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cGMP CALIBRATION – COMPLIANT PROGRAM CONSIDERATIONS

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

The Premise

After all the equipment has be qualified, and that qualification has included the calibration of the instruments and controls maintaining the process within specific parameters, our work is done, right? No, it is not. Just as with maintenance considerations, if left to itself, the Second Law of Thermodynamics tells us the instruments will naturally gravitate to a state of greater disorder and inaccuracy. As soon as the validation effort is complete, and the Final Reports signed, and the equipment put to use, instruments start wearing out and moving toward a state different than the state the instrument was in when qualified/validated. All instrument and controls must be maintained to counter the effects of the Second Law. The industries governed by cGMPs have the burden, beyond the financial burden experienced by all industries to maintain a facility in a validated state, adhering to the GMPs. 21 CFR 211.68 says:

> §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.

And the FDA's *Guidance for Industry, Quality Systems Approach to Pharmaceutical CGMP Regulations* state:

> Under the CGMP regulations, equipment must be qualified, calibrated, cleaned, and maintained to prevent contamination and mix-ups (§§ 211.63, 211.67, 211.68). *Note that the CGMP regulations require a higher standard for calibration and maintenance than most nonpharmaceutical quality system models.*

Calibration activities are a requirement of the regulations, a quality requirement, clearly laid out in the CFR and an obvious necessity to maintain the validated state.

What follows are considerations for 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.

Repeating, all instruments used to manufacture a drug or related product must be included in the calibration program. However, as part of a commonsense risk assessment, instruments in the program can be classified with a system that objectively identified the risk to product and patient. Note the FDA's *Guidance for Industry - Q9 Quality Risk Management* (June 2006) states:

> It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or internal procedures, e.g., standard operating procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable. Appropriate use of quality risk management can facilitate but does not obviate industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators.
>
> Is would be an excess burden to perform a FMEA for each instrument. An unnecessary complication, and complications without a compliance benefit is a compliance risk

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Following is an example of procedural based risk assessment program

Risk Assessment – Characterization and Classification

- 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 documented and objective criteria. Some organization use classification categories that include the word “critical” in multiple definitions and can lead to confusion or the need for more elaborate explanations and training.
- 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. As the CFR states, instruments used in our industries “shall be routinely calibrated, inspected, or checked”, not “routinely calibrated, inspected, checked, or *ignored*”.

Further implementation of a risk assessment program would use the Instrument classifications (e.g., GMP Critical, GMP Non-critical, GMP Utility) to determine calibration parameters such as frequency of calibration, Out-of-Tolerance investigations, limits and tolerances. These parameters should recognize and be based on 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

The Standards used to calibrate site instruments have some very necessary, scientifically sound requirements, e.g.:

- 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 – both by in house technicians and contracted services.
- Outside contracted services must have a system of mandatory recall, notifying you if/when one of their standards, used to calibrate your instruments, failed certification.
- 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. The determination of the accuracy of the standard must include any auxiliary components used with the standard to perform the calibration, e.g. RTDs, pressure attachments to a calibrator, etc.

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-

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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.

- 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 to help ensure linearity. Five points is often recommended by calibration experts. The more points, the more assurance of accuracy.
  - ♦ 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 between calibration activities.
  - ♦ Procedures prepared must determine when to challenge repeatability (precision) for each test point where repeatability errors can produce substantial errors, for example mechanical pressure indicators.
  - ♦ Procedures must be prepared and approved by the technical representative, the owner of the equipment or process and the Quality Unit describing the steps and forms required for the calibration and maintenance of a class or type of instrument.
  - ♦ The same level of device calibration procedure approvals applied to internal procedures must be applied to procedures used by external contracted calibration services.
  - ♦ A Calibration Sticker program should 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 using objective, documented criteria.

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- The calibration program must include a procedure for reporting any GMP Critical instrument that is found outside the Process Calibration Tolerance (or Calibration Limit if a Process Calibration Tolerance has not been established) during a calibration. This procedure must based on As-found data and 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
  - 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 the current technical manuals specific to device make and model.
- Notations in equipment logbooks by any calibration personnel must be completed in clear, understandable terms.

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Personnel Qualifications

- There must be a system for ensuring the qualification of technicians and mechanics employed in the calibration of GMP Instruments, including contracted services.
- 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 cGMPs, and operational issues as well as technical procedures.

This guide is offered as a basis for a Compliant Calibration Program and do not pretend to cover all the aspects of, e.g., when is using 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 Maintenance (or Calibration or Engineering) Programs. Please contact us at:

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