Life & Health

Pharmaceutical Communiqué

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CDER'S PRIORITIES FOR 2013-2014

It's always good to know where CDER is going – or at least where it says it wants to go. Late last year, Dr. Richard Moscicki, CDER's Deputy Center Director for Science Operations, set out CDER's priorities for the upcoming year.

According to Dr. Moscicki, CDER's big-picture priorities are:

- FDASIA:
  - Expedited reviews and breakthroughs
  - Antibiotic development
  - Rare diseases
  - Drug shortages
  - GDUFA goals
  - Electronic submissions
- Pharmacy compounding
- Rethinking pharmaceutical quality
- Improving drug labels
- Drug safety: Sentinel/IMEDS
- PDUFA V goals

(continued...)

CDER'S PRIORITIES FOR 2013-2014 *(Continued)*

Everything CDER does will have some impact on a Pharmaceutical company's quality and compliance functions but one of CDER's priorities jumps out as a bright, blinking light for the quality department: drug shortages and the interrelated issue of drug quality.

Drug Shortages and Quality

Drug shortages make the news and nobody comes out looking good – not regulators, enforcement agencies, manufacturers, prescribers, or even pharmacies. FDA's analysis of the causes for drug shortages points to some good reasons why the industry gets a bad reputation: two-thirds of the causes of drug shortages are quality manufacturing issues, either facility remediation efforts or product manufacturing problems.

Drug shortages go hand-in-hand with FDA's increased inspection of pharmaceutical manufacturing facilities. The product recalls and bans on products manufactured at both domestic and foreign plants with severe GMP violations point to the perhaps unintended consequence of increased GMP inspections and intensified global attention on drug quality.

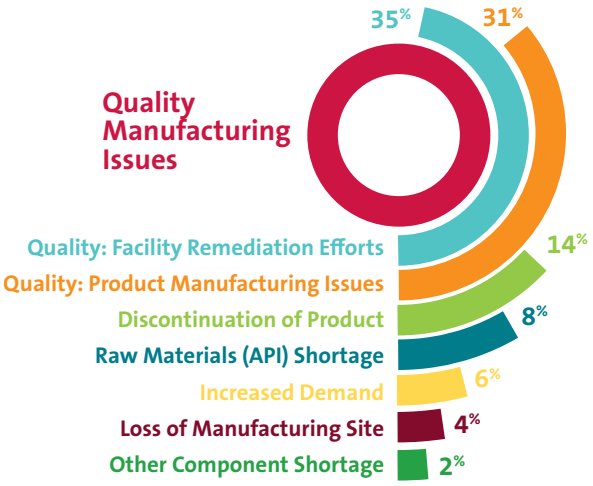
After too long at the kicking end of the drug shortage problem, FDA issued a strategic plan in October 2013. The plan focuses on notification by manufacturers of upcoming or potential drug shortages. The short-term effort is a risk-based analysis to determine ways of addressing the shortage, ranging from asking other manufacturers to ramp up their production to working with the notifying manufacturer to ensure adequate investigation into the root cause of the shortage. The long-term goal is improvement of manufacturing quality. According to Dr. Moscicki's December 11th presentation, early notification produced positive results even before FDA's formal strategic plan was issued. In 2012, 282 shortages were prevented. 2013 numbers are yet available.

Using Metrics for Drug Quality

Dr. Moscicki didn't specifically address the use of metrics for ensuring drug quality but Dr. Janet Woodcock, Director of CDER, did in speeches including one at the Parenteral Drug Association last September. Her unwavering focus on drug quality as the Center's overriding priority has been a constant theme in other presentations since then along with a plan to involve the pharmaceutical industry in establishing the metrics for FDA to plan and conduct facility inspections.

The use of metrics to identify potential product quality issues before they evolve into serious problems, threats to patient safety and candidates for recall or bans isn't new. What is new is Woodcock's methodical approach to identifying the metrics that make sense for the industry and FDA. To that end, she is calling on industry to collaborate with FDA in identifying metrics worth collecting and using to ensure drug quality. It's an ambitious request, given that she emphasizes the importance of collecting information from across the organization, from quality and compliance to facility maintenance, training, warehousing, production and procurement.

CAUSES OF DRUG SHORTAGES:



483s AND RECALLS

Hindsight has its value, especially for gaining insight into FDA's direction and focus going forward. Here's a brief look at FDA's inspectional observations in 2013.

The number of 483s dropped in 2013, according to FDA's annual inspections statistics report. In 2013, the agency issued 690 483s compared to 787 in 2012. For the most part, 2013's top citations are repeats of 2012's, with poor investigations into batch failures and lax procedural documentation leading the pack. There were, however, some differences worth noting. Deficiencies for positron emission tomography (PET) drugs doubled to more than two dozen in 2013. The increase in observed deficiencies correlates with FDA's 2012 plan to increase inspections of PET drugs. Another difference between 2012 and 2013 numbers was the significant rise in citations related to the prevention of microbiological contamination of sterile drug products. In 2012, lacking adequate procedures to prevent such contamination was the 15th most frequently cited observation; in 2012, it shot to sixth place. FDA attributes the change in part to its surprise investigations of compounding pharmacies.

The top 10 observations in 2013

155	Responsibilities and procedures for the quality control unit aren't in writing or fully followed
131	Failure to review and investigate the failure of a batch or any of its components
106	No written procedures for production and process controls
99	Laboratory controls are not scientifically sound or appropriate
77	Written procedures aren't established for maintenance of plant equipment
76	Procedures to prevent microbiological contamination of sterile products are not established, written or followed
71	Equipment and utensils are not cleaned, maintained or sanitized properly
66	Testing of drug products prior to release doesn't include appropriate laboratory determination of conformance to specifications for active ingredient
65	Control procedures aren't established to monitor or validate manufacturing processes
62	No written testing program established to assess stability

Source: FDA annual inspections statistics report

NEW FDA/EU COOPERATIVE PROGRAM

The US Food and Drug Administration (FDA) has established information-sharing agreements with many of its regulatory counterparts around the world as a critical step in protecting the global drug supply. No relationship is more important than the one the FDA has with the European Medicines Agency. The two agencies have worked together on initiatives involving site inspections and Quality-by-Design assessments.

In 2014, FDA and EMA are expanding their cooperative efforts to focus on generic drugs. The initiative centers on information-sharing about inspections of bioequivalence studies submitted in support of generic drug approvals. In addition to the FDA and EMA, other participants in the joint program are France, Germany, Italy, the Netherlands and the UK.

According to FDA, the key objectives of the new initiative are:

- To streamline information-sharing on inspections of bioequivalence studies conducted and planned for generic drug applications; inspectional information will be shared for clinical facilities, analytical facilities or both;
- To share information about negative inspection outcomes that reveal system problems at a facility;
- To conduct joint inspections at facilities all over the world;
- To provide training opportunities to improve bioequivalence inspections.

TRANSPARENCY MOVES FORWARD

Transparency into the GMP compliance of a Pharmaceutical company's facilities was pushed forward with the European Medicines Agency's (EMA) European Inspections database. The database was designed to give the EMA and member nations an overview of the status of Pharmaceutical manufacturers including Manufacturing and Importation Authorizations and Good Manufacturing Practices. In April 2013, the database was expanded to include information on Good Distribution Practices (GDP).

In late 2013, the EMA launched a new version of the EudraGMDP database which includes, for the first time, statements of non-compliance with Good Manufacturing Practices (GMPs). The statements are the result of inspections of manufacturing sites found to be non-compliant with GMPs. In those cases, inspectors issue a statement of non-compliance and enter the document into EudraGMDP. The non-compliance documents are available to the public, just as the positive GMP certificates have been.

The database contains statements of noncompliance issued from 2007 until the present. In 2013, there were 34 statements of non-compliance. India (14) and China (10) led the list of cGMP violations. Other countries fell far behind those two leaders. The UK and South Korea showed two statements of noncompliance each. Japan, Spain, Italy, France, Thailand and Brazil each showed only one statement of noncompliance.

NEW COMBINATION PRODUCTS COURSE
Now Available

In 2013, the US Food and Drug Administration (FDA) issued a new regulation (Final Rule) on cGMP requirements applicable to combination products. While this rule does not create new cGMP requirements, it does clarify which cGMP requirements apply for combination products, while also providing a streamlined regulatory framework for firms to use when demonstrating cGMP compliance for combination products.

To help your quality and manufacturing teams understand this regulation, UL has developed a new course, Combination Products – cGMP Requirements (PHDV93). This course is now available to annual GMP library subscribers.

This course focuses on the four different types of combination products as well as the scope of the new regulation in 21 CFR Part 4. Learners will also understand how post-marketing modifications are made, and how to report post-marketing adverse events. The course, which can be taken on a PC or iPad, was authored by Dave Peterson, renowned GMP expert and member of the UL EduNeering Advisory Services team.

Learn about New Courses and "Major" Course Changes

To learn about any new Life Science course, or why a course received a "major" update, visit UL EduNeering's Course Update Portal. This web page provides a three-month rolling summary of why a course received a "major" update.

Minor updates will not be included, as they are typically grammatical or aesthetic changes. In addition, new courses will be listed as well.

www.uleduneering.com/course-update-portal

This page will be updated at the end of each month, or sooner as major updates occur. Please provide feedback about the site and any course questions to your Account Director, or our Client Services team.

About UL EduNeering

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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®.

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, UL 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.