COMPLIANCE NEWSLETTER 02/2017

Compliance enforcement trends for the health care industry

FDA´s Changing Focus

The FDA was quite busy in the final days of the Obama administration as seen in the interesting Warning Letters posted in January. Under the Trump administration there is already a new acting Commissioner, but he has not stated what the new focus of the FDA should be. Besides protecting the public, it is obvious that it tries to ensure that the government is not held liable for injurious behavior in the private sector. With its recent globalized approach to enforcement, one could expect that it could be employed to protect the domestic manufacturing sector. In the past, domestic manufacturers had more to fear from the FDA than offshore producers.

Final GMP Guidance on Combination Products

Reducing the regulatory burden may not have had priority, which might explain why it took 4 years to provide final guidance on this subject after the FDA issued its regulation of combination products. A combination product has at least 2 components which are not of the same regulated type, i.e. drug, medical device, biological, or human tissue. A "streamlined approach" to managing quality is offered to reduce the regulatory burden because each of these product types has different GMPs. Some combination products are quite common in the industry, such as prefilled syringes and prefilled IV bags. The FDA could have attempted to harmonize all of these GMPs, but that task would have been a monumental effort to reduce "red tape".

With the streamlined approach, a single Quality Management System which includes a restricted list of GMP provisions for the less significant component can be employed. The significant component delivers the PMOA (primary mode of action), e.g. the drug in a prefilled syringe. Depending upon the manufacturing and organizational structure of the enterprise, the streamlined approach may not be allowed, as described in the Guidance.

FDA Cybersecurity Awareness

The FDA has been concerned about cybersecurity since 2005, as evident in the number of final guidances on this topic, which are still in force:

- Content of Premarket Submissions for Management of Cybersecurity in Medical Devices;
- Postmarket Management of Cybersecurity in Medical Devices;
- Cybersecurity for Networked Medical Devices Containing Off-the-Shelf (OTS) Software.

Hacking pacemakers is a cybersecurity threat that has captured the interest of the public. Perhaps the recent posting from M. Moe regarding St. Jude Medical pacemakers led Muddy Waters Capital to attack the firm with accusations of a cyberthreat. The FDA was perhaps then compelled to issue a safety warning regarding these pacemakers, in which it has determined "that the health benefits to patients from continued use of the device outweigh the cybersecurity risks". This is a rare instance where the FDA publicly takes on liability, with potential risks, but it is clear from the postmarket guideline, that the FDA expects the manufacturer to actively maintain and report a Cybersecurity Risk Management, with heavy reliance upon the "NIST Framework for Improving Critical Infrastructure Cybersecurity".

Overview of Recent Warning Letters

WLs in January demonstrate again, that there are plenty of firms who avoid the GMPs, or find them foreign. A lack of Data Integrity is a common finding. At Suzhou Pharmaceutical, the WL could not even reference noncompliance to the GMPs because the observations were so far-out. Here, they forge Certificates of Analysis via copying the results from their suppliers and pasting them on their own new CoAs. The supply chain is thereby concealed from the record. Shipping banned drugs to the USA by this method certainly eliminates any credibility of this firm.

Cixi Zhixin Bird Clean-Care only makes topicals, but they still must follow the GMPs for drugs, including batch release and process validation. Indian CTX Lifesciences is not excused from the GMPs just because their UV instrument is broken, so that they can make conditional batch releases, and then forget about completing the testing. At Japanese Sato Yakuhin Kogyo, the audit trail of the HPLC units revealed that they routinely repeat measurements, but only report the repeats. Strangely, the FDA found no OOS investigations, but this may not be strange in a culture, where it is impolite to say "no".

FACTA Farmaceutici does paper-based, double bookkeeping of testing results which certainly is a Data Integrity issue. There seems to be no awareness of the controls needed for paper records, especially the controlled forms used for recording. Shredding records during the inspection may have been the highlight. Another red flag is manually transcribing data as a routine operation in order to improve the appearance of the record.

When GMPs are in place, the FDA may still push the firm towards more quality management as seen in the WL to British Porton Biopharma. The FDA became aware of the particle contamination of lyophilized parenterals in 2015 and returned for a follow-up inspection in 2016. It expected effective investigations, with confirmed root causes, and implemented corrective actions. It found incomplete investigations, a more extensive particle problem, and "an overreliance on finished product visual inspection". The WL introduces new subjects as well:

- Porton changed the working cell bank without prior approval from either the FDA or its customer. Such a process change is not trivial, and product recalls could be an outcome of this finding;
- The Quality Agreement between Porton and Jazz Pharmaceuticals; "Regardless of this agreement, you and Jazz Pharmaceuticals are both responsible for the quality of drugs released and ultimately administered to patients."