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Supplier Quality – The New Frontier in Drug Manufacture

The globalization of the drug manufacturing industry has caused FDA to become increasingly concerned about supplier quality controls. By Morgan Lewis & Bockius partner Kathleen Sanzo.

FDA's Historical Approach to Supplier Quality

For many years, current Good Manufacturing Practices (cGMPs), recognized as broad and general, have provided the backbone of the regulatory structure around the manufacturing of drugs for US distribution. FDA relied on use of the term "current" as the basis for its expectation that industry would upgrade and modernize manufacturing techniques and controls as necessary. This worked relatively well for a number of decades in which the majority of drugs for the US market were made in North America or Europe, where regulatory authorities used similar paradigms for controlling manufacturing. In the last decade, however, the drug manufacturing business has changed significantly in ways that it has not been easy for FDA to manage. The building of Active Pharmaceutical Ingredients (API) manufacturing facilities in emerging markets by established pharma, followed by the complete outsourcing of API, excipients and packaging to third-party suppliers in emerging markets, has caused major strains on FDA resources, and caused sleepless nights among FDA regulators.

As a result of this expansion of global outsourcing of active ingredients and pharmaceutical excipients, FDA has become increasingly concerned about supplier quality. Recalls of products due to adulteration of actives and excipients with bacteriological contaminants such as mold and fungus and chemicals such as melamine further heightened the sense of urgency of the need for FDA to upgrade its regulatory requirements for supplier qualification and verification.

FDA began to signal there were gaps in supplier controls through a number of consent decrees and Warning Letters issued over the last several years. Since 2010, there have been five consent decrees issued to Ben Venue, Ranbaxy, Genzyme, McNeill, and Deltex that were based on cGMP deficiencies including in connection with materials issues at sites in the US and abroad. Warning Letters issued to a number of pharmaceutical companies between 2011 and 2013, contained references to multiple cGMP deficiencies, including failure to have controls to ensure that materials meet their relevant standards.[1] As a result, each of the Warning Letters to these companies requested that they conduct "comprehensive and global" assessments of their cGMPs compliance. The scope of this requirement clearly would include a review of the processes for managing sources for and testing of API and other raw materials as part of the companies' supply chain management.

Congress Strengthens Legal Authority for FDA Regulation of the Drug Supply Chain

Under Section 301 of the Federal Food, Drug, and Cosmetic Act ("FFDCA") 21 U.S.C. § 331, manufacturers are prohibited from introducing or causing the introduction of adulterated or misbranded drugs into US interstate commerce. A product is adulterated if it is not manufactured, processed, packed, or held pursuant to current cGMPs. See 21 U.S.C. 351(a)(2)(B). However, cGMP statutory provisions did not specifically mention suppliers. To address this gap, in 2012 Congress included a provision concerning supplier controls in the Food and Drug Administration Safety and Innovation Act (FDASIA). Part 711 of FDASIA amends the definition of cGMP in Section 501(a)(2)(B) of the Act specifically to include "the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacture of drugs, and finished drug products." See Pub. Law 112-144 (July 9, 2012). The term cGMP is now statutorily defined to require the oversight of raw materials used in drug products, thus requiring controls for the source of those products. FDA consequently now has a legal basis to require reliable and well-controlled processes relating to drug component suppliers and to take enforcement action for the failure to have these processes.

Where Do the cGMP Regulations Address Supplier Controls and Quality?

Notwithstanding the new legislation, the current cGMP regulations do not specifically identify "supplier quality" as an element of cGMP. Rather, cGMP regulations require that manufacturers have a quality control unit that has the responsibility and authority to approve or reject all components, containers, closures, in-process materials, packaging, labeling and drug product, as well as to approve or reject any product manufactured, processed, packaged, or held under contract by another party. 21 C.F.R.§ 211.22(a). Thus, manufacturers cannot outsource their responsibility to approve and release drug components and finished pharmaceuticals. In addition, the cGMP regulations require that manufacturers have adequate procedures and inspections/sampling controls to ensure the quality of raw materials. 21 C.F.R. § 211.80.

Recently, FDA issued a draft guidance on Quality Agreements for suppliers (May 2013)[2] which describes FDA's current thinking on defining and documenting the responsibilities of parties that are involved in the manufacture of a drug product. FDA

thus has issued a call to action. Both manufacturers and suppliers must now engage in a transparent way to enhance and better manage their relationships.

Legal Consequences of Absence of Supplier Controls

As noted above, the legal and regulatory consequences resulting from failure specifically to assure supplier quality can now be the basis for a cGMP violation during an inspection, resulting in an observation on a FDA Form 483 or more severe legal action if the violation results in adulterated or misbranded product. These consequences potentially include 1) issuance of an untitled or Warning Letter to the offending company, including refusal to approve any pending applications; 2) import alerts preventing the importation of potentially affected product; 3) recall or seizure of any affected product already in US distribution; 4) additional facility inspections, 5) imposition of a consent decree; and 6) civil and/or criminal prosecution and monetary fines of the company and/or individuals under the FFDCA and/or the False Claims Act (for selling adulterated or misbranded product to US healthcare programs), with resulting threat of personal or corporate exclusion from those programs. Other legal consequences can include class actions based on personal or economic injuries resulting from the adulterated product, and shareholder lawsuits. All such consequences would also likely receive significant negative media attention. Consequently, it is important for companies to implement and effectively manage a robust supplier quality process.

What Are the Elements of a Supplier Quality Program?

Based on FDA's new guidance, there are several essential elements of a well-managed supplier quality program.

Risk Evaluation of Suppliers and Services

FDA recommends that, before outsourcing a manufacturing activity, the owner should conduct a risk evaluation of both the extent of controls necessary for the particular activity and of the supplier. Factors that manufacturers should include in ranking the risk include the specific component being sourced (API, excipient, labels, inner versus outer packaging, laboratory testing), complexity of process and/or equipment, geographic location and regulatory oversight of the supplier's site, regulatory and quality history of the supplier, and the financial status of the supplier.

A Quality Agreement

FDA now requires that manufacturers have Quality Agreements with their suppliers. The Quality Agreement should be separate from the master services or other commercial agreement with the supplier and it should be written with active participation by the company's Quality Unit, i.e., not just the lawyers. Moreover, the Quality Agreement should have the following components:

- Comprehensive allocation of responsibilities of each party; note only the owner can approve final product release;
- Communication plan between the parties for oral and written communications;
- Routine and for-cause auditing rights;
- Facilities and equipment specifications, validation, and maintenance responsibilities;
- Materials management, including who will set specifications for raw materials, audit and qualify sub-suppliers, conduct sampling and testing, and inventory management (e.g., segregation, quarantine);
- Product-specific terms, including specifications, and operational requirements such as batch numbering, expiration dating, process validation, and technology transfer;
- Laboratory controls, including requirements for validating equipment and methods, sampling protocols and testing timelines, and investigating deviations and out-of-specification (OOS) results;
- Documentation and recordkeeping requirements, including as to electronic document systems and their validation; and
- Change control processes, including identification of changes requiring prior approval by the owner.

Other Relevant Standards for Supplier Qualification and Verification

In addition to its general cGMP regulation identified above, FDA issued in 2001 Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients,[3] the US version of the ICH Guideline on API manufacture.[4] The Materials Management section of the ICH Guideline states that "materials should be purchased against an agreed specification, from a supplier or suppliers approved by the quality units(s)," and that changing the source of supply of critical raw materials should be managed according to change control procedures.[5] These Guidelines are being updated in 2013 and 2014.[6] Recently, the European Union proposed to revise its cGMP Guidelines to require greater controls over and audits of suppliers of both active ingredients and excipients.[7] Moreover, several third-party organizations have issued more specific guidelines and programs on supply chain integrity and supplier qualification. These include the US Pharmacopeia (USP) Drug Substance Verification Program,[8] for active ingredients and similar industry guidelines for pharmaceutical excipients.[9] Industry has also organized a coalition of companies to share supplier audits.[10]

Considerations Relating to Enhanced Supplier Quality Programs

The regulatory expectation that relationships between Owners and suppliers will be more formalized, documented, and better managed will have significant commercial consequences that must be incorporated into the commercial relationships. These include:

- **Unreasonable Expectations.** Unequal bargaining power of the parties or uneven interest in the regulatory obligations—with the new expectation for additional formalization of the process—will cause some supplier companies to be tempted to offer more than they can reasonably provide, and some Owners to be tempted to ask suppliers for more than they can reasonably deliver in services and performance. Owners must therefore conduct adequate due diligence on the supplier to determine if it is actually capable of doing all it says it can do, or that Owners obligate it to do; and suppliers must be realistic in their strengths and capacities. Although it might be commercially advantageous for an Owner to strike a "hard deal" with the supplier, if the supplier fails, it will cause serious regulatory and financial consequences for the Owner.
- **Demands for Proprietary Information.** Owners will demand under the auspices of FDA's new guidance the need for significant information concerning suppli-

ers, and their quality systems and sources. Often this information is critical and proprietary to the supplier and not likely to be shared. The parties need to create mechanisms for the exchange of relevant information that protects both parties. Non-disclosure agreements, third party exchanges of information, i.e. through independent consultants or groups, password protected databases, use of Drug Master Files, or other mechanisms should be considered.

- **Timing.** In view of FDA's strong recommendation that Quality Agreements be separate from Master Service Agreements, and also be more detailed, the entire supply contract negotiation process will be extended. Additional time should be factored into the timeline for this part of the process, and establishment of a company policy precluding the interim or short-term use of any supplier that does not have a Quality Agreement should be considered.
- **Transparency about Filings.** Especially in partnerships involving new product filings or supplements, it is important to ensure that the supplier is kept up to date on filing developments and modifications so that there can be credible communications with FDA during pre-approval or other inspections and transfer of information into filings; failure to ensure all parties have the same information can cause misstatements to FDA and resulting data integrity concerns, failing inspections, and delayed or rejected approvals. Similar early information exchange is necessary by the supplier about changes it makes which may impact Owners' filings.
- **Use of Third-Party Auditors to Qualify Suppliers.** The parties must agree on whether, and the extent to which, they will rely on third party auditors, and who the auditors will represent. Suppliers often offer to Owners audits done by a third party paid for by the Supplier. This obviously raises potential conflicts of interest, and can result in significant gaps. For example, the significant peanut recall in the US that has now resulted in criminal action against the peanut supplier involved the reliance by many customers on GMP audit reports conducted by third-party auditors hired by the supplier.
- **Alternative Suppliers.** Many Owners have not made adequate preparations for alternative suppliers if there is a serious GMP deficiencies with a supplier. This can result in continued use of a supplier notwithstanding serious issues, or potential disruption of the business. Therefore, qualifying alternative suppliers or having redundancy is necessary for critical suppliers.
- **Diligence.** Both Owners and suppliers must be willing to dig deep into their sub-suppliers, and ask hard questions about history, experience, and performance, and demand documented evidence of quality operations.

Conclusion

Supplier quality is the new frontier. Supplier quality issues should be front and center for review and enhancement in all compliance and quality plans to avoid serious regulatory enforcement actions and business disruption, in 2013 and beyond.

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1 See letters to Joseph Jimenez, Novartis International AG, Basel, Switzerland, from FDA, CDER, dated Nov. 18, 2011, available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm281843.htm; Dr. Karl-Ludwig Kley, Merck KGaA, Darmstadt, Germany from FDA, CDER, dated December 15, 2011, available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2011/ucm291672.htm; Oliver Charmeil, Sanofi, Paris, France, from FDA, CBER, dated July 12, 2012; available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm312929.htm; and Dr. Gerhard Gigl, Boehringer-Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany, from FDA, CDER, dated May 6, 2013 available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm352325.htm.

2 See Draft Guidance for Industry, "Contract Manufacturing Arrangements for Drugs: Quality Agreements," Food and Drug Administration (May 2013) available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM353925.pdf.

3 See Food and Drug Administration, Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129098.pdf.

4 See ICH Harmonized Tripartite Guidelines, Good Manufacturing Guidelines for Active Pharmaceutical Ingredients Q7 (2000), available at http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html.

5 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Chapter 5 (Production), sections 26-28 (Jan. 2012). ("Changes were also introduced in sections 26 to 28 on the qualification of suppliers in order to reflect the legal obligation of manufacturing authorization holders to ensure that active substances are produced in accordance with GMP. The changes include supply chain traceability").

6 See ICH concept paper on updating QA7 document available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q7/Q7_IWG_Concept_Paper.pdf

7 See Request for public consultation on Rule Governing Medicinal Products in the European Union, Good Manufacturing Practice, chapter 5, Production, dated 17/01/2013 available at http://ec.europa.eu/health/human-use/quality/developements/index_en.htm.

8 See United States Pharmacopeia, Drug Substance Verification Program (2007) available at http://www.usp.org/sites/default/files/usp_pdf/EN/support/pivpparticipantmanual.pdf.

9 See International Pharmaceutical Excipient Council (IPEC) of Europe and America, Good Manufacturing Guide for Pharmaceutical Excipients (2006).

10 See Rx- 360 Consortium, an International Supply Chain consortium at www.Rx-360.org.