



COMPLIANCE NEWSLETTER

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Compliance enforcement trends for the health care industry

Globalization of the Medical Device Market

Starting in 2011, the International Medical Device Regulators Forum ([IMDRF](#)) has been driving globalization further than most political or economic organizations have achieved. The IMDRF includes in its membership representation from almost all significant markets for medical devices, (including Russia, but excepting India). The FDA has [devoted a website](#) to its activities, but basically defers in most cases to the IMDRF web site for content. There is no counterpart which appears to measure up to the scope of the IMDRF in the drug industry. It is a voluntary organization like GAMP, but formed directly by the regulators of the industry.

SAMDs (Software as a Medical Device)

One of the first activities of the IMDRF was the regulation of SAMDs. Key definitions were formulated in 2013 in the [final N10 Guide](#). The FDA recently posted a [draft clinical evaluation guide for SAMDs](#), (which is not yet available on the IMDRF site).

The term SAMD is supposed to classify all software that is used for medical purposes, but is not part of, (embedded in), a medical device. As such, a SAMD is limited to data processing and analysis, and its medical purpose can only support decision-making,

such as diagnosis, and possibly supporting indirectly the operation of a medical device. A database with analytical tools, used for monitoring and/or mitigation of disease in the general population, could be interpreted as a SAMD. Needless to say, SAMDs must be registered and controlled as a medical device.

Retrospective Computer Validation

A recent ISPE discussion in the GAMP community considered how to handle the situation where an inspection uncovers a system that has not been validated. Such a scenario guarantees that retrospective validation remains a current subject. The experts seem to agree that one must begin immediately with a new system risk assessment (addressing potential risks to patients, etc.). With low to moderate risk, the system in question can be justified to remain in operation, while the retrospective validation is performed. (It should be conducted with the same rigor as a prospective validation.

More Trouble at Valeant Pharmaceuticals

Valeant has been a darling on the stock market via its aggressive strategy of company buyouts, elevating prices of acquired products, and avoiding research and development expenses. Recent history has

demonstrated that this strategy was short-sighted, and a recent [WL to Valeant](#) points to more trouble; this time with products it acquired from the takeover of Bausch & Lomb in 2013.

The documentation requirements for medical devices apparently caught the Valeant Pharmaceuticals management by surprise. The design history files for at least one acquired medical device were not completely transferred, (e.g. missing clinical data). The FDA concluded: "Specifically, the organizational structure has not assured that acquired products are adequately integrated into your quality management system."

Other Warning Letters of Interest

The FDA appears to be having difficulty issuing timely Warning Letters, since it is common now to receive the WL as long as 1 year after the inspection. For acute problems, (e.g. sterility concerns), the FDA can start some enforcement actions before releasing the WL, as documented in the following examples.

The FDA extended its intense enforcement of data integrity to Europe with a WL to [Interpharm Praha](#) in the Czech Republic. Criminal intent was not documented here, and an import ban was not issued. Still, the common remedial measures, (listed in the last newsletter), are expected to avoid a further escalation.

The QC lab was the major focus, and it is clear that the inspectors used the 5 inspection days to critically analyze the audit trails on the systems. Particularly on the Empower-2 system with 8,906 entries, it was

found that: "well over half indicated some form of data deletion or manipulation, including at least 1,441 instances of deleted results, at least 3,643 instances of manual integration, and at least 194 instances of altered running sample sets. Your personnel confirmed that these actions are common during chromatographic data processing. We found that you did not have a procedure in place to indicate the requirements and level of restrictions for users of the automated system." The statement implies that data manipulation can be allowed, when it can be justified and defined.

In contrast, criminal intent in data falsification and concealment can be deduced in the WL to Chinese API manufacturer, [Beijing Taiyang Pharmaceutical](#), which received its import ban 5 months after the inspection.

Unauthorized destruction of paper records, (also a data integrity issue), was documented in the inspection of a Hungarian Pharmaceutical site. Not only were poor aseptic techniques multiply observed, investigations of frequent sterility testing failures gives the impression that sterile assurance is only wishful thinking. Here GMP concerns trump the data integrity problems, but both must be addressed before this import ban can be lifted.

Another interesting point in this extensive WL to consider is the FDA's phrase, "Your stand-alone computer systems lacked controls, ..." It implies that the FDA recognizes stand-alone systems as especially vulnerable to data manipulation. They expected the audit trails to have been internally reviewed although the procedure for doing so had only been implemented 10 days prior to the inspection.