

FDA'S NEW REQUIREMENTS ON PROCESS VALIDATION – AN OUTLOOK ON THE NEW FDA GUIDANCE (Parts I and II)

Oliver Schmidt

At the PAT Conference 2008, which was organised jointly by the University of Heidelberg and the European Compliance Academy (ECA), Jon Clark from the FDA gave an outlook on the upcoming new FDA Process Validation Guidance. The new Guidance will replace the current version of 1987.

The new approach of Process Validation considers validation as a series of activities taking place over the “life” of a product or process. Its key goal is hence to achieve process understanding. As a consequence the overall validation is not “complete” but ongoing. It requires a comprehensive process design to identify and mitigate significant sources of variability. The Process Validation may also incorporate risk management and recognises that more knowledge will be gained during commercial distribution. This is a fundamental change from the traditional three batches validation.

In his presentation Jon Clark mentioned that the life cycle approach to Process Validation consists of three elements:

- Process Design
- Process Qualification and
- Continued Process Verification

Process Design assures that the commercial process is defined based on knowledge gained through development and scale-up activities. Process Qualification consists of two aspects: Design of facilities including qualification of equipment and utilities and performance qualification. During his talk he defined the criteria for the Performance Qualification Protocol. This document specifies the manufacturing conditions, controls, testing and the expected outcomes. It should therefore include operating parameters, processing limits and component (raw material) inputs, the data to be collected and when and how these data have been evaluated. In addition the Protocol should include the test to be performed (in-process, release and characterisation) and acceptance criteria for each significant process step. Also the sampling plan including the sampling points, number of samples and the frequency of sampling for each unit operation and attribute needs to be considered. He emphasised that the number of samples should be adequate to provide sufficient statistical confi-

dence of both within a batch and between batches. As further components of the Performance Qualification Protocol he noted:

- Criteria that provide for a rational conclusion whether the process consistently produces quality products
- Design of facilities and the qualification of utilities and equipment, personnel training and qualification and verification of material sources
- Status of the validation of analytical methods used
- Review and approval by appropriate departments and the quality unit

He emphasised: “Before any batch from the process is commercially distributed for use by the consumer, a high degree of assurance in the performance of the manufacturing process, that it will consistently produce APIs and drug products, is needed. This is in fundamental opposite to the traditional three batches validation which is no longer sufficient. He goes on by saying that the high degree of assurance can only be obtained by providing data to demonstrate that the commercial manufacturing process is capable of consistently producing acceptable quality products within commercial manufacturing conditions including those conditions that pose a high risk of process failure. The continued process verification activities would include establishing a system for

- process monitoring
- trending and assessing of data
- process control strategy

Jon Clark used the term “validation in production”. He defines this as activities to continually assure that the process remains in a state of control. The management of changes as well as the monitoring of the process are key elements for the ongoing evaluation. As a consequence the term “Re-validation” will not be used in the revised Process Validation Guidance any more. In addition the “retrospective validation” does no longer exist. As a summary he defined the new validation approach as “the collection and evaluation of data from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products.” A fundamental change to the current industry practice is ahead.