Pharmaceutical Communiqué

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FDA IMPORT ALERTS & CGMP COMPLIANCE

With so much regulatory attention on the value chain, companies must remain diligent about their active pharmaceutical ingredient (API) suppliers globally.

April 2016 saw three more Chinese pharmaceutical companies added to the US FDA Import Alert list for either failing to meet current Good Manufacturing Practice (cGMP) standards, or for refusing an FDA manufacturing facility inspection.

That raised the total to 46 pharmaceutical manufacturing sites in China, along with 42 sites in India, that are included on the FDA's Import Alert list, as noted on the RAPS report, "An Analysis of Form 483s from 2015, Regulatory Affairs Professionals Society, published on February 10, 2016.

(continued...)

FDA IMPORT ALERTS & CGMP COMPLIANCE *(Continued)*

Basics of FDA Import Alerts

FDA Import Alerts provide notice to District Offices and import inspection and compliance officers that a foreign manufacturer and its products appear to be in violation of the U.S. Federal Food, Drug, and Cosmetic Act. In many cases, companies and products listed on an FDA Import Alert are automatically detained without the added step of an FDA conducted physical inspection, examination, or sampling of the product.

Import Alerts are the FDA's signal to the global marketplace that a drug manufacturer's products present potential health risks for consumers. These alerts are issued whenever it is determined that the FDA already has sufficient evidence to conclude that imported drug products appear to be adulterated, misbranded, or unapproved, and therefore may be refused admission or, in extreme cases, even seized.

In addition to helping prevent potentially tainted products from being distributed, Import Alerts free-up agency resources to examine other shipments, provide uniform coverage across the country, and place the responsibility back on the importer to ensure that the products being imported into the U.S. are in compliance with FDA laws and regulations.

How do companies find themselves on an Import Alert list? Often, it's not until FDA automatically detains that first affected shipment at a U.S. port of entry. The FDA, through its "due vigilance," reviews imported product labels and internet marketing websites looking for unapproved drugs. The FDA website explains: "Some imported products might look like they are only over-the-counter medicines, or alternative medical remedies, including homeopathic, Chinese and Ayurveda Medicinal products." However, if the FDA determines that label or internet marketing claims fall within drug claim categories (intending the products to diagnose, treat, mitigate, cure or prevent disease or to affect the structure or function of the body), those products will be added to the Import Alert list, of which there are two types:

- Red List: Companies the FDA has discovered (by testing imported products or inspecting documents or facilities) have previously exported unsafe, adulterated, misbranded, or unapproved products. Products cited will be automatically detained.
- Green List: Issues may be more pervasive in a specific country or region than in the rest of the world. This alert applies to certain products originating in that country or region, even if the company shipping the product has never had the problem.

How to Get Taken Off the List

How can companies be removed from an Import Alert? The decision to remove a company or product is predicated on submitting a fully documented, compelling, and persuasive petition, grounded in FDA cGMP standards, to the FDA's Division of Import Operations. The petition must provide evidence that establishes the conditions that generated the apparent violation, and demonstrate that steps have been taken to permanently remediate the issue.

To avoid unnecessary delays in petition review, companies are mandated to submit documentation that includes U.S. Customs Form 3461 or Form 7501, commercial Invoice, packing list, the Bill of Lading, and any other paperwork required by the regulator. It is mandatory to prove that the subsequent changes were effectively implemented, and that all future shipments will contain products that reflect only legal claims.

Getting taken off the FDA Import Alert List is labor intensive in the best of circumstances, and even more challenging when attempted from abroad – especially when revenue and profits are at stake. The FDA website provides guidelines to help manage the process. To better protect themselves, foreign companies often enlist law firms that specialize in U.S. customs policies. The best strategy, however, is preemptive. Trouble-shooting operations and increasing oversight can help identify potential infractions before they become actual violations, and ensure that cGMP complies with established FDA standards.

DATA INTEGRITY:
THE CHALLENGE OF CHANGE MANAGEMENT

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.

As discussed in the last Communique, the computerized system must be maintained in a validated state. Companies must have the proper infrastructure to assess system changes and determine how it will impact the validated state. The infrastructure should consider these four elements:

Product Enhancements

With custom configurable packages, maintenance becomes a key issue, particularly when software vendors issue new and improved versions of their software.

Personnel Qualifications

Personnel must be trained for the new role. The maintenance process must include personnel who are responsible for originating change requests, and also identify individuals responsible for approving changes to be made, as well as the reviewing/approval officials of the executed changes. These personnel may include anyone who uses or is affected by the system. A procedure must be in place that allows personnel to originate a change request.

Documentation

All changes must be properly documented, thoroughly tested, traced to show all affected areas, and implemented with the proper approvals. The process must always include evaluation of all system documentation to determine if other revisions are needed following change; i.e., does the change affect the intended use requirements document, system design document, user manuals, and, of course, traceability.

The documentation for a change must assure the investigator or auditor that the request for the change was properly approved and that the risks as a result of the change were considered, documented, and resolved prior to the change.

Testing

Was testing comprehensive as indicated by the traceability matrix? Was the traceability matrix updated and users of the system informed and trained on the functionality of the new change? Traceability enables each uniquely identified Intended Use Requirement to be traced through all respective and related functional specifications, design specifications, coding/ configurations, testing, qualifications, and test results.

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 October 31 to November 2, 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

SHARE EQUIPMENT AND CALIBRATION KNOWLEDGE

UL's Facilities & Equipment eLearning Program

UL has taken five facility and equipment maintenance courses within our current 90-course GMP library and made it easy for non-subscribers to gain access.

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.

The Facility and Equipment Compliance set includes these five courses:

- Understanding GMPs for Facilities and Equipment
- Environmental Control and Monitoring
- Gowning for Sterile Manufacturing
- Maintenance and Cleaning of Drug Manufacturing Equipment
- Essentials of an Effective Calibration Program

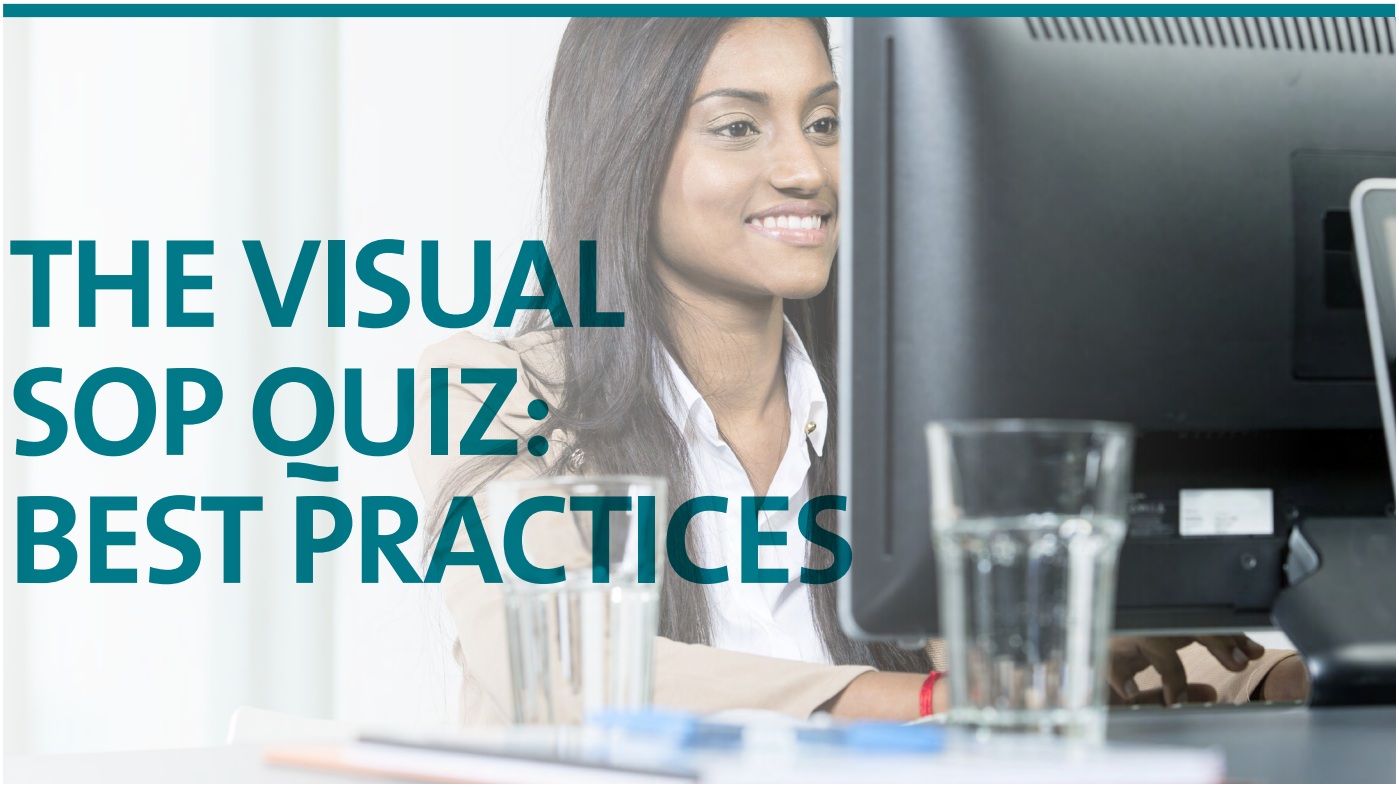
Click here to download

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®.



THE VISUAL SOP QUIZ: BEST PRACTICES

The following article is based on recent changes to the QuizCreator and ExamCreator tools in our ComplianceWire LMS.

As more Life Sciences companies add images to their policies and procedures, it only makes sense that these same images should be applied in related assessments. Clients add images to their SOPs to improve adherence to the procedures and work instructions. And studies have confirmed that the use of "illustrated text" improves retention, as opposed to the use of text alone.

To capture images for procedures or work instructions, clients typically document an "expert" performing an operation successfully, and also take pictures of each critical step.

In our 2015 November release of ComplianceWire, we made it easy for any training administrator to add images (up to 2 MB) to questions in our QuizCreator and ExamCreator tools. In this article, we share three common SOP quiz image best practices. We should point out that ComplianceWire clients must subscribe to "content hosting" to load these images to UL's secure servers. Here are just four critical SOP quiz topics that can be improved with the addition of images:

- Equipment Use (including maintenance)
- Document Recordkeeping
- Visual Inspection (OOS or rejections)
- Analytical Testing (QC Lab)

The "Right or Wrong Way" Challenge

One best practice for using images in an SOP quiz is to add a "right or wrong way" question in the assessment, and include photos that show the proper - or improper- approach for a specific task or operation. In this way, the learner gains a deeper link to the real-world experience of the operation or task.

The visual depiction helps to encourage proper behavior well after the training activity, as it clarifies "the right approach" related to any process or work instruction.

An example of the "right or wrong" question is displayed on the next page. This was done in our QuizCreator tool. In this example, the learner is shown a scanned picture of a sign-in sheet that depicts multiple violations of Good Documentation Practices. Based on the image, the learner must identify all of the violations.

During an actual documentation activity, the learner is more likely to recall the right or wrong way, thanks to seeing the visual in the assessment. In this way, the "quiz" itself serves as an extension of the learning activity.

(continued...)

THE VISUAL SOP QUIZ: BEST PRACTICES *(Continued)*

The "Identify/Match the Visual" Challenge

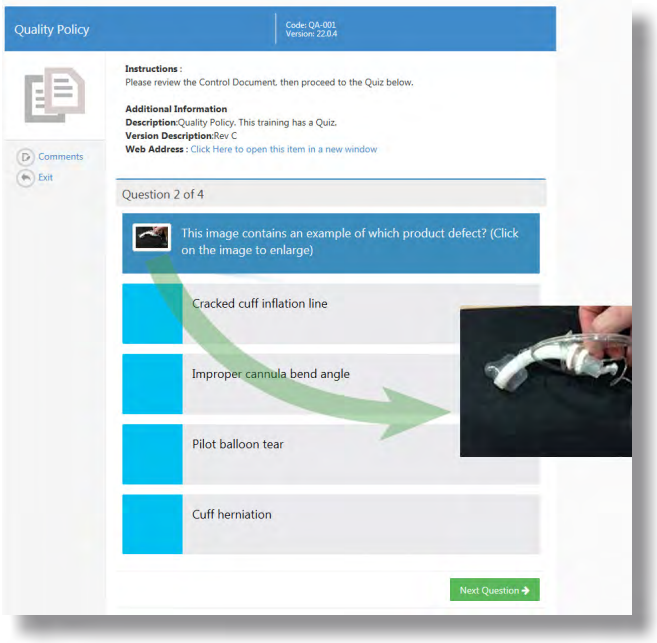
Another best practice is to challenge the learners's knowledge of product defects by presenting an image of the defect.

This can be a valuable way to assess learners on their visual inspection knowledge. QA teams can show the quiz as a way of demonstrating "training effectiveness" to auditors and regulatory investigators.

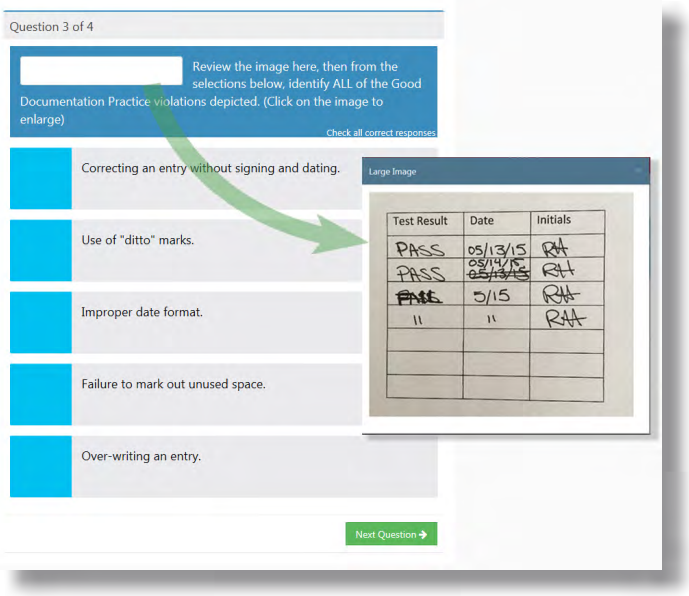
Trainers can add a single image, as shown to the right, or up to six images if they select the "matching" question type.

The trainer can then ask the learner to identify the issue depicted in the image, or match the type of defect to the image depicted. These questions provide two key benefits:

- Learners can recognize the product issue(s) as it would be presented in a real-world setting;
- Learners are able to correctly distinguish the precise issue(s) from a number of options.



Example of a "Identify/Match the Visual" Question



Example of a "Right or Wrong Way" Question

The "Sequence the Items" Challenge

For SOPs or work instructions related to equipment calibration or other steps, we are introducing a new "Sequence" question type in the July 2016 release of ComplianceWire. Training administrators can identify steps with images and have learners place the steps in the proper order. This serves as a great exercise that "surfaces" any sequence explanation within the SOP.

For all of the question types in ComplianceWire, a new "immediate feedback" feature was added to QuizCreator in 2015, in which feedback can be provided to a learner immediately after a correct or incorrect response is given.

If you are not a current subscriber to ComplianceWire, and want to see a demo of the QuizCreator tool and the image functionality, please contact Pat Thunell at pat.thunell@ul.com.

REPORTING POST-APPROVAL CHANGES TO FDA

Over the past few years, FDA has made available a number of documents to help manufacturers determine how to report post-approval changes in chemistry, manufacturing, and controls (CMC) of their products. Specifically, FDA's Scale-up and Post-Approval Changes (SUPAC) guidance has been aimed at specific dosage forms.

SUPAC documents provide "road maps" for making regulatory decisions and for developing supporting documentation for changes to CMC, such as modifications in dissolution and bioequivalence documentation.

Previously, FDA has provided guidances for immediate-release, modified-release, and semi-solid dosage forms, as well as for biologics. In 2014, FDA released "Guidance for Industry: CMC Post-Approval Manufacturing Changes to be Documented in Annual Reports," and gave recommendations to holders of NDAs and ANDAs regarding the types of changes to be documented in annual reports.

Because the "Changes to Approved NDA or ANDA" guidance does not provide extensive recommendations for component and composition changes, the SUPAC guidance documents can be beneficial, as they are specific for particular dosage forms. This approach is increasingly important because some dosage forms are more complex and, as a result, call for more specific requirements for evaluating post-approval changes.

The SUPAC guidance also applies to scale-up activities. For each dosage form, SUPAC guidance defines categories of change, recommended CMC tests to support each category of change, recommended in vitro release tests and/or in vivo bioequivalence tests to support each change, and documentation to support the change. Here is a summary of each reporting category of change:

Minor change:

SUPAC minor changes are those that have minimal potential to adversely affect the identity, strength, quality, purity, or potency of a product. It is the easiest type of change and requires the least amount of supporting data to be included in the submission. Minor changes should be described in the applicant's next annual report.

Moderate change:

SUPAC moderate changes are those that have moderate potential to adversely affect the identity, strength, quality, purity, or potency of a product. These changes may be covered under one of two categories of Changes Being Effected (CBE) supplements, depending on the type of moderate change being made.

Major change:

SUPAC major changes are those changes that are considered to have a substantial potential to adversely affect the identity, strength, purity, or potency of a product. The Agency wants to see this type of change ahead of time to determine if it is necessary. Major changes almost always require notification to FDA in the form of a prior approval supplement (PAS).

UL's "Understanding Post-Approval Changes" course focuses on categories of post-approval changes (PAC), the requirements for each, and PAC guidance. Topics in this course include: SUPAC, Components and Composition, Site of Manufacture, Scale of Manufacture, and Manufacturing.

After completing this course, learners will be able to:

- Recognize PAC guidance and how these documents are used to provide notification to FDA for post-approval changes to an approved drug application.
- Identify the categories of PAC and the recommended chemistry, manufacturing, and control (CMC) requirements for each change.
- Identify the tests and documents needed for each category of change.

To learn more about our Post-Approval Reporting course, contact Pat Thunell at pat.thunell@ul.com.

About UL EduNeering

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 EduNeering 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), EduNeering 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.