



COMPLIANCE NEWSLETTER

08/2016

Compliance enforcement trends for the health care industry

Original Records and True Copies

The economic pressure to go paperless has always been stymied by uncertainties regarding the disposition of paper records, which have been scanned or converted to PDF Files. Keep them just in case the copy is in doubt, or destroy them per company policy? With the recent guidances regarding Data Integrity, (see past issues), this uncertainty unfortunately remains, because there are nuances involved. In the MHRA guidance, a “static” record is simply paper or a scan of it, whereas a “dynamic” record is electronic and is more than just a display of information. When an electronic record is printed out and signed, the printout is often not a true copy and signing it just complicates the issue. If the record contains content which is not displayed in the printout, which can be as simple as a hyperlink, then the printout is not a true copy of the record, and signatures do not necessarily apply to the electronic record.

The only clear harmonized position on this issue is that true copies can be retained in place of the original, i.e. the original can be destroyed, e.g. 21CFR211.180d.

The MHRA just revised its [Data Integrity Guidance](#) after only a few months. Included is still the expectation; “Data must be retained in a dynamic form where this is critical to its integrity or later verification.” Further,

“Where the capability of the electronic system permits dynamic storage it is not appropriate for low-resolution or static (printed / manual) data to be collected in preference to high resolution or dynamic (electronic) data.” The regulatory push to paperless operations is obvious, and the uncertainty regarding destruction of paper documents may soon be lost to history. Still, caution is advised when creating documents with embedded objects and hyperlinks. So called, print renditions, of such documents are not true copies.

Look-Back EU Non-Compliance Reports

The recent publicly available website for [EU Non-Compliance Reports](#) can be browsed for the past year. Dating from May 2015, there are only 28 reports posted. Of these only 8 involved an EU location. Does this indicate that Compliance in the EU is very good? Hardly. Inspections are only marginally harmonized in the EU, and it is interesting to see which agencies issued reports. The UK, France and Italy issued the most reports, but Spain, Sweden, Croatia, Romania, the Czech Republic, and Poland also are represented. Not a single report was issued by Germany, which clearly has a large drug industry. The 8 EU locations with reports were cited by their own national authorities. Apparently, Germany is a good location when viewed in terms of compliance pressure.

Basic GMPs still Count

When a big Pharma concern like SmithKline Beecham gets a [Warning Letter](#) faulting basic GMPs, it shows that basic GMPs cannot be taken for granted. An antibiotics plant is involved here, and the main point is potential penicillin contamination of non-penicillin products. Dedicated facilities for penicillin production has been a regulatory expectation for many years, and SMK has apparently cut some corners in its facility design. The FDA points out that, "No safe level of penicillin contamination has been determined to be a tolerable risk."

Also of interest are the problems associated with CAPA investigations. Regarding Root Cause Analyses, the FDA came to its own conclusions:

- "In 16 of the 25 investigations, you concluded that the root cause was sampling error but had no supporting evidence." If the RCAs commonly yield human error as the cause and result in the corrective action, retraining, then the investigations are not adding much value.
- "... you attributed the high bioburden root cause to an extended (b)(4) hold time. ... Your firm has no established maximum (b)(4) hold time. You failed to include any supporting data to correlate your (b)(4) holding times with increased API bioburden. You did not extend your investigation into the (b)(4) other (b)(4) with similar or longer (b)(4) hold times." The FDA provides evidence that the problems are coming from the purified water system.
- Regarding investigations of foreign particle contamination, "It failed to include a root-cause evaluation of glass particles and the foreign materials found in these drugs. You also failed to evaluate the impact of the contaminants on all other drugs manufactured with the same equipment in the same facility." An RCA for foreign particles is always difficult, but a cross-check to other charges is simply due diligence.

Other Warning Letters of Interest

The WL to [medical device manufacturer Oscor](#) highlights some classical process validation concerns, particularly with regards to sterilization. The validation of a sterilization process for a product must include the definition of sterilizer loading, placement of sensors, and the critical control parameters. Each configuration must be validated, and no general operation will be recognized as validated.

There are other process validation problems at Oscor:

- 100 % inspection of product in lieu of validation was not accepted for an injection molding process, especially as there were customer complaints regarding defects;
- The UV curing process failed to address the UV intensity and has no specifications for the end product to support concluding that the process is validated.

Chinese [Guangzhou Haishi Biological Technology Co., Ltd.](#) has been able to produce and sell drugs without any apparent process or quality control. They were able to continue to export drugs to the US for 8 months after the inspection, and it took 1 year to issue the WL. Apparently, the FDA judged the risk to the consumer to be low.