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Advancing Industry Leaders

COMPLIANCE NEWSLETTER 07/2016

Compliance enforcement trends for the health care industry

Warning Letters 2016

The FDA finally created a search page for WLs in 2016, which already has +260 entries. Extrapolated and compared to previous years, this number is not out of line. About half of the WLs concern the healthcare industry. There is a notable difference in the details, when comparing 10 years back. The majority of these WLs do not concern the "classical" manufacturing industries for medical devices and drugs. Only 17 WLs to date concern drug or API manufacturing, but 57 address nutraceuticals or unapproved trend drugs, and 25 are directed to compounding pharmacies. These are domestic issues, whereas "classical" manufacturing is global. In this grouping (17 drug & 21 medical devices), 15 WLs go to foreign entities.

In the past decade the number of WLs delivered to the "classical" manufacturing sector has dropped, but the fraction involving a foreign entity has climbed to almost 50%. The FDA's attention appears less focused on this sector because of the rise in compounding and alternative medicines.

EU ramps up Enforcement

"Non Compliance Reports" from the EU are now something that even US manufacturers must reckon with. In the last 3 months 3 American sites have received such notices, which have consequences of import bans and recalls. At Bend Research, a manufacturer of oral dosage forms, 2 critical and 1 major deficiencies involved the lack of data integrity. Pharmaceutics International, Cockeysville, produces both sterile and non-sterile products, and has critical and major problems. Major deficiencies involved "inadequate investigation into previous data integrity failures". This same issue was also raised in the report for the Hunt Valley site. We see that data integrity can become a central inspectional issue.

Neither company has Warning Letters posted on the FDA website, which may either indicate that these are "offshore" firms for the EU, or the FDA was upstaged!

User Management Records

In a recent ISPE forum, a question was raised on how to oversee user management, which resulted in this quote from the recent FDA Guide on Data Integrity: "FDA recommends maintaining a list of authorized individuals and their access privileges for each CGMP computer system in use." If the list is simply created upon demand, (e.g. for an inspection), it only demonstrates that a list can be created. It does not document that user access is actively monitored. Maintaining historical lists of users, separate from the computer system, is an old FDA expectation, apparently still alive.

Warning Letters of Interest

There are 2 WLs recently posted to German firms. BBT Biotech is an API manufacturer with some serious GMP problems, as well as data integrity issues:

"your (b)(4) system used for (b)(4) and (b)(4) testing lacked access controls and audit trail capabilities. For example, all employees had administrator privileges and shared one user name, so actions could not be attributed or traced to specific individuals. This exposed your electronic data to manipulation and/or deletion without traceability.

Our investigator also noted that your firm copied raw data to a CD (b)(4), and then deleted the data from the (b)(4) system to free space on the hard drive. Files copied to the CD were selected manually; the selection process was not supervised. Without audit trail capabilities or supervised file selection, there was no assurance that all raw data files were copied to the CD before they were permanently deleted from the system."

Although both practices are probably still quite common, the WL shows that there is no tolerance with GxP critical systems. The FDA wants audit trails and a "supervised file management", i.e. no more simple manual handling of files.

Qiagen, a diagnostics manufacturer and supplier, was caught with an ineffective CAPA system, i.e. "Multiple CAPAs had been open due to repeated complaints" (of the same problem). Cross-checking for similar problems and effective root cause analyses appear to be lacking. The FDA took the CAPA issue further and determined that Qiagen's design and development process did not include opening a design change record for changing the design outputs, which were then not verified. The FDA also followed the multiple CAPAs back to Complaint Management and determined that it was ineffective because action is only initiated when an adverse trend is identified. The SOP provides no information on what an adverse trend is. Finally, Qiagen was faulted for not filing timely MDRs and Correction and Removal Reports for the failed product and recall associated with the complaints. Qiagen now has plenty of corrective actions to clarify with the FDA.

French Eolane Vailhauques, a medical device manufacturer tried to explain to no avail that process validation is not needed because it is compliant with ISO/IPC-610. FDA expectations are higher. They also have a custom software program, (for quality records), which has been in use since 2005, but never validated. Someone certified it for use, but there is no validation documentation. The word validation seems to have a different meaning in the French language.

The WL to Chinese Tai Heng Industry is another example of systematic data falsification and disregard of quality control. Data Integrity is naturally a central theme in this letter. Not only does QC retest samples until passing, it omits the failing results from the batch record. The analysts also manipulate the PC clocks on the HPLCs in order to create false timestamps. Operators use "mock" sheets to capture data during production, which is then massaged and entered into backdated batch production records. The FDA wants within 15 days a comprehensive investigation of the extent of the problem; a risk analysis of the current patient risks; and a management plan with a detailed corrective action plan. Given the statements in the WL, this request can only be viewed as unrealistic.