



## **GAMP Good Practice Guide**

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

**Second Edition**



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## **GAMP Good Practice Guide**

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

**Second Edition**

### **Disclaimer:**

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.

# Acknowledgements

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.

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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.

GAMP is an ISPE Community of Practice. For further information, see [www.ispe.org](http://www.ispe.org).

## 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.



## 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.



### 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

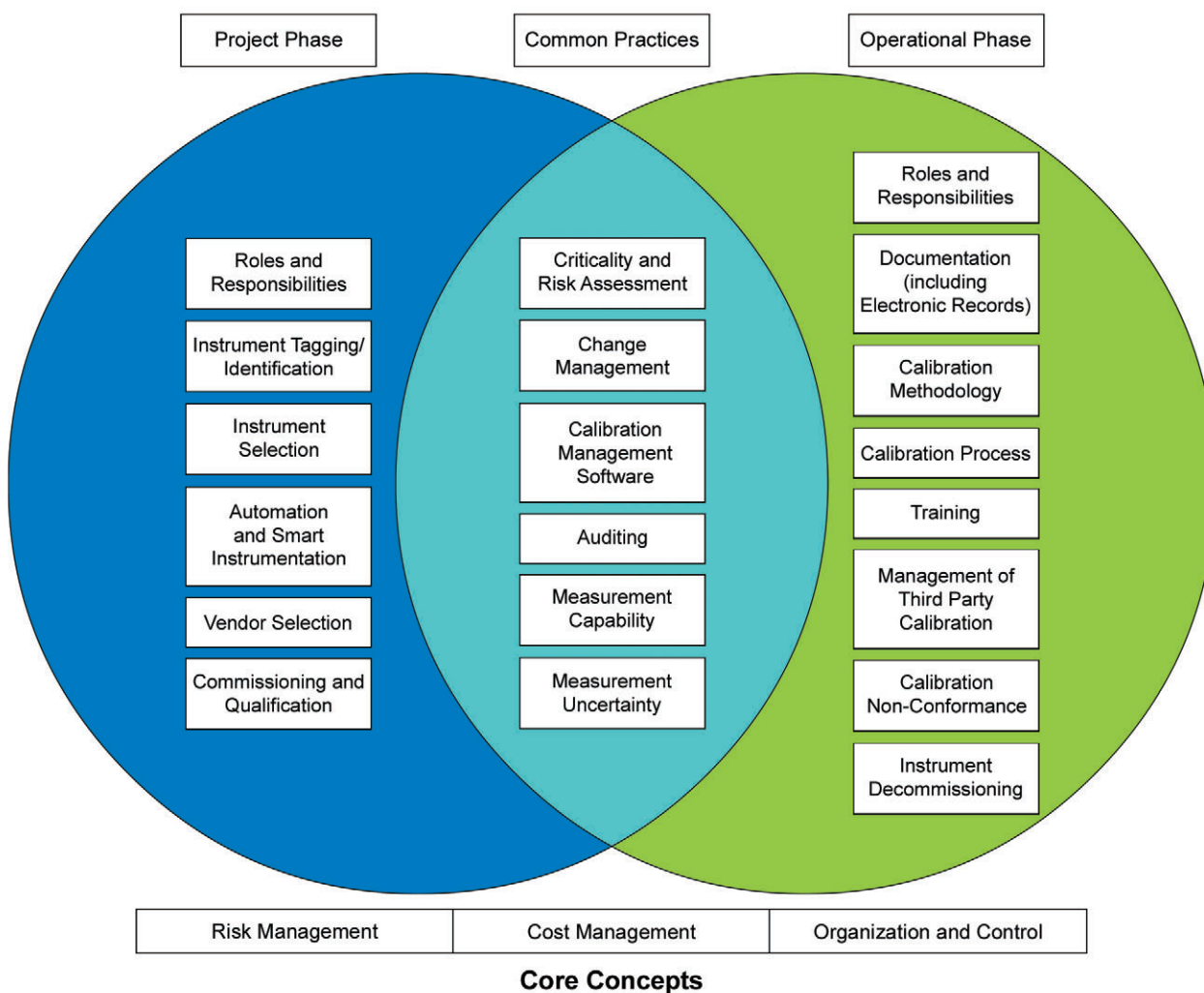
Expertise above may be available from less than three persons. It also may be necessary to involve specific expertise in other areas, when required to identify and to cover all relevant areas and other aspects, particularly for complex systems.

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

## 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.



## 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.

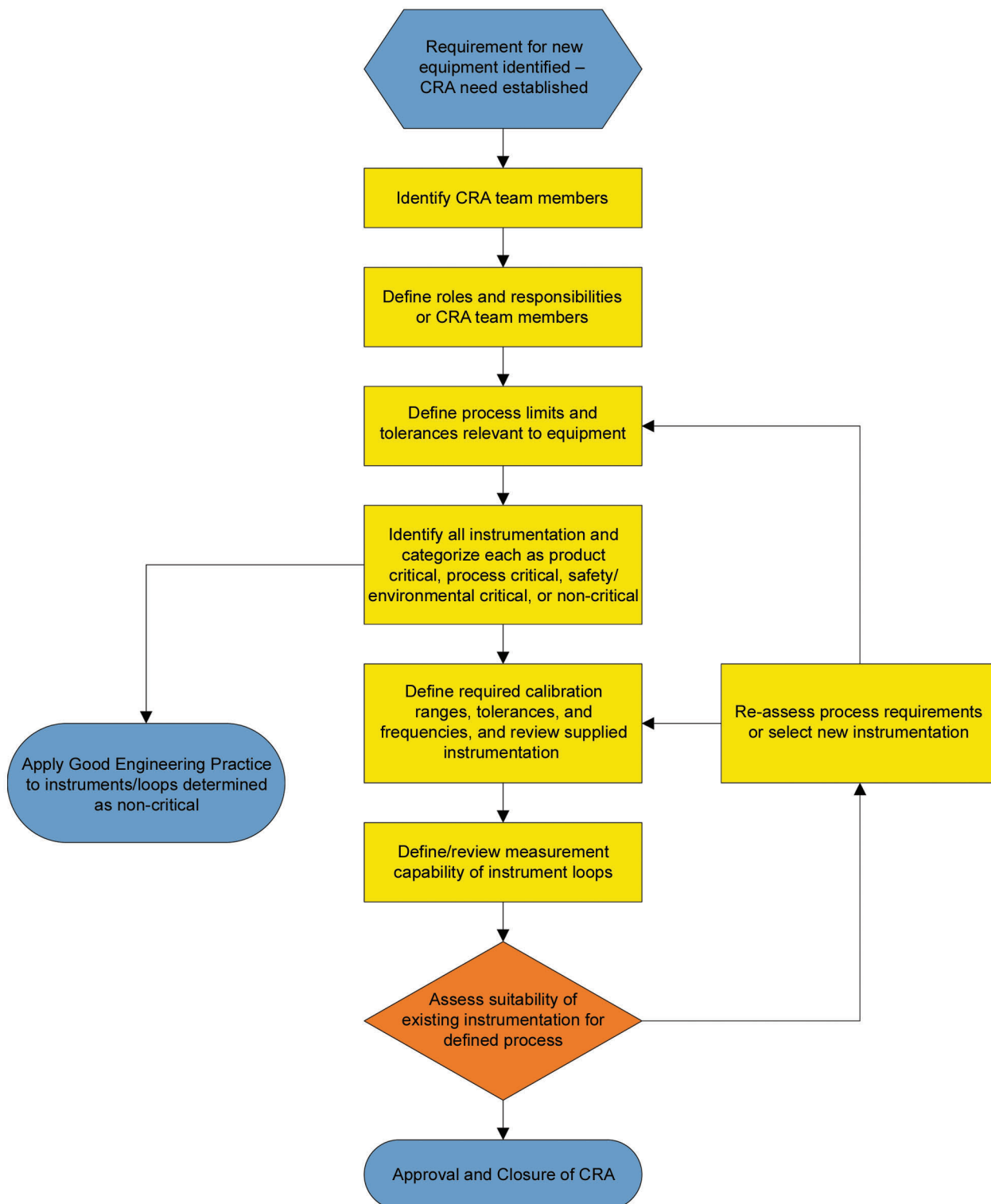
The CRA is a once through process; there should be periodic review of the results to ensure that the assumptions made are reflected in the actual performance of the instrumentation with change control used as necessary. The CRA also may be used as a continuous improvement tool to ensure the calibration 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:<br>• Drug registration file<br>• 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                          |
| <b>Note:</b> 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. |                                    |                            |                                      |

#### 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.

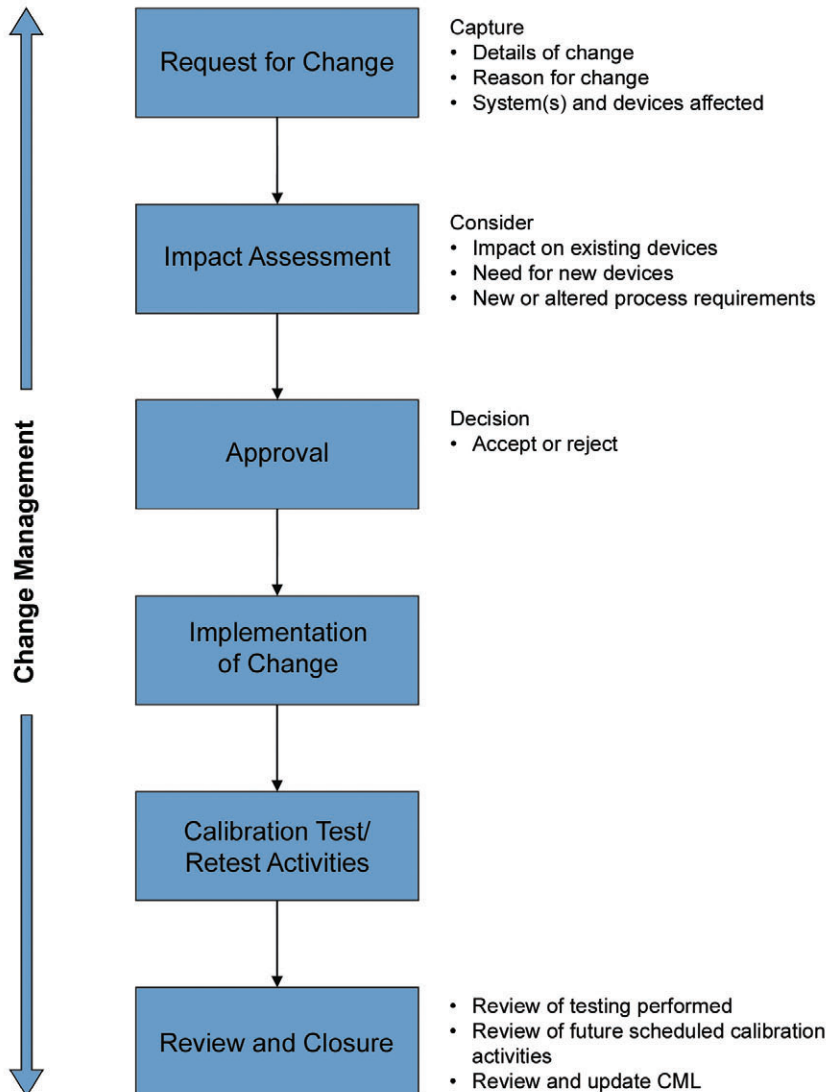
### **5.2.1 Key Requirements**

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).