Pharmaceutical Communiqué

Q4 2015

THE 10 MOST-USED eLEARNING GMP COURSES IN 2015

UL EduNeering has identified the "Top 10" GMP training topics for our Pharmaceutical clients, based on 2015 usage data.

1. PHDV73 – Orientation to GMP Compliance
2. PHDV74 – Handling an FDA Inspection
3. PHDV67 – Laboratory Safety
4. PHA74 – Principles of Good Documentation
5. PHDV63 – Understanding GMPs for Facilities and Equipment
6. PHDV71 – Principles of Aseptic Processing
7. PHDV79 – A Step-by-Step Approach to Process Validation
8. PHA64 – GMP Principles of SOPs
9. PHA35 – Change Control
10. PHA60 – GMP Principles for Batch Records

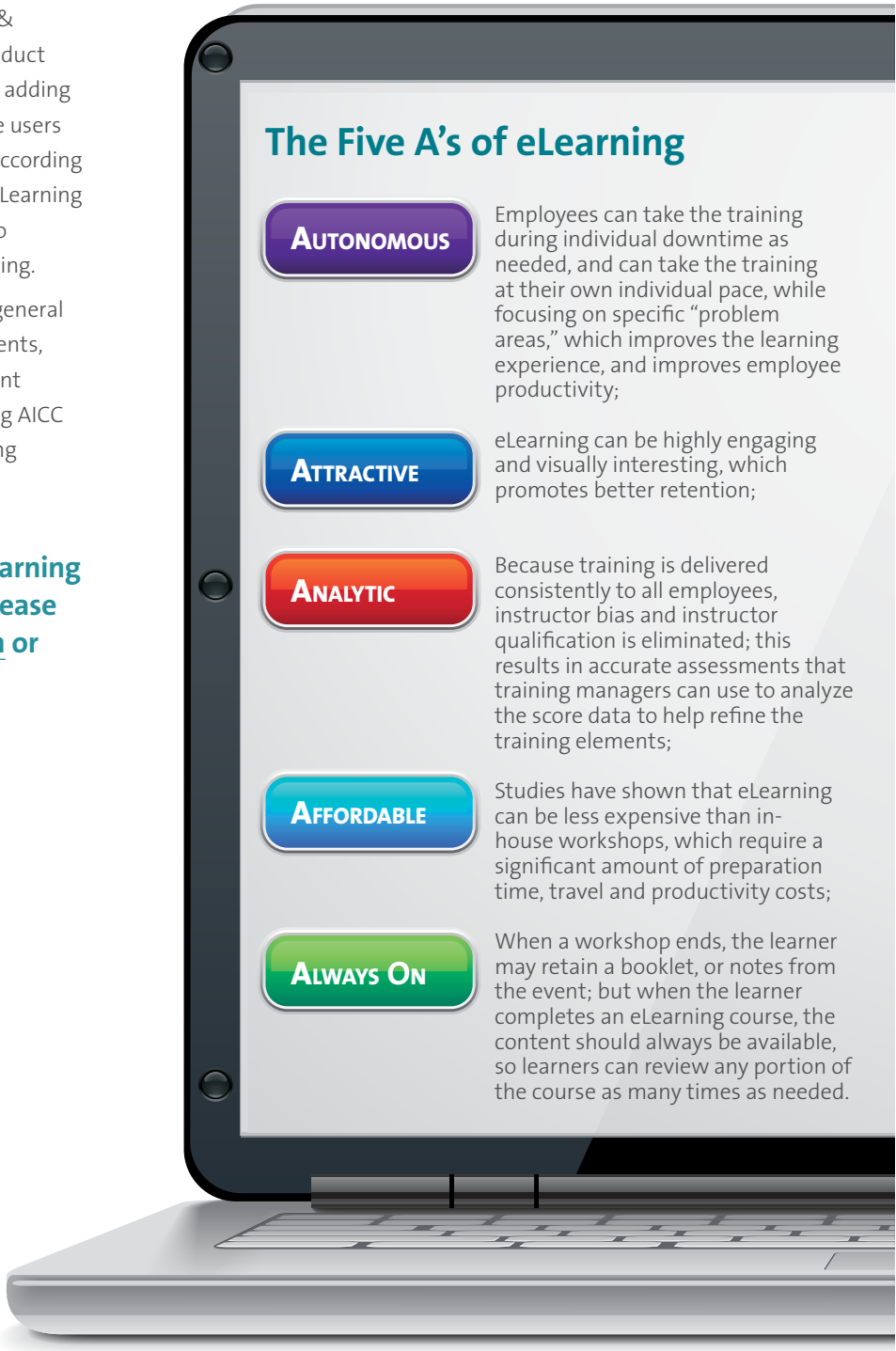
(continued...)

THE 10 MOST-USED eLEARNING GMP COURSES IN 2015 *(Continued)*

UL is now offering these courses as part of our Quality & Compliance Essentials sets. While many clients still conduct classroom and on-the-job training for most employees, adding eLearning enables training teams to reach more remote users at reduced costs. The advantage goes beyond dollars, according to our clients. A GMP training program that leverages eLearning courses also ensures an additional touch point, and also reduces the time spent on these topics during live training.

Each set contains five courses that are focused on the general topic, and the content is delivered as SCORM files to clients, so they can add them to their own learning management systems. Other delivery methods are available, including AICC and delivery through our own ComplianceWire® learning management system.

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



BATCH RECORDS:
DOCUMENTATION OF LABELING AND FILLING REQUIREMENTS

The filling and labeling operations are critical to ensure a quality product. Labeling errors are one of the most common causes of product recalls. There are several elements of the filling and labeling operations that must be documented in the packaging of batch records.

Filling

Here's what must be documented during filling operations:

- **Equipment and lines:** Major equipment and manufacturing or packaging lines used in the operation must be identified and documented.
- **Components:** It is critical that the correct packaging components are used. The batch record will list specific items and part numbers. The materials used, including lot numbers, must be documented and verified against the desired materials.
- **Parameters:** Verify the filling parameters. It is important to achieve fill weight specifications. Over or under filling containers can violate the drug application requirements. You should also verify other critical parameters, such as filler and capper/sealer settings, pressures, and machine adjustments specified in the batch record.
- **Results:** Carefully review the results of in-process testing at the required intervals, checking for such things as fill weights, vacuum, and proper seal. Make sure to document and investigate all deviations.

Labeling

Here's what must be documented during labeling operations:

- **Line clearance inspection:** This is the process of removing all materials from previous batches from the labeling line. The clearance process includes removing previous labels, containers, filled products, and other materials. Typically, a checklist is used to document line clearance. In some cases, companies should double-check the inspection. Line clearance inspection is expected before and after line use for both filling and labeling operations.
- **Correct label usage:** Verify that the correct labeling was used. The batch record should contain a unique identifier for the correct, required labels. The completed batch record includes documentation and samples of the actual labels used.
- **Label reconciliation:** This is the process of balancing and accounting for all uses of labels; it is required by cGMPs. The batch record must list the number of labels issued, then account for all used, unused, destroyed, and sample labels. If the shortfall exceeds a narrow preset limit, based on historical operating data, an investigation must be conducted into the reasons for the discrepancy.

We have updated our course, GMP Principles for Batch Records (PHA60), so that it's now mobile-friendly, and available in seven languages: English, Dutch, Spanish (Latin America), German, French (European), Japanese and Chinese.

The course explains key subparts of 21 CFR Part 211, so learners will understand how to properly create and maintain batch records. Topics in this course include: Record Requirements, Manufacturing Records, Packaging Records, Deviations, and Batch Record Review.

To review the course, contact Pat Thunell at 609-627-5320 or **pat.thunell@ul.com**.

A NEW APPROACH TO MEET YOUR LEARNING NEEDS

Introducing UL's New Quality & Compliance Essentials Program

To meet the needs of the Life Science industry – particularly smaller companies with fewer resources and need of only the core GMP training, UL has created an unprecedented solution.

Our new "Quality & Compliance Essentials" program provides sets of five of our most critical GMP courses targeted to specific areas of Life Science organizations.

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, clients can select a particular set of five courses – pay one affordable price – and receive unlimited usage.**

The *Pharmaceutical GMP Compliance* program includes these five courses (Learn more):

- Orientation to GMP Compliance
- Introduction to GMPs
- Principles of Good Documentation
- Maintenance and Cleaning of Drug Manufacturing Equipment
- Understanding the Practices and Principles of Process Controls

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®.

OFFICE OF PHARMACEUTICAL QUALITY WITHIN FDA'S CDER DIVISION

In the recently updated Awareness of FDA Inspections for Pharmaceutical Manufacturers course (PHA65), we focused on the Office of Pharmaceutical Quality (OPQ) within FDA's CDER Division. This new super-office was launched a few years ago and is organized to streamline regulatory processes, advance regulatory standards, align areas of expertise, and originate surveillance of drug quality.

Thus far, OPQ has promoted and encouraged the adoption of emerging pharmaceutical technology to enhance pharmaceutical quality and potentially reinvigorate the pharmaceutical manufacturing sector in the United States.

Within the OPQ is the Office of Surveillance (OS). Pharmaceutical "quality surveillance" pertains to quality oversight of approved and marketed products. Quality surveillance will greatly enhance FDA's ability to monitor quality across facilities, providing impetus for both FDA and industry to respond quickly to process trends before serious quality problems can occur. OPQ has identified a set of quality metrics for use in surveillance so that FDA can better monitor and prioritize facilities for risk-based surveillance inspection, and the FDA released draft guidance on quality metrics in July 2015.

The OS will maintain information on all facilities involved in the manufacturing of drugs destined for US patients and will conduct risk analysis and monitoring across the population of such facilities.

Surveillance of the product at site-specific levels will be conducted through assessment of facility inspection reports and problem reports for drug products. OS will generate and manage knowledge related reports to the state of quality of drug facilities and products, so that the entire drug supply chain can be better monitored and understood.

FDA conducts drug manufacturing inspections and maintains profiles or other monitoring systems, which ensure that each firm receives biennial (once every two years) inspectional coverage. FDA's District Office is responsible for determining the depth of coverage given to each firm and considers cGMP inspectional coverage sufficient to assess the state of compliance for each firm. The frequency and depth of inspection is determined by the statutory obligation, the firm's compliance history, the technology employed, and the characteristics of the products.

OFFICE OF PHARMACEUTICAL QUALITY WITHIN FDA'S CDER DIVISION *(Continued)*

Full Inspections vs. Abbreviated Inspections

The Full Inspection Option is a surveillance and systems-based approach to inspection that provides a broad and deep evaluation of the firm's cGMP compliance status. This is done when little or no information is known about a firm's cGMP compliance (e.g., for new firms); where there is doubt about the cGMP compliance in the firm (e.g., a firm whose history has documented short-lived compliance and repetitive violations); or as follow-up to previous regulatory actions.

The Full Inspection Option normally includes an inspection of at least four of these systems, one of which must be the Quality System (the system which includes Quality Assurance and Quality Control). The Abbreviated Inspection Option is a surveillance or compliance inspection that is meant to provide an efficient update evaluation of a firm's cGMP compliance status. An Abbreviated Inspection may revert to a Full Inspection if significant cGMP violations are discovered.

Key Inspection Types Used by FDA

cGMP Surveillance Inspection: An initial or biennial cGMP Surveillance Inspection utilizes the "Full Inspection Option." It's a broad and deep evaluation of a firm's cGMP compliance status that includes an inspection of at least four (4) subsystems, one of which must be the Quality System. Due to resource constraints, full cGMP inspections may not be conducted every two years. They may be conducted at less frequent intervals where Abbreviated Inspections are utilized to build comprehensive information on the firm's total manufacturing activities. An Abbreviated Inspection is considered adequate for routine coverage and typically satisfies the biennial inspectional requirement.

Pre-Approval Inspection: Prior to approval of an application for a new drug, FDA will conduct a Pre-Approval Inspection (PAI), which is part of FDA's "pre-approval oversight" responsibilities. PAIs are designed to prevent noncompliant, adulterated, or unsafe drug products from ever entering the market. If a firm fails a PAI, its application will not be approved until the necessary corrective actions are completed. This could result in the firm losing millions of dollars for each day that approval of the application is delayed. Once approved, new drug applications essentially become the "legal" contract with FDA. The application details how the drug will be manufactured, processed, and tested to ensure its quality and safety. Note: Pre-Approval Inspections resulted from the "generics scandal" of the late 1980s when FDA determined that it was necessary to verify that the manufacturing processes, practices, equipment, and testing used in support of a New Drug Application were actually in place as described in the application.

Post-Approval Inspection: Part of FDA's "Post-Approval Oversight" responsibilities, these inspections are used by FDA to follow up on compliance with such items as conditional application approval commitments and irregularities in documents and reports. They occur after the drug is approved and marketed.

Compliance Inspection: Evaluate or verify compliance corrective actions after a regulatory action has been taken. The inspections must be related to the areas found deficient and subjected to corrective actions. Special attention is given to "systems" because a determination must be made on the overall compliance status of the firm after the corrective actions are taken. The Full Inspection Option is typically used for a Compliance Inspection, especially if the Abbreviated Inspection Option was used during the routine inspection. There is no set frequency of Compliance Inspections. However, their frequency will be reflective of the firm's state of compliance – the more cGMP violations a firm has, the more compliance inspections they can expect.

For-Cause Inspection: Compliance inspections performed to investigate a specific problem that has come to the attention of the Agency (FDA). The problems may be indicated in Field Alert Reports, product complaints, adverse events reporting, recalls, or indicators of defective products. NOTE: For Cause Inspections may be expanded to a Full Inspection Option, if other more significant cGMP deficiencies are discovered.

WHAT EU EXPECTS FROM THE STERILIZATION PROCESS

One of the Pharmaceutical industry's top training needs is **Principles of Sterilization**. This includes the basics of sterilization and principles of several commonly used sterilization techniques, such as: Moist Heat, Dry Heat, Gas, Radiation, Chemical and Filtration. Here are examples of how EU regulations impact the Sterilization process and the methods used:

1. Re-Verifying the Sterilization Process

- Once validated, no changes should be made to the cycle parameters or equipment without evaluating if the proposed change requires additional validation work or a regulatory submission.
- Because changes can occur without our knowledge, it's important to re-verify that any sterilization process continues to work as expected over time. This involves conducting requalification studies to confirm, on a defined periodic basis (typically annually), that sterilization processes remain effective.

  EU regulation: EU specifically requires that sterilization processes be revalidated at least annually.

2. Moist Heat Method

- Moist heat, in the form of saturated steam under pressure, is the most widely used and the most dependable method of sterilization. Moist heat is used to sterilize liquids, cloth, small parts, sterilizing filters, stainless steel processing lines, and equipment.

  EU regulation: EU regulations state that the use of moist heat or dry heat is preferred. If one of these methods is not possible, written justification is expected.

3. Radiation Use

- Some materials cannot be sterilized using heat, and the use of gas sterilization may be impractical. In these cases, radiation sterilization may be used.
- Radiation works by breaking chemical bonds in DNA and other cell structures that lead to the destruction of the microorganism. It is generally more costly and requires the use of outside contract sterilizers. It has limited penetration, depending on the type of radiation used and causes some materials, such as polyvinyl chloride plastics (PVC), to yellow or become brittle when exposed to it.

  EU regulation: UV irradiation as a sterilization method is not acceptable in the EU.

4. Filtration

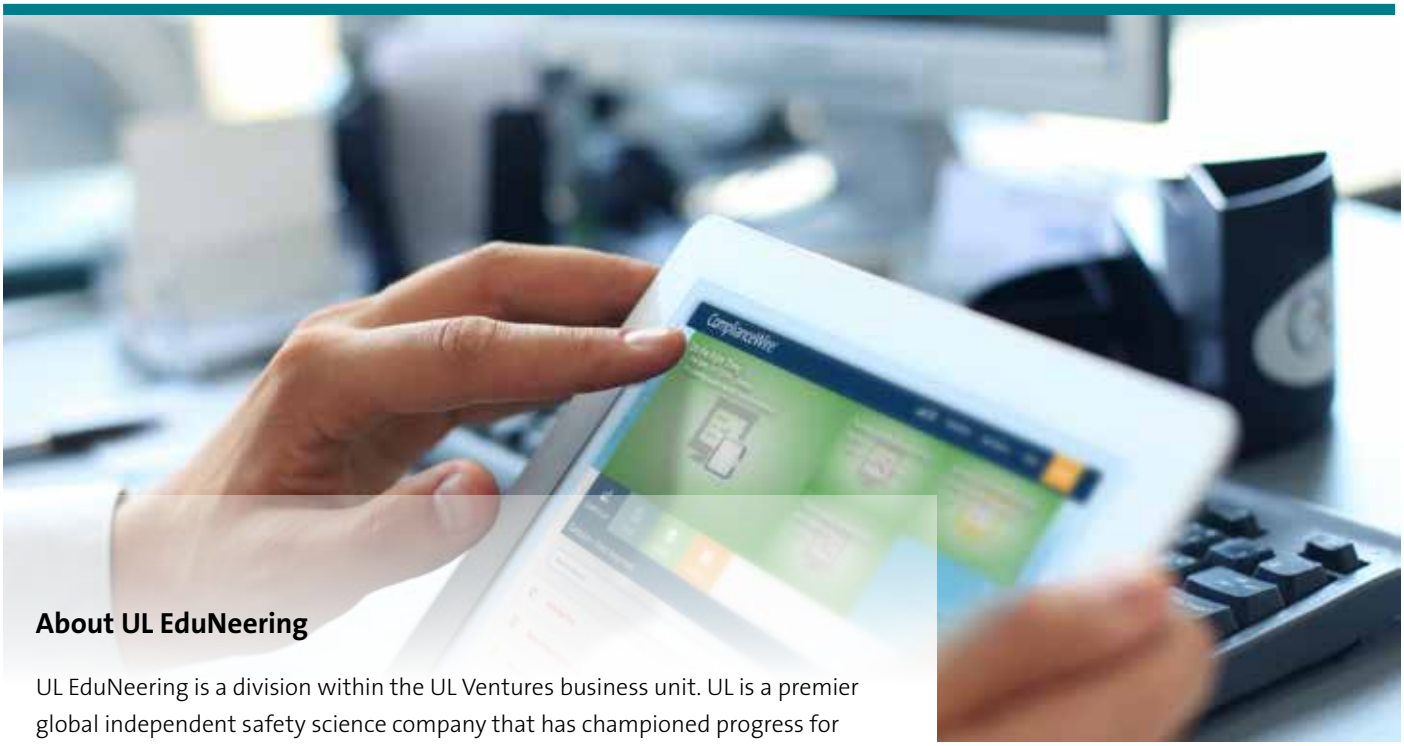
- Some liquid pharmaceutical products cannot withstand moist heat sterilization. In these cases, filtration is the sterilization method of choice. Filtration differs from other methods of sterilization in that microorganisms are physically removed from the product rather than being deactivated or killed.

  EU regulation: "Due to the potential additional risks of the filtration method as compared with other sterilization processes, a second filtration via a further sterilized microorganism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point."

UL's Principles of Sterilization course is one of our top 10 GMP eLearning topics in 2015. This course discusses the basics of sterilization and principles of several commonly used sterilization techniques, such as: Moist Heat, Dry Heat, Gas, Radiation, Chemical, and Filtration. Our subject matter expert for the course, Ann Early, of Early Mentoring Partners, has added commentary based on two EU regulations:

- EudraLex Vol. 4, EU Guidelines for GMP for Human and Veterinary Use - Annex 1 – Manufacture of Sterile Medicinal Products, 2008
- EudraLex Vol. 4, EU Guidelines for GMP for Human and Veterinary Use - Annex 2 (rev. 1) – Manufacture of Biological active substances and Medicinal Products for Human Use, 2013

To learn more about our Principles of Sterilization 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. Additionally, maintains exclusive partnerships with leading regulatory and industry trade organizations, including AdvaMed, the Drug Information Association, the Personal Care Products Council and the Duke Clinical Research Institute.