Pharmaceutical Communiqué

Q1 2016

CLEANING VALIDATION STEPS

In the past few years, US FDA has issued several Warning Letters to companies for issues related to inadequate cleaning validation.

FDA has cited deviations that include failure to use worst-case products, handling errors in swabbing tests, and missing swab recovery rates. The companies that received these Warning Letters failed to prove that their products were not contaminated.

One of UL EduNeering's most popular eLearning courses, Principles of Cleaning Validation (PHA37), written by Ann Early of Early Mentoring Partners, introduces the basic elements

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CLEANING VALIDATION STEPS *(Continued)*

of cleaning validation. The course focuses on the importance of assessing the cleaning procedure with product tested under a cleaning validation protocol. Importantly, FDA and EU expect the organization to have a written procedure describing how to validate cleaning methods. Here are cleaning validation steps that are provided in our eLearning course:

Cleaning Method

The cleaning procedure selected depends upon the equipment and products involved. Product solubility and physical characteristics must also be considered. In some cases, automated cleaning can occur, while manual cleaning is needed for others.

Sampling Method

You must determine how to sample the equipment or evaluate the process to assess cleanliness. Some techniques include visual examination, rinse solution testing, or swab sampling of equipment surfaces.

Method Validation

After determining how to assess cleanliness, you must document the testing procedure and prove that the method works. You must show that you are able to detect residues if they are present. Any residues from the cleaning process itself (e.g., detergents and solvents) must also be removed from the equipment.

Establish Limits

You must establish limits for cleanliness. Limits should be practical, achievable, and verifiable. They should be based on good risk management principles to assure the safety of products and consumers.

Cleaning Studies

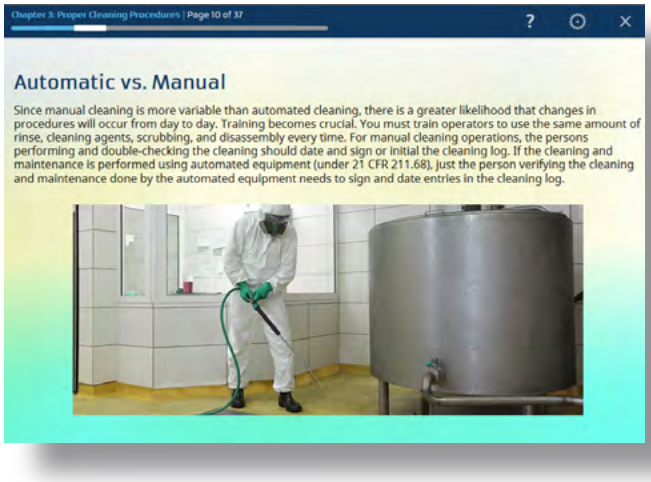
A cleaning validation protocol outlining the specifics of the testing procedure is prepared in advance of testing. The cleaning procedure is carried out on equipment following normal use with product. The equipment is cleaned as per SOP and the protocol sampling and testing is conducted. Multiple repeats of this cycle are typically performed to prove reproducibility.

The data should support a conclusion that residues have been reduced to an acceptable level. A final validation report stating that the cleaning process is valid must be approved by quality.

Control and Monitoring

After completing cleaning validation, you must continue to monitor the process to ensure that the method of cleaning has not changed or that other changes in product or equipment have not invalidated the method. Maintain a log of equipment cleaning and the results.

If you have any questions about our Principles of Cleaning Validation course, or any of our GMP eLearning courses, or would like to set up a demo, please contact Pat Thunell at pat.thunell@ul.com or visit uleduneering.com/QCE.



DATA INTEGRITY:
SEVEN CRITICAL VALIDATION DOCUMENTS AND RECORDS

The following excerpt is from an upcoming IT-focused Data Integrity course from UL, written by the experts at EduQuest. This new eLearning course will be part of UL's new Data Integrity Series, focusing on key GxP data integrity areas of the pharmaceutical manufacturer.

Overview

Auditing computer systems for compliance with FDA rules and international standards requires knowing what to look for in validation documentation. Production process control software must be validated for its intended use according to an established protocol. Auditors must be able to identify and review documented evidence of the validation process – including documented evidence of following the process and completing validation tasks - as well as the results of validation activities.

Computer system validation and the integrity of the data used and produced by computer systems is a global issue, as in 2015 U.K.'s MHRA issued definitions and guidance specifically for data integrity in GMPs. MHRA defines data integrity as "the extent to which all data are complete, consistent and accurate throughout the data life cycle."

The concept of data integrity refers to the accuracy and consistency of stored data. Data can be stored in a database, data warehouse, data mart or other construct. The term data integrity can be used to describe a state, a process or a function.

Here are seven critical software and system validation documents and records that should be included with any system:

1. Requirements documents describing the intended use(s) and user needs associated with the software and system;
2. Established validation protocol/plan describing the activities necessary to demonstrate that the requirements can be met;
3. Records of the results of the validation activities described in the validation protocol;
4. Records that show changes are appropriately controlled (where applicable);
5. Records that show appropriate software, system, and quality requirements were established and provided to the vendor, if developed elsewhere. The vendor must be qualified, and the purchasing data and validation results should support that the requirements were met;
6. Records of testing and verification activities, including proper installation;
7. Validation Report that summarizes the activities and documentation as described in the validation protocol/plan, including issues during development and testing.

EduQuest Workshop on Auditing of Computerized Systems

For more information about ensuring data integrity and meeting your regulatory obligations, EduQuest is presenting an "FDA Auditing of Computerized Systems and Part 11/Annex 11 Compliance" training class from April 4 to 6, 2016, in the Baltimore/ Washington DC area.

EduQuest also provides on-site consulting services for data integrity and regulatory compliance. To view more details on the class, visit:

http://www.eduquest.net/FDA_Auditing_Part_11_Training_Class.htm

PROVIDE FOUNDATIONAL EU REGULATORY KNOWLEDGE

UL's New EU Regulation eLearning Program

For companies that do business in the EU, it's critical that their global QA and auditing teams have foundational knowledge of EU directives and specifically, Annex 15 and 16.

Our new "Quality & Compliance Essentials" program for EU GMP Regulations provides five eLearning courses targeted to specific areas of EU regulations.

Current subscribers of our eLearning courses are already familiar with these courses, as they have targeted these courses to specific curricula and qualification programs. Now, with our new SCORM option, clients can select a particular set of five courses – pay one affordable price – and receive unlimited usage.

The EU GMP Regulations program includes these five courses:

- A Tour of Health Europe
- EU GMP Requirements for Computerised Systems
- EU Directives and Inspection Readiness
- Role of the Qualified Person
- Good Distribution Practices

Other Quality & Compliance Essentials sets are available, each focused on specific topics. Content is provided as SCORM files to host on your own learning management system. Other delivery methods are available, including AICC or hosting on our own industry-standard LMS – ComplianceWire®.

STANDARDIZING LEARNING WITH GOVERNANCE POLICIES

The following excerpt is from an upcoming UL whitepaper that will focus on LMS/DMS integration best practices.

As pharmaceutical companies face increased globalization, expanding supplier networks and internal harmonization requirements, they seek to build consistency and standardization into their learning and compliance programs.

UL Advisory Services has conducted a number of "Learning and Compliance Governance" projects for clients, which is the process of defining the roles and steps required to make sure the enterprise system is used and managed effectively. A Governance policy focuses on these activities:

- Captures Industry Best Practices
- Defines Enterprise System Ownership & Oversight
- Defines Procedural/Process Control
- Defines Administrative Control
- Describes the Roles of Training & Administrators
- Outlines System Use and Operation
- Captures Integration Processes (DMS, HRIS, MES, etc)
- Defines Monitoring and Metrics

Why Governance Is So Critical

There are two key major risks that companies face if they haven't formalized their governance policies. The first risk centers on "lost knowledge." When so much process and operational knowledge resides in a few people's heads, the organizations lose best practices when the people who implemented the learning system move to new functions. We have seen a new team take months to understand the process, but a governance policy would have made for a near-seamless transition.

Another risk occurs when companies expand rapidly, either through organic business growth or through acquisition. As new teams are added, they start to build their procedures for how to manage qualifications and training.

For example, they may start defining their own nomenclature for SOP training items. They may create their own policies around training management visibility for department managers. And at some point these siloed practices generate friction when senior management is seeking a consistent view across product lines and facilities.

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STANDARDIZING LEARNING WITH GOVERNANCE POLICIES (Continued)

The Governance Policy's Impact on Culture

With a governance policy in place, our clients have told us that this is how the policy builds a culture of quality:

- The policy develops a clear and scalable enterprise vision for the LMS, leveraging all feasible synergies;
- Drives regulatory compliance and/or business efficiency;
- Resolves issues and finds common ground;
- Recognizes and encourages the entrepreneurial culture by acting as a business partner via collaboration with learning communities;
- Promotes harmonization, standardization, continuous improvement and knowledge management across the wider organization.

Core "Governance" Procedures

The UL Advisory Services team can provide a number of procedural templates that help clients with controlling and maintaining the enterprise learning system. Here are just four "core" policies and procedures that our clients are using as part of their governance programs:

- Training Policy – this policy touches on scope, training responsibilities, procedures for GxP training and non - GxP area personnel, training curricula, training documentation, Annual GxP Training, External Training;
- Use and Operation Procedures – general use and operations instructions for Users and User e-signature certification;
- System Administration Procedures – including security roles, system admin roles and responsibilities, maintenance (including system releases), configuration changes requiring change control;
- Computer System Change Control – including standard operation procedures for system configuration changes, addition of new functionality, handling system releases.

An Example of Training Governance

Training policies detail how training is conducted, but also how activities are recorded. The training policy typically serves these purposes for department managers, employees and of course, quality assurance and auditing teams:

- Establishes that personnel must have the education, training, and experience (or any combination) to enable that person to perform his or her assigned functions.
- Notes that personnel must be trained in an operation before they perform these functions.
- States that personnel must be trained in the current good manufacturing practices (CGMP).
- Requires that training must be conducted on a continuing basis with sufficient frequency to assure that employees remain familiar with CGMP requirements.
- Defines the role of the employee and their manager when it comes to training activities.
- Defines the minimum elements/requirements for management of the training program.
- Explains the process that qualified individuals (or Qualified Persons, as defined in the EU) must use when conducting training.
- Explains the steps needed to conduct training effectiveness verification.
- States that training must be properly documented and maintained (e.g. date, content of training, trainer, length of training, etc).
- Refers to a separate "Training Record Retention Policy" in which the company's policy on record retention is defined.
- Identifies or points to a document that states Electronic Signature Policy (applicable if utilizing e-Signatures).

To learn more about UL Advisory Services and our Governance Policy services, contact Pat Thunell at pat.thunell@ul.com

COMBINATION PRODUCTS: GMP BASICS

Last year, US FDA released GMP Requirements for Combination Products draft guidance, which was added to our foundational "GMPs for Combination Products" course (see sidebar for course summary). We wanted to summarize the critical compliance options that combo product makers have to make.

FDA recognizes that there is much overlap between drug and device regulations. Efforts by firms to apply all the specific regulations for all combination product components could result in redundant work, so FDA offers a more streamlined approach to compliance.

For "single-entity" or "co-packaged" combination products, the manufacturer must follow one of two requirements. Firms must comply with either all requirements applicable to each constituent part, or all the manufacturing/compliance requirements applicable to one constituent part, and certain provisions noted in section 4.4(b) applicable to the other constituent part.

Co-packaged drug-device combination

A manufacturer of a "co-packaged" drug-device combination product may choose to fully implement both the drug cGMPs (21 CFR Parts 210 and 211) and device QSR requirements.

Alternatively, the manufacturer may choose to comply with the drug cGMPs, but would be required by the new regulations to also comply with specific QSR requirements (e.g., the requirements in 21 CFR 820.20 on Management responsibility, 820.30 on Design controls, and 820.200 on Servicing).

Compliance Options

The production of any combination product whose constituent parts include both a drug and a device must comply with one of the options set forth in section 4.4(b). Firms may choose any one of the options presented to be compliant.

- Full constituent part compliance: a firm may choose to fully comply with all requirements applicable to each constituent part, as if each were manufactured separately.
- Full drug compliance: a firm may choose to fully comply with all drug cGMPs. They must then follow the additional provisions of the QSR, as noted in section 4.4(b).
- Full device compliance: a firm may choose to fully comply with all QS regulations. They must then follow the additional provisions of the drug cGMPs, as noted in section 4.4(b).

For example, a manufacturer of an insulin pump decides they are going to satisfy the drug component's cGMPs and be in full compliance. The firm must then make sure that, according to section 4.4(b), they comply with the relevant QS regulations pertaining to the device constituent part.

UL's GMPs for Combination Products course introduces individuals to cGMP requirements and FDA rules that relate to combination products. Written by GMP expert Dave Peterson, the course covers these topics: Background, Final Rule, Compliance, The Office of Combination Products, and Post-Approval Modifications. Regulations and Guidance noted in this course include:

- 21 CFR Parts: 3, 4, 210, 211, 600-680, 820, 1271
- Draft Guidance: Submissions for Post-approval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA, issued January, 2013
- Guidance for Industry and Staff: Current Good Manufacturing Practice Requirements for Combination Products DRAFT GUIDANCE January, 2015
- Proposed rule: Post Marketing Safety Reporting for Combination Products, Federal Register, September 30, 2009

To learn more about our GMPs for Combinations Products course, contact Pat Thunell at pat.thunell@ul.com.

About UL EduNeering

UL EduNeering is a division within the UL Ventures business unit. UL is a premier global independent safety science company that has championed progress for 120 years. Its more than 10,000 professionals are guided by the UL mission to promote safe working and living environments for all people.

UL EduNeering develops technology-driven solutions to help organizations mitigate risks, improve business performance and establish qualification and training programs through a proprietary, cloud-based platform, ComplianceWire®. In addition, UL offers a talent management suite that provides companies the ability to improve workforce skills & competencies within established role-based talent training programs to drive business performance.

For more than 30 years, UL has served corporate and government customers in the Life Science, Health Care, Energy and Industrial sectors. Our global quality and compliance management approach integrates ComplianceWire, training content and advisory services, enabling clients to align learning strategies with their quality and compliance objectives.

Since 1999, under a unique partnership with the FDA's Office of Regulatory Affairs (ORA), UL has provided the online training, documentation tracking and 21 CFR Part 11-validated platform for ORA-U, the FDA's virtual university.