

A photograph showing a rowing team of eight people in white shirts and dark shorts, carrying a long, narrow white boat on their shoulders. They are standing on a sandy beach with water and trees in the background under a bright sky.

Compliance enforcement trends for the health care industry

Validation – Lost in the Woods?

The FDA concept of validation began with the recognition, that quality control is sometimes insufficient to detect and reject a critical defect, such as microbial contamination in a parenteral. Absolute methods of confirming sterilization required “destructive” testing, i.e. rendering the sample unfit for sale or use, and statistics had to be resorted to, in order to estimate the sterility of the production lot. Steam sterilization processes were among the first to require validation, and the concept of “overkill” was given to a process which reduced by 12 logs the potential concentration of the most thermally resistant bacterium known at the time. “Overkill” applied because any contamination potentially present was not so thermally resistant and not so extensive.

Once the validation concept was established, it was extended to other processes in which a defect would be difficult to detect, but potentially unacceptable. Particularly, computers came under question, because software defects can almost never be excluded as a possibility. Most such defects can be tolerated, i.e. compensated for, but the ethereal wish for perfection, or “overkill” in assurance, required validation. Interestingly, simple computer systems were recognized to behave deterministically, and statistics has not played a major role in computer validation.

The validation mindset is quite firmly established in most, but not all of the world. In these changing times, it will be called into question again, as established ways of thinking are challenged. The question which will be raised is; what makes sense today?

Stepping back from the dramatic, this question has been raised before. With the advent of biotech products, steam sterilization of parenterals had to be replaced with aseptic manufacturing. The FDA recognized that the sterility assurance attainable with an overkill sterilization process is very difficult for aseptic manufacturing processes to achieve and demonstrate. Still, the FDA accepted such processes, when validated, and has tried to enforce the same sterility assurance standard, (i.e. overkill); hence the relatively large number of WLs for aseptic operations.

Another change in mindset came with the new millennium regarding computer validation. An extreme approach to computer validation has been modified to a risk-based approach, as it was recognized that most software defects can be tolerated. As with all changes, there is something lost and something gained. Now, the owners must know and manage their risks.

If an “overkill” approach to CSV was still followed, cloud computing would be severely limited. Typically, a multi-tenant cloud system access is not controlled by persons

who are responsible for the content of electronic records that are on the system, thus not meeting the “closed system” definition.

“Close cooperation” between Process Owner, System Owner (which might be the cloud provider), qualified person and IT is essential according to Annex 11. Some of the roles can be renamed, but how do you cooperate closely with a distributed supplier workforce? This difficulty becomes even more evident, if auditors would ask to pay a visit to the cloud provider’s premises where the data resides (see Annex 11, 3.4). These obstacles could be eliminated by a specific SLA for life science customers.

While the underlying risks of these topics can simply be accepted (to be specific: can be accepted by the “manufacturer”), there remains one open flank, called “Change Control”, where it becomes almost impossible to control changes to the computerised system using a strict quality management system as it is lived at the LS&HC industry.

The good news is that most of the hurdles above can be mitigated and accepted afterwards within a company and project-specific validation framework. The “bad news” is the need for the regulated company to update their “legacy” QMS devoted to “classical” CSV in order to accommodate the age of cloud computing. Let’s name it CSV 4.0.

Also Agile Methods appear to be a relevant option for regulated industries. In several aspects its focus upon results, clarity, transparency and quality correspond better with the basic goals of computer validation than conventional methods. They are gaining more acceptance as an integral part of software development in the regulated environment and are increasingly integrated into the Quality Management System.

Validation Creep in Warning Letters

The [WL to Aplicare](#), a manufacturer of topical drugs demonstrates how feature creep can enter into the validation mindset. Here, we see a claim for sterility in these topicals, which is to be achieved via validated aseptic manufacturing. When such claims are made, (or expected), the FDA will follow-through with all of the expectations for a sterile parenteral.

The [WL to Canadian Intega Skin Sciences](#) illustrates the current validation expectations of the FDA. It is not demanded that topical drugs be sterile, but the processes must still be validated to, “demonstrate that they are capable of operating within established parameters to assure batch uniformity, integrity, and consistent drug quality”. Originally, Quality Control was considered sufficient when the risks to patients were low, but the current mindset requires validation for all manufacturing processes of drugs.

As if to refute this observation, FDA headquarters issued a similar [WL to Spanish Natura Bisse](#), which faulted poor quality control but did not even mention validation. Without good quality control, process validation makes no sense.

Quest for the Paperless Laboratory

A recent GAMP discussion reflected upon the quest for “achieving Paperless Laboratory by implementing LIMS application ... without an ELN”. None of the participants could report on a successfully completed project. Although software limitations are recognized as a problem, the greatest obstacle appears to be transforming the complex business processes, which are usually full of organizational hurdles. Finally, the consequences of a dynamic hardware environment, (interfaces, alternative equipment suppliers, etc.), makes maintaining such a laboratory a major operation. The perceived potential savings must be large when so many are on this quest.

Other Warning Letters of Interest

The [WL to Chinese Baoying County Fukang Medical Appliance](#) documents a defensive position taken against globalization and the free flow of information. Management refused to disclose information to the FDA inspectors in order to protect its “trade secrets”. The subject was microbiological testing procedures, which can only be included in the scope of trade secrets, when the science of microbiology is partly secret. Protection of trade secrets in a country, which is known for its procurement of such secrets, is an understandable and plausible argument within China.

The [WL to Indian API manufacturer Wockhardt](#) illustrates FDA positions on both aseptic manufacturing and computer validation. The FDA will even take the time to review smoke studies LAF benches, and can subsequently require the firm to review its facility design in this regard. Also, all computerized equipment in the QC lab still requires computer validation documentation. When lacking, an assessment of the historical data (retrospective validation) is required in addition to a prospective validation.

More to come: US FDA finalizes combination drug / device product guidance

The US FDA has finalized its [guideline on “Current Good Manufacturing Practice Requirements for Combination Products”](#).

A core requirement of the approach is that change control of each combination component must be aligned across all affected quality management systems:

“While not an issue unique to combination products, coordination of changes among manufacturers participating in the manufacture of a combination product is an important CGMP issue. Appropriate consideration should be given to any implications for the safety or effectiveness of the combination product that might arise from changes to the combination product or its constituent parts.”

As the buck stops with the market authorization holder it is foreseeable that CMO’s quality systems will be subject to intensive scrutiny and supervision.