COMPLIANCE NEWSLETTER 04/2017

Mutual Recognition Agreement – US and the EU

Maybe it shouldn´t be surprising that this almost dead initiative came back to life. It was listed as an "important priority" in CDER´s 2016 Priorities paper, but the initiative is as old as this century. The FDA press release provides some of the history, and it is evident that the Obama administration reactivated this latest round of negotiations. The Trump administration also needs to contain costs, and the mutual recognition of inspections avoids the need for foreign inspections. Furthermore, the FDA is now under a hiring freeze, (according to Trump).

Interestingly, this MRA will not apply to the UK, and both parties have the option to exclude a particular country or agency from the agreement. This is in line with Trump´s nationalistic approach. The MRA also applies only to CDER, which means it does not cover medical devices, blood products, and other specialities. Still, for drug or API manufacturers in the EU, the pressure will soon be off, (target Nov. 2017), at least in terms of Warning Letters or Import Bans. The EU needs such an advantage now, more than ever.

Recent EU Compliance Actions

With the MRA pending, it is of interest to note what the EU has been doing in the last 6 months regarding compliance enforcement. Only 4 Non-Compliance Reports were issued since last September, and only 2 involved sites within the EU. The Spanish agency cited 2 drug manufacturers using aseptic manufacturing methods in Spain. In both cases, their manufacturing licenses were suspended, because the findings were so extreme:

- EURO FAR ALERGI does not inspect and release raw materials, nor perform complete testing and release of final product. Process validation, particularly of the aseptic operations is missing, and the inspectors found general non-conformance to Annex 1 of the EU GMPs in the design and operation of aseptic manufacturing.
- ANGULEMA does not have an effective quality assurance, and releases its product without sterility testing. Also, process validation is simply not done, and especially with media fills, of terminal sterilization, and viral inactivation.

The other 2 active agencies were Ireland and Italy who found problems with foreign suppliers. What the other agencies are doing is generally not publicized.

Update on Controlling User Access to IT

Recent postings in the ISPE GAMP Forum provide insight and inform on some timely concerns:

- Passwords appear to be a universal component in identification. No one could provide experience with biometric IDs;

- When badges or RFIDs are used for identification, a password as a second component is always required for signatures, as specified in the regulation 21CFR11.200. However, CFR11 doesn´t specify how to perform an authority check to access the system for other purposes. The GAMP community is a bit uncomfortable with this situation, but apparently there are badges in use without an enforced password entry;
- The limit on the number of failed logons is open to question, and may no longer be relevant. There is no codified requirement for it, but a limit is probably still expected. There was some consensus with 15. Historically, 3 to 5 was a common requirement. That was before hacking efforts became possible, which could storm a site with brute force methods and potentially deactivate within a short time most or all of the user accounts.
- Password protection of accounts is alone insufficient; security monitoring is more important than ever.

Warning Letters Review

Excluding domestic compounding facilities, the FDA issued In February and March:

9 WLs to foreign drug facilities;
2 WLs to domestic drug facilities;
1 WL to a domestic and 1 WL to a foreign medical device manufacturer.

Despite the MRA, WLs can still be of interest, because domestic sites often belong to global concerns.

For example, the WL to Morton Grove Pharmaceuticals belongs to an Indian global concern, Wockhardt, (with no apparent German roots), which just recently received the “Best Enterprise” award from the “Europe Business Assembly”. A site inspection factors into an appraisal of the entire firm. The FDA notes in the WL, “seven Wockhardt facilities (including Morton Grove) are considered out of compliance with CGMP”. Although this extensive WL has plenty to offer, it is particularly instructive regarding handling of non-conformances and their investigations:

- A science-based health hazard analysis is needed when non-conforming product is on the market;
- A cross-check of all potentially affected batches is needed when a non-conformance is detected;
- Assigning operator error to an OOS result, repeating the test, and discarding the first results is not proper handling of such non-conformities;
- Classifying the investigation of quality problems as “internal audits”, so that the quality unit and its procedures are not involved is not acceptable.

Denttio is a medical device manufacture, selling computerized image processing systems. The WL lists 12 problems with the Quality System Regulation, including “Failure to perform device software validation and risk analysis as required by 21 CFR 820.30(g)”. Keep in mind that inspection of medical device manufacturers is not included within the scope of the pending MRA.