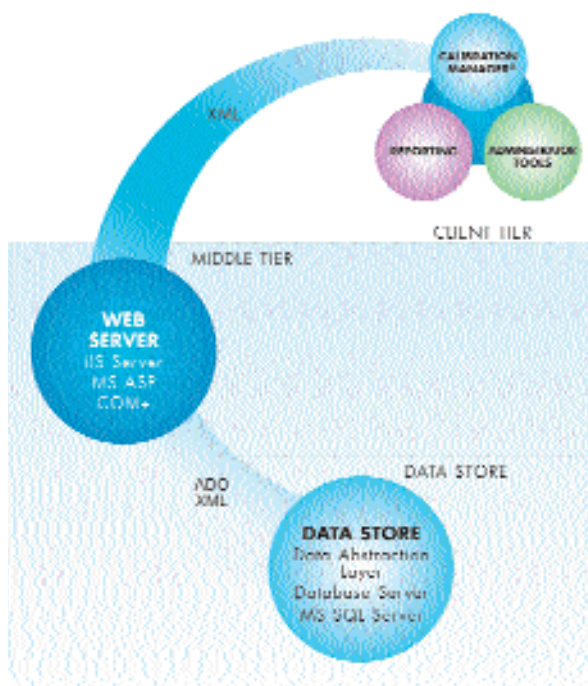


Establishing Global GMP Compliance with an Enterprise Calibration Management System

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The author describes the features of an effective Web-based calibration management system and discusses some of the benefits of its implementation.

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Driven by tough FDA enforcement, attention to GMP compliance is at an all-time high. In addition to having the responsibility for complying with increasing regulatory requirements, pharmaceutical manufacturers must find ways to improve their productivity. As a result of mergers and acquisitions, worldwide markets, and the complex nature of drug development, the need for cost-effective global compliance has never been more important.

FDA itself has acknowledged the changing times and has been working with industry to support new technologies for safe and cost-effective compliance. Two such initiatives are the electronic records and electronic signatures rule, 21 *CFR* Part 11, and a new program titled "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach" (available at www.fda.gov/oc/guidance/gmp.html), which are paving the way for productivity gains for manufacturers while allowing FDA to continue its quest for public safety. These activities are providing companies the opportunity to evaluate and improve their good manufacturing practices (GMP) management systems. Calibration management is one such GMP system that can readily take advantage of new regulatory advances. This article discusses how calibration management systems (CMS) can enable cost-effective global compliance when coupled with advances in information technology (IT).

Calibration management

Calibration management is mandated in 21 *CFR* Part 211 as a requirement for making reliable measurements in all aspects of development, manufacturing, and quality control (QC) of drug products. Because development, manufacturing, and QC have become more sophisticated, calibration has become more complex as well. Calibrated assets are found across the pharmaceutical organization, from analytical equipment in development and QC laboratories to process instrumentation in pilot plants and full-scale manufacturing. A typical pharmaceutical corporate campus may have as many as 20,000 instruments requiring periodic calibration, and global corporations may have hundreds of thousands of GMP-critical assets. As a result, calibration problems are always found among FDA 483 observations and warning letters. For the sheer volume and complexity of calibration management, specific software systems are required. It



Figure 1: (Left) Calibration Manager provides multiple event tracking. (Right) Functionality designed for Part 11 compliance.

is no longer practical or feasible to track, manage, schedule, and record these in generic maintenance management systems, let alone in a spreadsheet as many companies do. Specific best-in-class functionality is required for productive global calibration compliance.

CMS functionality can be classified into two groups: calibration management best practices and GMP/Part 11 functionality. The primary function of these systems is to track the instrument inventory, schedule the calibrations, and record the histories. More specifically, calibration standards, procedures, and technical measurement data must be captured. In addition, these systems must be validatable and have full Part 11 capability and record life-cycle maintenance.

Historically, CMS, department policies, and calibration procedures have been implemented within the same site or laboratory. However, the push for corporate standardization, the advances of new technology, and resulting productivity gains have created the need for Web-based enterprise calibration management software.

Web-based enterprise systems

Among several available enterprise systems, one CMS taking advantage of this new model is Calibration Manager 4e (Blue Mountain Quality Resources). Using a distributed Web architecture, this system enables pharmaceutical users to host the application centrally and allow worldwide access to separate departments and facilities. In a typical installation, the database application is hosted on centralized IT servers, configured and controlled by a corporate quality or metrology group, and used by working groups throughout the entire global enterprise. The software enables each working group to have its own dataset configured to its specific needs, including its own field labels, languages, or time zones, while centralizing the overall implementation configuration.

The technology that enables this is an *n*-tiered Web model. A Web-based, *n*-tier approach distributes the necessary user interaction, computation, and storage tasks between the layers of the architecture. Although some latitude exists in the exact number and structure of layers, the CMS is broken up into a client tier, a middle tier, and a data store. The data store is further segmented into a data abstraction layer (DAL) and a database server (see photo on opening page).

Client tier. The client tier is responsible for interaction with the user. In the past, all users of an application saw the same interface. Today's users access their data from a variety of devices with various screen sizes and input methods. The client tier must accommodate the user regardless of the device that bridges the user to the system.

Middle tier. The middle tier, also known as the business logic layer (BLL), is where the data are interpreted and where business

rules are applied. Certain types of security and access checks are also conducted at this level. The middle tier is considered the brain of the *n*-tiered system.

Data store. The data store is delegated the task of storage and retrieval of data. Once the choice of a database server has been made, a DAL is created to provide the interface between the middle tier and the database itself. The CMS uses Microsoft SQL Server 2000 or Oracle databases.

This architecture allows the centralized control and scalability needed to standardize policies and procedures at the corporate level while maintaining flexibility of use throughout the organization. This architecture also permits cleaner integrations with other systems by using less custom programming. Typically, the cost of integrating a CMS with other enterprise applications such as enterprise resource planning and enterprise asset management has been prohibitive. Now with enterprise implementations, this cost can be further reduced by amortizing it over a broader user base.

Part 11 compliance

GMPs state in numerous instances that records of calibration and maintenance information must be maintained, and those records are subject to document controls that include, among other things, signatures of the reviewing or approving party. This requirement mandates that the CMS allows for compliance to 21 *CFR* Part 11. Thus, implementing enterprise CMS is an effective method to administer and control the use of electronic records and signatures at the corporate level.

Effective 20 August 1997, FDA issued 21 *CFR* Part 11, setting forth criteria under which the agency will accept, under certain circumstances, electronic records and electronic signatures as equivalent to paper records and handwritten signatures. Part 11 allows firms to take advantage of electronic technology and to have electronic records considered equivalent to traditional paper records. Such systems must be validated to ensure accuracy, reliability, and consistency, and they must incorporate security checks and audit trails to verify that records are accurate and that changes are recorded. Electronic signatures are subject to additional requirements, including ensuring that a signature can only be used by its genuine owner and that the act of signing a document electronically is equivalent to a traditional handwritten signature. The following sections describe

some of the features that are useful in a Web-based CMS, using the Calibration Manager 4e system as an example.

Security. The security feature, designed for a multiple-level, password-based security system, allows an organization to limit system, database, and record access to authorized users. System administrators should be able to, if they desire, further limit authorized users' rights to add, edit, delete, or even view records. If an organization is using multiple datasets (for instance, one for production instruments and one for R&D), a user should be granted different rights to each dataset.

Audit trail. The software must feature an audit trail capability to track changes made to the system data. The audit trail records the date and time of a change as well as the original field value and the changed field value. In the Calibration Manager 4e system, password security is used, and the audit trail records the name of the user making changes and the reason for the change. Each record has its own audit trail record.

A fundamental aspect of an audit trail is the time stamp. For example, the previously described CMS allows configuration of the time stamp to be shown in multiple formats and is linked to the server's system clock. This is extremely important in an enterprise system in which user activities occur across multiple time zones.

In addition to the audit trail records for each equipment master and equipment history record, the software should maintain logs that reflect changes to each database and to the system as a whole. These logs are similar to audit trail records, in that they record an activity, its date and time, and the identification and name of the user responsible for the change.

History records. The CMS should record a separate history record for each activity performed on a piece of equipment. For instance, the previously described CMS system records each calibration performed on an instrument. In addition, if users track maintenance, inspections, and so forth, there is a history record for each of these activities. The history record includes the date of the activity and can include who performed the activity, comments, approvals, and measurement data. The history record also includes the electronic signature of a user, so that each calibration (or maintenance) record is linked to an electronic signature specific to that record.

Electronic signature. The Calibration Manager 4e software incorporates an electronic-signature mechanism (see Figure 1). When a user selects this mechanism, an "Electronic Signature" dialogue box will appear, prompting the user for the user ID and a password. To electronically sign a record, the user must enter information into both of these fields. Part 11 indicates that when a user signs additional records in a single, continuous period of controlled system access, the user ID field must be filled and the user should be prompted for a password. When the user ID and password have been entered, the user is prompted for a meaning for the signature (e.g., review, approval, responsibility, or authorship). Upon completion of a signature, a confirmation box appears. Each electronic signature and its

Resources

Calibration management

- 21 *CFR* Part 211: References to calibration
- Subpart D: Equipment, Sec. 211.68 (a) Automatic, mechanical, and electronic equipment.
- Subpart I: Laboratory Controls, Sec. 211.160 (4) General requirements.
- Subpart J: Records and reports, Sec. 211.194 Laboratory records.

Calibration

- NCSL Healthcare Metrology Committee
- ISPE/ AMP calibration guide
- www.eCalibration.com: general FDA calibration reference and calibration-specific 483s.

reason is linked to a specific history record. Records may be signed by multiple personnel and for multiple reasons.

Electronic signature log. A Web-based CMS should include an electronic signature-log capability. In the Calibration Manager 4e, the electronic signature log displays the date and time that the signature was executed, as well as the user ID and user name of the person signing the record, and the reason for the signature. This information is also recorded in the record's audit trail.

Validation. Section 11.10 of Part 11 requires persons using electronic recordkeeping systems to use procedures and controls to ensure the authenticity, integrity, and confidentiality of electronic records and electronic signatures. The primary mechanism for this is validation of the system to ensure accuracy, reliability, and consistent intended performance.

Facilitating validation efforts

Enterprise CMS can be a successful part of reducing the rising costs of validation and reducing overall validation efforts. From a return on investment (ROI) perspective, this can be one of the most compelling reasons for investing in an enterprise system. For example, implementing a CMS can enable one validation for the entire enterprise instead of requiring the validation of 10 sites using individual systems. Moreover, validation costs can far exceed software license fees. As result, this ROI is significant.

By following the traditional path of defining system user requirement statements, vendor qualification, and installation, operational, and performance qualification, validation of an enterprise CMS is not much different than validation of traditional systems. With a Web-based enterprise CMS, most of the validation effort is at the middle-tier and data-store levels. Client validation is minimized with a thin client (browser or Windows-based), in which most of the processing takes place on the server.

Network qualification is one area that does become more important. With an enterprise system, the connection between the hosting site and the users is through a corporation's internal network. It is this network—whether based on the Internet, a virtual private network, or other means—that must be qualified (1,2).

Benefits

A Web-based CMS is an investment that can yield high returns. By enforcing consistent calibration best practices throughout the corporation, companies may experience reduced FDA compliance issues from missed calibrations, improper use of procedures, local Part 11 interpretations, and inadequate software validation. Furthermore, by reducing redundancy in calibra-

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