Addressing Supplier Purchasing Controls

How to establish clear guidelines, and stay out of trouble.

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MANUFACTURERS BEAR responsibility for every step of their global supply chain, FDA Commissioner Margaret Hamburg has stated recently; and the Agency is taking strict enforcement action. In 2009, 12% of 483 Observations and 16 Warning Letters were issued citing inadequate supplier qualification [1]. The following reflects the perspectives of compliance consultants, a supplier and finished goods manufacturer (FGM) on how best to address supplier purchase control issues. (*Note:* A longer, more detailed article is available on Pharma-Manufacturing.com.) While two of our co-authors hail from the device industry, their insights apply equally to pharmaceutical FGMs and their suppliers.

REGULATIONS AND GUIDANCE DOCUMENTS

Manufacturers are wise to remember that the purpose of assessing the capability of suppliers is to ensure that supplier components meet FGM GMP requirements. FGMs need to provide a greater degree of assurance beyond that provided by receiving inspection and test. An appropriate component supplier and services quality assurance (QA) program should include a combination of assessment techniques.

One such technique and regulatory enforcement trend is supplier process validation. FGMs need to ensure that validation processes employed by their suppliers not only meet the supplier's own processes, but meet the validation processes requirements of the FGM as part of either: a) the qualification of the supplier by the FGM, and/or b) through the review of validation protocols conducted by the supplier for the manufacturer. This would include all aspects of the validation process, including process output performance levels, statistical requirements, review/resolution of deviations, etc.

The expectation of an Active Pharmaceutical Ingredient supplier is defined in ICH Q7A, and closely mirrors the same GMP regulations applied for FGMs—i.e., CFR 21 Part 211. Additionally, the requirements for API supplier validation are comprehensive, from equipment and facilities qualification, to analytical test methods, cleaning, and process validation.

The "gray" area is that the application of the guidance and cGMP requirements depends on the type of manufacturing, (e.g., chemical vs. API derived from animal or plant sources vs. biotechnology), cell culture and degree of manufacturing, (e.g., cutting, mixing, and/or initial processing vs. isolation and purification), where more complex and final processing of material has a higher degree of applicability.

The QS approach also calls for periodic auditing of suppliers based on risk assessment. According to the FDA's "Guidance for Industry Quality Systems Approach to Pharmaceutical cGMP Regulations," the audit should include an examination of the supplier's quality system to ensure that reliability is maintained and quality is built-in throughout its component manufacturing. Although this is only a guidance, it is up to the FGM to provide rationale, through a risk assessment, as to why such an approach was not used; or risk being cited for inadequate establishment of the reliability of the supplier's analyses (§ 211.84 d(2)).

In addition, the guidance recommends that changes to materials (e.g., specification, supplier, or materials handling) be implemented through a change control system with certain changes requiring review and approval by the Quality Unit per § 211.100(a). It is also important to have a system in place to respond to changes in materials from suppliers so that necessary adjustments to the FGM's process can be made and validated if appropriate; helping to avoid unintended consequences.

OUTSOURCING NEWS AND NOTES

Albany Molecular Research Inc. (Albany, N.Y.) has won the first **Pfizer** Route Design Innovation Award for innovative ideas for process chemistry and large scale production of API's.

Merck will team up with **Sinopharm** to market vaccines in China. Also, Merck will reacquire the Riverside, Penn. API facility it had sold to **PRWT** and **Cherokee Pharmaceuticals** in 2008.

Aesica (Newcastle upon Tyne, U.K.) will invest some £3 million in a new high-containment facility at its Queenborough site.

Roche has partnered with **Aileron Therapeutics** (Cambridge, Mass.) on drugs for inflammation and metabolic ailments.

Charles River Labs (Wilmington, Mass.) withdrew its $1.6 billion bid for **WuXi PharmaTech** after investors opposed the deal as "highly speculative."

SCM Pharma (Northumberland, U.K.) is adding sterility and bacterial endotoxin testing to its offerings.

Aspen Pharmacare (La Lucia Ridge, South Africa) is purchasing the drug-manufacturing division of **Sigma Pharmaceuticals**.

THEORETICAL APPLICATION

Current enforcement trends indicate that the minimum quality systems for all suppliers should include:

- Change Control (Design and Process)
- Process Control, including Process Validation where the product quality attributes, including stability, cannot be fully verified
- Supplier QA, for critical raw material suppliers

Other aspects of FGMs' quality assurance may also apply—e.g., Complaint Handling, Statistical Requirements. Ultimately, manufacturers must view all suppliers as if they were part of their in-house production.

PRAGMATIC REALISM

Manufacturers must identify high-risk component suppliers through a documented risk management process. Methodologies such as component category risk grid can be used to prioritize remediation based on degree of customization and impact to function and safety. With FDA's focus on purchasing controls, the following is clear:

- FDA expects FGMs to conduct remediation, or face regulatory action.
- Where remediation is required, utilize risk management to prioritize, but not eliminate, work.
- Develop a detailed Supply Quality Agreement documenting the FGM's quality system requirements and a supplier's areas of responsibility.
- Suppliers should not necessarily wait for direction from their FGM customers in this area.
- Collaboration between manufacturers and suppliers is critical to success; ideally, costs should be shared.

The effort required to come into full compliance can be significant depending upon the number of products a manufacturer has on the market, the complexity of outsourced processes, and the depth of the supply chain. The time to act is now. Manufacturers and suppliers who do can avoid regulatory action, improve business outcomes and, most important, decrease patient safety issues.

References

1. Avellanet, John. FDA Drug Enforcement: An Analysis of Warning Letter Trends. FDANews, March 2010.