# A REGULATORY EMPHASIS ON SUPPLIER COMPLIANCE

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The recent heparin contamination investigations have cast a spotlight on suppliers to the Pharmaceutical industry. As a result, the FDA is increasingly vigilant in inspecting overseas manufacturing facilities and in enforcing the manufacturers' responsibilities to ensure their supplier's compliance.

In April 2008, FDA issued a warning letter to an Active Pharmaceutical Ingredient (API) manufacturing facility in China. The firm had failed to have adequate systems for evaluating the suppliers of its crude materials and the crude materials themselves. This firm did not ensure that these materials are acceptable before use and the warning letter indicated that the firm had received materials from an unacceptable supplier and the materials were used in their API manufacturing process. Subsequently, the firm has acknowledged that there were inadequacies in its supplier qualification efforts. Although an audit was previously performed on the crude material supplier who was designated as "unacceptable", no corrective actions were taken with the crude supplier with respect to the processed material. However, the firm accepted and subsequently used crude materials from the supplier. The firm had also failed to establish appropriate specifications for the incoming crude materials.

Under the CGMP at CFR Part 211.84, the regulation permits a manufacturer to release a shipment of raw material and/or packaging material based on the supplier's certificate of analysis and a visual identification of the material or component. In order to accept a shipment based on the certificate of analysis, the past quality history of the supplier is key information for receiving APIs, excipients and components. The reliability of a supplier needs to be established through appropriate validation of the supplier's test results at appropriate intervals. An established supplier qualification program would provide adequate evidence that the supplier can consistently provide reliable and safe materials. Suppliers should be monitored and regularly scrutinized to assure ongoing reliability. It is the manufacturer's responsibility to ensure that their suppliers are suitable and qualified.

In order to be proactive, drug manufacturers must have a compliant supplier audit program. The program should be based on the quality systems approach as explained on FDA's Guidance for Industry issued in September 2006. A Quality System approach is one of the most important GxP requirements. The quality systems of a supplier will change as the manufacturer grows and as the company's products, operations and employees change. Thus, an effective supplier audit program is an ongoing monitoring program.

## SUPPLIER AUDIT REQUIREMENTS

The scope of the supplier audit program should include the suppliers for API, excipients, packaging materials, software for GxP systems, calibration laboratories and contractors.

A written supplier audit procedure should be in place. The details of the audit procedures will vary depending on the manufacturer size and nature of the manufacturing operations.

A supplier audit program should include, but not limited to the following:

Audit Objective – to ensure the quality systems of the suppliers will provide products that meet the safety, identity, strength, quality and purity of their products;
Audit Scope – includes all functions that impact the products or services;
Audit Schedules
Assignment of responsibilities
Evaluation of criteria
Management Review of results
Corrective action policies, schedules and due dates monitoring
As products and processes become increasingly complex, evidence from supplier audits and testing of incoming materials may no longer be sufficient to provide full assurance that the suppliers'

operations will consistently produce quality products/services. During supplier audits, a full quality system audit is required to ensure that the established quality systems are adequate for producing quality products and services. The quality system approach inspects if there are any company-wide problems, and will ensure that the product quality will consistently meet the specifications and expectations.

## AUDIT SCHEDULE

Manufacturers are responsible for deciding the frequency of supplier audits. The frequency should depend upon previous audit findings and the quality trends of products received from the supplier. If an audit reveals no problems, then audit intervals could be lengthened. If problems are identified, audits may need to be conducted more often. For a new supplier with many audit findings, a minimum of an annual audit is required. For an established supplier with good quality history, a biennial schedule is common for the pharmaceutical industry. For a supplier with excellent quality trends and good quality systems, a triennial audit is acceptable by most regulatory agencies.

## AUDIT PLANNING

The effectiveness of an audit begins with the planning. The manufacturer should start by defining the purpose and scope of their audits. The lead auditor and the audit team should be identified early in the planning process, and the members of this team should possess the skills and knowledge of quality system principles. Preparing an audit checklist will enable the team to properly cover the audit requirements, while review of previous audits and their responses will enable the audit team to evaluate their audit plans and scope. The background preparation should also include the review of the supplier's company policies, procedures and the full range of products, including those products that are not purchased by the manufacturer. The audit team should notify the suppliers before the audit. Furthermore, the audit team should hold a pre-audit conference to clarify exactly what the audit will include and what the objective(s) of their audit will be.

## AUDITORS

Manufacturers can have their own experienced auditors perform audits of their suppliers. This function can also be outsourced to a consultant, corporate or other independent auditor.

Individuals(s) responsible for conducting audits should be sufficiently trained. They should have the experience to detect variations and problems in the quality system. An auditor is expected to objectively see the overall quality approach, company culture and any systemic problems. For a manufacturing site, the auditing team should have a working knowledge in the product development and validation aspects, the manufacturing processes and process controls, the change controls, the applicable quality assurance principles, and the human relations aspect of auditing.

## COMMUNICATIONS

An experience auditor should ask questions clearly and listen actively during the audits. The lead auditor should present the audit findings opening and honestly. Any finding should be based on facts and support by rationale or regulations.

The supplier audit requires a written audit report, and auditors must have sufficient writing skills to effectively communicate findings and recommendations.

## AUDIT CRITERIA

When designing audit criteria, GMP requirements should be used as a baseline for the evaluation. Since the quality system regulation is broad, each manufacturer shall tailor the criteria to the manufacturing operations of their suppliers. Small manufacturers may need only minimal documentation. This may consist of an audit checklist with appropriate ancillary instructions to assure that all aspects of the quality system are covered.

An audit checklist may be a series of questions, phrases, trigger words, or any combination of these that will prompt auditors to cover the entire quality system. Checklist should cover requirements of the quality system applicable to the supplier's products, services, operations, and other areas of total quality system. Experienced auditors may not want to follow an audit checklist, but rather may follow the quality system or product/process flows during their audits.

## AUDIT RESULTS

A supplier audit program with sufficient depth can detect undesirable variations and trends in operating procedures. Management, upon becoming aware of these quality variations, should make decisions on using materials from unqualified suppliers. Manufacturers can also work with suppliers to correct and prevent unsafe, unreliable and inconsistent product or services from getting to the market. Audit results should be provided to the supplier management for their resources allocation for corrective actions.

Copies of the current audit reports should be maintained by the manufacturer. FDA has authority to review and copy all records required by the regulations.

Consequently, manufacturers must ensure that supplier audits have been conducted and the results documented.

Regulatory agencies are raising the compliance bar on supplier audits. Manufacturers should implement a rigorous and proactive supplier audit program, along with proper documentation. This will ensure product quality, patient safety and reduce citations from regulatory agencies. No company wants its products to be on the news and on the GxP history like the heparin case - neither as a negative example in a case study, nor causing any harm to consumers.

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