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Advancing Industry Leaders

COMPLIANCE NEWSLETTER 02/2018

Compliance enforcement trends for the health care industry

Q12 – the new ICH Guideline to harmonize Post-Approval Changes

The ICH is also concerned about promoting innovation, and this new draft guideline is supposed to enhance implementation of post-approval changes to Chemistry, Manufacturing and Controls (CMC), as defined in the drug licensing agreements. Regulatory oversight of changes is an acknowledged inhibitor of innovation.

A risk-based approach to regulating changes is already practiced, at least for some regions. What is new in this guideline is the definition and employment of some "ICH Q12 Regulatory Tools and Enablers", particularly:

- Definition of "Established Conditions (ECs)" and their use in defining proposed changes;
- The Post-Approval Change Management Protocol (PACMP) regulatory tool;
- The Product Lifecycle Management (PLCM) document.

ECs are considered necessary to assure product quality. Therefore any proposed change to an EC would require regulatory review. The concept of ECs overlaps with previously defined terms, such as critical and key process parameters, but is a broader concept, including both implicit and explicit ECs.

Once established, the ECs may promote innovation, but both regulators and submitters will have to expend some effort to adapt to this new concept.

Changing documentation requirements, such as adopting the PACMP and the PLCM, will also impart an initial heavy regulatory burden on companies to adjust their dosier practices.

FDA researches Nanomaterials

The FDA has been advancing "regulatory science" in this area, most recently with the creation of a dedicated site for nanotechnology, where one can obtain current positions on this subject as well as final guidance for industry. These concerns involve cosmetics, the food chain, (particularly animal feeds), as well as drugs. Since nanomaterials are often found in many conventional products, i.e. as unintentional constituents, these concerns only address engineered nanomaterials, designed to have certain properties or activities.

Although environmental contamination with nanoparticles has been in the news (via toothpastes), the focus of these Guides is upon safety of the patient or consumer,

especially toxicity. For cosmetics, the manufacturer is ultimately responsible for safety and no regulatory submissions are required, (but encouraged). However, food additives must be pre-approved, and food for animals should be classified as (GRAS), i.e. "generally accepted as safe", which requires regulatory review. The Guide for animal foods states that no engineered nanomaterial has yet been classified as GRAS, (dated 2015). An Environmental Impact assessment may be required. This applies to drugs as well, for which the application of nanotechnology should be included in the regulatory submission and review. Generally, safety of nanomaterials would be included in both the scope of non-clinical and clinical studies. In short, including nanomaterials in a drug preparation would significantly extend the scope of testing before market release, i.e. inhibit innovation in the eyes of some observers.

Warning Letters of Interest

The FDA started the year with 4 WLs issued to Asian drug / API manufacturers. Resulting in 4 Import Bans. Headquarters also acted against internet sales of drugs intended to alleviate opiate addiction, resulting in 11 WLs. The district offices issued 4 WLs to drug and 3 WLs to medical device manufacturers. Besides GMP and QSR issues, there were specialties, as can be read in the following links.

The WL to American CryoStem Corp. was elevated to a press release, in which the regulatory borderline between innovative medical practice, and manufacturing of biologicals applied autologously, is defined. Atcell is obtained from the patient´s adipose tissue, but the cells are extensively manipulated and can no longer be considered human tissue. This product is being applied experimentally for a number of conditions, without regulatory oversight, nor the minimum of GMPs. Unknown is how the FDA became aware of this activity, but professionals and consumers are encouraged in the press release to report any adverse effects.

Another press release puts Becton Dickinson in the spotlight related to the lead testing scandal of children. B-D is the supplier of the blood collection tubes for the lead testing kits, and changes to these tubes are considered to be a probable root cause of the recent failures of lead testing. Damning is the observation that manufacturer Magellan issued a complaint early-on, but B-D did not register this complaint and investigate. Blame was put on the poor validation of the complaint handling software, used globally, for which there is no user SOP.

Although the design change to the rubber stopper formulation was specified and validated, B-D did not consider possible changes to clinical performance. "... without clinical testing to demonstrate that the performance of the tubes was not affected by these design changes or evidence demonstrating that (b)(4) testing accurately and reliably predicts clinical performance, your firm has not performed adequate design validation." Here is a good example of where innovation can have unintended consequences, and where costly regulatory expectations basically inhibit minimal changes, such as changes to a rubber stopper formulation.

Finally, it should be noted that at the end of the year, Fresenius Kabi (Oncology), received a 2nd WL for another production site in India, which also involved falsely invalidating OOS results. (The first WL was reported in the previous issue of this newsletter.) The observations in this 2. WL are also repeat observations, which place even more pressure now on Fresenius Kabi´s global quality assurance.

More to come about the current Bayer WL in March.