

Compliance enforcement trends for the health care industry

Globalization: Still Progressing?

Several subjects were presented in the newsletters of this past year, which reflect a progressive globalization of the business environment for firms involved in health care:

- Drug Tracking and Tracing (ISO Standard)
- Data Integrity Guidelines (similar interpretations)
- International Medical Device Regulators Forum

However, some subjects indicate a trend of differentiation or even isolation of regional markets:

- Pharmacy Compounding (a thriving business in the USA)
- 21st Century Cures – the US and the EU have separate agendas, i.e. national interests
- EU Regulation for the protection of personal data (not supported in the US)

The changing political landscape in the “West” can be interpreted as potentially slowing or reversing globalization, as national interests take priority. China remains focused upon its national interests. Compliance will remain a responsibility of national authorities, and this subject though “harmonized”, probably cannot be expected to globalize. The major players are global and probably should not expect an easier future in achieving and maintaining compliance.

Have Good Vision and Judgement to assure a successful New Year and beyond!

New FDA Guidance

While on the subject of national interests, guidance was just issued on 2 pet FDA projects: [Contract Manufacturing - Quality Agreements](#) and [New FDA Quality Metrics Guide](#). Both of these ideas are still voluntary for the players, but FDA expectations behind them can lead to WLs, as illustrated in the next section.

Regarding quality metrics, collecting and analysing data is not voluntary, as “Current good manufacturing practice (CGMP) for human drugs require manufacturers to have an ongoing program to maintain and evaluate product and process data that relate to product quality.” Don’t be surprised if during the next inspection, questions are raised regarding data related to these metrics: Lot Acceptance Rate (LAR); Product Quality Complaint Rate (PQCR); and Invalidated Out-of-Specification (OOS) Rate (IOOSR).

European Good Distribution Practices

The recent creation of the [European GDP Association](#), under the umbrella of the [ECA Foundation](#), is another example of regional interests going alone on a global theme. Although harmonization of global interests is a goal of these groups, the definition of GDP has been primarily a European effort.

GMP Examples from Warning Letters

Compliance guidelines are in a continual state of revision, but basic GMP issues are relatively timeless, and perhaps best understood per anecdote.

Cleaning Validation is covered in the [WL to Spanish Interquim](#). Visible residues on production equipment used for different products is a red flag pointing to cross-contamination. Cleaning validation is a scientific study, which begins with estimating an allowable contamination level in a product and follows through with measurement methods that verify that this level is not reached after cleaning. With multi-product facilities, such studies can be extensive. Without cleaning validation, there is no evidence that cross-contamination is under control.

Potential contamination from corrosion or deterioration of product contact surfaces in equipment calls into question not only preventive maintenance as documented in the WL, but also equipment qualification. Product may need to be investigated for metals or leachables, as part of the investigation needed to satisfy the FDA on this point.

It is not clear how STI Pharma, which was formed in 2008, supplies its generic and proprietary drugs, but the [WL to STI Pharma](#) shows they are not equipped to process PADEs (postmarketing adverse drug experiences) reports, as they put undue reliance upon their contract manufacturers. A Quality Agreement

with the contractor(s), as defined in the previously cited guidance could have helped because it would not have included simply, "they provide regulatory submission services on your behalf."

The WL to Indian [CP Pharmaceuticals](#) identifies poor aseptic manufacturing practices at its British production site. Exposed sterile product is at heightened risk whenever there is air circulation caused by movements. Laminar air flows over the product is designed to direct sterile air, but are easily disrupted in proximity to such activity, allowing contaminated air to reach the product. That is why, the number of operators and equipment movements must be minimized. Facility design must have this goal, but there are some activities which require more action, and filling line setup is one, (in which the FDA takes a special interest). Inadequate disinfection procedures, as well as, inappropriate movements between environmental zones are also noted.

The [WL to Morton Drug Company](#) (a pharmacy compounder) also illustrates some hair-raising aseptic manufacturing practices. Clean rooms must be maintained at a higher pressure than the immediate environment, so that air ingress is minimized, and the pressure differential must be monitored. Cleaning activities, using unqualified (i.e. non-sterile) disinfectants with operators in street clothes, is not an option for clean rooms. Even if the room is subsequently gassed, it cannot probably be validated that all potential exposable surfaces have been sterilized, because the bioburden is not under control.