Life & Health

Pharmaceutical Communiqué

Q2 2013

1 Focusing on Counterfeits

2 GMPs are Top Area of Focus for DOJ in 2013

3 FDA's Final Rule for Combination Products

Focusing on Counterfeits

Dr. Margaret A. Hamburg, Commissioner of the US Food and Drug Administration (FDA), recently took to the blogosphere to reinforce the Agency's concern and response to the global threat of counterfeit drugs. She set the stage for her comments with the now-familiar numbers reflecting the risks posed to drug safety in the US because of globalization: 40 percent of the medicines used in the US are manufactured outside the country and 80 percent of the active ingredients in those drugs come from abroad.

"One of the greatest threats to safety involves substandard, falsified and counterfeit medical products in the supply chain. For the past several years, FDA has been engaged in global efforts to improve collaboration in preventing, detecting and responding to this threat." Hamburg references partnerships with the World Health Organization and the Asia Pacific Economic Community as well as FDA collaboration with agencies including the US Agency for International Development and the World Bank.

Focusing on Counterfeits *(Continued)*

Hamburg's update reinforces the Agency's belief that FDA's efforts are based in large part on the 2011 Institute of Medicine (IOM) report that examined how falsified and poor quality drugs affect the health of people around the world. The OIM report urges FDA to continue its collaboration with foreign counterparts in developing regulatory strategies to implement and control Good Manufacturing Practices globally.

The effort to crack down on counterfeit and substandard drugs isn't limited to regulators and government agencies. Recently, 29 of the world's largest Pharmaceutical companies and INTERPOL entered into a three-year agreement to create the INTERPOL Pharmaceutical Crime Program. The new Program, backed by EUR 4.5 million, builds on INTERPOL's Medical Product Counterfeiting and Pharmaceutical Crime unit. In addition to its focus on organized crime networks involved in Pharmaceutical crimes, the new program will work to prevent counterfeiting of branded and generic drugs.

While "counterfeiting" is often used to describe the production, illicit diversion and trafficking in fake drugs, Pharmaceutical companies know the risk of adulteration can infect their own product quality through the supply chain. The well-known Heparin tragedy highlights the safety risks to patients and the quality risks to manufacturers because of adulterated ingredients, even from trusted suppliers. Evidence indicates that global crime syndicates are playing a growing role in the production and distribution of counterfeit drugs, a problem estimated by the World Health Organization to infect some 10 percent of all medicines used globally.

The new partnership between INTERPOL and Pharmaceutical giants including Sanofi, Eli Lilly, GlaxoSmithKline and Amgen reflects the urgency of the problem. Plans for the program emphasize training, capacity building and targeted enforcement. For individual Pharmaceutical companies, the agreement reinforces the need for intensified quality assurance measures including training and testing. Equally important is the need to allocate sufficient resources – human, monetary and organizational – to increase surveillance and rapid response capabilities for substandard ingredients and excipients.

GMPS ARE A TOP AREA OF FOCUS FOR DOJ IN 2013

The US Department of Justice (DOJ) has a new "top area of focus" for 2013: Pharmaceutical current Good Manufacturing Practices (cGMPs). That was the word from Maame Ewusi-Mensah Frimpong, Deputy Assistant Attorney General for DOJ's Consumer Protection Branch (CPR) at the CBI Pharmaceutical Compliance Congress in January 2013.

CPR isn't one of the DOJ branches that automatically comes to mind when thinking about compliance, drug quality or GMPs. CPR has responsibility for the national consumer protection statutes of four federal agencies including the Federal Food, Drug and Cosmetic Act. CPR might not be the most recognizable of all DOJ divisions and branches, but it has been a central player in some of the Pharmaceutical industry's largest settlements, including last year's massive GlaxoSmithKline settlement agreement.

Misbranding will continue to be a priority for CBI but Frimpong added the adulteration of drugs as a top area of focus for the DOJ. "When companies fail to follow current good manufacturing practices," she said at the CBI Congress, "they often place patients at great risk of harm that neither they nor their doctors have any way of mitigating or even recognizing." She continued, "We will ... be taking an especially hard look whenever patients are placed at an unacceptably high risk of harm by ... violations of current good manufacturing practices."

Fortunately, Frimpong didn't stop her comments there but followed with a dollop of humor. "Now that you know that GMP will be one of our top areas of focus, many of you want to know the answer to a simple question: What is the DOJ looking for? How can I avoid ever having to deal with this woman or the US Attorneys on the panel after her?"

Central to her guidance was an emphasis on people. "In addition to focusing on plants and production lines and manuals and policies and testing and controls, I urge you to also focus on people. People are at the heart of what you do, and it is the

GMPS ARE A TOP AREA OF FOCUS FOR DOJ IN 2013 *(Continued)*

failures of people – often the combined failures of a number of people – which result in noncompliance." Here are some of the questions she offers for companies to ask:

1. **Do we have the right people?** "You need people with the right training and expertise to recognize problems that can arise when manufacturing pharmaceuticals."
2. **Do our people have the right incentives to see problems, to report problems and to fix problems?** "Internal communication – and systems to encourage that communication – are key."
3. **Are our people satisfied and engaged?** "We all know that having a reputation as being fair and honest can enhance employee morale and aid in recruiting and retaining the best and brightest employees, and this can be critical in maintaining a seamless and airtight culture of compliance."
4. **Are our people and policies working in harmony?** Put another way, do our policies acknowledge how real people work and what they are capable of? "Quality assurance processes that rely on unrealistic expectations are doomed to fail." Citing a past example, she explained, "... some of the safety problems resulted from relying on a policy of 100% visual inspection ... when visual inspection could not actually reveal problems given the speed of the production line."
5. **Do compliance officers personally have visibility into what our people are actually doing?** "...avoiding knowledge of problems in your organization will not shield you from liability." Frimpong noted that independent audits are one way to make sure that a company's systems are not masking any problems that exist.

Insights from the Field

Frimpong sounded an alarm for compliance officers in identifying GMPs as a top area of focus for 2013. Her recommendation to focus on people recognizes the role people play in compliance: they make or break the program. Our experience working with clients and colleagues throughout the pharmaceutical industry "add meat to the bones" of Frimpong's suggested questions.

1. **The goal of training is behavior change**, not filling in the boxes of hourly requirements.
2. **Effective training is learner-specific**, not only by targeting the content to the job function but also by testing proficiency in subject matter, immediately distributing remedial training when necessary, and tracking learner status to avoid unnecessary repetition that contributes to "training overload."
3. **Engaging the learner is not a feel-good feature**; engagement and interest are essential to effective learning. Scenario-based training and role-based training, for example, make lessons "real" instead of theoretical, encouraging a personal connection with the subject matter.
4. **Communication must be consistent, varied and real**. Simply repeating the company's mission statement will not resonate with most employees; using different communication techniques – mobile aps, newsletters, letters from the CEO, short videos, and recognition of employee contributions – will keep the message of compliance top of mind.
5. **GMPs are not simply "compliance requirements."** They are the first line of defense in ensuring that unsafe drugs do not move through the system and reach patients. Employees must be encouraged to take personal responsibility for quality and empowered to report actual or potential problems. Then, compliance departments have to follow through on those reports – quickly, thoroughly and seriously.

Knowing what DOJ wants and what our observations in the field have been is no guarantee that a company will never encounter a quality or GMP problem. But, as Frimpong noted, knowing what DOJ is looking for can help answer the question, "How can I avoid ever having to deal with this woman or the US Attorneys on the panel after her?"

FDA'S FINAL RULE FOR COMBINATION PRODUCTS

Life Science companies that manufacture combination products have until July 22, 2013 to comply with the Food and Drug Administration's (FDA) final rule on current Good Manufacturing Practices (cGMPs) for those products. The new rule (part of 21 CFR Part 4) clarifies several points that had plagued the industry, including those products and entities that are regulated under the new rule. The rule applies to manufacturers of combination products – and "manufacturing" is defined as an activity including repackaging, storing, testing and designing combination products.

What is a Combination Product?

The short version of FDA's definition for a combination product is a product comprising any combination of a device and a drug and/or a biological product. Combination products regulated under the new rule can be "single-entity" or "co-packaged." In addition, FDA specifically mentioned "convenience kits" in the preamble to the new rule, defining them as "... kits that solely include products that are; also legally marketed independently; and included in the kit as already packaged for independent marketing with the same labeling as for independent marketing."

Requirements For Compliance

The final rule is "largely identical to the proposed rule" that was released by the FDA in September 2009. Some important provisions of the final rule include:

1. A manufacturer of a single-entity or co-packaged drug/device combination product may comply with the cGMP or QSR requirements that apply to each constituent part.
2. A manufacturer of a single-entity or co-packaged drug/device combination product may comply with the requirements of one constituent part under conditions defined in the rule. A manufacturer may comply with either drug cGMPs or medical device QSRs, for example, but under the final rule it would also be required to comply with additional quality regulations included in the rule.
3. A manufacturer of a combination product that includes biological or human tissue components must comply with all cGMP and QSR requirements for each constituent part.
4. A manufacturer of a "convenience kit" has no cGMP requirements beyond those that apply to the assembly, packaging, labeling or sterilization of the kit. The final rule's new requirements do apply any of the kit's components is repackaged, relabeled or otherwise modified in order to be included in the kit.

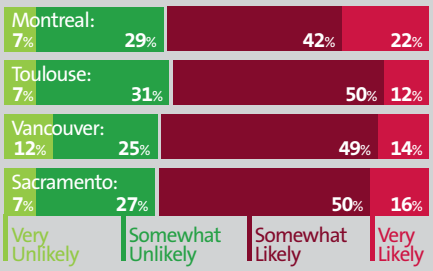
The final rule provides some guidance and clarification but it continues to pose some of the most challenging compliance issues that confront the Life Science industry. The FDA has promised to help with that by issuing guidance on the implementation of a streamlined, effective cGMP operating system for combination products. No date was given for that guidance, notwithstanding the July 22 effective date for the final rule.

DRUG SAFETY AND SALES

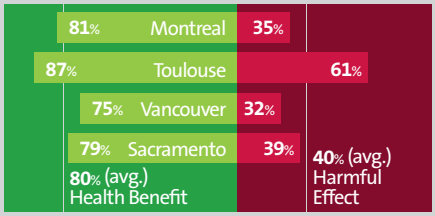
Product recalls, Good Manufacturing Practice (GMP) violations and counterfeit products have put drug safety squarely in the public eye. But a recent study points to an unexpected patient safety concern: Drug sales representatives were giving family physicians inadequate information about side effects of the drugs they promoted.

The study was conducted by a team of researchers from the University of British Columbia (UBC), the University of Montreal and York University in Canada; the University of California, Davis in the US; and the University of Toulouse in France. According to UBC's study, sales representatives failed to provide any information about common or serious side effects and the type of patients who should not use the medicine in 59 percent of the promotional visits with doctors. A release from the University noted, "Serious risks were mentioned in only six percent of the promotions, even though 57 percent of the medications involved in these visits came with US Food and Drug Administration 'black box' or Health Canada-boxed warnings – the strongest drug warning that can be issued by both countries."

While much attention has focused on the role of sales representatives in promoting drugs for purposes not approved by the FDA, there has been little scrutiny of the knowledge which prescribing physicians receive about the potential side effects posed by any individual drug. The recent study changes that, highlighting the potential risks to patients and drug manufacturers posed by inadequately-trained sales representatives.



In a UBC study, doctors surveyed shortly after a promotional visit by pharmaceutical sales representatives indicate they are likely to prescribe the medicine. The study also found that in the majority of these visits, doctors weren't informed of the harmful effects of the promoted medicines. (Source: UBC)



A new UBC study compares the amount of information about a medicine's health benefits and harmful effects given to a family physician during a visit from pharmaceutical sales representatives in Canada, the U.S. and France. (Source: UBC)

About UL Quality, Compliance and Learning

UL Quality, Compliance and Learning is a business line within UL Life & Health's Business Unit. UL is a global independent safety science company offering expertise across five key strategic businesses: Life & Health, Product Safety, Environment, Verification Services and Enterprise Services.

UL Quality, Compliance and Learning 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 Quality, Compliance and Learning 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.