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Herbal Drug Extracts

General Notices

Extracts

(Ph. Eur. monograph 0765)

Herbal Drug Extracts comply with the requirements of the European Pharmacopoeia. These requirements are reproduced in the British Pharmacopoeia.

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DEFINITION

Herbal drug extracts are liquid (liquid extraction preparations), semi-solid (soft extracts and oleoresins) or solid (dry extracts) preparations obtained from *Herbal drugs (1433)* using suitable solvents.

An extract is essentially defined by the quality of the herbal drug, by its production process (extraction solvent(s), method of processing, etc.) and by its specifications.

European Pharmacopoeia monographs for extracts cover the genuine (native) extract and, where present, excipients.

Different types of extract may be distinguished.

Standardised extracts

Are adjusted to a defined content of one or more constituents with known therapeutic activity. This is achieved by adjustment of the extract with inert excipients or by blending batches of the extract.

Quantified extracts

Are adjusted to one or more active markers, the content of which is controlled within a limited, specified range. Adjustments are made by blending batches of the extract.

Other extracts

Are not adjusted to a particular content of constituents. For control purposes, one or more constituents are used as analytical markers. The minimum content for these analytical markers is given in an individual monograph.

PRODUCTION

Herbal drugs, solvents and other materials used for the preparation of extracts are of suitable quality and where applicable comply with the requirements of any relevant monograph in the European Pharmacopoeia. Where justified, herbal drugs used for the production of extracts may exceed the limits for heavy metals specified in the monograph *Herbal drugs (1433)* provided that the resulting extract satisfies the requirements for heavy metals (see Tests).

Different batches of the herbal drug which are compliant with the relevant monograph, or in the absence of an individual monograph with other suitable specifications, may be combined prior to extraction, for example for the purpose of achieving the quantity of herbal drug required for the production process or, in the case of standardised and quantified extracts, to achieve a certain range of content for one or more constituents in the herbal drug to be extracted. The herbal drug may also undergo a preliminary treatment, for example, grinding, inactivation of enzymes or defatting. In addition, unwanted constituents (e.g. toxic constituents) or unwanted matter (e.g. insoluble matter) may be removed at a suitable stage in the production process.

Where solvents are recovered from the production process, such recovered or recycled solvents may be used, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before re-use or admixture with other approved materials. Water used for the production of extracts complies with the requirements of the monograph *Water for preparation of extracts (2249)*.

Where applicable, miscella (extraction liquors) are concentrated to the intended consistency using suitable methods, usually under reduced pressure and at a temperature at which deterioration of the constituents is reduced to a minimum. Essential oils that have been separated during processing may be restored to the extracts at an appropriate stage in the production process. Suitable excipients may be added at various stages of the production process for technological reasons (for example, as part of the drying process or to improve the homogeneity or consistency of an extract). For standardised extracts, suitable inert excipients may also be added to adjust one or more constituents to a defined content. For quantified extracts and 'other' extracts, the addition of inert excipients to adjust the content of assayed constituents is not permitted. Excipients are included for technological reasons only, and the manufacturer must declare the content of such excipients as a fixed percentage. In some applications, an excipient may be added in a narrow percentage range (e.g. silicon dioxide between 0.1-0.5 per cent, to improve flowability of the extract). The proposed range must be justified by the manufacturer. Suitable stabilisers, antioxidants and antimicrobial preservatives may be added to extracts where justified and authorised.

Extraction with a given solvent leads to a typical content of selected constituents in the extracted dry matter; during production of standardised and quantified extracts, purification procedures may be applied that increase the content of these selected constituents with respect to the expected values; such extracts are referred to as 'refined'.

IDENTIFICATION

Extracts are identified using suitable methods.

TESTS

Where applicable, as a result of analysis of the herbal drug used for production and in view of the production process, tests for microbiological quality (*5.1.4* or *5.1.8*), heavy metals (*2.4.27*), aflatoxins (*2.8.18*), ochratoxin A (*2.8.22*) and pesticide residues (*2.8.13*) in the extracts may be necessary. Where a test for heavy metals is carried out, the same limits for heavy metals as those given in the monograph *Herbal drugs (1433)* are applicable to extracts unless otherwise stated in an individual extract monograph or unless otherwise justified and authorised.

ASSAY

Extracts are assayed by a suitable method, unless otherwise justified.

Standardised extracts

The Definition section of an individual monograph on a standardised extract states the content of the assayed constituents as either a defined single content or within a defined range of content.

Defined single content For example, in the monograph *Ipecacuanha liquid extract, standardised (1875)*, the content of assayed constituents is stated as 1.80 per cent to 2.20 per cent. In this case, the declaration is based on a defined single content of 2.0 per cent with a tolerance of ± 10 per cent. The acceptable tolerance is usually within the range ± 5 per cent to ± 10 per cent taking into account the nature of the extract and the method of assay.

Defined range of content For example, in the monograph *Frangula bark dry extract, standardised (1214)*, the content of assayed constituents is stated as 15.0 per cent to 30.0 per cent. In this case, it is intended that an extract will consistently be produced to a defined single content selected from within the defined range taking into account an acceptable tolerance. Where there is an individual monograph in the pharmacopoeia for a standardised extract with a defined range of content, the acceptable tolerance will be stated in the individual monograph (for example, for *Frangula bark dry extract, standardised (1214)*, the acceptable tolerance is stated as ± 10 per cent relative to the declared content).

Quantified extracts

The content of assayed constituents must be within the values given in the Definition section of an individual monograph.

Other extracts

The content of assayed constituents must not be lower than the minimum value given in the Definition section of an individual monograph. Where justified and authorised, this does not preclude the selection of alternative constituents as a basis for assay using a corresponding validated analytical method, which may be more appropriate to the physical and/or chemical properties of the medicinal product into which the extract is to be incorporated. Where alternative constituents are selected for assay, a suitable minimum value for such constituents must be established.

LABELLING

The label states:

— the herbal drug used;

— where applicable, that fresh herbal drug has been used;

— the form of the extract (for example, liquid, tincture, soft, oleoresin or dry);

— where applicable, that the extract is standardised or quantified;

— for standardised extracts, the defined content of constituents with known therapeutic activity;

— for quantified extracts, the specified range of content of active markers;

— where applicable, that the extract is ‘refined';

— the first solvent or solvents used for extraction (for example, ethanol 60 per cent *V/V*);

— the name and amount of any excipients present in the extract (for example, diluents, stabilisers, antimicrobial preservatives, antioxidants);

— for quantified extracts and ‘other' extracts, the ratio of the quantity of herbal drug to the quantity of genuine (native) extract ($DER_{genuine}$) expressed on a mass/mass basis for soft extracts, oleoresins and dry extracts, and on either a mass/mass or a mass/volume basis for liquid extraction preparations;

— where applicable, the percentage of dry residue;

— the storage conditions.

LIQUID EXTRACTION PREPARATIONS - PRAEPARATIONES FLUIDAE AB EXTRACTIONE

Liquid extraction preparations are liquid preparations consisting of a diverse range of products which are described by their extraction solvents, methods of production and drug solvent ratios or drug extract ratios. Included in this range are products obtained using ethanol, water, glycerol, propylene glycol and fatty oils as extraction solvents. Liquid (fluid) extracts and tinctures belong to this category and are described below.

LIQUID (FLUID) EXTRACTS – EXTRACTA FLUIDA

DEFINITION

Quantified liquid (fluid) extracts and ‘other' liquid (fluid) extracts are liquid extraction preparations of which, in general, 1 part by mass or volume is equivalent to 1 part by mass of the dried herbal drug.

Standardised liquid (fluid) extracts are only defined by their content of constituents with known therapeutic activity.

PRODUCTION

Liquid extracts are prepared using ethanol of a suitable concentration and/or water together with, where necessary, other substances (e.g. glycerol or ammonia solution) to extract the herbal drug, or by dissolving a soft or dry extract of the herbal

drug (which has been produced using the same extraction solvent as would be used to prepare the liquid extract by direct extraction) in either ethanol of the required concentration or water.

Where the liquid extract contains ethanol, it is tested for 2-propanol (*2.9.11*), with a maximum of 0.05 per cent *V/V*, unless assurance of compliance with this limit is provided by a detailed knowledge of the ethanol supply chain and the extract manufacturing process.

Except for standardised liquid extracts, liquid extracts produced from soft or dry extracts do not contain any excipients other than those that would be present in the liquid extract prepared by direct extraction. However, exceptions may be justified in certain cases such as when the soft extract used to produce the liquid extract contains stabilisers, antioxidants or antimicrobial preservatives that have been added to ensure its stability.

Liquid extracts are adjusted, if necessary, so that they satisfy the requirements for content of solvent. Liquid extracts may be filtered, if necessary.

A slight sediment may form on standing.

TESTS

Relative density (*2.2.5*)

Where applicable, the liquid extract complies with the limits prescribed.

Ethanol (*2.9.10*)

For ethanolic liquid extracts, carry out the determination of ethanol content. The ethanol content complies with the limits prescribed.

Methanol (*2.9.11*)

Maximum 0.05 per cent *V/V* for ethanolic liquid extracts, unless otherwise prescribed or justified and authorised.

Dry residue (*2.8.16*)

Where applicable, the liquid extract complies with the limits prescribed.

STORAGE

Protected from light.

LABELLING

The label states in addition to the requirements listed above, the ethanol content in per cent *V/V*, where applicable.

TINCTURES – TINCTURAE

DEFINITION

Quantified tinctures and ‘other' tinctures are liquid extraction preparations that are obtained using either 1 part by mass of herbal drug and 10 parts by mass or volume of extraction solvent, or 1 part by mass of herbal drug and 5 parts by mass or volume of extraction solvent. Alternatively, they may be obtained using either 1 part by mass of herbal drug and sufficient extraction solvent to produce 10 parts by mass or volume of tincture or 1 part by mass of herbal drug and sufficient extraction solvent to produce 5 parts by mass or volume of tincture. Other ratios of herbal drug to extraction solvent may be used.

Standardised tinctures are only defined by their content of constituents with known therapeutic activity.

PRODUCTION

Tinctures are usually prepared by either maceration or percolation, using ethanol of a suitable concentration to extract the herbal drug, or by dissolving a soft or dry extract of the herbal drug (which has been produced using the same extraction solvent as would be used to prepare the tinctures by direct extraction) in ethanol of the required concentration.

The tincture is tested for 2-propanol (*2.9.11*), with a maximum of 0.05 per cent *V/V*, unless assurance of compliance with this limit is provided by a detailed knowledge of the ethanol supply chain and the tincture manufacturing process.

Except for standardised tinctures, tinctures produced from soft or dry extracts do not contain any excipients other than those that would be present in the tincture prepared by direct extraction. However, exceptions may be justified in certain cases such as when the soft extract used to produce the tincture contains stabilisers, antioxidants or antimicrobial preservatives that have been added to ensure its stability.

Tinctures are adjusted, if necessary so that they satisfy the requirements for content of solvent. Tinctures may be filtered if necessary.

Tinctures are usually clear. A slight sediment may form on standing.

TESTS

Relative density (*2.2.5*)

Where applicable, the tincture complies with the limits prescribed.

Ethanol (*2.9.10*)

The ethanol content complies with the limits prescribed.

Methanol (*2.9.11*)

Maximum 0.05 per cent *V/V*, unless otherwise prescribed or justified and authorised.

Dry residue (*2.8.16*)

Where applicable, the tincture complies with the limits prescribed.

STORAGE

Protected from light.

LABELLING

The label states, in addition to the requirements listed above, the ethanol content in per cent *V/V*.

SOFT EXTRACTS – EXTRACTA SPISSA

DEFINITION

Soft extracts are semi-solid preparations obtained by evaporation or partial evaporation of the solvent used for production.

TESTS

Dry residue (*2.8.16*)

The soft extract complies with the limits prescribed.

Solvents

Residual solvents are controlled as described in chapter *5.4*, unless otherwise prescribed or justified and authorised.

STORAGE

In an airtight container, protected from light.

OLEORESINS – OLEORESINA

DEFINITION

Oleoresins are semi-solid extracts composed of a resin in solution in an essential and/or fatty oil and are obtained by evaporation of the solvent(s) used for their production.

This monograph applies to oleoresins produced by extraction and not to natural oleoresins.

TESTS

Water (*2.2.13*)

The oleoresin complies with the limits prescribed.

Solvents

Residual solvents are controlled as described in chapter *5.4*, unless otherwise prescribed or justified and authorised.

STORAGE

In an airtight container, protected from light.

DRY EXTRACTS – EXTRACTA SICCA

DEFINITION

Dry extracts are solid preparations obtained by evaporation of the solvent used for their production.

Dry extracts usually have a loss on drying of not greater than 5 per cent *m/m*. Where justified and authorised, a loss on drying with a different limit or a test for water may be prescribed.

TESTS

Loss on drying (*2.8.17*)

Where applicable, the dry extract complies with the limits prescribed.

Water (*2.5.12*)

Where a test for loss on drying is not applicable, the dry extract complies with the limits prescribed.

Solvents

Residual solvents are controlled as described in chapter *5.4*, unless otherwise prescribed or justified and authorised.

STORAGE

In an airtight container, protected from light.

GLOSSARY - GLOSSA

Constituents with known therapeutic activity

Chemically defined substances or groups of substances which are generally accepted to contribute substantially to the therapeutic activity of a herbal drug, a herbal drug preparation or a herbal medicinal product.

Drug extract ratio (*DER*)

The ratio between the quantity of herbal drug used in the manufacture of an extract and the quantity of extract obtained. The number (given as the actual range) written before the colon is the relative quantity of the herbal drug; the number written after the colon is the relative quantity of the extract obtained. Two *DERs* can be differentiated:

— **Genuine (native) drug extract ratio ($DER_{genuine}$)**. The ratio between the quantity of herbal drug used in the manufacture of an extract and the quantity of genuine (native) extract obtained.

— **Total drug extract ratio (DER_{total})**. The ratio between the quantity of herbal drug used in the manufacture of an extract and the quantity of whole extract (including excipients) obtained.

For example, $DER_{genuine}$ 2.5-4.5:1 means that between 2.5 and 4.5 parts of herbal drug are required to produce 1 part of genuine (native) extract. Where processing aids are added to the genuine (native) extract to produce, for example, a dry extract, the DER_{total} and the $DER_{genuine}$ will have different values; where a dry extract is produced without the need for any processing aids, the DER_{total} and the $DER_{genuine}$ will be identical. Oleoresins are usually produced without the need to include processing aids, therefore the DER_{total} and the $DER_{genuine}$ are usually identical. For soft extracts and liquid extraction preparations, where the genuine (native) extract does not exist without excipients and/or processing aids (e.g. usually 20-30 per cent of water in soft extracts, ethanolic extraction solvent in tinctures), the DER_{total} and the $DER_{genuine}$ are identical.

Drug solvent ratio (*DSR*)

The ratio between the quantity of herbal drug, expressed in mass, used in the manufacture of an extract and the quantity of the first extraction solvent, expressed in mass or volume.

Extraction solvents

Solvents which are used for the extraction process.

Genuine (native) herbal drug extract

Refers to the extract without excipients, even if for technological reasons the genuine extract is not available. However, for soft extracts and liquid extraction preparations the genuine extract may contain variable amounts of (extraction) solvent.

Markers

Chemically defined constituents or groups of constituents of a herbal drug, a herbal drug preparation or a herbal medicinal product which are of interest for control purposes independent of whether they have any therapeutic activity. Markers serve to calculate the quantity of herbal drug(s) or herbal drug preparation(s) in the herbal medicinal product if the marker has been quantitatively determined in the herbal drug or herbal drug preparation.

There are 2 categories of markers:

— *active markers* are constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity;

— *analytical markers* are constituents or groups of constituents that serve solely for analytical purposes, irrespective of any pharmacological or therapeutic activity which they may be reported to possess.

Miscella (extraction liquor)

Liquid obtained from the extraction process.

Production of tinctures by maceration

A process whereby, unless otherwise prescribed, the herbal drug to be extracted is reduced to pieces of suitable size, mixed thoroughly with the prescribed extraction solvent and allowed to stand in a closed container for an appropriate time, with agitation where required. The residue is separated from the extraction solvent and, if necessary, pressed out. If the residue is pressed, the 2 liquids are combined.

Production of tinctures by percolation

A process whereby, unless otherwise prescribed, the herbal drug to be extracted is reduced to pieces of suitable size and mixed thoroughly with a portion of the prescribed extraction solvent and allowed to stand for an appropriate time. The mixture is transferred to a percolator and more extraction solvent is added until the herbal drug is covered with a layer of extraction solvent. The percolate is allowed to flow slowly from the base of the percolator while extraction solvent is slowly added to the top of the percolator, ensuring that the herbal drug to be extracted is constantly covered with extraction solvent, until all the extraction solvent has been added. Percolation continues until the percolate is recovered. If the residue is pressed, the 2 liquids are combined.