

A COMPLIANT CALIBRATION PROGRAM

The terms used in this paper are examples and are used throughout this document as points of reference.

CHARACTERIZATION AND CLASSIFICATION

- All facility, process, utility, and laboratory instruments used in the manufacturing, processing, packing, holding or testing of drug products, biologicals, medical devices, or nutritional products must be characterized as GMP or Non-GMP according to their use in the GMP environment. This characterization must recognize that in a pharmaceutical, biological, diagnostic or related area the majority of instruments exist to monitor or control some aspect of the manufacturing operation and are therefore GMP.
 - ◆ Instruments characterized as GMP should be further classified regarding their potential for direct impact on product quality (for example, GMP Critical, GMP Non-critical, GMP Utility), using objective criteria.
 - ◆ Non-GMP Instruments must be handled in accordance with good engineering practices and are not subject to the requirements of this program.
 - ◆ Note: All instruments must be evaluated and all GMP instruments included in the calibration program for calibration or operational verification/maintenance.
- Instrument classifications (e.g., GMP Critical, GMP Non-critical, GMP Utility) must be used to determine calibration parameters such as frequency of calibration, Out-of-Tolerance investigations, limits and tolerances. These parameters should recognize the criticality of the instrument, for example:
 - ◆ GMP Critical instruments should be calibrated more frequently than GMP Non-critical instruments to ensure product quality and reduce liability if an instrument is found OOT.
 - ◆ Out-of-Tolerance investigations can be limited to GMP Critical instruments
 - ◆ Process Calibration Tolerances (a secondary calibration limit set to initiate an Out-of-Tolerance investigation based on process tolerance – e.g. Action Limit) can be established for GMP Critical instruments using objective criteria.
 - ◆ GMP Utility instruments may have their maintenance limited to functional operational checks on a regular basis, rather than a quantitative calibration performed.

STANDARDS

- Calibration Standards (instruments and equipment) must be traceable to a national or international certified standard, where applicable. If national or international standards are not practical or available, an independent reproducible standard must be used.
- There must be a system of Reverse Traceability to track where standards were used to calibrate specific instruments
- In all cases the accuracy of a calibration standard must be greater than the accuracy of the device under calibration, generally by a 4:1 ratio, and this ratio must be verified at the time of calibration.

GENERAL PROGRAM ELEMENTS

- GMP Instruments must be assigned Calibration Limits to determine when adjustment is required. Critical GMP Instruments may also be assigned Process Calibration Tolerances to trigger Out-of-Tolerance notification. These Process Calibration Tolerances must be based on the requirements of the process and products and supplied by Process Development, Technical Services, or Operations personnel.

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- All GMP Instruments must be calibrated and maintained according to a written program designed to ensure and demonstrate ongoing accurate performance. This program must include the following elements:
 - ◆ Each GMP Instrument must be locally identified by a unique identification number and included on the Master GMP Instrument List.
 - ◆ There must be a procedure for establishing and maintaining Instrument History Files.
 - ◆ Calibration Parameters, e.g. characterization, classifications, calibration points, limits and tolerances, etc., must be approved by the Quality Unit, the department responsible for calibration, and the applicable user group (Production, Facilities and Utilities, Technical Services, or Laboratory).
 - ◆ Calibration should include at least three points across the full range of the instrument.
 - ◆ Procedures must be established for determining, changing, and approving calibration intervals, test points, Calibration Limits and, where required, Process Calibration Tolerances.
 - ◆ Where appropriate, procedures must be in place to verify and/or standardize accuracy and reliability of GMP Instruments such as analytical balances and pH meters.
 - ◆ Procedures prepared must determine when to challenge repeatability (precision) for each test point where repeatability errors can produce substantial errors.
 - ◆ Procedures must be prepared describing the steps and forms required for the calibration and maintenance of a class or type of instrument.
 - ◆ A Calibration Sticker program must be defined, including requirements for a calibration sticker. Auxiliary stickers, such as Out of Service stickers must be defined.
 - ◆ There must be a procedure for tracking scheduled calibration activities.
 - ◆ There must be a procedure for notifying users of calibration due dates, overdue calibrations and Out-of-Tolerance findings
 - ◆ There must be a procedure for disallowing the use of an instrument after its calibration due date if it has not been calibrated successfully.
 - ◆ The Quality Unit must review all systems and procedures.
 - ◆ Where a computerized calibration management system (CCMS) or computerized maintenance management systems (CMMS) is employed, it must be qualified for its intended use.
 - ◆ Calibration records and procedures must be reviewed to identify any trends and the need to change frequencies or tasks.
 - ◆ The calibration program must include a procedure for reporting any GMP Critical instrument that is found outside the Process Calibration Tolerance during a calibration. This procedure must be invoked whether the device is returned to a calibrated state at the time of calibration or not.
 - ◆ There must be calibration forms developed to record the results of the calibration. These forms must include, at a minimum:
 - Instrument Identification Number and:
 - Manufacturer
 - Model number
 - Serial number

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- Calibration procedure identification (specific to instrument type).
 - Calibration due date.
 - Calibration standard(s) used.
 - Next due date for the calibration of each standard.
 - Predetermined test inputs and test points.
 - As-found result for each test point.
 - Acceptable calibration limits (accuracy) for each test point in engineering terms and percentages, as appropriate.
 - Process Calibration Tolerance for each test point, as required, for Critical GMP Instruments.
 - As-left results, including precision verification for each test point.
 - Calibration performed by/date.
 - Calibration reviewed by/date.
- Exceptions to any of the standard program elements, e.g., two point calibration vs. the norm of three points, must be approved by a process outlined in a procedure designed to rigorously challenge the exception as necessary. These exceptions require approval by the Quality Unit, Responsible Operating Department, and Technical (Calibration) personnel
 - Laboratory instruments used in the manufacture, processing, packing, holding or testing of drug products must be incorporated into the process and facilities instrumentation calibration program or equivalent program.

RECORD KEEPING

- ◆ Records of all calibrations must be complete, current and understandable.
- ◆ Records of all calibration and maintenance of instruments must be maintained for a specified period beyond the longest expiration date of any product produced using the equipment.
- ◆ There must be a procedure established to maintain and make available to technicians current technical manuals specific to device make and model.
- ◆ Notations in equipment logbooks by any calibration personnel must be completed in clear, understandable terms.

PERSONNEL QUALIFICATIONS

- ◆ There must be a system for ensuring the qualification of technicians and mechanics employed in the calibration of GMP Instruments.
- ◆ There must be a written system established to ensure technicians and mechanics are properly trained on any significant new equipment installed in the facility.
- ◆ There must be a written procedure for the qualification of contracted mechanics and technicians used to supplement facility resources.
- ◆ There must be regular training sessions for all calibration personnel covering both cGMP's and operational issues as well as technical procedures.

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These guides are offered as a basis for a Compliant Calibration Program and do not pretend to cover all the aspects of, e.g., when is a Test Accuracy Ratio not appropriate, relating calibration limits to readability of the Unit Under Test, instrument versus equipment considerations, guidelines for determining classifications, etc. Developing a calibration program is a significant undertaking, best done as comprehensively as possible in the early stages to avoid redoing classifications, etc., at later dates.

Pharmaceutical Technical Services is ready to assist in your efforts to establish a compliant Calibration (or Maintenance or Engineering) Program. Contact us at:

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