INDIAN PHARMACOPOEIA 2022

Volume IV

Veterinary Monographs

Government of India
Ministry of Health & Family Welfare

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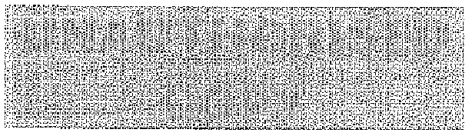

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General Notices

General Statements

The General Notices provide the basic guidelines for the interpretation and application of the standards, tests, assays, and other specifications of the Indian Pharmacopoeia (IP), as well as to the statements made in the monographs and other texts of the Pharmacopoeia.

A monograph is to be constructed in accordance with any general monograph or notice or any appendix, note or other explanatory material that is contained in this Pharmacopoeia and that is applicable to that monograph. All statements contained in the monograph, except where a specific general notice indicates otherwise and with the exceptions given hereafter, constitute standards for the official articles. An article is not of pharmacopoeial quality unless it complies with all of the requirements stated.

Exceptions to the General Notices do exist, and where they do, the wording in the individual monograph or an appendix takes precedence and specifically indicates directions or the intent. Thus, the specific wording of standards, tests, assays and other specifications is binding wherever deviations from the General Notices exist. Likewise, where there is no specific mention to the contrary, the General Notices apply.

Name. The full name or title of this book, including addenda thereto, is Indian Pharmacopoeia 2022, abbreviated to IP 2022. In the texts, the term "Pharmacopoeia" or "IP" without qualification means the Indian Pharmacopoeia 2022 and any amendments and thereto.

Official and Official Articles. The word 'official' wherever used in this Pharmacopoeia or with reference thereto, is synonymous with 'pharmacopoeial', with 'IP' and with 'compendial'. The designation IP in conjunction with the official title on the label of an article is an indication that the article purports to comply with IP standards.

The following terms are used where the articles for which monographs are provided are to be distinguished.

An official substance is a single drug or a drug entity or a pharmaceutical aid for which the monograph title includes no indication of the nature of a dosage form.

An official preparation is a drug product (dosage form) and is the finished or partially finished preparation or product of one or more official substances formulated for use on the patient.

An article is an item for which a monograph is provided, whether an official substance or an official preparation.

Official Standards. The requirements stated in the monographs apply to articles that are intended for medicinal use but not necessarily to articles that may be sold under the same name for other purposes.

An article is not of Pharmacopoeial quality unless it complies with all the requirements stated in the monograph. This does not imply that performance of all the tests in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the Pharmacopoeia before release of a product.

Pharmacopoeial requirements for articles used in veterinary medicine are established on the same basis as those used in human medicine. It should be noted that no requirement in the pharmacopoeia can be taken in isolation. A valid interpretation of any particular requirement depends upon it being read in context of the monograph as a whole, the specified method of analysis, the relevant General Notices and where appropriate the General Monographs.

Where a preparation that is the subject of a monograph in the Indian Pharmacopoeia is supplied for use in veterinary medicine, the standards of Indian Pharmacopoeia apply unless otherwise justified and authorized.

The active pharmaceutical ingredients (drug substances), excipients (pharmaceutical aids), pharmaceutical preparations (dosage forms) and other articles described in the monographs are intended for human and veterinary use (unless explicitly restricted to one of these uses). It may be noted, however, that in the event of doubt of interpretation in any text of Veterinary monographs of IP, Indian Pharmacopoeia Commission (IPC) should be consulted.

The requirements given in the monographs are not framed to provide against all possible impurities, contaminants or adulterants; they provide appropriate limitation of potential impurities only.

A preparation must comply with the requirements specified, throughout its shelf-life assigned to it by the manufacturer. For opened or broached containers, the maximum period of validity for use will be as may be stated in the individual monograph. Nevertheless, the responsibility for assigning the period of validity shall be with the manufacturer.

Added Substances. An official substance, as distinguished from an official preparation, contains no added substances except when specifically permitted in the individual monograph. Unless otherwise specified in the individual monograph, or elsewhere in the General Notices, suitable substances may be added to an official preparation to enhance its stability, preserve its properties, usefulness or elegance, or to facilitate its preparation. Such auxiliary substances shall be harmless in the amounts used, shall not exceed the minimum quantity required to provide their intended effect, shall not impair the therapeutic efficacy or the bioavailability or safety of the preparation and shall not interfere with any of the tests and assays prescribed for determining compliance with the official

standards. Particular care should be taken to ensure that such substances are free from harmful organisms. The freedom to the manufacturers to add auxiliary substances imposes on them the responsibility of satisfying the licensing authorities on the purpose of the addition and the innocuity of such substances. No substance shall be added to conceal any defect or damage or deficiency in the substance or formulation.

Alternative Methods. The tests and assays described are the official methods upon which the standards of the Pharmacopoeia are based. Alternative methods of analysis may be used for control purposes, provided that the methods used are shown to give results of equivalent accuracy and enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used. Automated procedures utilising the same basic chemistry as the test procedures given in the monograph may also be used to determine compliance. Such alternative or automated procedures must be validated and are subject to approval by the authority competent to authorised manufacturer of substance or product.

In the event of doubt or dispute, the methods of analysis of the Pharmacopoeia are alone authoritative and only the result obtained by the procedure given in this Pharmacopoeia is conclusive.

Meanings of Terms

Alcohol. The term "alcohol" without qualification means ethanol (95 per cent). Other dilutions of ethanol are indicated by the term "ethanol" or "alcohol" followed by a statement of the percentage by volume of ethanol (C_2H_6O) required.

Desiccator. A tightly-closed container of suitable size and design that maintains an atmosphere of low moisture content by means of silica gel or phosphorus pentoxide or other suitable desiccant.

Drying and ignition to constant weight. Two consecutive weighings after the drying or igniting operations do not differ by more than 0.5 mg, the second weighing following an additional period of drying or of ignition respectively appropriate to the nature and quantity of the residue.

Ethanol. The term "ethanol" without qualification means anhydrous ethanol or absolute alcohol.

Filtration. Unless otherwise stated, filtration is the passing of a liquid through a suitable filter paper or equivalent device until the filtrate is clear.

Freshly prepared. Made not more than 24 hours before it is used.

Label. Any printed packing material, including package inserts that provide information on the article.

Negligible. A quantity not exceeding 0.50 mg.

Solution. Where the name of the solvent is not stated, "solution" implies a solution in water. The water used complies with the requirements of the monograph on Purified Water.

Temperature. The symbol ° used without qualification indicates the use of the Celsius thermometric scale.

Water. If the term is used without qualification it means Purified Water of the Pharmacopoeia. The term 'distilled water' indicates Purified Water prepared by distillation.

Water-bath. A bath of boiling water unless water at another temperature is indicated. Other methods of heating may be used provided the required temperature is approximately maintained but not exceeded.

Provisions Applicable To Monographs and Test Methods

Expression of Contents. Where the content of a substance is defined, the expression "per cent" is used according to circumstances with one of two meanings:

— per cent w/w (percentage, weight in weight) expressing the number of grams of substance in 100 grams of final product,

— per cent v/v (percentage, volume in volume) expressing the number of millilitres of substance in 100 millilitres of final product.

The expression "parts per million" refers to the weight in weight, unless otherwise stated.

Where the content of a substance is expressed in terms of the chemical formula for that substance an upper limit exceeding 100 per cent may be stated. Such an upper limit applies to the result of the assay calculated in terms of the equivalent content of the specified chemical formula. For example, the statement 'contains not less than 99.0 per cent and not more than 101.0 per cent of $C_7H_6O_2$ implies that the result of the assay is not less than 99.0 per cent and not more than 101.0 per cent, calculated in terms of the equivalent content of $C_7H_6O_2$.

Where the result of an assay or test is required to be calculated with reference to the dried, anhydrous, ignited substance, or the substance free from solvent, the determination of loss on drying, water content, loss on ignition, content of the specified solvent, respectively is carried out by the method prescribed in the relevant test in the monograph.

Expression of Concentrations. The following expressions in addition to the ones given under Expression of Content are also used:

— per cent w/v (percentage, weight in volume) expressing the number of grams of substance in 100 millilitres of product,

— per cent v/w (percentage, volume in weight) expressing the number of millilitres of substance in 100 grams of product.

Usually, the strength of solutions of solids in liquids is expressed as percentage weight in volume, of liquids in liquids as percentage volume in volume, of solids in semi-solid bases (e.g. creams) and of gases in liquids as percentage weight in weight.

When the concentration of a solution is expressed as parts of dissolved substance in parts of solution, it means parts by weight (g) of a solid in parts by volume (ml) of the final solution; as parts by weight (g) of a gas in parts by weight (g) of the final solution.

When the concentration of a solution is expressed in molarity designated by the symbol M preceded by a number, it denotes the number of moles of the stated solute contained in sufficient Purified Water (unless otherwise stated) to produce 1 litre of solution.

Abbreviated Statements. Incomplete sentences are employed in parts of the monographs for directness and brevity (for example, Iodine Value. Not more than ……; Relative Density. ……to……..) Where the tests are abbreviated, it is to be understood that the test method referred to in brackets provides the method to be followed and that the values specified are the applicable limits.

Weights and Measures. The metric system of weights and measures is employed in the Pharmacopoeia. All measures are required to be graduated at 25° and all measurements in tests and assays, unless otherwise stated, are to be made at that temperature. Graduated glass apparatus used in analytical operations shall comply with the requirements stated in Chapter 2.1.6.

Monographs

General Monographs

General monographs on dosage forms include requirements of general application and apply to all preparations within the scope of the Introduction section of the general monograph, except where a preamble limits the application. The requirements are not necessarily comprehensive for a given specific preparation; additional requirements may sometimes be given in the individual monograph for it.

Production. Statements given under the heading Production relate to particular aspects of the manufacturing process and are not necessarily comprehensive. However, they are mandatory instructions to manufacturers. They may relate, for example, to source materials, to the manufacturing process and its validation and control, to any in-process testing that is to be carried out by the manufacturer on the final product either on selected batches or on each batch prior to release. All this cannot be verified on a sample of the final product by an independent analyst. It is for the licensing authority to verify that the instructions have been followed.

The absence of a section on Production does not imply that attention to features such as those given above is not required. An article described in a monograph of the Pharmacopoeia is to be manufactured in accordance with the principles of good manufacturing practice and in accordance with the requirements of the Drugs and Cosmetics Rules, 1945. The general principles applicable to the manufacture and quality assurance of drugs and preparations meant for human use apply equally to veterinary products as well.

Manufacture of Drug Products. The opening definitive statement in certain monographs for drug products is given in terms of the active ingredient(s) only. Any ingredient(s) other than those included in the statement, must comply with the general notice on Excipients and the product must conform to the Pharmacopoeial requirements.

Official preparations are prepared only from ingredients that comply with the requirements of the pharmacopoeial monographs for those individual ingredients for which monographs are provided.

Excipients. Any substance added in preparing an official preparation shall be innocuous, shall have no adverse influence in the therapeutic efficacy of the active ingredients and shall not interfere with the tests and assays of the Pharmacopoeia. Care should be taken to ensure that such substances are free from harmful organisms.

Individual Monographs

Drug products that are the subject of an individual monograph are also required to comply with the tests given in the general monographs.

Titles. The main title for a drug substance is the International Non-proprietary Name (INN) approved by the World Health Organization. Subsidiary names and synonyms have also been given in some cases; where included, they have the same significance as the main title.

The main titles of drug products are the ones commonly recognised in practice. Synonyms drawn from the full non-proprietary name of the active ingredient or ingredients have also been given. Where, however, a product contains one or the other of different salts of an active molecule, the main title is based on the full name of the active ingredient. For example, Chloroquine Phosphate Tablets and Chloroquine Sulphate Tablets.

Chemical Formulae. When the chemical structure of an official substance is known or generally accepted, the graphic and molecular formulae are normally given at the beginning of the monograph for information. This information refers to the chemically pure substance and is not to be regarded as an indication of the purity of the official material. Elsewhere, in statement of purity and strength and in descriptions of

processes of assay, it will be evident from the context that the formulae denote the chemically pure substances.

Where the absolute stereochemical configuration is specified, the International Union of Pure and Applied Chemistry (IUPAC) *R/S* and *E/Z* systems of designation have been used. If the substance is an enantiomer of unknown absolute stereochemistry, the sign of the optical rotation, as determined in the solvent and under the conditions specified in the monograph, has been attached to the systematic name. An indication of sign of rotation has also been given where this is incorporated in a trivial name that appears on an IUPAC preferred list.

Atomic and Molecular Weights. The atomic weight or molecular weight is shown, as and when appropriate at the top right hand corner of the monograph. The atomic and molecular weights and graphic formulae do not constitute analytical standards for the substances described.

Definition. The opening statement of a monograph is one that constitutes an official definition of the substance, preparation or other article that is the subject of the monograph. In certain monographs for pharmaceutical preparations the statement is given in terms of the principal ingredient(s).

In monographs on vegetable drugs, the definition indicates whether the subject of the monograph is, for example, the whole drug or the drug in powdered form.

Certain pharmaceutical substances and other articles are defined by reference to a particular method of manufacture. A statement that a substance or article is prepared or obtained by a certain method constitutes part of the official definition and implies that other methods are not permitted. A statement that a substance may be prepared or obtained by a certain method, however, indicates that this is one possible method and does not imply that other methods are not permissible.

Statement of content. The limits of content stated are those determined by the method described under Assay.

Category. The statement of category is provided for general information only and is indicative of the medical or pharmaceutical basis for recognition in the Pharmacopoeia. It generally represents an application of the best known pharmacological action of the article or of its active ingredient. The statement under the heading 'Category' are also subject to regulations under the D&C Act 1940 and rules theirunder. In the case of pharmaceutical aids it may indicate the more common usage of the article. The statement is not intended to limit in any way the choice or use of the article nor to indicate that it has no other activity or use.

Usual strength. The statement on the usual strength(s) of a preparation given in the individual monograph indicates the strength(s) usually marketed for information of the pharmacist and the medical practitioner. It does not imply that a strength other than the one(s) mentioned in the individual monograph meeting all the prescribed requirements cannot be manufactured and marketed with the approval of the appropriate authority.

Description. The statements under the heading Description are not to be interpreted in a strict sense and are not to be regarded as official requirements.

Solubility. Statements on solubility are given in Chapter 2.4.26 and are intended as information on the approximate solubility at a temperature between 15° and 30°, unless otherwise stated, and are not to be considered as official requirements. However, a test for solubility stated in a monograph constitutes part of the standards for the substance that is the subject of that monograph.

Residual solvents. The requirements, guidance and information on residual solvents for pharmaceutical use are given in the chapter entitled Residual Solvents (5.4).

All IP articles are subject to relevant control of residual solvents, even when no test is specified in the individual monograph. If solvents are used during production, they must be of suitable quality. In addition, the toxicity and residual level of each solvent shall be taken into consideration and the solvents limited according to the principles defined and the requirements specified in Chapter 5.4. Residual Solvent, using the general methods presented therein or other suitable methods.

Test Methods

References to general methods of testing are indicated by test method numbers in brackets immediately after the heading of the test or at the end of the text.

Identification. The tests given under the heading Identification are not necessarily sufficient to establish absolute proof of identity. They provide a means of verifying that the identity of the material under examination is in accordance with the label on the container.

In certain monographs alternative series of identification tests are given; compliance with either one or the other set of tests is adequate to verify the identity of the article.

When tests for infrared absorption are applied to material extracted from formulated preparations, strict concordance with the specified reference spectrum may not always be possible, but nevertheless a close resemblance between the spectrum of the extracted material and the specified reference spectrum should be achieved.

Tests and Assays

The tests and assays are the official methods upon which the standards of the Pharmacopoeia depend. The requirements are not framed to take into account all possible impurities. It is

not to be presumed, for example, that an impurity that is not detectable by means of the prescribed tests is tolerated. Material found to contain such an impurity is not of pharmacopoeial quality if the nature or amount of the impurity found is incompatible with good pharmaceutical practice.

Pharmacopoeial methods and limits should be used merely as compliance requirements and not as requirements to guarantee total quality assurance. Tests and assays are prescribed for the minimum sample available on which the attributes of the article should be measured. Assurance of quality must be ensured by the manufacturer by the use of statistically valid sampling and testing programmes.

Tests. Unless otherwise stated, the assays and tests are carried out at a temperature between 20° and 30°.

Where it is directed that an analytical operation is to be carried out 'in subdued light', precautions should be taken to avoid exposure to direct sunlight or other strong light. Where a procedure is directed to be performed 'protected from light' precautions should be taken to exclude actinic light by the use of low-actinic glassware, working in a dark room or similar procedures.

For preparations other than those of fixed strength, the quantity to be taken for a test or an assay is usually expressed in terms of the active ingredient. This means that the quantity of the active ingredient expected to be present and the quantity of the preparation to be taken are calculated from the strength stated on the label.

Other Tests. In the monographs on dosage forms and certain preparations, under the sub-heading 'Other tests' it is stated that the article complies with the tests stated under the general monograph of the relevant dosage form or preparation. Details of such tests are provided in the general monographs.

Limits. The limits given are based on data obtained in normal analytical practice. They take into account normal analytical errors, of acceptable variations in manufacture and of deterioration to an extent that is acceptable. No further tolerances are to be applied to the limits for determining whether or not the article under examination complies with the requirements of the monograph.

Quantities. Unless otherwise stated, the quantities to be taken for assays, limit tests and other tests are of the substance under examination.

In tests with numerical limits and assays, the quantity stated to be taken for testing is approximate. The amount actually used, which may deviate by not more than 10 per cent from that stated, is accurately weighed or measured and the result of analysis is calculated from this exact quantity. In tests where the limit is not numerical but usually depends upon comparison with the behaviour of a reference in the same conditions, the stated quantity is taken for testing. Reagents are used in the prescribed amounts.

Quantities are weighed or measured with an accuracy commensurate with the indicated degree of precision. For weighings, the precision is plus or minus 5 units after the last figure stated. For example, 0.25 g is to be interpreted as 0.245 g to 0.255 g. For the measurement of volumes, if the figure after the decimal point is a zero or ends in a zero, e.g. 10.0 ml or 0.50 ml, the volume is measured using a pipette, a volumetric flask or a burette, as appropriate; in other cases, a graduated measuring cylinder or a graduated pipette may be used. Volumes stated in microlitres are measured using a micropipette or microsyringe.

The term 'transfer' is used generally to indicate a quantitative operation.

Apparatus. Measuring and weighing devices and other apparatus are described in the chapter entitled 'Apparatus for Tests and Assays'. A specification for a definite size or type of container or apparatus in a test or assay is given merely as a recommendation.

Unless otherwise stated, comparative tests are carried out using identical tubes of colourless, transparent, neutral glass with a flat base, commonly known as Nessler cylinders.

Reagents and Solutions. The reagents required for the tests and assays of the Pharmacopoeia are defined in the various chapters showing their nature, degree of purity and the strengths of the solutions to be made from them. The requirements set out are not intended to imply that the materials are suitable for use in the test concerned; reagents not covered by monographs in the pharmacopoeia shall not be claimed to be of IP quality.

The term 'analytical reagent grade of commerce' implies that the chemical is of a high degree of purity wherein the limits of various impurities are known. Where it is directed to use a 'general laboratory reagent grade of commerce' it is intended that a chemically pure grade material, not necessarily required to be tested for limiting or absence of certain impurities, is to be used.

Indicators. Where the use of an indicator solution is mentioned in an assay or test, approximately 0.1 ml of the solution shall be added, unless otherwise directed.

Reference Substances. Certain monographs require the use of a chemical reference substance or a biological reference preparation or a reference spectrum. These are authentic specimens chosen and verified on the basis of their suitability for intended use as prescribed in the Pharmacopoeia and are not necessarily suitable in other circumstances.

IP Reference Substances, abbreviated to IPRS are issued by the Indian Pharmacopoeia Commission (IPC). They are the official standards to be used in cases of arbitration.

Biological Reference Substances, also abbreviated to IPRS and Standard Preparations of antibiotics are issued by

agencies authorised by the IPC. They are standardized against the International Standards and Reference Preparations established by the World Health Organization (WHO). The potency of these preparations is expressed in International Units.

Reference spectra are published by the IPC and they are accompanied by information concerning the conditions used for sample preparation and recording of the spectra.

Test Animals. The animal experiments are carried out in accordance with the provisions of 'The Prevention of Cruelty to Animals Act, 1960' and 'CPCSEA Guidelines' so as to prevent the infliction of unnecessary pain, suffering and prevention of cruelty to animals. Unless otherwise directed, animals used in a test or an assay shall be healthy and are drawn from a uniform stock, and have not previously been treated with any material that will interfere with the test or the assay.

Rounding Rules for Calculation of Results. The observed or calculated values should be rounded off to the number of decimal places that is in agreement with the limit expression. Numbers should not be rounded up or down until the final calculations for the reportable value have been completed. Intermediate calculations (e.g., slope for linearity) may be rounded for reporting purposes, but the original (not rounded) value should be used for any additional required calculations. Acceptance criteria are fixed numbers and are not rounded.

When rounding is required, consider only one digit in the decimal place to the right of the last place in the limit expression. If this digit is 4 or smaller, it is eliminated and the preceding digit is left unchanged. If this digit is 5 to 9, it is eliminated and the preceding digit is increased by 1.

Table 1 – Illustration of Rounding Numerical values for comparison with Requirements

Pharmacopoeial Requirement	Unrounded Value (per cent)	Rounded Result (per cent)	Conforms
Assay limit	97.96	98.0	Yes
≥ 98.0 per cent	97.92	97.9	No
	97.95	98.0	Yes
Assay limit	101.55	101.6	No
≤ 101.5 per cent	101.46	101.5	Yes
	101.45	101.5	Yes
Limit test	0.025	0.03	No
≤ 0.02 per cent	0.015	0.02	Yes
	0.027	0.03	No
Limit test ≤ 3 ppm	3.5 ppm	4 ppm	No
	3.4 ppm	3 ppm	Yes
	2.5 ppm	3 ppm	Yes

Storage. Statements under the side-heading 'Storage' constitute non-mandatory advice. The articles of the Pharmacopoeia are to be stored under conditions that prevent contamination and, as far as possible, deterioration. Precautions that should be taken in relation to the effects of the atmosphere, moisture, heat and light are indicated, where appropriate, in the individual monograph.

Specific directions are given in some monographs with respect to the temperatures at which Pharmacopoeial articles should be stored, where it is considered that usage at a lower or higher temperature may produce undesirable results. The storage conditions are defined by the following terms:

— Store in a dry, well-ventilated place at a temperature not exceeding 30°
— Store in a refrigerator (2° to 8°). Do not freeze
— Store in a freezer (-2° to -18°)
— Store in a deep freezer (Below -18°)

Storage conditions not related to temperature are indicated in the following terms:

— Store protected from light
— Store protected from light and moisture

Where no specific storage directions or limitations are given in the monograph or in the D&C rules 1945 or by the manufacturer, it is to be understood that the storage conditions include protection from moisture, direct sunlight, freezing and excessive heat (any temperature above 40°).

Storage Containers. The requirements, guidance and information on containers for pharmaceutical use are given in the chapter entitled Containers (6.2).

In general, an article should be packed in a well-closed container i.e. one that protects the contents from contamination by extraneous solids, liquids, moisture or vapours and from loss of the article under normal conditions of handling and storage and preserves the properties of the drug. Containers, unless otherwise specified, or of the nature such as capsule shall, foils of strips etc, shall allow examination of the contents inside. Closures used shall also of suitable properties and quality to protect the drug from any contamination and shall not be the source of contamination by themselves. Notices as may be needed in respect of Radiopharmaceuticals may also be incorporated.

Where, additionally, loss or deterioration of the article from effervescence, deliquescence or evaporation under normal conditions of storage is likely, the container must be capable of being tightly closed, and re-closed after use.

In certain cases, special requirements of pack have been indicated in some monographs under Storage, using expressions that have been defined in chapter 6.2.

Labelling. The labelling of drugs and pharmaceuticals is governed by the Drugs and Cosmetics Rules, 1945. The statements that are given in the monographs under the side-heading 'Labelling' are not comprehensive. Only those that are necessary to demonstrate compliance or otherwise with the monograph have been given and they are mandatory. For example, in the monograph on Betamethasone Sodium Tablets the labelling statement is "The label states the strength in terms of the equivalent amount of betamethasone".

Notice

For monographs of drugs detailed elsewhere in this edition of the IP, only the ususal strength etc as may be applicable for veterinary use are stated in this volume. The users have to refer to the relevant monograph in the other volumes of this edition of IP. The monographs included in this volume of the Indian Pharmacopoeia 2022 are applicable exclusively for drugs intended for animal use only unless otherwise justified and authorised.

VETERINARY GENERAL MONOGRAPHS

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Veterinary Diagnostics 4807
Veterinary Immunosera 4808
Veterinary Liquid Preparations for Cutaneous Application 4811
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General Monographs

General Requirements

The general requirements relating to a specific type of dosage form of an active pharmaceutical ingredient or ingredients, that have been given in the chapter on General Monographs on Dosage Forms of Active Pharmaceutical Ingredients apply to all veterinary dosage forms or preparations of the type defined. However, a valid interpretation of the appropriateness of a test or requirement should be done in the context of the monograph as a whole and of the relevant General Notices.

The requirement for compliance with the tests given under each dosage form or preparation is indicated in each monograph of a drug product or preparation under the heading 'Other tests'. These tests are mandatory and are additional to the tests given in the individual monograph.

Intramammary Infusions

Intramammary Infusions for Veterinary Use; Intramammary Injections.

Intramammary Infusions are sterile products intended for injection into the mammary gland through the teat canal. They are solutions, emulsions or suspensions or semi-solid preparations containing one or more active ingredients in a suitable vehicle. They may contain stabilizing, emulsifying, suspending and thickening agents. If a sediment is formed in a suspension, it is readily dispersible on shaking. In emulsions, phase separation may occur but this is readily miscible on shaking.

There are two main types of Intramammary Infusions. One is intended for administration to lactating animals as qualified by the term Lactating Cow/Buffalo and the other, qualified as Non-lactating or Dry Cow/Buffalo, is intended for administration to animals at the end of lactation or during the non-lactating period for the prevention or treatment of infection during the dry period.

Intramammary Infusions are prepared by dissolving or suspending the sterile medicaments in the sterilized vehicle using aseptic precautions, unless a process of terminal sterilisation is employed.

Containers. Intramammary Infusions are usually supplied in single dose containers for administration into a single teat canal of an animal. If supplied in multiple dose containers, aqueous preparations contain an antimicrobial preservative in adequate concentration except when the preparation itself has antimicrobial properties. The containers are made from materials that meet the requirements for Parenteral Preparations intended for use in human beings.

The containers are sealed so as to exclude microorganisms and each container is fitted with a smooth, tapered nozzle to facilitate the introduction of the infusion into the teat canal. The containers are sterilised and filled aseptically unless the preparation is subjected to a process of terminal sterilisation.

Tests

Sterility. Intramammary Infusions comply with the test for sterility (2.2.11), using Method A or B, as appropriate, using the contents of 10 containers mixed thoroughly before use in the test. Use for each medium 0.5 to 1.0 g or 0.5 to 1.0 ml, as appropriate, of the mixed sample.

Storage. Store in sterile, single dose or multiple dose, tamper-evident containers.

Labelling. The label states (1) the strength in terms of the weight or the number of Units of activity of the active ingredient(s) or that may be expressed from the container using normal techniques; (2) whether the preparation is intended for use in lactating cow/buffalo or in dry or non-lactating cow/buffalo; (3) for Intramammary Infusions (Non-lactating or Dry Cow/Buffalo), that the preparation is not intended for use in lactating animals; (4) in the case of infusions in multiple dose containers, the name of any added antimicrobial preservative.

Intrauterine Preparations

Intrauterine Preparations for veterinary use are liquid, semi-solid or solid preparations intended for the direct administration to the uterus (cervix, cavity or fundus), usually in order to obtain a local effect. They contain one or more active substances in a suitable base.

Where appropriate, containers for intrauterine preparations for veterinary use comply with the requirements for Containers for Pharmaceutical Products (6.2).

Production

During the development of an intrauterine preparation for veterinary use, the effectiveness of any added antimicrobial preservative shall be demonstrated to the satisfaction of the competent authority. A suitable test method together with criteria for judging the preservative properties of the formulation are provided under Effectiveness of Antimicrobial Preservative (2.2.2).

In the manufacture, packaging, storage and distribution of intrauterine preparations for veterinary use, suitable means are taken to ensure their microbial quality.

Sterile intrauterine preparations for veterinary use are prepared using materials and methods designed to ensure sterility and to avoid the introduction of contaminants and the growth of microorganisms.

During development, it must be demonstrated that the nominal content can be withdrawn from the container of liquid and semi-solid intrauterine preparations for veterinary use presented in single-dose containers.

Tests

Uniformity of content (2.5.4). Unless otherwise prescribed or justified and authorised, solid single-dose preparations with a content of active substance less than 10 mg or less than 10 per cent of the total mass comply with test A (intrauterine tablets) or test B (intrauterine capsules) for uniformity of content of single-dose preparations. If the preparation has more than one active substance, the requirement applies only to those substances which correspond to the above conditions.

Uniformity of weight (2.5.3). Solid single-dose intrauterine preparations for veterinary use comply with the test for uniformity of weight of single-dose preparations. If the test for uniformity of content is prescribed for all the active substances, the test for uniformity of weight is not required.

Dissolution (2.5.2). A suitable test may be carried out to demonstrate the appropriate release of the active substance(s) from solid single-dose intrauterine preparations for veterinary use, for example one of the tests described in *Dissolution test for solid dosage forms*.

When dissolution test is prescribed, disintegration test may not be required.

Sterility (2.2.11). Sterile intrauterine preparations for veterinary use comply with the test for sterility. Applicators supplied with the preparation also comply with the test for sterility. Remove the applicator with aseptic precautions from its package and transfer it to a tube of culture medium so that it is completely immersed.

Labelling. The label states (1) the name of any added antimicrobial preservative; (2) where applicable, that the preparation is sterile.

Intrauterine Tablets

Intrauterine tablets are solid preparations each containing a single dose of one or more active substances. They generally conform to the definition given in the monograph on *Tablets*.

A suitable applicator may be used for application into the uterus.

Tests

Disintegration (2.5.1). Unless intended for prolonged local action, they comply with the test for disintegration of suppositories and pessaries. Examine the state of the tablets after 30 minutes.

Intrauterine Capsules

Intrauterine capsules are solid, single-dose preparations. They are generally similar to soft capsules, differing only in their shape and size. Intrauterine capsules have various shapes, usually ovoid. They are smooth and have a uniform external appearance.

A suitable applicator may be used for application into the uterus.

Tests

Disintegration (2.5.1). Unless intended for prolonged local action, they comply with the test for disintegration of suppositories and pessaries. Examine the state of the capsules after 30 minutes.

Intrauterine Solutions, Suspensions and Emulsions

Intrauterine Solutions, Suspensions and Emulsions are liquid preparations. Concentrates for intrauterine solutions are intended for administration after dilution.

They may contain excipients, for example to adjust the viscosity of the preparation, to adjust or stabilize the pH, to increase the solubility of the active substances or to stabilise the preparation. The excipients do not adversely affect the intended medical action, or, at the concentrations used, cause undue local irritation.

Intrauterine emulsions may show evidence of phase separation, but are readily redispersed on shaking. Intrauterine suspensions may show sediment that is readily dispersed on shaking to give a suspension which remains sufficiently stable to enable a homogeneous preparation to be delivered.

They may be supplied in single-dose containers. The container is adapted to deliver the preparation to the uterus or it may be accompanied by a suitable applicator.

Production

In the manufacture of intrauterine suspensions, measures are taken to ensure a suitable and controlled particle size with regard to the intended use.

Tablets for Intrauterine Solutions and Suspensions

Tablets intended for the preparation of intrauterine solutions and suspensions are single-dose preparations which are

dissolved or dispersed in water at the time of administration. They may contain excipients to facilitate dissolution or dispersion or to prevent caking.

Tablets for intrauterine solutions or suspensions comply with the requirements given in the monograph on *Tablets*.

After dissolution or dispersion, they comply with the requirements for intrauterine solutions or intrauterine suspensions, as appropriate.

Tests

Disintegration (2.5.1). Tablets for intrauterine solutions or suspensions disintegrate within 3 minutes when tested according to the test for disintegration of tablets and capsules, but using *water* at 37° ± 2°.

Labelling. The label states (1) the method of preparation of the intrauterine solution or suspension; (2) the conditions and duration of storage of the solution or suspension after reconstitution.

Veterinary Diagnostics

Veterinary Diagnostics are antigenic materials of bacterial or viral origin employed for various tests. These will also include polyclonal or monoclonal antibodies. The preparations are examined for their purity at various critical stages of production. The diagnostic kits may be prepared using bacterial or viral antigens and antisera.

Proper Name

The proper name of any diagnostic agent is the name of microorganism which it is made, followed by the word 'antigen', or it may be derived from the name of the organism responsible for the causation of the disease, or the name approved by the licensing authority.

Production

Diagnostic agents of bacterial origin are prepared from selected cultures after their careful examination for the identity, specificity, purity and antigenicity. They may be prepared in the following manner.

A. Formolised antigens- the selected pure culture strain grown in a suitable medium at an optimum temperature for an appropriate period. The pure growth is then exposed to the action of a solution of formaldehyde in a suitable concentration and an appropriate temperature for a suitable period.

B.In some cases, the diagnostic agents are prepared by growing the organisms on suitable media and then deriving specific protein constituents of the bacteria by various methods.

Tests

Veterinary Diagnostics, reconstituted where necessary, comply with the following tests unless otherwise stated in the individual monograph.

Identification

Unless otherwise stated in the individual monograph, Veterinary Diagnostics exhibits specific agglutination when mixed with the serum of the animals infected with homologous organisms or give specific reaction when injected into the skin of a healthy white guinea-pig or rabbit that has not been previously treated with any material that will interfere with the test but fails to produce this reaction when mixed with a sufficient quantity of the specific antitoxin or antiserum.

Sterility. Unless otherwise stated, in the individual monograph Veterinary Diagnostics comply with the test for sterility (2.2.11), except that in the case of preparations containing living bacteria there may be growth of the organism from which the diagnostic was prepared.

Use suitable solid media for streaking the preparation under examination and incubate at 30° to 35° for 72 hours for detecting bacteria and at 20° to 25° for 72 hours for detecting fungi. The media selected will depend upon the nature of the product to be tested. The contents of each randomly selected sealed container of the preparation under examination or portions or dilutions thereof, as appropriate, are used for the test.

Other tests to determine the nature and identity of contaminating microorganisms, if any, detected during the test include examination for mobility of the organisms, fermentation reactions, thermo-agglutination tests and dye inhibitor tests (in the case of *Brucella* cultures).

Unless otherwise stated in the monograph, the preparation passes the test if no growth of microorganisms, other than those from which the veterinary diagnostic was prepared, is observed in any of the media during the incubation period. Repeat the tests if growth of organisms, other than those from which the veterinary diagnostic was prepared, is observed. The diagnostic passes the test if no growth of microorganisms, other than those from which the diagnostic was prepared, is observed in any of the media. The preparation fails the test if growth of a microorganism that was seen after the first test, other than those from which the veterinary diagnostic was prepared, is observed. If growth of a different microorganism is observed, the test may be repeated a second time. The preparation passes the test if no growth of a microorganism, other than those from which the veterinary diagnostic was prepared, is observed in any of the media.

The number of containers recommended to be drawn by the manufacturer for performing the test for sterility depends on the environmental conditions of manufacture, the volume of preparation per container and any other special considerations

applicable to the preparation concerned. For preparations intended for veterinary use, 1 per cent of the containers in a batch, with a minimum of three and a maximum of ten, is considered a suitable number assuming that the preparation has been manufactured under appropriately validated conditions designed to exclude contamination.

Storage. Store protected from light in a refrigerator (2° to 8°) unless otherwise stated in the individual monograph.

Labelling. The label states (1) the name and quantity of any antibacterial substance added; (2) for a dried preparation, the nature and quantity of the liquid to be used for reconstitution.

Veterinary Immunosera

Immunosera for veterinary use are preparations containing immunoglobulins, purified immunoglobulins or immunoglobulin fragments obtained from serum or plasma of immunised animals. They may be preparations of crude polyclonal antisera or purified preparations.

The immunoglobulins or immunoglobulin fragments have the power of specifically neutralising the antigen used for immunisation. The antigens include microbial or other toxins, bacterial and viral antigens, venoms of snakes and hormones. The preparation is intended for parenteral administration to provide passive immunity.

Production

General Provisions. Immunosera are obtained from the serum or plasma of healthy animals immunised by administration of one or more suitable antigens. The production method shall have been shown to yield consistently batches of immunosera of acceptable safety and efficacy (2.7.12).

Donor Animals. The animals used are exclusively reserved for production of immunoserum. They are maintained under conditions protecting them from the introduction of disease, as far as possible. The donor animals, and any animals in contact with them, are tested and shown to be free from a defined list of infectious agents and re-tested at suitable intervals. The list of agents for testing includes not only those agents that are relevant to the donor animal, but also those that are relevant to the recipient target species for the product. Where the donor animals have not been demonstrated to be free from a relevant pathogen, a justification must be provided and a validated inactivation or purification procedure must be included in the manufacturing procedure. The feed originates from a controlled source. Where the donor animals are chickens, use chickens from a flock free from specified pathogens (2.7.7). Where applicable for the species used, measures are taken to avoid contamination with agents of transmissible spongiform encephalopathies.

As far as possible, animals being introduced into the herd are from a known source and have a known breeding and rearing history. The introduction of animals into the herd follows specified procedures, including defined quarantine measures. During the quarantine period the animals are observed and tested to establish that they are free from the list of agents relevant for the donor animals. It may be necessary to test the animals in quarantine for freedom from additional agents, depending on their known breeding and rearing history or any lack of information on their source. Any routine or therapeutic medicinal treatment administered to the animals in quarantine or thereafter must be recorded.

Immunising Antigen. The principles described in the Veterinary Vaccines: General Requirements are applied to the production of the immunogen. The antigen used is identified and characterised. The starting materials used for antigen preparation must be controlled to minimise the risk of contamination with extraneous agents. The antigen may be blended with a suitable adjuvant. The immunogen is produced on a batch basis. The batches must be prepared and tested in such a manner that assures that each batch will be equally safe and free from extraneous agents and will produce a satisfactory, consistent immune response.

Immunisation. The donor animals are immunised according to a defined schedule. For each animal, the details of the dose of immunising antigen, route of administration and dates of administration are recorded. Animals are kept under general health surveillance and the developments of specific antibodies are monitored at appropriate stages of the immunisation process.

Collection of Blood or Plasma. Animals are thoroughly examined before each collection. Only healthy animals may be used as a donor animal. Collection of blood is made by venepuncture or plasmapheresis. The puncture area is shaved, cleaned and disinfected. The method of collection and the volume to be collected on each occasion are specified. The blood or plasma is collected in such a manner as to maintain sterility of the product. If the serum or plasma is stored before further processing, precautions are taken to avoid microbial contamination.

The blood or plasma collection is conducted at a site separate from the area where the animals are kept or bred and the area where the immunoserum is further processed. Clear criteria are established for determining the time between immunisation and first collection of blood or plasma as well as the time between subsequent collections and the length of time over which collections are made. The criteria applied must take into account the effect of the collections on the health and welfare of the animal as well as the effect on the consistency of production of batches of the finished product, over time.

The rate of clearance of any residues that may arise from the immunising antigen or medication given needs to be taken into account. In the case of the risk of residues from chemical substances, consideration could be given to the inclusion of a withdrawal period for the finished product. If the immunising agent consists of a live organism, the time between immunisation and collection may need to take into account the time required for the donor to eliminate the immunogen, particularly if any residual live organisms might be harmful to the recipient.

Preparation of the Finished Product. Several single plasma or serum collections from one or more animals may be pooled to form a bulk for preparation of a batch. The number of collections that may be used to produce a bulk and the size of the bulk are defined. Where pooling is not undertaken, the production procedure must be very carefully controlled to ensure that the consistency of the product is satisfactory. The active substance is subjected to a purification and/or inactivation procedure unless omission of such a step has been justified and agreed with the competent authority. The procedure applied must have been validated and be shown not to adversely impair the biological activity of the product. The validation studies must address the ability of the procedure to inactivate or remove any potential contaminants such as pathogens that could be transmitted from the donor to the recipient target species and infectious agents such as those that cause ubiquitous infections in the donor animals and cannot be readily eliminated from these donor animals. For purified immunosera, the globulins containing the immune substances may be obtained from the crude immunoserum by enzyme treatment and fractional precipitation or by other suitable chemical or physical methods.

Antimicrobial preservatives. Antimicrobial preservatives are used to prevent spoilage or adverse effects caused by microbial contamination occurring during use of a product. Antimicrobial preservatives are not included in freeze-dried products but, if justified, taking into account the maximum recommended period of use after reconstitution, they may be included in the diluent for multidose freeze-dried products. For single-dose liquid preparations, inclusion of antimicrobial preservatives is not normally acceptable, but may be acceptable, for example where the same product is filled in single-dose and multidose containers and is for use in non-food producing species. For multidose liquid preparations, the need for effective antimicrobial preservation is evaluated taking into account likely contamination during use and the maximum recommended period of use after broaching of the container. During development studies the effectiveness of the antimicrobial preservative throughout the period of validity shall be demonstrated to the satisfaction of the competent authority.

The efficacy of the antimicrobial preservative is evaluated as described in chapter; for a multidose preparation, additional samples are taken, to monitor the effect of the antimicrobial preservative over the proposed in-use shelf-life. If neither the (a) criteria nor the (b) criteria of interpretation in Effectiveness of Antimicrobial Preservatives (2.2.2) can be met, then in justified cases the following criteria are applied to antisera for veterinary use: bacteria, no increase at 24 hours and 7 days, 3 log reduction at 14 days, no increase at 28 days; fungi, no increase at 14 days and 28 days.

Addition of antibiotics as antimicrobial preservative is not acceptable.

Unless otherwise prescribed in the monograph, the final bulk is distributed aseptically into sterile, tamper-proof containers which are then closed so as to exclude contamination.

The preparation may be freeze-dried.

In-process tests. Suitable tests are carried out in-process, such as on samples from collections before pooling to form a bulk.

Batch Tests

The tests that are necessary to demonstrate the suitability of a batch of a product will vary and are influenced by a number of factors, including the detailed method of production. The tests to be conducted by the manufacturer on a particular product are agreed with the competent authority. If a product is treated by a validated procedure for inactivation of extraneous agents, the test for extraneous agents can be omitted on that product with the agreement of the competent authority. If a product is treated by a validated procedure for inactivation of mycoplasmas, the test for mycoplasmas can be omitted on that product with the agreement of the competent authority. Only a batch that complies with each of the relevant requirements given under Identification, Tests and Potency and/or in the relevant specific monograph may be released for use. With the agreement of the competent authority, certain tests may be omitted where in-process tests give an equal or better guarantee that the batch would comply or where alternative tests validated with respect to the Pharmacopoeia method have been carried out. Certain tests, e.g. for antimicrobial preservatives, for foreign proteins and for albumin, may be carried out by the manufacturer on the final bulk rather than on the batch, batches or sub-batches of finished product prepared from it. In some circumstances, e.g. when collections are made into plasmapheresis bags and each one is, essentially, a batch, pools of samples may be tested, with the agreement of the competent authority.

It is recognised that, in accordance with General Notice, for an established antiserum the routine application of the safety test will be waived by the competent authority in the interests of animal welfare when a sufficient number of consecutive

batches have been produced and found to comply with this test, thus demonstrating consistency of the manufacturing process. Significant changes to the manufacturing process may require resumption of routine testing to re-establish consistency. The number of consecutive batches to be tested depends on a number of factors such as the type of antiserum, the frequency of production of batches, and experience with the immunoserum during developmental safety testing and during application of the batch safety test. Without prejudice to the decision of the competent authority in the light of information available for a given antiserum, testing of 10 consecutive batches is likely to be sufficient for the majority of products. For products with an inherent safety risk, it may be necessary to continue to conduct the safety test on each batch.

Animal tests. If it is indicated that an animal is considered to show positive, infected etc. when typical clinical signs occur then as soon as sufficient indication of a positive result is obtained the animal in question shall be either euthanised or given suitable treatment to prevent unnecessary suffering. In accordance with the General chapter, alternative test methods may be used to demonstrate compliance with the monograph and the use of such tests is particularly encouraged when this leads to replacement or reduction of animal use or reduction of suffering.

pH (2.4.24). The pH of crude and purified immunosera is shown to be within the limits approved for the products.

Free Formaldehyde (2.3.20). If formaldehyde is used for production of immunoserum, a test for free formaldehyde is carried out as prescribed under Tests in individual monographs.

Test for inactivating agents. When other inactivation methods are used, appropriate tests are carried out to demonstrate that the inactivating agent has been removed or reduced to an acceptable residual level.

Batch potency test. If a specific monograph exists for the product, the test described under Potency is not necessarily carried out for routine testing of batches of antiserum. The type of batch potency test to be carried out will depend on the claims being made for the product. Wherever possible, *in vitro* tests must be used. The type of test required may include measurement of antibodies against specific infectious organisms, determination of the type of antibody (e.g. neutralising or opsonising). All tests must be validated. The criteria for acceptance must be set with reference to a batch that has been shown to comply with the requirements specified under Potency if a specific monograph exists for the product, and which has been shown to have satisfactory efficacy, in accordance with the claims being made for the product.

Total immunoglobulins. A test for the quantities of total immunoglobulins and/or total gammaglobulins and/or specific immunoglobulin classes is carried out. The results obtained must be within the limits set for the product and agreed with the competent authority. The batch contains not more than the level shown to be safe in the safety studies and, unless the batch potency test specifically covers all appropriate immunoglobulins, the level in the batch is not less than that in the batch or batches shown to be effective in the efficacy studies.

Total solids. Native antisera should not contain more than 10 per cent solid matter.

Total protein. (2.3.49). For products where claims are being made which relate to the protein content, as well as demonstrating that the batch contains not more than the stated upper limit, the batch shall be shown to contain not less than that in the batch or batches shown to be effective in the efficacy studies. The total protein is determined by a suitable method. The content is within the limits approved for the specific product.

Extraneous agents (2.7.10). In addition to the test described under Tests, specific tests may be required depending on the nature of the preparation, its risk of contamination and the use of the product. In particular, specific tests for important potential pathogens may be required when the donor and recipient species are the same and when these agents would not be detected reliably by the general screening test described under Tests.

Water (2.3.43). Where applicable, the freeze-drying process is used for determination of water and shown to be within the limits approved for the product.

Identification

The identity of the product is established by immunological tests and, where necessary, by determination of biological activity. The potency test may also serve for identification.

Tests

The following requirements refer to liquid immunosera and reconstituted freeze-dried immunosera.

Foreign proteins. When examined by precipitation tests with specific antisera against plasma proteins of a suitable range of species, only protein from the declared animal species is shown to be present.

Albumin. Purified immunosera comply with a test for albumin. Unless otherwise prescribed in the monograph, when examined electrophoretically, purified immunosera show not more than a trace of albumin, and the content of albumin is in any case not more than 3.0 per cent of the reconstituted preparation applicable.

Total protein. Dilute the preparation under examined with a 0.9 per cent solution of *sodium chloride* to obtain a solution containing about 15 mg of protein in 2 ml. To 2 ml of this solution in a round-bottomed centrifuge tube add 2 ml of a 7.5 per cent solution of *sodium molybdate* and 2 ml of a mixture of 1 volume of *nitrogen-free sulfuric acid* and 30 volumes of *water*. Shake, centrifuge for 5 minutes, discard the supernatant liquid and allow the inverted tube to drain on filter paper. Determine the nitrogen in the residue by the method of sulphuric acid digestion and calculate the content of protein by multiplying by 6.25. The results obtained are not more than the upper limit stated on the label.

Antimicrobial preservative. Determine the amount of antimicrobial preservative by a suitable physicochemical method. The amount is not less than the minimum amount shown to be effective and is not more than 115 per cent of that stated on the label.

Free Formaldehyde (2.3.20). Where formaldehyde has been used in the preparation, the concentration of free formaldehyde is not more than 0.05 per cent, unless a higher amount has been shown to be safe.

Sterility (2.2.11). Complies with test for sterility.

Mycoplasmas (2.7.9). Complies with the test for mycoplasmas.

Safety. A test is conducted in one of the species for which the product is recommended. Unless an overdose is specifically contraindicated on the label, twice the maximum recommended dose for the species used is administered by a recommended route. If there is a warning against administration of an overdose, a single dose is administered. For products to be used in mammals, use two animals of the minimum age for which the product is recommended. For avian products, use not less than ten birds of the minimum age recommended. The birds are observed for 21 days. The other species are observed for 14 days. No abnormal local or systemic reaction occurs.

Extraneous agents (2.7.3). Complies with requirements stated under veterinary immunosera. A test for extraneous agents is conducted by inoculation of cell cultures sensitive to pathogens of the species of the donor animal and into cells sensitive to pathogens of each of the recipient target species stated on the label. Observe the cells for 14 days. During this time, carry out at least one passage. The cells are checked daily for cytopathic effect and are checked at the end of 14 days for the presence of a haemadsorbing agent. The batch complies with the test if there is no evidence of the presence of an extraneous agent.

For immunosera of avian origin, if a test in cell culture is insufficient to detect potential extraneous agents, a test is conducted by inoculation of embryonated eggs from flocks free from specified pathogens (2.7.7) or by some other suitable method for example polymerase chain reaction (PCR).

Potency. Carry out test for potency. Where a specific monograph exists, carry out the biological assay prescribed in the monograph and express the result in IU per ml when such exist.

Storage. Store protected from light, at a temperature not exceeding 2° to 8°. The liquid immunosera must not be allowed to freeze.

Labelling. The label states (1) that the preparation is for veterinary use; (2) whether or not the preparation is purified; (3) the minimum number of Units per ml, where applicable; (4) the volume of the preparation in the container; (5) the indications for the product; (6) the instructions for use including the interval between any repeat administrations and the maximum number of administrations that is recommended; (7) the recipient target species for the immunoserum; (8) the dose recommended for different species; (9) the route(s) of administration; (10) the name of the species of the donor animal; (11) the maximum quantity of total protein; (12) the name and amount of any antimicrobial preservative or other substance added to the immunoserum; (13) any contra-indications to the use of the product including any required warning on the dangers of administration of an overdose; (14) For freeze-dried immunosera: the name or composition and the volume of the reconstituting liquid to be added; and the period within which the immunoserum is to be used after reconstitution.

Veterinary Liquid Preparations for Cutaneous Application

Veterinary liquid preparations for cutaneous application are liquid preparations intended to be applied to the skin to obtain a local and/or systemic effect. They are solutions, suspensions or emulsions which may contain one or more active substances in a suitable vehicle. They may be presented as concentrates in the form of wetable powders, pastes, solutions or suspensions, which are used to prepare diluted suspensions or emulsions of active substances. They may contain suitable antimicrobial preservatives, antioxidants and other excipients such as stabilisers, emulsifiers and thickeners.

Pour-On Preparations

Pour-on preparations contain one or more active substances for the prevention and treatment of ectoparasitic and/or endoparasitic infestations of animals. They are applied in volumes which are usually more than 5 ml by pouring along the animal's dorsal midline.

Spot-On Preparations

Spot-on preparations contain one or more active substances for the prevention and treatment of ectoparasitic and/or

endoparasitic infestations of animals. They are applied in volumes which are usually less than 10 ml, to a small area on the head or back, as appropriate, of the animal.

Veterinary Oral Liquids

Veterinary oral liquids intended for administration in large animals may also be called Drenches.

Veterinary Oral Pastes

Veterinary Oral Pastes are semi-solid preparations containing one or more active substances in a suitable vehicle. They are administered to the oral cavity and are intended to be swallowed for delivery of active substances to the gastrointestinal tract.

Veterinary Oral Pastes may contain suitable antimicrobial preservatives and other excipients such as dispersing, suspending, thickening, emulsifying, buffering, wetting, solubilising, stabilising, flavouring and sweetening agents.

Where applicable, containers for Veterinary Oral Pastes comply with the requirements for Containers (6.2).

Veterinary Oral Pastes are presented in multi-dose containers which are designed to allow the accurate dosing of animals according to their bodyweight.

Tests

Dissolution (2.5.2). A suitable test may be carried out to demonstrate the appropriate release of the active substances, for example, the test using apparatus 1.

Storage. If the preparation contains water or other volatile ingredients, store in an airtight container.

Labelling. The label states the name and quantity of active substance in a suitable amount by weight or volume. The label also states the directions for use of the Veterinary Oral Paste.

Veterinary Oral Powders

Veterinary Oral Powders are intended for oral administration, usually after dilution in drinking water or the feed. They may be in the form of soluble or wettable powders.

Storage. Store protected in air tight container.

Labelling. The label states (1) for single dose containers, the name and quantity of active medicament(s) per container; (2) for multiple dose containers, the name and quantity of active medicament(s) by weight; (3) the name of any added antimicrobial preservative(s); (4) the directions for use of the preparation.

Veterinary Parenteral Preparations

Veterinary Parenteral Preparations prepared with oily vehicles are not meant for intravenous administration but are suitable for intramuscular or subcutaneous use.

Veterinary Parenteral Preparations comply with the appropriate requirements for Parenteral Preparations (Injections) that are given in the chapter on General Monographs on Dosage Forms of Active Pharmaceutical Ingredients.

Veterinary Tablets and Boluses

Veterinary tablets and boluses are usually solid, circular cylinders the end surfaces of which are flat or biconvex and the edges of which are bevelled except that those weighing 5 g of more may be elongated or biconical.

Tests

Disintegration (2.5.1). The test may have to be suitably modified in the case of large tablets and boluses; the discs may have to be omitted because they would otherwise be dislodged from the disintegration tubes. It may also be necessary to adjust the volume of the disintegration medium so that the tablet does not break the surface of the medium at the top of the up-stroke, care being taken to apply the minimum practical volume of liquid for this purpose. For certain tablets where the diameter of the tablet may not permit adequate movement of the disintegration medium, the apparatus and the method should be suitably modified.

Veterinary Vaccines: General Requirements

Vaccines are a heterogeneous class of medicinal products containing immunogenic substances capable of inducing specific, active and protective immunity against infectious diseases. They may be prepared from bacteria, viruses, parasites or other suitable organisms or their toxins. Vaccines may contain live attenuated or avirulent or inactivated or killed micro-organisms as antigens. Some vaccines consist of antigenic fractions or substances produced by the same pathogenic organisms but rendered harmless whilst retaining their immunogenicity. Vaccines may be prepared from one

species or from two or more species of microorganisms. The antigen may be produced by recombinant DNA technology.

Vaccines may be prepared by the method described in the individual monograph or by any other appropriate method provided the identity of the antigen is maintained and the preparations are free from microbial contamination and extraneous agents. Suitable adjuvants may be added during preparation of vaccines. The addition of antibiotics during the manufacturing process is normally restricted to cell culture fluids and other media, egg inocula and material harvested from skin or other tissues. A suitable bactericide /preservative may be added to vaccines, if necessary. The final products are distributed aseptically into sterile containers that are then sealed to exclude extraneous microorganisms. Unless otherwise indicated in the monograph, the final vaccine may be filled into single dose or multiple dose containers. When filled in multidose containers which must contain a bactericide/ preservative.

Bacterial Vaccine

Bacterial Vaccines are made from any microorganism pathogenic to man or other animal and from other microorganisms which have antigenic value. A bacterial vaccine means a sterile suspension of a killed culture of the microorganism from which the vaccine derives its name or a sterile extract or derivative of a microorganism, or a pure suspension of living microorganisms which have been previously made avirulent.

They may be simple vaccines prepared from one species or may be combined or polyvalent vaccines prepared by blending two or more monovalent vaccines from different species or strains. Bacterial vaccines may be prepared from cultures grown on suitable solid or liquid media.

Proper Name. The proper name of any vaccine shall be the name of the microorganism from which it is made followed by the word "Vaccine" or some other name as approved by the licensing authority. For example Anthrax Spore Vaccine, Live, Blackquarter Vaccine, Brucella abortus (Strain 19) Vaccine, Live.

Bacteria

Cultures used in the preparation of the vaccine should be a standard or reference strain/serotype/species being manipulated into a vaccine should be thoroughly tested for identity by the generally accepted tests applicable to particular microorganisms.

Preparation

Bacterial vaccines, simple or polyvalent, are prepared from selected cultures after careful examination for their identity, specificity, purity and antigenicity. They may be prepared in following manner.

a) Formal cultures or bacterins

b) Vaccine of bacterial products or bacterial derivatives

c) Live bacterial vaccines

Live Bacterial Vaccines

Live bacterial vaccines are prepared from avirulent or attenuated strains of the specific bacteria that are capable of stimulating immune response against pathogenic strains of the same or of antigenically related species of bacteria.

Inactivated Bacterial Vaccines

Inactivated bacterial vaccines are either prepared from bacteria or their immunogenic components that have been inactivated in a suitable way that they retain adequate immunogenicity.

Combined Vaccine

Consist of two or more monovalent vaccines of different diseases, or antigens combined by the manufacturer at the final formulation stage. Such vaccines are intended to protect against either more than one disease, or against one disease caused by different strains or serotypes of the same organism. Monovalent vaccines when combined will be known as Polyvalent vaccine.

Multicomponent vaccine

A multicomponent preparation is formulated so that different antigens are administered simultaneously. The different antigenic components are intended to protect against different strains or types of the same organism and/or different organisms.

Bacterial Toxoids

Bacterial toxoids are prepared from toxins by diminishing their toxicity to low level or by completely eliminating it by physical or chemical means whilst retaining adequate immunizing potency. The toxins are obtained from selected strains of specific microorganisms, grown in a suitable media devoid of agents capable of inducing undesirable immunological reactions in animals. Bacterial toxoids may be liquid or may be prepared by adsorbing on suitable agents such as aluminium phosphate, aluminium hydroxide or any other suitable adsorbents. Bacterial toxoids are clear or slightly opalescent liquids, colourless or slightly yellow. Adsorbed toxoids may be white or greyish-white suspensions or pale yellow liquids

with sediment at the bottom of container. Freeze-dried preparations are greyish-white or yellowish-white powders or pellets.

Bacterial Seed Lots

General requirements

The genus and species (and varieties where appropriate) of the bacteria used in the vaccine are stated. Bacteria used in manufacture are handled in a seed-lot system wherever possible. Each master seed lot is tested as described below. A record of the passage history and storage conditions is maintained for each master seed lot. Each master seed lot is assigned a specific code or number for identification purposes.

Propagation. The minimum and maximum number of subcultures of each master seed lot prior to the production stage are specified. The methods used for the preparation of seed cultures, preparation of suspensions for seeding, techniques for inoculation of seeds, cfu and concentration of inocula and the media used, are documented. The conditions under which each seed lot has to be stored are documented.

Identity and purity. Each master seed lot is shown to contain only the species and strain of bacterium stated. A brief description of the method of identifying each strain by biochemical or molecular, serological and morphological characteristics and distinguishing it as far as possible from related strains is recorded, as is also the method of determining the purity of the strain. If the master seed lot is shown to contain living organisms of any kind other than the species and strain stated, then it is unsuitable for vaccine production. Once the master seed and working seed are identified by the above means, it is not necessary to carry out the testing on every lot of the batch produced provided traceability is established and documented by the firm. In such cases, this testing also serves the identity purposes where applicable for a batch release. However, purity needs to be shown for every lot of the batch during production stages.

Batch Tests

Vaccine complies with the tests prescribed in the individual monographs including, where applicable, the following.

Aluminium (*if present*) (2.3.9). Not more than 1.25 mg of aluminium (Al) per single dose, unless otherwise stated.

Calcium (*if present*) (2.3.11). Not more than 1.3 mg of Calcium (Ca) per single dose, unless otherwise stated.

Free formaldehyde (*if present*) (2.3.20). Not more than 0.05 per cent of free formaldehyde is present in the final product, unless otherwise stated.

Phenol (*if present*) (2.3.36). Not more than 0.5 per cent is present in the final product, unless otherwise stated.

Test for purity for live bacterial vaccines. Petri-dishes containing suitable media are streaked with the final product and incubated at 37° for 72 hours. The vaccine passes the test if no growth of micro-organisms other than those from which the vaccine was prepared is observed.

Viable count for living bacterial vaccines. As described in the individual monograph, the vaccine when plated on suitable medium should show presence of minimum number of viable bacteria of the strain used at the time of bottling and at any time before issue.

Inactivation. Inactivated vaccines are subjected to validated inactivation procedure. The testing of inactivation kinetics described below is carried out once for given inactivation process.

Inactivation Kinetics. The inactivating agent and inactivation procedure shall be shown, under conditions of manufacture, to inactivate the vaccine micro-organisms. Adequate data on inactivation kinetics shall be obtained. Normally, the time required for inactivation shall be not more than 67 per cent of the duration of inactivation process. Once inactivation kinetics is established for each applicable vaccine, it can be omitted as a test during the bioprocess unless otherwise stated in the individual monograph.

Water (2.3.43). For freeze-dried vaccines, not more than 3.0 per cent, unless otherwise stated.

Pyrogen. Unless otherwise stated in the individual monograph, when the volume to be injected in a single dose is 10 ml or more, injections comply with the tests for pyrogens (2.2.8), otherwise the test for bacterial endotoxins (2.2.3) is prescribed.

Thiomersal (*if present*) (2.2.12) (2.3.48). Where thiomersal has been used in the preparation of the vaccine, not more than 0.02 per cent w/v.

Dyes. Approved dye may be used in sterile diluents for monitoring non-parenteral vaccination procedures. Use of dye should be supported by stability of the vaccine(s) intended for reconstitution with the diluents.

Residual Live Virus/Bacteria Testing. The test for complete inactivation is performed after completion of inactivation. The test shall be appropriate to the vaccine bacteria/virus being used and must consist of atleast two passages in appropriate solid / liquid media, cells, embryonated eggs or where no other suitable method is available, in animals. The quantity of cell samples, eggs or animals shall be sufficient to ensure appropriate sensitivity of test. For test in cell cultures, not less than 150 cm^2 of cell culture monolayer is inoculated with 1.0 ml of inactivated harvest. The product complies with the test, if no evidence/presence of live virus or other micro-organisms is observed.

Viruses

The seed virus used in the preparation of vaccine shall, before being used for preparing a batch, be thoroughly tested for purity, safety, sterility and antigenicity by generally accepted tests applicable to a particular virus. It shall not be more than five passages away from the stock seed virus, unless otherwise prescribed for a particular virus. The stock seed virus shall be maintained by seed-lot system at specified passage level and tested for bacterial, mycoplasmal and extraneous viral contamination.

Viral Vaccine

Viral vaccines, live or inactivated are made from any virus pathogenic to domestic animals and poultry and made from other modified viruses which have any antigenic value. A viral vaccine means sterile suspension or a freeze dried powder containing the modified living or inactivated virus particles, which in its original unaltered stage, causes disease from which the vaccine derives its name and which has been prepared from the blood or tissues of a suitable host in which it has been grown *in vivo* or from tissue culture.

Proper Name. The proper name of a viral vaccine shall be the name of the disease which is caused by a particular virus from which the vaccine is produced followed by the word "Vaccine" or some other name as approved by the licensing authority. For example Avian Infectious Bronchitis Vaccine, Inactivated, Avian Infectious Bronchitis Vaccine, Live as included in Pharmacopoeia.

General standards. Following tests are given.

a) Description

b) Identification

c) Tests for sterility

d) Virus titre

e) Safety test

f) Potency test

Test for Absence of Avian Mycoplasmas (2.7.9). The master seed lot complies with the test for Mycoplasmas (culture method and indicator cell culture method or Nucleic acid Amplification Test (NAT) Method B (2.7.4)).

Extraneous agents. Monograph prescribes set of measures that taken together give an acceptable degree of assurance that the final product does not contain infectious extraneous agents. These measures includes:

1) Production within seed lot system and cell seed system, wherever possible.

2) Extensive testing of seed lots and cell seed for extraneous agents.

3) Requirements for SPF flocks used for providing substrate for vaccine production.

4) Testing of substances of animal origin, which must wherever possible, undergo inactivation procedure.

5) For live vaccines, testing of final product for infectious extraneous agents, such tests are less extensive than those carried out at earlier stages because of guarantees given by in-process testing.

Abnormal Toxicity. Where stated in the individual monograph vaccines comply with the following test. Inject 0.5 ml subcutaneously into each of five mice and 2 ml intraperitoneally into each of two guinea pigs. If the vaccine being examined contains an adjuvant, inject 2 ml of the vaccine subcutaneously into each guinea pig. Observe the animals for 7 days. None of the animals shows significant local or systemic reaction. If one animal dies or shows signs of ill health during the observation period repeat the test. None of the animals of the second group dies or show signs of ill health.

Sterility (2.2.11). Unless otherwise stated in the individual monograph, use Method A. Incubate the media for not less than 14 days at 30° to 35° in the test for detecting bacteria and at 20° to 25° in the test for detecting fungi. However, for live bacterial vaccines growth of the organisms from which the vaccine was prepared is permitted.

The number of containers to be drawn for the test should be 1 per cent of the containers in a batch, with minimum of 3 and a maximum of 10, assuming that the preparation has been manufactured under appropriately validated conditions designed to exclude contamination.

For avian live viral vaccines, for non-parenteral use only, the requirement for sterility is usually replaced by requirements for absence of pathogenic micro-organisms and for a maximum of one (1) non-pathogenic micro-organism per dose.

Safety Test. Unless otherwise stated in the individual monograph, vaccines other than live viral vaccines intended for poultry comply with following test.

Inject at least 2 healthy, susceptible animals of one of the species in which the vaccine is intended to be used by the route recommended by the manufacturer for field use. The quantity to be injected in each animal is twice the appropriate vaccinating dose. Observe the animals for not less than 7 days. No animal exhibits an abnormal reaction.

Potency. Determine the potency of the vaccine using the method described in the individual monograph. The vaccine complies with the level of immune response specified in the monograph. A combined vaccine complies with the level specified in the respective monographs for each individual component. If the immunogenicity (Potency test) has been performed with satisfactory results on representative batch of live vaccines from the same seed lot, it may omitted as a

Viruses

The seed virus used in the preparation of vaccine shall, before being used for preparing a batch, be thoroughly tested for purity, safety, sterility and antigenicity by generally accepted tests applicable to a particular virus. It shall not be more than five passages away from the stock seed virus, unless otherwise prescribed for a particular virus. The stock seed virus shall be maintained by seed-lot system at specified passage level and tested for bacterial, mycoplasmal and extraneous viral contamination.

Viral Vaccine

Viral vaccines, live or inactivated are made from any virus pathogenic to domestic animals and poultry and made from other modified viruses which have any antigenic value. A viral vaccine means sterile suspension or a freeze dried powder containing the modified living or inactivated virus particles, which in its original unaltered stage, causes disease from which the vaccine derives its name and which has been prepared from the blood or tissues of a suitable host in which it has been grown *in vivo* or from tissue culture.

Proper Name. The proper name of a viral vaccine shall be the name of the disease which is caused by a particular virus from which the vaccine is produced followed by the word "Vaccine" or some other name as approved by the licensing authority. For example Avian Infectious Bronchitis Vaccine, Inactivated, Avian Infectious Bronchitis Vaccine, Live as included in Pharmacopoeia.

General standards. Following tests are given.

a) Description

b) Identification

c) Tests for sterility

d) Virus titre

e) Safety test

f) Potency test

Test for Absence of Avian Mycoplasmas (2.7.9). The master seed lot complies with the test for Mycoplasmas (culture method and indicator cell culture method or Nucleic acid Amplification Test (NAT) Method B (2.7.4)).

Extraneous agents. Monograph prescribes set of measures that taken together give an acceptable degree of assurance that the final product does not contain infectious extraneous agents. These measures includes:

1) Production within seed lot system and cell seed system, wherever possible.

2) Extensive testing of seed lots and cell seed for extraneous agents.

3) Requirements for SPF flocks used for providing substrate for vaccine production.

4) Testing of substances of animal origin, which must wherever possible, undergo inactivation procedure.

5) For live vaccines, testing of final product for infectious extraneous agents, such tests are less extensive than those carried out at earlier stages because of guarantees given by in-process testing.

Abnormal Toxicity. Where stated in the individual monograph vaccines comply with the following test. Inject 0.5 ml subcutaneously into each of five mice and 2 ml intraperitoneally into each of two guinea pigs. If the vaccine being examined contains an adjuvant, inject 2 ml of the vaccine subcutaneously into each guinea pig. Observe the animals for 7 days. None of the animals shows significant local or systemic reaction. If one animal dies or shows signs of ill health during the observation period repeat the test. None of the animals of the second group dies or show signs of ill health.

Sterility (2.2.11). Unless otherwise stated in the individual monograph, use Method A. Incubate the media for not less than 14 days at 30° to 35° in the test for detecting bacteria and at 20° to 25° in the test for detecting fungi. However, for live bacterial vaccines growth of the organisms from which the vaccine was prepared is permitted.

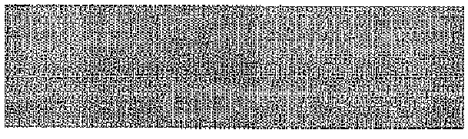
The number of containers to be drawn for the test should be 1 per cent of the containers in a batch, with minimum of 3 and a maximum of 10, assuming that the preparation has been manufactured under appropriately validated conditions designed to exclude contamination.

For avian live viral vaccines, for non-parenteral use only, the requirement for sterility is usually replaced by requirements for absence of pathogenic micro-organisms and for a maximum of one (1) non-pathogenic micro-organism per dose.

Safety Test. Unless otherwise stated in the individual monograph, vaccines other than live viral vaccines intended for poultry comply with following test.

Inject at least 2 healthy, susceptible animals of one of the species in which the vaccine is intended to be used by the route recommended by the manufacturer for field use. The quantity to be injected in each animal is twice the appropriate vaccinating dose. Observe the animals for not less than 7 days. No animal exhibits an abnormal reaction.

Potency. Determine the potency of the vaccine using the method described in the individual monograph. The vaccine complies with the level of immune response specified in the monograph. A combined vaccine complies with the level specified in the respective monographs for each individual component. If the immunogenicity (Potency test) has been performed with satisfactory results on representative batch of live vaccines from the same seed lot, it may omitted as a



routine control test during production of other batches of the vaccine prepared from the same seed lot.

Antimicrobial agents. The addition of antibiotics during the manufacturing process is normally restricted to cell culture, fluids and other media, egg inocula and material harvested from skin or other tissues. A suitable bactericide may be added to sterile and inactivated vaccines. The final products are distributed aseptically into sterile containers that are then sealed to exclude extraneous microorganisms. Unless otherwise indicated in the monograph, the final vaccine may be filled into single dose or multiple dose containers; however, inactivated vaccines in multiple dose containers must invariably contain a bactericide if necessary and as long as stability/potency of the product is not compromised.

Adjuvant. Substance that is intended to enhance immune response by the vaccine.

Stability. Stability is the ability of a vaccine to retain its chemical, physical, microbiological and biological properties within specified limits throughout its shelf life.

Labelling. The label states (1) for liquid vaccines, the total number of ml in the container and for freeze dried vaccines, the number of doses in the container; (2) unless otherwise indicated the minimum number of units per dose or per ml of, for viral vaccines, the minimum viral titre; (3) the dose and route of administration; (4) the name and proportion of any antibacterial preservative for other auxiliary substances added to the vaccine; (5) the date after which the vaccine is not intended to be used; (6) the conditions under which it should be stored; (7) for freeze dried vaccine, the liquid to be used for the reconstitution and its volume; (8) that the vaccine should be used immediately after reconstitution; (9) unless otherwise directed. That the vaccine should be shaken well before use; (10) any contraindication to the use of the vaccine.

Name and percentage of agent contained in vaccine, if vaccine is issued for sale contains any substance other than diluents, the nature and strength of such substance

Storage. Liquid vaccines must be stored at a temperature between 2° to 8° and should not be allowed to freeze unless otherwise specified in the individual monograph. Freeze-dried preparation must be stored at temperature between 2° to 8° and for long term storage at a temperature of -20°. The vaccine may be protected from light. At higher temperature vaccines deteriorate rapidly.

Condition of housing of animals

1. The animals used in the production of vaccine must be housed in hygienic conditions in premises satisfactory for purpose.
2. Only healthy animals may be used in the production of vaccines. Each animal intended to be used as a source of vaccine must, before being passed for the production of vaccine be subjected to period of observation in quarantine for atleast seven days. During the period of quarantine the animal must remain free from any sign of disease and must be well kept.
3. The poultry birds from which eggs and cell culture for production of vaccines are obtained should be housed in a manner so as to keep them from extraneous infection and shall be screened at frequent intervals for common bacterial, mycoplasmal and viral infections. The record of tests and their results shall be maintained by the manufacturers. Should comply to Appendix XI of Drugs and Cosmetics Act, 1940 and CPCSEA guidelines.

Inclusion and Exclusion Criteria of Veterinary Drugs Monographs in Indian Pharmacopoeia

Inclusion criteria

- Drugs approved for veterinary use by Central Drugs Standard Control Organization (CDSCO).
- Fixed Dose Combination approved by CDSCO and recommended by the Indian Pharmacopoeia Commission (IPC).
- Drugs considered appropriate from animal health perspective by IPC.

Exclusion criteria

- Drugs banned in India.
- Obsolete drugs.
- Drugs considered inappropriate by IPC.

Terminology used in Monographs of Veterinary Vaccines

Seed-lot system. A seed-lot system is a system according to which successive batches of a product are derived from the master seed lot. For routine production, a working seed-lot may be prepared from the master seed lot. The origin and the passage history of the master seed lot and working seed lot are maintained in records.

Master seed lot. A culture of microorganism distributed from a single bulk into containers and processed together in a single operation in such a manner as to ensure uniformity and stability and to prevent contamination. A master seed lot in liquid form is usually stored at or below -70°. A freeze-dried master seed lot is stored at a temperature known to ensure stability.

Working seed lot. A culture of a microorganism derived from the master seed lot and intended for use in production. Working seed lots are distributed into containers and stored as described above for the master seed lots.

Cell-bank system (Cell-seed system). A system whereby successive final lots (batches) of a product are manufactured by culture in cells derived from the same master cell bank (master cell seed). A number of containers from the master cell bank are used to prepare a working cell bank (working cell seed). The cell bank system (Cell-seed system) is validated for the highest passage level achieved during routine production.

Master cell bank (Master cell-seed). A culture of cells distributed into containers in a single operation, processed together and stored in such a manner as to ensure uniformity and stability, and to prevent contamination. A master cell bank is usually stored at or below -70°.

Working cell bank (Working cell seed). A culture of cells derived from the master cell bank (master cell seed) and intended for use in the preparation of production cell cultures. The working cell bank is distributed into containers, processed and stored as described for the master seed bank (master cell seed).

Primary cell cultures. Cultures of cells obtained by trypsinization of suitable tissue or organ. The cells are essentially identical to those of the tissues of origin and are no more than five *in vitro* passages from the initial preparation from the animal tissue.

Cell lines. Cultures of cells that have a high capacity for multiplication *in vitro*. In diploid cell lines, the cells essentially have the same characteristics as those of the tissue of origin. In continuous cell lines, the cells are able to multiply indefinitely in culture and may be obtained from healthy or tumoral tissue. Some continuous cell lines have oncogenic potential under certain conditions.

Production cell culture. A culture of cells intended for use in production; it may be derived from one or more containers of the working cell bank (working cell seed) or it may be a primary cell culture.

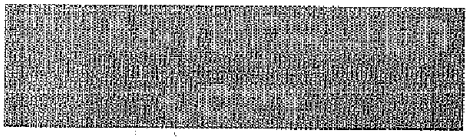
Control cells. A quantity of cells set aside at the time of virus inoculation as uninfected cell cultures. The uninfected cells are incubated under similar conditions to those used for the production cell cultures.

Single harvest. Material derived on one or more occasions from a single production cell culture inoculated with the same working seed lot or a suspension derived from the working seed lot, incubated, and harvested in a single production run.

Monovalent pooled harvest. Pooled material containing a single strain or type of microorganism or antigen and derived from a number of eggs, cell culture containers etc. that are processed at the same time.

Final bulk vaccine. Material that has undergone all the steps of production except for the final filling. It consists of one or more monovalent pooled harvests, from cultures of one or more species or types of microorganism, after clarification, dilution or addition of any adjuvant or other auxiliary substance. It is treated to ensure its homogeneity and is used for filling the containers of one or more final lots (batches).

Final lot (Batch). A collection of closed, final containers or other final dosage units that are expected to be homogeneous and equivalent with respect to risk of contamination during filling or preparation of final product. The dosage units are filled, or otherwise prepared, from the same final bulk vaccine, freeze-dried together (if applicable) and closed in one continuous working session. They bear a distinctive number or code identifying the final lot (batch). Where a final bulk vaccine is filled and/or freeze-dried on several separate sessions, there results a related set of final lots (batches) that are usually identified by use of a common part in the distinctive number or code; these related final lots are sometimes referred to as sub-batches, sub-lots or filling lots.



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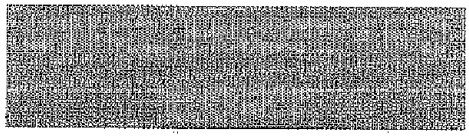

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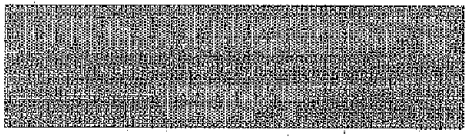
Ornidazole 4907
Oxfendazole 4907
Oxfendazole Veterinary Oral Suspension 4908
Oxyclozanide 4908



Oxyclozanide Veterinary Oral Suspension 4909
Oxyclozanide Premix 4910
Oxytetracycline Injection 4911
Oxytetracycline Hydrochloride 4911
Oxytetracycline Hydrochloride Injection 4911
Oxytetracycline Veterinary Oral Powder 4912
Paclitaxel Injection 4913
Pentobarbitone Sodium 4913
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Fortified Procaine Penicillin Injection 4914
Progesterone 4914
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Trimethoprim and Sulphamethoxazole Injection 4935
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Tylosin Injection 4937
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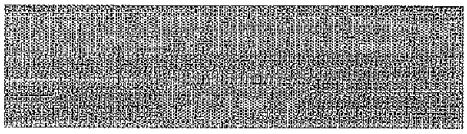
Tylosin Tartrate 4939
Tylosin Tartrate and Sulphathiazole Sodium Veterinary Oral Powder 4940
Xylazine Hydrochloride 4942
Zinc Oxide Cream 4943



Acepromazine Maleate

Category. Sedative; preanaesthetic.

For Description, Identification and Tests refer to IP Volume II.

Acepromazine Injection

Acepromazine Maleate Injection

Acepromazine Injection is a sterile solution of Acepromazine Maleate in Water for Injections.

Acepromazine Injection contains not less than 92.5 per cent and not more than 107.5 per cent of the stated amount of acepromazine, $C_{19}H_{22}N_2OS$.

Usual strengths. The equivalent of 10 mg of acepromazine per ml.

Identification

NOTE — Carry out the tests in subdued light.

A. To a volume containing 20 mg of acepromazine, add 2 ml of *water* and 3 ml of *2 M sodium hydroxide*, extract with two quantities, each of 5 ml, of *cyclohexane* and remove the solvent under reduced pressure. The residue complies with the following test.

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *acepromazine maleate IPRS* treated in the same manner or with the reference spectrum of acepromazine.

B. To 5 mg of the residue obtained in test A, add 2 ml of *sulphuric acid*; a yellow colour is produced which changes to deep orange on warming for 2 minutes.

C. Determine by thin-layer chromatography (2.4.17), coating the plate with *kieselguhr G*.

Mobile phase. A mixture of 100 volumes of *light petroleum (40° to 60°)*, 2 volumes of *diethylamine* and 6 to 8 volumes of *2-phenoxyethanol*. Shake and use the supernatant liquid.

Test solution. Extract a volume containing 20 mg of acepromazine with two quantities, each of 5 ml, of *dichloromethane* and use the combined extracts.

Reference solution. A 0.2 per cent w/v solution of *acepromazine maleate IPRS* in *dichloromethane*.

Impregnate the dry plate by placing it in a tank containing a shallow layer of a mixture of 85 volumes of *acetone*, 10 volumes of *2-phenoxyethanol* and 5 volumes of *polyethyleneglycol 300* so that the plate dips about 5 mm below the surface of the liquid and allow the impregnating solvent to ascend almost to the top. Use the plate immediately after removing it from the tank. Apply to the plate 1 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 365 nm. The principal spot in the chromatogram obtained with the test solution corresponds to the spot in the chromatogram obtained with the reference solution. A secondary spot due to maleic acid is also observed in both chromatograms. Spray the plate with *ethanolic sulphuric acid (10 per cent v/v)*. The spot in the chromatogram obtained with the test solution corresponds to the spot in the chromatogram obtained with the reference solution.

D. To a volume containing 25 mg of acepromazine add 2 ml of *5 M sodium hydroxide* and shake with three quantities, each of 3 ml, of *ether*. Discard the ether extracts. Add 2 ml of *bromine solution* to the aqueous solution, warm in a water-bath for 10 minutes, heat to boiling, cool and add 0.25 ml to a solution of 10 mg of *resorcinol* in 3 ml of *sulphuric acid*; a bluish-black colour is produced on heating for 15 minutes in a water-bath.

Tests

pH (2.4.24). 4.5 to 5.5.

Bacterial endotoxins (2.2.3). Not more than 4.5 Endotoxin Units per mg of acepromazine.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. To a measured volume containing 40 mg of acepromazine add 5 ml of *1 M sodium hydroxide* and extract with three or more quantities, each of 50 ml, of *dichloromethane* until the dichloromethane extract is colourless. Wash the extracts with the same 10 ml of *water* and filter through a plug of absorbent cotton previously moistened with *dichloromethane*. Evaporate the combined extracts to dryness, dissolve the residue in 15 ml of *acetic anhydride*. Titrate with *0.02 M perchloric acid*, using *crystal violet solution* as indicator. Carry out a blank titration.

1 ml of *0.02 M perchloric acid* is equivalent to 0.006529 g of $C_{19}H_{22}N_2OS$.

Storage. Store protected from light.

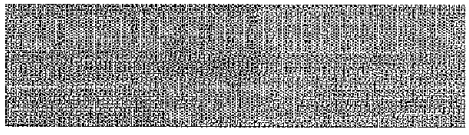
Labelling. The label states the strength in terms of the equivalent amount of acepromazine.

Acepromazine Tablets

Acepromazine Maleate Tablets

Acepromazine Tablets contain not less than 92.5 per cent and not more than 107.5 per cent of the stated amount of acepromazine, $C_{19}H_{22}N_2OS$.

Usual strengths. 10 mg; 25 mg.



Identification

NOTE — Carry out the tests in subdued light.

A. To a quantity of the powdered tablets containing 20 mg of acepromazine add 2 ml of *water* and 3 ml of *2 M sodium hydroxide*. Extract with two quantities, each of 5 ml, of *cyclohexane* and remove the solvent under reduced pressure. The residue complies with the following test.

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *acepromazine maleate IPRS* treated in the same manner or with the reference spectrum of acepromazine.

B. To 5 mg of the residue obtained in test A add 2 ml of *sulphuric acid*; a yellow colour is produced which changes to deep orange on warming for 2 minutes.

C. Determine by thin-layer chromatography (2.4.17), coating the plate with *kieselguhr G*.

Mobile phase. A mixture of 100 volumes of *light petroleum (40° to 60°)*, 2 volumes of *diethylamine* and 6 to 8 volumes of *2-phenoxyethanol*. Shake and use the supernatent liquid.

Test solution. Extract a quantity of powdered tablets containing 20 mg of acepromazine with two quantities, each of 5 ml, of *dichloromethane* and use the combined extracts.

Reference solution. A 0.2 per cent w/v solution of *acepromazine maleate IPRS* in *dichloromethane*.

Impregnate the dry plate by placing it in a tank containing a shallow layer of a mixture of 85 volumes of *acetone*, 10 volumes of *2-phenoxyethanol* and 5 volumes of *polyethyleneglycol 300* so that the plate dips about 5 mm below the surface of the liquid and allow the impregnating solvent to ascend almost to the top. Use the plate immediately after removing it from the tank. Apply to the plate 1 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 365 nm. The principal spot in the chromatogram obtained with the test solution corresponds to the spot in the chromatogram obtained with the reference solution. A secondary spot due to maleic acid is also observed in both chromatograms. Spray the plate with *ethanolic sulphuric acid (10 per cent v/v)*. The spot in the chromatogram obtained with the test solution corresponds to the spot in the chromatogram obtained with the reference solution.

D. Dissolve a quantity of the powdered tablets containing 25 mg of acepromazine as completely as possible in a mixture of 3 ml of *water* and 2 ml of *5 M sodium hydroxide* and shake with three quantities, each of 3 ml, of *ether*. Discard the ether extracts. Add 2 ml of *bromine solution* to the aqueous solution, warm in a water-bath for 10 minutes, heat to boiling, cool and add 0.25 ml of a solution of 10 mg of *resorcinol* in 3 ml of *sulphuric acid*; a bluish-black colour is produced on heating for 15 minutes in a water-bath.

Tests

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Solvent mixture. 95 volumes of *methanol* and 5 volumes of *diethylamine*.

Mobile phase. A mixture of 75 volumes of *hexane*, 17 volumes of *2-butanol* and 8 volumes of *diethylamine*.

Test solution. Shake a quantity of the powdered tablets containing 50 mg of acepromazine with 10 ml of *dichloromethane*, filter, evaporate to dryness and dissolve the residue in 5 ml of *methanol* containing 0.5 per cent v/v of *strong ammonia solution*.

Reference solution. Dilute 1.0 ml of the test solution to 100 ml with *methanol* containing 0.5 per cent v/v of *strong ammonia solution*.

Apply to the plate 10 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. Any secondary spot in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with the reference solution.

Other tests. Comply with the tests stated under Tablets.

Assay. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 60 mg of acepromazine, add 5 ml of *water* and extract with three or more quantities, each of 50 ml, of *dichloromethane* until the dichloromethane extract is colourless. Wash the extracts with the same 10 ml of *water* and filter through a plug of absorbent cotton previously moistened with *dichloromethane*. Evaporate the combined extracts to dryness, dissolve the residue in 15 ml of *acetic anhydride*. Titrate with *0.02 M perchloric acid*, using *crystal violet solution* as indicator. Carry out a blank titration.

1 ml of *0.02 M perchloric acid* is equivalent to 0.006529 g of $C_{19}H_{22}N_2OS$.

Labelling. The label states the strength in terms of the equivalent amount of acepromazine.

Adrenaline Tartrate

For Description, Identification and Tests refer to IP Volume II.

Albendazole Veterinary Oral Powder

Albendazole Veterinary Oral powder is a mixture of Albendazole and a suitable diluents and stabilizing agents.

Albendazole Veterinary Oral powder contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of albendazole, $C_{12}H_{15}N_3O_2S$

Usual strength. 5 per cent w/w.

Identification

A. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 60 volumes of *chloroform*, 10 volumes of *ether* and 10 volumes of *glacial acetic acid*.

Test solution. Disperse a quantity of powder containing 200 mg of Albendazole in 20 ml of a mixture of 18 volumes of *chloroform* and 1 volume of *formic acid*, warm the suspension on a water-bath for 15 minutes, cool and filter. Dilute 10 ml of the filtrate with an equal volume of *glacial acetic acid*.

Reference solution. A 0.5 per cent w/v solution of *albendazole IPRS* in *glacial acetic acid*.

Apply to the plate 10 µl of each solution. After development, dry the plate in a current of warm air and examine under ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with the reference solution.

B. Extract a quantity of powder containing 100 mg of Albendazole with 100 ml of *0.1 M methanolic hydrochloric acid*, filter and dilute 1.0 ml of the filtrate to 100 ml with *0.1 M sodium hydroxide*. The absorbance of the resulting solution at the maximum at about 309 nm (2.4.7) is about 0.74. When examined in the range 250 nm to 350 nm (2.4.7), the solution obtained in the Assay exhibits maxima only at about 309 nm.

Tests

Other tests. Comply with the tests stated under Veterinary Oral Powders.

Assay. Weigh a quantity of the powder containing 0.1 g of Albendazole, add 150 ml *0.1 M methanolic hydrochloric acid*, shake for 15 minutes and dilute to 250.0 ml with *0.1 M methanolic hydrochloric acid*, mix and filter, rejecting the first few ml of filtrate. Further dilute 5.0 ml of the filtrate to 250.0 ml with *0.1 M sodium hydroxide*. Measure the absorbance of the resulting solution at the maximum at about 309 nm (2.4.7). Calculate the content of $C_{12}H_{15}N_3O_2S$ taking 742 as the specific absorbance at 309 nm.

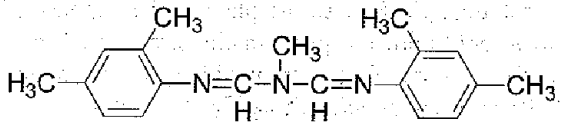
Storage. Store protected from light and moisture at a temperature below 30°.

Albendazole Oral Suspension

Usual strengths. 125 mg per 5 ml; 250 mg per 5 ml; 500 mg per 5 ml.

For Identification and Tests refer to IP Volume II.

Amitraz



$C_{19}H_{23}N_3$ Mol. Wt. 293.4

Amitraz is *N,N*-di-(2,4-xylyliminomethyl)methylamine.

Amitraz contains not less than 95.0 per cent and not more than 101.5 per cent of $C_{19}H_{23}N_3$, calculated on the anhydrous basis.

Category. Acaricide.

Description. A white to buff powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *amitraz IPRS* or with the reference spectrum of amitraz.

B. In the test for Related substances, the principal spot in the chromatogram obtained with test solution (b) corresponds to that in the chromatogram obtained with reference solution (a).

C. In the Assay, the principal peak in the chromatogram obtained with the test solution (b) corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel HF254*.

Mobile phase. A mixture of 50 volumes of *cyclohexane*, 30 volumes of *ethyl acetate* and 20 volumes of *triethylamine*.

Test solution (a). Dissolve 1 g of the substance under examination in 10 ml of *toluene*.

Test solution (b). Dissolve 20 mg of the substance under examination in 10 ml of *toluene*.

Reference solution (a). A 0.2 per cent w/v solution of *amitraz IPRS* in *toluene*.

Reference solution (b). A 0.03 per cent w/v solution of *2,4-dimethylaniline* in *toluene*.

Impregnate the plate to a depth of about 3.5 cm with a solution prepared by dissolving 35 g of *acetamide* in 100 ml of *methanol*, adding 100 ml of *triethylamine* and diluting to 250 ml with *methanol*, before standing it in a stream of cold air for about 30 seconds. Immediately apply to the plate, at a level 1 cm below the top of the impregnated zone, 2 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. Any secondary spot in the

chromatogram obtained with test solution (a) is not more intense than the spot in the chromatogram obtained with reference solution (a). Expose the plate to the vapours of *hydrochloric acid* until the plate smells strongly of acid. Expose to the vapours of nitrogen dioxide (prepared by the action of *nitric acid* on *granulated zinc*) for 10 minutes, remove the excess of nitrogen dioxide with air and spray with a 0.5 per cent w/v solution of *N-(1-naphthyl)ethylenediamine dihydrochloride* in a 50 per cent v/v solution of *methanol*. Any secondary spot corresponding to 2,4-dimethylaniline in the chromatogram obtained with test solution (a) is not more intense than the corresponding spot in the chromatogram obtained with reference solution (b).

Water (2.3.43). Not more than 0.1 per cent, determined on 5 g and using *anhydrous pyridine* in place of *anhydrous methanol*.

Sulphated ash (2.3.18). Not more than 0.2 per cent.

Assay. Determine by gas chromatography (2.4.13).

Internal standard solution. A 1.0 per cent v/v solution of *squalane* in *methyl acetate*.

Test solution (a). Dissolve 0.8 g of the substance under examination in 100.0 ml of *methyl acetate*.

Test solution (b). Dissolve 0.8 g of the substance under examination in 100.0 ml of the internal standard solution.

Reference solution. A 0.8 per cent w/v solution of *amitraz IPRS* in the internal standard solution.

Chromatographic system
- a fused silica capilllary column 15 m x 0.53 mm coated with a 1.5 µm film of methyl silicone gum,
- temperature:
  column: 220°,
  inlet port: 230°,
- flame ionization detector at a temperature of 300°,
- flow rate: 12 ml per minute, using nitrogen as the carrier gas,
- injection volume: 1 µl.

Calculate the content of $C_{19}H_{23}N_3$.

Storage. Store in containers which may contain paraformaldehyde packed in separate sachets as stabiliser.

Amitraz Dip Concentrate Liquid

Amitraz Dip Concentrate Liquid contains Amitraz in a suitable emulsifiable vehicle. It may contain a suitable stabilising agent.

Amitraz Dip Concentrate Liquid contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of amitraz, $C_{19}H_{23}N_3$.

Usual strength. 12.5 per cent w/v.

Identification

A. In the test for Related substances, the principal spot in the chromatogram obtained with test solution (b) corresponds to that in the chromatogram obtained with reference solution (a).

B. In the Assay, the principal peak in the chromatogram obtained with the test solution (b) corresponds to the peak in the chromatogram obtained with reference solution (b).

Tests

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel HF254*.

Mobile phase. A mixture of 50 volumes of *cyclohexane*, 30 volumes of *ethyl acetate* and 20 volumes of *triethylamine*.

Test solution (a). Dilute the dip concentrate with *toluene* to obtain 5.0 per cent w/v of Amitraz.

Test solution (b). Dilute the dip concentrate with *toluene* to obtain 0.2 per cent w/v of Amitraz.

Reference solution (a). A 0.2 per cent w/v solution of *amitraz IPRS* in *toluene*.

Reference solution (b). A 0.03 per cent w/v solution of *2,4-dimethylaniline* in *toluene*.

Impregnate the plate to a depth of about 3.5 cm in a solution prepared by dissolving 35 g of *acetamide* in 100 ml of *methanol*, adding 100 ml of *triethylamine* and diluting to 250 ml with *methanol*, before standing it in a stream of cold air for about 30 seconds. Immediately apply to the plate, at a level 1 cm below the top of the impregnated zone, 2 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. Any secondary spot in the chromatogram obtained with the test solution (a) is not more intense than the spot in the chromatogram obtained with the reference solution (a). Expose the plate to the vapours of *hydrochloric acid* until the plate smells strongly of acid. Expose to the vapours of nitrogen dioxide (prepared by the action of *nitric acid* on *granulated zinc*) for 10 minutes, remove the excess of nitrogen dioxide with air and spray with a 0.5 per cent w/v solution of *N-(1-naphthyl)ethylenediamine dihydrochloride* in a 50 per cent v/v solution of *methanol*. Any secondary spot corresponding to 2,4-dimethylaniline in the chromatogram obtained with test solution (a) is not more intense than the corresponding spot in the chromatogram obtained with reference solution (b).

Water (2.3.43). Not more than 0.15 per cent w/v, determined in 5 ml of the dip concentrate and using *anhydrous pyridine* in place of *anhydrous methanol*.

Other tests. Comply with the tests stated under Dip Concentrates.

Assay. Determine by gas chromatography (2.4.13).

Internal standard solution. A 1.0 per cent v/v solution of *squalane* in *methyl acetate*.

Test solution (a). Dissolve a measured volume of the dip concentrate containing 80 mg of Amitraz in 10 ml of *methyl acetate*.

Test solution (b). Dissolve a measured volume of the dip concentrate containing 80 mg of Amitraz in 10 ml of the internal standard solution.

Reference solution. A 0.8 per cent w/v solution of *amitraz IPRS* in the internal standard solution.

Chromatographic system
- a fused silica capillary column 15 m x 0.53 mm coated with a 1.5 µm film of methyl silicone gum,
- temperature:
  column: 220°,
  inlet port: 230°,
- flame ionization detector at a temperature of 300°,
- flow rate: 12 ml per minute, using nitrogen as the carrier gas,
- injection volume: 1 µl.

Calculate the content of $C_{19}H_{23}N_3$.

Amitraz Dip Concentrate Powder

Amitraz Dip Concentrate Powder consists of Amitraz mixed with suitable wetting, dispersing and suspending agents. It may contain a suitable stabilising agent.

Amitraz Dip Concentrate Powder contains not less than 92.0 per cent and not more than 108.0 per cent of the stated amount of amitraz, $C_{19}H_{23}N_3$.

Usual strengths. 25 per cent w/w and 50 per cent w/w.

Identification

A. Shake a quantity of the powder containing 0.1 g of Amitraz with 10 ml of *acetone* for 5 minutes, filter and evaporate the filtrate to dryness. The residue complies with the following test.

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *amitraz IPRS* or with the reference spectrum of amitraz.

B. In the test for Related substances, the principal spot in the chromatogram obtained with test solution (b) corresponds to that in the chromatogram obtained with reference solution (a).

C. In the Assay, the principal peak in the chromatogram obtained with the test solution (b) corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel HF254*.

Mobile phase. A mixture of 50 volumes of *cyclohexane*, 30 volumes of *ethyl acetate* and 20 volumes of *triethylamine*.

Test solution (a). The supernatant liquid obtained by shaking a quantity of the powder containing 0.5 g of Amitraz with 10 ml of *toluene* for 5 minutes and centrifuging the suspension.

Test solution (b). The supernatant liquid obtained by shaking a quantity of the powder containing 20 mg of Amitraz with 10 ml of *toluene* for 5 minutes and centrifuging the suspension.

Reference solution (a). A 0.2 per cent w/v solution of *amitraz IPRS* in *toluene*.

Reference solution (b). A 0.03 per cent w/v solution of *2,4-dimethyl-aniline* in *toluene*.

Impregnate the plate to a depth of about 3.5 cm in a solution prepared by dissolving 35 g of *acetamide* in 100 ml of *methanol*, adding 100 ml of *triethylamine* and diluting to 250 ml with *methanol*, before standing it in a stream of cold air for about 30 seconds. Immediately apply to the plate, at a level 1 cm below the top of the impregnated zone, 2 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. Any secondary spot in the chromatogram obtained with the test solution (a) is not more intense than the spot in the chromatogram obtained with the reference solution (a). Expose the plate to the vapours of *hydrochloric acid* until the plate smells strongly of acid. Expose to the vapours of nitrogen dioxide (prepared by the action of *nitric acid* on *granulated zinc*) for 10 minutes, remove the excess of nitrogen dioxide with air and spray with a 0.5 per cent w/v solution of *N-(1-naphthyl)ethylenediamine dihydrochloride* in a 50 per cent v/v solution of *methanol*. Any secondary spot corresponding to 2,4-dimethylaniline in the chromatogram obtained with test solution (a) is not more intense than the corresponding spot in the chromatogram obtained with reference solution (b).

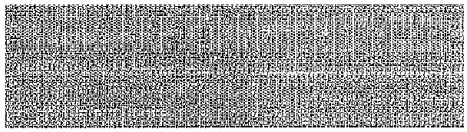
Other tests. Comply with the tests stated under Dip Concentrates.

Assay. Determine by gas chromatography (2.4.13).

Internal standard solution. A 1.0 per cent v/v solution of *squalane* in *methyl acetate*.

Test solution (a). Shake a quantity of the powder containing 80 mg of Amitraz with 10 ml of *methyl acetate*, centrifuge and use the supernatant liquid.

Test solution (b). Shake a quantity of the powder containing 80 mg of Amitraz with 10 ml of the internal standard solution, centrifuge and use the supernatant liquid.



Reference solution. A 0.8 per cent w/v solution of *amitraz IPRS* in the internal standard solution.

Chromatographic system

- a fused silica capilllary column 15 m x 0.53 mm coated with a 1.5 µm film of methyl silicone gum,
- temperature:
  column: 220°,
  inlet port: 230°,
- flame ionization detector at a temperature of 300°,
- flow rate: 12 ml per minute, using nitrogen as the carrier gas,
- injection volume: 1 µl.

Calculate the content of $C_{19}H_{23}N_3$.

Amitraz Pour-on

Amitraz Pour-on is a pour-on solution. It contains amitraz in a suitable vehicle. It may contain a suitable stabilising agent.

Amitraz Pour-on contains not less than 90.0 per cent and not more than 105.0 per cent of the stated amount of amitraz, $C_{19}H_{23}N_3$.

Usual strength. 2 .0 per cent w/v.

Identification

In the Assay, the principal peak in the chromatogram obtained with test solution (a) corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

Water (2.3.43). Not more than 0.05 per cent w/v, determine in the 5 ml of the preparation being examined and a mixture of equal volumes of *chloroform and 2-chloroethanol* in place of *anhydrous methanol*.

Assay. Determine by gas chromatography (2.4.13).

Internal standard solution. A 0.1 per cent w/v solution of *benzyl butyl phthalate* in *methyl acetate*.

Test solution (a). Dilute a quantity of the pour-on containing 15 mg of amitraz in sufficient *methyl acetate* to produce 25 ml.

Test solution (b). Dilute a quantity of the pour-on containing 15 mg of amitraz in 10 ml of the internal standard solution and add sufficient *methyl acetate* to produce 25 ml.

Reference solution. Dissolve 15 mg of *amitraz IPRS* in 10 ml of the internal standard solution and add sufficient *methyl acetate* to produce 25 ml.

Chromatographic system

- a fused silica capillary column 15 m × 0.53 mm, coated with a 1.2 µm film of poly [(cyanopropyl) methylphenyl-methylsiloxane],
- temperature:

column	time (min.)	temperature (°)
	0	145
	15	145
	18	195
	48	195

- inlet port at 220° and detector 250°,
- flame ionization detector,
- flow rate: 13 ml per minute using nitrogen as a carrier gas,
- injection volume: 1.5 µl.

Inject the reference solution. The test is not valid unless the resolution between the peaks corresponds to benzyl butyl phthalate and amitraz is not less than 3.0.

Inject the reference solution and test solution (b).

Calculate the content of $C_{19}H_{23}N_3$.

Amoxycillin Injection

Usual strengths. 250 mg; 500 mg; 1 g; 2 g; 3 g; and 4 g vials.

For Identification and Tests refer to IP Volume II.

Amoxycillin Oral Powder

Amoxycillin Oral Powder is a mixture consisting of Amoxycillin Trihydrate and Lactose or other suitable diluent and a stabilizing agent.

Amoxycillin Oral Powder contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of amoxycillin, $C_{16}H_{19}N_3O_5S$.

Usual strengths. 20 per cent w/w; 75 per cent w/w.

Identification

A. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF 254*.

Mobile phase. A mixture of 90 volumes of a 15.4 per cent w/v solution of *ammonium acetate* adjusted to pH 5.0 with *glacial acetic acid* and 10 volumes of *acetone*.

Test solution. Dissolve a quantity of powder containing 0.25 g of amoxycillin in sufficient *sodium hydrogen carbonate solution* and dilute to 100 ml.

Reference solution (a). A 0.25 per cent w/v solution of *amoxycillin trihydrate IPRS* in *sodium hydrogen carbonate solution*.

Reference solution (b). A 0.25 per cent w/v solution each of *amoxycillin trihydrate IPRS* and *ampicillin trihydrate IPRS* in *sodium hydrogen carbonate solution.*

Apply to the plate 1 µl of each solution. Allow the mobile phase to rise 15 cm. Dry the plate in air, expose to the vapour of iodine and examine in daylight. The principal spots in the chromatogram obtained with test solution correspond to that in the chromatogram obtained with the reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows two clearly separated spots.

B. Shake a quantity of the powder containing the equivalent of 0.5 g of amoxycillin with 5 ml of *water* for 5 minutes, filter, wash the residue first with *ethanol* and then with *ether* and dry at a pressure not exceeding 0.7 kPa for 1 hour. Suspend 10 mg of the residue in 1 ml of *water* and add 2 ml of a mixture of 2 ml of *cupri-tartaric solution* and 6 ml of *water*; a magenta colour is produced immediately.

C. Prepare a solution by dissolving 0.1 ml of *aniline* in a mixture of 1 ml of *hydrochloric acid* and 3 ml of *water*, cool in ice, add 1 ml of a freshly prepared 20.0 per cent w/v solution of *sodium nitrite*, add the mixture drop wise to a solution of 0.1 g of residue obtained in test B in 2 ml of *5 M sodium hydroxide*, the solution becomes deep cherry-red and dark brown precipitated.

Tests

Other tests. Comply with the tests stated under Veterinary Oral Powders.

Assay. Determine by liquid chromatography (2.4.14).

Solution A. A mixture of 99 volumes of a 25.0 per cent v/v solution of *0.2 M potassium dihydrogen orthophosphate* and 1 volume of *acetonitrile* and adjusted to pH 5.0 with *2 M sodium hydroxide.*

Solution B. A mixture of 80 volumes of a 25.0 per cent v/v solution of *0.2 M potassium dihydrogen orthophosphate* and 20 volumes of *acetonitrile* and adjust to pH 5.0 with *2 M sodium hydroxide.*

Test solution. Disperse a quantity of the veterinary oral powder containing the equivalent of 60 mg of amoxycillin in 80 ml solution A and shake for 15 minutes and mix with the aid of ultrasound for 1 minute and dilute to produce 100 ml, mix and filter.

Reference solution (a). A 0.07 per cent w/v solution of *amoxycillin trihydrate IPRS* in solution A.

Reference solution (b). A 0.0004 per cent w/v of *cefadroxil IPRS* and 0.003 per cent w/v solution of *amoxycillin trihydrate IPRS* in solution A.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with deactivated octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 92 volumes of solution A and 8 volumes of solution B.
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm.
- injection volume: 50 µl.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to amoxycillin and cefadroxil is not less than 2.0. If necessary, adjust the composition of the mobile phase to achieve the required resolution.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{16}H_{19}N_3O_5S$ in the veterinary oral powder.

Amoxycillin Tablets/Boluses

Amoxycillin Trihydrate Tablets/Boluses

Amoxicillin Tablets/Boluses contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of Amoxicillin, $C_{16}H_{19}N_3O_5S$.

Usual strengths. 250 mg, 300 mg, 500 mg, 600 mg, 875 mg, and 1500 mg tablets/boluses.

Identification

A. In Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

B. Shake a quantity of the powdered tablets/boluses containing about 0.5 g of amoxycillin with 5 ml of *water* for 5 minutes, filter, wash the residue first with *ethanol* and then with *ether* and dry at a pressure not exceeding 0.7 kPa for 1 hours. Suspend 10 mg of the residue in 1 ml of *water* and add 2 ml of a mixture of 2 ml of *cupric tartaric solution* and 6 ml of *water*. A magenta colour is produced immediately.

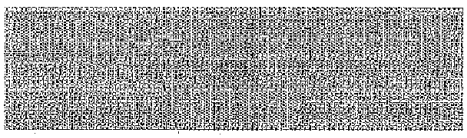
C. Dissolve 0.1 ml of *aniline* in a mixture of 1 ml of *hydrochloric acid* and 3 ml of *water*. Cool the solution in ice and add 1 ml of a freshly prepared 20 per cent w/v solution of *sodium nitrite*. Add the resulting mixture drop wise to a cold solution of 0.1 g of the residue obtained in test B in 2 ml of *5 M sodium hydroxide*. The solution becomes deep cherry red and a copious dark brown precipitate is produced.

Tests

Other tests. Complies with the tests stated under Tablets/Boluses.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Weigh and powder 20 tablets/boluses. Weigh a quantity of the powder containing 60 mg of Amoxicillin in to



100-ml volumetric flask. Add 80 ml of the *mobile phase A* and shake for 15 minutes. Dissolve with the aid of ultrasound for 1 minute and dilute to 100.0 ml with the *mobile phase A* and mix well. Filter through 0.45µm filter, rejecting the first few ml of filtrate.

Reference solution (a). A 0.07 per cent w/v solution of *amoxicillin trihydrate IPRS* in *mobile phase A.*

Reference solution (b). A 0.0004 per cent w/v solution of *cefadroxil IPRS* and 0.003 per cent w/v solution of *amoxicillin trihydrate IPRS* in *mobile phase A.*

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5µm),
- mobile phase: a mixture of 92 volumes of mobile phase A and 8 volumes of mobile phase B.

  A : a mixture of 99 volumes of a 25 per cent v/v solution of *0.2 M potassium dihyrogen orthophosphate* and 1 volume of *acetonitrile* and adjusted to pH 5.0 with *2 M sodium hydroxide*,

  B : a mixture of 80 volumes of a 25 per cent v/v solution of *0.2 M potassium dihyrogen orthophosphate* and 20 volumes of *acetonitrile* and adjusted to pH 5.0 with *2 M sodium hydroxide*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 50 µl.

Inject reference solution (b). The test is not valid unless in the chromatogram obtained with reference solution (b) the resolution factor between the peaks due to amoxicillin and cefadroxil is not less than 2.0. If necessary, adjust the composition of the mobile phase to achieve the required resolution.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{16}H_{19}N_3O_5S$ in the tablets/boluses.

Storage. Store protected from light and moisture, at a temperature below 30°.

Ampicillin Sodium

For Description, Identification and Tests refer to IP Volume II.

Ampicillin Injection

Usual strengths. 250 mg; 500 mg; 1 g; 2 g; 3 g and 4 g vials.

For Identification and Tests refer to IP Volume II.

Ampicillin and Cloxacillin Intramammary Infusion (Lactating Cow/Buffalo)

Ampicillin Sodium and Cloxacillin Sodium Intramammary Infusion (LC/B)

Ampicillin and Cloxacillin Intramammary Infusion (Lactating Cow/Buffalo) is a sterile suspension of Ampicillin Sodium and Cloxacillin Sodium in a suitable vehicle containing suitable suspending agents.

Ampicillin and Cloxacillin Intramammary Infusion (Lactating Cow/Buffalo) contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of each of ampicillin, $C_{16}H_{19}N_3O_4S$, and cloxacillin, $C_{19}H_{18}ClN_3O_5S$.

Usual strength. The equivalent of 75 mg of ampicillin and 200 mg of cloxacillin.

Identification

A. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G.*

Mobile phase. A mixture of 10 volumes of *butyl acetate*, 6 volumes of *glacial acetic acid*, 1 volume of *1-butanol* and 2 volumes of solution A (see below).

Test solution. Extract a quantity of the infusion containing 50 mg of ampicillin with three successive quantities, each of 15 ml, of *light petroleum (120° to 160°).* Discard the extracts, wash the residue with 10 ml of *ether* and dry in a current of air. Dissolve the residue in 50 ml of *phosphate buffer pH 7.0*, shake well, filter and use the filtrate.

Reference solution. A 0.12 per cent w/v solution of *ampicillin trihydrate IPRS* in *phosphate buffer pH 7.0.*

Impregnate the plate by spraying it with a 0.1 per cent w/v solution of *disodium edetate* in a 5 per cent w/v solution of *sodium dihydrogen phosphate* (solution A), allow the plate to dry in air and heat it at 105° for 1 hour. Apply to the plate 1 µl of each solution. After development, dry the plate in air and heat at 150° for 10 to 15 minutes and spray with a mixture of 100 volumes of *starch mucilage*, 6 volumes of *glacial acetic acid* and 2 volumes of a 1 per cent w/v solution of *iodine* in a 4 per cent w/v solution of *potassium iodide.* The principal spot in the chromatogram obtained with the test solution corresponds to the spot in the chromatogram obtained with the reference solution.

B. Determine by thin-layer chromatography (2.4.17), coating the plate with *silanised silica gel GF254.*

Mobile phase. A mixture of 70 volumes of *0.05 M potassium hydrogen phthalate*, 30 volumes of *acetone* and 1 volume of *formic acid* that has been adjusted first to pH 6.0 with *5 M*

sodium hydroxide and then to pH 9.0 with *0.1 M sodium hydroxide*.

Test solution. Extract a quantity of the infusion containing 130 mg of cloxacillin with three successive quantities, each of 15 ml, of *light petroleum (120° to 160°)*. Discard the extracts, wash the residue with 10 ml of *ether* and dry in a current of air. Dissolve the residue in 50 ml of *phosphate buffer pH 7.0*, shake well, filter and use the filtrate.

Reference solution. A 0.28 per cent w/v solution of *cloxacillin sodium IPRS* in *phosphate buffer pH 7.0*.

Apply to the plate 1 µl of each solution. After development, dry the plate in air and heat at 150° for 10 to 15 minutes and spray with a mixture of 100 volumes of *starch mucilage*, 6 volumes of *glacial acetic acid* and 2 volumes of a 1 per cent w/v solution of *iodine* in a 4 per cent w/v solution of *potassium iodide*. The principal spot in the chromatogram obtained with the test solution corresponds to the spot in the chromatogram obtained with the reference solution.

C. Extract a quantity containing 50 mg of ampicillin with three successive quantities, each of 15 ml, of *light petroleum (120° to 160°)*. Discard the extracts, wash the residue with 10 ml of *ether* and dry the residue at 55°. The residue produces an intense, persistent yellowish orange colour when introduced into a non-luminous flame on a platinum wire moistened with *hydrochloric acid*.

Tests

Water (2.3.43). Not more than 1.0 per cent , determined on 1.5 g using a mixture of 70 volumes of *dichloromethane* and 30 volumes of *anhydrous methanol* as the solvent.

Other tests. Comply with the tests stated under Intramammary Infusions.

Assay. Weigh and mix the contents of 10 containers. Weigh a quantity of the mixed contents containing 50 mg of ampicillin and extract with three successive quantities, each of 15 ml, of *light petroleum (120° to 160°)* previously saturated with ampicillin sodium and cloxacillin sodium. Discard the extracts, wash the residue with *ether* previously saturated with ampicillin sodium and cloxacillin sodium, dry in a current of air, dissolve in *water* and dilute to 100.0 ml with *water*. Centrifuge and use the clear supernatant liquid (solution B).

For ampicillin — Dilute 2.0 ml of solution B to 50.0 ml with *cupric sulphate solution pH 5.2 buffered*, transfer 10.0 ml of the resulting solution to a stoppered test-tube and heat in a water-bath at 75° for 30 minutes. Cool to room temperature rapidly, dilute to 20.0 ml with *cupric sulphate solution pH 5.2 buffered* and measure the absorbance of the resulting solution at the maximum at about 320 nm (2.4.7), using as the blank a solution prepared by diluting 2.0 ml of solution B to 100.0 ml with *cupric sulphate solution pH 5.2 buffered*.

Calculate the content of $C_{16}H_{19}N_3O_4S$ in a container of average content from the absorbance obtained by carrying out the procedure simultaneously using 2.0 ml of a solution prepared by dissolving 60 mg of *ampicillin trihydrate IPRS* in 100.0 ml of *water*, diluting to 50.0 ml with *cupric sulphate solution pH 5.2 buffered* and beginning at the words "transfer 10.0 ml.....".

For cloxacillin — Dilute 2.0 ml of solution B to 100.0 ml with *1 M hydrochloric acid*. Measure the absorbance of the resulting solution at 20° after exactly 12 minutes at the maximum at about 350 nm (2.4.7), using *1 M hydrochloric acid* as the blank. Calculate the content of $C_{19}H_{18}ClN_3O_5S$ in a container of average content from the absorbance obtained by carrying out the procedure simultaneously using 2.0 ml of a solution prepared by dissolving 0.14 g of *cloxacillin sodium IPRS* in 100.0 ml of *water*.

Labelling. The label states the quantity of Ampicillin Sodium in terms of the equivalent amount of ampicillin and the quantity of Cloxacillin Sodium in terms of the equivalent amount of cloxacillin.

Ampicillin and Cloxacillin Benzathine Intramammary Infusion (Dry Cow/ Buffalo)

Ampicillin and Cloxacillin Benzathine Intramammary Infusion (Dry Cow/Buffalo) is a sterile suspension of Ampicillin Trihydrate and Cloxacillin Benzathine in a suitable vehicle containing suitable suspending agents.

Ampicillin and Cloxacillin Benzathine Intramammary Infusion (Dry Cow/Buffalo) contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amounts of ampicillin, $C_{16}H_{19}N_3O_4S$, and cloxacillin, $C_{19}H_{18}ClN_3O_5S$.

Usual strength. The equivalent of 250 mg of ampicillin and 500 mg of cloxacillin.

Identification

A. Extract a quantity containing 250 mg of ampicillin with three quantities, each of 15 ml, of *light petroleum (120° to 160°)*. Discard the extracts, wash the residue with 10 ml of *ether* and dry in a current of air. Shake with 10 ml of *dichloromethane* and filter. Keep both the residue and the filtrate.

Wash the residue with two quantities, each of 5 ml, of *dichloromethane* and dry in a vaccum desiccator.

On the residue determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *ampicillin trihydrate IPRS* or with the reference spectrum of ampicillin trihydrate.

B. Wash the filtrate with two quantities, each of 5 ml, of *water*, dry the dichloromethane layer with *anhydrous sodium sulphate*, filter and dilute the filtrate to 20 ml with *dichloromethane*.

On the filtrate determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *cloxacillin benzathine IPRS* or with the reference spectrum of cloxacillin benzathine.

Tests

Water (2.3.43). Not more than 3.0 per cent, determined on 1.5 g using a mixture of 70 volumes of *dichloromethane* and 30 volumes of *anhydrous methanol* as the solvent.

Other tests. Comply with the tests stated under Intramammary Infusions.

Assay. Weigh and mix the contents of 10 containers. Weigh a quantity of the mixed contents containing 60 mg of ampicillin and extract with three quantities, each of 15 ml, of *light petroleum (120° to 160°)* previously saturated with *ampicillin trihydrate* and *cloxacillin benzathine*. Discard the extracts, wash the residue with *ether* previously saturated with *ampicillin trihydrate* and *cloxacillin benzathine*, dry in a current of air, dissolve in 50 ml of *methanol* and dilute to 100.0 ml with *water*. Centrifuge and use the clear supernatant liquid (solution A).

For ampicillin — Dilute 2.0 ml of solution A to 50.0 ml with *cupric sulphate solution pH 5.2 buffered* , transfer 10.0 ml to a stoppered test-tube and heat in a water-bath at 75° for 30 minutes. Cool to room temperature rapidly, dilute to 20.0 ml with *cupric sulphate solution pH 5.2 buffered* and measure the absorbance of the resulting solution at the maximum at about 320 nm (2.4.7), using as the blank the unheated buffered solution of the infusion.

Calculate the content of $C_{16}H_{19}N_3O_4S$ in a container of average content from the absorbance obtained by carrying out the procedure simultaneously using 2.0 ml of a solution prepared by dissolving 70 mg of *ampicillin trihydrate IPRS* in 100.0 ml of a 50 per cent v/v solution of *methanol*, diluting to 50.0 ml with *buffered cupric sulphate solution pH 5.2*, and beginning at the words "transfer 10.0 ml:....".

For cloxacillin — Dilute 2.0 ml of solution A to 100.0 ml with *1 M hydrochloric acid* and measure the absorbance of the resulting solution at 20° after exactly 12 minutes at the maximum at about 350 nm, (2.4.7), using *1 M hydrochloric acid* as the blank. Calculate the content of $C_{19}H_{18}ClN_3O_5S$ in a container of average content from the absorbance obtained by carrying out the procedure simultaneously using 2.0 ml of a solution prepared by dissolving 0.165 g of *cloxacillin benzathine IPRS* in 100.0 ml of a 50 per cent v/v solution of *methanol*.

Labelling. The label states the strength of Ampicillin Trihydrate in terms of the equivalent amount of ampicillin and that of Cloxacillin Benzathine in terms of the equivalent amount of cloxacillin.

Ampicillin Trihydrate

For Description, Identification and Tests refer to IP Volume II.

Ampicillin Veterinary Oral Powder

Ampicillin Trihydrate Veterinary Oral Powder

Ampicillin Veterinary Oral Powder is a mixture of Ampicillin Trihydrate and Lactose or other suitable diluent.

Ampicillin Veterinary Oral Powder contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of ampicillin, $C_{16}H_{19}N_3O_4S$.

Usual strength. The equivalent of 10 per cent w/w of ampicillin.

Description. A fine granular powder.

Identification

A. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*

NOTE — Prepare the solutions immediately before use.

Mobile phase. A mixture of 10 volumes of *butyl acetate*, 6 volumes of *glacial acetic acid*, 2 volumes of a 0.1 per cent w/v solution of *disodium edetate* in *mixed phosphate buffer pH 4.0* and 1 volume of *1-butanol*.

Test solution. Shake a quantity of the powder containing 0.1 g of ampicillin with 50 ml of *phosphate buffer pH 7.0* for 15 minutes, filter and use the filtrate.

Reference solution. A 0.2 per cent w/v solution of *ampicillin trihydrate IPRS* in *phosphate buffer pH 7.0*.

Impregnate the dry plate by placing it in a tank containing a shallow layer of a 0.1 per cent w/v solution of *disodium edetate* in *mixed phosphate buffer pH 4.0*, allowing the solvent to ascend to the top, removing the plate from the tank and allowing the solvent to evaporate. Use the plate with the flow of the mobile phase in the direction in which impregnation was carried out. Before use heat the plate at 100° for 1 hour and allow to cool. Apply to the plate 1 µl of each solution. After development, dry the plate in air and spray with a mixture of 100 volumes of a 1 per cent w/v solution of *starch*, 6 volumes of *glacial acetic acid* and 2 volumes of a 1 per cent w/v

solution of *iodine* in a 4 per cent w/v solution of *potassium iodide*. The principal spot in the chromatogram obtained with the test solution corresponds to the spot in the chromatogram obtained with the reference solution.

B. To a quantity of the powder containing 10 mg of ampicillin add sufficient *water* to produce 10 ml, shake for 15 minutes and filter. Place 0.1 ml of a 0.1 per cent w/v solution of *ninhydrin* on a filter paper, dry at 105°, superimpose 0.1 ml of the solution of the preparation under examination, heat for 5 minutes at 105° and allow to cool; a mauve colour is produced.

C. Suspend a quantity of the powder containing 10 mg of ampicillin in 1 ml of *water* and add 2 ml of a mixture of 2 ml of *potassium cupri-tartrate solution* and 6 ml of *water*; a magenta-violet colour is immediately produced.

Tests

Uniformity of weight. When supplied in containers intended for use on one occasion, complies with the requirements *of uniformity of weight of single dose preparations* (2.5.4).

Other tests. Comply with the tests stated under Veterinary Oral Powders.

Assay. Determine by liquid chromatography (2.4.14).

NOTE — Prepare the solutions immediately before use.

Solvent mixture. Mix 10 ml of *1 M monobasic potassium phosphate* and 1 ml of *1 M acetic acid* and dilute to 1000 ml with *water*.

Test solution. Dissolve a weighed quantity of powder containing about 100 mg of ampicillin in the solvent mixture by shaking and mixing if necessary, with the aid of ultrasound and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). Weigh a suitable quantity of *ampicillin IPRS*, dissolve in the solvent mixture by shaking and mixing if necessary, with the aid of ultrasound to obtain a solution having a known concentration of about 1 mg per ml.

Reference solution (b). Dissolve *caffeine IPRS* in reference solution (a) to obtain a solution containing about 0.12 mg per ml.

Chromatographic system
- a stainless steel column 30 cm x 4.0 mm, packed with octadecylsilane bonded to porous silica or ceramic microparticles (5 µm),
- mobile phase: a mixture of 90 volumes of *water*, 8 volumes of *acetonitrile*, 1 volume of *1 M monobasic potassium phosphate* and 1 volume of *1 M acetic acid*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

Inject reference solution (b). The test is not valid unless the resolution between the caffeine and ampicillin peaks is not less than 2.0. The relative retention time with reference to caffeine for ampicillin is about 0.5.

Inject reference solution (a). The test is not valid unless the capacity factor is not more than 2.5, the tailing factor is not more than 1.4 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

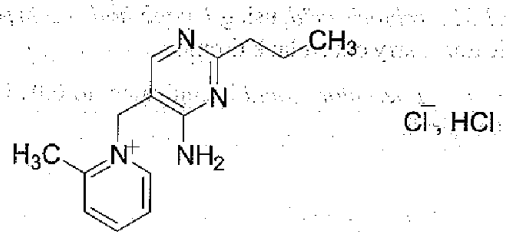
Inject reference solution (a) and the test solution.

Calculate the content of $C_{16}H_{19}N_3O_4S$ in oral powder.

Storage. Store protected from moisture, at a temperature not exceeding 30°.

Labelling. The label states the strength in terms of the equivalent concentration of ampicillin.

Amprolium Hydrochloride



$C_{14}H_{19}ClN_4.HCl$ Mol. Wt. 315.3

Amprolium Hydrochloride is hydrochloride salt of 1-[(4-amino-2-propyl-5-pyrimidinyl)methyl]-2-methylpyridinium chloride.

Amprolium Hydrochloride contains not less than 97.5 per cent and not more than 101.0 per cent of $C_{14}H_{19}ClN_4.HCl$, calculated on the dried basis.

Category. Coccidiostat.

Description. A white or almost white powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *amprolium hydrochloride IPRS* or with the reference spectrum of amprolium hydrochloride.

B. When examined in the range 230 nm to 360 nm (2.4.7), a 0.002 per cent w/v solution in *0.1 M hydrochloric acid* exhibits maxima at about 246 nm and 262 nm; absorbance at about 246 nm, about 0.84 and at about 262 nm, about 0.80.

C. To 1 mg add 5 ml of *naphthalenediol reagent*; a deep violet colour is produced.

D. It gives the reactions of chlorides (2.3.1).

Tests

Picoline. Dissolve 1.5 g in 30 ml of *water* in a distillation flask, add 20 ml of a saturated solution of *potassium carbonate sesquihydrate*, connect the flask to a ground-glass aerator extending to the bottom of a 100-ml graduated cylinder containing 50 ml of *0.05 M hydrochloric acid* and pass air, which has previously been passed through *sulphuric acid* and glass wool, through the system for 60 minutes. To 5 ml of the *hydrochloric acid solution* add sufficient *0.05 M hydrochloric acid* to produce 200 ml. Absorbance of the resulting solution at about 262 nm (2.4.7), not more than 0.52.

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Loss on drying (2.4.19). Not more than 1.0 per cent, determined on 1.0 g by drying to constant weight at 100° at a pressure not exceeding 0.7 kPa.

Assay. Weigh 0.3 g, dissolve in 20 ml of *anhydrous glacial acetic acid*, add 10 ml of *mercuric acetate solution*. Titrate with *0.1 M perchloric acid*, using *1-naphtholbenzein solution* as indicator. Carry out a blank titration.

1 ml of *0.1 M perchloric acid* is equivalent to 0.01577 g of $C_{14}H_{19}ClN_4,HCl$.

Amprolium Oral Powder

Amprolium Oral Powder is a mixture consisting of Amprolium Hydrochloride with excipients.

Amprolium Oral Powder contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of amprolium hydrochloride, $C_{14}H_{19}ClN_4$, HCl.

Usual strength. 20.0 per cent w/w.

Identification

In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (b).

Tests

Other tests. Complies with the tests stated under Veterinary Oral Powders.

Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. 5 volumes of *acetonitrile*, 45 volumes of *methanol* and 50 volumes of *water*.

Test solution. Weigh and transfer a quantity of powder containing 50 mg of Amprolium Hydrochloride in to 100.0 ml volumetric flask. Add 75 ml of the *solvent mixture* and dissolve with the aid of ultra sound for about 10 minutes and dilute to 100.0 ml with the *solvent mixture* and mix well. Filter through 0.45 µm filter.

Reference solution (a). A 0.05 per cent w/v solution of *amprolium hydrochloride IPRS* and 0.02 per cent w/v solution of *2-picoline* in the *solvent mixture*.

Reference solution (b). A 0.05 per cent w/v solution of *amprolium hydrochloride IPRS* in the *solvent mixture*.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with trimethylsilane bonded to porous silica (3-5µm),
- mobile phase: dissolve 6 g of *sodium 1-hexanesulphonate* in 500.0 ml of *water*, add 12.0 ml of *glacial acetic acid*, 2.0 ml of *triethylamine*, 450 ml of *methanol* and 50.0 ml of *acetonitrile*,
- flow rate: 0.6 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 µl.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to amprolium and 2-picoline is not less than 7.0 in the chromatogram obtained with reference solution (a), the column efficiency is not less than 6500 theoretical plates, the tailing factor is not more than 2.3 and the relative standard deviation is not more than 1.0 per cent in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and the test solution.

Calculate the content of $C_{14}H_{19}ClN_4$, HCl in the oral powder.

Storage. Store protected from moisture, at a temperature below 30°.

Amprolium Hydrochloride and Ethopabate Premix

Amprolium Hydrochloride and Ethopabate Premix contains Amprolium Hydrochloride and Ethopabate.

Amprolium Hydrochloride and Ethopabate Premix contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amounts of amprolium hydrochloride, $C_{14}H_{19}ClN_4$,HCl and of ethopabate, $C_{12}H_{15}NO_4$.

Usual strength. 25 per cent w/w of Amprolium Hydrochloride and 1.6 per cent w/w of Ethopabate.

Identification

A. Shake a quantity containing 20 mg of Amprolium Hydrochloride with 90 ml of *methanol* and filter. Add 5 ml of the filtrate to 5 ml of *naphthalenediol reagent*; a deep violet colour is produced.

B. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

NOTE — Prepare the solution immediately before use.

Mobile phase. A mixture of 90 volumes of *dichloromethane* and 10 volumes of *methanol*.

Test solution. Shake continuously for 10 minutes a quantity containing 10 mg of Ethopabate with 25 ml of *acetone* that has been warmed to 50°, filter and use the filtrate.

Reference solution. A 0.04 per cent w/v solution of *ethopabate IPRS* in *acetone*.

Apply to the plate 2 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution corresponds to the spot in the chromatogram obtained with the reference solution.

Tests

pH (2.4.24). 2.5 to 4.0, determined in a 25 per cent w/v slurry in *carbon dioxide-free water*.

Assay. *For amprolium hydrochloride* — Weigh a quantity containing 50 mg of Amprolium Hydrochloride, shake continuously for 20 minutes with 100.0 ml of a mixture of 2 volumes of *methanol* and 1 volume of *water* and filter. Dilute 5.0 ml of the filtrate to 100.0 ml with the methanol-water mixture. To 4.0 ml of the resulting solution add 10.0 ml of *naphthalenediol reagent*, allow to stand for 20 minutes and measure the absorbance of the resulting solution at the maximum at about 520 nm (2.4.7), using as the blank a solution obtained by mixing 4.0 ml of a mixture of 2 volumes of *methanol* and 1 volume of *water* with 10.0 ml of *naphthalenediol reagent* and allowing to stand for 20 minutes. Calculate the content of $C_{14}H_{19}ClN_4$,HCl from the absorbance obtained by carrying out the procedure simultaneously, using 4.0 ml of a 0.0025 per cent w/v solution of *amprolium hydrochloride IPRS* in a mixture of 2 volumes of *methanol* and 1 volume of *water* and beginning at the words, "To 4.0 ml of the resulting solution add 10.0 ml of.....".

For ethopabate — Weigh a quantity containing 6 mg of Ethopabate, add 75 ml of *methanol*, shake continuously for 20 minutes, dilute to 100.0 ml with *methanol* and filter. To 10.0 ml of the filtrate add 10 ml of *1 M sodium hydroxide* and evaporate to dryness. Dissolve the residue in 10.0 ml of *water*, heat on a water-bath for 15 minutes, add 10 ml of *2 M hydrochloric acid*, dilute to 100.0 ml with *water* and filter. To 25.0 ml of the filtrate, add 2.5 ml of *2 M hydrochloric acid* and 5 ml of a 0.1 per cent w/v solution of *sodium nitrite* prepared immediately before use. Allow to stand for 3 minutes and add 2.0 ml of a freshly prepared 0.5 per cent w/v solution of *ammonium sulphamate*. Allow to stand for 2 minutes, add 5.0 ml of a freshly prepared 0.1 per cent w/v solution of *N-(1-naphthyl)ethylenediamine dihydrochloride*, allow to stand for 10 minutes and dilute to 50.0 ml with *water*. Measure the absorbance of the resulting solution at the maximum at about 540 nm (2.4.7), using as the blank a solution obtained by repeating the procedure with 25 ml of *water* and beginning at the words "add 2.5 ml of *2 M hydrochloric acid*.....".

Calculate the content of $C_{12}H_{15}NO_4$ from the absorbance obtained by carrying out the procedure simultaneously, using 10.0 ml of a 0.006 per cent w/v solution of *ethopabate IPRS* in *methanol* and beginning at the words "add 10 ml of *1 M sodium hydroxide* and evaporate to dryness.....".

Amprolium, Ethopabate and Sulphaquinoxaline Premix

Amprolium Hydrochloride, Ethopabate and Sulphaquinoxaline Premix

Amprolium, Ethopabate and Sulphaquinoxaline Premix contains Amprolium Hydrochloride, Ethopabate and Sulphaquinoxaline.

Amprolium, Ethopabate and Sulphaquinoxaline Premix contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amounts of amprolium hydrochloride, $C_{14}H_{19}ClN_4$,HCl, of ethopabate, $C_{12}H_{15}NO_4$, and of sulphaquinoxaline, $C_{14}H_{12}N_4O_2S$.

Usual strength. 20 per cent w/w of Amprolium Hydrochloride, 1 per cent w/w of Ethopabate and 12 per cent w/w of Sulphaquinoxaline

Identification

A. Shake a quantity containing 20 mg of Amprolium Hydrochloride with 90 ml of *methanol* and filter. Add 5 ml of the filtrate to 5 ml of *naphthalenediol reagent*; a deep violet colour is produced.

B. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

NOTE — Prepare the solution immediately before use.

Mobile phase. A mixture of 90 volumes of *dichloromethane* and 10 volumes of *methanol*.

Test solution. Shake continuously for 10 minutes a quantity containing 10 mg of Ethopabate with 25 ml of *acetone* that has been warmed to 50°, filter and use the filtrate.

Reference solution (a). A 0.04 per cent w/v solution of *ethopabate IPRS* in *acetone*.

Reference solution (b). A 0.4 per cent w/v solution of *sulphaquinoxaline IPRS* in *acetone*.

Apply to the plate 2 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution corresponds to the spot in the chromatogram obtained with reference solutions (a) and (b).

Tests

pH (2.4.24). 2.5 to 4.0, determined in a 25 per cent w/v slurry in *carbon dioxide-free water*.

Assay. *For amprolium hydrochloride* — Weigh a quantity containing 50 mg of Amprolium Hydrochloride, shake continuously for 20 minutes with 100.0 ml of a mixture of 2 volumes of *methanol* and 1 volume of *water* and filter. Dilute 5.0 ml of the filtrate to 100.0 ml with the methanol-water mixture. To 4.0 ml of the resulting solution add 10.0 ml of *naphthalenediol reagent*, allow to stand for 20 minutes and measure the absorbance of the resulting solution at the maximum at about 520 nm (2.4.7), using as the blank a solution obtained by mixing 4.0 ml of a mixture of 2 volumes of *methanol* and 1 volume of *water* with 10.0 ml of *naphthalenediol reagent* and allowing to stand for 20 minutes. Calculate the content of $C_{14}H_{19}ClN_4$,HCl from the absorbance obtained by carrying out the procedure simultaneously, using 4.0 ml of a 0.0025 per cent w/v solution of *amprolium hydrochloride IPRS* in a mixture of 2 volumes of *methanol* and 1 volume of *water* and beginning at the words, "To 4.0 ml of the resulting solution add 10.0 ml of.....".

For ethopabate — Weigh a quantity containing 6 mg of Ethopabate, add 75 ml of *methanol*, shake continuously for 20 minutes, dilute to 100.0 ml with *methanol* and filter. To 10.0 ml of the filtrate add 10 ml of *1 M sodium hydroxide* and evaporate to dryness. Dissolve the residue in 10.0 ml of *water*, heat on a water-bath for 15 minutes, add 10 ml of *2 M hydrochloric acid*, dilute to 100.0 ml with *water* and filter. To 25.0 ml of the filtrate, add 2.5 ml of *2 M hydrochloric acid* and 5 ml of a 0.1 per cent w/v solution of *sodium nitrite* prepared immediately before use. Allow to stand for 3 minutes and add 2.0 ml of a freshly prepared 0.5 per cent w/v solution of *ammonium sulphamate*. Allow to stand for 2 minutes, add 5.0 ml of a freshly prepared 0.1 per cent w/v solution of N-*(1-naphthyl)ethylenediamine dihydrochloride*, allow to stand for 10 minutes and dilute to 50.0 ml with *water*. Measure the absorbance of the resulting solution at the maximum at about 540 nm (2.4.7), using as the blank a solution obtained by repeating the procedure with 25 ml of *water* and beginning at the words "add 2.5 ml of *2 M hydrochloric acid*.....". Calculate the content of $C_{12}H_{15}NO_4$ from the absorbance obtained by carrying out the procedure simultaneously, using 10.0 ml of a 0.006 per cent w/v solution of *ethopabate IPRS* in *methanol* and beginning at the words "add 10 ml of *1 M sodium hydroxide* and evaporate to dryness.....".

For sulphaquinoxaline — Weigh a quantity containing 40 mg of Sulphaquinoxaline, shake continuously for 10 minutes with a mixture of 75 ml of *water* and 4 ml of *2 M sodium hydroxide*, dilute to 250.0 ml with *water* and centrifuge. To 10.0 ml of the supernatant liquid add 5 ml of *2 M hydrochloric acid* and dilute to 200.0 ml with *water*. To 10.0 ml of the diluted solution add 2.5 ml of *2 M hydrochloric acid* and 5 ml of a freshly prepared 0.1 per cent w/v solution of *sodium nitrite* and allow to stand for 3 minutes. Add 5.0 ml of a freshly prepared 0.5 per cent w/v solution of *ammonium sulphamate* and allow to stand for 2 minutes. Add 5.0 ml of a freshly prepared 0.1 per cent w/v solution of N-*(1-naphthyl) ethylenediamine dihydrochloride*, allow to stand for 10 minutes and dilute to 50.0 ml with *water*. Measure the absorbance of the resulting solution at the maximum at about 540 nm (2.4.7), using as the blank the solution obtained by repeating the procedure with 10 ml of *water* and beginning at the words "add 2.5 ml of *2 M hydrochloric acid*.....". Calculate the content of $C_{14}H_{12}N_4O_2S$ from the absorbance obtained by carrying out the procedure simultaneously, using 10.0 ml of a 0.0008 per cent w/v solution of *sulphaquinoxaline IPRS* in *0.001M sodium hydroxide* and beginning at the words "To 10.0 ml of the diluted solution add 2.5 ml of *2 M hydrochloric acid*.....".

Benzocaine

Category. Local anesthetic (for gastric sedation and topical wound dressing).

For Description, Identification and Tests refer to IP Volume II.

Benzyl Benzoate Application

Category. Topical acaricide anti-parasitic (for treatment of scabies) and insecticide.

CAUTION — Not to be used in cats.

For Identification and Tests refer to IP Volume II.

Benzylpenicillin Potassium

For Description, Identification and Tests refer to IP Volume II.

Benzylpenicillin Sodium

For Description, Identification and Tests refer to IP Volume II.

Benzylpenicillin Injection

For Identification and Tests refer to IP Volume II.

Betamethasone Sodium Phosphate

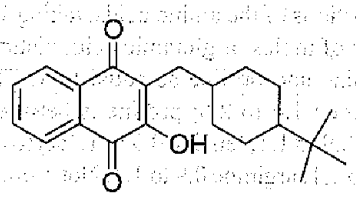
For Description, Identification and Tests refer to IP Volume II.

Betamethasone Injection

Usual strength. The equivalent of 2 mg of betamethasone per ml.

For Identification and Tests refer to IP Volume II.

Buparvaquone



$C_{21}H_{26}O_3$ Mol. Wt. 326.4

Buparvaquone is 2-(trans-4-t-butylcyclohexylmethyl)-3-hydroxy-1,4-naphthaquinone.

Buparvaquone contains not less than 98.0 per cent and not more than 101.0 per cent of $C_{21}H_{26}O_3$.

Category. Antiprotozoal.

Description. A pale greenish-yellow to brownish-yellow powder.

Identification

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *buparvaquone IPRS* or with the reference spectrum of buparvaquone.

Related Substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF 254*.

Mobile phase. A mixture of 65 volumes of *toluene*, 35 volumes of *hexane* and 5 volumes of *glacial acetic acid*.

Test solution (a). A 4.0 per cent w/v solution of the substance under examination in *dichloromethane*.

Test solution (b). A 0.01 per cent w/v solution of the substance under examination in *dichloromethane*.

Apply to the plate 5 µl of test solution (a) and 1, 2 and 4 µl of test solution (b). Allow the mobile phase to rise 15 cm. After development, dry the plate in a current of warm air and examine under ultraviolet light at 254 nm. Any secondary spot in the chromatogram obtained with the test solution (a) is not more intense than the spot in the chromatogram obtained with the test solution (b).

Sulphated ash (2.3.18). Not more than 0.2 per cent.

Assay. Weigh accurately about 0.45 g and dissolve in 60 ml of *ethanol*. Titrate with *0.1M methanolic sodium hydroxide* using a glass/calomel electrode conditioned by storing in an equal-volume mixture of *ethylene glycol* and *propanol*, determining the end-point potentiometrically (2.4.25). Carry out a blank titration.

1 ml of *0.1 M methanolic sodium hydroxide* is equivalent to 0.03254 g of buparvaquone, $C_{21}H_{26}O_3$.

Calculate the content of $C_{21}H_{26}O_3$ correcting the content of toluene and petroleum spirit.

Storage. Store cool and dry place in close containers, protected from light and moisture.

Buparvaquone Injection

Buparvaquone injection is a sterile solution of Buparvaquone in ethyl oleate or other suitable ester, in a suitable fixed oil or in a mixture of these.

Buparvaquone Injection contains not less than 90.0 per cent and not more than 110.0 per cent of stated amount of buparvaquone, $C_{21}H_{26}O_3$.

Usual strength. 50 mg per ml.

Identification

In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with the reference solution.

Tests

Other tests. Comply with tests stated under Parenteral Preparations (Injections).

Sterility (2.2.11). Complies with test for sterility.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a volume containing 50 mg of Buparvaquone to 250.0 ml with *methanol*. Dilute 10.0 ml of the solution to 100.0 ml with *methanol*.

Reference solution. Weigh accurately 50.0 mg *buparvaquone IPRS* into a 250 ml volumetric flask. Dissolve and dilute to volume. Dilute 10.0 ml of the solution with *methanol* to 100.0 ml.

Chromatographic system :

- a stainless steel column 12.5 cm x 4 mm, packed with 100 RP 8 (5 µm),
- mobile phase: a mixture of 90 volumes of *methanol*, 10 volumes of *water* and 0.1 volume of concentrated *orthophosphoric acid*,
- column temperature. 25°,
- flow rate: 1.0 ml per minute,
- spectrophotometer set at 245 nm,
- injection volume:10 µl.

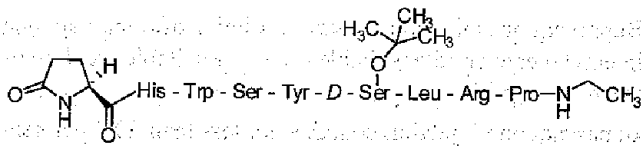
Inject reference solution. The retention time of with reference to Buparvaquone is about 2.5 minutes.

Inject reference solution and test solution.

Calculate the content of $C_{21}H_{26}O_3$ in the injection from the peak response of Buparvaquone obtained with the reference solution and test solution respectively.

Storage. Store protected from light and at a temperature not exceeding 25°.

Buserelin



$C_{60}H_{86}N_{16}O_{13}$ Mol Wt.1239.4

Buserelin is 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-O-(1,1-dimethylethyl)-D-seryl-L- leucyl-L-arginyl-N-ethyl-L-prolinamide.

Synthetic nonapeptide analogue of human gonadotropin releasing hormone GnRH with agonistic acivity to gonadorelin hormone. It is obtained by chemical synthesis and is available as an acetate.

Buserelin contains not less than 95.0 per cent and not more than 102.0 percent of $C_{60}H_{86}O_{13}$, calculated on the anhydrous acetic acid free basis.

Category. Gonadotropin releasing hormone (gonadorelin) analogue; treatment of prostate cancer.

Description. A white or slightly yellowish hygroscopic powder.

Identification

Test B may be omitted if tests A and C are carried out. Test C may be omitted if tests A and B are carried out

A. In the Assay, the principal peak in the chromatogram obtained with test solution corresponds to the peak in the chromatogram obtained with reference solution (b).

B. Determine by nuclear magnetic resonance spectrometery (2.4.34).

Solvent mixture. 20 volumes of *deuterated acetic acid* and 80 volumes of *deuterium oxide*.

Test solution. A 0.4 per cent w/v solution in solvent mixture.

Reference solution. A 0.4 per cent w/v solution of *buserelin IPRS* in solvent mixture

Operating conditions:

- Field strength: minimum 300 MHz;
- temperature: 27°.

Record the ^{1}H NMR spectrum from 0 to 9 ppm, the ^{1}H NMR spectrum obtained is qualitatively similar to the ^{1}H NMR spectrum obtained with *buserelin IPRS*.

C. **Amino acid analysis** (2.2.18). Method 1 for hydrolysis and method 1 for analysis are suitable.

Calculate the content of each amino acid in moles and the relative proportions of the amino acids, taking 1/6 of the sum of the number of moles of glutamic acid, histidine, tyrosine, leucine, arginine and proline as equal to 1. The values for serine is between 1.4 to 2.0; proline is between 0.8 to 1.2; glutamic acid 0.9 to 1.1; leucine 0.9 to 1.1; tyrosine 0.9 to 1.1; histidine 0.9 to 1.1; arginine 0.9 to 1.1. Not more than traces of other amino acids are present.

Tests

Appearance of solution (2.4.1). A 1.0 per cent w/v solution is clear and not more intensly coloured than reference solution YS7.

Specific absorbance (2.4.7). A 0.01per cent w/v solution in *0.01 M hydrochloric acid*, at 278 nm shows specific absorbance from 49.0 to 56.0, calculated on the *anhydrous acetic acid* free basis.

Specific optical rotation (2.4.22). – 58° to – 49°, calculated on the anhydrous acetic acid free basis determined in a 1.0 per cent solution.

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 5.0 mg of the substance under examination in mobile phase.

Reference solution (a). Dissolve the contents of avial of *D-His-buserelin IPRS* in the mobile phase. Dilute an

appropriate volume of the solution with the mobile phase to obtain a final concentration of 1 mg per ml. Add 1.0 ml of the test solution to 1.0 ml of the solution.

Reference solution (b). Dissolve *buserelin IPRS* in the mobile phase, dilute an appropriate volume of the solution in the mobile phase to obtain a final concentration of 1 mg per ml of the solution.

Reference solution (c). Dilute 1.0 ml of the test solution to 100.0 ml with the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x 4.0 mm, packed with octadecylsilane bonded to porous silica (5µm),
- mobile phase: a mixture of 70 volumes of 1.12 per cent w/v solution of *orthophosphoric acid* and 20 volumes of *acetonitrile*, adjusted to pH 2.5 with *triethylamine*,
- flow rate: 0.8 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 10 µl.

Name	Relative retention time
Buserelin impurity B[1]	0.76
Buserelin impurity C[2]	0.83
Buserelin impurity A[3]	0.90
Buserelin impurity D[4]	0.94
Buserelin impurity E[5]	0.94
Buserelin (Retention time: about 36 minutes)	1.0

[1][4-D-serine] buserelin,
[2]buserelin-(3-9)-peptide,
[3][2-D-histidine] buserelin,
[4][5-D-tyrosine] buserelin,
[5][1-(5-oxo-D-proline)] buserelin.

Inject reference solution (a). The test is not valid unless the resolution between the peaks due to buserelin impurity A and buserelin is not less than 1.5.

Inject reference solution (c) and the test solution. In the chromatogram obtain with the test solution, the sum of the D and E impurties is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (3.0 per cent). The area of any other impurity is not more than 3 times the area of principlal peak in the chromatogram obtained with reference solution (c) (3.0 per cent). The sum of the secondry peak is not more than 5 times the area of the the principal peak in the chromatogram obtained with reference solution (c) (5.0 per cent). Ignore any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

Acetic acid . 3.0 per cent to 7.0 per cent. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 20 mg of the substance under examination in a mixture of 95 volumes of mobile phase A and 5 volumes of mobile phase B and dilute to 10.0 ml with the same mixture of solvents.

Reference solution. A 0.01 per cent w/v solution of *glacial acetic acid* in a mixture of 95 volumes of mobile phase A and 5 volumes of mobile phase B.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm; packed with octadecylsilane bonded to porous silica (5µm),
- mobile phase: A. dilute 0.7 ml *orthophosphoric acid* to 1000 ml with *water*, adjusted to pH 3.0 with *sodium hydroxide solution*,
  B. *methanol*,
- a gradient programme using the conditions given below,
- flow rate: 1.2 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	95	5
5	95	5
10	50	50
20	50	50
22	95	5
30	95	5

Inject the reference solution and the test solution. In the chromatogram obtained with reference solution and test solution, the retention time for buserlin corresponding to acetic acid is between 3 and 4 minutes. The baseline presents a steep rise after the start of the linear gradient, which corresponds to the elution of the peptide from the column. Determine the content of acetic acid in the peptide.

Water (2.3.43). Not more than 4.0 per cent, determined on 80 mg.

Buserelin intended for use in the manufacture of parenteral preparations without a father appropriate procedure for removal of bacterial endotoxin with following additional requirements.

Bacterial endotoxins (2.2.3). Not more than 55.5 Endotoxin Units per mg of buserelin.

Assay. Determine by liquid chromatography (2.4.14).

Use the chromatographic system as described under Related substances.

Inject the reference solution and the test solution.

Calculate the content of $C_{60}H_{86}N_{16}O_{13}$.

Labelling. The label states (1) the mass of peptide in the container; (2) that the substance is suitable for use in the manufacture of parenteral preparations.

Storage. Store protected from light, in an airtight container, at a temperature 2° to 8°. If the substance is sterile, store in an airtight, sterile, tamper-evident containers.

Buserelin Injection

Buserelin Acetate Injection

Buserelin Injection is a sterile solution of Buserelin Acetate in Water for Injections.

Buserelin Injection contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of buserelin, $C_{60}H_{86}N_{16}O_{13}$.

Usual strength. 4.0 mcg per ml.

Identification

In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

pH (2.4.24). 4.5 to 6.7.

Bacterial endotoxins (2.2.3). Not more than 350.0 Endotoxin units per mg of buserelin.

Sterility (2.2.11). Complies with the test for sterility.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Use the injection.

Reference solution. Weigh 20 mg of *buserelin IPRS*, dissolve in 100 ml of mobile phase. Dilute 1.0 ml of the solution to 50 ml with mobile phase.

Chromatographic system
- a stainless steel column 25 cm x 4.0 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- column temperature: 25°,
- mobile phase: a mixture of 200 volumes of *acetonitrile* and 700 volumes of 1.12 per cent w/v solution of *orthophosphoric acid*, adjusted to pH 2.5 with *triethylamine*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 100 µl.

Inject reference solution and test solution. The test is not valid unless the column efficiency is not less than 1000 theoretical plates and tailing factor is not more than 2.0. The relative standard deviation for replicate injections is not more than 2.0 per cent.

Calculate the content of $C_{60}H_{86}N_{16}O_{13}$ in injection.

Calcium Borogluconate Injection

Calcium Borogluconate Injection is a sterile solution of Calcium Gluconate and Boric Acid in Water for Injections. The solution may contain up to 0.2 per cent w/v of Chlorocresol.

Calcium Borogluconate Injection contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of calcium, Ca, and boric acid, H_3BO_3, equivalent to not more than 2.3 times the stated content of calcium.

Category. Hypocalcaemic.

Usual strength. 25 per cent w/v solution equivalent to 1.9 per cent w/v of calcium (approximately).

Identification

A. Dilute 1 ml with sufficient *water* to produce a solution containing about 0.75 per cent w/v of calcium and add 0.05 ml of *ferric chloride test solution*; an intense yellow or yellowish green colour is produced.

B. It gives the reactions of calcium salts (2.3.1).

C. To 1 ml add 0.15 ml of *sulphuric acid* and 5 ml of *methanol* and ignite; the mixture burns with a flame tinged with green.

Tests

pH (2.4.24). 3.0 to 4.0, determined in a solution diluted if necessary with *carbon dioxide-free water* to produce a solution containing 1.5 per cent w/v of calcium.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. *For calcium* — Dilute a measured volume containing 45 mg of calcium to about 50 ml with *water*. Titrate with *0.05 M disodium edetate* to within a few ml of the expected end-point, add 4 ml of a 40 per cent w/v solution of *sodium hydroxide* and 10 mg of *calcon mixture* and continue the titration until the colour changes from pink to blue.

1 ml of *0.05 M disodium edetate* is equivalent to 0.002004 g of Ca.

For boric acid — Dilute a measured volume containing 0.1 g of boric acid to 50 ml with *water*, add 3 g of *mannitol* and titrate with *0.1 M sodium hydroxide* using *phenolphthalein solution* as indicator.

1 ml of *0.1 M sodium hydroxide* is equivalent to 0.006183 g of H_3BO_3.

Storage. Store protected from light, at a temperature not exceeding 30°.

Labelling. The label states (1) the strength in terms of the equivalent amount of calcium in a suitable dose-volume; (2) the proportion of boric acid present; (3) the proportion of chlorocresol, if present.

Calcium Levulinate Injection

Usual strength. Each ml contains Calcium levulinate 76.4 mg along with Cholecalciferol and Vitamin B_{12}.

For Identification and Tests refer to IP Volume III.

Calcium Magnesium Borogluconate Injection

Calcium Magnesium Borogluconate Injection is a sterile solution of Calcium Gluconate, Boric Acid, Magnesium Hypophosphite and Dextrose in Water for Injections. It may contain upto 0.2 per cent w/v of Chlorocresol.

Calcium Magnesium Borogluconate Injection contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amounts of calcium, Ca, of magnesium, calculated as magnesium hypophosphite, $Mg(H_2PO_2)_2,6H_2O$, and of dextrose, $C_6H_{12}O_6$, and the content of boric acid, H_3BO_3, is not more than 2.3 times the stated content of calcium.

Usual strengths. Equivalent to 1.86 per cent w/v; 2.25 per cent w/v; 3.0 per cent w/v of Ca.

Identification

A. Dilute 1 ml with sufficient *water* to produce a solution containing about 0.75 per cent w/v of calcium and add 0.05 ml of *ferric chloride TS*; an intense yellow or yellowish green colour is produced.

B. It gives the reactions of calcium salts (2.3.1).

C. It gives the reactions of magnesium salts (2.3.1).

D. To 1 ml add 5 ml of *water*, neutralise to pH 7.0 with *dilute ammonia solution* and add 5 ml of *silver nitrate solution*. A yellow precipitate is produced which does not change colour on boiling but dissolves on addition of *dilute ammonia solution*.

E. To 1 ml add 0.15 ml of *sulphuric acid* and 5 ml of *methanol* and ignite; the mixture burns with a flame tinged with green.

F. To 1 ml add 2 ml of *2 M sodium hydroxide solution* and 0.05 ml of *copper sulphate solution*. The solution is blue and clear. Heat to boiling. A copious red precipitate is produced.

Tests

pH (2.4.24). 3.0 to 4.0, determined in a solution diluted, if necessary, with *carbon dioxide-free water* so as to contain 1.5 per cent w/v of calcium.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Bacterial endotoxins (2.2.3). Not more than 0.5 Endotoxin Unit per ml.

Assay. *For calcium* — Dilute a volume containing 45 mg of calcium to about 50 ml with *water*. Add 1 ml of *1 M sodium hydroxide solution*. Titrate with *0.05 M disodium edetate* to within a few ml of the expected end-point, add 5 ml of *strong ammonia-ammonium chloride solution* and 10 mg of *calcon mixture* as indicator and continue the titration until the colour changes from pink to blue. Calculate the volume of *0.05 M disodium edetate* consumed by substracting the volume of *0.05 M disodium edetate* consumed in the assay for *magnesium*.

1 ml of *0.05 M disodium edetate* is equivalent to 0.002004 g of Ca.

For magnesium — Dilute a volume containing 10 mg of magnesium to about 50 ml with *water*. Add 1 g of *ammonium chloride* and 1 g of *ammonium oxalate*. Neutralise to litmus paper with *dilute ammonia solution* and add 5 ml in excess. Boil for 5 minutes and allow to stand for 1 hour. Filter and wash the residue with hot *water*. Collect the filtrate and washings and add 5 ml of *strong ammonia-ammonium chloride solution*. Titrate with *0.05 M disodium edetate* using *eriochrome black T mixture* as indicator.

1 ml of *disodium edetate* is equivalent to 0.001216 g of magnesium or 0.01312 g of magnesium hypophosphite, $Mg(H_2PO_2)_2,6H_2O$.

For boric acid — Dilute a volume containing 0.1 g of boric acid to 50 ml with *water*, add 3 g of *mannitol* and titrate with *0.1 M sodium hydroxide* using *phenolphthalein solution* as indicator.

1 ml of *0.1 M sodium hydroxide* is equivalent to 0.006183 g of H_3BO_3.

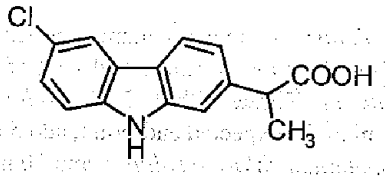
For dextrose — Dilute a volume containing 200 mg of dextrose to 50 ml with *water*; add 30 ml of *0.1 M iodine solution* and 10 ml of a 5 per cent w/v solution of *sodium carbonate* and allow to stand for 20 minutes. Add 15 ml of *1 M hydrochloric acid* and titrate the excess of iodine with *0.1 M sodium thiosulphate solution* using *starch solution* as indicator. Carry out a blank titration.

1 ml of *0.1 M iodine solution* is equivalent to 0.009008 g of dextrose, $C_6H_{12}O_6$.

Storage. Store protected from light.

Labelling. The label states (1) the strength in terms of the equivalent amount of calcium, magnesium and dextrose in a suitable dose-volume; (2) the proportion of boric acid to calcium; (3) the percentage of any added stabilising agent.

Carprofen



$C_{15}H_{12}ClNO_2$ Mol. Wt. 273.7

Carprofen is (*RS*)-2-(6-Chloro-9*H*-carbazol-2-yl)propanoic acid.

Carprofen contains not less than 98.5 per cent and not more than 101.5 per cent of $C_{15}H_{12}ClNO_2$, calculated on the dried basis.

Category. Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Description. A white or almost white crystalline powder. It shows polymorphism (2.5.11).

Identification

Determine by infrared abortion spectrometry (2.4.6). Compare the spectrum with that obtained *carprofen IPRS* or with the reference spectrum of carprofen.

If the spectra obtained in solid state show differences, dissolve the substance under examination and the reference substance separately in *acetone*, evaporate to dryness and record new spectra using the residues.

Tests

Appearance of solution (2.4.1). A 4.0 per cent w/v solution in *methanol* is clear and not more intensely coloured than reference solution BYS3 (2.4.1).

Related substances. Determine by liquid chromatography (2.4.14).

NOTE— Carry out the following procedure protected from light.

Test solution. Dissolve 25 mg of the substance under examination in 50.0 ml of mobile phase.

Reference solution (a). Dissolve 2.5 mg of *carprofen IPRS* containing impurity C (1 *RS*)-1-(6-chloro-9*H*-carbazol-2-yl)ethanol) in 10.0 ml of mobile phase.

Reference solution (b). Dilute 1.0 ml of the test solution to 100.0 ml with mobile phase. Dilute 1.0 ml of the solution to 10.0 ml with mobile phase.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with endcapped polar-embedded octadecylsilane amorphous organosilica polymer (5 µm),
- mobile phase: a mixture of 30 volumes of solution containing 0.136 per cent *potassium dihydrogen phosphate*, adjusted to pH 3.0 with *orthophosphoric acid* and 70 volumes of *methanol*,
- flow rate: 1.3 ml per minute,
- spectrophotometer set at 235 nm,
- injection volume: 20 µl.

Inject reference solution (a). Run the chromatogram 4 times the retention time of the carprofen. The test is not valid unless the resolution between the peaks due to carprofen impurity C and carprofen is not less than 1.5. The retention time of carprofen is about 10.0 minutes.

Inject reference solution (b) and the test solution. The area of any other secondary peak for each impurity not more than 2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.20 per cent). The sum of the areas of the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Heavy metals (2.3.13). Dissolve 1.0 g in *ethanol (95 per cent)* and dilute to 20 ml with the same solvent. 12 ml of the solution complies with the limit test of heavy metals, Method D (20 ppm), using 10 ml of *lead standard solution (1 ppm Pb)*.

Sulphated ash (2.3.18). Not more than 0.1 per cent, determined on 1.0 g.

Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105° for 2 hours.

Assay. Dissolve 0.20 g in 50.0 ml of *ethanol (95 per cent)* and add 1.0 ml of *0.1 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide*, determining the end point potentiometrically (2.4.25). Read the volume added between the 2 points of inflexion.

1 ml of *0.1 M sodium hydroxide* is equivalent to 0.02737 g of $C_{15}H_{12}ClNO_2$.

Storage. Store protected from light.

Cefoperazone Sodium Intramammary Suspension

Cefoperazone Sodium Intramammary Suspension is a sterile suspension of Cefoperazone Sodium in a suitable oil vehical

Cefaperazone contains not less than 90.0 per cent and not more than 120.0 per cent of Cefoperazone, $C_{25}H_{27}N_9O_8S_2$.

Usual strength. 250 mg.

Identification

In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

Uniformity of content. Complies with the test for the content of packaged dosages form (2.5.6).

Sterility (2.2.11). Complies with the test for sterility.

Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. Transfer 7.0 ml *triethylamine* and 3.0 ml *glacial acetic acid* to a 100-ml volumetric flask, dilute to 100 ml with *water*. Dilute 2.0 ml of the solution to 1000 ml with *water*.

Test solution. Disperse a quantity of suspension containing 125 mg of cefoperazone in 25 ml *tetrahydrofuran* and 25 ml *methanol* with the aid of ultrasound for 10 minutes. Add 162.5 ml of *tetrahydrofuran*, sonicate for 10 minutes and dilute to 250 ml with *methanol*. Dilute 1.0 ml of the solution to 20.0 ml with the mobile phase and filter.

Reference solution. Weigh 26 mg *cefoperazone sodium IPRS* in 100 ml of the mobile phase, dissolve with aid of ultrasound. Dilute 5.0 ml of the solution to 50 ml with the mobile phase.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- column temperature: 40°,
- mobile phase: a mixture of 80 volumes of the solvent mixture and 20 volumes of *acetonitrile*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 266 nm,
- injection volume: 20 µl.

Inject the reference solution and the test solution. The test is not valid unless the column efficiency is not less than 1000 theoretical plates and the tailing factor is not more than 2.0. The relative standard deviation for replicate injections is not more than 2.0 per cent.

Calculate the content of $C_{25}H_{27}N_9O_8S_2$ in suspension.

Storage. Store protect from light.

Cefpodoxime Oral Suspension

Usual strength. 600 mg per bottle.

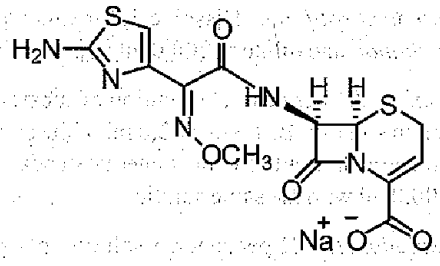
For Identification and Tests refer to IP Volume II.

Cefpodoxime Tablets

Usual strengths. Each uncoated tablet contains Cefpodoxime. 100 mg ; 200 mg.

For Identification and Tests refer to IP Volume II.

Ceftizoxime Sodium



$C_{13}H_{12}N_5NaO_5S_2$ Mol. Wt 405.4

Ceftizoxime Sodium is Sodium 7-[(*Z*)-2-(2-Amino-1,3-thiazol-4-yl)-2-(methoxyimino)acetamido]-3-cephem-4-carboxylate.

Ceftizoxime Sodium contains not less than 850 µg and not more than 995 µg of ceftizoxime $C_{13}H_{13}N_5O_5S_2$, per mg, calculated on the anhydrous basis.

Category. Antibacterial.

Description. A white to pale yellow crystalline powder.

Identification

A. In the Assay, the retention time of the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

B. It gives reaction (A) of sodium salts (2.3.1).

Tests

pH (2.4.24). 6.0 to 8.0, determined in 10 per cent w/v solution.

Water (2.3.43). Not more than 8.5 per cent.

Ceftizoxime Sodium is intended for use in the manufacture of parenteral preparations without a further appropriate procedure for removal of bacterial endotoxins complies with the following additional requirement.

Bacterial endotoxins (2.2.3). Not more than 0.10 Endotoxin unit per mg of ceftizoxime.

Ceftizoxime Sodium is intended for use in the manufacture of parenteral preparations without a further appropriate sterilization procedure complies with the following additional requirement.

Sterility (2.2.11). Complies with the test for sterility.

Assay. Determine by liquid chromatography (2.4.14).

Solution A. Dissolve 1.42 g of *citric acid monohydrate* and 1.73 g of *dibasic sodium phosphate* in *water*, dilute to 1000 ml with *water*.

Solution B. Dissolve 3.63 g of *monobasic potassium phosphate* and 10.73 g of *dibasic sodium phosphate* in *water*, dilute to 1000 with *water*.

Internal standard solution. Dissolve 1.2 g *salicylic acid* in 10 ml of *methanol*, and dilute to 200.0 ml with solution B.

Test solution. A 0.01 per cent w/v solution of substance under examination in solution B. Transfer 2.0 ml of the solution to a 100-ml volumetric flask, add 5.0 ml of Internal standard solution. Dilute to 100.0 ml with the same solution.

Reference solution. A 0.01 per cent w/v solution of *ceftizoxime IPRS* in solution B. Transfer 2.0 ml of the solution to a 100 ml volumetric flask, add 5.0 ml of Internal standard solution. Dilute to 100.0 ml with the same solution.

Chromatographic system
- a stainless steel column 30 cm x 4.0 mm; packed with octadecylsilane bonded to porous silica (5 to 10 µm),
- mobile phase: a mixture of 90 volumes of solution A and 10 volumes of *acetonitrile*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 µl.

Inject the reference solution and the test solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates, the tailing factor is not more than 2.0 and the resolution between the peaks due to principal peak and internal standard is not less than 4.0. The relative standard deviation for the replicate injections is not more than 2.0 per cent. The relative retention time for ceftizoxime is 0.6 and for salicylic acid is 1.0.

Calculate the content of $C_{13}H_{13}N_5O_5S_2$.

Labelling. The label states where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.

Storage. Store in tightly-closed containers.

Ceftizoxime Injection

Ceftizoxime Injection contains not less than 90.0 per cent and not more than 115.0 per cent of stated amount of ceftizoxime, $C_{13}H_{13}N_5O_5S_2$.

Usual strengths. 1.5 g; 2.5 g.

Identification

A. In the Assay, the retention time of the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

B. It gives reaction (A) of sodium salts (2.3.1).

Tests

pH (2.4.24). 6.0 to 8.0, determined in 10 per cent w/v solution.

Water (2.3.43). Not more than 8.5 per cent.

Bacterial endotoxins (2.2.3). Not more than 0.10 Endotoxin unit per mg of ceftizoxime.

Sterility (2.2.11). Complies with the test for sterility.

Other tests. Comply with the tests stated under Parenteral Preparations (Injection).

Assay. Determine by liquid chromatography (2.4.14).

Solution A. Dissolve 1.42 g of *citric acid monohydrate* and 1.73 g of *dibasic sodium phosphate* in *water*, dilute to 1000 ml with *water*.

Solution B. Dissolve 3.63 g of *monobasic potassium phosphate* and 10.73 g of *dibasic sodium phosphate* in *water*, dilute to 1000 with *water*.

Internal standard solution. Dissolve 1.2 g *salicylic acid* in 10 ml of *methanol*, and dilute to 200 ml with solution B.

Test solution. A 0.01 per cent w/v solution of substance under examination in solution B. Transfer 2.0 ml of the solution to a 100-ml volumetric flask, add 5.0 ml of Internal standard solution. Dilute to 100.0 ml with the same solution.

Reference solution. A 0.01 per cent w/v solution of *ceftizoxime IPRS* in solution B. Transfer 2.0 ml of the solution to a 100-ml volumetric flask, add 5.0 ml of Internal standard solution. Dilute to 100.0 ml with the same solution.

Chromatographic system
- a stainless steel column 30 cm x 4.0 mm; packed with octadecylsilane bonded to porous silica gel (5µm),
- mobile phase: a mixture of 90 volumes of solution A and 10 volumes of *acetonitrile*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 µl.

Inject the reference solution and the test solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates. The tailing factor is not more than 2.0.The resolution between the peaks due to principal peak and internal standard is not less than 4.0. The Relative standard deviation for the replicate injections is not more than 2.0 per cent. The relative retention time for ceftizoxime is 0.6 and for salicylic acid is 1.0.

Calculate the content of $C_{13}H_{13}N_5O_5S_2$.

Storage. Store in tightly-closed containers for sterile solids.

Ceftriaxone Injection

Usual strengths. 250 mg, 500 mg, 1 g, 2 g, 3 g, 4 g and 5 g per Vials.

For Identification and Tests refer to IP Volume II.

Cefuroxime Intramammary Infusion

Cefuroxime Sodium Intramammary Infusion is a sterile suspension of Cefuroxime Sodium in a suitable vehicle.

Cefuroxime Sodium Intramammary Infusion contains not less than 90.0 per cent and not more than 110.0 per cent of cefuroxime, $C_{16}H_{16}N_4O_8S$.

Usual strength. Cefuroxime 250 mg.

Tests

Other tests. Comply with the tests stated under Intramammary Infusion.

Water (2.3.43). Not more than 0.5 per cent.

Specific gravity. At 25° between 0.88 to 0.92.

Viscosity (2.4.28). 3000 to 5000 cps determined at 25°.

Uniformity of weight. Complies with the test for the content of packaged dosage form.

Sterility (2.2.11). Complies with the test for sterility.

Assay

Test solution. Weigh accurately a quantity equivalent to 20 mg Cefuroxime Sodium, add 100 ml *ether*, disperse as completely as possible. Add 20 ml *water*, shake on a magnetic stirrer for 1 minute, retransfer to a 500 ml separator, allow separating. Discard the *ether* layer and collect the water layer into a 250 ml volumetric flask. Keep it on a steam bath to expel *ether* traces. Cool and make up to volume with distilled water. Dilute 10.0 ml to 100.0 ml with *water*.

Reference solution. Dissolve 20 mg *cefuroxime sodium IPRS* in *water* and dilute to 250.0 ml with the same solvent. Dilute 10.0 ml of the solution to 100.0 ml with *water*.

Measure the absorbance of both solutions at the maximum at about 271 nm (2.4.7). Calculate the content of cefuroxime in suspension.

Storage. Store protected from light.

Cephalexin Intrauterine Powder for Suspension

Cephalexin Intrauterine Powder for Suspension is a mixture consisting of Cephalexin with excipients. The suspension is constituted by dispersing the contents in Water for Injections immediately before use.

Cephalexin Intrauterine powder contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of cephalexin, $C_{16}H_{17}N_3O_4S$.

Usual strengths. 37.5 per cent w/w.

Identification

A. In the Assay, the principal peak in the chromatogram obtained with test solution corresponds to the peak in the chromatogram obtained with the reference solution (a).

B. Weigh a quantity containing 0.1 g of anhydrous cephalexin, shake with 20 ml of *methanol*, filter and evaporate the filtrate to dryness using a rotary evaporator. Dissolve the residue in the minimum volume of a 1 per cent v/v solution of *glacial acetic acid*, decolorize, if necessary, by the addition of sufficient *decolorising charcoal*, shake and filter. To 0.25 ml of the resulting solution add 0.1 ml of 1 per cent w/v solution of *cupric sulphate* and 0.05 ml of *2 M sodium hydroxide*; an olive green colour is produced.

Tests

Other tests. Comply with the tests stated under Intrauterine Preparations.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Shake an accurately weighed quantity of the powder containing about 0.25 g of anhydrous cephalexin with 100 ml of *water* for 30 minutes, add sufficient quantity of *water* to produce 250.0 ml and filter. Dilute 25.0 ml of the filtrate to 50.0 ml with *water*.

Reference solution (a). A 0.05 per cent w/v solution of *cephalexin IPRS* in *water*.

Reference solution (b). A solution containing 0.01 per cent w/v each of *cephalexin IPRS* and *cephradine IPRS* in *water*.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 2 volume of *methanol*, 5 volume of *acetonitrile*, 10 volume of 1.36 per cent solution of *potassium dihydrogen phosphate* and 83 volume of *water*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

Inject reference solution (b). The test is not valid unless the resolution between the peaks corresponding to cephalexin and cephradine is not less than 4.0.

Inject reference solution (a). The relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{16}H_{17}N_3O_4S$ in the powder.

Storage. Store protected from light at a temperature not exceeding 30°.

Cephalexin Veterinary Oral Powder

Cephalexin Veterinary Oral powder is a mixture of Cephalexin and a suitable diluent.

Cephalexin Veterinary Oral powder contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of cephalexin, $C_{16}H_{17}N_3O_4S$.

Usual strength. 7.5 per cent w/w.

Identification

A. In the assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution (a).

B. Weigh a quantity containing 0.1 g of anhydrous cephalexin, shake with 20 ml of *methanol*, filter and evaporate the filtrate to dryness using a rotary evaporator. Dissolve the residue in the minimum volume of a 1 per cent v/v solution of *glacial acetic acid*, decolorise if necessary by the addition of sufficient *decolorising charcoal*, shake and filter. To 0.25 ml of the resulting solution add 0.1 ml of a 1 per cent w/v solution of *cupric sulphate* and 0.05 ml of *2 M sodium hydroxide*; an olive-green colour is produced.

Tests

Other tests. Comply with the tests stated under Veterinary Oral Powders.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Shake an accurately weighed quantity of the powder containing about 0.25 g of anhydrous cephalexin with 200.0 ml of *water* for 30 minutes, add sufficient quantity of *water* to produce 500.0 ml and filter.

Reference solution (a). A 0.05 per cent w/v solution of *cephalexin IPRS* in *water*.

Reference solution (b). A solution containing 0.01 per cent w/v each of *cephalexin IPRS* and *cephradine IPRS* in *water*.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 2 volumes of *methanol*, 5 volumes of *acetonitrile*, 10 volumes of 1.36 per cent solution of *potassium dihydrogen phosphate* and 83 volumes of *water*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

Inject reference solution (b). The test is not valid unless the resolution between the peaks corresponding to cephalexin and cephradine is not less than 4.0.

Inject reference solution (a). The test is not valid unless the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{16}H_{17}N_3O_4S$ in the oral powder.

Storage. Store protected from light at a temperature not exceeding 30°.

Activated Charcoal

Strength. Activated Charcoal 100 mg per ml

For Description, Identification and Tests refer to IP Volume II.

Chloramphenicol

For Description, Identification and Tests refer to IP Volume II.

Chloramphenicol Injection

Chloramphenicol Injection is a sterile suspension of Chloramphenicol in Water for Injections containing suitable suspending and stabilising agents.

Chloramphenicol Injection contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of chloramphenicol, $C_{11}H_{12}Cl_2N_2O_5$.

Usual strengths. 4.5 g in 30 ml; 5.0 g in 50 ml; 11.25 g in 75 ml; 15 g in 100 ml; 20 g in 100 ml.

Identification

Centrifuge a volume containing 0.15 g of Chloramphenicol; wash the residue with water and dry over *self-indicating silica gel* and then for 1 hour at 105°. The dried residue complies with the following tests.

A. Wash 75 mg of the residue with two quantities, each of 10 ml, of *light petroleum (60° to 80°)* and allow to dry. The residue complies with the following test.

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *chloramphenicol IPRS* or with the reference spectrum of chloramphenicol.

B. In the test for Related substances, the principal spot in the chromatogram obtained with 1 µl of test solution corresponds to that in the chromatogram obtained with reference solution (a).

C. To 5 ml of a 0.1 per cent w/v *solution* add a few drops of *silver nitrate solution*; no precipitate is produced. Heat about 50 mg with 3 ml of *ethanolic potassium hydroxide solution* on a water-bath for 15 minutes, add 15 mg of *decolorising charcoal*, shake and filter. The filtrate gives the reactions of chlorides (2.3.1).

Tests

pH (2.4.24). 3.5 to 6.5.

Consistence. Chloramphenicol Injection containing 150 mg per ml passes readily through a 23G hypodermic needle.

2-Amino-1-(4-nitrophenyl)propane-1,3-diol Determine by liquid chromatography (2.4.14).

Test solution. Dilute the injection with sufficient of the mobile phase to produce a solution containing 0.03 per cent w/v of Chloramphenicol.

Reference solution. A 0.00225 per cent w/v of *2-amino-1-(4-nitrophenyl) propane-1,3-diol IPRS* in the mobile phase.

Chromatographic system

- a stainless steel column 10 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a filtered and degassed mixture of 85 volumes of *0.012 M sodium pentane- sulphonate*, 15 volumes of *acetonitrile* and 1 volume of *glacial acetic acid*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 272 nm,
- injection volume: 20 µl.

Inject the reference solution and the test solution. In the chromatogram obtained with test solution the area of any peak corresponding to 2-amino-1-(4-nitrophenyl)- propane-1, 3-diol is not more than the area of the peak obtained with the reference solution.

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 90 volumes of *dichloromethane*, 10 volumes of *methanol* and 1 volume of *water*.

Test solution. A 1.0 per cent w/v solution of the dried residue obtained in the test for identification in *acetone*.

Reference solution (a). A 1.0 per cent w/v solution of *chloramphenicol IPRS* in *acetone*.

Reference solution (b). Dilute 1 ml of reference solution (a) to 200 ml with *acetone*.

Apply to the plate 1 µl and 20 µl of the test solution, 1 µl of reference solution (a) and 20 µl of reference solution (b). After development, dry the plate in air and examine under ultraviolet light at 254 nm. Any secondary spot in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with reference solution (b).

Bacterial endotoxins (2.2.3). Not more than 0.2 Endotoxin Unit per mg of chloramphenicol.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. To a measured volume containing 0.75 g of chloramphenicol add sufficient *water* to produce 1000.0 ml and shake until a clear solution is obtained. Dilute 5.0 ml of the solution to 200.0 ml with *water* and measure the absorbance of the resulting solution at the maximum at about 278 nm (2.4.7). Calculate the content of $C_{11}H_{12}Cl_2N_2O_5$ in the injection taking 297 as the specific absorbance at 278 nm.

Storage. Store protected from light. Do not freeze.

Labelling. The label states (1) the name of any added suspending agent; (2) that the injection is for intramuscular injection only; (3) the date after which the contents are not intended to be used.

Chloramphenicol Sodium Succinate

For Description, Identification and Tests refer to IP Volume II.

Chlorpheniramine Injection

Usual strengths. Each ml contains Chlorpheniramine Maleate 10 mg.

For Identification and Tests refer to IP Volume II.

Chlorpromazine Hydrochloride

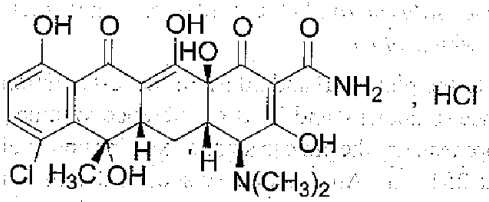
For Description, Identification and Tests refer to IP Volume II.

Chlorpromazine Injection

Usual strengths. 10 mg in 1 ml; 25 mg in 1 ml.

For Identification and Tests refer to IP Volume II.

Chlortetracycline Hydrochloride



$C_{22}H_{23}ClN_2O_8,HCl$ Mol. Wt. 515.3

Chlortetracycline Hydrochloride is [4*S*-(4α,4aα,5aα,6β,12aα)]-7-chloro-4- dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide hydrochloride.

Chlortetracycline Hydrochloride contains not less than 89.5 per cent of chlortetracycline hydrochloride and the sum of the contents of chlortetracycline hydrochloride and tetracycline hydrochloride is not less than 94.5 per cent and not more than 100.5 per cent, calculated on the anhydrous basis.

Category. Antibacterial.

Description. Yellow powder.

Identification

A. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel H*.

NOTE — Use freshly prepared solution.

Mobile phase. A mixture of 59 volumes of *dichloromethane*, 35 volumes of *methanol* and 6 volumes of *water*.

Test solution: Dissolve 50 mg of the substance under examination in 100 ml of *methanol*.

Reference solution (a). A 0.05 per cent w/v of *chlortetracycline hydrochloride IPRS* in *methanol*.

Reference solution (b). A solution containing 0.05 per cent w/v each of *chlortetracycline hydrochloride IPRS*, *tetracycline hydrochloride IPRS* and *metacycline hydrochloride IPRS* in *methanol*.

Adjust the pH of a 10 per cent w/v solution of *disodium edetate* to 8.0 with *10 M sodium hydroxide* and spray this solution evenly on the plate (about 10 ml for a plate of 100 mm by 200 mm size). Allow the plate to dry in a horizontal position for at least 1 hour. Dry the plate in an oven at 100° for 1 hour before use. Apply to the plate 1 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 365 nm. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows three clearly separated spots.

B. To about 2 mg add 5 ml of *sulphuric acid*; a deep blue colour develops which becomes bluish green. Add the solution to 2.5 ml of *water*; the colour changes to brownish.

C. It gives reaction (A) of chlorides (2.3.1).

Tests

pH (2.4.24). 2.3 to 3.3, determined in a 1 per cent w/v solution in *carbon dioxide-free water* prepared by slight heating, if necessary.

Specific optical rotation (2.4.22). –250° to –235°, determined at 20° in a 0.25 per cent w/v solution in *water*, calculated on the anhydrous basis.

Light absorption. When examined at 460 nm of a 0.5 per cent w/v solution in *water* is not more than 0.40.

Related substances. Carry out the method described under Assay injecting test solution, reference solutions (e) and (f). The test is not valid unless the peak in the chromatogram obtained with reference solution (f) is properly integrated. In the chromatogram obtained with test solution the area of the peak corresponding to 4-epichlortetracycline is not more than the area of the peak corresponding to 4-epichlortetracycline in the chromatogram obtained with reference solution (e) (4 per cent) and the total area of any secondary peaks, other than the peaks due to tetracycline and 4-epichlortetracycline, is not more than 25 per cent of the area of the peak corresponding to 4-epichlortetracycline in the chromatogram obtained with reference solution (e) (1 per cent). Ignore any peak with an area smaller than that of the principal peak in the chromatogram obtained with reference solution (f) (0.1 per cent).

Tetracycline hydrochloride. Not more than 8.0 per cent, calculated on the anhydrous basis and determined as described under the Assay, injecting separately test solution and reference solution (e).

Heavy metals (2.3.13). 0.5 g complies with the limit test for heavy metals, Method D (50 ppm), using 2.5 ml of lead standard solution (10 ppm Pb) as the standard.

Sulphated ash (2.3.18). Not more than 0.5 per cent.

Water (2.3.43). Not more than 2.0 per cent, determined on 0.3 g.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 100 mg of the substance under examination in 100.0 ml of *0.01 M hydrochloric acid*.

Reference solution (a). A 0.1 per cent w/v solution of *chlortetracycline hydrochloride IPRS* in *0.01 M hydrochloric acid*.

Reference solution (b). A 0.04 per cent w/v of *4-epichlortetracycline hydrochloride IPRS* in *0.01 M hydrochloric acid*.

Reference solution (c). A 0.08 per cent w/v of *tetracycline hydrochloride IPRS* in *0.01 M hydrochloric acid*.

Reference solution (d). Mix 5 ml of reference solution (a) and 10 ml of reference solution (b) and dilute to 25 ml with *0.01 M hydrochloric acid*.

Reference solution (e). Mix 5 ml of reference solution (b) and 5 ml of reference solution (c) and dilute to 50 ml with *0.01 M hydrochloric acid*.

Reference solution (f). Dilute 1 ml of reference solution (c) to 20 ml with *0.01 M hydrochloric acid* and dilute 2.5 ml of the solution to 100 ml with *0.01 M hydrochloric acid*.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octylsilane groups (5 µm),
- column temperature 35°,
- mobile phase: a filtered and degassed mixture of 450 ml of *dimethyl sulphoxide*, 50 ml of *1 M perchloric acid* and 500 ml of *water*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Inject reference solution (d) and adjust the instrument so that the peak heights correspond to at least 50 per cent of the full scale deflection of the recorder. If necessary, adjust the dimethyl sulphoxide content in the mobile phase. The test is not valid unless the resolution factor between the first peak (4-epichlortetracycline) and the second (chlortetracycline) is not less than 2.0 and the symmetry factor for the second peak is not more than 1.3.

Inject reference solution (a). The test is not valid unless the relative standard deviation of the peak area for chlortetracycline hydrochloride is not more than 1.0 per cent. If necessary, adjust the integrator parameters.

Inject alternately the test solution and reference solution (a).

Calculate the content of $C_{22}H_{23}ClN_2O_8,HCl$.

Chlortetracycline Hydrochloride intended for use in the manufacture of Parenteral Preparations without a further appropriate procedure for removal of bacterial endotoxins complies with the following additional requirement.

Bacterial endotoxins (2.2.3). Not more than 1.1 Endotoxin Units per mg of chlortetracycline hydrochloride.

Chlortetracycline Hydrochloride intended for use in the manufacture of Parenteral Preparations without a further appropriate sterilisation procedure complies with the following additional requirement.

Sterility (2.2.11). Complies with the test for sterility.

Storage. Store protected from light. If it is intended for use in the manufacture of Parenteral Preparations, the container should be sterile, tamper-evident and sealed so as to exclude micro-organisms.

Labelling. The label states (1) the date after which the material is not intended to be used; (2) the storage conditions; (3) where applicable, that the material is sterile and free from Bacterial endotoxins.

Chlortetracycline Veterinary Oral Powder

Chlortetracycline Hydrochloride Veterinary Oral Powder; Chlortetracycline Soluble Powder

Chlortetracycline Veterinary Oral Powder is a mixture of Chlortetracycline Hydrochloride and Lactose or other suitable diluent.

Chlortetracycline Veterinary Oral Powder contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of chlortetracycline hydrochloride, $C_{22}H_{23}ClN_2O_8,HCl$

Usual strength. 5.5 per cent w/w.

Identification

A. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel H*.

NOTE — Use freshly prepared solutions.

Mobile phase. A mixture of 59 volumes of *dichloromethane*, 35 volumes of *methanol* and 6 volumes of *water*.

Test solution. The supernatant liquid obtained by extracting a quantity containing 5 mg of Chlortetracycline Hydrochloride with 10 ml of *methanol* and centrifuging.

Reference solution (a). A 0.05 per cent w/v of *chlortetracycline hydrochloride IPRS* in *methanol*.

Reference solution (b). A solution containing 0.05 per cent w/v each of *chlortetracycline hydrochloride IPRS*,

tetracycline hydrochloride IPRS and *metacycline hydrochloride IPRS* in *methanol.*

Adjust the pH of a 10 per cent w/v solution of *disodium edetate* to 8.0 with *10 M sodium hydroxide* and spray this solution evenly on the plate (about 10 ml for a plate of 100 mm by 200 mm size). Allow the plate to dry in a horizontal position for at least 1 hour. Dry the plate in an oven at 100° for 1 hour before use. Apply to the plate 1 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 365 nm. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows three clearly separated spots.

B. To a quantity containing 10 mg of Chlortetracycline Hydrochloride, add 20 ml of warm *ethanol (95 per cent)*, allow to stand for 20 minutes, filter and evaporate to dryness on a water-bath. Dissolve the residue in sufficient *phosphate buffer pH 7.6* to produce a 0.1 per cent w/v solution and heat at 100° for 1 minute; it exhibits a strong blue fluorescence in ultra-violet light.

Tests

Other tests. Comply with the tests stated under Veterinary Oral Powders.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 100 mg of the substance under examination in 100.0 ml of *0.01 M hydrochloric acid.*

Reference solution (a). A 0.1 per cent w/v solution of *chlortetracycline hydrochloride IPRS* in *0.01 M hydrochloric acid.*

Reference solution (b). A 0.04 per cent w/v solution of *4-epichlortetracycline hydrochloride IPRS* in *0.01 M hydrochloric acid.*

Reference solution (c). A 0.08 per cent w/v solution of *tetracycline hydrochloride IPRS* in *0.01 M hydrochloric acid.*

Reference solution (d). Mix 5.0 ml of reference solution (a) and 10.0 ml of reference solution (b) and dilute to 25 ml with *0.01 M hydrochloric acid.*

Reference solution (e). Mix 5.0 ml of reference solution (b) and 5.0 ml of reference solution (c) and dilute to 50 ml with *0.01 M hydrochloric acid.*

Reference solution (f). Dilute 1.0 ml of reference solution (c) to 20 ml with *0.01 M hydrochloric acid.* Further, dilute 2.5 ml of the solution to 100.0 ml with *0.01 M hydrochloric acid.*

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octylsilane bonded to porous silica (5 µm),
- column temperature 35°,
- mobile phase: a mixture of 45 ml of *dimethyl sulphoxide*, 5 ml of *1 M perchloric acid* and 50 ml of *water*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Inject reference solution (d). Adjust the instrument so that the peak heights correspond to at least 50 per cent of the full scale deflection of the recorder. If necessary, adjust the *dimethyl sulphoxide* content in the mobile phase. The test is not valid unless the resolution factor between the first peak (4-epichlortetracycline) and the second (chlortetracycline) is not less than 2.0 and the symmetry factor for the second peak is not more than 1.3.

Inject reference solution (a). The test is not valid unless the relative standard deviation of the peak area for chlortetracycline hydrochloride is not more than 1.0 per cent.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{22}H_{23}ClN_2O_8,HCl$.

Storage. Store protected from moisture, at a temperature not exceeding 30°.

Labelling. The label states the strength in terms of the concentration of Chlortetracycline Hydrochloride

Cholecalciferol

For Description, Identification and Tests refer to IP Volume III.

Chorionic Gonadotropin

For Description, Identification and Tests refer to IP Volume II.

Ciprofloxacin Injection

Usual strengths. 40 mg in 1 ml; 100 mg in 1 ml.

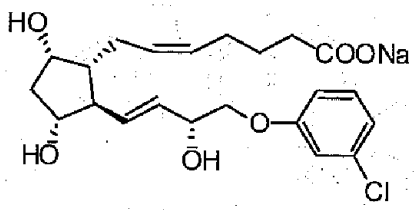
For Identification and Tests refer to IP Volume II.

Ciprofloxacin Tablets/Boluses

Usual strengths. 250 mg; 500 mg; 1500 mg tablets/boluses .

For Identification and Tests refer to IP Volume II.

Cloprostenol Sodium



$C_{22}H_{28}ClNaO_6$ Mol.Wt. 446.9

Category. Prostaglandin ($PGF_{2\alpha}$) analogue.

Cloprostenol Sodium is (5*Z*)-7-((1*R*,2*R*,3*R*,5*S*)-2-((*R*,*E*)-4-(3-chlorophenoxy)-3-hydroxybut-1-enyl)-3,5-dihydroxycyclopentyl)hept-5-enoic acid.

Cloprostenol Sodium contains not less than 97.5 per cent and not more than 102.5 per cent of $C_{22}H_{28}ClNaO_6$, calculated on the anhydrous basis.

NOTE—Cloprostenol sodium is extremely potent and extraordinary care should be taken in any procedure in which it is used.

Description. A white or almost white, amorphous hygroscopic powder.

Identification

A. Determine by infrared absorption spectrometry (2.4.6). Compare the spectrum with that obtained *cloprostenol sodium IPRS* or with the reference spectrum of cloprostenol sodium.

B. It gives reaction (A) of sodium salts (2.3.1).

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. A 2.0 per cent w/v solution of cloprostenol sodium in *ethanol*.

Reference solution. A 0.05 per cent w/v solution of *cloprostenol sodium IPRS* in *ethanol*.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with silica gel (5 µm),
- mobile phase: a mixture of 93 volumes of *hexane*, 7 volumes of *ethanol* and 0.1 volume of *glacial acetic acid*,
- flow rate: 1.8 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 5 µl.

Inject the reference solution and the test solution. Run the chromatogram two times the retention time of the peak due to cloprostenol. The sum of the areas of any secondary peaks is not more than the area of the principal peak in the chromatogram obtained with reference solution (2.5 per cent).

Water (2.3.43). Not more than 3.0 per cent, determine in 0.5 g dissolved in 1 ml of *ethanol*.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. A 0.08 per cent w/v solution of cloprostenol sodium in *ethanol*.

Reference solution. A 0.08 per cent w/v solution of *cloprostenol sodium IPRS* in *ethanol*.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with silica gel (5 µm),
- mobile phase: a mixture of 90 volumes of *hexane*, 10 volumes of *ethanol* and 0.1 volume of *glacial acetic acid*.
- flow rate: 1.8 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 20 µl.

Inject the reference solution and the test solution.

Calculate the content of $C_{22}H_{28}ClNaO_6$.

Storage. Store protected from light and moisture.

Cloprostenol Injection

Cloprostenol Injection is a sterile solution of Cloprostenol Sodium in Water for Injections.

Cloprostenol Injection contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of cloprostenol, $C_{22}H_{29}ClO_6$.

Category. Prostaglandin ($PGF_{2\alpha}$) analogue.

Usual strength. 250 mcg per ml.

Identification

In the Assay, the principal peak in the chromatogram obtained with test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dilute the injection equivalent to 0.009 per cent w/v of cloprostenol with the *ethanol*.

Reference solution (a). A 0.00018 per cent w/v solution of *cloprostenol sodium IPRS* in *ethanol*.

Reference solution (b). Dissolve 5 mg of *hydrocortisone acetate IPRS* and 2.5 mg of *cloprostenol sodium IPRS* in *ethanol* and dilute to 10.0 ml with the mobile phase.

Chromatographic system

- a stainless steel column 25 cm x 5 mm, packed with base-deactivated octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 27 volumes of *acetonitrile* and 73 volumes of 0.24 per cent w/v solution of *sodium dihydrogen orthophosphate*, adjusted to pH 2.5 with *orthophosphoric acid*,
- flow rate: 1.8 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 20 µl.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to hydrocortisone acetate and that of cloprostenol is not less than 6.

Inject reference solution (a) and the test solution. Run the chromatogram 1.5 times the retention time of the cloprostenol. The sum of the areas of the secondary peaks obtained with test solution is not more than 1.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.5 per cent).

Bacterial endotoxins (2.2.3). Not more than 2500 Endotoxin Units per mg of cloprostenol.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dilute the injection equivalent to 0.009 per cent w/v of cloprostenol with the *ethanol*.

Reference solution (a). A 0.009 per cent w/v solution of *cloprostenol sodium IPRS* in *ethanol*.

Reference solution (b). Dissolve 5 mg of *hydrocortisone acetate IPRS* and 2.5 mg of *cloprostenol sodium IPRS* in *ethanol* and dilute to 10 ml with the mobile phase.

Use the Chromatographic system as described under Related substances.

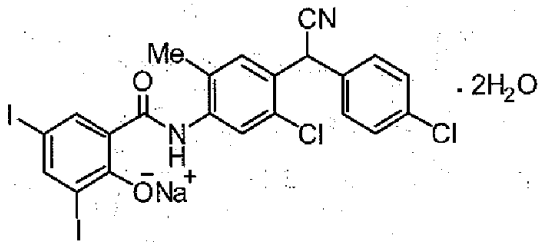
Inject reference solution (b). The test is not valid unless the resolution between the peaks due to hydrocortisone acetate and that of cloprostenol is not less than 6.

Calculate the content of cloprostenol, $C_{22}H_{29}ClO_6$, in the injection.

Storage. Store protected from light.

Labelling. The label states that the strength is stated as the equivalent amount of cloprostenol in a suitable dose-volume.

Closantel Sodium Dihydrate



$C_{22}H_{13}Cl_2I_2N_2NaO_2, 2H_2O$ Mol. Wt. 721.0

Closantel Sodium Dihydrate is *N*-[5-chloro-4-[(*RS*)-(4-chlorophenyl) cyanomethyl]-2-methylphenyl]-2-hydroxy-3,5-diiodobenzamide sodium salt dihydrate.

Closantel Sodium Dihydrate contains not less than 98.5 per cent and not more than 101.5 per cent of $C_{22}H_{13}Cl_2I_2N_2NaO_2, 2H_2O$, calculated on the anhydrous basis.

Category. Antihelminthic.

Description. A yellow powder, slightly hygroscopic. It shows polymorphism (2.5.11).

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *closantel sodium dihydrate IPRS* or with the reference spectrum of closantel sodium dihydrate.

B. Dissolve 0.1 g in 2 ml of *ethanol (95 per cent)*. It gives reaction (A) of sodium (2.3.1).

Tests

Appearance of solution (2.4.1). A 1.0 per cent w/v solution in *ethanol (95 per cent)* is clear and not more intensely coloured than reference solution GYS4.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE—Prepare the solution immediately before use and protected from light.

Test solution. Dissolve 0.1 g of the substance under examination in 10 ml of *methanol*.

Reference solution (a). Dissolve 10 mg of *closantel for system suitability IPRS* (containing impurities A to J) in 1 ml of *methanol*.

Reference solution (b). Dilute 1.0 ml of test solution to 100.0 ml with *methanol* and dilute 5.0 ml of the solution to 25.0 ml with *methanol*.

Chromatographic system

- a stainless steel column 10 cm x 4.6 mm, packed with base-deactivated octadecylsilane bonded to porous silica (3 µm),

- column temperature: 35°;
- mobile phase: A. a mixture of 10 volumes of 0.77 per cent *ammonium acetate* solution, adjusted to pH 4.3 with *acetic acid*, 5 volumes of *acetonitrile* and 85 volumes of *water*,

  B. a mixture of 10 volumes of 0.77 per cent *ammonium acetate* solution, adjusted to pH 4.3 with *acetic acid*, 5 volumes of *water* and 85 volumes of *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 240 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	50	50
2	50	50
22	20	80
27	20	80

Name	Relative retention time	Correction factor
Closantel impurity A[1]	0.07	1.5
Closantel impurity B[2]	0.48	1.3
Closantel impurity C[3]	0.62	—
Closantel impurity D[4]	0.65	—
Closantel impurity E[5]	0.82	—
Closantel impurity F[6]	0.89	—
Closantel impurity G[7]	0.93	—
Closantel (Retention time: about 16 minutes)	1.0	—
Closantel impurity H[8]	1.13	—
Closantel impurity I[9]	1.16	—
Closantel impurity J[10]	1.55	—

[1]2-hydroxy-3,5-diiodobenzoic acid,

[2](2*RS*)-(4-amino-2-chloro-5-methylphenyl)(4-chlorophenyl) ethanenitrile,

[3](2*RS*)-[2-chloro-4-[(2-hydroxy-3,5-diiodobenzoyl)amino]-5-methylphenyl](4-chlorophenyl)acetic acid,

[4]*N*-[4-[(1*RS*)-2-amino-1-(4-chlorophenyl)-2- oxoethyl]-5-chloro-2-methylphenyl]-2-hydroxy-3,5-diiodobenzamide,

[5]3-chloro-*N*-[5-chloro-4-[(*RS*)-(4-chlorophenyl)cyanomethyl]-2-methylphenyl]-2-hydroxy-5-iodobenzamide,

[6]*N*-[5-chloro-4-(4-chlorobenzoyl)-2-methylphenyl]-2- hydroxy-3,5-diiodobenzamide,

[7]methyl (2*RS*)-2-[2-chloro-4-[(2-hydroxy-3,5- diiodobenzoyl)amino]-5-methylphenyl]-2-(4-chlorophenyl)acetimidate,

[8]methyl (2*RS*)-[2-chloro-4-[(2-hydroxy-3,5- diiodobenzoyl)amino]-5-methylphenyl](4-chlorophenyl)acetate,

[9]*N*-[5-chloro-4-[(*RS*)-(4-chlorophenyl)cyanomethyl]-2-methylphenyl]-2-hydroxy-5-iodobenzamide,

[10]*N*-[5-chloro-4-[[4-[[2-chloro-4-[(2-hydroxy-3,5-diiodobenzoyl) amino]-5-methylphenyl]cyanomethyl]phenyl](4-chlorophenyl) cyanomethyl]-2-methylphenyl]- 2-hydroxy-3,5-diiodobenzamide.

Inject reference solution (a). The test is not valid unless there is clear base line separation between the peaks due to impurity G and closantel.

Inject reference solution (b) and the test solution. The chromatogram obtained with test solution is correspond to the chromatogram obtained with reference solution (b), the area of any peak corresponding to each impurity A, B, C, D, E and J, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent), the area of peak for each impurity F, H and I, each of, is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent) and the area of peak for impurity G is not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent). The area of any other secondary peak is not more than the area of principle peak in the chromatogram obtained with reference solution (b) (0.2 per cent). The sum of the areas of the secondary peak is not more than 7.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent). Ignore any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (2.3.43). 4.8 to 5.8 per cent, determined on 0.25 g.

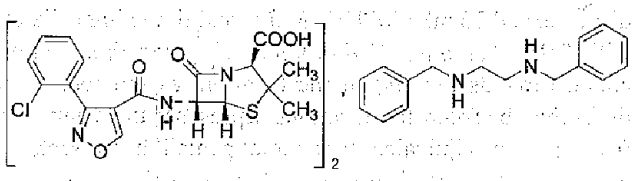
NOTE—Use a mixture of 1 volume of dimethylformamide and 4 volumes of methanol as the solvent.

Assay. Dissolve 0.5 g in 50 ml of a mixture of 1 volumes of *anhydrous glacial acetic acid* and 7 volumes of *methyl ethyl ketone*. Titrate with *0.1 M perchloric acid*, determining the end point potentiometrically (2.4.25). Carry out a blank titration.

1 ml of *0.1 M perchloric acid* is equivalent to 0.0685 g of $C_{22}H_{13}Cl_2I_2N_2NaO_2$.

Storage. Store protected from light, in an air tight container.

Cloxacillin Benzathine



$(C_{19}H_{18}ClN_3O_5S)_2,C_{16}H_{20}N_2$ Mol. Wt. 1112.1

Cloxacillin Benzathine is *N,N'*-dibenzylethylene-diammonium bis-[(6*R*)-6-{3-(2-chlorophenyl)-5-methyl-isoxazole-4-carboxamido}penicillanate].

Cloxacillin Benzathine contains not less than 92.0 per cent of $(C_{19}H_{18}ClN_3O_5S)_2.C_{16}H_{20}N_2$ and not less than 20.0 per cent and not more than 22.0 per cent of benzathine, $C_{16}H_{20}N_2$, both calculated on the anhydrous basis.

Category. Antibacterial.

Description. A white or almost white powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *cloxacillin benzathine IPRS* or with the reference spectrum of cloxacillin benzathine.

B. Shake 0.1 g with 1 ml of *1 M sodium hydroxide* for 2 minutes, add 2 ml of *ether*, shake for 1 minute and allow to separate. Evaporate 1 ml of the ether layer to dryness, dissolve the residue in 2 ml of *glacial acetic acid* and add 1 ml of *dilute potassium dichromate solution*; a golden yellow precipitate is produced.

C. Shake 50 mg with 10 ml of *water* and filter. To 5 ml of the filtrate add a few drops of *silver nitrate solution*; no precipitate is produced. Heat 50 mg with 2 ml of *ethanolic potassium hydroxide solution* on a water-bath for 15 minutes, add 15 mg of *decolorising charcoal*, shake and filter. Acidify the filtrate with *2 M nitric acid*; the solution gives reaction (A) of chlorides (2.3.1).

Tests

Water (2.3.43). Not more than 5.0 per cent w/w, determined on 0.5 g.

Assay. *For cloxacillin benzathine* — Weigh 60 mg, add 40 ml of *methanol*, shake to dissolve, add 25 ml of *1 M sodium hydroxide* and allow to stand for 30 minutes. Add 27.5 ml of *1 M hydrochloric acid* and sufficient *water* to produce 100.0 ml, mix, transfer 20.0 ml of the solution to a stoppered conical flask, add 30.0 ml of *0.01 M iodine*, close the flask with a wet stopper and allow to stand for 15 minutes protected from light. Titrate the excess of iodine with *0.02 M sodium thiosulphate*, using *starch mucilage*, added towards the end of the titration, as indicator. Add a further 12 mg of the substance under examination to 10 ml of *water*, swirl to disperse, add 30 ml of *0.01 M iodine* and titrate immediately with *0.02 M sodium thiosulphate*, using *starch mucilage*, added towards the end of the titration, as indicator. The difference between the titrations represents the volume of *0.01 M iodine* equivalent to the total penicillins present.

Calculate the content of $(C_{19}H_{18}ClN_3O_5S)_2.C_{16}H_{20}N_2$ from the difference obtained by carrying out the procedure simultaneously using *cloxacillin benzathine IPRS*.

For benzathine — Weigh 1 g, add 30 ml of a saturated solution of *sodium chloride* and 10 ml of *5 M sodium hydroxide*, shake well and extract with four quantities, each of 50 ml, of *ether*. Wash the combined extracts with three quantities, each of 10 ml, of *water*, extract the combined washings with 25 ml of *ether* and add the extract to the main ether solution. Evaporate the ether solution to low volume, add 2 ml of *ethanol* and evaporate to dryness. To the residue add 50 ml of *anhydrous glacial acetic acid*. Titrate with *0.1 M perchloric acid*, using 0.1 ml of *1-naphtholbenzein solution* as indicator. Carry out a blank titration.

1 ml of *0.1 M perchloric acid* is equivalent to 0.01202 g of $C_{16}H_{20}N_2$.

Cloxacillin Benzathine intended for use in the manufacture of either parenteral preparations or intramammary infusions without a further appropriate sterilisation procedure complies with the following additional requirement.

Sterility (2.2.11). Complies with the test for sterility.

Storage. Store protected from moisture. If it is intended for use in the manufacture of parenteral preparations or intramammary infusions, the container should be sterile, tamper-evident and sealed so as to exclude micro-organisms.

Cloxacillin Benzathine Intramammary Infusion (Dry Cow/ Buffalo)

Cloxacillin Benzathine Intramammary Injection; Cloxacillin Intramammary Infusion (Dry Cow/Buffalo); Cloxacillin Intramammary Infusion (DC/B)

Cloxacillin Benzathine Intramammary Infusion (Dry Cow/ Buffalo) is a sterile suspension of Cloxacillin Benzathine in a suitable non-aqueous vehicle containing suitable suspending agents.

Cloxacillin Benzathine Intramammary Infusion (Dry Cow/ Buffalo) contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of cloxacillin, $C_{19}H_{18}ClN_3O_5S$.

Usual strength. The equivalent of 500 mg of cloxacillin.

Identification

Extract a quantity containing 75 mg of cloxacillin with three quantities, each of 15 ml, of *light petroleum (120° to 160°)*. Discard the extracts, wash the residue with 10 ml of *ether* and dry in a current of air. The residue complies with the following tests.

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *cloxacillin benzathine IPRS* or with the reference spectrum of cloxacillin benzathine.

B. Shake 50 mg with 1 ml of *1 M sodium hydroxide* for 2 minutes, add 2 ml of *ether*, shake for 1 minute and allow to separate. Evaporate 1 ml of the ether layer to dryness, dissolve the residue in 2 ml of *glacial acetic acid* and add 1 ml of *dilute potassium dichromate solution*; a golden yellow precipitate is produced.

Tests

Water (2.3.43). Not more than 2.0 per cent, determined on 3 g and using a mixture of 70 volumes of *dichloromethane* and 30 volumes of *anhydrous methanol* as the solvent.

Other tests. Comply with the tests stated under Intramammary Infusions.

Assay. Weigh and mix the contents of 10 containers. Weigh a quantity of the mixed contents containing 80 mg of cloxacillin and extract with three quantities, each of 15 ml, of *light petroleum (120° to 160°)* previously saturated with cloxacillin benzathine. Discard the extracts, wash the residue with *ether* previously saturated with cloxacillin benzathine. Dry in a current of air, dissolve in 25 ml of *methanol* and dilute to 50.0 ml with *water*. Dilute 2.0 ml of the solution to 100.0 ml with *buffered cupric sulphate solution pH 2.0*, transfer 10.0 ml to a stoppered test-tube and heat in a water-bath at 70° for 20 minutes. Cool to room temperature rapidly, dilute to 20.0 ml with *ethanol* and measure the absorbance of the resulting solution at the maximum at about 338 nm (2.4.7), using as the blank 10.0 ml of the unheated buffered solution of the substance under examination after dilution to 20.0 ml with *ethanol*.

Calculate the content of $C_{19}H_{18}ClN_3O_5S$ in a container of average weight from the absorbance obtained by carrying out the procedure simultaneously using 2.0 ml of a solution prepared by dissolving 105 mg of *cloxacillin benzathine IPRS* in 50.0 ml of a mixture of equal volumes of *methanol* and *water*.

Labelling. The label states the strength in terms of the equivalent amount of cloxacillin in the sealed container.

Cloxacillin Sodium

For Description, Identification and Tests refer to IP Volume II.

Cloxacillin Injection

Cloxacillin Sodium Injection

Usual strengths. 250 mg; 500 mg; 1 g; 2 g; 3 g and 4 g Vials.

For Identification and Tests refer to IP Volume II.

Cloxacillin Sodium Intramammary Infusion (Lactating Cow/Buffalo)

Cloxacillin Intramammary Injection; Cloxacillin Intramammary Infusion (Lactating Cow/Buffalo); Cloxacillin Intramammary Infusion (LC/B)

Cloxacillin Sodium Intramammary Infusion (Lactating Cow/Buffalo) is a sterile suspension of Cloxacillin Sodium in a suitable non-aqueous vehicle containing suitable suspending and dispersing agents.

Cloxacillin Sodium Intramammary Infusion (Lactating Cow/Buffalo) contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of cloxacillin, $C_{19}H_{18}ClN_3O_5S$.

Usual strength. Equivalent of 200 mg of cloxacillin.

Identification

Extract a quantity containing 75 mg of cloxacillin with three quantities, each of 15 ml, of *light petroleum (120° to 160°)*. Discard the extracts, wash the residue with 10 ml of *ether* and dry in a current of air. The residue complies with the following tests.

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *cloxacillin sodium IPRS* or with the reference spectrum of cloxacillin sodium.

B. It gives reaction (A) of sodium salts (2.3.1).

Tests

Water (2.3.43). Not more than 1.0 per cent, determined on 3 g using a mixture of 70 volumes of *dichloromethane* and 30 volumes of *anhydrous methanol* as the solvent.

Other tests. Comply with the tests stated under Intramammary Infusions.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Disperse a quantity of mixed contents of 10 containers containing about 50 mg of cloxacillin with 15 ml of *petroleum spirit (boiling range 120° to 160°)*, centrifuge and discard the supernatant liquid. Repeat the extraction with a further two 15 ml quantities of *petroleum spirit (boiling range 120° to 160°)*. Shake the residue with 20 ml of *ether*, centrifuge and dry in a current of air until the solvent get evaporated. Dissolve the final residue in 50 ml of the mobile phase. Dilute 5.0 ml of the solution to 50.0 ml with the mobile phase.

Reference solution (a). A 0.011 per cent w/v each of *cloxacillin sodium IPRS* in the mobile phase.

Reference solution (b). A solution containing 0.01 per cent w/v each of *cloxacillin sodium IPRS* and *flucloxacillin sodium IPRS* in the mobile phase.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 25 volumes of *acetonitrile* and 75 volumes of 0.27 per cent w/v solution of *potassium dihydrogen orthophosphate*, adjusted to pH 5.0 with *2 M sodium hydroxide*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 225 nm,
- injection volume:20 µl.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to cloxacillin and flucoxacillin is not less than 2.5.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{19}H_{18}ClN_3O_5S$.

1 mg of $C_{19}H_{17}ClN_3NaO_5S$ is equivalent to 0.952 mg of $C_{19}H_{18}ClN_3O_5S$.

Labelling. The label states the strength in terms of the equivalent amount of cloxacillin.

Cyanocobalamin

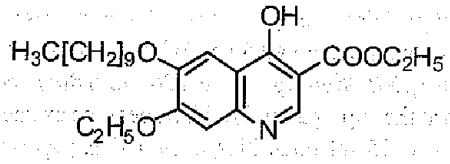
For Description, Identification and Tests refer to IP Volume III.

Cyanocobalamin Injection

Usual strengths. 500 mcg per ml; 10 ml; 30 ml vial.

For Identification and Tests refer to IP Volume II.

Decoquinate



$C_{24}H_{35}NO_5$ Mol. Wt. 417.6

Decoquinate is ethyl 6-(decyloxy)-7-ethoxy-4-hydroxyquinoline-3-carboxylate.

Decoquinate contains not less than 99.0 per cent and not more than 101.0 per cent of $C_{24}H_{35}NO_5$, calculated on the dried basis.

Category. Antiprotozoal.

Description. A cream to buff-coloured, microcrystalline powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *decoquinate IPRS* or with the reference spectrum of decoquinate.

B. When examined in the range of 220 nm to 350 nm (2.4.7), the solution used in light absorption shows absorption maxima at about 265 nm.

Tests

Light absorption (2.4.7). Dissolve 40 mg substances in 10 ml of hot *chloroform*, keep the solution warm, cool and dilute to 100 ml with *ethanol*. Dilute 10.0 ml of the solution to 100.0 ml with *ethanol* immediately. To 10.0 ml solution, add 10.0 ml of *0.1 M hydrochloric acid* and dilute to 100.0 ml with absolute *ethanol*. The absorbance of the resulting solution at the maximum at about 265 nm is 0.38 to 0.42, calculated on the dried basis.

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 5 volumes of *anhydrous formic acid*, 10 volumes of *ethanol* and 85 volumes of *chloroform*.

Test solution. A 1.0 per cent w/v solution of the substance under examination in *chloroform*.

Reference solution (a). A 0.005 per cent w/v solution of *diethyl 4-decyloxy-3- ethoxy aniline methylene malonate IPRS* in *chloroform*.

Reference solution (b). A 0.010 per cent w/v solution of the substance under examination in *chloroform*.

Apply to the plate 10 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. Any secondary spot correspondence in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.5 per cent) and any other secondary spot is not more intense than the spot in reference solution (b) (1.0 per cent).

Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105°.

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Assay. Dissolve 1.0 g in 50 ml of *chloroform* and 50 ml of *anhydrous acetic acid*. Titrate with *0.1 M perchloric acid*, using *crystal violet solution* as indicator. Carry out a blank titration.

1 ml of *0.1 M perchloric acid* is equivalent to 0.04176 g of $C_{24}H_{35}NO_5$.

Decoquinate Premix

Decoquinate Premix contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of decoquinate, $C_{24}H_{35}NO_5$.

Usual strength. 6.0 per cent w/w.

Identification

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 30 volumes of *ethanol (95 per cent)* and 70 volumes of *chloroform*.

Test solution. Take 0.1 g of decoquinate in 40 ml *chloroform*, heat for 20 minutes on a water bath under a reflux condenser, cool and filter.

Reference solution. A 0.25 per cent w/v solution of *decoquinate IPRS* in *chloroform*.

Apply to the plate 10 µl of each solution. Allow the mobile phase to rise 15 cm. Dry the plate in air and examine under ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with reference solution.

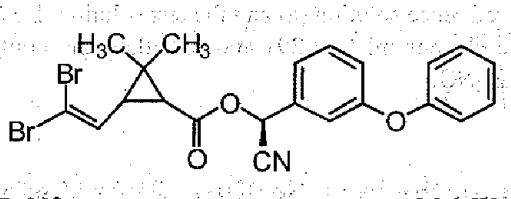
Tests

Assay. *Test solution*. Weigh a quantity containing 0.2 g of decoquinate, add 50 ml of *chloroform* reflux on water-bath for one hour. Cool and add sufficient *chloroform* to produce 100.0 ml, and dilute 5.0 ml to 100.0 ml with *ethanol*. To 5.0 ml add 10.0 ml of *0.1 M hydrochloric acid* and dilute to 100.0 ml with *ethanol*.

Reference solution. Dissolve 50 mg of *decoquinate IPRS* in 10.0 ml of hot *chloroform* and keep the solution warm, add slowly 70.0 ml of *ethanol*, cool and dilute to 100.0 ml with *ethanol* and immediately dilute 10.0 ml of the solution to 100.0 ml with *ethanol*. To 10.0 ml of the solution, add 10.0 ml of *0.1 M hydrochloric acid* and dilute to 100.0 ml with *ethanol*. Measure the absorbance of the resulting solution at the maximum at about 265 nm (2.4.7).

Calculate the content of $C_{24}H_{35}NO_5$ in the premix.

Deltamethrin



$C_{22}H_{19}Br_2NO_3$ Mol. Wt. 505.2

Deltamethrin is (*S*)-α-cyano-3-phenoxybenzyl-(1*R*,3*R*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate.

Deltamethrin contains not less than 97.0 per cent and not more than 101.0 per cent of $C_{22}H_{19}Br_2NO_3$.

Category. Insecticide.

Description. A white to buff-coloured, crystalline powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *deltamethrin IPRS* or with the reference spectrum of deltamethrin.

B. In the test for Related substances, the principal spot in the chromatogram obtained with test solution (b) corresponds to that in the chromatogram obtained with reference solution.

Tests

Specific optical rotation (2.4.22). +55.5° to +61.5°, determined in a 4.0 per cent w/v solution in *toluene*.

Becisthemic acid chloride. Not more than 0.2 per cent.

Dissolve 2.0 g in 100 ml of *methanol* heat on water bath, and cool. Titrate with *0.02 M potassium hydroxide*, using a solution containing 0.8 per cent w/v of *dimethyl yellow* and 0.08 per cent w/v of *methylene blue* in *methanol* as indicator, until a green colour is produced.

1 ml of *0.02 M potassium hydroxide* is equivalent to 0.006329 g of becisthemic acid chloride, $C_8H_9Br_2ClO$.

Becisthemic acid and becisthemic anhydride. Not more than 1.0 per cent, determine by the following method.

Becisthemic acid. Dissolve 2.0 g in 100 ml of *ethanol (95 per cent)*, heat on water bath. Cool in an ice-bath and immediately titrate with *0.02 M sodium hydroxide*, using a 1.0 per cent w/v solution of *1-naphtholbenzein* in *ethanol (95 per cent)* solution as indicator, until a green colour is produced. Correct the volume of titrant for any contribution due to the becisthemic acid chloride content from the expression.

$$V \times \frac{P_2}{P_1}$$

where, V = titration volume obtained in the becisthemic acid chloride test,

P_1 = weight of sample used in the becisthemic chloride test,

P_2 = weight of sample used in this test.

1 ml of *0.02 M sodium hydroxide* is equivalent to 0.005959 g of becisthemic acid, $C_8H_{10}Br_2O_2$.

Becisthemic anhydride. To 1.0 g add 10 ml of *0.01 M aniline* in *cyclohexane* and 10 ml of *glacial acetic acid*. Stopper the flask and allow standing at room temperature for 1 hour. Titrate

with *0.01 M perchloric acid*, using *crystal violet solution* as indicator. Carry out a blank titration. Correct the volume of titrant for any contribution due to twice the becisthemic acid chloride content calculated from the expression above.

1 ml of *0.01 M perchloric acid* is equivalent to 0.005779 g of becisthemic anhydride, $C_{16}H_{18}Br_4O_3$.

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silca gel GF254*.

Mobile phase. A mixture of 20 volumes of *di-isopropyl ether* and 80 volumes of *hexane*.

Test solution (a). A 2.0 per cent w/v solution of substance under examination in *toluene*.

Test solution (b). A 0.5 per cent w/v solution of substance under examination in *toluene*.

Test solution (c). A 0.02 per cent w/v solution of substance under examination in *toluene*.

Test solution (d). A 0.01 per cent w/v solution of substance under examination in *toluene*.

Reference solution. A 0.5 per cent w/v solution of *deltamethrin IPRS* in *toluene*.

Apply to the plate 10 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. Any secondary spot in the chromatogram obtained with the test solution (a) is not more intense than the spot in the chromatogram obtained with test solution (c) (1.0 per cent) and not more than two such spots are more intense than the spot in the chromatogram obtained with test solution (d) (0.5per cent).

Assay. Determine by liquid chromatography (2.4.14).

Test solution. A 0.1 per cent w/v solution of the substance under examination in mobile phase.

Reference solution (a). A 0.1 per cent w/v solution of *deltamethrin IPRS* in mobile phase.

Reference solution (b). A 0.1 per cent w/v solution of *deltamethrin impurity IPRS* in reference solution (a).

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with porous silica (5 µm),
- mobile phase: a mixture of 0.04 volumes of *propan-2-ol*, 2 volumes of *acetonitrile*, 10 volumes of *dichloromethane* and 100 volumes of *hexane*,
- flow rate: 1.3 ml per minute,
- spectrophotometer set at 278 nm,
- injection volume: 20 µl.

Inject reference solution (b). The test is not valid unless the peak due to deltamethrin appears immediately before the peak due to deltamethrin impurity.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{22}H_{19}Br_2NO_3$.

Deltamethrin Pour-on

Deltamethrin Pour-on is a pour-on solution. It contains deltamethrin in a suitable, oily vehicle.

Deltamethrin contains not less than 90.0 per cent and not more than 110.0 per cent of stated amount of deltamethrin, $C_{22}H_{19}Br_2NO_3$.

Usual strengths. 10 mg per ml; 125 mg per ml; 175 mg per ml.

Identification

In the Assay, the chromatogram obtained with test solution corresponds to that in the chromatogram obtained with reference solution (a).

Tests

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Weigh a quantity containing 30 mg of deltamethrin, add sufficient *hexane* to produce 100.0 ml. Dilute 5 ml of the solution to 20 ml with *hexane*.

Reference solution (a). A 0.0075 per cent w/v solution of *deltamethrin IPRS* in *hexane*.

Reference solution (b). A 0.0075 per cent w/v solution of *deltamethrin impurity IPRS* in reference solution (a).

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with silica gel modified with chemically-bonded nitrophenyl groups (5 µm),
- mobile phase: a mixture of *hexane* containing 0.25 per cent v/v of *propan-2-ol*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 230 nm,
- injection volume: 20 µl.

Inject reference solution (b). The test is not valid unless a peak due to deltamethrin appears immediately before the peak, due to deltamethrin impurity.

Inject reference solution (a) and the test solution. Determine the weight per ml (2.4.29) and calculate the content of $C_{22}H_{19}Br_2NO_3$.

Dexamethasone Sodium Phosphate

For Description, Identification and Tests refer to IP Volume II.

Dexamethasone Injection

Usual strengths. The equivalent of 4 mg of dexamethasone per ml in 2 ml, 5 ml and 10 ml vials.

For Identification and Tests refer to IP Volume II.

Diazepam

Category. Anticonvulsant and in the treatment of behavioural disorders.

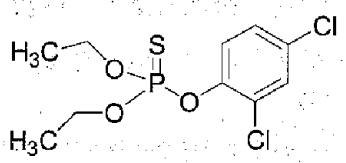
For Description, Identification and Tests refer to IP Volume II.

Diazepam Injection

Usual strengths. 10 mg in 2 ml; 20 mg in 4 ml.

For Identification and Tests refer to IP Volume II.

Dichlofenthion



$C_{10}H_{13}Cl_2O_3PS$ Mol. Wt. 315.2

Dichlofenthion is *O*-2,4-dichlorophenyl-*O*,*O*-diethyl phosphorothioate.

Dichlofenthion contains not less than 95.0 per cent and not more than 100.5 per cent of $C_{10}H_{13}Cl_2O_3PS$.

Category. Insecticide.

Description. A colourless or pale yellow, oily substance.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *dichlofenthion IPRS* or with the reference spectrum of dichlofenthion.

B. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*.

Mobile phase. A mixture of 95 volumes of *hexane* and 5 volumes of *2-butanone*.

Test solution. Dissolve 0.5 g of the substance under examination in 100 ml of *methanol*.

Reference solution. A 0.5 per cent w/v solution of *dichlofenthion IPRS* in *methanol*.

Apply to the plate 2 µl of each solution. After development, dry the plate in air and spray with a 2 per cent w/v solution of *4-(4-nitrobenzyl)pyridine* in *ethyl acetate*. Heat the plate at 130° for 10 minutes, allow to cool and spray with a 2 per cent w/v solution of *lithium hydroxide* in a mixture of 8 volumes of *methanol*, 1 volume of *diethylene glycol* and 1 volume of *water*. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with the reference solution.

C. Burn 50 mg by the oxygen-flask method (2.3.34), using 20 ml of *1 M sodium hydroxide* as the absorbing liquid. The solution obtained, after acidification with *2 M nitric acid* gives reaction (A) of chlorides and reaction C of phosphates (2.3.1).

Tests

Refractive index (2.4.27). 1.530 to 1.533.

Weight per ml (2.4.29). 1.296 to 1.316 g.

Assay. Determine by gas chromatography (2.4.13).

Test solution (a). Dissolve 0.3 g of the substance under examination in 100 ml of *dichloromethane*.

Test solution (b). A solution containing 0.3 per cent w/v of the substance under examination and 0.2 per cent w/v of *methyl stearate* (internal standard) in *dichloromethane*.

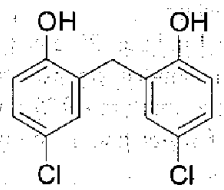
Reference solution. A solution containing 0.3 per cent w/w of *dichlofenthion IPRS* and 0.2 per cent w/v of *methyl stearate* (internal standard) in *dichloromethane*.

Chromatographic system

- a glass column 1.5 m × 4 mm, packed with 3 per cent w/w of phenyl methyl silicone fluid (50 per cent phenyl) on acid-washed, silanised diatomaceous support (80 to 100 mesh) (such as OV-17),
- temperature:
  column 190°,
  inlet port and detector 280°,
- flow rate: 30 ml per minute of the carrier gas.

Calculate the content of $C_{10}H_{13}Cl_2O_3PS$.

Dichlorophen



$C_{13}H_{10}Cl_2O_2$ Mol. Wt. 269.1

Dichlorophen is 2,2'-methylenebis(4-chlorophenol).

Dichlorophen contains not less than 97.0 per cent and not more than 101.0 per cent of $C_{13}H_{10}Cl_2O_2$, calculated on the dried basis.

Category. Anthelmintic and fungicide.

Description. A white or almost white powder.

Identification

A. When examined in the range 220 nm to 360 nm (2.4.7), a 0.002 per cent w/v solution in *0.1 M sodium hydroxide* shows absorption maxima at about 245 nm and 304 nm. The absorbances of the solution after further dilution with an equal volume of *0.1 M sodium hydroxide* at these maxima are about 0.65 and 0.27 respectively.

B. Dissolve 0.2 g in 10 ml of *2.5 M sodium hydroxide*, cool in ice and add a solution prepared by mixing 1 ml of *sodium nitrite solution* with a cold solution containing 0.15 ml of *aniline* in a mixture of 4 ml of *water* and 1 ml of *hydrochloric acid*; a reddish-brown precipitate is produced.

C. Fuse 0.5 g with 2 g of *anhydrous sodium carbonate*, cool, extract the residue with *water* and filter. The filtrate gives reaction (A) of chlorides (2.3.1).

D. Melting point (2.4.21). about 175°.

Tests

Chlorides (2.3.12). Shake 3.0 g with 6 ml of *ethanol (95 per cent)*, dilute with *water* to 100 ml, allow to stand for 5 minutes and filter. 25 ml of the filtrate complies with the limit test for chlorides (330 ppm).

Sulphates (2.3.17). Shake 1.0 g with 20 ml of *water* for 2 minutes and filter. 5 ml of the filtrate complies with the limit test for sulphates (600 ppm).

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 100 mg of the substance under examination in 10 ml of the mobile phase.

Reference solution (a). A 1.0 per cent w/v solution of *dichlorophen impurity IPRS* in the mobile phase.

Reference solution (b). A 0.0010 per cent w/v solution of *4-chlorophenol* in the mobile phase.

Chromatographic system

- a stainless steel column 20 cm × 5 mm, packed with octadecylsilane bonded to porous silica (10 µm),
- mobile phase: a mixture of 75 volumes of *methanol*, 25 volumes of *water* and 1 volume of *glacial acetic acid*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Inject the test solution and reference solution (b). In the chromatogram obtained with the test solution the area of the peak corresponding to 4-dichlorophenol is not more than the area of the principal peak in the chromatogram obtained with reeference solution (b). The content of 4,4′-dichloro-2,2′-(2-hydroxy-4-chloro-*m*-xylene-a,a-diyl)diphenol in the substance under examination does not exceed 8.0 per cent w/w and the sum of the contents of any other impurities, excluding 4-chlorophenol, is not more than 2.0 per cent w/w.

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Loss on drying (2.4.19). Not more than 3 per cent, determined on 1.0 g by drying in an oven at 105°.

Assay. Weigh 0.5 g, dissolve in 20 ml of *2-propanol*. Titrate with *0.1 M tetrabutylammonium hydroxide*, determining the end-point potentiometrically (2.4.25). Carry out a blank titration.

1 ml of *0.1 M tetrabutylammonium hydroxide* is equivalent to 0.02691 g of $C_{13}H_{10}Cl_2O_2$.

Labelling. The label states that the substance is intended for animal treatment only.

Dichlorophen Veterinary Aerosol

Dichlorophen Veterinary Aerosol Spray; Dichlorophen Veterinary Spray

Dichlorophen Veterinary Aerosol is a solution of Dichlorophen in a suitable solvent to which suitable propellants have been added. It may contain a suitable dye as a marker.

Dichlorophen Veterinary Aerosol contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of dichlorophen, $C_{13}H_{10}Cl_2O_2$.

Usual strengths. 2 per cent w/w; 7 per cent w/w; 7.5 per cent w/w; 10 per cent w/w.

Identification

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 60 volumes of *hexane* and 40 volumes of *acetone*.

Test solution. Solution A obtained in the Assay diluted with *methanol* to contain the equivalent of 1 per cent w/v of Dichlorophen.

Reference solution. A 1.0 per cent w/v solution of *dichlorophen IPRS* in *methanol*.

Apply to the plate 5 µl of each solution. After development, dry the plate in air and spray with a freshly prepared solution containing 3.5 per cent w/v of *ferric chloride* and 0.25 per cent w/v of *potassium ferricyanide*. The principal spot in the

chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with the reference solution.

Tests

Other tests. Comply with the tests stated under Veterinary Aerosols.

Assay. Weigh the intact container. Place the container in an ice-bath for 15 minutes. Make a small hole about 1 cm from the top of the body of the container and let the propellant escape. When the flow of propellant stops, enlarge the hole. Transfer the contents of the container to a tared vessel capable of being fitted with a reflux condenser. Remove the top of the container carefully retaining all fragments. Wash the container with suitable solvents and add the washings to the tared vessel. Dry the container and reweigh to obtain the net weight of the contents. Heat the contents of the tared vessel under reflux for 30 minutes, cool and weigh (solution A). Dilute an accurately measured volume of the resulting solution containing about 0.25 g of Dichlorophen to 100.0 ml with *acetone*. Dilute 2.0 ml of the solution to 200.0 ml with *ammonia buffer pH 10.9* and mix. To 10.0 ml of the resulting solution add 20 ml of *ammonia buffer pH 10.9* and 2 ml of a freshly prepared 2 per cent w/v solution of *4-aminophenazone*, mix, and add 2 ml of a freshly prepared 8 per cent w/v solution of *potassium ferricyanide*. Dilute to 50.0 ml with *ammonia buffer pH 10.9* and allow to stand for 15 minutes. Measure the absorbance of the resulting solution at the maximum at about 510 nm (2.4.7), using as the blank a solution obtained in a similar manner by carrying out the procedure simultaneously, beginning at the words "To 10.0 ml of the resulting solution....." but omitting the *4-aminophenazone solution*. Calculate the weight of $C_{13}H_{10}Cl_2O_2$ in the container from the absorbance obtained by repeating the operation using a 0.25 per cent w/v solution of *dichlorophen* in *acetone* beginning at the words "Dilute 2.0 ml.....".

Labelling. The label states (1) the weight of Dichlorophen present in the container; (2) the total weight of contents; (3) the name and proportion of any added dye.

Dichlorophen Tablets

Dichlorophen Tablets contain not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of dichlorophen, $C_{13}H_{10}Cl_2O_2$.

Usual strength. 500 mg.

Identification

A. Shake a quantity of the powdered tablets containing 0.1 g of Dichlorophen with 50 ml of *0.1 M sodium hydroxide* for 15 minutes, add sufficient *0.1 M sodium hydroxide* to produce 100 ml, centrifuge and dilute a suitable volume of the supernatant liquid with *0.1 M sodium hydroxide* to produce a solution containing 0.002 per cent w/v of Dichlorophen.

When examined in the range 220 to 360 nm (2.4.7), the resulting solution shows absorption maxima at about 245 nm and 304 nm; absorbances at about 245 nm and 304 nm, about 1.3 and 0.54 respectively.

B. Shake a quantity of the powdered tablets containing 0.2 g of Dichlorophen with a mixture of 5 ml of *water* and 5 ml of *5 M sodium hydroxide*, filter, cool in ice and add a solution prepared by mixing 1 ml of *sodium nitrite solution* with a cold solution containing 0.15 ml of *aniline* in a mixture of 4 ml of *water* and 1 ml of *hydrochloric acid*; a reddish-brown precipitate is produced.

C. Fuse a quantity of the powdered tablets containing 0.5 g of Dichlorophen with 2 g of *anhydrous sodium carbonate*, cool, extract the residue with *water* and filter. The filtrate gives reaction (A) of chlorides (2.3.1).

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Shake a quantity of the powdered tablets containing 0.50 g of Dichlorophen with 20 ml of *methanol* for 10 minutes, filter, add 7 ml of *water* and dilute to 50.0 ml with the mobile phase.

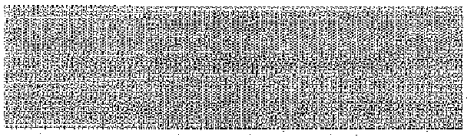
Reference solution (a). A 1.0 per cent w/v solution of *dichlorophen impurity standard IPRS* in the mobile phase.

Reference solution (b). A 0.0010 per cent w/v solution of *4-chlorophenol* in the mobile phase.

Chromatographic system

- a stainless steel column 20 cm × 5 mm, packed with octadecylsilane bonded to porous silica (10 µm),
- mobile phase: a filtered and degassed mixture of 75 volumes of *methanol*, 25 volumes of *water* and 1 volume of *glacial acetic acid*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

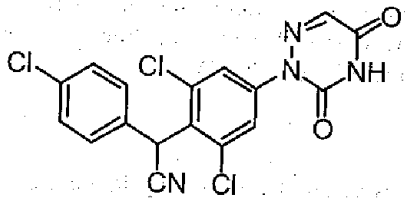
Inject the test solution and reference solution (b). In the chromatogram obtained with the test solution the area of the peak corresponding to 4-chlorophenol is not more than the area of the principal peak in the chromatogram obtained with reeference solution (b). The content of 4,4′-dichloro-2,2′-(2-hydroxy-4-chloro-*m*-xylene-a,a′-diyl) diphenol in the substance under examination does not exceed 8.0 per cent w/w and the sum of the contents of any other impurities, excluding 4-chlorophenol, is not more than 2.0 per cent w/w.



Other tests. Comply with the tests stated under Tablets.

Assay. Weigh and powder 20 tablets. Weigh a quantity of the powder containing 0.1 g of Dichlorophen, shake with 50 ml of *0.1 M sodium hydroxide* for 15 minutes and add sufficient *0.1 M sodium hydroxide* to produce 100.0 ml. Centrifuge and dilute 10.0 ml of the clear supernatant liquid to 100.0 ml with *0.1 M sodium hydroxide*. Dilute 20.0 ml of the solution to 100.0 ml with *0.1 M sodium hydroxide* and measure the absorbance of the resulting solution at the maximum at about 304 nm (2.4.7). Calculate the content of $C_{13}H_{10}Cl_2O_2$ taking 275 as the specific absorbance at 304 nm.

Diclazuril



$C_{17}H_9Cl_3N_4O_2$ Mol. Wt. 407.6

Diclazuril is (*RS*)-4-Chlorophenyl-[2,6-dichloro-4-(2,3,4, 5-tetrahydro-3,5-dioxo-1,2,4-triazin-2-yl)phenyl]acetonitrile.

Diclazuril contains not less than 99.0 per cent and not more than 101.0 per cent of $C_{17}H_9Cl_3N_4O_2$, calculated on the dried basis.

Category. Antiprotozoal, coccidiosis.

Description. A white or light yellow powder.

Identification

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *diclazuril IPRS* or with the reference spectrum of diclazuril.

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 20 mg of the substance under examination in 20 ml of *dimethylformamide*.

Reference solution (a). Dissolve 5 mg of *diclazuril for system suitability IPRS* in 5 ml of *dimethylformamide*.

Reference solution (b). Dilute 1.0 ml of test solution to 100 ml with *dimethylformamide* and dilute 5.0 ml of the solution to 20 ml with *dimethylformamide*.

Chromatographic system

- a stainless steel column 10 cm x 4.6 mm, packed with base-deactivated octadecylsilane bonded to porous silica (3 µm),
- column temperature: 35°,
- mobile phase: A. a mixture of 10 volumes of a solution containing 0.63 per cent *ammonium formate*, adjusted to pH 4.0 with *anhydrous formic acid*, 15 volumes of *acetonitrile* and 75 volumes of *water*,
  B. a mixture of 10 volumes of a solution containing 0.63 per cent *ammonium formate*, adjusted to pH 4.0 with *anhydrous formic acid*, 85 volumes of *acetonitrile* and 5 volumes of *water*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 230 nm,
- injection volume: 5 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
20	0	100
25	0	100

Name	Correction factor
Diclazuril impurity H[1]	1.4
Diclazuril impurity D[2]	1.9

[1](*RS*)-(4-chlorophenyl)(2,6-dichlorophenyl)acetonitrile,

[2]2-[3, 5-dichloro-4-(4-chlorobenzoyl)phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)- dione.

Inject reference solution (a). The peaks to valley ratio of H_p and H_v is not less than 1.5, where H_p= height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to diclazuril.

Inject reference solution (b) and the test solution. The area of the peak corresponding to diclazuril for impurity D is not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent), the area of any other secondary peak is not more than the area of principle peak in the chromatogram obtained with reference solution (b) (0.25 per cent) and the sum of the areas of the secondary peaks is not more than 4.0 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent). Ignore any peak with an area 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105° for 4 hours.

Assay. Dissolve 0.15 g in 75 ml of *dimethylformamide*. Titrate with *0.1 M tetrabutylammonium hydroxide*, determining the end point potentiometrically (2.4.25). Read the volume added at the second inflexion point. Carry out a blank titration.

1 ml of *0.1 M tetrabutyl ammonium hydroxide* is equivalent to 0.02038 g of $C_{17}H_9Cl_3N_4O_2$.

Storage. Store protected from light.

Dicloxacillin Sodium

For Description, Identification and Tests refer to IP Volume II.

Diethylcarbamazine Citrate

For Description, Identification and Tests refer to IP Volume II.

Diethylcarbamazine Injection

Diethylcarbamazine Citrate Injection.

Diethylcarbamazine Injection is a sterile solution of Diethylcarbamazine Citrate in Water for Injections.

Diethylcarbamazine Injection contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of diethylcarbamazine citrate, $C_{10}H_{21}N_3O,C_6H_8O_7$.

Usual strength. 400 mg in 1 ml.

Identification

A. To a volume containing 0.5 g of Diethylcarbamazine Citrate add 2 ml of *water* and make alkaline with *5 M sodium hydroxide*. Extract with four quantities, each of 5 ml, of *dichloromethane*, reserve the aqueous solution for test B, wash the combined *dichloromethane* extracts with *water* and remove the *dichloromethane* by evaporation. Add 0.5 ml of *iodoethane* to the residue and heat gently under a reflux condenser for 5 minutes. Remove the excess *iodoethane* with a current of air, dissolve the viscous yellow oil in 2 ml of *ethanol (95 per cent)* and add, with continuous stirring, sufficient *ether* to precipitate the quaternary ammonium salt. Decant off the ether, dissolve the residue in 2 ml of *ethanol (95 per cent)*, reprecipitate with *ether* and dry at 105°; the residue melts at about 152° (2.4.21).

B. Neutralise the aqueous solution obtained in test A with *1 M sulphuric acid*, add an excess of *mercuric sulphate solution*, boil and add a few drops of *potassium permanganate solution*; a white precipitate is produced.

Tests

pH (2.4.24). 6.0 to 7.0.

N,N'-Dimethylpiperazine* and *N-methylpiperazine. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*.

Mobile phase. A mixture of 65 volumes of *methanol*, 30 volumes of *2-butanone* and 5 volumes of *strong ammonia solution*.

Test solution. Dilute a volume of the injection with sufficient *methanol* to produce a solution containing the equivalent of 5.0 per cent w/v of Diethylcarbamazine Citrate.

Reference solution (a). A 5.0 per cent w/v solution of *diethylcarbamazine citrate IPRS* in *methanol*.

Reference solution (b). A 0.010 per cent w/v solution of *N,N'-dimethylpiperazine* in *methanol*.

Reference solution (c). A 0.010 per cent w/v solution *N-methylpiperazine* in *methanol*.

Apply to the plate 10 µl of each solution. Allow the mobile phase to rise 12 cm. Dry the plate at 105° and expose it to iodine vapours for 30 minutes. Any spots corresponding to N,N'-dimethylpiperazine and N-methylpiperazine in the chromatogram obtained with the test solution are not more intense than the spots in the chromatograms obtained with reference solutions (b) and (c) respectively.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. To a measured volume containing 8 g of Diethylcarbamazine Citrate add sufficient *water* to produce 100.0 ml. To 10.0 ml of the solution add 2 ml of *5 M sodium hydroxide* and extract with four quantities, each of 25 ml, of *dichloromethane*. Wash each extract with the same two quantities, each of 20 ml, of *water* and with a third quantity if the second becomes alkaline to *phenolphthalein solution*. Extract the combined *dichloromethane* extracts in succession with 25.0 ml of *0.05 M sulphuric acid* and 15 ml and 10 ml of *water*. Combine the acid and water extracts, remove the dichloromethane, by warming, cool and titrate the excess of acid with *0.1 M sodium hydroxide* using *bromocresol green solution* as indicator.

1 ml of *0.05 M sulphuric acid* is equivalent to 0.03914 g of $C_{10}H_{21}N_3O,C_6H_8O_7$.

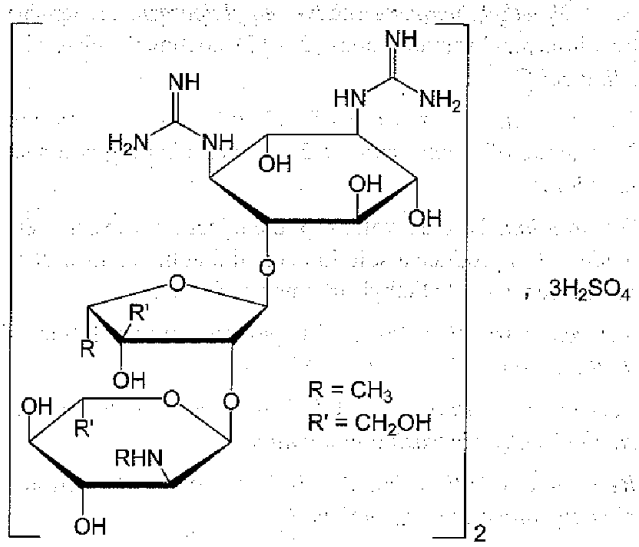
Storage. Store protected from light.

Diethylcarbamazine Tablets

Usual strengths. 50 mg; 100 mg; 200 mg.

For Identification and Tests refer to IP Volume II.

Dihydrostreptomycin Sulphate



$(C_{21}H_{41}N_7O_{12})_2,3H_2SO_4$ Mol. Wt. 1461.4

Dihydrostreptomycin sulphate is *O*-2-deoxy-2-methylamino-*d*-L-lyxofuranosyl-(1→4)-N^1,N^3-diamidino-D-streptamine sulphate.

Dihydrostreptomycin Sulphate contains not less than 95.0 per cent and not more than 102.0 per cent sum of $C_{42}H_{88}N_{14}O_{36}S_3$ and $C_{42}H_{84}N_{14}O_{36}S_3$, calculated on dried basis.

Category. Antibacterial.

Description. A white or almost white powder.

Identification

A. Determine by thin-layer chromatography (2.4.17), coating the plate in the following manner. Mix 0.3 g of *carbomer* with 240 ml of *water*, allow to stand with moderate stirring for 1 hour, adjust to pH 7.0 by the gradual addition with constant shaking of *2 M sodium hydroxide* and add 30 g of *silica gel H*. Spread a uniform layer of the resulting suspension 0.75 mm thick. Heat the plate at 110° for 1 hour, allow to cool and use immediately.

Mobile phase. A 7.0 per cent w/v solution of *potassium dihydrogen phosphate*.

Test solution. Dissolve 100 mg of the substance under examination in 100 ml of *water*.

Reference solution (a). A 0.1 per cent w/v solution of *dihydrostreptomycin sulphate IPRS* in *water*.

Reference solution (b). A solution containing 0.1 per cent w/v of *dihydrostreptomycin sulphate IPRS*, 0.1 per cent w/v of *neomycin sulphate IPRS* and 0.1 per cent w/v of *kanamycin sulphate IPRS* in *water*.

Apply to the plate 10 µl of each solution. Allow the mobile phase to rise 12 cm. Dry the plate in a current of warm air, spray it with a mixture of equal volumes of a 0.2 per cent w/v solution of *naphthalene-1,3-diol* in *ethanol (95 per cent)* and a 46 per cent w/v solution of *sulphuric acid* and heat at 150° for 5 to 10 minutes. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows three clearly separated spots.

B. Dissolve 0.1 g in 2 ml of *water* and add 1 ml of *dilute 1-naphthol solution* and 2 ml of a mixture of equal volumes of *sodium hypochlorite solution (3 per cent Cl)* and *water*; a red colour is produced.

C. Dissolve 10 mg in 5 ml of *water* and add 1 ml of *1 M hydrochloric acid*. Heat in a water-bath for 2 minutes. Add 2 ml of a 0.5 per cent w/v solution of *1-naphthol* in *1 M sodium hydroxide* and heat in a water-bath for 1 minute; a violet-pink colour is produced (distinction from streptomycin).

D. It gives the reactions of sulphates (2.3.1).

Tests

Appearance of solution. A 25 per cent w/v solution in *carbon dioxide-free water* is not more intensely coloured than degree 4 of the appropriate range of reference solutions (2.4.1). The solution, after standing protected from light at a temperature of about 20° for 24 hours, is not more opalescent than opalescence standard OS2 (2.4.1).

pH (2.4.24). 5.0 to 7.0, determined in a 25 per cent w/v solution.

Specific optical rotation (2.4.22). −91° to −83°, calculated on the dried basis, determined in a 2 per cent w/v solution in *water*.

Sulphate. 18.0 per cent to 21.5 per cent, calculated on the dried basis.

Dissolve 0.25 g in 100 ml of *water*, adjust the pH to 11 with *strong ammonia solution* and add 10.0 ml of *0.1 M barium chloride* and 0.5 mg of *metalphthalein*. Titrate the excess of barium chloride with *0.1 M disodium edetate*, adding 50 ml of *ethanol (95 per cent)* when the colour of the solution begins to change and continuing the titration until the violet-blue colour disappears.

1 ml of *0.1 M barium chloride* is equivalent to 0.009606 g of sulphate, SO_4.

Streptomycin. Weigh 0.10 g and dissolve in sufficient *water* to produce 5.0 ml. Add 5.0 ml of *0.2 M sodium hydroxide* and heat for exactly 10 minutes in a water-bath. Cool in ice for exactly 5 minutes, add 3 ml of a 1.5 per cent w/v solution of

ferric ammonium sulphate in *0.25 M sulphuric acid* and sufficient *water* to produce 25.0 ml, and mix. Exactly 20 minutes after the addition of the ferric ammonium sulphate solution, measure the absorbance of a 2-cm layer at the maximum at about 525 nm (2.4.7), using as the blank a solution prepared in the same manner, omitting the substance under examination. The absorbance is not more than that obtained by carrying out the procedure simultaneously using 5.0 ml of a solution prepared by dissolving 10 mg, accurately weighed, of *streptomycin sulphate IPRS* in sufficient *water* to produce 50 ml and beginning at the words "Add 5.0 ml...", both absorbances being calculated on the dried basis.

Methanol. Determine by gas chromatography (2.4.13).

Test solution. Dissolve 4.0 g of the substance under examination in 100.0 ml of *water*.

Reference solution. A 0.008 per cent w/v solution of *methanol*.

Chromatographic system
- a glass column 1.5 to 2.0 m × 2 to 4 mm, packed with ethylvinylbenzenedivinylbenzene copolymer (150 to 180 mm) porous polymer beads (such as Porapak Q),
- temperature:
  column 50°,
  inlet port and detector. 280°,
- flow rate: 30 to 40 ml per minute of the carrier gas.

The area of any peak corresponding to methanol in the chromatogram obtained with test solution is not more than that of the peak in the chromatogram obtained with reference solution (0.2 per cent).

Sulphated ash (2.3.18). Not more than 1.0 per cent.

Loss on drying (2.4.19). Not more than 5 per cent, determined on 1 g by drying over *phosphorus pentoxide* at 60° at a pressure not exceeding 0.1 kPa for 4 hours.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 50 mg of the substance under examination in 10 ml of *water*.

Reference solution. Dissolve the contents of a vial of *dihydrostreptomycin sulphate IPRS* (containing impurities A,B,C) in 5.0 ml of *water*.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5µm),
- coloumn temperature. 45°,
- mobile phase: mix 4.6 g of *anhydrous sodium sulphate*, 1.5 g of *sodium octanesulphonate*, 120 ml of *acetonitrile* and 50 ml of 2.72 per cent w/v solution of *potassium dihydrogen phosphate* and dilute to 1000 ml with *water*, adjusted to pH 3.0 with 2.25 per cent *orthophosphoric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 205 nm,
- injection volume: 20 µl.

The relative retention time with reference to dihydrostreptomycin for impurity A is about 0.2, for impurity B is about 0.8, for streptomycin is about 0.9 and for impurity C is about 0.95.

Inject the reference solution. Run the chromatogram 1.5 times the retention time of dihydrostgreptomycin.

Inject the reference solution and the test solution.

Calculate the content of $C_{42}H_{88}N_{14}O_{36}S_3$ and of $C_{42}H_{84}N_{14}O_{36}S_3$. Calculate the sum of these contents.

Dihydrostreptomycin Sulphate intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins complies with the following additional requirement.

Bacterial endotoxins (2.2.3). Not more than 0.5 Endotoxin Unit per mg of dihydrostreptomycin sulphate.

Dihydrostreptomycin Sulphate intended for use in the manufacture of parenteral preparations without a further appropriate sterilization procedure complies with the following additional requirement.

Sterility (2.2.11). Complies with the test for sterility.

Storage. Store protected from light, at a temperature not exceeding 30°. If it is intended for use in the manufacture of parenteral preparations or intramammary infusions, the container should be sterile and sealed so as to exclude micro-organisms.

Labelling. The label states (1) the number of Units per mg; (2) the name and quantity of any added stabiliser; (3) whether or not the contents are intended for use in the manufacture of Parenteral Preparations or intramammary infusions; (4) that the substance is meant for veterinary use only; (5) the storage conditions; (6) the date after which the contents are not intended to be used.

Dihydrostreptomycin Injection

Dihydrostreptomycin Sulphate Injection

Dihydrostreptomycin Injection is a sterile solution of Dihydrostreptomycin Sulphate in Water for Injections. It is prepared by dissolving the contents of a sealed container in the requisite amount of Water for Injections immediately before use.

Dihydrostreptomycin Injection contains not less than 90.0 per cent and not more than 115.0 per cent of the stated amount of dihydrostreptomycin, $C_{21}H_{41}N_7O_{12}$, calculated on the dried basis.

Usual strength. The equivalent of 250 mg of dihydrostreptomycin.

Description. A white or almost white powder which yields a clear, colourless or faintly yellow solution when dissolved in *water*.

The injection complies with the tests stated under Parenteral Preparations (Powders for Injection).

The contents of the sealed container comply with the following requirements.

Identification

A. Determine by thin-layer chromatography (2.4.17), prepared by mixing 0.3 g of *carbomer* with 240 ml of *water*, allow to stand with moderate stirring for 1 hour, adjust to pH 7.0 by the gradual addition with constant shaking of *2 M sodium hydroxide* and add 30 g of *silica gel H*. Spread a uniform layer of the resulting suspension 0.75 mm thick. Heat the plate at 110° for 1 hour, allow to cool and use immediately.

Mobile phase. A 7.0 per cent w/v solution of *potassium dihydrogen phosphate*.

Test solution. Dissolve 100 mg of the sunbstance under examination in 100 ml of *water*.

Reference solution (a). A 0.1 per cent w/v solution of *dihydrostreptomycin sulphate IPRS* in *water*.

Reference solution (b). A solution containing 0.1 per cent w/v of *dihydrostreptomycin sulphate IPRS*, 0.1 per cent w/v of *neomycin sulphate IPRS* and 0.1 per cent w/v of *kanamycin sulphate IPRS* in *water*.

Apply to the plate 10 µl of each solution. Allow the mobile phase to rise 12 cm. Dry the plate in a current of warm air, spray it with a mixture of equal volumes of a 0.2 per cent w/v solution of *naphthalene-1,3-diol* in *ethanol (95 per cent)* and 46 per cent w/v solution of *sulphuric acid* and heat at 150° for 5 to 10 minutes. The principal spot in the chromatogram obtained with test solution corresponds to that in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows three clearly separated spots.

B. Dissolve 0.1 g in 2 ml of *water* and add 1 ml of *dilute 1-naphthol solution* and 2 ml of a mixture of equal volumes of *sodium hypochlorite solution (3 per cent Cl)* and *water*; a red colour is produced.

C. Dissolve 10 mg in 5 ml of *water* and add 1 ml of *1 M hydrochloric acid*. Heat in a water-bath for 2 minutes. Add 2 ml of a 0.5 per cent w/v solution of *1-naphthol* in *1 M sodium hydroxide* and heat in a water-bath for 1 minute; a violet-pink colour is produced (distinction from streptomycin).

D. It gives the reactions of sulphates (2.3.1).

Tests

Appearance of solution. A 25 per cent w/v solution in *carbon dioxide-free water* is not more intensely coloured than degree 4 of the appropriate range of reference solutions. The solution, after standing protected from light at a temperature of about 20° for 24 hours, is not more opalescent than opalescence standard OS2 (2.4.1).

pH (2.4.24). 5.0 to 7.0, determined in a 25 per cent w/v solution.

Specific optical rotation (2.4.22). −91° to −83°, calculated on the dried basis, determined in a 2 per cent w/v solution in *water*.

Sulphate. 18.0 per cent to 21.5 per cent, calculated on the dried basis.

Dissolve 0.25 g in 100 ml of *water*, adjust the pH to 11 with *strong ammonia solution* and add 10.0 ml of *0.1 M barium chloride* and 0.5 mg of *metalphthalein*. Titrate the excess of barium chloride with *0.1 M disodium edetate*, adding 50 ml of *ethanol (95 per cent)* when the colour of the solution begins to change and continuing the titration until the violet-blue colour disappears.

1 ml of *0.1 M barium chloride* is equivalent to 0.009606 g of sulphate, SO_4.

Streptomycin. Weigh 0.10 g and dissolve in sufficient *water* to produce 5.0 ml. Add 5.0 ml of *0.2 M sodium hydroxide* and heat for exactly 10 minutes in a water-bath. Cool in ice for exactly 5 minutes, add 3 ml of a 1.5 per cent w/v solution of *ferric ammonium sulphate* in *0.25 M sulphuric acid* and sufficient *water* to produce 25.0 ml, and mix. Exactly 20 minutes after the addition of the *ferric ammonium sulphate solution*, measure the absorbance of a 2 cm layer at the maximum at about 525 nm (2.4.7), using as the blank a solution prepared in the same manner, omitting the substance under examination. The absorbance is not more than that obtained by carrying out the procedure simultaneously using 5.0 ml of a solution prepared by dissolving 10 mg, accurately weighed, of *streptomycin sulphate IPRS* in sufficient *water* to produce 50 ml and beginning at the words "Add 5.0 ml....", both absorbances being calculated on the dried basis.

Methanol. Determine by gas chromatography (2.4.13).

Test solution. Dissolve 4.0 g of the substance under examination in 100 ml of *water*.

Reference solution. A 0.008 per cent w/v solution of *methanol*.

Chromatographic system

- a glass column 1.5 to 2.0 m × 2 to 4 mm, packed with ethylvinylbenzene-divinylbenzene copolymer (150 to 180 mm) porous polymer beads (such as Porapak Q),
- temperature:
  column 50°,
  inlet port and detector 280°,
- flow rate: 30 to 40 ml per minute of the carrier gas.

The area of any peak corresponding to methanol in the chromatogram obtained with test solution is not more than that of the peak in the chromatogram obtained with reference solution (0.2 per cent).

Sulphated ash (2.3.18). Not more than 1.0 per cent.

Loss on drying (2.4.19). Not more than 5 per cent, determined on 1 g by drying over *phosphorus pentoxide* at 60° at a pressure not exceeding 0.1 kPa for 4 hours.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. On the mixed contents of ten containers carry out the microbiological assay, Method A or B (2.2.10), and express the result in Units of dihydrostreptomycin per mg.

Dihydrostreptomycin Sulphate intended for use in the manufacture of Parenteral Preparations without a further appropriate procedure for the removal of bacterial endotoxins complies with the following additional requirement.

Bacterial endotoxins (2.2.3). Not more than 0.5 Endotoxin Unit per mg of dihydrostreptomycin sulphate.

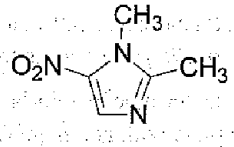
Dihydrostreptomycin Sulphate intended for use in the manufacture of Parenteral Preparations without a further appropriate sterilization procedure complies with the following additional requirement.

Sterility (2.2.11). Complies with the test for sterility.

Storage. Store protected from light. Use the injection within 7 days of the preparation of the solution when stored in a cool place or within 1 month when stored in a cold place.

Labelling. The label states (1) the strength in terms of the equivalent amount of dihydrostreptomycin in a suitable dose-volume; (2) that the contents are meant for veterinary use only; (3) the storage conditions; (4) the date after which the contents are not intended to be used.

Dimetridazole



$C_5H_7N_3O_2$ Mol. Wt. 141.1

Dimetridazole is 1,2-dimethyl-5-nitro-1*H*-imidazole.

Dimetridazole contains not less than 98.0 per cent and not more than 101.0 per cent of the stated amount of dimetridazole, $C_5H_7N_3O_2$, calculated on the anhydrous basis.

Category. Antiprotozoal.

Description. An almost white to brownish yellow powder; darkens on exposure to light, odourless or almost odourless.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *dimetridazole IPRS* or with the reference spectrum of dimetridazole.

B. When examined in the range of 230 to 360 nm (2.4.7), a 0.002 per cent w/v solution in *methanol* shows a well-defined absorption maximum only at about 309 nm; absorbance at about 309 nm, about 1.3.

C. Dissolve 0.1 g in 20 ml of *ether*, add 10 ml of a 1 per cent w/v solution of *picric acid* in *ether*, induce crystallisation by scratching the sides of the vessel and allow to stand. Wash the precipitate obtained with *ether* and dry at 105°; the residue melts at about 160° (2.4.21).

Tests

2-Methyl-5-nitroimidazole. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 90 volumes of *dichloromethane* and 10 volumes of *2-propanol*.

Test solution. Dissolve 2 g of the substance under examination in 100 ml of *dichloromethane*.

Reference solution. A 0.01 per cent w/v solution of *2-methyl-5-nitroimidazole IPRS* in *dichloromethane*.

Apply to the plate 5 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. Any spot corresponding to 2-methyl-5-nitroimidazole in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with the reference solution.

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Water (2.3.43). Not more than 1.0 per cent, determined on 1 g.

Assay. Weigh 0.3 g, dissolve in 30 ml of *anhydrous glacial acetic acid*. Titrate with *0.1 M perchloric acid*, using *crystal violet solution* as indicator. Carry out a blank titration.

1 ml of *0.1 M perchloric acid* is equivalent to 0.01411 g of $C_5H_7N_3O_2$.

Storage. Store protected from light.

Dimetridazole Premix

Dimetridazole Premix contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of dimetridazole, $C_5H_7N_3O_2$.

Usual strength. 22.5 per cent w/w.

Identification

Mix a quantity containing 0.1 g of Dimetridazole with 20 ml of *ether*, shake and filter. To the filtrate add 10 ml of a 1 per cent w/v solution of *picric acid* in *ether*, stir to induce crystallisation and allow to stand. Wash the precipitate obtained with *ether* and dry at 105°; the residue melts at about 160° (2.4.21).

Tests

Assay. Weigh a quantity containing 0.45 g of Dimetridazole, transfer to a sintered glass funnel (porosity No. 4), add 10 ml of *dichloromethane*, stir for 1 minute, and apply gentle suction. Repeat the extraction with four further quantities, each of 10 ml, of *dichloromethane*. To the combined dichloromethane extracts add 50 ml of *anhydrous glacial acetic acid* previously neutralised to *crystal violet solution* by the dropwise addition of *0.1 M perchloric acid*. Titrate with *0.1 M perchloric acid*, using *crystal violet solution* as indicator. Carry out a blank titration.

1 ml of *0.1 M perchloric acid* is equivalent to 0.01411 g of $C_5H_7N_3O_2$.

Storage. Store protected from light.

Dimetridazole Veterinary Oral Powder

Dimetridazole Veterinary Oral Powder is a mixture of Dimetridazole and a suitable water-soluble diluent.

Dimetridazole Veterinary Oral Powder contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of dimetridazole, $C_5H_7N_3O_2$.

Usual strength. 40 per cent w/w.

Identification

Mix a quantity containing 0.1 g of Dimetridazole with 20 ml of *ether*, shake and filter. To the filtrate add 10 ml of a 1 per cent w/v solution of *picric acid* in *ether*, stir to induce crystallisation and allow to stand. Wash the precipitate obtained with *ether* and dry at 105°; the residue melts at about 160° (2.4.21).

Tests

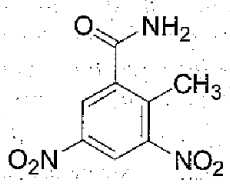
Other tests. Comply with the tests stated under Veterinary Oral Powders.

Assay. Weigh a quantity containing 0.4 g of Dimetridazole, transfer to a sintered glass funnel (porosity No. 4), add 10 ml of *dichloromethane*, stir for 1 minute, and apply gentle suction. Repeat the extraction with four further quantities, each of 10 ml, of *dichloromethane*. To the combined dichloromethane extracts add 50 ml of *anhydrous glacial acetic acid* previously neutralised to *crystal violet solution* by the dropwise addition of *0.1 M perchloric acid*. Titrate with *0.1 M perchloric acid*, using *crystal violet solution* as indicator. Carry out a blank titration.

1 ml of *0.1 M perchloric acid* is equivalent to 0.01411 g of $C_5H_7N_3O_2$.

Storage. Store protected from light.

Dinitolmide



$C_8H_7N_3O_5$ Mol. Wt. 225.2

Dinitolmide is 3,5-dinitro-2-methylbenzamide.

Dinitolmide contains not less than 98.0 per cent and not more than 100.5 per cent of $C_8H_7N_3O_5$, calculated on the dried basis.

Category. Coccidiostat.

Description. A cream to light tan powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *dinitolmide IPRS* or with the reference spectrum of dinitolmide.

B. Heat 1 g with 20 ml of *9 M sulphuric acid* under a reflux condenser for 1 hour, cool, add 50 ml of *water* and filter. The residue after washing with *water* and drying at 105° melts at about 205° (2.4.21).

Tests

Acid value (2.3.23). Not more than 5.0, determined on 0.5 g and using 50 ml of *ethanol (95 per cent)* as the solvent.

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 85 volumes of *dichloromethane*, 10 volumes of *methanol* and 5 volumes of *glacial acetic acid*.

Test solution. Dissolve 2.5 g of the substance under examination in 100 ml of *acetone*.

Reference solution (a). A 0.0125 per cent w/v of the substance under examination in *acetone*.

Reference solution (b). A 0.0125 per cent w/v of *o-toluic acid* in *acetone*.

Apply to the plate 10 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. Spray with *titanium trichloride solution*, diluted 5 times with *water*, heat at 100° for 5 minutes and spray with *ethanolic dimethylaminobenzaldehyde solution*. When viewed under ultraviolet light at 254 nm the spot in the chromatogram obtained with reference solution (b) is more intense than any corresponding spot in the chromatogram obtained with the test solution. By both methods of visualisation any secondary spot in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with reference solution (a).

Loss on drying (2.4.19). Not more than 1.0 per cent, determined on 1.0 g by drying in an oven at 105°.

Assay. Weigh 0.15 g, dissolve in *acetone* and dilute to 50.0 ml. To 10.0 ml of the solution add 10 ml of *glacial acetic acid* and 15 ml of a 40 per cent w/v solution of *sodium acetate*. Maintain a stream of carbon dioxide through the flask throughout the determination. Add 25.0 ml of *0.1 M titanium trichloride* and allow to stand for 5 minutes. Add 10 ml of *hydrochloric acid*, 10 ml of *water* and 1 ml of *potassium thiocyanate solution*. Titrate with *0.1 M ferric ammonium sulphate* until the solution becomes first colourless and then orange. Repeat the operation without the substance under examination. The difference between the titrations represents the amount of titanium trichloride required.

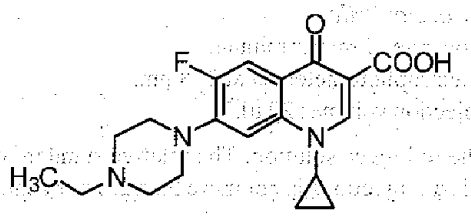
1 ml of *0.1 M titanium trichloride* is equivalent to 0.001876 g of $C_8H_7N_3O_5$.

Docetaxel Injection

Usual strengths. 20 mg; 80 mg.

For Identification and Tests refer to IP Volume II.

Enrofloxacin



$C_{19}H_{22}FN_3O_3$ Mol. Wt. 359.4

Enrofloxacin is 1-Cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolonecarboxylic acid.

Enrofloxacin contains not less than 98.5 per cent and not more than 101.5 per cent of $C_{19}H_{22}FN_3O_3$, calculated on the dried basis.

Category. Antibacterial.

Description. A pale yellowish or light yellow, crystalline powder.

Identification

Determined by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *enrofloxacin IPRS* or with the reference spectrum of enrofloxacin.

Tests

Appearance of solution (2.4.1). Dissolve 1.0 g in 10 ml of 2.5 per cent solution of *potassium hydroxide* in *water*. The solution is not more opalescent than opalescence standard OS2 and not more intensely coloured than reference solution GYS4.

Impurity A. Determined by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 50 volumes of *ethyl acetate*, 20 volumes of *anhydrous acetic acid*, 15 volumes of *butanol* and 15 volumes of *water*.

Solvent mixture. 50 volumes of *methanol* and 50 volumes of *methylene chloride*.

Test solution. Dissolve 0.10 g of the substance under examination in the solvent mixture and dilute to 5.0 ml with the solvent mixture.

Reference solution. Dissolve 5 mg of *ciprofloxacin impurity A IPRS* (enrofloxacin impurity A) in the solvent mixture and dilute to 50.0 ml with the solvent mixture. Dilute 4.0 ml of the solution to 10.0 ml with the solvent mixture.

Apply to the plate 10 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. Any spot due to impurity A is not more intense than the spot in the chromatogram obtained with the reference solution (0.2 per cent).

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 50 mg of the substance under examination in the mobile phase and dilute to 50.0 ml with the mobile phase.

Reference solution (a). Dissolve 10 mg of *enrofloxacin IPRS* (containing impurities B and C) and dilute to 10.0 ml with the mobile phase.

Reference solution (b). Dilute 1.0 ml of the test solution to 50.0 ml with the mobile phase. Dilute 1.0 ml of the solution to 10.0 ml with the mobile phase.

Chromatographic system
- a stainless steel column 15 cm × 4.6 mm, packed with base-deactivated endcapped octadecylsilane bonded to porous silica (5 µm),
- column temperature: 40°,
- mobile phase: a mixture of 15 volumes of *methanol* and 85 volumes of a 0.29 per cent solution of *phosphoric acid*, previously adjusted to pH 2.3 with *triethylamine*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 270 nm,
- injection volume: 10 µl.

Name	Relative retention time
Enrofloxacin impurity C[1]	0.6
Enrofloxacin impurity B[2]	0.8
Enrofloxacin (Retention time: about 16 minutes)	1.0

[1]1-cyclopropyl-7-(4-ethylpiperazin-1-yl)-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid,

[2]ciprofloxacin.

Inject reference solution (a). The test is not valid unless the resolution between the peeks due to impurity B and enrofloxacin is not less than 2.0.

Inject reference solution (b) and the test solution. Run the chromatogram three times the retention time of enrofloxacin. In the chromatogram obtained with test solution, the area of the peak corresponding to impurity B is not more than 2.5 times of the area of principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent), the area of peak corresponding to impurity C is not more than the area of principle peak in the chromatogram obtained with reference solution (b) (0.2 per cent), the area of each secondary peak is not more than the area of the principle peak in the chromatogram obtained with reference solution (b) (0.2 per cent) and the sum of area of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent). Ignore any peak with an area less than 0.5 times the area of principle peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Heavy metals (2.3.13). Dissolve 1.5 g in a mixture of 5 ml of *2 M acetic acid* and 10 ml of *water*, Filter. 12 ml of the filtrate, complies with the limit test for heavy metals, Method D (20 ppm), using 10 ml of *lead standard solution (2 ppm Pb)*.

Sulphated ash (2.3.18). Not more than 0.1 per cent, determined on 1.0 g.

Loss on drying (2.4.19). Not more than 1.0 per cent, determined on 2.0 g by drying in an oven at 120° for 6 hours.

Assay. Dissolve 0.25 g in 100 ml of *anhydrous acetic acid* and titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.4.25).

1 ml of *0.1 M perchloric acid* is equivalent to 0.03594 g of $C_{19}H_{22}FN_3O_3$.

Storage. Store protected from light.

Enrofloxacin Injection

Enrofloxacin is a sterile solution of Enrofloxacin in Water for Injections. It may contain suitable pharmaceutical aids.

Enrofloxacin Injection contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of enrofloxacin, $C_{19}H_{22}FN_3O_3$.

Usual strength. 10.0 per cent w/v.

Identification

In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution.

Tests

pH (2.4.24). 9.0 to 12.0.

Bacterial endotoxins (2.2.3). Not more than 0.5 Endotoxin Unit per mg of enrofloxacin.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a volume of the injection with mobile phase to obtain a solution containing 0.002 per cent w/v of enrofloxacin.

Reference solution. A 0.002 per cent w/v solution of *enrofloxacin IPRS* in mobile phase.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 85 volumes of 0.1 percent v/v solution of *orthophosphoric acid* and 15 volumes of *acetonitrile*,
- flow rate : 1 ml per minute,
- spectrophotometer set at 278 nm,
- injection volume : 20 µl.

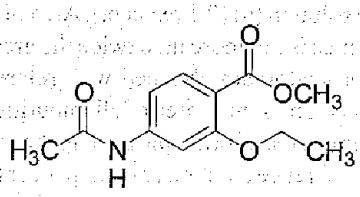
Inject the reference solution. The relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{19}H_{22}FN_3O_3$ in the injection.

Storage. Store protected from light.

Ethopabate



$C_{12}H_{15}NO_4$ Mol. Wt. 237.3

Ethopabate is methyl 4-acetamido-2-ethoxybenzoate.

Ethopabate contains not less than 96.0 per cent and not more than 104.0 per cent of ethopabate, $C_{12}H_{15}NO_4$, calculated on the dried basis.

Category. Coccidiostat.

Description. A white or pinkish white powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *ethopabate IPRS* or with the reference spectrum of ethopabate.

B. When examined in the range 230 to 360 nm (2.4.7), a 0.0016 per cent w/v solution in *methanol* shows absorption maxima at about 268 nm and at about 299 nm; absorbance at about 268 nm, about 1.3 and at about 299 nm, about 0.58.

C. Melts at about 148° (2.4.21).

Tests

Diazotisable substances. Dissolve 0.2 g in 10 ml of *dichloromethane* and extract in succession with 100 ml and 90 ml of *0.1 M hydrochloric acid*, combine the acid extracts, wash with 5 ml of *dichloromethane*, dilute to 200 ml with *0.1 M hydrochloric acid* and filter. To 5 ml, add 6 ml of *1 M hydrochloric acid* and 1 ml of a 0.1 per cent w/v solution of *sodium nitrite*, mix, and allow to stand for 4 minutes. Add 1 ml of a 0.5 per cent w/v solution of *ammonium sulphamate*, mix and allow to stand for 3 minutes. Add 1.0 ml of a 0.1 per cent w/v solution of *N-(1-naphthyl)ethylenediamine dihydrochloride*, mix, and allow to stand for 30 minutes. Absorbance of the resulting solution at about 545 nm (2.4.7), not more than 0.70.

Phenolic substances. Dissolve 0.25 g in 15 ml of *methanol* and add sufficient *methanol* to produce 25 ml. To 5 ml add 5 ml of a 3 per cent w/v solution of *anhydrous ferric chloride*, mix and allow to stand for 10 minutes. Absorbance of the resulting solution at about 525 nm (2.4.7), not more than 0.70, using as the blank a solution prepared by adding 5 ml of a 3 per cent w/v solution of *anhydrous ferric chloride* to 5 ml of *methanol*.

Sulphated ash (2.3.18). Not more than 0.5 per cent.

Loss on drying (2.4.19). Not more than 1.0 per cent, determined on 1.0 g, by drying in an oven at 105° at a pressure not exceeding 0.7 kPa.

Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. Equal volumes of *methanol* and *water*.

Test solution. Dissolve 20 mg of the substance under examination in 100 ml of the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (a). A 0.002 per cent w/v solution of *ethopabate IPRS* in the solvent mixture.

Reference solution (b). A solution containing 0.002 per cent w/v of *ethopabate IPRS* and 0.01 per cent w/v of *methyl-4-acetamido- 2-hydroxybenzoate IPRS* in the solvent mixture.

Chromatographic system

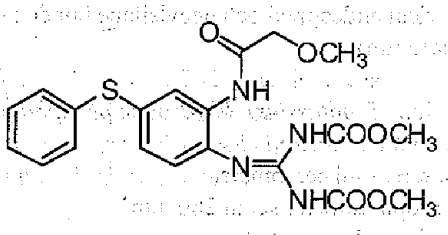
- a stainless steel column 30 cm x 3.9 mm, packed with silica particles the surface of which has been modified with chemically bonded phenyl groups (10 µm),
- column temperature: 45°,
- mobile phase: a mixture of 3 volumes of *acetonitrile*, 15 volumes of *methanol* and 45 volumes of *0.15 M sodium hexanesulphonate*, adjusted to pH 2.5 with *orthophosphoric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 268 nm,
- injection volume: 20 µl.

Inject reference solution (b). The test is not valid unless the resolution factor between the peaks due to ethopabate and methyl-4-acetamido-2 hydroxybenzoate is not less than 1.2.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{12}H_{15}NO_4$.

Febantel



$C_{20}H_{22}N_4O_6S$ Mol. Wt. 446.5

Febantel is *N*-[2-[*N,N'*-Bis(methoxycarbonyl)guanidino]-5-phenylthio]-2-methoxyacetanilide.

Febantel contains not less than 97.5 per cent and not more than 102.0 per cent of $C_{20}H_{22}N_4O_6S$, calculated on the dried basis.

Category. Antihelminthic.

Description. A white or almost white, crystalline powder. It shows polymorphism (2.5.11).

Identification

Determined by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *febantel IPRS* or with the reference spectrum of febantel.

NOTE— If the spectra obtained in the solid state show differences, dissolve the substance under examination and the reference substance separately in acetone, evaporate to dryness and record new spectra using the residues.

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 50 volumes of *acetonitrile* and 50 volumes of *tetrahydrofuran.*

Test solution (a). Dissolve 0.1 g of the substance under examination in the solvent mixture and dilute to 10.0 ml with the solvent mixture.

Test solution (b). Dilute 5.0 ml of test solution (a) to 100.0 ml with the solvent mixture.

Reference solution (a). Dilute 1.0 ml of test solution (a) to 100.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (b). Dissolve 50 mg of *febantel IPRS* in the solvent mixture and dilute to 10.0 ml with the solvent mixture. Dilute 5.0 ml of solution to 50.0 ml with the solvent mixture.

Reference solution (c). Dissolve 5 mg of *febantel system suitability IPRS* (containing impurities A, B and C) in 1.0 ml of the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm × 4.0 mm, packed with spherical endcapped octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 65 volume of a 0.68 per cent solution of *potassium dihydrogen phosphate* in *water* and 35 ml of *acetonitrile.*
- flow rate: 1 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 10 µl.

Inject reference solution (c). The test solution is not valid unless the resolution between the peaks due to impurities A and B is not less than 3.0 and between the peaks due to impurities B and C is not less than 4.0.

Inject reference solution (a) and the test solution. Run the chromatogram 1.5 times the retention time of febantel. Area of any peak due to impurities A, B and C, each of, is not more than the area of principle peak in the chromatogram obtained with reference solution (a) (0.1 per cent). Area of any peak due to other impurities is not more than twice the area of principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent). The sum of area of all impurities is not more than the 5 times of area of principle peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Ignore any peak with an area less than 0.5 times the area of principal peak obtained in the chromatogram of reference solution (a) (0.05 per cent).

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent, determined on 1.0 g.

Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105° for 2 hours.

Assay. Determined by liquid chromatography (2.4.14) as described under test for Related substances with the following modification.

Inject reference solution (b) and the test solution (b).

Calculate the percentage content of $C_{20}H_{22}N_4O_6S$.

Fenbendazole Granules

Fenbendazole Granules contain Fenbendazole mixed with suitable diluents.

Fenbendazole Granules contains not less than 95.0 per cent and not more than 105.0 per cent of stated amount of fenbendazole, $C_{15}H_{13}N_3O_2S$.

Category. Anthelminthic.

Usual strength. 20 per cent w/w.

Identification

A. In the Assay, the principal peak in the chromatogram obtained with test solution corresponds to peak in the chromatogram obtained with reference solution.

B. Determined by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254.*

Mobile phase. A mixture of 65 volumes of *toluene,* 26 volumes of *13.5 M ammonia,* 6.5 volumes of *acetone,* and 2.5 volumes of *water.*

Test solution. Dissolve a quantity of the powdered granules containing 80 mg of Fenbendazole with 80 ml of *0.1 M methanolic hydrochloric acid* with the aid of ultrasound for 90 minutes, cool, dilute to 100 ml with *0.1 M methanolic hydrochloric acid,* filter and use the filtrate.

Reference solution. A 0.08 per cent w/v solution of *fenbendazole IPRS* in *0.1 M methanolic hydrochloric acid*.

Apply to the plate 5 µl of each solution. After development, dry the plate in air for 10 minutes, heat at 100° for 5 minutes and examine under ultraviolet light at 254 nm and 365 nm. The principal spot in the chromatogram obtained with test solution corresponds to that in the chromatogram obtained with reference solution.

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve a quantity of the powdered granules containing 0.1 g of Fenbendazole with 50 ml of *0.1 M methanolic hydrochloric acid* with the aid of ultrasound for 30 minutes, cool, dilute to 100 ml with *methanol (65 per cent)*, and filter.

Reference solution (a). Dilute 1 volume of a 0.001 per cent w/v solution of *fenbendazole impurity A IPRS* (methyl (1*H*-benzimidazol-2-yl) carbamate) in *0.1 M methanolic hydrochloric acid* to 2 volumes with *methanol (65 per cent)*.

Reference solution (b). Dilute 1 volume of a 0.001 per cent w/v solution of *fenbendazole impurity B IPRS* (methyl (5-chloro-1*H*-benzimidazol-2-yl) carbamate) in *0.1 M methanolic hydrochloric acid* to 2 volumes with *methanol (65 per cent)*.

Reference solution (c). Dilute 1 volume of a 0.0010 per cent w/v solution of *fenbendazole impurity 1 IPRS* (5-phenylthio)-2-aminobenzimidazole) in *0.1 M methanolic hydrochloric acid* to 2 volumes with *methanol (65 per cent)*.

Reference solution (d). Dilute 1 volume of a solution containing 0.002 per cent w/v each of *fenbendazole impurity A IPRS, fenbendazole impurity B IPRS, fenbendazole impurity 1 IPRS* and 0.20 per cent *w/v of fenbendazole IPRS* in *0.1 M methanolic hydrochloric acid* to 2 volumes with *methanol (65 per cent)*.

Chromatographic system
- a stainless steel column 25 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 350 volumes of a 0.5 per cent w/v solution of *sodium dihydrogen orthophosphate* and 650 volumes of *methanol* containing 1.88 g of *sodium hexanesulphonate*, adjusted to pH 3.5 with *orthophosphoric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Inject reference solution (d). The test is not valid unless the peak in the chromatogram obtained with reference solution (d) corresponds to the reference chromatogram obtained with *fenbendazole IPRS*.

Inject reference solutions (a), (b), (c) and the test solution. The areas of any peaks in the chromatogram obtained with test solution corresponding to fenbendazole impurity A, fenbendazole impurity B and fenbendazole impurity 1 (5-(phenylthio)-2-aminobenzimidazole) are not more than the areas of the corresponding peaks in the chromatograms obtained with reference solutions (a), (b) and (c) respectively (0.5 per cent each).

Other tests. Comply with the requirements stated under Granules.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve a quantity of powdered granules containing 0.1 g of Fenbendazole with 50 ml of *0.1M methanolic hydrochloric acid* with the aid of ultrasound for 30 minutes, cool, dilute to 100 ml with *methanol (65 per cent)*, and filter. Dilute 5 volumes of the resulting solution to 50 volumes with *0.1 M hydrochloric acid* in *methanol (85 per cent)*.

Reference solution. A 0.01 per cent w/v of *fenbendazole IPRS* in a mixture of 1 volume of *0.1 M hydrochloric acid* and 1 volume of *methanol (85 per cent)*.

Use the Chromatographic system as described under Related substances.

Calculate the content of $C_{15}H_{13}N_3O_2S$ in the granules.

Fenbendazole Oral Paste

Fenbendazole Oral Paste contains Fenbendazole finely dispersed in a suitable basis.

Fenbendazole Oral Paste contains not less than 95.0 per cent and not more than 105.0 per cent of stated amount of fenbendazole, $C_{15}H_{13}N_3O_2S$.

Usual strength. 100 mg per g.

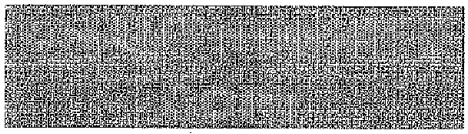
Identification

In the Assay, the retention time of the principal peak in the chromatogram obtained with test solution corresponds to the retention time of the principal peak in the chromatogram obtained with reference solution.

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve a quantity of the oral paste containing 0.1 g of Fenbendazole with 50 ml of *0.1 M methanolic hydrochloric acid* with the aid of ultrasound for 30 minutes, cool, dilute to 100 ml with *methanol (65 per cent)*, and filter.



Reference solution (a). Dilute 1 volume of a 0.001 per cent w/v solution of *fenbendazole impurity A IPRS* (methyl (1*H*-benzimidazole-2-yl) carbamate) in *0.1 M methanolic hydrochloric acid* to 2 volumes with *methanol (65 per cent)*.

Reference solution (b). Dilute 1 volume of a 0.001 per cent w/v solution of *fenbendazole impurity B IPRS* (methyl (5-chloro-1*H*-benzimidazole-2-yl) carbamate) in *0.1 M methanolic hydrochloric acid* to 2 volumes with *methanol (65 per cent)*.

Reference solution (c). Dilute 1 volume of a 0.001 per cent w/v solution of *fenbendazole impurity 1 IPRS* ((5-phenylthio)-2-aminobenzimidazole) in *0.1 M methanolic hydrochloric acid* to 2 volumes with *methanol (65 per cent)*.

Reference solution (d). Dilute 1 volume of a solution containing 0.002 per cent w/v each of *fenbendazole impurity A IPRS, fenbendazole impurity B IPRS, fenbendazole impurity 1 IPRS* and 0.20 per cent w/v of *fenbendazole IPRS* in *0.1 M methanolic hydrochloric acid* to 2 volumes with *methanol (65 per cent)*.

Chromatographic system
- a stainless steel column 25 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 35 volumes of a 0.5 per cent w/v solution of *sodium dihydrogen orthophosphate* and 65 volumes of *methanol* containing 1.88 g of *sodium hexanesulphonate*, adjusted to pH 3.5 with *orthophosphoric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Inject reference solution (d). The test is not valid unless the chromatogram obtained with reference solution (d) corresponds to the chromatogram obtained with *fenbendazole IPRS*.

Inject reference solutions (a), (b), (c) and the test solution. The areas of any peaks in the chromatogram obtained with test solution corresponding to fenbendazole impurity A (methyl (1*H*- benzimidazol-2-yl)carbamate), fenbendazole impurity B (methyl (5-chloro-1*H*- benzimidazol-2-yl) carbamate) and fenbendazole impurity 1 ((5-phenylthio)-2- amino-benzimidazole) are not more than the areas of the corresponding peaks in the chromatograms obtained with reference solutions (a), (b) and (c) respectively (0.5 per cent each).

Other tests. Comply with tests stated under Veterinary Oral Pastes.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve a quantity of oral paste containing 0.1 g of Fenbendazole with 50 ml of *0.1 M methanolic hydrochloric acid* with the aid of ultrasound for 30 minutes, cool, dilute to 100 ml with *methanol (65 per cent)*, and filter. Dilute 5 volumes of the resulting solution to 50 volumes with *0.1 M hydrochloric acid* in *methanol (85 per cent)*.

Reference solution. A 0.01 per cent w/v of *fenbendazole IPRS* in a mixture of 1 volume of *0.1 M hydrochloric acid* and 1 volume of *methanol (85 per cent)*.

Use the Chromatographic system as described under Related substances.

Inject the reference solution and the test solution.

Calculate the content of $C_{15}H_{13}N_3O_2S$ in the veterinary oral paste.

Fenbendazole Oral Powder

Fenbendazole Oral Powder contains Fenbendazole mixed with suitable diluents.

Fenbendazole Oral Powder contains not less than 95.0 per cent and not more than 105.0 per cent of stated amount of fenbendazole, $C_{15}H_{13}N_3O_2S$.

Usual strengths. 22 per cent w/w; 22.2 per cent w/w.

Identification

A. In the Assay, the principal peak in the chromatogram obtained with test solution corresponds to the peak in the chromatogram obtained with reference solution.

B. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 65 volumes of *toluene*, 26 volumes of *13.5 M ammonia*, 6.5 volumes of *acetone*, and 2.5 volumes of *water*.

Test solution. Dissolve a quantity of the powder containing 80 mg of Fenbendazole with 80 ml of *0.1 M methanolic hydrochloric acid* with the aid of ultrasound for 90 minutes, cool, dilute to 100 ml with *0.1 M methanolic hydrochloric acid*, filter and use the filtrate.

Reference solution. A 0.08 per cent w/v solution of *fenbendazole IPRS* in *0.1 M methanolic hydrochloric acid*.

Apply to the plate 5 µl of each solution. After development, dry the plate in air for 10 minutes, heat at 100° for 5 minutes and examine under ultraviolet light at 254 nm and 365 nm. The principal spot in the chromatogram obtained with test solution corresponds to that in the chromatogram obtained with reference solution.

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve a quantity of the powder containing 0.1 g of Fenbendazole with 25 ml each of *dimethylformamide* and *methanol* and 1 ml of *5 M hydrochloric acid* with the aid of ultrasound until a clear solution is produced, cool, dilute to 100 ml with *methanol (65 per cent)*.

Reference solution (a). Dilute 1 volume of a 0.001 per cent w/v solution of *fenbendazole impurity A IPRS* in *0.1 M methanolic hydrochloric acid* to 2 volumes with *methanol (65 per cent)*.

Reference solution (b). Dilute 1 volume of a 0.001 per cent w/v solution of *fenbendazole impurity B IPRS* in *0.1 M methanolic hydrochloric acid* to 2 volumes with *methanol (65 per cent)*.

Reference solution (c). Dilute 1 volume of a 0.001 per cent w/v solution of *fenbendazole impurity 1 IPRS* in *0.1 M methanolic hydrochloric acid* to 2 volumes with *methanol (65 per cent)*.

Reference solution (d). Dilute 1 volume of a solution containing 0.002 per cent w/v each of *fenbendazole impurity A IPRS, fenbendazole impurity B IPRS, fenbendazole impurity 1 IPRS* and 0.20 per cent w/v of *fenbendazole IPRS* in *0.1 M methanolic hydrochloric acid* to 2 volumes with *methanol (65 per cent)*.

Chromatographic system

- a stainless steel column 25 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 35 volumes of a 0.5 per cent w/v solution of *sodium dihydrogen orthophosphate* and 65 volumes of *methanol* containing 1.88 g of *sodium hexanesulphonate*, adjusted to pH 3.5 with *orthophosphoric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Inject reference solution (d). The test is not valid unless the chromatogram obtained with reference solution (d) corresponds to the reference chromatogram obtained with *fenbendazole IPRS*.

Inject reference solutions (a), (b), (c) and the test solution. The areas of any peaks in the chromatogram obtained with test solution corresponding to fenbendazole impurity A (methyl (1*H*-benzimidazol-2-yl)carbamate), fenbendazole impurity B (methyl (5-chloro-1*H*-benzimidazol-2-yl) carbamate) and fenbendazole impurity 1 (5-(phenylthio)-2-minobenzimidazole) is not more than the areas of the corresponding peaks in the chromatograms obtained with reference solutions (a), (b) and (c) respectively (0.5 per cent each). Ignore any peaks due to preservatives.

Other tests. Comply with the tests stated under Veterinary Oral Powders.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve a quantity of powder containing 0.1 g of Fenbendazole in 25 ml each of *dimethylformamide* and *methanol* and 1 ml of *5M hydrochloric acid* with the aid of ultrasound until a clear solution is produced, cool, dilute to 100 ml with *methanol (85 per cent)*. Dilute 5 volumes of the resulting solution to 50 volumes with *0.1 M hydrochloric acid* in *methanol (85 per cent)*.

Reference solution. A 0.01 per cent w/v of *fenbendazole IPRS* in a mixture of 1 volume of *0.1M hydrochloric acid* and 1 volume of *methanol (85 per cent)*.

Use the Chromatographic system as described under Related substances.

Inject the reference solution and the test solution.

Calculate the content of $C_{15}H_{13}N_3O_2S$ in the oral powder.

Fenbendazole Oral Suspension

Fenbendazole Oral Suspension is an aqueous suspension of Fenbendazole.

Fenbendazole Oral Suspension contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of fenbendazole, $C_{15}H_{13}N_3O_2S$.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Usual strength. 100 mg per ml.

Identification

In the Assay, the retention time of the principal peak in the chromatogram obtained with test solution corresponds to the retention time of the principal peak in the chromatogram obtained with reference solution.

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve a quantity of oral suspension containing 0.1 g of Fenbendazole with 50 ml of *0.1 M methanolic hydrochloric acid* with the aid of ultrasound for 30 minutes, cool, dilute to 100 ml with *methanol (65 per cent)*, and filter.

Reference solution (a). Dilute 1 volume of a 0.001 per cent w/v solution of *fenbendazole impurity A IPRS* (methyl (1*H*-benzimidazol-2-yl) carbamate) in *0.1 M methanolic hydrochloric acid* to 2 volumes with *methanol (65 per cent)*.

Reference solution (b). Dilute 1 volume of a 0.001 per cent w/v solution of *fenbendazole impurity B IPRS* (methyl (5-

chloro-1*H*-benzimidazol-2-yl) carbamate) in *0.1 M methanolic hydrochloric acid* to 2 volumes with *methanol (65 per cent)*.

Reference solution (c). Dilute 1 volume of a 0.001 per cent w/v solution of *fenbendazole impurity 1 IPRS* (5-phenylthio)-2-aminobenzimidazole) in *0.1 M methanolic hydrochloric acid* to 2 volumes with *methanol (65 per cent)*.

Reference solution (d). Dilute 1 volume of a solution containing 0.002 per cent w/v each of *fenbendazole impurity A IPRS, fenbendazole impurity B IPRS, fenbendazole impurity 1 IPRS* and 0.20 per cent *w/v of fenbendazole IPRS* in *0.1 M methanolic hydrochloric acid* to 2 volumes with *methanol (65 per cent)*.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 350 volumes of a 0.5 per cent w/v solution of *sodium dihydrogen orthophosphate* and 650 volumes of *methanol* containing 1.88 g of *sodium hexanesulfonate*, adjusted to pH 3.5 with *orthophosphoric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Inject reference solution (d). The test is not valid unless the peak in the chromatogram obtained with reference solution (d) corresponds to the reference chromatogram obtained with *fenbendazole IPRS*.

Inject reference solutions (a), (b), (c) and the test solution. The areas of any peak in the chromatogram obtained with test solution corresponding to fenbendazole impurity A (methyl (1*H*- benzimidazol-2-yl)carbamate), fenbendazole impurity B (methyl(5-chloro-1*H*- benzimidazol-2-yl)carbamate) and fenbendazole impurity 1 ((5-phenylthio)-2- amino-benzimidazole) is not more than the areas of the corresponding peaks in the chromatograms obtained with reference solutions (a), (b) and (c) respectively (0.5 per cent each).

Other tests. Comply with the tests stated under Veterinary Oral Liquid.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve a quantity of the oral suspension containing 0.1 g of Fenbendazole in 50 ml of *0.1 M methanolic hydrochloric acid* with the aid of ultrasound for 30 minutes, cool, dilute to 100 ml with *methanol (65 per cent)*, and filter. Dilute 5 volumes of the resulting solution to 50 volumes with *0.1 M hydrochloric acid* in *methanol (85 per cent)*.

Reference solution. A 0.01 per cent w/v of *fenbendazole IPRS* in a mixture of 1 volume of *0.1 M hydrochloric acid* and 1 volume of *methanol (85 per cent)*.

Use chromatographic system as described under Related substances.

Inject the reference solution and test solution. The test is not valid unless the chromatogram obtained with reference solution (d) corresponds to the reference chromatogram obtained with *fenbendazole IPRS*.

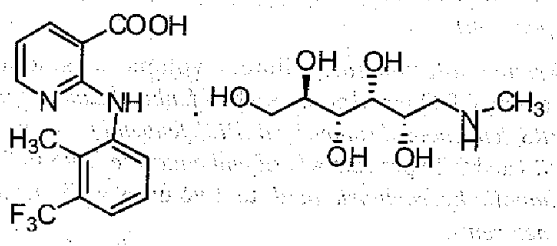
Calculate the content of $C_{15}H_{13}N_3O_2S$ in the oral suspension.

Ferrous Fumerate Boluses

Usual strength. 1500 mg.

For Identification and Tests refer to IP Volume III.

Flunixin Meglumine



$C_{21}H_{28}F_3N_3O_7$ Mol. Wt. 491.5

Flunixin Meglumine is 2-(3-(Trifluoromethyl)-2-methyl-phenylamino)pyridine-3-carboxylic acid meglumine.

Flunixin Meglumine contains not less than 99.0 per cent and not more than 101.0 per cent of $C_{21}H_{28}F_3N_3O_7$, calculated on dried basis.

Category. Cyclo-oxygenase inhibitor; analgesic; anti-inflammatory.

Description. A white or almost white, crystalline powder.

Identification

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *flunixin meglumine IPRS* or with the reference spectrum of flunixin meglumine.

Tests

Appearance of solution (2.4.1). A 5.0 per cent w/v in *carbon dioxide- free water is* clear and not more intensely coloured than reference solution YS7.

pH (2.4.24). 7.0 to 9.0, determined in 5.0 per cent w/v solution in *carbon dioxide-free water*.

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 50 mg of the substance under examination in 10.0 ml of mobile phase.

Reference solution (a). Dissolve 5 mg of *flunixin impurity B IPRS* in 1.0 ml of test solution and dilute to 50.0 ml with mobile phase.

Reference solution (b). Dissolve 5 mg of *flunixin impurity A IPRS (2-chloronicotinic acid)* in mobile phase and dilute to 50.0 ml with the mobile phase. To 2.0 ml of the solution add 2.0 ml of reference solution (a) and dilute to 20.0 ml with the mobile phase.

Reference solution (c). Dissolve 50 mg of *flunixin impurity C IPRS* in 100.0 ml with the mobile phase.

Chromatographic system

- a stainless steel column 12.5 cm x 4.0 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- column temperature: 35°,
- mobile phase: a mixture of 300 volumes of *water* and 700 volumes of *acetonitrile,* add 0.25 volumes of *phosphoric acid.*
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 µl.

Name	Relative retention time	Correction factor
Flunixin impurity A[1]	0.4	—
Flunixinimpurity C[2]	0.6	1.9
Flunixin impurity B[3]	0.7	—
Flunixin(Retention time: about 3.1 minutes)	1.0	—
Flunixinimpurity D[4]	4.2	—

[1]2-chloropyridine-3-carboxylic acid,

[2]ethyl 2-chloropyridine-3-carboxylate,

[3]2-methyl-3-(trifluoromethyl) aniline,

[4]ethyl 2-[[2-methyl-3-(trifluoromethyl) phenyl] amino] pyridine-3-carboxylate.

Inject reference solution (a). Run the chromatogram 5 times the retention time of the flunixin. The test is not valid unless the resolution between the peaks due to impurity B and flunixin is not less than 3.5.

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to flunixin impurity A and flunixin impurity B, each of, is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.2 per cent), the area of peak corresponding to impurity C and D, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent), the area of any other secondary peak is not more than the area of principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent) and the sum of the areas of the secondary peak is not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent). Ignore any peak with an area 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105° for 4 hours.

Assay. Dissolve 0.175 g in 50 ml of *anhydrous acetic acid.* Titrate with *0.1 M perchloric acid,* determining the end point potentiometrically (2.4.25). Carry out a blank titration.

1 ml of *0.1 M perchloric acid* is equivalent to 0.02457 g of $C_{21}H_{28}F_3N_3O_7$.

Frusemide Injection

Frusemide Injection is a sterile solution of Frusemide in Water for Injection prepared with the aid of Diethanolamine or Monoethanolamine.

Frusemide Injection contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of Frusemide $C_{12}H_{11}ClN_2O_5S$.

Usual strength: 50 mg per ml.

pH. 7.0 to 7.8, if it contains diethanolamine; or between 8.0 to 9.3, if it contains monoethanolamine.

Labelling. The label states whether preparation 1.0 per cent prepared using Diethanolamine or with Monoethanolamine.

For Identification and Tests refer to IP Volume II.

Furazolidone

Category. Antibacterial.

For Description, Identification and Tests refer to IP Volume II.

Furazolidone Veterinary Oral Suspension

Furazolidone Veterinary Mixture; Furazolidone Mixture; Furazolidone Drench

Furazolidone Veterinary Oral Suspension is an aqueous suspension of Furazolidone.

Furazolidone Veterinary Oral Suspension contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of furazolidone, $C_8H_7N_3O_5$.

Usual strengths. 5 per cent w/v; 7.5 per cent w/v.

Identification

A. Add 0.2 ml to a mixture of 15 ml of *dimethylformamide* and 1 ml of *0.5 M ethanolic potassium hydroxide*; a blue colour is produced.

B. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G F254*.

Mobile phase. A mixture of 50 volumes of *dichloromethane* and 40 volumes of *nitromethane* and 10 volumes of *methanol*.

Test solution. Shake a quantity of the suspension containing 5 mg of Furazolidone with 1 ml of *acetone*, allow to stand, and use the supernatant liquid.

Reference solution. A 0.5 per cent w/v solution of *furazolidone IPRS* in *acetone*.

Apply to the plate 10 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with the reference solution.

Tests

Other tests. Comply with the tests stated under Veterinary Oral Liquids.

Assay. *NOTE—Protect the solutions from light throughout the assay.*

Weigh a quantity of the well-shaken suspension containing 35 mg of Furazolidone, add slowly and with stirring, 50 ml of *dimethylformamide*. Warm on a water-bath, with occasional stirring, until most of the solid is dissolved. Decant the supernatant liquid and extract the residue further with two quantities, each of 50 ml, of *dimethylformamide*, decanting the supernatant solution. No yellow colour should be visible in the third extract. Cool the combined dimethylformamide extracts, add sufficient *water* to produce 500.0 ml and filter. To 10.0 ml of the filtrate add sufficient *water* to produce 100.0 ml and measure the absorbance of the resulting solution at the maximum at about 367 nm (2.4.7). Calculate the content of $C_8H_7N_3O_5$ taking 754 as the specific absorbance at 367 nm.

Determine the weight per ml of the suspension (2.4.29), and calculate the content of furazolidone, weight in volume.

Labelling. The label states that the oral suspension should be administered undiluted.

Furazolidone Premix

Furazolidone Premix contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of furazolidone, $C_8H_7N_3O_5$.

Usual strengths. 4.4 per cent w/w; 22.4 per cent w/w.

Identification

A. To a mixture of 15 ml of *dimethylformamide* and 1 ml of *0.5 M ethanolic potassium hydroxide* add 5 mg of the premix; a blue colour is produced.

B. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G F254*.

Mobile phase. A mixture of 50 volumes of *dichloromethane* and 40 volumes of *nitromethane* and 10 volumes of *methanol*.

Test solution. The supernatant liquid obtained by shaking a quantity of the premix containing 5 mg of furazolidone with 1 ml of *acetone*.

Reference solution. A 0.5 per cent w/v solution of *furazolidone IPRS* in *acetone*.

Apply to the plate 10 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with the reference solution.

Tests

Assay. *NOTE — Protect the solutions from light throughout the assay.*

Weigh a quantity of the premix containing 35 mg of Furazolidone, add 50 ml of *dimethylformamide* and shake for 20 minutes. Add sufficient *water* to produce 500.0 ml and filter. To 10.0 ml of the filtrate add sufficient *water* to produce 100.0 ml and measure the absorbance of the resulting solution at the maximum at about 367 nm (2.4.7). Calculate the content of $C_8H_7N_3O_5$ taking 754 as the specific absorbance at 367 nm.

Storage. Store protected from light and moisture.

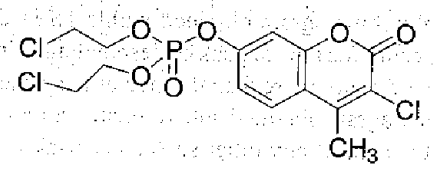
Gentamicin Injection

Category. Antibacterial.

Strengths. 40 mg and 100 mg per ml.

For Identification and Tests refer to IP Volume II.

Haloxon



$C_{14}H_{14}Cl_3O_6P$ Mol. Wt. 415.6

Haloxon is phosphoric acid bis(2-chloroethyl) 3-chloro-4-methyl-2-oxo-2*H*-1-benzopyran-7-yl ester.

Haloxon contains not less than 95.0 per cent and not more than 100.5 per cent of $C_{14}H_{14}Cl_3O_6P$, calculated on the dried basis

Category. Anthelmintic.

Description. A white or almost white powder.

Identification

A. Dissolve about 20 mg in 10 ml of *dioxan*, add 0.5 ml of *0.1 M hydrochloric acid* and dilute to 25 ml with *methanol*. Dilute 1 ml to 25 ml with *methanol*.

When examined in the range 230 to 360 nm (2.4.7), the resulting solution exhibits a maximum at about 290 nm and a less well defined maximum at about 312 nm. Ratio of the absorbance at about 312 nm to that at about 290 nm, about 1.08.

B. Dissolve 0.1 g in 5 ml of *5 M sodium hydroxide* with the aid of warming, cool, acidify 1 ml of the solution by the addition of *2 M nitiric acid* and add 1 ml of *silver nitrate solution*, a white precipitate is formed. The precipitate is soluble in *5 M ammonia* giving a brown solution which exhibits a green fluorescence when viewed under screened ultraviolet light.

C. Melting range (2.4.21). 88° to 93°.

Tests

Acidity. Dissolve 0.1 g in 10 ml of *ethanol (95 per cent)* previously neutralised to *methyl red solution*; the solution requires for neutralisation not more than 0.1 ml of *0.1 M sodium hydroxide*.

3-Chloro-4-methylumbelliferone. Not more than 2.0 per cent.

NOTE — Prepare the solutions immediately before use and protected from light.

Dissolve 0.20 g in 50 ml of *0.01 M methanolic hydrochloric acid* and dilute 5 ml of the solution to 100 ml with *0.01 M methanolic hydrochloric acid*. Measure the fluorescence of the resulting solution (2.4.5), using an excitation wavelength of about 345 nm and an emission wavelength of about 400 nm and setting the spectrofluorimeter to zero with *0.01 M methanolic hydrochloric acid* and to 100 with a standard solution prepared by dissolving 25 mg of *3-chloro-4-methylumbelliferone IPRS* in sufficient *0.01 M methanolic hydrochloric acid* to produce 250 ml (solution A) and diluting 5 ml to 100 ml with *0.01 M methanolic hydrochloric acid*. Calculate the content of *3-chloro-4-methylumbelliferone* from a calibration curve prepared by measuring the fluorescence of suitable dilutions of solution A.

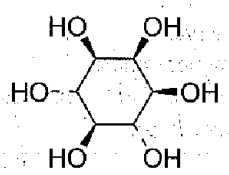
Loss on drying (2.4.19). Not more than 1.0 per cent, determined on 1.0 g by drying in an oven at 80° at a pressure not exceeding 0.7 kPa.

Assay. Weigh 0.25 g and dissolve in sufficient *acetonitrile* to produce 10 ml and record the infrared absorption of a 0.2 mm layer of the solution at the maximum at about 1155 cm^{-1} (2.4.6). Construct a base line between the minima at about 1125 cm^{-1} and 1180 cm^{-1}. Calculate the content of $C_{14}H_{14}Cl_3O_6P$ from the absorption obtained by repeating the procedure using *haloxon IPRS* in place of the substance under examination.

Storage. Avoid contact with metals.

Inositol

myo-Inositol



$C_6H_{12}O_6$ Mol. Wt. 180.2

Inositol is cyclohexane-1,2,3,5/4,6-hexol.

Inositol contains not less than 97.0 per cent and not more than 102.0 per cent of $C_6H_{12}O_6$, calculated on the anhydrous basis.

Category. Vasodilator.

Description. A white or almost white, crystalline powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *inositol IPRS* or with the reference spectrum of inositol.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the principal peak in the chromatogram obtained with reference solution (a).

Tests

Solution A. A 10 per cent w/v solution in *distilled water*.

Appearance of solution. Solution A is clear (2.4.1), and colourless (2.4.1).

Conductivity. Not more than 30 µS per cm. Dissolve 10.0 g in *carbon dioxide-free water* with gentle warming if necessary, and dilute to 50.0 ml with the same solvent. Measure the conductivity of the solution while gentle stirring with a magnetic stirrer.

Related substances. Determine by liquid chromatography (2.4.14):

Test solution. Dissolve 0.5 g of the substance under examination in 10.0 ml of *water*.

Reference solution (a). Dissolve 0.5 g of *inositol IPRS* in 10.0 ml of *water*.

Reference solution (b). Dilute 2.0 ml of test solution to 100.0 ml with *water* and dilute 5.0 ml of the solution to 100.0 ml with *water*.

Reference solution (c). Dissolve 0.5 g of *inositol IPRS* and 0.5 g of *mannitol IPRS* in 10.0 ml of *water*.

Chromatographic system

- a stainless steel column 30 cm x 7.8 mm, packed with strong cation-exchange resin (calcium form) (9 µm),
- column temperature: 85°,
- mobile phase: *water*,
- flow rate: 0.5 ml per minute,
- refractometer at a constant temperature,
- injection volume: 20 µl.

Name	Relative retention time
Inositol impurity A[1]	1.3
Inositol impurity B[2]	1.4
Inositol (Retention time: about 17.5 minutes)	—

[1]D- mannitol,

[2]propane-1,2,3-triol (glycerol).

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to inositol impurity A and *myo*-inositol is not less than 4.0.

Inject reference solution (b) and the test solution. In the chromatogram obtained with test solution, the area of the peak corresponding to each impurity A and B, each of, is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent). The area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the sum of the areas of the secondary peaks is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Barium. To 10 ml of solution A add 1.0 ml of dilute *sulphuric acid*. When examined after 1 hour, the solution is not more opalescent than a mixture of 1.0 ml of *distilled water* and 10.0 ml of solution A.

Lead (2.3.15). Not more than 0.5 ppm, determined by the following method.

Prepare the test solution by dissolving 20.0 g of the substance to be examined in 100 ml of *water*, heat if necessary, and dilute to 200.0 ml with *dilute acetic acid*.

Water (2.3.43). Not more than 0.5 per cent.

Assay. Determine by liquid chromatography (2.4.14) as described under Related substances.

Inject reference solution (a) and the test solution.

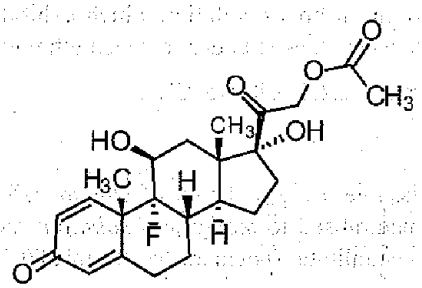
Calculate the content of $C_6H_{12}O_6$.

Iron Dextran Injection

Usual strengths. 250 mg per ml contains, 50 mg elemental iron.

For Identification and Tests refer to IP Volume II.

Isoflupredone Acetate



$C_{23}H_{29}FO_6$ Mol Wt. 420.5

Isoflupredone Acetate is Pregna-1, 4-diene-3, 20-dione, 21-(acetyloxy)-9-fluoro-11, 17-dihydroxy-(11β)-.

9-Fluoro-11β, 17, 21-trihydroxypregna-1, 4-diene-3, 20-dione 21-acetate.

Isoflupredone Acetate contains not less than 97.0 per cent and not more than 103.0 per cent of $C_{23}H_{29}FO_6$, calculated on the dried basis.

Category. Antiinflammatory; immunosuppressive.

Description. A white to pale yellow crystalline powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *isoflupredone acetate IPRS* or with the reference spectrum of isoflupredone acetate.

B. The absorbance of a 0.00125 per cent w/v solution in *ethanol (95 per cent)* at 240 nm (2.4.7) is 0.440 to 0.480.

Tests

Specific optical rotation (2.4.22). +110° to +120°, determined in a 1.0 per cent w/v solution in *dioxane*.

Related substances. Determine by liquid chromatography (2.4.14).

Solution A. a mixture of 500 volumes of *water*, 350 volumes of *methanol*, 150 volumes of *acetonitrile* and 3 volumes of *glacial acetic acid*.

Solution B. a mixture of 500 volumes of *acetonitrile*, 500 volumes of *methanol* and 3 volumes of *water*.

Test solution. A 0.03 per cent w/v solution of substance under examination in solution A.

NOTE—Use this solution within same day.

Reference solution. A solution containing 0.003 per cent w/v solution, each of, *isoflupredone acetate IPRS* and *prednisolone acetate IPRS* in solution A.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica particles (1.5 to 10 µm),
- mobile phase: A. Solution A,
  B. Solution B,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 50 µl.

Time (in min.)	Solution A (per cent v/v)	Solution B (per cent v/v)
0	100	0
32.5	100	0
47.5	0	100
50.5	0	100
51.5	100	0
61.5	100	0

Inject the reference solution. The test is not valid unless the resolution between the peaks due to isoflupredone acetate and prednisolone acetate is not less than 1.2 and the column efficiency determined from isoflupredone is not less than 6000 theoretical plates. The retention time for isoflupredone acetate is between 21 and 26 minutes and the relative retention time for prednisolone acetate is 1.1 and for isoflupredone acetate is 1.0.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than 0.1 times the area of the principle peak in the chromatogram obtained with reference solution (1.0 per cent). The sum of areas of all the secondary peaks is not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (2.0 per cent). Ignore any peak the area is 0.005 times the area of the principle peak in the chromatogram obtained with the reference solution (0.05 per cent).

Sulphated ash (2.3.18). Not more than 0.5 per cent.

Loss on drying (2.4.19). Not more than 1.0 per cent, determined on 1.0 g by drying in an oven at 105° for 4 hours.

Assay. Determine by liquid chromatography (2.4.14).

Internal Standard Solution. Dissolve a quantity of *fluoxymesterone* in *water-saturated chloroform* to obtain a solution having a known concentration of about 0.9 mg per ml.

Test solution. Dissolve 4 mg of substance under examination in 8.0 ml of internal standard solution and 32.0 ml of *water-saturated chloroform*, centrifuge and use the clear chloroform portion.

Reference solution. Dissolve 4 mg of *isoflupredone acetate IPRS* in 8.0 ml of internal standard solution and 32.0 ml of *water-saturated chloroform*.

Chromatographic system

- a stainless steel column 30 cm x 4.0 mm, packed with octadecylsilane bonded to porous micro silica particles (1.5 to 10 µm),
- mobile phase: a mixture of 475 volumes of *n-butyl chloride*, 475 volumes of *water-saturated n-butyl chloride*, 70 volumes of *tetrahydrofuran*, 35 volumes of *methanol* and 30 volumes of *glacial acetic acid*,
- flow rate: 0.7 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 12 µl.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to isoflupredone acetate and fluoxymesterone is not less than 2.0, and the relative standard deviation for the replicate injection is not more than 2.0 per cent. The relative retention time for isoflupredone acetate is 1.0 and for fluoxymesterone is 1.2.

Inject the reference solution and the test solution.

Calculate the content of $C_{23}H_{29}FO_6$.

Isoflupredone Acetate intended for use in the manufacture of parenteral preparations without a further appropriate procedure for removal of bacterial endotoxin complies with the following additional requirements.

Bacterial endotoxins (2.2.3). Not more than 125 Endotoxin units per mg of isoflupredone acetate.

Isoflupredone Acetate intended for use in the manufacture of parenteral preparations without a further appropriate sterilization procedure complies with the following additional requirements.

Sterility (2.2.11). Complies with the test for sterility.

Storage. Store protected from light.

Labeling. The Label states (1) where it is intended for use in preparing injectable dosage forms; (2) it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.

Isoflupredone Acetate Injectable Suspension

Isoflupredone Injection contains not less than 90.0 per cent and not more than 115.0 per cent of the stated amount of isoflupredone acetate, $C_{23}H_{29}FO_6$.

Usual strength. 2 mg per ml.

Identification

Determine by infrared absorption spectrophotometry (2.4.6.). Transfer about 25 mg of substance under examination to a centrifuge tube, add 20 ml of *water* and shake well. Centrifuge, and discard the liquid layer. Repeat this washing step with three additional 20 ml portions of *water* and dry at 105° for 3 hours.

Tests

pH (2.4.24). 5.0 to 7.5.

Bacterial endotoxins (2.2.3). Not more than 125 Endotoxin Units per mg of isoflupredone acetate.

Sterility (2.2.11). Complies with the test for sterility.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. Determine by liquid chromatography (2.4.14).

Internal standard solution. Dissolve a quantity of *fluoxymesterone* in *water-saturated chloroform* to obtain a solution having a known concentration of about 0.9 mg per ml.

Test solution. Dilute a volume of injection containing about 4 mg of Isoflupredone Acetate with 8.0 ml of internal standard solution and 32.0 ml of *water-saturated chloroform*, centrifuge and use the clear chloroform portion.

Reference solution. Dissolve 4 mg of *isoflupredone acetate IPRS* in 8.0 ml of internal standard solution and 32.0 ml of *water-saturated chloroform*.

Chromatographic system

- a stainless steel column 30 cm x 4.0 mm, packed with octadecylsilane bonded to porous micro silica particles (1.5 to 10 µm),
- mobile phase: a mixture of 475 volumes of *n-butyl chloride*, 475 volumes of *water-saturated n-butyl chloride*, 70 volumes of *tetrahydrofuran*, 35 volumes of *methanol* and 30 volumes of *glacial acetic acid*,
- flow rate: 0.7 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 12 µl.

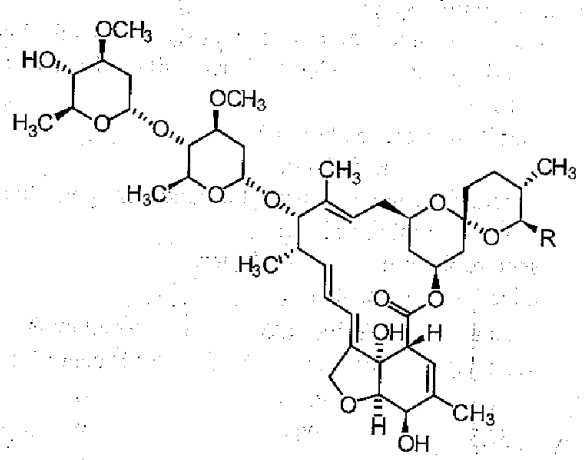
Inject the reference solution. The test is not valid unless the resolution between the peaks due to isoflupredone acetate and fluoxymesterone is not less than 2.0, and the relative standard deviation for the replicate injection is not more than 2.0 per cent. The relative retention time for isoflupredone acetate is 1.0 and for fluoxymesterone is 1.2.

Inject the reference solution and the test solution.

Calculate the content of $C_{23}H_{29}FO_6$.

Storage. Store in a single dose or multi dose sterile container, preferably of type I glass.

Ivermectin



B_{1a}	B_{1b}
R = [alkyl] = (*S*)-sec. butyl	R = [alkyl] = *iso*.propyl
$C_{48}H_{74}O_{14}$, H_2B_{1a}	Mol.Wt. 875.1
$C_{47}H_{72}O_{14}$, H_2B_{1b}	Mol.Wt. 861.1

Ivermectin contains not less than 95.0 per cent and not more than 102.0 per cent of H_2B_{1a} + H_2B_{1b}, calculated on the anhydrous and solvent free basis.

The ratio $H_2B_{1a}/(H_2B_{1a} + H_2B_{1b})$, determined by liquid chromatography is not less than 90.0 per cent.

Category. Anthelmintic.

Description. A white or yellowish white powder, slightly hygroscopic.

Identification

A. Determine by infrared absorption spectrophotometery (2.4.6). Compare the spectrum with that obtained with *ivermectin IPRS*.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Tests

Appearance of solution. A 2.0 per cent w/v solution in toluene is clear (2.4.1) and not more intensely colored than reference solution BYS7 (2.4.1).

Specific optical rotation (2.4.22). – 20.0° to – 17.0°, determined on a 2.5 per cent w/v solution in *methanol*.

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 40 mg of the substance under examination in 50 ml of *methanol*.

Reference solution (a). A 0.08 per cent w/v solution of *ivermectin IPRS* in *methanol*.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100 ml with *methanol*.

Reference solution (c). Dilute 5 ml of reference solution (b) to 100 ml with *methanol*.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 15 volumes of *water*, 34 volumes of *methanol* and 51 volumes of *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

Inject reference solution (a). This test is not valid unless resolution between the component H_2B_{1b} (first peak) and component H_2B_{1a} (second peak) is not less than 3.0.

Inject the test solution and reference solution (b). In the chromatogram obtained with the test solution the impurity with a relative retention of 1.3 to 1.5 with reference to the principal peak is not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (2.5 per cent). The area of any other peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent) and the sum of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (5.0 per cent).

Ethanol and formamide. Ethanol. Not more than 5.0 per cent and formamide. Not more than 3.0 per cent, determined by gas chromatography (2.4.13).

Internal standard solution. Dilute 0.5 ml of *propanol* to 100 ml with *water*.

Test solution. Dissolve 0.120 g of the substance under examination in 2.0 ml of *m-xylene* by heating on a water-bath at 40 to 50°, add 2.0 ml of *water*, mix thoroughly and centrifuge. Remove the upper layer and extract it with 2.0 ml of *water*. Discard the upper layer and combine the aqueous layers. Add 1.0 ml of the internal standard solution. Centrifuge and discard any remaining *m-xylene*.

Reference solution (a). Dilute 3.0 g of *ethanol* to 100 ml with *water*.

Reference solution (b). Dilute 1.0 g of *formamide* to 100 ml with *water*.

Reference solution (c). Dilute 5.0 ml of reference solution (a) and 5 ml of reference solution (b) to 50.0 ml with *water*. Transfer 2.0 ml of the solution to a centrifuge tube, add 2 ml of *m-xylene*, mix thoroughly and centrifuge. Remove the upper layer and extract it with 2.0 ml of *water*. Discard the upper layer and combine the aqueous layers. Add 1.0 ml of the internal standard solution. Centrifuge and discard any remaining *m-xylene*.

Reference solution (d). Dilute 10.0 ml of reference solution (a) and 10.0 ml of reference solution (b) to 50.0 ml with *water*. Transfer 2.0 ml of the solution to a centrifuge tube, add 2 ml of *m-xylene*, mix thoroughly and centrifuge. Remove the upper layer and extract it with 2.0 ml of *water*. Discard the upper layer and combine the aqueous layers. Add 1.0 ml of the internal standard solution. Centrifuge and discard any remaining *m-xylene*.

Chromatographic system
- a glass column 30 m × 0.53 mm, packed with fused silica with macrogol 20,000 with film thickness 1 mm,
- temperature
  column 80° increase @ 60° per minute to 240°,
  injection port 220° and detector 280°,
- flow rate: 7.5 ml per minute of nitrogen or helium as carrier gas.

Inject 1 µl of the test solution and reference solutions (c) and (d).

Calculate the content of *ethanol* is not more than 5.0 per cent and *formamide* not more than 3.0 per cent.

Heavy metals (2.3.13). 1 g complies with the limit test for heavy metals, Method C (20 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Water (2.3.43). Not more than 1.0 per cent, determined on 0.5 gm.

Assay. Determine by liquid chromatography (2.4.14), as described under Related substances.

Inject reference solution (a) and the test solution.

Calculate the percentage contents of ivermectin ($H_2B_{1a} + H_2B_{1b}$) and the ratio $H_2B_{1a}/(H_2B_{1a} + H_2B_{1b})$.

Storage. Store protected from moisture.

Ivermectin Injection

Ivermectin Injection is a sterile solution of Ivermectin with or with out one or more anaesthetics, preservatives and solvents.

Ivermectin Injection contains not less than 90 per cent and not more than 110 per cent of H_2B_1a, and not more than 5 per cent of H_2B_1b.

The content of $H_2B_{1a} + H_2B_{1b}$ is not less than 95 per cent and not more than 110 per cent of the stated amount of Ivermectin.

Description. A clear, colourless to yellow colour solution.

Identification

When examined in the range 220 nm to 360 nm (2.4.7), a 0.001 per cent w/v solution in *methanol* shows an absorption maximum at about 245 nm.

Tests

Bacterial endotoxins (2.2.3). Not more than 0.016 Endotoxin Unit per µg of ivermectin.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. Determine by liquid chromatography (2.4.14).

Test solution: Dilute a volume of the injection containing 5mg of Ivermectin to 100 ml with *methanol*.

Reference solution. A 0.005 per cent w/v solution of *ivermectin IPRS* in *methanol*.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 9 volumes of *methanol* and 1 volume of *water*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 245 nm,
- injection volume: 20 µl.

Inject the reference solution. The test is not valid unless the tailing factor is not less than 2.0

Inject the reference solution and the test solution.

Calculate the content of ivermectin in the injection.

Storage. Store protected from light.

Labelling. The label states (1) the strength in mg of Ivermectin per ml; (2) that the contents are to be used for subcutaneous use only; (3) the names of any preservatives used.

Ivermectin Oral Paste

Ivermectin Oral Paste contains Ivermectin in a suitable basis.

Ivermectin Oral Paste contains not less than 95.0 per cent and not more than 110.0 per cent of the sum of H_2B_{1a} ($C_{48}H_{74}O_{14}$) and H_2B_{1b} ($C_{47}H_{72}O_{14}$).

The ratio of the contents H_2B_{1a} / (H_2B_{1a} + H_2B_{1b}) is not less than 90.0 per cent of the stated amount of ivermectin.

Usual strengths. 120 mg per 6.42 g; 18.7 mg per g (for horse).

Identification

A. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel 60 GF254*.

Mobile phase. A mixture of 1 volume of *strong ammonia*, 9 volumes of *methanol* and 90 volumes of *dichloromethane*.

Test solution. Dilute the substance under examination containing 5 mg of Ivermectin in 10 ml of *methanol* and mix with the aid of ultrasound.

Reference solution. A 0.05 per cent w/v solution of *ivermectin IPRS* in *methanol*.

Apply to the plate 2 µl of each solution. After development, dry the plate in air and examine under ultraviolet light 254 nm and 366 nm. The principal spot in the chromatogram obtained with test solution corresponds to that in the chromatogram obtained with reference solution.

B. In the Assay, the principal peak in the chromatogram obtained with test solution corresponds to the peak in the chromatogram obtained with reference solution.

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve a quantity of the oral paste in *methanol* to produce a solution containing 0.04 per cent w/v of Ivermectin with the aid of ultrasound.

Reference solution (a). A 0.04 per cent w/v solution of *ivermectin IPRS* in *methanol*.

Reference solution (b). A 0.0004 per cent w/v solution of *ivermectin IPRS* in *methanol*.

Reference solution (c). A 0.00002 per cent w/v solution of *ivermectin IPRS* in *methanol*.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 39 volumes of *water*, 55 volumes of *methanol* and 106 volumes of *acetonitrile*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 245 nm,
- injection volume: 20 µl.

Inject reference solution (a). The test is not valid unless the resolution between the first peak (component H_2B_{1b}) and the second peak (component H_2B_{1a}) is not less than 3.0.

Inject reference solution (b), reference solution (c) and the test solution. The area of the peak obtained with test solution

the retention time of 1.3 to 1.5 relative to that of the principal peak is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent). The area of any other secondary peak is not more than the area of principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent). The sum of the areas of the secondary peaks is not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (6.0 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Other tests. Comply the tests stated under the Oral Paste.

Assay. Determine by liquid chromatography (2.4.14) as described under Related substances with following modification.

Test solution. Dissolve a quantity of oral paste in *methanol* with the aid of ultrasound and prepare 0.04 per cent w/v solution of ivermectin.

Reference solution. Prepare 0.04 per cent w/v solution of *ivermectin IPRS* in *methanol.*

Inject the reference solution and the test solution .

Calculate the content of ivermectin ($H_2B_{1a} + H_2B_{1b}$) in the oral paste and the ratio $H_2B_{1a} / (H_2B_{1a} + H_2B_{1b})$.

Ivermectin Pour-on

Ivermectin Pour-on is a pour-on solution. It contains Ivermectin in a suitable non-aqueous vehicle.

Ivermectin Pour-on contains not less than 95.0 per cent and not more than 105.0 per cent of the sum of H_2B_{1a} ($C_{48}H_{74}O_{14}$) and H_2B_{1b} ($C_{47}H_{72}O_{14}$).

The ratio of the contents $H_2B_{1a} / (H_2B_{1a} + H_2B_{1b})$ is not less than 90.0 per cent of the stated amount of Ivermectin.

Usual strengths. 500 mg per 100 ml (for cattle).

Identification

A. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel 60 GF254.*

Mobile phase. A mixture of 1 volume of *strong ammonia,* 9 volumes of *methanol* and 90 volumes of *dichloromethane.*

Test solution. Dissolve a quantity of the substance under examination containing 5 mg of Ivermectin in 10 ml of *methanol.*

Reference solution. A 0.05 per cent w/v solution of *ivermectin IPRS* in *methanol.*

Apply to the plate 2 µl of each solution. After development, dry the plate in air and examine under ultraviolet light 254 nm and 366 nm. The principal spot in the chromatogram obtained with test solution corresponds that in the chromatogram obtained with reference solution.

B. In the Assay, the principal peak in the chromatogram obtained with test solution corresponds to the peak in the chromatogram obtained with reference solution.

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve a quantity of the pour-on in *methanol* to produce a solution containing 0.04 per cent w/v of Ivermectin.

Reference solution (a). A 0.04 per cent w/v solution of *ivermectin IPRS* in *methanol.*

Reference solution (b). A 0.0004 per cent w/v solution of *ivermectin IPRS* in *methanol.*

Reference solution (c). A 0.00002 per cent w/v solution of *ivermectin IPRS* in *methanol.*

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 39 volumes of *water,* 55 volumes of *methanol* and 106 volumes of *acetonitrile,*
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 245 nm,
- injection volume: 20 µl.

Inject reference solution (a). The test is not valid unless the resolution between the first peak (component H_2B_{1b}) and the second peak (component H_2B_{1a}) is not less than 3.0.

Inject reference solution (b), reference solution (c) and the test solution. The area of the peak obtained with test solution he retention time of 1.3 to 1.5 relative to that of the principal peak is not more than 2.7 times the area of the principal peak in the chromatogram obtained with reference solution (b) (2.7 per cent). The area of any other secondary peak is not more than the area of principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent). The sum of the areas of the secondary peak is not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (6.0 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Assay. Determine by liquid chromatography (2.4.14) as described under Related substances with following modification.

Test solution. Dissolve a quantity of oral pour-on in *methanol* with the aid of ultrasound and prepare 0.04 per cent w/v solution of ivermectin.

Reference solution. Prepare 0.04 per cent w/v solution of *ivermectin IPRS* in *methanol*.

Inject the reference solution and the test solution .

Calculate the content of ivermectin ($H_2B_{1a} + H_2B_{1b}$) in the pour-on and the ratio $H_2B_{1a} / (H_2B_{1a} + H_2B_{1b})$.

Light Kaolin

For Description, Identification and Tests refer to IP Volume II.

Kaolin Veterinary Oral Suspension

Kaolin Veterinary Mixture; Kaolin Mixture

Light Kaolin	200 g
Light Magnesium Carbonate	50 g
Sodium Bicarbonate	50 g
Water to produce	1000 ml

Kaolin Veterinary Oral Suspension should be freshly prepared, unless the Light Kaolin has been sterilised.

Kaolin Veterinary Oral Suspension contains not less than 1.04 per cent w/w and not more than 1.25 per cent w/w of the stated amount of magnesium, Mg and not less than 4.05 per cent w/w and not more than 4.65 per cent w/w of the stated amount of sodium bicarbonate, $NaHCO_3$.

Tests

Acid-insoluble matter. 13.8 to 18.4 per cent w/w, determined by the following method. Weigh 3 g, add 15 ml of *water* and make acid to *litmus paper* by the cautious addition of *2 M hydrochloric acid*; boil for 5 minutes, replacing water lost by evaporation, cool and decant the supernatant layer through a filter. Boil the residue with 20 ml of *water* and 10 ml of *2 M hydrochloric acid*, cool, filter through the same filter, and wash the residue with *water* until the washings are free from chloride, reserving the filtrate and washings for the Assay *for magnesium*. Dry and ignite the residue to constant weight at red heat.

Other tests. Comply with the tests stated under Veterinary Oral Liquids.

Assay. *For magnesium* — Dilute the combined filtrate and washings reserved in the determination of acid-insoluble matter to 100.0 ml with *water*. To 20.0 ml add 0.1 g of *ascorbic acid*, make slightly alkaline to *litmus paper* with *5 M ammonia* and add 10 ml of *triethanolamine*, 10 ml of *ammonia buffer pH 10.9* and 1 ml of *potassium cyanide solution*. Titrate with *0.05 M disodium edetate* using *eriochrome black T solution* as indicator.

1 ml of *0.05 M disodium edetate* is equivalent to 0.001215 g of Mg.

For sodium bicarbonate — Weigh 10 g, boil with 100 ml of *water* for 5 minutes and filter. Boil the residue with 100 ml of *water* for 5 minutes and filter. Cool the combined filtrates and titrate with *0.5 M hydrochloric acid* using *methyl orange-xylene cyanol FF solution* as indicator. Add 10 ml of *ammonia buffer pH 10.9* and titrate with *0.05 M disodium edetate* using *eriochrome black T solution* as indicator.

1 ml of *0.5 M hydrochloric acid* after subtracting one fifth of the volume of *0.05 M disodium edetate* is equivalent to 0.0420 g of $NaHCO_3$.

Levamisole Hydrochloride

For Description, Identification and Tests refer to IP Volume II.

Levamisole Injection

Levamisole Hydrochloride Injection

Leavamisole Injection is a sterile solution of Levamisole Hydrochloride in Water for Injections.

Levamisole Injection contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of levamisole hydrochloride, $C_{11}H_{12}N_2S,HCl$.

Usual strength. 75 mg in 1 ml.

Identification

A. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*.

Mobile phase. A mixture of 100 volumes of *ethyl acetate*, 10 volumes of *methanol* and 1 volume of *strong ammonia solution*.

Test solution. Dilute a volume of the injection to produce a solution containing 1.0 per cent w/v of Levamisole Hydrochloride in *methanol*.

Reference solution. A 1.0 per cent w/v of *levamisole hydrochloride IPRS* in *methanol*.

Apply to the plate 1 µl of each solution. After development, dry the plate in air and spray with *potassium iodoplatinate solution*. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with the reference solution.

B. Dilute a volume of the injection containing 0.75 g of Levamisole Hydrochloride to 20 ml with *water* and add 6 ml of *1 M sodium hydroxide*. Extract with 20 ml of *dichloromethane*, discard the aqueous layer and wash the dichloromethane layer with 10 ml of *water*. Dry by shaking with *anhydrous sodium sulphate*, filter and evaporate the solvent at room temperature. The residue, after drying over *phosphorus pentoxide* at a pressure of 1.5 to 2.5 kPa at a temperature not exceeding 40°, melts at about 59° (2.4.21).

C. The injection is laevorotatory.

D. It gives reaction (B) of chlorides (2.3.1).

Tests

pH (2.4.24). 3.0 to 4.0.

2,3-Dihydro-6-phenylimidazo[2,1-*b*]thiazole hydrochloride. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*.

Mobile phase. A mixture of 45 volumes of *toluene*, 8 volumes of *methanol* and 4 volumes of *anhydrous glacial acetic acid*.

Test solution. Dilute a volume of the injection with *methanol* to produce a solution containing 5.0 per cent w/v of Levamisole Hydrochloride.

Reference solution. A 0.025 per cent w/v of *2,3-dihydro-6-phenylimidazo[2,1-b]thiazole hydrochloride IPRS* in *methanol*.

Apply to the plate 10 µl of each solution. After development, dry the plate in air and spray with *potassium iodoplatinate solution*. Any spot corresponding to 2,3-dihydro-6-phenylimidazo[2,1-b]thiazole hydrochloride in the chromatogram obtained with test solution is not more intense than the spot in the chromatogram obtained with reference solution.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a volume of the injection containing 150 mg of Levamisole Hydrochloride in *water* to obtain a solution of 0.0075 per cent w/v of Levamisole Hydrochloride.

Reference solution. A 0.0075 per cent w/v solution of *levamisole hydrochloride IPRS* in *water*.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 70 volumes of a buffer solution prepared by dissolving 5.0 g of *ammonium dihydrogen phosphate* in 1000 ml of *water* and 30 volumes of *acetonitrile*, adjusted to pH 6.5 with *1 M sodium hydroxide*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 215 nm,
- injection volume: 20 µl.

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{11}H_{12}N_2S,HCl$ in the injection.

Storage. Store protected from light.

Levamisole Hydrochloride Veterinary Oral Solution

Levamisole Hydrochloride Veterinary Mixture; Levamisole Veterinary Oral Solution; Levamisole Veterinary Mixture

Levamisole Hydrochloride Veterinary Oral Solution is an aqueous solution of Levamisole Hydrochloride containing suitable stabilising agents.

Levamisole Hydrochloride Veterinary Oral Solution contains not less than 92.5 per cent and not more than 107.5 per cent of the stated amount of levamisole hydrochloride, $C_{11}H_{12}N_2S,HCl$.

Usual strength. 0.25 per cent w/w; 1.5 per cent w/w.

Identification

A. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*.

Mobile phase. A mixture of 100 volumes of *ethyl acetate*, 10 volumes of *methanol* and 1 volume of *strong ammonia solution*.

Test solution. Dilute a volume of the preparation under examination with *methanol* to produce a solution containing 1.0 per cent w/v of Levamisole Hydrochloride.

Reference solution. A 1.0 per cent w/v of *levamisole hydrochloride IPRS* in *methanol*.

Apply to the plate 1 µl of each solution. After development, dry the plate in air and spray with *potassium iodoplatinate solution*. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with the reference solution.

B. To a quantity containing 0.3 g of Levamisole Hydrochloride add 10 ml of *water* and 6 ml of *1 M sodium hydroxide*. Extract with 20 ml of *dichloromethane*, discard the aqueous layer and wash the *dichloromethane* layer with 10 ml of *water*. Dry by shaking with *anhydrous sodium sulphate*, filter and allow the *dichloromethane* to evaporate at room temperature. The

residue, after drying over *phosphorus pentoxide* at a pressure of 1.5 to 2.5 kPa at a temperature not exceeding 40°, melts at about 59° (2.4.21).

C. The solution is laevorotatory.

Tests

2,3-Dihydro-6-phenylimidazo[2,1-*b*]thiazole hydrochloride. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*.

Mobile phase. A mixture of 45 volumes of *toluene*, 8 volumes of *methanol* and 4 volumes of *anhydrous glacial acetic acid*.

Test solution. Dilute a volume of the preparation under examination with *methanol* to produce a solution containing 1.0 per cent w/v of Levamisole Hydrochloride.

Reference solution. A 0.025 per cent w/v of *2,3-dihydro-6-phenylimidazo[2,1-b]thiazole hydrochloride IPRS* in *methanol*.

Apply to the plate 50 µl of the test solution and 10 µl of the reference solution. After development, dry the plate in air and spray with *potassium iodoplatinate solution*. Any spot corresponding to *2,3-dihydro-6-phenylimidazo[2,1-b]thiazole hydrochloride* in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with the reference solution.

Other tests. Comply with the tests stated under Veterinary Oral Liquids.

Assay. Weigh a quantity containing 0.75 g of Levamisole Hydrochloride add 15 ml of *2 M sodium hydroxide*, extract with three quantities each of 25 ml, 20 ml and 15 ml of *dichloromethane*, wash the combined extracts with two quantities, each of 10 ml, of *water* and discard the washings. To the clear *dichloromethane solution*, after drying with *anhydrous sodium sulphate*, add 50 ml of *anhydrous glacial acetic acid*. Titrate with *0.1 M perchloric acid*, using *1-naphtholbenzein solution* as indicator. Carry out a blank titration.

1 ml of *0.1 M perchloric acid* is equivalent to 0.02408 g of $C_{11}H_{12}N_2S,HCl$.

Levofloxacin Hemihydrate

For Description, Identification and Tests refer to IP Volume II.

Lignocaine Hydrochloride

For Description, Identification and Tests refer to IP Volume II.

Lignocaine Injection

Usual strengths. 200 mg in 10 ml; 2 g in 100 ml.

For Identification and Tests refer to IP Volume II.

Lincomycin Hydrochloride

For Description, Identification and Tests refer to IP Volume II.

Lincomycin Premix

Lincomycin Hydrochloride Premix.

Lincomycin Premix contains Lincomycin Hydrochloride.

Lincomycin Premix contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of lincomycin, $C_{18}H_{34}N_2O_6S$.

Usual strength. 4.4 per cent w/w.

Identification

In the Assay, the chromatogram obtained with the test solution corresponds to the chromatogram obtained with the reference solution.

Tests

Lincomycin B. Examine test solution as described under Assay but increasing the sensitivity by 8 to 10 times while recording the peak due to the trimethylsilyl derivative of lincomycin B, which is eluted immediately before the trimethylsilyl derivative of lincomycin. The area of the peak due to the trimethylsilyl derivative of lincomycin B, after correction for the sensitivity factor, is not more than 5 per cent of the area of the peak due to the trimethylsilyl derivative of lincomycin.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve a quantity of premix containing about 12 mg of Lincomycin Hydrochloride in 10 ml of the mobile phase.

Reference solution. A 0.12 per cent w/v solution of *lincomycin hydrochloride IPRS* in the mobile phase.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octylsilane bonded to porous silica (5 µm),
- column temperature. 45°,
- mobile phase: a mixture of 78 volumes a solution prepared by diluting 13.5 ml of *orthophosphoric acid* to 1000 ml of *water*, adjusted to pH 6.0 with *ammonium*

hydroxide, 15 volumes of *acetonitrile* and 15 volumes of *methanol*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 20 µl.

The relative rentention time with reference to lincomycin for lincomycin B is about 0.5.

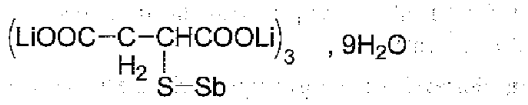
Inject the reference solution. The test is not valid unless the tailing factor is not more than 1.3; the column efficiency is not less than 4000 theoretical plates and relative standard devation for replicate injections is not more than 2.0.

Inject the reference solution and the test solution.

Calculate the content of $C_{18}H_{34}N_2O_6S$ in premix.

Labelling. The label states the strength in terms of the equivalent amount of lincomycin.

Lithium Antimony Thiomalate



$C_{12}H_9Li_6O_{12}S_3Sb,9H_2O$ Mol. Wt. 766.9

Lithium Antimony Thiomalate contains not less than 15.5 per cent and not more than 16.5 per cent of Sb and not less than 5.1 per cent and not more than 5.7 per cent of Li, calculated on the dried, solvent-free basis.

Category. Anthelmintic against trematodes.

Description. A pinkish white or creamy powder; hygroscopic.

Identification

A. To 0.2 g dissolved in 5 ml of *water* add 2 ml of *hydrochloric acid* and 5 ml of *sodium sulphide solution*; a yellowish- orange precipitate is produced which does not dissolve on addition of *dilute ammonia solution*.

B. When moistened with *hydrochloric acid* and introduced on a platinum wire it imparts a red colour to a non-luminous flame.

Tests

Appearance of solution. A 6 per cent w/v solution in *carbon dioxide-free water* is clear (2.4.1), and not more intensely coloured than reference solution RS3 (2.4.1).

pH (2.4.24). 9.0 to 10.5, determined in a 6 per cent w/v solution in *carbon dioxide-free water*.

Assay. *For antimony* — Weigh 0.5 g, add 35 ml of *water* and swirl to dissolve. Add 5 g of *ammonium persulphate*, 10 ml of *sodium hydroxide solution* and 3 or 4 glass beads (approximately 0.5 cm diameter). Place a small funnel in the neck of the flask and boil gently for 20 minutes at such a rate that the volume is not reduced appreciably. Cool, add through the funnel 0.25 ml of *phenolphthalein solution* and sufficient *0.1 M hydrochloric acid* until the last trace of pink colour disappears. Add 25 ml of a 10 per cent w/v solution of *oxalic acid* through the funnel and boil vigorously for 3 minutes. Rinse the funnel, with a small quantity of *water*, remove it and add 5 ml of *hydrochloric acid* and 2 g of *potassium iodide*. Allow to stand for 10 minutes and boil until the solution becomes yellow and shows no further decrease in colour, but taking care to see that the volume is not reduced to less than about 30 ml. Cool and remove a small drop of the solution with a sealed capillary melting point tube and add to *starch iodide paper*. If a bluish colour is produced, add 1 drop of *0.1 M sodium thiosulphate* while swirling and again test with *starch iodide paper*. Repeat if necessary until a bluish colour is no longer produced.

Add 5 g of *sodium potassium tartrate*, cool to about 15° to 20° and cautiously add small portions of *sodium bicarbonate* until no further effervescence is produced. Add 2 to 4 g more of *sodium bicarbonate* and titrate with *0.1 M iodine* until the first permanent light yellow colour is produced.

1 ml of *0.1 M iodine* is equivalent to 0.006088 g of Sb.

For lithium — Weigh 0.2 g, dissolve in 50 ml of *glacial acetic acid*. Titrate with *0.1 M perchloric acid*, using 1 ml of *crystal violet solution* as indicator. Carry out a blank titration.

1 ml of *0.1 M perchloric acid* is equivalent to 0.000694 g of Li.

Storage. Store protected from light and moisture.

Lithium Antimony Thiomalate Injection

Lithium Antimony Thiomalate Injection is a sterile solution of Lithium Antimony Thiomalate in Water for Injections containing a suitable antimicrobial preservative.

Lithium Antimony Thiomalate Injection contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of lithium antimony thiomalate, $C_{12}H_9Li_6O_{12}S_3Sb,9H_2O$.

Usual strength. 6 per cent w/v.

Identification

A. Dilute a volume containing 0.2 g of Lithium Antimony Thiomalate to 5 ml with *water*. Add 2 ml of *hydrochloric acid* and 5 ml of *sodium sulphide solution*; a yellowish orange precipitate is produced which does not dissolve on addition of *dilute ammonia solution*.

B. Dilute 0.2 ml of the injection under examination to 10 ml with a 5 per cent w/v solution of *sodium potassium tartrate*.

To 2 ml of the solution add few drops of *hydrochloric acid* and add *sodium sulphide solution* dropwise; a reddish orange precipitate is produced. The precipitate dissolves on adding *dilute sodium hydroxide solution*.

Tests

Appearance of solution. The solution is clear (2.4.1), and not more intensely coloured than reference solution RS3 (2.4.1).

pH (2.4.24). 9.0 to 10.5.

Pyrogens. Complies with the test for pyrogens (2.2.8), using per 1.5 kg of the rabbit's weight, a volume containing 0.012 g of Lithium Antimony Thiomalate.

Sterility (2.2.11). Complies with the test for sterility.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. Dilute 10.0 ml with 25 ml of *water*, add 7.5 g of *ammonium persulphate* and 16 ml of *sodium hydroxide solution*, boil gently for 20 minutes, cool and add 0.5 ml of *phenolphthalein solution*. Neutralise the solution with *dilute hydrochloric acid* and boil for 3 minutes. Add 50 ml of a 10 per cent w/v solution of *oxalic acid*, 7.5 ml of *hydrochloric acid* and sufficient *water* to make up the volume, if necessary. Add 2 g of *potassium iodide* to the hot solution, allow to stand for 10 minutes and boil until it acquires a pale yellow colour (about 10 minutes). Cool and remove the colour by adding *0.1 M sodium thiosulphate* using *starch iodide solution* as an external indicator. Add 7.5 g of *sodium potassium tartrate* and dilute to 200 ml. Add *sodium bicarbonate* carefully (avoiding loss by spurting due to effervescence) till alkaline to *litmus paper* and titrate with *0.05 M iodine* using 1 ml of *starch solution*, added towards the end of the titration, as indicator.

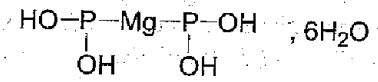
1 ml of *0.05 M iodine* is equivalent to 0.03834 g of $C_{12}H_9Li_6O_{12}S_3Sb,9H_2O$.

Storage. Store protected from light.

Light Magnesium Carbonate

For Description, Identification and Tests refer to IP Volume III.

Magnesium Hypophosphite



$Mg(H_2PO_2)_2,6H_2O$ Mol. Wt. 262.4

Magnesium Hypophosphite contains not less than 98.5 per cent and not more than 101.0 per cent of $Mg(H_2PO_2)_2,6H_2O$.

Category. Supplement in deficiency conditions; nerve tonic.

Description. Colourless crystals or white crystalline powder.

Identification

A. It gives the reactions of magnesium salts (2.3.1).

B. Dissolve about 50 mg in 5 ml of *water* and add 0.5 ml of *mercuric chloride solution*; a white precipitate is produced.

C. Dissolve about 50 mg in 5 ml of *water* and acidify with *sulphuric acid*. Add 0.5 ml of *cupric sulphate solution* and warm; a red precipitate is produced.

Tests

Appearance of solution. A 5 per cent w/v solution is clear (2.4.1) and colourless (2.4.1).

Heavy metals (2.3.13). Dissolve 1.0 g in 20 ml of *water*, add 2 ml of *dilute hydrochloric acid* and sufficient *water* to produce 25 ml. The resulting solution complies with the limit test for heavy metals, Method A (20 ppm).

Chlorides (2.3.12). To 5 g add 200 ml of *water* and filter. 10 ml of the filtrate complies with the limit test for chlorides (0.1 per cent).

Sulphates (2.3.17). 1 g complies with the limit test for sulphates (0.015 per cent).

Assay. Weigh 0.2 g, dissolve in 50 ml of *water*, add 5 ml of *strong ammonia-ammonium chloride solution* and titrate with *0.05 M disodium edetate* using 0.1 g of *mordant black II mixture* as indicator, until a blue colour is obtained.

1 ml of *0.05 M disodium edetate* is equivalent to 0.01312 g of $Mg(H_2PO_2)_2,6H_2O$.

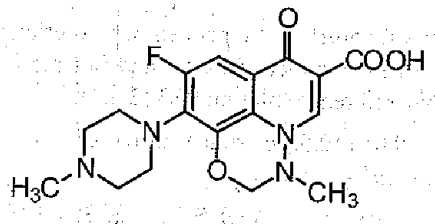
Storage. Store protected from moisture.

Magnesium Sulphate

Category. Laxative; hypomagnesaemia prophylactic.

For Description, Identification and Tests refer to IP Volume III.

Marbofloxacin



$C_{17}H_{19}FN_4O_4$ Mol. Wt. 362.4

Marbofloxacin is 9-Fluoro-2,3-dihydro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-7*H*-pyrido[3,2,1-ij][4,1,2]benzoxadiazine-6-carboxylic acid.

Marbofloxacin contains not less than 99.0 per cent and not more than 101.0 per cent of $C_{17}H_{19}FN_4O_4$ calculated on the dried basis.

Category. Fluroquinolone antibacterial.

Description. A light yellow, crystalline powder.

Identification

Determine by infrared absorption spectrophotometery (2.4.6). Compare the spectrum with that obtained with *marbofloxacin IPRS* or with the reference spectrum of marbofloxacin.

Tests

Light absorption (2.4.7). Absorbance of 4.0 per cent w/v solution in *borate buffer solution* pH 10.4, at about 450 nm is not more than 0.20.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE—Carry out the test protected from light.

Solvent mixture. 23 volumes of *methanol* and 77 volumes of *water*.

Test solution. Dissolve 0.1 g of the substance under examination in 80 ml of the solvent mixture, dissolve with the aid of ultrasound and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). Dilute 5.0 ml of the test solution to 100.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 50.0 ml with the solvent mixture.

Reference solution (b). Dissolve 10 mg of *marbofloxacin IPRS* (containing impurities A, B, C, D and E) in solvent mixture and dilute to 10.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with endcapped polar-embeded octadecylsilane amorphous organosilica polymer (3.5µm),
- mobile phase: a mixture of 230 volumes of *methanol* and 5 volumes of *glacial acetic acid* with 770 volumes of a 0.27 per cent w/v solution of *sodium dihydrogen phosphate* containing 0.35 per cent w/v solution of *sodium octanesulphonate* and previously adjusted to pH 2.5 with *phosphoric acid*.
- column temperature: 40°,
- flow rate: 1.2 ml per minute,
- spectrophotometer set at 315 nm,
- injection volume: 10 µl.

Name	Relative retention time	Correction factor
Marbofloxacin impurity B[1]	0.5	—
Marbofloxacin impurity A[2]	0.7	—
Marbofloxacin impurity C[3]	0.9	—
Marbofloxacin (Retention time: about 33 minutes)	1.0	—
Marbofloxacin impurity D[4]	1.3	—
Marbofloxacin impurity E[5]	1.5	1.5

[1]9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[3,2,1-*ij*][4,1,2]benzoxadiazine-6-carboxylic acid,

[2]6,7-difluoro-8-hydroxy-1-(methylamino)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,

[3]6,8-difluoro-1-(methylamino)-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,

[4]6-fluoro-8-hydroxy-1-(methylamino)-7-(4-methylpiperazin-1-yl)-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid,

[5]8-ethoxy-6-fluoro-1-(methylamino)-7-(4-methylpiperazin-1-yl)-4-oxo- 1, 4-dihydroquinoline-3-carboxylic acid.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to impurity C and marbofloxacin is not less than 1.5 and between the peaks due to impurity D and marbofloxacin is not less than 4.0. Run the chromatogram 2.5 times the retention time of the marbofloxacin. Identify the impurities in the chromatogram obtained with *marbofloxacin IPRS* and identify the peaks due to impurities A, B, C, D and E in the chromatogram obtained with reference solution (b).

Inject reference solution (a) and the test solution. The area of the peak for each impurity C, D, and E, each of, is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of the peak for each impurity A and B, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the area of any other secondary peak for each impurity is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent). The sum of the areas of the entire peak is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Ignore any peak the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent, determined on 1.0 g.

Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105° for 4 hours.

Assay. Dissolve 0.3 g in 80 ml of *glacial acetic acid.* Titrate with *0.1 M perchloric acid,* determining the end point potentiometrically (2.4.25). Carry out a blank titration.

1 ml of *0.1M perchloric acid* is equivalent to 0.03624 g of $C_{17}H_{19}FN_4O_4$.

Storage. Store protected from light.

Marbofloxacin Injection

Marbofloxacin Injection is a sterile solution of Marbofloxacin in water for injections.

Marbofloxacin Injection contains not less than 90.0 per cent and not more than 110.00 per cent of the stated amount of marbofloxacin, $C_{17}H_{19}FN_4O_4$.

Usual strength. 100 mg per ml.

Description. A clear colourless solution.

Identification

In the Assay, the retention time of the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

pH (2.4.24). 3.0 to 5.0.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Bacterial endotoxins (2.2.3). Not more than 0.625 Endotoxin Unit per mg of marbofloxacin.

Sterility (2.2.11). Complies with the test for sterility.

Assay. Determine by liquid chromatography (2.4.14).

NOTE — Carry out the test protected from light.

Solvent mixture. 23 volumes of *methanol* and 77 volumes of *water.*

Test solution. To a volume of the injection containing 100 mg marbofloxacin in 100 ml volumetric flask, add 50 ml solvent mixture and sonicate for about 15 minutes. Dilute to 100 ml with solvent mixture and filter.

Reference solution. Dissolve 10 mg of *marbofloxacin IPRS* in solvent mixture and dilute 10.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with endcapped polar-embeded octadecylsilane amorphous organosilica polymer (3.5 µm),
- mobile phase: a mixture of 230 volumes of *methanol;* 5 volumes of *glacial acetic acid* with 770 volumes of a 0.27 per cent w/v solution of *sodium dihydrogen phosphate* containing 0.35 per cent w/v solution of *sodium octanesulphonate* and previously adjusted to pH 2.5 with *phosphoric acid,*
- column temperature: 40°,
- flow rate: 1.2 ml per minute,
- spectrophotometer set at 315 nm,
- injection volume: 10 µl.

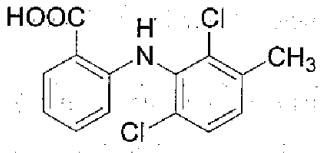
Inject the reference solution. The test is not valid unless the column efficiency is not less than 1500 theoretical plate, the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{17}H_{19}FN_4O_4$ in injection.

Storage: Store in a cool and dry place, protected from light.

Meclofenamic Acid



$C_{14}H_{11}Cl_2NO_2$ Mol. Wt. 296.2

Meclofenamic acid is *N*-(2,6-dichloro-3-methylphenyl) anthranilic acid.

Meclofenamic Acid contains not less than 98.5 per cent and not more than 100.5 per cent of the stated amount of $C_{14}H_{11}Cl_2NO_2$, calculated on the dried basis.

Category. Anti-inflammatory; analgesic; antipyretic.

Description. A white or almost white, crystalline powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *meclofenamic acid IPRS* or with the reference spectrum of meclofenamic acid.

B. When examined in the range 220 nm to 360 nm (2.4.7), a 0.002 per cent w/v solution in *0.1 M sodium hydroxide* shows absorption maxima at about 279 nm, and 371 nm; absorbance at about 279 nm, about 0.45, and at about 317 nm, about 0.33.

C. Dissolve 25 mg in 15 ml of *dichloromethane*; the solution exhibits a strong blue fluorescene when examined under ultraviolet light.

D. Dissolve 1 mg in 2 ml of *sulphuric acid* and add 0.05 ml of *0.02 M potassium dichromate*; an intense purple colour is produced, which rapidly fades to purple brown.

Tests

Appearance of solution. A 5.0 per cent w/v solution in *1 M sodium hydroxide* is not more opalescent than reference suspension OS2 and is not more intensely coloured than reference solution BYS5 (2.4.1).

Light absorption (2.4.7). Absorbance of a 0.002 per cent w/v solution in *0.01 M methanolic hydrochloric acid* at the maximum at about 279 nm, not less than 0.400 and not more than 0.445, and at the maximum at about 335 nm, not less than 0.440 and not more than 0.490.

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 1.0 g of the substance under examination in 100 ml of *ethanol*.

Reference solution (a). A 0.0035 per cent w/v solution of *ethyl meclofenamate IPRS* (internal standard) in *ethanol*.

Reference solution (b). A solution containing 1.0 per cent w/v of the substance under examination and 0.0035 per cent w/v of *ethyl meclofenamate IPRS* (internal standard) in *ethanol*.

Chromatographic system
- a stainless steel column 20 cm × 4 mm, packed with octadecasilane bonded to porous silica (10 µm),
- mobile phase: a mixture of 75 volumes of *methanol*, 25 volumes of *water* and 1 volume of *glacial acetic acid*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

Inject reference solution (a). The test is not valid unless the column efficiency is not less than 900 theoretical plates.

Inject reference solution (b). The area of the peak immediately preceding the peak due to meclofenamic acid is not more than one-seventh of the area of the peak due to the internal standard. The area of any other peak is not more than the area of the peak due to the internal standard.

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105°.

Assay. Weigh 0.6 g, dissolve in 100 ml of warm *ethanol* previously neutralised to *phenol red solution* and titrate with *0.1 M sodium hydroxide*, using *phenol red solution* as indicator.

1 ml of *0.1 M sodium hydroxide* is equivalent to 0.02962 g of $C_{14}H_{11}Cl_2NO_2$.

Storage. Store protected from moisture.

Meloxicam Injection

Meloxicam Injection is a sterile solution of Meloxicam in Water for Injections.

Meloxicam Injection contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of meloxicam, $C_{14}H_{13}N_3O_4S_2$.

Usual strengths. 5 mg per ml, 20 mg per ml.

Identification

A. Determined by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 80 volumes of *dichloromethane*, 20 volumes of *methanol* and 1 volume of *13.5 M ammonia*.

Test solution. Dilute a volume of the injection containing 10 mg of *meloxicam* with 20.0 ml *acetone*, stir for 15 minutes and filter.

Reference solution. Dissolve 10 mg of *meloxicam IPRS* in 10 ml *acetone*, add 2 ml of *water* and dilute to 20.0 ml with *acetone*.

Apply to the plate 20 µl of each solution. Allow the mobile phase to rise 8 cm, dry the plate in air and examine under ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution corresponds to the spot in the chromatogram with reference solution.

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Tests

pH (2.4.24). 8.0 to 9.0.

Related substance. Determine by liquid chromatography (2.4.14).

Test solution (a). Add 0.3 ml of *0.4 M sodium hydroxide* to a volume of the injection containing 40 mg meloxicam and dilute to 10 ml with *methanol (40 per cent)*.

Test solution (b). Dilute 2 ml of test solution (a) to 100 ml with *methanol (40 per cent)*, dilute 1.0 ml of the solution to 10 ml with *methanol (40 per cent)*.

Reference solution. Add 0.3 ml of *0.4 M sodium hydroxide* to 40 mg *meloxicam impurity IPRS* and dilute with *methanol* (40 per cent) to produce 10 ml.

Chromatographic system
- a stainless steel column 10 cm x 4.0 mm packed with octadecylsilane bonded to porous silica (10 µm),
- mobile phase: A. a 0.1 per cent w/v solution of *potassium dihydrogen orthophosphate*, adjusted to pH 6.0 with *2M sodium hydroxide*;

B. *methanol*,

- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 260 nm and 350 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	60	40
2.5	60	40
12	30	70
25	30	70
26	60	40
30	60	40

Inject the reference solution and the test solution (a). The test is not valid unless the chromatogram obtained with reference solution closely resembles the chromatogram supplied with *meloxicam impurity IPRS* at 260 nm and 350 nm. The resolution between the peaks due to meloxicam and impurity A at 350 nm is not less than 3.0 and the resolution between the peaks due to impurity B and meloxicam at 260 nm is not less than 3.0.

Inject the reference solution and the test solution (b). Multiply the area of any peak corresponding to impurity A at 350 nm by a correction factor of 2.0. The area of any peak corresponding to impurity A at 350 nm is not more than the area of the principal peak in the chromatogram obtained with test solution (b) (0.2 per cent). The area of any peak corresponding to impurity C at 350 nm is not more than the area of the principal peak in the chromatogram obtained with test solution (b) (0.2 per cent). The area of any peak corresponding to impurity B at 260 nm is not more than 2.5 times the area of the principal peak in the chromatogram obtained with test solution (b) (0.5 per cent). The area of any other secondary peak is not more than the area of the peak in the chromatogram obtained with test solution (b) at that wavelength (0.2 per cent). The total content of any such impurities is not more than 2.0 per cent. Ignore any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with test solution (b) at the same wavelength (0.05 per cent).

Other tests. Comply with the test stated under Parenteral Preparations (Injection).

Assay. Determine by liquid chromatography (2.4.14).

Test solution. To a volume of the injection containing 40 mg meloxicam add 0.3 ml of *0.4M sodium hydroxide* and dilute to 10 ml with *methanol (40 per cent)*. Dilute 1.0 ml of the resulting solution to 10.0 ml with *methanol (40 per cent)*.

Reference solution (a). A 0.04 per cent w/v solution of *meloxicam IPRS* in *methanol (40 per cent)*.

Reference solution (b). Take 40 mg of *meloxicam impurity IPRS* add 0.3 ml of *0.4M sodium hydroxide*, dilute to 10 ml with *methanol (40 per cent)*.

Use the chromatographic system as described under Related substances with following modification.

Spectrophotometer set at 350 nm.

Inject the reference solution (b) and the test solution. The test is not valid unless the chromatogram obtained with reference solution (b) closely resembles the chromatogram supplied with *meloxicam impurity IPRS* at 350 nm. The resolution between the peaks due to meloxicam and impurity A at 350 nm is not less than 3.0.

Calculate the content of $C_{14}H_{13}N_3O_4S_2$ in the injection.

Mepyramine Maleate

For Description, Identification and Tests refer to IP Volume II.

Mepyramine Injection

Mepyramine Maleate Injection; Pyrilamine Maleate Injection; Pyrilamine Injection

Mepyramine Injection is a sterile solution of Mepyramine Maleate in Water for Injections.

Mepyramine Injection contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of mepyramine maleate, $C_{17}H_{23}N_3O,C_4H_4O_4$.

Usual strengths. 25 mg in 1 ml; 50 mg in 1 ml.

Description. Colourless or almost colourless solution.

Identification

A. To a volume containing 0.1 g of Mepyramine Maleate add 2 ml of *5 M sodium hydroxide* and shake with three quantities, each of 3 ml, of *ether*. Warm the aqueous layer in a water-bath for 10 minutes with 2 ml of *bromine solution*, heat to boiling, cool, and add 0.2 ml to a solution of 10 mg of *resorcinol* in 3 ml of *sulphuric acid*; a blue-black colour develops on heating for 15 minutes in a water-bath.

B. Dilute a volume containing 20 mg of mepyramine maleate to 2 ml with *water*, add 1 ml of *cyanogen bromide solution* and 5 ml of a 2 per cent w/v solution of *potassium hydrogen phthalate*, mix, allow to stand for 15 minutes and add 1 ml of a 4 per cent solution of *aniline* in *ethanol (95 per cent)*; a yellow colour is produced.

Tests

pH (2.4.24). 5.5 to 6.5.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. To a measured volume containing about 25 mg of mepyramine maleate add sufficient *0.01 M hydrochloric acid* to produce 100.0 ml. Dilute 10.0 ml of the solution to 100.0 ml with *0.01 M hydrochloric acid* and measure the absorbance of the resulting solution at the maximum at about 316 nm (2.4.7). Calculate the content of $C_{17}H_{23}N_3O,C_4H_4O_4$, taking 206 as the specific absorbance at 316 nm.

Methylergometrine Injection

Usual strength. 1 mg in 1 ml.

For Identification and Tests refer to IP Volume II.

Methylprednisolone Acetate

For Description, Identification and Tests refer to IP Volume II.

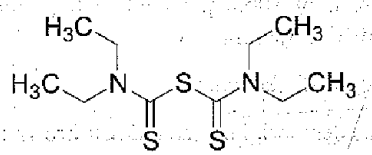
Methylprednisolone Acetate Injection

Usual strengths. 40 mg in 1 ml; 200 mg in 5 ml.

For Identification and Tests refer to IP Volume II.

Monosulfiram

Sulfiram



$C_{10}H_{20}N_2S_3$ Mol. Wt. 264.5

Monosulfiram is bis(diethylthiocarbamoyl)sulphide.

Monosulfiram contains not less than 98.0 per cent and not more than 101.0 per cent of $C_{10}H_{20}N_2S_3$, calculated on the anhydrous basis.

Category. Insecticide.

Description. A yellow or yellowish-brown soft solid; odour, sulphurous.

Identification

A. When examined in the range 230 nm to 360 nm (2.4.7), a 2-cm layer of a 0.001 per cent w/v solution in *methanol* shows a well-defined absorption maximum only at about 281 nm; absorbance at about 281 nm, about 1.3.

B. Dissolve 0.1 g in a mixture of 0.15 ml of a 1 per cent w/v solution of *cupric sulphate* and 5 ml of *ethanol (95 per cent)*, evaporate on a water-bath and dissolve the residue in *dichloromethane*; a deep yellowish brown colour is produced.

C. Boil 0.1 g with *2 M hydrochloric acid*; hydrogen sulphide is evolved which has a characteristic odour and turns filter paper treated with *lead acetate solution*, black.

Tests

Freezing point (2.4.11). 28.5° to 32.0°.

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

NOTE — Carry out the test in subdued light.

Mobile phase. A mixture of 70 volumes of n-*hexane* and 30 volumes of *butyl acetate*.

Test solution. Dissolve 2.5 g of the substance under examination in 100 ml of *ethyl acetate*.

Reference solution (a). A 0.125 per cent w/v solution of *disulfiram IPRS* in *ethyl acetate*.

Reference solution (b). A 0.050 per cent w/v solution of the substance under examination in *ethyl acetate*.

Apply to the plate 5 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. In the chromatogram obtained with the test solution any secondary spot is not more intense than the spot in the chromatogram obtained with reference solution (a) and any other spot, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b).

Water (2.3.43). Not more than 1.0 per cent, determined on 1 g.

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Assay. Dissolve 0.35 g in 8 ml of *nitrogen-free sulphuric acid* and carry out the method for the determination of nitrogen (2.3.30).

1 ml of *0.05 M sulphuric acid* is equivalent to 0.01322 g of $C_{10}H_{20}N_2S_3$.

Storage. Store protected from light.

Monosulfiram Soap

Monosulfiram Soap contains not less than 5 per cent w/w of monosulfiram in a toilet soap base which may be perfumed.

Monosulfiram Soap contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of monosulfiram, $C_{10}H_{20}N_2S_3$.

Usual strength. 5 per cent w/w.

Identification

In the test for Related substances, the principal spot in the chromatogram obtained with test solution (b) corresponds to that in the chromatogram obtained with reference solution (c).

Tests

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

NOTE — Carry out the test in subdued light.

Mobile phase. A mixture of 70 volumes of *n-hexane* and 30 volumes of *butyl acetate*.

Test solution (a). Shake a quantity of the finely shredded soap containing 20 mg of Monosulfiram with 10 ml of *dichloromethane*, filter and wash the filtrate with *dichloromethane*. Evaporate the combined filtrate and washings just to dryness at room temperature in a current of *nitrogen* and dissolve the residue in 1 ml of *ethanol (95 per cent)*.

Test solution (b). Dilute 0.5 ml of test solution (a) to 10 ml with *ethanol (95 per cent)*.

Reference solution (a). A 0.10 per cent w/v solution of *disulfiram IPRS* in *ethanol (95 per cent)*.

Reference solution (b). A 0.040 per cent w/v solution of *monosulfiram IPRS* in *ethanol (95 per cent)*.

Reference solution (c). A 0.10 per cent w/v solution of *monosulfiram IPRS* in *ethanol (95 per cent)*.

Apply to the plate 5 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. In the chromatogram obtained with test solution any spot running ahead of the principal spot and corresponding in position to disulfiram is not more intense than the spot in the chromatogram obtained with reference solution (a) and any spot running behind the principal spot is not more intense than the spot in the chromatogram obtained with reference solution (b). Ignore any subsidiary spots due to the soap basis which may also be observed ahead of the principal spot in the chromatogram obtained with test solution (a).

Assay. Determine by gas chromatography (2.4.13).

NOTE —Protect the solutions from light throughout the assay.

Test solution (a). Weigh a quantity of the finely shredded soap containing about 0.25 g of Monosulfiram, shake for 10 minutes with 50 ml of *dimethylformamide*, centrifuge and use the supernatant liquid.

Test solution (b). Weigh a quantity of the finely shredded soap containing about 0.25 g of Monosulfiram, shake for 10 minutes with 50 ml of *dimethylformamide* containing 0.125 g of *N-phenylcarbazole* (internal standard), centrifuge and use the supernatant liquid.

Reference solution. A solution containing 0.5 per cent w/v of *monosulfiram IPRS* and 0.25 per cent w/v of *N-phenylcarbazole* (internal standard) in *dimethylformamide*.

Chromatographic system

- a glass column 1.5 m x 4 mm, packed with 2 per cent w/w of methyl silicone gum on acid-washed, silanised diatomaceous support (80 to 100 mesh) (such as SE 30),
- temperature:
  column 180°,
  inlet port 180° and detector 280°,
- flow rate: 30 ml per minute, using nitrogen as the carrier gas.

Calculate the content of $C_{10}H_{20}N_2S_3$.

Labelling. The label states (1) the proportion of Monosulfiram in the preparation; (2) the method of use of the preparation.

Monosulfiram Solution

Monosulfiram Solution is a solution of Monosulfiram in Ethanol (95 per cent) containing a suitable dispersing agent.

In making Monosulfiram Solution the ethanol (95 per cent) may be replaced by Industrial Methylated Spirit provided that the statutory requirements governing the use of Industrial Methylated Spirit are observed.

Monosulfiram Solution contains not less than 94.0 per cent and not more than 106.0 per cent of the stated amount of monosulfiram, $C_{10}H_{20}N_2S_3$.

Usual strength. 25 per cent w/w.

Description. Clear, bright, deep reddish-brown liquid; crystals from which may deposit slowly at low temperatures but dissolve on warming. Yields a pale yellow dispersion on dilution with *water*.

Identification

In the test for Related substances, the principal spot in the chromatogram obtained with test solution (b) corresponds to that in the chromatogram obtained with reference solution (c).

Tests

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

NOTE — Carry out the test in subdued light.

Mobile phase. A mixture of 70 volumes of n-*hexane* and 30 volumes of *butyl acetate.*

Test solution (a). Dilute a quantity of the solution under examination with *ethanol (95 per cent)* so as to contain of 2.0 per cent w/v of Monosulfiram.

Test solution (b). Dilute 0.5 ml of test solution (a) to 10 ml with *ethanol (95 per cent).*

Reference solution (a). A 0.10 per cent w/v solution of *disulfiram IPRS* in *ethanol (95 per cent).*

Reference solution (b). A 0.040 per cent w/v solution of *monosulfiram IPRS* in *ethanol (95 per cent).*

Reference solution (c). A 0.10 per cent w/v solution of *monosulfiram IPRS* in *ethanol (95 per cent).*

Apply to the plate 5 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. In the chromatogram obtained with the test solution any spot running ahead of the principal spot and corresponding in position to disulfiram is not more intense than the spot in the chromatogram obtained with reference solution (a) and any spot running behind the principal spot is not more intense than the spot in the chromatogram obtained with reference solution (b).

Assay. Determine by gas chromatography (2.4.13).

NOTE—Protect the solutions from light throughout the assay.

Test solution (a). Dilute the solution under examination in *dimethylformamide* containing the equivalent of 0.5 per cent w/v of Monosulfiram.

Test solution (b). Weigh a quantity of the finely shredded soap containing 0.25 g of Monosulfiram, shake for 10 minutes with 50 ml of *dimethylformamide* containing 0.125 g of *N-phenylcarbazole* (internal standard), centrifuge and use the supernatant liquid.

Reference solution. A solution containing 0.5 per cent w/v of *monosulfiram IPRS* and 0.25 per cent w/v of *N-phenylcarbazole* (internal standard) in *dimethylformamide.*

Chromatographic system

- a glass column 1.5 m x 4 mm, packed with 2 per cent w/w of methyl silicone gum on acid-washed, silanised diatomaceous support (80 to 100 mesh) (such as SE 30),
- temperature:
  column 180°,
  inlet port 180° and detector 280°,
- flow rate: 30 ml per minute, using nitrogen as the carrier gas.

Calculate the content of $C_{10}H_{20}N_2S_3$.

Labelling. The label states (1) the percentage w/w of monosulfiram; (2) the method of use of the preparation.

Morphine Sulphate

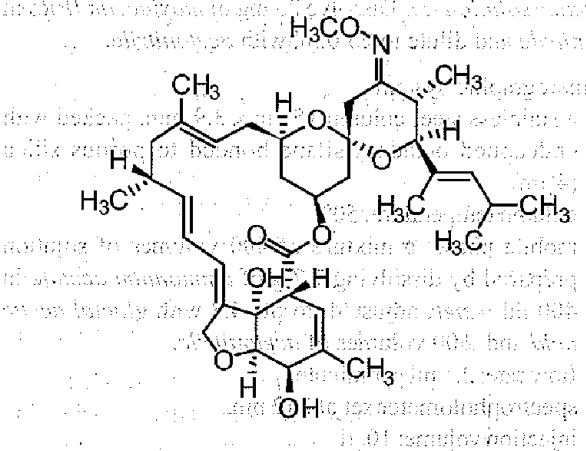
For Description, Identification and Tests refer to IP Volume II.

Morphine Injection

Usual strengths. 10 mg, 15 mg, 20 mg and 30 mg in 1 ml; 60 mg in 2 ml.

For Identification and Tests refer to IP Volume II.

Moxidectin



$C_{37}H_{53}NO_8$ Mol. Wt. 639.8

Moxidectin is (6*R*,15*S*)-5-*O*-Demethyl-28-deoxy-25-[(*E*)-1,3-dimethylbut-1-enyl]-6,28-epoxy-23-oxomilbemycin B(*E*)-23-*O*-methyloxime.

Moxidectin is a semi-synthetic product derived from a fermentation product. It may contain suitable stabilisers such as antioxidants.

Moxidectin contains not less than 92.0 per cent and not more than 102.0 per cent of $C_{37}H_{53}NO_8$, on anhydrous basis.

Category. Antihelminthic; ectoparasiticide.

Description. A white or pale yellow, amorphous powder.

Identification

Determine by infrared absorption spectrometry (2.4.6). Compare the spectrum with that obtained *moxidectin IPRS* or with the reference spectrum of moxidectin.

Tests

Appearance of solution (2.4.1). Dissolve 0.40 g in *benzyl alcohol* and dilute to 20 ml with the same solvent. The solution

is clear and not more intensely coloured than reference solution GYS5.

Related substances. Determine by liquid chromatography (2.4.14).

Method A

Test solution. Dissolve 25 mg of the substance under examination in *acetonitrile* and dilute to 25.0 ml with the same solvent.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml *acetonitrile*.

Reference solution (b). Dissolve 5 mg of *moxidectin for system suitability IPRS* (containing impurities A, B, C, D, E, F, G, H, I, J and K) in 5 ml of *acetonitrile*.

Reference solution (c). Dissolve 25 mg of *moxidectin IPRS* in *acetonitrile* and dilute to 25.0 ml with *acetonitrile*.

Chromatographic system
- a stainless steel column 15 cm x 3.9 mm, packed with endcapped octadecylsilane bonded to porous silica (4 µm),
- column temperature: 50°,
- mobile phase: a mixture of 400 volumes of solution prepared by dissolving 7.7 g of *ammonium acetate* in 400 ml *water*, adjusted to pH 4.8 with *glacial acetic acid* and 600 volumes of *acetonitrile*,
- flow rate: 2.5 ml per minute,
- spectrophotometer set at 242 nm,
- injection volume: 10 µl.

Name	Relative retention time
Moxidectin impurity A[1]	0.5
Moxidectin impurity B[2]	0.7
Moxidectin impurity C[3]	0.75
Moxidectin impurity D[4]	0.94
Moxidectin (Retention time: about 12 minutes)	1.0
Moxidectin impurity E[5] and F[6]	1.3-1.5
Moxidectin impurity G[7]	1.6

[1]25-des [(1*E*)-1,3-dimethylbut-1-enyl]-25-[(1*E*)-1-methylprop-1-enyl] moxidectin,

[2]24-desmethylmoxidectin,

[3]25-des[(1*E*)-1,3-dimethylbut-1-enyl]-25-[(1*E*)-1-methylbut-1-enyl] moxidectin,

[4]2-*epi*-moxidectin,

[5](4*S*)-2-dehydro-4-hydromoxidectin,

[6]one of groups is C_2H_5, the others are CH_3: x-desmethyl-x-ethylmoxidectin,

[7](23*E*, 25S)-5*O*-desmethyl-28-deoxy-25-[(1*E*)-1,3-dimethylbut-1-enyl]-23-(methoxyimino)milbemycin B.

Inject reference solution (b). Run the chromatogram 2.0 times the retention time of the moxidectin. Identify the impurities in the chromatogram obtained with *moxidectin IPRS* and identify the peaks corresponding to impurities A, B, C, D, E, F and G in the chromatogram obtained with reference solution (b).

The peaks to H_p and H_v valley ratio is not less than 3.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to moxidectin.

Inject reference solution (a) and the test solution. The area of the peak for impurity D is not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.5 per cent), the area of the peak for impurity B is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent), the area of the peak for each impurity A, C and G, each of, is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent) and the area of any other secondary peak for each impurity eluting before impurity G is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). The sum of the areas of the peak for impurity E and F is not more than 1.7 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.7 per cent). Ignore any peak of the area is 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and peak due to stabiliser.

Method B

Test solution. Dissolve 75 mg of the substance under examination in *acetonitrile* and dilute to 25.0 ml with the same solvent.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml *acetonitrile*.

Reference solution (b). Dissolve 5 mg of *moxidectin for system suitability IPRS* (containing impurities A, B, C, D, E, F, G, H, I, J and K) in 5 ml of *acetonitrile*.

Chromatographic system
- a stainless steel column 15 cm x 3.9 mm, packed with endcapped octadecylsilane bonded to porous silica (4 µm),
- column temperature: 35°,
- mobile phase: a mixture of 250 volumes of solution prepared by dissolving 3.8 g of *ammonium acetate* in 250 ml *water*, adjusted to pH 4.2 with *glacial acetic acid* and 750 volumes of *acetonitrile*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 242 nm,
- injection volume: 10 µl.

Name	Relative retention time
Moxidectin (Retention time: about 4 minutes)	1.0
Moxidectin impurity G[7]	1.4
Moxidectin impurity H[8]	2.0
Moxidectin impurity I[9]	2.0
Moxidectin impurity J[10]	2.2
Moxidectin impurity K[11]	3.4

[8]2,5-didehydro-5-deoxymoxidectin,

[9](23*S*)-23-des (methoxyimino)-23-[(methylsulfanyl)methoxy] moxidectin,

[10]7-*O*-[(methylsulfanyl)methyl]moxidectin,

[11]5-*O*-(4-nitrobenzoyl)moxidectin.

Inject reference solution (b). Run the chromatogram 10 times the retention time of the moxidectin. Identify the impurities in the chromatogram obtained with *moxidectin IPRS* and identify the peaks due to impurities H+I, J and K, each of, in the chromatogram obtained with reference solution (b). The resolution between the peaks due to impurities H, I and J is separation baseline.

Inject reference solution (a) and the test solution. The area of the peak for each impurity J and K is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent) and the area of any other secondary peak for each impurity eluting after impurity G is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). The sum of the areas of the peak for impurity H and I is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak of the area is 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and peak due to stabiliser.

Calculate the sum of the impurities eluting from the start of the run to impurity G in test A, and from impurities H+I to the end of the run in test B. The total of all impurities is not more than 7.0 per cent.

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Water (2.3.43). Not more than 1.3 per cent, determined on 0.5 g.

Sulphated ash (2.3.18). Not more than 0.2 per cent.

Assay. Determine by liquid chromatography (2.4.14) as described under test A for Related substances with the following modification.

Inject reference solution (c) and the test solution.

Calculate the content of $C_{37}H_{53}NO_8$.

Moxidectin Injection

Moxidectin Injection is a sterile solution of Moxidectin.

Moxidectin injection contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of moxidectin, $C_{37}H_{53}NO_8$.

Identification

A. Determined by thin-layer chromatography (2.4.17), coating the plate with *silica gel*.

Mobile phase. A mixture of 8 volumes of a 15.0 per cent w/v solution of *ammonium acetate*, adjusted to pH 9.6 with *ammonia*, 19 volumes of *propan-2-ol* and 43 volumes of *ethyl acetate*.

Test solution. A 0.04 per cent w/v solution of the substance under examination in *methanol*.

Reference solution. A 0.04 per cent w/v of *moxidectin IPRS* in *methanol*.

Apply to the plate 5 µl of each solution. Allow the mobile phase to rise 15 cm. After development, dry the plate in air, spray with *anisaldehyde solution*, heat at 110° for 10 minutes and allow to cool. The principal spot in the chromatogram obtained with the test solution corresponds to the spot in the chromatogram with reference solution.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Tests

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. Determined by liquid chromatography (2.4.14).

Test solution. A 0.1 per cent w/v solution of moxidectin in *acetonitrile*. If the solution is cloudy, shake, allow to settle and use the supernatant.

Reference solution (a). A 0.1 per cent w/v solution of *moxidectin IPRS* in *acetonitrile*.

Reference solution (b). A 0.1 per cent w/v solution of *moxidectin for system suitability IPRS* in *acetonitrile*.

Chromatographic system

- a stainless steel column 15 cm × 3.9 mm, packed with endcapped octadecylsilane bonded to porous silica (4 µm),
- column temperature: 50°,
- mobile phase: a mixture of 40 volumes of a 1.925 per cent w/v solution of *ammonium acetate* in *water*, adjusted to pH 4.8 with *glacial acetic acid*, and 60 volumes of *acetonitrile*,

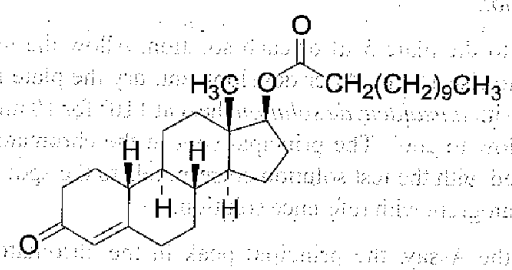
– flow rate: 2.5 ml per minute;
– spectrophotometer set at 242 nm;
– injection volume: 10 µl.

Inject reference solution (b). The test is not valid unless the peaks to valley ratio of H_p and H_v is not less than 3.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to moxidectin.

Inject reference solution (b) and the test solution. The relative retention time of moxidectin is about 12 and the retention time of impurity D relative to that of moxidectin is about 0.94.

Calculate the content of $C_{37}H_{53}NO_8$ in the injection.

Nandrolone Laurate



$C_{30}H_{48}O_3$ Mol. Wt. 456.7

Nandrolone Laurate is 3-oxoestr-4-en-17β-yl-dodecanoate.

Nandrolone Laurate contains not less than 97.0 per cent and not more than 103.0 per cent of $C_{30}H_{48}O_3$, calculated on the dried basis.

Category. Anabolic steroid; androgen.

Description. A white to creamy white, crystalline powder; odour, faint and characteristic.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *nandrolone laurate IPRS* or with the reference spectrum of nandrolone laurate.

B. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*, surface of which has been modified by chemically bonded octadecylsilyl groups (such as Whatman KC 18F plates).

Mobile phase. A mixture of 60 volumes of *2-propanol*, 40 volumes of *acetonitrile* and 20 volumes of *water*.

Test solution. Dissolve 0.5 g of the substance under examination in *dichloromethane*.

Reference solution (a). A 0.5 per cent w/v of *nandrolone laurate IPRS* in *dichloromethane*.

Reference solution (b). A mixture of equal volumes of the test solution and reference solution (a).

Apply to the plate 5 µl of each solution. After development, dry the plate in air until the odour of the solvent is no longer detectable and heat at 100° for 10 minutes. Allow to cool and examine under ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with the reference solution (a). The test is not valid unless the principal spot in the chromatogram obtained with reference solution (b) appears as a single, compact spot.

C. Melts at about 47° (2.4.21).

Tests

Specific optical rotation (2.4.22). +31.0° to +35.0°, determined in a freshly prepared 2 per cent w/v solution in *dioxan*.

Nandrolone. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*.

Mobile phase. A mixture of 70 volumes of *n-heptane* and 30 volumes of *acetone*.

Test solution. Dissolve 1.5 g of the substance under examination in *dichloromethane*.

Reference solution. A 0.03 per cent w/v of *nandrolone IPRS* in *dichloromethane*.

Apply to the plate 1 µl of each solution. After development, dry the plate in air until the odour of the solvent is no longer detectable, spray with a 10 per cent v/v solution of *sulphuric acid* in *ethanol (95 per cent)*, heat at 105° for 30 minutes and examine under ultraviolet light at 365 nm. Any spot in the chromatogram obtained with the test solution corresponding to nandrolone is not more intense than the spot in the chromatogram obtained with the reference solution.

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 1.0 g by drying over *phosphorus pentoxide* at a pressure not exceeding 0.7 kPa for 24 hours.

Assay. Weigh 0.1 g, dissolve in sufficient *ethanol* to produce 100.0 ml and dilute 10.0 ml to 100.0 ml with *ethanol*. Dilute 10.0 ml of the solution to 100.0 ml with *ethanol* and measure the absorbance of the resulting solution at the maximum at about 240 nm (2.4.7). Calculate the content of $C_{30}H_{48}O_3$ taking 380 as the specific absorbance at 240 nm.

Storage. Store protected from light.

Nandrolone Laurate Injection

Nandrolone Laurate Injection is a sterile solution of Nandrolone Laurate in Ethyl Oleate or other suitable ester, in a suitable fixed oil, or in any mixture of these.

Nandrolone Laurate Injection contains not less than 92.5 per cent and not more than 107.5 per cent of the stated amount of nandrolone laurate, $C_{30}H_{48}O_3$.

Usual strengths. 25 mg in 1 ml; 50 mg in 1 ml.

Identification

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*, surface of which has been modified by chemically bonded octadecylsilyl groups (such as Whatman KC 18F plates).

Mobile phase. A mixture of 60 volumes of *2-propanol*, 40 volumes of *acetonitrile* and 20 volumes of *water*.

Test solution. Dilute a suitable volume with *dichloromethane* to produce a solution containing 0.5 per cent w/v of Nandrolone Laurate .

Reference solution (a). A 0.5 per cent w/v of *nandrolone laurate IPRS* in *dichloromethane*.

Reference solution (b). A mixture of equal volumes of the test solution and reference solution (a)

Apply to the plate 5 µl of each solution. After development, dry the plate in air until the odour of the solvent is no longer detectable and heat at 100° for 10 minutes. Allow to cool and examine under ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with the reference solution (a). The test is not valid unless the principal spot in the chromatogram obtained with reference solution (b) appears as a single, compact spot.

Tests

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. To a measured volume containing about 0.1 g of Nandrolone Laurate add sufficient *dichloromethane* to produce 100.0 ml. Dilute 3.0 ml of the resulting solution to 50.0 ml with *dichloromethane*. To 5.0 ml of the solution add 10 ml of *isoniazid solution* and sufficient *methanol* to produce 20.0 ml. Allow to stand for 45 minutes and measure the absorbance of the resulting solution at the maximum at about 380 nm (2.4.7), using as the blank 5 ml of *dichloromethane* treated in a similar manner. Calculate the content of $C_{30}H_{48}O_3$ from the absorbance obtained by repeating the procedure using a suitable quantity of *nandrolone IPRS*.

1 mg of $C_{18}H_{26}O_2$ is equivalent to 0.001664 g of $C_{30}H_{48}O_3$.

Storage. Store protected from light.

Neomycin Sulphate

For Description, Identification and Tests refer to IP Volume III.

Niclosamide

For Description, Identification and Tests refer to IP Volume III.

Niclosamide Veterinary Oral Powder

Niclosamide Dispersible Powder for Veterinary Use

Niclosamide Veterinary Oral Powder contains Niclosamide with suitable auxiliary substances.

Niclosamide Veterinary Oral Powder contains not less than 97.0 per cent and not more than 103.0 per cent of the stated amount of niclosamide, $C_{13}H_8Cl_2N_2O_4$.

Usual strength. 75 per cent w/w.

Identification

Heat 50 mg with 5 ml of *1 M hydrochloric acid* and 0.1 g of *zinc powder* in a water-bath for 10 minutes, cool and filter. To the filtrate add 0.5 ml of a 1 per cent w/v solution of *sodium nitrite* and allow to stand for 10 minutes. Add 2 ml of a 2 per cent w/v solution of *ammonium sulphamate*, shake, allow to stand for 10 minutes and add 2 ml of a 0.5 per cent w/v solution of N-*(1-naphthyl)ethylenediamine dihydrochloride*; a deep red colour is produced.

Tests

2-Chloro-4-nitroaniline. Boil a quantity containing 0.10 g of Niclosamide with 20 ml of *methanol* for 2 minutes, cool, add sufficient *1 M hydrochloric acid* to produce 50 ml and filter. To 10 ml of the filtrate add 0.5 ml of a 0.5 per cent w/v solution of *sodium nitrite* and allow to stand for 10 minutes. Add 1 ml of a 2 per cent w/v solution of *ammonium sulphamate*, shake, allow to stand for 10 minutes and add 1 ml of a 0.5 per cent w/v solution of *N-(1-naphthyl)ethylenediamine dihydrochloride*. Any pinkish violet colour produced is not more intense than that obtained in a solution prepared simultaneously using 10.0 ml of a solution prepared by diluting 2.0 ml of a 0.0002 percent w/v solution of *2-chloro-4-nitroaniline* in *methanol* to 20 ml with *1 M hydrochloric acid*.

5-Chlorosalicylic acid. Boil a quantity containing 0.50 g of Niclosamide with 10 ml of *water* for 2 minutes, cool and filter. To the filtrate add a few drops of *ferric chloride solution*; no red or violet colour is produced.

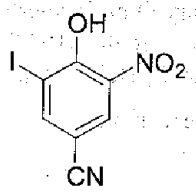
Loss on drying (2.4.19). Not more than 1.0 per cent, determined on 1 g by drying in an oven at 105° for 4 hours.

Other tests. Comply with the tests stated under Veterinary Oral Powders.

Assay. Weigh a quantity containing about 0.3 g of Niclosamide, dissolve in 60 ml of *dimethylformamide* with the aid of gentle heat, cool. Titrate with *0.1 M tetrabutyl-ammonium hydroxide*, maintaining a stream of *nitrogen* through the solution throughout the titration, and determining the end-point potentiometrically (2.4.25). Carry out a blank titration.

1 ml of *0.1 M tetrabutylammonium hydroxide* is equivalent to 0.03271 g of $C_{13}H_8Cl_2N_2O_4$.

Nitroxynil



$C_7H_3IN_2O_3$ Mol. Wt. 290.0

Nitroxynil is 4-hydroxy-3-iodo-5-nitrobenzonitrile.

Nitroxynil contains not less than 98.0 per cent and not more than 101.0 per cent of $C_7H_3IN_2O_3$, calculated on the dried basis.

Category. Anthelmintic.

Description. A yellow to yellowish brown powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *nitroxynil IPRS* or with the reference spectrum of nandrolone nitroxynil.

B. When examined in the range 220 nm to 360 nm (2.4.7), a 0.002 per cent w/v solution in *0.01 M sodium hydroxide* exhibits maxima at about 225 nm and at about 271 nm; absorbance at about 271 nm, about 1.3.

C. When heated with *sulphuric acid*, iodine vapours are evolved.

D. Melting range (2.4.21). 136° to 139°.

Tests

Inorganic iodide. To 0.40 g add 0.35 g of *N-methylglucamine* and 10 ml of *water*. Shake to dissolve and add sufficient *water* to produce 50 ml. To 10 ml of the resulting solution add 4 ml of *1 M sulphuric acid* and extract with three quantities, each of 10 ml, of *dichloromethane*. Add to the aqueous extract 1 ml of *hydrogen peroxide solution (100 vol)* and 1 ml of *dichloromethane*, shake for 2 minutes and allow to separate. Any purple colour in the dichloromethane layer is not more intense than that obtained by adding 2 ml of a 0.0026 per cent w/v solution of *potassium iodide* to a mixture of 4 ml of *1 M sulphuric acid* and 8 ml of *water*, adding 10 ml of *dichloromethane*, shaking for 2 minutes, adding to the aqueous layer 1 ml of *hydrogen peroxide solution (100 vol)* and 1 ml of *dichloromethane*, shaking for 2 minutes and allowing to separate (500 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Loss on drying (2.4.19). Not more than 1.0 per cent, determined on 1 g by drying in an oven at 105° for 4 hours.

Assay. Carry out the oxygen flask method for iodine (2.3.34), using 25 mg.

1 ml of *0.02 M sodium thiosulphate* is equivalent to 0.0009667 g of $C_7H_3IN_2O_3$.

Storage. Store protected from light.

Nitroxynil Injection

Nitroxynil Injection is a sterile solution of the *N*-ethylglucamine salt of Nitroxynil in Water for Injections.

Nitroxynil Injection contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of nitroxynil, $C_7H_3IN_2O_3$.

Usual strengths. 200 mg in 1 ml; 340 mg in 1 ml.

Identification

A. When examined in the range 230 nm to 360 nm (2.4.7), of the final solution obtained in the Assay exhibits a maximum at about 271 nm.

B. Heat 0.5 ml with 3 ml of *sulphuric acid*; iodine vapours are evolved.

Tests

pH (2.4.24). 5.0 to 7.0, determined by using a 20 per cent w/v solution of *N-ethylglucamine hydrochloride* instead of a saturated solution of *potassium chloride* as the liquid junction solution.

Inorganic iodide. To a volume containing 0.4 g of Nitroxynil add 0.35 g of *N-methylglucamine* and dilute to 100 ml with *water*. To 10 ml of the diluted solution add 4 ml of *1 M sulphuric acid* and extract with three quantities, each of 10 ml, of *dichloromethane*. Add to the aqueous extract 1 ml of *hydrogen peroxide solution (100 vol)* and 1 ml of *dichloromethane*, shake for 2 minutes and allow to separate. Any purple colour in the dichloromethane layer is not more intense than that obtained by adding 2 ml of a 0.0026 per cent w/v solution of

potassium iodide to a mixture of 4 ml of *1 M sulphuric acid* and 8 ml of *water*, adding 10 ml of *dichloromethane*, shaking for 2 minutes, adding to the aqueous layer 1 ml of *hydrogen peroxide solution (100 vol)* and 1 ml of *dichloromethane*, shaking for 2 minutes and allowing to separate (0.1 per cent w/v of iodide).

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. To a measured volume containing 1.7 g of Nitroxynil add sufficient *0.01 M sodium hydroxide* to produce 500.0 ml. Dilute 20.0 ml of the solution to 500.0 ml with *0.01 M sodium hydroxide*. To 5.0 ml of the solution add sufficient *0.01 M sodium hydroxide* to produce 100.0 ml and measure the absorbance of the resulting solution at the maximum at about 271 nm (2.4.7). Calculate the content of $C_7H_3IN_2O_3$ taking 660 as the specific absorbance at 271 nm.

Storage. Store protected from light.

Oestradiol Benzoate

For Description, Identification and Tests refer to IP Volume III.

Oestradiol Injection

Usual strengths. 1 mg in 1 ml; 2 mg in 1 ml; 5 mg in 1 ml.

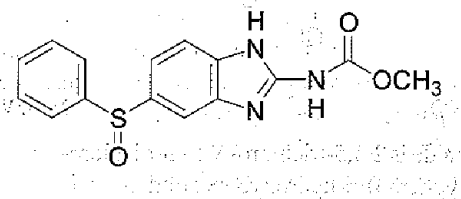
Storage. Store in light resistant containers. Solid matter that may separate on standing should be redissolved by warming before use.

For Identification and Tests refer to IP Volume III.

Ornidazole

For Description, Identification and Tests refer to IP Volume III.

Oxfendazole



$C_{15}H_{13}N_3O_3S$ Mol. Wt. 315.4

Oxfendazole is methyl 5-(phenylsulphinyl)-2-benzimidazolecarbamate.

Oxfendazole contains not less than 97.0 per cent and not more than 100.5 per cent of $C_{15}H_{13}N_3O_3S$, calculated on the dried basis.

Category. Anthelmintic.

Description. A white or almost white powder.

Identification

A. Dissolve 0.1 g in 50 ml of *methanol*, evaporate to a volume of about 2 ml, cool, filter, wash the residue with 2 ml of *water* and dry at 105° at a pressure not exceeding 2.7 kPa. The residue complies with the following test.

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *oxfendazole IPRS* or with the reference spectrum of oxfendazole.

B. When examined in the range 220 nm to 360 nm (2.4.7), a 0.001 per cent w/v solution in *methanol* exhibits two maxima at about 228 nm and about 297 nm; absorbances at about 228 nm, about 1.4 and at about 297 nm, about 0.55.

Tests

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Solvent mixture. 40 volumes of *ethyl acetate* and 10 volumes of *glacial acetic acid*.

Mobile phase. A mixture of 95 volumes of *ethyl acetate* and 5 volumes of *glacial acetic acid*.

Test solution. Dissolve 0.5 g of the substance under examination in 100 ml of solvent mixture.

Reference solution (a). A 0.010 per cent w/v solution of the substance under examination in solvent mixture.

Reference solution (b). A 0.0050 per cent w/v solution of *methyl 5-phenylthio-1H-benzimidazol-2-yl carbamate IPRS* in solvent mixture.

Apply to the plate 20 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. Any spot corresponding to methyl 5-phenylthio-1*H*-benzimidazol-2-yl carbamate in the chromatogram obtained with test solution is not more intense than the spot in the chromatogram obtained with reference solution (b). Any other secondary spot in the chromatogram obtained with test solution is not more intense than the spot in the chromatogram obtained with reference solution (a).

Sulphated ash (2.3.18). Not more than 0.2 per cent.

Loss on drying (2.4.19). Not more than 1.0 per cent, determined on 1 g by drying in an oven at 105° for 2 hours at a pressure not exceeding 0.7 kPa.

Assay. Weigh 0.3 g, dissolve in 20 ml of *glacial acetic acid*, add 3 g of *potassium iodide* and 1 ml of *acetyl chloride* and

stir for 10 minutes. Add 50 ml of *1 M hydrochloric acid* and 10 ml of *dichloromethane* and titrate immediately with *0.1 M sodium thiosulphate*, shaking after each addition, until the dichloromethane layer is colourless. Repeat the operation omitting the substance under examination; the difference between the titrations represents the amount of sodium thiosulphate required.

1 ml of *0.1 M sodium thiosulphate* is equivalent to 0.01577 g of $C_{15}H_{13}N_3O_3S$.

Storage. Store protected from light.

Oxfendazole Veterinary Oral Suspension

Oxfendazole Veterinary Mixture; Oxfendazole Mixture; Oxfendazole Oral Suspension

Oxfendazole Veterinary Oral Suspension is an aqueous suspension of Oxfendazole containing suitable suspending or dispersing agents.

Oxfendazole Veterinary Oral Suspension contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of oxfendazole, $C_{15}H_{13}N_3O_3S$.

Usual strengths. 2.265 per cent w/v; 9.06 per cent w/v.

Identification

Shake a quantity containing 0.1 g of Oxfendazole with 50 ml of *methanol* for 15 minutes, centrifuge, evaporate the supernatant liquid to a volume of about 2 ml, cool, filter and wash the residue with 2 ml of *water* and dry at 105° for 1 hour at a pressure not exceeding 2.7 kPa. The residue complies with the following tests.

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *oxfendazole IPRS* or with the reference spectrum of oxfendazole.

B. When examined in the range 220 nm to 360 nm (2.4.7), a 0.001 per cent w/v solution in *1 M hydrochloric acid* exhibits three maxima, at about 226, 284 and 291 nm.

Tests

pH (2.4.24). 4.3 to 5.3.

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Solvent mixture. 40 volumes of *ethyl acetate* and 10 volumes of *glacial acetic acid*.

Mobile phase. A mixture of 95 volumes of *ethyl acetate* and 5 volumes of *glacial acetic acid*.

Test solution. Shake a quantity containing 0.1 g of Oxfendazole with 20 ml of solvent mixture and filter.

Reference solution (a). Dilute 1 volume of test solution to 50 volumes with the solvent mixture.

Reference solution (b). A 0.0050 per cent w/v solution of *methyl 5-phenylthio-1H-benzimidazol-2-yl carbamate IPRS* in solvent mixture.

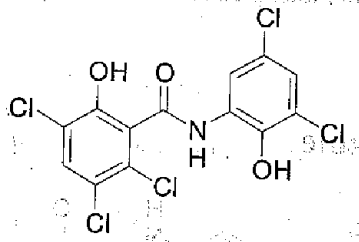
Apply to the plate 20 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. Any spot corresponding to methyl 5-phenylthio-1*H*-benzimidazol-2-yl carbamate in the chromatogram obtained with test solution is not more intense than the spot in the chromatogram obtained with reference solution (b). Any other secondary spot in the chromatogram obtained with test solution is not more intense than the spot in the chromatogram obtained with reference solution (a).

Other tests. Comply with the tests stated under Veterinary Oral Liquids.

Assay. Weigh a quantity of the well-mixed suspension containing about 0.1 g of Oxfendazole and disperse in 15 ml of *water*. Add 200 ml of *methanol* and mix in an ultrasonic bath for 15 minutes, cool, add sufficient *methanol* to produce 500.0 ml and filter. Dilute 2 ml of the solution to 50 ml with *methanol* and measure the absorbance of the resulting solution at the maximum at about 296 nm (2.4.7). Calculate the content of $C_{15}H_{13}N_3O_3S$ taking 550 as the specific absorbance at 296 nm.

Determine the weight per ml of the suspension (2.4.29), and calculate the content of oxfendazole, weight in volume.

Oxyclozanide



$C_{13}H_6Cl_5NO_3$ Mol. Wt. 401.5

Oxyclozanide is 2,3,5-trichloro-*N*-(3,5-dichloro-2-hydroxyphenyl)-6-hydroxybenzamide.

Oxyclozanide contains not less than 98.0 per cent and not more than 101.0 per cent of $C_{13}H_6Cl_5NO_3$, calculated on the dried basis.

Category. Anthelmintic.

Description. A pale cream to cream-coloured powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *oxyclozanide IPRS* or with the reference spectrum of oxyclozanide.

B. When examined in the range 230 nm to 360 nm (2.4.7), a 0.003 per cent w/v solution in *1 M methanolic hydrochloric acid* exhibits a maximum only at about 300 nm, is about 0.76.

C. Melting range (2.4.21). 208° to 211°.

Tests

Ionisable chlorine. Dissolve 2 g in 100 ml of *methanol*, add 10 ml of *1.5 M nitric acid* and titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (2.4.25). Not more than 1.4 ml is required (0.25 per cent).

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. A 0.1 per cent w/v solution of the substance under examination prepared by dissolving it in a suitable volume of *methanol* and slowly diluting with *water* containing 0.1 per cent v/v of *phosphoric acid* to give a solution containing about the same proportion of methanol to water as in the mobile phase.

Reference solution. Dilute 1.0 ml of test solution to 100.0 ml with the mobile phase.

Chromatographic system

- a stainless steel column 20 cm x 5 mm, packed with octadecylsilane bonded to porous silica (5 µm) (such as Hypersil ODS),
- mobile phase: a filtered and degassed mixture of 62 volumes of *methanol* and 38 volumes of *water* containing 0.1 per cent v/v of *phosphoric acid*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 300 nm,
- injection volume: 20 µl.

Inject the reference solution and the test solution. In the chromatogram obtained with test solution the area of any secondary peak with a retention time less than that of the principal peak is not more than one-third of the area of the principal peak in the chromatogram obtained with reference solution and the area of any secondary peak with a retention time greater than that of the principal peak is not more than the area of the principal peak in the chromatogram obtained with reference solution.

Sulphated ash (2.3.18). Not more than 0.2 per cent.

Loss on drying (2.4.19). Not more than 1.0 per cent, determined on 1 g by drying in an oven at 60° at a pressure not exceeding 0.7 kPa.

Assay. Weigh 0.25 g, dissolve in 75 ml of *anhydrous pyridine* and pass a stream of *nitrogen* through the solution for 5 minutes. Titrate with *0.1 M tetrabutyl-ammonium hydroxide*, maintaining a stream of *nitrogen* through the solution throughout the titration, determining the end-point potentiometrically (2.4.25). Carry out a blank titration.

1 ml of *0.1 M tetrabutylammonium hydroxide* is equivalent to 0.02007 g of $C_{13}H_6Cl_5NO_3$.

Oxyclozanide Veterinary Oral Suspension

Oxyclozanide Oral Suspension; Oxyclozanide Suspension; Oxyclozanide Mixture; Oxyclozanide Drench

Oxyclozanide Veterinary Oral Suspension is an aqueous suspension of Oxyclozanide containing suitable suspending or dispersing agents.

Oxyclozanide Veterinary Oral Suspension contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of oxyclozanide, $C_{13}H_6Cl_5NO_3$.

Usual strength. 3.4 per cent w/v.

Identification

In test A for Related substances, the principal spot in the chromatogram obtained with 10 ml of test solution corresponds to that in the chromatogram obtained with reference solution (b).

Tests

Related substances. A. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*.

Mobile phase. A mixture of 60 volumes of *light petroleum (60° to 80°)*, 20 volumes of *acetone* and 5 volumes of *glacial acetic acid*.

Test solution. Dilute a quantity with *acetone* to contain 1.0 per cent w/v of Oxyclozanide, centrifuge and use the supernatant liquid.

Reference solution (a). A 0.050 per cent w/v solution of *3,5,6-trichloro-2-hydroxybenzoic acid IPRS* in *acetone*.

Reference solution (b). A 1.0 per cent w/v solution of *oxyclozanide IPRS* in *acetone*.

Apply to the plate 40 µl and 10 µl of test solution, 4 µl of reference solution (a) and 10 µl of reference solution (b). After development, dry the plate in air and spray with a 3 per cent w/v solution of *ferric chloride* in *methanol*. In the chromatogram obtained with 40 µl of test solution any spot corresponding to *3,5,6-trichloro-2-hydroxybenzoic acid* is not more intense than that in the chromatogram obtained with reference solution (a).

B. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*.

Mobile phase. A mixture of 100 volumes of *ethyl acetate*, 10 volumes of *methanol* and 1 volume of *strong ammonia solution*.

Test solution. Dilute a quantity with *acetone* to contain 1.0 per cent w/v of Oxyclozanide, centrifuge and use the supernatant liquid.

Reference solution. A 0.040 per cent w/v of *2-amino-4,6-dichlorophenol IPRS* in *acetone*.

Apply to the plate 40 µl of test solution and 4 µl of reference solution. After development, dry the plate in air and spray with *lithium and sodium molybdotungstophosphate solution*. In the chromatogram obtained with the test solution any spot corresponding to 2-amino-4,6-dichlorophenol is not more intense than that in the chromatogram obtained with reference solution.

Other tests. Comply with the tests stated under Veterinary Oral Liquids.

Assay. Protect the solutions from light throughout the procedure. Weigh a quantity containing 60 mg of Oxyclozanide, add 60 ml of *acidified methanol* and boil gently on a water-bath. Shake continuously for 20 minutes, cool to 20° and dilute to 100.0 ml with *acidified methanol*. Filter, dilute 5.0 ml of the filtrate to 100.0 ml with *acidified methanol* and measure the absorbance of the resulting solution at the maximum at about 300 nm (2.4.7). Calculate the content of $C_{13}H_6Cl_5NO_3$ taking 254 as the specific absorbance at 300 nm.

Determine the weight per ml of the suspension (2.4.29), and calculate the content of oxyclozanide, weight in volume.

Oxyclozanide Premix

Oxyclozanide Granules.

Oxyclozanide Premix contains Oxyclozanide.

Oxyclozanide Premix contains not less than 92.5 per cent and not more than 107.5 per cent of the stated amount of oxyclozanide, $C_{13}H_6Cl_5NO_3$.

Usual strength. 5 per cent w/w.

Identification

In test A for Related substances, the principal spot in the chromatogram obtained with 10 ml of test solution corresponds to that in the chromatogram obtained with reference solution (b).

Tests

Related substances. A. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*.

Mobile phase. A mixture of 60 volumes of *light petroleum (60° to 80°)*, 20 volumes of *acetone* and 5 volumes of *glacial acetic acid*.

Test solution. Extract the finely powdered preparation under examination with sufficient *acetone* to produce a mixture containing 1.0 per cent w/v of Oxyclozanide, centrifuge and use the supernatant liquid.

Reference solution (a). A 0.050 per cent w/v solution of *3,5,6-trichloro-2-hydroxybenzoic acid IPRS* in *acetone*.

Reference solution (b). A 1.0 per cent w/v solution of *oxyclozanide IPRS* in *acetone*.

Apply to the plate 40 µl and 10 µl of test solution, 4 µl of reference solution (a) and 10 µl of reference solution (b). After development, dry the plate in air and spray with a 3 per cent w/v solution of *ferric chloride* in *methanol*. In the chromatogram obtained with 40 µl of test solution any spot corresponding to 3,5,6-trichloro-2-hydroxybenzoic acid is not more intense than that in the chromatogram obtained with reference solution (a).

B. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*.

Mobile phase. A mixture of 100 volumes of *ethyl acetate*, 10 volumes of *methanol* and 1 volume of *strong ammonia solution*.

Test solution. Extract the finely powdered preparation under examination with sufficient *acetone* to produce a mixture containing 1.0 per cent w/v of Oxyclozanide, centrifuge and use the supernatant liquid.

Reference solution. A 0.04 per cent w/v of *2-amino-4,6-dichlorophenol IPRS* in *acetone*.

Apply to the plate 40 µl of test solution and 4 µl of reference solution. After development, dry the plate in air and spray with *lithium and sodium molybdotungstophosphate solution*. In the chromatogram obtained with test solution any spot corresponding to 2-amino-4,6-dichlorophenol is not more intense than that in the chromatogram obtained with reference solution.

Assay. Protect the solutions from light throughout the procedure. Weigh a quantity of the finely powdered preparation

under examination containing 60 mg of Oxyclozanide, add 60 ml of *acidified methanol* and boil gently on a water-bath. Shake continuously for 20 minutes, cool to 2° and dilute to 100.0 ml with *methanol acidified*. Filter, dilute 5.0 ml of the filtrate to 100.0 ml with *methanol acidified* and measure the absorbance of the resulting solution at the maximum at about 300 nm (2.4.7). Calculate the content of $C_{13}H_6Cl_5NO_3$ taking 254 as the specific absorbance at 300 nm.

Labelling. The label states (1) the proportion of oxyclozanide in the premix and (2) the method of use of the preparation.

Oxytetracycline Injection

Oxytetracycline Dihydrate Injection

Usual strength. 200 mg per ml

For Identification and Tests refer to IP Volume III.

Oxytetracycline Hydrochloride

For Description, Identification and Tests refer to IP Volume III.

Oxytetracycline Hydrochloride Injection

Oxytetracycline Hydrochloride Injection is a sterile solution of Oxytetracycline Hydrochloride with or without one or more suitable buffering agents, anaesthetics, preservatives, antioxidants, complexing agents and solvents.

Oxytetracycline Hydrochloride Injection contains not less than 90.0 per cent and not more than 115.0 per cent of the stated amount of anhydrous oxytetracycline, $C_{22}H_{24}N_2O_9$.

Usual strengths. 50 mg per ml; 125 mg per ml.

Description. A clear, yellow colour liquid.

Identification

A. Determine by thin-layer chromatography (2.4.17), coating the plate with the substance prepared by mixing 25 g of *silica gel G* with 50 ml of a mixture of 2.5 ml of *glycerin* and 47.5 ml of *0.1 M disodium edetate* previously adjusted to pH 7.0 with *dilute ammonia solution*. After spreading the plate, allow it to stand at room temperature till it is dry (70 to 90 minutes).

Mobile phase. The lower layer formed after shaking 200 ml of a mixture of 2 volumes of *ethyl acetate*, 2 volumes of *chloroform* and 1 volume of *acetone* with 25 ml of *0.1 M disodium edetate* previously adjusted to pH 7.0 with *dilute ammonia solution*.

Test solution. Shake a quantity equivalent to 10 mg of oxytetracycline with 20 ml of *methanol*, centrifuge if necessary and use the clear supernatant liquid.

Reference solution (a). A 0.05 per cent w/v solution of *oxytetracycline hydrochloride IPRS* in *methanol*.

Reference solution (b). A solution containing 0.05 per cent w/v each of *demethylchlortetracycline hydrochloride IPRS*, *oxytetracycline hydrochloride IPRS* and *tetracycline hydrochloride IPRS* in *methanol*.

Apply to the plate 1 µl of each solution, freshly prepared. After development, dry the plate in air, expose to the vapours of ammonia and examine under ultraviolet light at 365 nm. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows three clearly separated spots.

B. Add 0.1 ml to 2 ml of *sulphuric acid*; a red colour is produced. Add the solution to 1 ml of *water*; the colour changes to yellow.

Tests

pH (2.4.24). 8.0 to 9.0.

Bacterial endotoxins (2.2.3). Not more than 0.4 Endotoxin Unit per mg of oxytetracycline.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. Determine by liquid chromatography (2.4.14).

Phosphate buffer pH 7.5. A mixture of 85 volumes of *0.33 M dibasic potassium phosphate* and 15 volumes of *0.33 M monobasic sodium phosphate*, adjusted to pH 7.5.

Test solution. Dilute a volume of the injection containing 100 mg of oxytetracycline to 500.0 ml with *0.01 M hydrochloric acid*.

Reference solution (a). A 0.02 per cent w/v solution of *oxytetracycline IPRS* in *0.01 M hydrochloric acid*.

Reference solution (b). A 0.02 per cent w/v solution of *tetracycline hydrochloride IPRS* in *0.01 M hydrochloric acid*. To 3.0 ml of the solution, add 1.5 ml of reference solution (a) and dilute to 25.0 ml with *water*.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with styrene-divinylbenzene co-polymer (5 to 10 µm),
- column temperature: 60°,

- mobile phase: a solution prepared by mixing 50 g of *tertiary butyl alcohol* with 200 ml of *water* in 1000-ml volumetric flask, add 60 ml of phosphate buffer pH 7.5, 50 ml of 1.0 per cent w/v solution of *tetrabutylammonium hydrogen sulphate*, adjusted to pH 7.5 with *1M sodium hydroxide* and 10 ml of a 0.04 per cent w/v solution of *disodium edetate*, adjusted to pH 7.5 with *2 M sodium hydroxide* and dilute to volume with *water*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

The relative retention time with reference to tetracycline for oxytetracycline is about 0.6.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peak due to oxytetracycline and tetracycline is not less than 5.0 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 1.25 and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of $C_{22}H_{24}N_2O_9$ in the injection.

Storage. Store protected from light.

Oxytetracycline Veterinary Oral Powder

Oxytetracycline Hydrochloride Veterinary Oral Powder; Oxytetracycline Hydrochloride Soluble Powder; Oxytetracycline Soluble Powder

Oxytetracycline Veterinary Oral Powder is a mixture of Oxytetracycline Hydrochloride and Lactose or other suitable diluent.

Oxytetracycline Veterinary Oral Powder contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of oxytetracycline hydrochloride, $C_{22}H_{24}N_2O_9,HCl$.

Usual strength. 5.6 per cent w/w of Oxytetracycline Hydrochloride.

Identification

A. Determine by thin-layer chromatography (2.4.17), coating the plate with a substance prepared by mixing 25 g of *silica gel G* with 50 ml of a mixture of 2.5 ml of *glycerin* and 47.5 ml of *0.1 M disodium edetate* previously adjusted to pH 7.0 with *dilute ammonia solution*. After spreading the plate, allow it to stand at room temperature till it is dry (70 to 90 minutes).

Mobile phase. The lower layer formed after shaking 200 ml of a mixture of 2 volumes of *ethyl acetate*, 2 volumes of *dichloromethane* and 1 volume of *acetone* with 25 ml of *0.1 M disodium edetate* previously adjusted to pH 7.0 with *dilute ammonia solution*.

Test solution. Extract a quantity of the oral powder containing 10 mg of Oxytetracycline Hydrochloride with 20 ml of *methanol*, centrifuge and use the supernatant liquid.

Reference solution (a). A 0.05 per cent w/v solution of *oxytetracycline hydrochloride IPRS* in *methanol*.

Reference solution (b). A solution containing 0.05 per cent w/v each of *demethylchlortetracycline hydrochloride IPRS*, *oxytetracycline hydrochloride IPRS* and *tetracycline hydrochloride IPRS* in *methanol*.

Apply to the plate 1 µl of each solution. After development, dry the plate in air, expose to the vapours of ammonia and examine under ultraviolet light at 365 nm. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows three clearly separated spots.

B. To a quantity of the powder containing 0.4 mg of Oxytetracycline Hydrochloride add 5 ml of a 1 per cent w/v solution of *sodium carbonate*, shake and add 2 ml of *diazotised sulphanilic acid solution*; a light brown colour is produced.

C. Shake a quantity of the powder containing 100 mg of Oxytetracycline Hydrochloride with 10 ml of *2 M nitric acid* and filter. To the filtrate add *activated charcoal* to decolorise it and filter again. The filtrate gives the reactions of chlorides (2.3.1).

Tests

Other tests. Comply with the tests stated under Oral Powder.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve a quantity of the oral powder containing about 50 mg of Oxytetracycline Hydrochloride in 100.0 ml of *0.01 M hydrochloric acid*. Dilute 1.0 ml of the solution to 10.0 ml with *0.01 M hydrochloric acid*.

Reference solution (a). A 0.005 per cent w/v solution of *oxytetracycline IPRS* in *0.01 M hydrochloric acid*.

Reference solution (b). A 0.1 per cent w/v solution of *4-epioxytetracycline IPRS* in *0.01 M hydrochloric acid*.

Reference solution (c). A 0.1 per cent w/v solution of *tetracycline hydrochloride IPRS* in *0.01 M hydrochloric acid*.

Reference solution (d). Dilute 1.5 ml of a 0.1 per cent w/v solution of *oxytetracycline IPRS* in *0.01 M hydrochloric acid*, 1.0 ml of reference solution (b) and 3.0 ml of reference solution (c) to 25.0 ml with *0.01 M hydrochloric acid*.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with styrene divinylbenzene copolymer (8 to 10 µm),
- column temperature. 60°,
- mobile phase: to 50 g of *2 methylpropan-2-ol*, add 200 ml of *water*, 60 ml of *0.33 M phosphate buffer pH 7.5*, 50 ml of 1.0 per cent w/v solution of *tetrabutylammonium hydrogen sulphate* previously adjusted to pH 7.5 with *2 M sodium hydroxide* and 10 ml of a 0.04 per cent w/v solution of *disodium edetate* previously adjusted to pH 7.5 with *2 M sodium hydroxide* and dilute to 1000 ml with *water*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

Inject reference solution (d). The test is not valid unless the resolution between the peaks due to 4-epioxytetracycline and oxytetracycline is not less than 4.0, the resolution between the peak due to oxytetracycline and tetracycline is not less than 5.0 and the tailing factor of the principal peak due to oxytetracycline is not more than 1.25.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{22}H_{24}N_2O_9$,HCl in the oral powder.

1 mg of $C_{22}H_{24}N_2O_9$ is equivalent to 1.079 mg of $C_{22}H_{24}N_2O_9$,HCl.

Storage. Store at a temperature not exceeding 15°.

Paclitaxel Injection

Usual strengths. 30 mg; 60 mg.

For Identification and Tests refer to IP Volume III.

Pentobarbitone Sodium

Category. Hypnotic and general anaesthetic.

For Identification and Tests refer to IP Volume III.

Pentobarbitone Injection

Pentobarbitone Sodium Injection; Pentobarbital Sodium Injection

Pentobarbitone Injection is a sterile solution of Pentobarbitone Sodium in a suitable vehicle.

Solutions containing 20 per cent w/v of Pentobarbitone Sodium in 100-ml and 500-ml containers are also available for use other than for injection. Such solutions may be coloured and need not be sterile but must comply with all other requirements of this monograph.

Pentobarbitone Injection contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of pentobarbitone sodium, $C_{11}H_{17}N_2NaO_3$.

Usual strength. 60 mg in 1 ml.

Description. A clear, colourless or almost colourless solution.

Identification

In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

pH (2.4.24). 10.0 to 11.5.

Isomer. To a volume of the injection containing 0.3 g of Pentobarbitone Sodium diluted, if necessary, to 5 ml with *water* add 0.3 g of *4-nitrobenzyl bromide* dissolved in 10 ml of *ethanol (95 per cent)*. Heat under a reflux condenser for 30 minutes, cool to 25°, scratch the sides of the vessel with a glass rod if necessary to induce crystallisation, filter and wash the residue with five quantities, each of 5 ml, of *water*. Transfer the residue as completely as possible to a small flask, add 25 ml of *ethanol (95 per cent)* and heat under a reflux condenser for 10 minutes. Filter the hot solution, cool to 25° and scratch the sides of the vessel with a glass rod to induce crystallisation. Filter and wash the residue with two quantities, each of 5 ml, of *water* and dry at 105° for 30 minutes. The dried residue melts completely between 136° and 148° (2.4.21).

Bacterial endotoxins (2.2.3). Not more than 0.8 Endotoxin Unit per mg of pentobarbitone.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a volume of the injection with the mobile phase to obtain a solution containing 0.01 per cent w/v of Pentobarbitone.

Reference solution. A 0.01 per cent w/v solution of *pentobarbitone IPRS* in the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Gemini C18),
- mobile phase: a mixture of 65 volumes of *0.01M monobasic potassium phosphate* and 35 volumes of *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 214 nm,
- injection volume: 10 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 15000 theoretical plates, the tailing factor is not more than 1.5 and the relative standard deviation of replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

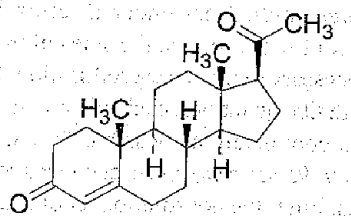
Calculate the content of $C_{11}H_{17}N_2NaO_3$ in the injection.

Fortified Procaine Penicillin Injection

Usual strength. Procaine Penicillin G 15 lacs IU & Penicillin G Sodium 5 lacs IU

For Identification and Tests refer to IP Volume III.

Progesterone



$C_{21}H_{30}O_2$ Mol. Wt. 314.5

Progesterone is pregn-4-en-3,20-dione.

Progesterone contains not less than 97.0 per cent and not more than 103.0 per cent of $C_{21}H_{30}O_2$, calculated on the dried basis.

Category. Progestogen.

Description. Colourless crystals or a white or almost white crystalline powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *progesterone IPRS* or with the reference spectrum of progesterone. If the spectra are not concordant, prepare spectra using 5 per cent w/v solutions in *chloroform IR*.

B. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 66 volumes of *dichloromethane* and 33 volumes of *ethyl acetate*.

Solvent mixture. 90 volumes of *dichloromethane* and 10 volumes of *methanol*.

Test solution. Dissolve 0.1 g of the substance under examination in 100 ml of the solvent mixture.

Reference solution. A 0.1 per cent w/v solution of *progesterone IPRS* in the solvent mixture.

Apply to the plate 5 µl of each solution. After removal of the plate, dry the plate in air and examine under ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with the reference solution. Spray the plate with *ethanolic sulphuric acid* (20 per cent), heat at 120° for 15 minutes, allow to cool and examine in day light and under ultraviolet light at 365 nm. The principal spot in the chromatogram obtained with the test solution corresponds in position, colour in day light, fluorescence under ultraviolet light and size to that in the chromatogram obtained with the reference solution.

Tests

Specific optical rotation (2.4.22). +186° to +194°, determined in a 1.0 per cent w/v solution in *ethanol (95 per cent)*.

Related substances. Determine by thin layer chromatography (2.4.17), coating the plate with *silica gel G*.

Mobile phase. A mixture of 66 volumes of *dichloromethane* and 33 volumes of *ethyl acetate*.

Solvent mixture. 90 volumes of *dichloromethane* and 10 volumes of *methanol*.

Test solution. Dissolve 0.1 g of the substance under examination in 10.0 ml of the solvent mixture.

Reference solution. Dilute 1.0 ml of the test solution to 100.0 ml with the solvent mixture.

Apply the plate 5 µl of each solution. After development, dry the plate in air and spray with a saturated solution of *potassium dichromate* in *sulphuric acid* (70 per cent), heat at 130° for 30 minutes and allow to cool. Any secondary spot in the chromatogram obtain with test solution is not more intense than the spot in the chromatogram obtain with reference solution.

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 0.5 g by drying in an oven at 105° for 2 hours.

Assay. Weigh 10 mg and dissolve in 100.0 ml of *ethanol (95 per cent)*. Dilute 5.0 ml of the solution to 50.0 ml with *ethanol (95 per cent)*. Measure the absorbance of the resulting solution at the maximum at about 241 nm (2.4.7). Calculate the content of $C_{21}H_{30}O_2$ taking 535 as the specific absorbance at 241 nm.

Storage. Store protected from light.

Progesterone Injection

Progesterone Injection is a sterile solution of Progesterone in Ethyl Oleate or other suitable ester, in a suitable fixed oil or in any mixture of these. It may contain suitable alcohols.

Progesterone Injection contains not less than 92.5 per cent and not more than 107.5 per cent of the stated amount of progesterone, $C_{21}H_{30}O_2$.

Usual strength 250 mg per ml.

Identification

Dissolve a volume containing 50 mg of Progesterone in 8 ml of *light petroleum (40° to 60°)* and extract with three quantities, each of 8 ml, of a mixture of 7 volumes of *glacial acetic acid* and 3 volumes of *water* until the solution becomes turbid, allow to stand in ice for 2 hours and filter. The precipitate, after washing with *water* and drying at 105°, complies with the following tests.

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *progesterone IPRS* or with the reference spectrum of progesterone. If the spectra are not concordant, prepare spectra using 5 per cent w/v solutions in *chloroform IR*.

B. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*.

Solvent mixture. A mixture of 90 volumes of *acetone* and 10 volumes of *1,2-propanediol*.

Mobile phase. A mixture of equal volumes of *cyclohexane* and *light petroleum (40° to 60°)*.

Test solution. Dissolve 25 mg of the substance under examination in 10 ml of the solvent mixture.

Reference solution (a). A 0.25 per cent w/v solution of *progesterone IPRS* in the solvent mixture.

Reference solution (b). Mix equal volumes of the test solution and reference solution (a).

Place the dry plate in a tank containing a shallow layer of the solvent mixture, allow the solvent mixture to ascend to the top, remove the plate from the tank and allow the solvent to evaporate. Use within 2 hours, with the flow of the mobile phase in the direction in which the aforementioned treatment was done.

Apply to the plate 2 µl of each solution. Allow the mobile phase to rise 12 cm. Dry the plate in a current of warm air, allow the solvent to evaporate, heat at 120° for 15 minutes and spray the hot plate with *ethanolic sulphuric acid (20 per cent v/v)*. Heat at 120° for a further 10 minutes, allow to cool and examine in daylight and in ultraviolet light at 365 nm. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with reference solution (a). The principal spot in the chromatogram obtained with reference solution (b) appears as a single, compact spot.

Tests

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. To a measured volume containing about 50 mg of Progesterone add sufficient *dichloromethane* to produce 100.0 ml. Dilute 3.0 ml to 50.0 ml with *dichloromethane*. To 5.0 ml of the solution add 10 ml of *isoniazid solution* and sufficient *methanol* to produce 20.0 ml. Allow to stand for 45 minutes and measure the absorbance of the resulting solution at the maximum at about 380 nm (2.4.7), using as the blank 5 ml of *dichloromethane* treated in the same manner. Calculate the content of $C_{21}H_{30}O_2$ from the absorbance obtained by repeating the procedure using a 0.003 per cent w/v solution of *progesterone IPRS* in *dichloromethane* and beginning at the words "To 5.0 ml of the solution.....".

Storage. Store protected from light. If solid matter separates on standing, it should be redissolved by heating before use.

Labelling. The label states (1) the composition of the solvent; (2) that the preparation is intended for veterinary use by subcutaneous or intramuscular injection only.

Promazine Hydrochloride

Category. Sedative.

For Description, Identification and Tests refer to IP Volume III.

Promazine Injection

Promazine Hydrochloride Injection

Promazine Injection is a sterile solution of Promazine Hydrochloride in Water for Injections free from dissolved air and containing suitable buffering and stabilising agents. The solution is distributed in containers, the air in which is replaced by nitrogen or other suitable gas.

Promazine Injection contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of promazine hydrochloride, $C_{17}H_{20}N_2S,HCl$.

Usual strengths. 50 mg in 1 ml; 100 mg in 2 ml.

Description. A colourless or almost colourless liquid.

Identification

A. To a volume containing 0.1 g of Promazine Hydrochloride add 20 ml of *water* and 2 ml of *10 M sodium hydroxide*. Shake

and extract the mixture with 25 ml of *ether*. Wash the ether extract with two quantities, each of 5 ml, of *water*, dry with *anhydrous sodium sulphate* and evaporate the ether. A 10 per cent w/v solution of the oily residue in *chloroform* complies with the following test.

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *promazine hydrochloride IPRS*, treated in the same manner.

B. To a volume containing 5 mg of Promazine Hydrochloride add carefully 2 ml of *sulphuric acid* and allow to stand for 5 minutes; an orange colour is produced.

C. To a volume containing 0.2 g of Promazine Hydrochloride add 1 ml of *1 M sodium hydroxide* and extract with four quantities, each of 10 ml, of *ether*. Wash the combined extracts with 10 ml of *water*, remove the ether and dissolve the residue in 4 ml of *methanol*. Heat on a water-bath almost to boiling, immediately add 2 ml of a boiling 3.5 per cent w/v solution of *picric acid* in *methanol* and boil for 2 minutes. Cool in ice, filter, wash the crystals thrice with *methanol*, dissolve in 10 ml of hot *methanol* and repeat the crystallisation and washing. The rust-red crystals so obtained, after drying at 105° for 1 hour, melt at about 144° (2.4.21).

Tests

pH (2.4.24). 4.4 to 5.2.

Related substances. Carry out the test for identification of related substances in phenothiazines (2.3.5), using *mobile phase A* and applying separately to the plate 10 µl of each of the following freshly-prepared solutions.

Test solution. Dilute a volume of the injection with sufficient *methanol* to produce a solution containing the equivalent of 1.0 per cent w/v of Promazine Hydrochloride.

Reference solution (a). Dilute 1 volume of the test solution to 40 volumes with *methanol*.

Reference solution (b). Dilute 1 volume of the test solution to 200 volumes with *methanol*.

Any secondary spot in the chromatogram obtained with the test solution is more intense than the spot in the chromatogram obtained with reference solution (a) and not more than one such spot is more intense than the spot in the chromatogram obtained with reference solution (b).

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay.

NOTE—Protect the solutions from light throughout the procedure.

To an accurately measured volume containing about 50 mg of Promazine Hydrochloride, add 5 ml of *2 M hydrochloric acid* and sufficient *water* to produce 1000.0 ml. To 10.0 ml add 10 ml of *0.1 M hydrochloric acid*, dilute to 100.0 ml with *water* and measure the absorbance of the resulting solution at the maximum at about 251 nm (2.4.7). Calculate the content of $C_{17}H_{20}N_2S,HCl$ taking 935 as the specific absorbance at 251 nm.

Storage. Store protected from light.

Promethazine Hydrochloride

For Description, Identification and Tests refer to IP Volume III.

Promethazine Injection

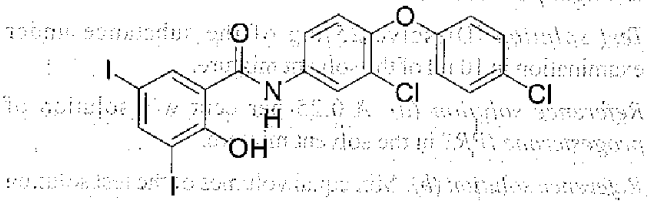
Usual strengths. 25 mg in 1 ml; 50 mg in 1 ml.

For Identification and Tests refer to IP Volume III.

Pyridoxine Hydrochloride

For Description, Identification and Tests refer to IP Volume III.

Rafoxanide



$C_{19}H_{11}Cl_2I_2NO_3$ Mol. Wt. 626.0

Rafoxanide is *N*-[3-chloro-4-(4-chlorophenoxy)phenyl]-2-hydroxy-3,5-diiodobenzamide.

Rafoxanide contains not less than 98.0 per cent and not more than 101.0 per cent of $C_{19}H_{11}Cl_2I_2NO_3$, calculated on the dried basis.

Category. Anthelmintic.

Description. A greyish-white to brown powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *rafoxanide IPRS* or with the reference spectrum of rafoxanide.

B. When examined in the range 230 nm to 360 nm (2.4.7), a 0.004 per cent w/v solution in *0.1 M methanolic hydrochloric acid* shows absorption maxima at about 280 nm and at 335 nm; absorbance at about 280 nm, about 0.97 and at about 335 nm, about 0.59.

C. Burn 20 mg by the oxygen-flask method (2.3.34), using 5 ml of *2 M sodium hydroxide* as the absorbing liquid, and dilute to 25 ml with *water*. To 5 ml add 1 ml of *silver nitrate solution*; a yellow precipitate is produced; add 5 ml of *5 M ammonia*, shake, filter, and acidify the filtrate with *nitric acid*; a white precipitate is produced.

D. Shake 10 mg with 10 ml of *ethanol (80 per cent)* and add 0.1 ml of *ferric chloride test solution*; a violet colour is produced.

E. Melts at about 175° (2.4.21).

Tests

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

NOTE — Carry out the test in subdued light and use freshly prepared solutions.

Mobile phase. A mixture of 170 volumes of *dichloromethane*, 30 volumes of *methanol* and 2 volumes of *strong ammonia solution*.

Test solution. Dissolve 2 g of the substance under examination in 100 ml in *dichloromethane*.

Reference solution. A 0.010 per cent w/v of *rafoxanide IPRS* in *dichloromethane*.

Apply to the plate 5 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. Any secondary spot in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with the reference solution.

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 90° at a pressure not exceeding 0.7 kPa for 2 hours.

Assay. To 50 ml of *dioxan* add 1 ml of *phenolphthalein solution*, replace the air in the flask with *nitrogen* and titrate with *0.1 M sodium hydroxide*. Weigh 1.25 g, dissolve it in the mixture and again titrate with *0.1 M sodium hydroxide*. The difference between the titrations represents the amount of *0.1 M sodium hydroxide* required.

1 ml of *0.1 M sodium hydroxide* is equivalent to 0.06260 g of $C_{19}H_{11}Cl_2I_2NO_3$.

Storage. Store protected from light.

Rafoxanide Veterinary Oral Suspension

Rafoxanide Suspension; Rafoxanide Veterinary Mixture; Rafoxanide Mixture

Rafoxanide Veterinary Oral Suspension is an aqueous suspension of Rafoxanide containing suitable suspending and dispersing agents and antimicrobial preservatives.

Rafoxanide Veterinary Oral Suspension contains not less than 90.0 per cent and not more than 110.0 per cent of rafoxanide, $C_{19}H_{11}Cl_2I_2NO_3$.

Usual strength. 3 per cent w/v.

Identification

A. Evaporate a volume containing 0.2 g of Rafoxanide to dryness on a water-bath and heat the residue over a Bunsen burner flame; the vapours turn moistened *starch-iodide paper* blue.

B. In addition to the absorbance at about 335 nm, measure the absorbance at about 280 nm (2.4.7), of the final solution obtained in the Assay. The ratio of the absorbance at about 280 nm to that at about 335 nm is 1.59 to 1.69.

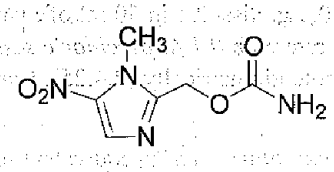
Tests

Other tests. Comply with requirements stated under Veterinary Oral Liquids.

Assay. Weigh a quantity of the well-mixed suspension containing 0.12 g of Rafoxanide in a stoppered 50-ml test tube and add 15 ml of *0.1 M sodium hydroxide* and 15 ml of *ether*. Shake for 5 minutes and centrifuge. Remove the ether layer and repeat the extraction with three further quantities, each of 15 ml, of *ether*. Dilute the combined ether solutions to 250.0 ml with *ether* and mix. Dilute 5.0 ml of the solution to 100.0 ml with *0.1 M methanolic hydrochloric acid*, mix and measure the absorbance of the resulting solution at about 335 nm (2.4.7). Calculate the content of $C_{19}H_{11}Cl_2I_2NO_3$ taking 149 as the specific absorbance at 335 nm.

Determine the weight per ml of the suspension (2.4.29), and calculate the content of rafoxanide, weight in volume.

Ronidazole



$C_6H_8N_4O_4$ Mol. Wt. 200.2

Ronidazole is 1-methyl-2-[(carbamoyloxy)methyl]-5-nitroimidazole.

Ronidazole contains not less than 98.5 per cent and not more than 101.0 per cent of $C_6H_8N_4O_4$, calculated on the anhydrous basis.

Category. Antiprotozoal.

Description. A white to yellowish-brown powder; odourless or almost odourless.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *ronidazole IPRS* or with the reference spectrum of ronidazole.

B. When examined in the range 230 nm to 360 nm (2.4.7), a 0.002 per cent w/v solution in *0.1 M methanolic hydrochloric acid* shows an absorption maximum only at about 270 nm; absorbance at about 270 nm, about 0.64.

C. Melts at about 167° (2.4.21).

Tests

Appearance of solution. A 0.5 per cent w/v solution in *methanol* is not more intensely coloured than reference solution YS6 (2.4.1).

(1-Methyl-5-nitroimidazol-2-yl)methanol. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 80 volumes of *toluene*, 5 volumes of *methanol* and 5 volumes of *glacial acetic acid*.

Test solution. Dissolve 1 g of the substance under examination in 100 ml in *acetone*.

Reference solution. A 0.0050 per cent w/v of *(1-methyl-5-nitroimidazol-2-yl)methanol IPRS* in *acetone*.

Apply to the plate 20 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. Any secondary spot in the chromatogram obtained with the test solution corresponding to (1-methyl-5-nitroimidazol-2-yl)methanol is not more intense than the spot in the chromatogram obtained with the reference solution.

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Water (2.3.43). Not more than 0.5 per cent.

Assay. Weigh 0.3 g, dissolve in 50 ml of *anhydrous glacial acetic acid*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (2.4.25). Carry out a blank titration.

1 ml of *0.1 M perchloric acid* is equivalent to 0.02002 g of $C_6H_8N_4O_4$.

Storage. Store protected from light.

Ronidazole Veterinary Oral Powder

Ronidazole Veterinary Oral Powder is a mixture of Ronidazole with suitable diluents.

Ronidazole Veterinary Oral Powder contains not less than 92.5 per cent and not more than 107.5 per cent of the stated amount of ronidazole, $C_6H_8N_4O_4$.

Usual strength. 10 per cent w/w.

Identification

A. Shake a quantity of the powder containing 0.1 g of Ronidazole with 10 ml of *acetone* for 15 minutes, filter and evaporate the filtrate to dryness. The residue complies with the following test.

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *ronidazole IPRS* or with the reference spectrum of ronidazole.

B. When examined in the range 230 nm to 360 nm (2.4.7), the final solution obtained in the Assay shows an absorption maximum only at about 281 nm.

Tests

(1-Methyl-5-nitroimidazol-2-yl)methanol. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 80 volumes of *toluene*, 5 volumes of *methanol* and 5 volumes of *glacial acetic acid*.

Test solution. Shake a quantity of the powder containing 0.1 g of Ronidazole with 10 ml of *acetone* for 15 minutes and filter.

Reference solution. A 0.0050 per cent w/v of *(1-methyl-5-nitroimidazol-2-yl)methanol IPRS* in *acetone*.

Apply to the plate 20 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. Any secondary spot in the chromatogram obtained with the test solution corresponding to (1-methyl-5-nitroimidazol-2-yl)methanol RS is not more intense than the spot in the chromatogram obtained with the reference solution.

Other tests. Comply with the tests stated under Veterinary Oral Powders.

Assay. Weigh a quantity of powder containing 0.2 g of Ronidazole, dissolve in 450 ml of *water* and add sufficient *water* to produce 500.0 ml. Dilute 5.0 ml of the solution to 100.0 ml with *0.1 M hydrochloric acid* and measure the absorbance of the resulting solution at the maximum at about 281 nm (2.4.7). Calculate the content of $C_6H_8N_4O_4$ taking 279 as the specific absorbance at 281 nm.

Storage. Store protected from light.

Serum Gonadotrophin for Veterinary Use

Equine Serum Gonadotrophin for Veterinary Use

Serum Gonadotrophin for Veterinary Use is a dry preparation of a glycoprotein fraction, obtained from the serum or plasma of pregnant mares in their 60th to 75th day of pregnancy, which stimulates the formation of follicles and induces leutinising activity.

Serum Gonadotrophin for Veterinary Use contains not less than 1000 Units per mg, calculated on the anhydrous basis.

Category. Gonadotrophic hormone.

Description. A white or pale grey, amorphous powder.

Identification

Causes enlargement of the ovaries of immature female rats when administered as directed in the Assay.

Tests

Water (2.3.43). Not more than 10.0 per cent, determined on 80 mg.

Assay. Carry out the biological assay of serum gonadotrophin described below.

The potency of serum gonadotrophin for veterinary use is determined by comparing its effect in increasing the weight of the ovaries of immature rats with that of the Standard Preparation of serum gonadotrophin under the conditions of the following method of assay.

Standard Preparation

The Standard Preparation is the 2nd International Standard for serum gonadotrophin, equine, for bioassay, established in 1966, consisting of the freeze-dried active principle from the serum of pregnant mares, with lactose (supplied in ampoules containing 1600 Units), or other suitable preparation the potency of which has been determined in relation to the International Standard.

Method

Test animals. Use immature female rats of the same strain, 21 to 28 days old, differing in age by not more than 3 days and of approximately equal weights such that the difference between the heaviest and the lightest rat is not more than 10 g. Assign the rats at random to six equal groups of not less than five animals. If sets of six litter-mates are available, allot one litter-mate from each set at random to each group and mark according to the litter.

Procedure. Choose three doses of the Standard Preparation and three doses of the preparation under examination such that the smallest dose is sufficient to produce a positive response in some of the rats and the largest dose does not produce a maximal response in all of the rats. Use doses in geometric progression. As an initial approximation total doses of 8, 12 and 18 Units may be tried although the dose will depend on the sensitivity of the animals used, which may vary widely. Dissolve separately the total quantities of the preparation under examination and of the Standard Preparation corresponding to the doses to be used in sufficient of a sterile *saline solution* containing 1 mg of *bovine albumin* per ml such that each single dose may be administered by the injection of 6 equally-divided portions, in the same volume of about 0.2 ml. Store the solutions at a temperature 2° to 8°. Inject subcutaneously into each rat the dose allocated to its group. Repeat the injections 18, 21, 24, 42 and 48 hours after the first injection. Kill the rats between 40 hours and 72 hours after the last injection and remove the ovaries. Remove any extraneous fluid and tissue and immediately weigh the two ovaries from each rat.

Calculate the result of the assay by standard statistical methods using the combined weight of the two ovaries of each animal as the response.

Limits of error - The estimated potency is not less than 80 per cent and not more than 125 per cent of the stated potency. The fiducial limits of error ($P = 0.95$) of the estimated potency are not less than 64 per cent and not more than 156 per cent of the stated potency.

Serum Gonadotrophin for Veterinary Use intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins complies with the following additional requirement.

Bacterial endotoxins (2.2.3). Carry out the test, Method C. Not more than 0.035 Endotoxin Unit per mg of serum gonadotrophin.

Serum Gonadotrophin for Veterinary Use intended for use in the manufacture of parenteral preparations without a further appropriate sterilisation procedure complies with the following additional requirement.

Sterility (2.2.11). Complies with the test for sterility.

Storage. Store protected from moisture and light in a refrigerator (2 to 8). If the contents are sterile, the containers should be sterile, tamper-evident and sealed so as to exclude micro-organisms.

Labelling. The label states (1) the number of Units per mg; (2) the total number of Units in the container; (3) the date after which the material is not intended to be used; (4) the storage conditions; (5) whether or not it is intended for use in the manufacture of parenteral preparations.

Serum Gonadotrophin Injection for Veterinary Use

Serum Gonadotrophin Injection for Veterinary Use is a sterile material consisting of Serum Gonadotrophin for Veterinary Use with or without buffering agents and other excipients. It is filled in a sealed container.

The injection is constituted by dissolving the contents of the sealed container in the requisite amount of sterile Water for Injections, immediately before use.

The constituted solution complies with the requirements for Clarity of solution and Particulate matter stated under Parenteral Preparations (Injections).

Storage. The constituted solution should be used immediately after preparation but, in any case, within the period recommended by the manufacturer.

Serum Gonadotrophin Injection for veterinary Use contains not less than 80.0 per cent and not more than 125.0 per cent of the stated potency.

The contents of the sealed container comply with the requirements stated under Parenteral Preparations (Powders for Injection) and with the following requirements.

Usual strength. 1000 Units.

Identification

Causes enlargement of the ovaries of immature female rats when administered as directed in the Assay.

Tests

Appearance of solution. A solution containing 5000 Units per ml (solution A) is clear (2.4.1), and colourless (2.4.1).

pH (2.4.24). 6.0 to 8.0, determined on solution A.

Water (2.3.43). Not more than 10.0 per cent, determined on 80 mg.

Assay. Carry out the biological assay of serum gonadotrophin described below.

The potency of serum gonadotrophin for veterinary use is determined by comparing its effect in increasing the weight of the ovaries of immature rats with that of the Standard Preparation of serum gonadotrophin under the conditions of the following method of assay.

Standard Preparation

The Standard Preparation is the 2nd International Standard for serum gonadotrophin, equine, for bioassay, established in 1966, consisting of the freeze-dried active principle from the serum of pregnant mares, with lactose (supplied in ampoules containing 1600 Units), or other suitable preparation the potency of which has been determined in relation to the International Standard.

Test animals. Use immature female rats of the same strain, 21 to 28 days old, differing in age by not more than 3 days and of approximately equal weights such that the difference between the heaviest and the lightest rat is not more than 10 g. Assign the rats at random to six equal groups of not less than five animals. If sets of six litter-mates are available, allot one litter-mate from each set at random to each group and mark according to the litter.

Procedure. Choose three doses of the Standard Preparation and three doses of the preparation under examination such that the smallest dose is sufficient to produce a positive response in some of the rats and the largest dose does not produce a maximal response in all of the rats. Use doses in geometric progression. As an initial approximation total doses of 8, 12 and 18 Units may be tried although the dose will depend on the sensitivity of the animals used, which may vary widely. Dissolve separately the total quantities of the preparation under examination and of the Standard Preparation corresponding to the doses to be used in sufficient of a sterile *saline solution* containing 1 mg of *bovine albumin* per ml such that each single dose may be administered by the injection of 6 equally-divided portions, in the same volume of about 0.2 ml. Store the solutions at a temperature 2° to 8°. Inject subcutaneously into each rat the dose allocated to its group. Repeat the injections 18, 21, 24, 42 and 48 hours after the first injection. Kill the rats between 40 hours and 72 hours after the last injection and remove the ovaries. Remove any extraneous fluid and tissue and immediately weigh the two ovaries from each rat.

Calculate the result of the assay by standard statistical methods using the combined weight of the two ovaries of each animal as the response.

Limits of error. The estimated potency is not less than 80 per cent and not more than 125 per cent of the stated potency. The fiducial limits of error ($P = 0.95$) of the estimated potency are not less than 64 per cent and not more than 156 per cent of the stated potency.

Bacterial endotoxins (2.2.3). Carry out the test, Method C. Dissolve the sealed container in *water BET* to give a solution containing 1000 Units of serum gonadotrophin per ml. The solution contains not more than 35 Endotoxin Unit per ml.

Storage. Store protected from light in a refrigerator (2° to 8°).

Labelling. The label states the number of Units contained in the sealed container.

Sodium Acid Phosphate Injection

Sodium Acid Phosphate Injection is a sterile solution of Sodium Acid Phosphate in Water for Injections.

Sodium Acid Phosphate Injection contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of sodium acid phosphate, $NaH_2PO_4, 2H_2O$.

Usual strength. Elemental Phosphorus 8 per cent w/v.

Identification

Dilute 2.5 ml of the solution with sufficient *carbon dioxide-free water* to produce 10 ml (Solution A).

A. Solution A neutralised with 10 per cent w/v solution of *potassium hydroxide* gives reaction of *sodium salts* (2.3.1).

B. Solution A gives reactions of *phosphates* (2.3.1).

Tests

Sterility (2.2.11). Complies with the test for sterility.

Bacterial endotoxins (2.2.3). Not more than 75.75 Endotoxin Unit per mg of sodium acid phosphate.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. Transfer 2.0 ml of measured volume of the sample to a glass-stoppered flask containing about 40 ml of *water* and titrate with *1 M sodium hydroxide*, determining the end-point potentiometrically. Carry out a blank titration.

1 ml of *1M sodium hydroxide* is equivalent to 0.156 g of $NaH_2PO_4, 2H_2O$.

Storage. Store protected from light.

Monobasic Sodium Phosphate

Sodium Dihydrogen Phosphate Dihydrate

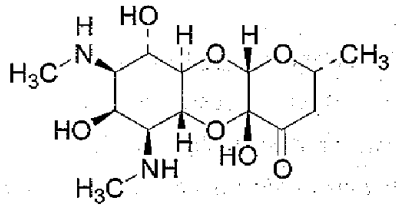
Used in Veterinary as a source of Phosphorous in form of Injection.

For Description, Identification and Tests refer to IP Volume III.

Sodium Thiosulphate

For Description, Identification and Tests refer to IP Volume III.

Spectinomycin Hydrochloride



, 2HCl, $5H_2O$

$C_{14}H_{24}N_2O_7,2HCl,5H_2O$ Mol. Wt. 495.4

Spectinomycin Hydrochloride is [2*R*-(2α,4aβ,5aβ,6β,7β,8β,9α,9aα,10aβ)]-decahydro-4a,7,9-trihydroxy-2-methyl-6,8-bis(methylamino)-4*H*-pyrano[2,3-*b*] [1,4]benzodioxin-4-one dihydrochloride pentahydrate.

Spectinomycin Hydrochloride contains not less than 95.0 per cent and not more than 100.5 per cent of $C_{14}H_{24}N_2O_7,2HCl$, calculated on the anhydrous basis.

Category. Antibacterial.

Description. A white or almost white, crystalline powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *spectinomycin hydrochloride IPRS* or with the reference spectrum of spectinomycin hydrochloride.

B. It gives reaction (A) of chlorides (2.3.1).

Tests

Appearance of solution. A 10 per cent w/v solution is clear (2.4.1), and colourless (2.4.1).

pH (2.4.24). 3.8 to 5.6, determined in a 10 per cent w/v solution.

Specific optical rotation (2.4.22). +15.0° to +21.0°, determined in a 10 per cent w/v solution within 20 minutes of preparation, on the anhydrous basis.

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*

Mobile phase. A mixture of 50 volumes of *1-propanol*, 40 volumes of *water*, 5 volumes of *glacial acetic acid* and 5 volumes of *pyridine*.

Test solution. Dissolve 2 g of the substance under examination in 100 ml *water*.

Reference solution. A 0.020 per cent w/v solution of the substance under examination in *water*.

Apply to the plate 10 µl of each solution. After development, dry the plate in air and spray with a 5 per cent w/v solution of *potassium permanganate*. Allow the plate to stand for 2 to

3 minutes. Any secondary spot in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with the reference solution (1 per cent).

Sulphated ash (2.3.18). Not more than 1.0 per cent.

Water (2.3.43). 16.0 to 20.0 per cent, determined on 0.2 g.

Assay. Determine by gas chromatography (2.4.13).

NOTE — Use the solutions within 1 hour after preparation.

Test solution (a). Take 60 mg of the substance under examination in a glass-stoppered conical flask, add 10.0 ml of *dimethylformamide* and 2.0 ml of *hexamethyl- disilazane*, shake intermittently for 1 hour and dilute to 20.0 ml with *dimethylformamide*.

Test solution (b). Take 60 mg of the substance under examination in a glass-stoppered conical flask, add 10.0 ml of a solution containing 0.15 per cent w/v of *phenazone* (internal standard) in *dimethylformamide* and 2.0 ml of *hexamethyl-disilazane*, shake intermittently for 1 hour and dilute to 20.0 ml with *dimethylformamide*.

Reference solution. Take 60 mg of the *spectinomycin hydrochloride IPRS* in a glass-stoppered conical flask, add 10.0 ml of a solution containing 0.15 per cent w/v of *phenazone* (internal standard) in *dimethylformamide* and 2.0 ml of *hexamethyl- disilazane*, shake intermittently for 1 hour and dilute to 20.0 ml with *dimethylformamide*.

Chromatographic system

- a glass column 1.5 m x 4 mm, packed with acid-washed, silanised diatomaceous support (100 to 120 mesh) coated with 3 per cent w/w of *phenylmethylsilicone fluid (50 per cent phenyl)*,
- temperature:
  column 200°,
  inlet port 200° and detector 230°,
- flow rate: 45 ml per minute of the carrier gas.

Inject the chosen volumes of test solutions (a) and (b). The test is not valid unless the resolution factor between the peak due to the internal standard and the principal peak in the chromatogram obtained with test solution (b) is not less than 8.0.

Inject the reference solution and test solution (b).

Calculate the content of $C_{14}H_{24}N_2O_7$,2HCl.

Spectinomycin Hydrochloride intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins complies with the following additional requirement.

Bacterial endotoxins (2.2.3). Not more than 0.09 Endotoxin Unit per mg determined in a 0.42 per cent w/v solution of *sodium bicarbonate*.

Spectinomycin Hydrochloride intended for use in the manufacture of parenteral preparations without a further appropriate sterilisation procedure complies with the following additional requirement.

Sterility (2.2.11). Complies with the test for sterility.

Storage. Store protected from moisture, at a temperature not exceeding 30°. If the substance is sterile, the container should be sterile, tamper-evident and sealed so as to exclude micro-organisms.

Labelling. The label states (1) the date after which the material is not intended to be used; (2) the storage conditions; (3) whether or not it is intended to be used for manufacture of parenteral preparations.

Spectinomycin Injection

Spectinomycin Hydrochloride Injection

Spectinomycin Injection is a sterile material consisting of Spectinomycin Hydrochloride with or without auxiliary substances. It is filled in a sealed container.

The injection is constituted by suspending the contents of the sealed container in the requisite amount of sterile Water for Injections, immediately before use.

Storage. The constituted suspension should be used immediately after preparation but, in any case, within the period recommended by the manufacturer.

Spectinomycin Injection contains not less than 90.0 per cent and not more than 110.0 per cent the stated amount of spectinomycin, $C_{14}H_{24}N_2O_7$.

The contents of the sealed container comply with the requirements stated under Parenteral Preparations (Powders for Injection) and with the following requirements.

Usual strength. Equivalent of 2 g of spectinomycin.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *spectinomycin hydrochloride IPRS* or with the reference spectrum of spectinomycin hydrochloride.

B. It gives reaction (A) of chlorides (2.3.1).

Tests

pH (2.4.24). 4.0 to 7.0, determined in a suspension of the contents of a sealed container in the volume of the liquid stated on the label.

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*

Mobile phase. A mixture of 50 volumes of *1-propanol*, 40 volumes of *water*, 5 volumes of *glacial acetic acid* and 5 volumes of *pyridine*.

Test solution. Prepare a solution containing the equivalent of 1.4 per cent w/v of spectinomycin in *water*.

Reference solution. A 0.015 per cent w/v solution of *spectinomycin hydrochloride IPRS* in *water*.

Apply to the plate 10 µl of each solution. After development, dry the plate in air and spray with a 5 per cent w/v solution of *potassium permanganate*. Allow the plate to stand for 2 to 3 minutes. Any secondary spot in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with reference solution.

Water (2.3.43). Not more than 20.0 per cent, determined on 0.2 g.

Bacterial endotoxins (2.2.3). Not more than 0.09 Endotoxin Unit per ml, determined on a solution prepared by dissolving the contents in a solution containing *0.05 M sodium bicarbonate* in *water BET* to give a solution containing the equivalent of 1 mg of spectinomycin per ml (solution A), and using the maximum valid dilution of solution A calculated from the declared sensitivity of the lysate used in the test.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. Determine by gas chromatography (2.4.13).

NOTE — Use the solutions within 1 hour after preparation.

Test solution (a). Weigh and mix the contents of the 10 containers. To a weighed quantity containing about 60 mg of Spectinomycin Hydrochloride in a glass-stoppered conical flask, add 10.0 ml of *dimethyl-formamide* and 2.0 ml of *hexamethyl- disilazane*, shake intermittently for 1 hour and dilute to 20.0 ml with *dimethyl-formamide*.

Test solution (b). To a weighed quantity containing about 60 mg of Spectinomycin Hydrochloride in a glass-stoppered conical flask, add 10.0 ml of a solution containing 0.15 per cent w/v of *phenazone* (internal standard) in *dimethylformamide* and 2.0 ml of *hexamethyl- disilazane*, shake intermittently for 1 hour and dilute to 20.0 ml with *dimethylformamide*.

Reference solution. T0 about 60 mg, weighed, of *spectinomycin hydrochloride IPRS* in a glass-stoppered conical flask, add 10.0 ml of a solution containing 0.15 per cent w/v of *phenazone* (internal standard) in *dimethylformamide* and 2.0 ml of *hexamethyl-disilazane*, shake intermittently for 1 hour and dilute to 20.0 ml with *dimethylformamide*.

Chromatographic system

- a glass column 1.5 m x 4 mm, packed with acid-washed, silanised diatomaceous support (100 to 120 mesh) coated with 3 per cent w/w of *phenylmethylsilicone fluid (50 per cent phenyl)*,
- temperature:
  column 200°,
  inlet port 200° and detector 230°,
- flow rate: 45 ml per minute of the carrier gas.

Inject the chosen volumes of test solutions (a) and (b). The test is not valid unless the resolution factor between the peak due to the internal standard and the principal peak in the chromatogram obtained with test solution (b) is not less than 8.0.

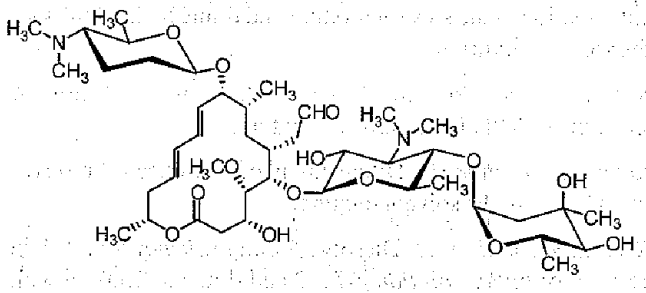
Inject the reference solution and test solution (b).

Calculate the content of $C_{14}H_{24}N_2O_7$.

Storage. Use the injection immediately after preparation but, in any case, within the period recommended by the manufacturer provided it is prepared and stored in accordance with the manufacturer's instructions.

Labelling. The label states the strength in terms of the equivalent amount of spectinomycin.

Spiramycin



$C_{43}H_{74}N_2O_{14}$ Mol. Wt. 843.1

Spiramycin is (4*R*,5*S*,6*R*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-10-{[(2*R*,5*S*,6*R*)-5-(Dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl]oxy}-9,16-dimethyl-5-methoxy-2-oxo-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-6-yl-3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-3-(dimethylamino)-α-D-glucopyranoside.

Spiramycin contains not less than 3900 Units per mg, calculated on the dried basis.

Category. Antibacterial.

Description. A white or slightly yellowish powder; slightly hygroscopic.

Identification

A. When examined in the range 220 nm to 360 nm (2.4.7), a 0.001 per cent w/v solution in *methanol* shows an absorption maximum only at about 232 nm; absorbance at about 232 nm, about 0.34.

B. Dissolve 0.5 g in a mixture of 10 ml of *0.05 M sulphuric acid* and 25 ml of *water*. Adjusted to pH 8.0 with *0.1 M sodium hydroxide* and dilute to 50 ml with *water*. To 5 ml of the resulting solution add 2 ml of a mixture of 1 volume of *water* and 2 volumes of *sulphuric acid*; a brown colour is produced.

Tests

pH (2.4.24). 8.5 to 10.5, determined in a solution prepared by dissolving 0.5 g in 5 ml of *methanol* and diluting to 100 ml with *carbon dioxide-free water*.

Specific optical rotation (2.4.22). –85.0° to –80.0°, determined in a 2 per cent w/v solution in *0.2 M acetic acid*.

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Related substances. Determine by liquid chromatography (2.4.14).

NOTE–Prepare the solutions immediately before use.

Solvent mixtue. 30 volumes of *methanol* and 70 volumes of *water*.

Test solution. Dissolve 25 mg of the substance under examination in the solvent mixture and dilute to 25.0 ml with the solvent mixture.

Reference solution (a). A 0.1 per cent w/v solution of *spiramycin IPRS* in the solvent mixture.

Reference solution (b). Dilute 2.0 ml of reference solution (a) to 100 ml with the solvent mixture.

Reference solution (c). Dissolve 5.0 mg *spiramycin IPRS* in 15.0 ml of *buffer solution pH 2.2* and dilute to 25.0 ml with *water*, heat on water-bath at 60° for 5 minutes and cool.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, endcapped polar embedded octadecylsilane amorphous organosilica polymer (5 µm) (polar embedded octadecylsilane methylsilica (12.5 µm),
- mobile phase: a mixture of 5.0 volumes of 3.48 per cent solution of *dipotassium hydrogen phosphate*, adjusted to pH 6.5 with 2.72 per cent w/v solution of *potassium dihydrogen phosphate*, 40 volumes of *acetonitrile* and 55 volumes of *water*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 232 nm,
- injection volume: 20 µl.

Inject reference solution (a) and (c). Run the chromatogram three times the retention times of spiromycin peak. The relative rentention time with reference to spiramycin I for impurity F is about 0.41, for impurity A is about 0.45, for impurity D is about 0.5, for impurity G is about 0.66, for impurity B is about 0.73, for impurity H is about 0.87, for spiramycin II is about 1.4, for spiramycin III is about 2.0 and for impurity E is about 2.5. The test is not valid unless in the chromatogram obtained with reference solution (c), the resolution between the peaks due to impurity A and spiramycin I is not less than 10.0.

Inject reference solution (b) and the test solution. The area of secondary peak due to impurity A, B, C, D, E, F, G and H, each of, is not more than the area of principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent). The area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent) and the sum of areas of all the secondary peaks is not more than 5 times the area of principal peak in the chromatogram obtained with reference solution (b) (10.0 per cent). Ignore any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the peak due to blank, Spiramycin I, II, III.

Sulphated ash (2.3.18). Not more than 0.1 per cent w/v.

Loss on drying (2.4.19). Not more than 3.5 per cent, determined on 0.5 g by drying over *phosphorus pentoxide* at 80° at a pressure not exceeding 0.7 kPa for 6 hours.

Assay. Determine by the microbiological assay of antibiotics (2.2.10).

Storage. Store protected from moisture.

Streptomycin Sulphate

For Description, Identification and Tests refer to IP Volume III.

Sulphadiazine

For Description, Identification and Tests refer to IP Volume III.

Sulphadiazine and Trimethoprim Injection

Trimethoprim and Sulphadiazine Injection; Co-trimazine Injection

Sulphadiazine and Trimethoprim Injection is a sterile suspension in Water for Injections containing Sulphadiazine and Trimethoprim in the proportion of five parts to one part respectively.

Sulphadiazine and Trimethoprim Injection contains not less than 90.0 per cent and not more than 110.0 per cent of the

stated amounts of sulphadiazine, $C_{10}H_{10}N_4O_2S$ and of trimethoprim, $C_{14}H_{18}N_4O_3$.

Usual strengths. 400 mg of Sulphadiazine and 80 mg of Trimethoprim in 1 ml; 200 mg of Sulphadiazine and 40 mg of Trimethoprim in 1 ml.

Identification

A. When examined in the range 230 nm to 360 nm (2.4.7), the solution obtained in the Assay for *trimethoprim* shows an absorption maximum only at about 271 nm.

B. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 75 volumes of *ethyl acetate*, 15 volumes of *dimethylformamide* and 5 volumes of *water*.

Test solution. Add 4 ml of *hydrochloric acid* to 2.5 ml of the well-mixed contents of the container and dilute to 50 ml with *1.4 M methanolic ammonia*.

Reference solution (a). A 2.0 per cent w/v of *sulphadiazine IPRS* in *1.4 M methanolic ammonia*.

Reference solution (b). A 0.4 per cent w/v of *trimethoprim IPRS* in *1.4 M methanolic ammonia*.

Apply to the plate 1 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. One of the principal spots in the chromatogram obtained with the test solution corresponds to the principal spot in the chromatogram obtained with reference solution (a) and the other corresponds to the principal spot in the chromatogram obtained with reference solution (b).

C. To 5 ml of the filtrate obtained in the Assay *for sulphadiazine* add 10 ml of *water* and 5 ml of *thiobarbituric acid-citrate buffer*. Mix and heat on a water-bath for 30 minutes; a pink colour is produced.

Tests

pH (2.4.24). 10.0 to 10.5.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. *For sulphadiazine* — Disperse the trimethoprim evenly throughout the injection solution by gently inverting the container several times without foam formation. Transfer an accurately measured quantity of the injection containing 2 g of Sulphadiazine to a separating funnel containing 50 ml of *0.1 M sodium hydroxide* and extract with two quantities, each of 100 ml and 50 ml of *dichloromethane*, washing the extract with the same 25-ml quantity of *0.1 M sodium hydroxide*. Reserve the combined dichloromethane extracts for the assay for trimethoprim.

Dilute the combined aqueous solutions and washings to 250.0 ml with *water* and filter, and dilute 5.0 ml of the filtrate to 200.0 ml with *water*. Dilute 10.0 ml of the solution to 100.0 ml with *water*. To 3.0 ml of the resulting solution add 1 ml of *2 M hydrochloric acid* and 1 ml of a 0.1 per cent w/v solution of *sodium nitrite* and allow to stand for 2 minutes. Add 1 ml of a 0.5 per cent w/v solution of *ammonium sulphamate* and allow to stand for 3 minutes. Add 1 ml of a 0.1 per cent w/v solution of *N-(1-naphthyl)ethylenediamine dihydrochloride*, allow to stand for 10 minutes, add sufficient *water* to produce 25.0 ml and measure the absorbance of the resulting solution at the maximum at about 538 nm (2.4.7). Calculate the content of $C_{10}H_{10}N_4O_2S$ from the absorbance obtained by carrying out the procedure simultaneously, using 3.0 ml of a solution prepared by dissolving 200 mg of *sulphadiazine IPRS* in 50 ml of *0.1 M sodium hydroxide*, adding sufficient *water* to produce 200.0 ml, diluting 5.0 ml to 250.0 ml with *water* and beginning at the words "add 1 ml of *2 M hydrochloric acid*.....".

For trimethoprim — Extract the dichloromethane solution reserved in the Assay *for sulphadiazine* with three quantities, each of 100 ml, 50 ml and 50 ml, of *1 M acetic acid* and dilute the combined extracts to 500.0 ml with *1 M acetic acid*. To 5.0 ml add 35 ml of *1 M acetic acid* and sufficient *water* to produce 200.0 ml and measure the absorbance of the resulting solution at the maximum at about 271 nm (2.4.7). Calculate the content of $C_{14}H_{18}N_4O_3$ taking 204 as the specific absorbance at 271 nm.

Labelling. The label states the content of Sulphadiazine and Trimethoprim in a suitable dose-volume.

Sulphadiazine and Trimethoprim Veterinary Oral Powder

Trimethoprim and Sulphadiazine Veterinary Oral Powder; Sulphadiazine and Trimethoprim Dispersible Powder; Co-trimazine Veterinary Oral Powder

Sulphadiazine and Trimethoprim Veterinary Oral Powder consists of Sulphadiazine and Trimethoprim in the proportion of five parts to one part respectively, mixed with suitable wetting, dispersing and suspending agents.

Sulphadiazine and Trimethoprim Veterinary Oral Powder contains not less than 92.5 per cent and not more than 107.5 per cent of the stated amounts of sulphadiazine, $C_{10}H_{10}N_4O_2S$, and of trimethoprim, $C_{14}H_{18}N_4O_3$.

Usual strength. 10 per cent w/w of Sulphadiazine and 2 per cent w/w of Trimethoprim.

Identification

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 75 volumes of *ethyl acetate*, 15 volumes of *dimethylformamide* and 5 volumes of *water*.

Test solution (a). The supernatant liquid obtained by shaking a quantity of the powder containing 0.2 g of Sulphadiazine with sufficient *1.4 M methanolic ammonia* to produce 100 ml and centrifuging.

Test solution (b). The supernatant liquid obtained by shaking a quantity of the powder containing 0.2 g of Trimethoprim with sufficient *1.4 M methanolic ammonia* to produce 100 ml and centrifuging.

Reference solution (a). A 0.2 per cent w/v solution of *sulphadiazine IPRS* in *1.4 M methanolic ammonia*.

Reference solution (b). A 0.2 per cent w/v solution of *trimethoprim IPRS* in *1.4 M methanolic ammonia*.

Apply to the plate 5 µl of each solution. After development, dry the plate in air and spray with a 0.1 per cent w/v solution of *4-dimethylaminobenzaldehyde* in a mixture of 1 ml of *hydrochloric acid* and 100 ml of *ethanol (95 per cent)*, allow to dry and spray with *dilute potassium iodobismuthate solution*. The spot in the chromatogram obtained with test solution (a) having R_f value of about 0.7 corresponds to the principal spot in the chromatogram obtained with reference solution (a). The spot in the chromatogram obtained with test solution (b) having R_f value of about 0.3 corresponds to the principal spot in the chromatogram obtained with reference solution (b).

Tests

Other tests. Comply with the tests stated under Veterinary Oral Powders.

Assay. *For sulphadiazine* — Weigh a quantity of the powder containing 0.125 g of Sulphadiazine, transfer into a separator containing 20 ml of *0.1 M sodium hydroxide* and extract with four quantities, each of 50 ml, of *dichloromethane*. Wash each dichloromethane extract with the same two quantities, each of 10 ml, of *0.1 M sodium hydroxide*. Combine the aqueous washings and the aqueous layer from the separator and reserve the combined dichloromethane extracts for the Assay for trimethoprim.

Dilute the combined aqueous solutions to 250.0 ml with *water*, filter and dilute 10.0 ml of the filtrate to 200.0 ml with *water*. To 2.0 ml of the resulting solution add 0.5 ml of *4 M hydrochloric acid* and 1 ml of a 0.1 per cent w/v solution of *sodium nitrite* and allow to stand for 2 minutes. Add 1 ml of a 0.5 per cent w/v solution of *ammonium sulphamate* and allow to stand for 3 minutes. Add 1 ml of a 0.1 per cent w/v solution of *N-(1-naphthyl)ethylenediamine dihydrochloride*, allow to stand for 10 minutes. Dilute the solution to 25.0 ml with *water* and measure the absorbance of the resulting solution at the maximum at about 538 nm (2.4.7), using as the blank a solution prepared in the same manner using 2 ml of *water* and beginning at the words "add 0.5 ml of *4 M hydrochloric acid*.....". Calculate the content of $C_{10}H_{10}N_4O_2S$ from the absorbance obtained by carrying out the procedure simultaneously, with 2.0 ml of a 0.0025 per cent w/v solution of *sulphadiazine IPRS* in *0.0005 M sodium hydroxide* and beginning at the words "add 0.5 ml of *4 M hydrochloric acid*.....".

For trimethoprim — Extract the combined dichloromethane extracts from the Assay for sulphadiazine with four quantities, each of 50 ml, of a 5 per cent v/v solution of *6 M acetic acid*; wash the combined aqueous extracts with 5 ml of *dichloromethane*, discard the dichloromethane layer and dilute to 250.0 ml with a 5 per cent v/v solution of *6 M acetic acid*. Dilute 20.0 ml to 100.0 ml with *water* and determine the absorbance of the resulting solution at the maximum at about 271 nm (2.4.7). Calculate the content of $C_{14}H_{18}N_4O_3$ taking 204 as the specific absorbance at 271 nm.

Sulphadiazine and Trimethoprim Veterinary Oral Suspension

Sulphadiazine and Trimethoprim Mixture; Trimethoprim and Sulphadiazine Veterinary Oral Suspension; Co-trimazine Oral Suspension; Co-trimazine Mixture

Sulphadiazine and Trimethoprim Veterinary Oral Suspension is a suspension of Sulphadiazine and Trimethoprim in the proportion of five parts to one part respectively, containing suitable suspending and dispersing agents. It may contain suitable antimicrobial preservatives.

Sulphadiazine and Trimethoprim Veterinary Oral Suspension contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amounts of sulphadiazine, $C_{10}H_{10}N_4O_2S$, and of trimethoprim, $C_{14}H_{18}N_4O_3$.

Usual strengths. 40 per cent w/v of Sulphadiazine and 8 per cent w/v of Trimethoprim; 4.55 per cent w/v of Sulphadiazine and 0.91 per cent w/v of Trimethoprim.

Identification

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 75 volumes of *ethyl acetate*, 15 volumes of *dimethylformamide* and 5 volumes of *water*.

Test solution (a). A dilution of the oral suspension in *1.4 M methanolic ammonia* containing the equivalent of 0.2 per cent w/v of Sulphadiazine.

Test solution (b). A dilution of the oral suspension in *1.4 M methanolic ammonia* containing the equivalent of 0.2 per cent w/v of Trimethoprim.

Reference solution (a). A 0.2 per cent w/v solution of *sulphadiazine IPRS* in *1.4 M methanolic ammonia*.

Reference solution (b). A 0.2 per cent w/v solution of *trimethoprim IPRS* in *1.4 M methanolic ammonia*.

Apply to the plate 5 µl of each solution. After development, dry the plate in air and spray with a 0.1 per cent w/v solution of *4-dimethylaminobenzaldehyde* in a mixture of 1 ml of *hydrochloric acid* and 100 ml of *ethanol (95 per cent)*, allow to dry and spray with *dilute potassium iodobismuthate solution*. The spot in the chromatogram obtained with test solution (a) having R_f value of about 0.7 corresponds to the principal spot in the chromatogram obtained with reference solution (a). The spot in the chromatogram obtained with test solution (b) having R_f value of about 0.3 corresponds to the principal spot in the chromatogram obtained with reference solution (b).

Tests

Other tests. Comply with the tests stated under Veterinary Oral Liquids.

Assay. *For sulphadiazine* — Transfer a weighed quantity of the oral suspension containing about 0.125 g of Sulphadiazine, into a separator containing 20 ml of *0.1 M sodium hydroxide* and extract with four quantities, each of 50 ml, of *dichloromethane*. Wash each dichloromethane extract with the same two quantities, each of 10 ml, of *0.1 M sodium hydroxide*. Combine the aqueous washings and the aqueous layer from the separator and reserve the combined dichloromethane extracts for the Assay for trimethoprim.

Dilute the combined aqueous solutions to 250.0 ml with *water*, filter and dilute 10.0 ml of the filtrate to 200.0 ml with *water*. To 2.0 ml of the resulting solution add 0.5 ml of *4 M hydrochloric acid* and 1 ml of a 0.1 per cent w/v solution of *sodium nitrite* and allow to stand for 2 minutes. Add 1 ml of a 0.5 per cent w/v solution of *ammonium sulphamate* and allow to stand for 3 minutes. Add 1 ml of a 0.1 per cent w/v solution of *N-(1-naphthyl)ethylenediamine dihydrochloride*, allow to stand for 10 minutes. Dilute the solution to 25.0 ml with *water* and measure the absorbance of the resulting solution at the maximum at about 538 nm (2.4.7), using as the blank a solution prepared in the same manner using 2 ml of *water* and beginning at the words "add 0.5 ml of *4 M hydrochloric acid*.....".

Calculate the content of $C_{10}H_{10}N_4O_2S$ from the absorbance obtained by carrying out the procedure simultaneously, with 2.0 ml of a 0.0025 per cent w/v solution of *sulphadiazine IPRS* in *0.0005 M sodium hydroxide* and beginning at the words "add 0.5 ml of *4 M hydrochloric acid*.....".

For trimethoprim — Extract the combined dichloromethane extracts from the Assay for sulphadiazine with four quantities, each of 50 ml, of a 5 per cent v/v solution of *6 M acetic acid*; wash the combined aqueous extracts with 5 ml of *dichloromethane*, discard the dichloromethane layer and dilute to 250.0 ml with a 5 per cent v/v solution of *6 M acetic acid*. Dilute 20.0 ml to 100.0 ml with *water* and determine the absorbance of the resulting solution at the maximum at about 271 nm (2.4.7). Calculate the content of $C_{14}H_{18}N_4O_3$ taking 204 as the specific absorbance at 271 nm.

Determine the weight per ml of the suspension (2.4.29), and calculate the contents of sulphadiazine and trimethoprim, weight in volume.

Labelling. The label states the strength in terms of the amounts of Sulphadiazine and Trimethoprim.

Sulphadiazine and Trimethoprim Tablets/Boluses

Trimethoprim and Sulphadiazine Tablets/Boluses; Co-trimazine Tablets/Boluses

Sulphadiazine and Trimethoprim Tablets/Boluses consist of Sulfadiazine and Trimethoprim in the proportion of five parts to one part respectively.

Sulphadiazine and Trimethoprim Tablets/Boluses contains not less than 92.5 per cent and not more than 107.5 per cent of the stated amounts of sulphadiazine, $C_{10}H_{10}N_4O_2S$ and of trimethoprim, $C_{14}H_{18}N_4O_3$.

Usual strengths. Sulphadiazine 1000 mg and Trimethoprim 200 mg; Sulphadiazine 400 mg and Trimethoprim 80 mg; Sulphadiazine 200 mg and Trimethoprim 40 mg tablets/boluses.

Identification

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 75 volumes of *ethyl acetate*, 15 volumes of *dimethylformamide* and 5 volumes of *water*.

Test solution (a). Shake a quantity of the finely powdered tablets/boluses in *1.4 M methanolic ammonia* containing the equivalent of 0.2 per cent w/v of Sulfadiazine. Centrifuge if necessary.

Test solution (b). Shake a quantity of the finely powdered tablets/boluses in *1.4 M methanolic ammonia* containing the equivalent of 0.2 per cent w/v of Trimethoprim. Centrifuge if necessary.

Reference solution (a). A 0.2 per cent w/v solution of *sulfadiazine IPRS* in *1.4 M methanolic ammonia*.

Reference solution (b). A 0.2 per cent w/v solution of *trimethoprim IPRS* in *1.4 M methanolic ammonia*.

Apply to the plate 5 µl of each solution. After development, dry the plate in air and spray with a 0.1 per cent w/v solution of *4-dimethylaminobenzaldehyde* in a mixture of 1 ml of *hydrochloric acid* and 100 ml of *ethanol (95 per cent)*, allow to dry and spray with *dilute potassium iodobismuthate solution*. The spot in the chromatogram obtained with test solution (a) corresponds to the principal spot in the chromatogram obtained with the reference solution (a). The spot in the chromatogram obtained with test solution (b) corresponds to the principal spot in the chromatogram obtained with reference solution (b).

Tests

Other tests. Comply with the tests stated under Tablets/Boluses.

Assay. *For sulphadiazine* — Weigh a quantity of the powdered tablets/boluses containing 0.125 g of Sulphadiazine, transfer in to a separator containing 20 ml of *0.1 M sodium hydroxide* and extract with four quantities, each of 50 ml, of *dichloromethane*. Wash each dichloromethane extract with the same two quantities, each of 10 ml, *of 0.1 M sodium hydroxide*. Combine the aqueous washings and the aqueous layer from the separator and reverse the combined dichloromethane extracts for the Assay for trimethoprim.

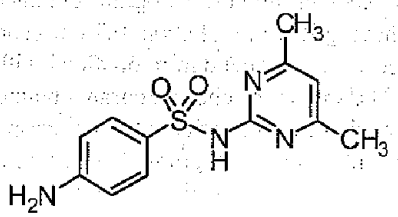
Dilute the combined aqueous solutions to 250.0 ml with *water*, filter and dilute 10.0 ml of the filtrate to 200.0 ml with *water*. To 2 ml of the resulting solution add 0.5 ml of *4 M hydrochloric acid* and 1 ml of a 0.1 per cent w/v solution of *sodium nitrite* and allow to stand for 2 minutes. Add 1 ml of a 0.5 per cent w/v solution of *ammonium sulphamate* and allow to stand for 3 minutes. Add 1 ml of a 0.1 per cent w/v solution of *N-(1-naphthyl) ethylene diamine dihydrochloride*; allow to stand for 10 minutes. Dilute the solution to 25.0 ml with *water* and measure the *absorbance* of the resulting solution at the maximum at about 538 nm (2.4.7), using as the blank a solution prepared in the same manner using 2 ml of *water* and beginning at the words "add 0.5 ml of *4 M hydrochloric acid*.....". Calculate the content of $C_{10}H_{10}N_4O_2S$ in the injection from the absorbance obtained by carrying out then procedure simultaneously, with 2.0 ml of a 0.0025 per cent w/v solution of *sulfadiazine IPRS* in *0.0005 M sodium hydroxide* and beginning at the words "add 0.5 ml of *4 M hydrochloric acid*.....".

For trimethoprim—Extract the combined dichloromethane extracts from the assay the Assay for sulfadiazine with four quantities, each of 50 ml, of a 5.0 per cent v/v solution of *6 M acetic acid*; wash the combined extracts with 5 ml of *dichloromethane*, discard the dichloromethane layer and dilute to 250.0 ml with a 5.0 per cent v/v solution of *6 M acetic acid*. Dilute 20.0 ml of the solution to 100.0 ml with *water* and determine the absorbance of resulting solution at the maximum at about 271 nm (2.4.7). Calculate the content of $C_{14}H_{18}N_4O_3$ taking 204 as the specific absorbance at 271.

Labelling. The label states the strength in terms of the amounts of Sulfadiazine and Trimethoprim.

Sulphadimidine

Sulfamathazine



$C_{12}H_{14}N_4O_2S$ Mol. Wt. 278.3

Sulphadimidine is 4-amino-*N*-(4, 6-dimethylpyridin-2-yl) benzenesulphonamide.

Sulphadimidine contains not less than 99.0 per cent and not more than 101.0 per cent of $C_{12}H_{14}N_4O_2S$, calculated on the dried basis.

Category. Sulphonamide antibacterial.

Description. A white or almost white powder or crystals.

Identification

Test C and D may be omitted if test A and B are carried out. Tests A may be omitted if test B, C and D are carried out.

A. In the test for Related substances, the principal spot in the chromatogram obtained with test solution (a) corresponds to that in the chromatogram obtained with reference solution (a).

B. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *sulphadimidine IPRS* or with the reference spectrum of sulphadimidine.

C. Take 3.0 g in a dry tube. Immerse the lower part of the tube, inclined at 45°, in a silicone oil bath and heat to about 270°. The substance under examination decomposes and a white or yellowish-white sublimate is formed which, after recrystallisation from *toluene* and drying at 100°, melts (2.4.21) at 150° to 154°.

D. Dissolve 5 mg in 10 ml of *1 M hydrochloric acid*. Dilute 1.0 ml of the solution to 10 ml with *water*, the solution, without further acidification, gives the reaction of primary aromatic amines (2.3.1).

Tests

Appearance of solution (2.4.1). Dissolve 0.5 g of substance under examination, in a mixture of 5.0 ml of *dilute sodium*

hydroxide solution and 5.0 ml of *water*, the remaining solution is not more intensely coloured than reference solution YS5, BYS5 or GYS5.

Acidity. Shake 1.25 g finely powdered substance with 25.0 ml of *carbon dioxide-free water*. Heat at about 70° for 5 minutes. Cool in iced water for about 15 minute and filter. To 20 ml of the filtrate, add 0.1 ml of *bromothymol blue solution*. Not more than 0.2 ml of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 3 volumes of *dilute ammonia*, 5 volumes of *water*, 40 volumes of *nitromethane* and 50 volumes of *dioxin*.

Test solution (a). Dissolve 20 mg of the substance under examination in 5 ml of a mixture of 2 volumes of *strong ammonia* and 48 volumes of *methanol*.

Test solution (b). Dissolve 0.10 g of the substance under examination in 0.5 ml of *strong ammonia* and dilute to 5.0 ml with *methanol*. If the solution is not clear, heat gently until dissolution is complete.

Reference solution (a). Dissolve 20 mg of *sulphadimidine IPRS* in 5 ml of a mixture of 2 volumes of *strong ammonia* and 48 volumes of *methanol*.

Reference solution (b). Dilute 1.25 ml of test solution (a) to 50.0 ml with a mixture of 2 volumes of *strong ammonia* and 48 volumes of *methanol*.

Apply to the plate 5µl of each solution. Allow the mobile phase to rise 15 cm. After development, dry the plate, heat at 100° to 105° and examine under ultraviolet light at 254 nm. Any secondary spot in the chromatogram obtained with the test solution (b) is not more than intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent).

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent.

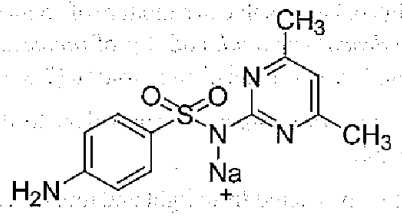
Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105°.

Assay. Dissolve 0.25 g in a mixture of 20 ml of *dilute hydrochloric acid* and 50 ml of *water*. Cool the solution in iced water. Carry out the determination of primary aromatic amino-nitrogen, determining the end-point electrometrically. Carry out a blank titration.

1 ml of *0.1 M sodium nitrite* is equivalent to 0.02783 g of $C_{12}H_{14}N_4O_2S$.

Storage. Store protected from light.

Sulphadimidine Sodium



$C_{12}H_{13}N_4NaO_2S$ Mol. Wt. 300.3

Sulphadimidine Sodium is the sodium salt of *N¹*–(4,6-dimethylpyrimidin-2-yl) sulphanilamide.

Sulphadimidine Sodium contains not less than 98.0 per cent and not more than 101.0 per cent of $C_{12}H_{13}N_4NaO_2S$, calculated on the dried basis.

Description. A white or creamy white crystals or powder; hygroscopic.

Identification

A. Dissolve 0.1 g in 10 ml *water*, acidify with *1 M hydrochloric acid*, filter, wash the precipitate with *water* and dry the residue at 105°.

On the residue determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *sulphadimidine IPRS* or with the reference spectrum of sulphadimidine.

B. Acidify a solution of 0.1 g in 5 ml of *water with 6 M acetic acid*. A precipitate is produced which, after washing with cold *water* and drying at 105°, gives the reaction of primary aromatic amines (2.3.1), producing a bright orange-red precipitate.

C. The washed and dried precipitate obtained in test B melts at about 198° (2.4.21).

D. Incinerate 0.5 g. The residue, when moistened with *hydrochloric acid* and introduced on a platinum wire into the flame of a Bunsen burner, imparts a yellow colour to the flame.

Tests

Appearance of solution. A 33.3 per cent w/v solution is clear (2.4.1), and not more intensely coloured than reference solution YS4 (2.4.1).

pH (2.4.24). 10.0 to 11.0, determined in a 10.0 per cent w/v solution.

Related substances (2.3.7). Complies with test A, but using as the test solution a solution prepared by dissolving the substance under examination in 1 volume of *strong ammonia solution* and then diluting with 9 volumes of *ethanol (95 per cent)* to produce a 1.0 per cent w/v solution.

Loss on drying (2.4.19). Not more than 2.0 per cent, determined on 1.0 g by drying in an oven at 105°.

Assay. Weigh 0.3 g, dissolve in a mixture of 75 ml of *water* and 10 ml of *hydrochloric acid*, add 3 g of *potassium bromide*, cool in ice and carry out the nitrite titration (2.3.31).

1 ml of *0.1 M sodium nitrite* is equivalent to 0.03003 g of $C_{12}H_{13}N_4NaO_2S$.

Storage. Store protected from light and moisture.

Sulphadimidine Injection

Sulphadimidine Sodium Injection

Sulphadimidine Injection is a sterile solution of Sulphadimidine Sodium in Water for Injections free from dissolved air.

Sulphadimidine Injection contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of Sulphadimidine sodium, $C_{12}H_{13}N_4NaO_2S$.

Usual strength. 33.33 per cent w/v.

Identification

A. Acidify a volume of injection containing 0.1 g of Sulphadimidine sodium with *6 M acetic acid*, filter, wash the residue with *water* and dry at 105°. The residue complies with the following test.

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *sulphadimidine IPRS* or with the reference spectrum of sulphadimidine.

B. The residue obtained in test A gives the reaction of *primary aromatic amines* (2.3.1) producing a bright red precipitate.

Tests

Appearance of solution (2.4.1). Dissolve an injection containing 1.0 g of Sulphadimidine sodium in 3.0 ml *water*, the solution is not more intensely coloured than reference solution YS4.

pH (2.4.24). 10.0 to 11.0.

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel H*.

Mobile phase. A mixture of 18 volumes of *10 M ammonia* and 90 volumes of *butan-1-ol*.

Test solution. A 0.20 per cent w/v solution of Sulphadimidine sodium in the *water*.

Reference solution. A 0.0020 per cent w/v solution of *sulfanilamide* in a mixture of 1 volume of *13.5 M ammonia* and 9 volumes of *ethanol (95 per cent)*.

Apply to the plate 10 µl of each solution. Allow the mobile phase to rise 15 cm. After development, dry the plate at 105° for 10 minutes, spray with 0.1 per cent solution of *4-dimethyl aminobenzaldehyde* in *ethanol (95 per cent)* containing a 1.0 per cent v/v of *hydrochloric acid*. Any secondary spot in the chromatogram obtained with the test solution is not more than intense than the spot in the chromatogram obtained with reference solution (1.0 per cent).

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. Transfer a volume containing about 0.50 g of Sulphadimidine sodium dilute to 75 ml with *water*, add 10 ml of *hydrochloric acid* and pass air slowly through the solution until the vapours do not turn moistened *starch iodate paper* blue. Add 3.0 g of *potassium bromide* and cool the solution in ice. Titrate slowly with *0.1 M sodium nitrite*, stirring constantly and determine the end-point electrometrically. Carry out a blank titration.

1 ml of *0.1 M sodium nitrite* is equivalent to 0.03003 g of $C_{12}H_{13}N_4NaO_2S$.

Storage. Store protected from light.

Labelling. The label states that the strength is stated as the amount of Sulphadimidine sodium in a suitable dose-volume.

Sulphadimidine Boluses

Sulphadimidine Boluses contain not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of Sulphadimidine, $C_{12}H_{14}N_4O_2S$.

Usual strength. 2.5 g; 5.0 g.

Identification

A. Take a quantity of the powdered boluses containing 0.5 g of Sulphadimidine, extract with two quantities, each of 5 ml of *chloroform* and discard the *chloroform*. Shake the residue with 10 ml of *5 M ammonia* for 5 minutes, add 10 ml of *water* and filter. Warm the filtrate until most of the ammonia has been removed, cool, acidify with *6 M acetic acid*, wash the residue with *water* and dry at 105°. The residue complies with the following test.

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *sulphadimidine IPRS* or with the reference spectrum of sulphadimidine.

B. In the test for Related substances, the principal spot in the chromatogram obtained with test solution (b) corresponds to that in the chromatogram obtained with reference solution.

C. The residue obtained in test A gives the reaction of *primary aromatic amines* (2.3.1).

Tests

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 3 volumes of *6 M ammonia*, 5 volumes of *water*, 40 volumes of *nitromethane* and 50 volumes of *1,4-dioxan*.

Solvent mixture. 1 volume of *13.5 M ammonia* and 24 volumes of *methanol*.

Test solution (a). Shake a quantity of the powdered boluses containing 0.5 g of Sulphadimidine with 25 ml of a mixture of 1 volume of *13.5 M ammonia* and 9 volumes of *methanol* for 10 minutes and filter.

Test solution (b). Dilute 1.0 volume of test solution (a) to 5.0 volumes with a solvent mixture.

Test solution (c). Dilute 1.0 volume of test solution (a) to 200.0 volumes with a solvent mixture.

Reference solution. A 0.40 per cent w/v solution of *sulphadimidine IPRS* in solvent mixture.

Apply to the plate 5 µl of each solution. Allow the mobile phase to rise 15 cm. After development, dry the plate at 105° and examine under ultraviolet light at 254 nm. Any secondary spot in the chromatogram obtained with the test solution (a) is not more intense than the spot in the chromatogram obtained with test solution (c) (0.5 per cent).

Other tests. Comply with the tests stated under Boluses.

Assay. Weigh and powder 20 boluses. Disperse a quantity of the powder containing 0.5 g of Sulphadimidine, add 50 ml of *water*, 10 ml of *hydrochloric acid* and 3.0 g of *potassium bromide*, cool the solution in ice. Titrate slowly with *0.1 M sodium nitrite*, stirring constantly and determine the end-point electrometrically. Carry out a blank titration.

1 ml of *0.1 M sodium nitrite* is equivalent to 0.02783 g of $C_{12}H_{14}N_4NaO_2S$.

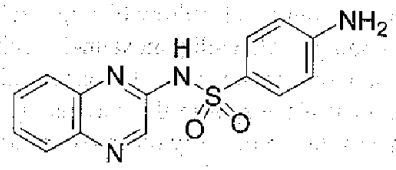
Storage. Store protected from light.

Sulphamethoxazole and Trimethoprim Boluses

Usual strength. Sulphamethoxazole 2 g and Trimethoprim 400 mg per bolus.

For Identification and Tests refer to IP Volume III.

Sulphaquinoxaline



$C_{14}H_{12}N_4O_2S$ Mol. Wt. 300.3

Sulphaquinoxaline is 4-amino-*N*-2-quinoxalinylbenzene-sulphonamide.

Sulphaquinoxaline contains not less than 98.0 per cent and not more than 101.0 per cent of $C_{14}H_{12}N_4O_2S$, calculated on the dried basis.

Category. Antibacterial.

Description. A yellow colour powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *sulphaquinoxaline IPRS* or with the reference spectrum of sulphaquinoxaline.

B. When examined in the range 230 nm to 360 nm (2.4.7), a 0.001 per cent w/v solution in *0.01 M sodium hydroxide* shows an absorption maximum only at about 252 nm; about 1.1.

C. Dissolve 4 mg in 2 ml of warm *2 M hydrochloric acid*. The solution gives the reaction of primary aromatic amines (2.3.1).

Tests

Acidity. To 2 g add 100 ml of *water*, heat at 70° for 5 minutes, cool to 20°, and filter. Titrate 50 ml of the filtrate to pH 7.0 with *0.1 M sodium hydroxide*; not more than 0.2 ml of *0.1 M sodium hydroxide* is required.

Heavy metals. Dissolve the residue obtained in the test for Sulphated ash in 1 ml of *2 M hydrochloric acid* and dilute to 14 ml with *water*. 12 ml of the solution complies with limit test for heavy metals, Method D (2.3.13) (20 ppm).

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 60 volumes of *dichloromethane*, 40 volumes of *methanol* and 20 volumes of *strong ammonia solution*.

Test solution. Dissolve 0.2 g of the substance under examination in 2 ml of *1 M sodium hydroxide* and add sufficient *methanol* to produce 50 ml.

Reference solution (a). A 0.012 per cent w/v solution of *N^1,N^2-diquinoxalin- 2-ylsulphanilamide IPRS* in *methanol*.

Reference solution (b). A 0.004 per cent w/v solution of *sulphanilamide IPRS* in *methanol*.

Apply to the plate 5 µl of each solution. After development, dry the plate in air until the odour of the solvent is no longer detectable and examine under ultraviolet light at 254 nm. Any spot corresponding to N^1, N^2-diquinoxalin-2-ylsulphanilamide in the chromatogram obtained with the test solution not more intense than that of the spot in the chromatogram obtained with reference solution (a). Any other secondary spot in the chromatogram obtained with the test solution is not more intense than that in the chromatogram obtained by reference solution (b).

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Loss on drying (2.4.19). Not more than 1.0 per cent, determined on 1.0 g by drying in an oven at 105°.

Assay. Weigh 0.65 g and dissolve in 10 ml of a mixture of equal volumes of *1 M sodium hydroxide* and *water*. Add 20 ml of *glycerin*, 20 ml of *9 M sulphuric acid* and 5 g of *potassium bromide*, cool in ice and carry out the nitrite titration (2.3.31).

1 ml of *0.1 M sodium nitrite* is equivalent to 0.03003 g of $C_{14}H_{12}N_4O_2S$.

Storage. Store protected from light.

Sulphaquinoxaline Sodium Solution

Sulphaquinoxaline Sodium Solution is an aqueous solution of sulphaquinoxaline sodium prepared by the interaction of Sulphaquinoxaline and Sodium Hydroxide.

Sulphaquinoxaline Sodium Solution contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of sulphaquinoxaline, $C_{14}H_{12}N_4O_2S$.

Usual strength. The equivalent of 96 mg of Sulphaquinoxaline in 1 ml.

Description. A clear, yellow to brown solution.

Identification

A. To a volume containing 1 g of Sulphaquinoxaline add 10 ml of *water* and 3 ml of *2 M hydrochloric acid*, filter, wash the precipitate with *water* and dry for 2 hours at 105°. The residue complies with the following test.

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *sulphaquinoxaline IPRS* or with the reference spectrum of sulphaquinoxaline.

B. Dissolve 4 mg of the residue obtained in test A in 2 ml of warm *2 M hydrochloric acid*. The solution gives the reaction of primary aromatic amines (2.3.1).

C. Acidify with *6 M acetic acid*, filter and evaporate the filtrate to dryness. The incinerated residue, when moistened with *hydrochloric acid* and introduced on a platinum wire into a Bunsen burner flame, gives a yellow colour to the flame.

Tests

pH (2.4.24). 12.2 to 12.8, determined in a 9.6 per cent w/v solution in *carbon dioxide-free water*.

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 60 volumes of *dichloromethane*, 40 volumes of *methanol* and 20 volumes of *strong ammonia solution*.

Test solution. Dilute a solution containing 0.2 g of Sulphaquinoxaline to 50 ml with *methanol*.

Reference solution (a). A 0.012 per cent w/v solution of N^1, N^2-*diquinoxalin- 2-ylsulphanilamide IPRS* in *methanol*.

Reference solution (b). A 0.004 per cent w/v solution of *sulphanilamide IPRS* in *methanol*.

Apply to the plate 5 µl of each solution. After development, dry the plate in air until the odour of the solvent is no longer detectable and examine under ultraviolet light at 254 nm. Any spot corresponding to N^1,N^2-diquinoxalin-2-ylsulphanilamide in the chromatogram obtained with the test solution not more intense than that in the chromatogram obtained with reference solution (a). Any other secondary spot in the chromatogram obtained with the test solution is not more intense than that of the spot in the chromatogram obtained with reference solution (b).

Other tests. Comply with the tests stated under Veterinary Oral Liquids.

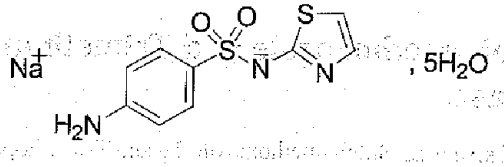
Assay. To a measured volume containing about 0.48 g of Sulphaquinoxaline add 30 ml *water*, 20 ml of *glycerin*, 20 ml of *9 M sulphuric acid* and 5 g of *potassium bromide*, cool in ice and carry out the nitrite titration (2.3.31).

1 ml of *0.1 M sodium nitrite* is equivalent to 0.03003 g of $C_{14}H_{12}N_4O_2S$.

Storage. Store protected from light.

Labelling. The label states the strength in terms of the equivalent amount of Sulphaquinoxaline in a suitable dose-volume.

Sulphathiazole Sodium



$C_9H_8N_3NaO_2S_2,1^1/_2H_2O$ Mol. Wt. 304.3

$C_9H_8N_3NaO_2S_2,5H_2O$ Mol. Wt. 367.4

Sulphathiazole Sodium is sodium salt of 4-amino-*N*-2-thiazolylbenzenesulphonamide with five or one and half molecules of water.

Sulphathiazole Sodium contains not less than 99.0 per cent and not more than 101.0 per cent of $C_9H_8N_3NaO_2S_2$, calculated on the dried basis.

Category. Antibacterial.

Description. A white or yellowish white, crystalline powder or granules.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *sulphathiazole sodium IPRS* or with the reference spectrum of sulphathiazole sodium.

B. Dissolve 1 g in 25 ml of *water* and add 2 ml of *6 M acetic acid*. Wash the precipitate formed with *water* and dry for 4 hours at 105°. The residue melts at about 201° (2.4.21).

C. The precipitate obtained in test B gives the reaction of primary aromatic amines (2.3.1).

Tests

pH (2.4.24). 9.0 to 10.0, determined in a 1 per cent w/v solution.

Heavy metals. Dissolve 2.5 g of the substance under examination in 10 ml of *water*, add 15 ml of *2 M acetic acid*, shake for 30 minutes and filter. 12 ml of the solution complies with the limit test for heavy metals, Method D (2.3.13) (20 ppm).

Related substances. Complies with test A for related substances in sulphonamides (2.3.7).

Loss on drying (2.4.19). Not less than 6.0 per cent and not more than 10.0 per cent (sesquihydrate) or not less than 22.0 per cent and not more than 27.0 per cent (pentahydrate), determined on 1.0 g by drying in an oven at 105°.

Assay. Weigh 0.5 g, dissolve in a mixture of 75 ml of *water* and 10 ml of *hydrochloric acid*, add 3 g of *potassium bromide*, cool in ice and carry out the nitrite titration (2.3.31).

1 ml of *0.1 M sodium nitrite* is equivalent to 0.02773 g of $C_9H_8N_3NaO_2S_2$.

Storage. Store protected from light.

Labelling. The label states whether the substance is the sesquihydrate or the pentahydrate.

Testosterone Propionate

For Description, Identification and Tests refer to IP Volume III.

Testosterone Propionate Injection

Usual strengths. 5 mg in 1 ml; 10 mg in 1 ml; 50 mg in 1 ml.

For Identification and Tests refer to IP Volume III.

Thiabendazole

For Description, Identification and Tests refer to IP Volume III.

Thiabendazole Veterinary Oral Suspension

Thiabendazole Oral Suspension; Thiabendazole Mixture; Thiabendazole Drench

Thiabendazole Veterinary Oral Suspension is an aqueous suspension of Thiabendazole containing suitable suspending agents and antimicrobial preservatives.

Thiabendazole Veterinary Oral Suspension contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of thiabendazole, $C_{10}H_7N_3S$.

Usual strength. 13.3 per cent w/v.

Identification

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 50 volumes of *toluene*, 20 volumes of *glacial acetic acid*, 8 volumes of *acetone* and 2 volumes of *water*.

Test solution. Add 50 ml of *ethyl acetate* and 2 ml of *glacial acetic acid* to a volume of the well-mixed oral suspension containing about 0.25 g of Thiabendazole. Shake for 5 minutes, heat to boiling, cool, shake for a further 15 minutes and filter.

Reference solution. Dissolve 0.25 g of *thiabendazole IPRS* in 50 ml of *ethyl acetate* and add 2 ml of *glacial acetic acid*.

Apply to the plate 10 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with reference solution.

Tests

Other tests. Comply with the tests stated under Veterinary Oral Liquids.

Assay. Weigh a quantity of the well-mixed oral suspension containing about 1 g of Thiabendazole, add to 700 ml of *0.1 M*

hydrochloric acid, shake for 30 minutes, add sufficient *0.1 M hydrochloric acid* to produce 1000.0 ml, mix and filter. Dilute 10.0 ml of the filtrate to 100.0 ml with *0.1 M hydrochloric acid*. Dilute 5.0 ml of the solution to 100.0 ml with *0.1 M hydrochloric acid* and measure the absorbance of the resulting solution at the maximum at about 302 nm (2.4.7). Calculate the content of $C_{10}H_7N_3S$ taking 1230 as the specific absorbance at 302 nm.

Determine the weight per ml of the suspension (2.4.29), and calculate the content of thiabendazole, weight in volume.

Labelling. The label states that the suspension should be administered undiluted.

Thiabendazole and Rafoxanide Veterinary Oral Suspension

Thiabendazole and Rafoxanide Suspension; Thiabendazole and Rafoxanide Mixture

Thiabendazole and Rafoxanide Veterinary Oral Suspension is an aqueous suspension of Thiabendazole and Rafoxanide containing suitable suspending and dispersing agents.

Thiabendazole and Rafoxanide Veterinary Oral Suspension contains not less than 92.5 per cent and not more than 107.5 per cent of the stated amount of thiabendazole, $C_{10}H_7N_3S$, and not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of rafoxanide, $C_{19}H_{11}Cl_2I_2NO_3$.

Usual strength. 13.3 per cent w/v of Thiabendazole and 2.27 per cent w/v of Rafoxanide.

Identification

A. Mix a volume containing 20 mg of Thiabendazole with 5 ml of *0.1 M hydrochloric acid*, add 3 mg of *4-phenylenediamine dihydrochloride*, mix, add 0.1 g of *zinc powder* and allow to stand for 2 minutes. Add 10 ml of *ferric ammonium sulphate solution*; a deep blue or blue violet colour is produced.

B. In addition to the absorbance at about 335 nm, measure the absorbance at about 280 nm (2.4.7), of the final solution obtained in the Assay. The ratio of the absorbance at about 280 nm to that at about 335 nm is 1.59 to 1.69.

Tests

Other tests. Comply with the tests stated under Veterinary Oral Liquids.

Assay. *For thiabendazole* — Weigh a volume of the well-mixed suspension containing about 85 mg of Thiabendazole, add 20 ml of *water* and 9 ml of *0.1 M hydrochloric acid* and warm on a water-bath for 30 minutes with occasional stirring. Transfer the suspension to a flask, rinse the vessel with *water* and add the washings to the flask. Cool, add sufficient *water* to produce 1000.0 ml and filter. Dilute 5.0 ml of the filtrate to 100.0 ml with *0.1 M hydrochloric acid* and measure the absorbance of the resulting solution at the maximum at about 302 nm (2.4.7). Calculate the content of $C_{10}H_7N_3S$ taking 1230 as the specific absorbance at 302 nm.

For rafoxanide — Protect the solutions from light throughout the determination.

Weigh a volume of the well-mixed suspension containing about 0.1 g of Rafoxanide in a 500-ml stoppered flask and add sufficient *water* to produce 100 ml. Swirl to disperse, add 20 ml of *1 M hydrochloric acid*, mix well and add 300 ml of *ethyl acetate*. Shake the mixture for 1 hour, set aside for separation of the immiscible layers and centrifuge a portion of the ethyl acetate layer. Transfer 15.0 ml of the clear solution to a 50-ml centrifuge tube, add 20 ml of *0.1 M hydrochloric acid*, stopper the tube, shake for 15 minutes, and centrifuge. Remove and discard the aqueous layer. Repeat the washing with two quantities, each of 20 ml, of *0.1 M hydrochloric acid*. Evaporate the ethyl acetate solution almost to dryness in a warm water-bath, passing a stream of *nitrogen* over the surface of the liquid. Add 10 ml of *water*, warm on a water-bath for 10 minutes, add 5 ml of *1 M sodium hydroxide* and mix. Add 15 ml of *ether*, shake for 15 minutes, centrifuge, and remove the ether layer. Repeat the extraction with two quantities, each of 15 ml, of *ether*. Evaporate the combined ether extracts almost to dryness on a warm water-bath, passing a stream of *nitrogen* over the surface of the liquid. Dissolve the residue in sufficient *0.1 M methanolic hydrochloric acid* to produce 200.0 ml and measure the absorbance of the resulting solution at the maximum at about 335 nm (2.4.7).

Calculate the content of $C_{19}H_{11}Cl_2I_2NO_3$ from the absorbance obtained by carrying out the procedure simultaneously, using 0.1 g of *rafoxanide IPRS* and beginning at the words, "add sufficient *water* to produce 100 ml:....".

Determine the weight per ml of the suspension (2.4.29), and calculate the content of thiabendazole and rafoxanide, weight in volume.

Thiabendazole Premix

Thiabendazole Premix contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of thiabendazole, $C_{10}H_7N_3S$.

Usual strengths. 22.5 per cent w/w; 33.3 per cent w/w.

Identification

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. A mixture of 50 volumes of *toluene*, 20 volumes of *glacial acetic acid*, 8 volumes of *acetone* and 2 volumes of *water*.

Test solution. To a quantity of the premix containing 0.25 g of Thiabendazole, finely powdered if necessary, add 50 ml of *ethyl acetate* and 2 ml of *glacial acetic acid*, shake for 5 minutes, heat to boiling, cool, shake for a further 15 minutes and filter.

Reference solution. Dissolve 0.25 g of *thiabendazole IPRS* in 50 ml of *ethyl acetate* and add 2 ml of *glacial acetic acid*.

Apply to the plate 10 µl of each solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with the reference solution.

Tests

Assay. Weigh a quantity containing about 0.1 g of Thiabendazole, add 700 ml of *0.1 M hydrochloric acid*, shake for 30 minutes, dilute to 1000.0 ml with *0.1 M hydrochloric acid* and filter. Dilute 5.0 ml of the filtrate to 100.0 ml with *0.1 M hydrochloric acid* and measure the absorbance of the resulting solution at the maximum at about 302 nm (2.4.7). Calculate the content of $C_{10}H_7N_3S$, taking 1230 as the specific absorbance at 302 nm.

Tinidazole Tablets

Usual strengths. 300 mg; 1800 mg.

For Identification and Tests refer to IP Volume III.

Tocopheryl Acetate

For Description, Identification and Tests refer to IP Volume III.

Triamcinolone Acetonide Injection

Usual strength. 6 mg in 1 ml.

For Identification and Tests refer to IP Volume III.

Trifluprom azine Hydrochloride Injection

Usual strength. 20 mg in 1 ml.

For Identification and Tests refer to IP Volume III.

Trimethoprim

For Description, Identification and Tests refer to IP Volume III.

Trimethoprim and Sulphamethoxazole Injection

Sulphamethoxazole and Trimethoprim Injection

Trimethoprim and Sulphamethoxazole Injection is a sterile solution in water for injection containing Trimethoprim and Sulphamethoxazole in the proportion of five parts to part respectively.

Trimethoprim and Sulphamethoxazole injection contains not less than 90.0 per cent not more than 110.00 per cent of the stated amounts of trimethoprim, $C_{14}H_{18}N_4O_3$, and sulphamethoxazole, $C_{10}H_{11}N_3O_3S$.

Usual strength. 80 mg of Trimethoprim and 400 mg of Sulphamethoxazole per ml.

Description. A clear colourless to pale yellow solution.

Identification

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*.

Mobile Phase. A mixture of 20 volumes of *chloroform*, 2 volumes of *methanol* and 1 volume of *dimethylformamide*.

Test solution. A volume of the injection containing 0.16 g Sulphamethoxazole, with 8 ml of *methanol* and filter.

Reference solution (a). A 2.0 per cent w/v solution of *sulphamethoxazole IPRS* in *methanol*.

Reference solution (b). A 0.4 per cent w/v solution of *trimethoprim IPRS* in solvent mixture.

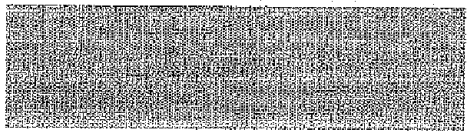
Apply to the plate 5 µl of each solution. After development, dry the plate in air, spray with *dilute potassium iodobismuthate* solution. One of the principal spots in the chromatogram obtained with test solution corresponds to that in the chromatogram obtained with reference solution (a) and the other corresponds to that in the chromatogram obtained with solution (b).

Tests

pH (2.4.24). 9.5 to 11.0.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Bacterial endotoxins (2.2.3). Not more than 0.20 Endotoxin Units per mg.



Sterility (2.2.11). Complies with the test for sterility.

Assay. *For Trimethoprim* — Take 5 ml volume of injection, add 30 ml of *0.1 M sodium hydroxide*, shake and extract with four quantities, each of 50 ml of *chloroform*, washing each extract with the same two quantities, each of 10 ml of *0.1 M sodium hydroxide*. Reserved the combined aqueous solution and washing for the Assay for Sulphamethoxazole. Extract the combined *chloroform* extracts with four quantities, each of 50 ml, of *1 M acetic acid*. Wash the combined extracts with 5 ml of *chloroform* and dilute the extracts to 250.0 ml with *1 M acetic acid*. To 10.0 ml of the solution add 10 ml of *1M acetic acid* and sufficient *water* to produce 100.0 ml; mix and measure the absorbance of the resulting solution at the maximum at about 271 nm (2.4.7).

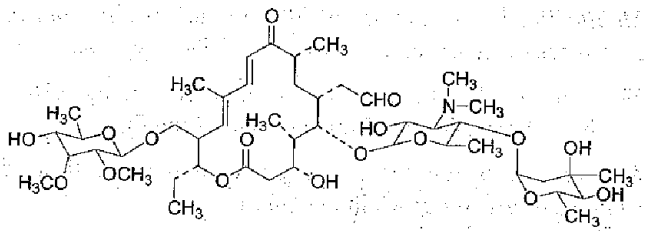
Calculate the content of $C_{14}H_{18}N_4O_3$ taking 204 as the specific absorbance at 271 nm.

For Sulphamethoxazol — Take 2 ml volume of injection, add 10 ml of *water* and 10 ml of *hydrochloric acid*. Cool in ice and carry out the nitrite titration (2.3.31) using *starch* indicator.

1 ml of *0.1 M sodium nitrite* is equivalent to 0.02533 g of $C_{10}H_{11}N_3O_3S$.

Storage. Store in a cool and dry place, protected from light.

Tylosin



$C_{46}H_{77}NO_{17}$ Mol. Wt. 916.1

Tylosin is a macrolide antibiotic isolatede from a strain of Stryptomycetes fradiae found in soil from Thailand.

Tylosin has a potency of not less than 900 Units per mg, calculated on the dried basis. The content of tylosin A is not less than 80.0 per cent and the sum of the contents of tylosin A, tylosin B, tylosin C and tylosin D is not less than 95.0 per cent.

Category. Antibacterial.

Description. Almost white or slightly yellow powder.

Identification

Tests B and C may be omitted if tests A, D and E are carried out. Tests D and E may be omitted if tests A, B and C are carried out.

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *tylosin IPRS* or with the reference spectrum of Tylosin.

B. When examined in the range 230 nm to 360 nm (2.4.7), a 0.004 per cent w/v solution in *0.1 M hydrochloric acid* (solution A) shows an absorption maximum only at about 290 nm; absorbance at about 290 nm, about 0.94.

C. To 10 ml of solution A add 1 ml of *2 M sodium hydroxide*, heat on a water-bath for 20 minutes and cool. When examined in the range 250 nm to 430 nm (2.4.7), of the resulting solution shows an absorption maximum only at about 332 nm.

D. In the test for Tylosin A and other tylosins, the retention time and size of the principal peak in the chromatogram obtained with the test solution are approximately the same as those of the principal peak in the chromatogram obtained with reference solution (a).

E. Dissolve about 30 mg in a mixture of 0.15 ml of *water*, 2.5 ml of *acetic anhydride* and 7.5 ml of *pyridine*. Allow to stand for 10 minutes; no green colour develops.

Tests

pH (2.4.24). 8.5 to 10.5, determined in a 2.5 per cent w/v suspension in *carbon dioxide-free water*.

Heavy metals. To the residue obtained in the test for Sulphated ash add 2 ml of *hydrochloric acid* and evaporate slowly to dryness on a water-bath. Moisten the residue with 0.05 ml of *hydrochloric acid*, add 10 ml of boiling *water* and heat for 10 minutes on a water-bath. Cool and dilute to 20 ml with *water*. 12 ml of the solution complies with the limit test for heavy metals, Method D (2.3.13) (20 ppm) using 10 ml of either lead standard solution(1 ppm Pb).

Tyramine. Dissolve 50 mg in 5 ml of *0.03 M phosphoric acid* in a 25-ml volumetric flask, add 1 ml of *pyridine* and 2 ml of a saturated solution of *ninhydrin* in *water* (approximately 4 per cent w/v). Close the flask by covering with a piece of aluminium foil and heat in a water-bath at 85° for at least 20 minutes. Cool rapidly and add sufficient *water* to produce 25 ml. Mix and measure without delay the absorbance of the solution at about 570 nm (2.4.7), using as the blank a solution prepared in a similar manner but omitting the substance under examination. The absorbance is not more than that obtained by carrying out the procedure simultaneously, using 5 ml of a solution in *0.03 M phosphoric acid* containing 35 mg of *tyramine* per litre and beginning at the words "add 1 ml of *pyridine*....." (0.35 per cent).

Sulphated ash (2.3.18). Not more than 3.0 per cent.

Loss on drying (2.4.19). Not more than 5.0 per cent, determined on 1.0 g by drying at 60° at a pressure not exceeding 0.7 kPa for 3 hours.

Tylosin A and other tylosins. Determine by liquid chromatography (2.4.14).

NOTE — Use freshly prepared solutions.

Test solution. Dissolve 20 mg of the substance under examination in 100 ml of a mixture of equal volumes of *acetonitrile* and *water*.

Reference solution (a). A 0.02 per cent w/v solution of *tylosin IPRS* in a mixture of equal volumes of *acetonitrile* and *water*.

Reference solution (b). A solution containing 0.02 per cent w/v each of *tylosin A IPRS* and *tylosin D IPRS* in a mixture of equal volumes of *acetonitrile* and *water*.

Chromatographic system

- a stainless steel column 20 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- column temperature 35°,
- mobile phase: a filtered and degassed mixture of 60 volumes of *0.85 M sodium perchlorate* and 40 volumes of *acetonitrile* adjusted to pH 2.5 with *1 M hydrochloric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 290 nm,
- injection volume: 20 µl.

Inject reference solution (b). If necessary, adjust the molarity of the sodium perchlorate or increase the temperature of the column to a maximum of 50° so as to obtain a retention time of about 12 minutes for tylosin A. The test is not valid unless the resolution between the peaks due to tylosin A and tylosin D is not less than 2.0.

Inject reference solution (a). The column efficiency, determined using the peak due to tylosin A, should be not less than 22,000 theoretical plates per metre.

Inject reference solution (a) and the test solution. The order of elution of the major components of the substance under examination is desmycinosyltylosin, tylosin C, tylosin B, tylosin D, tylosin A aldol and tylosin A.

Calculate the percentage content of components from the areas of the peaks in the chromatogram obtained with the test solution by normalisation.

Assay. Carry out the microbiological assay of antibiotics (2.2.10).

Tylosin intended for use in the manufacture of Parenteral Preparations without a further appropriate sterilisation procedure complies with the following additional requirement.

Sterility (2.2.11). Complies with the test for sterility.

Storage. Store protected from light. If it is intended for use in the manufacture of Parenteral Preparations, the container should be sterile, tamper-evident and sealed so as to exclude micro-organisms.

Labelling. The label states (1) the number of Units per mg; (2) the date after which the material is not intended to be used; (3) the storage conditions; (4) where applicable, that it is suitable for use in the manufacture of Parenteral Preparations; (5) that the preparation is intended for veterinary use.

Tylosin Injection

Tylosin Injection is a sterile solution of Tylosin or Tylosin Tartarate in a mixture of equal volumes of Propylene Glycol and Water for Injections.

Tylosin Injection contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of tylosin. The content of tylosin A is not less than 80.0 per cent and the sum of the contents of tylosin A, tylosin B, tylosin C and tylosin D is not less than 90.0 per cent.

Usual strengths. 2.5 g in 50 ml; 20 g in 100 ml.

Description. A pale yellow to amber-coloured solution.

Identification

A. To a volume containing 0.1 g of Tylosin add sufficient *water* to obtain a solution containing 0.02 per cent w/v of Tylosin. To 5 ml of the solution add 10 ml of *0.1 M sodium hydroxide* and extract with 10 ml of *dichloromethane*. Separate the dichloromethane layer and extract it with 25 ml of *0.1 M hydrochloric acid*. Discard the dichloromethane layer, wash the aqueous layer with 3 ml of *dichloromethane*, discard the washings and filter. When examined in the range 230 nm to 360 nm (2.4.7), of the resulting solution exhibits a maximum only at about 290 nm; absorbance at about 290 nm, about 0.94.

B. To 10 ml of the filtrate obtained in test A add 1 ml of *2 M sodium hydroxide*, heat in a water-bath for 20 minutes and cool. When examined in the range 250 nm to 430 nm (2.4.7), exhibits a maximum only at about 332 nm.

Tests

Tyramine. Dilute a volume containing 100 mg of Tylosin with 5 ml of *0.03 M phosphoric acid* in a 25-ml volumetric flask, add 1 ml of *pyridine* and 2 ml of a saturated solution of *ninhydrin* in *water* (approximately 4 per cent w/v). Close the flask by covering with a piece of aluminium foil and heat in a water-bath at 85° for at least 20 minutes. Cool rapidly and add sufficient *water* to produce 25 ml. Mix and measure without delay the absorbance of the resulting solution at about 570 nm (2.4.7), using as the blank a solution prepared in a similar manner but omitting the preparation under examination. The absorbance is not more than that obtained by carrying out the procedure simultaneously, using 5 ml of a solution in *0.03 M phosphoric acid* containing 30 mg of *tyramine* per

litre and beginning at the words "add 1 ml of *pyridine*....." (0.15 per cent).

Tylosin A and other tylosins. Determine by liquid chromatography (2.4.14).

NOTE — Use freshly prepared solutions.

Test solution. Dilute the injection with sufficient of a mixture of equal volumes of *acetonitrile* and *water* to produce a solution containing 0.02 per cent w/v of Tylosin.

Reference solution (a). A 0.02 per cent w/v solution of *tylosin IPRS* in a mixture of equal volumes of *acetonitrile* and *water*.

Reference solution (b). A solution containing 0.02 per cent w/v each of *tylosin A IPRS* and *tylosin D IPRS* in a mixture of equal volumes of *acetonitrile* and *water*.

Chromatographic system
- a stainless steel column 20 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- column temperature 35°,
- mobile phase: a filtered and degassed mixture of 60 volumes of *0.85 M sodium perchlorate* and 40 volumes of *acetonitrile* adjusted to pH 2.5 with *1 M hydrochloric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 290 nm,
- injection volume: 20 µl.

Inject reference solution (b). If necessary, adjust the molarity of the sodium perchlorate or increase the temperature of the column to a maximum of 50° so as to obtain a retention time of about 12 minutes for tylosin A. The test is not valid unless the resolution between the peaks due to tylosin A and tylosin D is at least 2.0.

Inject reference solution (a). The column efficiency, determined using the peak due to tylosin A, should be not less than 22,000 theoretical plates per metre.

Inject reference solution (a) and test solution. The order of elution of the major components of the substance under examination is desmycinosyltylosin, tylosin C, tylosin B, tylosin D, tylosin A aldol and tylosin A.

Calculate the percentage contents of components from the areas of the peaks in the chromatogram obtained with the test solution.

Bacterial endotoxins (2.2.3). Not more than 0.28 Endotoxin Unit per mg of tylosin.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Assay. Determine by the microbiological assay of antibiotics (2.2.10). Calculate the content of tylosin in the injection, taking each 1000 Units found to be equivalent to 1 mg of tylosin.

Storage. Store protected from light.

Labelling. The label states that the preparation is intended for veterinary use by intramuscular injection only.

Tylosin Tablets

Tylosin Tablets contain not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of tylosin. The content of tylosin A is not less than 80.0 per cent and the sum of the contents of tylosin A, tylosin B, tylosin C and tylosin D is not less than 90.0 per cent.

Usual strength. 200 mg.

Identification

A. Triturate a quantity of the powdered tablets containing 0.2 g of Tylosin with 20 ml of *dichloromethane* and filter. Dry the dichloromethane extract by shaking with *anhydrous sodium sulphate*, filter and evaporate the filtrate to dryness. Dry the residue over *phosphorus pentoxide* at a pressure not exceeding 0.7 kPa for 1 hour.

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *tylosin IPRS* or with the reference spectrum of tylosin.

B. Triturate a quantity of the powdered tablets containing 0.2 g of Tylosin with two quantities, each of 10 ml, of *0.1 M hydrochloric acid*, filter and dilute the filtrate to 100 ml with *0.1 M hydrochloric acid*. Dilute 10 ml of the resulting solution to 50 ml with the same solvent. Dilute 5 ml of the solution further to 50 ml with the same solvent.

When examined in the range 230 nm to 360 nm (2.4.7), the resulting solution shows an absorption maximum only at about 290 nm; absorbance at about 290 nm, about 0.94.

C. To 10 ml of the final solution obtained in test B add 1 ml of *2 M sodium hydroxide*, heat in a water-bath for 20 minutes and cool. When examined in the range 250 nm to 430 nm (2.4.7), exhibits a maximum only at about 332 nm.

Tests

Tyramine. Shake a quantity of the powdered tablets containing 50 mg of Tylosin with 5 ml of *0.03 M phosphoric acid*. Filter into a 25-ml volumetric flask, add 1 ml of *pyridine* and 2 ml of a saturated solution of *ninhydrin* in *water* (approximately 4 per cent w/v). Close the flask by covering with a piece of aluminium foil and heat in a water-bath at 85° for at least 20 minutes. Cool rapidly and add sufficient *water* to produce 25 ml. Mix and measure without delay the absorbance of the solution at about 570 nm (2.4.7), using as the blank a solution prepared in a similar manner but omitting the substance under

examination. The absorbance is not more than that obtained by carrying out the procedure simultaneously, using 5 ml of a solution in *0.03 M phosphoric acid* containing 35 mg of *tyramine* per litre and beginning at the words "add 1 ml of *pyridine*....." (0.35 per cent).

Tylosin A and other tylosins. Determine by liquid chromatography (2.4.14).

NOTE —Use freshly prepared solutions.

Test solution. Shake a quantity of the powdered tablets containing 0.2 g of Tylosin with 50 ml of *methanol*, filter and dilute 5 ml of the filtrate to 100 ml with a mixture of equal volumes of *acetonitrile* and *water*.

Reference solution (a). A 0.02 per cent w/v solution of *tylosin IPRS* in a mixture of equal volumes of *acetonitrile* and *water*.

Reference solution (b). A solution containing 0.02 per cent w/v each of *tylosin A IPRS* and *tylosin D IPRS* in a mixture of equal volumes of *acetonitrile* and *water*.

Chromatographic system
- a stainless steel column 20 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (such as Nucleosil C18),
- column temperature 35°,
- mobile phase: a filtered and degassed mixture of 60 volumes of *0.85 M sodium perchlorate* and 40 volumes of *acetonitrile* adjusted to pH 2.5 with *1 M hydrochloric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 290 nm,
- injection volume: 20 µl.

Inject reference solution (b). If necessary, adjust the molarity of the sodium perchlorate or increase the temperature of the column to maximum of 50° so as to obtain a retention time of about 12 minutes for tylosin A. The test is not valid unless the resolution between the peaks due to tylosin A and tylosin D is at least 2.0.

Inject reference solution (a). The column efficiency, determined using the peak due to tylosin A, should be not less than 22,000 theoretical plates per metre.

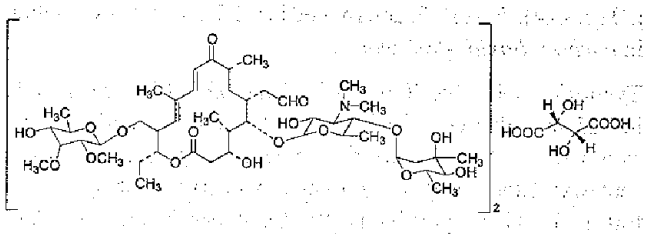
Inject reference solution (a) and the test solution. The order of elution of the major components of the substance under examination is desmycinosyltylosin, tylosin C, tylosin B, tylosin D, tylosin A aldol and tylosin A.

Calculate the percentage content of components from the areas of the peaks in the chromatogram obtained with test solution.

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by the microbiological assay of antibiotics (2.2.10). Calculate the content of tylosin in the tablets, taking each 1000 Units found to be equivalent to 1 mg of tylosin.

Tylosin Tartrate



$(C_{46}H_{77}NO_{17})_2, C_4H_6O_6$ Mol. Wt. 1983.3

Tylosin Tartrate is the tartrate of Tylosin, which is a mixture of antimicrobial macrolides produced by the growth of certain strains of *Streptomyces fradiae* or by any other means. It consists largely of tylosin A tartrate but tartrates of tylosin B (desmycosin), tylosin C (macrocin) and tylosin D (relomycin) may also be present.

Tylosin Tartrate contains not less than 800 Units per mg, calculated on the dried basis. The content of tylosin A is not less than 80.0 per cent and the sum of the contents of tylosin A, tylosin B, tylosin C and tylosin D is not less than 95.0 per cent.

Category. Antibacterial.

Description. An almost white or slightly yellow, hygroscopic powder.

Identification

Tests B and C may be omitted if tests A, D and E are carried out. Tests D and E may be omitted if tests A, B and C are carried out.

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *tylosin tartrate IPRS* or with the reference spectrum of tylosin tartrate.

B. When examined in the range 230 nm to 360 nm (2.4.7), a 0.004 per cent w/v solution in *0.1 M hydrochloric acid* (solution A) shows an absorption maximum only at about 290 nm; absorbance at about 290 nm, about 0.88.

C. To 10 ml of solution A add 1 ml of *2 M sodium hydroxide*, heat on a water-bath for 20 minutes and cool.

When examined in the range 250 nm to 430 nm (2.4.7), the resulting solution shows an absorption maximum only at about 332 nm.

D. In the test for Tylosin A and other tylosins, the retention time and size of the principal peak in the chromatogram obtained with the test solution are approximately the same as those of the principal peak in the chromatogram obtained with the reference solution.

E. Dissolve 30 mg in a mixture of 0.15 ml of *water*, 2.5 ml of *acetic anhydride* and 7.5 ml of *pyridine*. Allow to stand for 10 minutes; a green colour develops.

Tests

pH (2.4.24). 5.0 to 7.2, determined in a 2.5 per cent w/v solution in *carbon dioxide-free water*.

Tyramine. Dissolve 50 mg in 5 ml of *0.03 M phosphoric acid* in a 25-ml volumetric flask, add 1 ml of *pyridine* and 2 ml of a saturated solution of *ninhydrin* in *water* (approximately 4 per cent w/v). Close the flask by covering with a piece of aluminium foil and heat in a water-bath at 85° for at least 20 minutes. Cool rapidly and add sufficient *water* to produce 25 ml. Mix and measure without delay the absorbance of the solution at about 570 nm (2.4.7), using as the blank a solution prepared in a similar manner but omitting the substance under examination. The absorbance is not more than that obtained by carrying out the procedure simultaneously, using 5 ml of a solution in *0.03 M phosphoric acid* containing 35 mg of *tyramine* per litre and beginning at the words "add 1 ml of *pyridine*....." (0.35 per cent).

Sulphated ash (2.3.18). Not more than 2.5 per cent.

Loss on drying (2.4.19). Not more than 4.5 per cent, determined on 1.0 g by drying at 60° at a pressure not exceeding 0.7 kPa for 3 hours.

Tylosin A and other tylosins. Determine by liquid chromatography (2.4.14).

NOTE — Use freshly prepared solutions.

Test solution. Dissolve a quantity containing 20 mg of tylosin in 100 ml of a mixture of equal volumes of *acetonitrile* and *water*.

Reference solution (a). A 0.02 per cent w/v solution of *tylosin IPRS* in a mixture of equal volumes of *acetonitrile* and *water*.

Reference solution (b). A solution containing 0.02 per cent w/v each of *tylosin A IPRS* and *tylosin D IPRS* in a mixture of equal volumes of *acetonitrile* and *water*.

Chromatographic system
- a stainless steel column 20 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (such as Nucleosil C18),
- column temperature: 35°,
- mobile phase: a filtered and degassed mixture of 60 volumes of *0.85 M sodium perchlorate* and 40 volumes of *acetonitrile* adjusted to pH 2.5 with *1 M hydrochloric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 290 nm,
- injection volume: 20 µl.

Inject reference solution (b). If necessary, adjust the molarity of the sodium perchlorate or increase the temperature of the column to a maximum of 50° so as to obtain a retention time of about 12 minutes for tylosin A. The test is not valid unless the resolution between the peaks due to tylosin A and tylosin D is at least 2.0.

Inject reference solution (a). The column efficiency, determined using the peak due to tylosin A, should be not less than 22,000 theoretical plates per metre.

Inject the reference solution (a) and the test solution. The order of elution of the major components of the substance under examination is desmycinosyltylosin, tylosin C, tylosin B, tylosin D, tylosin A aldol and tylosin A.

Calculate the percentage content of components from the areas of the peaks in the chromatogram obtained with test solution.

Assay. Carry out the microbiological assay of antibiotics (2.2.10).

Tylosin Tartrate intended for use in the manufacture of parenteral preparations complies with the above requirements with the following modification.

Tyramine. Carry out the procedure described under test for Tyramine but using 100 mg in 5 ml of *0.03 M phosphoric acid*. Measure the absorbance of the solution under the conditions described under test. The absorbance is not more than that obtained by simultaneously carrying out the procedure using 5 ml of a solution in *0.03 M phosphoric acid* containing 30 mg of *tyramine* per litre and beginning at the words "add 1 ml of *pyridine*....." (0.15 per cent).

Tylosin Tartrate intended for use in the manufacture of parenteral preparations without a further appropriate sterilisation procedure complies with the following additional requirement.

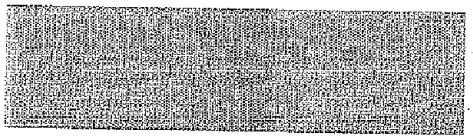
Sterility (2.2.11). Complies with the test for sterility.

Storage. Store protected from light. If it is intended to be used in the manufacture of parenteral preparations, the container should be sterile, tamper-evident and sealed so as to exclude micro-organisms.

Labelling. The label states (1) the number of Units per mg; (2) the quantity of Tylosin Tartrate in terms of equivalent amount of tylosin; (3) the date after which the material is not intended to be used; (4) the storage conditions; (5) where applicable, that it is suitable for use in the manufacture of parenteral preparations; (6) that the preparation is intended for veterinary use.

Tylosin Tartrate and Sulphathiazole Sodium Veterinary Oral Powder

Tylosin Tartrate and Sulphathiazole Sodium Veterinary Oral Powder is a mixture of Tylosin Tartrate and Sulphathiazole Sodium. It contains 3 parts of Sulphathiazole Sodium for 1 part, by weight, of Tylosin.



Tylosin Tartrate and Sulphathiazole Sodium Veterinary Oral Powder contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amounts of tylosin and sulphathiazole sodium sesquihydrate, $C_9H_8NaO_2S_2,1^1/_2H_2O$.

Usual strength. The equivalent of 25 g of tylosin as Tylosin Tartrate and the equivalent of 75 g of sulphathiazole sodium sesquihydrate as Sulphathiazole Sodium.

Identification

A. Triturate a quantity of the powder containing 0.25 g of Tylosin with two quantities, each of 25 ml, of *dichloromethane* and filter. Reserve the dichloromethane-insoluble matter for test B. Wash the combined filtrates by shaking for 1 minute with 20 ml of *0.1 M sodium hydroxide* and dry the dichloromethane layer by the addition of *anhydrous sodium sulphate*. Evaporate the filtrate to dryness and dry the residue over *phosphorus pentoxide* at a pressure not exceeding 0.7 kPa for 1 hour. The residue complies with the following test.

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *tylosin IPRS* or with the reference spectrum of Tylosin.

B. Dry the dichloromethane-insoluble matter reserved in test A at 105° for 1 hour. The residue complies with the following test.

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *sulphathiazole sodium IPRS* or with the reference spectrum of Sulphathiazole sodium.

Tests

Sulphonamide-related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel H*.

Solvent mixture. A mixture of 9 volumes of *ethanol (95 per cent)* and 1 volume of *strong ammonia solution*.

Mobile phase. A mixture of 90 volumes of *1-butanol* and 18 volumes of *10 M ammonia*.

Test solution. Shake a quantity of the powder containing 0.1 g of sulphathiazole sodium sesquihydrate with 10 ml of the solvent mixture.

Reference solution. A 0.005 per cent w/v solution of *sulphanilamide* in the solvent mixture.

Apply to the plate 10 µl of each solution. After development, dry the plate by heating it at 105° for 10 minutes and spray with a 0.1 per cent w/v solution of *4-dimethylaminobenzaldehyde* in a mixture of 99 volumes of *ethanol (95 per cent)* and 1 volume of *hydrochloric acid*. Any secondary spot in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with reference solution (0.5 per cent).

Tylosin A and other tylosins. Determine by liquid chromatography (2.4.14).

NOTE — Use freshly prepared solutions.

Test solution. Dissolve a quantity containing 20 mg of tylosin in 100 ml of a mixture of equal volumes of *acetonitrile* and *water*.

Reference solution (a). A 0.02 per cent w/v solution of *tylosin IPRS* in a mixture of equal volumes of *acetonitrile* and *water*.

Reference solution (b). A solution containing 0.02 per cent w/v each of *tylosin A IPRS* and *tylosin D IPRS* in a mixture of equal volumes of *acetonitrile* and *water*.

Chromatographic system

- a stainless steel column 20 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (such as Nucleosil C18),
- column temperature: 35°,
- mobile phase: a filtered and degassed mixture of 60 volumes of *0.85 M sodium perchlorate* and 40 volumes of *acetonitrile* adjusted to pH 2.5 with *1 M hydrochloric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 290 nm,
- injection volume: 20 µl.

Inject reference solution (b). If necessary, adjust the molarity of the sodium perchlorate or increase the temperature of the column to a maximum of 50° so as to obtain a retention time of about 12 minutes for tylosin A. The test is not valid unless the resolution between the peaks due to tylosin A and tylosin D is at least 2.0.

Inject reference solution (a). The column efficiency, determined using the peak due to tylosin A, should be not less than 22,000 theoretical plates per metre.

Inject the reference solution (a) and the test solution. The order of elution of the major components of the substance under examination is desmycinosyltylosin, tylosin C, tylosin B, tylosin D, tylosin A aldol and tylosin A.

Calculate the percentage content of components from the areas of the peaks in the chromatogram obtained with the test solution by normalisation. In the chromatogram obtained with the test solution the content of tylosin A is not less than 80.0 per cent and the sum of the contents of tylosin A, tylosin B, tylosin C and tylosin D is not less than 95.0 per cent.

Other tests. Comply with the tests stated under Veterinary Oral Powders.

Assay. *For tylosin activity* — Weigh a quantity of the powder containing about 0.2 g of Tylosin, transfer to a 100-ml volumetric flask with three quantities, each of 10 ml, of

methanol, swirl to dissolve and add sufficient sterile *phosphate buffer pH 7.0* to produce 100.0 ml. Filter and dilute 5.0 ml of the filtrate to 100.0 ml with sterile *phosphate buffer pH 7.0*. Carry out the microbiological assay of antibiotics (2.2.10). Calculate the content of tylosin taking each 1000 Units found to be equivalent to 1 mg of tylosin.

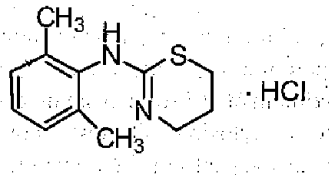
For sulphathiazole sodium — Weigh a quantity of the powder containing about 0.4 g of sulphathiazole sodium sesquihydrate, dissolve in a mixture of 75 ml of *water* and 10 ml of *hydrochloric acid*, add 3 g of *potassium bromide*, cool in ice and titrate slowly with *0.1 M sodium nitrite*, stirring constantly and determine the end-point potentiometrically (2.4.25).

1 ml of *0.1 M sodium nitrite* is equivalent to 0.03043 g of $C_9H_8N_3NaO_2S_2,1\frac{1}{2}H_2O$.

Storage. Store protected from moisture.

Labelling. The label states the strength of Tylosin Tartrate in terms of the equivalent amount of tylosin and that of Sulphathiazole Sodium in terms of the equivalent amount of sulphathiazole sodium sesquihydrate.

Xylazine Hydrochloride



$C_{12}H_{17}ClN_2S$ Mol. Wt. 256.8

Xylazine is *N*-(2,6-Dimethylphenyl)-5,6-dihydro-4*H*-1,3-thiazin-2-amine hydrochloride.

Xylazine contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{12}H_{17}ClN_2S$, calculated on the dried basis.

Category. Analgesic.

Description. A white or almost white, crystalline hygroscopic powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *xylazine hydrochloride IPRS* or with the reference spectrum of xylazine hydrochloride.

B. It gives reaction (B) of chlorides (2.3.1).

Tests

Solution A. Prepare the 10.0 per cent w/v solution in *carbon dioxide-free water*, heating at 60°, if necessary, allow to cool.

Appearance of solution (2.4.1). Solution A is colourless and not more opalescent than opalescence standard OS2.

pH (2.4.24). 4.0 to 5.5, determined in Solution A.

Impurity A. Not more than 100 ppm. Carry out the test by following procedure.

Solution A. Dissolve 0.25 g of the substance under examination in 10 ml of *methanol*.

Solution B. Dissolve 50 mg of *2,6-dimethylaniline* in 100 ml of *methanol*. Dilute 1.0 ml of the solution to 100.0 ml with *methanol*.

Using 2 flat-bottomed tubes with an inner diameter of about 10 mm, place in the first tube 2.0 ml of solution A, and in the second tube 1.0 ml of solution B and 1.0 ml of *methanol*. To each tube, add 1.0 ml of fresh prepared solution containing 1 per cent w/v of *dimethylaminobenzaldehyde* in *methanol* and 2.0 ml of *glacial acetic acid* and allow standing at room temperature for 10 minutes. Compare the colours in diffused daylight, viewing vertically against a white background. Any yellow colour in the test solution is not more intense than that in the reference solution.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE— Prepare the solutions immediately before use.

Solvent mixture. 8 volumes of *acetonitrile*, 30 volumes of *methanol* and 62 volumes of 0.272 per cent *potassium dihydrogen phosphate* solution, adjusted to pH 7.2 with *dilute sodium hydroxide solution*.

Test solution. Dissolve 0.10 g of the substance under examination in the 20 ml of solvent mixture.

Reference solution (a). Dissolve 5 mg of the substance under examination, 5 mg of *2,6-dimethylaniline* (impurity A) and 5 mg of *xylazine* (impurity C) and 5 mg of *xylazine* (impurity E) in 100 ml of *acetonitrile*. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (b). With the aid of ultrasound, dissolve the contents of a vial of *xylazine IPRS* impurities mixture (impurities B and D) in 1.0 ml of the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm x 3.9 mm, packed with octadecylsilane silica gel with polar incorporated groups (5 µm),
- column temperature: 40°.
- mobile phase: A. a mixture of 30 volumes of *methanol* and 70 volumes of 0.272 per cent *potassium dihydrogen phosphate* solution, adjusted to pH 7.2 with *dilute sodium hydroxide solution*.

  B. a mixture of 30 volumes of *methanol* and 70 volumes of *acetonitrile*.
- a gradient programme using the conditions given below,

- flow rate: 1 ml per minute,
- spectrophotometer set at 230 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	89	11
15	28	72
21	28	72

Equilibrate the column for not less 30 minutes using 28 volumes of mobile phase A and 72 volumes of mobile phase B.

Name	Relative retention time
Xylazine impurity D[1]	0.5
Xylazine impurity A[2]	0.8
Xylazine (Retention time: about 7.5 minutes)	1.0
Xylazineimpurity B[3]	1.3
Xylazine impurity E[4]	1.6
Xylazine impurity C[5]	2.2

[1]*N*-(2,6-dimethylphenyl)-*N*'-(3-hydroxypropyl)thiourea.

[2]2,6-dimethylaniline (2,6-xylidine).

[3]*N,N*'-bis(2,6-dimethylphenyl)thiourea.

[4]methyl (2,6-dimethylphenyl)carbamodithioate.

[5]2,6-dimethylphenyl isothiocyanate.

Inject reference solution (a) and (b). The chromatogram obtained with *xylazine* impurity mixture and identify the peaks due to impuritties B and D in the chromatogram obtained with reference solution (b) and identify the peaks due to impurities A , C and E in the chromatogram obtained with reference solution (a). The test is not valid unless the resolution between the peaks due to impurity A and xylazine is not less than 4.0.

Inject reference solution (a) and the test solution . The area of the peak corresponding to xylazine for each impurity B, C, D and E, each of, is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent). The area of any other secondary peak is not more than twice the area of principle peak in the chromatogram obtained with reference solution (a) (0.2 per cent). The sum of the areas of the entire secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent) and peak due to blank.

Heavy metals (2.3.13). 12 ml of solution A complies with the limit test for heavy metals, Method D (10 ppm), using 10 ml of *lead standard solution (1 ppm Pb)*.

Sulphated ash (2.3.18). Not more than 0.1 per cent, determined on 1.0 g.

Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105° for 2 hours.

Assay. Weight 0.2 g of substance under examination, dissolve in 25.0 ml of *ethanol (95 per cent)*, and add 25.0 ml of *water*. Titrate with *0.1 M sodium hydroxide*, determining the end point potentiometrically (2.4.25). Carry out a blank titration.

1 ml of *0.1 M sodium hydroxide* is equivalent to 0.02568 g of $C_{12}H_{17}ClN_2S$.

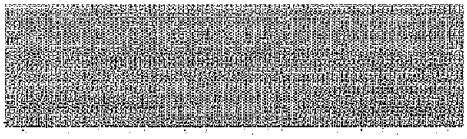
Storage. Store protected from light, in an airtight container.

Zinc Oxide Cream

For Identification and Tests refer to IP Volume III.

VETERINARY BIOLOGICAL MONOGRAPHS

Anthrax Spore Vaccine, Live 4947
Avian Infectious Bronchitis Vaccine, Inactivated 4948
Avian Infectious Bronchitis Vaccine, Live 4949
Avian Infectious Laryngotracheitis Vaccine, Live 4950
Avian Spirochaetosis Vaccine 4952
Blackquarter Vaccine 4952
Bluetongue Vaccine, Inactivated 4953
Brucella Abortus (Strain 19) Vaccine, Live 4955
Canine Adenovirus Vaccine, Live 4956
Canine Coronavirus Vaccine, Inactivated 4957
Canine Distemper Vaccine, Live 4959
Canine Leptospirosis Vaccine, Inactivated 4960
Canine Parainfluenza Virus Vaccine, Live 4961
Canine Parvovirus Vaccine, Inactivated 4962
Canine Parvovirus Vaccine, Live 4964
Classical Swine Fever Vaccine, Live 4965
Multicomponent Clostridium Vaccine, Inactivated 4966
Clostridium Novyi (Type B) Vaccine for Veterinary Use 4966
Clostridium Septicum Vaccine, Inactivated 4968
Duck Pasteurella Vaccine, Inactivated 4970
Duck Plague Vaccine, Live 4970
Egg Drop Syndrome 76 (Adenovirus) Vaccine, Inactivated 4971
Enterotoxaemia Vaccine, Inactivated 4971
Foot-and-Mouth Disease Vaccine, Inactivated 4972
Fowl Cholera Vaccine, Inactivated 4974
Fowl Pox Vaccine, Live 4976
Goat Pox Vaccine, Live 4976
Haemorrhagic Septicaemia Vaccine, Inactivated 4978
Haemorrhagic Septicaemia Vaccine-Alum Treated 4979
Inclusion Body Hepatitis (IBH) Vaccine, Inactivated 4979
Infectious Avian Encephalomyelitis Vaccine, Live 4980



Infectious Bursal Disease Vaccine, Inactivated 4981
Infectious Bursal Disease Vaccine, Live 4982
Infectious Canine Hepatitis Vaccine, Inactivated 4983
Infectious Chicken Anemia Vaccine, Inactivated 4984
Infectious Chicken Anemia Vaccine, Live 4985
Infectious Coryza Vaccine 4985
Marek's Disease Vaccine, Live 4986
Peste Des Petits Ruminants Vaccine, Live 4987
Rabies Veterinary Vaccine, Inactivated (Cell Culture) 4987
Ranikhet Disease Vaccine, Inactivated 4989
Ranikhet Disease Vaccine, Live (Lentogenic Strain) 4990
Ranikhet Disease Vaccine, Live (Mesogenic Strain) 4991
Reo Virus Vaccine, Inactivated 4991
Reo Virus Vaccine, Live 4992
Salmonella Abortus Equi Vaccine 4993
Salmonella Vaccine, Inactivated 4993
Sheep Pox Vaccine, Live Attenuated 4994
Tetanus Veterinary Vaccine 4995
Theileriosis Vaccine, Live 4998

Anthrax Spore Vaccine, Live

Anthrax Spore Vaccine is a suspension of an un-capsulated avirulent strain of *Bacillus anthracis* in 50 per cent glycerin saline.

Production

Preparation of vaccine. Avirulent (Cap⁻ Tox⁺) *B. anthracis* of known immunogenicity is grown on a suitable medium at pH 7.4 in Roux flasks. After 72 hours of incubation at 37°, the pure growth showing 70 to 80 per cent sporulation is harvested with *normal saline* and glycerinated to the extent of 50 per cent by weight of culture harvest. The whole suspension is kept at room temperature for 21 days to allow for the stabilization of spores. Total spore count of the glycerinated spore stock is determined by appropriate method. The stock is then appropriately diluted with glycerin saline to contain desirable number of viable spores as per the dose.

Choice of vaccine strain. A reference strain obtained from an authentic source shall be used for the vaccine production. The strain used may either be not lethal to guinea-pig or the mouse, or lethal to guinea-pig but not to the rabbit or lethal to some rabbits. A reference strain of *B. anthracis* obtained from an authentic source should be used.

Tests on Master seed lot

The master seed lot of the vaccine strain of *B. anthracis* is maintained as glycerin suspension of spores or it may be freeze-dried. The master seed lot complies with the tests of purity and identity for the organism and a batch of vaccine prepared from the master seed lot should comply with full range of control tests, i.e. identification, safety and potency.

Vaccine composition

The vaccine contains spores of an un-capsulated avirulent strain of *B. anthracis* in 50 per cent glycerin saline. The vaccine is shown to be satisfactory with respect to identification, safety and immunogenicity for the animal species for which it is intended.

Identification

Uncapsulated *B. anthracis* (Cap⁻ Tox⁺) which is avirulent may be isolated from the vaccine and identified by means of morphological, serological, cultural and biochemical tests.

Tests

Safety and Potency. The following safety and potency test is suggested on representative batch prepared from master seed lot.

Use eight sheep and eight goats each weighing not less than 18 kg. Inject animals in the following manner.

For safety, each of two sheep is injected with 10 ml of vaccine containing not less than 10 million spores per ml through subcutaneous route. Similarly, each of the two goats receives 5 ml of vaccine through subcutaneous route. The animals are observed for 10 days. Master seed lot passes the test if no abnormal systematic reaction is produced and no animal dies of anthrax. A mild local reaction may however be observed at the site of inoculation. Discontinue the animals used for safety test from the experiment.

For immunogenicity, each of six sheep and six goats are inoculated with one million spore suspended in 50 per cent glycerin saline through subcutaneous route. Twenty one days after inoculation, all the vaccinated animals are challenged with 100 minimum lethal dose (MLD) of virulent *B. anthracis* spores. Two healthy sheep and 2 healthy goats, used as unvaccinated controls are challenged with 10 MLD of the organism at the same time. All animals are observed for 10 days. The master seed lot passes the test if all vaccinated animals survive the challenge, and all the controls die from anthrax during the observation period.

If a vaccinated animal dies after challenge, repeat the test. If in the second test, a vaccinated animal dies, the master seed lot fails the test.

Manufacturer's tests

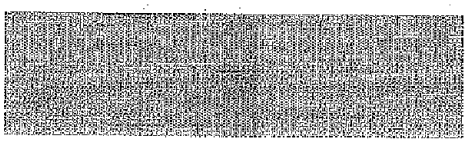
Following tests may be carried out on the final bulk vaccine rather than on the batch or batches prepared from it.

Sterility and purity. The vaccine is a live culture of *B. anthracis* spores. The final bulk must be tested for freedom from contamination by inoculating it on a suitable solid medium. Pure growth of the vaccinal bacterium obtained after incubation must be ignored.

Viable spore count. The spore count of the final bulk when plated on suitable medium must be not less than 2-10 x 10^6 per dose for cattle and 1-5 x 10^6 per dose for sheep and goat at the time of filling.

Safety. Carry out safety test on one of the species for which the vaccine is intended. If the vaccine is intended for several species including goats, carry out the test on goats. Administer 2 million spores subcutaneously or intramuscularly to each of two animals weighing not less than 18 kg. Observe the animals for 10 days. No abnormal systemic reaction is produced but a mild local reaction may occur at the site of inoculation. None of these animals should die of anthrax.

Potency. If the immunogenicity tests have been performed with satisfactory results on a representative batch of the vaccine from the seed lot, they may be omitted as a routine control test during production on other batches of the vaccine prepared from the same seed lot through the same production process.



Batch tests

Description. It is slightly opalescent or pale-brown semi-viscous liquid.

Identification

The vaccine complies with the requirements of the test mentioned under the section of Tests on master seed lot.

Viable spore count. The spore count of vaccine when plated on suitable medium should not be less than 80 per cent of that stated on the label.

Sterility and purity. Viable spore count may serve as the test for purity and freedom from contamination.

Safety and Potency. The vaccine complies with the tests for safety and potency mentioned under section of master seed lot.

Labelling and Storage. Should comply with the requirements of 'Labelling and Storage' as laid down in the General Monograph on Veterinary Vaccines: General Requirement.

Expiry. Not more than six months from the date of manufacture.

Avian Infectious Bronchitis Vaccine, Inactivated

Avian Infectious Bronchitis Vaccine, Inactivated consists of an emulsion or a suspension of one or more serotypes of avian infectious bronchitis virus which have been inactivated in such a manner that the immunogenic activity is retained. This monograph applies to vaccines intended to protect birds against drop in egg production or quality; for vaccines also intended for protection against respiratory signs and nephropathic symptoms, a demonstration of efficacy additional to that described under potency is required.

Production

The virus is propagated in embryonated hen's eggs obtained from healthy flocks or in suitable cell culture derived from SPF eggs (2.7.7). The master seed lot complies with the tests for extraneous agents as described in the General monograph for Veterinary Vaccines (2.7.10). The vaccine may contain one or more suitable adjuvant.

Inactivation

An amplification test for residual live avian infectious bronchitis virus is carried out on each batch of antigen immediately after inactivation. The test is carried out in fertilised hen's eggs from flocks free from specified pathogens (SPF) or in suitable cell culture derived from SPF eggs (2.7.7) and the quantity of inactivated virus used is equivalent to not less than $2/5^{th}$ doses of vaccine. No live virus is detected.

A. **In embryonated eggs.** For vaccine prepared with embryo-adapted strains of virus, inject quantity of inactivated virus equivalent to $2/5^{th}$ doses of vaccine into the allantoic cavity of ten 9 to 11-day-old fertilized hen eggs from an SPF flock and incubate. Observe for 5 to 6 days and pool separately the allantoic fluid from eggs containing live embryos and that from eggs containing dead embryos, excluding those that die within the first 24 hours after injection. Examine for abnormalities in all embryos which die after 24 hours of inoculation or which survive 5 to 6 days. No death or abnormality attributable to the vaccine virus occurs.

Inject into the allantoic cavity of each of ten 9 to 11-day-old fertilized hen eggs from SPF flock, 0.2 ml of the pooled allantoic fluid from the live embryos and into each of 10 similar eggs 0.2 ml of the pooled liquid from the dead embryos and incubate for 5 to 6 days. Examine for abnormalities in all embryos which die after 24 hours of injection or which survive 5 to 6 days. No death or abnormality attributable to the vaccine virus occurs.

If more than 20 per cent of the embryos die at either stage repeat the test from that stage. The vaccine complies with the test if there is no death or abnormality attributable to the vaccine virus. Antibiotics may be used to control extraneous bacterial infection.

B. **In cell culture.** For vaccine prepared with cell-culture-adapted strains of virus, inoculate quantity of inactivated virus equivalent to $2/5^{th}$ doses of vaccine into suitable cell culture derived from SPF eggs (2.7.7). Incubate at 36° ± 1° for 7 days. Make a passage on another set of cell culture derived from SPF eggs (2.7.7) and incubate at 36° ± 1° for 7 days. None of the cultures shows signs of infection.

Identification

In susceptible birds, the vaccine stimulates the production of specific antibodies against each of the virus strain incorporated in the vaccine, detectable by suitable serological method.

Tests

Sterility (2.2.11). Complies with the test for sterility.

Safety. Inject intramuscularly a quantity equivalent to 2 doses into each of ten SPF chickens (2.7.7) or healthy susceptible chickens, 2 to 4 weeks old. Observe the chickens for 14 days. No abnormal systemic or local reaction is seen.

Potency. Inject one dose by the route stated on the label into each of 10 SPF chickens (2.7.7, Table 3) or healthy susceptible chickens, 3 to 4 weeks old. Use 5 similar chickens as controls and house them together with the vaccinated chickens. After 28 days, collect serum samples from each of the vaccinated and control chickens and perform haemagglutination inhibition

(HI) test on each serum using 4 haemagglutinating (HA) units of antigen and chicken erythrocytes, testing all serum samples at the same time. The vaccine passes the test if the mean antibody titre of the vaccinated group is not less than 1:64 and no specific antibody is detected in the control chickens. Alternatively, serum neutralization test may be carried out in SPF eggs (2.7.7). Serum neutralization titre should not be less than 10^2 neutralization units.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 2 years from the date the potency was determined.

Labelling. The label states (1) the strain of virus used in preparing the vaccine; (2) the route of administration.

Avian Infectious Bronchitis Vaccine, Live

Infectious Bronchitis Vaccine, Live, Avian Infectious Bronchitis Vaccine Living

Avian Infectious Bronchitis Vaccine, Live is a preparation of one or more suitable strains of avian infectious bronchitis virus.

Production

The vaccine virus is grown in embryonated hens' eggs or in cell culture derived from SPF eggs (2.7.7).

Substrate for virus propagation

If the vaccine virus is grown in embryonated hen's eggs they are obtained from SPF flock (2.7.7) or in cell culture derived from SPF flocks (2.7.7).

The production is based on an approved seed lot system. Each lot of stock seed virus is tested for immunogenicity in chicken of the same age and source by the method described under immunogenicity test. If the immunogenicity test has been performed with satisfactory results on the representative batch of vaccine from the seed lot, it may be omitted as a routine control of other batches of the vaccine prepared from the same seed lot.

The master seed lot complies with the tests for extraneous agents as described in the General monograph for Veterinary Vaccines (2.7.10).

Identification

Carry out either the test A or B.

A. Inoculate 0.2 ml undiluted vaccine in the allantoic sac of SPF embryonated eggs and incubate at 36° ± 1° for 5 to 6 days. Lesions typical of infectious bronchitis (IB) are observed in the embryos and the allantoic fluid does not agglutinate chicken erythrocytes.

B. Specific antiserum against the strain or each of the strains of the avian infectious bronchitis virus used in the vaccine should neutralise corresponding IB virus. When mixed with specific antiserum, the vaccine no longer infects 9-11 day old embryonated SPF eggs (2.7.7).

Tests

Water (2.3.43). Not more than 3.0 per cent.

Mycoplasmas (2.7.9). Complies with the test for mycoplasmas.

Safety. Inject 10 times the dose by the route stated on the label into each of 10 SPF chickens (2.7.7, Table 3) or healthy susceptible chickens of 5 to 10 days old. Observe the birds for 21 days. Not more than one of the vaccinated chickens shows symptoms of or dies from infectious bronchitis. If during the period of observation more than 2 of the vaccinated chickens die from causes not attributable to the vaccine, repeat the test.

Sterility (2.2.11). Vaccines intended for administration by injection comply with the test for sterility prescribed in the monograph (2.2.11).

Virus titre. Titrate the vaccine in cell culture derived from SPF eggs (2.7.7) derived from SPF embryos or by inoculating into the allantoic sac of SPF embryonated eggs, 9 to 11 days old. One dose of the vaccine contains not less than $10^{3.5}$ $TCID_{50}/EID_{50}$.

Immunogenicity. Carry out a test for each route of administration recommended on the label and for each serotype against which protection is claimed and of the minimum age stated for vaccination. Administer to each of 20 SPF chickens (2.7.7, Table 3) or healthy susceptible chickens, 3 to 4 weeks old, for each of the stated routes a volume of reconstituted vaccine containing a quantity of virus equivalent to the minimum titre stated on the label. Ten additional SPF chickens (2.7.7, Table 3) or healthy susceptible chickens of same flock for each serotype against which protection is claimed are used as unvaccinated controls. Three to four weeks later, administer by eye drop a virulent strain of bronchitis virus with a titre of at least $10^{3.5}$ EID_{50} per ml to all the vaccinated and control birds. Between the fourth to seventh day after the challenge, take tracheal swabs from each of the vaccinated and control birds. Place each swab in a sterile test tube containing 3 ml of tryptose phosphate broth and antibiotics. Swirl the tubes containing swabs thoroughly and store at -20° pending inoculation into eggs. For each tracheal swab, inoculate at least 5 chicken embryos, 9 to 11 days old, with 0.2 ml of the broth from each tube into the allantoic cavity. All the embryos surviving on the third day after inoculation are used in the evaluation. A tracheal swab is

considered positive for recovery of the virus if any of the embryos shows typical infectious bronchitis lesions such as stunting, curling, kidney urates, clubbing down or death between the fourth and seventh day after inoculation. The vaccine complies with the test if not less than 80 per cent of the controls and not more than 20 per cent of the vaccinated chickens are positive for virus recovery. If less than 80 per cent of the vaccinated chickens are negative for virus recovery the stock seed is unsatisfactory.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 18 months from the date the virus titre was determined. The reconstituted vaccine should be used immediately after preparation.

Labelling. The label/insert states (1) the minimum virus titre per dose; (2) the dose of vaccine.

Avian Infectious Laryngotracheitis Vaccine, Live

Laryngotracheitis Vaccine, Live

Avian Infectious Laryngotracheitis Vaccine, Live is a preparation of a suitable strain of avian infectious laryngotracheitis virus (gallid herpesvirus 1). This monograph applies to vaccines intended for administration to chickens for active immunisation.

Production

The vaccine virus is grown in embryonated hens' eggs, from SPF flock (2.7.7) or in cell cultures derived from SPF eggs (2.7.7).

Substrate for virus propagation

The vaccine virus is grown in embryonated hens' eggs, they are obtained from flocks free from specified pathogens (SPF) (2.7.7) or in cell cultures for the production of veterinary vaccines (2.7.13).

Seed Lot

Extraneous agents. The master seed lot complies with the tests for extraneous agents in seed lots (2.7.10). In these tests on the master seed lot, the organisms used are not more than 5 passages from the master seed lot at the start of the tests.

Choice of vaccine virus

The following tests for index of respiratory virulence, safety, increase in virulence and immunogenicity may be used during the demonstration of safety and immunogenicity. The vaccine virus shall be shown to be satisfactory with respect to safety and efficacy (2.7.12) for the chickens for which it is intended.

Tests

Index of respiratory virulence. Use for the test not less than sixty 10-day-old chickens from an SPF flock (2.7.7). Divide them randomly into 3 groups, maintained separately. Prepare 2 tenfold serial dilutions starting from a suspension of the vaccine virus having a titre of 10^5 EID_{50} or 10^5 $CCID_{50}$ per 0.2 ml or, if not possible, having the maximum attainable titre. Use vaccine virus at the least attenuated passage level that will be present in a batch of the vaccine. Allocate the undiluted virus suspension and the 2 virus dilutions each to a different group of chickens. Administer by the intratracheal route to each chicken 0.2 ml of the virus suspension attributed to its group. Observe the chickens for 10 days after administration and record the number of deaths. The index of respiratory virulence is the total number of deaths in the 3 groups divided by the total number of chickens.

The vaccine virus complies with the test if its index of respiratory virulence is not more than 0.33.

Safety. Carry out the test for each route and method of administration to be recommended for vaccination, using in each case chickens not older than the youngest age to be recommended for vaccination. Use vaccine virus at the least attenuated passage level that will be present between the master seed lot and a batch of the vaccine. For each test use not less than 20 chickens, from an SPF flock (2.7.7). Administer to each chicken a quantity of the vaccine virus equivalent to not less than 10 times the maximum virus titre likely to be contained in 1 dose of the vaccine. Observe the chickens daily for 21 days.

The test is not valid if more than 10 per cent of the chickens die from causes not attributable to the vaccine virus. The vaccine virus complies with the test if no chicken shows notable clinical signs of avian infectious laryngotracheitis or dies from causes attributable to the vaccine virus.

Increase in virulence. The test for increase in virulence consists of the administration of the vaccine virus at the least attenuated passage level that will be present between the master seed lot and a batch of the vaccine to a group of 5 chickens not more than 2 weeks old, from an SPF flock (2.7.7), sequential passages, 5 times where possible, to further similar groups and testing of the final recovered virus for increase in virulence. If the properties of the vaccine virus allow sequential passage to 5 groups via natural spreading, this method may be used, otherwise passage as described below is carried out and the maximally passage virus that has been recovered is tested for increase in virulence. Care must be taken to avoid contamination by virus from previous passages. Administer by eye-drop a quantity of the vaccine virus that will allow

recovery of virus for the passages described below. After the period shown to correspond to maximum replication of the virus, prepare a suspension from the mucosae of suitable parts of the respiratory tract of each chicken and pool these samples. Administer 0.05 ml of the pooled samples by eye-drop to each of 5 other chickens that are 2 weeks old and from an SPF flock (2.7.7). Carry out this passage operation not less than 5 times; verify the presence of the virus at each passage. If the virus is not found at a passage level, carry out a second series of passages. Determine the index of respiratory virulence using the unpassaged vaccinevirus and the maximally passage virus that has been recovered; if the titre of the maximally passage virus is less than 10^5 EID_{50} or $10^5 CCID_{50}$; prepare the tenfold, serial dilutions using the highest titre available.

The vaccine virus complies with the test if no indication of increase in virulence of the maximally passage virus compared with the unpassaged virus is observed. If virus is not recovered at any passage level in the first and second series of passages, the vaccine virus also complies with the test.

Immunogenicity. A test is carried out for each route and method of administration to be recommended using in each case chickens not older than the youngest age to be recommended for vaccination. The quantity of the vaccine virus administered to each chicken is not more than the minimum virus titre to be stated on the label and the virus is at the most attenuated passage level that will be present in a batch of the vaccine. Use for the test not less than 30 chickens of the same origin and from an SPF flock (2.7.7). Vaccinate by a recommended route not less than 20 chickens. Maintain not less than 10 chickens as controls. Challenge each chicken after 21 days by the intratracheal route with a sufficient quantity of virulent infectious laryngotracheitis virus. Observe the chickens daily for 7 days after challenge. Record the deaths and the number of surviving chickens that show clinical signs of disease. At the end of the observation period euthanise all the surviving chickens and carry out examination for macroscopic lesions: mucoid, haemorrhagic and pseudomembraneous inflammation of the trachea and orbital sinuses.

The test is not valid, if during the observation period after challenge less than 90 per cent of the control chickens die or show severe clinical signs of avian infectious laryngotracheitis or notable macroscopic lesions of the trachea and orbital sinuses or if during the period between the vaccination and challenge more than 10 per cent of the vaccinated or control chickens show notable clinical signs of disease or die from causes not attributable to the vaccine.

The vaccine virus complies with the test if during the observation period after challenge not less than 90 per cent of the vaccinated chickens survives and shows no notable clinical signs of disease and/or macroscopical lesions of the trachea and orbital sinuses.

Batch Tests

Identification

The vaccine, diluted if necessary and mixed with a monospecific infectious laryngotracheitis virus antiserum, no longer infects embryonated hens' eggs from an SPF flock (2.7.7) or susceptible cell cultures into which it is inoculated.

Sterility (2.2.11). Complies with the test for sterility.

NOTE—Vaccines intended for administration by injection comply with the test for sterility in the monograph Vaccines for veterinary use.

Vaccines not intended for administration by injection either comply with the test for sterility prescribed in the monograph Vaccines for veterinary use or with the following test: carry out a quantitative test for bacterial and fungal contamination; carry out identification tests for micro-organisms detected in the vaccine; the vaccine does not contain pathogenic micro-organisms and contains not more than 1 non- pathogenic micro-organism per dose.

Any liquid supplied with the vaccine complies with test for sterility in the monograph Vaccines for veterinary use.

Mycoplasmas (2.7.9). Complies with the test for mycoplasmas.

Extraneous agents (2.7.11). The vaccine complies with the tests for extraneous agents in batches of finished product.

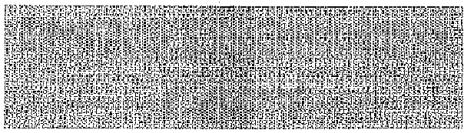
Safety. Use not less than 10 chickens from an SPF flock (2.7.7) and of the youngest age recommended for vaccination. Administer by eye-drop to each chicken 10 doses of the vaccine. Observe the chickens daily for 21 days.

The test is not valid if more than 20 per cent of the chickens show abnormal clinical signs or die from causes not attributable to the vaccine. The vaccine complies with the test if no chicken shows notable clinical signs of disease or dies from causes attributable to the vaccine.

Virus titre. Titrate the vaccine virus by inoculation into embryonated hens' eggs from an SPF flock (2.7.7) or into suitable cell cultures (2.7.7).

The vaccine complies with the test if 1 dose contains not less than the minimum titre stated on the label.

Potency. The vaccine complies with the requirements of the test prescribed under Immunogenicity when administered according to the recommended schedule by a recommended route and method. It is not necessary to carry out the potency test for each batch of the vaccine if it has been carried out on a representative batch using a vaccinating dose containing not more than the minimum virus titre stated on the label.



Avian Spirochaetosis Vaccine

Avian spirochaetosis Vaccine is a suspension prepared from viscera and membranes of developing chicken embryos of SPF eggs (2.7.7) infected with antigenic strains of *Borrelia anserina,* which has been inactivated in a such a manner that it's immunogenic activity is retained.

Production

Substrate for propagation

The organism is grown in embryonated eggs derived from SPF flocks.

Inactivation

An amplification test for residual live *Borrelia anserina spirochates*, batch of antigen after inactivation should be carried out in clean fertilised hen's eggs from apparently healthy flocks. Inoculate quantity of inactivated antigen equivalent to 2/5th dose of vaccine in fertilized hens eggs. Prepare smears from liver and heart tissue on 72 hours post inoculation and perform Fontana Silver Impregnation staining for detection of spirochates. The smears should be negative for presence of spirochaetes.

Identification

Protects chickens against infection with *B. anserina.*

Tests

Safety. Inject subcutaneously a quantity equivalent to 2 doses into each of 10 SPF chickens (2.7.7, Table 3) or healthy susceptible chickens of the recommended age at which vaccine is to be used. Observe the chickens for 14 days, no abnormal systemic or local reaction is seen.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Inject at least 10 SPF chickens (2.7.7, Table 3) or healthy susceptible chickens, 8 to 12 week old, with the minimum dose of vaccine by the route stated on the label. Use 5 chickens of the same stock as controls. Ten days later challenge all the chickens intra peritoneally with an adequate dose of a virulent culture of *B. anserina* used to prepare the vaccine or with a suspension of liver or kidney tissues obtained from infected chickens. Observe the chickens for 10 days. The vaccinated chickens do not show any symptoms of the disease and presence of *B. anserina* organism in the blood smears of the vaccinated group. The test is not valid unless the control chickens show typical symptoms of spirochaetosis with detection of spirochetes in the blood smears.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 2 years from the date the potency was determined.

Labelling. The label/insert states (1) strain of the bacteria used; (2) the route of administration.

Blackquarter Vaccine

Blackleg Vaccine; Clostridium Chauvoei Vaccine

Blackquarter Vaccine is a culture of a suitable strain or strains of *Clostridium chauvoei* grown in a suitable anaerobic fluid medium and rendered sterile and non-toxic by addition of *formaldehyde* in such a manner that it retains its immunizing properties. The vaccine may contain a suitable adjuvant. This monograph applies to the vaccines intended for active immunization of animals against disease caused by *C. chauvoei.*

Production

Preparation of vaccine. *C. chauvoei* strain used for production is grown in a suitable anaerobic fluid medium and the whole cultures are inactivated by addition of suitable quantity of *formaldehyde*. A suitable adjuvant may be added to the inactivated cultures.

Choice of vaccine strain. A reference strain of *C. chauvoei* obtained from an authentic source should be used. However, a local isolate from a particular area may also be used if the strain is shown to be satisfactory with respect to safety and immunogenicity for the animals for which the vaccine is intended.

Tests on Master seed lot

The master seed lot of the vaccine strain of *C. chauvoei* is maintained within three passages in artificial media from the culture obtained after target animal passage. The master seed lot complies with the tests of purity and identity for the organism and a batch of vaccine prepared from the master seed lot should comply with full range of control tests, i.e. identification, safety and potency.

Vaccine composition. The vaccine contains inactivated strain or strains of immunogenic *C. chauvoei* with or without a suitable adjuvant. The vaccine is shown to be satisfactory with respect to identification, safety and immunogenicity for the animal species for which it is intended.

Identification

The vaccine protects susceptible animals against infection with *C. chauvoei.* The potency test may also serve for identification.

Safety. Carry out safety test either on sheep or on cattle as per the following procedure.

Sheep. Inoculate three one-year-old sheep not vaccinated against Blackquarter vaccine with double the dose of the vaccine product by subcutaneous route at the inner face of the thigh. Observe for ten days and record their temperature in the morning and evening.

Cattle. Inoculate three one-year-old cattle not vaccinated against Blackquarter vaccine with double the dose of the product in the neck by subcutaneous route. Observe the inoculated animals for ten days and record their temperature twice a day in the morning and evening.

The seed-lot passes the test if there is no untoward reaction except slight swelling at the site of inoculation which subsides in four to five days.

Potency. Inoculate each of ten healthy guinea-pigs weighing between 350 g and 450 g subcutaneously with 2 ml of the vaccine or a quantity of the vaccine not greater than the minimum dose stated on the label as a primary dose. After 7 days, re-inoculate these guinea-pigs with 2 ml of the vaccine or a quantity of the vaccine not greater than the minimum dose stated on the label as a secondary dose. None of the vaccinated guinea-pigs shows any systemic reaction. However a minimal local reaction may be observed in the animals.

Fourteen days after the second vaccination, challenge all vaccinated guinea-pigs along with five controls by intramuscular route with 0.2 ml of virulent culture or 25 viable spore suspension of viable culture of virulent *C. chauvoei* in saline suspension containing 2.5 per cent *calcium chloride*.

The vaccine complies with the test if not more than 10 per cent of the vaccinated guinea-pigs die from the *C. chauvoei* infection within 5 days, and all control guinea-pigs die from the *C. chauvoei* infection within 72 hours of challenge.

If more than 10 per cent but less than 20 per cent of the vaccinated animals die, repeat the test. The vaccine complies with the test if not more than 10 per cent of the second group of vaccinated guinea-pigs die from the *C. chauvoei* infection within 5 days, and all of the animals of the control group die from the *C. chauvoei* infection within 72 hours of challenge. To avoid unnecessary sufferings following virulent challenge, moribund animals are euthanized and are considered to have died from *C. chauvoei* infection.

Manufacturer's tests

Certain tests may be carried out on the final bulk vaccine rather than on the batch or batches prepared from it.

Safety and potency. Each of a lot of at least 6 healthy adult guinea-pigs weighing between 350 g and 450 g is injected subcutaneously with 3 ml of the vaccine followed a week later by a second injection with the same dose. None of the vaccinated guinea-pigs shows any systemic reaction though, a minimal local reaction may be observed in the animals.

Fourteen days after the second vaccination, challenge all vaccinated guinea-pigs along with 2 controls by intramuscular route with 20 viable spores or virulent culture of *C. chauvoei* in saline suspension containing 2 per cent *calcium chloride*.

The vaccine complies with the test if at least 4 of the 6 vaccinated guinea-pigs survive from the *C. chauvoei* infection for 7 days, and the two control guinea-pigs die from the infection within 72 hour of challenge.

Batch tests

Description. An off-white to yellowish-brown liquid containing dead bacteria in suspension.

Identification

The vaccine complies with the requirements of the test mentioned under the section of Test on Master seed lot.

Sterility (2.2.11). Complies with the test for sterility.

Safety and Potency. The vaccine complies with the test for safety and potency mentioned under section of Manufacturer's tests.

Labelling and Storage. Should comply with the requirements of 'Labelling and Storage' as laid down in the General Monograph on Veterinary Vaccines: General Requirements.

The label states. (1) whether the product is a toxoid vaccine prepared from one or two strains of bacteria; (2) the immunizing effects produced in each target species (for example, protects against signs of disease or infection); (3) dose and route of inoculation.

Expiry. Not more than 24 months from the date of manufacture.

Bluetongue Vaccine, Inactivated

Bluetongue Vaccine (BTV), Inactivated is a preparation containing bluetongue virus serotypes that have been inactivated in such a manner that is immunogenic activity is retained. This monograph applies to vaccines intended for the active immunization of sheep against bluetongue. The vaccine can also be used in other susceptible animals such as goats, cattle and wild animals.

Production

Each serotype of BTV is grown separately in suitable cell culture. Each BTV serotypes should have a $TCID_{50}$ of $10^{5.5}$ per ml. The harvested virus is inactivated using Binary Ethyleneimine–Formaldehyde or Ethyleneimine in suitable condition. The inactivated BTV serotypes are blended. The vaccine contains a suitable adjuvant.

Identification

When injected into susceptible sheep, the vaccine stimulates the production of specific neutralizing antibodies against the BTV serotypes. Besides this test, before inactivation, identity on the antigen lot by means of molecular methods is also carried out.

Tests on master seed

Inactivation

Carry out inactivation of BTV serotypes separately. During inactivation of the virus, take the sample at regular intervals for the purpose of monitoring the rate and linearity of inactivation process. Virus titres in the samples are determined by inoculation into sensitive cell culture. The infectivity of the timed samples are plotted against time. The last sample taken does not show cytopathic effect or the presence of BTV in the inoculated sensitive cell culture. The inactivation procedure is considered satisfactory if the inoculated sensitive cell culture does not show the presence of BTV. The inoculated sensitive cell culture does not show the presence of dsRNA bands in Agarose gel electrophoresis. The sample taken at 24 hours after inactivation does not show even the traces of dsRNA bands in Agarose gel electrophoresis.

Safety

Carry out the test for each route and method of administration to be recommended for the vaccination. Representative batches prepared from the master seed shall be injected per batch into each of 6 sheep with double doses of the vaccine and by the route stated on the label. Observe the sheep for 14 days. None of the sheep shows abnormal local or systemic reactions. Such animals used in the test may be free of bluetongue antibodies for the serotypes present in the vaccine.

Potency

Inject each of 10 susceptible sheep that have been previously tested and shown to be free from bluetongue antibodies for the serotypes present in the vaccine with the minimum dose and the route stated on the label. After 14 days, administer a booster dose. Fourteen days later, collect the serum from each sheep and carry out serum neutralization test in suitable cell cultures using 100 $TCID_{50}$ of each of the BTV serotypes separately. Include 3 sheep as unvaccinated controls.

The vaccine passes the test if mean antibody titer of the vaccinated group is more than 1:20. The test is valid only if no specific antibodies are found in the control sheep. If the potency test has been performed with satisfactory result on representative batches of the vaccine from the seed lot, it may be tested on one in ten batches during production.

Manufacturer's tests

The tests mentioned under the tests on master seed need not be repeated if the tests are carried out at initial stage of development.

Cell culture innocuity test

Carry out cell culture innocuity test with each serotype after inactivation in suitable cells with an interval of 4 to 5 days spread over 3 passages. Use an equivalent of 10 doses per each serotype. The culture harvest collected at each passage should be negative for any cytopathic effects.

Identification

When injected into the susceptible sheep, the vaccine stimulates the production of specific neutralizing antibodies against the BTV serotypes. Potency test serves the purpose of identification also.

Batch tests

Cell culture innocuity test

Carry out cell culture innocuity test with each serotype after inactivation in suitable cells with an interval of 4 to 5 days spread over 3 passages. Use an equivalent of 10 doses per each serotype. The culture harvest collected at each passage should be negative for any cytopathic effects.

Safety

Inject two susceptible sheep with two doses of the vaccine and by the route stated on the label and observe the sheep for 14 days. None of the sheep shows abnormal local or systemic reactions.

Identification

When injected into the susceptible sheep, the vaccine stimulates the production of specific neutralizing antibodies against the BTV serotypes. Potency test serves the purpose of identification also.

Sterility (2.2.11). Complies with the test for sterility.

Potency

If the potency test has been performed with satisfactory result on representative batches of the vaccine from the seed lot. It may be tested on one in ten batches during production provided the vaccine is prepared from the same seed lot.

Labelling: The label states (1) BTV serotypes used; (2) recommended age for vaccination; (3) dose and route of administration; (4) storage conditions; (5) expiry period.

Brucella Abortus (Strain 19) Vaccine, Live

Contagious Abortion (Strain 19) Vaccine, Live; Contagious Brucella Vaccine (Strain 19) Live

Brucella Abortus (Strain 19) Vaccine, Live is a suspension of pure smooth culture of *Brucella abortus* strain 19 of low virulence in normal *saline solution*. The vaccine may be issued as a liquid, or prepared immediately before use by reconstitution from the freeze-dried preparation with *saline solution*.

Production

Preparation of vaccine

Wash 48 to 72 hour old growth of *B. abortus* on potato agar medium in Roux flasks with buffered normal *saline solution* pH 6.4, and pooled together the pure growth from the flasks. Mix 0.5 ml of pooled bulk harvest with 4.5 ml of normal *saline solution* at pH 6.4 in graduated centrifuge tubes and centrifuge at 3000 rpm for one hour. Determine the percentage of cell deposit. Dilute the concentrated suspension with buffered normal *saline solution* so that the final product contains 0.7 per cent bacterial cell deposit.

Vaccine strain

Brucella abortus strain 19 having normal properties of a biovar 1 strain of *B. abortus*, but does not require CO_2 for growth, does not grow in presence of benzylpenicillin (3 µg per ml = 5 IU per ml), thionin blue (2 µg per ml) and i-erythritol (1 mg per ml) concentrations.

Master seed lot

If facilities to prepare and maintain seed lots does not exist in the manufacturing unit, procure fresh original seed from a reference laboratory, each time a new vaccine batch is started. If the number of batches being produced makes it impracticable, then freeze-dried seed lot may be prepared. The seed lot of the vaccine strain should comply with the tests for purity and identity for the organism and, a batch of vaccine prepared from the master seed lot should comply with full range of control tests i.e. identification, safety and immunogenicity.

Vaccine composition

The vaccine contains 4×10^{10} to 8×10^{10} *B. abortus* organisms per dose in buffered saline. It complies with the tests for identification, and immunogenicity.

Identification

B. abortus strain 19 present in vaccine is identified by means of morphological, biochemical and serological tests. The potency test on vaccine batch may also serve for identification.

Tests

Safety. Inject each of a group of at least 10 healthy adult guinea-pigs with the test vaccine diluted in buffered saline (pH 6.4), containing 5×10^9 viable organisms or $1/10^{th}$ of calf dose intramuscularly and observe for 10 days.

The master seed lot passes the safety test if none of the animals shows notable adverse reactions or death attributable to vaccination.

Immunogenicity. The following test for immunogenicity may be used for the demonstration of efficacy in guinea-pig.

Inject each of a group of 10 healthy adult guinea-pigs drawn from a uniform stock and each weighing 300 g to 450 g, intramuscularly with $1/15^{th}$ of the calf dose of the test vaccine. Nine weeks later, challenge each of the vaccinated guinea-pigs with 1 ml suspension of 5000 fully virulent *B. abortus* strain 544 organisms. Use 6 guinea-pigs of the same stock and weight as unvaccinated controls. Six weeks later, sacrifice the all guinea-pigs and prepare cultures from their spleens. The master seed lot passes the test if not more than 25 per cent of the vaccinated animals contain demonstrable *B. abortus* organisms in spleens.

The test is not valid unless the spleens of all control animals are infected.

Manufacturer's tests

Following tests may be carried out on the final bulk of vaccine rather than on the batch or batches prepared from it.

Identification

Complies with the requirements of the test mentioned under section of Master seed lot. The identity of each single harvest and of each bulk should also be tested by agglutination tests with antiserum to *B. abortus*.

Bacteria and Fungi. Carry out the test by microscopic examination and by inoculation of suitable growth media. The bulk does not contain contaminating bacteria and fungi.

Enumeration of live bacteria and determination smoothness. Conduct viable count on final bulk by plate count method using a suitable medium (serum-dextrose agar or trypticase-soy agar or potato infusion agar). The final bulk vaccine complies with the test, if it contains 4×10^{10} to 8×10^{10} *B. abortus* organisms per dose. At least 90 per cent of the *B. abortus* should be in smooth phase.

Recommended dose for vaccination is not less than 4×10^{10} *B. abortus* organisms per dose.

Safety. Use 2 healthy adult guinea-pigs each weighing 300 g to 450 g for the test. The final bulk vaccine complies with the requirements of the mentioned under section of Master seed lot.

Batch tests

Description. Almost white, turbid liquid containing live bacterial suspension.

Identification

Complies with the requirements of the test mentioned under section of Master seed lot.

Viable count and smoothness. The vaccine complies with the requirements of the test, if the number of live *B. abortus* organisms is not less than 4×10^{10} per dose stated on label and at least 90 per cent of the organisms are in smooth phase.

Bacteria and Fungi. The batch complies with the requirements of the test as mentioned under section of Manufacturer's tests.

Safety. If the batch has been prepared through the same manufacturing process from the same seed lot which has shown good results for safety, it is not necessary to conduct the test on each batch of vaccine.

Potency. If the batch has been prepared through the same manufacturing process from the same seed lot which has shown good results for potency, it is not necessary to conduct the test on each batch of vaccine.

Labelling and Storage. Should comply with the requirements of 'Labelling and Storage' as laid down in the General Monograph on Veterinary Vaccines: General Requirements. The liquid vaccine should be issued fresh as far as possible without allowing any period of storage after manufacture.

Expiry. Not more than 5 weeks from the date of manufacture for liquid vaccine.

Canine Adenovirus Vaccine, Live

Canine Infectious Tracheobronchitis Vaccine, Live; Canine Adenovirus-2 (CAV-2) Vaccine, Live

Canine Adenovirus Vaccine, Live is a freeze dried preparation containing one or more attenuated strains of canine adenovirus-2 (CAV-2).

Production

The virus is propagated in suitable cell culture. The cell culture complies with the requirements for cell culture for production of veterinary vaccines (2.7.13). The harvested virus culture is titrated and may be mixed with a suitable stabilizing solution. The vaccine is then freeze-dried and can be used with any suitable diluent or used after reconstitution with licensed liquid canine vaccine components.

Choice of vaccine strain. A reference strain obtained from an authentic source shall be used for the vaccine production. The master seed which has been established as pure, safe and immunogenic for the species for which it is intended shall be used for vaccine production.

Identification

The vaccine mixed with the monospecific serum against CAV-2, no longer infects susceptible cell culture.

Tests

Extraneous agents. Neutralize the vaccine virus with a suitable mono specific antiserum against canine adenovirus-2 and inoculate into cell cultures known for their susceptibility to viruses pathogenic for the dog. Carry out 2 passages with an interval of 6 to 8 days and maintain the cultures for a total 14 days. The vaccine complies with the test if no cytopathic effect develops.

Mycoplasmas (2.7.8). Complies with the test for freedom from mycoplasmas.

Sterility (2.2.11). Complies with the test for sterility.

Safety. Carry out the test for each route and methods of administration to be recommended for vaccination. Use vaccine virus at least attenuated passage level that will be present between the master seed lot and a batch of the vaccine. Use not less than 5 dogs of the minimum age recommended for vaccination that do not have antibodies against canine adenovirus. Administer to each dog a quantity of vaccine virus equivalent to not less than 10 times of the maximum virus titre likely to be contained in one dose of the vaccine. Observe the dog daily for 14 days. The vaccine complies with the test if no dogs shows abnormal local and/ or systemic reactions, sign of diseases or dies from causes attributed to the vaccine virus.

Increase in virulence. The test for increase in virulence consists of the administration of the vaccine virus at least attenuated passage level that will be present between the master seed lot and a batch of the vaccine to two dogs, 5 to 7 weeks old that do not have antibodies against canine adenovirus. Administer to each dog by a route to be recommended a quantity of vaccine virus that will allow recovery of virus for the passage described below.

Administer the virus by the route recommended for the vaccination most likely to lead to reversion of virulence. After 4 to 6 days of administration kill the puppies and prepare a suspension from nasal and pharyngeal mucosa, tonsil, lungs and spleen and if they are likely to contain virus, liver and kidney of each dog and pool the sample. Administer 1 ml of the pooled sample by suitable route to each of the 2 dogs of the same age. Carry out this passage operation not less than 5 times; verify the presence of virus in each passage. If the virus is not found at a passage level, carry out a second series

of passage. Carry out the test for safety using unpassaged vaccine virus and maximally passage virus that has been recovered.

The vaccine virus complies with the test if no indication of increased in virulence of the maximally passage virus compared with the unpassaged virus is observed. If virus is not recovered at any passaged level in the first and second series of passages, the vaccine virus also complies with the test.

Immunogenicity. A test is carried out of each route and method of administration to be recommended for vaccination using dogs of the minimum age to be recommended. The quantity of vaccine virus to be administered to each dog is not more than the minimum titre to be stated on the label and the virus is at the most attenuated passage level that will be present in a batch of vaccine.

Use 20 dogs of the minimum age recommended for vaccination and that do not have antibodies against canine adenovirus-2. Vaccinate not less than 10 dogs according to the route and schedule to be recommended. Use not less than 10 dogs as controls. Challenge each dog after 21 days by the intranasal route with the quantity of a suspension of virulent strain of canine adenovirus-2 sufficient to cause typical signs of respiratory disease in a susceptible dog. Observe the dogs daily for a further 10 days. Record the incidence of signs of respiratory and general disease in each dog (for example, sneezing, coughing, nasal and lachrymal discharge, loss of appetite). Collect nasal swabs or washings from each dog daily from days 2 to 10 after challenge and test these samples to determine the presence and titre of excreted virus.

The vaccine complies with the test if there is a notable decrease in the incidence and severity of clinical signs and in virus excretion in vaccinates compared to controls.

Virus titre. Not less than 10^3 $TCID_{50}$ of the virus per dose, determining the titre of the vaccine in a suitable cell culture with suitable medium.

Manufacturer's tests

Virus titre. Virus titre is determined in final bulk harvest in a suitable cell culture with suitable medium.

Identification

Vaccine complies the requirements of the test mentioned under production.

Extraneous agents. Vaccine complies the requirements of the test mentioned under production.

Mycoplasmas (2.7.8). Complies with the test for freedom from mycoplasmas.

Sterility (2.2.11). Complies with the test for sterility.

Batch tests

Identification

Vaccine complies the requirements of the test mentioned under production. Alternatively, identification on the final lot by molecular techniques is acceptable and can be used in the routine batch release tests after proper validation (2.8.1).

Water (2.3.43). Not more than 3.0 per cent.

Extraneous agents. Vaccine complies the requirements of the test mentioned under production. Alternatively, molecular techniques for detection of pathogenic viruses of dog are acceptable batch release test after proper validation (2.8.1).

Mycoplasmas (2.7.8). Complies with the test for freedom from mycoplasmas. Alternatively, molecular techniques for detection of mycoplasma nucleic acid are acceptable batch release test after proper validation (2.8.1).

Virus titre. Not less than 10^3 $TCID_{50}$ of the virus per dose, determining the titre of the vaccine in a suitable cell culture with suitable medium or one dose of vaccine contains not less than quantity of virus equivalent to the minimum virus titre stated on the label.

Sterility (2.2.11). Complies with the test for sterility.

Safety. Inject intramuscularly 10 times the minimum dose stated on the label into each of two dogs of the minimum age recommended for vaccination. Observe the animals for 21 days. None of the dogs shows abnormal local or systemic reactions or dies of any causes attributable to the vaccine.

Potency. The vaccine complies with the requirements of test mentioned under immunogenicity when administered by a recommended route and method. It is not necessary to carry out the potency test for each batch of the vaccine if it has been carried out on a representative batch of the vaccine using a vaccinating dose containing not more than the minimum titre stated on the label. The virus titre is considered for a routine batch release provided the traceability of the vaccine strains used is from the same master seed.

Labelling. The label states (1) the minimum dose; (2) the recommended routes of administration; (3) storage temperature; (4) virus titre; (5) expiry period.

Canine Coronavirus Vaccine, Inactivated

Canine Coronavirus Vaccine, Inactivated is a preparation containing canine coronavirus, inactivated in such a manner that its immunogenic activity is retained. It may be issued as a liquid or as a freeze-dried preparation to be reconstituted with

a suitable liquid immediately before use. The liquid vaccine may contain a suitable adjuvant.

Production

The virus is grown in suitable cell culture systems. The cell culture complies with the requirements for cell culture for production of veterinary vaccines (2.7.13). The vaccine may contain a suitable adjuvant.

Choice of vaccine strain. A reference strain obtained from an authentic source shall be used for the vaccine production. The master seed which has been established as pure, safe and immunogenic shall be used for vaccine production.

Identification

When inoculated into dogs, the vaccine stimulates the production of specific neutralizing antibodies against canine coronavirus as determined by suitable serological tests.

Tests

Safety. Carry out the test for each route and method of administration to be recommended for the vaccination. Double dose of the batch prepared from the master seed shall be injected to ten healthy dogs in the age group and by the route stated on the label. Observe the animals for 14 days and no abnormal systemic or local reaction occurs. Such animals used in the test shall be preferably free of canine coronavirus antibodies. At least three representative batches from the master seed shall be tested for safety.

Potency. Inject each of 6 healthy susceptible dogs between 8 and 14 weeks old having antibody titer less than 6 SN_{50} per 50 µl of serum with a representative batch with the dose recommended on the label. Use 2 dogs of the same age as control. If a second dose is recommended, the second dose shall be administered at the time specified on the label. Not less than 14 days booster or not less than 21 days after single vaccination, challenge all the animals through appropriate route with a virulent virus strain of canine coronaovirus. Observe the animals for 14 days. The vaccine complies with the test if the 5 vaccinated dogs remain healthy and show no sign of disease. The test is not valid unless the controls die or show clinical signs of canine coronavirus infection.

Manufacturer's tests

Identification

Vaccine complies the requirements of the test mentioned under production.

Potency. If is not necessary to carry out the potency test for each batch of the vaccine if it has been carried out using a batch of vaccine with a minimum potency. Where the test is not carried out, an alternative validated methods is used, the criteria for acceptance being set with reference to a batch of vaccine that has been given satisfactory results in the test described under potency.

Batch tests

Identification

Vaccine complies the requirements of the test mentioned under production. Alternatively, identification on the final lot by validated molecular techniques is acceptable and can be used in the routine batch release tests after proper validation of antigen extraction protocol from adjuvanted vaccine and test applied (2.8.1).

Water (2.3.43). Not more than 3.0 per cent (for freeze dried vaccine only).

Safety. Inject each of two healthy susceptible dogs in the recommended age group free from canine coronavirus antibodies with a quantity equivalent to 2 doses by the route stated on the label. Observe the animals for 14 days. No abnormal systemic or local reaction occurs.

Sterility (2.2.11). Complies with the test for sterility.

Potency. *Carry out either the test A or B.*

A. Inject each of five healthy susceptible guinea-pigs, each weighing between 350 and 450 g, with half the minimum dose and by the route stated on the label. Repeat the injection after14 days. Fourteen days after the second injection collect blood samples and obtain the serum from each guinea-pig separately. Inactivate each serum by heating at 56° for 30 minutes. Examine the serum samples for antibodies by the following method.

Prepare 2-fold serial dilutions of serum in a medium suitable for canine cells. Add to each dilution an equal volume of a virus suspension containing approximately 10^2 $TCID_{50}$ and incubate the mixtures at 37° for 1 hour. Inoculate a suitable volume of canine cells into at least 4 replicates of serum virus mixtures and incubate at 37° for 4 days. Examine for evidence of specific cytopathic effects and calculate the antibody titre. The vaccine complies with the test if the mean antibody titre is not less than 45 SN_{50} per 50 µl of serum.

B. Inject each of 2 healthy susceptible dogs between 8 and 14 weeks old having antibody titer less than 6 SN_{50} per 50 µl of serum with a representative batch with the dose recommended on the label. If a second dose is recommended, the second dose shall be administered at the time specified on the label. For single dose schedule, collect blood after 21 days or for two dose schedule, collect blood 14 days after booster from each dog. Inactivate each serum sample by heating at 56° for 30 minutes. Examine the serum sample individually for the

neutralizing antibodies. Prepare 2-fold serial dilutions of the serum in a suitable for canine cells. Add to each dilution an equal volume of a virus suspension containing approximately 10^2 $TCID_{50}$ and incubate the mixture at 37° for 1 hour. Inoculate a suitable volume of canine cells into at least 4 replicates of serum virus mixture and incubate at 37° for 4 days. Examine for evidence of specific cytopathic effects and calculate the mean antibody titer. Vaccine complies with the test, if the mean antibody titer in vaccinated dogs is not less than 45 SN_{50} per 50 µl of serum.

Labelling. The label states (1) the recommended routes of administration; (2) that the preparation should be shaken well before use; (3) that the liquid preparation should not be allowed to freeze; (4) that the vaccine should be used immediately after reconstitution for freeze dried vaccine; (5) storage temperature; (6) expiry date.

Canine Distemper Vaccine, Live

Canine Distemper Vaccine, Live is a freeze-dried preparation of a strain of canine distemper virus that has been attenuated for dogs and is grown either in suitable cell cultures or SPF eggs.

Production

The virus is propagated in suitable cell culture or SPF eggs. The cell culture or SPF eggs complies with the requirements for cell culture or egg for production of veterinary vaccines (2.7.13). The viral suspension is harvested, titrated and may be mixed with a suitable stabilizing agents. The vaccine is then freeze-dried and can be used with any suitable diluent or used after reconstitution with licensed liquid vaccine components.

Choice of vaccine strain. A reference strain obtained from an authentic source shall be used for the vaccine production. The master seed which has been established as pure, safe and immunogenic for the species for which it is intended shall be used for vaccine production.

Identification

Carry out either the test A or B.

A. The vaccine reconstituted as stated on the label and mixed with a mono-specific serum against canine distemper virus no longer infects chorioallantoic membranes of SPF embryonated eggs.

B. The vaccine reconstituted as stated on the label and mixed with a mono-specific serum against canine distemper virus no longer provokes cytopathic effects in susceptible cell cultures.

Tests

Mycoplasma (2.7.8). Complies with the test for freedom from mycoplasmas.

Extraneous agents. *Carry out either the test A or B.*

A. Neutralize the vaccine virus with a suitable mono-specific antiserum against canine distemper virus and inoculate into cell cultures known for their susceptibility to viruses pathogenic for the dog. Carry out 2 passages with an interval of 6 to 8 days. The vaccine complies with the test if no cytopathic effect develops for 10 days.

B. Use a sufficient number of mice, not less than ten, each weighing between 11 and 15 g and administer each mouse intracerebrally with 30 µl of the vaccine. Observe for 21 days. Not more than two mice die within the first 48 hours. If more than two mice die within the first 48 hours, repeat the test. From the third day to 21 days after the injection, the mice do not show any abnormalities attributable to the vaccine.

Sterility (2.2.11). Complies with the test for sterility.

Safety. Reconstitute the vaccine as recommended on the label and carry out the following tests.

A. *For chicken embryo-adapted vaccine only.* Inject 30 µl intracerebrally into each of a group of eight mice, between 3 and 4 weeks old, and 0.5 ml intraperitoneally into each of another eight mice of the same age group. Observe both the groups for 7 days. Not more than one mouse in either group shows any abnormal local or systemic reaction attributable to the vaccine.

B. The test is carried out for each recommended route of administration. Use five susceptible puppies of the minimum age recommended for vaccination and that do not have antibodies against canine distemper virus. Administer to each puppy by a recommended route a quantity of virus corresponding to not less than ten times the maximum titre that may be expected in a dose of vaccine. Observe the puppies for 42 days. The puppies remain in good health and there is no abnormal local or systemic reaction.

Increase in virulence. Administer by a recommended route to each of two puppies, 5 to 7 weeks old and which do not have antibodies against canine distemper virus a quantity of virus corresponding to one dose of vaccine. Kill the puppies 5 to 10 days later, remove nasal mucosa, tonsils, thymus, spleen and the lungs and their local lymph nodes from each puppy and pool the samples; administer intranasally 1 ml of the pooled organ suspension to each of two other puppies of the same age and susceptibility; carry out these operations at least five times; verify the presence of the virus at each passage by direct or indirect means. If the virus has disappeared, carry out a second series of passages. Inoculate virus from the highest recovered passage level to puppies, observe for

42 days and compare any reactions that occur with those seen in the test for safety described above. There is no indication of an increase of virulence as compared with the non passaged virus.

Immunogenicity. Inject each of five susceptible dogs, between 8 and 14 weeks old, that have been previously tested and shown to be free from canine distemper virus neutralizing antibodies with a volume of the reconstituted vaccine containing a quantity of the virus equivalent to the minimum titre and by stated on the label. Use another two dogs of the same age group as unvaccinated controls. Observe the animals for a further 21 days. Inject intravenously each of the seven animals with a quantity of virulent strain of canine distemper virus sufficient to cause death or produce typical signs of the disease in a susceptible dog. Observe the animals for a further 21 days. The vaccinated animals survive and show no clinical signs of canine distemper. The test is not valid unless the control dogs die or show symptoms typical of canine distemper. If one of the control animals does not show any sign of canine distemper, repeat the test. The vaccinated animals of the second group remain in normal health and the control animals die from canine distemper or show symptoms typical of canine distemper.

If the potency test has been performed with satisfactory results on a representative batch of the vaccine from the seed lot, it may be omitted as a routine control test during production on other batches of the vaccine prepared from the same seed lot.

Virus titre. Not less than 10^3 $TCID_{50}$/$CCID_{50}$/EID_{50} of the virus per dose, determining the titre of the vaccine in a suitable cell culture with suitable medium.

Manufacturer's tests

Virus titre. Virus titre is determined in final bulk harvest in a suitable cell culture with suitable medium.

Identification. Vaccine complies the requirements of the test mentioned under production.

Extraneous agents. Vaccine complies the requirements of the test mentioned under production.

Mycoplasmas (2.7.8). Complies with the test for freedom from mycoplasmas.

Sterility (2.2.11). Complies with the test for sterility.

Batch tests

Identification

Vaccine complies the requirements of the test mentioned under production. Alternatively, identification on the final lot by molecular techniques is acceptable and can be used in the routine batch release tests after proper validation (2.8.1).

Water (2.3.43). Not more than 3.0 per cent.

Extraneous agents. Vaccine complies the requirements of the test mentioned under Production. Alternative, molecular techniques for detection of pathogenic viruses of dog are acceptable batch release test after proper validation (2.8.1).

Mycoplasmas (2.7.8). Complies with the test for freedom from mycoplasmas. Alternatively, molecular techniques for detection of mycoplasma nucleic acid are acceptable batch release test after proper validation (2.8.1).

Virus titer. Not less than 10^3 $TCID_{50}$ of the virus per dose, determining the titre of the vaccine in a suitable cell culture with suitable medium or one dose of vaccine contains not less than quantity of virus equivalent to the minimum virus titre stated on the label.

Sterility (2.2.11). Complies with the test for sterility.

Safety. Inject intramuscularly 10 times the minimum dose stated on the label into each of two dogs of the minimum age recommended for vaccination. Observe the animals for 21 days. None of the dogs shows abnormal local or systemic reactions or dies of any causes attributable to the vaccine.

Potency. The vaccine complies with the requirements of test mentioned under immunogenicity when administered by a recommended route and method. It is not necessary to carry out the potency test for each batch of the vaccine if it has been carried out on a representative batch of the vaccine using a vaccinating dose containing not more than the minimum titre stated on the label. The virus titer is considered for a routine batch release provided the traceability of the vaccine strains used is from the same master seed.

Labelling. The label states (1) the minimum dose; (2) the recommended routes of administration; (3) storage temperature; (4) virus titer; (5) expiry period.

Canine Leptospirosis Vaccine, Inactivated

Canine Leptospirosis Vaccine (Inactivated) is a suspension of inactivated whole organisms and/or antigenic extract(s) of one or more suitable strains of one or more of *Leptospira interrogans* serovar canicola, serovar *icterohaemorrhagiae* or any other epidemiologically appropriate serovar, inactivated and prepared in such a way that adequate immunogenicity is maintained.

Production

The seed material is cultured in a suitable medium; each strain is cultivated separately. During production, various parameters

such as growth rate are monitored by suitable methods; the values are within the limits approved for the particular product. Purity and identity are verified on the harvest using suitable methods. After cultivation, the bacterial harvests are collected separately and inactivated by a suitable method. The antigen may be concentrated. The vaccine may contain an adjuvant.

Inactivation

Carry out a test for inactivation by inoculation on to a specific medium. Inoculate 1 ml of the vaccine into 100 ml of the medium. Incubate at 30° for 14 days, subculture into a further quantity of the medium and incubate both media at 30° for 14 days: no growth occurs in either medium. At the same time, carry out a control test by inoculating a further quantity of the medium with the vaccine together with a quantity of a culture containing approximately 100 leptospirae and incubating at 30° growth of leptospirae occurs within 14 days.

Identification

When administered to experimental animals causes the appearance of agglutinating antibodies against the serotype or serotypes used to prepare the vaccine.

Tests

Safety. Use two dogs of the minimum age recommended for vaccination and which do not have antibodies to the leptospira serovar(s) present in the vaccine. Administer 2 doses of the vaccine to each dog by a recommended route. Observe the animals for 14 days. The animals remain in good health and no abnormal local or systemic reaction occurs.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Carry out a separate potency test for each serotype if the vaccine is prepared with different serotypes. Inject each of five hamsters not more than 3 months old, the animals being drawn from the same stock, subcutaneously with 1/40 of the dose of the vaccine stated on the label for dogs. Use an equal number of animals of the species used for the test as controls. After 15 to 20 days inject intraperitoneally into each of the vaccinated and control animals an adequate dose of a virulent culture of leptospirae of the serotype used to prepare the vaccine or a suspension of liver or kidney tissue obtained from animals infected with the serotype used to prepare the vaccine. Observe the animals for 14 days after the injection. Not less than four of the control animals die showing typical leptospira infection. Not less than four of the vaccinated animals remain in good health for not less than 14 days after the death of the four control animals.

Labelling. The label states (1) the strain used for the preparation; (2) the name of any added adjuvant.

Canine Parainfluenza Virus Vaccine, Live

Canine Parainfluenza Virus Vaccine, Live is a freeze-dried preparation containing one or more attenuated strains of canine parainfluenza virus grown in suitable cell cultures.

Production

The virus is propagated in suitable cell culture. The viral suspension is harvested, titrated and may be mixed with a suitable stabilizing agent. The vaccine is then freeze-dried and can be used either with any suitable diluent or after reconstitution with licensed liquid canine vaccine components.

Choice of vaccine strain. A reference strain obtained from an authentic source shall be used for the vaccine production. The master seed which has been established as pure, safe and immunogenic for the species for which it is intended shall be used for vaccine production.

Identification

When inoculated into dogs, the vaccine stimulates the production of specific neutralizing antibodies against canine parainfluenza virus determined by suitable serological tests.

Tests

Mycoplasmas (2.7.8). Complies with the test for mycoplasma.

Extraneous agents. Neutralize the vaccine virus with a suitable mono specific antiserum against canine parainfluenza virus and inoculate into cell cultures known for their susceptibility to viruses pathogenic for the dog. Carry out 2 passages with an interval of 6 to 8 days. The vaccine complies with the test if no cytopathic effect develops.

Sterility (2.2.11). Complies with the test for sterility.

Safety. Carry out the test for each route and methods of administration to be recommended for vaccination. Use vaccine virus at least attenuated passage level that will be present between the master seed lot and a batch of the vaccine. Inject 10 times the minimum dose into each of 6 dogs of the minimum recommended age that are shown to be preferably free of canine parainfluenza virus antibodies. Observe the dogs for 21 days. None of the dogs shows abnormal local or systemic reactions or dies of any causes attributable to the vaccine.

Increase in virulence. Administer intranasally and by a recommended route to each of 2 puppies, 5 to 7 weeks old and which do not have antibodies against parainfluenza virus of canine origin, a quantity of virus that will allow recovery of virus for the passages described below. Use vaccine virus at the least attenuated passage level that will be present in a

batch of the vaccine. Collect nasal swabs from each dog daily from 3 to 10 days after inoculation. Inoculate the suspension from the swabs into suitable cell cultures to verify the presence of virus. Use the suspension from the swabs that contain the maximum amount of virus and administer intranasally 1 ml of the suspension into each of 2 other puppies of the same age and susceptibility. This operation is then repeated at least 5 times. If the virus is not recovered at a given passage level, a second series of passages is carried out. Inoculate virus from the highest recovered passage level to not fewer than 5 puppies, observe for 21 days and compare any reactions that occur with those seen in the test for safety described above. There is no indication of an increase in virulence as compared with the non-passaged virus.

Immunogenicity. Inject each of eight susceptible dogs, between 8 and 14 weeks old that have been previously tested and shown to be preferably free from canine parainfluenza virus antibodies with a dose of the vaccine stated on the label. Use another two dogs of the same age group as unvaccinated controls. Observe the animals for a further 21 days. Challenge all the dogs with sufficient quantity of a suspension of canine parainfluenza virus by intranasal route. Observe the animals for a further 14 days. Collect nasal swabs from day 5 to 10 days after challenge and test the samples for the presence of excreted virus. Use a scoring system for recording the incidence of coughing in each dog. The control dogs show typical signs of coughing or excretion of the virus. The vaccine complies with the test if the scores for coughing or virus excretion in the vaccinated dogs are significantly lower than the controls.

If the potency test has been performed with satisfactory results on a representative batch of the vaccine from the seed lot, it may be omitted as a routine control test during production on other batches of the vaccine prepared from the same seed lot.

Virus titre. Not less than 10^3 $TCID_{50}$/$CCID_{50}$ per dose, determining the titre of the vaccine in a suitable cell culture with suitable medium.

Manufacturer's tests

Virus titre. Virus titre is determined in final bulk harvest in a suitable cell culture with suitable medium.

Identification. Vaccine complies the requirements of the test mentioned under production.

Extraneous agents. Vaccine complies the requirements of the test mentioned under production.

Mycoplasmas (2.7.8). Complies with the test for freedom from mycoplasmas.

Sterility (2.2.11). Complies with the test for sterility.

Batch tests

Identification

Vaccine complies the requirements of the test mentioned under production. Alternatively, identification on the final lot by molecular techniques are acceptable and can be used in the routine batch release tests after proper validation (2.8.1).

Water (2.3.43). Not more than 3.0 per cent.

Extraneous agents. Vaccine complies the requirements of the test mentioned under production. Alternatively, molecular techniques for detection of pathogenic viruses of dog are acceptable batch release test after proper validation (2.8.1).

Mycoplasmas (2.7.8). Complies with the test for freedom from mycoplasmas. Alternatively, molecular techniques for detection of mycoplasma nucleic acid are acceptable batch release test after proper validation (2.8.1).

Virus titer. Not less than 10^3 $TCID_{50}$ of the virus per dose, determining the titre of the vaccine in a suitable cell culture with suitable medium or one dose of vaccine contains not less than quantity of virus equivalent to the minimum virus titre stated on the label.

Sterility (2.2.11). Complies with the test for sterility.

Safety. Inject each of two susceptible dogs, between 8 and 14 weeks old, free from canine parainfluenza virus antibodies with a dose of the vaccine reconstituted with the sterile diluent equivalent to 10 times the dose and by the route stated on the label. Observe the animals for 14 days. None of the dogs shows any systemic or local reactions.

Potency. The vaccine complies with the requirements of test mentioned under immunogenicity when administered by a recommended route and method. It is not necessary to carry out the potency test for each batch of the vaccine if it has been carried out on a representative batch of the vaccine using a vaccinating dose containing not more than the minimum titre stated on the label. The virus titer is considered for a routine batch release provided the traceability of the vaccine strains used is from the same master seed.

Labelling. The label states (1) the minimum dose; (2) the recommended routes of administration; (3) storage temperature; (4) virus titre; (5) expiry period.

Canine Parvovirus Vaccine, Inactivated

Canine Parvovirus Vaccine, Inactivated is a liquid or freeze dried preparation of canine parvovirus inactivated by a suitable method so that its immunogenic activity is retained.

Production

The virus is grown in suitable cell culture systems. The cell culture complies with the requirements for cell culture for production of veterinary vaccines (2.7.13). The vaccine may contain a suitable adjuvant.

Choice of vaccine strain. A reference strain obtained from an authentic source shall be used for the vaccine production. The master seed which has been established as pure, safe and immunogenic shall be used for vaccine production.

Identification

When inoculated into dogs, the development of specific neutralizing antibodies against canine parvovirus can be demonstrated by suitable serological tests.

Tests

Safety. Carry out the test for each route and method of administration to be recommended for the vaccination. Double dose of the batch prepared from the master seed shall be injected to six healthy dogs in the age group and by the route stated on the label. Observe the animals for 14 days and no abnormal systemic or local reaction occurs. Such animals used in the test shall be preferably free of canine parvovirus antibodies. At least three representative batches from the master seed shall be tested for safety.

Potency. Inject each of 5 healthy susceptible dogs between 8 and 14 weeks having antibody titer less than 4 ND_{50} per 0.1 ml of serum with a batch prepared from master seed with the dose recommended on the label. Use 2 dogs of the same age as control. If a second dose is recommended, the second dose shall be administered at the time specified on the label. Not less than 14 days booster or not less than 21 days after single vaccination, challenge all the animals through oronasal route with a virulent virus strain of canine parvovirus. Observe the animals for 14 days. Vaccine complies with the test if the 5 vaccinated dogs remain healthy and show no sign of disease or leucopenia. The test is not valid unless the controls die or show clinical signs of canine parvovirus infection.

Manufacturer's tests

Identification

Vaccine complies the requirements of the test mentioned under production.

Potency. It is not necessary to carry out the potency test for each batch of the vaccine if it has been carried out using a batch of vaccine with a minimum potency. Where the test is not carried out, an alternative validated method is used, the criteria for acceptance being set with reference to a batch of vaccine that has been given satisfactory results in the test described under potency.

Batch tests

Identification

Vaccine complies the requirements of the test mentioned under production. Alternatively, identification on the final lot by validated molecular techniques is acceptable and can be used in the routine batch release tests after proper validation of antigen extraction protocol from adjuvanted vaccine and test applied (2.8.1).

Water (2.3.43). Not more than 3.0 per cent (for freeze dried vaccine only).

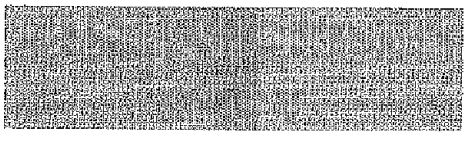
Sterility (2.2.11). Complies with the test for sterility.

Safety. Inject each of two healthy susceptible dogs in the recommended age group preferably free from canine parvovirus antibodies with a quantity equivalent to 2 doses by the route stated on the label. Observe the animals for 14 days. No abnormal systemic or local reaction occurs.

Potency. *Carry out either the test A or B.*

A. Inject subcutaneously each of the 5 healthy susceptible guinea-pigs, weighing between 350 to 450 g with half dose stated on the label. After 14 days, inject again half dose stated on the label. Fourteen days after the second injection collect blood samples and obtain serum from each guinea-pig separately. Inactivate the serum samples individually at 56° for 30 minutes and treat 1 volume of each serum sample with 9 volumes of a 20 per cent of light kaolin in phosphate buffer saline. Shake each mixture for 20 minutes and centrifuge at 2000 rpm for 10 minutes. Collect the supernatant and mix with 1 volume of a concentrated suspension of pig erythrocytes and allow to stand at 4° for 1 hour. Centrifuge at 2000 rpm for 10 minutes and collect the supernatant serum obtained is 10 fold dilution. Using each serum, prepare a series of 2-fold dilutions. To 25 µl of each of the later dilutions, add 25 µl of a suspension of canine parvovirus antigen containing 4 HA units. Leave at 37° for 30 minutes and add 50 µl of a suspension of pig erythrocytes containing 3×10^7 cells per ml. Incubate at 4° for 90 minutes and note the last dilution of the serum that completely inhibits the haemagglutination. The vaccine complies with the test if the mean antibody titer of the sera collected after the second vaccination is not less than 1:80.

B. Inject each of 2 healthy susceptible dogs between 8 and 14 weeks having antibody titer less than 4 ND_{50} per 0.1 ml of serum with a batch prepared from master seed with the dose recommended on the label. If a second dose is recommended, the second dose shall be administered at the time specified on the label. For single dose schedule, collect blood after 21 days or for two dose schedule, collect blood 14 days after booster from each dog. Collect the serum samples from each of the dog separately and inactivate the serum samples individually at 56° for 30 minutes. Examine the serum samples individually for the neutralizing antibodies.



Prepare 2-fold serial dilutions of the serum in a medium suitable for canine cells. Add to each dilution an equal volume of a virus suspension containing approximately 10^2 $TCID_{50}$ and incubate the mixture at 37° for 1 hour. Inoculate a suitable volume of canine cells into at least 4 replicates of serum virus mixture and incubate at 37° for 7 days. Examine for evidence of specific cytopathic effects and calculate the mean antibody titer. The vaccine complies with the test if the serum mean antibody titer in vaccinated dogs is not less than 32 ND_{50} per 0.1 ml of serum. If any dog fails to respond, repeat the test using 3 more dogs and calculate the mean titer of the dogs that have responded.

Labelling. The label states (1) the recommended routes of administration; (2) that the preparation should be shaken well before use; (3) that the liquid preparation should not be allowed to freeze; (4) that the vaccine should be used immediately after reconstitution for freeze dried vaccine; (5) storage temperatures; (6) expiry date.

Canine Parvovirus Vaccine, Live

Canine Parvovirus Vaccine, Live is a freeze-dried preparation of a strain of canine parvovirus that is attenuated for the target species of dogs.

Production

The attenuated virus is grown in suitable cell culture systems. The cell culture complies with the requirements for cell culture for production of veterinary vaccines (2.7.13). The viral harvest is titrated and mixed with a suitable stabilizing solution. The vaccine is then freeze dried and can be used with any suitable diluent or used after reconstitution with licensed liquid canine vaccine components.

Choice of vaccine strain. A reference strain obtained from an authentic source shall be used for the vaccine production. The master seed which has been established as pure, safe and immunogenic for the species for which it is intended shall be used for vaccine production.

Identification

When inoculated into dogs, the development of specific neutralizing antibodies against canine parvovirus can be demonstrated by suitable serological tests. The vaccine is grown in a susceptible cell line. A proportion of the cells are tested with a monoclonal antibody specific for canine parvovirus and a proportion of the cells tested with a monoclonal antibody specific for feline parvovirus. Canine parvovirus should be detected but no feline parvovirus is detected in the cells inoculated with the vaccine.

Tests

Extraneous agents. Neutralize the vaccine virus with a suitable mono specific antiserum against canine parvovirus and inoculate into cell cultures known for their susceptibility to viruses pathogenic for the dog. Carry out 2 passages with an interval of 6 to 8 days. The vaccine complies with the test if no cytopathic effect develops.

Mycoplasmas (2.7.8). Complies with the test for freedom from mycoplasmas.

Sterility (2.2.11). Complies with the test for sterility.

Safety. Carry out test for each route and method of administration recommended for the vaccination. Inject 10 times the minimum dose into each of 6 dogs of the minimum recommended age that are shown to be free of canine parvovirus antibodies. None of the dogs shows abnormal local or systemic reactions or dies of any causes attributable to the vaccine.

Reversion of virulence. Use 2 susceptible puppies of the minimum age recommended for vaccination and which do not have haemagglutination-inhibiting antibodies against canine parvovirus. Administer to each puppy, by a recommended route, a quantity of virus corresponding to 10 times the maximum titre that may be expected in a batch of vaccine. From the second to the tenth day after administration of the virus, the faeces are collected from each puppy and checked for the presence of the virus; faeces containing virus are pooled. 1 ml of the suspension of pooled faeces is administered by the oronasal route to each of 2 other puppies of the same age and susceptibility; this operation is carried out 4 times. The presence of virus is verified at each passage. If the virus is not found, a second identification of passages is carried out; if the virus is not found in one of the second identification of passages, the vaccine strain complies with the test. No puppy dies or shows signs attributable to the vaccine. No indication of increase of virulence compared to the original vaccinal virus is observed; account is taken, notably, of the count of white blood cells, of results of histological examination of the thymus and of the titre of excreted virus.

Immunogenicity. Inject each of seven dogs between 8 and 14 week of old free of canine parvovirus haemagglutinating antibodies subcutaneously with the minimum dose of the vaccine stated on the label. Use 2 dogs of the same age as controls. Not less than 21 days after vaccination, challenge all the animals through oronasal route with a virulent virus strain of canine parvovirus. Observe the animals for 14 days. Not less than 5 out of the seven vaccinated dogs survive. The test is not valid unless the controls die or show clinical signs of canine parvovirus infection. Once the potency has been carried out on the representative batch of the vaccine it may be omitted as a routine test during the production of the other batches of vaccine prepared from the same seed lot.

Virus titre. Not less than 128 HA unit per dose, determining the titre of the vaccine in a suitable cell culture with suitable medium.

Manufacturer's tests

Virus titre. Virus titre is determined in final bulk harvest in a suitable cell culture with suitable medium.

Identification

Vaccine complies the requirements of the test mentioned under production.

Extraneous agents. Vaccine complies the requirements of the test mentioned under production.

Mycoplasmas (2.7.9). Complies with the test for freedom from mycoplasmas.

Sterility (2.2.11). Complies with the test for sterility.

Batch tests

Identification

Vaccine complies the requirements of the test mentioned under production. Alternatively, identification on the final lot by molecular techniques is acceptable and can be used in the routine batch release tests after proper validation (2.8.1).

Water (2.3.43). Not more than 3.0 per cent.

Extraneous agents. As per the method described earlier in this monograph. Alternative, molecular techniques for detection of pathogenic viruses of dog is acceptable batch release test after proper validation (2.8.1).

Mycoplasmas (2.7.8). Complies with the test for freedom from mycoplasmas. Alternatively, molecular techniques for detection of mycoplasma nucleic acid are acceptable batch release test after proper validation (2.8.1).

Sterility (2.2.11). Complies with the test for sterility.

Virus titre. Not less than 128 HA units per dose when tested using suitable RBC after culturing the virus in a suitable cell culture or one dose of vaccine contains not less than quantity of virus equivalent to the minimum virus titre stated on the label.

Safety. Inject each of two susceptible dogs, between 8 and 14 weeks old, free from canine parvovirus hemagglutinating antibodies, a quantity of the vaccine reconstituted with the sterile diluents equivalent to 10 times the dose and by the route stated on the label. Observe the animals for 21 days. No abnormal systemic or local reaction occurs.

Potency. if the potency has been carried out with satisfactory results on the representative batch of the vaccine, this test may be omitted as a routine control on the other batches of the vaccine prepared from the same seed lot, subjected to the approval by the competent authorities.

Labelling. The label states (1) the minimum dose; (2) the recommended routes of administration; (3) virus titre; (4) storage temperature; (5) expiry period.

Classical Swine Fever Vaccine, Live

Classical Swine Fever Vaccine, Live is a preparation of a modified strain of classical swine fever virus, which is devoid of pathogenicity for the pig by adaptation either to cell cultures or to the rabbit. It is prepared immediately before use by reconstitution from the dried vaccine with a suitable diluents.

Production

For vaccine prepared in rabbits, the seed-lot (or the vaccine) is made from the homogenised spleen and lymph nodes of rabbits sacrificed at the peak of temperature rise (104 to 106° F) following intravenous inoculation of the virus. The vaccine is freeze dried.

For cell culture vaccine, the virus is propagated in suitable cell culture. The viral suspension is harvested, titrated and mixed with a suitable stabilizing agent. The vaccine is then freeze dried.

Choice of vaccine strain. A reference strain obtained from an authentic source shall be used for the vaccine production. Only a virus strain shown to be satisfactory with respect to identification, safety, test for extraneous pathogens, test for mycoplasma, virus titre and potency may be used in the preparation of the vaccine.

Identification

Lapinised vaccine. Administer 0.5 ml intravenously into one or more non-immunised rabbits, immunized either with an identical dose of a vaccine of the same type injected by the same route between 10 and 60 days before hand or with a sufficient dose of antiserum administered a few hours before the injection of the vaccine. Twenty-four hours after the injection, start recording the temperature of the rabbits in the mornings and the evenings until the fifth day after the injection. The immunised rabbits do not exhibit a rise in temperature of more than 1.5° . The test is not valid unless the non-immunised rabbits exhibit a rise in temperature of not less than 1.5°.

Cell culture vaccine. For non–lapinised vaccines prepared in cell cultures, on administration to pigs immunised with the vaccine, specific neutralizing antibodies develop.

Tests

Test for extraneous pathogens.

Use method A or B.

A. The vaccine mixed with a mono specific antiserum does not cause cytopathic effects in susceptible cell cultures. The

cells also show no evidence of the presence of haemadsorbing agents and the cell-culture fluids are free of haemagglutinating agents when tested with chicken erythrocytes.

B. Inject intracerebrally 30 µl of the vaccine, reconstituted in a manner that 1.0 ml contains one dose, into each of ten mice, weighing between 11g and 15g. Observe the mice for 21 days. If more than two mice die within the first 48 hours, repeat the test. The mice show no abnormalities attributable to the vaccine within the third and twenty-first days after the injection.

Mycoplasmas (2.7.8). Complies with the test for mycoplasmas.

Water (2.3.43). Not more than 3.0 per cent.

Safety. Inject intramuscularly 10 times the minimum does stated on the label into each of three healthy piglets, between 10 to 12 weeks old, free from swine fever virus antibodies. Observe the animals for 21 days. Temperature curve should be normal and animals remain in apparent good health and display normal growth.

Virus titre. Not less than 100 PD_{50} per dose or alternately, not less than $10^{3.0}$ $TCID_{50}$ per dose (in Fluorescent Antibody test using CSFV monoclonal antibody).

Sterility (2.2.11). Complies with the test for sterility.

Potency. All the animals are healthy and must have had no contact with swine fever virus and serologically must be free from CSF and BVDV antibodies. Use four healthy piglets, 10 to 12 weeks old, for each of the 1/40 and 1/160 dilutions of a single dose of the vaccine prepared in a suitable diluents or buffer. Inject intramuscularly 1 ml of these dilutions into each of the piglets in respective groups. Use two healthy susceptible piglets of the same stock and age as control animal group. After 28 days, inoculate intramuscularly with a sufficient quantity of the challenge virus in each vaccinated piglet and in each of the two unvaccinated control animals so that at least one of the two unvaccinated control animals dies within 7 to 14 days. Observe the vaccinated animals for 14 days. Calculate the number of PD_{50} contained in the vaccine by standard statistical methods from the number of animals, which survive without showing any signs of swine fever. The vaccine contains not less than 100 PD_{50} per dose. The test is not valid unless the control animals die within 7 to 14 days after inoculation. PD_{50} correlation studies with virus titres can replace the potency test on routine basis.

Cell culture vaccines can be alternatively tested for potency by virus titration in PK-15 cells by Fluorescent Antibody Test using CSF monoclonal antibodies. A vaccine passes the potency if it contains a virus titre of at least $10^{3.0}$ $TCID_{50}$ per dose which is equivalent to 100 PD_{50}.

Labelling. The label states (1) the minimum dose (LD_{50} or $TCID_{50}$); (2) the recommended routes of administration; (3) cell line used; (4) expiry date.

Multicomponent Clostridium Vaccine, Inactivated

Multicomponent Clostridium Vaccine, Inactivated consists of five highly antigenic components containing the toxoids of *C. perfringens* type 'B', *C. perfringens* type 'C', *C. perfringens* type 'D', *C. oedematiens* and *C. septicum* which are prepared in double strength and then combined in such a proportion that would invoke adequate anti-toxin response in the vaccinated sheep against each antigen incorporated in the vaccine.

Identification

When injected into susceptible animals, it stimulates the production of epsilon and beta antitoxin against *C. perfringens* types 'B', 'C' and 'D' and also antitoxins against *C. septicum* and toxin of *C. oedematiens.*

Tests

Safety. Four sheep each are inoculated with two times the dose of vaccine subcutaneously and are observed for 7 days during which period the animals do not show any local or systemic reaction.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Eight sheep each are inoculated with 2 doses of vaccine subcutaneously at an interval of 21 to 28 days and bled on 10th day after second inoculation for collection of serum for assessing the antitoxin titre against each antigen incorporated in the vaccine. The post-inoculation serum contains not less than 5 IU of epsilon antitoxin and 10 units of beta antitoxins of *C. perfringens types 'B' and 'C'* and 2.5 IU of *C. septicum* antitoxin and 3.5 IU of *C. oedematiens* antitoxin.

Labelling. The label states (1) the types of Clostridia contained in the vaccine; (2) the preparation should be shaken before use.

Clostridium novyi (Type B) Vaccine Inactivated for Veterinary Use

Clostridium novyi (Type B) Vaccine Inactivated for Veterinary Use is prepared from a liquid culture of a suitable strain of *Clostridium novyi* Type B.

Production

The whole culture or its filtrate or a mixture of the two is inactivated in such a manner that toxicity is eliminated and immunogenic activity is retained. Toxoids and/or inactivated

cultures may be treated with a suitable adjuvant, after concentration, if necessary.

Choice of vaccine composition. The vaccine is shown to be satisfactory with respect to safety and efficacy (2.7.12). For the latter, it shall be demonstrated that for each target species the vaccine, when administered according to the recommended schedule, stimulates an immune response (for example, induction of antibodies) consistent with the claims made for the product.

Batch testing

Safety. Administer by a recommended route, to each of 2 sheep that have not been vaccinated against *C. novyi* Type B twice the maximum dose of the vaccine stated on the label. Observe the animals for not less than 14 days. No abnormal local or systemic reaction occurs.

Residual toxicity. Inject 0.5 ml of the vaccine subcutaneously into each of 5 mice, each weighing between 17 and 22 g. Observe the animals for 7 days. No abnormal local or systemic reaction occurs.

Identification

The vaccine stimulates the formation of *C. novyi* Type B alpha antitoxin when injected into animals.

Tests

Sterility (2.2.11). Complies with the test for sterility.

Potency. Inject subcutaneously into each of not less than 10 healthy rabbits, 3 to 6 months old, a quantity of vaccine not exceeding the minimum dose stated on the label as the first dose. After 21 to 28 days, inject into the same animals a quantity of the vaccine not exceeding the minimum dose stated on the label as the second dose. 10 to 14 days after the second injection, bleed the rabbits and pool the sera.

The alpha antitoxin titre of the pooled sera is not less than 3.5 IU per ml.

The International Unit is the specific neutralising activity for *C. novyi* alpha toxin contained in a stated amount of the International standard, which consists of a quantity of dried immune horse serum. The equivalence in International Units of the International standard is stated by the World Health Organisation.

The potency of the pooled sera obtained from the rabbits is determined by comparing the quantity necessary to protect mice or other suitable animals against the toxic effects of a fixed dose of *C. novyi* alpha toxin with the quantity of a reference preparation of *Clostridium novyi* alpha antitoxin, calibrated in International Units, necessary to give the same protection. For this comparison, a suitable preparation of *C. novyi* alpha toxin for use as a test toxin is required. The dose of the test toxin is determined in relation to the reference preparation; the potency of the serum under examination is determined in relation to the reference preparation using the test toxin.

Preparation of test toxin. Prepare the test toxin from a sterile filtrate of an approximately 3 to 5 day culture in liquid medium of *C. novyi* Type B and dry by a suitable method. Select the test dose of the toxin in mice by determining the L+ 10 dose and the LD_{50} the observation period being 72 hours.

A suitable alpha test toxin contains not less than one L+/10 dose in 0.05 mg and not less than 10 LD_{50} in each L+/10 dose.

Determination of test dose of toxin. Prepare a solution of the reference preparation in a suitable liquid so that it contains 1 IU per ml. Prepare a solution of the test toxin in a suitable liquid so that 1 ml contains a precisely known amount such as 1 mg. Prepare mixtures of the solution of the reference preparation and the solution of the test toxin such that each mixture contains 1.0 ml of the solution of the reference preparation (1 IU), one of a series of graded volumes of the solution of the test toxin and sufficient of a suitable liquid to bring the total volume to 2.0 ml. Allow the mixtures to stand at room temperature for 60 minutes. Using not less than 2 mice, each weighing between 17 and 22 g, for each mixture, inject a dose of 0.2 ml subcutaneously into each mouse. Observe the mice for 72 hours. If all the mice die, the amount of toxin present in 0.2 ml of the mixture is in excess of the test dose. If none of the mice dies, the amount of toxin present in 0.2 ml of the mixture is less than the test dose. Prepare fresh mixtures such that 2.0 ml of each mixture contains 1.0 ml of the solution of the reference preparation (1 IU) and one of a series of graded volumes of the solution of the test toxin separated from each other by steps of not more than 20 per cent and covering the expected end-point. Allow the mixtures to stand at room temperature for 60 minutes. Using not less than two mice for each mixture, inject a dose of 0.2 ml subcutaneously into each mouse. Observe the mice for 72 hours. Repeat the determination at least once and combine the results of the separate tests that have been made with mixtures of the same composition so that a series of totals is obtained, each total representing the mortality due to a mixture of a given composition.

The test dose of toxin is the amount present in 0.2 ml of that mixture which causes the death of one half of the total number of mice injected with it.

Determination of the potency of the serum obtained from rabbits

Preliminary test. Dissolve a quantity of the test toxin in a suitable liquid so that 1 ml contains 10 times the test dose (solution of the test toxin). Prepare a series of mixtures of the

solution of the test toxin and of the serum under examination such that each mixture contains 1.0 ml of the solution of the test toxin, one of a series of graded volumes of the serum under examination and sufficient of a suitable liquid to bring the final volume to 2.0 ml. Allow the mixtures to stand at room temperature for 60 minutes. Using not less than 2 mice for each mixture, inject a dose of 0.2 ml subcutaneously into each mouse. Observe the mice for 72 h. If none of the mice dies, 0.2 ml of the mixture contains more than 0.1 IU. If all the mice die, 0.2 ml of the mixture contains less than 0.1 IU.

Final test. Prepare a series of mixtures of the solution of the test toxin and of the serum under examination such that 2.0 ml of each mixture contains 1.0 ml of the solution of the test toxin and one of a series of graded volumes of the serum under examination, separated from each other by steps of not more than 20 per cent and covering the expected end-point as determined by the preliminary test. Prepare further mixtures of the solution of the test toxin and of the solution of the reference preparation such that 2.0 ml of each mixture contains 1.0 ml of the solution of the test toxin and one of a series of graded volumes of the solution of the reference preparation, in order to confirm the test dose of the toxin. Allow the mixtures to stand at room temperature for 60 minutes. Using not less than 2 mice for each mixture, proceed as described in the preliminary test. The test mixture which contains 0.1 IU in 0.2 ml is that mixture which kills the same or almost the same number of mice as the reference mixture containing 0.1 IU in 0.2 ml. Repeat the determination at least once and calculate the average of all valid estimates. The test is valid only if the reference preparation gives a result within 20 per cent of the expected value.

The confidence limits (P = 0.95) have been estimated to be (a) 85 per cent and 114 per cent when 2 animals per dose are used; (b) 91.5 per cent and 109 per cent when 4 animals per dose are used; (c) 93 per cent and 108 per cent when 6 animals per dose are used.

Labelling. The label states (1) whether the product is a toxoid, a vaccine prepared from a whole inactivated culture or a mixture of the two; (2) that the preparation is to be shaken before use; (3) for each target species, the immunising effect produced (for example, antibody production, protection against signs of disease or infection).

Clostridium Septicum Vaccine, Inactivated

Clostridium Septicum Vaccine, Inactivated is a suspension of a culture of a highly toxigenic strain of *C. septicum* grown in an anaerobic medium, or a filtrate from such a culture.

Production

The whole culture or its filtrate or a mixture of the two is inactivated in such a manner that toxicity is eliminated and immunogenic activity is retained. Toxoid and/or inactivated cultures may be treated with a suitable adjuvant.

Batch testing

Residual toxicity. Inject 0.5 ml of the vaccine subcutaneously into each of 5 mice, each weighing between 17 and 22 g. Observe the animals for 7 days. No abnormal local or systemic reaction occurs.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Inject subcutaneously each of eight healthy susceptible sheep, between 8 and 12 months old, or ten rabbits, between 3 and 6 months old, with the minimum dose of the vaccine stated on the label. Repeat the dose after an interval of 21 to 28 days. 10 to 14 days after the second inoculation, bleed the animals. Pool the sera samples from individual animals and determine the antitoxin titre by the biological assay of *C. septicum* antitoxin described below.

1 ml of serum contains not less than 2.5 Units of *C. septicum* antitoxin by biological assay of *C. septicum* antitoxin.

The potency of *C. septicum* antitoxin is determined by comparing the dose of antitoxin necessary to protect mice or other suitable animals against the lethal effects of *C. septicum* toxin with the dose of a Standard preparation of *C. septicum* antitoxin necessary to give the same protection. For this purpose, the Standard preparation of *C. septicum* antitoxin and a suitable preparation of *C. septicum* toxin for use as a test toxin are required.

Identification

When injected into healthy susceptible animals, it stimulates the production of antitoxins to *C. septicum*.

Tests

The test dose of the toxin is determined in relation to the Standard preparation of antitoxin and the potency of antitoxin under examination is then determined in relation to the Standard preparation using the test toxin.

Assay

Standard preparation

The Standard preparation is the Third International Standard, established in 1957, consisting of dried hyperimmune horse serum (supplied in ampoules containing 500 Units) or another suitable preparation the potency of which has been determined in relation to the International standard.

Safety. Inject subcutaneously each of two healthy susceptible sheep, between 8 and 12 months old, with twice the dose stated on the label. Observe the animals for 7 days; none of the animals shows any systemic or local reaction. Observe the animals for 14 days.

Test animals. Use healthy mice having body weights such that the difference between the lightest and heaviest is not more than 5 g.

Preparation of test toxin. Prepare *C. septicum* toxin by growing *C. septicum* in a liquid culture medium, filtering the supernatant aseptically and precipitating with *ammonium sulphate*. The resulting precipitate, which contains the toxin, is collected, dried over *phosphorus pentoxide* at a pressure of 1.5 to 2.5 kPa, powdered and kept dry.

Selection of test toxin. Select toxin for use as the test toxin by determining the following quantities.

L+/5 dose. This is the smallest quantity of the toxin which when mixed with 0.2 Unit of antitoxin and injected intravenously into mice causes the death of the animals within 72 hours.

LD_{50}. This is the quantity of toxin which when injected intravenously into mice causes the death of one-half of the animals within 72 hours.

A suitable *C. septicum* toxin is one that has an L+/5 dose in 1 mg or less and contains not less than 10 LD_{50} in an L+/5 dose.

Determination of test dose of toxin. Weigh accurately a quantity of the dried toxin and dissolve it in a suitable liquid so that 1.0 ml contains a precise known amount, such as 4 mg. Prepare a solution of the standard preparation in a suitable liquid such that 1.0 ml contains 1 Unit.

Prepare mixtures such that 5.0 ml of each mixture contains 2.0 ml of the solution of the standard preparation (2 Units) and one of a series of graded volumes of the solution of the toxin. Dilute each mixture with a suitable liquid to the same final volume (5.0 ml). Allow the mixtures to stand at room temperature, protected from light, for 60 minutes and then inject a dose of 0.5 ml of each mixture intravenously into each of not less than 2 mice. Observe the mice for 72 hours. If all the mice die the amount of toxin present in 0.5 ml of the mixture is in excess of the test dose. If none of the mice dies, the amount of toxin present in 0.5 ml of the mixture is less than the test dose. Prepare similar fresh mixtures such that 5.0 ml of each mixture contains 2.0 ml of the solution of the Standard preparation (2 Units) and one of a series of graded volumes of the solution of the toxin separated from each other by steps of not more than 20 per cent and covering the expected end-point.

Allow the mixtures to stand at room temperature, protected from light, for 60 minutes. Inject a dose of 0.5 ml of each mixture intravenously into each of not less than two mice. Observe the mice for 72 hours. Repeat the determinations at least once and add together the results of the separate tests that have been made with mixtures of the same composition such that a series of totals is obtained, each total representing the mortality due to a mixture of a given composition.

The test dose of toxin is the amount present in 0.5 ml of that mixture that causes the death of one-half of the total number of mice injected within 72 hours.

Determination of potency of the antitoxin

Preliminary test. Dilute the test toxin with a suitable liquid such that 2.0 ml contains 10 times the test dose. Prepare mixtures such that 5.0 ml of each mixture contains 2.0 ml of the solution of the toxin and one of a series of graded volumes of the preparation under examination. Adjust each mixture to the same final volume with a suitable liquid.

Allow the mixtures to stand at room temperature, protected from light, for 60 minutes. Inject a dose of 0.5 ml of each mixture intravenously into each of not less than two mice and observe the mice for 72 hours. If all the mice die, 0.5 ml of the mixture contains less than 0.2 Unit of antitoxin. If none of the mice dies, 0.5 ml of the mixture contains more than 0.2 Unit of antitoxin.

Final test. Prepare similar fresh mixtures such that 5.0 ml of each mixture contains 2.0 ml of the solution of the toxin and one of a series of graded volumes of the preparation under examination, separated from each other by steps of not more than 20 per cent and covering the expected end-point. Prepare further mixtures of 5.0 ml containing 2.0 ml of the solution of the toxin and graded volumes of the standard preparation to confirm the test dose of the toxin.

Allow the mixtures to stand at room temperature, protected from light, for 60 minutes. Inject a dose of 0.5 ml of each mixture intravenously into each of not less than two mice and observe the mice for 72 hours. The mixture of the antitoxin under examination which contains 0.2 Unit in 0.5 ml is that mixture which causes the death of the same or almost the same number of mice as the mixture containing 0.2 Unit of the Standard preparation in 0.5 ml. Repeat the determinations at least once and calculate the average of all valid estimates. Estimates are not valid unless the Standard preparation gives a result within 20 per cent of the expected value.

Limits of error. For the suggested method, the limits of error (P = 0.95) have been estimated to be (a) 85 per cent and 114 per cent when 2 animals per dose are used; (b) 91.5 per cent and 109 per cent when 4 animals per dose are used; (c) 93 per cent and 108 per cent when 6 animals per dose are used.

The vaccine passes the test if the pooled serum contains 2.5 IU of *C. septicum* antitoxins.

Labelling. The label states (1) whether the preparation is a toxoid or a vaccine prepared from a whole inactivated culture, or a mixture of the two; (2) that the preparation is to be shaken before use; (3) for each target species, the immunising effect produced (for example, antibody production, protection against signs of disease or infection).

Duck Pasteurella Vaccine, Inactivated

Duck Pasteurella Vaccine, Inactivated consists of an emulsion or suspension of a virulent strain of *Pasteurella multocida* which has been inactivated in such a manner that the pathogenicity is eliminated and the immunogenic activity is retained.

Identification

Protects susceptible ducks against infection with *P. multocida*.

Tests

Safety. Either test A or test B may be carried out.

A. Inject 5 ml subcutaneously into each of four healthy rabbits, weighing between 1.0 and 1.5 kg. Observe the animals for 7 days. No untoward reaction except slight and transient local swelling occurs.

B. Inject 5 ml subcutaneously into each of two healthy rabbits, each weighing between 1.0 and 1.5 kg, and 0.5 ml subcutaneously into each of six mice, each weighing between 25 and 30 g. Observe the animals for 7 days. No untoward reaction except slight and transient local swelling occurs in both species of animals.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Either test A or test B may be carried out.

A. Inject subcutaneously with the minimum dose of the vaccine stated on the label three healthy susceptible ducks, between 4 and 6 weeks old. Use another two ducks of the same stock and age as unvaccinated controls. Three weeks later, challenge each of the vaccinated and control ducks, subcutaneously with 10^2 mouse LD_{50} viable organisms in 0.2 ml of a suitably diluted 18-hour broth culture of the homologous virulent strain of *P. multocida*. Observe the ducks for 7 days. Not less than two of the vaccinated ducks remain in normal health and both the controls die of pasteurellosis.

B. Inject subcutaneously each of six mice, each weighing between 25 and 30 g, with 0.2 ml of the vaccine under examination. Use another six mice of the same stock and weight range as unvaccinated controls. Three weeks later, challenge each of the vaccinated and control mice subcutaneously with 0.2 ml of a suitably diluted 18-hour broth culture of the homologous virulent strain of *P. multocida* containing 50 mouse LD_{50} viable organisms. Observe the animals for 7 days. All the vaccinated mice survive. The test is not valid unless all the control mice die of pasteurellosis during the observation period.

Labelling. The label states (1) the type of strain; (2) the recommended age for vaccination.

Duck Plague Vaccine, Live

Duck Plague Vaccine, Live is a preparation of attenuated strain of duck plague virus. This monograph applies to vaccines intended for administration to duck for active immunisation against duck plague disease.

Production

The vaccine virus is grown in SPF eggs (2.7.7) or in cell cultures. The master seed lot complies with the tests for extreneous agents in seed lot (2.7.10).

Substrate for virus propagation

The vaccine virus is grown in embryonated hens' eggs or in cell cultures obtained from flocks free from specified pathogens SPF (2.7.7). If the vaccine virus is grown in cell cultures, they comply with the requirements for cell cultures for production of veterinary vaccines. The vaccine virus is filled with suitable stabilizing agent and freeze dried.

Identification

Protects ducks against duck plague.

Tests

Water (2.3.43). Not more than 3.0 per cent.

Safety. Inject subcutaneously each of four healthy susceptible ducks, between 8 and 12 weeks old and each weighing not less than 600 g, with 1 ml of a 1 : 10 dilution of the reconstituted vaccine. Observe the ducks for 14 days. None of the ducks shows any untoward reaction.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Inject subcutaneously each of four healthy susceptible ducks, between 8 and 12 weeks old and each weighing not less than 600 g, with a volume of the reconstituted vaccine containing a quantity of the virus equivalent to the minimum dose stated on the label. Fourteen days later, challenge each of the vaccinated ducks and each of two control ducks of the same stock and weight range, subcutaneously with 10^2 ID_{50} of virulent duck plague virus. Observe the ducks for 21 days. None of the vaccinated ducks dies or shows any

clinical symptoms of plague. The test is not valid unless the control ducks die from duck plague or show typical signs of serious infection during the observation period.

If potancy test has been performed with satisfactoery results on a representative batch of the vaccine, it may be omitted as a vaccine test during production on the other batches of vaccine prepared from the same seed lot.

Labelling. The label states (1) the minimum virus titre per dose; (2) the recommended age of the birds in which the vaccine is to be used.

Egg Drop Syndrome'76 (Adenovirus) Vaccine, Inactivated

Egg Drop Syndrome'76 (Adenovirus) Vaccine,

Egg Drop Syndrome'76 (Adenovirus) Vaccine, Inactivated consists of an emulsion or a suspension of a suitable strain of egg drop syndrome'76 virus (haemagglutinating avian adenovirus) which has been inactivated in such a manner that immunogenic activity is retained.

Production

The vaccine strain is propagated in embryonated duck eggs from healthy flocks or in suitable cell culture derived from SPF eggs (2.7.7). The master seed lot complies with the tests for extraneous agents as described in the General monograph for Veterinary Vaccines (2.7.10).

Test for inactivation

The test for inactivation is carried out in fertilized duck eggs from a flock free from egg drop syndrome '76 virus infection or hen eggs from a flock free from specified pathogens, or in suitable cell culture derived from SPF eggs (2.7.7), whichever is the most sensitive for the vaccine strain; the quantity of virus used in the test is equivalent to not less than ten doses of the vaccine. No live virus is detected.

The vaccine may contain a suitable adjuvant.

Identification

When inoculated into chicken, the development of specific neutralizing antibodies against egg drop syndrome '76 (adenovirus) can be demonstrated by suitable serological tests.

Tests

Safety. Inject each of ten SPF chickens (2.7.7, Table 3) or healthy susceptible chickens between 2 and 4 weeks old, with two doses and by the route stated on the label. Observe the chicken for 14 days. None of the chicken shows any abnormal local or systemic reaction.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Inject each of twenty SPF chickens (2.7.7, Table 3) or healthy susceptible chickens, 3 to 4 weeks old, with the dose and by the route stated on the label. After 21 days, collect serum samples from each of the birds as well as ten-control chickens of the same stock and perform haemagglutination inhibition test on each serum using 4 haemagglutinating units of antigen and chicken erythrocytes. The vaccine passes the potency test if the mean antibody titre of the vaccinated group is greater than 1:128. The test is valid only if no specific antibody is found in the control chicken.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 2 years from the date the potency was determined.

Labelling. The label/insert states (1) the strain used for the preparation; (2) the route of administration.

Enterotoxaemia Vaccine, Inactivated

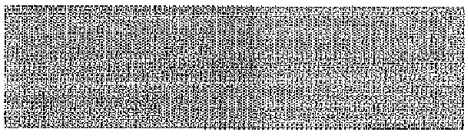
Clostridium welchii Type D Vaccine, *Clostridium perfringens* Type D Vaccine, Pulpy Kidney Vaccine

Enterotoxaemia Vaccine is a culture of highly toxigenic strain of *Clostridium perfringens* Type D grown in an anaerobic medium and rendered sterile and non-toxic by the addition of a suitable quantity of *formaldehyde* in such a manner that it retains its immunizing properties. The toxoid and/or inactivated culture may contain a suitable adjuvant. This monograph applies to the vaccines intended for active immunization of animals against enterotoxaemia caused by *C. perfringens* Type D.

Production

Choice of vaccine strain. A reference, highly toxigenic strain of *C. perfringens* Type D, obtained from an authentic source should be used. However, a local isolate from a particular area may also be used if the strain is shown to be satisfactory with respect to safety and immunogenicity for the animals for which the vaccine is intended.

Preparation of vaccine. Selected toxigenic *C. perfringens* Type D strain used for production is grown in a suitable anaerobic fluid medium under conditions which ensure maximum epsilon (ε) toxin production. The culture is tested for purity and trypsinized to activate the ε prototoxin. The epsilon (ε) toxin titer is determined by mice inoculation. Solution of *formaldehyde* is added in a suitable concentration and the formalized culture is kept at 37° till the product is sterile and non-toxic. A suitable adjuvant may be added.



Tests on Master seed lot

The master seed lot of the vaccine strain of *C. perfringens* Type D is maintained in an anaerobic fluid medium without glucose. The master seed lot complies with the tests of purity and identity for the organism and a batch of vaccine prepared from the master seed lot should comply with full range of control tests, i.e. *identification, safety* and *potency*.

Vaccine composition. The vaccine contains a highly toxigenic, inactivated strain of *C. perfringens* Type D with or without a suitable adjuvant. The vaccine is shown to be satisfactory with respect to *identification, safety* and *immunogenicity* for the animal species for which it is intended.

Identification

When injected into susceptible animals, the vaccine stimulates production of ε antitoxin of *C. perfringens* Type D. The potency test may also serve for identification.

Safety and Potency. At least 8 sheep each weighing not less than 18 kg are used for testing safety and potency of master seed lot. Each of two sheep receives subcutaneously 10 ml of the test product. Each of the remaining six sheep receives 2.5 ml of the test product through subcutaneous route. The animals are observed for 5 days.

The product passes the safety test if only a minimum of local reaction and no systemic reaction is observed in the animals. Sheep receiving 10 ml of the product are withdrawn from the experiment after 5 days.

Inoculate each of the remaining 6 sheep with a second dose of 2.5 ml after an interval of 14 to 21 days of first inoculation. Bleed the animals 10 to 14 days after the second dose and determine the ε antitoxin titer in the pooled serum sample by testing on mice as follows.

1 ml of the pooled serum is mixed with 1.0 ml of ε toxin of *C. perfringens* Type D, containing 300 mouse-minimum-lethal doses (mouse m.l.d.) and kept at room temperature for 30 minutes. At least 2 mice each weighing not less than 18 g are each injected intravenously 0.2 ml of the mixture. Each of two control mice, each weighing not less than 18 g receive 0.2 ml of toxin containing 300 mouse m.l.d. per ml diluted with equal volume of *normal saline*. The control mice should die within 1 to 2 hours while the mice receiving the mixture of serum and toxin should survive for at least 2 days. Serum containing one International Unit (IU) of ε antitoxin per ml will be able to neutralize 150 mouse m.l.d. of ε toxin of *C. perfringens* Type D.

The product passes the test if the post-inoculation pooled sheep serum contains not less than 2 IU of ε antitoxin per ml.

Manufacturer's tests

Certain tests may be carried out on the final bulk vaccine rather than on the batch or batches prepared from it.

Safety and potency. The tests may be carried out on rabbits. Use at least 12 rabbits each weighing not less than 1 kg. Each of the rabbit is immunized with 10 ml of the preparation through subcutaneous route. The animals are observed for 5 days during which they should not show any systemic reaction. Only a minimum local reaction may be observed. After one month, each of the animals is inoculated with second dose of 10 ml of the product through the same route. Bleed the animals 10 to 14 days after the second dose and determine the ε antitoxin titer in the pooled serum sample by testing on mice as described for sheep.

The product passes the test if the post-inoculation pooled serum contains not less than 2 IU of ε antitoxin per ml.

Batch tests

Description. An off-white to yellowish-brown liquid containing dead bacteria in suspension.

Identification

The vaccine complies with the requirements of the test mentioned under the section of Tests on master seed lot.

Sterility (2.2.11). Complies with the test for sterility.

Safety and Potency. The vaccine complies with the test for safety and potency mentioned under section of Manufacturer's tests.

Labelling and Storage. Should comply with the requirements of 'Labelling and Storage' as laid down in the General Monograph on Bacterial Vaccines.

Expiry. Not more than 1 year from the date of manufacture.

Foot-and-Mouth Disease Vaccine, Inactivated

Foot-and-Mouth Disease Vaccine, Inactivated is a liquid preparation containing one or more types of foot-and-mouth disease virus that have been inactivated in such a manner that its immunogenic activity is retained. Depending on the number of types of virus incorporated, the vaccine is described as monovalent, bivalent, trivalent or polyvalent.

Production

The virus is grown in suitable cell cultures. The virus is separated from cellular material by filtration or other suitable

procedures and the virus is inactivated using binary ethyleneimine (BEI) in suitable conditions. The antigen may be concentrated and purified. The antigen is used for the preparation of vaccine. The vaccine contains a suitable adjuvant. Only an inactivated antigen suspension that complies with the requirements mentioned under final bulk vaccine may be used in the preparation of the final lot. For a given antigen, the quantity of 146S antigen blended in each batch of the vaccine is not less than that of a batch of the vaccine that has shown to be satisfactory with respect to immunogenicity.

Identification

When inoculated into sero negative animals, the vaccine stimulates the production of specific neutralizing antibodies against the serotypes incorporated as determined by suitable serological tests. Alternately before inactivation, identity on the antigen lot by means of molecular methods is acceptable.

Tests on master seed

Antigen content estimation

The 146S antigen content per each batch of bulk inactivated antigens is determined by an *in vitro* method for example by sucrose density gradient centrifugation and ultraviolet spectrophotometry at 259 nm.

Residual live virus

During inactivation of the virus, samples should be taken at regular intervals for the purpose of monitoring the rate and linearity of the inactivation process. Virus titre in the samples is determined by inoculation into sensitive cell culture. The infectivity of the timed samples is plotted against time, and the inactivation procedure is not considered to be satisfactory unless the extrapolation indicates that there would be less than one infectious particle per 10^4 litres of liquid preparation at the end of the inactivation period. A proportion of each batch of bulk inactivated antigen representing at least 200 doses is tested for freedom from infectious virus by inoculation in to sensitive cell culture. A sample of inactivated antigen is concentrated to volumes adequate for inoculation into cell cultures and it must show that the concentrated antigen does not interfere with the sensitivity or reading of the assay. The sample is passaged 2 times at an interval of 24 to 48 hours and inoculated cell cultures are examined for the presence of foot-and-mouth disease virus by suitable tests. No cytopathic changes attributable to foot-and-mouth disease virus replication should be detected. If infectious foot-and-mouth disease virus is detected, the bulk antigen is rejected. Only a final bulk vaccine that complies with the following requirements may be used in the preparation of the final lot.

Safety

Carry out the test for each route and method of administration to be recommended for the vaccination and in animals of each species for which the vaccine is intended. For each test, use not less than 10 animals that are sero negative for foot and mouth disease antibodies. Administer to each animal a double dose of the vaccine. Observe the animals for 14 days and no abnormal systemic or local reaction occurs.

Sterility (2.2.11). Complies with the test for sterility.

Immunogenicity

Use three groups of not less than five cattle per group, not less than 6 months old, which have never been vaccinated and are free from antibodies neutralizing the different types of foot-and-mouth disease virus in the vaccine. Vaccinate the 3 groups by the prescribed route stated on the label. Use different doses of the vaccine for each group without diluting the vaccine. For example, if 3 ml is one dose, a 1/3 dose of vaccine would be obtained by injecting 1 ml, and a 1/10 dose would be obtained by injecting 0.3 ml. Three to four weeks later, challenge all the vaccinated animals and a control group of two cattle susceptible to foot-and-mouth disease, with a suspension of virus that is fully virulent and of the same type as that used for preparation of the vaccine by inoculating 10,000 ID_{50} (50 per cent bovine infectious dose) intradermally into two sites into the tongue (0.1 ml per site). Observe the animals for 8 days and then sacrifice them. Unprotected animals show lesions at sites other than the tongue. Protected animals may display lingual lesions. The test is not valid unless control animals show lesions on at least three feet. From the number of animals protected in each group, calculate the PD_{50} content of the vaccine. The potency of the vaccine is expressed as the number of 50 per cent cattle protective doses (PD_{50}) contained in the dose stated on the label. The vaccine must contain at least 3 PD_{50} per dose for cattle.

Alternatively, percentage of protection against generalized foot infection (PGP) test can be carried out. A group of 16 cattle of six months age which have never been vaccinated and are free from antibodies neutralizing the different types of foot-and-mouth disease virus in the vaccine are vaccinated with a full vaccine dose by the route recommended by the manufacturer. These animals and a control group of two non-vaccinated animals susceptible to foot-and-mouth disease are challenged three to four weeks after vaccination with a suspension of virus that is fully virulent and of the same type as that used for preparation of the vaccine by inoculating 10,000 ID_{50} (50 per cent bovine infectious dose) intradermally into two sites into the tongue (0.1 ml per site). Observe the animals for 8 days and then sacrifice them. Unprotected animals show lesions at sites other than the tongue. Protected animals may display lingual lesions. The test is not valid unless control

animals show lesions on at least three feet. The vaccine passes the test if a minimum of 12 animals out of 16 vaccinated are protected.

Test animals shall be bleed on day 0, 21 or 28 days post vaccination for screening the animals for sero-negative status and for estimation of the antibody titres post vaccination. Indirect tests, including post vaccination measurement of virus neutralizing antibodies in cell culture or ELISA antibodies, may be used to assess the potency of a vaccine provided that a statistical evaluation has established a satisfactory correlation between the results obtained by the test on the relevant vaccine serotype and the potency test in cattle. Subject to condition that it has been established and approved by the competent authority.

The description applies to the testing of a monovalent vaccine. The potency of polyvalent vaccines may be tested by challenging each valency as described above. Immunogenicity test carried out in cattle species serves the purpose for other ruminants species like sheep and goats.

Manufacturer's tests

The tests mentioned under the tests on master seed need not be repeated if the tests are carried out at initial stage of development.

Batch tests

Residual live virus

During inactivation of the virus, samples should be taken at regular intervals for the purpose of monitoring the rate and linearity of the inactivation process. Virus titre in the samples is determined by inoculation into sensitive cell culture. The infectivity of the timed samples is plotted against time, and the inactivation procedure is not considered to be satisfactory unless the extrapolation indicates that there would be less than one infectious particle per 10^4 litres of liquid preparation at the end of the inactivation period. A proportion of each batch of bulk inactivated antigen representing about 200 doses is tested for freedom from infectious virus by inoculation in to sensitive cell culture. A sample of inactivated antigen is concentrated to volumes adequate for inoculation into cell cultures and it must show that the concentrated antigen does not interfere with the sensitivity or reading of the assay. The sample is passaged 2 times at an interval of 24 to 48 hours and inoculated cell cultures are examined for the presence of foot-and-mouth disease virus by suitable tests. No cytopathic changes attributable to foot-and-mouth disease virus replication should be detected. If infectious foot-and-mouth disease virus is detected, the bulk antigen is rejected. Only a final bulk vaccine that complies with the following requirements may be used in the preparation of the final lot.

Identification

The serum of a foot-and-mouth disease susceptible animal that has been immunized with the vaccine neutralizes the types of virus used to prepare the vaccine, when tested by a suitable method.

Sterility (2.2.11). Complies with the test for sterility.

Safety. Use two cattle, not less than six months old, that do not have antibodies against foot-and-mouth disease virus. Administer to each animal a double dose of the vaccine by the prescribed route of administration stated on the label. Observe the animals daily for at least 14 days. The vaccine complies with the test if no animal shows abnormal local or systemic reactions or dies from causes attributable to the vaccine.

Potency

Indirect tests, including post vaccination measurement of virus neutralizing antibodies in cell culture or ELISA antibodies, may be used to assess the potency of a vaccine provided that a statistical evaluation has established a satisfactory correlation between the results obtained by the test on the relevant vaccine serotype and the potency test in cattle.

Labelling. The label states (1) the recommended routes of administration; (2) the serotypes used in the vaccine; (3) that the preparation should be shaken well before use; (4) that the liquid preparation should not be allowed to freeze; (5) storage temperatures; (6) expiry date

Fowl Cholera Vaccine, Inactivated

Fowl Cholera Vaccine, Inactivated is a formolized preparation of suitable strain or strains of one or more immunogenic serotypes of *Pasteurella multocida*. The preparation may contain a suitable adjuvant. This monograph applies to the vaccines intended for active immunization of chickens, turkeys, ducks and geese against fowl cholera caused by *P. multocida*.

Production

Preparation of Vaccine. The vaccine strains are grown separately in a suitable medium at 37° for suitable time and harvested separately. Pure harvest of each is inactivated by addition of *formaldehyde* in a suitable concentration. The harvests are mixed in equal proportions. The vaccine may contain a suitable adjuvant.

Choice of vaccine strain. A reference strain/or strains of *P. multocida* obtained from an authentic source should be used. However, local isolate from a particular area may also be used if the strain is shown to be satisfactory with respect to safety and immunogenicity for the bird species for which the vaccine is intended.

Tests on Master seed lot

The master seed lots of the vaccine strains of *P. multocida* are maintained within three passages in/on artificial media from the culture obtained after passage in susceptible bird species. The master seed lots complies with the tests of purity and identity for the organism and a representative batch of vaccine prepared from the master seed lot should comply with full range of control tests, i.e. identification, safety and potency.

Vaccine composition. The vaccine contains inactivated strain or strains of immunogenic *P. multocida* with or without a suitable adjuvant. The vaccine is shown to be satisfactory with respect to identification, safety, and immunogenicity against all incorporated serotypes of *P. multocida* for all bird species for which it is intended.

Identification

Protects susceptible bird species against infection with *P. multocida*. The potency tests may also serve for identification.

Safety. Administer double dose of the vaccine by the recommended route of administration into each of 20 SPF (2.7.7) chickens or healthy susceptible chickens of 4 to 6 weeks age. In case of turkeys, ducks or geese use not less than 20 unvaccinated birds that do not have antibodies against *P. multocida* and that are not older than the minimum age recommended for vaccination. If the recommended schedule requires a second dose, administer 1 dose after the recommended interval. Observe the birds daily for 21 days after the last administration of the vaccine. The test is not valid if more than 10 per cent of the birds show abnormal signs of disease, or die from the cause not attributable to the vaccine. The vaccine complies with the test if no bird shows abnormal signs of disease or dies from causes attributable to the vaccine. The test is carried out for each route of administration to be recommended for vaccination.

Potency: Carry out potency test in each of the bird species in which the vaccine is intended to be used against virulent challenge with all the serotypes of *P. multocida* incorporated in the vaccine.

When potency is conducted in chickens, use not fewer than 30 SPF (2.7.7) or healthy susceptible chickens of 4 to 6 weeks age for each *P. multocida* serotype incorporated in the vaccine. For each test, administer to each of not fewer than 20 birds a quantity of vaccine not greater than one dose. If revaccination is recommended, administer the same dose after the recommended interval. Maintain 10 unvaccinated controls. Challenge each of the birds of both groups 21 days after the last administration by appropriate dose of virulent strain of *P. multocida* that shall kill at least 80 per cent of the unvaccinated susceptible chickens. Observe birds for 14 days after the challenge. There should be not less than 70 per cent protection of the vaccinated birds. The test is invalid unless 80 per cent of the unvaccinated control birds die of *P. multocida* infection.

Manufacturer's tests

Certain tests may be carried out on the final bulk vaccine rather than on the batch or batches prepared from it.

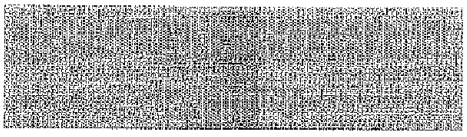
Inactivation. The test shall consist of at least 2 passages in production medium; or if solid medium has been used for production, in suitable liquid medium. Incubate inoculated medium at 30° to 35° for 72 hours. The bulk complies with the test if no evidence of presence of live *P. multocida* is observed.

Safety. For vaccines recommended for use in chickens, use 10 chickens of the minimum age recommended for vaccination from an SPF (2.7.7) or healthy susceptible chicken flock. For vaccines recommended for use only in turkeys, ducks or geese, use 10 birds of the species likely to be most sensitive to fowl cholera, which do not have antibodies against *P. multocida* and of the minimum age recommended for vaccination. Administer to each bird by a recommended route a double dose of the vaccine. Observe the birds daily for 21 days. The vaccine complies with the test if no bird shows abnormal signs of disease or dies from causes attributable to the vaccine. The test is not valid if more than 20 per cent of the birds show abnormal signs or die from causes not attributable to the vaccine.

Potency. It is not necessary to carry out Potency test for each batch of vaccine if it has been produced through same production process and from the same master seed lot that has shown satisfactory results.

Where potency test is not carried out, an alternative validated method is used. The criteria of acceptance being set with reference to a batch of vaccine prepared from the same master seed lot that has given satisfactory results in test described under potency test on master seed lot.

Use not less than 15 SPF chickens (2.7.7), 3 to 4 weeks old. Collect serum samples from each chicken just before vaccination and check for the absence of antibodies against each serotype of *P. multocida* in the vaccine. Administer each of 10 chickens 1 dose of the vaccine by subcutaneous route. Maintain remaining 5 chickens as unvaccinated controls. Collect serum samples 5 weeks after the vaccination from each vaccinated and control bird. Using a suitable validated serological method, measure the titers of serum antibodies against each serotype of *P. multocida* incorporated in the vaccine. Calculate the mean titers for the group of vaccinates. The vaccine complies with the test if the mean antibody titers of the group of vaccinates are equal to or greater than the titers obtained with the reference batch prepared from the master seed lot that has given satisfactory results in test described under potency test on master seed lot.



The test is invalid if specific *P. multocida* antibodies are detected before vaccination in one or more sera from chickens to be vaccinated or from controls; in 1 or more sera from control chickens 5 weeks after the day of administration of the vaccine.

Batch tests

Description. Homogenous suspension of inactivated bacteria.

Identification

The vaccine complies with the requirements of the test mentioned under the section of master seed lot.

Sterility (2.2.11). Complies with the test for sterility.

Safety. The vaccine complies with the requirements of the test mentioned under section of Manufacturer's tests.

Potency. The vaccine complies with the requirements of the test mentioned under section of master seed lot.

Labelling and Storage. Should comply with the requirements of 'Labelling and Storage' as laid down in the General Monograph on Veterinary Vaccines: General Requirements.

The label states: (1) the serotypes and the strains of bacteria used to prepare vaccine; (2) adjuvant used (3) dose and route of inoculation.

Expiry. Not more than 1 year from the date of manufacture.

Fowl Pox Vaccine, Live

Pigeon Pox Vaccine, Live

Fowl Pox Vaccine, Live is a preparation of a suitable strain(s) of pigeon pox virus or fowl pox virus. This monograph applies to vaccines intended for administration to chickens for active immunization against avian pox virus.

Production

The vaccine virus is grown in embryonated hens' eggs from SPF flock (2.7.7) or in cell cultures derived from SPF eggs (2.7.7) or cell lines. The master seed lot complies with the tests for extraneous agents as described in the General monograph for Veterinary Vaccines (2.7.10).

Substrate for virus propagation

The vaccine virus is grown either in embryonated hens' eggs from flocks free from specified pathogens SPF (2.7.7) or in avian cell cultures obtained from flocks free from specified pathogens SPF (2.7.7) or cell lines.

Identification

Carry out an immunostaining or neutralization test in cell culture derived from SPF eggs (2.7.7) to demonstrate the presence of the vaccine virus or inoculate the vaccine into eggs and notice the characteristic lesions.

Tests

Water (2.3.43). Not more than 3.0 per cent.

Mycoplasmas (2.7.9). Complies with the test for mycoplasmas.

Safety. Administer 10 doses of the vaccine to each of ten SPF chickens (2.7.7, Table 3) or healthy susceptible chickens 6 to 8 weeks old by the route stated on the label. Observe the birds for 21 days. No chicken dies from causes attributable to the vaccine or shows signs of toxicity other than mild, transient, local reactions. If during the observation period more than two chickens die from causes not attributable to the vaccine, repeat the test.

Virus titre. Not less than 10^2 $EID_{50}/TCID_{50}$ of the virus per dose, determining the titre by inoculation into the chorio-allantoic membrane of SPF embryonated eggs, between 9-11 days old, or one or more route for virus titration depending upon the strain.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Carry out a separate potency test for each of the routes of administration stated on the label. Use not less than ten SPF chickens (2.7.7, Table 3) or healthy susceptible chickens, 6 to 8 weeks old. Use ten birds from the same flock and weight range as controls. Administer to each chicken a volume of the reconstituted vaccine containing a quantity of the virus equivalent to the minimum titre stated on the label. After 21 days, challenge each chicken by intrafollicular administration or by scarification with a virulent strain of fowl poxvirus. Observe the birds for 14 days. The vaccinated chickens survive and show no signs of disease except transient local reactions of fowl pox within 6 days following the challenge. All control chickens show lesions of fowl pox.

If the potency test has been performed with satisfactory results on a representative batch of the vaccine it may be omitted as a routine test during production of the other batches of the vaccine prepared from the same seed lot.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 18 months from the date the virus titre was determined. The reconstituted vaccine should be used immediately after preparation.

Labelling. The label/insert states (1) the minimum virus titre; (2) the dose of vaccine.

Goat Pox Vaccine, Live

Goat Pox Vaccine, Live attenuated is a freeze dried preparation obtained by producing attenuated goat pox virus in a suitable

cell culture and mixed with a suitable stabilizer and freeze dried. The freeze dried vial is reconstituted with a suitable diluent and used immediately.

Production

The virus is propagated in suitable cell cultures and the freeze dried vaccine reconstituted with a suitable liquid and diluted if necessary to provide a concentration appropriate to the particular test and the master seed used for vaccine preparation must be free from extraneous pathogens.

Master seed lot

The master seed lot complies with the tests of identity for the organism and a batch of vaccine prepared from the master seed lot should comply with full range of control tests, i.e. identification, safety and immunogenicity. Once immunogenicity is established on the initial 3 batches, this test can be omitted as a routine test for the batch release and virus titer is considered for a batch release provided the traceability of the vaccine strains used is from the same master seed.

Identification

Vaccine administration in the target species like goats does not cause goat pox but immunizes them with specific neutralizing antibodies. The potency test serves the identification also. Alternately, identification on the final antigen lot by molecular approaches is acceptable and can be used in the routine batch release tests also.

Virus titer

Not less than 10^3 $TCID_{50}$ of the virus per dose, determining the titre in a suitable cell culture with suitable medium.

Extraneous agents

Neutralize the vaccine virus with a suitable mono specific antiserum against goat pox and inoculate into cell suitable cultures. Carry out 2 passages with an interval of 4 to 6 days. The vaccine complies with the test if no cytopathic effect is observed.

Sterility (2.2.11). Complies with the test for sterility.

Mycoplasmas. Complies with the test for Mycoplasma either by cell culture or by molecular based method.

Safety. Inject 100 doses of the vaccine contained in 1 ml of the reconstituted vaccine subcutaneously into each of 6 susceptible goats, 6 to 8 months old. Observe the goats for 14 days. None of the animals shows abnormalities other than local erythema of not more than 3 cm in diameter around the site of injection.

Immunogenicity

Use nine susceptible goats, 8 to 10 months old. Inject subcutaneously with one dose of the vaccine stated on the label into each goat. Use 3 goats as unvaccinated controls which should be kept along with the inoculated goats. Observe the animals for 14 days and record the rectal temperature daily of each goat during the observation period. None of the vaccinated goats shows any thermal reaction or local or generalized lesion. After 21 days, challenge the vaccinated and control animals with sufficient quantity of a virulent goat pox virus by intradermal injection. Observe the animals for 14 days and record the rectal temperature daily of each goat during the observation period. None of the vaccinated goats shows any thermal reaction or local or generalized lesion. The test is valid only if the control animals develop high fever or show local or generalized lesions. If the test for potency has been carried out with satisfactory results on a representative batch of vaccine, this test may be omitted as a routine control on other batches of vaccine prepared from the same seed lot.

Manufacturer's tests

The tests stated under Master seed lot i.e. virus titer, extraneous agents, safety and immunogenicity need not be carried out provided the these tests are demonstrated at the development stage with the vaccine. However, the identity test needs to be carried out for every antigen lot before conversion to the final vaccine.

Batch tests

Identification

Suitable methods like molecular approaches are suggested for identification of the final antigen lot apart from any validated identification methods. Upon administration to goats immunized with the vaccine, specific neutralizing antibodies develop.

Water (2.3.43). Not more than 3.0 per cent.

Virus titer. Not less than 10^3 $TCID_{50}$ of the virus per dose, determining the titre of the vaccine in a suitable cell culture using suitable medium.

Sterility (2.2.11). Complies with the test for sterility.

Safety. Inject intramuscularly with 10 times the minimum dose stated on the label into each of 2 goats of the minimum age recommended for vaccination. Observe the animals for 21 days. None of the animals shows abnormal local or systemic reactions or dies of any causes attributable to the vaccine.

Labelling. The label states (1) the minimum dose; (2) the recommended routes of administration; (3) virus titer per dose (4) the storage temperature of the vaccine (5) expiry period.

Haemorrhagic Septicaemia Vaccine, Inactivated

Haemorrhagic Septicaemia Vaccine, Inactivated is a preparation of *Pasteurella multocida*. The whole culture is inactivated by *formaldehyde* and a suitable adjuvant (gel or mineral oil) is added. This monograph applies to the vaccines intended for active immunization of cattle and buffaloes against Haemorrhagic septicaemia.

Production

Preparation of Vaccine. Pure suspension of a highly immunogenic strain of Haemorrhagic septicaemia causing *Pasteurella multocida* grown in phase I on a suitable medium by a suitable method (Agar wash or Fermenter) is inactivated by a suitable quantity of *formaldehyde*. The suspension is adjusted to a desired Brown's opacity scale or any other suitable method before addition of adjuvant (Alum or Aluminium hydroxide gel or oil adjuvant) so that the finished product contains not less than 2.5 mg of antigenic mass per dose.

Choice of vaccine strain. A reference strain of Haemorrhagic septicaemia causing *Pasteurella multocida*, obtained from an authentic source is used.

Tests on Master seed lot

The master seed lot of the vaccine strain of *P. multocida* is not more than one passage on an artificial medium from the culture obtained after target animal passage. The master seed lot complies with the tests of *purity* and *identity* for the organism and, a representative batch of vaccine prepared from the master seed lot complies with full range of control tests, i.e. identification, safety and potency.

Vaccine composition. The vaccine contains inactivated immunogenic strain of Haemorrhagic septicaemia causing *Pasteurella multocida* grown in phase I along with a suitable adjuvant. The preparation is shown to be satisfactory with respect to antigenic mass per dose and, complies with the tests for identification, safety and immunogenicity for the animal species for which it is intended.

Antigenic mass. The following method is suggested for adjusting the antigenic mass.

Centrifuging at least 100 ml of the final inactivated bulk suspension in each of 4 pre-weighed (up to milligram level) centrifuge tubes at 5000 rpm for 30 minutes. Discard supernatant and, dry the pallets by an appropriate method. Determine the dry weight of the pallets in the tubes. Calculate volume of *phenol saline* to be added to the bulk so that the dry weight of the cell mass is between 140 to 150 mg per 100 ml.

Identification. The vaccine prepared from the master seed lot protects susceptible animals against infection with Haemorrhagic septicaemia causing *P. multocida*. The potency test may also serve for identification.

Safety. Inject at least 2 apparently healthy buffalo or male cow claves with twice the dose of the product through appropriate route (subcutaneous for Alum gel or intramuscular for oil adjuvant) and observe for 10 days. The master seed lot passes the safety test if none of the animal shows any obvious adverse reaction and die of *P. multocida* infection.

Immunogenicity. Use 3 apparently healthy buffalo or male cow calves which have been tested free from anti-*P. multocida* antibodies and ageing between 6 months and 2 years. Inoculate 2 ml (animals having body weight less than 140 kg) or 3 ml (animals having body weight more than 140 kg) of the test product from 5 pooled samples through route recommended for the vaccine. (Inject Alum gel vaccine through subcutaneous and oil adjuvant vaccine through intramuscular route). Challenge the vaccinated animals along with 2 healthy controls tested free from anti-*P. multocida* antibodies with at least 50 million mouse minimum lethal dose of a virulent *P. multocida* culture after 21 days. Observe the animals for 7 days.

The master seed lot passes the immunogenicity test if both the controls die of Haemorrhagic septicaemia and at least 2 out of the 3 vaccinated, survive the challenge.

Manufacturer's tests

Certain tests may be carried out on the final bulk vaccine rather than on the batch or batches prepared from it.

Antigenic mass. Determine the antigenic mass of the inactivated bulk harvest before adjuvantation according to the method suggested for master seed lot.

Safety. Inject intraperitoneally into each of 6 healthy mice weighing not less than 18 g with 0.5 ml of the preparation under test and observe for 5 days. No abnormal reaction occurs and none of the mice dies of *P. multocida* infection.

Potency. Carry out test for potency in one of the animal species as described.

A. *Test on mice.* Inject 50 mice of either sex weighing not less than 18 g, subcutaneously with 0.2 ml of Alum gel vaccine or intramuscularly with 0.2 ml of the oil adjuvant vaccine from 5 pooled samples. Repeat the dose similarly after 14 days. After 7 day of the second vaccination divide the vaccinated mice into 10 groups of 5 each. Use 50 mice of the same from the same stock as controls divided similarly into 10 groups of 5 each. Challenge each of the vaccinated and the control mice of each group with 0.2 ml of a dilution of 12 to 18 hours old broth culture of a virulent strain of *P. multocida* ranging from

10^{-1} to 10^{-10} through subcutaneous route. Observe the mice for 5 days and record the mortalities in vaccinated and control groups. Calculate the 50 per cent lethal dose of the challenge organism for vaccinated and control mice by Spearman and Karber method.

The protection provided by the vaccine is determined as Protective Index (PI), using following formula:

Protective Index (PI) = LD_{50} in control mice ÷ LD_{50} in vaccinated mice

The vaccine passes the test if it provides a minimum PI of 4 log_{10}.

B. *Buffalo or Cow Calves.* The vaccine complies with the test for potency on target animals mentioned under section of master seed lot.

Conduct a potency test on the target animal species on every fifth batch of vaccine produced from the same MSL.

Batch tests

Description. Homogenous suspension of inactivated bacteria.

Identification

The vaccine complies with the requirements of the test mentioned under the section of master seed lot.

Sterility (2.2.11). Complies with the test for sterility.

Safety. The vaccine complies with the requirements of the test mentioned under section of Manufacturer's tests.

Potency. The vaccine complies with requirements of the test mentioned under section of master seed lot.

Labelling and Storage. Should comply with the requirements of 'Labelling and Storage' as laid down in the General Monograph on Veterinary Vaccines: General Requirements.

The label states (a) the serotype and the strain of bacteria used to prepare vaccine; (b) adjuvant used (c) dose and route of inoculation.

Expiry. Not more than 12 months from the date of manufacture.

Haemorrhagic Septicaemia Vaccine-Alum Treated

Pasteurella multocida/ (*Yersinia multocida*) Vaccine - Alum Treated

Haemorrhagic Septicaemia Vaccine Alum Treated is a formalized culture of *Pasteurella multocida* in nutrient broth treated with potash alum. The vaccine is a white suspension containing dead bacteria and alum.

Production

The highly potent strain of *Pasteurella multocida* type 1 in phase 1 is grown on nutrient broth at 37°. The pure growth is killed by the addition of a solution of Formalin in suitable concentration (0.5 per cent). This is treated with potash alum to give a final concentration of 1.0 per cent.

Identification

The vaccine protects susceptible animals against infection with *Pasteurella multocida.*

Tests

Safety. Inject 5 ml of the vaccine subcutaneously in to each of four healthy rabbits, each weighing 1 to 1.5 kg. Observe the animals for 7 days; no abnormal, local or systematic reaction occurs for except slight local swelling, or two rabbits and six mice may be taken. Inject 0.5 ml into each mice and rabbits.

Sterility (2.2.11). Complies with the test for sterility.

Labelling. The label states (1) the method of preparation; (2) the type and strains of bacteria use to prepare the vaccine; (3) expiry date should not be more than six months.

Inclusion Body Hepatitis (IBH) Vaccine, Inactivated

Hydropericardium Syndrome (HPS)

Inclusion Body Hepatitis (IBH) Vaccine, Inactivated consists of an emulsion or a suspension of avian adenovirus(es) which have been inactivated in such a manner that the immunogenic activity is retained. The vaccine may contain one or more suitable adjuvants.

Production

Substrate for virus propagation

Vaccine virus is multiplied in healthy susceptible chicks or SPF eggs (2.7.7) or in cell culture derived from SPF eggs (2.7.7).

The master seed lot complies with the tests for extraneous agents as described in the General monograph for Veterinary Vaccines (2.7.10).

Test for Inactivation

To confirm inactivation an amplification test for residual live IBH/HPS virus is carried out on each batch of antigen immediately after inactivation or on the final bulk (if the vaccine contains a mixture of inactivated antigens). The test is conducted on healthy susceptible chickens demonstrated to be free from antibodies to IBH/HPS virus or in fertilized eggs

(two passage) derived from specific pathogen free flocks (2.7.7) if the vaccine virus has been propagated in embryos. The quantity of inactivated virus used in the test is equivalent to not less than 2/5th doses of the vaccine. No live virus is detected.

Identification

Protects chickens against infection of IBH/HPS.

Tests

Safety. Inject subcutaneously a quantity equivalent to 2 doses into each of 10 SPF chickens (2.7.7, Table 3) or healthy susceptible chickens of the recommended age at which vaccine is to be used. Observe the chickens for 14 days, no abnormal systemic or local reaction is seen.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Either test A or test B may be carried out.

A. Inject one dose by the route stated on label into each of 20 SPF chickens (2.7.7, Table 3) or healthy susceptible chickens at the age recommended by manufacturer. Use 10 similar chickens from same source as unvaccinated controls. After 10 days of immunization challenge the birds with 10 per cent IBH positive infected liver suspension 0.5 ml per bird. Observe the birds for ten days. The vaccine passes the potency test when there is 90 per cent protection in vaccinated bird and 80 per cent deaths in unvaccinated controls.

B. At least five, 3-6 week old SPF chickens (2.7.7, Table 3) or healthy susceptible chickens are vaccinated with one field dose of vaccine by intramuscular route. Blood samples are collected between 3 and 5 weeks and the antibody response measured by ELISA. The mean antibody titre should be at least 10 $\log_2$ ELISA units.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 2 years from the date the potency was determined.

Labelling. The label/insert states (1) strain used for vaccine production; (2) the route of administration.

Infectious Avian Encephalomyelitis Vaccine, Live

Encephalomyelitis Vaccine Live: Epidemic Tremor Vaccine Live

Infectious Avian Encephalomyelitis Vaccine, Live is a freeze-dried preparation of an attenuated strain of infectious avian encephalomyelitis virus.

Production

The virus is grown in SPF embryonated eggs (2.7.7) or in suitable cell culture derived from SPF eggs (2.7.7). The master seed lot complies with the tests for extraneous agents as described in the General monograph for Veterinary Vaccines (2.7.10).

Identification

Inoculate 0.1 ml of the undiluted reconstituted vaccine into the yolk sac of SPF embryonated eggs, between 5 to 6 days old. Keep them in an incubator and transfer to the setter for hatching. Observe the hatched chickens for 7 days. Not less than 50 per cent of the chickens show the typical symptoms characteristic of infectious avian encephalomyelitis-like weakness or paralysis of legs, sitting posture on hock joints and tremors.

Tests

Water (2.3.43). Not more than 3.0 per cent.

Mycoplasmas (2.7.9). Complies with the test for mycoplasmas.

Safety. Administer ten SPF chickens (2.7.7, Table 3) or healthy susceptible chickens by ten doses of the vaccine by the recommended route. Observe the chickens for 21 days. No chicken develops signs of the disease or dies from causes attributable to the vaccine. Repeat the test if more than two chickens die from causes not attributable to the vaccine during the observation period.

Virus titre. Not less than $10^{2.5}$ $TCID_{50}/EID_{50}$ of the virus per dose, determining the titre of the virus in cell culture derived from SPF eggs (2.7.7) or by inoculation into the yolk sac of SPF embryonated hen eggs (2.7.7), between 5 to 6 days old.

Sterility (2.2.11). Vaccines intended for administration by injection comply with the test for sterility prescribed in the monograph (2.2.11). Vaccines not intended for administration by injection either comply with the test for sterility prescribed in the monograph (2.2.11) or with the following test: carry out the quantitative test for bacterial and fungal contamination; carry out identification tests for microorganisms detected in the vaccine; the vaccine does not contain pathogenic microorganisms and contain not more than 1 non pathogenic microorganisms per dose.

Potency. Carry out a separate potency test for each of the routes of administration stated on the label. For each of the stated routes, use not less than ten SPF chickens (2.7.7, Table 3) or healthy susceptible chickens, 3 weeks old. Administer to each chicken a volume of the reconstituted vaccine containing a quantity of the virus equivalent to the minimum virus titre stated on the label. Use ten chickens of the same flock and age as controls. After 21 days, challenge each chicken in the vaccinated and control groups with intracerebral injection of

a suitable quantity of a virulent avian encephalomyelitis virus. Observe the chickens for another 21 days. Not less than 80 per cent of the vaccinated chickens survive or show no signs of disease and not less than 70 per cent of the controls die or develop signs or paralytic lesions of avian encephalomyelitis.

If the potency test has been performed with satisfactory results on representative batch of the vaccine from the same seed lot, it may be omitted as a routine control test during production of other batches of the vaccine prepared from the same seed lot.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 18 months from the date the virus titre was determined. The reconstituted vaccine should be used immediately after preparation.

Labelling. The label/insert states (1) the minimum virus titre; (2) the dose of vaccine.

Infectious Bursal Disease Vaccine, Inactivated

Infectious Bursal Disease Vaccine, Inactivated consists of an emulsion or a suspension of a suitable strain of infectious bursal disease virus which has been inactivated in such a manner that immunogenic activity is retained. The vaccine may contain one or more suitable adjuvant.

Production

The virus is propagated in fertilized eggs obtained from healthy flock or in suitable cell culture derived from SPF eggs (2.7.7) or in healthy susceptible chicken.

The master seed lot complies with the tests for extraneous agents as described in the General monograph for Veterinary Vaccines (2.7.10).

Inactivation

An amplification test for residual live infectious bursal disease virus is carried out on each batch of antigen immediately after inactivation and the test is carried out in fertilized hen eggs obtained from SPF flocks (2.7.7) or in suitable cell culture derived from SPF eggs (2.7.7) or, where chickens have been used for production of the vaccine, in chickens from a flock free from specified pathogens. The quantity of inactivated virus used in the test is equivalent to not less than $2/5^{th}$ doses of the vaccine. No live virus is detected.

Test for inactivation

For vaccine prepared with embryo-adapted strains of the virus. Inject quantity of inactivated virus equivalent to $2/5^{th}$ doses of vaccine into the allantoic cavity or onto the chorio-allantoic membrane of the SPF embryonated hen eggs, between 9 to 11 days old, and incubate at 36° ± 1°. Observe for 6 days and pool separately the allantoic fluid from eggs containing live embryos, and that from eggs containing dead embryos, excluding those dying from non-specific causes within the first 24 hours after inoculation.

Inject into the allantoic cavity or Chorio-allantoic membrane of each of the SPF embryonated hen eggs, between 9 to 11 days old, 0.2 ml of the pooled allantoic fluid or Chorio-allantoic membrane from the live embryos or membrane from the dead embryos and incubate at 36°±1° for 6 days. Examine each embryo for lesions of infectious bursal disease. The vaccine complies with the test if, there is no evidence of lesions of infectious bursal disease.

The test is valid only if not more than 20 per cent of the embryos die at either stage of the test. If more than 20 per cent of the embryos die at either one of the stages of the test, repeat that stage. In any repeat test, not more than 20 per cent of the embryos die from non-specific causes. Antibiotics may be used to control extraneous bacterial infection.

For vaccine prepared with strains of virus not adapted to embryos. Inject two doses intramuscularly into each of twenty chickens, between 14 and 28 days old, complying with the requirements stated under Test on chicken flocks free from pathogens for the production and quality control of vaccines (2.7.7). Four days later, kill ten of the chickens and remove bursa of fabricius from each chicken, pool the bursa and homogenise in an equal volume of a suitable liquid. Inject 1 ml of the homogenate into each of a further ten chickens of the same flock and age. After 21 days, examine microscopically the bursa of each chicken from the first group and the second group. No evidence of infectious bursal disease is seen and no abnormal local reaction develops.

For vaccine prepared with cell culture-adapted strains of the virus. The formaldehyde in the test sample is neutralizes with sodium metabisulphite. One ml is tested for the presence of infective Gumboro Disease virus by inoculation of at least 150 square cm primary or secondary CEF. The cultures are incubated for 3 to 4 days at a temperature of 37°. After one cycle of freezing and thawing the supernatant from these cultures is passaged to a fresh CEF cultures. Three to four days latter this is repeated. Three to four days after final inoculation the cultures are inspected for CPE. A vital stain and overlay may be used. If no traces of CPE is detected, the inactivation of the antigen suspension is accepted to be completed.

Identification

Protects susceptible chickens against infectious bursal disease by producing specific antibodies on inoculation.

Tests

Safety. Inject each of ten healthy chickens, 14 to 28 days old with twice the minimum vaccinating dose and by one of the routes stated on the label. Observe the chickens for 14 days. No abnormal local or systemic reaction is seen.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Inject each of ten SPF chickens (2.7.7) or healthy susceptible chickens, 3 to 4 weeks old, with the minimum dose and by the route stated on the label. Use ten chickens of the same flock and age as controls. After 21 days, collect serum samples from each bird including the ten-control chickens and perform quantitative agar gel precipitation test or serum neutralizing test on each serum sample. The mean antibody titre of sera in vaccinated group shall be 1:8 by agar gel diffusion test and 10000 units per ml by serum neutralization test and there are no IBD specific antibodies in the sera of control chickens.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 2 years from the date the potency was determined.

Labelling. The label states (1) the type of strain; (2) the route of administration.

Infectious Bursal Disease Vaccine, Live

Infectious Bursal Disease Vaccine, Live is a freeze dried preparation of attenuated strain of infectious bursal disease (IBD) virus. This monograph applies to vaccines intended for administration to chickens for active immunization.

Production

Infectious Bursal Disease Vaccine, Live is a suitable strain of Infectious Bursal Disease virus. The master seed lot complies with the tests for extraneous agents as described in the General monograph for Veterinary Vaccines (2.7.10).

Substrate for virus propagation

The vaccine virus is grown in embryonated eggs obtained from SPF flocks or in cell culture derived from SPF eggs (2.7.7) or susceptible cell lines.

Identification

When mixed with monospecific infectious bursal disease virus antiserum the vaccine no longer infects susceptible cell culture derived from SPF eggs (2.7.7) or embryonated hen eggs, 9 to 11 days old.

Tests

Water (2.3.43). Not more than 3.0 per cent.

Mycoplasmas (2.7.9). Complies with the test for mycoplasmas.

Safety. Use not less than ten SPF chickens (2.7.7, Table 3) or healthy susceptible chickens, 10 to 15 days old. According to the type of viral vaccine strain incorporated in the product - Invasive - Moderately invasive- it may be necessary to conduct the safety test on chicks possessing moderate level of maternal antibodies.

Administer by eye drop to each chicken ten doses of the vaccine reconstituted so as to obtain a concentration suitable for the test. Observe the chickens for 21 days. If during the period of observation more than 2 chickens die from causes not attributable to the vaccine, repeat the test. The vaccine complies with the test if non of the chickens shows signs of the disease, if no chicken dies from causes attributable to the vaccine and if 21 days after inoculation of the vaccine, no chicken shows lesions of the bursa of fabricius.

Sterility (2.2.11). Vaccines intended for administration by injection comply with the test for sterility prescribed in the monograph (2.2.11).

Vaccines intended for administration by injection either comply with the test for sterility prescribed in the monograph (2.2.11) or with the following test: carry out the quantitative test for bacterial and fungal contamination; carry out identification tests for microorganisms detected in the vaccine; the vaccine does not contain pathogenic microorganisms and contain not more than 1 non pathogenic microorganisms per dose.

Virus titre. Infectious Bursal Disease Vaccine, Live (using IBD Intermediate Strain): Not less than $10^{3.0}$ $TCID_{50}/EID_{50}$ of the IBD virus titre per dose; Infectious Bursal Disease Vaccine, Live (using IBD Intermediate plus Strain): Not less than $10^{2.0}$ $TCID_{50}/EID_{50}$ of the IBD virus titre per dose. Determining the titre in cell cultures derived from SPF embryo or onto the chorio- allantonic membrane of SPF embryonated hen eggs between 9 to 11 days old.

Potency. Use 20 SPF chickens (2.7.7, Table 3) or healthy susceptible chickens 10 to 15 day old. Administer to each chicken one dose of the vaccine by recommended route. Use 10 chickens of the same flock and age as controls. Fourteen days after immunization challenge chicken of both groups by intraocular route administration of a suitable quantity of virulent infectious bursal disease virus. Observe the birds for 10 days after challenge. Not more than 4 of vaccinated chickens die or show signs of the infectious bursal disease or on histological examination show severe bursal lesions. The test is not valid unless not less than 50 per cent of the control birds die or show signs of IBD and all the surviving controls show severe bursal lesions on histological examination.

If at least 90 per cent of the follicles show greater than 75 per cent depletion of lymphocytes, the bird is considered as one showing severe bursal lesions.

If the potency test has been performed with satisfactory results on a representative batch of the vaccine from the seed lot, it may be omitted as a routine control test during production on other batches of the vaccine prepared from the same seed lot.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 18 months from the date the virus titre was determined. The reconstituted vaccine should be used immediately after preparation.

Labelling. The label/ insert states (1) minimum virus titre; (2) the dose of vaccine (3) Intermediate or Intermediate Plus IBD strain.

Infectious Canine Hepatitis Vaccine, Inactivated

Canine Adenovirus Vaccine-1, Inactivated

Infectious Canine Hepatitis Vaccine, Inactivated is a preparation of one or more suitable strains of canine contagious hepatitis (CAV 1) virus, inactivated in such a manner that its immunogenic activity is retained. It may be freeze dried preparation or a liquid preparation containing a suitable adjuvant.

Production

Preparation of the vaccine. The virus is grown in suitable cell culture system, The cell culture complies with the requirements for cell culture for production of veterinary vaccines (2.7.13). The vaccine may contain a suitable adjuvant.

Choice of vaccine strain. A reference strain obtained from an authentic source shall be used for the vaccine production. The master seed which has been established as pure, safe and immunogenic shall be used for vaccine production.

Identification

When inoculated into dogs, the development of specific neutralizing antibodies against canine adenovirus-1 can be demonstrated by suitable serological tests.

Tests

Safety. Carry out the test for each route and methods of administration to be recommended for vaccination. Use a batch of vaccine containing not less than the maximum potency that may be expected in a batch of vaccine. Use not less than 10 dogs of the minimum age to be recommended for vaccination and that do not have antibodies against canine adenovirus-1. Administer double dose of vaccine prepared from master seed to each dog. If the schedule to be recommended requires a second dose, administer double dose after the interval to be recommended. Observe the dogs daily at least until 14 days after the last administration. The vaccine complies with the test, if no dogs shows abnormal local or/ and systemic reactions, sign of diseases or dies from causes attributed to the vaccine virus.

Potency. A test is carried out of each route and method of administration to be recommended for vaccination using dogs of the minimum age to be recommended. The vaccine administered to each dog is of minimum potency. Use 7 susceptible dogs, between 8 to 14 weeks old that do not have antibodies against CAV-1. Vaccinate 5 dogs according to the schedule and dose to be recommended. Use another 2 dogs of the same age group as unvaccinated controls. If a second dose is recommended, the second dose shall be administered at the time specified on the label. For single dose schedule, challenge each dog after 21 days or for two dose schedule, 14 days after booster by the intravenous route with a quantity of a suspension of virulent strain of canine contagious hepatitis virus sufficient to cause death or typical signs of disease in susceptible dogs. Observe the animals for a further 21 days. Dogs show typical sign of serious infection with canine adenovirus-1 are euthanized to avoid unnecessary suffering.

The test is not valid if during the observation period after challenge, less than 100 per cent of the control dogs die or show notable sign of infectious canine hepatitis. The vaccine complies with the test if during observation period after challenge all the vaccinated dogs survive and show no signs of disease.

Manufacturer's tests

Identification

Vaccine complies the requirements of the test mentioned under production.

Potency. It is not necessary to carry out the potency test for each batch of the vaccine if it has been carried out using a batch of vaccine with a minimum potency. Where the test is not carried out, an alternative validated methods is used, the criteria for acceptance being set with reference to a batch of vaccine that has been given satisfactory results in the test described under potency.

Batch tests

Identification

Vaccine complies the requirements of the test mentioned under production. Alternatively, identification on the final lot by validated molecular techniques is acceptable and can be used in the routine batch release tests after proper validation of antigen extraction protocol from adjuvanted vaccine and test applied (2.8.1).

Water (2.3.43). Not more than 3.0 per cent (for freeze dried vaccine only).

Safety. Inject each of two healthy susceptible dogs in the recommended age group free from canine contagious hepatitis virus antibodies with a quantity equivalent to 2 doses by the route stated on the label. Observe the animals for 14 days. No abnormal systemic or local reaction occurs.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Inject each of two healthy susceptible dogs, between 8 to 14 weeks old that have been previously tested and shown to be free from canine contagious hepatitis virus antibodies, with the minimum dose and the route stated on the label. If a second dose is recommended, the second dose shall be administered at the time specified on the label. For single dose schedule, collect blood after 21 days or for two dose schedule, collect blood 14 days after booster from each dog.

Inactivate each serum sample by heating at 56° for 30 minutes and prepare serial dilutions in a suitable medium. Add to each dilution an equal volume of serum-virus suspension containing approximately 10^2 $TCID_{50}$. Incubate the mixture at 37° for 1 hour. Add suitable cell culture with minimum of four replicates for each dilution and incubate at 37° for 4 to 8 days. Examine each culture for evidence of specific cytopathic effect and calculate the antibody titer. Vaccine complies with the test; if serum from each vaccinated dog contains not less than 80 SN_{50} per 0.05 ml of serum tested.

Labelling. The label states (1) the recommended routes of administration; (2) that the preparation should be shaken well before use; (3) that the liquid preparation should not be allowed to freeze; (4) that the vaccine should be used immediately after reconstitution for freeze dried inactivated vaccine; (5) storage temperatures; (6) expiry date.

Infectious Chicken Anemia Vaccine, Inactivated

Infectious Chicken Anemia Vaccine (ICAV), Inactivated is a preparation of a suitable strain of chicken anemia virus, inactivated in such a manner that the immunogenic activity is retained. This monograph applies to vaccines intended for administration to chickens for immunization.

Production

Substrate for virus propagation

The vaccine is grown in embryonated hen's egg obtained from SPF flocks or in suitable cell culture derived from SPF eggs (2.7.7) or susceptible cell line. Harvested virus is inactivated using suitable inactivating agent. The master seed lot complies with the tests for extraneous agents as described in the General monograph for Veterinary Vaccines (2.7.10).

Inactivation

An amplification test for residual live chicken infectious anemia virus is carried out on each batch of antigen immediately after inactivation. The test is carried out in suitable cell culture derived from SPF eggs (2.7.7) or using susceptible cell lines. The quantity of inactivated virus used in the test is equivalent to not less than $2/5^{th}$ doses of the vaccine. No live virus is detected.

Test for Inactivation

Inoculate $2/5^{th}$ doses of vaccine virus using suitable cell culture derived from SPF eggs (2.7.7) or in susceptible cell lines or SPF eggs (2.7.7). Incubate at 36°±1° for 7 days. Make a passage on another set of cell culture derived from SPF eggs (2.7.7) or in cell lines or embryonated SPF eggs (2.7.7) and incubate at 36° ± 1° for 7 days. None of the cultures shows signs of CPE.

Identification

In susceptible chicks, the vaccine stimulates the production of specific antibodies against vaccine virus detected by suitable serological tests.

Tests

Safety. Inject a double dose of vaccine by recommended route in to each of 10, 14 to 28 day-old SPF chickens (2.7.7, Table 3) or healthy susceptible chickens. Observe the chickens for 21 days. No abnormal local or systemic reactions occur.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Carry out a potency test for the route of administration stated on the label. Vaccinate, 10, 21 to 28 day old SPF chickens (2.7.7, Table 3) or healthy susceptible chickens with one dose of vaccine. Keep 10 unvaccinated birds of the same age group as controls. Observe the birds for 28 days. Collect serum samples from each bird including the ten-control chickens. Detect the virus specific antibodies by serological methods i.e. Enzyme Linked Immunoassay or Serum Neutralization test. The mean serum neutralization antibody titre of sera in vaccinated group shall be 5000 units per ml and there are no CAV specific antibodies in the sera of control chickens.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 2 years from the date the potency was determined.

Labelling. The label states (1) strains used for preparation; (2) the route of administration.

Infectious Chicken Anemia Vaccine, Live

Infectious Chicken Anemia Vaccine, Live is a preparation of a suitable strain of chicken anemia virus. This monograph applies to vaccines intended for administration to breeder chicken for active immunization, to prevent excretion of virus, to prevent or reduce transmission through eggs.

Production

Substrate for propagation

Vaccine is grown either in embryonated hen's egg obtained from SPF flocks (2.7.7) or in cell culture obtained from flocks free from specified pathogens (2.7.7) or susceptible cell lines. The master seed lot complies with the tests for extraneous agents as described in the General monograph for Veterinary Vaccines (2.7.10).

Identification

The vaccine, diluted if necessary and mixed with a monospecific chicken anemia virus (CAV) antiserum, no longer infects susceptible cell culture derived from SPF eggs (2.7.7) or egg from SPF flock (2.7.7) into which it is inoculated.

Tests

Water (2.3.43). Not more than 3.0 per cent.

Mycoplasmas (2.7.9). Complies with the test for mycoplasmas.

Safety. Use not less than 10 SPF chickens (2.7.7, Table 3) or healthy susceptible chickens, not older than the minimum age recommended for vaccination (2.7.7). Administer by a recommended route to each chickens 10 doses of the vaccine. Observe the chickens daily for 21 days. The test is not valid if more than 20 per cent of the chickens show abnormal clinical signs or die from causes not attributable to vaccine. The vaccine complies with the test if no chicken shows notable clinical signs of disease or dies from causes attributable to the vaccine.

Virus titre. Titrate the vaccine virus by inoculating into suitable cell lines or eggs from SPF flocks (2.7.7). One dose vaccine contains not less than $10^{3.0}$ $TCID_{50}$/ EID_{50} per dose.

Sterility (2.2.11). Vaccines intended for administration by injection comply with the test for sterility prescribed in the monograph (2.2.11).

Potency. Carry out potency test for each of the routes of administration stated on the label. Vaccinate ten, 21 to 28 day old SPF chickens (2.7.7, Table 3) or healthy susceptible chickens with one dose of vaccine. Keep 10 unvaccinated birds of the same age group as controls. Two to three weeks post vaccination challenge both the groups by intramuscular route with 10^2 CID_{50} CAV virus or the dilution at which 70 per cent of unvaccinated birds get infected or show clinical signs of coryza. Observe the birds for 14 days. Bleed individual birds for haematocrit value, thymus atrophy and bone marrow tissue discolouration.

The vaccine complies with the test if during the observation period after challenge not less than 90 per cent of the vaccinated chickens survive and show no notable clinical signs of disease and/or macroscopic lesions of the bone marrow and thymus.

It is not necessary to carry out the potency test for each batch of the vaccine if it has been carried out on a representative batch using a vaccinating dose containing not more than the minimum virus stated on the label.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 18 months from the date the virus titre was determined. The reconstituted vaccine should be used immediately after preparation.

Labelling. The label/insert states (1) strain of virus used; (2) the dose of vaccine.

Infectious Coryza Vaccine

Infectious Coryza Vaccine is a suspension of inactivated culture of suitable strains of one or more serotype/s or preferably locally prevalent strain/s of *Avibacterium (Haemophilus) paragallinarum* in a suitable medium.

Production

The seed material is inoculated in a suitable medium. If the vaccine contains more than one strain of bacterium, the different strains are grown and harvested separately. The bacterial harvests are inactivated with a suitable agent. The vaccine may contain suitable adjuvant.

Inactivation

The test shall consists at least two passages in production medium or if solid medium has been used for production, in suitable liquid medium. Incubate inoculated medium at 35° to 37° and 4.5 to 5.5 per cent carbon dioxide for 72 hours. The product complies with the test if no evidence of presence of live *Avibacterium paragallinarum* is observed.

Identification

Protects susceptible chicken against infection with *Avibacterium paragallinarium*.

Tests

Sterility (2.2.11). Complies with the test for sterility.

Safety. Inject double dose of vaccine subcutaneously into each of 10 healthy susceptible chickens at the minimum age group at which vaccine is intended. Observe these birds for 7 days; no bird shows untoward reactions other than slight transient local swelling.

Potency. Inject subcutaneously each of 10 SPF chickens (2.7.7, Table 3) or healthy susceptible chickens of the minimum age group at which vaccine is used for each strain incorporated in vaccine, with minimum dose stated on the label. Repeat the vaccination after 2 to 4 weeks. Use 10 healthy chickens of same age group and of same stock as controls. Two to three weeks later, challenge vaccinated and control chickens by instillation with 0.2 ml of 18 hour broth culture of homologous strain of *A. paragallinarium* diluted suitably so as to contain 1×10^6 colony forming units by infra-orbital sinus instillation. Observe the chickens for 7 days for eye swelling, nasal discharge. There should be not less than 70 per cent protection of vaccinated birds. The test is not valid unless 70 per cent of control chickens exhibit typical symptoms of eye swelling and nasal discharge typical of infectious coryza.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 2 years from the date of potency testing.

Labelling. The label/insert states (1) strains used for preparation; (2) the route of administration.

Marek's Disease Vaccine, Live

Marek's Disease, Freeze Dried/Cell Associated Vaccine, Live is a preparation of a suitable serotype(s) of Marek's Disease Virus (Avian Herpes Virus) or combinations their off.

Production

The vaccine virus is grown in cell cultures obtained from SPF (2.7.7) eggs. If the vaccine contains more than one type of virus, the different types are grown separately. The vaccine may be freeze-dried or stored in liquid nitrogen.

The master seed lot complies with the tests for extraneous agents as described in the General monograph for Veterinary Vaccines (2.7.10).

Substrate for virus propagation

Cell culture derived from SPF eggs (2.7.7) obtained from SPF hens (2.7.7) eggs.

Identification

Carry out either the test A or B.

A. The vaccine on inoculation in susceptible cell cultures derived from SPF embryos causes cytopathic effects typical of Marek's Disease virus.

B. When mixed with a specific avian herpes virus antiserum the vaccine loses its capability to produce cytopathic effects or plaques in susceptible cell cultures derived from SPF embryos.

Tests

Water (2.3.43). Not more than 3.0 per cent (For Freeze dried vaccine only).

Mycoplasams (2.7.9). Complies with the test for mycoplasmas.

Safety. Use ten one-day-old SPF chickens (2.7.7, Table 3) or healthy susceptible chickens. Administer by recommended route and method to each chicken or chicken embryo 10 doses of the vaccine. Observe the chicken for 21 days. No chicken shows persistent clinical signs, dies or, at autopsy, shows macroscopic lesions from causes attributable to the vaccine. If during the observation period more than two chickens die from causes not attributable to the vaccine, repeat the test.

Sterility (2.2.11). Complies with the test for sterility.

Virus titre. Vaccine containing one type of virus: Titrate the vaccine virus by inoculation into suitable cell culture derived from SPF eggs (2.7.7). If the virus titre is determined in plaque forming units (PFU), only primary plaques are taken into consideration. The vaccine complies with the test if one dose contains not less than 10^3 PFU per dose.

Vaccine containing more than one type of virus: For vaccine containing more than one type of virus, titrate each virus by inoculation into suitable cell culture derived from SPF eggs (2.7.7), reading the results by immunostaining using antibodies. Vaccine complies with the test if one dose contains for each vaccine virus not less than 10^3 PFU of virus per dose.

Potency. Carry out a separate potency test for each of the routes of administration stated on the label. For each of the stated routes, use not less than thirty susceptible one-day-old SPF chickens (2.7.7, Table 3) or healthy susceptible chickens.

Administer each chicken a volume of the vaccine containing a quantity of the virus equivalent to the minimum titre stated on the label. Use thirty chickens of the same flock and age as controls. After 9 days, challenge each chicken by a suitable route with a suitable quantity of virulent Marek's disease virus. Observe the birds for 10 weeks. Record the deaths and kill the survivors to carry out autopsies on both dead and sacrificed chicken for specific macroscopic lesions of Marek's disease. For each of the stated routes of administration, the total number of vaccinated birds that show specific macroscopic lesions is reduced by not less than 80 per cent as compared with the control birds and the challenge virus produces specific macroscopic lesions in not less than 70 per cent of the control birds.

If the potency test has been performed with satisfactory results on representative batch of the vaccine from the same seed lot, it may be omitted as a routine control test during production of other batches of the vaccine prepared from the same seed lot.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 2 years from the date the virus titre was determined. The reconstituted vaccine should be used immediately after preparation.

Labelling. The label states (1) the minimum virus titre; (2) the dose of vaccine.

The frozen vaccine has to be dispensed in glass ampoules suitable for liquid nitrogen storage and if the above information cannot be printed on the small size ampoule, the product should be accompanied by suitable insert which clarifies the prescribed contents of the labels.

Peste Des Petits Ruminants Vaccine, Live

Peste Des Petits Ruminants (PPR) Vaccine, Live is a preparation of a suitable strain of PPR vaccine that is attenuated for sheep and goats.

Production

The vaccine strain is grown in suitable cell cultures. The viral suspension is harvested, mixed with a suitable stabilizing liquid and freeze-dried.

Choice of vaccine strain. A reference strain obtained from an authentic source shall be used for the vaccine production. Only a virus strain shown to be satisfactory with respect to identification, safety, test for extraneous pathogens, test for mycoplasma and virus titre may be used in the preparation of the vaccine.

Identification

When injected into target animals, the vaccine stimulates the production of specific PPR virus neutralization antibodies.

Tests

Safety. Inject two susceptible goats of one year old free from antibodies to PPR by subcutaneous route with a 100 times the dose of vaccine stated on the label. Observe the animals for 21 days. No sign of illness attributable to PPR is noticed.

Water (2.3.43). Not more than 3.0 per cent.

Virus titre. Not less than $10^{2.5}$ $TCID_{50}$ per dose.

Extraneous viruses. The reconstituted vaccine when mixed with specific anti-PPR serum should not produce cytopathic effects in susceptible cell cultures and the cells should show no evidence of the presence of haemadsorbing agents.

Mycoplasma (2.7.4 or 2.7.8). Complies with the test for mycoplasma.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Use not less than six healthy goats and six healthy sheep of 1 year old free from antibodies to PPR virus. Collect sera from animals before the time of vaccination and 3 weeks after vaccination and just before challenge. Vaccinate two goat and two sheep subcutaneously with 1/10 dose each and two goat and two sheep subcutaneously with one dose of the vaccine. Keep the remaining animals as the in-contact controls. Monitor each animal for clinical signs, in particular respiratory symptoms and record temperature daily for three weeks. Three weeks after vaccination collect sera samples from all vaccinated as well as control animals and challenge the vaccinated and in-contact controls group with a suspension of virus containing either 10^3 LD_{50} pathogenic PPRV or 2.5 ml of a 10 per cent splenic suspension by subcutaneous route. The animals are observed for clinical signs and the body temperatures are recorded daily for two weeks. The vaccine passes the test if all vaccinated animals resist challenge infection and all the in-contact controls develop signs of PPR. The serum neutralization test must be positive for PPR antibody in vaccinated animals only, in samples taken three weeks after vaccination.

If potency test has been performed with satisfactory results on a representative batch of the vaccine from the seed lot, it may be omitted as a routine control test during production on other batches of the vaccine prepared from the same seed lot.

Labelling. The label/insert states (1) the cell line used for vaccine manufacture; (2) the virus titre per dose; (3) the recommended age for vaccination.

Expiry. As per label claim approved by National Control Laboratory/ National Regulatory Authority.

Rabies Veterinary Vaccine, Inactivated (Cell Culture)

Rabies Vaccine for Veterinary Use is a preparation of rabies fixed virus adapted to and propagated in cell culture and inactivated by a suitable method. It may be issued as a liquid containing a suitable adjuvant or as a freeze-dried preparation to be reconstituted with a suitable liquid immediately before use.

Production

The vaccine is prepared from virus grown either in suitable cell lines or in primary cell cultures from healthy animals. The virus suspension is harvested on one or more occasions within 28 days of inoculation. Multiple harvests from a single production cell culture may be pooled and considered as a single harvest. The rabies virus is inactivated by a suitable method. The vaccine may contain one or more adjuvants.

Inactivation

A. The test for residual live rabies virus is carried out by inoculation of the inactivated virus into the same type of cell culture as that used in the production of the vaccine or a cell culture shown to be at least as sensitive. The quantity of inactivated virus used in the test is equivalent to not less than 25 doses of the vaccine. After incubation for 4 days, a subculture is made using trypsinised cells; after incubation for a further 4 days, the cultures are examined for residual live rabies virus by an immunofluorescence test. No live virus is detected.

B. Inject each of twenty suckling mice, each weighing between 12 and 16 g, intracerebrally with not less than 0.03 ml of the vaccine or antigen under examination. Observe the animals for 21 days. None of the mice dies or shows any abnormalities attributable to the vaccine. If more than two mice die within 48 hours, repeat the test.

Identification

When injected into animals, the vaccine stimulates production of specific neutralising antibodies.

Tests

Water (2.3.43). Not more than 3.0 per cent (for freeze dried vaccine only).

Safety. Inject each of twenty mice, each weighing between 12 and 16 g, intracerebrally with not less than 0.03 ml of the vaccine under examination. Observe the animals for 21 days. None of the mice dies or shows any abnormalities attributable to the vaccine. If more than two mice die within 48 hours repeat the test. If the vaccine is intended for more than one species including one belonging to the order of Carnivore, carry out the test in dogs. Otherwise use one of the species for which the vaccine is intended. Administer, by a recommended route, a double dose of vaccine to each of 2 animals having no antibodies against rabies virus. Observe the animals for 14 days. No abnormal local or systemic reaction occurs.

Sterility (2.2.11). Complies with the test for sterility.

Potency. The potency of rabies vaccine is determined by comparing the dose necessary to protect mice against the clinical effects of the dose of rabies virus defined below, administered intracerebrally, with the quantity of a reference preparation, calibrated in International Units, necessary to provide the same protection.

Preparation of the challenge suspension. Inoculate a group of mice intracerebrally with the CVS strain of rabies virus and when the mice show signs of rabies, but before they die, kill the mice and remove the brains and prepare a homogenate of the brain tissue in a suitable diluent. Separate gross particulate matter by centrifugation and use the supernatant liquid as challenge suspension. Distribute the suspension in small volumes in ampoules, seal and store at a temperature below − 60°. Thaw one ampoule of the suspension and make serial dilutions in a suitable diluent. Allocate each dilution to a group of 10 mice and inject intracerebrally into each mouse 0.03 ml of the dilution allocated to its group. Observe the animals for 14 days and record the number in each group that, between the fifth and the fourteenth day, develop signs of rabies. Calculate the ID_{50} of the undiluted suspension.

Determination of potency of the vaccine

Use in the test, healthy mice about 4 weeks old and from the same stock. Distribute the mice into at least 10 groups of not less than 10 mice. Prepare at least three serial dilutions of the vaccine under examination and three similar dilutions of the reference preparation. Prepare the dilutions such that those containing the largest quantity of vaccine may be expected to protect more than 50 per cent of the animals into which they are injected and those containing the smallest quantities of vaccine may be expected to protect less than 50 per cent of the animals into which they are injected. Allocate each dilution to a different group of mice and inject intraperitoneally into each mouse 0.5 ml of the dilution allocated to its group. Fourteen days after the injection prepare a suspension of the challenge virus such that, on the basis of the preliminary titration, it contains about 50 ID_{50} in each 0.03 ml. Inject intracerebrally into each vaccinated mouse 0.03 ml of this suspension. Prepare 3 suitable serial dilutions of the challenge suspension. Allocate the challenge suspension and the 3 dilutions one to each of 4 groups of 10 unvaccinated mice and inject intracerebrally into each mouse 0.03 ml of the suspension or one of the dilutions allocated to its group. Observe the animals in each group for 14 days. The test is not valid if more than 2 mice of any group die within the first 4 days after challenge. Record the numbers in each group that show signs of rabies in the period 5 to 14 days after challenge.

The test is not valid unless (a) for both the vaccine under examination and the reference preparation the 50 per cent protective dose lies between the smallest and the largest dose given to the mice; (b) the titration of the challenge suspension shows that 0.03 ml of the suspension contained at least 10 ID_{50} and not more than 50 ID_{50}; (c) the confidence limits

(P = 0.95) are not less than 25 per cent and not more than 400 per cent of the estimated potency; (d) the statistical analysis shows a significant slope and no significant deviations from linearity or parallelism of the dose-response lines.

The vaccine complies with the test if the estimated potency is not less than 1 IU in the smallest prescribed dose.

Labelling. The label states (1) the strain used for the preparation; (2) the name of any added adjuvant.

Ranikhet Disease Vaccine, Inactivated

Newcastle Disease Vaccine, Inactivated

Ranikhet Disease Vaccine, Inactivated consists of an emulsion or a suspension of a suitable strain of Newcastle disease virus (avian paramyxovirus 1) that has been inactivated in such a manner that immunogenic activity is retained.

Production

Substrate for virus propagation

The vaccine virus is grown either in embryonated hens' eggs or in cell culture derived from SPF eggs (2.7.7) or suitable cell line.

The master seed lot complies with the tests for extraneous agents as described in the General monograph for Veterinary Vaccines (2.7.10).

Inactivation

Inject quantity of inactivated virus equivalent to 2/5th doses of vaccine into the allantoic cavity of each of 10 embryonated 9 to 11 days old SPF eggs (2.7.7), and incubate. Observe for 6 days and pool separately the allantoic fluid from eggs containing live embryos and that from eggs containing dead embryos, excluding those dying within 24 hours of the injection. Examine embryos that die after 24 hours of injection for the presence of Newcastle disease virus. Test the allantoic fluid from each egg for the presence of haemagglutinins using chicken erythrocytes.

Inject into the allantoic cavity of each of 10 SPF eggs (2.7.7), 9 to 11 days old, 0.2 ml of the pooled allantoic fluid from the live embryos and, into each of 10 similar eggs, 0.2 ml of the pooled fluid from the dead embryos and incubate for 5 to 6 days. Test the allantoic fluid from each egg for the presence of haemagglutinins using chicken erythrocytes.

The vaccine complies with the test if there is no evidence of haemagglutinating activity and if not more than 20 per cent of the embryos die at either stage. If more than 20 per cent of the embryos die at one of the stages, repeat that stage; the vaccine complies with the test if there is no evidence of haemagglutinating activity and not more than 20 per cent of the embryos die at that stage.

Antibiotics may be used in the test to control extraneous bacterial infection.

Identification

When injected into susceptible healthy chicken, the vaccine stimulates the production of specific antibodies against Newcastle disease virus.

Tests

Safety. Inject ten SPF chickens (2.7.7, Table 3) or healthy susceptible chickens of the age stated on the label with twice the dose and by the route stated on the label. Observe the birds for 21 days. No abnormal local or systemic reactions are observed.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Either test A or test B may be carried out.

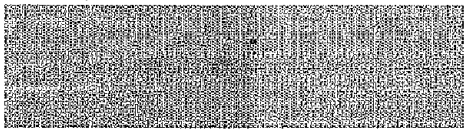
A. Inject intramuscularly each of ten SPF chickens (2.7.7, Table 3) or healthy susceptible chickens, between 3 - 4 weeks old, with a volume of the vaccine equivalent to one-fiftieth of a dose. Use ten chickens of the same stock and age group as controls. After 21 days, collect serum samples from each of the vaccinated and unvaccinated chicken. Perform haemagglutination inhibition test using the method described below. Use the positive control serum calibrated against a Standard preparation of anti-Newcastle disease serum. The vaccine passes the test if a mean HI titre of the vaccinated group is equal to or greater than 1:16 and that of the unvaccinated controls is equal to or less than 1:4.

If the HI titre are not satisfactory, carry out the test B.

Standard preparation

The Standard preparation is the 1st International reference preparation, established in 1966, consisting of freeze-dried chicken serum (supplied in ampoules containing 320 Units), or another suitable preparation, the potency of which has been determined in relation to the International reference preparation.

Suggested method of haemagglutination inhibition test. Inactivate the serum samples by heating at 56° for 30 minutes. Add 0.05 ml of *saline solution* to all the wells in a microtitre plate and 0.05 ml of the test sera to the first row of wells. Prepare two-fold dilutions of the serum samples across the plate. Add 0.05 ml of a suspension of Newcastle disease virus containing 4 haemagglutinating units of inactivated Newcastle disease virus. Incubate the plate at 4° for one hour. Add 0.05 ml of a 1 per cent suspension of erythrocytes collected from chicken, between 3-4 weeks old, susceptible to Newcastle disease.



Incubate the plate at 4° for one hour. It must be ensured that negative and positive control sera are included in the test. The positive control serum must show a titre of 300 to 400 Units determined by calibration against the Standard reference Preparation.

B. Inject intramuscularly each of three groups of twenty SPF chickens (2.7.7, Table 3) or healthy susceptible chickens, between 3 - 4 weeks old, with five fold ($1/25^{th}$, $1/50^{th}$ and $1/100^{th}$) dilution of vaccine. Use minimum three dilutions. Allocate a different volume to each vaccination group. Vaccinate each chicken by the intramuscular route with the volume of vaccine allocated to its group. Maintain not less than 10 chickens as controls. Challenge each chicken after 21 days by the intramuscular route with 10^6 chick LD_{50} of the virulent strain of avian Paramyxovirus 1. Observe the chickens at least daily for 7 days after challenge. At the end of the observation period, calculate the PD_{50} by standard statistical methods from the number of chickens that survive in each vaccinated group without showing any signs of Newcastle disease during the 7 days. The vaccine complies with the test if the smallest dose stated on the label corresponds to not less than 50 PD_{50} and the lower confidence limit is not less than 35 PD_{50} per dose. If the lower confidence limit is less than 35 PD_{50} per dose, repeat the test; the vaccine must be shown to contain not less than 50 PD_{50} in the repeat test. The test is not valid unless all the control birds die within 6 days of challenge.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 2 years from the date the potency was determined.

Labelling. The label/insert states (1) strain of virus used; (2) the route of administration.

Ranikhet Disease Vaccine, Live (Lentogenic Strain)

Newcastle Disease Vaccine, Live (Lentogenic strain)

Ranikhet Disease Vaccine Live (Lentogenic Strain) is a preparation of a suitable strain of Newcastle disease/Ranikhet disease virus (avian paramyxovirus 1). This monograph applies to vaccines intended for administration to chickens and/or other avian species for active immunization.

Production

Substrate for virus propagation

The vaccine virus is grown in embryonated SPF eggs (2.7.7) or in cell cultures derived from SPF flocks (2.7.7).

The master seed lot complies with the tests for extraneous agents as described in the General monograph for Veterinary Vaccines (2.7.10).

Identification

The vaccine, diluted if necessary and mixed with a monospecific Newcastle disease virus antiserum, no longer provokes haemagglutination of chicken red blood cells or infects embryonated hens' eggs from SPF flock or susceptible cell culture derived from SPF eggs (2.7.7) into which it is inoculated.

Tests

Water (2.3.43). Not more than 3.0 per cent.

Mycoplasmas (2.7.9). Complies with the test for mycoplasmas.

Safety. For vaccines recommended for use in healthy susceptible chickens, use not less than 10 SPF chickens (2.7.7, Table 3) or healthy susceptible chickens demonstrated to be free from antibodies to Newcastle disease virus and of the youngest age recommended for vaccination. For vaccines recommended for use only in avian species other than the chicken, use not less than 10 birds of the species likely to be most sensitive to Newcastle disease, which do not have antibodies against Newcastle disease virus and of the minimum age recommended for vaccination. Administer to each bird by eye-drop, or parenterally if only parenteral administration is recommended, 10 doses of the vaccine in a volume suitable for the test. Observe the birds at least daily for 21 days. The test is not valid if more than 20 per cent of the birds show abnormal clinical signs or die from causes not attributable to the vaccine. The vaccine complies with the test if no bird shows notable clinical signs of disease or dies from causes attributable to the vaccine.

Virus titre. Not less than 10^6 $TCID_{50}/EID_{50}$ of the virus per dose, determining the titre in suitable cell culture derived from SPF eggs (2.7.7) or by inoculation into the allantoic cavity of SPF embryonated eggs, 9 to 11 days old.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Carry out a potency test for each of the routes of administration stated on the label. For each of the stated routes, use at least ten SPF chickens (2.7.7, Table 3) or healthy susceptible chickens and of the minimum age recommended for vaccination.

Administer each chicken with a volume of the reconstituted vaccine containing a quantity of the virus equivalent to the minimum titre stated on the label. Use ten chickens of the same flock and age as controls. After 14 to 21 days, challenge each chicken by intramuscular injection with 10^5 LD_{50} of a virulent strain of Newcastle disease virus. Observe the chickens for 14 days. The vaccine complies with the test if not

more than two of the vaccinated chickens die or show signs of disease. The test is valid only if all the control birds die within 6 days of inoculation of the virulent challenge strain.

If the potency test has been performed with satisfactory results on a representative batch of the vaccine from the seed lot, it may be omitted as a routine control test during production on other batches of the vaccine prepared from the same seed lot.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 18 months from the date the virus titre was determined. The reconstituted vaccine should be used immediately after preparation.

Labelling. The label/insert states (1) strain of virus used; (2) the dose of vaccine.

Ranikhet Disease Vaccine, Live (Mesogenic Strain)

Ranikhet Disease Vaccine, Live (Mesogenic Strain) is a preparation of a suitable strain of Newcastle disease virus (naturally modified avian Paramyxovirus 1). This monograph applies to vaccines intended for administration to chickens for active immunization.

Production

Substrate for virus propagation

The vaccine virus is grown in embryonated SPF eggs (2.7.7) or in cell cultures derived from SPF flocks (2.7.7) or susceptible cell lines. The master seed lot complies with the tests for extraneous agents as described in the General monograph for Veterinary Vaccines (2.7.10).

Identification

The vaccine, diluted if necessary and mixed with a monospecific Newcastle disease virus antiserum, no longer provokes haemagglutination of chicken red blood cells or infects embryonated hens' eggs from SPF flock (2.7.7) or susceptible cell culture derived from SPF eggs (2.7.7) into which it is inoculated.

Tests

Water (2.3.43). Not more than 3.0 per cent.

Mycoplasmas (2.7.9). Complies with the test for mycoplasmas.

Safety. Administer fifteen SPF chickens (2.7.7, Table 3) or healthy susceptible chickens, 8 to 9 weeks old, with a minimum 10 doses and by the route stated on the label. Observe the chickens for 21 days. Not more than 2 chicken show abnormal clinical signs or die due to causes attributable to the vaccine. If more than two chickens die during the period of observation due to causes other than those attributable to the vaccine, repeat the test.

Virus titre. Not less than 10^5 $TCID_{50}$/EID_{50} of the virus per dose, determining the titre in suitable cell culture derived from SPF eggs (2.7.7) or by inoculation into the allantoic cavity of SPF embryonated eggs (2.7.7), between 9 -11 days old.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Carry out potency test for each of the routes of administration stated on the label. For each of the stated routes, use not less than ten SPF chickens (2.7.7, Table 3) or healthy susceptible chickens of the minimum age recommended for vaccination. Administer each chicken with a volume of the reconstituted vaccine containing a quantity of the virus equivalent to the minimum titre stated on the label. Use ten chickens of the same flock and age as controls. After 14 to 21 days, challenge each chicken by intramuscular injection with 10^5 LD_{50} of a virulent strain of Newcastle disease virus. Observe the birds for 14 days. The vaccine complies with the test if not more than two of the vaccinated chickens die or show signs of disease. The test is valid only if all the control chickens die within 6 days of inoculation of the virulent challenge strain.

If the potency test has been performed with satisfactory results on a representative batch of the vaccine from the seed lot, it may be omitted as a routine control test during production on other batches of the vaccine prepared from the same seed lot.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 18 months from the date the virus titre was determined. The reconstituted vaccine should be used immediately after preparation.

Labelling. The label/insert states (1) strain of virus used; (2) the dose of vaccine.

Reo Virus Vaccine, Inactivated

Reo virus vaccine, Inactivated consists of an emulsion or a suspension of a suitable strains of Reo virus which has been inactivated in such a manner that immunogenic activity is retained. The vaccine may contain one or more strains and a suitable adjuvant.

Production

Substrate for virus propagation

The virus is propagated in fertilized eggs obtained from healthy flock or in suitable cell culture derived from SPF flocks (2.7.7) or susceptible cell line.

The master seed lot complies with the tests for extraneous agents as described in the General monograph for Veterinary Vaccines (2.7.10).

Inactivation

An amplification test for residual live infectious avian reo virus is carried out on each batch of antigen immediately after inactivation and the test is carried out in fertilized SPF hen eggs or in suitable cell culture derived from SPF eggs (2.7.7). The quantity of inactivated virus used in the test is equivalent to not less than 2/5th doses of the vaccine. No live virus is detected.

A. **In cell culture derived from SPF eggs** (2.7.7). Inoculate 2/5th doses of vaccine into suitable cell culture derived from SPF eggs (2.7.7). Incubate at 36° ± 1° for 7 days. Make a passage on another set of cell culture derived from SPF eggs (2.7.7) and incubate at 36° ± 1° for 7 days. None of the cultures shows signs of infection i.e. CPE.

B. **In embryonated eggs.** Inject quantity of inactivated virus equivalent to 2/5th doses of vaccine into the allantoic cavity of the SPF embryonated hen eggs, between 9-11 days old, and incubate at 36° ± 1°. Observe for 6 days and pool separately the allantoic fluid from eggs containing live embryos, and that from eggs containing dead embryos, excluding those dying from non-specific causes within the first 24 hours after inoculation. Inject into the allantoic cavity of each of the SPF embryonated hen eggs, between 9-11 days old, 0.2 ml of the pooled allantoic fluid from the live embryos or membrane from the dead embryos and incubate at 36° ± 1° for 6 days. Examine each embryo for lesions of Reo virus. The vaccine complies with the test if there is no evidence of lesions of Reo virus. The test is valid only if not more than 20 per cent of the embryos die at either stage of the test. If more than 20 per cent of the embryos die at either one of the stages of the test, repeat that stage. In any repeat test, not more than 20 per cent of the embryos die from non-specific causes. Antibiotics may be used to control extraneous bacterial infection.

Identification

In susceptible chickens, the vaccine stimulates the production of specific antibodies against each of the virus serotypes in the vaccine detected by virus neutralization.

Tests

Safety. Inject each of ten SPF chickens (2.7.7, Table 3) or healthy susceptible chickens, 14 to 28 days old with twice the minimum vaccinating dose and by one of the routes stated on the label. Observe the chickens for 14 days. No abnormal local or systemic reaction should be seen.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Inject each of twenty SPF chickens (2.7.7, Table 3) or healthy susceptible chickens, 3 to 4 weeks old, with the minimum dose and by the route stated on the label. Use ten chickens of the same flock and age as controls. After 21 days, collect serum samples from each bird including the ten-control chickens and perform quantitative agar gel precipitation test or serum neutralization test on each serum sample. The mean antibody titre of sera in vaccinated group shall be 1:8 by Agar gel diffusion test and 10000 units per ml by serum neutralization test and there should be no specific antibodies in the sera of control chicken.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 2 years from the date the potency was determined.

Labelling. The label/insert states (1) strains used for preparation; (2) the route of administration.

Reo Virus Vaccine, Live

Reo Virus Vaccine, Live is a preparation of a suitable strain(s) of Reo virus known to be safe and immunogenic. This monograph applies to vaccines intended for administration to chickens for protection against Malabsorption Syndrome and /or proventriculitis and /or Tenosynovitis in birds.

Production

Substrate for virus propagation

The vaccine virus is grown in embryonated SPF hens' eggs or in cell cultures derived from SPF flocks (2.7.7) or suitable cell line.

The master seed lot complies with the tests for extraneous agents as described in the General monograph for Veterinary Vaccines.

Identification

When mixed with monospecific Reo virus antiserum, the vaccine no longer induces cytopathic effect in susceptible cell culture derived from SPF eggs (2.7.7) or carry out immunostaining test in cell culture derived from SPF eggs (2.7.7) to identify the vaccine virus.

Tests

Water (2.3.43). Not more than 3.0 per cent.

Mycoplasmas (2.7.9). Complies with the test for mycoplasmas.

Safety. Final container samples of completed product from each serial shall be tested as follows:

A. For vaccines intended for use in very young chickens, each of 10, one day old SPF chickens (2.7.7, Table 3) or healthy

tenosynovitis/malabsorption/proventriculitis susceptible chickens shall be vaccinated with the equivalent of 10 doses by one method recommended on the label.

B. For vaccines intended for use in older chickens, each of ten, 4-week-old or older SPF chickens (2.7.7, Table 3) or healthy tenosynovitis susceptible chickens shall be vaccinated with the equivalent of 10 doses by one method recommended on the label.

The vaccinates shall be observed each day for 21 days. If unfavourable reactions occur which are attributable to the product, the serial is unsatisfactory. If unfavorable reactions occur in more than two vaccinates which are not attributable to the product, the test is inconclusive and may be repeated. If the test is not repeated, the serial is unsatisfactory.

Virus titre. Titrate the vaccine in cell cultures derived from SPF embryos or in SPF eggs (2.7.7). One dose of the vaccine contains not less than 10^3 $TCID_{50}$ / EID_{50} per dose.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Reo susceptible healthy chickens of same age and from the same source shall be used as test birds. Vaccine intended for use in very young chickens shall be administered to chickens of the youngest age for which vaccine is recommended. Vaccines intended for use in older chickens shall be administered to 4 weeks or older birds. Ten SPF chickens (2.7.7, Table 3) or healthy susceptible chickens vaccinates shall be used for each method of administration. One dose will be injected to vaccinates. Ten chicks shall be held as unvaccinated controls.

Potency test of each age group shall be conducted separately. Twenty one days post vaccination each vaccinate and control shall be challenged by injecting virulent virus into one foot pad. The vaccinates and controls shall be observed for 14 days post challenge. If at least 90 per cent of the controls do not develop swelling and discolouration in the phalangeal joint area of injected foot pad typical of infection of Reo virus, the test is inconclusive and may be repeated. If at least 18 out of 20 vaccinates do not remain free of these signs, disregarding transient swelling which subsides within 5 days post challenge, the serial is unsatisfactory.

The serial is satisfactory when it gives 90 per cent protection to vaccinated group and 90 per cent controls develop positive Reo virus lesions on challenge.

If the potency test has been performed with satisfactory results on a representative batch of the vaccine from the seed lot, it may be omitted as a routine control test during production on other batches of the vaccine prepared from the same seed lot.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 18 months from the date the virus titre was determined. The reconstituted vaccine should be used immediately after preparation.

Labelling. The label/insert states (1) strain of virus used; (2) the dose of vaccine.

Salmonella Abortus Equi Vaccine

Salmonella abortus equi Vaccine is a suspension of killed mixture of equal parts of pure formalized cultures of smooth laboratory strains of *Salmonella abortus equi*.

Production

The whole culture or its filtrate or a mixture is inactivated in such a manner that pathogenecity is eliminated and immunogenic activity is retained. The inactivated cultures may be treated with a suitable adjuvant.

Identification

It protects susceptible animals against infection with *Salmonella abortus equi*.

Tests

Safety. Inject 0.5 ml of the vaccine intraperitoneally to each of six mice, each weighing not less than 18 g. Observe the mice for 96 hours, none of the mice dies of salmonellosis.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Inject each of twelve mice, each weighing not less than 18 g, subcutaneously with 0.5 ml of the preparation under examination. Use another twelve mice of the same weight range and from the same stock as controls. Three weeks later, challenge the mice from both groups by injecting intraperitoneally each animal with 0.5 ml of a suspension of an 18-hour old culture containing 10 LD_{50} virulent organisms of *S. abortus equi*. Observe the mice for 7 days. The vaccine passes the test if not less than nine mice of the vaccinated group survive. The test is not valid unless not less than nine of the control mice succumb to the challenge.

Labelling. The label states (1) the method of preparation; (2) the strains of bacteria used to prepare the vaccine.

Salmonella Vaccine, Inactivated

Salmonella Vaccine, Inactivated is a preparation of 1 or more suitable strains of 1 or more serovars of *Salmonella* organism, inactivated while maintaining adequate immunogenic properties.

This monograph applies to vaccines intended for the active immunization of chickens against infection/s of *Salmonella* in chickens and reducing *Salmonella* colonization and fecal excretion in chickens.

Production

The seed material is inoculated in a suitable medium. If the vaccine contains more than 1 strains of bacterium, the different strains are grown and harvested separately. During production, parameters such as growth rate, purity and identity is verified on harvests using suitable culture. The bacterial harvests are inactivated with suitable agent. The vaccine may contain suitable adjuvant.

Inactivation

The test shall consists at least two passages in production medium or if solid medium has been used for production, in suitable liquid medium. Incubate inoculated medium at 30° to 35° for 72 hours. The product complies with the test if no evidence of presence of live *Salmonella* is observed.

Identification

Vaccine stimulates production of strain specific antibodies against *Salmonella* organisms in susceptible birds.

Tests

Safety. Administer double dose of vaccine subcutaneously into each of ten SPF chickens (2.7.7, Table 3) or healthy susceptible chickens of minimum age recommended for vaccination. Observe the birds at least for 21 days. The test is not valid if more than 20 per cent of the chickens show abnormal signs or die from causes not attributable to the vaccine. The vaccine complies with the test if no chicken shows notable clinical signs of disease or dies from causes attributable to the vaccine.

Sterility (2.2.11). Complies with the test for sterility.

Potency. Carry out separate potency test for each strain of *Salmonella* organism incorporated in the vaccine preparation. Use not less than 10 SPF chickens (2.7.7, Table 3) or healthy susceptible chickens of the minimum age recommended for vaccination. Administer 1 dose of vaccine by a recommended route. Maintain 10 chickens as unvaccinated controls from the same source and flock used for vaccination for each strain used in vaccine. Repeat the vaccination with the same dose and route after 21 days to vaccinated birds. Challenge both the groups, 2 weeks after last administration of vaccine, by oral administration to each chicken a sufficient quantity of a homologous strains of *Salmonella* organisms that is able to colonize chickens. Observe the birds daily for 14 days. Collect fecal samples on 14th day for detection of presence of *Salmonella* organisms by direct plating. The vaccine complies with the test, if the number of *Salmonella* organisms in fresh fecal samples after challenge is significantly lower in vaccinated birds than in unvaccinated controls.

Storage. When stored under the prescribed conditions, the vaccine may be expected to retain its potency for not less than 2 years from the date the potency was determined.

Labelling. The label states (1) strains used for preparation; (2) the route of administration.

Sheep Pox Vaccine, Live Attenuated

Sheep Pox Vaccine, Live attenuated is a freeze dried preparation obtained by producing attenuated sheep pox virus in a suitable cell culture and mixed with a suitable stabilizer and freeze dried. The freeze dried vial is reconstituted with a suitable diluent and used immediately.

Production

A reference vaccine strain obtained from an authentic source should be used. The virus is propagated in suitable cell cultures and the freeze dried vaccine reconstituted with a suitable liquid and diluted if necessary to provide a concentration appropriate to the particular test and the master seed used for vaccine preparation must be free from extraneous pathogens.

Master seed lot

The master seed lot complies with the tests of identity for the organism and a batch of vaccine prepared from the master seed lot should comply with full range of control tests, i.e. identification, safety and immunogenicity. Once immunogenicity is established on the initial 3 batches, this test can be omitted as a routine test for the batch release and virus titer is considered for a batch release provided the traceability of the vaccine strains used is from the same master seed.

Identification

Vaccine administration in the target species like sheep does not cause sheep pox but immunizes them with specific neutralizing antibodies. The potency test serves the identification also. Alternately, identification on the final antigen lot by molecular approaches is acceptable and can be used in the routine batch release tests also.

Mycoplasmas. Complies with the test for Mycoplasma either by cell culture or by molecular based method.

Extraneous agents

Neutralize the vaccine virus with a suitable mono specific antiserum against sheep pox and inoculate into cell suitable

cultures. Carry out 2 passages with an interval of 4 to 6 days. The vaccine complies with the test if no cytopathic effect is observed.

Sterility (2.2.11). Complies with the test for sterility.

Virus titre. Not less than 10^3 $TCID_{50}$ of the virus titer per dose, determining the titer of the vaccine in a suitable cell culture using suitable medium.

Safety. Carry out test for each route and method of administration recommended for the vaccination. Inoculate not less than 6 sheep of 8 to 12 months old, free from neutralizing antibodies against sheep pox virus, with ten times the field dose of the vaccine contained in 1 ml by the route stated on the label. Observe the animals for 14 days. The vaccine complies the test if none of the vaccinated animals show deep necrotic lesion and generalization.

Immunogenicity. Administer each of three sheep, between 8 and 12 months old, free from sheep pox neutralizing antibodies, with the dose of the vaccine and by the route stated on the label. Use two sheep as un-vaccinated controls. Shave the animals closely on the flank from the shoulder to the proctodal area. Challenge each animal after 21 days post-vaccination by inoculating intradermally with 0.1 ml of a suspension six ten fold dilution of the sheep pox challenge virus. Make five separate inoculations in a vertical line for each serial dilution from the anterior to the posterior of the animals. The titer of the challenge virus is calculated using a standard statistical method for the vaccinated and control sheep by the number of pox lesions observed in each dilution. The titer of the challenge virus is calculated for the vaccinated and control animals. The vaccine passes the test if there is a difference of log titer of more than $\log 10^{2.5}$.

If the potency test has been performed with satisfactory results on a representative batch of the vaccine from the seed lot, it may be omitted as a routine control test during production on other batches of the vaccine prepared from the same seed lot.

Manufacturer's tests

The tests stated under Master seed lot such as virus titer, extraneous agents, safety and immunogenicity need not be carried out provided the above tests are demonstrated at the development stage with the vaccine. However, the identity test needs to be carried out for every antigen lot before conversion to the final vaccine.

Batch tests

Identification

Suitable methods like molecular approaches are suggested for identification of the final antigen lot apart from any validated identification methods. Upon administration to sheep immunized with the vaccine, specific neutralizing antibodies develop.

Water (2.3.43). Not more than 3.0 per cent.

Virus titer. Not less than 10^3 $TCID_{50}$ of the virus per dose, determining the titre of the vaccine in a suitable cell culture using suitable medium.

Sterility (2.2.11). Complies with the test for sterility.

Safety. Inject intramuscularly with 10 times the minimum dose stated on the label into each of two sheep of the minimum age recommended for vaccination. Observe the animals for 21 days. None of the animals shows abnormal local or systemic reactions or dies of any causes attributable to the vaccine.

Labelling: The label states (1) the minimum dose; (2) the recommended routes of administration; (3) virus titer per dose; (4) the storage temperature; (5) expiry period.

Tetanus Veterinary Vaccine

Tetanus Vaccine for Veterinary use is a preparation of the neurotoxin of *Clostridium tetani* treated in a manner that eliminates toxicity while maintaining adequate immunogenic properties

Production

The *C. tetani* strain used for production is cultured in a suitable medium and a facility having tetanus vaccine for human use can be sourced for further production processes. The antigenic purity is determined in Lf units of tetanus toxoid per milligram of protein and shown to be not less than the value approved for the particular product.

Choice of vaccine composition

The *C. tetani* strain used in the preparation of the vaccine is shown to be satisfactory with respect to the production of the neurotoxin. The vaccine is shown to be satisfactory with respect to safety and immunogenicity for each species of animal for which it is intended. As part of the studies to demonstrate these characteristics, the tests described below may be used.

Detoxified harvest

Absence of toxin and irreversibility of toxoid. Carry out a test for reversion to toxicity on the detoxified harvest using 2 groups of 5 guinea-pigs, each weighing between 350 to 450 g; if the vaccine is adsorbed, carry out the test with the shortest practical time interval before adsorption. Prepare a dilution of the detoxified harvest so that the guinea-pigs each receive 10 times the amount of toxoid (measured in Lf units) that will be present in a dose of vaccine. Divide the dilution into 2 equal

parts. Keep one part at 5 ± 3° and the other at 37° for 6 weeks. Attribute each dilution to a separate group of guinea-pigs and inject into each guinea-pig the dilution attributed to its group. Observe the animals for 21 days. The toxoid complies with the test if no guinea-pig shows clinical signs of disease or dies from causes attributable to the neurotoxin of *C. tetani*.

Tests on Master seed lot

The master seed lot of *C. tetani* is maintained at recommended storage temperatures. Production of the neurotoxin of *C. tetani* is verified by a suitable immunochemical method carried out on the neurotoxin obtained from the vaccine strain under the condition used for the production of the vaccine. The master seed lot complies with the tests of purity and identity for the organism and a batch of vaccine prepared from the master seed lot should comply with full range of control tests, i.e. identification, safety and potency. For identification, molecular approaches are acceptable.

Identification. Carry out test A if permitted by the nature of the adjuvant. Otherwise carry out test B.

A. Separate the toxoid from the adjuvant. For vaccines adsorbed on aluminium hydroxide, the following treatment is suitable. Dissolve sufficient *sodium citrate* in the vaccine under examination to give a 10 per cent w/v concentration. Maintain at 37° for about 16 hours and centrifuge. The clear supernatant liquid reacts with a suitable tetanus antitoxin and yields a precipitate.

B. When inoculated into healthy susceptible animals, the vaccine stimulates the formation of antitoxin to the neurotoxin of *C. tetani* or protects the animals against the paralytic effects of the toxin. When identification test is carried out on master seed or working seed, it can be omitted as a routine test on in process or finished product provided traceability is established.

Safety. Carry out the test for each recommended route of administration and species of animal for which the vaccine is intended; use animals of the minimum age recommended for vaccination and of the most sensitive category of the species.

Use not less than 15 animals, free from antitoxic antibodies for each test. Administer a double dose of vaccine to each animal. Administer a single dose of vaccine to each animal after the interval stated on the label. Observe the animals until 14 days after the last administration. The vaccine complies with the test if no animal shows abnormal local or systemic signs of disease or dies from causes attributable to the vaccine.

Potency. *Test A may be omitted if test B is carried out. Test B may be omitted if test A is carried out.*

A. Inject subcutaneously each of ten guinea pigs, each weighing between 350 and 450 g, with a quantity of the vaccine not more than the minimum dose stated on the label as the primary dose, and 28 days later with a quantity of the vaccine not more than the minimum dose stated on the label as the secondary dose. Fourteen days after the second dose, collect the blood from each guinea pig, pool the sera and determine the antitoxin titre by the biological assay of *C. tetani* antitoxin described below.

1 ml of serum contains not less than 7.5 IU per ml or, for vaccine intended for use in equine, not less than 30 IU per ml.

When *C. tetani* vaccine is presented as a component of a mixed vaccine intended for use in animals other than equine and the potency test of the other component or components normally carried out using rabbits, the potency test described above may be carried out using ten healthy rabbits, between 3 and 6 months old. 1 ml of serum contains not less than 2.5 Units.

Biological assay of *C. tetani* antitoxin

The potency of *C. tetani* antitoxins is determined by comparing the dose necessary to protect mice or other suitable animals against the toxic effects of a fixed dose of *C. tetani* toxin with the quantity of a Standard preparation of *C. tetani* antitoxin necessary to give the same protection. For this purpose, the Standard preparation of *C. tetani* antitoxin and a suitable preparation of *C. tetani* toxin are required. The test dose of the toxin is determined in relation to the Standard preparation of antitoxin and the potency of the preparation under examination is then determined in relation to the Standard preparation using the test toxin.

C. tetani antitoxin standard preparation

It is recommended to obtain the international standards or reference standard from any recognized international labs or any other suitable preparation, the potency of which has been determined in relation to the international standard method.

Suggested method

NOTE— The severity of tetanic paralysis to be regarded as the end-point is such that the paralysis is readily recognized but not sufficiently extensive to cause significant suffering.

In practice, when using high levels of toxin to determine the test dose, or when using low levels of antitoxin in the preliminary and final tests, the development of paralysis is so rapid that the defined end-point is usually synchronous with death. Where death occurs, the combined totals of animals dying or reaching the paralytic end-point are used in the calculations.

Preparation of test toxin. Prepare *C. tetani* toxin by growing *C. tetani* in liquid culture for 8 to 10 days and then adding 1 volume of a sterile filtrate of the culture to 1 or 2 volumes of *glycerine*. Store at 0° or at temperatures slightly below it. The toxin may be dried by a suitable method.

Selection of test toxin. Select toxin for use as the test toxin by determining the following quantities:

LP/10 dose (Limes paralyticum). This is the smallest quantity of toxin that when mixed with 0.1 Unit of antitoxin and injected subcutaneously into mice (or guinea pigs) causes tetanic paralysis in the animals on or by the fourth day after injection.

Paralytic dose 50. This is the quantity of toxin that when injected subcutaneously into mice (or guinea pigs) causes tetanic paralysis in one-half of the animals injected on or by the fourth day after injection. A suitable toxin is one that contains not less than 1000 paralytic dose 50 in an LP/10 dose.

Determination of test dose of toxin. Measure or weigh a quantity of the test toxin and dilute with or dissolve in a suitable liquid. Reconstitute or dilute the Standard preparation with a suitable liquid to give a solution containing 0.5 Unit in 1 ml.

Prepare mixtures of the solution of the Standard preparation and the solution of the test toxin such that each mixture contains 0.1 Unit of antitoxin in the volume selected for injection and one of a series of graded volumes of the solution of the toxin, separated from each other by steps of not more than 20 per cent and covering the expected end-point. Adjust each mixture to the same final volume (0.4 to 0.6 ml if mice are used or 4.0 ml if guinea-pigs are used) with a suitable liquid. Allow the mixtures to stand at room temperature, protected from light, for 60 minutes and then inject a dose of the selected volume of each mixture subcutaneously into each of not less than 2 animals of the group to which each mixture has been allocated. Observe the animals for 4 days and record daily the degree of tetanus developing in each group of animals. Repeat the determination at least once, add together the results of the separate tests that have been made with mixtures of the same composition such that a series of totals is obtained and determine the mean values. The test dose of the toxin is the amount present in that mixture that causes tetanic paralysis in one-half of the total number of animals injected with it. When the test dose of the test toxin has been determined, a concentrated solution of the test toxin may be prepared in a mixture consisting of 1 volume of *saline solution* and 1 or 2 volumes of *glycerine*. This concentrated solution may be stored frozen and diluted as required. The specific activity of such a solution must be determined at frequent intervals.

Determination of potency of the antitoxin

Preliminary test. Measure or weigh a quantity of the test toxin and dilute with or dissolve in a suitable liquid such that the solution contains 5 test doses per ml. Prepare mixtures of the solution of the test toxin and the preparation under examination such that for each mixture the volume selected for injection contains the test dose of toxin and one of a series of graded volumes of the preparation under examination. Adjust each mixture to the same final volume with a suitable Liquid. Allow the mixtures to stand at room temperature, protected from light, for 60 minutes. Inject a dose of the selected volumes of each mixture subcutaneously into each of not less than two animals of the group to which each mixture has been allocated. Observe the animals for 4 days and record daily the degree of tetanus developing in each group of animals. From the results select suitable mixtures for the final test.

Final test. Prepare similar fresh mixtures of the test toxin and the preparation under examination such that for each mixture the volume selected for injection contains the test dose of toxin and one of a series of graded volumes of the preparation under examination, separated from each other by steps of not more than 20 per cent and covering the expected end-point as determined in the preliminary test. Prepare further mixtures with the same amount of test toxin and graded volumes of the Standard preparation, centered on 0.1 Unit in the volume selected for injection to confirm the test dose of the toxin. Adjust each mixture to the same final volume with a suitable liquid. Allow the mixture to stand at room temperature, protected from light, for 6 minutes. Inject a dose of the selected volume of each mixture subcutaneously into each of not less than two animals of the group to which each mixture has been allocated. Observe the animals for 4 days and record daily the degree of tetanus developing in each group of animals. The mixture of antitoxin under examination that contains 0.1 Units in the volume injected is that mixture which causes tetanic paralysis in the same, or almost the same number of animals as the mixture containing 0.1 Unit of the Standard preparation in the volume injected. Repeat the determination at least once and calculate the average of all valid estimates. Estimates are not valid unless the Standard preparation gives a result within 20 per cent of the expected value.

Limits of error. For the suggested method, the limits of error (P = 0.95) have been estimated to be 85 to 114 per cent when two animals are used for the test, 91.5 to 109 percent when three animals are used and 93 to 108 percent when six animals are used per the dose.

B. Carry out the biological assay of adsorbed tetanus vaccine as stated under Tetanus Vaccine (Adsorbed).

This method may only be used for those preparations for which it has been shown to be suitable and in particular may not be suitable for vaccine with an oil adjuvant.

Where this alternative method is used the estimated potency is not less than 150 IU in the smallest dose stated on the label.

Labelling (1) the name of the adjuvant used; (2) preparation should be shaken before use; (3) storage temperature; (4) expiry period.

Theileriosis Vaccine, Live

Theileriosis Vaccine, Live is a lymphoblast cell culture containing *Theileria annulata* macroschizonts attenuated by passage in such a manner that it remains avirulent while it retains its immunogenicity. The concentrate of the vaccine is diluted with a suitable diluent after thawing and used immediately preferably within 1 hour of reconstitution.

Production

A reference vaccine strain obtained from an authentic source should be used for the production. The vaccine is recommended to be stored at -196° in liquid nitrogen containers and must be transported in the same temperature till it is used in the target animals. If any alternate methods of storage are employed, number of schizonts/lymphoblast culture cells in the vaccine must be in the range suggested for the vaccine production per dose till the vaccine is used in the target animals.

Master seed lot

The master seed lot complies with the tests of identity for the organism and a batch of vaccine prepared from the master seed lot should comply with full range of control tests, i.e. identification, safety and immunogenicity. Once immunogenicity is established on the representative batch, this test can be omitted as a routine test for the batch release and the count per dose is considered for a batch release provided the traceability of the vaccine strains used is from the same master seed.

Identification

Vaccine administration in the target species like cattle does not cause theileriosis but immunizes them against the infection. Alternately, identification on the final antigen lot by molecular approaches is acceptable and can be used in the routine batch release tests also.

Sterility (2.2.11). Complies with the test for sterility.

Cell count. Contains not less than 2 million live lymphoblast cells in each dose.

Safety. Carry out test for each route and method of administration recommended for the vaccination. Inoculate not less than 6 cattle in the age group of 4 to 9 months with double dose of the vaccine. Observe the animals for 30 to 45 days. None of the animals shows systemic reactions other than mild pyrexia and mild swelling of superficial lymph nodes. No schizonts/piroplasms should be seen in the blood smears/lymph node smear.

Immunogenicity. Inject each of three susceptible cattle not less than 9 to 12 months old with the minimum dose by the route stated on the label. Use two cattle of the same age as controls. After 30 to 35 days, challenge each of the vaccinated as well as the control animals with a preparation of gut homogenate of ticks containing suitable quantity of sporozoites to infect adult cattle. Observe the animals for 30 days; none of the vaccinated, animals shows any abnormal signs. The test is not valid unless both the control animals show typical signs of theileriosis. If these tests have been performed with satisfactory results on a representative batch of the vaccine from the seed lot, they may be omitted by the manufacturer as a routine control on other batches of the vaccine prepared from the same seed lot.

Identification

Molecular means of identification are recommended for the identification test.

Manufacturer's tests

The tests stated under Master seed lot such as identification and immunogenicity need not be carried out provided the above tests are demonstrated at the development stage with the vaccine.

Batch tests

Cell count. Contains not less than 2 million live lymphoblast cells in each dose.

Sterility (2.2.11). Complies with the test for sterility.

Safety. Carry out test for each route and method of administration recommended for the vaccination. Inoculate not less than 2 cattle in the age group of 4 to 9 months with double dose of the vaccine. Observe the animals for 30 to 45 days. None of the animals shows systemic reactions other than mild pyrexia and mild swelling of superficial lymph nodes. No schizonts/piroplasms should be seen in the blood smears/lymph node smear.

Labelling. The label states (1) the minimum dose; (2) the recommended routes of administration; (3) count per dose; (4) storage temperature; (5) the reconstituted vaccine should be used within 1 hour after thawing and reconstitution; (6) expiry period.

VETERINARY DIAGNOSTICS MONOGRAPHS

Avian Mycoplasma Antigen 5001

Avian Tuberculin Purified Protein Derivative (PPD) 5001

Brucella Abortus Milk Ring Test Antigen, Hematoxylin Stained 5002

Brucella Abortus Milk Ring Test Antigen, Tetrazolium Stained 5002

Brucella Abortus Plain Antigen 5003

Brucella Abortus Rose Bengal Plate Test Antigen (Strain 99) 5003

Brucella Abortus Working Standard Serum 5003

Johnin Purified Protein Derivative 5004

Mallein Purified Protein Derivative 5005

Purified Protein Derivative (PPD), Bovine Tuberculin 5005

Salmonella Abortus Equi H Antigen 5006

Salmonella Pullorum Coloured Antigen 5006

Salmonella Pullorum Plain Antigen 5007

Salmonella Pullorum Positive Serum 5007

Avian Mycoplasma Antigen

Mycoplasma antigen shall be prepared either from *Mycoplasma gallisepticum* or *Mycoplasma synoviae*, grown in broth cultures that are inactivated and standardized. Plate antigen shall be stained with an acceptable dye. Each intermediate antigen lot shall be tested for purity, density, and preservative.

Purity. Intermediate antigen lot sample should be free from extraneous organisms as determined by microscopic examination and Gram staining.

Density. A 2.5 ml of sample of intermediate lot shall be diluted with 2.5 ml of buffer solution, formulated in the same manner as the vehicle of the antigen being tested in a modified Hopkins tube and then sedimented by centrifugation at 4000 rpm for 1 hour. If the packed cell volume of the sample is not 1.2 ± 0.4 per cent, the intermediate antigen lot is unsatisfactory.

Preservative. Phenol content of antigen lot shall be 0.25 ± 0.05 per cent.

A batch of finished product should be tested for Identification, Homogeneity and pH. The batch of finished product found unsatisfactory for any prescribed test shall not be released.

Identification

Gives specific agglutination when mixed with the serum of birds infected with *M. gallisepticum* or *M. synoviae* but fails to react with serum from healthy birds.

Tests

Homogeneity. Antigen shall show no evidence of auto agglutination or unusual appearance such as presence of large visible particles.

pH (2.4.24). The pH of *Mycoplasma gallisepticum* antigen shall be 6.0 ± 0.2. The pH of *Mycoplasma synoviae* antigen shall be 7.0 ± 0.2.

Labelling. The label states (1) strains used for preparation; (2) the dose of test.

Expiry. Not less than 1 year from the date of manufacture.

Avian Tuberculin Purified Protein Derivative (PPD)

Avian Tuberculin Purified Protein Derivative (PPD) is a preparation obtained from the heat-treated products of growth and lysis of *Mycobacterium avium* capable of revealing a delayed hypersensitivity in an animal sensitised to micro-organisms of the same species.

Production

It is obtained from the water-soluble fractions prepared by heating in free-flowing stream and subsequently filtering cultures of *Mycobacterium avium* grown in a fluid synthetic medium.The active fraction of the filtrate, consisting mainly protein, is isolated by precipitation;washed and re-dissolved. An antimicrobial preservative that does not give rise to false positive reactions, such as *phenol* may be added. The final sterile product free from mycobacteria is distributed in sterile, tamper-evident glass containers, which are then closed to prevent contamination with extraneous microorganisms. The preparation may be freeze-dried.

NOTE—Identification, the tests and the determination of potency apply to the liquid form and to the freeze-dried form after reconstitution as stated on the label.

Identification

Inject intradermally a range of graded doses at different sites into suitable sensitised albino guinea-pigs, each weighing not less than 250 g. After 24-28 hours, reaction appears at the points of injections, in the form of oedematous swellings with erythema with or without necrosis. The size and severity of the reactions vary according to the dose. Unsensitised guinea-pigs show no reactions to similar injections.

Tests

pH (2.4.24). 6.5 to 7.5.

Phenol *(if present)* (2.3.36). Not more than 0.5 per cent w/v.

Sensitivity. Use a group of 3 guinea-pigs that have not been treated with any material that will interfere with the test. On 3 occasions at intervals of 5 days inject intradermally 0.1 ml equivalent to 500 IU of the product under examination into each guinea-pig. Inject the same dose (500 IU) intradermally into these animals and into a control group of 3 guinea-pigs of the same mass 15-21 days after the 3rd injection which have not previously received injections of tuberculin. 24-28 hours after the last injections, the reactions of the 2 groups are not significantly different.

Other tests. Complies with the tests stated under Veterinary Diagnostics.

Sterility (2.2.11). Complies with the test for sterility.

Abnormal toxicity (2.2.1). Inject subcutaneously 0.5 ml of the preparation under examination into each of two guinea-pigs weighing not less than 250 g that have not previously been treated with any material that will interfere with the test. Observe the animals for 7 days. No abnormal effects are produced.

Potency. The potency of avian tuberculin purified protein derivative is determined by comparing the reactions produced in sensitised guinea-pigs by the intradermal injection of a series of dilutions of the preparation to be examined with those produced by known concentrations of the Standard preparation calibrated in International Units. The International Units is the activity contained in a stated amount of the International Standard. The equivalence in International Units of the International Standard is stated by the World Health Organization.

Sensitise not less than 8 albino guinea-pigs, each weighing between 400 and 600 g by the deep intramuscular injection of a suitable dose of inactivated or live *M. avium*. Not less than 4 weeks after the sensitisation of the guinea-pigs, shave their flanks to provide space for not more than 4 injection sites on each side. Prepare dilutions of the preparations to be examined and of the reference preparation using consist of isotonic *phosphate-buffered saline* pH 6.5-7.5, containing *polysorbate 80* (0.0005 per cent). Use not less than 3 doses of the reference preparation and not less than 3 doses of the preparation to be examined. Choose the doses such that the lesions produced have a diameter of not less than 8 mm and not more than 25 mm. Allocate the dilutions randomly to the sites, for example using a Latin square design. Inject each dose intradermally in a constant volume of 0.1 ml or 0.2 ml. Measure the diameters of the lesions after 24-28 hours and calculate the results of the test using the usual statistical methods and assuming that the diameters of the lesions are directly proportional to the logarithm of the concentration of the tuberculins.

The test is not valid unless the confidence limits (P = 0.95) is not less than 50 per cent and not more than 200 per cent of the estimated potency. The estimated potency is not less than 75 per cent and not more than 133 per cent of the stated potency. The stated potency is not less than 20, 000 IU/ml.

Storage. Protected from light, store at 2 to 8°.

Labelling. The label states (1) the potency in international units per ml; (2) the name and volume of the reconstituting liquid to be added; (3) the name and quantity of any excipient; (4) for freeze-dried preparations; (5) the product is to be used immediately after reconstitution.

Brucella Abortus Milk Ring Test Antigen, Hematoxylin Stained

Brucella abortus Milk Ring Test Antigen, Hematoxylin Stained is a suspension of a pure smooth culture of *Brucella abortus* strain 99 bacteria stained with hematoxylin and suspended in *saline solution* containing 0.5 per cent w/v of *phenol*, the reaction of which is adjusted to pH 4.0 with *0.1 M citric acid* or with *0.5 M disodium hydrogen phosphate*, as appropriate.

For standardisation, the stained suspension is washed by centrifugation in a solution containing 6.4 g of *sodium chloride*, 1.5 ml of *lactic acid* and 4.4 ml of 10 per cent w/v solution of *sodium hydroxide* in 1,600 ml of *distilled water*, the pH of the solution being adjusted to 4.0. The washed cells are resuspended in *phenol saline solution* and the packed cell volume of the final product is adjusted to 4 per cent v/v.

Identification

The antigen forms a blue-coloured ring in the cream layer when mixed with milk from animals suffering from Brucellosis.

Tests

Sterility (2.2.11). Complies with the tests for sterility.

Other tests. Complies with the tests stated under Veterinary Diagnostics.

Sensitivity. It has the same sensitivity as that of a standard antigen when tested by the milk ring test.

Storage. As stated under Veterinary Diagnostics.

Labelling. As stated under Veterinary Diagnostics.

Brucella Abortus Milk Ring Test Antigen, Tetrazolium-Stained

Brucella abortus Milk Ring Test Antigen, Tetrazolium-Stained is a suspension of a pure smooth culture of *Brucella abortus* strain 99 bacteria stained supravitally with *2,3,5-triphenyl-tetrazolium chloride* in *saline solution* containing 1 per cent v/v of *glycerin* and 1 per cent w/v of *phenol*. Smooth strain of *Brucella abortus* strain 99 is grown on *potato infusion agar* for 48 to 72 hours in roux flasks, at 37°. Condensation fluid if any is pipetted off before washing. Each flask is washed with about 20 ml of *normal saline*. The pooled washing is filtered through a gauze and the filtrate is collected in a measuring cylinder. To every 500 ml of the filtrate 1g of *2, 3, 5 triphenyl-tetrazolium chloride* is added immediately. The container is shaken for thirty minutes till the *tetrazolium salt* is dissolved. The product is taken out and kept in at 37° for two hours. After incubation the product is heated at 65° in a *water* bath for thirty minutes. It is cooled and centrifuged at 3,000 rpm for one hour. The supernatant is pipetted off and sediment is suspended in *normal saline* containing 1 per cent *glycerol* and 1 per cent *phenol* and filtered through sterile cotton wool. This forms concentrated antigen.

For the standardisation of the stained antigen, 1.0 ml of an aliquot of the suspension representing the initial undiluted suspension is taken in each of 6 test-tubes to which increasing quantities (0.6, 0.8, 1.0, 1.2, 1.4 and 1.6 ml) of *saline solution* containing 1 per cent v/v of *glycerin* and 1per cent w/v of

phenol are added. The contents of each tube are then diluted 10-fold with the same diluent and serve as antigen for the tube agglutination test with the reference standard antiserum. Thus six sero-reactions will be carried out. During this procedure the concentrated stained microbial suspension is kept at a temperature between 2° and 8°. The agglutination reactions are read after 48 hours. The dilution which gives 50 per cent agglutination with a 1 in 500 final dilution of the standard antiserum is taken as the final dilution for the preparation.

Identification

The antigen forms a cherry-red ring in the cream layer when mixed with milk from animals infected with Brucellosis.

Tests

Sterility (2.2.11). Complies with the tests for sterility.

Other tests. Complies with the tests stated under Veterinary Diagnostics.

Storage. As stated under Veterinary Diagnostics.

Labelling. As stated under Veterinary Diagnostics.

Brucella Abortus Plain Antigen

Brucella abortus Plain Antigen is a suspension of a pure smooth culture of killed *Brucella abortus* strain 99 bacteria in *phenol-saline solution*.

Identification

Gives specific agglutination reaction when mixed with the serum of animals infected with *Brucella abortus* organisms.

Tests

Sterility (2.2.11). Complies with tests for sterility.

Other tests. Complies with the tests stated under Veterinary Diagnostics.

Sensitivity. Gives 50 per cent agglutination on incubation at 37° for 20 ± 1 hours with a 1 in 500 dilution of a standard *Brucella antiserum* containing 1,000 International Units.

Storage. As stated under Veterinary Diagnostics.

Labelling. As stated under Veterinary Diagnostics.

Brucella Abortus Rose Bengal Plate Test Antigen (Strain 99)

Brucella abortus Rose Bengal Plate Test Antigen (Strain 99) is a suspension of inactivated bacteria from a pure smooth culture of *Brucella abortus* strain 99. The bacteria being stained with *Rose Bengal*, in a *buffered solution* prepared by adding 540 ml of *lactic acid* to 2,000 ml of *phenol saline solution* and diluting to 6,000 ml.

The antigen is used when an approximate idea of the extent of the infection in a herd is required to be assessed with minimum effort and maximum speed or as a screening test to assess whether an outbreak of abortions is due to Brucellosis.

Identification

Gives the specific agglutination reaction when mixed with the serum of animals infected with *Brucella* organisms.

Tests

pH (2.4.24). 3.6 to 3.7.

Sterility (2.2.11). Complies with tests for sterility.

Other tests. Complies with the tests stated under Veterinary Diagnostics.

Assay. To 0.5 ml quantities taken in each of six Hopkin's graduated tubes or graduated haematocrit tubes, add 4.5 ml of saline solution in each tube, mix and centrifuge at 3,000 rpm for 60 minutes. The packed bacterial cell volume is not less than 8 per cent.

Storage. As stated under Veterinary Diagnostics.

Labelling. As stated under Veterinary Diagnostics.

Brucella Abortus Working Standard Serum

Brucella abortus Working Standard Serum is serum of cattle infected with *Brucella abortus* biotype I, or serum raised in rabbits against smooth cultures of *B. abortus* strain 99 or strain 544 which is suitably diluted with healthy cattle serum or rabbit serum as appropriate. It contains 0.01 per cent w/v of *thiomersal* as antibacterial preservative.

The serum is suitably standardised so that a 1 in 500 dilution gives 50 per cent agglutination in tube agglutination test in comparison with the *Brucella abortus* standard serum.

Identification

Gives specific agglutination reaction when mixed with a pure smooth culture of *Brucella abortus* organisms.

Tests

Sterility (2.2.11). Complies with tests for sterility.

Other tests. Complies with the tests stated under Veterinary Diagnostics.

Assay. When tested with standardised *Brucella abortus* tube test antigen, gives 50 per cent agglutination at 1 in 500 final serum dilution in tube agglutination test in comparison with the *Brucella abortus* standard serum.

Storage. As stated under Veterinary Diagnostics.

Labelling. As stated under Veterinary Diagnostics.

Johnin Purified Protein Derivative

Johnin Purified Protein Derivative is a preparation of a fluid synthetic medium in which *Mycobacterium paratuberculosis* has been grown and which has been freed of the bacilli by filtration. The active fraction of the filtrate, which is predominantly protein in nature, is isolated by precipitation, washed and re-dissolved. It is then distributed in sterile glass containers and sealed so as to exclude microorganisms. It may contain a suitable preservative. It reveals delayed hypersensitivity in animals sensitised by *M. paratuberculosis*.

Description. A yellowish-brown liquid.

Identification

Inject intradermally small doses of the preparation into suitable guinea-pigs that have been sensitised with *M. paratuberculosis;* hot, painful oedematous swellings occur at the sites of inoculation after 48 hours.

Tests

pH (2.4.24). 6.5 to 7.5.

Phenol (2.3.36) (*if present*). Not more than 0.5 per cent w/v.

Sterility (2.2.11). Complies with the tests of sterility, Method A.

Abnormal toxicity (2.2.1). Inject 0.5 ml subcutaneously into each of two guinea-pigs. Observe the animals for 7 days; none of the guinea pigs shows significant local or systemic reaction.

Potency. Carry out the biological assay of Johnin Purified Protein Derivative described below:

Biological assay of Johnin purified protein derivative

The potency of Johnin purified protein derivative is determined by comparing the reactions produced in sensitised guinea-pigs by intradermal injection of a series of dilutions of the preparation under examination with those produced by known concentrations of the Standard preparation.

Standard preparation

The Standard preparation is Johnin purified protein derivative, maintained by the Indian Veterinary Research Institute, Izatnagar, or another suitable preparation, the potency of which has been determined in relation to the Standard preparation.

Suggested method

Sensitise five guinea-pigs, each weighing between 300 and 450 g, by deep intramuscular injection of 0.5 ml of a suspension in *saline solution* containing 0.1 µg of moist growth from solid slants of live *M. paratuberculosis*. After a period of not less than 3 weeks carry out the following test. Use two healthy animals of the same weight range and from the same stock as controls. Shave the flanks to provide space for not more than 4 injection sites on each side. Prepare 1:500, 1:1000, 1:2000 and 1:4000 dilutions of each of the Standard preparation and the preparation under examination in *phosphate-buffered saline pH 7.4* containing 0.005 per cent w/v of *polysorbate* 80. Using not less than 2 doses of each dilution of the Standard preparation and the preparation under examination, inject each dose intradermally in the same volume (0.1 to 0.2 ml) to the available sites in a random manner in Latin-square design.

The sensitised guinea-pigs exhibit hot, painful and oedematous swellings typical of *M. paratuberculosis* at the sites of injection persisting for not less than 72 hours. The test is not valid unless the control animals fail to produce such reactions. With the help of callipers, measure the skin thickness around the sites of injection, 72 hours after inoculation.

Calculate the potency using standard statistical methods on the basis that the skin thickness are directly proportional to the logarithms of the concentrations of the Johnin Purified Protein Derivative.

Assay. To 5 ml add 2.5 ml of water and 2.5 ml of a 40 per cent w/v solution of *trichloro acetic acid*, mix, allow to stand for 30 minutes and centrifuge for 15 minutes. Discard the supernatant liquid and dissolve the residue in 0.5 ml of *5 M sodium hydroxide* solution. Transfer the solution to a Kjeldhal flask with the aid of 6 ml of *water*. Add about 0.1 g of a mixture of 100 parts of *potassium sulphate*, 10 parts of *cupric sulphate* and 5 parts of *selenium dioxide* and 1 ml of *nitrogen-free sulphuric acid*. Heat until the water evaporates. Continue the heating until a brown deposit appears. Dissolve the deposit in 0.5 ml of *hydrogen peroxide* solution, continue heating until white fumes appear and boil rapidly for at least 10 minutes. If a brown deposit again appears add a further 0.5 ml of *hydrogen peroxide* solution. Transfer to an ammonia distillation apparatus with the aid of 5 ml of water and add 5 ml of a 50 per cent w/v solution of *sodium hydroxide* to form a lower layer. Distil for 3 minutes, collecting the distillate in a mixture of 5 ml of a 2 per cent w/v solution of *boric acid* and 0.05 ml of a solution containing 0.066 per cent w/v of *methyl red* and 0.033 per cent w/v of *bromocresol green* in *ethanol (95 per cent)*. Titrate with *0.00447 M sulphuric acid*. Repeat the operation using 5 ml of the water in place of the preparation under examination. The difference between the titrations represents the ammonia liberated by the substance under examination.

1 ml of *0.00447 M sulphuric acid* is equivalent to 0.875 mg of purified protein derivative.

Storage. As stated under Veterinary Diagnostics.

Labelling. The label complies with the requirements stated under Veterinary Diagnostics and also states (1) the total volume in the container; (2) the name and percentage of any added preservative.

Mallein Purified Protein Derivative

Mallein Purified Protein Derivative is a preparation of a fluid synthetic medium in which *Pseudomonas mallei* (*Burkholderia mallei*) has been grown and which has been freed of the bacilli by filtration. The active fraction of the filtrate, which is predominantly protein in nature, is isolated by precipitation, washed and re-dissolved in *phosphate buffered saline* at about neutral pH. It is then distributed in sterile containers that are inert towards the contents and sealed so as to exclude microorganisms.

For standardisation, four ponies previously sensitised with *P. mallei* and two healthy ponies are injected intradermo-palpebrally with 0.2 ml of the preparation near the rim of the lower eye-lid of one eye. Typical reaction such as painful swelling of the palpebral tissue with mucopurulent discharge from the eye of sensitised animals and no such reaction in the healthy ponies should be seen. A similar test is performed with the Standard preparation maintained by the Indian Veterinary Research Institute, Izatnagar. When the reactions of the two preparations are comparable the batch is considered fit for use.

Mallein Purified Protein Derivative contains not less than 0.95 mg per ml and not more than 1.05 mg per ml of purified protein derivative.

CAUTION — Mallein Purified Protein Derivative is not dangerous to humans, but the organism from which it is prepared is pathogenic to man and may be fatal if an infection is not treated properly. Treatment should begin promptly if an infection is suspected.

Description. A yellowish to brown, viscous liquid.

Identification

Inject intradermally small doses of the preparation into suitable guinea-pigs that have been sensitised with killed *P. mallei* in an oily adjuvant; hot, tense, painful oedematous swellings occur at the sites of inoculation after 48 hours.

Tests

pH (2.4.24). 6.5 to 7.5.

Phenol (2.3.36) (*if present*). Not more than 0.5 per cent w/v.

Sterility (2.2.11). Complies with the test of sterility, with modifications stated under Johnin Purified Protein Derivative.

Abnormal toxicity (2.2.1). Inject 0.5 ml subcutaneously into each of two guinea pigs. Observe the animals for 7 days; none of the guinea pigs shows significant local or systemic reaction.

Assay. Carry out the Assay described under Johnin Purified Protein Derivative using 2.5 ml.

Storage. As stated under Veterinary Diagnostics.

Labelling. The label complies with the requirements stated under Veterinary Diagnostics and also states (1) the total volume in the container; (2) the name and percentage of any added preservative.

Purified Protein Derivative (PPD), Bovine Tuberculin

Purified Protein Derivative (PPD), Bovine Tuberculin is a preparation of a fluid synthetic medium in which reference *Mycobacterium bovis* strain has been grown and which has been freed from the bacilli by filtration. The final sterile product is distributed in sterile, tamper-evident glass containers, which are then sealed to prevent contamination with extraneous microorganisms.

Description. A yellowish-brown viscous liquid, or dry yellowish-brown powder or pellet.

Identification

Inject intradermally a range of graded doses at different sites into suitable albino guinea-pigs sensitised with tuberculosis. Depending upon the allergic status of the animal, the magnitude of dose and specificity of the product, reactions occur at the points of injection as diffused oedematous swellings with erythema with or without necrosis. When similar injections are given to non-sensitised guinea pigs no such reactions occur.

Tests

The preparation, reconstituted if necessary with a suitable liquid and diluted to provide a concentration appropriate to the particular test, complies with the requirements stated under Veterinary Diagnostics with the following modifications.

pH (2.4.24). 6.5 to 7.5.

Phenol (*if present*) (2.3.36). Not more than 0.5 per cent w/v.

Other tests. Complies with the tests stated under Veterinary Diagnostics.

Abnormal toxicity (2.2.1). Inject subcutaneously 0.5 ml of the preparation under examination into each of two guinea-pigs weighing not less than 250 g. No abnormal effects are produced within 7 days.

Potency. Carry out the biological assay of bovine tuberculin purified protein derivative described below:

Biological assay of bovine tuberculin purified protein derivative

The potency of bovine tuberculin purified protein derivative is determined by comparing the reactions produced in sensitised guinea-pigs by intradermal injection of a series of dilutions of the preparation under examination with those produced by known concentrations of the Standard preparation calibrated in International Units. Sensitise not less than 9 albino guinea-pigs each weighing between 300 and 450 g by deep intramuscular injection of 0.0001 mg of wet mass of living *M. bovis* strain suspended in 0.5 ml of *normal saline solution*. Not less than 4 weeks after the sensitisation of the guinea-pigs, shave their flanks to provide space for not more than 4 injection sites on each side. Alternatively, inactivated bacilli of *M. bovis*, 5 to7 weeks before the assay may be used to sensitize the guinea-pigs. The bacilli are suspended in buffer and made into an emulsion with Freund's incomplete adjuvant. A deep intramuscular injection is made on the medial side of the thigh, using a dose of 0.5 ml.

Standard preparation

The International Standard for Purified Protein derivative (PPD) of *Mycobacterium bovis* Tuberculin was donated to National Institute for Biological Standards and Control, Potters Bar, Hertfordshire, UK by Central Diergeneeskundig, Netherlands. With effect from 1st June 1998, the National Institute for Biological Standards and Control (NIBSC), Potters Bar, UK is the custodian and distributor of this material. Each ampoule contains 58,000 International Units of PPD and when reconstituted with 1.8 ml of diluting fluid will contain 1 mg PPD and 32,500 I.U. per ml or Indian standard of PPD.

Suggested method

Sensitise nine guinea-pigs, each weighing not less than 400 g. Inject each animal intramuscularly on the medial side of thigh with 0.0001 mg wet mass of living *M. bovis* strain suspended in 0.5 ml *physiological saline*. Test three dilutions of each of 3 preparations. Since it is practicable to give only 8 injections to an individual animals, a balanced incomplete Latin Square design is used, in which a different one of the 9 dilution is omitted from each animal. The remaining 8 dilutions are allocated to 4 sites.

Diluting fluid for assay

The diluent consists of isotonic *phosphate-buffered saline pH 7.3*, containing *tween 80* (0.0005 per cent) and is prepared by adding 0.5 ml of 1 per cent w/v solution of *tween 80* in *distilled water* to 1 litre of the following solution: *sodium phosphate dibasic dihydrate* - 7.60 g; *potassium dihydrogen phosphate* - 1.45 g; *sodium chloride* - 4.80 g; *distilled water* - 1 litre. Tuberculin diluted 1 in 100, 1 in 500 and 1 in 2,500 with 0.1 ml inoculum or 1 in 200, 1 in 1,000 and 1 in 5,000 ml with 0.2 ml inoculum generally will produce satisfactory results in guinea-pigs.

Measure the skin thickness at each site at the time of injection and after 72 hours. Calculate the results using standard statistical methods on the basis that the diameters of the lesions are directly proportional to the logarithms of the concentrations of the tuberculin.

Storage. As stated under Veterinary Diagnostics.

Labelling. The label/insert states (1) the number of units per dose of 0.1 ml or per ml or per mg; (2) the total volume in the container (for liquid preparation); (3) the name and proportion of any added substances; (5) the strain used; (6) the storage conditions; (7) the date after which the contents are not intended to be used.

Salmonella Abortus Equi H Antigen

Salmonella abortus Equi H Antigen is a suspension of killed organisms derived from a pure smooth culture of actively motile *Salmonella abortus equi*.

Identification

Gives specific agglutination when mixed with the serum of animals infected with *S. abortus equi* organisms.

Tests

Sterility (2.2.11). Complies with tests for sterility.

Opalescence of suspension. The opalescence of the preparation under examiantion corresponds to Brown's opacity standard tube No. 2.

Other tests. Complies with the tests stated under Veterinary Diagnostics.

Storage. As stated under Veterinary Diagnostics.

Salmonella Pullorum Colored Antigen

Salmonella pullorum Coloured Antigen is suspension of a pure smooth culture of representative strains of *Salmonella pullorum* in a solution containing 1.0 per cent *formalin*, 1.0 per cent *potassium dihydrogen phosphate*, 0.85 per cent *sodium chloride*, and stained with 1 per cent aqueous solution of *crystal violet* 3 ml to each 100 ml of the suspension.

Identification

Gives specific agglutination reaction when mixed with the serum of birds infected with *S. pullorum* or *S. gallinarum* but fails to react with serum from healthy birds.

Tests

Homogeneity. Antigen shall show no evidence of auto agglutination or unusual appearance such as presence of flakes.

pH (2.4.24). The pH of stained antigen shall be 4.6 ± 0.4. No pH level is specified for pullorum tube antigen but after dilution, as recommended for use it shall have a pH of 8.2 to 8.5.

Purity. Intermediate lot sample should be free from extraneous organisms as determined by microscopic examination and Gram staining.

Sterility (2.2.11). Complies with tests for sterility.

Assay. Centrifuge the preparation in a graduated hematocrit tube at 4000 rpm for 30 minutes. The packed cell volume is not less than 10 per cent.

Labelling. The label states (1) strains used for preparation; (2) the dose of test.

Expiry. Not less than 1 year from the date of manufacture.

Salmonella Pullorum Plain Antigen

Salmonella pullorum Plain Antigen is a suspension of dead bacterial cells of a pure smooth culture of a suitable strain of *Salmonella pullorum* in *saline solution* containing 0.5 per cent w/v of *phenol.*

Identification

Gives specific agglutination reaction when mixed with the serum of birds infected with of *S. pullorum* or *S. gallinarium* but fails to react with serum from healthy birds. It show positive reaction with known positive serum.

Tests

Opalescence of suspension. The opalescence of the preparation under examination corresponds to Brown's opacity standard tube No. 1.

Sterility (2.2.11). Complies with tests for sterility.

Other tests. Complies with the tests stated under Veterinary Diagnostics.

Storage. As stated under Veterinary Diagnostics.

Labelling. As stated under Veterinary Diagnostics.

Salmonella Pullorum Positive Serum

Salmonella pullorum Positive Serum is a liquid or freeze-dried antiserum raised against a suitable smooth strain of *S. pullorum* in rabbits. The liquid preparation contains 0.01 per cent w/v of *thiomersal* or other suitable preservative.

Identification

Gives specific agglutination reaction when mixed with a smooth strain of *S. pullorum* and gives a titre 1:1000 with tube test antigen.

Tests

Sterility (2.2.11). Complies with tests for sterility.

Other tests. Complies with the tests stated under Veterinary Diagnostics.

Storage. As stated under Veterinary Diagnostics.

Labelling. As stated under Veterinary Diagnostics.

VETERINARY IMMUNOSERA MONOGRAPHS

Clostridium Novyi Alpha Antitoxin 5011
Clostridium Perfringens Antitoxins 5012
Clostridium Perfringens Beta Antitoxin 5012
Clostridium Perfringens Epsilon Antitoxin 5014
Clostridium Tetani Antitoxin 5015

Clostridium Novyi Alpha Antitoxin

Clostridium Novyi Alpha Antitoxin for veterinary use is a preparation containing the globulins that have the power of specifically neutralising the alpha toxin formed by *Clostridium novyi*. It consists of the serum or a preparation obtained from the serum of animals immunised against *C. novyi* alpha toxin.

Production

Choice of Composition

The antitoxin is shown to be satisfactory with respect to safety and efficacy (2.7.12). For the latter, it shall be demonstrated, for each target species, that the product, when administered at the minimum recommended dose and according to the recommended schedule(s), provides a response or responses consistent with the claims made for the product.

Batch potency test

The test described under Potency is not necessarily carried out for routine testing of batches of antitoxin. It is carried out on one or more occasions as decided by or with the agreement of the competent authority. Where the test is not carried out, a suitable validated alternative test is carried out, the criteria for acceptance being set with reference to a batch of antitoxin that has given satisfactory results in the test described under Potency and that has been shown to be satisfactory with respect to immunogenicity in the target species. The following test may be used after a satisfactory correlation with the test described under Potency has been established.

Determine the level of antibodies against *C. novyi* alpha toxin in the batch of antitoxin using a suitable method such as an immunochemical method (2.2.14) or neutralisation in cell cultures. Use a homologous reference serum calibrated in International Unit of *Clostridium novyi* alpha antitoxin.

The International Unit is the specific neutralising activity for *C. novyi* alpha toxin contained in a stated amount of the International Standard, which consists of a quantity of dried immune horse serum. The equivalence in International Unit of the International Standard is stated by the World Health Organisation.

The potency of the finished product is expressed in International Units per ml and is shown to be not less than the minimum number stated on the label.

Identification

The antitoxin is shown, by a suitable immunochemical method (2.2.14), to react specifically with the alpha toxin formed by *C. novyi*.

Potency. The potency of *Clostridium novyi* alpha antitoxin is determined by comparing the dose necessary to protect mice or other suitable animals against the toxic effects of a fixed dose of *C. novyi* alpha toxin with the quantity of a reference preparation of *Clostridium novyi* alpha antitoxin, calibrated in International Units, necessary to give the same protection. For this comparison, a suitable preparation of *C. novyi* alpha toxin for use as a test toxin is required. The dose of the test toxin is determined in relation to the reference preparation; the potency of the antitoxin to be examined is determined in relation to the reference preparation using the test toxin.

Preparation of test toxin. Prepare the test toxin from a sterile filtrate of an approximately 5 days culture in liquid medium of *C. novyi* type B and dry by a suitable method. Select the test toxin by determining for mice the L+/10 dose and the LD_{50}, the observation period being 72 hours. A suitable alpha toxin contains not less than one L+/10 doses in 0.05 mg and not less than 10 LD_{50} in each L+/10 dose.

Determination of test dose of toxin. Prepare a solution of the reference preparation in a suitable liquid so that it contains 1 IU per ml. Prepare a solution of the test toxin in a suitable liquid so that 1 ml contains a precisely known amount such as 1 mg. Prepare mixtures of the solution of the reference preparation and the solution of the test toxin such that each mixture contains 1.0 ml of the solution of the reference preparation (1 IU), one of a series of graded volumes of the solution of the test toxin and sufficient of a suitable liquid to bring the total volume to 2.0 ml. Allow the mixtures to stand at room temperature for 60 minutes. Using not less than 2 mice, each weighing 17-22 g, for each mixture, inject a dose of 0.2 ml intramuscularly or subcutaneously into each mouse. Observe the mice for 72 hours. If all the mice die, the amount of toxin present in 0.2 ml of the mixture is in excess of the test dose. If none of the mice die, the amount of toxin present in 0.2 ml of the mixture is less than the test dose. Prepare similar fresh mixtures such that 2.0 ml of each mixture contains 1.0 ml of the solution of the reference preparation (1 IU) and 1 of a series of graded volumes of the solution of the test toxin separated from each other by steps of not more than 20 per cent and covering the expected end-point. Allow the mixtures to stand at room temperature for 60 minutes. Using not less than 2 mice for each mixture; inject a dose of 0.2 ml intramuscularly or subcutaneously into each mouse. Observe the mice for 72 hours. Repeat the determination at least once and combine the results of the separate tests that have been carried out with mixtures of the same composition so that a series of totals is obtained, each total representing the mortality due to a mixture of a given composition. The test dose of toxin is the amount present in 0.2 ml of that mixture which causes the death of one half of the total number of mice injected with it.

Determination of the potency of the antitoxin to be examined

Preliminary test. Dissolve a quantity of the test toxin in a suitable liquid so that 1 ml contains 10 times the test dose

(solution of the test toxin). Prepare mixtures of the solution of the test toxin and of the antitoxin to be examined such that each mixture contains 1.0 ml of the solution of the test toxin, one of a series of graded volumes of the antitoxin to be examined and sufficient of a suitable liquid to bring the final volume to 2.0 ml. Allow the mixtures to stand at room temperature for 60 minutes. Using not less than 2 mice for each mixture, inject a dose of 0.2 ml intramuscularly or subcutaneously into each mouse. Observe the mice for 72 hours. If none of the mice die, 0.2 ml of the mixture contains more than 0.1 IU. If all the mice die, 0.2 ml of the mixture contains less than 0.1 IU.

Final test. Prepare mixtures of the solution of the test toxin and of the antitoxin to be examined such that 2.0 ml of each mixture contains 1.0 ml of the solution of the test toxin and one of a series of graded volumes of the antitoxin to be examined, separated from each other by steps of not more than 20 per cent and covering the expected end-point as determined by the preliminary test. Prepare further mixtures such that 2.0 ml of each mixture contains 1.0 ml of the solution of the test toxin and one of a series of graded volumes of the solution of the reference preparation, in order to confirm the test dose of the toxin. Allow the mixtures to stand at room temperature for 60 minutes. Using not less than two mice for each mixture proceed as described in the preliminary test. The test mixture which contains 0.1 IU in 0.2 ml is that mixture which kills the same or almost the same number of mice as the reference mixture containing 0.1 IU in 0.2 ml. Repeat the determination at least once and calculate the average of all valid estimates. Estimates are valid only if the reference preparation gives a result within 20 per cent of the expected value.

The confidence limits (P = 0.95) have been estimated to be (a) 85 per cent and 114 per cent when 2 animals per dose are used; (b) 91.5 per cent and 109 per cent when 4 animals per dose are used; (c) 93 per cent and 108 per cent when 6 animals per dose are used.

The potency of the finished product is expressed in International Units per ml and is shown to be not less than the minimum number stated on the label.

Clostridium Perfringens Antitoxins

Clostridium Perfringens Antitoxins are preparations containing either the individual antitoxic globulins or a combination of the antitoxic globulins that have the specific power of neutralising either the beta toxin or the beta and epsilon toxins produced by *C. perfringens type B*, the beta toxin produced by *C. perfringens type C* or the epsilon toxin produced by *C. perfringens type D*.

The name Clostridium Perfringens Beta Antitoxin may be used for preparations stated to contain beta antitoxins only.

The names Clostridium Perfringens Epsilon Antitoxin or Clostridium Perfringens Type D Antitoxin may be used for preparations stated to contain epsilon antitoxins only.

The name Clostridium Perfringens Type B Antitoxin (synonym Lamb Dysentery Antiserum) may be used for preparations stated to contain both beta and epsilon antitoxin.

The antitoxins comply with the requirements stated under Veterinary Immunosera with the modifications below and with the requirements of one or both of the following two monographs according to the composition of the antitoxin as stated on the label.

Labelling. The label states (1) whether the preparation contains beta or epsilon antitoxin or both; (2) the type or types of *C. perfringens* against which the antitoxin will provide protection.

Clostridium Perfringens Beta Antitoxin

Clostridium Perfringens Beta Antitoxin for veterinary use is a preparation containing principally the globulins that have the power of specifically neutralising the beta toxin formed by *Clostridium perfringens* (types B and C). It consists of the serum or a preparation obtained from the serum of animals immunised against *C. perfringens* beta toxin.

Production

Choice of Composition

The antitoxin is shown to be satisfactory with respect to safety and efficacy (2.7.12). For the latter, it shall be demonstrated, for each target species, that the product, when administered at the minimum recommended dose and according to the recommended schedule(s), provides a response or responses consistent with the claims made for the product.

Batch Potency Test

The test described under Potency is not necessarily carried out for routine testing of batches of antitoxin. It is carried out on one or more occasions as decided by or with the agreement of the competent authority. Where the test is not carried out, a suitable validated alternative test is carried out, the criteria for acceptance being set with reference to a batch of antitoxin that has given satisfactory results in the test described under Potency and that has been shown to be satisfactory with respect to immunogenicity in the target species. The following test may be used after a satisfactory correlation with the test described under Potency has been established.

Determine the level of antibodies against *C. perfringens* beta toxin in the batch of antitoxin using a suitable method such as

an immunochemical method (2.2.14) or neutralisation in cell cultures. Use a homologous reference serum calibrated in International Units of C. perfringens beta antitoxin.

The International Unit is the specific neutralising activity for *C. perfringens* beta toxin contained in a stated amount of the International Standard, which consists of a quantity of dried immune horse serum. The equivalence in International Units of the International Standard is stated by the World Health Organisation.

The potency of the finished product is expressed in International Unit per ml and is shown to be not less than the minimum number stated on the label.

Identification

The antitoxin is shown, by a suitable immunochemical method (2.2.14), to react specifically with the beta toxin formed by *C. perfringens*.

Potency. The potency of *Clostridium perfringens* beta antitoxin is determined by comparing the dose necessary to protect mice or other suitable animals against the toxic effects of a fixed dose of *C. perfringens* beta toxin with the quantity of a reference preparation of Clostridium perfringens beta antitoxin, calibrated in International Units, necessary to give the same protection. For this comparison, a suitable preparation of *C. perfringens* beta toxin for use as a test toxin is required. The dose of the test toxin is determined in relation to the reference preparation; the potency of the antitoxin to be examined is determined in relation to the reference preparation using the test toxin.

Preparation of test toxin. Prepare the test toxin from a sterile filtrate of an early culture in liquid medium of *C. perfringens* type B or type C and dry by a suitable method. Select the test toxin by determining for mice the L+ dose and the LD_{50}, the observation period being 72 hours. A suitable beta toxin contains not less than one L+ dose in 0.2 mg and not less than 25 LD_{50} in each L+ dose.

Determination of test dose of toxin. Prepare a solution of the reference preparation in a suitable liquid so that it contains 5 IU per ml. Prepare a solution of the test toxin in a suitable liquid so that 1 ml contains a precisely known amount such as 10 mg. Prepare mixtures of the solution of the reference preparation and the solution of the test toxin such that each mixture contains 2.0 ml of the solution of the reference preparation (10 IU), one of a series of graded volumes of the solution of the test toxin and sufficient of a suitable liquid to bring the total volume to 5.0 ml. Allow the mixtures to stand at room temperature for 30 minutes. Using not less than two mice, each weighing 17-22 g, for each mixture, inject a dose of 0.5 ml intravenously or intraperitoneally into each mouse. Observe the mice for 72 hours. If all the mice die, the amount of toxin present in 0.5 ml of the mixture is in excess of the test dose. If none of the mice die, the amount of toxin present in 0.5 ml of the mixture is less than the test dose. Prepare similar fresh mixtures such that 5.0 ml of each mixture contains 2.0 ml of the solution of the reference preparation (10 IU) and 1 of a series of graded volumes of the solution of the test toxin separated from each other by steps of not more than 20 per cent and covering the expected end-point. Allow the mixtures to stand at room temperature for 30 minutes. Using not less than two mice for each mixture, inject a dose of 0.5 ml intravenously or intraperitoneally into each mouse. Observe the mice for 72 hours. Repeat the determination at least once and combine the results of the separate tests that have been carried out with mixtures of the same composition so that a series of totals is obtained, each total representing the mortality due to a mixture of a given composition. The test dose of toxin is the amount present in 0.5 ml of that mixture which causes the death of one half of the total number of mice injected with it.

Determination of the potency of the antitoxin to be examined

Preliminary test. Dissolve a quantity of the test toxin in a suitable liquid so that 2.0 ml contains 10 times the test dose (solution of the test toxin). Prepare mixtures of the solution of the test toxin and of the antitoxin to be examined such that each mixture contains 2.0 ml of the solution of the test toxin, one of a series of graded volumes of the antitoxin to be examined and sufficient of a suitable liquid to bring the final volume to 5.0 ml. Allow the mixtures to stand at room temperature for 30 minutes. Using not less than 2 mice for each mixture, inject a dose of 0.5 ml intravenously or intraperitoneally into each mouse. Observe the mice for 72 hours. If none of the mice die, 0.5 ml of the mixture contains more than 1 IU. If all the mice die, 0.5 ml of the mixture contains less than 1 IU.

Final test. Prepare mixtures of the solution of the test toxin and of the antitoxin to be examined such that 5.0 ml of each mixture contains 2.0 ml of the solution of the test toxin and one of a series of graded volumes of the antitoxin to be examined, separated from each other by steps of not more than 20 per cent and covering the expected end-point as determined by the preliminary test. Prepare further mixtures such that 5.0 ml of each mixture contains 2.0 ml of the solution of the test toxin and one of a series of graded volumes of the solution of the reference preparation, in order to confirm the test dose of the toxin. Allow the mixtures to stand at room temperature for 30 minutes. Using not less than 2 mice for each mixture proceed as described in the preliminary test.

The test mixture which contains 1 IU in 0.5 ml is that mixture which kills the same or almost the same number of mice as the reference mixture containing 1 International Unit in 0.5 ml. Repeat the determination at least once and calculate the

average of all valid estimates. Estimates are valid only if the reference preparation gives a result within 20 per cent of the expected value.

The confidence limits (P = 0.95) have been estimated to be (a) 85 per cent and 114 per cent when 2 animals per dose are used; (b) 91.5 per cent and 109 per cent when 4 animals per dose are used; (c)93 per cent and 108 per cent when 6 animals per dose are used.

The potency of the finished product is expressed in International Units per ml and is shown to be not less than the minimum number stated on the label.

Clostridium Perfringens Epsilon Antitoxin

Clostridium Perfringens Epsilon Antitoxin for veterinary use is a preparation containing the globulins that have the power of specifically neutralising the epsilon toxin formed by *C. perfringens* type D. It consists of the serum or a preparation obtained from the serum of animals immunised against *C. perfringens* epsilon toxin.

Production

Choice of Composition

The antitoxin is shown to be satisfactory with respect to safety and efficacy (2.7.12). For the latter, it shall be demonstrated, for each target species, that the product, when administered at the minimum recommended dose and according to the recommended schedule(s), provides a response or responses consistent with the claims made for the product.

Batch potency test

The test described under Potency is not necessarily carried out for routine testing of batches of antitoxin. It is carried out on one or more occasions as decided by or with the agreement of the competent authority. Where the test is not carried out, a suitable validated alternative test is carried out, the criteria for acceptance being set with reference to a batch of antitoxin that has given satisfactory results in the test described under Potency and that has been shown to be satisfactory with respect to immunogenicity in the target species. The following test may be used after a satisfactory correlation with the test described under Potency has been established.

Determine the level of antibodies against *C. perfringens* epsilon toxin in the batch of antitoxin using a suitable method such as an immunochemical method (2.2.14) or neutralisation in cell cultures. Use a homologous reference serum calibrated in International Units of Clostridium perfringens epsilon antitoxin.

The International Unit is the specific neutralising activity for *C. perfringens* epsilon toxin contained in a stated amount of the International Standard, which consists of a quantity of dried immune horse serum. The equivalence in International Units of the International Standard is stated by the World Health Organisation.

The potency of the finished product is expressed in International Units per ml and is shown to be not less than the minimum number stated on the label.

Identification

The antitoxin is shown, by a suitable immunochemical method (2.2.14), to react specifically with the epsilon toxin formed by *C. perfringens*.

Potency. The potency of Clostridium Perfringens epsilon antitoxin is determined by comparing the dose necessary to protect mice or other suitable animals against the toxic effects of a fixed dose of *C. Perfringens* epsilon toxin with the quantity of a reference preparation of Clostridium perfringens epsilon antitoxin, calibrated in International Units, necessary to give the same protection. For this comparison, a suitable preparation of *C. perfringens* epsilon toxin for use as a test toxin is required. The dose of the test toxin is determined in relation to the reference preparation, the potency of the antitoxin to be examined is determined in relation to the reference preparation using the test toxin.

Preparation of test toxin. Prepare the test toxin from a sterile filtrate of an early culture in liquid medium of *C. perfringens* type D and dry by a suitable method. Select the test toxin by determining for mice the L+/10 dose and the LD_{50}, the observation period being 72 hours. A suitable epsilon toxin contains not less than one L+/10 dose in 0.005 mg and not less than 20 LD_{50} in each L+/10 dose.

Determination of test dose of toxin. Prepare a solution of the reference preparation in a suitable liquid so that it contains 0.5 IU per ml. Prepare a solution of the test toxin in a suitable liquid so that 1 ml contains a precisely known amount such as 1 mg. Prepare mixtures of the solution of the reference preparation and the solution of the test toxin such that each mixture contains 2.0 ml of the solution of the reference preparation (1 IU), one of a series of graded volumes of the solution of the test toxin and sufficient of a suitable liquid to bring the total volume to 5.0 ml. Allow the mixtures to stand at room temperature for 30 minutes. Using not less than 2 mice, each weighing 17-22 g, for each mixture, inject a dose of 0.5 ml intravenously or intraperitoneally into each mouse. Observe the mice for 72 hours. If all the mice die, the amount of toxin present in 0.5 ml of the mixture is in excess of the test dose. If none of the mice die, the amount of toxin present in 0.5 ml of the mixture is less than the test dose. Prepare similar fresh mixtures such that 5.0 ml of each mixture contains 2.0 ml of the

solution of the reference preparation (1 IU) and 1 of a series of graded volumes of the solution of the test toxin, separated from each other by steps of not more than 20 per cent and covering the expected end-point. Allow the mixtures to stand at room temperature for 30 minutes. Using not less than 2 mice for each mixture, inject a dose of 0.5 ml intravenously or intraperitoneally into each mouse. Observe the mice for 72 hours. Repeat the determination at least once and combine the results of the separate tests that have been made with mixtures of the same composition so that a series of totals is obtained, each total representing the mortality due to a mixture of a given composition. The test dose of the toxin is the amount present in 0.5 ml of that mixture which causes the death of one half of the total number of mice injected with it.

Determination of the potency of the antitoxin to be examined

Preliminary test. Dissolve a quantity of the test toxin in a suitable liquid so that 2.0 ml contains 10 times the test dose (solution of the test toxin). Prepare mixtures of the solution of the test toxin and of the antitoxin to be examined such that each mixture contains 2.0 ml of the solution of the test toxin, one of a series of graded volumes of the antitoxin to be examined and sufficient of a suitable liquid to bring the final volume to 5.0 ml. Allow the mixtures to stand at room temperature for 30 minutes. Using not less than two mice for each mixture, inject a dose of 0.5 ml intravenously or intraperitoneally into each mouse. Observe the mice for 72 hours. If none of the mice die, 0.5 ml of the mixture contains more than 0.1 IU. If all the mice die, 0.5 ml of the mixture contains less than 0.1 IU.

Final test. Prepare mixtures of the solution of the test toxin and of the antitoxin to be examined such that 5.0 ml of each mixture contains 2.0 ml of the solution of the test toxin and one of a series of graded volumes of the antitoxin to be examined, separated from each other by steps of not more than 20 per cent and covering the expected end-point as determined by the preliminary test. Prepare further mixtures such that 5.0 ml of each mixture contains 2.0 ml of the solution of the test toxin and one of a series of graded volumes of the solution of the reference preparation to confirm the test dose of the toxin. Allow the mixtures to stand at room temperature for 30 minutes. Using not less than two mice for each mixture proceed as described in the preliminary test. The test mixture which contains 0.1 IU in 0.5 ml is that mixture which kills the same or almost the same number of mice as the reference mixture containing 0.1 IU in 0.5 ml. Repeat the determination at least once and calculate the average of all valid estimates. Estimates are valid only if the reference preparation gives a result within 20 per cent of the expected value.

The confidence limits (P = 0.95) have been estimated to be (a) 85 per cent and 114 per cent when 2 animals per dose are used; (b) 91.5 per cent and 109 per cent when 4 animals per dose are used; (c) 93 per cent and 108 per cent when 6 animals per dose are used.

The potency of the finished product is expressed in International Unit per ml and is shown to be not less than the minimum number stated on the label.

Clostridium Tetani Antitoxin

Tetanus Antitoxin

Tetanus antitoxin for veterinary use is a preparation containing principally the globulins that have the power of specifically neutralising the neurotoxin formed by *Clostridium tetani*. It consists of the serum or a preparation obtained from the serum of animals immunised against tetanus toxin.

Production

Choice of Composition

The antitoxin is shown to be satisfactory with respect to safety and efficacy (2.7.12). For the latter, it shall be demonstrated, for each target species, that the product, when administered at the minimum recommended dose and according to the recommended schedule(s), provides a response or responses consistent with the claims made for the product. The ability of the product to neutralise the neurotoxin formed by *C. tetani* must also be demonstrated, e.g. by conducting the test in mice as described below.

Demonstration of neurotoxin neutralisation

The ability of tetanus antitoxin to neutralise the neurotoxin of *C. tetani* is determined by establishing the dose necessary to protect mice (or guinea-pigs) against the toxic effects of a fixed dose of tetanus toxin. The test must be conducted in parallel with a test of a reference preparation of tetanus antitoxin, calibrated in International Units, using a quantity expected to give the same protection. The ability of the test antitoxin to neutralise the neurotoxin (potency) can then be expressed in International Units. For this study, a suitable preparation of tetanus toxin for use as a test toxin is required. The dose of the test toxin is determined in relation to the reference preparation; the potency of the antitoxin to be examined is determined in relation to the reference preparation using the test toxin.

Preparation of test toxin. Prepare the test toxin from a sterile filtrate of an 8-10 days culture in liquid medium of *C. tetani*. A test toxin may be prepared by adding this filtrate to *glycerol* in the proportion of 1 volume of filtrate to 1 to 2 volumes of *glycerol*. The solution of test toxin may be stored at or slightly below 0°. The toxin may also be dried by a suitable method.

Select the test toxin by determining for mice the Lp/10 dose and the paralytic dose 50 per cent. A suitable toxin contains not less than 1000 times the paralytic dose 50 per cent in 1 Lp/10 dose.

Lp/10 dose (Limes paralyticum). This is the smallest quantity of toxin which when mixed with 0.1 International Unit of antitoxin and injected subcutaneously into mice (or guinea-pigs) causes tetanic paralysis in the animals on or before the 4th day after injection.

Paralytic dose 50 per cent. This is the quantity of toxin which when injected subcutaneously into mice (or guinea-pigs) causes tetanic paralysis in one half of the animals on or before the 4th day after injection.

Determination of test dose of toxin. Reconstitute or dilute the reference preparation with a suitable liquid so that it contains 0.5 IU per ml. Measure or weigh a quantity of the test toxin and dilute with or dissolve in a suitable liquid. Prepare mixtures of the solution of the reference preparation and the solution of the test toxin so that each mixture will contain 0.1 IU of antitoxin in the volume chosen for injection and one of a series of graded volumes of the solution of the test toxin, separated from each other by steps of not more than 20 per cent and covering the expected end-point. Adjust each mixture with a suitable liquid to the same final volume (0.4 ml to 0.6 ml if mice are used for the test or 4.0 ml if guinea-pigs are used). Allow the mixtures to stand at room temperature for 60 minutes. Using not less than 2 animals for each mixture, inject the chosen volume subcutaneously into each animal. Observe the animals for 96 hours and make daily records of the degree of tetanus developing in each group of animals. Repeat the test at least once and calculate the test dose as the mean of the different tests. The test dose of the toxin is the amount present in that mixture which causes tetanic paralysis in one half of the total number of animals injected with it.

Determination of the neutralising ability of the antitoxin to be examined

Preliminary test. Measure or weigh a quantity of the test toxin and dilute with or dissolve in a suitable liquid so that the solution contains 5 test doses per ml (solution of the test toxin). Prepare mixtures of the solution of the test toxin and of the antitoxin to be examined so that for each mixture the volume chosen for injection contains the test dose of toxin and one of a series of graded volumes of the antitoxin to be examined. Adjust each mixture to the same final volume with a suitable liquid. Allow the mixtures to stand at room temperature for 60 minutes. Using not less than 2 animals for each mixture, inject the chosen volume subcutaneously into each animal. Observe the animals for 96 hours and make daily records of the degree of tetanus developing in each group of animals. Using the results, select suitable mixtures for the final test.

Final test. Prepare mixtures of the solution of the test toxin and of the antitoxin to be examined so that for each mixture the volume chosen for the injection contains the test dose of toxin and one of a series of graded volumes of the antitoxin to be examined, separated from each other by steps of not more than 20 per cent and covering the expected end-point as determined in the preliminary test. Prepare further mixtures with the same amount of test toxin and graded volumes of the reference preparation, centred on 0.1 IU in the volume chosen for injection, to confirm the test dose of the toxin. Adjust each mixture to the same final volume with a suitable liquid. Allow the mixtures to stand at room temperature for 60 minutes. Using not less than 2 animals for each mixture, inject the chosen volume subcutaneously into each animal. Observe the animals for 96 hours and make daily records of the degree of tetanus developing in each group of animals. The test mixture which contains 0.1 IU in the volume injected is that mixture which causes tetanic paralysis in the same, or almost the same, number of animals as the reference mixture containing 0.1 IU in the volume injected. Repeat the determination at least once and calculate the mean of all valid estimates. Estimates are valid only if the reference preparation gives a result within 20 per cent of the expected value.

The confidence limits (P = 0.95) have been estimated to be: (a) 85 per cent and 114 per cent when 2 animals per dose are used; (b) 91.5 per cent and 109 per cent when 3 animals per dose are used; (c) 93 per cent and 108 per cent when 6 animals per dose are used.

Identification

The antitoxin is shown, by a suitable immunochemical method (2.2.14), to react specifically with the neurotoxin formed by *C. tetani*. The potency test may also serve for identification.

Potency. Determine the titre of antibodies against the neurotoxin formed by *C. tetani* using a suitable immunochemical method (2.2.14) such as a toxin-binding-inhibition test (ToBI test) and a homologous reference serum, calibrated in International Units per ml.

The International Unit is the specific neutralising activity for tetanus toxin contained in a stated amount of the International Standard which consists of a quantity of dried immune horse serum. The equivalence in International Units of the International Standard is stated by the World Health Organisation.

The potency of the finished product is expressed in International Unit per ml and is shown to be not less than the minimum number stated on the label.

VETERINARY SURGICAL MONOGRAPHS

Sterile Braided Silk Suture in Distributor 5019
Sterile Catgut in Distributor 5019
Sterile Linen Thread in Distributor 5020
Sterile Non-absorbable Strands in Distributor 5020
Sterile Poly (Ethylene Terephthalate) Suture in Distributor ... 5022
Sterile Polyamide 6 Suture in Distributor 5023
Sterile Polyamide 6/6 Suture, in Distributor 5023

Sterile Braided Silk Suture in Distributor

Sterile Braided Silk Suture in Distributor for veterinary use is obtained by braiding a variable number of threads, according to the diameter required, of degummed silk obtained from the cocoons of the silkworm *Bombyx mori L.* It may be coloured with colouring matter authorised by the competent authority. The suture is sterilised.

Identification

A. Dissect the end of a strand, using a needle or fine tweezers, to isolate a few individual fibres. The fibres are sometimes marked with very fine longitudinal striations parallel to the axis of the strand. Examined under a microscope, a cross-section is more or less triangular or semi-circular, with rounded edges and without a lumen.

B. Impregnate isolated fibres with *iodinated potassium iodide solution*. The fibres are coloured pale yellow.

Tests

It complies with the tests prescribed in the monograph on strands, sterile non-absorbable, in distributor of veterinary use.

Storage. Store protected from light and heat.

Labelling. The label states (1) The gauge number; (2) the length in centimetres or in metres; (3) where appropriate, that the strand is coloured and intended to remain so during use.

Sterile Catgut in Distributor

Sterile Catgut in Distributor for veterinary use consists of strands prepared from collagen taken from the intestinal membranes of mammals. After cleaning, the membranes are split longitudinally into strips of varying width, which, when assembled in small numbers, according to the diameter required, are twisted under tension, dried, polished, selected and sterilised. The strands may be treated with chemical substances such as chromium salts to prolong absorption and glycerol to make them supple, provided such substances do not reduce tissue acceptability.

The strand is presented in a distributor that allows the withdrawal and use of all or part of it in aseptic conditions. The design of the distributor is such that with suitable handling the sterility of the content is maintained even when part of the strand has been withdrawn. It may be stored dry or in a preserving liquid to which an antimicrobial preservative but not an antibiotic may be added.

Tests

If stored in a preserving liquid, remove the strand from the distributor and measure promptly and in succession the length, diameter and breaking load. If stored in the dry state, immerse the strand in alcohol or a 90 per cent v/v solution of 2-propanol for 24 hours and proceed with the measurements as indicated above.

Length. Measure the length without applying to the strand more tension than is necessary to keep it straight. The length is not less than 95 per cent of the length stated on the label. If the strand consists of several sections joined by knots, the length of each section is not less than 2.5 m.

Diameter. Carry out the test using a suitable instrument capable of measuring with an accuracy of at least 0.002 mm and having a circular pressure foot 10 mm to 15 mm in diameter. The pressure foot and the moving parts attached to it are weighted so as to apply a total load of 100 ± 10 g to the strand being tested. When making the measurements, lower the pressure foot slowly to avoid crushing the strand. Make not less than one measurement per 2 m of length. If the strand consists of several sections joined by knots, make not less than three measurements per section. In any case make not less than twelve measurements. Make the measurements at points evenly spaced along the strand or along each section. The strand is not subjected to more tension than is necessary to keep it straight during measurement. The average of the measurements carried out on the strand being tested and not less than two-thirds of the individual measurements are within the limits given in the column A under in Table 1 for the gauge number concerned. None of the measurements is outside the limits given in the columns under B in Table 1 for the gauge number concerned.

Minimum breaking load. The minimum breaking load is determined over a simple knot formed by placing one end of a strand held in the right hand over the other end held in the left hand, passing one end over the strand and through the loop so formed and pulling the knot tight.

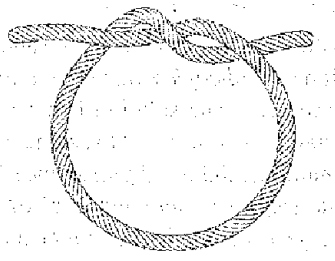


Fig.1: Simple knot

Make not less than one measurement per 2 m of length. If the strand consists of several sections joined by knots, make not less than three measurements per section and, in any case,

not less than one measurement per 2 m of length at points evenly spaced along the strand or along each section. Determine the breaking load using a suitable tensilometer. The apparatus has two clamps for holding the strand, one of which is mobile and is driven at a constant rate of 30 cm per minute. The clamps are designed so that the strand being tested can be attached without any possibility of slipping. At the beginning of the test the length of strand between the clamps is 12.5 cm to 20 cm and the knot is midway between the clamps. Set the mobile clamp in motion and note the force required to break the strand. If the strand breaks in a clamp or within 1 cm of it, the result is discarded and the test repeated on another part of the strand. The average of all the results, excluding those legitimately discarded, is equal to or greater than the value in column C and no value is less than that given in column D in Table 1 for the gauge number concerned.

Table-1

Gauge number	Diameter (millimeters)				Breaking load (newtons)	
	A		B		C	D
	Min.	Max.	Min.	Max.		
1	0.100	0.149	0.085	0.175	1.8	0.4
1.5	0.150	0.199	0.125	0.255	3.8	0.7
2	0.200	0.249	0.175	0.275	7.5	1.8
2.5	0.250	0.299	0.225	0.325	10	3.8
3	0.300	0.349	0.275	0.375	12.5	7.5
3.5	0.350	0.399	0.325	0.450	20	10
4	0.400	0.499	0.375	0.550	27.5	12.5
5	0.500	0.599	0.450	0.650	38.4	20.0
6	0.600	0.699	0.550	0.750	45.0	27.5
7	0.700	0.799	0.650	0.850	60.0	38.0
8	0.800	0.899	0.750	0.950	70.0	45.0

Soluble chromium compounds. Place 0.25 g in a conical flask containing 1 ml of water per 10 mg of catgut. Stopper the flask; allow standing at 37 ± 0.5° for 24 hour and cool, decant the liquid. Transfer 5 ml to a small test tube and add 2 ml of a 1 per cent solution of *diphenylcarbazide* in *alcohol* and 2 ml of *dilute sulphuric acid*. The solution is not more intensely coloured than a standard prepared at the same time using 5 ml of a solution containing 2.83 µg of *potassium dichromate* per ml, 2 ml of dilute *sulphuric acid* and 2 ml of a 10 per cent solution of *diphenylcarbazide* in *alcohol* (1 ppm of Cr).

Sterility (2.2.11). Complies with the test for sterility.

Storage. Store protected from light and heat.

Labelling. The label states (1) The gauge number; (2) the length in centimetres or in metres.

Sterile Linen Thread in Distributor

Sterile Linen Thread in Distributor for veterinary use consists of the pericyclic fibres of the stem of *Linum usitatissimum* L. The elementary fibres, 2.5 cm to 5 cm long, are assembled in bundles 30 cm to 80 cm long and spun into continuous lengths of suitable diameter. The thread may be creamy-white or may be coloured with colouring matter authorised by the competent authority. The thread is sterilised.

Identification

A. Dissect the end of a thread, using a needle or fine tweezers, to isolate a few individual fibres. Examined under a microscope, the fibres are seen to be 12 µm to 31 µm wide and, along the greater part of their length, have thick walls, sometimes marked with fine longitudinal striations, and a narrow lumen. The fibres gradually narrow to a long, fine point. Sometimes there are unilateral swellings with transverse lines.

B. Impregnate isolated fibres with *iodinated zinc chloride solution*. The fibres are coloured violet-blue.

Tests

It complies with the tests prescribed in the monograph on Strands, sterile non- absorbable, in distributor.

If stored in a dry state, expose to an atmosphere with a relative humidity of 65 ± 5 per cent at 20° ± 2° for 4 hours immediately before measuring the diameter and for the determination of minimum breaking load immerse in water at room temperature for 30 minutes immediately before carrying out the test.

Storage. Store protected from light and heat.

Labelling. The label states (1) The gauge number; (2) the length in centimetres or in metres; (3) where appropriate, that the strand is coloured and intended to remain so during use.

Sterile Non-absorbable Strands in Distributor

The statements in this monograph are intended to be read in conjunction with the individual monographs on sterile non-absorbable strands in distributor for veterinary use in the Pharmacopoeia. The requirements do not necessarily apply to sterile non- absorbable strands which are not the subject of such monographs.

Sterile Non-absorbable Strands in Distributor for veterinary use are strands which, when introduced into a living organism, are not metabolised by that organism and sterile non-absorbable strands vary in origin, which may be animal,

vegetable or synthetic. They occur as cylindrical monofilaments or as multifilament strands. Multifilament strands consist of elementary fibres which are assembled by twisting, cabling or braiding. Such strands may be sheathed. Sterile non- absorbable strands may be treated to render them non-capillary, and they may be coloured with colouring matter or pigments authorised by the competent authority, the strands are sterilised.

They are presented in a suitable distributor that allows the withdrawal and use of all or part of the strand in aseptic conditions. The design of the distributor is such that with suitable handling the sterility of the content is maintained even when part of the strand has been removed. They may be stored dry or in a preserving liquid to which an antimicrobial preservative but not an antibiotic may be added.

Tests

Remove the strand from the distributor and measure promptly and in succession the length, diameter and minimum breaking load.

Length. Measure the length in the condition in which the strand is presented and without applying more tension than is necessary to keep it straight. The length of the strand is not less than 95 per cent of the length stated on the label.

Diameter. Unless otherwise prescribed, measure the diameter by the following method using the strand in the condition in which it is presented. Use a suitable instrument capable of measuring with an accuracy of at least 0.002 mm and having a circular pressor foot 10 mm to 15 mm in diameter. The pressure foot and the moving parts attached to it are weighted so as to apply a total load of 100 ± 10 g to the strand being tested. When making the measurements, lower the pressure foot slowly to avoid crushing the strand. Make not less than one measurement per 2 m of length and in any case not less than 12 measurements at points evenly spaced along the strand. During the measurement submit monofilament strands to a tension not greater than that required to keep them straight. Submit multifilament strands to a tension not greater than one-fifth of the minimum breaking load shown in column C of Table 1 appropriate to the gauge number and type of material concerned or 10 N whichever is less. For multifilament strands of gauge number above 1.5 make two measurements at each point, the second measurement being made after rotating the strand through 90°. The diameter of that point is the average of the two measurements.

The average of the measurements carried out on the strand being tested and not less than two-thirds of the individual measurements are within the limits given in the columns under A in Table 1 for the gauge number concerned. None of the

Table-1

Gauge number	Diameter (millimeters)				Minimum breaking load (newtons)			
					Linen thread		All other non-absorbablestrands	
	A		B		C	D	C	D
	Min.	Max.	Min.	Max.				
0.5	0.050	0.069	0.045	0.085	---	—	1.0	0.35
0.7	0.070	0.099	0.060	0.125	1.0	0.3	1.5	0.60
1	0.100	0.149	0.085	0.175	2.5	0.6	3.0	1.0
1.5	0.150	0.199	0.125	0.255	5.0	1.0	5.0	1.5
2	0.200	0.249	0.175	0.275	8.0	2.5	9.0	3.0
2.5	0.250	0.299	0.225	0.325	9.0	5.0	13.0	5.0
3	0.300	0.349	0.275	0.375	11.0	8.0	15.0	9.0
3.5	0.350	0.399	0.325	0.450	15.0	9.0	22.0	13.0
4	0.400	0.499	0.375	0.550	18.0	11.0	27.0	15.0
5	0.5000	0.599	0.450	0.650	26.0	15.0	35.0	22.0
6	0.600	0.699	0.500	0.750	37.0	18.0	50.0	27.0
7	0.700	0.799	0.650	0.850	50.0	26.0	62.0	35.0
8	0.800	0.899	0.750	0.950	65.0	37.0	73.0	50.0

measurements is outside the limits given in the columns under B in Table 1 for the gauge number concerned.

Minimum breaking load

Unless otherwise prescribed, determine the minimum breaking load by the following method using the strand in the condition in which it is presented. The minimum breaking load is determined over a simple knot formed by placing one end of a strand held in the right hand over the other end held in the left hand, passing one end over the strand and through the loop so formed see and pulling the knot tight.

Make not less than one measurement per 2 meter of length at points evenly spaced along the strand. Determine the breaking load using a suitable tensilometer. The apparatus has two clamps for holding the strand, one of which is mobile and is driven at a constant rate of 30 cm per minute. The clamps are designed so that the strand being tested can be attached with-out any possibility of slipping. At the beginning of the test the length of strand between the clamps is 12.5 cm to 20 cm and the knot is midway between the clamps. Set the mobile clamp in motion and note the force required to break the strand. If the strand breaks in a clamp or within 1 cm of it, the result is discarded and the test repeated on another part of the strand. The average of all the results, excluding those legitimately dis-carded, is equal to or greater than the value in column C and no value is less than that given in column D in Table 1 for the gauge number and type of material concerned.

Extractable colour

Strands that are dyed and intended to remain so during use comply with the test for extractable colour. Place 0.25 g of the strand to be examined in a conical flask, add 25.0 ml of *water* and cover the mouth of the flask with a short-stemmed funnel. Boil for 15 minutes, cool and adjust to the original volume with *water*. Depending on the colour of the strand, prepare the appropriate reference solution as described in Table 2 using the primary colour solutions (2.4.1).

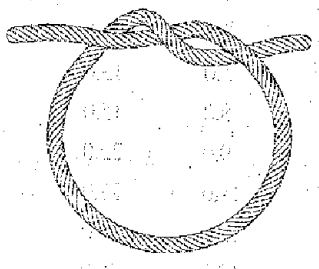


Fig.1: Simple knot

Table 2

Colour of strand	Composition of reference solution (parts by volume)			
	Cobalt Chloride Colorimetric Solution (CCS)	Ferric Chloride Colorimetric Solution (FCS)	Cupric Sulphate Colorimetric Solution CSS)	Water
Yellow-brown	0.2	1.2	—	8.6
Pink-red	1.0	—	—	9.0
Green-blue	—	—	2.0	8.0
Violet	1.6	—	8.4	—

The test solution is not more intensely coloured than the appropriate reference solution.

Sterility (2.2.11). Complies with the test for sterility.

Storage. Store protected from light and heat.

Labelling. The label states (1) The gauge number; (2) the length in centimetres or in metres; (3) where appropriate, that the strand is coloured and intended to remain so during use.

Sterile Poly (Ethylene Terephthalate) Suture in Distributor

Sterile Poly (Ethylene Terephthalate) Suture in Distributor for veterinary use is obtained by drawing poly (ethylene terephthalate) through a suitable die. The suture is prepared by braiding very fine filaments in suitable numbers, depending on the gauge required. It may be whitish in colour, or may be coloured with authorised colouring matter or pigments authorised by the competent authority. The suture is sterilised.

Description. It is practically insoluble in most of the usual organic solvents, but is attacked by strong alkaline solutions. It is incompatible with phenols.

Identification

A. It dissolves with difficulty when heated in *dimethyl-formamide* and in *dichlorobenzene*.

B. To 50 mg add 10 ml of *hydrochloric acid*. The material remains intact even after immersion for 6 hours.

Tests

It complies with the tests prescribed in the monograph on Sterile Non-absorbable Strands in distributor.

Storage. Store protected from light and heat.

Labelling. The label states (1) The gauge number; (2) the length in centimetres or in metres; (3) where appropriate, that the strand is coloured and intended to remain so during use.

Sterile Polyamide 6 Suture in Distributor

Sterile Polyamide 6 Suture in Distributor for veterinary use is obtained by drawing through a suitable die a synthetic plastic material formed by the polymerisation of caprolactam. It consists of smooth, cylindrical monofilaments or braided filaments, or lightly twisted strands sheathed with the same material. It may be coloured with colouring matter authorised by the competent authority. The suture is sterilised.

Description. It is practically insoluble in the usual organic solvents, it is not attacked by dilute alkaline solutions (for example 10 per cent solution of *sodium hydroxide*) but is attacked by dilute mineral acids (for example 2.0 per cent *sulphuric acid*), by hot *glacial acetic acid* and by 70 per cent *m/m formic acid.*

Identification

A. Heat about 50 mg with 0.5 ml of *hydrochloric acid* in a sealed glass tube at 110° for 18 hours and allow to stand for 6 hours, no crystals appear.

B. Take 50 mg add 10 ml of *hydrochloric acid*, the material disintegrates in the cold and dissolves completely within a few minutes.

C. It dissolves in a 70 per cent *m/m* solution of *anhydrous formic acid.*

Tests

It complies with the tests prescribed in the monograph on Strands Sterile Non-absorbable in distributor.

Monomer and oligomers. In a continuous-extraction apparatus, treat 1.0 g with 30 ml of *methanol* at a rate of at least three extractions per hour for 7 hours. Evaporate the extract to dryness, dry the residue at 110° for 10 minutes and allow cooling in a desiccator and weighing. The residue weighs not more than 20 mg, (2.0 per cent).

Storage. Store protected from light and heat.

Labelling. The label states (1) The gauge number; (2) the length in centimetres or in metres; (3) where appropriate, that the strand is coloured and intended to remain so during use.

Sterile Polyamide 6/6 Suture, in Distributor

Sterile Polyamide 6/6 Suture in Distributor for veterinary use is obtained by drawing through a suitable die a synthetic plastic material formed by the polycondensation of hexamethylenediamine and adipic acid. It consists of smooth, cylindrical monofilaments or braided filaments, or lightly twisted strands sheathed with the same material. It may be coloured with authorised colouring matter or pigments authorised by the competent authority. The suture is sterilised.

Description. It is practically insoluble in the usual organic solvents; it is not attacked by dilute alkaline solutions (for example 10.0 per cent solution of *sodium hydroxide*) but is attacked by dilute mineral acids (for example 2.0 per cent *sulphuric acid*) by hot *glacial acetic acid* and by 80 per cent *m/m formic acid.*

Identification

A. In contact with a flame it melts and burns, forming a hard globule of residue and gives off a characteristic odour resembling that of celery.

B. Place 50 mg in an ignition tube held vertically and heat gently until thick fumes are evolved. When the fumes fill the tube, withdraw it from the flame and insert a strip of *nitrobenzaldehyde paper*. A violet-brown colour slowly appears on the paper and fades slowly in air; it disappears immediately on washing with dilute *sulphuric acid.*

C. Take 50 mg add 10 ml of *hydrochloric acid.* The material disintegrates in the cold and dissolves within a few minutes.

D. It does not dissolve in a 70 per cent *m/m* solution of *anhydrous formic acid* but dissolves in an 80 per cent *m/m* solution of *anhydrous formic acid.*

Tests

It complies with the tests prescribed in the monograph on strands, sterile non-absorbable, in distributor.

Storage. Store protected from light and heat.

Labelling. The label states (1) The gauge number; (2) the length in centimetres or in metres; (3) where appropriate, that the strand is coloured and intended to remain so during use.

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