This article presents the infrastructure of a GMP compliant Calibration Program based on technical and metrology mythology.

Recommendations for Implementing a Calibration Program

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Introduction

This article is limited to the principles of organization for calibration work in relation to cGMP and other pharmaceutical standards. Calibration and metrology methods related to actual calibration techniques, statistics, and theories are not explored in our discussions.[1] Each class of instruments requires specific techniques and approaches to achieve stated accuracies. All members of the calibration team should be educated in metrology techniques and skills necessary for the successful calibration work.

In pharmaceutical applications, performance and accuracy of instrumentation devices are governed by Current Good Manufacturing Practices (cGMPs). Verification of proper process instrumentation operation is an important factor for finished product in Quality Assurance (QA) programs. In GPM processes, outside of validated parameters weighing additions, sterilization temperatures, compounding pressures, and other factors are most likely not recoverable and costly to the business. Mistakenly released products within an established QA program could be detrimental to patients' health and manufacturers' reputation, including legal implications.[5]

Proper operation of process systems and laboratory equipment in the pharmaceutical environment is critical for product quality, manufacturing cost, and research development. Processes controlled by instrumentation outside of defined tolerances, presumably irreversible, will lead to distraction of affected materials and rise of production costs. Incorrect data of laboratory instrumentation and measurements could delay development and

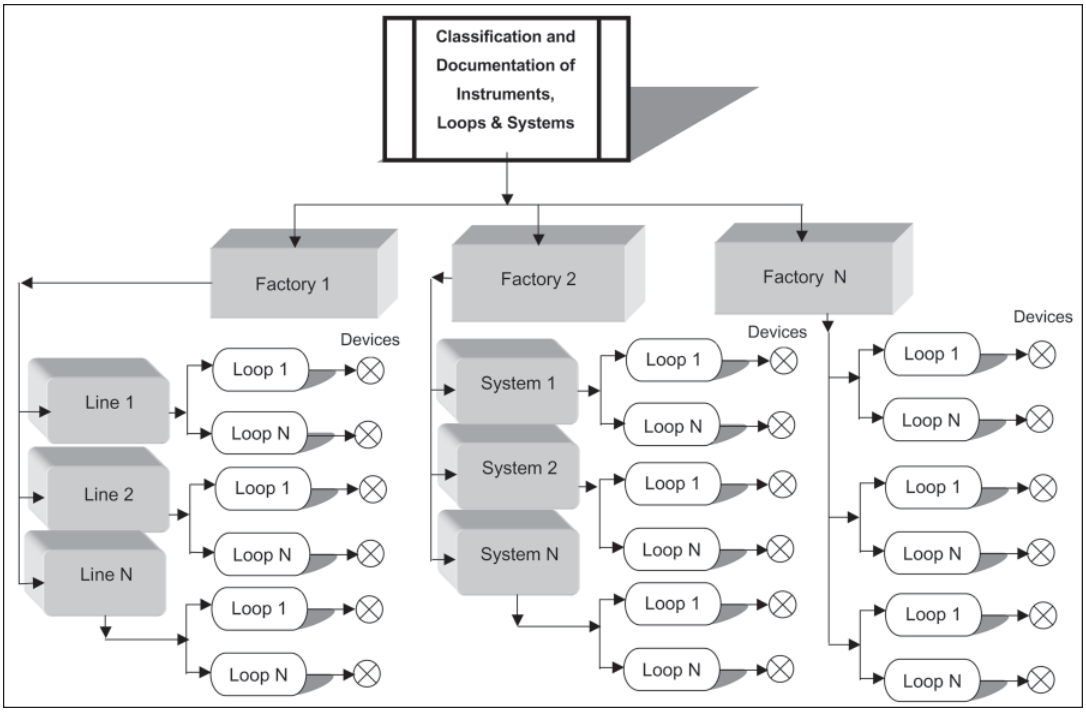

Figure 1. Facility instrumentation configuration diagram.

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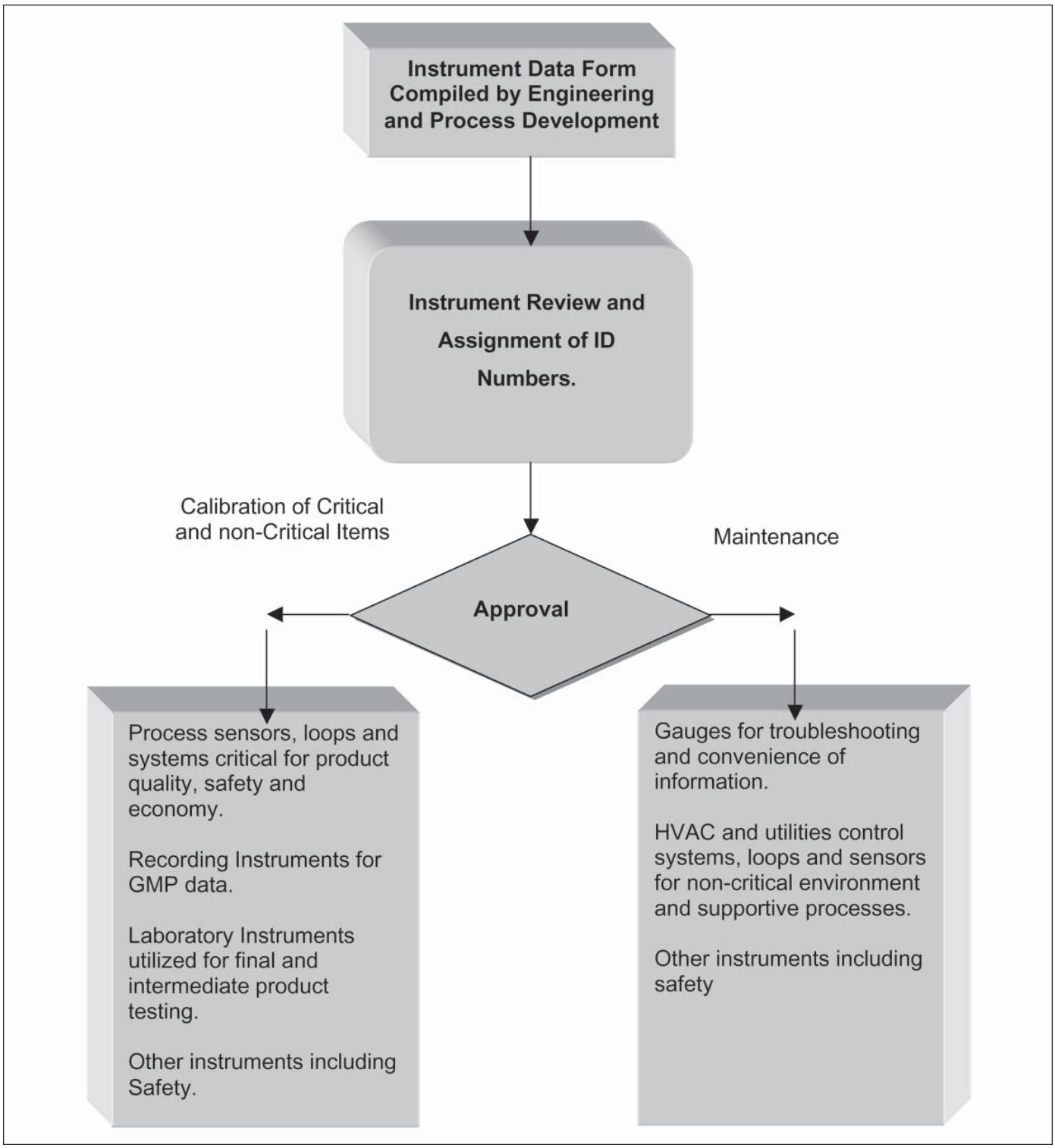

Figure 2. Interactions between preventative maintenance and calibration programs.

release of new products resulting in potential losses of the market share.

The Product Master File and Batch Records contain information concerning weighing specifications, sterilization requirements, compounding parameters, and other details of scientifically developed process tolerances. Production recipes include sequential order of all process activities and permitted fluctuations. Maximum and minimum temperatures for sterilization, weights of each chemical addition, mixing time, and feeding rates are examples of windows for validated parameters critical in determination of final pharmaceutical product quality.[2]

Precision of data in research and development applications is one of the requirements associated with current Good Laboratory Practices (cGLPs). Good calibration record keeping and maintenance of standards and instruments are

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Selected Functions of Calibration Program	Functions of Preventative Maintenance Program in relation to Instrumentation and Measurements	Description of Differences or Comments
Field calibrators are certified as traceable to NIST. Failures of field calibrators will result in product hold and investigations.	Field calibrators are functional but not necessarily traceable to NIST. Calibrators functional or calibration failures will be limited to equipment retests only.	Instruments subjected to calibration program require greater functional analysis than devices under preventative maintenance program. For example, failure of calibrators used for sterilization processes and calibrators used for balancing temperature in office areas will generate different responses.
Calibration and process tolerances are specified for the process operating range and instrument operating range.	Instruments and loops functional performance are defined for control and monitoring processes of non-GMP areas.	Product quality could be directly or indirectly affected by out of tolerance instruments in the Calibration program. Instruments under preventative maintenance program have functions of convenience, energy cost, effectiveness or comforts.
Documentation of performed calibration is filed under calibration program.	Documentation of performed preventative maintenance is filed under preventative maintenance calibration program.	There should be no difference in documentation filing and retrieval between calibration and preventative maintenance programs.
Calibration schedules and frequencies are under periodic review and approval.	Preventative Maintenance schedules and frequencies are under periodic review and approval.	Both programs could be defined by one database and divided by Critical, non-Critical and Maintenance categories.
Instruments, loops and systems calibration failures will trigger notification, investigations, product hold, etc.	Instruments, loops and systems functional failures will necessitate repairs and possible notifications.	Calibrated instruments and loops are traceable to calibrators and standards. It is a good practice to use calibrated instrument in preventative maintenance work. However, strict instrumentation traceablilety is not necessary.

Table A. Similarities and differences between calibration and preventative maintenance programs.

necessary for expected reliability of experimental outcomes. Introductions of new drugs to the market could be affected by failures of upholding metrology standards in science laboratories.

The purpose of this article is to review in a general format a Calibration Program suitable for the pharmaceutical industry. In addition, a discussion of engineering methods for process specifications and theory of calibration requirements in reference to pharmaceutical process procedures, operation/laboratory methods, and standards for instrumentation

tolerances will be outlined.

Weighing additions of chemical components, process temperatures, pressures, flows, etc., will naturally fluctuate from batch to batch. Therefore, cGMP requires that Standard Operating Procedures (SOPs) for validated pharmaceutical processes will cover maximum allowed fluctuations for specified parameters. Products made outside of critical control defined specifications will oblige sanctions of product "on hold" for investigation. An almost certain outcome from investigations will lead to destruction or rework of manufactured material.

Permitted variations in processes need to agree with the equipment and instrumentation capabilities. Qualification tests and procedures for instruments in validated processes will provide the necessary assurance of accurate process executions. Verification of the instrument's compliance to the process requirements is an important phase for the system qualification and validation. Selections of calibration procedures, calibration frequencies, and certification methods for instruments, sensors, control loops, and systems depend on applications, accuracies, and characteristics of instruments stability.

Data of pharmaceutical manufacturing processes and laboratory testing are limited by the instrumentation accuracy. Product quality compliance requires calibration standard certification traceable to National Institute of Standards and Technology (NIST). Calibration procedures work with formats of records to establish documentation layout and flow designed to assure traceability of collected data. Verification of instrumentation measuring devices performance is comprised from two parts. One is a calibration certification and the other is a calibration check. The calibration certification summarizes a methodical process defined by a written and approved procedure developed for a range of measurements. A calibration check is a simplified confirmation of the instrument, loop, or device performance. Usually calibration checks are represented by one or two test measurements.

A successfully executed calibration procedure confirms that manufacturing processes and laboratory experiments are not affected by the tested instrument within the last calibration time interval. Calibration failure in the "as found" data will necessitate an investigation of the product produced within the last calibration period. In the laboratory environment, all tested lots will be affected by an instrument calibration failure. Strict procedures are required for notification of calibration failures. Adjustments of the instruments found out of tolerance should be controlled by Standard Operating Procedures (SOPs). Each SOP should contain instructions for adjustments or reference them to published literature. For investigation purposes, some instruments could require additional testing and may not be adjusted or repaired inimitably. Investigational tests may be needed to determine a magnitude of losses or requirements for application/design/replacement of an instrument.

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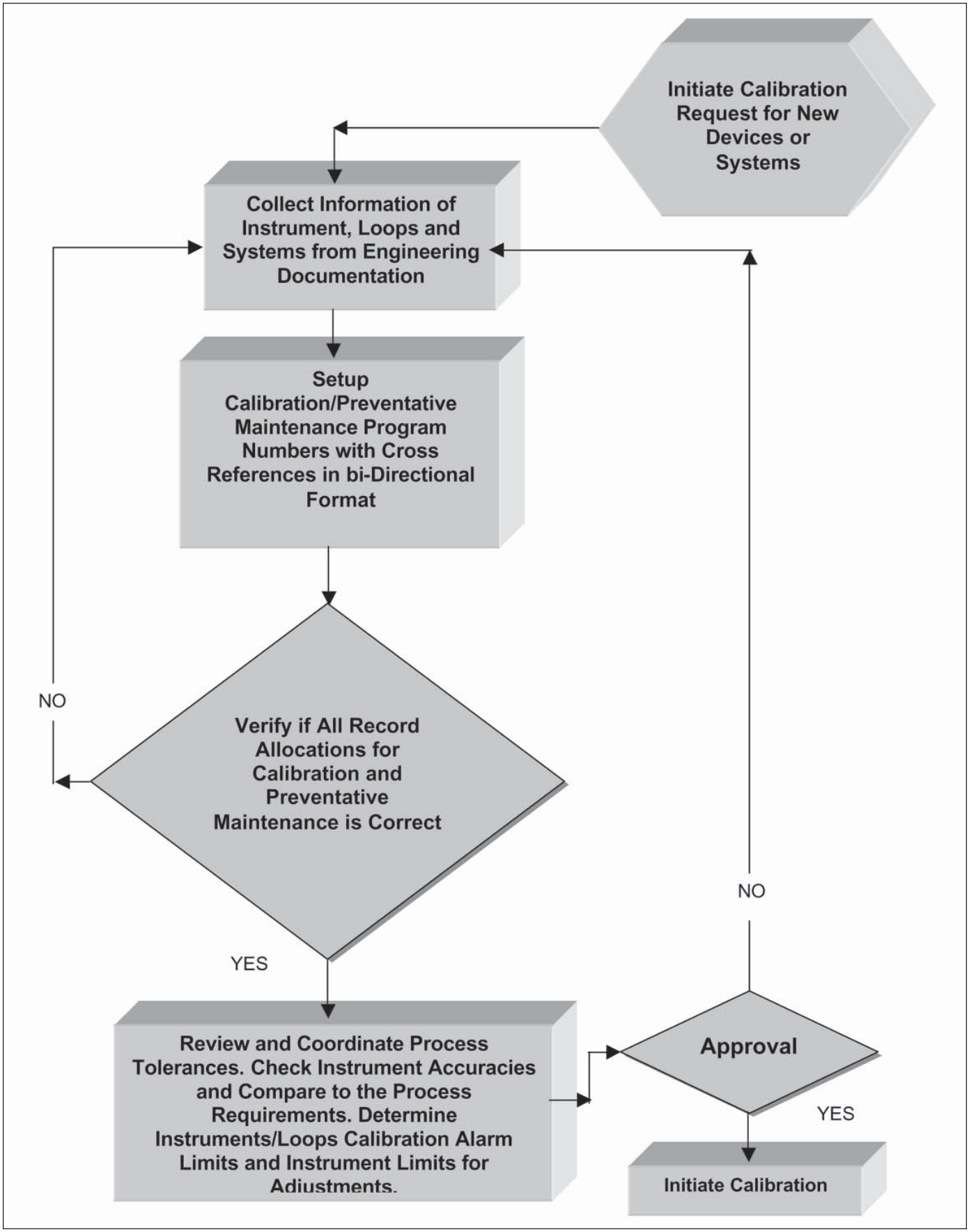

Figure 3. Process of calibration request approval.

Properly established instrumentation tolerances, calibration procedures, and instruments functional tests are very important issues for product development, quality assurance programs, and production costs. CGMP/cGLP metrology program issues related to laboratory instruments, manufacturing capabilities, process tolerances, and calibration methodology are addressed in this article. Actual calibration techniques and metrology requirements related to standards, uncertainty rations, instruments bias, precision, and accuracy are outside of the scope of work for this article.

Managing a Calibration Program

A modern pharmaceutical facility is dependant on thousands of instruments installed in operations, utilities, laboratories, and development areas. Proper functions and accuracies of those instruments are maintained by a Calibration Program. Tasks of a Calibration Program are interfaced with a Preventative Maintenance Program and Quality Assurance activities.[6]

The process of review and approval of Preventive Maintenance activities needs to address requirements of pre and post calibration data. The critical path formula of Pre-Calibration, Preventive Maintenance work, and Post-Calibration is necessary for the system integrity assurance. Calibration and Preventive Maintenance programs cannot function as independent programs. In many cases, Preventive Maintenance could disturb instrumentation and unfortunate discoveries during Calibration work will lead to quality investigations, production loses, and poor business reviews.

Interfacing of Calibration and Preventive Maintenance work requires maintenance, engineering, and quality reviews. Preventive Maintenance and Calibration tasks for all systems and devices need initial and periodic evaluations for assurances of production/experimental consistency and repeatability. The outcome of these reviews should be outlined in specific procedures. For example, Preventive Maintenance work associated with control valves, removal, and reinstallation of instruments will necessitate coordination with calibration activities. Bearing greasing, belts replacements, and other mechanical work may not require links to the calibration program.

An established Calibration Program needs to address the following functions:

I. Documentation records of instruments for traceability and application requirements in accordance with the industry standards of metrology.

II. Continued enforcement of approved calibration SOPs. Reviews and recommendations for modifications of calibration SOPs based on the inputs from Preventative Maintenance and Quality Assurance. Development of new SOPs.

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III. Notification of calibration failures to appropriate departments. Investigations of calibration failures and assistance to affected departments by providing technical expertise and improvements.

IV. Maintaining calibration schedules and coordination with production and maintenance activities.

Each of the above functional topics represents specific responsibilities and procedures of a comprehensive calibration program.[3] Descriptions of internal and external configuration correlated to functional topics are very important for understanding the scope of calibration work.

I. Documentation Records of Instruments for Traceability and Application Requirements in Accordance with the Industry Standards of Metrology

All instruments should be recorded on an approved single format Instrument Data Form. The form should be able to describe and identify a single instrument, sensor, loop, display, system, etc. The information from the manuals and cutsheets of instruments include manufacturing model, serial number, input/output units of measurement, resolution, and accuracy. This information should be properly placed on an Instrument Data Form. Consequences of instrument performances and failures related to processes should be provided by engineering, process development groups, and technical services. This information is needed to identify each instrument as critical or not critical, calibration frequency, and tolerances in reference to the final product quality requirements.

Each of the critical and non-critical instrumentation could be divided into several subcategories. That division may be necessary to establish multi-level procedures for calibration failure notification and actions. The following sections of this article will provide a general discussion of critical and non-critical categories without subcategories.

Instrument review procedures in a calibration program need to identify each device, loop, and system with a calibration number. This number will stay with each instrument, loop, or system and will be retired from the program after removal of the instrument or loop/system modification. Calibration numbers need to work within an establish database to assure historical traceability (replacements and modifications) for all control elements of production and research equipment. Figure 1 represents a sample diagram for configuration of facility instrumentation. The Instrument Data Form requires the location of an instrument, loop, and system (including interconnected references) to be recorded. For example, a form for a temperature sensor, transmitter, or controller should identify the location in the loop, system, and plant area (factory). Each loop or system needs to reference instruments and devices employed in the application. Bi-directional referencing is a very important factor for effective performance of a calibration program.

Instrument calibration numbers need to be interfaced or in many cases integrated with the preventative maintenance program for production machines and devices. It is acceptable for the function verification of non-critical instruments to be addressed by the plant preventative maintenance program. Non-critical gauges and displays utilized for reference only could be checked or periodically replaced within a preventative maintenance program. The Calibration Program could employ a separate category of maintenance devices. For example, some HVAC control loops may be covered by the preventative maintenance (calibration) program. Table A demonstrates similarities and differences between calibration and preventative maintenance functions in relation to instrumentation testing.

The process of an instrument calibration review flow chart is presented in Figure 2. The Maintenance and Calibration work need integration for the following reasons:

- Calibration schedules must be coordinated with preventative maintenance schedules. Preventative maintenance of a system immediately after calibration will void all calibration efforts. Calibration should be a conclusion of preventative maintenance work.

- All instruments require performance verification. However, the detailed periodic calibration with documented traceable standards is not necessary for maintenance

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gauges, HVAC controls, and many other devices. The preventative maintenance functions within the Calibration Program can satisfy the need for verification for such devices without traceable documentation for standards and detailed records.

Figure 3 summarizes the necessary steps for finalizing and approving calibration documentation. In the process of development or modification of a calibration program, those steps could be subdivided or combined to satisfy company policies, personal need of technical staff, or availability of equipment and software. A brief description for each step is presented below:

1. The first step is dedicated for instrument identification with cross-reference to control loops, systems, and locations. References of the instruments to loops and system should be bi-directional. In this step, information is recorded about manufacturing operational data, devices models, operating software, serial numbers, I/O inputs, etc.
2. The second step requires review of the instrument's impact on product quality. This step will collect information necessary to determine instruments, loops, and system alliance and placement under calibration or preventative maintenance programs.
3. This step is allocated for instruments under calibration program and will require coordination of tolerances. Calibration limits will be determined from coordination of tolerances. Recorded and approved calibration limits will be used to initiate suitable procedures to notify appropriate departments of calibration failures.

Coordination of tolerances is a very important factor for setting process calibration limits.[4] This information should be extracted from engineering and process development information. Based on instrument/loop capabilities and process requirements, calibration procedures should include two sets of limits. After exceeding the first set of limits the instrument or loop should be subjected to adjustments. No calibration failure notices will be necessary. If the instrument or loop calibration data exceeds the second level of limits then calibration failure notifications will be necessary. For graphical interpretations see Figure 4. Calibration limits usually are determined by experience, but process limits are established from the process requirements and engineering calculations.

II. Continued Enforcement of Approved Calibration SOPs. Reviews and Recommendations for Modifications of Calibration SOPs Based on the Inputs From Preventative Maintenance and Quality Assurance. Development of new SOPs.

Periodic SOP reviews and GMP training are very important factors for a successful calibration program. SOP reviews should reflect changes in facility processes, quality assurance, and preventative maintenance programs. GMP training is a requirement for maintaining personnel qualifications at an acceptable level.

New and modified processes will require creation or modifications of specific SOPs. Periodic reviews will assure that single changes of one SOP have not created contradictions and discrepancies in the integrity of the calibration program. Those reviews or audits should be conducted by quality, engineering, and production representatives.

Training of personnel should be focused on actual documentation procedures and metrology techniques. It is advisable for members of a calibration team to join professional societies. Participation in the Instrument Society of America and National Conference of Weights and Measurements will improve and broaden technical skills of technicians and engineers. The staff responsible for implementation of technical tasks within the frame of a calibration program must maintain and continuously improve their knowledge in instrumentation and metrology.[3]

III. Notification of Calibration Failures to Appropriate Departments. Investigations of Calibration Failures and Assistance to Affected Departments by Providing Technical Expertise and Improvements.

Procedures of a calibration program for pharmaceutical applications should be able to categorize instruments, loops, and systems in several levels of criticality. Instruments involved in the final product quality tests will be the most critical and devices collecting duplicate data will be less critical. Different organizations may adapt specific and most appropriate terminology for a system to categorize instruments.

The majority of calibration programs choose the use of primary standards. Primary standards are instruments, materials, and devices utilized for testing (calibrating) field calibrators. Primary standards are directly traceable to NIST traceable laboratories. Field calibrators are traceable to primary standards. Sometimes primary standards are used for field calibration also. All instruments, loops, and devices must be traceable to calibrators. Calibration failures of primary or field calibrators will trigger investigations of processes affected by instruments traceable to failed calibrators.

A failure of an instrument or a loop calibration indicates that all product or testing material affected by the instrument requires investigation for quality of compliance. Investigation periods will be extended to the date of the previous calibration. All products manufactured and tested between the last acceptable calibration and the current failure of calibration require an investigation.

Instruments of a failed calibration in different applications will require:

a) immediate adjustment, repair, or replacement, or
b) no adjustment or repairs until additional testing of the failed instrument and process is conducted

The actions above must be pre-selected for each instrument,

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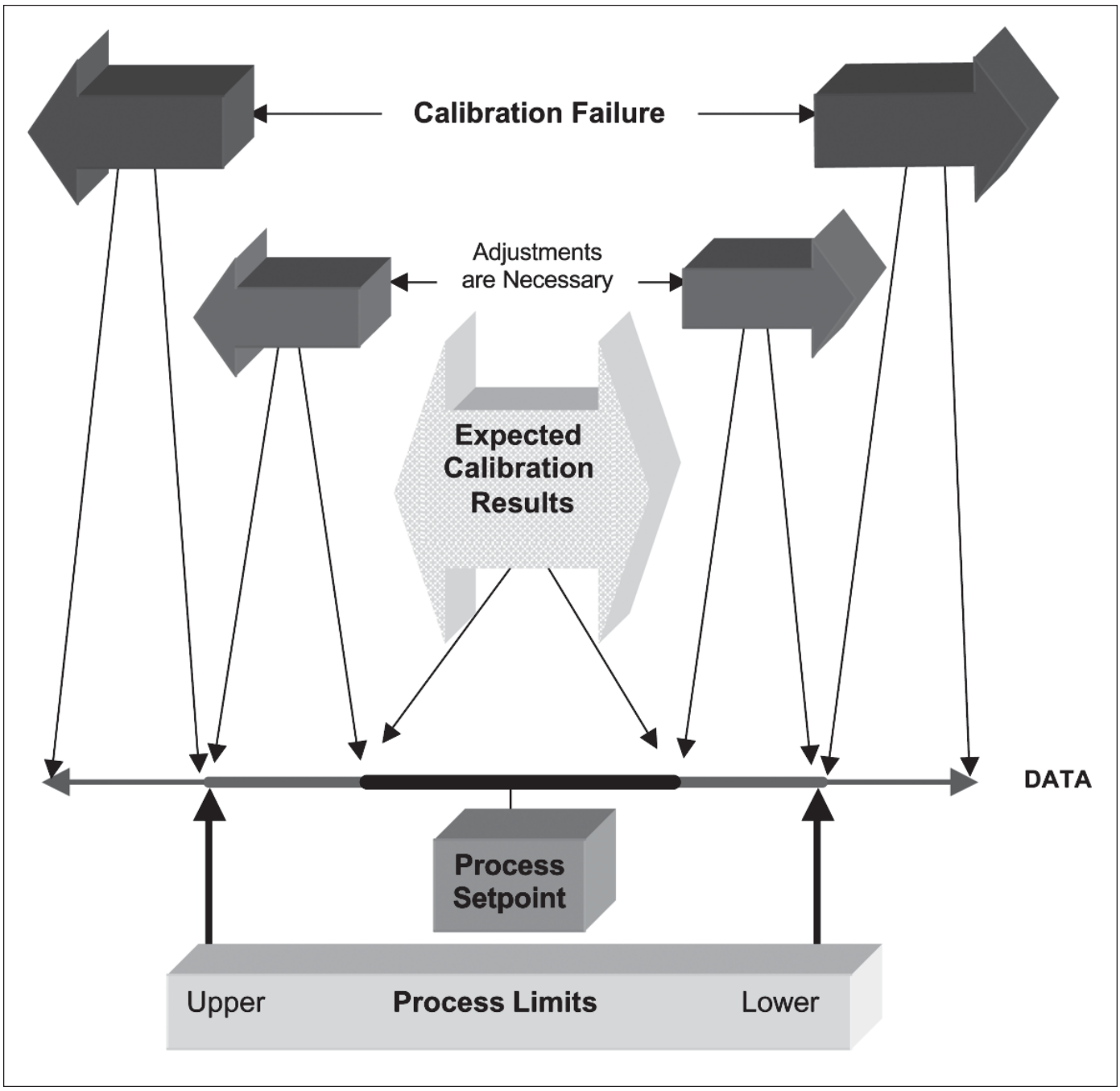

Figure 4. Limits of calibration process and tolerances.

loop, and system, and clearly identified by specific SOPs. The actions 'a' and 'b' could be associated with the level of criticality of instruments and processes. Therefore, instrument calibration frequencies should be set with considerations and risk assessments of processes.

Calibration failures will affect all processes and instruments calibrated with the defective calibrator. Calibration failure of instruments in a quality assurance laboratory could have the same or larger specter of issues. Calibration failures of critical instrumentation could put product on hold, recall and/or destruction.

Properly engineered systems with correctly selected instruments and a practical calibration program will effectively minimize nuisance calibration failures. One part of the calibration program consists of continuous/periodic evaluations of the processes and instrumentation to assure good cGMP compliance.

IV. Maintaining Calibrations Schedules and Coordination with Production and Maintenance Activities

Calibration instruments, loops, and system must be carefully scheduled for calibration. Calibration work requires shutdown of production and laboratory testing. In production environments, calibration of water systems, continuous sterilizers, and other systems will necessitate a major shutdown.

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Calibration work requires diligence, dedication, and objectivity. Therefore, system shutdowns should be scheduled with adequate time delegated for calibration and coordination with other perhaps preventative maintenance activities.

Calibration schedules must be very closely monitored. Overdue scheduled calibrations should be considered as serious events and treated with commitments to avoid any possible future delays. If an instrument calibration is overdue, then production/laboratory stop notices should be immediately forwarded to appropriate departments for shutdown of instruments and associated processes. Accidentally manufactured products or laboratory work performed with instruments affected by a calibration overdue date will require investigation and hold of products.

If a cGMP equipment or system is due for removal or modification then calibration work should be scheduled before work begins. Calibration should be conducted immediately after production ends and before project work starts. To assure product integrity calibration work is necessary to verify instrumentation performance as production ends. After project completion (in case of modification), calibration work will be part of commissioning or validation. If equipment is removed, then the last calibration report will be a record that product manufacturing was performed under specified controls.

Conclusion

Calibration work in a pharmaceutical plant should be focused on the specific applications and not on the capability of instruments in wide varieties of their potential performances. The rules of calibration cannot require that all instruments must be calibrated over the full range of the instrument to the expected manufacturing accuracies and with a complete ignorance to the processes. Each system, loop, and instrument should be carefully reviewed for calibration methodology and applicable techniques.

Process instrument calibrations should be done in place, without instrument removal, and within the loops. Loop calibration is one of the most desirable methods. Calibration of instruments before installation and manufacturing certification should be considered as a reference only and acceptable for commissioning. In regulatory environments, calibration procedures of an approved program must be exercised prior to the beginning of qualifications and validations.

The relationship between an instrument range, process limit, and instrument tolerances is very important. Process limits cannot exceed instrumentation ranges and range of instruments cannot exceed the required process resolution. For example, gauges with ranges of 0 to 1000 psi and 0 to 25 psi cannot be used in the processes of 20- 30 psi.

In a large number of pharmaceutical processes, an application loop calibration at process limits is acceptable and considered as a reliable verification of the controlled accuracy. Loop calibrations could be supplemented by individual device calibrations. For example, if frequency of a loop calibration is quarterly or semiannual then device calibrations could be set for an annual schedule. After completion of individual device calibrations, a loop calibration should be done to assure proper operation of the loop. Functionalities of alarms, emergency algorithmic, and sequence of operations at critical points could be included in calibration procedures.

This article in a general format outlines an infrastructure of a Calibration Program dedicated to a pharmaceutical facility. The purpose of the program is an assurance of instrumentation integrity. A successful calibration program must be interfaced and integrated with other functional programs of engineering, production, and quality departments. At the present time, a facility calibration program is one of the most important factors in the plant compliance and business performance.

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