Life & Health

Pharmaceutical Communiqué

Q2 2014

SHARE INSPECTION INFORMATION – OR NOT?

The US Food and Drug Administration (FDA) knows that it can't alone police all drugs entering the US for quality, safety and compliance with US regulatory requirements. Over the past several years, senior FDA officials including CDER Director Janet Woodcock have emphasized the need to cooperate with regulatory counterparts in other countries, particularly when it involves the inspection of drug manufacturing plants. But, despite statements and speeches, the road to cooperative information-sharing still remains bumpy. Those bumps in the road mean the global Pharmaceutical industry continues to face the prospect of multiple inspections from various national regulatory agencies.

(continued...)

UL and the UL logo are trademarks of UL LLC © 2014.

SHARE INSPECTION INFORMATION – OR NOT? *(Continued)*

In May 2014 Howard Sklamberg, FDA's Deputy Commissioner for Global Regulatory Operations and Policy posted on FDA Voice, the agency's official blog, the need for global cooperation into context, noting that 40 percent of the US' finished drugs are imported and approximately 80 percent of the manufacturers of active Pharmaceutical ingredients used in the US are located outside the country's national borders. He repeats the caution so often expressed by FDA and industry insiders, stating that anywhere along the massive global supply chain of most Pharmaceutical products, things can go wrong, leading to products that are improperly formulated, manufactured or packaged; contaminated; or counterfeited. Sklamberg admits securing the global supply chain demands more than FDA's foreign inspection.

The Food and Drug Administration Safety and Innovation Act (FDASIA) contained some provisions designed to aid FDA in addressing its global challenge to improve the safety and integrity of imported drugs sold in the US. High on the list of FDASIA's tools is FDA's ability to partner with foreign regulatory authorities through increased information-sharing and recognition of foreign inspections. The US has more than 60 agreements with foreign counterparts to share certain information in inspection reports and other non-public information.

Sklamberg's post introduced an expansion of FDA's global efforts through an initiative of cooperation with the European Commission (EC) and the European Medicines Agency (EMA). He explains, "FDA will aim to deepen our reliance on trusted regulators outside of the US to provide equivalent public safety and quality protection." He continues confidently, "And together we will be more efficient and effective in targeting our resources for inspecting Pharmaceutical operations."

That statement may have been overly confident. Just a week later, an article in *FiercePharma Manufacturing* recounted a Wall Street Journal (WSJ) report about the US sharing information with its European counterpart. According to the Firecepharma article which is referring to the WSJ points out, "the US is just not ready to agree that all inspection agencies in the 28-member EU are created equal." Regulatory standards and systems are not identical across the EU, which continues to expand as new countries are admitted to the EU. Regulators, including some outside the US, may be reconsidering how much confidence they have in inspections conducted under those various regulatory programs.

While the US and other governments work on hammering out trade agreements that could include US acceptance of inspections conducted by other countries, the global Pharmaceutical industry waits – and continues to commit resources too often to facility inspections by multiple international regulatory agencies.

FDA GETS HEAT FOR DOMESTIC API INSPECTION PLAN

Sometimes, FDA can't win. After years of being skewered by the US Congress, government watchdogs and patient advocates for its track record of inspecting foreign Pharmaceutical manufacturing facilities, the FDA was hit by concerns over its plan to increase foreign inspections while reducing domestic inspections of API plants.

Society of Chemical Manufacturers and Affiliates' (SOCMA) affiliate Bulk Pharmaceuticals Task Force (BPTF) zapped off a letter to Kathleen Uhl, M.D., Acting Director of Generic Drugs in FDA's Center for Drug Evaluation and Research. The letter followed BPTF's review of FY 2015 FDA budget justification and expressed concern that domestic API manufacturers would be penalized under the Generic Drug User Fee Act (GDUFA) if such a plan was implemented. In the letter, John DiLoreto, Executive Director of BPTF writes:

> *"It is of great concern to the BPTF that a recent Health and Human Services FY 2015 budget justification disclosed that the FDA will be scaling back by 40% the number of domestic routine surveillance inspections it plans to conduct in fiscal years 2014 and 2015. It is our understanding that the agency is reducing the number of domestic inspections in order to elevate the number of foreign inspections."*

BPTF's argument is justified, as noted by DiLoreto, who references major program goals contained in the GDUFA Commitment Letter (Human Generic Drug Performance Goals and Procedures Fiscal Years 2013 through 2017): "FDA will conduct risk-adjusted biennial cGMP surveillance inspections of generic API and generic finished dosage form manufacturers, with the goal of achieving parity of inspection frequency between foreign and domestic firms in FY 2017." DiLoreto continues, "In the Commitment Letter ... all statements indicated that inspections of API sites would be performed within 3 years of the previous site inspection. However ... the agency estimated that for fiscal year 2013, only 80% of domestic API facilities had received a cGMP routine surveillance inspection in the last three years. If the inspection rate is reduced by 40%, this could cause over half of domestic API manufacturers to fail to receive an inspection within the 3-year cycle. "

The problem, according to BPTF, is that the most cGMP-compliant API manufacturers and their customers (the manufacturers of finished dosage form drug products) would be penalized because FDA's risk-based approach may not put a well-performing facility on the "pending" list for a surveillance inspection. Again referring to the Commitment Letter, DiLoreto cites, "FDA intends to continue the practice of using a risk-based assessment in determining the length of time since the last inspection, guided by a 2-year cycle for finished dosage product sites and a 3-year cycle for API sites and consideration of the type of finished product or API in the application." Many countries (including countries in the EU, Canada, Australia and South Korea) require marketers to recertify their products every five years and regulators in those countries require that API suppliers for those products must have been successfully inspected within the previous three years. Without evidence of the inspection, the drug product could fail to receive timely renewal of its marketing authorization.

How FDA deals with its inspection scheduling dilemma remains unknown, but with thousands of domestic and foreign manufacturing facilities to oversee and limited resources to meet that goal, the FDA has to feel properly battered no matter which way it turns.

DEALING WITH DRUG SHORTAGES

Nobody wins when there is a drug shortage. Manufacturers, regulators, pharmacies, insurance plans, and even prescribing physicians are all blamed by patients when they encounter a drug recall or shortage, regardless of the cause. A 2014 Report to Congressional Addressees by the US Government Accountability Office (GAO) produced findings that put the issue into context.

According to the report, entitled "Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability," the number of drug shortages remains high. GAO notes, "The immediate cause of drug shortages can generally be traced to a manufacturer halting or slowing production to address quality problems, triggering a supply disruption." GAO identified other factors that contributed to drug shortages, but quality problems remain the main cause. Here are some of the report's other findings:

- More than half of the 1,132 shortages reported since January 1, 2007, were for drugs that were in shortage more than once.
- The duration of the shortages varied for that period, ranging from one day to more than five years. The majority of shortages (68%) lasted one year or less – just barely at 340 days.
- Although the number of shortages reported has declined recently, the number of active shortages remains high, with the total number of active shortages each year increasing steadily since 2007. In fact, the number of active shortages each year between 2007 and 2012 nearly tripled. During the first half of 2013, there were 361 active shortages.
- 44% of the drug shortages reported between June 1, 2011 and June 30, 2013 were critical shortages involving generic sterile injectable drugs. Of the 96 shortages in that percentage, 63 were for drugs available only in generic form.
- Anti-infective, anesthetic, cardiovascular, nutritive and central nervous system therapeutic classes represented 53% of critical drug shortages.

DEALING WITH DRUG SHORTAGES *(Continued)*

Drug shortages can cause a variety of problems directly related to patient care. Noted in the GAO study, "... Recent research on the effects of drug shortages identified an increase in adverse outcomes among pediatric cancer patients treated with an alternative drug." For providers, drug shortages can also cause significant problems including delays in or rationing of care, difficulties finding alternative drugs, risks associated with medication errors, higher costs, reduced time for patient care and hoarding or stockpiling drugs in short supply.

As noted, quality issues represent the primary cause of drug shortages. 35% of all shortages are caused by quality issues tied to facility remediation efforts; another 31% are due to product manufacturing issues. A presentation by Douglas C. Throckmorton, M.D., Deputy Director for Regulatory Programs at CDER, for International Society for Pharmaceutical Engineering (ISPE) in June 2014 identified examples of quality manufacturing issues:

- Sterility: bacterial and fungal contamination
- Particulates: glass, metal or fiber in vials
- Crystallation: drug may form crystals
- Precipitation: reaction between drug and container or diluent
- Impurities: can be toxic (heavy metals)
- Degradants: lead to less effective drug products
- Equipment breakdown and the need for remediation
- Natural disasters

The FDA has developed a strategic plan for preventing and mitigating drug shortages. Among the proposed long-term solutions contained in the Strategic Plan, one deserves specific mention: FDA proposes to develop methods to incentivize and prioritize manufacturing quality. How? The Number 1 proposed endeavor is to examine the broader use of manufacturing quality metrics to assist in the evaluation of product manufacturing quality.

The use of quality metrics is something FDA has emphasized recently and is a topic of considerable focus by many members of the Life Science community. One industry-wide initiative was launched this year by ISPE. ISPE introduced its Quality Metrics Pilot Program, which it designed to "... define and operationalize standard metrics reporting to the US Food and Drug Administration. The year-long program will test a series of leading and lagging indicators that support an FDA risk-based inspection program in lieu of biennial inspections ..." Participation in the pilot program is open to companies. Even without that participation, however, the need for developing and applying metrics as an essential tool to improve and assure product quality is taken seriously by Pharmaceutical industries around the world. It's an issue that will continue to escalate in importance, visibility and negative consequences, not only to patients but also to the company's reputation and stakeholders. Reviewing the presentation by Throckmorton, particularly the examples of quality manufacturing issues (listed above), is a good step in beginning or reinforcing a company's existing quality plan and metrics applications.

GIVING LEARNERS A "HOW TO" COURSE IN RISK MANAGEMENT

UL EduNeering's new course, Risk Management in Pharmaceutical Manufacturing (PHA72), offers an introduction to the practical application of Risk Management principles, published in "Guidance for Industry: Q9", through case studies applied to process design and manufacturing.

FDA's "Guidance for Industry: Q9 Quality Risk Management," published in June 2006, addresses risk management and lists some tools that can be implemented. However, FDA has not mandated a specific risk-based approach for Pharmaceuticals. The Pharmaceutical industry can experiment with various risk-based approaches, decide which ones work best, and make sure that the selected approaches will both protect patients and add value to our business. Our new course focuses on risk assessment and risk control, and also provides two case studies.

What is Risk Assessment?

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. QRMs begin with a well-defined problem description or risk question. When the risk in question is well-defined, an appropriate risk management tool and the types of information that will address the risk question will be more readily identifiable. As an aid to clearly defining the risks for risk assessment purposes, three fundamental questions are often helpful.

- What might go wrong?
- What is the likelihood (probability) it will go wrong?
- What are the consequences (severity)?

GIVING LEARNERS A "HOW TO" COURSE IN RISK MANAGEMENT *(Continued)*

In our PHA72 course, we explain the three components to risk assessment:

Risk Identification: Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, requirements/design specifications, potential process failures, and the concerns of stakeholders. Risk identification addresses the "What might go wrong?" question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process. The identification process might include a Design of Experiment (DoE), showing what actually affects the production of a product (hazard identification).

Risk Analysis: Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harm. In some risk management tools, the ability to detect the harm also factors into the estimation of risk.

Risk Evaluation: Risk evaluation compares the identified and analyzed risk against given risk criteria. On the basis of risk analysis and taking into account factors such as social, economic, and environmental aspects, judgments are made on the acceptability of the risk during risk evaluation.

For more information about the PHA72 course, please contact your Account Director or send a request for a demo of the course to EduNeeringInquiry@UL.com.

About UL EduNeering

UL EduNeering is a business line within UL Life & Health's 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®.

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.