Validation & Monitoring Solutions

Calibration Program Setup and Management

in the Life Sciences / FDA Regulated Industry

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About the Author

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Steve Lauver has worked in the FDA Regulated Industry since 1992 always with a desire to continuously learn and improve.

Twelve years were initially spent as a Calibration/Instrumentation Technician prior to focusing on managing Calibration and Preventive Maintenance (PM) Programs. Steve worked on two FDA Consent Decree projects remediating Calibration Programs. Since then Steve has worked on myriad projects across the country helping many companies both large and small.

Steve joined Ellab in July 2019 taking on an initial assignment as Project Manager at AveXis in Longmont Colorado. AveXis was starting up the site to produce Zolgensma®, a gene therapy medication used to treat spinal muscular atrophy. Ellab was responsible for the initial validation of over 150 Controlled Temperature Chambers to support the site's production needs. Steve managed Ellab Validation Engineers handling project logistics, collaboration, workflow planning, problem solving, status tracking, and related Project Management duties.

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About Ellab

Ellab offers a wide range of complete solutions for various validation, calibration, and monitoring applications.
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Purpose

This booklet was written to help anyone tasked with setting up and managing a Calibration Program in the Life Sciences/FDA Regulated Industry.

The information contained herein is based on the author's personal experiences through 25+ years of working in the industry, involvement in two FDA Consent Decree projects remediating Calibration Programs (at Wyeth Labs and at McNeil Consumer Healthcare), countless hours collaborating with national and international colleagues, and the author's passion for the subject matter.

Applying the information in this guide will ensure you have, and maintain, a robust, compliant, and sustainable Calibration Program.

A Starting Point: the FDA

Let's begin by looking at the requirements from the agency that regulates our industry: the FDA.

The FDA has governance over the Life Sciences Industry and publishes their regulations in the Code of Federal Regulations (CFRs). Title 21 covers Food and Drugs and Parts 210 & 211 cover cGMP (current Good Manufacturing Practices) in Manufacturing, Processing, Packing, or Holding of Drugs and Finished Pharmaceuticals. If you are reading this, you are likely very familiar with these requirements.

If you are new to this get ready to learn!

Let's take a brief look at the core requirements specific to Calibration Programs for some general understanding about what these tell us we must do. Let's just look at two key statements and break those down: Part 211.68 and Part 820.72:

§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.*

From these statements we learn the following:

- I need to *assess* my plant to identify instruments that I must test.
- I need *written procedures* defining what I will do during that testing.
- I need to *maintain* and *preserve* the documentation of those test events.

§820.72 Inspection, measuring, and test equipment.

(a) Control of inspection, measuring, and test equipment. Each manufacturer shall ensure that all inspection, measuring, and test equipment, including mechanical, automated, or electronic inspection

and test equipment, is *suitable for its intended purposes* and is capable of producing valid results. Each manufacturer shall establish *and maintain procedures* to ensure that equipment is *routinely calibrated, inspected, checked, and maintained*. The procedures shall include provisions for handling, preservation, and storage of equipment, so that its accuracy and fitness for use are maintained. These activities *shall be documented.*

(b) Calibration. Calibration *procedures* shall include specific directions and limits for *accuracy and precision*. When accuracy and precision limits are not met, there shall be provisions for remedial action to reestablish the limits and to evaluate whether there was any *adverse effect* on the device's quality. These activities shall be documented.

(1) Calibration *standards*. Calibration standards used for inspection, measuring, and test equipment shall be *traceable* to national or international standards. If national or international standards are not practical or available, the manufacturer shall use an independent reproducible standard. If no applicable standard exists, the manufacturer shall establish and maintain an in-house standard.

(2) Calibration records. The equipment *identification, calibration dates*, the *individual performing each calibration*, and the *next calibration date shall be documented*. These records shall be displayed on or near each piece of equipment or shall be *readily available* to the personnel using such equipment and to the individuals responsible for calibrating the equipment.

From these statements we learn the following:

- Test equipment/instruments must be *fit-for-purpose*.
- I need *procedures* defining how I will be testing my instruments.
- I need to test my instruments for *accuracy* and *precision*.
- If any requirements are not met, I must *investigate* and follow-up.
- My calibration standards must be *traceable* to other standards.
- I must *create* and *maintain* records of all calibration events.
- Those records must be *easy to find*.

While the FDA CFRs have much to say, the two sections referenced above comprise the core statements that we must follow when creating and maintaining a Calibration Program.

Following these rules *consistently* and following up based on audits and CAPA (more on this later) is the key to successfully managing any Calibration Program!

Let's begin!

Now that we understand why we must have a Calibration Program (it is required by the FDA), and understand the core needs of that program, let's build the framework of a Calibration Program. Your Calibration Program can be broken down into the following core functions:

Let's review each of these describing what we need to do for each.

- Training
- Onboarding assets
- Asset numbering
- Classification & Criticality
- Labels & Tags
- Calibration specifications
- Standard Operating Procedures (SOPs)
- Lifecycle
- CMMS – your Calibration Program IT Solution
- Documentation
- Out-of-Tolerance (OOT) and Overdue response
- Metrics
- Audits and CAPA response

Before we explore each of these in some detail let's summarize what you always need to do to be audit ready when it comes to managing your Calibration Program:

- Be in control of your program.
- Assess risk to product and patient.
- Have rationale for your decisions.
- Document all decisions.

Additionally, while the core focus of this booklet is managing a Calibration Program, it is important to understand the close relationship this has to the site's *Preventive Maintenance Program, Certification Program,* and Validation Program. Many of the fundamentals in this guide work across all these platforms with respect to the *service needs* of your plant's equipment.

Let's take a moment to mention that throughout this booklet the terms *equipment* and *instrument* are meant to be interchangeable. We can view an Autoclave as an equipment that has instruments on it. A Balance can be thought of as being an instrument, like a Pipette or pH meter. These are all assets managed by the site's Calibration Program.

Training

Technicians performing calibration need any combination of *education*, *training*, and *experience* to be considered qualified to perform their job role. It is important to have and maintain robust training of your Technicians and have training records to show all training is complete *and* up to date. This is basic audit readiness! Auditors will ask for training records and if you have gaps, such as overdue training, it looks bad because quality cannot be assured without robust training that is properly documented.

It is very important that everyone performing calibrations have the proper training and qualifications *before* performing their work and all this is documented and defendable. What I mean by defendable is this: are you confident the person can do a given job based on their education, training, and experience? If they only read a procedure and said, "Got it!" is that good enough? The short answer is No! Technicians need to show they can perform a job role through competency testing, on the job training, or even by bringing a history with them (they've done this work previously and their work experiences and competencies can be verified).

End Users in the organization also need to be properly trained in the Calibration Program. They need to understand when it is OK, *and when it is not OK*, to use a piece of equipment. If calibration is expired they need to be able to recognize that, so they do not use expired equipment. They need to understand they *must not move certain assets* without going through a process. This way the equipment can be calibrated before and after it is moved. They also need to ensure equipment can be found when calibration is due. We often need help from End Users in locating equipment due for calibration. This all speaks to having control over your Calibration Program from End Users to the Technicians performing the calibration work.

Onboarding assets

Onboarding is a process of *assessing* your facilities' equipment and instruments, *determining* their service needs, *documenting* those needs, and *approving* those decisions.

Onboarding starts with a need: imagine our End User says, "I need an Autoclave to do my job." This leads to something called User Requirement Specifications (URS) that define everything this Autoclave is expected to do. In this way you ensure the equipment ultimately procured is suited for the purpose for which it is intended. The site's Calibration Subject Matter Experts (SMEs) might be asked for guidance or approval to avoid purchasing equipment that fails to meet the expected needs. I've seen cases where a lower priced unit was purchased without much oversight and when it came time to qualify that unit it didn't pass the acceptance criteria it needed to. *It was not fit for purpose*. The savings, in that case, were wasted causing unnecessary delays.

Once this is all approved and the equipment arrives onsite the official Calibration Program onboarding begins. So much to do…where do we start?

We begin with a document…

That document may be paper based or an electronic workflow in your Computerized Maintenance Management System (CMMS). More on IT solutions later. In either case, the function of this document, let's call this a *Master Equipment Record (MER*), serves as the starting point for what service(s) we expect to do to this asset during its usable lifecycle.

On this document we capture relevant information for the equipment such as manufacturer, model, serial, description, location, and additional important information (perhaps owner's name or department).

We also can capture what service(s) are needed on this equipment and who will perform those services. For example: does this new Autoclave need calibration? Validation? PM? Perhaps all of those? Remember how the Calibration Program can be considered along with these other service functions? Why not combine some, or all, of these needs into one document? By using our MER form to document these decisions we then can drill down deeper into the specifics so we can *paint an entire story around the service needs of each asset.*

Additional forms, besides our MER, may include:

- Master Instrument Record (MIR) – documents calibration requirements.
- Master PM Record (MPMR) – documents PM requirements.
- Equipment Change Form – documents changes to service needs.
- Adverse Event Notification Form – documents asset failures.
- Reactivation Form – documents return to service of inactive assets.

Forms tracking

It is very important that all forms are logged and tracked to ensure they are processed in a timely manner. Some forms will surely get stuck awaiting approval. Only through vigorous tracking will those stuck forms be identified so they can be located, and the approval process completed in a timely manner. The Calibration SME is often the best gatekeeper for this task.

Forms approval

The forms are approved by the various cross-functional SMEs that are involved in your Calibration Program. They each have a role to play in the approval of these documents and your program design will determine the complexity of your Calibration Program. The cross-functional people working together form a *Calibration Committee*. Here are some common approving departments and their role(s):

The number of SMEs on your Calibration Committee will vary depending on size of your site, complexity of your process, and risk to product or patient. In the very least you should include a Calibration SME, End User, and QA and expand according to the site's needs and risk.

Calibration:

- Are the specifications appropriate for the instrument?
- Do we have standards and apparatus needed to perform a calibration?
- Do we have a procedure for the calibration?

Validation:

- Are the specifications aligned to the acceptance criteria?
- Do these specifications align to the process needs?
- Is this aligned to the site's Validation Master Plan?

Engineering:

- Do these specifications align to the equipment design needs?

End User:

- Do these specifications align to the process needs?

EH&S:

- Do these specifications address any EH&S requirements?

QA:

- Does the form meet all GMP/GDP (Good Documentation Practices) requirements?

You may want to include checkpoints on your forms to ensure they are properly processed. I've seen this used as a great tool to avoid missing an update! In a very robust process, you may even have a second person verify that the form was processed properly by looking up in the CMMS after the form is processed to catch errors before they have a negative impact to your process.

Asset numbering

We use the MER/MIR forms to assign assets a unique ID used to track the equipment and services performed on it. Numbering schemes can be as simple as a number "00001" or perhaps include some information describing the item "BAL-001" (for Balance #001).

Keep in mind if you use a "smart" ID numbering scheme this can lead to challenges when changes happen. Smart ID numbering may include the building, department, criticality, or other information about the asset. *If the use of that equipment changes, the ID number might no longer be valid*. Changing an ID can be done but it complicates things! You'll need a way to track ID changes and reverse lookup an ID even if someone gives you an ID that has since been changed. Keep in mind a lot of documents might be impacted by an ID changing such as validation documents. *It is recommended to avoid smart ID numbering schemes for these reasons.*

It is common to have *parent* and *child* numbering schemes. For example: An Autoclave may be 00001 and the instruments on the Autoclave be 00001-001, 00001-002, 00001-003, etc. to easily link those instruments to their parent asset, in this case the Autoclave.

Classification & Criticality

It is important to understand that the equipment in your plant are not all equal in terms of importance. A pressure gauge on a line supplying air to valves won't be as critical as a pH meter used by the QC Laboratory for GMP testing purposes. Some instruments will need vigorous testing while others might need very simple testing, if any at all. You can only make this determination by *assessing* your equipment, *documenting* your decisions, and having cross-functional disciplines *approve* those decisions.

This is called doing a *Risk Assessment.*

Classification and Criticality Assessment is a way to make decisions, so you know what to test and, very importantly, what to do when a test fails or when an item is overdue for scheduled service.

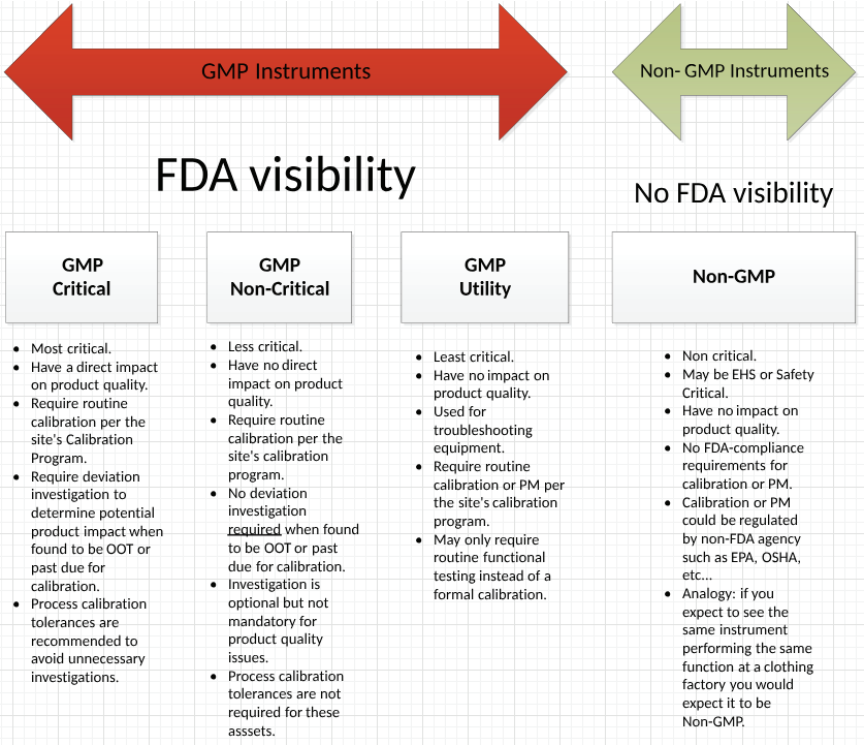
Let's use an example: you have a meter used at your wastewater processing plant that fails calibration. Does this warrant notification to your site QA department? No! There is no potential impact to product or patient in this case. There might, however, be an impact to the environment; therefore, your EHS Officer should be notified. QA's purpose is to protect the product and the patient, and you only want to use them when it is appropriate.

By performing Risk Assessment and classifying your equipment during the onboarding phase you make important decisions about *future responses*.

So how do you perform Classification and Risk Assessment? *Characterization* can divide instruments into simply GMP (FDA visibility applies) and non-GMP (no FDA visibility applies). *Classification* can further divide your GMP instruments into sub-categories each with slightly different requirements depending on the potential for risk to product or patient. Some common classifications are:

- GMP Critical
- GMP non-Critical
- GMP Utility

Here is an infographic to help visualize this:



Who makes these decisions? Your site SMEs. They should be a cross-section of experts and include End Users, Validation, Engineering, Calibration, and a QA representative. This is our *Calibration Committee* we spoke about earlier.

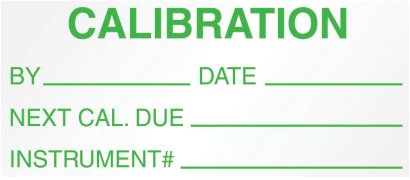
The scale and complexity of your site will determine how many SMEs you need but the more collaboration during onboarding the more robust your Calibration Program will be. You need to have good rationale for your decisions so do a good job here and document and approve your decisions.

Know that Risk Assessment is subjective *and* objective at the same time! *There can always be disagreements about some of these decisions!* But if you have knowledgeable SMEs involved and you *document and approve your decisions* you will be in a strong position when it is audit time.

Labels

Labels are permanent (ID numbers) or semi-permanent (service labels) and display information right at the equipment. Your use of labels will depend on how much information you need to convey directly at the equipment. At the minimum you will need to have ID labels showing the assigned unique ID and a label showing the status of the calibration, PM, certification, or validation.

Here are some examples:



You may have a few other *special-use labels* at your site to include:

- Criticality assigned to the asset.
- Limited calibration label.
- Minimum acceptable weight (for Scales and Balances).
- Calibration Not Required / For Reference Only.

Tags

Tags are temporary and tell End Users if the equipment is out-of-service and therefore not to be used for GMP purposes due to being inactivated, unable to meet approved specifications, or because repairs are needed or in progress.

Calibration specifications

This is where you define what calibration testing is required for the instrument. This is some of the nuts-and-bolts of the operation and is a very important part of your Calibration Program.

Remember the MER and IMR documents that define the requirements?

- Do I need to calibrate the instrument?
- Do I need to perform PM on the instrument?
- Do any parts need to be routinely replaced?
- Do we need to perform certification activities (Cleanrooms, Biological Safety Cabinets, Fume Hoods)?
- Do I need to validate the equipment?

Those requirements may be:

What do you need to document?

Let's cover the basics (this may be enough to start with and grow when additional needs and complex cases arise):

- Calibration Interval (monthly, quarterly, semi-annually, annually, other?).
- Instrument Range.
- Instrument Resolution.
- Calibration Test Point(s).
  - *1-point at operating point (oftentimes this point is documented).*
  - *Multi-point (including all points to be tested).*
- Limited calibration.
  - *A special case where only a partial range/function may be tested due to special requirements or inability to perform full testing.*
- Calibration Tolerance.
  - *May include a Process Calibration Tolerance which defines when a GMP instrument requires Out-of-Tolerance notification and QA response.*
- Source for Calibration Tolerance:
  - *Manufacturer's tolerance.*
  - *Industry standard (such as ISO).*
  - *End User-defined.*
- Calibration performed by:
  - *Internal Technician.*
  - *Calibration Service Provider.*
  - *OEM (Original Equipment Manufacturer)*
- Calibration SOP (and perhaps Work Instruction) to use during calibration.

Remember: these decisions must be *documented* and *approved* so you have evidence to show Auditors how you selected these requirements.

Standard Operating Procedures (SOPs)

Your Calibration Program SOPs will fall into two categories:

- Managing the Calibration Program:
  - › *Documenting the processes described in this guide.*
- Technical procedures:
  - › *Documenting how the calibration is performed on an instrument such as Temperature, Pressure, pH, Relative Humidity, etc...*

Your SOPs should be clearly written, easy to understand, and provide enough detail to perform the job satisfactorily.

Not following your SOPs is a common GMP violation so it is worth your investment to get this right!

Your Calibration Program management SOP(s) will spell out how you run your program, onboard your equipment, manage changes, interface with your IT solution, retire equipment, reactivate equipment, and manage Out-of-Tolerance discoveries and overdue service events.

Your technical SOPs will explain the technical calibration procedure for a given equipment type, such as a Pipette. What standards do I need? How do I perform the calibration? How do I adjust, clean, or repair the unit?

A good practice is to put the requirements in your *SOP* and the how-to in a companion *Work Instruction*. The SOPs require tight controls and should be revised only as needed. The Work Instructions can be more fluid-like evolving over time more rapidly as you improve your process methods.

For example: Your SOP might require a Past Due metric report be generated on the first day of each month and forwarded to the Facility Manager and QA for review and assessment. Your Work Instruction would describe *how* to obtain that metric report from your CMMS. The process in the CMMS might change with software changes and therefore may be updated more frequently. The metric report is the critical output. How you obtain that is less critical provided the output is the *proper* output containing the *proper* data!

Lifecycle

Lifecycle refers to managing our assets from cradle to grave. From initial receipt, to the phase throughout routine usage, through possible periods of inactivity, and eventually to final disposition (retired). Throughout the lifecycle it is common to have changes that need to be managed: the unit may get relocated, parts will fail and need to be replaced, test points may need to change (an Incubator may have its operating point adjusted), the item may not be needed for some period of time but be kept for potential future use (inactive), and for similar reasons.

Changes must be controlled to ensure the equipment remains fit for its intended purpose. If a critical part is replaced with a non-conforming part the unit may no longer be fit for its intended purpose. Therefore, it is vital that *all changes be documented and approved*. This can be done on a Change Form managed in the Calibration Program or is some more complex cases this may come under the site's overarching Change Control process. Either way is acceptable and is a site decision. *The key is ensuring all equipment changes are managed!*

Remember that during periods of status changes it is important this is reflected at the equipment using an appropriate label or tag. An equipment that is inactive is no longer OK for GMP use and therefore any calibration labels should be removed, and an Out of Service tag applied so all End Users are aware of the current status to avoid improperly using an inactive equipment for GMP purposes.

Equipment status can be separated into:

CMMS – your Calibration Program IT Solution

Your Calibration Program will be managed to varying degrees by a software package. This software may be very as basic as an Excel spreadsheet* or may be part of an enterprise software package such as SAP.

Key provisions of your Calibration Program software are:

- Must be validated.
- Meets FDA requirements for digital signatures (CFR Part 11, Electronic Records; Electronic Signatures).
- Have controlled access and user rights to prevent unauthorized changes.
- May include some read-only access.
- Have an audit log to document data entry and changes.
- Manages key Calibration Program requirements:
  - › *Service requirements.*
  - › *Service intervals.*
  - › *Schedule due dates.*
- Have outputs for metrics and reports.
- Requires data backup functionality.
- May include workflows for forms routing, tracking, and approval.

** Note that use of an Excel spreadsheet to manage your Calibration Program is inherently risky and this should only be used in the very early stages of a program setup until a robust and compliant IT solution is in place.*

Work Instructions should exist to explain how to use the software to add assets, modify data, generate reports, etc.…

Many such software packages exist, and any internet search will reveal many such offerings. These can be offline or online applications. Offline programs can operate without an internet connection and require a syncing functionality to upload and download changes to the cloud whereas online programs only operate with an internet connection. Both offer advantages and disadvantages and which you have depends on needs, budget, and corporate vision and direction.

Documentation

In the FDA Regulated Industry, a common statement is *if it isn't documented, it did not happen!* So documentation is a key part of any Calibration Program.

Documentation in your Calibration Program includes:

- Forms (MERs, MIRs, Change Forms, etc.…).
- Service events (calibration records).
- Other outputs such as metrics and reports.

These records are often stored in physical or digital file folders referred to as *Equipment History Files*. The file folder may be sub-divided into separate calibration and PM folders. Forms may be separated as well so they are easily found when viewing a specific file folder. Documents are stored chronologically in the Equipment History Files.

These documents must be stored in a secure area, such as in a site Records Retention Department, where access is controlled and restricted. Documentation must not be allowed to be removed from the secure area without being logged. This is critical: missing documentation demonstrates a lack of control and of course during an audit a requested record will be the one that is missing!

The documentation storage area must be protected against fire and water damage and access must be tightly controlled, monitored, and restricted. Oftentimes original documents will NOT be allowed to be removed from this area! In these cases, a copier may be inside the controlled storage area so only official copies can be removed. Records must be kept per the site's Records Retention procedures; often that is for many years. Records may be stored offsite in some cases: very old, inactive, retired records. Those need to be logged so they can be retrieved if there is a need to view those later.

Out-of-Tolerance and Overdue response

Most calibration service events pass with no adjustments required. In these cases, the Calibration Technician performed the required tests, found the instrument was within all stated specifications, and no adjustments were made to the instrument. These are the easy records to deal with! The more challenging events are those where the instrument was found outside the expected specification, a failure happened, or the equipment went overdue for calibration service. When this happens, more work is involved to determine

what, if anything, needs to be done as a result of this adverse finding.

Remember us talking about Risk Assessment and Criticality Assessment earlier? If you did that properly you will know which failures require notification to QA for assessment. Not all failures will require QA notification and follow-up. If the equipment is not critical, we already know we don't need to notify QA. Here is another special case: initial calibration. If a unit is being calibrated for the first time and did not pass calibration, there is no need to notify QA and perform an investigation: the unit was not used for GMP purposes. *Be sure to mention this scenario in your Calibration Program SOP.*

QA will, upon notification of Out-of-Tolerance or calibration overdue, need to investigate if there is any potential impact to product or patient as a result of this discovery. This is via QA Deviation Investigation and may be simple or complex depending on the situation. For example: if it is determined the equipment was not used since its last calibration, then there is clearly no potential impact. It is vital, therefore, to know if your equipment was used for GMP purposes through some mechanism, be that a logbook or other means, to help with this determination.

Besides determining potential impact to patient or product there is also assessment of what we might want to do with the equipment to reduce the change of reoccurrence in the future. *See CAPA below for more information on that.*

Overdue response requires evaluation as well. In some cases, an equipment may be overdue because it is offsite for calibration and wasn't returned by the due date. Is this OK? Usually yes: the equipment is undergoing routine calibration and isn't being used for GMP purposes *but keep in mind* if the unit is offsite for an extended length of time that could cause great pains if it is eventually discovered to be Out-of-Tolerance. That delay could be a big problem therefore it is vital to monitor equipment that is overdue and keep a watchful eye to ensure a timely completion. Depending on the length of delay your product may have shipped and been used by a lot of people! This is part of our Risk Assessment: managing equipment that is sent offsite for service such as calibration.

Thus, *keeping track* of calibration events and *monitoring* and *responding* to delays is a key part of managing any Calibration Program.

Metrics

Metrics and Key Performance Indicators can paint a very clear picture of the overall health of your Calibration Program. Some things you can tell from your metrics and reports:

- How many forms are in processing but not yet returned?
- Which calibrations were completed last month?
- How many calibrations are due this month?
  - *How many of those are still due?*
  - *Are they scheduled for service?*
  - *Are any missing?*
- How many calibrations are currently overdue for service?
- What assets are currently active, inactive, and retired?
- How many Out-of-Tolerance discoveries were made during a given timespan (such as last month, this month, etc.….).
- What is the status of the follow-up to the Out-of-Tolerance and overdue discoveries?

Sometimes site metrics may include verification that the process is running properly. This might entail, for example, verification of a statistical sampling of complete calibration service events in the Equipment History Files to ensure they have all been processed and filed properly.

The more manual handling of paperwork that is in your process, the more chances you have of some missing records. Be mindful of your documentation: having strong oversite will be a huge benefit for your site. *Do not neglect in this critical area!*

Audits and CAPA response

Audits are a method of evaluation the compliance of your Calibration Program and can assess:

- Training records of Calibration Technicians.
- Compliance to all SOP requirements.
- Review of Out-of-Tolerance and Overdue response.
- Documentation review.
- Field labels and tags are being used properly.

Audits can be of varying levels and include:

- Self-audit.
- QA internal audit.
- External audit (FDA or another regulatory agency).

CAPA refers to *Corrective Action and Preventive Action* and takes effect when we have Out-of-Tolerance and Past Due response.

Corrective action is the re-work/rectification activity of the non-conforming products. Corrective actions are implemented in response to Out-of-Tolerance and Overdue Response.

Short answer: *Corrective Action is immediate response to fix the problem.*

Preventive action is any proactive methodology used to determine potential discrepancies before they occur and to ensure that they do not happen. Preventive Maintenance is a Preventive Action by nature.

Short answer: *Preventive Action is proactive response to avoid having a problem.*

Some FAQs

The managing of a Calibration Program is not a black-and-white process! It requires constant evaluation and decision making. Often there is no perfect decision. Strong collaboration is the key along with having someone managing your Calibration Program that brings a lot of experience and skills to the table! It is critical you document your decisions (in SOPs and on forms) and have a good rationale for them. Even with all this in place you may still be challenged by Auditors that insist on doing things differently! This cannot be avoided and is normal.

Let's review some special cases that often come up when discussing Calibration Program management and some things to consider when dealing with these.

Let's address these as Frequently Asked Questions.

- Monitoring sensors: place in air or a small bottle of liquid?
- How do we manage Test Accuracy Ratio (TAR)?
- Precision testing: when is this needed?
- Are single-point calibrations acceptable?
- What should my test points be?
- Calibrate or replace?
- Should we include switch testing in the Calibration Program?
- Should my service due dates be the last day of each month?
- Do we need to retain expired service labels?
- What is the difference between daily checks/standardization versus calibration?
- Do I need to calibrate each device if we perform loop calibrations?
- When to attempt adjustment?
- Can I use N/A checkboxes on forms?

Monitoring sensors: place in air or a small bottle of stabilizing fluid?

Refrigerators and some -20°C freezers may include a small bottle of glycol, or similar liquid, into which your monitoring temperature probes may go to provide some dampening/smoothing of the temperature measurement. These bottles only contain a small amount of liquid, but the slight dampening effect more closely reflects the temperature of materials stored inside the unit compared to having the probe directly exposed to the air.

Note you should not place controlling temperature probes inside a fluid stabilizing bottle. Controlling sensors need to sense temperature changes quickly and thus slowing down their response time would have a negative impact on the control of the unit.

Some companies may prefer to avoid this based on "How much fluid is the correct amount?" This is valid and, depending on the product being stored, this may be a consideration that leads to the decision to avoid this.

Having your monitoring probe in a small quantity of fluid is often preferred compared to having the probe in air. This can be managed by noting this in your SOP(s) and perhaps by including a checkbox on your MER form noting the presence of a bottle for the monitoring probes.

Remember: if you decide to go this route, include this in your SOP, and possibly indicate the presence of this bottle on your MER form (or maybe even in your CMMS software) and you will be in a strong defendable position! You have your decision documented and approved. That is solid footing and common industry practice.

How do we manage Test Accuracy Ratio (TAR)?

Test Accuracy Ratio compares the accuracy of the Calibration Reference Standard to the Unit Under Test (UUT). A good rule of thumb is to ensure a TAR of 4:1 when performing calibrations. This means your Calibration Reference Standard is 4 times more accurate than the UUT. This won't always be possible or practical and managing this can get tricky. As instruments get more and more accurate obtaining standards that are 4 times better can be quite complicated (and expensive!). In high risk calibrations maintaining a higher TAR may be very important despite the potentially high cost to procure and maintain those standards. As the TAR drops your confidence in the readings also drops. Eventually a TAR of 1:1 means both standard and UUT have the same accuracy. At this point are you still performing a meaningful calibration? No!

You may hear TUR mentioned as well: this is Test Uncertainty Ratio and accounts for possible sources of error in the calibration process that TAR does not.

No matter which of these terms you use knowing what your TAR is during a calibration event and where high accuracy / high risk calibrations are is critical. Maintaining as high a TAR as possible is a consideration that requires expertise to manage.

Precision testing: when is it needed?

Precision is a measure of the reproducibility, or closeness in value, of repeated measurements. You will need to determine if and where you will need to perform precision testing. Common items tested for precision include mechanical gauges (such as temperature and pressure), Pipettes, and mechanical Scales. The more critical the device the more important it will be to consider performing precision testing on it. Pipettes calibrated to ISO 8655 guidelines include precision testing.

Additional terms that are often spoken about are repeatability and hysteresis. Hysteresis refers to the instrument's ability to read accurately during ascending testing versus descending testing. Some transducers will exhibit a mechanical binding effect that will cause the upscale readings to be different than the downscale reading. If you've ever seen someone tapping a gauge, they were trying to vibrate out any hysteresis and view a true reading. These terms are all close enough in meaning not to split hairs over regarding the need to test.

The bottom line is where, if anywhere, do you need to test for precision in your process? You may have very little need for this or quite a lot depending on the instruments you have and the criticality of those instruments. This is often restricted to mechanical instruments such as pressure gauges as well as Pipettes. You may decide to manage this on your MER form by having a checkbox to indicate whether precision testing is required.

Are single-point calibrations acceptable?

The number of calibration test points you test per instrument is dependent on the process being monitored, the criticality of that process, and even the ability to perform the testing. Often a question may be asked: Do you allow one-point calibrations at your site? You may find that in some cases you will.

If your process is *controlled* at a *static setpoint* such as for a Freezer or Refrigerator, then a one-point calibration of the monitoring probe at the operating point may be sufficient and even prudent. I've seen Auditors reject this saying that multi-point calibrations are always required; however, there isn't anything in the FDA CFRs that states this is so. Just know that each Auditor will bring with him or her some expectations they will press each site to comply with. Be ready to cite your approved SOPs as rationale for why you do something and allow the site's escalation process to take any issues up the chain of command if the Auditor insists on changing your process when you've covered your bases.

I've experienced situations where multi-point calibrations were performed by simulating the sensor using a Process Calibrator to test everything except the sensor; however, *I do not see great value in this*. The sensor is often a point of error so eliminating the sensor from the calibration greatly reduces the effectiveness of the overall calibration.

Some devices don't lend themselves well to more than a single-point calibration. A Cryo Freezer, for example, operates around -196°C (liquid nitrogen temperature) and without removing the probe there is no practical way to check it at other temperatures. Is this OK? Sure, provided your SOP and documentation allow for this!

Thermoforming plates can have embedded heating elements and temperature sensors. These may be used on a production line and swapped out when they fail. Calibration of these is very tricky: you need to know where to place your Calibration Standard and performing multi-point calibrations may be impossible. Performing only a simulation calibration of the instrumentation may be your best and only practical course of action.

Always remember *risk* and *criticality* drive your decisions! If you have a high-risk instrument in your process you may need more robust calibration testing despite that testing being more complicated, time consuming, and costly to perform.

What should my test points be?

Know that there is no standard to apply here. For years I was accustomed to calibrating many instruments at three points: 10%, 50%, and 90% of range. One day I encountered global guidance that this was improper, and that calibration must be performed at 0%, 50%, and 100% of range. The rationale was if the signal went below 10% or above 90% it would be in an *uncalibrated* part of the range. While it is best practice to operate *between* calibration points, it isn't wrong to calibrate at 10%, 50%, and 90% of range and consider the entire range of the instrument to be calibrated. Changing the process to calibrate at 0%, 50%, and 100% of range led to new trouble as we discovered some input devices didn't read below the 0% input or above the 100% input thus we had to avoid this new guidance and move away from this requirement.

In the end both methods are acceptable and if this is what is being picked on during audits this is a good thing because it means your Calibration Program is tight and the Auditor is looking for technical issues to pick apart.

You might even find some people saying you need to test at more points: perhaps up to five points across the range. Again, you won't find this recommendation in the CFRs and you should only do this if your internal Risk Assessment deems this truly necessary.

Even something as innocent as the tapping of a mechanical gauge during calibration may be debated by various experts in the industry. These are all very subtle reminders that there will always be debate on the specific ways we can calibrate an instrument. If you have a strong, well documented Calibration Program in place, you document and approve your decisions, and do that consistently, you are doing great!

If an Auditor insists on changing the way you perform some technical aspect of calibration you will have to decide if you want to accept that or push back through your site's escalation process.

Calibrate or replace?

I've seen a trend where some companies prefer to purchase calibrated portable digital timers and replace those when the factory calibration expires rather than performing re-calibration on those units.

Here is an example you should recognize:

Be cautious with this reasoning: if your timers are used for a critical process parameter neglecting to perform a final calibration may be challenged by your Auditors. You may say "Timers never fail!" and feel confident with that; however, Auditors may not share in your enthusiasm and ask why you aren't performing a final calibration on a critical instrument prior to retiring it. And if you DO perform a final calibration, why not simply calibrate your timers rather than replace them?

I've seen this replace-don't-calibrate scheme also be applied to certain portable dataloggers that can be purchased calibrated with a "guaranteed for one year" certificate whereby they get used a year and replaced with "new" units, sometimes with the expired units being returned to the supplier for recycling/ reuse. The choice to do this is very risky: what is your rationale for not calibrating when the campaign is over, prior to returning these to the OEM? How can you be certain they were in tolerance throughout the period you used them *unless you test them after using them?*

Remember calibration is done before and after GMP use. This gives us the highest level of assurance the instrument was in tolerance throughout its period of GMP use. Bypassing the after-use calibration is a very risky position to be in! Use with care and be prepared to be questioned about this practice!

Should we include switch testing in the Calibration Program?

Sometimes switches serve a critical function and it may be beneficial to include those in your Calibration Program to ensure continued proper operation. For example: mechanical pressure switches on an Autoclave to prevent the door from opening unless the chamber is at atmospheric pressure (a safety function). This testing may be considered a functional verification and not a true calibration, but switches should be checked and adjusted, if possible and where necessary, during calibration testing. If adjustment is not possible and they are not tripping at the expected point, they should be replaced.

Keep in mind switch verification and adjustment may be managed under the site's PM program as well. Either way is fine, just be consistent with your approach, document and approve your decisions, all based on Risk Assessment.

Preventive Maintenance programs are designed around visual checks, lubrication, cleaning, and routine parts replacement so it seems logical to have switches managed under the Calibration Program but just be sure you evaluate your plant's critical switches and cover them *somewhere* if you have critical switches in your facility.

Should my service due dates be the last day of each month?

Calibration due dates can be To-The-Day (TTD) or End-Of-Month (EOM).

If a calibration was performed on January 5th on an equipment having an annual calibration requirement, when is it overdue for calibration?

In a TTD example it would be January 6th of the following year.

In an EOM example it would be February 1st of the following year.

It is most common to use EOM due date methodology; however, you may run into an Auditor that says that is not allowed. They might say "12 months from January 5th is January 5th, NOT January 31st!"

The FDA CFRs do not address this in any way. *It is often common practice in the industry to allow EOM due dating for calibration and PM events.*

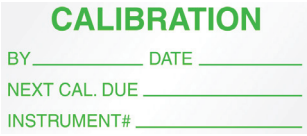
One consideration is if you have short calibration intervals such as 1-month. In this case you *could* calibrate the device on January 1st and next on February 28th and be compliant despite having nearly 2 months in between those successive calibration events. Conversely you could perform calibration on January 31st and again on February 1st and still be compliant with your rule of one calibration event per month. In both of these cases you would be following the letter of the law but not the spirit of the law; therefore, if you have short calibration intervals you may need to apply some rules around those to avoid having successive service events either too close together or too far apart.

I always suggest using EOM due dating. Put this in your SOP as your definition for calibration due dates and oftentimes this is adequate to address this despite some cases where you may be challenged on this by an Auditor that insists this is unacceptable practice.

Do we need to retain expired service labels?

When a calibration is completed a new label is applied to the equipment showing the calibration status at a glance.

Recall our sample calibration label:



When we install our new label, *what should we do with the expired/old label?*

Here is what you should consider: this label provides a quick status to the End User at the equipment. What might happen if a Technician forgot to place or replace a label? Upon discovery the Technician should be notified and investigate and if it is determined that the label was missed it should be corrected in a timely manner.

Retaining the expired/old labels is not recommended and creates unnecessary GDP challenges. If you keep the old labels, they need to be attached to the calibration certificate and how do you manage that if you are operating in a paperless system? If you require maintaining your old calibration labels you would have to explain any lost labels, potentially creating a Deviation when this happens. Is this necessary? Think of this: if your CMMS is the *source* of your service due dates these service labels are only tools to aid End Users.

The best approach is to be mindful of calibration labels ensuring they are replaced after each calibration and address any field label discrepancies as timely as possible. These field labels are not GMP documents! *They are only status labels and occasionally will be missed by the Technician.* This is easily fixed, however, by creating a proper label and applying it on the equipment. Having a requirement to retain all expired/old labels is not a best practice and is simply not necessary.

Labels can also be verified periodically by self-audits. Finally, End Users should be looking at these labels prior to using the instrument (such as a Balance) and where they notice an expired label they should notify Calibration as soon as possible and not use the instrument until the problem is sorted out. If the label was missed it can be fixed easily. If the unit is out of date and was not caught by the Calibration Program, that needs to be investigated (perhaps the unit was reported to be missing and therefore couldn't be calibrated on time).

What is the difference between daily checks/ standardizations versus calibration?

Sometimes the End User will test an equipment to get some confidence it is OK for use. Here are some examples where this can take place:

- pH meter – standardized with buffer solutions.
- Conductivity meter – standardized with conductivity solutions.
- Balance – verified with test weights.

In these cases, the End User will check their equipment prior to use, record their results, and only use the equipment if the readings are within the specifications noted in the logbook/SOP.

In the case of our pH and conductivity examples above our routine calibration testing may only verify the meter itself (since the End User tests the entire pH meter including the probe before use). We may only simulate the sensor using mV for pH or resistance for conductivity and confirm the meter is working properly. We could include probe testing as well but keep in mind that probes fail and are often replaced in the field directly by the End User.

If the End User can standardize their probes properly this is acceptable and further involvement by Calibration isn't required. We don't, for example, track the serial numbers of the probes being used by the End User by the Calibration Department. This, however, may be documented in the logbook by the End User for tracking purposes.

If a Balance fails "before use" testing, a Work Order should be created to have the Balance calibrated to determine why it failed the daily check.

Do I need to calibrate each device if we perform loop calibrations?

A common instrument setup is:

Sensor >>> Transmitter >>> PC input

The PC input may be a Programmable Logic Controller (PLC) or similar device that scales and displays the information from the transmitter.

The transmitter will read the sensor and covert those readings to the signal the PC input requires.

Each of these devices will have some error and taken as a system these errors will be additive and impact the final readings. Here is a question: "Do we need to calibrate the individual devices or is calibration of the loop (all the devices working together) acceptable?"

Say we put this sensor, assume it is a temperature sensor, into a stable bath such as an ice bath (0.0°C) and note the PC input displays 0.25°C. In this case we have a SYSTEM error of 0.25°C. If our system tolerance is ±0.5°C our measured error of 0.25°C is well within that tolerance. *Note that we do know where the error(s) exist but is that necessary?* We may check this system at one, two, or three points. If all points tested are within our specified tolerance this is acceptable despite not knowing the errors of the individual instruments.

I've seen some companies want to verify the individual devices in this loop; however, this really isn't necessary if we test the loop as a complete system.

When to attempt adjustment?

During a calibration when should the Technician attempt an adjustment? Only if the specification is exceeded? What if we are right at the specification limit? Or very close to the limit? Where is the *line in the sand* that defines when an adjustment attempt is required?

This is impossible to define for all cases! I've seen rules applied such as "If you are above 50% of the tolerance, you must adjust" but what if that is unrealistic? If the manufacturer's tolerance is applied to the instrument can we expect the instrument to be better than TWICE what the manufacture specifies for the instrument?

What about 75% of tolerance? We have the same issue.

Here are some considerations:

- The Calibration Technician may only be able to check the device and cannot adjust the device (it requires special OEM software to adjust).
- The unit may be non-linear and no matter how much adjustment we attempt we will never get it better than it already is.
- The unit has a history of stable in tolerance readings and messing around with it may make it worse, not better.
- We may wish to trend the results over time. Adjusting resets this data analysis.

What I want you to think about: avoid zero tolerance policies in this area and train your Technicians to decide when adjustment is advised and allow Technicians to make informed decisions based on their experience and expertise. In some cases, you may prefer to adjust often and optimize the instrument at each calibration. This is OK and this may be shared with the Technician via a Work Instruction.

Can I use N/A checkboxes on forms?

Good Documentation Practices (GDP) requires the lining out of unused sections and spaces of documents and forms. Following GDP guidelines, we line out the section/space, add N/A, initial and date, and include an explanation if not completely obvious. To reduce excessive lining out on our forms we may use N/A checkboxes on some forms. It may help to add verbiage on the form nearby an N/A checkbox to "leave this section blank."

Just be careful if doing this to ensure a consistent response! You don't want some people using a N/A checkbox while leaving the section/space blank, and others manually lining out the section. *Consistency* is important in the managing of your Calibration Program!

Final Thoughts

I hope you found information in this booklet helpful!

I have spent considerable time discussing the topics contained herein and if I am able to help others understand the fundamentals of building and managing a Calibration Program in the Life Sciences/FDA Regulated Industry I consider the efforts to create this well worth the investment.

Managing a Calibration Program requires knowledge, collaboration, and commitment from the site's leadership to support the Team and approve the resources including people, equipment, IT solutions, etc.

The company should drive a culture where compliance is a *requirement*, not an option!

Ellab can help your company setup and manage your Calibration Program.

We can:

- Perform gap assessment of your current Calibration Program.
- Review and update your equipment database accuracy.
- Create swim lane process flowcharts.
- Create custom Calibration Program SOPs and Forms.
- Help with Risk Assessment and documentation processing.
- Setup, review, and even manage your Calibration Program.

Ellab can also provide you with Consulting Support: from short-term projects to full time staffing.

Be sure to visit us at *www.ellab.com* for more information.

Acknowledgements

I've had the great fortunate of working with many passionate, smart, driven, and knowledgeable people that engaged me to think to better myself and in term to better the companies and people I've had the opportunity of working with along my career journey.

Here are a few people that inspired me to ask questions and engage in lifelong learning that I want to thank:

- Timothy Arms
- John Ashley
- Jim Bell
- Kendric Bert
- Jim Bufano
- Joeseph Busfield
- Sharon Christian
- Gene Conn
- Raymond Cox
- Gregory Delporte
- Rudy Dupont
- Jason Finney
- Laura Abrams Garver
- Leo Garza
- Matt Goth
- Richard Henderson
- Angel Mercado
- Michael Parente
- Peter Roles
- Joe Siebenaler
- Kevin Tuel
- Richard Tumbusch

…and so many others…

Considerable thank you to Peter Stevenson, without whom this presentation wouldn't have been possible. Peter is a VP, Usability & Marketing, and made this content presentable. I sincerely appreciate Peter's contributions to this booklet!

A heartfelt thank you to my family: my wife, Shari, who inspires me to do my best on every project I undertake, and my sons, Doug and Greg, that have grown into fine men, keep me grounded, and make me proud to be their father!

Finally, thank you, for taking your time to read this material. I sincerely hope you enjoyed the content and gained some new knowledge. I wish you the best in your career journey!

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