Life & Health

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QUALITY, CONTRACTS AND THE FDA

The US Food and Drug Administration (FDA)'s overriding message to drug manufacturers over the past several years has been both consistent and unbending: you are ultimately responsible for the quality of your products. Regardless of the number or location of your suppliers, contracted manufacturers or distributors, you cannot outsource that ultimate responsibility. Ironically, the FDA faces a similar message from US law and the US Congress: you are responsible for the safety of patients who use drugs sold in the US.

The FDA has made no secret of the challenge it faces. More than 40% of the finished drugs sold in the US are made overseas; more than 80% of the APIs going into those drugs are made overseas; and, despite an increased focus on foreign facilities and escalating pressure from the US Congress, the FDA has inspected fewer than 15% of foreign Drug Manufacturing plants for compliance with Good Manufacturing Practices (GMPs). Even with the inspection collaboration of the FDA's counterparts around the world, the ability of regulators to police the exploding Drug Manufacturing industry is limited.

QUALITY, CONTRACTS AND THE FDA *(Continued)*

Acknowledging the complexity and size of the global drug industry and its own inspection limitations, the FDA continually emphasizes the accountability of the industry for ensuring GMP compliance and product safety. In May 2013, a particularly bright light focused on the relationship between drug companies and their contract manufacturing partners with the publication of the FDA's draft guidance, "Contract Manufacturing Arrangements for Drugs: Quality Agreements." The guidance describes the FDA's thinking on "... defining, establishing and documenting the responsibilities of each party (or all parties) involved in the contract manufacturing of drugs subject to current Good Manufacturing Practice (cGMP)." The FDA describes how Quality Agreements can be used to define those responsibilities:

- "This guidance applies to the commercial manufacturing of Active Pharmaceutical Ingredients (APIs or drug substances, or their intermediaries), finished drug products, combination products and biological drug products."
- "...the term 'manufacturing' includes processing, packing, holding, labeling operations, testing and operations of the Quality Unit."

The FDA defines the organization that "... introduces (or causes the introduction) of a drug into interstate commerce..." as the "Owner" of the drug while outside entities performing manufacturing operations for the product Owner are identified as Contracted Facilities. From that starting point, "FDA believes that implementing a written Quality Agreement facilitates compliance with §211.22(d). Therefore, FDA recommends that owners and Contracted Facilities establish a written Quality Agreement ..."

The Quality Agreement

The purpose of the recommended written Quality Agreement is to describe the roles and responsibilities of the Owner and the Contracted Facility. FDA recommends that the Quality Agreement be separate (or at least severable) from commercial contracts such as Master Services Agreements or Supply Agreements. In fact, the FDA specifically notes that Quality Agreements are not commercial or business agreements, noting that while it does not routinely request or review business documents or business agreements on inspections, the FDA does routinely request and review evidence – or the absence – of Quality Agreements.

A well-crafted Quality Agreement, according to the FDA, uses clear language to define key quality roles and responsibilities, establish communication expectations, provide key points of contact for both parties, specify what products and/or services the Contracted Facility will provide, and establish who has final approval of various activities. Basic sections of most Quality Agreements include the purpose/scope, terms (including effective date and termination clause), dispute resolution, responsibilities (including communication mechanisms and contacts) and change control and revisions. Among the recommended provisions of the Quality Agreement are two of particular note.

The first centers on inspections and audits. Quality Agreements should provide for Owners to evaluate and audit Contracted

QUALITY, CONTRACTS AND THE FDA *(Continued)*

Facilities to ensure cGMP compliance. Specifically, this provision of the Agreement should cover both routine quality audits conducted on a regular basis and for-cause audits. Quality Agreements should address regulatory inspections and the parties' respective obligations for reporting inspectional observations and findings. Of Particular interest, FDA writes, "Because Contracted Facilities often simultaneously or sequentially provide services to multiple product Owners, special consideration should be given to reporting information about objectionable conditions observed during inspections and audits of the Contracted Facility" regardless of which products were covered on inspection.

Another notable condition focuses on change control including subcontractors. Compliance and quality officers know all too well the risks posed by "invisible" suppliers or subcontractors. The FDA Quality Agreement states that the Contracted Facility should notify the Owner of changes including raw materials and starting materials and their suppliers; establishment locations; manufacturing processes; additional products brought into the line, train or facility; testing procedures; major manufacturing equipment; shipping methods; lot numbering schemes; container closure systems; tamper evidence features; key personnel and product discontinuation.

FDA's Guidance provides several "hypothetical scenarios" that highlight common problems in contract manufacturing arrangements. Although unnamed, the scenarios bear strong resemblance to recent, real-life situations. The four scenarios are short, pointed and worth reading for insight into the problems in Owner/Contract relationships and the risks that may face Owners because of the actions of Contractors. A good contract manufacturing agreement can help manage those risks but effective risk management starts before any agreement is considered with a good risk assessment, not only of your potential partner but of your own operations. In the end, the old admonition still applies: Choose your partners carefully.

DRUG SAFETY AND API REGULATIONS

The global concern about counterfeit and substandard drugs has focused attention on the quality of Active Pharmaceutical Ingredients (APIs), fueling a flurry of international regulations that affect API, excipient and finished pharmaceutical manufacturers.

The European Union set the new regulatory framework in 2011 with enactment of the Falsified Medicines Directive, which began rolll-out by member states in 2013. Among the four core elements of the Directive is regulating pharmaceutical APIs and excipients entering the European Union (EU). The goal is to ensure product quality and patient safety by preventing falsified medicines from entering the legitimate supply of drugs sold in the EU. The EU's strategy for achieving that goal requires (as of July 1, 2013) that all APIs imported into the EU carry written confirmation from regulators in the exporting country that the product was manufactured under GMP standards equivalent with those in the EU. The confirmation applies to both API and the manufacturing plant that produced it. Countries that meet the benchmark of equivalent GMP standards are exempt from issuing written confirmations.

Many observers assumed that the US would get an automatic exception from the written requirements.

DRUG SAFETY AND API REGULATIONS *(Continued)*

Wrong assumption. The US's formal request to be listed as an exempt country because of equivalent GMPs was filed in January 2013 and granted on June 21, 2013. As of that date, the US joined just three other non-EU countries – Australia, Japan and Switzerland – exempt from the written confirmation requirement.

For API manufacturers exporting products to the EU, the Falsified Medicines Act is just the starting point for an emerging set of new regulations, risks and challenges. Here are a few recent developments:

- **Canada:** In 2013, Canada amended its food and drug regulations, extending requirements for Good Manufacturing Practices (GMPs) to Active Ingredients (AIs) used in pharmaceutical drugs. The amendments go into effect in autumn 2013. Canada's definition of an AI, according to a press release issued by Health Canada on May 8, 2013, is "An AI is the ingredient or combination of ingredients in a drug that delivers a health benefit to a patient. An example of a common AI is acetaminophen, which is used as a pain reliever." The amendments, which include a new record-keeping requirement designed to improve traceability of active ingredients through the system, will apply to all AI manufacturers, packagers, labelers and importers.
- **Mexico:** In 2013, Mexico updated its GMP requirements for APIs, with the intent of bringing them in line with the API requirements under the EU's Falsified Medicines Act. As of mid-July, Mexico had not yet been included on the EU's list of nations exempt from written confirmation requirements.
- **India:** In June 2013, India submitted written confirmation to the EU for API manufacturers that complied with GMP regulations required by the Falsified Medicines Act. According to an article posted on In-Pharma Technologist, the number of approved manufacturers was less than anticipated. The report cites European Medicines Agency International (EMA) cooperation head Emer Cooke, who claimed India's decision to limit the number of written confirmations was proof that the new API system worked to improve quality assurances for APIs imported to the EU.

The EU's API import regulations stand out as the most important and far-reaching of the new GMP rules. Even more significant, they set a trend of regulatory tightening over concerns about product quality.

WHAT INSPECTORS EXPECT

What do regulatory inspectors want? What do they expect? The answers are as different as the regulations and regulatory agencies themselves, but the European Medicines Agency (EMA) has clarified what its inspectors expect in the audit reports from API manufacturers or suppliers inside the EU.

EMA's answer is contained in its updated Questions & Answers on GMPs (#9). After introducing the structure of the audit – address of the site, full name of auditor, sponsor of the audit and similar conditions – the section focuses on the audit's scope. "The scope of the audit should be clearly stated e.g. what activities (against European Union GMP part II/International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH Q7 chapters) were covered."

From there, the guidance drills into particulars:

"Audits should identify the high risk areas for audit specific to the site or products being audited. For example, these could include but not be limited to:

- Process, cleaning or validation;
- Risk of cross-contamination with other active substances or other substances;
- Potential for generation of unknown impurities;
- Risk of mix-up of materials and products through materials handling or packing;
- Change control;
- Deviation recording or management;
- Security sealing of active substance containers and security or temperature control of shipments."

A list of all active substances included in the audit scope, plus other active substances or intermediates (or other products) manufactured at the site should be maintained. Beyond these elements, the audit should include information about previous audits, key findings, responses to the audit, corrective and preventive action taken for any noted deficiency, and any proposed reassessment period. The final report should be signed and dated by, at least, the lead auditor.

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