Compliance Newsletter

IDS Scheer Consulting – Pharmaceuticals & Life Sciences

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Foreign API Suppliers Face Increasing Oversight

In a global market, most API (active pharmaceutical ingredient) suppliers are foreign to at least one region. Besides the rising expectation, (see previous issue), that their pharmaceutical customers should regularly audit them for GMPs, they also should expect more frequent inspections from the regulators. The associated costs for complying with these inspections and audits are certainly on the rise.

Recently, a New York Times scoop revealed a pending agreement between the FDA and generic drug manufacturers, in which the manufacturers will fund via annual fees an inspection program of foreign suppliers. The FDA has been inhibited in the past by a lack of resources in conducting foreign inspections, (see past 11/2010 issue). Now, with foreign partners and offices already established, and a funding mechanism planned, the goal of inspecting foreign entities every 2 years may be achievable. The agreement is limited to foreign APIs and suppliers for generic drugs intended for the US market. Specifically outside of scope are non-prescription, (OTC), drugs and ingredients, probably because of the reduced risk.

The FDA, the EMA, and the TGA (Australian agency) just recently completed their pilot program for coordinated inspections of foreign API manufacturers. Based upon the final report from the EMA, there is the promise for greater coordination between regulators regarding inspections. This could hopefully lead to fewer inspections for a particular site, but the impact of such inspections could be global.

How this inspectional intensification fits with the EU expectation that pharmaceutical manufacturers should audit their API suppliers is unclear. Can a successful inspection be sufficient evidence for a favourable supplier audit report? Most likely.

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New Regulatory Guidances for GDPs

The EU has updated its Good Distribution Practice Guide (GDP) to meet its goal of combating counterfeiting (see previous newsletter). GDP applies to all wholesalers and distributing manufacturers operating in the EU. It hammers them with the full Quality Management System (QMS) approach, including CAPA, change management, management reviews, and QRM methodologies. A "Responsible Person" analogous to a manufacturer's Qualified Person is to be named and made responsible for ensuring that QMS is implemented and maintained. Computerised systems must be qualified and documented, but the term validation is not mentioned.

There are very specific operational requirements in this guide, such as the need for temperature mapping of storage areas, which certainly adds to the compliance work (and does nothing against counterfeiting). Also noteworthy is the new requirement FEFO (first expired, first out) regarding picking. After final revision, the new GDP is intended to come into force in 2012.

Although the EU does not intend to publish its own GMPs and GDPs for **excipients** at this time, drug manufacturers are expected to define requirements as needed. Industrial groups have jumped to the occasion with suggested draft guidelines to consider. Particularly, the Excipact™ certification scheme has formulated GMPs and GDPs for excipients.

GAMP Interpretation of the Impact of the New Annex 11

Recently the ISPE GAMP issued to its members an interpretation of the impact expected from the recently revised EU GMP Guideline for Computerized Systems (Annex 11). I reviewed the revision in the past Feb. issue and expected some impact. However, "The GAMP CoP believes that there is nothing in the revised Annex 11 - if interpreted in a pragmatic and reasonable way - that should cause major concern or problems to any regulated company that was complying with the previous Annex 11, and generally following good practice as defined in GAMP 5 and associated key Good Practice Guides." Is that reassuring? Furthermore, regarding audit trails, "Routine review of all audit trail content is not required, and is not consistent with a risk-based approach. The cost and effort is not justified by any likely benefit." Now, if your inspector makes the same interpretations, you may have nothing new to consider. Good Luck.

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Warning Letters and Enforcement Actions of Interest

As a follow-up to the WL issued to Dr. Reddy's Laboratories, as reported in the last issue, the FDA has placed an import ban on Dr. Reddy's but only to one site. I have seen this situation before with India's Ranbaxy. Serious local quality problems are not visibly escalated to global issues by the FDA for global firms, although their global oversight has clearly failed. Maybe heads do roll, but quietly.

The FDA just published a report, which summarizes WLs issued to medical device manufacturers over the period from 2003 until 2010. There is no noticeable trend in the numbers of WLs issued. Problems with CAPA and complaint handling clearly dominate the list of observations found in 2010, which I have also noted in previous years.

The WL to GYN Disposables, a medical device manufacturer, highlights responsibilities when a contract manufacturer is relied upon. The contract manufacturer sterilizes the products and performs the final acceptance and release activities. That can be delegated, but not the oversight. GYN Disposables was not able to provide validation documentation for the sterilization process, and is thus not in a position to confirm to the authorities that the process is validated. GYN Disposables tried the following corrective measures, all inadequate for oversight:

> "You updated the Certificate of Compliance to include requirements for documenting sterility status (pass/fail) and method (b)(4). This certificate alone is insufficient to determine the validity of the sterilization process. You intended to incorporate the monitoring/process parameter requirements in the Supplier Evaluation procedure (SOP 7.4.1). The Evaluation Procedure (SOP 7.4.1) lacks instructions for how the sterilization process will be monitored and what parameters will be controlled. You also intended to conduct an annual audit no later than August 2011, to cover detail reviews of the process data, sterilization and packaging validation activities, and monitoring. However, you have not established a procedure to conduct this audit."

Beckman Coulter, a manufacturer of lab instruments, also provides diagnostic devices, and was caught with faulty design controls, (21CFR 820.30). For example, verification studies performed after validation and risk mitigation strategies which are not completed are not really helpful for demonstrating control of the design. This is another example of extensive procedures without the resources to fulfil them.

The recent WLs to Chinese drug manufacturers highlight the FDA's concerns with foreign manufacturers in countries without an established regulatory environment. Lack of laboratory records, quality control of raw materials, and complaint handling practices at both Nanjing Maohai Biotech and Zhejiang Casing Animal By-Products were cited. Especially alarming to the inspectors, (after previous Chinese scandals), is the lack of quality control for raw materials at Zhejiang. The certificate of analyses are simply accepted without prior evaluation of the supplier nor identity testing of the goods receipts.

Germany's B. Braun Melsungen received a WL for its medical device operations in Brazil. Problems were found with procedures for handling non-conforming product and complaints. Especially irritating was the removal of documentation of non-conforming product, once the product was discarded and without initiating any investigation into the non-conformities. That looks like hiding quality defects from the FDA. Braun also got into trouble with interpretation of the complex rules for MDR reporting.

You might find the WL to Seattle Sperm Bank amusing regarding the rejection criteria for donors. Donor screening in the world of biologicals is a strict GMP requirement. The FDA expects residency in Europe to trigger a donor rejection, especially if the donor has resided in England, (risk of mad cow disease).

Sincerely Yours

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