

Technical Document Review: GAMP® Good Practice Guide: Calibration Management

Introduction

The GAMP® forum is a body formed in 1991 primarily to promote the understanding of pharmaceutical computer controlled systems. The first document issued by the GAMP® forum was “The GAMP® Guide to Validation of Automated Systems in Pharmaceutical Manufacture.” This document was released in 1994 and has grown and been revised to meet the changing requirements from the pharmaceutical market. In 2000, GAMP® became formally affiliated with ISPE as a technical sub-committee within the organization. The “Calibration Management” Good Practice Guide (Jan 2002) is the first document released by the GAMP® forum which aims to assist pharmaceutical manufacturers in both devising and managing a good calibration strategy.

This document aims to review the GAMP® Good Practice Guide for Calibration Management; January 2002, published by the ISPE. To learn more about GAMP® or to place an order, visit www.ispe.org The content of this summary hopes to identify the top level requirements of the steps undertaken to establish a calibration management strategy.

This document focuses on the requirements of the pharmaceutical manufacturers and offers a path to them to implement a calibration management strategy. The scope of the document is for any instrument, which is employed by a pharmaceutical manufacturer, and for readership by engineers, Quality Assurance and any other personnel involved in the calibration management of a pharmaceutical system. The impact for the supplier is that this guideline is undoubtedly the direction in which the pharmaceutical market will direct its calibration efforts and that by understanding the requirements we will be better placed to meet them.

The key message of the document is *“that with good control and prioritization of instrument calibration there is a high degree of confidence that the [manufacturing] process has remained within the desired range and the accuracy of measurement has been maintained within tolerances.”*

Key Pharmaceutical Requirements

The key pharmaceutical requirements for critical instruments are that they meet the following criteria:

Each instrument should have a record in a permanent master history file.

All instruments are assigned a unique number and are tagged with that number.

The calibration method should be defined and approved.

Calibration frequency and process limits should be defined for each instrument.

The calibration status should be identified on the instrument (status sticker).

All records shall be maintained.

All and any electronic records must meet 21CFR part 11.

The calibration standards must be more accurate to a closer tolerance than the instrument being tested.

Each standard must be traceable to a recognized standard.

All instruments must be fit for purpose.

Training records for all personnel involved in the calibration must be maintained.

A change control system must be in place.

The instruments must meet all GMP requirements, as defined by the FDA or MCA.

Criticality Assessment

All instruments directly, or indirectly, involved with the process should be individually assessed for their criticality to the process. A group to assess this criticality list is formed (Criticality Assessment Team – CAT) and assigns a category to each instrument.

Product Critical Instruments

An instrument whose failure may have a direct impact on product quality.

Process / System Critical Instruments

An instrument whose failure may affect the process or system performance but does not directly impact product quality.

Safety / Environmental Critical Instruments

An instrument whose failure may affect either safety or the environment.

Non- Critical Instruments

An instrument whose failure has no impact on product quality, systems or the environment.

Calibration Frequency

Frequency of calibration is determined by the following factors.

Manufacturers recommendations

- Duty of instrument
- Relevant standards and regulations
- Historical information
- Consequence of calibration failure
- Experience

In general, critical instruments should be recalibrated every 6 months until sufficient data allows for annual calibrations to be performed. Non-critical instruments may only require periodic checks on performance and not require calibration.

Instrument Lifecycle

Each instrument, which enters use at a pharmaceutical application, follows three basic phases.

- Project Phase
- Pre-Operational Phase
- Operational Phase

PROJECT PHASE

This is where an application is identified as requiring an instrument. From this requirement a specification can be drafted. Typically three groups are involved in the selection and specification of an instrument: Process, Engineering and Quality.

The specification of an instrument is based upon:

- Specification (manufacturers specifications are treated only as guidance)
- Accumulation errors due to non-linearity
- Hysteresis
- Temperature effects
- Repeatability

The range and accuracy for the instrument is defined, as are the expectations of the instrument calibration accuracy. The instrument should be calibrated 'on bench' and where integrated into a system should also be loop calibrated.

PRE-OPERATIONAL PHASE

This phase is the documentation of the project phase to verify that the Operational Phase can progress.

OPERATIONAL PHASE

Responsibilities should be defined before the operational phase begins, an instrument owner, QA representative, and calibrators, all need identifying. The calibrator is responsible for ensuring that the procedure, test equipment and standards are all available and in date.

Cleaning and decontamination should be performed prior to calibration to ensure that no biohazard exists.

5.3.1 Calibration Process

Bench calibrations should be performed to an approved procedure, and, where applicable, a total loop calibration performed. If deviations are found during the loop calibrations the loop should be broken to identify the problem area. The types of loop calibration defined are:

- The live sensor put into a stable conditions (temp bath, pressure generator)
- Signal injection from a 'Known' source
- Sensor disconnected and a Known/Traceable source installed.
- Bench test the sensor loop verify the rest (last resort...)

5.3.2 Non-Conformance Investigation

These are performed when the 'as found' data lies outside of acceptable drift, the following should be done when a sensor raises a non-compliance report.

- Sensor marked as 'out of calibration'
- Failure logged
- Non-conformance report generated
- Actions defined for repair
- QA informed and investigation to recall or reject product

5.3.3 Third Party Calibration

Third parties can be used to perform the calibration, however all the rules still apply, plus the additions, which must be identified in the contract. It is highly likely the third party will be audited.

5.3.4 Calibration Records

All calibration records must be unambiguous and be readily available; a unique number must identify the document. Any instrument removal should be documented and the

replacement has a full documented history. The removed instrument should be calibrated immediately to ascertain the cause or impact of failure. The following is a list of key documents plus the content for each document.

CALIBRATION REQUEST

- Scheduled date for calibration and frequency
- Instrument ID
- Calibration range
- Special instructions
- Accuracy and failure limits

CERTIFICATE OF CALIBRATION

- Reference to calibration request
- Instrument ID
- All test hardware and traceability
- Calibration range
- Calibration accuracy and failure limits
- As found and as left data
- Instrument status (PASS/FAIL)
- Calibrator and Approver
- Combination of errors / uncertainties
- All calculations and corrections
- Environmental data

NON-CONFORMANCE REPORT

- Unique ID for instrument
- Failure or errors leading to the non-conformance
- Actions for repair
- Final approval

Training

All persons involved in training should have a full training record; the record should include the following sections: name; employee number; qualifications; experience/competency records, and job description.

Documentation Practices

Good documentation Practice should be followed to ensure that the key documents are created and maintained.

Standardized for layout

Version Control

Reviewed and approved

Approved documents available at required locations

Subject to review

Approval signatories identified

Changes to record should be identified

Master document file to track each document

Other Considerations

With ever improving instrumentation and internal self-calibrations, the calibration record is ever more important. Do not believe an internal self-test, only acceptable output is a hardware failure message. New software for calibration management (Instrument Asset Maintenance Software IAMS) must be 21 CFR 11 compliant.

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Mark Hallworth



Particle Measuring Systems Headquarters
5475 Airport Blvd., Boulder, CO 80301
1-303-443-7100 1-800-238-1801 Fax: 1-303-546-7331
Instrument Service & Support: 1-800-557-6363
Customer Response Center: 1-877-475-3317

Particle Measuring Systems Europe
Tel: +44 1684 581000
PMSEurope@pmeasuring.com

Particle Measuring Systems Japan
PMSJapan@pmeasuring.com

Particle Measuring Systems Asia Pacific
PMSAsiaPacific@pmeasuring.com

Particle Measuring Systems Singapore
Tel: +65-6496 0330
PMSSingapore@pmeasuring.com

Particle Measuring Systems China
PMSChina@pmeasuring.com

Particle Measuring Systems Mexico
PMSMexico@pmeasuring.com

Particle Measuring Systems Puerto Rico
PMSPuertoRico@pmeasuring.com

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