

INTRODUCTION

Calibration, maintenance and validation activity, despite operating within the same department in some organizations, have generally been managed separately, each with their own procedures and their own computerized management systems. Since even calibration and maintenance professionals tend to access records differently and track different types of information, these separate and unconnected systems made sense. However with new regulatory pressures and in search of greater productivity and efficiency, leaders in the life science industries have explored and experimented with different ways to harmonize these systems. Until recently, the available options have required significant compromises to be made. This paper discusses the evolution of the driving forces and the available solutions for harmonizing calibration, maintenance and validation, concluding with the latest technologies designed to eliminate the need for the departmental compromises previously required to achieve harmonization.

THE SYSTEMS

Calibration

The ever-present forces of entropy, as explained in the Second Law of Thermodynamics, mean that even the most perfectly engineered instrument sitting undisturbed on the shelf will lose precision over time, let alone the instruments and equipment in regular use. Therefore, to have confidence in the performance and readings of instruments and equipment, they must be regularly calibrated back to within an acceptable level of accuracy, as dictated not only by common sense but also GxP guidelines.

Regulatory agencies, such as the Food and Drug Administration (FDA) in the United States, expect to see evidence that regular calibrations are being performed, that the instrument or equipment – in production, QC laboratory, or research area – was working properly as part of the complete production process, and that it is, perhaps after some adjustments, ready to return to active use. This process requires taking readings using an approved standard at different set points both before and after any adjustments or calibrations are made to determine whether the asset was and is performing within the process tolerances. If the asset is found to have been out of calibration then product and processes affected by that asset need to be discovered and remediated.

With the addition and continual evolution of electronic signature functionality to meet 21 CFR Part 11 requirements, most calibration departments have come to rely on Computerized Calibration Management Systems (CCMS) to simplify many of the tasks associated with managing and documenting calibration activity. These systems are generally designed to conform to calibration's instrument-centric approach to managing work and have naturally evolved to include many features specific to calibrations, including measurement data collection and reverse traceability.

Maintenance

While on the surface the principles of maintenance management can appear straight forward, they involve some very sophisticated trade-offs and decisions tied to the management of limited human resources and nearly limitless work that could be done. Not only does this mean determining the optimal frequency for preventive maintenance – balancing costs of preventive maintenance with the costs and downtime from emergency service, but also managing a complex pool of craftspeople, making sure the right person is available for the job. These sorts of questions can make a huge difference on the bottom line when dealing with a multi-million dollar piece of equipment or process line.

When working in a validated environment, issues of change control and like-for-like replacements also come into play. To manage all the complicating issues in maintenance management, companies are turning to Computerized Maintenance Management Systems (CMMS). Unlike in calibration management systems, activity in the CMMS tends to be organized around work orders. With endless potential preventive maintenance, the challenge becomes to prioritize the work based on risk (for example, GMP versus non-GMP) and costs.

Validation

Ultimately the regulatory agencies want documented evidence that the complete production system results in consistent output. This means performing the initial qualifications – including design, install, operation, and performance – of new instruments, equipment, processes, methods and systems; and then documenting that ongoing activity, including calibrations and maintenance, keep the complete process in the validated state. When something does change, it needs to be documented and approved, demonstrating that there is no effect on the final product.

To achieve their ends, validation specialists use a wide range of systems and tools, including project management systems, CCMS, CMMS, document management systems and change control systems. In each case changes to records need to pass through a specific approval process before the change can be accepted as part of the validated state.

HARMONIZATION

It is easy to see why there have been so many different systems, since each department works with assets their own way. In some cases, in fact, there are assets that are unique to one department that they don't want the other departments to work with. However, new regulatory and business pressures are encouraging many companies to consider greater harmonization.

Regulatory pressures

The FDA and other similar regulatory agencies have started to take a top-down, system-based approach to inspections and audits called the Quality Systems Inspection Technique (QSIT). Instead of looking at the end results of processes for small abnormalities, they are focusing instead on the elements of the total quality system that are most important to meeting requirements. As part

of the implementation of this new technique, the regulatory agencies are training their inspectors in new areas of focus, including, for example, metrology.

The FDA has grouped **Facility and Equipment** controls into one of the seven subsystems that make up a complete quality system. According to the FDA, the Facilities and Equipment category "includes the measures and activities which provide an appropriate physical environment and resources used in the production of the drugs and drug products. (FDA Compliance Program Guidance Manual program (7356.002) February 1, 2002)

To the right is a list of elements that the FDA has included in the terms "Facilities" and "Equipment", including such additional activity as environmental monitoring and IT asset management. A similar approach for each of these activities and responsibilities would seem to be the first step toward a complete and integrated facility and equipment system, on which regulatory audits will pivot.

Business pressures

Business pressures, including the constant need to maintain and improve profitability, are not new. For years companies in the life sciences came to rely on their new products to drive profits, with attention on improving the cost-effectiveness of the development process. Now, particularly in the pharmaceutical industry where growing numbers of products coming off patent and the impact of healthcare reform efforts are placing a downward pressure on prices and affecting profitability, the cost-savings measures are spreading to other departments and steps in the product life cycle. The increased pressure for greater cost efficiency in production is one of the driving forces in the development of Process Analytical Technology (PAT), which in turn is requiring greater rigor in understanding and controlling equipment and processes.

With greater attention paid to the procedures and systems in place for production, similarities between the activities performed by calibration, maintenance and quality personnel were revealed. For the most part, each group is working with the same set of assets, collecting a lot of the same profile information on the asset: description, ID, manufacturer, applications, etc. The fact that calibration, maintenance and quality personnel each store similar information about the same assets brought up questions not only of efficiency but also compliance concerns when identical information,

Facilities

- Cleaning and maintenance
- Facility layout
- Areas of manufacturing operations
- Air handling systems
- Control system for implementing building changes
- Lighting, potable water, washing and toilet, sewage and refusal disposal
- Sanitation of the building

Equipment

- Adequacy of equipment design, size and location
- Equipment installation and operational qualification
- Equipment qualification
- Equipment calibration
- Equipment maintenance
- Computer qualification and security
- Equipment identification practices
- Documented investigation into discrepancies

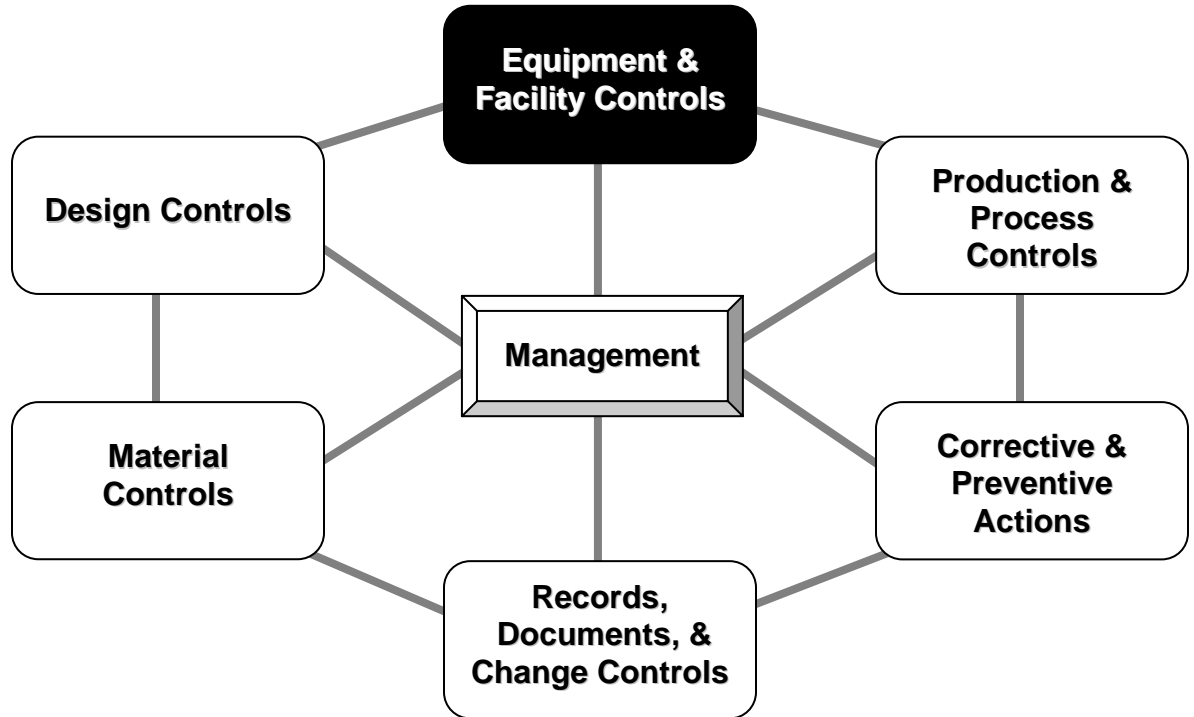


Diagram 1: Quality Systems Inspection Technique

with possible variations due to errors, is being stored in multiple locations. There are also similarities between how the groups work with assets: maintenance, calibration and validation events occur for many assets on a set schedule, with a procedure or collection of procedures to follow for each event, and requirements for documented evidence that the event took place.

Not only are there some real similarities for the management of these activities, but ultimately the goal is also the same for everyone: to keep the process working as designed in order to preserve the controlled and validated state. In this effort, there is interaction that takes place. For example, during the initial commissioning of a new piece of equipment, it passes through a complete validation cycle that includes calibration. Once in production, routine maintenance is usually performed on it that in many cases will require recalibration before it can re-enter production. When routine maintenance isn't enough to fix a problem or replacement parts are no longer available, the asset enters a change control process that will require revalidation and calibration once a solution has been worked out. (See Diagram 2 for a typical system life cycle)

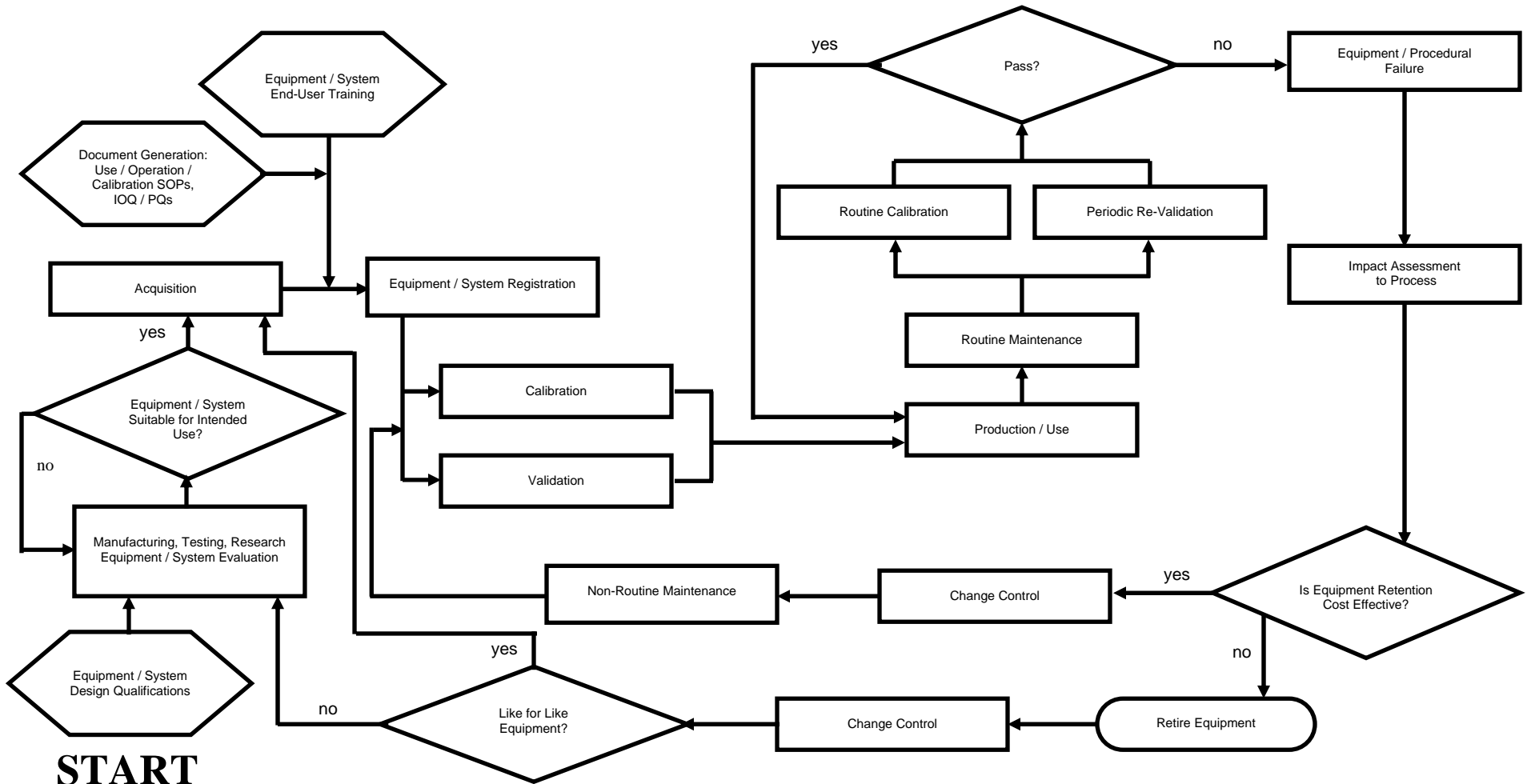


Diagram 2: Typical System Lifecycle

REGULATORY ASSET MANAGEMENT

The combination of calibration, maintenance and validation forms the core of Regulatory Asset Management: the management, scheduling, data collection and documentation associated with keeping processes, instruments and equipment in the validated state in regulated production and critical research environments. In the last few years, as companies realize the similarities, the interaction and the common goal within these activities, the options available for the harmonization of regulatory asset management systems have expanded.

For years the most practical option for companies that required best-in-class applications for both calibration and maintenance was simply to use two separate point solutions with the only coordination going on outside of the applications through personal communications between the different roles or departments. To check for inconsistent entry due to duplication, workarounds and other manual systems were often put in place.

More recently, companies have commissioned software integration between their separate point solutions to reduce or eliminate duplicated entry and to offer a certain level of collaboration between departments. This solution allows each department to work with their best-in-class applications while automating some of the duplicated entry of data for greater efficiency and compliance. However even if each application has been installed and validated separately, this option can be costly to fully implement and validate. A great deal of effort has to be put into the specification of the nature and regularity of updates between systems, and the integration development process should be monitored carefully. Once the integration has been completed and implemented, all connection points will need to be validated, making sure that the integration did not affect the regular operations of either system.

Additionally, the upgrade path for such integrated applications is more complicated. The integration is built on the current versions of both systems. Future versions of either system will not likely be fully compatible with the integration, requiring redevelopment work for the integration when either of the systems is upgraded. This can serve as a practical obstacle to upgrading to the latest technology.

Many companies have found that they can, with some compromise, use the application designed to manage one department to manage activity for multiple departments. For example, companies have been using calibration management systems to manage preventive maintenance for years. As a result, many of the developers of these applications have started to add functionality to their point solutions to serve multiple purposes. The latest versions of CCMS applications now include basic work order functionality, which is the cornerstone to how maintenance events are tracked. Although the unique data collection requirements in calibration have made the use of CMMS applications for calibration impractical, new calibration modules being added on to maintenance applications recently have encouraged many companies to explore this option. Many of these attempts still yielded disappointing results, forcing these companies back to separate point solutions.

Depending on the exact requirements and the chosen vendor, implementing a point solution with add-on functionality to serve multiple departments can involve significant compromises to efficiency.

For example, a CCMS would lack the sophisticated work order system or inventory management that a CMMS would have. Likewise, a CMMS, driven by work orders, generally requires additional steps and time for each calibration, not trivial when you realize that some companies perform tens of thousands of calibrations a year. The CMMS also generally lacks sophisticated reverse standards traceability, out of calibration notifications and handfuls of other calibration-specific features common to CCMS.

It is for such point solutions with add-ons that the most diligent risk-based analysis is demanded. Presumably the system handles one of the functions very well, ideally even designed specifically for the unique requirements and regulations of life sciences. However it is important to determine what the impact on compliance and productivity for the other department would be. Favoring one department over another will require detailed documentation or otherwise could result in resentment and animosity, which is counterproductive to the harmonizing goals of the system.

Comprehensive integrated solution

The issue with using a single solution for multiple departments has been that the existing solutions, being built on an existing single point framework, have been unable to consistently satisfy all departments. For example, a best-in-class CMMS is great for managing maintenance, with more functionality than even most maintenance people could dream of using, but it doesn't offer a practical framework for add-on calibration management functionality. To get the sort of flexibility required to satisfy each department, a new framework is required, one designed specifically for this harmonization.

A comprehensive integrated Regulatory Asset Management system, designed to meet the compliance standards of life sciences, provides such a framework. This new class of enterprise software, without the legacy of being first created for a single department, allows each department to manage and work with the assets efficiently while still permitting the interaction between activities and personnel. Maintenance, calibration and validation can be scheduled in sequence, through a single interface, to reduce the amount of downtime experienced. Unscheduled maintenance can result in automatic notifications to facilitate quicker scheduling of recalibration and or revalidation activity.

Beyond allowing all personnel to work with and manage the assets in their own way and the collaboration benefits explained above, additional benefits of a comprehensive integrated solution include elimination of redundant data entry on profile and other shared information, single system to validate, lower computer hardware and system maintenance costs, clean and simple upgrade path, single system to explain during audits, fewer vendors and lower overall costs of ownership.

CONCLUSION

As regulatory and productivity requirements in life sciences have evolved so too has the technology available to meet those needs. In the past few years, software companies have responded to changes in the market by adding new modules and additional flexibility to existing systems. While this has worked for many companies, the high profile compliance and productivity implications specifically of calibration, maintenance and validation have made the compromises required to use these systems unacceptable to many companies. More recently, a new class of software has emerged that eliminates the need for departments to compromise on their productivity to fit into a single system.

The new regulatory asset management systems are unique, not only in their ability to more completely satisfy the distinct requirements of calibration, maintenance and validation personnel, but also with their holistic approach to the compliance and productivity issues common to life science companies.

ABOUT BLUE MOUNTAIN QUALITY RESOURCES

Blue Mountain Quality Resources has been developing technologically advanced software applications for asset management at FDA-regulated and ISO-compliant companies since 1989. The company's Blue Mountain Regulatory Asset Manager™ was the first regulatory asset management system, designed specifically as a harmonization of calibration, maintenance and validation systems into a single comprehensive solution for life science companies. Blue Mountain Regulatory Asset Manager's advanced browser-based system simplifies deployment and validation without the compromises to performance that typify browser-based applications based on previous technologies.

Blue Mountain's Calibration Manager®, a point solution for calibration management, has over 1500 worldwide implementations and is broadly considered the industry standard CCMS for life science and other regulated industries. A leader in the market, Calibration Manager was the first validatable, the first Windows-based, the first 21 CFR Part 11 compliant, and the first web-based CCMS.

The company's suite of implementation services was specifically designed to leverage their experience toward reducing costs and risks in implementing and validating these systems. Companies that outsource these activities to Blue Mountain Quality Resources are not only up and running with the software quicker, but they also achieve a higher return on investment by utilizing more of the functionality of the system.

For more on products and services available from Blue Mountain Quality Resources call us at 800-982-2388, email us at bluemountain@coolblue.com, or visit www.coolblue.com.

