



Gamp

GAMP Good Practice Guide

**A Risk-Based
Approach to Calibration
Management**

Second Edition

Weiler Engineering... IT'S SAFER INSIDE

1395 Gateway Drive
Elgin, Illinois 60124 USA
PHONE: 847-697-4900
FAX: 847-697-4915



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GAMP Good Practice Guide

A Risk-Based Approach to Calibration Management

Second Edition

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This Guide is meant to assist pharmaceutical companies in managing calibration. The GAMP COP Calibration Special Interest Group cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

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Preface

Calibration is an essential element in ensuring compliance in the pharmaceutical and associated regulated life science industries. To ensure success, calibration should be managed effectively, by appropriately qualified and competent personnel. If neglected, calibration is capable of compromising product and process quality, facility, safety, environmental and patient safety, and dramatically increasing costs.

The GAMP® Good Practice Guide: A Risk-Based Approach to Calibration Management provides guidance in setting up a calibration management system, which will give a structured approach to instrument risk assessment, calibration program management, documentation, and corrective actions, essential to regulatory compliance.

It is intended to cover both process and laboratory instrumentation.

There has been a change in regulatory expectations and in associated industry guidance documents. The FDA has been actively promoting a risk-based approach to GMP as part of the 21st Century Initiative. The change in approach to validation and compliance now puts more focus on the integrity, security, and reliability of process control systems and the instrumentation supporting them. The benefit will be a focused calibration effort that concentrates on risks to product quality and public safety. Such a focus also should be cost-effective.

The process of establishing clear procedures and performing risk assessments will allow calibration activities to be managed to concentrate the most resource where it is most needed. This Guide offers a pragmatic approach, based on risk assessment, to provide effectiveness and regulatory compliance as cost effectively as possible.

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The following members of the GAMP COP Calibration Special Interest Group (SIG) worked on one or more of the sections of this document and volunteered countless hours to attend meetings and review the many drafts, which were produced over an 18 month period.

Chair

Mark Foss	Sciurus Consultancy	United Kingdom
-----------	---------------------	----------------

Special Interest Group Core Team

James Culyer	Napp Pharmaceuticals	United Kingdom
--------------	----------------------	----------------

Stephen Dawson	Eli Lilly & Co. Ltd.	United Kingdom
----------------	----------------------	----------------

Matthew Dornan	CompuCal Software Solutions	Ireland
----------------	-----------------------------	---------

Niketa Gandhi	Abbott Laboratories	USA
---------------	---------------------	-----

Ian Hall	Pfizer	UK
----------	--------	----

Ray Hewett	GSK	United Kingdom
------------	-----	----------------

Additional Material/Comments Requested From:

Ivan Diamond	IAGT Group	United Kingdom
--------------	------------	----------------

Miguel Cerezo	Amgen	USA
---------------	-------	-----

Mark Newton	Eli Lilly	USA
-------------	-----------	-----

John Murray	US Food and Drug Administration, CDRH	USA
-------------	---------------------------------------	-----

Lorrie Vuolo Schuessler	GSK	USA
-------------------------	-----	-----

Robert Tollefsen	US Food and Drug Administration	USA
------------------	---------------------------------	-----

Document Specialist

Tim Smith	Boehringer Ingelheim	United Kingdom
-----------	----------------------	----------------

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**ENGINEERING
PHARMACEUTICAL
INNOVATION**

ISPE Headquarters

3109 W. Dr. Martin Luther King Jr. Blvd., Suite 250, Tampa, Florida 33607 USA
Tel: +1-813-960-2105, Fax: +1-813-264-2816

ISPE Asia Pacific Office

73 Bukit Timah Road, #04-01 Rex House, Singapore 229832
Tel: +65-6496-5502, Fax: +65-6336-6449

ISPE China Office

Suite 2302, Wise Logic International Center
No. 66 North Shan Xi Road, Shanghai, China 200041
Tel +86-21-5116-0265, Fax +86-21-5116-0260

ISPE European Office

Avenue de Tervueren, 300, B-1150 Brussels, Belgium
Tel: +32-2-743-4422, Fax: +32-2-743-1550

www.ISPE.org

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1 Introduction

The ISPE GAMP® Good Practice Guide: A Risk-Based Approach to Calibration Management discusses controlling risk to product quality and patient safety.

It discusses issues in calibration management along with existing industry good practice to address those issues. It also considers enhancing business benefits by managing and documenting calibration.

This Guide describes a risk-based approach to calibration management, and seeks to be in clear alignment with other related ISPE Guides and initiatives.

It is not a prescriptive method or a standard, but rather provides pragmatic guidance, approaches, and tools for the practitioner.

Application of this Guide should help to ensure a consistent approach to calibration management in line with regulatory expectations; therefore, the overall risk of compliance failures may be reduced. When applied with expertise and good judgment, this Guide offers a robust, cost effective approach to calibration management.

The approach described considers the full life cycle of instrument management, covering requirements to satisfy regulators and giving guidance on good practice in the pharmaceutical industry. It is a building block for use in qualification, verification, and validation.

The approach described is designed to be compatible with a wide range of other models, methods, and schemes, including:

- Quality systems standards, such as those of the Institute of Electrical and Electronics Engineers (IEEE), (Reference 14, Appendix 16)
- Certification schemes, such as the International Organization for Standardization (ISO) 9001 Series (Reference 11, Appendix 16)
- ANSI/ISA standard approaches to labeling and tagging (Reference 9, Appendix 16)

Where possible, terminology is harmonized with standard international sources such as International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and ISO.

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1.1 Rationale

Making the correct decisions depends largely on whether the correct information is acquired. This information is often gathered through measurement; therefore, it is critical that the information is reliable, accurate, and traceable.

The calibration of process control instruments may drift, due to the complexity of their construction and the environmental conditions in which they operate. This drift may be significant within a short period of time and accounts for the requirement for periodic recalibration.

Concentrating resources in the most important areas will maximize their effectiveness. The process of risk assessment will help in achieving this and in reducing costs.

This Guide discusses the importance of calibration and the need/benefits of focusing on critical instruments. If a parameter is not measured, control cannot be assured. Effective calibration management is essential in assuring control and compliance.

The performance of an instrument should be such that there is high confidence that the process has remained within the desired range, i.e., indicated value and associated measurement uncertainty will remain within desired limits.

Instruments should be assessed for potential impact on product quality and patient safety, as well as their accuracy and their stability. Effective calibration is essential in achieving a high degree of confidence that a manufacturing process remains within the defined operating limits.

1.2 New and Revised Material

The GAMP Good Practice Guide: A Risk Based Approach to Calibration Management Second Edition has been updated to address the changing environment, while still satisfying international GxP regulatory expectations, current at time of publication. The scope has been widened to include related industries, laboratory, and analytical instrumentation.

This Guide has been significantly updated to align with the concepts and terminology of regulatory and industry developments including:

- ICH Guidance Q8 (R2), Q9, and Q10: setting out expectations for the application of science and risk-based approaches to drug development and manufacture supported by pharmaceutical quality systems (References 1, 2, and 3, Appendix 16)
- US Food and Drug Administration (FDA) current Good Manufacturing Practices (cGMPs) for the 21st Century Initiative and associated guidance (Reference 5, Appendix 16): promoting science based risk management
- Product Quality Lifecycle Implementation (PQLI): an initiative launched by ISPE to help industry to implement ICH guidance (Reference 15, Appendix 16)

This Guide aims to be fully compatible with the approach described in the American Society for Testing and Materials (ASTM) E2500 (Reference 19, Appendix 16).

This Guide represents industry good practice at time of publication and remains compatible with the principles presented in the first edition of this Guide, ISPE GAMP Good Practice Guide: Calibration Management (2002).

The Following Areas Have Been Addressed as Part of this Revision:

1. Alignment with current thinking on the risk-based approach, including the concepts of design and control space.
2. Software systems for supporting calibration both as scheduling and data recording tools. Software system should include the provision of historical data to assist in calibration optimization, e.g., Historical Analysis Graphs, Failure Alarms via email or text, Drift Analysis to predict failures.
3. internal and external auditing of systems and the use of supplier systems and documentation
4. changes in the cGMP, including:
 - SOP requirements
 - contractor competency assessment

- documentation sign off (paper or electronic)
 - verification versus qualification
5. guidance on the application of measurement uncertainty estimates and assumptions
 6. physical labeling and tagging schemes (including tagging structure)
 7. integration of instrumentation into process control systems
 8. use of programmable/configurable intelligent instruments
 9. use of electronic calibration devices
 10. inclusion of laboratory and analytical instrumentation as part of the scope of the Guide
 11. update of example documents in line with current industry thinking, including:
 - multi function calibration certificate
 - unique calibration certificate numbering
 - loop commissioning
 - non-routine verification
 - audit check lists
 - activity reference standards

1.3 Purpose

The purpose of this Guide is to provide a cost effective framework of good calibration management practice to ensure that activities that affect product quality and patient safety are supported by a robust calibration management system which is fit for purpose and compliant with applicable regulations. The framework aims to safeguard patient safety, product quality, Environment, Health, and Safety (EHS), and data integrity while also delivering business benefit.

Patient safety is affected by the integrity of critical records, data, and decisions, as well as those aspects affecting physical attributes of the product. The phrase 'product quality and patient safety' is used throughout this document to underline this point.

This Guide is intended for use by regulated companies, suppliers, and regulators. Suppliers include providers of calibration activities, recording systems, and support services, both internal and external to the regulated company.

The GAMP Good Practice Guide: A Risk-Based Approach to Calibration Management is intended for use by engineers, Quality Assurance (QA), and personnel involved in the management of calibration in a regulated environment for use by a wide range of disciplines and responsibilities, including:

- management
- quality unit
- research

- development
- manufacture
- distribution
- laboratory
- engineering
- support staff
- all associated suppliers

The objective of this Guide is to provide a practical approach to calibration management within the pharmaceutical and associated regulated life science industries, to satisfy relevant regulatory bodies, and improve operational effectiveness.

1.4 Scope

The scope of the Guide includes quality, safety, and environmental issues as well as the regulatory requirements of the pharmaceutical and associated regulated life science industries.

This Guide focuses on the regulatory implications of designing guidelines following the principles established by GAMP Council in 2005. Technical processes of calibration management are outside the scope of this Guide, which focuses on the management of activities required to achieve regulatory compliance.

This Guide describes a system of calibration management, which defines what needs to be done, when, by whom, and why. This Guide also describes the principles and suggests a prioritized, effective method for meeting the calibration needs of the pharmaceutical industry and satisfying the requirements of regulatory authorities.

This Guide applies to calibration used in regulated activities covered by:

- Good Manufacturing Practice (GMP) (pharmaceutical, including Active Pharmaceutical Ingredient (API), veterinary, and blood processing)
- Good Clinical Practice (GCP)
- Good Laboratory Practice (GLP)
- Good Distribution Practice (GDP)
- Medical Device Regulations (with the exception of software embedded within medical devices)

These are collectively known as GxP regulations.

GAMP documents are guides and not standards. It is the responsibility of regulated companies to establish policies and procedures to meet applicable regulatory requirements.

Not all the activities defined in this Guide will apply to every system. It is recognized that there are acceptable methods other than those described in this Guide. The Guide is not intended to place any constraints on innovation and development and adoption of new concepts and technologies.

The Guide does not cover the detail of test methodology.

1.5 Regulatory Requirements

There are clear regulatory GxP requirements for calibration that must be met. These include:

- establishing and maintaining procedures to ensure that equipment is routinely calibrated
- such procedures should include specific directions and limits for accuracy and precision
- calibration standards used for inspection, measuring, and test equipment should be traceable to appropriate standards
- the equipment identification, calibration dates, the individual performing each calibration, and the next calibration date should be documented

It is recommended that regulated companies carefully read and understand the specific regulations relevant to them. Further information may be found in Appendix 5.

1.6 Business Benefits

Specific benefits to both regulated companies and suppliers include:

- consistent approach leading to better understanding by operations staff, support staff, and regulators
- focus of activities based on risk, impact, and criticality
- reduction of cost and time taken to achieve and maintain compliance
- early defect identification and resolution leading to reduced impact on cost and schedule
- cost effective calibration, operation, and maintenance
- effective change management and continuous improvement
- providing frameworks and templates for user/supplier cooperation
- assisting suppliers to produce required documentation and services
- promotion of common language and terminology
- providing practical guidelines and examples
- promoting pragmatic interpretation of regulatory requirements
- staff safety and protection

1.7 Structure

The Guide is structured to follow a life cycle approach and is intended to cover initial calibration as well as periodic inspection, testing, and ongoing calibration.

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2 Key Concepts and Terms

2.1 Key Concepts

This section introduces three Key Concepts which are applied throughout this Guide.

Instrument Life Cycle

The instrument life cycle consists of two distinct phases; the Project Phase and the Operation Phase. These are supported by Common Practices. For further information, see Sections 5, 6, and 7 of this Guide.

There are a number of key roles and responsibilities associated with the instrument life cycle. For further information, see Section 3 of this Guide.

Risk-Based Understanding

An understanding of the supported process is fundamental to determining system requirements. Product and process understanding should be used as the basis for making science and risk-based decisions to assure that a system is fit for its intended use.

Efforts to ensure regulatory compliance should focus on those aspects of systems that are critical to product quality and patient safety. These critical aspects should be identified, specified, and verified. A calibration strategy should focus on the instruments that confirm or control these parameters. Instruments used to assure safety and environmental protection also should be considered.

Process requirements may depend on a thorough understanding of product characteristics. Critical Quality Attributes (CQAs) associated with the product and related Critical Process Parameters (CPPs) should be identified to enable process control requirements to be defined. CQAs and CPPs can be used in the categorization of measurement instruments.

Calibration should focus on critical aspects.

Scaling of Calibration Activities

The level of effort, formality, and documentation of the calibration management process should be commensurate with the level of risk to product quality and patient safety.

2.2 Key Terms

This section introduces three key terms used in this Guide.

Consistent definitions should be used for terms used within a calibration management system.

Calibration

The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

Measurand

Quantity intended to be measured.

Measuring Instrument

Device used for making measurements, alone or in conjunction with one or more supplementary devices.

Measurement Precision

Closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions.

Measurement Repeatability

Measurement precision (as defined above) under a set of conditions that includes the same: measurement procedure, operators, measuring system, and location over a short period of time.

Measurement Reproducibility

Measurement precision (as defined above) under a set of conditions that includes different: measurement procedures, operators, measuring systems, and locations.

Measurement Accuracy

Closeness of agreement between a measured quantity value and a true quantity value of a measurand.

Measurement Uncertainty

Non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used. *Note: this is not inconsistent with the more commonly quoted definition given in the first edition of the VIM, i.e., "an estimate characterizing the range of values within which the true value of the measurand lies."*

Metrological Traceability

Property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty.

Test Equipment

Instrument or device used to calibrate other instruments, the calibration of which is traceable to recognized national or international standards or where this is not practicable (e.g., where only in-house reference materials/solutions are available), to a reproducible standard. The test equipment should have better precision, accuracy, and repeatability than the instrument under calibration.

Measurement Standard

A means by which to realize the definition of a given quantity, with stated quantity value and an associated measurement uncertainty, used as a reference.

Primary Measurement Standard (Primary Standard)

Measurement standard established using a reference measurement procedure not requiring a measurement standard for a quantity of the same kind or created as an artifact chosen by convention.

Secondary Measurement Standard (Secondary Standard)

Measurement standard established through calibration with respect to a Primary Measurement Standard for a quantity of the same kind.

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3 Key Roles and Responsibilities

Assessment and management of calibration requirements can involve different expertise and roles. This section covers the main responsibilities for these roles.

Calibration assessment is normally part of the Project Phase for new installations and part of the periodic review during the Operation Phase.

Primary areas of required expertise (e.g., appropriate Subjects Matter Experts (SMEs)), particularly when performing risk assessments (see Section 5 of this Guide) may be available in-house or can be delivered via a contracted service. Primary areas of required expertise include:

1. Process/Science/Technology:
 - identifying critical attributes, parameters, and process variables
 - defining process limits and tolerances
 - approving calibration specifications and frequencies
 - approval of criticality impact risk assessment
 - may have responsibility for the system as well as process, including process control strategy
2. Quality Assurance (Quality Unit):
 - ensuring that defined process limits and tolerances meet regulatory submission
 - involvement in deriving and approving calibration specifications and frequencies
 - approval of criticality risk assessment
 - approving timely investigations of out of tolerance conditions
 - auditing the calibration management process/system
 - involvement in the selection and approval of third party contractors
3. Engineering:
 - initiation and management of the criticality risk assessment process
 - involvement in deriving and approving calibration specifications and frequencies
 - selection/approval of instrumentation, including loop design, to meet required specification with respect to; range accuracy, precision, drift, hysteresis, and uncertainty as well as any corporate standardization requirements
 - approval of criticality risk assessment
 - planning and defining calibration strategies, defining acceptance criteria, selection of appropriate test methods, execution of tests, and reviewing results

- responsibility for calibration process or system

Expertise above may be available from less than three persons. It also may be necessary to involve specific expertise in other areas, when required to identify and to cover all relevant areas and other aspects, particularly for complex systems.

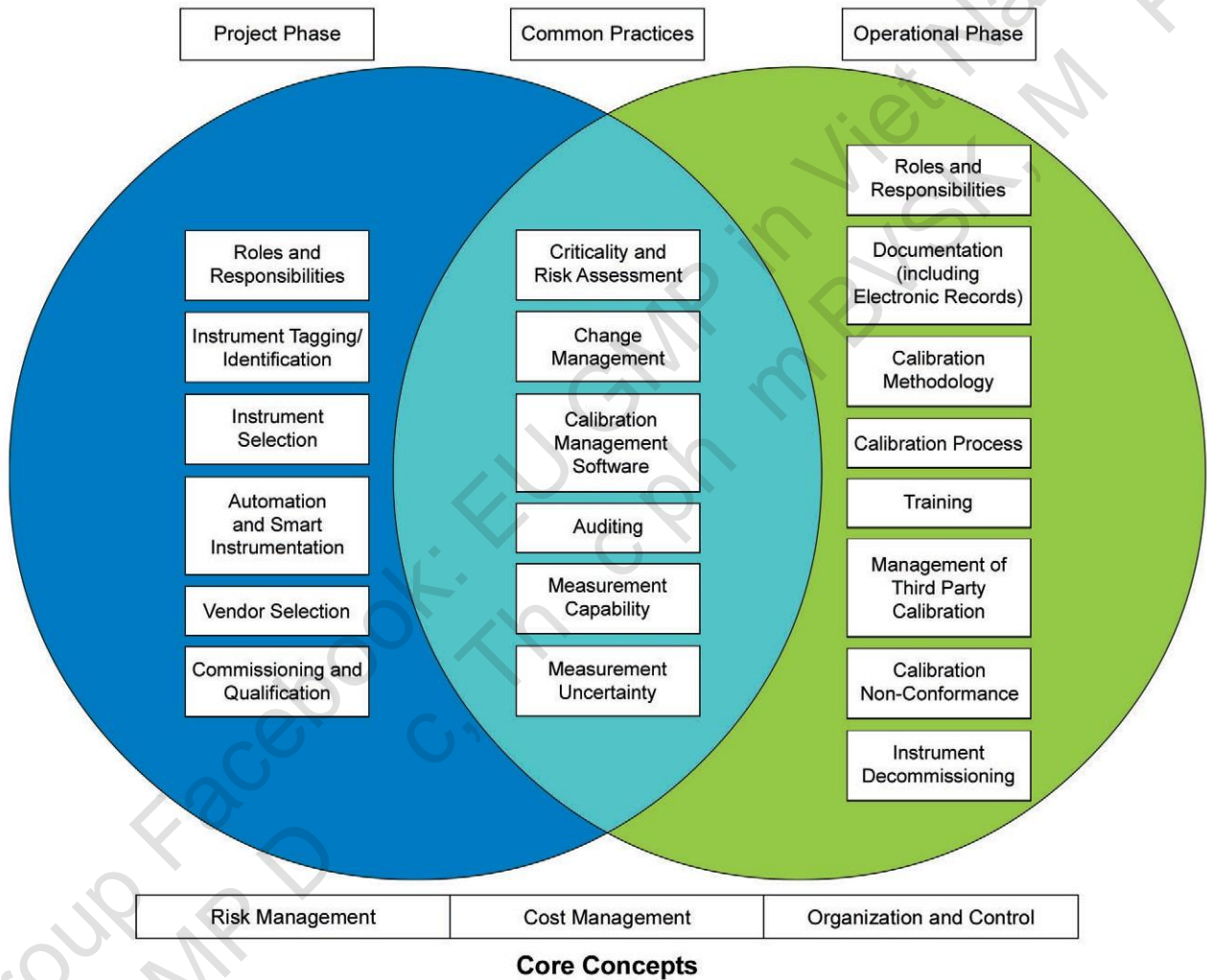
Additional responsibilities which apply during the Project or Operation Phases are considered in the relevant sections of this Guide.

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4 Instrumentation Life Cycle Approach

The instrument life cycle consists of two distinct phases; the Project Phase and the Operation Phase. These are supported by Common Practices.

Figure 4.1: Instrument Life Cycle



The calibration process is part of the overall instrument life cycle.

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5 Common Practices

Common Practices provide a foundation for the Project and Operation Phases. This approach is based on that defined in the ISPE Good Practice Guide: Good Engineering Practice (Reference 20, Appendix 16). The life cycle for an instrument is similar to that for other maintainable assets, but with the potential additional complexity of the calibration cycle.

Common Practices for instrumentation are augmented by:

- Criticality Risk Assessment
- Change Management
- Calibration Management Software
- Auditing
- Measurement Capability
- Measurement Uncertainty

5.1 Criticality Risk Assessment

5.1.1 Introduction

This section describes an assessment approach that should be applied to evaluate instrumentation criticality.

The Criticality Risk Assessment (CRA) (from the Common Practices) acts as the key to calibration activities. It helps to define the limits and frequency of subsequent calibration.

Following the initiation of the calibration cycle, the CRA can be used as an effective tool for modifications to programs, such as:

- change of use, due to alterations to the process or measurement criteria
- modification to the tolerances
- amendments to the frequency of calibration
- instrument replacement, where it is not a like for like change
- Non-Conformance Report
- Corrective and Preventive Action (CAPA) action item

If alterations are anticipated to maintain regulatory compliance or equipment efficiencies as part of the routine calibration program, the CRA may be initiated by any of the parties involved in reviewing of such alterations. Amendments may require approval from all functions involved in the original CRA activity.

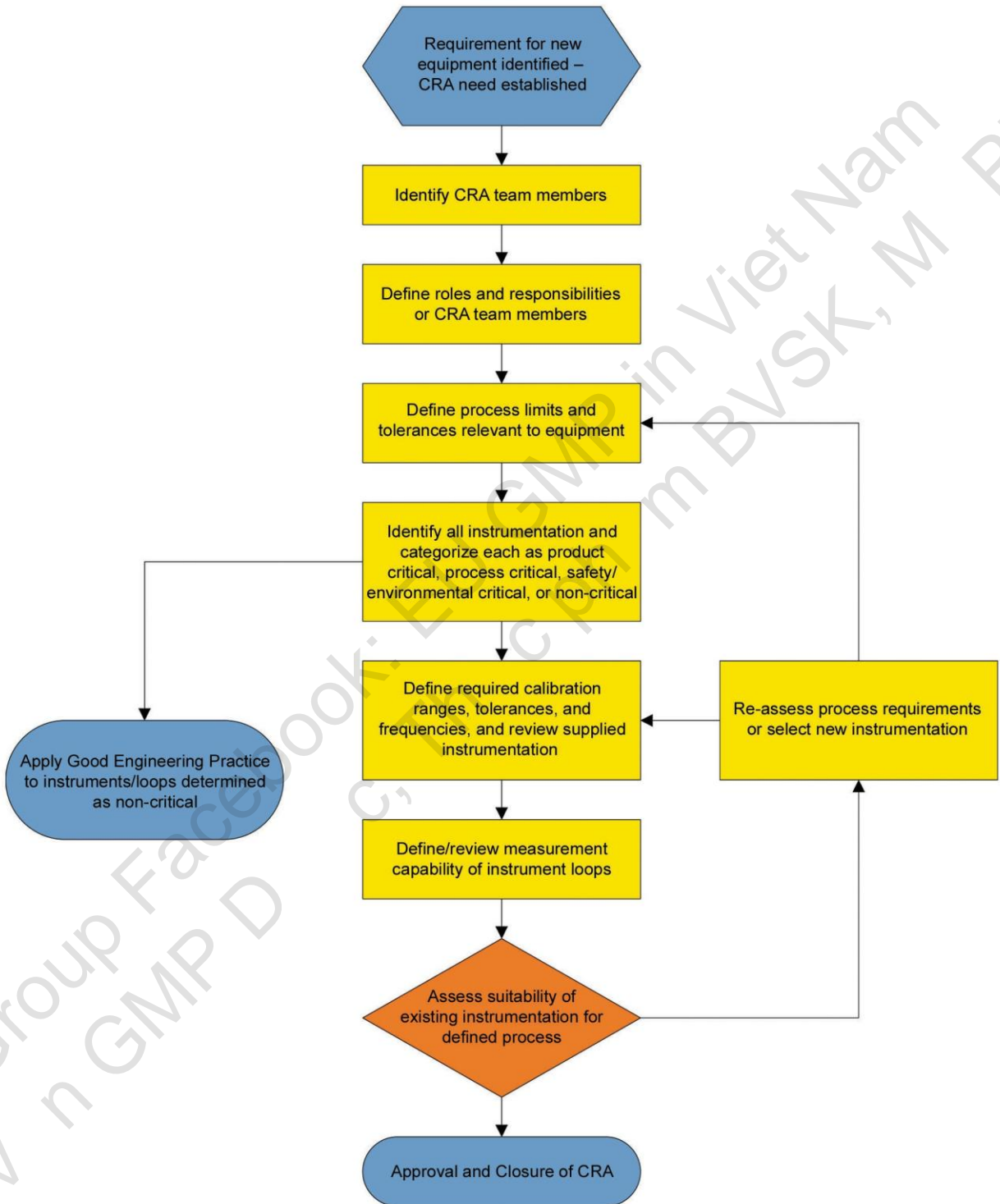
The CRA is a once through process; there should be periodic review of the results to ensure that the assumptions made are reflected in the actual performance of the instrumentation with change control used as necessary. The CRA also may be used as a continuous improvement tool to ensure the calibration program is fit for purpose and adding value to the business.

Instrument loops used in GxP applications should be individually assessed against their specific use to establish their potential impact on the process. Once this process has been conducted, those loops should be further assessed for suitability for the application and should have appropriate calibration regimes defined. Non-critical loops should be calibrated according to GEP norms or organizational standards.

The CRA is part of the Project Phase of introduction of new equipment and should be completed prior to handover of the equipment to routine operations. The outcome of the assessment should provide the calibration requirements for individual instruments, such as the range, tolerance, and calibration frequency. This information can be used to populate a Calibration Master List (CML) and calibration methodology. The CML should be considered as a controlled document with appropriate approvals and revision history.

The CRA should consider the impact of the instrumentation on product safety, identity, strength, purity, or quality, as well as plant/environmental safety or business efficiencies. The assessment should be performed by a multidisciplinary team including, but not limited to, representatives from Production (Process Owner or Expert), Quality Assurance, and Engineering.

Figure 5.1: Criticality and Risk Assessment Overview



5.1.2 **Operation of the Criticality Risk Assessment Team:**

The CRA for instrumentation requires the involvement of, as a minimum:

1. Production (Process Owner)
2. Quality Assurance
3. Engineering

Specific expertise in other areas should be called upon when required.

The roles and responsibilities of each Criticality Risk Assessment Team member should be defined either in an SOP or as part of the individual CRA activity.

The role definitions and responsibilities suggested in section 2.3 should be considered as good generic guidance for the responsibilities of the respective parties. Organizations should decide the best allocation of responsibilities based on individual organizational structure.

5.1.3 **Determination of Process Limits and Tolerances**

Where they exist, registered values associated with the manufacturing process, method, or task for which the instrument was specified should be considered when establishing process limits in accordance with GxP requirements.

Where multiple process ranges may be used within operation of the equipment or instrument, the worst case should be used as the calibrated range encompassing all values between the highest high limit and the lowest low limit.

When the same instrument is used for multiple process ranges that are tight, but very different, it may not be appropriate to calibrate for one wide range covering all process ranges, as accuracy may be diminished. In such circumstances, the instrument loop may need to be re-ranged between campaigns. Therefore, separate CRA assessments may need to be established for each scenario and strict Change Control invoked to manage the change of duties and to ensure calibration data is captured before, during, and at the end of each campaign cycle.

If there are no registered limits, the following hierarchy may be used as guidance when defining process limits and associated tolerances.

Table 5.1

Decision Step	Reference Source	Comments	Requirement
1	International and National Standards	Example sources include: USP, EP, ISO*, EN* (*International Standards selected should not contravene GMPs).	Process limits must be defined in accordance with International/ National standards.
2	Registered and Internal Developed Standards	Example sources include: <ul style="list-style-type: none"> • Drug registration file • Specific internal standards* based on evidence and knowledge (*Internal standards must not contravene GMP and international standards).	Where no applicable International/ National standard exists, process limits and tolerances must be defined in accordance with registered information submitted to regulators, e.g., FDA, MHRA.
3	Performance Data	Example sources include: testing results and raw data providing information relating to process ranges. Trending of raw data may be held to determine limits and tolerances.	Where no registered or internal standards have been defined the process, limits and tolerances may be defined based upon process understanding/performance data.
4	Vendor Specification	Example sources include: instrument data sheets and supplier performance data	Where no performance data have been defined, the process limits and tolerances may be defined upon equipment/instrument specification data.

In specific cases, the full range of the equipment or instrument may prove most appropriate for the calibration range. Conversely, for equipment and instruments that have a full calibrating range much greater than the actual operating values it will be appropriate to reduce the maximum and minimum calibration range closer such that they bracket the standard operating values.

Suitable test points across the process range must be defined to ensure that instrument accuracy and precision is clearly demonstrated.

Note: Where performance and operating history of instrumentation is not available, it is recommended that full scale calibration ranges should be adopted for the initial calibrations performed. As suitable evidence or trend data accumulates, a review may be performed, and where appropriate, adjustments to the calibration limits can be justified.

It is recommended that 'Alert' limits should be defined and applied to operational processes. Alert limits should be correctly defined relating to the process or task in which the instrument will perform and should ensure adequate notification **before** the process tolerance is exceeded.

When defining the action and alert limits, the instrument measurement capability should be taken into account. For further information, see Section 5 of this Guide.

Process Tolerances

Process tolerances should be:

- correctly defined, relating to the process or task in which the equipment or instrument will perform

- in accordance with registered values associated with GxP requirements
- defined as a maximum and minimum value and should not be confused with operating set point values

Table 5.2 provides examples of process tolerances that may be applied.

Table 5.2: Process Tolerances

Normal Operating Ranges	Operating Set Points in Normal Use	Process Tolerance Required	Minimum and Maximum Operating Ranges
22°C – 38°C	22°C, 33°C, 36°C,	±2°C	20°C – 40°C
<p>Note: Equipment and instrument uncertainty should be better than the process tolerance defined. In this case, an uncertainty of ±1°C would give a coverage factor of 2 which may be appropriate for many measurement processes. The CRA should establish the required uncertainty.</p>			

5.1.4 Determination of Instrument Categorization

The level of effort, formality, and documentation of the calibration management process should be commensurate with the level of risk to product quality and patient safety. Other aspects such as business risks or effectiveness, operator safety, or environmental concerns also should be considered.

A separate and specific risk assessment is not required if an adequate risk assessment has already been performed as part of previous process or engineering activities.

It may be useful, but is not mandatory, to classify instruments when making such judgments. Such classification is highly dependent on the nature of the product and the role of the instrument in the process, and may vary from case to case, even between identical instruments used at the same facility, but for different purposes.

The following example classification scheme is suggested in this Guide:

Product Critical Instrument

A product critical instrument is an instrument whose accuracy or failure has a high potential impact on product quality or patient safety.

Business Critical Instrument

A business critical instrument is an instrument whose accuracy or failure has a high potential impact on process effectiveness or other business aspect.

Safety/Environmental Critical Instrument

A safety/environmental critical instrument is an instrument whose accuracy or failure has a high potential impact on operator safety or the environment.

(A specific instrument within the context of a particular process may fall into one, two, three, or none of the above classes.)

All other instruments may be regarded as non-critical instruments. For such instruments, their specification, design, and verification may proceed following Good Engineering Practice with instrument ranges and overall performance specifications, calibration frequencies, etc., determined by process requirements and company standards or preferences.

5.1.5 *Defining Required Instrument Calibration Ranges and Limit*

When deciding on calibration ranges and limits, the instrument ranges, the manufacturer's accuracy, and the process requirements should be taken into account. Process ranges, tolerances, alert, and action limits are interrelated.

The full range of an instrument may prove most appropriate for the calibration range. Conversely, for instruments that have a full calibrating range much greater than the actual operating values, it may be appropriate to reduce the maximum and minimum calibration range closer to that of the standard operating values.

Suitable test points across the process range should be defined to ensure that instrument accuracy and precision is clearly demonstrated. For a critical loop, these should include rising and falling values, and wherever possible, values close to operating setpoints and any critical decision limits.

Where performance and operating history of instrumentation is not available, it is recommended that full scale calibration ranges should be adopted for the initial calibrations performed. As suitable evidence and trend data accumulates, a review may be performed, and where appropriate, adjustments to the calibration limits can be justified.

See Appendix 1 for an overview of the relationship between Process Limits and Calibration Ranges and Tolerances.

5.1.6 *Instrument Calibration Frequency*

Instruments measure process variables based on "true" values of the process and therefore, calibration should be planned and executed to suitable calibration frequencies. In order to define suitable calibration frequencies, the risk and consequences of an incorrect indication should be risk assessed.

Key considerations include:

- What is the expected performance of the instrument compared to the demands of the process?
- What calibration frequency is suggested by this comparison?
- How much confidence is there in the instrument meeting expectations?
- What are the implications of the instrument performance not meeting expectations?

The following questions should be answered to address the above issues:

- What is an acceptable tolerance? i.e., how wrong can it be before there is a problem?
- What is the actual instrument performance? i.e., based on historical evidence or supplier data?
- What are the operating conditions for the instrument? i.e., adverse or moderate?

The level of measurement uncertainty against the context of the true value indicated or controlled should be considered. The level of uncertainty also may determine that more frequent calibrations should be performed.

To determine the required calibration frequency, a risk assessment against the expected instrument performance should be performed. As part of the risk assessment process, the following should be considered:

- What are the implications of an unacceptable error? i.e., wrong decisions being made affecting patient safety, Environment, Health, and Safety (EHS) compliance or business performance?

- What are the implications of the error not being detected and continuing operation of the process, method, or system outside established operating parameters without knowing?
- What are the procedures associated with the process that would uncover unacceptable error?

See Appendix 1 for an overview of this process outlining the recommended steps for assessing instrument risk and calibration frequency.

Where the probability of error detection is low and the consequences high, a high calibration frequency should be adopted. Where error detection and consequences are considered to be moderate, a lower calibration frequency may be adopted.

5.1.7 Selection of Instrumentation and Closure of Criticality Risk Assessment

Once the above processes have been completed and the required ranges, tolerances, and calibration frequencies have been defined, the instrumentation required for the process can be selected. This may take the form of an approval of existing instruments or may require sourcing of new or replacement instrumentation. This should be performed in accordance with Section 6 of this Guide.

If new instrumentation is selected, a review of the calibration frequencies should be performed, based on the expected performance of the new instrumentation.

The findings of the risk assessment, the calibration ranges, tolerances, and frequencies defined should be agreed. Closure of the CRA should include approval by all members of the team.

5.2 Change Management

Change Management is the process of controlling the life cycle of all changes. Organizations may prefer separate change management activities for the calibration process. Where an effective and auditable change control process exists within an organization, which allows for assessment of the impact of changes to the calibration status and requirements of devices, this system should be used.

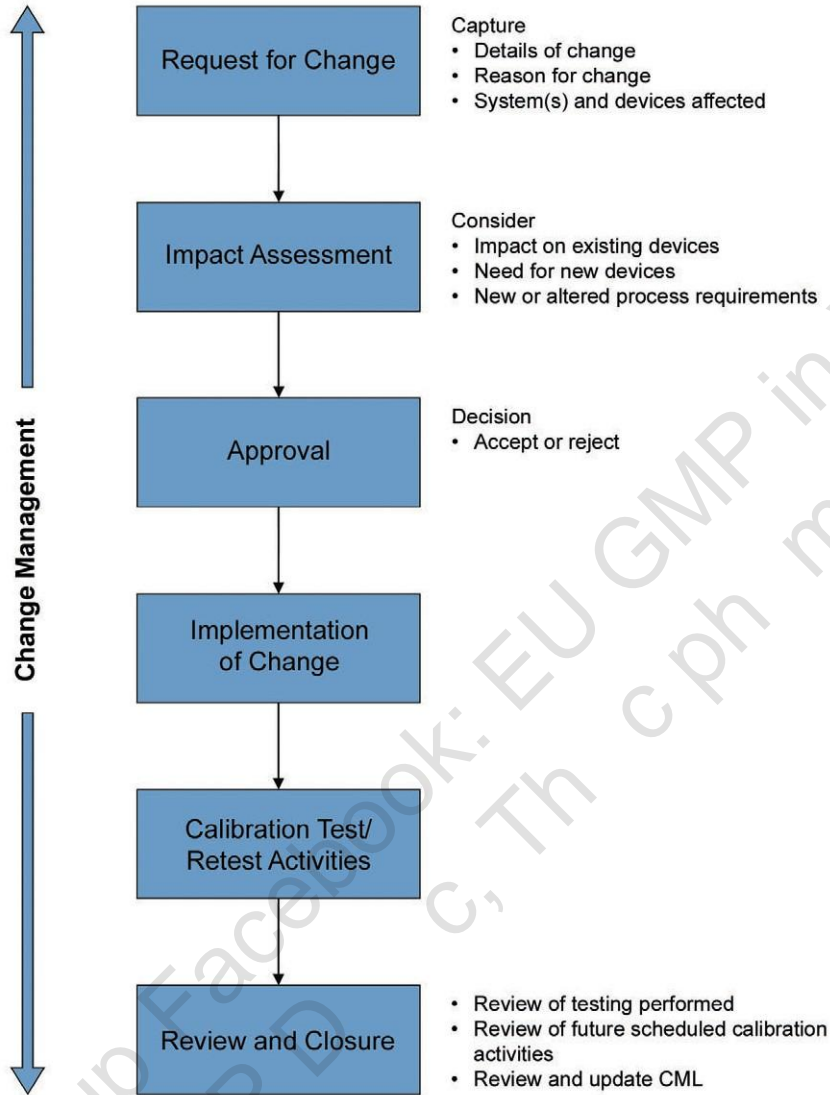
5.2.1 Key Requirements

Change Control process used for handling changes to calibrated devices should include:

- a formal process for recording the change and the reason for making it
- an authorization of the change
- an impact and risk assessment of the change on calibration statuses and requirements
- a process for defining test/retest requirements to mitigate identified risks
- a process for recording the outcome of calibration activities
- a process for completion and closure of the change

5.2.2 Process

Figure 5.2: Change Management Process



5.2.3 Risk Assessment

The following should be considered when performing the risk assessment for changes affecting calibrated systems:

- new or changed process requirements necessitating changes to calibration ranges, tolerances, or frequencies
- changes to environmental conditions affecting suitability of the instrumentation or calibration frequencies
- changes to equipment necessitating changes to defined calibration methodologies
- changes to equipment or processes that require previously critical or non-critical devices to be re-classified and subsequently calibrated or not calibrated

The outcome of the impact assessment should define the necessary action relating to the calibrated instrumentation.

5.2.4 *Increasing or Reducing Instrument Calibration Frequency*

Instrument manufacturers may provide information on suitable periods between calibrations; however, the environment and operation of the instrument should be considered and an assessment of the implications of uncertainty should be performed. When data has been obtained to show the stability of operation of an instrument in a particular environment, it may be feasible to review the periods between calibrations.

Statistically acceptable data should be available to justify decreasing the instrument calibration frequency. For example, data of at least three successive calibration periods without instrument adjustment under normal operating conditions may be deemed sufficient based on the instrumentation specification and related process requirements and criticality. The exact amount of data points necessary should be determined by the CRA team on a case by case basis. For further information, see Section 5 of this Guide.

Different statistical methods exist for revising calibration frequency using the available data. This Guide recommends following International Laboratory Accreditation Cooperation (ILAC), ILAC-G24:2007/OIML D10:2007 (E) (Reference 18, Appendix 16). This ILAC guidance includes the range of available methods and when they should be applied.

Any change of calibration frequency should be fully supported by the historical evidence. The ongoing review of the historical evidence should be logged and evaluated for the new calibration frequency.

In cases when instrumentation has behaved in an unpredictable manner, the criteria for increasing the calibration frequency can be difficult to define as its future behavior can be difficult to forecast. Consequently, the decision to increase the calibration frequency (and to what extent) should remain based on the judgment of experienced calibration staff and personnel familiar with the criticality of the operation and the instrument performance. It may be more appropriate to remove or replace instruments with new instruments, rather than increasing the calibration frequency. It may be necessary to consider the impact of reducing calibration frequency on any uncertainty calculations. See section 5 of this Guide.

Refer to Appendix 1 for an example of a change to a calibration frequency.

5.3 **Calibration Management Software**

Options for electronic management of calibration activities include:

- use of custom spreadsheets
- commercial off the shelf packages
- bespoke developed solutions, produced either in-house or externally supplied

Options should be adequately controlled, proceduralized and where necessary, validated.

The software options for calibration management may be an integral part of an instrument asset management system, a separate software tool dedicated to this one function, or a modular part of a computerized maintenance management system. However, the development of intelligent instruments that can provide diagnostic calibration alerts suggests that calibration management software should have communication capability with smart instrumentation in order to utilize these advanced diagnostic capabilities. Likewise, the use of mobile devices for capture of calibration data in remote location (e.g., Personal Digital Assistants (PDAs) or other handheld devices) should be a perceived benefit of such systems.

Electronic systems should operate within the same constraints and methodology as paper systems although they may benefit from the ability to transfer data electronically from the smart instrument or test equipment.

The advent of electronic authorization/approval with multilevel security access, e.g., account and password/biometric input, provides the opportunity to have a highly compliant and controlled calibration procedures, systems, and data archives.

Benefits of using a Calibration Management Software application include:

- demonstration of compliance
- automated planning and scheduling
- automate calibration procedures through the work flow
- reduced time to review for system improvements
- automated reporting
- storage of all data in a central secure location
- reduced management and administration effort
- reduced time preparing for audits
- reduction in follow up audits
- provision of rapid access to calibration history
- reduced time required to perform calibration frequency reviews

When choosing a calibration management software application, all requirements should be clearly listed. This will become the basis for the User Requirement Specification (URS) and will be essential in the final specification and validation of the application.

It is considered good practice to research applications that are available and functionality that can be provided. This also should feed into the URS and to ensure that the application required is available as an off the shelf configurable application. See Appendix 3 for more details on the URS; an example of a URS template is provided.

5.3.1 Validation

Software implemented for calibration management activities should be validated in accordance with the approaches defined in GAMP 5 (Reference 16, Appendix 16).

5.4 Auditing

5.4.1 Audit Compliance Expectations

There must be a calibration program, described in a sufficiently detailed written procedure(s). The program should include the following:

- Mechanism, such as an Equipment Master List, for differentiating critical from non-critical equipment/instrumentation.
- Requirement that equipment/instrumentation be calibrated prior to initial use.

- System for identifying equipment (e.g., ID number).
- Mechanism for establishing calibration tolerances, which takes into consideration the allowable or existing process tolerance and the capability of the equipment being calibrated.
- System for assigning calibration frequencies. This should include the time window within which the calibration must be performed (e.g., every six months \pm two weeks). Frequencies may be documented on the Equipment Master List or in individual calibration procedures.
- Requirement for the use of suitably recognized standards and the requirement for maintaining certificates of traceability for all reference standards used in calibrations.
- Requirement that there be a calibration procedure for each piece or type of equipment/instrument. Each procedure should include:
 - standard(s) to be used
 - step by step calibration instructions
 - calibration tolerance
 - provisions for adjustments, if necessary
 - requirement for recording actual measurements found both before and after adjustment
- Format for the Calibration Record, including appropriate provisions for approval(s) of data.
- Provision for timely investigation of any Out of Tolerance (OOT) conditions, including:
 - an assessment of all production/work performed using the OOT equipment instrumentation since the previous acceptable calibration or verification/accuracy check
 - a review of that work to evaluate the possible impact upon product quality
 - a documented rationale, approved by the quality function, as to why product/work was or was not impacted
- Requirement that any OOT equipment/instrumentation be labeled 'Out of Service' and not be used until it is adjusted and found to be within the required tolerances.
- Following appropriate supervisory review and approval, calibration records should be retained on a schedule commensurate with site record retention policies. Records should be retained at least as long as other records associated with product manufactured using the equipment/instrumentation.
- An appropriate change control system, to cover:
 - change in a calibration tolerance
 - change in calibration frequency
 - change in a calibration procedure
 - addition/deletion of equipment/instrumentation to/from the calibration program
 - changes in location of equipment/instrumentation

(An example of audit checklist is shown in Attachment 11, provided on the ISPE Web site – see Appendix 6.)

5.4.2 Calibration Management Auditing

Auditing should verify that the relevant procedures are being followed correctly, by appropriately trained personnel. The scope of the audit should be clearly defined.

Auditing should verify that procedures and systems are being operated and completed successfully. The audit report should:

1. serve as the formal record of the audit and its findings
2. provide a major input when determining corrective action

The audit report should present an accurate objective record of what was audited and the findings. References made in the audit report to documentation examined during the audit should be unambiguous (e.g., by title, reference, date, version, copy number, author).

An audit report normally will contain:

1. an introduction
2. Scope information
3. organization of audit, including agenda, criteria, representatives
4. detailed findings
5. record of closing meeting
6. conclusions

Audit reports should be responded to with agreed actions and retained as part of the overall validation for a process.

5.4.3 Service Supplier Auditing

When considering a supplier to provide calibration contract services, a clear understanding of their capability should be achieved before any work is undertaken. This can be achieved by:

- formal supplier audit
- postal audit
- combination of formal supplier and postal audits

The appropriate selection should be based on the criticality of the activity, extent of the works, or business impact of the activity. (An example of a typical postal audit document is included in Attachment 22, provided on the ISPE Web site – see Appendix 6.)

5.5 Measurement Capability and the Potential Influence of Measurement Uncertainty

5.5.1 Basic Concepts of Measurement Uncertainty and Traceability

The concepts of measurement uncertainty and measurement traceability should be understood so that the quality and validity of a measurement or an instrument calibration can be appreciated.

This, hopefully, gives an insight to uncertainty, the relevance of an associated level of confidence, and how uncertainty increases as the length of the traceability chain increases. It also should be clear that the magnitude of the uncertainty estimate decreases as the skill of the operator or the reliability of the measurement process increases.

5.5.2 Measurement Uncertainty

Measurement uncertainty may be described as 'the possible deviation between a measurement result and the true (unknown) value – expressed with a given confidence.

For a given measurement, independent influencing factors tend to combine to give a normal probability distribution for the measurement results. Methods of combining of these factors have been developed which give more realistic values, but with some limitation in confidence for those values.

5.5.3 Measurement Traceability

One way of describing measurement traceability could be 'the property of a measurement whereby it can be related to national standards through an unbroken chain of calibrations; each link having stated uncertainties.'

Uncertainty increases as the length of the traceability chain increases and without an uncertainty estimate for each part of the chain, measurement traceability does not exist.

5.5.4 Relationship between Measurement Uncertainty and Traceability

The larger the allowance for error in a measurement, the greater the confidence in the allowance. For a given process, as the estimate of uncertainty increases, the confidence increases until, at some value, 100 % confidence is achieved.

The international measurement community has standardized on a level of confidence equivalent to approximately 95% (for further information on this and the selection of 'coverage factors,' refer to ISO Guide 98 – 3: (Reference 12, Appendix 16).

A confidence level of 95% means that in 19 out of 20 cases, the estimate of uncertainty is sufficiently large to cover the possible deviation between the result and true value, and conversely, in one out of 20 cases, it is not. If the confidence level were any higher, it would give rise to excessively pessimistic uncertainty estimates.

The potential range of this uncertainty should be evaluated and characterized only by persons with appropriate expertise.

Reasons for uncertainty, which are considered as uncertainty components, typically include:

- the uncertainty of the calibration of the reference device
- any change in the reference device over time
- the influence of environmental variations (temperature, humidity, pressure, etc.)
- the smallest resolvable difference in instrument indications

- the ability of the operator to repeat the process

Once evaluated for magnitude, these components should be combined statistically to derive a figure which can be quoted. This combination should be conducted in accordance with the relevant standards (e.g., ISO Guide: 98-3:2008 (Reference 12, Appendix 16)).

The combined figure is called 'the combined standard uncertainty,' and should be multiplied by a factor 'k' (which depends on the consistency, and therefore, the reliability of the data established during the evaluation) to give a figure referred to as the 'expanded uncertainty,' i.e., one expressed with a confidence of approximately 95%.

Typically, during combination, independent factors are combined using the root-sum-square technique, which has the effect of reducing the overall estimate, but amplifying the influence of the more dominant components. If such calculations are made using software tools, this allows for an investigation of the magnitude of each component on the final estimate. This allows focus to be placed on dominant factors, allowing them to be mitigated by improvements in the measurement method.

Traditional uncertainty analysis does not include known errors, such as errors reported on the certificate of calibration for a reference instrument. These 'known' errors should either be corrected or added, in full, to the uncertainty estimate.

5.5.5 Introduction to the Application of Measurement Uncertainty

When measuring a critical parameter, measurement uncertainty should be understood, in order to evaluate the potential risk associated with obtaining either a false pass or a false fail. Approaches to this evaluation include:

- the detailed scientific analysis of each source of uncertainty, throughout the measurement chain – building up to an uncertainty estimate for each individual measurement
- the backward looking 'if a safety margin (or buffer zone) of X% is allowed on the final pass/fail limits, this will have allowed more than enough for uncertainty'

Both approaches can be tailored to allow appropriate analysis work, dependent on the associated risk of an incorrect pass/fail decision.

A pragmatic approach may include a blend of the two approaches where the starting point is the consideration of the maximum limits of error that can be tolerated in the final measurement. Where it is possible to set failure limits that are significantly within the limits of error, it may be quicker to establish if the generically-assigned uncertainty, associated with the prevailing instrument and its associated calibration hierarchy, is acceptable. Sources of uncertainty should be considered.

An example showing how to view the suitability of typical system uncertainties against failure margins (or buffer zones) is provided in Appendix 2.

Working instruments used in pharmaceutical sites or in analytical laboratories are usually calibrated against "test instruments" or "reference standards," which have been calibrated by an external calibration organization. The quality of the indication given by a working instrument normally depends upon:

- the properties and condition of the reference standard(s) used to calibrate the working instrument
- the quality of the reference standard's own calibration data
- the appropriateness/compatibility of the methods used by the external organization to calibrate the test instrument and those used to calibrate the working instrument on plant or in the laboratory, particularly the level of environmental control

- the knowledge or skill of the staff involved during each calibration stage
- the properties of the working instrument

These factors lead to an estimate of measurement uncertainty concerning the validity of any reported measurement or calibration results. This estimate should be quoted in conjunction with a statement of “confidence probability” (usually 95%).

5.5.6 Steps Involved in the Evaluation of Measurement Uncertainty

The aim of this guidance is to promote a pragmatic approach which can establish some worst-case estimates of the calibration and measurement capability for critical parameters.

5.5.7 Review of Third Party Calibration Certificates for Reference Standards

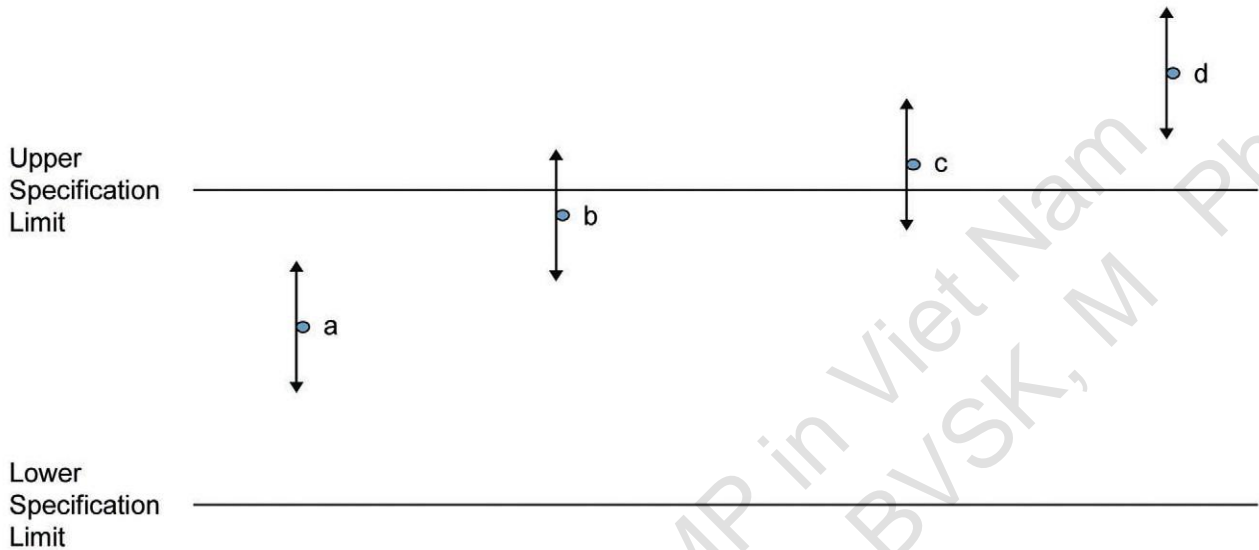
Appropriate reference standards should be selected. Equipment should have the required level of performance and be able to maintain this performance under real world conditions (for further information, see Section 6 of this Guide). Reliability and stability are key factors. Accurate equipment may be technically unsuitable or too fragile for use outside of a laboratory environment.

Reference standards should be calibrated by a competent (appropriately qualified) organization (for further information, see Section 6 of this Guide). The calibration ranges, test points, and configuration should be suitable for the intended use. It is considered good practice to capture this information in a specific Calibration Master List for test equipment.

The received “imported” calibration certificate should be checked. The certificate should clearly state: traceability to national/international standards, the method used, and all relevant prevailing environmental conditions. It also should show the errors at each test point, prior to and following any adjustment, along with a statement of the estimated measurement uncertainty.

The certificate should be checked to determine whether residual errors are within agreed limits. This assessment should include consideration of the potential influence of measurement uncertainty when trying to determine pass or fail decisions (see Figure 5.3).

Figure 5.3: A Representation of Various Influence Conditions



Instrument error results a to d – overlaid on the specification limits. For each result the respective measurement uncertainty estimates are shown by the arrows.. This represents the 4 possible influence conditions of measurement uncertainty when making statements of compliance with specification.

Notes for Figure 5.3:

- Result (a), the error – including an allowance for the extremes of reported measurement uncertainty – lies within both specification limits. In this case, therefore, it is reasonable to make a compliance statement such as *“this result is within specification.”*
- Result (b), the reported error is closer to the upper specification limit such that if the unknown true result was really at the uppermost extreme of the range of measurement uncertainty, it would not comply with specification. In this case, therefore, it is reasonable to make a compliance statement such as *“this result is probably within specification”* as the probability of the true result being close to the reported result is normally higher than it being at the outer limits of the measurement uncertainty range.
- Result (c), it is reasonable to make a compliance statement such as *“probably outside specification.”*
- Result (d), it is reasonable to make a compliance statement such as *“outside specification.”*

Given the ambiguity and inconsistency this can generate, it is considered good practice to have a policy on dealing with these various influence conditions. Outlines of three alternative policies are:

- A simple and conservative approach is to limit statements of compliance to the condition shown for result (a) above, i.e., only if the reported error when extended by the quoted measurement uncertainty still lies within specification can the result be declared a pass. Where measurement uncertainty values are quoted at a 95% confidence probability (see Appendix 2), there is still a very small risk that the true result differs from that reported by more than the estimate of measurement uncertainty, but this is a low risk and, therefore, the policy should still be considered conservative.

- A higher risk approach is to accept as compliant all results falling into the category of results (a) and (b) above. Essentially, this approach ignores the potential influence of measurement uncertainty and has been common practice in industry. The significance of a false pass decision, however, increases the further the band of uncertainty extends beyond the specification limit. If this policy is adopted, therefore, it would be prudent to include a requirement for an experienced Control and Instrumentation (C&I) person to confirm the compliance decision for cases where this situation occurs.
- An even higher risk approach is to accept as compliant all results that fall into categories of results (a) to (c) on the basis that even in case (c) the result does not conclusively demonstrate an out of compliance condition. This is a high risk approach which should be evaluated in light of the performance requirements for the test equipment and the accuracy limits set at each stage of the traceability chain – down to the point of measurement on site or in the laboratory.

Where external calibration organizations are asked to make the necessary compliance decisions on behalf of the pharmaceutical organization, the contract should state how the specification limits are selected and how the potential influence of measurement uncertainty will be treated. (**Note:** it is usually considered better to select larger tolerances than the manufacturer's specification, where the application allows, as compliance with manufacturer's specification may be difficult to achieve or demonstrate in the long term.)

Measurement uncertainty can lead to the incorrect or false acceptance and rejection of calibration results. Terms which may be used by pharmaceutical organizations include:

- False accept occurs when an instrument appears to pass specification limits when it actually fails:
 - Declaring an instrument to be within tolerance when it is out of tolerance has the potential for the instrument's reading to cause product to be made outside the intended process range.
- False reject occurs when an instrument appears to fail specifications when it actually passes:
 - False rejects may have a significant impact on business efficiency. For critical measurements, the calibration false accept rate should be considered.

When reviewing certificates for test equipment, it is considered good practice to refer to the previous certificate to monitor the level of drift between calibrations.

This information is useful in the next step and can give an early warning of reliability issues. Care should be taken when making conclusions, as any difference may be attributable to changes in traceability route or as a function of measurement uncertainty.

5.5.8 Establishing Generic Worst Case Uncertainties for In-House Calibration

The measurement capability of test equipment may not be fully expressed by its accuracy specification or by the estimated measurement uncertainty reported on its certificate of calibration.

The "real life" measurement capability may be determined by the ability to employ the test equipment under appropriate conditions, such that its associated calibration data remains valid.

For example, errors can occur when using a resistance decade box to simulate a resistance temperature probe when calibrating a temperature transmitter. If the transmitter is not configured for 4-wire measurement, the resistance of a poor connection could introduce an error equivalent to more than °C. Without the ability to correct for known errors or to ensure that the working instrument and the test instrument are measuring exactly the same parameter (i.e., they are in equilibrium) the true capability may be significantly degraded. In order to evaluate the measurement capability under real world conditions, it is necessary to consider a wide range of potential influence factors, such as:

- measurement uncertainty associated with the calibration of each piece of test equipment (**Note:** although not necessarily good practice, test probes and indicators are often calibrated separately)
- uncorrected errors reported on the calibration certificate(s) for the test equipment
- any uncorrected errors due to the method (e.g., alignment errors or the failure to correct for offsets such as stray resistance or fluid head)
- ambient temperature of use – compared to that prevailing during the test equipment's own calibration
- temperature gradients in use
- failure to achieve equilibrium, i.e., instability and gradients of any simulated sources
- long term drift of the test equipment
- resolution of the test equipment
- ambient pressure (especially fluctuations if measurements are referenced to atmospheric)
- sampling rate differences between working and test instrument (if stability of the source cannot be assured)
- interference sources, e.g., thermoelectric, electromagnetic, gravitational influences, and potential cross-sensitivities
- stability and resolution of the working instrument
- repeatability of the calibration method

It is suggested that as a minimum, the C&I representative on the Criticality Assessment Team should have an appreciation of the factors that contribute to measurement uncertainty at each stage of a traceability chain. The representative should be able to advise if suitable test instruments or calibration methods are available to ensure that the calibration limits, and the performance limits set for the working instruments, can be realized in practice.

It can be helpful to compile a list of factors that may influence a measurement. A standard generic list can help to ensure that each factor is considered although some may not be applicable. (An example of such a list is shown in Attachment 17, provided on the ISPE Web site – see Appendix 6.)

Were feasible, the maximum possible deviations in value of measured parameters should be assigned for each factor. This can usually either be found or estimated, e.g., an estimate of drift for the reference instrument can be established by examining differences between successive calibrations. The manufacturer's specification for the test equipment should provide details of the resolution on each range and the potential influence of ambient temperature. It also may provide guidance on sources of interference.

This process should provide a collection of lists which identify the typical measurement capability for each parameter. This summary of capabilities can be used in reviewing working instrument performance limits at CRA meetings. Failure limits which are no larger than the uncertainty of the calibration capability should be avoided.

If the capability appears inappropriate (i.e., the uncertainty is too large), a more detailed uncertainty analysis should be performed or influence factors should be more tightly controlled by using more advanced calibration methods. If neither of these suggest that pass or fail decisions can be met without fear of compromise from the influence of measurement uncertainty, a specialist supplier service may be required or the expected performance limits for the working instrument may need to be challenged as unrealistic.

The final stage of the on-site calibration exercise is to establish if the calibration results are compliant with the limits agreed. Again the policy with respect to measurement uncertainty should be clear. If an approach is to ignore the influence of uncertainty is adopted, the failure limits should be set in consideration of the limitations of the measurement capability (i.e., a level of guard-banding should have been introduced, assuming smaller process tolerances than are actually allowed).

5.5.9 True Performance of Working Instruments

In use, the measurement capability of each working instrument will be worse than the capability of the test equipment or procedure used for its calibration, even if it has a similar or better specification.

Factors such as the uncorrected calibration errors, differences in environmental conditions, failure to achieve equilibrium and drift play a significant part in degrading the measurement capability of an instrument once it is in service. Other factors will be determined in the early stages of process design, instrument selection, or protocol application.

Sampling points should be representative and response times/sampling rates and other critical factors should be suitable to monitor the parameter of interest. These may be grouped under the heading of "failure to achieve equilibrium." It may be necessary to take advice from the validation team/process development team regarding the likely magnitude of this uncertainty component. In addition to the measurement capability of test equipment and the method used to calibrate the working instrument, factors which should be considered include:

- uncorrected errors reported on the calibration certificate for the working instrument
- uncorrected errors due to the method of use (e.g., errors associated with the use of "standard" probes not included as part of the working instrument calibration)
- any uncorrected errors (due to alignment or the failure to correct for offsets)
- ambient temperature of use – compared to that prevailing during calibration
- temperature gradients in use compared to those during calibration (especially important in low differential pressure applications)
- failure to achieve equilibrium, i.e., instability and gradients in the process
- long term drift of the working instrument
- resolution of the working instrument
- ambient pressure (especially fluctuations if measurements are referenced to atmospheric)
- interference sources, e.g., thermoelectric, electromagnetic, gravitational influences, and potential cross-sensitivities

Formal uncertainty evaluation may be required, see Appendix 2.

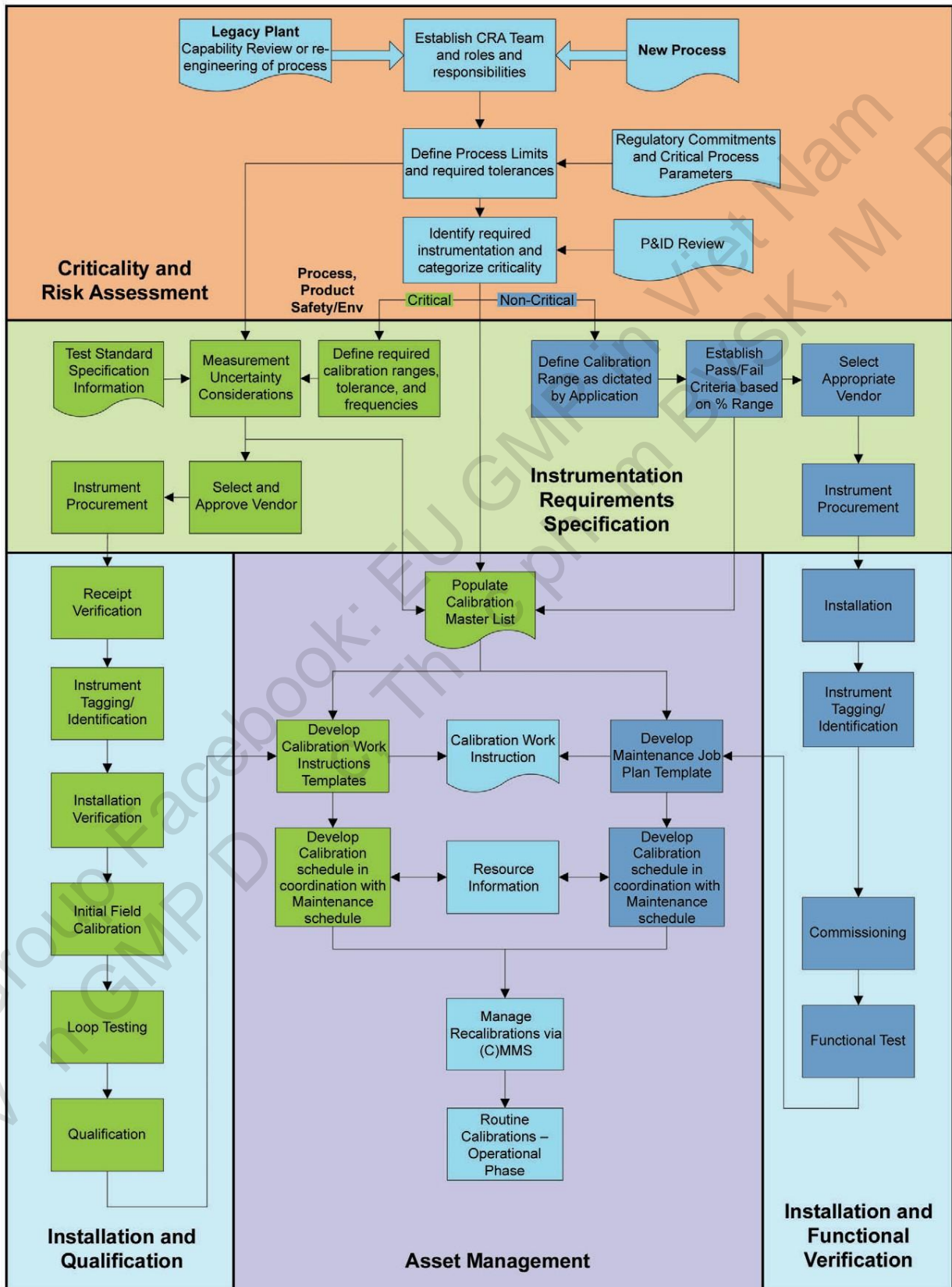
6 Project Phase

Most definitions of Calibration Management requirements will be initiated as part of a new project and include the requirement to perform a Criticality Risk Assessment (CRA) and use the data generated to specify appropriate instrumentation. The key requirements generated through these activities should be captured in a Calibration Master List (CML), which will become the master document referenced throughout verification activities and also will drive subsequent routine calibration activities in the Operation Phase.

The CRA activity is a Common Practice which can be invoked on legacy processes following a process change, process capability review, or cGMP remediation activity. For further information, see Section 5 of this Guide.

Figure 6.1 highlights the critical activities involved in managing the calibration of instrument assets through a Project Phase according to a documented risk assessment, the different approaches that may be applied when setting to work critical and non-critical loops, and the subsequent handover of key information for the management of those assets in the Operation Phase.

Figure 6.1: Project Phase Workflow



6.1 Roles and Responsibilities in the Project Phase

Representation from all elements of:

- Process/Science/Technology
- Quality Unit
- Engineering

The above are defined in Section 3 of this Guide.

Operations/Environment, Health, and Safety (EHS), expertise listed in Section 6 of this Guide should be established at the Project Phase. It typically falls upon the project group to organize and schedule the Criticality Risk Assessment. All areas should contribute to this process, as it establishes the foundation for all risk-based decision processes that follow. System Impact and Component Criticality Assessments can be a significant exercise and should be planned, managed, and documented accordingly.

6.1.1 Science, Technology, and Laboratory

Science, Technology, and Laboratory representatives should ensure that all process parameters included in regulatory commitment documents, identified as having the potential to impact product quality and patient safety or having the potential to seriously affect plant efficiencies are identified and have their proven acceptable range's defined. Science and Technology representatives should ensure that these parameters are captured in the Process Flow Document and any changes required due to process scale up, etc., are accurately accounted for and justified. For established legacy processes, this data may need to be derived from a review of batch production records, Standard Operating Procedures (SOPs) and historical plant/batch data.

6.1.2 Process Engineering

Process Engineering representatives should lead the effort of the System Impact and Component Criticality Assessment Team(s) in accordance with the guidelines contained in the ISPE Baseline Guide on Commissioning and Qualification (Reference 21, Appendix 16). They should ensure that the instruments selected are appropriate to the application and have been defined to the appropriate criticality, range, and accuracy. Process Engineering should sign the CML to accept that the specification of the listed instrument and its limits are appropriate to the related product and process.

6.1.3 Project Engineering

Project Engineering representatives should ensure that all instruments are recorded and specified appropriately for an application. Project Engineering representatives should ensure that instruments are installed and identified correctly in accordance with manufacturers' specifications. Appropriate calibration methods should be identified, and test facilities and calibration equipment provided to enable efficient execution of calibration activities. When required, Project Engineering representatives may provide measurement uncertainty calculations that demonstrate that the confidence level in the measurement and calibration processes is appropriate for the intended application.

Project Engineering representatives should sign the CML to qualify that the specification of the listed instrument and its limits have been defined and checked as appropriate to the related product and process.

Any loops that are identified as non-critical in the criticality risk assessment should be installed and inspected according to good engineering practice. This should include inspections to ensure that the correct instrument is received and installed in the correct location in accordance with manufacturer's instructions. If this exercise is performed by competent personnel, the level of documentation and quality oversight may be minimal. It helps to define the limits and frequency of subsequent calibration.

Project Engineering representatives also may check and sign each critical calibration certificate to ensure that it has been completed correctly and that any resulting actions are followed through in a timely fashion.

6.1.4 Operations

The Operations Group should be satisfied that the instruments fitted to the equipment supplied have been defined to the appropriate criticality, accuracy, and the frequency of future calibrations is appropriate to the planned operating modes of the facility. Operations Group representatives should sign the CML to accept that the specification of the listed instrument and its limits are appropriate to the related product and process and that they agree with and can work to the proposed calibration methods.

They should ensure that appropriate control measures and procedures are established, such that the department is advised of any deviations or non-conformances in a timely manner. The calibration system, records, and procedures also should be regularly reviewed and audited to ensure that management and control is still appropriate to the current process requirement. This applies especially to change control and out-of-specification results.

An engineer or competent person within the operations group should check and sign each critical calibration certificate to ensure that it has been completed correctly and that any resulting actions are followed through in a timely fashion.

Operations representatives should ensure that all instrument technicians, contractors, and calibration laboratories or service contract providers are qualified to a suitable level of competency to carry out calibrations to the required standard (see Section 7 of this Guide).

6.1.5 Quality Unit

Quality Unit representatives should ensure that the instruments fitted to the equipment have been defined to the appropriate criticality and that the frequency of calibrations is appropriate and justified. They also should ensure that appropriate procedures are established to ensure that the departments are advised of any deviations or non-conformances in a timely manner. They also should be satisfied that all calibration records, change control records, and procedures are maintained and updated, and that personnel performing calibration are properly trained and qualified to do so.

Quality Unit representatives may wish to counter sign calibration certificates when carrying out internal audits on the calibration system. Quality Unit representatives should sign the CML to qualify that the specification of the listed instrument and its limits are appropriate to the related product and process. Quality Unit representatives have the final signature to approve the CML fit for use.

On completion of the above activities, the Criticality Risk Assessment should be formally approved by all members of the team and stored as a controlled document in accordance with Good Documentation Practices (GDP).

6.2 Instrument Tagging/Identification

As a minimum, product, process, safety, and environmental critical instruments should be uniquely identifiable. The calibration status of product, process, safety, and environmental critical instruments should be available to the user. Sites may utilize calibration labels, a calibration database, or other site resources for making calibration status information available to the user or others.

Process instrumentation should be allocated instrument tagging, which gives information on process system/equipment allocation, measured variables, and function. Tagging should be completed in line with approved organizational procedures.

It is recommended that the following standards are referenced:

- ANSI/ISA S5.1 “Instrumentation Symbols and Identification” (Reference 9, Appendix 16)
- BS 1646: Part 1: 1979 “Symbolic Representation for Process Measurement Control Functions and Instrumentation.” Reference 7, Appendix 16)

Tagging systems may be developed using information from the associated Process and Instrumentation Diagram (P&ID) giving the type, equipment, and a numerical identifier, see Table 6.1.

Table 6.1: Example Tagging Information

TT-RE011-002		
TT = Type Temperature Transmitter	RE011 = Plant Equipment Reactor 011	002 = Numerical Identifier Taken from the P&ID
PIT-HVAC05-005		
PIT = Type Pressure Indicator Transmitter	HVAC05 = Plant Equipment HVAC 05	005 = Numerical Identifier Taken from the P&ID

A tag may be more like a maintenance identifier with the plant equipment ID first and then the other details, i.e., RE011-TT-002

Tagging system should be used if implementing a computerized management system. This provides useful search criteria when searching through historical data and compiling reports, comparing similar types of instrument, and associated to specific plant equipment.

Additionally, instrument (or calibrated equipment) serial numbers (or other Unique ID) should be recorded to enable traceability of the instrument history.

Example of an instrument tagging SOP is shown in Appendix 4.

6.3 Instrument Selection

Instrumentation plays a key role in successful pharmaceutical research and manufacturing operations. From laboratories to manufacturing plant, accurate measurements are an essential pre-requisite to understanding and controlling the process. Modern data processing/analysis systems are capable of significant levels of data fusion, process modeling, and visualization techniques. The selection, configuration, and maintenance of appropriate sensors and instrumentation are fundamental in achieving consistent product quality.

Parameters to be measured should be clearly defined. For example, the measurement of humidity could be either relative (which is inherently linked to temperature) or absolute (a representation of the amount of water vapor in a sample of gas). The anticipated range of values and the required precision should be identified. How the parameter is likely to change with time/position should be known, i.e., how dynamic and spatially consistent the conditions are likely to be. The application may call for rapid, accurate, tracking of a fast-changing parameter, or alternatively, the ability to average a value over time or space. This information helps to identify the characteristics for the sensor(s) and processing elements of the instrument system and the most likely measurement principle and instrument design.

Instrument features can be grouped into two categories:

1. inherent properties, i.e., the specified performance under ideal conditions

2. susceptibility to application/environmental influence factors

6.3.1 *Inherent Properties*

- measurement range (including ability to re-range)
- accuracy
- linearity
- short term stability (repeatability)
- long term stability (drift)
- resolution (for the selected range and output)
- hysteresis
- response time including damping/averaging capability
- reliability

6.3.2 *Susceptibility to Application/Environmental Influence Factors*

- ambient temperature range
- temperature gradients – both within the process media and ambient
- rate of temperature change
- humidity – both ambient and around the process media
- atmospheric air pressure
- relative air pressure due to height differences
- pressure fluctuation due to air movement or temperature change in sealed systems
- sensor contamination/fouling
- sensor specificity and response factor
- rate of change of measurement parameter
- orientation with respect to gravity
- electromagnetic interference
- various sources of cross-sensitivity
- vibration (may affect on some devices, e.g., mechanical gauges and coriolis flow meters)
- installation conditions (e.g., swirl-inducing upstream bends in flow metering applications)

- compatibility of materials – especially those in contact with product
- access limitations – for calibration/maintenance
- the need to have the sensor in a remote sampling location
- supply limitations/hazardous area compatibility requirements
- variability of a factor of the measure to used to measure the final measure under control (e.g., tare vs. gross to estimate the net weight)
- linearity among different instruments working in parallel in the same equipment (e.g., N weighing cells in N controls lines of a stand-alone checkweigher)

6.3.3 **Review of Instrument Specifications**

Additional data from manufacturers/suppliers and other suitable sources may be required to ensure an equivalent range of performance specifications is available for each instrument considered. Calculation of the specifications for values at the extremes of the operational range may be needed, such that comparable data in physical units (not % of range, etc.) is available.

This data should be used to establish which of the instruments available will measure the intended parameter, have the appropriate characteristics, cope with the prevailing conditions, and achieve an adequate accuracy throughout the operational envelope.

The “in use” performance specification (accuracy and failure limits) should be compared with the available calibration capability (see Appendix 2). This should ensure that the process limit requirements can be supported by the instrument **when the instrument itself is supported by the available calibration capability**. A limited in-house calibration capability will negate the high end performance of the best instruments.

When setting performance limits, process limits are not compromised. (For further information, see Section 6 of this Guide.)

6.3.4 **Common Selection Considerations**

6.3.4.1 *Range*

The range of an instrument should not significantly exceed the required operating range. Where an instrument is used in more than one application, it may be necessary to set a larger range so that it exceeds all the requirements. It is also a regulatory expectation that at least one test point is within the operating range of an instrument used in a product critical application. The operating range should be defined.

6.3.4.2 *Accuracy and Other Inherent Properties*

Accuracy is a major consideration when selecting an instrument. The measurement accuracy should be defined for each application, as the acceptable limits of a measurement are required to control or confirm a parameter and to assess whether a calibration has identified a pass or failure. (For further information, see Section 6 of this Guide.)

Normally two limits are required to define an instrument’s accuracy performance:

1. for normal operational accuracy
2. as a limit beyond which a failure is deemed to have occurred

Once the required accuracy limit for a measurement application has been defined in the criticality assessment process, the instrument details should be checked to ensure that it is capable of meeting that requirement consistently and without a level of drift that would result in a failure between calibration campaigns.

The selected instrument should have sufficient resolution, be able to track changes in the measurement parameter adequately (i.e., have an appropriate response time/sampling frequency), and be suitably free from hysteresis.

6.3.4.3 Application Considerations

Details of proposed applications may affect the performance of instrumentation and compromise measurement systems. Experienced personnel should review proposed applications to determine whether equipment will struggle to meet accuracy specifications in a particular application.

A wide range of factors should be considered and appropriate personnel should contribute to decisions related to applications. Examples issues include:

Example 1:

Hysteresis in measurement systems, such as tank gauging applications or lyophilizer shelf movements. Such applications require careful consideration regarding the required accuracy for movements in each direction and may require separate transducers covering each direction of movement or compensating control algorithms to ensure overall accuracy is not compromised by hysteresis.

Example 2:

Rate of change of ambient temperature: filled capillary level transmitters are particularly susceptible to changes in temperature. Care should be taken to understand the effects of any imbalance in the filled legs on the device's accuracy, before it is approved for use.

Example 3:

Sensor fouling: this can affect the periodicity of calibrations and may significantly affect the accuracy and response time of the measurement loop over time. Its effects on critical measurements should be understood so that they can be managed.

Example 4:

Wrong calculation of instrument accuracy: where a weighing cell is used to measure the gross weight of an object whose net weight is to be controlled and used to select conforming units from non-conforming units, the variability of the tare weight should be considered. For gross weighing systems, the device accuracy may be considered without taking into account the variability of the tare weights, leading to an incorrect calculation and causing inappropriate selection of equipment for weight control of the final product.

Numerical example:

If a weighing cell has an accuracy of ± 2 mg, this should be added to the variability of the tare weight, e.g., ± 4 mg for capsules size 3 used to encapsulate pharmaceutical product. This leads to a total accuracy of ± 6 mg. This is the accuracy that should be used to compare gross weight control systems with net weight control systems that directly control the net weight eliminating tare variability.

For documentation systems, the calibration certificate should consider that some calibrations will require tests to be performed on rising and falling values. This should be addressed in both pre- and post-calibration checks. A specific calibration certificate or an additional results sections on a standard sheet can be used to can meet this requirement.

6.4 Automation and Smart Instrumentation

Smart Instrumentation with communication capabilities to host systems allows additional measurement and diagnostic information from a field device to be made available. The use of Smart Instrumentation presents both opportunities and challenges in managing field instrument configuration, diagnosis, and calibration.

Self monitoring facilities may be used to enhance confidence between calibrations, but should not replace calibration activities. Accuracy should be assessed by performing a conventional calibration check where the sensor is exposed to a known physical parameter.

6.4.1 Requirements for Employing Smart Instrumentation

Smart Instrumentation that provide predictive diagnostic alerts need to communicate their status to appropriate personnel. Meter displays on the instrument itself are useful for local indication; however, a host system is needed to provide permanent monitoring capability.

Host systems can be hand held communicators, control systems, or dedicated Instrument Asset Management Systems (IAMS). Control system capabilities vary widely in their ability to support communications with intelligent instruments and in the degree of data integration. Advanced systems may use a single database for control system configuration and instrument configuration. This allows, e.g., a change to a transmitter's range to be automatically replicated in the control system's configuration, thus avoiding duplicate data entry and the risk of associated errors.

IAMS typically provide instrumentation management capabilities, including:

- management of configuration and specification data for both intelligent and conventional non-smart instrumentation, including integration with mobile hand-held communicators and diagnostic tools
- automatic recording of events for audit purposes of intelligent instrumentation configuration changes and diagnostic status changes
- diagnostic interrogation of intelligent instruments
- a window for preventative or predictive maintenance alerts for intelligent instruments that provide these capabilities

IAMS may include an integrated calibration management capability.

6.4.2 Final Stages of Selection

The final stage of instrument selection should be based upon an understanding of the:

- level of accuracy required from the loop
- issues presented by the application
- available calibration capability
- full cost of ownership, particularly the implications of periodic failure
- Quality Assurance procedures employed by the manufacturer, specifically adherence to the principles surrounding control of design and spare parts

6.5 Supplier Selection

Suppliers used for supply of calibration instrumentation or services should be assessed and approved for use. The nature and extent of the assessment should be risk-based and appropriate to the equipment or service being provided. The purpose of the assessment is to ensure that the equipment or service provided meets the quality standards expected of the pharmaceutical industry. The postal audit document (Attachment 22, provided on the ISPE Web Site – see Appendix 6) is useful in three ways:

1. To give an initial assessment of companies who could provide a service. For low criticality/risk, this could be all that will be necessary, particularly if there is relevant experience of working in the pharmaceutical industry.
2. To use as the basis for a physical audit and elicit those areas requiring more focus.
3. It may disqualify a potential provider before the expenditure of an on-site audit.

6.5.1 Calibration Laboratories

Calibration laboratories should provide measurements that are traceable to a recognized national or international standard. Laboratories selected to perform the calibration of critical or reference instruments should operate a quality management system in accordance with the principles of (Reference 10, Appendix 16) 17025, and preferably, should be formally accredited (for the relevant measurement field with an appropriate measurement capability), by the officially-appointed national body (e.g., UKAS in the UK) belonging to International Laboratory Accreditation Cooperation (ILAC).

Evidence of accreditation is normally sufficient to ensure that an effective Quality Management System is in place and a further assessment may not be deemed necessary. However, further assessments may be required to ensure that specific aspects of management, appropriate to the pharmaceutical industry, are in place. For example, systems for GxP awareness and contamination control plus any other company specific requirements would not form part of normal accreditation.

6.5.2 Instrumentation Suppliers

Although there are no specific requirements to assess the Quality Management System of instrumentation suppliers, it may be beneficial. It is desirable to have clear evidence for:

- a. change control systems, particularly with regard to the control/inspection of materials for wetted parts
- b. systems to ensure the calibration of supplied product (where required) is adequate and meets the traceability requirements
- c. complex instrumentation, software, and hardware processes are properly documented

6.5.3 Calibration Services

Suppliers providing on-site calibration activities should be assessed to ensure that the following elements of effective calibration and quality management are in place:

- quality management systems in compliance with ISO 9001 and ideally ISO 17025 (References 11 and 10, Appendix 16)
- training and competence of engineers/technicians performing the calibration activities
- management of reference standards

- methods of assuring the quality of data (e.g., routine cross checks on test equipment in addition to periodic calibration)
- development and control of calibration methods and control of calibration methods and the provision of these for authorization by the quality unit
- integrity and traceability of raw data obtained during calibration activities and generation of calibration reports
- definition of uncertainties of measurement
- management of third parties and sub-contractors
- de-contamination methods for test equipment

6.5.4 Types of Assessments

There are three main options for performing a supplier assessment:

1. basic assessment based on available information (e.g., ISO 17025 certification (Reference 10, Appendix 16))
2. postal audit, using a questionnaire (Attachment 22, provided on the ISPE Web site – see Appendix 6)
3. onsite audit, by relevant specialist, auditor, or audit team

The option selected depends on the available information and the risk presented by the supplier.

Risk-Based Decisions and Activities

The outcome of the supplier assessment will determine if use of that supplier is a high, medium, or low risk to the end user. End users should document why a given supplier has been selected, including mitigation of risks.

When selecting a supplier, the adequacy of their quality management system and their experience of regulated GxP industries should be considered.

6.6 Instrument Verification

Calibration may take place at various points during installation, commissioning, and testing of the instrument. Where possible, the instrumentation should be tested as part of the acceptance testing and during commissioning or site installation testing. Where this is not possible, calibration should be part of installation testing.

Instruments concerned with flow, load, or volume may be associated with 'wet' commissioning or functional testing.

As part of installation, documented verification is required that instrument specifications, accuracy, and installation practices conform to design documentation requirements. When possible, instruments should be delivered calibrated to the required specification.

The calibration certificate along with any other deliverables, e.g., hazardous area certification or product contact material certificates should be filed with the commissioning and verification documentation at the start of the instrument life cycle.

Each instrument loop should be verified and documented to confirm the connected instrument is correct, is installed in correct location, and that the installation conforms to the Process Flow Diagram, Engineering Line Diagram, Instrument hook-up, and Instrument Loop Drawing, where applicable. The instrument loop should be powered up and functionally checked during commissioning or installation testing stage.

Calibration methods should be developed for field calibrations and verified at the start of functional testing to ensure the measurement capability of the instrument and/or loop fulfills accuracy and range requirements. These methods should be captured within maintenance management plans together with range, tolerance, and calibration frequency derived from the risk assessment.

Once the maintenance management plan is populated and active, then records of the initial field calibrations (and functional tests performed on Non Critical loops) performed during commissioning and other verification activities can be entered into the maintenance management system as a record of the initial status of the equipment.

Process systems should be verified to provide documented evidence that the controlled variables of interest can be consistently maintained within the defined proven acceptable range of the critical process parameter and that operation at the limits of that range still manufactures product meeting quality requirements. The ability to meet environmental, safety, and business requirements also should be verified.

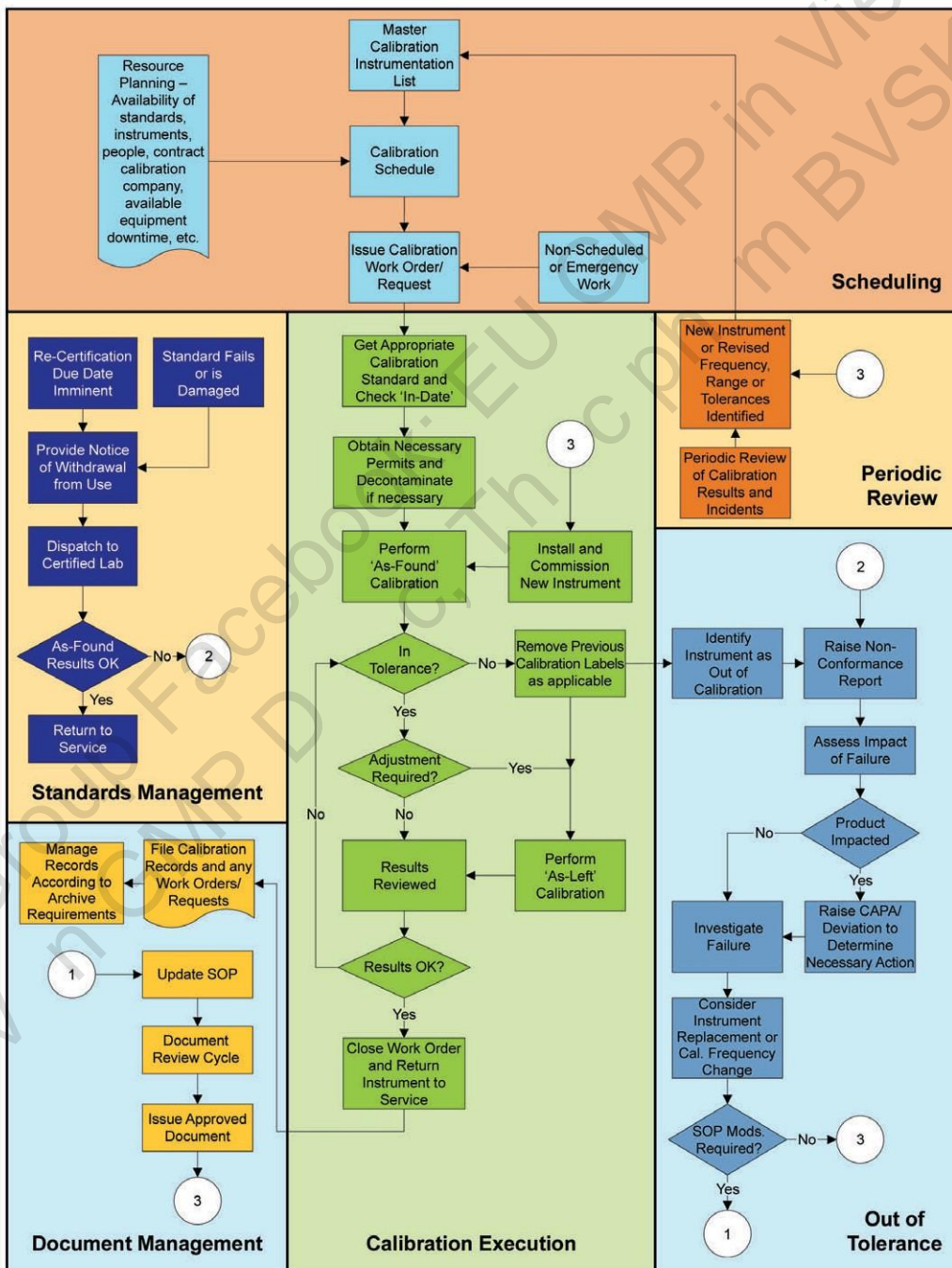
The documentation associated with supplied instrumentation should be provided to as defined in site calibration management procedures. This does not necessarily mean the use of site forms and data entry, but the closer the information is to these the easier the task of integrating new systems into the site calibration management process.

7 Operation Phase

This section describes the activities required for the management of calibration activities in the Operation Phase. The purpose of this section is to ensure that the processes required for instrument management, scheduling of activities, management of internal and external personnel, non-conformance handling, and management of all associated documentation are defined.

Figure 7.1 provides a high level overview of these activities and their interactions.

Figure 7.1: Operation Phase Workflow



7.1 Roles and Responsibilities in the Project Phase

Overall, departmental responsibilities for the management of the calibration process are defined in Section 3 of this Guide.

This section describes detailed tasks which have individual responsibilities referred to in individual calibration procedures.

7.1.1 Instrument Calibrator

Instrument calibrators should be appropriately trained in the calibration procedure and should ensure that:

- the equipment to be calibrated has been made available by Process Owner Department
- the relevant calibration procedures and test equipment are available and in date
- all safety precautions are followed
- any deviations from procedure are recorded and justified
- any amendments required to the procedure are communicated to the relevant SOP owner/author
- the Process Owner is alerted **immediately** when results are outside acceptance criteria
- the instrument calibration status is appropriately reflected, via labeling or other means
- equipment is left in an appropriate state to return to the customer
- all calibration documentation is completed and returned for approvals

7.1.2 Manager Responsible for Calibration

The manager responsible for calibration should ensure that:

- calibration regimes are adhered to and appropriate systems, equipment, resources, and materials are available to support these
- instrument calibrators have ongoing calibration-specific training and assessment to maintain competency
- calibration procedures are current and reflect latest calibration practice
- corrective actions for non-conformances are completed
- calibration records are maintained appropriately
- criticality risk assessment team members are informed of calibration management process changes
- all calibration standards/transfer standards and associated records are maintained
- periodic assessments are carried out for training and operation of management systems

7.1.3 Calibration Records Review

Two signatures should be required, as a minimum, to finalize the calibration status of any product critical instrument used in a GxP related process. These should be provided by:

- the instrument calibrator
- a reviewer (who is deemed competent to perform this activity by formal documented assessment). This signatory should review the calibration certificate in line with relevant SOPs.

7.2 Calibration Documentation

The purpose of good documentation practices in calibration management is to ensure that key documents are created, reviewed, approved, distributed, and stored in a controlled manner. This should ensure that key documents, such as calibration master lists and reports are used properly and establish a traceable and manageable basis for verification, including qualification and validation, activities.

Examples of documentation are supplied in attachments to this Guide, provided on the ISPE Web site (see Appendix 6).

Calibration documentation should demonstrate that instrument calibration has been completed in line with planned or breakdown repair requirements, detail the instrument status at the time of calibration, remedial actions (if any), and the results of non-conformance investigations.

An instrumentation calibration record should show the capability of a measuring instrument or system/loop to measure a variable within a required accuracy, over a specific range of values.

The calibration record, including the prime data, should be unambiguous and retrievable.

Hand-written data should be in indelible ink with errors crossed out with a single line. A brief justification should be added, and the amended data should be signed and dated. Ditto marks, including the word 'ditto' (or other similar markings or wording), should not be used.

7.2.1 Instrument Calibration Documentation

- **Calibration request documentation** (e.g., Computerized Maintenance Management System (CMMS) work order, unplanned work request, change control)
- **Calibration records** (results sheets, for example certificate of calibration, calibration test sheet)
- **Calibration report** (summary of calibration activities and calibration status with respect to the calibration request documentation)
- **Non-conformance documentation** (if a critical instrument calibration fails)

Documentation should be uniquely identifiable.

7.2.2 Calibration Request Documentation

Calibration request documents should reference:

- the scheduled date(s) of the calibration(s)
- identification of the instrument(s) under test

- the frequency at which the calibration should be carried out
- reference to any procedures or special instructions used for the calibration
- calibrated range and required calibration accuracies and failure limits

7.2.3 Calibration Records

Certificates of calibration should contain:

- unique reference to the request document
- unique identification of the instrument under test
- unique identification and next calibration due date of all measurement standards utilized during the calibration process
- range of calibration values
- required calibration accuracy and failure limits
- calibration procedure identification, including version
- 'as found' results, and if adjusted, the final 'as left' results
- date calibration was completed on
- indication of equipment status following calibration (pass/fail)
- name of the person carrying out the calibration
- name of the person reviewing the calibration record
- any necessary calculations or corrections used during the calibration process

Records may contain a measurement uncertainty value. See Appendix 2.

7.2.4 Calibration Report

The calibration report should contain:

- unique identification of the instrument under test
- unique reference to the request document
- date calibration was completed on
- indication of equipment status following calibration (pass/fail)
- description of any adjustments or repairs performed

7.2.5 Non-Conformance Documentation

Non-conformance documentation should contain:

- unique identification of the instrument under test
- failure or errors leading to the non-conformance
- actions resulting from the non-conformance

7.2.6 Review and Approval of Calibration Documentation

Calibration Records are completed by the instrument calibrator at the time and place of execution on original documentation and are approved by appropriately qualified, independent reviewers.

Review should include confirmation that:

- errors have been calculated correctly and are within Tolerances
- procedures used were correct and current
- valid test equipment was used
- the calibration activity was carried out in the appropriate schedule window
- the Pass/Fail status has been correctly assigned based upon the documented results
- any follow-up actions/observations or procedure/document corrections are followed up in a timely manner

7.2.7 Maintenance of Critical Instrumentation Calibration Documentation

Documentation should be stored in a suitable environment with restricted access to unauthorized personnel.

Documentation should be retained for an appropriate period of time, defined by approved company procedures, or linked to product shelf-life and clearly marked, indexed, and securely stored for ease of retrieval if or when required.

Instrument calibrations should follow approved written procedures, controlled in line with company policy.

Procedures, where appropriate, should reference requirements for EHS, GxP compliance, and Cleaning/Decontamination.

7.2.8 Electronic Records

Electronic records and signatures provide the opportunity to have a paperless calibration procedure, system, and data archive. A compliant system will produce electronic records, signatures (and/or hand-written signatures executed to electronic records) that are considered trustworthy, reliable, and generally, equivalent to paper records. Such records can be used in lieu of paper records.

The requirements of 21 CFR Part 11 and other international regulations for the use of electronic records and electronic signatures should be considered (Reference 4, Appendix 16).

The GAMP Good Practice Guide: A Risk-Based Approach to Compliant Electronic Records and Signatures provides further guidance on this topic (Reference 17, Appendix 16).

7.3 Calibration Methodology

Calibration methods may be determined by the instrument/device type, their process environment, their physical location, specification/process requirements, and available test equipment.

This section of the guide provides an overview and considerations of several different approaches.

7.3.1 Loop Calibration

Process:

The individual instrument or primary element (within an instrument loop) is removed from the process.

Using a stable calibration source monitored by traceable test equipment, known values are applied to the instrument/element and resulting indicated values/errors recorded.

Readings are taken at suitable points across the process range from the various points of indication in the loop, e.g., local indicator, control system, chart recorder. If a loop is successfully calibrated, separation of the loop and performance of sub-component calibrations may not be necessary.

When an instrument or primary element cannot be withdrawn from the process or is not routinely accessible, other calibration options should be considered. In these cases, additional uncertainties should be accounted for and accommodated.

One option is comparison calibration, where the test equipment may be positioned in close proximity to the device or in parallel with the loop in order to measure the value seen by device being compared, under the same conditions.

Another option is calibration using signal injection. The primary element is disconnected from the loop and an equivalent, traceable signal is injected into the loop. The signal is adjusted to cover the full process range of the loop. At a minimum, a single point system calibration at the operating point should be performed. If this is not possible, design modifications should be considered that enable the test equipment to measure the same quantity as the process element.

The risks versus the benefits for signal injection should be considered. The element should be only a small component of error in loop. If this is the recommended strategy, the risk assessment, including the impact of false accepts, should be re-evaluated. If this approach is selected, the uncertainty of the element should be assessed individually and combined with the loop uncertainty.

Considerations:

If errors are present that are greater than the specified loop accuracy, measurements should be taken at intermediate junctions between instruments to ascertain the source of the error.

Components of the loop may require individual calibration to bring the loop back into specification across its range.

Where it is not possible or reasonable to carry out a full loop calibration, the primary element and transmitter (if fitted) should be removed and calibrated on the bench, where possible.

The remaining loop components should be tested by signal injection as in loop calibration methodologies.

7.3.2 Bench Calibration

Process:

The individual instrument is entirely removed from the process to a more controllable environment, either within the manufacturing environment, engineering workshop, or calibration laboratory.

Where instrument or sensor has been removed for calibration purposes, once replaced, the loop should be calibrated at a single point to ensure that all connections are correct and to assess the total loop accuracy.

Advantages:

The instrument can be calibrated in a controlled set of conditions, temperature, humidity, etc., giving a more consistent test process.

Access to the instrument is not an issue; inputs can be simulated and outputs measured within the test environment more easily.

Contamination or corrosion can be readily observed. Decontamination of the instrument can be more tightly controlled prior to delivery and return to/from the calibrator.

Considerations:

This method of calibration may take longer, resulting in longer downtime for the equipment, a replacement instrument may need to be used and the calibration of the replacement instrument considered.

The calibration does not necessarily occur in the same environmental conditions as the process, resulting in differences in performance of the instrument.

Disconnection and subsequent reconnection of the instrument could result in introduction of errors caused by the connections, thus requiring a single point check following reconnection/reinstallation of the instrument.

7.3.3 Performance Evaluation

Overview:

This is a series of accuracy or performance checks performed periodically or following changes, typically within the laboratory environment, to detect deterioration in performance of instrumentation between calibration events.

Measurements can be taken at single points or over defined ranges and values obtained assessed against predefined acceptance criteria.

These checks could be linked to preventative maintenance activities to ensure performance has not been adversely affected by the maintenance activity.

An example would be performance evaluation of an HPLC system which may include:

- pump flow rate accuracy checks
- injector reproducibility
- detector accuracy/linearity
- column heater/chiller accuracy

These checks would be additional to full system calibration activities which would involve greater use of reference standards. Performance evaluation checks would involve more generation and evaluation of system outputs, e.g., peak heights/areas for High Pressure Liquid Chromatography (HPLC) systems.

Considerations:

The frequency and triggers for these events should be defined along with the acceptance criteria for each evaluation check.

The procedure to be followed in the event of a failure should be defined with clear links to the relevant Deviation or Corrective and Preventive Action (CAPA) systems to assess impact of the failure on product tested/manufactured.

7.3.1 Instrument Verification Checks

Overview:

These are tests performed on a frequent basis to detect and adjust for drift in calibrated systems prone to high levels of drift, e.g., balances, scales, or pH meters.

These checks can occur at a variety of frequencies, daily, weekly, monthly, or before each use, dependent on:

- the amount/speed of drift present in the system
- the frequency of use of the system
- the criticality of the system
- intended use of the system

These should be considered when setting the frequency of checks and the number of test points, e.g., single point, maximum/minimum, or across the operating range.

The outcome of these checks should be recorded and their performance verified.

If an adjustment is necessary, a full calibration, including 'as found' and 'as left' data should be performed and documented.

(Examples of procedures currently in use for the calibration of balances are shown in Attachments 18 and 19, provided on the ISPE Web site – see Appendix 6.)

7.4 Calibration Process

7.4.1 Request Documentation Issued to Instrument Calibrator

Request documentation should clearly state or reference calibration activities to be undertaken and all relevant pass/fail criteria.

7.4.2 Delivery from Process Owner

7.4.2.1 Cleaning and Decontamination

If appropriate, the Process Owner should ensure that instrument(s) are free from any materials hazardous to health prior to release for calibration, inspection, servicing, or repair. Typical hazards include:

- blood, body fluids, respired gases, pathological samples
- other biohazards
- actives, chemicals, substances hazardous to health
- other hazards include, e.g., radiation

A formal record of cleaning/decontamination of instruments should be maintained.

The requirements for cleaning/decontamination after calibration should be considered.

(An example checklist for decommissioning of instrumentation is included in Attachment 10, provided on the ISPE Web site – see Appendix 6.)

7.4.2.2 *Other Health and Safety Requirements*

Processes/equipment or facilities should be in an appropriately safe condition to enable calibration activities.

The impact of final control element movement, which could occur during the calibration process, should be considered and measures undertaken to disable or control this action if it poses a risk.

7.4.3 **Completion of Instrument Calibration**

7.4.3.1 *Test Equipment Requirements*

Calibration test equipment should have a better accuracy than that of the instrumentation to be calibrated. Test equipment should be traceable to national standards or equivalent international standards. Certified instruments also may be acceptable.

7.4.3.2 *Determination of Calibration Status*

Unambiguous data should be available to the instrument calibrator to ensure that the pass/fail status of calibration can be determined. This should be based on the 'as found' results.

If the 'as found' results are in tolerance, this is generally considered a passing calibration. An instrument may be found in tolerance, but still be adjusted; however, this should not be considered a failed calibration.

If the 'as found' results are out of tolerance, this is generally considered a failed calibration.

7.4.3.3 *Visibility of Instrumentation Calibration Status*

The calibration status for an instrument should be clearly identified to enable the plant operations personnel to readily ascertain if the instrument is 'critical' and able to be used. This should be either by direct labeling of the instrument or by referenced local identification.

The use of color coded labels incorporating details of the next calibration due date is a well established method of identifying product critical instruments. Management of the label update process should be robust and ascertaining the calibration status of an inaccessible device may not always be practical.

Other methods of off-line status identification could include status boards located in control rooms or adjacent to the equipment concerned, or maintenance management systems that are easily accessible to the user and present status information in an easily understood manner. This may be facilitated by labeling, status boards, or electronic means, e.g., bar-coding, linking to calibration management software, or a CMMS.

7.4.3.4 *Other Activities Arising from Instrument Calibration*

The impact of calibration activities on configurable instrumentation should be considered. On completion of calibration/adjustments, configuration parameter changes may be updated or recorded.

Specific calibration requirements should be considered when changes occur in operation, following maintenance, and when there is any physical intervention.

7.4.3.5 *Instrument Release*

It is expected that instrumentation is returned to the Process Owner in appropriate condition. When this is not possible, Process Owner/quality authorization should be readily determinable and documented. This should be captured by a suitable formal method, such as CAPA.

7.5 Training

Personnel, including contractors, involved in calibration activities should be given appropriate training covering all calibration related GxP requirements and specific calibration methodologies.

Training SOPs covering roles, responsibilities, plans, and records should be established covering GxP requirements for the calibration activities.

7.5.1 *Training Records*

Training records should be maintained to provide evidence of individual competency.

The following may form part of the training records, as appropriate:

- Trainee's full name
- copy of trainee's role and responsibilities
- specific training requirements for the role and responsibilities
- records of training undertaken by individual including activities/competencies
- date training undertaken
- expiry date of training, where re-certification may be required
- additional training activities, such as 'on the job' or job shadowing
- evidence of attendance at courses and presentations relevant to the role and responsibilities undertaken
- written assessments where appropriate that demonstrate understanding of a procedure – validation/evaluation of the training given

Periodic reviews of training records should be reviewed periodically.

7.6 Management of Third Party Calibration

Calibration may be carried out by third parties (e.g., contractors or instrument suppliers), but the responsibility for ensuring that calibration procedures have been correctly followed remains with the instrument owner (i.e., the regulated company).

The regulated company should assess the competence of the 3rd party contractors (the supplier) by performing an audit or by other appropriate means, and should use only competent contractors approved in this way (see Section 6 of this Guide).

The supplier should maintain suitable premises (if applicable), equipment, knowledge, and experienced/competent personnel. They should not pass to a sub-contractor any of the work entrusted to them nor change any of the agreed tests/methods, standards, or limits without the regulated company's prior evaluation and approval of the arrangements.

There should be a written contract covering the work to be carried out by the supplier and any technical arrangements made concerning it. This contract should be drawn up with the involvement of suitably qualified and experienced personnel and should cover:

1. Specify the respective responsibilities of the regulated company and supplier.
2. Describe (or reference) the tests to be done and the standards and limits to be applied.
3. Describe, or make reference to, the quality system to be applied by the supplier.
4. Specify the documentation to be used, produced, and retained by the supplier and to be supplied by the regulated company
5. Permit the regulated company and specified regulatory authorities to visit the premises of the supplier for the purposes of performing audits relevant to the calibration activities.
6. Specify the arrangements for handling, packing, and transporting the item(s) to be calibrated to minimize the potential for damage in transit.
7. Describe any hazards associated with the use or testing of the item(s).
8. Determine the return requirements and specifically cleaning requirements for product contact parts.
9. Specify the notification to the regulated company of any out of tolerance conditions found on test instruments used to calibrate item(s) belonging to the regulated company.

Documentation, supplied by the supplier to the regulated company on completion of calibration, should clearly identify the item(s) concerned, show the initial test results, indicate any adjustments made, and (where relevant) the test results after adjustment.

Any raw data from the tests should be supplied to the regulated company (unless it has been specifically agreed that the supplier should securely retain these). The documentation should record the test methods, standards, and limits applied, or give references to these. There should be a clear statement, signed by a responsible person, indicating whether or not items have been left in full working order.

When the regulated company receives items returned from the supplier, the items should be carefully examined for possible damage in transit. An appropriately qualified and trained person should review the documentation from the supplier. Where appropriate, this person should record in writing the acceptance of the items with signature and date.

7.7 Calibration Non-Conformance

A non-conformance investigation should be conducted when a product critical instrument has failed calibration.

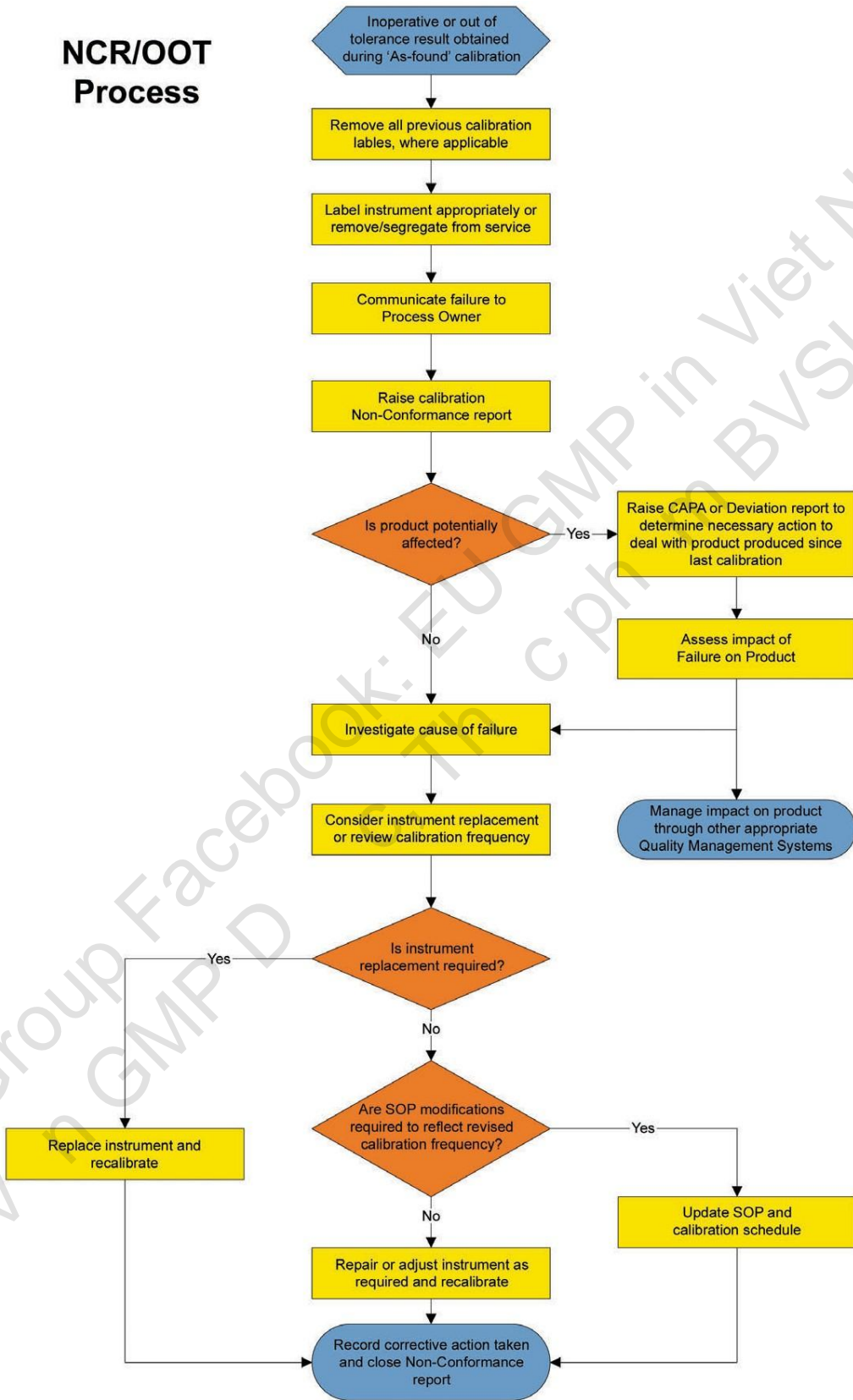
If the 'as found' results indicate that the instrument is inoperative or outside the tolerances, the following actions should be taken:

1. Previous calibration labels should be removed, where applicable.
2. An appropriate label should be attached (e.g., 'out of calibration' or 'do not use') or the instrument should be removed from service and/or segregated to prevent its use.
3. The failure of the instrument should be logged and this information should be readily available.
4. A non-conformance report should be raised for all failed product critical instruments as soon as possible.
5. The action to repair, adjust, or replace the instrument should be followed by a complete calibration check.
6. In the event of non-conformance, the Quality Unit should be contacted to assess the potential risk to product quality which should ultimately link to the protection of the patient.
7. An investigation should take place to analyze the effect of readjustment on the process and the control system that the instrument feeds information into. In the case of test instruments, utilize Reverse Traceability to determine which critical instruments were calibrated by this instrument during the selected time period, and evaluate the potential impact on the process.
8. Previous calibrations should be investigated to ascertain the performance of the instrument. It also should be noted that failure of the instrument may be caused by external forces, process medium, and fitness for purpose or incorrect installation. Fitting a like for like instrument may not be the only solution. Many modern calibration management software programs will provide historical analysis to assist with this investigation.
9. The non-conformance report should be completed, approved, and filed.

The non-conformance report should initiate and be a function of a CAPA process; this assists in ensuring that the calibration management process operates as an integrated component of the overall quality program.

Figure 7.2

NCR/OOT Process



7.8 Decommissioning of Instruments

Decommissioning of an instrument should be initiated and controlled using appropriate internal change control procedures to document the change to the equipment and to represent the need for a final, unscheduled, calibration event. Instruments that are determined as unable to be located should be decommissioned in a timely manner.

Within the change control documentation, the parent equipment, the instruments being decommissioned, and the reason for decommissioning should be clearly and accurately described to ensure full traceability in the event that the specific instrumentation is put back into use. It should be verified that the specific instrumentation can be identified and linked to a specific calibration identification number via the use of labeling or tagging.

Prior to removal and decommissioning, the instrumentation should be subjected to a final calibration event, per a defined and approved procedure, following all standard precautions relating to decontamination and 'making-safe' of the instrument. This should ensure that the Health and Safety risk is managed both during the calibration event and following subsequent removal of the instrument, potentially to storage for future re-use.

An 'as-found' calibration event is normally required for the final calibration, i.e., no adjustment of the instrument is needed prior to removal. If the final calibration cannot be performed (i.e., instrument cannot be located or is inoperative) or the instrument is found to be out of tolerance, the standard non-conformance procedure should be followed to determine the impact on product produced since the last calibration.

If the final calibration proves the instrument to be in tolerance, the instrument can be decommissioned, the calibration schedule updated to reflect the status of the instrument, and the calibration records archived in accordance with good documentation practices for retention of records. The instrument identification should not be deleted permanently from any electronic calibration management systems or re-used for other instrumentation.

Where an instrument may be re-used, a full calibration history and audit trail for the instrument should exist and should be maintained.

(An example checklist for decommissioning of instrumentation is included in Attachment 10, provided on the ISPE Web site – see Appendix 6.)

7.8.1 Record Retention, Archive, and Retrieval

It may be necessary to archive instrument data when a system or plant item is decommissioned. This data is likely to be associated with a CMMS.

The process for control system record retention, archiving, and retrieval should be followed in line with GAMP 5 Appendix O13 and the GAMP Good Practice Guide: Electronic Data Archiving (References 16 and 17, Appendix 16). Considerations for CMMSs include:

- Systems may have specific formats or require specific system hardware in order to retrieve records, particularly as systems age, methods for maintaining record readability, along with options for data/record migration or conversion to another format, e.g., to printed paper records should be considered.
- CMMSs may include historical trend data; such databases can become very large, particularly where significant analogue data trends are taken at frequent intervals, and alarm and event information is recorded.
- The timing for archiving historical data from the live system should be considered: it may be more convenient to keep this on the system as this allows ready analysis of trends, but may be an issue in relation to on-line storage capacity.
- The impact of daylight saving time on data historian trends and events should be considered.

- Local buffering of data should be considered, e.g., where there is a central historian server, the requirements for local systems would be in terms of data buffering if the historian connection be unavailable.

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8 Laboratory and Analytical Equipment

Laboratory and analytical equipment contain a sensor that reads a particular parameter(s) and reports the information into a display in human readable format. Between the sensor and the display there may be conditioning or conversion of the signal prior to display.

The calibration process must use a known standard (i.e., primary or secondary standard), against the primary sensing element with the resultant reading captured from either the instrument or secondary instrument.

The calibration process may require a number of replicate readings to confirm the statistical probability of the result.

After calibration, specific types of laboratory and analytical equipment require requalification to verify the instrument is fit for intended use.

The following calibration requirements should be considered for laboratory and analytical equipment:

- **Method** – how do the routine processes for operation link to the requirements to ensure traceability to a known reference standard for critical measurement parameters?
- **Criticality and Risk Assessment** – of the complete system and the contributions of the component parts to data integrity.
- **Calibration Type** – at time of use versus periodic.
- **Verification** – most analytical instruments are a combination of measurement, control, and computing. These systems will need a coordinated approach to link calibration into the overall scheme of verification. Guidance may be found in GAMP 5 (Reference 17, Appendix 16).

A large variety of laboratory and analytical systems, ranging from simple to complex multiple-function technologies are used in the pharmaceutical industry to acquire data. An analyst's objective is to use systems that are fit for intended use that meet regulatory requirements. Because calibration is a fundamental early step to ensure the fitness for intended use, there is a direct correlation between the quality of calibration and the quality of the result.

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9 Other Considerations

9.1 Fieldbus

Modern fieldbus instrumentation provides many attributes that can reduce the calibration burden. The digital signal format ensures that:

- overall loop performance may be characterized just by the transmitter accuracy
- the accuracy of the loop is not compromised by converters in analogue input cards, etc.

The control system can be used to verify that the correct instrument is placed in the allocated position and range and configuration parameters can be set remotely. This can help to reduce commissioning.

Fieldbus instruments may provide access to secondary internal measurement parameters; a single instrument may provide several measurements. The level of criticality assessment for the parameter which requires the most stringent criticality risk assessment should be applied to the entire instrument.

Individual measurement uncertainty calculations should be generated for each critical measurement.

Non-critical measurements may require more stringent calibration management and it may be more cost effective to employ separate instruments for non-critical measurement loops.

The accuracy of secondary measurements may not be adequate for critical loops. Hidden functionality and hidden measurements, e.g., temperature measurements within conductivity meters, should be considered.

9.2 Auto Calibration

The outputs of smart instruments which have 'self calibration' functionality may be set remotely via a supervisory computer either in the Distributed Control System (DCS), as part of an asset management system, or via hand held communications devices or PCs running suitable communications software. These features can assist control system commissioning activities, but do not constitute a calibration function.

Transmitters or instrument loops should be calibrated by comparison with known standards.

Internal calibration references in smart instruments should maintain accurate process readings and output from the device. Asset management systems may provide alerts/alarms on the internal reference and other diagnostic information. Internal references normally cannot be turned on or off. Calibrations should be performed with the internal reference active as it is during process measurement. Use of Statistical Process Monitoring should prove the stability between calibrations.

Example of Self-Calibration Performed by Comparison With a Known Standard

Capsule filler equipped with in-line capacitive sensors used to measure the mass of pharmaceutical product dosed into each capsule (100%). Sensors measure the variation of an electrical field that is related to the mass of the product. The measure from the capacitive sensor must be transformed in weight (mg) through a calibration factor.

This factor is initially calculated using analytical scales as "known standards" and is continuously maintained under control by means of the self-calibration algorithm. Real time measures coming from capacitive sensors are continuously checked against analytical scale results in order to evaluate if the calibration factor is valid or needs to be re-calculated.

Manufacturers may promote instruments which use control algorithms to automatically monitor and adjust internal parameters to compensate for drift in electronic circuits. The risk involved in leaving this functionality operational should be considered. There is no 'as-found' and 'as-left' audit trail to confirm that the instrument has performed predictably between calibrations. A pragmatic approach may be to turn off these features on instruments used in regulated environments.

9.3 On-Line Alerts

On-line alerts can be configured to alert operators or maintenance personnel when its accuracy may be compromised by system degradation, sensor problems, or process conditions outside of its design parameters. If these alerts are monitored by online (24/7) asset management systems which can be used to initiate corrective action, they may be used to generate data to support extension of calibration periods.

Routine time based calibration activities on non-critical loops may be replaced; however, the impact of identifying loop deficiencies after a protracted time should be considered, as a significant amount of product may have been put at risk. Alarms or alerts should be acknowledged with the acknowledgement time and date stamped.

The asset management system audit trail should capture the time and date stamp when action was taken for a given device.

9.4 Self Documenting Calibrators/Asset Management Systems

Self documenting calibrators which can interface with fieldbus systems provide the benefits of reducing the likelihood of transcription errors and providing improved audit trail facilities during calibration.

If integrated with asset management systems, these systems may declare the pass or fail status of a calibration activity automatically and independently of the operator. Validation of the result by the system operator should be considered. A physical review and authorization step usually is required for pharmaceutical operations.

The asset management system may provide tools to analyze loop calibration performance over time and recommend adjustments to calibration frequency, as well as identify suspect loops which are failing calibration regularly, and therefore, require investigation.

9.5 Process Analytical Technology

Process Analytical Technology (PAT) employs multivariate measurement analysis to control and demonstrate that processes are being operated within a defined 'Design Space' proven to consistently produce product meeting all regulatory and quality parameters. Such measurements should be classified as process critical.

Each loop in a PAT measurement strategy should be calibrated to the same schedule. The status of critical measurements contributing to this quality control strategy should:

- be known to have been within specification at relevant check points
- support disposition decisions made on product manufactured between successful calibration points

Examples of the use of instruments following PAT philosophy include:

- Near Infrared (NIR) spectrometers to check blend or content uniformity

- In-line or on-line weight control system (100% or statistical) that correlates the measures to the physical devices producing them and immediately performs a feedback action to the process (e.g., all weights are lower than the target, and therefore, increases the volume of product to be dosed).
- In-line or on-line systems provide higher level of process knowledge than at-line or stand-alone systems that just select the production without an effective feedback to the process.

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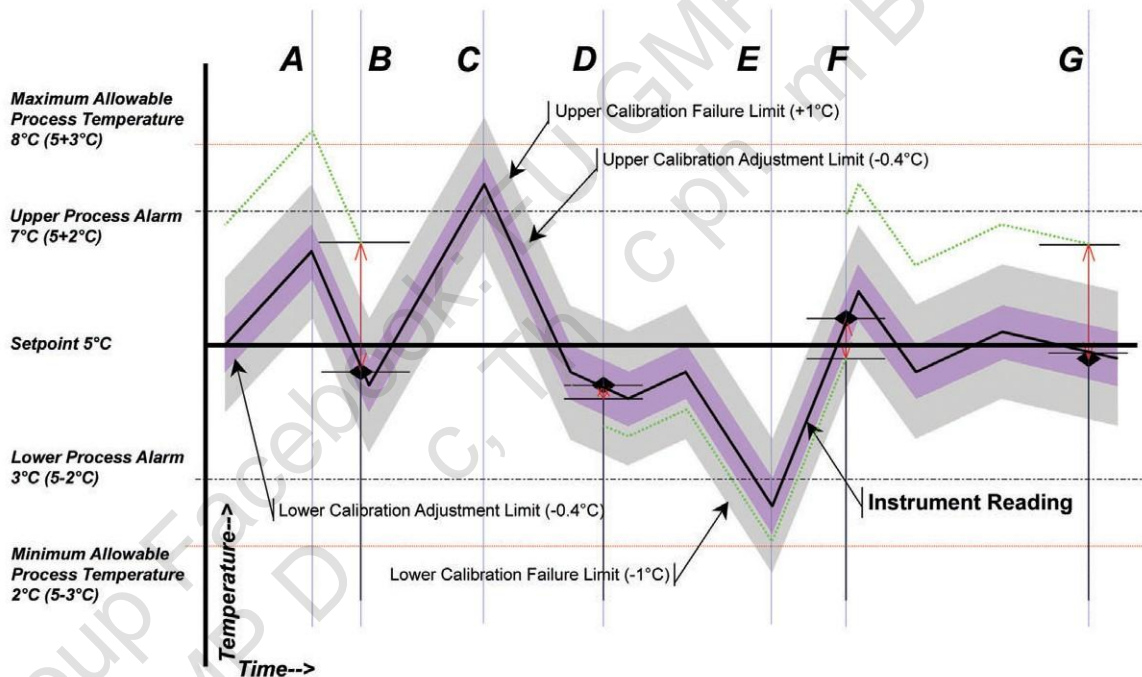
10 Appendix 1 – Worked Example Showing Tolerance

Setting and using process alarm, calibration adjustment, and tolerance.

Figure 10.1 provides an example for a fictional case where the product being processed needs to be controlled to 5°C ±3°C. Processing outside this temperature range will result in out of spec material. It is known that the control system can consistently achieve ±2°C, this allows ±1°C for the instrument. The instrument itself is capable of achieving ±0.4°C. The settings are therefore:

- Process Alarm Limit ±2°C
- Tolerance: ±1°C
- Calibration Adjustment Limit: ±0.4°C

Figure 10.1: Example – Control to 5°C ±3°C





C and E: Process Control

The shown/recorded reading has exceeded the **Process Alarm Limit**; adding in the allowable error for the temperature instrument (1°C), it can be seen that the absolute allowable value may have been exceeded and an alarm must be raised to test the quality of the product made at that time.

B, D, F, and G: Scheduled Calibrations

Calibrations are carried out at regular, timed intervals, indicated at points **B, D, F, and G** and marked:

-  The arrows: indicate the 'as found reading' error.
-  The dotted line then indicates what the **actual** value may have been assuming the found error to have been present at all times since the previous calibration.

Calibration checks at **B** and **G** show that the tolerance has been exceeded and an exception report should be raised and an investigation carried out on the product made and/or process conditions since the previous calibration.

The calibration check at **B** will trigger an investigation of the process conditions between **B** and the previous calibration check. In this case, a potential problem at **A** will be highlighted, indicating that the **actual** temperature may have exceeded the **absolute alarm condition of 8°C**. Product made at this time will need to be tested for quality.

The calibration check at **G** will trigger an investigation of the process conditions between **G** and the previous calibration check at **F**. In this case, it can be seen that there is no potential for the product processing temperature to have exceeded the absolute alarm condition, and all that is needed is an investigation of the instrument before adjusting it to within its calibration adjustment limits or replacing/repairing it.

The calibration check at **F** shows that the tolerance has not been exceeded, but that the calibration adjustment limits have been exceeded and the instrument can be simply adjusted to within its adjustment limits.

The calibration check at **D** shows that the instrument has not exceeded its adjustment limits and no further action is required.

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Figure 10.2: Relationship Between Process Tolerances, Alert, and Action Alarm Limits

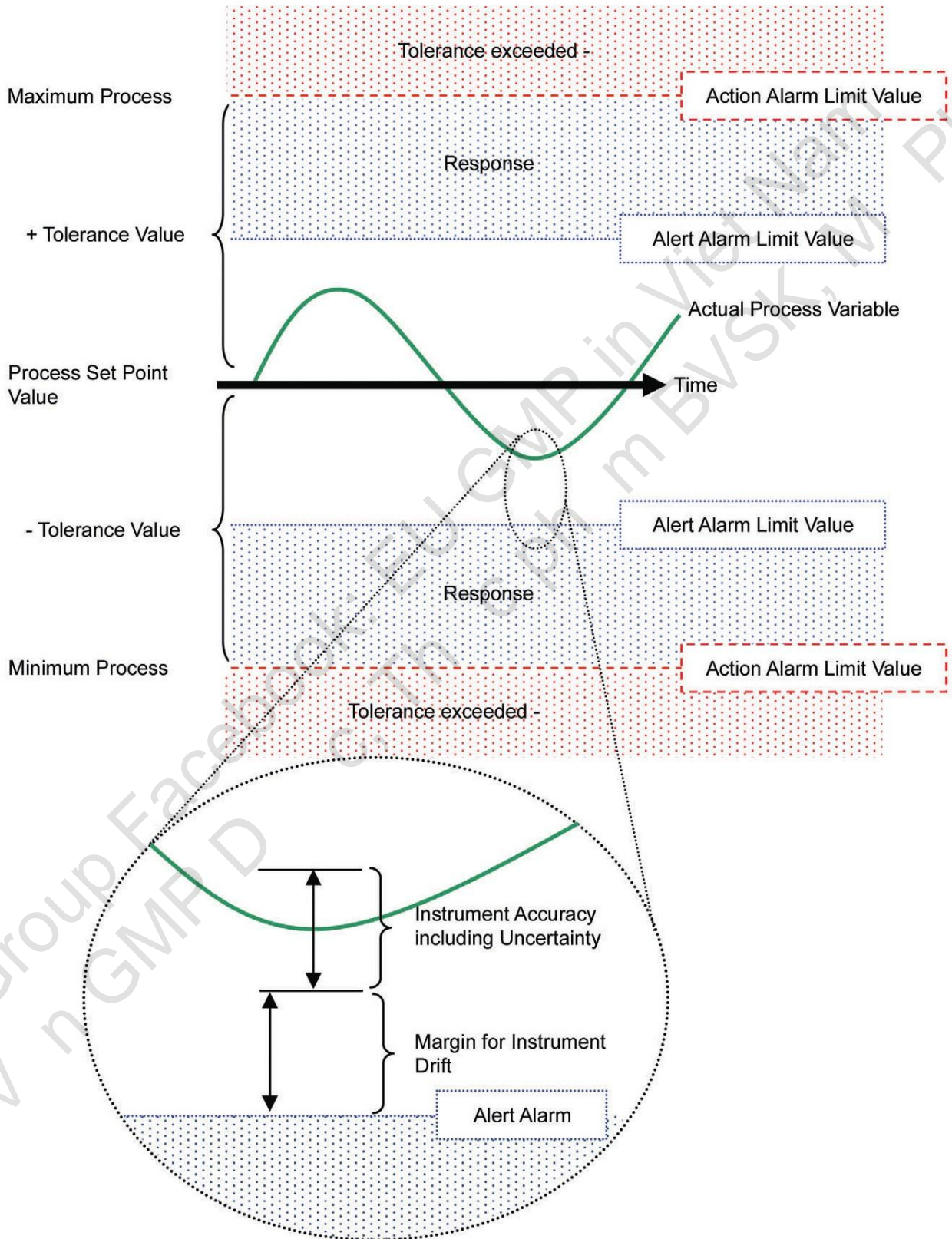


Figure 10.3 shows an **example** of using risk management to determine the setting of calibration frequency. It is not intended to be prescriptive.

Figure 10.3: Example Risk Management and Setting of Calibration Frequency

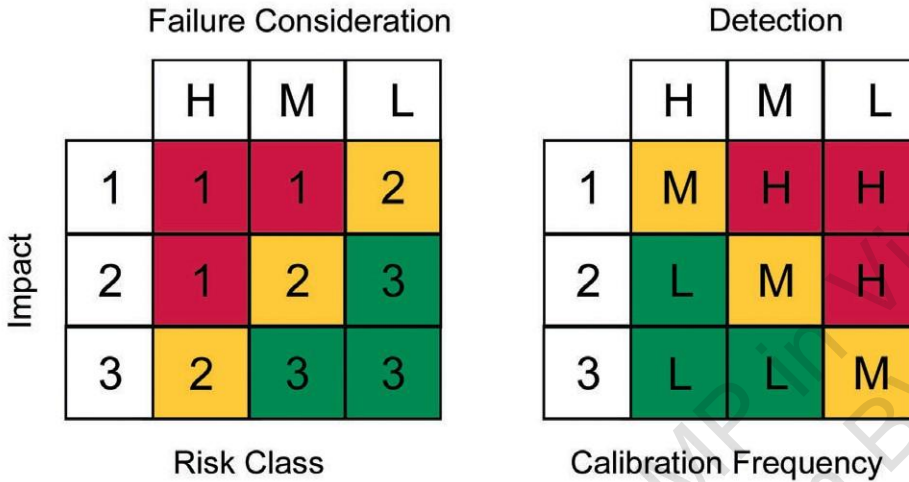


Table 10.1: Impact of Instrument Failure

1	High Impact
2	Medium Impact
3	Low Impact

Table 10.2: Failure Consideration

High	Unknown instrument pedigree without supporting information relating to stable performance and/or operation or Challenging process conditions with high measurement and control demands that apply on a routine daily/weekly basis
Medium	Known instrument pedigree with supporting information from supplier relating to stable performance and operation and/or operation or Stable process conditions with measurement/control demands that apply on a routine monthly basis
Low	Established instrument pedigree with both supporting information from supplier and historical data relating to performance and/or operation or Stable process conditions with measurement and control demands that apply on a quarterly/bi annual basis

Table 10.3: Failure Detection

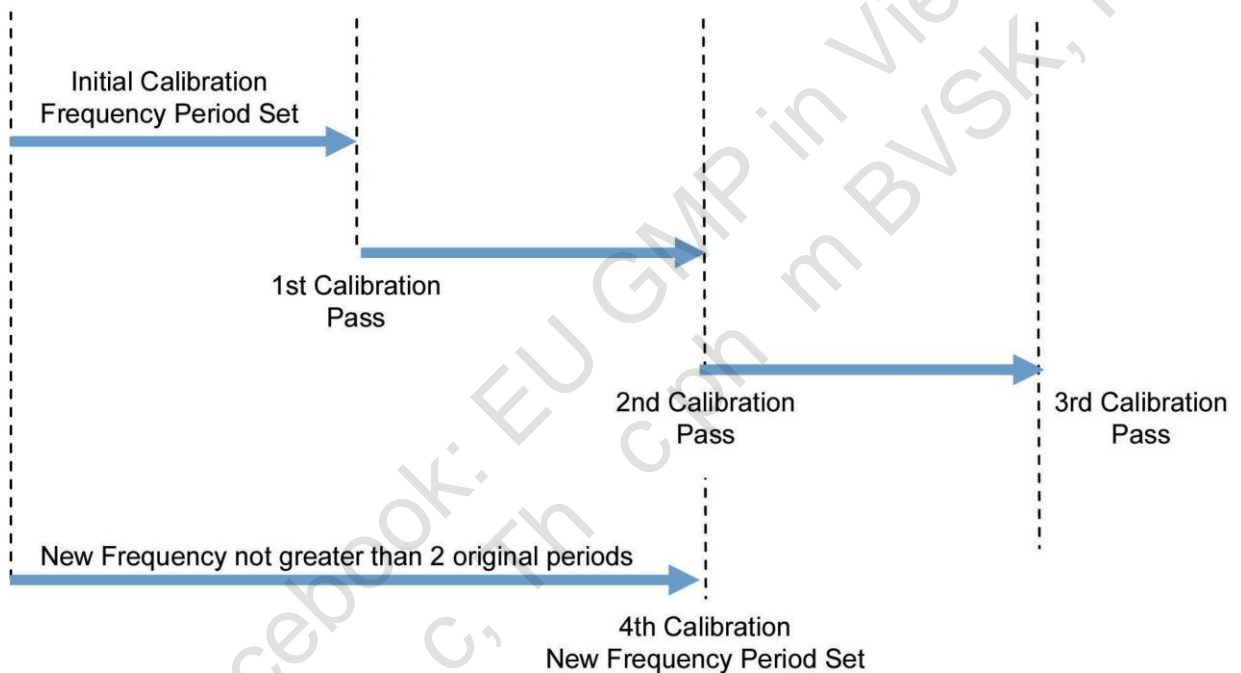
High	Clearly visible and fail safe detection.
Medium	Detectable through process testing or final results.
Low	Detectable through product or safety failure only.

Table 10.4: Calibration Frequency

High	Initially on a Quarterly basis. Frequency may be extended upon review of results.
Medium	Initially on a six month basis. Frequency may be extended upon review of results.
Low	Initially on an annual or bi annual basis. Frequency may be extended upon review of results.

The calibration frequency values, i.e., quarterly, six monthly, annual may be adjusted to suit the organization and/or process application applicable to the instrument in use.

Figure 10.4: Extending Calibration Frequency



Extending Calibration Frequency

The extension of calibration frequency periods should be used with caution. If applied without sufficient consideration, the calibration frequency could extend beyond the point where deteriorative effects of age could affect an instrument.

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11 Appendix 2 – Measurement Uncertainty Calculation – Examples

The following examples consider the measurement uncertainty associated with the calibration of a temperature indicator (an electronics unit with an associated probe) against a reference probe and indicator using a dry block style temperature bath.

Taking a simple approach, as suggested in Section 5 of this Guide, the factors that need to be considered should be identified. These factors are shown in Table, and relate to both the indicator and the probe. The maximum impact of each factor is estimated in terms of the measurement unit (°C) and summed as shown in Table 11.1.

Table 11.1: Summation of Uncertainty Components

Uncertainty Component	Value ± °C
Uncertainty – Test Indicator (from certificate)	0.03
Max Drift (of worst case point between calibrations) – Test Indicator	0.02
Resolution of Test Indicator (from mfrs literature)	0.01
Hysteresis of Test Indicator (< 1 LSD)	0.01
Non-linearity of Test Indicator (included in errors below)	0.00
Uncertainty – Test Probe (from certificate)	0.05
Max Drift (of worst case point between calibrations) – Test Probe	0.04
Resolution of Test Probe (negligible)	0.00
Hysteresis of Test Probe (from certificate – rising and falling readings)	0.02
Non-linearity of Test Probe (included in errors below)	0.00
Ambient Temperature Effect on Test Indicator (20 +/-10°C)	0.05
Ambient Temperature Effect on Test Probe (stem conduction)	0.02
Ambient Humidity (negligible – indicator and probe)	0.00
Ambient Pressure (negligible – indicator and probe)	0.00
Gravitational Influence (negligible – indicator and probe)	0.00
Interference/Cross Sensitivity (thermo electric/other noise)	0.01
Equilibration – Gradient (between bath wells)	0.20
Equilibration – Gradient (immersion depth)	0.20
Equilibration – Fluctuation (bath temperature)	0.02
Test Instrument Resolution	0.10
Summation of Uncertainty Components	0.78
Maximum Error – Test Indicator (from certificate)	0.02
Maximum Error – Test Probe (from certificate)	0.06
Total Uncertainty including Uncorrected Errors	0.86

The total uncertainty includes the maximum errors shown on the certificate for both the indicator and the probe.

This summation technique gives a pessimistic estimate. In real applications, some factors will not play a significant role or they will act in opposition to others. It demonstrates that despite having equipment with apparent errors of less than 0.06°C, the overall uncertainty of the calibration can be much larger, possibly by a more than an order of magnitude.

The most significant components are associated with problems in achieving equilibrium, even though a temperature block is used. If the measurement were to be made by comparing the two probes in air as is often the case in storage rooms, the potential gradients and fluctuations would be much larger and the uncertainty would be even larger.

In Table, the same data is incorporated into a more traditional uncertainty analysis where the probability distribution for each factor is identified and used to moderate the components such that they can be combined using the root-sum-square method.

In the case of a traditional uncertainty analysis, one additional factor is required to cover the natural variability of the measurement/calibration process. The value of this factor is established by repeating the process a number of times. From these trial results, the population standard deviation is established and divided by the square root of the number of trials to give the standard uncertainty of the mean. This value is then included in the analysis.

For this exercise, some simplifications are employed. Probability distributions for each of the factors are all assumed to be rectangular (i.e., worst case), unless they are derived from statistical trials or imported certificates (i.e., normal distributions). Assigning a worst case or rectangular distribution (i.e., a divisor of $\sqrt{3}$ or approximately 1.732) is the simplest and most conservative approach. Where normally distributed components such as expanded uncertainty estimates quoted on certificates are used, they should be divided by the coverage factor (normally 2 – see later) before inclusion. This is to ensure they are included at a level of confidence equivalent to one standard deviation.

The sensitivity column in the table is included to allow components to be converted into the same quantity, such as ohms into temperature (°C). In this example, all components are already expressed in °C and therefore, the sensitivity value is unity.

The calculated uncertainty (combined uncertainty) has an associated level of confidence equivalent to one standard deviation (approximately 67%). Therefore, to express the value with a level of confidence equivalent to 95%, it must be multiplied by a coverage factor “k” (normally 2). Further detail on probability distributions, degrees of freedom, and coverage factors is outside the scope of this document (refer to suggested further reading).

The combined uncertainty once multiplied by the coverage factor gives the “expanded uncertainty” which is expressed at a level of confidence equivalent to 95%. However, this does not allow for any known errors; therefore, either the errors must be corrected or added to the expanded uncertainty to obtain a useable uncertainty estimate.

Note that using this method, the expanded uncertainty is $\pm 0.376^\circ\text{C}$ – approximately half the value obtained by the summation method. However, this still does not account for known errors. If the expanded uncertainty is added to the uncorrected errors for the test indicator and the probe, the overall uncertainty is $\pm 0.456^\circ\text{C}$ (i.e., approximately $\pm 0.5^\circ\text{C}$). This compares with a value of $\pm 0.86^\circ\text{C}$, obtained by the total summation method, and demonstrates how summation is acceptable, but can lead to slightly pessimistic estimates.

It should be noted that the traditional method of combination involves a root sum square calculation. The impact of this is to amplify the significance of the larger components, and therefore, it is these components that may need to be moderated or eliminated should it be necessary to improve the measurement capability. For example, if the component associated with ambient temperature is a major contribution, setting some ambient temperature limits for the period when the calibration can proceed may be an option. Equally, before changing the method to moderate the impact of equilibration issues (thermal gradients), having two reference probes or swapping probes over and averaging results can help reduce the uncertainty.

Table 11.2: Uncertainty Analysis – Calibration of Temperature Indicator Using Reference Indicator and Probe and Dry Block

Source	Uncertainty Component	Value ±	Unit	Probability Distribution	Divisor	Sensitivity c_i	Standard Uncertainty (u_i)	u_{i2}	Deg. of Freedom (v_i)	u^2/v_i
Imported u/c	Uncertainty – Test Indicator (from certificate)	0.03	°C	normal	2.0	1	0.015	0.0002	i	0
Certificates	Max Drift (between cals) – Test Indicator	0.02	°C	rectangular	1.7	1	0.012	0.0001	i	0
Mfr's Spec	Resolution of Test Indicator	0.01	°C	rectangular	1.7	1	0.006	0.0000	i	0
Trials	Hysteresis of Test Indicator (1 LSD)	0.01	°C	rectangular	1.7	1	0.006	0.0000	i	0
	Non-linearity of Test Indicator	0.00	°C	rectangular	1.7	1	0.000	0.0000	i	0
Imported u/c	Uncertainty – Test Probe (from certificate)	0.05	°C	normal	2.0	1	0.025	0.0006	i	0
Certificates	Max Drift (between cals) – Test Probe	0.04	°C	rectangular	1.7	1	0.023	0.0005	i	0
Mfr's Spec	Resolution of Test Probe (N/A)	0.00	°C	rectangular	1.7	1	0.000	0.0000	i	0
Trials	Hysteresis of Test Probe	0.02	°C	rectangular	1.7	1	0.012	0.0001	i	0
	Non-linearity of Test Probe	0.00	°C	rectangular	1.7	1	0.000	0.0000	i	0
Mfr's Spec	Ambient Temp Effect on Indicator (20 ±10°C)	0.05	°C	rectangular	1.7	1	0.029	0.0008	i	0
Assumption	Ambient Temp Effect – Test Probe (stem conduction)	0.02	°C	rectangular	1.7	1	0.012	0.0001	i	0
Mfr's Spec	Ambient Humidity (N/A – indicator and probe)	0.00	°C	rectangular	1.7	1	0.000	0.0000	i	0
Assumption	Ambient Pressure (N/A – indicator and probe)	0.00	°C	rectangular	1.7	1	0.000	0.0000	i	0
Assumption	Gravitational Influence (N/A – indicator and probe)	0.00	°C	rectangular	1.7	1	0.000	0.0000	i	0
Trials	Interference/Cross Sensitivity (thermoelectric and other noise)	0.01	°C	rectangular	1.7	1	0.006	0.0000	i	0
Trials	Equilibration – Gradient (between bath wells)	0.20	°C	rectangular	1.7	1	0.115	0.0133	i	0
Trials	Equilibration – Gradient (immersion depth)	0.20	°C	rectangular	1.7	1	0.115	0.0133	i	0
Trials	Equilibration – Fluctuation (bath temperature)	0.02	°C	rectangular	1.7	1	0.012	0.0001	i	0
Mfr's Spec	Test Instrument Resolution	0.10	°C	rectangular	1.7	1	0.058	0.0033	i	0
Pop sd/ \sqrt{n}	Trial Repeatability – 5 Measurements	0.05	°C	normal	1.0	1	0.050	0.0025	4	0.000002
uc	Combined Uncertainty $\sqrt{\sum u_i^2}$		°C	normal			0.188	0.0354	800	0.000002
U	Expanded Uncertainty (k = 2)		°C	normal			0.376			

T V n GMP D c, Th c ph m BVSK, M Ph m
Group Facebook: EU GMP in Viet Nam

12 Appendix 3 – Calibration Management Software

Software for calibration management may be an integral part of an IAMS, a separate software tool dedicated to this one function, or a modular part of a computerized maintenance management system. The development of intelligent instruments that can provide diagnostic calibration alerts; however, suggests that calibration management software should have communication capability with Smart Instrumentation in order to utilize these advanced diagnostic capabilities.

The electronic system should operate within the same constraints and methodology as paper systems although it may benefit from the ability to transfer data electronically from the Smart Instrument or test equipment.

The advent of electronic authorization/approval with multilevel security access, e.g., account and password/biometric input, provides the opportunity to have a 'paperless' calibration procedure, system, and data archive.

12.1 User Requirements Specification

When choosing a calibration management software, application requirements should be clearly set out through an approved URS. This document should be realistic in its expectations and should match current procedures. Software alone may not provide all of the functions required so what is available in the market should be researched to ensure that requirements can be met.

A study of the current management program should be performed and the improvements that will be achieved when moving to a software management solution should be identified.

Each section of this document should be numerically identified to be used for comparison in a traceability matrix for validation purposes. This matrix should clearly identify that all requirements have been met and will become an essential tool when being audited.

Examples of Functionality

The items listed below provide guidance on some of the functionality that can be used to assist in the assessment of a software application and to help identify some key areas when auditing compliant software suppliers:

- automated scheduling and planning
- user friendly interface
- secure database
- ability to restrict access by user login
- ability to issue unplanned calibrations
- issue work orders in bulk to assist with shutdowns
- unique user access
- compliance with 21 Part 11 for Electronic Signatures and Electronic Records (Reference 4, Appendix 16) or Annex 11 (Reference 8, Appendix 16)
- time and date stamped audit trail

- display details of edit changes in the audit trail
- unique instrument and loop tagging
- ability to set up components as part of a loop
- ability to manage all reference instruments
- manage external calibrations
- store all historical data
- trending and reporting of historical data
- report on instrument performance
- automatic deviation handling
- flexibly work flow
- ability to group instruments and loop into types, i.e., TT, TI, PT, PI
- links to corporate email systems/automatic notifications
- scalability for instrumentation and users
- generation and management of forms or labels
- links to approved calibration methods
- process for definition and control of instrument status; in calibration, due calibration, calibration expired, etc.

General requirements:

- should be validated
- users should be trained
- Formal procedures should be established for use and management of users and data
- system description should be available
- disaster recovery/business continuity procedures should be established

Example of a User Requirements Template

This example of a URS shows how the requirements can be clearly identified. This table also can be used to assist in the supplier selection process. Each vendor would complete the table indicating which requirements can be met with their solution. This makes it a lot easier to select the right solution that best meets you requirements.

Mandatory = must be covered in the functionality

Good to have = would provide extra benefits, but is not mandatory

Nice to have = would be nice to have, but would not provide any extra benefits and is not mandatory (wish list)

Table 12.1

#	Requirement Description	Req. Met (Yes/No)	Req. By	Mand.	Good to Have	Nice to Have	Comments
1	Provides the ability to automatically schedule calibrations		JM	ii			
2	Provide facility to enter values for instrument and loops		HT	ii			
3	Has two tolerance levels and displays values that are outside the instrument (amber) and process (red) tolerance by changing color		JM	ii			
4	Provide the ability to add references used for calibrations		JM	ii			
5	Must have the ability to attach multiple components to a loop tag		JM	ii			
6	Automatically create a deviation if a calibration error exceeds the process tolerance value		JM	ii			
7	Must have full system in-house validation documentation		JM	ii			
8	Can interface with MES		HT		ii		
9	Must have user manuals and training packs available		HT	ii			
10	Must provide the ability to print labels for calibrations		JM	ii			
11	Must provide a full audit trail with the old and new values displayed		JM	ii			
12	Must require a valid login before allowing access to the system		JM	ii			
13	Provide inventory management		JM			ii	

Application of software provides an essential support tool for instrument calibration. End users may require simple calibration tasks to be managed by calibration software tool, such as routine scheduling through to complex tasks such as instrument performance analysis and uncertainty calculation.

While suppliers of calibration software are often very familiar with the core activities, it is essential for the pharmaceutical company in the first instance to clearly identify its own calibration process and specific needs before making a decision toward a particular solution. It is recommended that the calibration process should be formally documented within a User Requirements Specification (URS) and remain technically independent of any particular software preference. Failing to adequately understand the calibration process could result in a software solution that does not satisfy the core calibration needs.

As part of identifying the calibration process, it is recommended that at a high level process mapping exercise should be performed considering the specific activities within the following heading areas:

- Calibration inputs – identification of calibration triggers, stakeholders, and demands.
- Calibration process – defining the calibration activities performed.
- Calibration outputs – identification of calibration results and deliverables.
- Calibration interfaces – understanding which processes/systems are linked to calibration.
- Calibration reporting – identification of what records and reports are required.

With respect to stake holders of the calibration software, it is important to consider who within the pharmaceutical organization may require access to the system e.g., Production, Quality Assurance, Engineering, as their needs from the system will be different, such as forward schedules, compliance reports, works orders, and certificates.

Other requirements that should be considered for inclusion within the URS for the calibration software also may include:

- asset management fields, such risk assessment category, unique identifier, trace history
- label printing needs
- limits and alarms
- documentation references and linkages
- logical arrangements between systems, equipment, loops, and instruments
- data analysis and trending needs
- out of specification notifications
- query and reporting capabilities
- user access groups and profile management (external and internal users)
- volume and diversity of equipment and instruments
- electronic signature approvals
- electronic record audit trails
- import and export data requirements
- ease of use and type of graphic user interface

The process of performing instrument calibrations is a requirement of both EU and USA Pharmaceutical GxP regulations; therefore, calibration software must be considered as GxP critical and subject to appropriate validation.

Validation of calibration software should be based upon GAMP 5 lifecycle principles, including a suitable risk assessment to determine areas of high risk that require controls and suitable verification testing. In addition, where the pharmaceutical organization is supplying products to USA/FDA regulated markets, the requirements of 21 CFR Part 11 (Reference 4, Appendix 16) must be addressed within the validation approach.

Qualification considerations with respect to the IT infrastructure upon which the calibration software will operate also must be addressed, including the following:

- operational support activities and procedures
- security and account management practices
- data storage including format and archive capabilities
- concurrent user demands and system performance
- future updates and patch management

Critical to the operational success of calibration software is the integrity and accuracy of instrument data entered onto the system. Where a new calibration software system is to be implemented, the data must be checked as part of the validation approach. An assessment of legacy instrument data fields and content accuracy must be considered as it may be necessary for data to be 'normalized' for consistency and where applicable incomplete field information addressed.

Entering instrument data onto a calibration software system may involve electronic 'migration' that must be checked to ensure the data integrity and completeness is assured. Where manual steps are adopted for instrument data entry, a suitable second check verification method must be applied.

Cutover or 'Go Live' onto a calibration software system requires particular care as this will involve a change in operational practices. Procedures relating to the calibration software and appropriate user training is critical. Where possible, it is recommended that a measure of the system performance should be performed in order to demonstrate the following:

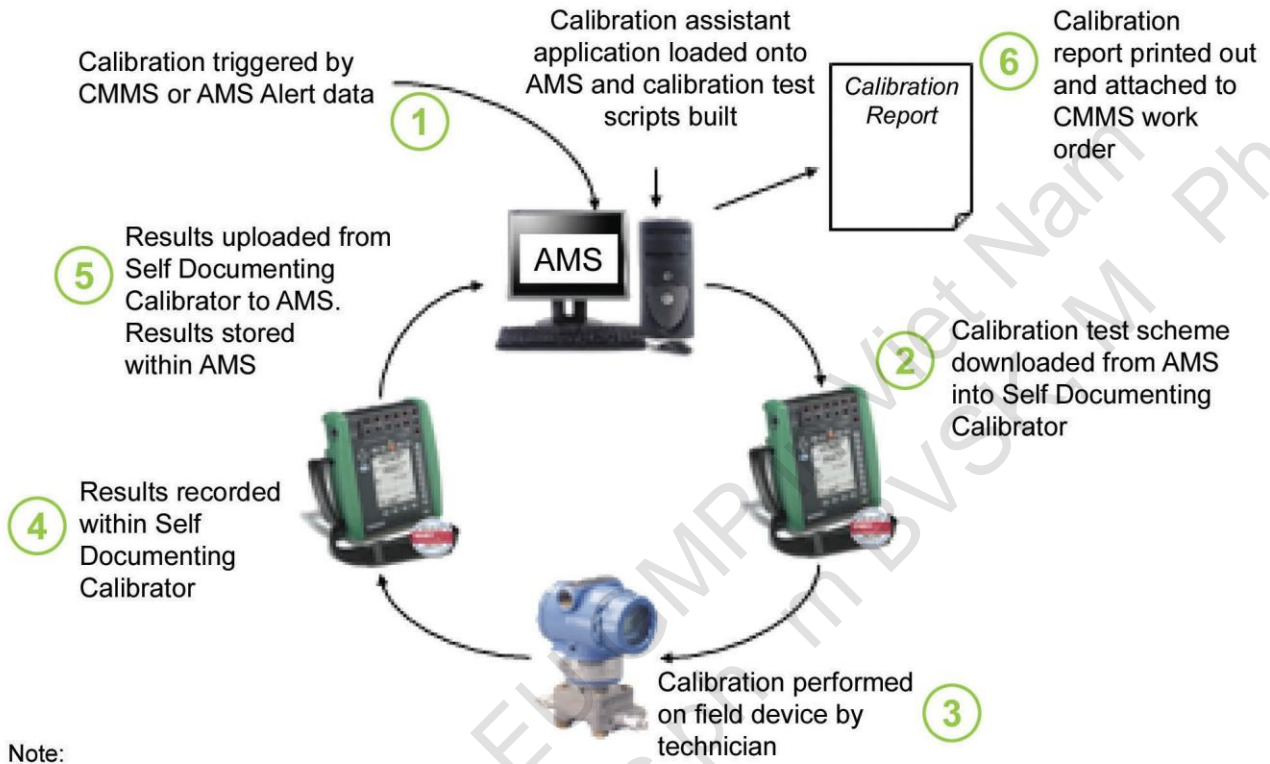
- satisfactory compliance of GxP regulatory requirements
- that original requirements are satisfied by the solution
- operational user access and competence of use
- stable and reliable use of the system
- backup and continuity plans are effective

Setup of a suitable Service Level Agreement (SLA) with the calibration software supplier should be considered. Dependent upon the operational criticality of the calibration software, i.e., high usage versus low usage, together with the supplier's ability to respond in a timely manner to issues will determine the type of SLA necessary to maintain compliant use. As part of the SLA, future software upgrades and patches also may be included, but must be managed as part of a change control process for the validated system.

AMS Systems

There are a number of advantages in using the correct software in controlling documentation in a calibration system.

Figure 12.1: Benefits – Automated Calibration Process



Note:
CMMS = Computerized Maintenance Management System
AMS = Asset Management System

Figure 12.2: Benefits – Improved Calibration Records

CMMS Hand Written checklist (with errors)

Work Order: 287257
Occurrence No: W O R K O R D E R
Work Order Job (1): 01
Belongs To: 27-208-2007 08-11
ID: 524574
Location Hierarchy: DL/061118/0611180601/0611180601/1

Regulatory Code(s):
ISO Impact: 003

Procedure Name: 21AR16

1.007	0.000/0.000	0.000/0.000
0.504	0.000/0.000	0.000/0.000

AS FOUND RESULTS:

Test	Pass	Fail	Operator	Loop	Error
Value of D.D.	0.00	0.00			0.00
0.000	0	0.005			0
1.12	1.27	0.05			1.15
0.500	0.500	0.05			0.500

3.1 Is the worst loop error within the process tolerance?
IF "FAIL" Contact the owner/user: **FAIL/FAIL**

3.2 Is the worst transmitter display error within the transmitter tolerance?
IF "FAIL" Contact the owner/user: **FAIL/FAIL**

3.3 Use the table below to assess the 'Loop Error' tolerance code.

NOTE: Use the worst loop error result

Code P: <+1/2 > Required Equipment Loop Tolerance
Code A: <+1/2 <+1 > Required Equipment Loop Tolerance
Code B: <+1 <+2 > Required Equipment Loop Tolerance
Code C: <+2 > Required Equipment Loop Tolerance

As Found Tolerance Code: **As Found**

PAGE: 5 OF 9

Improved Calibration Records

AMS Generated Calibration Report

Calibration Data For: DL118TT306A_D
Calibrated at: 1/17/2008 1:57:00 PM
Calibration Result: PASSED

Device Identification		
AMS Tag	DL118TT306A_D	
Device Tag	TRANSDUCER	
Manufacturer	Rosemount	
Model Name	844 Fieldbus Temperature Transmitter	
Device Identifier	001151044-FB-TEMP-06C339098	
Block Name	TRANSDUCER100	

Device Calibration Data		
Date/Time Calibrated:	1/17/2008 1:57:00 PM	Max Error Limit: 0.53 % of Span
Technician	YDZ 1099	Notification Limit: 0.27 % of Span
Layer	YDZ 1099	Adjustment Limit: 0.27 % of Span
Ambient	0.00 deg C	Calibration Interval: Not required
Temperature Standard	ITS-90	Critical Service: Yes
Work Order Number:	Demo	Input Range: -0.00 - 150.00 degC
Service Reason:	Routine PM	Output Range: -0.00 - 150.00 degC
Service Index:	Linear	
Relationship:	Linear	

Calibration Test Equipment				
AMS Tag	Manufacturer	Model	Serial Number	Last Calibration
SS450471	Beamex	MC5	25516941	Not required

Errors (%)				
Error	Limit	Actual	As Found	As Left
Maximum	0.5300	0.6667	(Fail)	0.0000 (Pass)
Zero	(N/A)	(N/A)	(N/A)	(N/A)
Span	(N/A)	(N/A)	(N/A)	(N/A)
Linearity	(N/A)	(N/A)	(N/A)	(N/A)
Hysteresis	(N/A)	(N/A)	(N/A)	(N/A)

13 Appendix 4 – Instrument Tagging Process

Department:	Doc No.	Issue No.	Date	Total Pages	Page
XXXXXX	XXXXXX	XXX	XXXXXX	93	70
Title: Standard for Identification of Instruments					

1 Introduction

This standard has been compiled to supply the guidelines for giving an instrument an individual code of identification.

Purpose

- To provide the mechanism by which an instrument can be uniquely identified.

2 Scope

This standard must apply to all instruments and associated equipment to be installed on the XXXXX Site.

This standard embodies the format of construction for an instrument identity or 'Tag Number' recommended in the Instrument Society of America Standard ISA-S5.1.

3 Definitions

3.1 Instrument

A device or combination of devices used directly or indirectly to measure, display, and/or control a variable.

The term includes primary elements, final control elements, computing devices, and electrical devices. The term does not apply to parts that are internal components of an instrument (e.g., a resistor, diode, etc).

3.2 Instrumentation

A collection of instruments or their application for the purpose of observation, measurement, control, or any combination of these.

3.3 Loop

A combination of two or more instruments or control functions arranged so that signals pass from one to another for the purpose of measurement and/or control of a process variable.

3.4 Tag or Tag Number

The identification code allocated to each device existing within an instrument loop. The tag number is constructed using various combinations of numeric and alphabetical characters.

3.5 **Field**

For the purpose of the standard, the definition of this term is a section within an identification code or tag number.

3.6 **P and ID**

Process and Instrument Diagram.

3.7 **Function**

The purpose of or an action performed by a device.

3.8 **Variable**

A physical quantity or condition, connected with a process which is varying, or is capable of varying.

- For individual instrument and instrument equipment definitions, refer to ISA Standard S5.1.

4 **Responsibilities**

The originator (instrument designer/draughtsman or project controller) for allocating a tag number to an instrument and ensuring that no duplication of records occurs.

5 **Standard**

5.1 **Allocating a Tag Number/Identification Code**

All instrument devices and associated equipment must be identified using an alphanumeric code which is constructed from four fields.

5.2 **First Field**

The Site Area/Building Code within which the instrument device/equipment is to be used.

5.3 **Second Field**

5.3.1

The functional identification of an instrument device or its functional equivalent consisting of letters from pages 6 and 7 and including one first letter (designating the measured or initiating variable) and one or more succeeding – letters (identifying the functions performed).

5.3.2

The functional identification of an instrument is made according to the function and not according to the construction. Thus, a differential pressure recorder used for flow measurement is identified by FR.

5.3.3

The first letter or the functional identification is selected according to the measured or initiating variable, and not according to the manipulated variable. Thus, a valve varying flow according to the dictates of a level controller is an LV, not an FV.

5.3.4

The succeeding letters of the functional identification designate one or more read out or passive functions and/or output functions. A modifying letter may be used, if required, in addition to one or more other succeeding letters.

Modifying letters may modify either a first letter or succeeding letters, as applicable.

Thus, TDAL contains two modifiers. The letter D changes the measured variable T into a new variable, temperature differential. The letter L restricts the read out function A, alarm, to represent a low alarm only.

5.3.5

A table of typical letter combinations for the functional identification of an instrument is available on pages 7 and 8.

5.4 **Third Field**

The unique numeric identification for an instrument loop. Each instrument situated within a loop must be allocated the same number.

An instrument which is common or functional to more than one loop should carry the identification number of the loop which is considered to be predominant.

5.5 **Fourth Field**

The loop position identification for an instrument. If an instrument loop comprises of two or more devices, a sequential numeric suffix for each device must be attached to the tag number.

5.6

5.6.1 *Recording the Tag Number*

The Site Engineering computer-network-database will be utilized to accurately record all instrument tag numbers.

Directories of the database will be compiled using the first and third fields of the tag number.

Example:

Network Database

Site Area/Building Code Directory à 6A

Instrument Functional Identification à 6A-PCV

Sequential Loop Number Sub-Directory à 6A-PCV-1234

Instrument Loop Positional Identification à 6A-PCV-1234.2

5.6.2

If the Site Area/Building Code has sub-divisions identified by a suffix to the number, i.e., 6, 6A, 6B, etc. The sequential number allocation will apply to the area/building code number regardless of sub-divisions.

Example:

6A	–	PCV	–	1234.1
6D	–	TRC	–	1235.1
6B	–	FIT	–	1236.1
6	–	PDI	–	1237.1

5.6.3

If all the instrument tag numbers detailed on a P&ID or schedule are common to the same site area or building, the code (first field) may be omitted for clarity as this identification will be within the documents number as detailed in Procedure for Numbering of Design Drawings and Documents (EDO301).

6 Referenced Documents

ISA-S5.1

The Instrument Society of America Standard for Instrumentation Symbols and Identification.

EDO301

Procedure for Numbering of Design Drawings and Documents.

Table 13.1: Function Identification Letters

	First-Letter		Succeeding-Letters		
	Measured or Initiating Variable	Modifier	Readout or Passive Function	Output Function	Modifier
A	Actuated		Alarm		
B	Burner, Combustion				Barrier
C	User's Choice			Control	
D	Density	Differential		Disc	
E	Voltage		Element (Primary)		
F	Flow Rate	Fraction (Ratio)			
G	User's Choice		Glass, Viewing Device		
H	Hand				High, High-High
I	Current (Electrical)		Indicate		
J	Power	Scan			
K	Time, Time Schedule	Time Rate of Change		Control Station	
L	Level		Light		Low, Low-Low
M	User's Choice	Momentary			Middle, Intermediate
N	User's Choice		User's Choice	User's Choice	User's Choice
O	User's Choice		Orifice, Restriction		
P	Pressure, Vacuum		Point (Test) Connection		
Q	Quality	Quantity			
R	Rupture, Relief		Record		
S	Speed, Frequency	Safety		Switch	
T	Temperature			Transmit	
U	Position, Proximity				
V	Vibration, Mechanical Analysis			Valve, Damper, Louver	
W	Weight, Force		Well		
X	Unclassified		Unclassified	Unclassified	Unclassified
Y	Event, State or Presence			Relay, Compute, Convert	
Z	Unclassified			Zener	

Table 13.2: Typical Letter Combinations

First-Letter	Initiating or Measured Variable	Controllers				Readout Devices		Switches and Alarm Devices*			Transmitters			Solenoids Relays, Computing Devices	Primary Element	Test Point	Well or Probe Glass	Viewing Device,	Safety Device	Final Element
		Recording Indicating Blind		Self-Actuated Control	Recording Indicating	High**	Low**	Comb	Recording Indicating Blind											
A	Actuated		AIC	AC					AS											AV
B	Burner/Combustion	BRC	BIC	BC		BR	BI	BSH	BSL	BSHL	BRT	BIT	BT	BY	BE		BW	BG		
C	User's Choice																			
D	User's Choice																			
E	Voltage	ERC	EIC	EC		ER	EI	ESH	ESL	ESHL	ERT	EIT	ET	EY	EE					
F	Flow Rate	FRC	FIC	EC	FCV FICV	FR	FI	FSH	FSL	FSHL	FRT	FIT	FT	FY	FE	FP		FG		FV
FQ	Flow Quantity	FQRC	FQIC			FQR	FQI	FQSH	FQSL			FQIT	FQT	FQY	FQE					FQV
FF	Flow Ratio	FFRC	FFIC	FFC		FFR	FFI	FFSH	FFSL						FE					FFV
G	User's Choice																			
H	Hand		HIC	HC						HS										HV
I	Current	IRC	IIC			IR	II	ISH	ISL	ISHL	IRT	IIT	IT	IY	IE					
J	Power	JRC	JIC			JR	JI	JSH	JSL	JSHL	JRT	JIT	JT	JY	JE					JV
K	Time	KRC	KIC	KC	KCV	KR	KI	KSH	KSL	KSHL	KRT	KIT	KT	KY	KE					KV
L	Level	LRC	LIC	LC	LCV	LR	LI	LSH	LSL	LSHL	LRT	LIT	LT	LY	LE		LW	LG		LV
M	User's Choice																			
N	User's Choice																			
O	User's Choice																			
P	Pressure/Vacuum	PRC	PIC	PC	PCV	PR	PI	PSH	PSL	PSHL	PRT	PIT	PT	PY	PE	PP				
PD	Pressure, Differential	PDRC	PDIC	PDC	PDCV	PDR	PDI	PDSH	PDSL		PDRT	PDIT	PDT	PDY	PE	PP				PDV
Q	Quality	QRC	QIC			QR	QI	QSH	QSL	QSHL	QRT	QIT	QT	QY	QE					
R	Rupture/ Relief														RE				RD	RV
S	Speed/ Frequency	SRC	SIC	SC	SCV	SR	SI	SSH	SSL	SSHL	SRT	SIT	ST	SY	SE					SV
T	Temperature	TRC	TIC	TC	TCV	TR	TI	TSH	TSL	TSHL	TRT	TIT	TT	TY	TE	TP	TW		TSE	TV
TD	Temperature, Differential	TDRC	TDIC	TDC	TDCV	TDR	TDI	TDSH	TDSL		TSRT	TDIT	TDT	TDY	TE	TP	TW			TDV
U	Position/Proximity					UR	UI							UY						
V	Vibration/ Machinery Analysis					VR	VI	VSH	VSL	VSHL	VRT	VIT	VT	VY	VE					
W	Weight/Force	WRC	WIC	WC	WCV	WR	WI	WSH	WSL	WSHL	WRT	WIT	WT	WY	WE					
WD	Weight/Force, Differential	WDRC	WDIC	WDC	WDCV	WDR	WDI	WDSH	WDSL		WDRT	WDIT	WDT	WDY	WE					
X	Unclassified																			
Y	Event/State/ Presence		YIC	YC		YR	YI	YSH	YSL				YT	YY	YE					
Z	Unclassified																			

Note: This table is not all-inclusive.

* A – alarm, the annunciating device, may be used in the same fashion as S - switch, the actuating device.

** The letters H and L may be omitted in the undefined case. HH and LL combinations may be used.

Table 13.2: Typical Letter Combinations (continued)

Other Possible Combinations:			
FO	(Restriction Office)	PFR	(Ratio)
FRK, HIK	(Control Station)	TSB	(Switch Barrier)
FX	(Accessories)	PZB	(Zener Barrier)
TJR	(Scanning Recorder)	WKIC	(Rate-of-Weight Controller)
LLH	(Pilot Light)	HMS	(Hand Momentary Switch)

T V n GMP D c, Th c ph m BVSK, M Ph m
Group Facebook: EU GMP in Vietnam

T V n GMP D c, Th c ph m BVSK, M Ph m
Group Facebook: EU GMP in Viet Nam

14 Appendix 5 – Indicative Regulatory Requirements

The following are indicative regulatory requirements related to calibration (which has been highlighted throughout the text in bold). This list is not intended to be definitive and reference should be made to regional regulations. It is the responsibility of the regulated company to determine which regulations apply in specific circumstances.

EudraLex – Volume 4 Good Manufacturing Practice (GMP) Guidelines

Part I – Basic Requirements for Medicinal Products

- 3.41 Measuring, weighing, recording and control equipment should be **calibrated** and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.
- 4.15 The Processing Instructions should include:
- a statement of the processing location and the principal equipment to be used;
 - the methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, **calibrating**, sterilising);
 - detailed stepwise processing instructions (e.g. checks on materials, pre-treatments, sequence for adding materials, mixing times, temperatures);
 - the instructions for any in-process controls with their limits;
 - where necessary, the requirements for bulk storage of the products; including the container, labelling and special storage conditions where applicable;
 - any special precautions to be observed.
- 4.26 There should be written procedures and the associated records of actions taken or conclusions reached, where appropriate, for:
- validation;
 - equipment assembly and **calibration**;
 - maintenance, cleaning and sanitation;
 - personnel matters including training, clothing, hygiene;
 - environmental monitoring;
 - pest control;
 - complaints;
 - recalls;
 - returns.

- 4.28 Log books should be kept for major or critical equipment recording, as appropriate, any validations, **calibrations**, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out.
- 6.7 Laboratory documentation should follow the principles given in Chapter 4. An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department:
- specifications;
 - sampling procedures;
 - testing procedures and records (including analytical worksheets and/or laboratory notebooks);
 - analytical reports and/or certificates;
 - data from environmental monitoring, where required;
 - validation records of test methods, where applicable;
 - procedures for and records of the **calibration** of instruments and maintenance of equipment.

Part II – Basic Requirements for Active Substances used as Starting Materials

2.3 Responsibilities of the Quality Unit(s)

- 2.32 The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing and should include but not necessarily be limited to:
1. Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company;
 2. Establishing a system to release or reject raw materials, intermediates, packaging and labelling materials;
 3. Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution;
 4. Making sure that critical deviations are investigated and resolved;
 5. Approving all specifications and master production instructions;
 6. Approving all procedures impacting the quality of intermediates or APIs;
 7. Making sure that internal audits (self-inspections) are performed;
 8. Approving intermediate and API contract manufacturers;
 9. Approving changes that potentially impact intermediate or API quality;
 10. Reviewing and approving validation protocols and reports;
 11. Making sure that quality related complaints are investigated and resolved;
 12. Making sure that effective systems are used for maintaining and **calibrating** critical equipment;
 13. Making sure that materials are appropriately tested and the results are reported;

14. Making sure that there is stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates where appropriate; and
15. Performing product quality reviews (as defined in Section 2.5)

2.4 Responsibility for Production Activities

The responsibility for production activities should be described in writing, and should include but not necessarily be limited to:

1. Preparing, reviewing, approving and distributing the instructions for the production of intermediates or APIs according to written procedures;
2. Producing APIs and, when appropriate, intermediates according to preapproved instructions;
3. Reviewing all production batch records and ensuring that these are completed and signed;
4. Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded;
5. Making sure that production facilities are clean and when appropriate disinfected;
6. Making sure that the necessary **calibrations** are performed and records kept;
7. Making sure that the premises and equipment are maintained and records kept;
8. Making sure that validation protocols and reports are reviewed and approved;
9. Evaluating proposed changes in product, process or equipment; and
10. Making sure that new and, when appropriate, modified facilities and equipment are qualified.

5.3 Calibration

- 5.30 Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs should be **calibrated** according to written procedures and an established schedule.
- 5.31 Equipment **calibrations** should be performed using standards traceable to certified standards, if existing.
- 5.32 Records of these **calibrations** should be maintained.
- 5.33 The current **calibration** status of critical equipment should be known and verifiable.
- 5.34 Instruments that do not meet **calibration** criteria should not be used.
- 5.35 Deviations from approved standards of **calibration** on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful **calibration**.

6.6 Laboratory Control Records

- 6.61 Complete records should also be maintained for:
 - Any modifications to an established analytical method,

- Periodic **calibration** of laboratory instruments, apparatus, gauges, and recording devices;
- All stability testing performed on APIs; and
- Out-of-specification (OOS) investigations.

19.3 Equipment and Facilities

19.30 During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is **calibrated**, clean and suitable for its intended use.

19.6 Validation

19.60 Process validation for the production of APIs for use in clinical trials is normally inappropriate, where a single API batch is produced or where process changes during API development make batch replication difficult or inexact. The combination of controls, **calibration**, and, where appropriate, equipment qualification assures API quality during this development phase.

Title 21--Food and Drugs
Chapter I--Food and Drug Administration
Department of Health and Human Services
Subchapter C--Drugs: General

Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals

Subpart D--Equipment

Sec. 211.68 Automatic, mechanical, and electronic equipment.

- (a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely **calibrated**, inspected, or checked according to a written program designed to assure proper performance. Written records of those **calibration** checks and inspections shall be maintained.

Subpart I--Laboratory Controls

Sec. 211.160 General requirements.

- (b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:
- (1) Determination of conformity to applicable written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.
 - (2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.

- (3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.
- (4) The **calibration** of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.

Subpart J--Records and Reports

Sec. 211.194 Laboratory records.

- (d) Complete records shall be maintained of the periodic **calibration** of laboratory instruments, apparatus, gauges, and recording devices required by 211.160(b)(4).

Title 21--Food and Drugs

Chapter I--Food and Drug Administration Department of Health and Human Services Subchapter H--Medical Devices

Part 820 Quality System Regulation

Subpart G--Production and Process Controls

Sec. 820.72 Inspection, measuring, and test equipment.

- (a) *Control of inspection, measuring, and test equipment.* Each manufacturer shall ensure that all inspection, measuring, and test equipment, including mechanical, automated, or electronic inspection and test equipment, is suitable for its intended purposes and is capable of producing valid results. Each manufacturer shall establish and maintain procedures to ensure that equipment is routinely **calibrated**, inspected, checked, and maintained. The procedures shall include provisions for handling, preservation, and storage of equipment, so that its accuracy and fitness for use are maintained. These activities shall be documented.
- (b) **Calibration.** **Calibration** procedures shall include specific directions and limits for accuracy and precision. When accuracy and precision limits are not met, there shall be provisions for remedial action to reestablish the limits and to evaluate whether there was any adverse effect on the device's quality. These activities shall be documented.
 - (1) **Calibration standards.** **Calibration** standards used for inspection, measuring, and test equipment shall be traceable to national or international standards. If national or international standards are not practical or available, the manufacturer shall use an independent reproducible standard. If no applicable standard exists, the manufacturer shall establish and maintain an in-house standard.
 - (2) **Calibration records.** The equipment identification, **calibration** dates, the individual performing each **calibration**, and the next **calibration** date shall be documented. These records shall be displayed on or near each piece of equipment or shall be readily available to the personnel using such equipment and to the individuals responsible for **calibrating** the equipment.

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15 Appendix 6 – List of Attachments

A set of attachments to this Guide are available on the ISPE Web Site, www.ispe.org/GAMP_Calibration_Management_Attachments.

These attachments comprise a number of documents contributed by organizations active in pharmaceutical manufacture. They are a sample of what currently exists as good practice in the management of calibration and have not been modified other than to provide anonymity for the donor organizations.

Their development precedes the production of this guidance and may not be fully aligned. The content of the attachments is not endorsed by ISPE.

- Attachment 1** Example Calibration Master List
- Attachment 2** Example Declaration of Decontamination Status
- Attachment 3** Example Non-Conformance Report (2 Versions)
- Attachment 4** Example Calibration Certificate – Type 1
- Attachment 5** Example Calibration Certificate – Type 2
- Attachment 6** Example Loop Calibration Certificate
- Attachment 7** Example Standard Operating Procedure: Calibration by Work Order
- Attachment 8** Example Calibration Report Standard Operating Procedure
- Attachment 9** Example Calibration Work Instruction Standard Operating Procedure
- Attachment 10** Decommissioning Checklist
- Attachment 11** Audit Checklist
- Attachment 12** Analytical Equipment Calibration SOP
- Attachment 13** Analytical Equipment Calibration Certificate
- Attachment 14** NCR/CAPA SOP
- Attachment 15** Uncertainty Opt Out Worksheet
- Attachment 16** Uncertainty CML Worksheet
- Attachment 17** Measurement Uncertainty Calculation and Application – Global Engineering Standard
- Attachment 18** Balances and Weigh Scales
- Attachment 19** Calibration of Scales and Balance Procedure
- Attachment 20** Analytical Instrument and Laboratory Equipment Qualification Process
- Attachment 21** Analytical Instrument Verification Process
- Attachment 22** Postal Audit Document
- Attachment 23** Criticality Assessment

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17 Appendix 8 – Glossary

17.1 Abbreviations and Acronyms

C&I	Control and Instrumentation
CAPA	Corrective and Preventive Action
CMMS	Computerized Maintenance Management System
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRA	Critical Risk Assessment
EHS	Environment, Health, and Safety
GxP	Comprises: <ul style="list-style-type: none">GCP Good Clinical PracticeGDP Good Distribution PracticeGEP Good Engineering PracticeGLP Good Laboratory PracticeGMP Good Manufacturing PracticeGQP Good Quality Practice
HVAC	Heating, Ventilation, and Air Conditioning
ILAC	International Laboratory Accreditation Cooperation
IAMS	Instrument Asset Management System
OOT	Out of Tolerance
PAT	Process Analytical Technology
P&ID	Process and Instrumentation Diagram
SLA	Service Level Agreement
SOP	Standard Operating Procedure
URS	User Requirements Specification
VIM	Vocabulaire International de Métrologie / International Vocabulary of Metrology

17.2 Definitions

Acceptance Criteria (IEEE)

The criteria that a system, component must satisfy in order to be accepted by a user, customer or other authorized entity.

Acceptance Test (IEEE)

Testing conducted to determine whether or not a system satisfies its acceptance criteria and to enable the customer to determine whether or not to accept the system. See also Factory Acceptance Test (FAT), Site Acceptance Test (SAT).

Application Software (ISO)

Software or a program that is specific to the solution of an application problem.

Appropriately Trained Personnel

Persons who have been trained and their competence assessed to a suitable level of expertise to carry out defined activities.

Audit (ISO)

Systematic, independent, and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which agreed criteria are fulfilled.

Calibration (ISO 10012)

The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure or a reference material, and the corresponding values of a quantity realized by a reference standard.

Calibration Accuracy

The agreed specified working accuracy of the instrument.

Calibration Master List

Lists all instruments which must be considered for calibration showing the device, process system, calibration, criticality, etc.

Calibration Periodicity

Frequency of scheduled calibrations.

Calibration Range

Specified range over which the instrument is calibrated. This should be greater than the process range.

Calibration Report

Document summarizing the results of a calibration activity.

Calibration Status

Indication of instrument compliance at a fixed point in time.

Change Control (PDA)

A formal process by which qualified representatives from appropriate disciplines review proposed or actual changes to a computer system. The main objective is to document the changes and ensure that the system is maintained in a state of control.

Computer System (IEEE)

A system containing one or more computers and associated software.

Computerized System

A broad range of systems including, but not limited to, automated manufacturing equipment, automated laboratory equipment, process control and process analytical, manufacturing execution, laboratory information management, manufacturing resource planning, clinical trials data management, vigilance and document management systems. The computerized system consists of the hardware, software, and network components, together with the controlled functions and associated documentation.

Computerized System Validation

Achieving and maintaining compliance with applicable GxP regulations and fitness for intended use by:

- the adoption of principles, approaches, and life cycle activities within the framework of validation plans and reports
- the application of appropriate operational controls throughout the life of the system

Customer

A recipient of a product provided by the supplier.

Critical Process Parameter (ICH Q8 (R2))

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces desired quality.

Critical Quality Attribute (ICH Q8 (R2))

A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure product quality.

Design (IEEE)

The process of defining the architecture, components, interfaces, and other characteristics of a system or component.

Design Review (IEEE)

A process or meeting during which a system, hardware, or software design is presented to project personnel, managers, users, customers, or other interested parties for comment or approval. Types include critical design review, preliminary design review, and system design review.

Design Space (ICH)

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

Detectability (ICH Q9)

The ability to discover or determine the existence, presence, or fact of a hazard.

Factory Acceptance Test (FAT) (IEEE)

An Acceptance Test in the Supplier's factory, usually involving the Customer. See also Acceptance Test. Contrast to Site Acceptance Test.

GxP Compliance

Meeting all applicable pharmaceutical and associated life-science regulatory requirements.

GxP Regulated Computerized System

Computerized systems that are subject to GxP regulations. The regulated company must ensure that such systems comply with the appropriate regulations.

GxP Regulation

The underlying international pharmaceutical requirements, such as those set forth in the US FD&C Act, US PHS Act, FDA regulations, EU Directives, Japanese regulations, or other applicable national legislation or regulations under which a company operates. These include but are not limited to:

- Good Manufacturing Practice (GMP) (pharmaceutical, including Active Pharmaceutical Ingredient (API), veterinary, and blood)
- Good Clinical Practice (GCP)
- Good Laboratory Practice (GLP)
- Good Distribution Practice (GDP)
- Good Quality Practice (GQP)
- Good Pharmacovigilance Practice
- Medical Device Regulations
- Prescription Drug Marketing Act (PDMA)

Harm (ICH Q9)

Damage to health, including the damage that can occur from loss of product quality or availability.

Hazard (ICH Q9)

The potential source of harm (ISO/IEC Guide 51).

Hysteresis

The difference between the readings obtained when a given value of the measured variable is approached from opposite directions.

Incident

Operational event which is not part of standard operation.

Instrument

Device or devices used to carry out a measurement.

Instrument Loop

A group of instruments connected together to monitor or control a process variable.

Life Cycle – see Product Lifecycle, Software Life Cycle (ISO/IEC: 99:2007)

Quantity intended to be measured.

Master Document File

A file containing the original signed documents or procedures.

Measurand (ISO/IEC: 99:2007)

Quantity intended to be measured.

Measuring Instrument (ISO/IEC: 99:2007)

Device used for making measurements, alone or in conjunction with one or more supplementary devices.

Measurement Precision (ISO/IEC: 99:2007)

Closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions.

Measurement Repeatability

Measurement precision (as defined above) under a set of conditions that includes the same: measurement procedure, operators, measuring system, and location over a short period of time.

Measurement Reproducibility

Measurement precision (as defined above) under a set of conditions that includes different: measurement procedures, operators, measuring systems, and locations.

Measurement Accuracy (ISO/IEC: 99:2007)

Closeness of agreement between a measured quantity value and a true quantity value of a measurand.

Measurement Uncertainty (ISO/IEC: 99:2007)

Non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used. *Note: this is not inconsistent with the more commonly quoted definition given in the first edition of the VIM, i.e., “an estimate characterizing the range of values within which the true value of the measurand lies.”*

Metrological Traceability (ISO/IEC: 99:2007)

Property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty.

National Standard

Reference standard for a particular country or community, traceable to a specific reference.

Non-Critical Instrument

An instrument whose accuracy/failure is deemed to have no effect on product quality, process/system performance, safety, or the environment.

Non-Conformance

A deviation from defined procedures. Failure to meet defined criteria also may be referred to as exception or deviation report.

Periodic Review

A documented assessment of the documentation, procedures, records, and performance of a computer system to determine whether it is still in a validated state and what actions, if any, are necessary to restore its validated state. The frequency of review is dependent upon the systems complexity, criticality, and rate of change.

Primary Element

Device used to convert the process parameter into a measured signal.

Process (ISO)

A set of interrelated or interacting activities which transform inputs into outputs.

Process Analytical Technology (ICH Q8 (R2))

A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

Process Limits

Extent of the process range.

Process Range

Specified range within which the process should operate.

Process/System Critical Instruments

A process/system critical instrument is an instrument whose accuracy/failure may have a direct effect on process or system performance, without affecting final product quality or safety.

Process Validation (FDA)

Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.

Process Owner

The person ultimately responsible for the business process or processes being managed.

Product Contact Parts

A part used for a qualified item of equipment or system that is in direct contact.

Product Critical Instruments

A product critical instrument is an instrument whose accuracy/failure may have a direct effect on product quality.

Product Lifecycle (ICH Q9)

All phases in the life of the product from the initial development through marketing until the product's discontinuation.

Production Report

Information in human readable form, presented via electronic, paper, or hybrid format for activities such as review, disposition, investigation, audit, and analysis.

Qualification (MHRA)

Action of proving that any instrument or equipment works correctly and actually leads to the expected results. The word 'validation' is sometimes widened to incorporate the concept of qualification.

Quality (ICH Q9)

The degree to which a set of inherent properties of a product, system or process fulfils requirements (see ICH Q6a definition specifically for "quality" of drug substance and drug (medicinal) products.)

Quality (Product) (ICH Q8 (R2))

The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity (from ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances).

Quality-by-Design (QbD) (ICH Q8 (R2))

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Quality Management System (ISO)

Management system to direct and control an organization with regard to quality.

Quality Plan (ISO)

Document specifying which procedures and associated resources shall be applied by whom and when to a specific project, product, process, or contract.

Quality Risk Management (ICH Q9)

A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

Quality System (ICH Q9)

The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met.

Requirement (ISO)

Need or expectation that is stated, generally implied, or obligatory.

Risk (ICH Q9)

The combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51).

Risk Analysis (ICH Q9)

The estimation of the risk associated with the identified hazards.

Risk Assessment (ICH Q9)

A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

Risk Communication (ICH Q9)

The sharing of information about risk and risk management between the decision maker and other stakeholders.

Risk Control (ICH Q9)

Actions implementing risk management decisions (ISO Guide 73).

Risk Evaluation (ICH Q9)

The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.

Risk Identification (ICH Q9)

The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description.

Risk Management (ICH Q9)

The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating, and reviewing risk.

Risk Reduction (ICH Q9)

Actions taken to lessen the probability of occurrence of harm and the severity of that harm.

Risk Review (ICH Q9)

Review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk.

Safety/Environmental Critical Instruments

A safety/environmental critical instrument is an instrument whose accuracy/failure may have a direct effect on safety/environment.

Self Tune

Action of an instrument to automatically adjust its characteristics to compensate for changes in operational parameters (sometimes referred to as self-calibration).

Severity (ICH Q9)

A measure of the possible consequences of a hazard.

Site Acceptance Test (SAT) (IEEE)

An Acceptance Test at the Customer's site, usually involving the Customer. See also Acceptance Test, contrast to Factory Acceptance Test.

Smart Instrumentation

Microprocessor based instrumentation often with communication capabilities.

Specification (IEEE)

A document that specifies, in a complete, precise, verifiable manner, the requirements, design, behavior, or other characteristics of a system or component, and often, the procedures for determining whether these provisions have been satisfied.

Subject Matter Expert

Those individuals with specific expertise in a particular area or field. Subject Matter Experts should take the lead role in the verification of computerized systems. Subject Matter Expert responsibilities include planning and defining verification strategies, assessing risk and impact of calibration equipment, defining acceptance criteria, selection of appropriate test and calibration methods, execution of verification tests, and reviewing results.

Supplier

An organization or individual internal or external to the user associated with the supply and/or support of products or services at any phase throughout a systems life cycle.

System Owner

The person ultimately responsible for the availability and support and maintenance of a system and for the security of the data residing on that system.

Test Equipment

Instrument or device used to calibrate other instruments, the calibration of which is traceable to recognized national or international standards. The test equipment should have better precision, accuracy, and repeatability, than the instrument under calibration. Including ancillary equipment and/or devices used in support of calibration activities (e.g., environmental sources, chambers, and baths)."

Testing, Functional (IEEE)

(1) Testing that ignores the internal mechanism or structure of a system or component and focuses on the outputs generated in response to selected inputs and execution conditions. (2) Testing conducted to evaluate the compliance of a system or component with specified functional requirements and corresponding predicted results. Syn: black-box testing, input/output driven testing. Contrast with testing, structural.

Testing, Structural (IEEE)

(1) Testing that takes into account the internal mechanism [structure] of a system or component. Types include branch testing, path testing, statement testing. (2) Testing to ensure each program statement is made to execute during testing and that each program statement performs its intended function. Contrast with functional testing. Syn: white-box testing, glass-box testing, logic driven testing.

Test Case (IEEE)

A set of test inputs, execution conditions, and expected results developed for a particular objective, such as to exercise a particular program path or to verify compliance with a specific requirement.

Test Plan (IEEE)

A document describing the scope, approach, resources, and schedule of intended test activities. It identifies test items, the features to be tested, the testing tasks, who will do each task, and any risks requiring contingency planning.

Test Procedure (IEEE)

Detailed instructions for the set-up, execution, and evaluation of results for a given test case.

Tolerance

Tolerance is the permissible deviation from a specified value.

Validation

Establishing documentary evidence, which provides a high degree of assurance that a process will consistently produce a product meeting its predetermined specifications and quality attributes (FDA).

Verification (ISO) (1) (ASTM) (2)

(1) Confirmation, through the provision of objective evidence that specified requirements have been fulfilled. (2) A systematic approach to verify that manufacturing systems, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly. This is an umbrella term that encompasses all types of approaches to assuring systems are fit for use such as qualification, commissioning and qualification, verification, system validation, or other.

User

The pharmaceutical customer or user organization contracting a supplier to provide a product. In the context of this document, it is therefore, not intended to apply only to individuals who use the system, and is synonymous with customer.

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