COMPLIANCE NEWSLETTER 01/2018

Compliance enforcement trends for the health care industry

Promoting Innovation via less Regulatory Review

As mentioned in the last issue, the FDA has issued 3 new guides which address SW that could be considered a SAMD (software as a medical device). As we know, it is relatively easy to develop a software-only product, and SAMDs are proliferating, resulting in a growing regulatory burden. By excluding as many products as possible from the medical device classification, the FDA is not only managing this burden, but also promoting innovation.

Clinical decision support (CDS) software can be design-limited so that it fails to meet the criteria for a SAMD classification. The draft guide on CDS SW delineates what features it must have to be considered a medical device. As a first assumption, consider it to be a SAMD when the intended user is not the patient, i. e. a specialist. Fitness bands can be considered to involve PDS (patient decision support) SW, which are generally **not** SAMDs.

The 2nd guide is a draft which further clarifies exclusions of SW from medical device regulations. Of particular interest, is the determination that a LIMS, when used in a health care facility, is not a SAMD, and has no oversight from the FDA. Obviously, a LIMS in a drug manufacturing facility, which is involved in product release, is not a SAMD, but is still quality relevant and must be validated along with the manufacturing operations. Validation issues may arise when the SW supplier is clinic-oriented.

When the SW product is a SAMD, the FDA "adopts the internationally converged principles agreed upon by the IMDRF", for regulating the product as a medical device, as recorded in the recently finalized Guide on SAMDs. It defines a risk-based approach, but also specifies that analytical and clinical validation are required for all SAMDs. "As part of the risk-based approach … clinical evidence of certain low-risk SaMD may be less important and the manufacturer may 'self-declare' the appropriateness of the evidence."

EU Annex 1 Revision

The EMA is not slowing down in its proliferation of the EU GMP Guidelines. With the latest expanded Annex 1 draft, the EMA continues to comprehensively address all technologies and GMP issues associated with the production of sterile products and beyond, i.e. "may be used to support the manufacture of other products that are not intended to be sterile (such as certain liquids, creams, ointments and low bioburden biological intermediates) but where the control of microbial, par-

ticulate and pyrogen contamination, to reduce it as far as possible, is considered important". It is in this sense a good starting point for coming to grips with GMP.

Also the section, Pharmaceutical Quality System (PQS) raises to the forefront the following activities: risk management; root cause analyses; and investigations of non-conformities. Particularly by such investigations, the "reasons for including or excluding product from the scope of the investigation should be clearly recorded and justified within the investigation". It is now expected to routinely cross-check what other products or batches could be affected when a non-conformity is detected, and to expand the investigation as appropriate, to determine if these other products are impacted, i.e. not conform.

Insight on EU Inspections

The EMA Annual Inspectors Report 2016 is a bit late to be called current, but provides insight into what the inspectional authorities in the EU have been doing and where their interest lies. The source of this report, the GMP / GDP Inspectors Working Group (GMDP IWG), has become the forum for "harmonisation of Good Manufacturing Practice (GMP) inspections in the European Community and practical implementation of Mutual Recognition Agreements (MRAs)". Its mandate is focused upon cooperation within the EU, and this report is addressed to the national regulatory bodies, (not the public).

It is understandable then, that compliance within member states and differences between them are not only not in focus, but are avoided as topics. Reported is a respectable number of 2293 inspections, from which 24 "non-compliance" statements were issued. A check with EU Non-Conformance Reporting yields a similar number (18), from which only one addressed a site within the EU. Comparing the total 24 non-compliances with the reported 19 found outside of the EU, one could infer that about 5 non-compliance reports were issued within the EU in 2016. This yields a miniscule 0.25% chance of obtaining a non-compliance finding within the EU. Thanks to the MRA with the US, the EU is on the high ground in terms of compliance risk, scandals excluded.

Warning Letters of Interest

Fresenius Kabi AG is a global concern with many production sites. When it receives a WL, in which repeat deviations are determined, the FDA will conclude: "These repeated failures demonstrate that your facility's oversight and control over the manufacture of drugs is inadequate." As a global concern, the expected corrective measures are not limited to the site in India. Rather, "It is essential that you initiate an immediate and comprehensive assessment of your company's global manufacturing operations to ensure that systems and processes, and ultimately, the products manufactured, conform to FDA requirements at all your sites."

Specifically, the strongly recommended external GMP consultant, "should comprehensively assess your laboratory and manufacturing systems, retrospectively review all OOS investigations, and assist with remediating overall quality oversight at your firm." This is a heavy price to pay for poor laboratory practices at an API site in India, and which might only exist at this one site. In terms of regulatory risk, global concerns are only as strong as the weakest site (which supplies the US market).