Life & Health

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Drawing Lessons from FDA in 2012

The US Food and Drug Administration (FDA) ended 2012 with rising recalls, site inspections and 483s. Looking back at the record can provide insight into issues, trends and problems that have plagued the industry and are likely to be priorities for FDA going forward.

Product recalls have been rising, with 2011 setting records for contamination-related problems. Cross-contamination in particular has become an issue, not only for the FDA but also for the European Commission, which specifically addressed the issue of cross-contamination in the revised Good Manufacturing Processes (GMPs) issued in 2012. The most publicized recall of 2011 involved the possible cross-contamination of penicillin in products repackaged in Aidapak Services' Washington facility.

While product recalls fill headlines, FDA 483s and Warning Letters grab the attention of manufacturers. Although not all 483s are noted in FDA's enforcement report, the Agency issued 483s to 787 Pharmaceutical companies for the period between 10/1/2011 and 9/30/2012. Of the top ten reasons for 483s, written procedures and documentation stand out: procedures not in writing or fully followed, absence of written procedures, written

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procedures not established/followed and SOPs not followed/documented. Even that doesn't show the full scope of poor compliance with requirements to provide written procedures and carry through with thorough documentation. "Control procedures to monitor and validate performance" stands out in the top ten, with FDA's explanation noting that control procedures were not established which monitor the output or validate the performance of manufacturing processes. Similarly, "Calibration/inspection/checking are not done" is described this way: "Routine calibration, inspection, checking of automatic, mechanical, electronic equipment is not performed according to a written program ..." Even training (operations, GMPs, written procedures), which is listed as #8 on FDA's citation list, notes the absence of written procedures required by current Good Manufacturing Practices (cGMPs). Finally, SOPs not followed/documented shows the explanation of "Written production and process control procedures are not followed ... or documented at the time of performance."

Written procedures are fundamental to compliance not only because of the specific requirement that they be developed and available but because they can't be effectively executed by employees if they aren't current, accurate, understandable and relevant. Equally important, the procedures must be easily accessible to employees and FDA inspectors.

Documentation is another problem often cited by the FDA. Based on our surveys and conversations with companies in the industry, lack of accurate, up-to-date and compliant documentation is often related to technology as much as employee knowledge and quality department oversight. An industry-specific technology platform should support rapid access to written procedures, automatic distribution of required and remedial training, proficiency testing and documentation of training status, and validation according to Part 11 standards. Too frequently, Pharmaceutical companies lack a comprehensive technology infrastructure that supports those compliance requirements and enables compliance monitoring and operational oversight.

The trends demonstrated by the most recent year's list of 483s point to the likelihood that FDA will continue to focus its attention on written procedures and documentation. Companies working to ensure compliance and improve their own operations should audit their procedures for generating up-to-date SOPs and other written procedures, ensuring that employees are trained on those procedures and that proper documentation exists. Documentation has to be accessible to FDA inspectors but it should also be organized and accessible for the Quality Unit in order to ensure ongoing oversight and rapid response to potential issues.

THE EVOLUTION OF GLOBAL GMPS

In a world of transnational supply chains, determined counterfeiters, aggressive competition and increasingly complex production processes, maintaining consistent quality is a demanding proposition for any Pharmaceutical company. Good Manufacturing Practices form the foundation of product quality but a shifting global landscape of regulations, laws and enforcement strategies now affect not only a company's GMP compliance but also its market access, global competitiveness and reputation.

Regulators including the US Food and Drug Administration (FDA) have warned manufacturers of their ultimate responsibility for the quality of their products, regardless of the source of the product's ingredients. GMP compliance for the manufacture of finished pharmaceuticals is a fact of life for global Pharmaceutical companies. A new generation of regulations is changing that "fact of life" for manufacturers of finished pharmaceuticals and the companies that produce ingredients that go into those products.

Here's a look at some of the most important game-changers in the world of global GMP compliance.

ICH Q11

The US FDA has announced adoption of the Q11 guidance released by the International Conference on Harmonisation (ICH) in 2012. According to the FDA's notice in the Federal Register, the guidance – Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological Biological Entities) – is intended to apply only to the manufacture of drug notable changes in the Q11 guidance: the emphasis on purification processes in drug substance manufacture; revisions related to design space for chemical entities and biotechnological/biological drug substances; and the discussion of control strategy. ICH Q11 expands and clarifies the approach of earlier ICH guidelines Q8 (Guidelines on Pharmaceutical Development), Q9 (Quality Risk Management), and Q10 (Pharmaceutical Quality Systems).

EC'S GMP REVISIONS

The European Commission (EC) has revised four chapters of its GMP Guidelines. Among the most important revisions are those in Chapters 3 and 5. Chapter 3 centers on reducing cross-contamination in facilities that manufacture multiple product lines. The new Chapter urges companies to follow Quality Risk Management principles, noting specifically that risk assessment should include a toxicological evaluation of the products that are manufactured. Even then, some facilities will not be allowed to manufacture multiple product lines. Chapter 5 builds on Chapter 3, adding guidance about where products should (and shouldn't) be manufactured. Chapter 5 also addresses active pharmaceutical ingredients (APIs) and excipients, requiring that all suppliers and starting ingredients have to be qualified to ensure traceability throughout the supply chain. Manufacturing Authorization Holders (MAHs) are required to ensure that their suppliers meet GMP and Good Distribution Practices (GDPs) through audits of active substance manufacturers and distributors. The new GMPs are now open to public consultation until July 18, 2013.

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GMP/ICH Q10 ALIGNMENT

Chapter 1 of the European Union (EU) Guidelines for GMPs for Medicinal Products for Human and Veterinary has been amended to "... align with the concepts and terminology described in the ICH Q10 tripartite guideline on Pharmaceutical Quality System." The new Chapter 1, titled "Pharmaceutical Quality System," was set for implementation on January 31, 2013. Integration of the guidelines into legislation of member states is likely to take months or even years and is not guaranteed to be consistent across jurisdictions. Nevertheless, Pharmaceutical manufacturers are put on notice that a risk-based approach is central to an ICH-compliant quality system and Chapter 1 of the EU Quality System Guidelines.

EU FALSIFIED MEDICINAL PRODUCTS DIRECTIVE

Sometimes overshadowed by the Directive's well-publicized emphasis on preventing counterfeit drugs from reaching patients, the Falsified Medicinal Products Directive will have a significant impact on organizations including Pharmaceutical companies, API and excipient manufacturers, and Contract Manufacturing Organizations (CMOs). The directive requires any drug, active substance or excipient used in a final product that is sold within the EU to be manufactured according to GMPs. The Directive also imposes multiple recordkeeping, reporting and auditing requirements not only on the finished Pharmaceutical manufacturer but also by suppliers, importers and distributors.

CGMPS FOR COMBINATION PRODUCTS

The FDA has issued a final rule on cGMPs for combination products, which contain two or more products (pharmaceutical, biologic, medical device) designed to be used together. The final rule is intended to unify the standards previously used in the manufacture of medical products that have been regulated by different Centers in the FDA.

CHINA'S EXCIPIENT REGULATIONS

China's State Food and Drug Administration (SFDA) set a February 1, 2013 implementation date for new rules regulating the production and use of pharmaceutical excipients. The regulation places new requirements on Pharmaceutical manufacturers and suppliers of excipients, which will be divided into two categories based on risk. Notable provisions include the requirement that suppliers audit their own raw material suppliers and notify their customers of any changes that might affect excipient quality. The SFDA has given itself a very tight deadline for issuing the rule and list of excipients, but it is unlikely that the implementation schedule will remain as is.

Additional legislation and regulations are under consideration for development around the world. While the individual rules and regulatory agencies differ, two underlying factors fuel virtually all of them. First is recognition of the reality of modern drug manufacturing, which is reliant on a network of suppliers and in turn their suppliers, who have often operated in shadows, protected by brokers and agents pursuing low-cost alternative sources. Second is the growing risk of substandard and counterfeited drugs, APIs and excipients, whether driven by intention or inadequate controls. Manufacturers of finished pharmaceuticals are responsible for the quality of the supplies that go into their products but new regulatory actions are adding the responsibility for ensuring the GMP compliance of their suppliers.

About UL

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