Compliance Newsletter

IDS Scheer Consulting – Pharmaceuticals & Life Sciences

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EU Takes Lead on Combating Counterfeiting

Back in 2005 I reported in newsletters how the FDA and the EU were attempting to combat counterfeiting. At the time, RFID technology was actively considered for tracking and tracing drugs through the supply chain, but was resisted by distributors. The RFID technical solution was never fully mandated, and the supply chain has remained vulnerable to the growing counterfeiting problem. In 2009 the FDA proposed unique identifiers to be included on packaging or introduced as trace chemicals in the product, but again issued no specific requirements. Now the EU has started a new initiative addressing counterfeiting via a major revision of the EC Directive for regulation of medicinal products. The member states have 18 months to implement the concepts into national laws. The ECA's review of the legislation is worth reading. Here is a link to the revision of Directive 2001/83/EC.

In the legislation, you will not find a requirement for a specific technical solution, such as RFID tagging. The description of the mandated "safety features" indicates that a unique identifier, printed on the packaging would be suitable.

The major emphasis of this legislation is to force registration of all members of the supply chain. Members are required to verify that its business partners are also registered, and to actively verify the authenticity and quality of not only the drug products, but active ingredients and even excipients (Article 46) which it handles. The Directive calls for manufacturers and wholesalers to adhere to "Good Distribution Practices" and promises to issue guidelines on this subject. APIs seem to be the main focus of the new "GDPs".

Manufacturers are now required (Article 8) to provide upon demand, "written confirmation that the manufacturer of the medicinal product has verified compliance of the

manufacturer of the active substance with principles and guidelines of good manufacturing practice by conducting **audits**..."

Finally, there is to be a mandatory registration of on-line pharmacies in the EU. Each member state is to maintain a listing of registered pharmacies, and the pharmacy websites are to be outfitted with a special EU logo and contact information to the regulatory bodies, (Title VIIa), (to provide authenticity to the public).

At the minimum, this directive promises to expand the record keeping requirements for all players in the drug industry. It will be no easy task to transform these expectations into national laws. Belgium, Greece and Italy have already claimed, that they already, "have systems in place that allow the identification at the point of dispense of all individual packs of medicinal products subject to reimbursement". They are allowed an additional 6 years for implementation of any future EU "safety feature". There is probably plenty of time to contemplate how to verify the registration of one's business partners.

Changes at the FDA

The FDA leaked to the public its intention to elevate its internal enforcement arm, the Office of Compliance to a "Super Office", i.e. on par with the Office of Pharmaceutical Science. It is also making transparent the compliance ratings of manufacturers and suppliers, via a web-accessible Inspection Classification Database. Given that an inspection resulted in a compliance finding, the pertinent observation report (483 Report) can also be reviewed by the public (via request).

The FDA has started an initiative to regulate nanotechnology with respect to protecting the public. Registration of drugs and medical devices will now also have to address the issues raised in the draft guideline. It is only a small step, and may not amount to much if hazards from nanotechnology become better understood. It reminds me of the original safety concerns with biotechnology, which are no longer in regulatory focus.

Warning Letters and Enforcement Actions of Interest

OTC drug manufacturer H&P Industries and its distributor the Triad Group entered into a consent decree because of poor GMPs. You can view the 483 reports, via the link in the preceding section. The decree followed a $6 million seizure of goods in April.

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Howard Solomon of Forest Laboratories Inc. was recently notified that the US government intends to exclude him as a business partner. Since Forest Laboratories supplies drugs via federal programs such as Medicare, it must basically remove Solomon as CEO in order to stay in business. This is another enforcement approach for compliance. GMP and drug licensing problems go back here to a WL in 2003.

The FDA published 65 WLs issued in May, and this year appears to be approaching record totals. A bad example of process validation can be found in the WL to Pointcare Technologies. When 2 of the 3 validation lots did not meet specifications, non-conformance reports were approved and the specifications relaxed. That is not something to show an inspector; “process validation is performed to assure that you are able to consistently meet your defined specifications, not develop the specifications.”

Philips Medical Systems is in trouble again with complaint and CAPA handling. I noted previously similar WLs issued to Philips sites in 2008 and 2009, and promised to report if these WLs had been “closed”. They are not. Between the lines one can see that Philips extensively manages requirements, defects, CAPAs and complaints using business software for its extensive line of complex medical devices. These WLs make it also apparent, that Philips is not successful at actively managing the data and the workflows organized around them. The FDA easily finds requirements which are not verified, incomplete or deficient CAPA records, and inattention to risk management via investigating its complaint handling systems. As to be expected, MDR reports are also not filed on time.

Philips’ problems are apparently not software-based, but rather procedural. The firm has promised now for a number of years to improve its procedures. Interestingly, change control as a process was mentioned only once in this WL, and it was noted; “The change control board is in the process of being developed and established”. The FDA is known for its patience, but the costs for such ongoing internal process improvements must be substantial. Philips is expected now to start a GMP certification project with an outside expert. I’m sure the FDA will be able to recommend someone.

In the WL to API manufacturer, Dr. Reddy's Laboratories, one sees typical GMP problems in manufacturing, particularly with validation of analytical methods, cleaning validation, and OOS (out-of-specification) investigations. Since this firm is an internationally operating API supplier, I would expect that this WL should have international repercussions. A review of the last supplier audit, regarding these GMP issues might be a good idea.

CBER lives up to its reputation in exploring the science behind compliance problems at international biological manufacturer, CSL Biotherapies. CSL had to investigate a spike in adverse events in children to its vaccine. CSL did not document its investigation and could only provide some studies which could have relevance. “There was no analysis of all critical parameters and critical processing steps to try to determine differences in the 2010 lots associated with Adverse Event reports compared to lots from previous seasons.”

Despite known earlier problems with “dark particles”, an investigation into dark particles found in a particular product, was not extended to other related products. Here, the FDA faulted reliance upon a retrospective study of the data, rather than additional measurements. Also only 2 lots at the end of their shelf life were included in a leaching study, without “statistical rationale for use of this sample size”. Finally, these dark particles appear to be linked to a particular stopper, but CSL concluded that the dark particles are not foreign to the product because they couldn’t identify a foreign substance directly. That didn’t convince CBER and shouldn’t convince any scientist either.

The FDA found numerous faults with OOS investigations, production and laboratory controls. Here, we see expectations that decisions, specifications and acceptance criteria are based upon more information than the simple arguments and studies which the FDA found. The FDA now wants to get actively involved in the remediation work. CBER has more clout than CDER; it can revoke or suspend CSL’s manufacturing license (without a consent decree).

Sincerely Yours

Dr. Paul Thomas Noble

Mobile: +49 172 6868 591

Email: PaulThomas.Noble@softwareag.com

If you have any further questions or comments, please don't hesitate to contact me directly via phone or email! www.softwareag.com