Pharmaceutical Communiqué

Q3 2016

QC LAB CONTROL REQUIREMENTS

All laboratory analysts must follow cGMPs in order to create effective products and comply with all quality standards.

In this article, we focus on five analytical laboratory practices, which are covered in our course, Application of cGMPs to Analytical Laboratories (PHDV78), which is reviewed by the experts at Raland Compliance Partners.

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QC LAB CONTROL REQUIREMENTS *(Continued)*

Handling and Identifying Reagents

Reagents such as chemicals, solutions, and materials used to conduct laboratory analyses are mandated to have labels. These labels should state the material and its concentration. If the reagent is prepared in the lab, additional labeling requirements include who prepared it, reference to documentation of preparation, when it was prepared, and its expiration date. It's important that you have data that supports the assigned expiration date.

Labeling reagents helps identify exactly what they are and how long they can be used. It can also be useful in determining who prepared the material and how it was prepared, so any questions that may arise can be answered. Following these procedures keeps companies compliant with cGMP regulations and maintains proper control over samples.

Documentation Practices

Laboratories test hundreds of different materials in a variety of methods. With all the analysts using the same equipment and materials, mix-ups can easily occur if materials are not properly labeled. Without proper documentation practices, data integrity can potentially be compromised. cGMPs require specific documentation to ensure this does not occur.

Controlling Laboratory Reference Standards

Laboratory reference standards must be carefully controlled in the lab. A reference standard serves as a benchmark (e.g., represents purity) against which each batch of product is compared. It is also critical for laboratory reference standards to be properly stored under controlled conditions. Some requirements may include proper refrigeration or freezer storage. Other standards may require storage at room temperature but require controlled humidity in a desiccator.

For this reason, it is important to follow the requirements listed on the label. Always check that the refrigerator, freezer, thermometer, and desiccator are compliant with your company's SOPs. Only use reference standard solutions that have been freshly prepared and properly stored unless they have a defined shelf-life. In some cases, testing the purity of working standards or verification of purity with a Certificate of Analysis can be done. Be careful with all standards; be sure to take time and properly handle them according to SOP.

Cleaning

Cross-contamination of samples or reagents may generate faulty results. To take measures to prevent this, validated glassware cleaning procedures are used and, in some cases, dedicated equipment and glassware are required. For example, SOPs must be in place for glass washer instruments, particularly if an analyst is required to wash glassware on their own. Manual glassware cleaning practices are difficult to validate. Be prepared to explain how you have verified manual glassware cleaning.

An example is the use of High-Performance Liquid Chromatography (HPLC) columns. Because these are especially prone to retain minute quantities of previously tested materials, these columns are dedicated to specific products. Unless it is proven that instrument and column flush procedures are effective, this is an essential practice to guarantee accurate results.

Written Approval

Unless you have written supervisory approval to deviate from a procedure, you must carefully comply with all guidelines within that procedure. The Code of Federal Regulations (CFRs) state that all methods/SOPs that a company has must be followed. Once a company writes an SOP, procedure, or process they become cGMP rules of the FDA/CFR for that company.

DATA INTEGRITY:
CHANGING BEHAVIOR IN THE LAB

The following excerpt is from a new "Data Integrity in the Lab" course from UL, to be released in November. Written by our GMP expert, Dave Peterson, the course is part of UL's new Data Integrity Series, to serve as a GxP data integrity education program for clients.

As discussed in the last Communique, companies must have the proper infrastructure to assess system changes and determine how they will impact the validated state. In this issue, we are going to shift our focus to raising data integrity awareness in the lab.

In the last three years alone, FDA has issued 30+ Warning Letters and Form 483 inspectional observations related to electronic records, and many of these are lab-related.

Critical Data Integrity Observations

The following issues have been found in FDA 483s as they related to data integrity:

Data recording - not recording data contemporaneously (at the time of the activity). Backdating stability test results to meet timeline commitments.

Fabricating data - creating false information not technically justified. Manually adjusting HPLC baselines to obtain desired results. Integration parameters are not controlled.

Manipulation of data or procedures - using existing data from one batch and copying to another batch. Manipulation or misuse of poorly written analytical procedures to obtain passing results.

Rerunning samples - continuing testing until an acceptable result is obtained, then discarding previous results.

Disposition - releasing product with failed results.

Record keeping - failure to maintain paper or electronic records. Failure to store and maintain raw data files (metadata) and reporting only passing results.

Security and computer system controls - laboratories have failed to exercise adequate controls over data, and unauthorized access to modify, delete, or not save electronic data is not prevented; use of shared passwords does not provide identification of who created or modified data.

Investigations - inadequate failure investigations - not identifying true root causes.

21 CFR Part 11 - disabling audit trails in order to delete or modify undesired lab data.

Qualification and Validation - inadequate or non-existent compliance with equipment qualification and process validation

Similar observations and concerns have been expressed by EU, Health Canada, and World Health Organization (WHO) authorities.

Five Actions that Can Improve Data Integrity

Here are five actions that can improve data integrity in the lab:

1. Checklist - develop specific internal audit procedure checklists to investigate for data integrity concerns.
2. Observations - identify trends from data integrity internal audit observations, then provide general feedback and training.
3. Data control - assure there are clear procedures and controls over electronic data management and software administration, and train on these procedures.
4. Contemporaneous data entry - assure that data is recorded at the time of the activity.
5. Corrections or changes - assure that modified data is justified by explanation, and reviewed and approved by supervision.

EDUCATE YOUR ENTIRE GXP WORKFORCE ON DATA INTEGRITY

UL's Data Integrity Program

Written by industry-leading subject matter experts, our program enables companies to build awareness to the entire GxP audience, including QA, QC Lab and IT professionals.

The program includes two full-length courses, which each takes about 40 minutes to complete, as well as three "short courses" targeted to professionals within QA, QC Lab and Clinical, so they gain an understanding of how to ensure data integrity within their specific job functions.

Click here to download

QA teams can deliver these courses to as many learners as possible, to stretch their training budget and eliminate the need to develop this regulatory training content on their own, without sacrificing the quality of the training content.

The Data Integrity program includes these five courses:

- Introduction to Data Integrity
- Auditing of Computer System Validation to Ensure Data Integrity
- Data Integrity for QA (launching Q4 2016)
- Data Integrity in the QC Labs (launching Q4 2016)
- Data Integrity in Clinical Trials (launching Q4 2016)

Sign up for a course demo via our Essentials Demo Site.

Here you can view other Quality & Compliance Essentials sets that are available, each focused on specific topics.

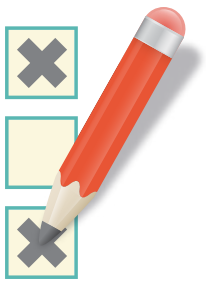
Content is provided as SCORM files to host on your own learning management system.

In addition, other delivery methods are available, including AICC or hosting on UL's LMS, ComplianceWire®.

IMPROVING SOP MANAGEMENT PROCESSES

The following article is based on a 2016 UL whitepaper, co-written with the document management experts at Veeva Systems.

As Life Sciences companies expand globally, opening new facilities or adding new suppliers, they face three main document and training management risks:



The first, and perhaps the most costly risk, is compliance. Global regulatory agencies, including US FDA, have made procedural control a top enforcement issue. In fact, the most cited US FDA observation of pharmaceutical companies in 2015 was "Procedures not in writing, fully followed" (21 CFR 211.22(d)).

The second risk centers on "lost knowledge." When most of the operational knowledge resides with a few people, organizations are at risk to lose best practices. It could take many months for a new team to define and map the governance process when crucial individuals move to new job roles, draining organizational resources and impacting operational efficiency.

The third risk is change management. Companies are expanding rapidly, either through organic business growth or acquisition. As business areas evolve, new procedures on managing SOPs, employee qualifications, and training are being implemented.

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IMPROVING SOP MANAGEMENT PROCESSES *(Continued)*

When companies add new people to a process, a governance strategy that captures and enforces key policies and operational rules is critical to success. A DMS to LMS workflow requires such a policy. The DMS to LMS process demands feedback from stakeholders including documentation personnel, subject matter experts, and department and training managers.

Many leading Life Sciences companies have defined governance models based on these key areas in document and training management policies, such as the SOP Management Policy, which focuses on document creation and SOP reviewer responsibilities, nomenclature, and definition of stages including: Pending, Approval, and Effective definitions. In addition, a Training Policy describes the scope, training responsibilities, procedures for GxP trained and non-GxP personnel, training curricula, training documentation, annual GxP training, and external training.

Cloud-Based DMS to LMS Workflow

Document management systems (DMS) eliminate many of the "paper shuffling" tasks, reducing regulatory risk and allowing document owners to devote more time developing SOPs. Automating routing of documents and version control, and easily providing a full document history, streamlines the approval and filing process.

Cloud-based DMS applications enable document owners to securely collaborate — in real-time — with authorized employees and partners anywhere in the world, speeding up the document review and approval process.

Integrating DMS and LMS applications facilitates timely SOP management and training. Well-integrated, modern solutions improve the process, making it more efficient and effective.

When developing a governance strategy that spans both systems, organizations need to consider how it will impact existing processes and ensure the DMS to LMS integration supports the alignment approach.

There are four types of "system governance" questions commonly asked during the design phase:

- How will we define oversight within QA, IT, operations, and other relevant departments?
- What nomenclature will we follow to support the DMS to LMS integration? Which document metadata fields can be used to prompt training work flows in the LMS?
- How will we define roles across both systems including document creators, reviewers, training managers, and administrators?
- What is the change management process when there are new document properties, additional training requirements, etc.?

Top 10 Capabilities of Well-Integrated DMS/LMS

With today's technology advances, companies can leverage best-of-breed DMS and LMS applications to enable seamless SOP management and training. Improving productivity of all job roles involved in the process, the top ten capabilities of well-integrated, modern solutions include:

1. Real-Time Integration
2. Training Item Status Flow
3. Flexible System Security Roles (Managers, Trainers, etc.)
4. Supports Alternative Training Items (Quizzes, Classrooms, etc.)
5. Audit Trails (To meet Annex 11 and 21 CFR Part 11)
6. Rapid Implementation Time
7. Ease of "Change Control"
8. Accelerated Validation
9. Ease-of-Use
10. Visibility into Compliance Risk

To learn more about the ComplianceWire CW Connector for the Veeva DMS, please contact Pat Thunell at pat.thunell@ul.com.

MANAGEMENT REVIEWS: SAMPLE CHECKLIST

Management responsibility is the cornerstone of any Quality System, according to the US Food and Drug Administration (FDA) and international quality standards.

The most sophisticated and compliant Quality System will not remain that way without vigorous and continuous management review and support. And unlike other duties, management cannot delegate its responsibility for quality.

US FDA does not expect management reviews to be just number-crunching exercises, such as tallying the number of open CAPAs or the amount of complaints. Instead, a management review should focus on what the quality data reveal about the overall health of the Quality System.

As a general rule, FDA will not request to see the results of a management review. However, FDA may want to confirm reviews actually take place and determine who attends them to ensure company procedures and schedules are being followed.

Here are the broad components of management reviews of the Quality System.

- Measurement: Reviews must measure a company's Quality System against FDA requirements and the company's own stated quality objectives as defined in its quality policy.
- Frequency: Management reviews must be conducted at defined intervals and with sufficient frequency. If there are too many quality issues not known or not addressed by executive-level management, reviews should occur more frequently.
- Documentation of procedures: Companies should have written procedures and schedules for doing the reviews. Companies also should document when reviews are held, along with their results.

Here is a sample checklist of what management reviews should cover:

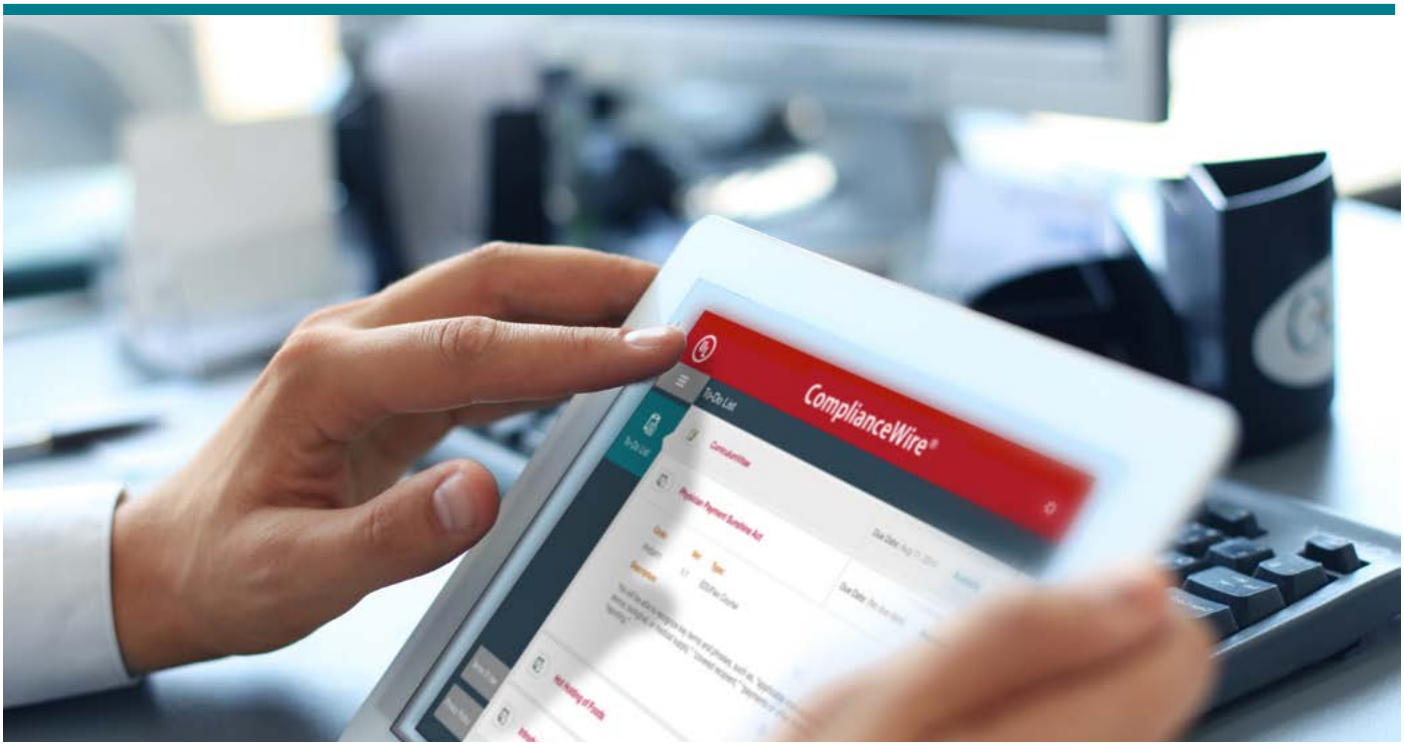
- ☐ Appropriateness of the quality policy and objectives.
- ☐ Results of audits and other assessments.
- ☐ Customer feedback (including complaints).
- ☐ Results of data trending analysis.
- ☐ Preventive action to avoid serious issues or recurrence of issues.
- ☐ Follow-up action from previous management reviews.
- ☐ Changes to business practices or environment.
- ☐ Ways product characteristics are (or are not) meeting customer needs.
- ☐ Document and date the decisions and results coming out of your management reviews.

UL Course: Management Responsibility for Quality: What FDA Expects (PHDV101)

Under FDA law and regulations, an effective and compliant Quality System literally begins and ends with management. This course explains who is considered management by FDA and management's responsibilities under FDA Good Manufacturing Practices.

Written by the experts at consulting firm EduQuest (www.eduquest.net), this course may be appropriate for managers and senior executives within Life Sciences organizations, to help them recognize how and why a successful Quality System depends on active management support and involvement to ensure safe and effective products reach patients and customers.

To preview the Management Responsibility course, contact Pat Thunell at pat.thunell@ul.com.



About UL Compliance to Performance

UL Compliance to Performance (formerly UL EduNeering) provides knowledge and expertise that empowers Life Sciences organizations globally to accelerate growth and move from compliance to performance. Our solutions help companies enter new markets, manage compliance, optimize quality and elevate performance by supporting processes at every stage of a company's evolution. UL provides a powerful combination of advisory solutions with a strong modular SaaS backbone that features ComplianceWire®, our award-winning learning and performance platform.

UL is a premier global independent safety science company that has championed progress for 120 years. It's more than 12,000 professionals are guided by the UL mission to promote safe working and living environments for all people.

For more than 30 years, UL Compliance to Performance has served corporate and government customers in the Life Science, Health Care, Energy and Industrial sectors. Since 1999, under a unique partnership with the FDA's Office of Regulatory Affairs (ORA), UL Compliance to Performance has provided the online training, documentation tracking and 21 CFR Part 11-validated platform for ORA-U, the FDA's virtual university. Additionally, UL maintains exclusive partnerships with leading regulatory and industry trade organizations.