Process validation from an 
FDA Perspective - Part 2

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New terms and definitions in the 
FDA Guidance for process validation

In January 2011 the FDA published the 
revision of the Guidance for Industry 
"Process Validation: General Principles 
and Practices".

In this guidance process validation is pre-
sented as a 3-stage life cycle model which 
contains the basic principles of the ICH 
Guidelines Q8(R2), Q9 and Q10 (see FDA 
Process Validation Guideline - Part 1 in 
LOGFILE No. 5).

In addition to these basic principles which 
have been compiled by the FDA, a num-
ber of technical terms have been intro-
duced in the guideline or assigned a dif-
ferent meaning. The most important inno-
vations are described below:

- The term "qualification" is also used for 
processes
- Processes must be both validated and 
qualified.
- "Process validation" is the generic term 
for all activities in the product life cycle, 
while "process qualification" is the 
second stage in the process validation 
procedure.
- The term "process qualification" has 
been introduced as the generic term for 
the second process validation stage. It 
includes on the one hand building and 
plant qualification, and on the other, 
process performance qualification 
(PPQ).
- "Process performance qualification" 
(PPQ) corresponds mainly to the con-
tent defined to date with "process vali-
dation". This term was only introduced 
by the FDA in the final version of the 
guideline – as a response to numerous 
complaints against the first draft in 
which "process qualification" (stage 2) 
evisaged a mixture of system qualifi-
cation and classical process validation 
which was difficult for the user to un-
derstand.

At first glance the new terms seem to con-
found everything that was known to date. 
However, if the three new validation stag-
es are compared directly with the familiar 
procedures, as illustrated in Figure 1 (see 
p. 2), it can be seen that as the end result 
only the vocabulary has changed.

Terms no longer used

Some familiar technical terms from the 
subject of validation are no longer included 
in the FDA Guidance:

- Prospective / retrospective/ 
concurrent validation:
Retrospective validation will presumably 
be a thing of the past and will no longer be 
mentioned by the FDA. The term concur-
rent validation has been replaced by "con-
current release of PPQ batches". This 
makes it clear that there are no longer 
different approaches to validation, but just 
a single one: the life cycle model. Within 
this strategy there is - under very strict 
boundary conditions which must be justi-
fied in individual cases - the option of re-
leasing validation batches for the market 
before stage 2, "Process qualification", has 
been completed.

- IQ / OQ:
According to the life cycle concept, qualifi-
cation of rooms and equipment is part of 
process validation (see below). However, 
the FDA Guidance makes no statements 
regarding details of plant qualification and 
its individual stages - because good, tried 
and tested methods have already been 
established for this and there is no further 
requirement for interpretation on the part 
of the FDA.

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Critical Quality Attribute (CQA) / Critical Process Parameter (CPP):

The FDA Guidance does not distinguish explicitly between "critical" and "uncritical" attributes or process parameters. Instead, the "criticality" is to be assessed continuously in the product life cycle on risk-based terms. This approach makes sense, but deviates from the information in ICH Q8 (R2): there great importance is ascribed to identifying critical material attributes and process parameters and assigning these to quality-determining product attributes in the context of development – namely as a prerequisite for defining "Design Spaces".

Worst case:
The investigation or examination only of extreme values or extreme cases is not necessary in a concept which demands in-depth scientific understanding of the process.

Qualification as part of process validation

What is actually new in terms of content and takes some time getting used to is the shifting of room and equipment qualification into the process validation cycle. Proof of the suitability of rooms, installations and equipment has to date been regarded as a necessary requirement for process validation; according to the FDA concept it must now be seen as an integral part. That is understandable when the idea of regarding the three stages of the FDA process validation model as a strict temporal sequence is dispensed with. If the three stages are seen rather as a logical sequence of actions which necessitate each other, this rearrangement appears less strange: also the established approach for process validation requires a check in the context of validation planning whether the

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Figure 1 Interpretation: Validation in the life cycle of a product (Dr. C. Oechslein)

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rooms, plants and equipment needed for the process examined are in a qualified status and the result must be documented in the validation plan.

Nevertheless the new assignment for plant qualification in "stage 2" proposed by the FDA gives rise to the question of whether the upstream "process design" stage makes sense or is possible without qualified rooms and plants. After all, if "process design" is to be understood as more than theoretical mathematical test design, according to prevalent GMP opinion the development equipment used at this stage should also be suitable for its purpose, the suitability customarily being proven by qualification. Only in this way can the data obtained be used for the following validation stages.

On the other hand the explanations in the FDA Guidance relating to the "Design of a Facility and Qualification of Utilities and Equipment" do not refer specifically to production plants, but are so general that they can also be used for development equipment. However, this means that room and equipment qualification is not to be seen so unambiguously as part of the second process validation stage, but – as before – remains a requirement for all validation activities.

**Particular focuses of the FDA Guidance**

Apart from the changed concepts and the presentation of process validation as a three-stage strategy, in its Guidance the FDA specifies a few focuses which will play a role in planning, implementing and inspecting process validation in the future:

- **Attributes and parameters to be examined**

  Whereas in the past primarily the attributes and parameters of processes were examined, the FDA has now extended the focus of validation expressly to product, material and quality attributes, and also to process, operation and equipment parameters. Attributes and parameters are not to be divided according to whether they are "critical" or "uncritical". In the product or process life cycle the finding regarding how "critical" something is to be regarded as is in a process of ongoing change and must be re-assessed in risk-based terms. The terms "Critical Quality Attribute" or "Critical Process Parameter" are consequently not used in the FDA Guidance.

- **Variations**

  The founding fathers of the idea of quality management already recognised the meaning of variations for quality ("Variation is the enemy of quality", E. Deming). However, as all processes in the animate and inanimate universe execute with variations, it is of prime importance that we should not be at the mercy of such variations but should have them "under control".

  The following measures are required to get a grip on variations:

  - Understanding the causes of variations
  - Recognising their occurrence and scope
  - Understanding their effects on the process and on the product attributes
  - Reaction and control in a manner which is commensurate with the quality risk

  The FDA Guidance emphasises the importance of gathering precise knowledge about processes and their variations in the context of development and validation so that the "Strategy for Process Control" for routine production can be derived from this process understanding. For this purpose the FDA makes the suggestion that a high level of control is required for attributes and parameters which represent a high risk.

- **Increased use of statistical methods**

  The use of statistical methods to assess the variation from batch to batch has been demanded as mandatory by the FDA since
1978 in the CFR Preamble and in 21 CFR 211.110(b). The guidance for process validation now explicitly names application examples in the validation procedure in which the FDA requires the use of statistical procedures. Which aspects are to be examined in which life cycle stage with the help of statistical methods is summarised in the overview below.

**Stage 1: Process Design:**
- Test planning and evaluation, e.g. in the context of “Design of Experiments” (DoE)

**Stage 2: Process Performance Qualification (PPQ):**
- Definition of the number of samples which must be taken during PPQ
- Assessment of all data collected and statements with respect to process capability

**Stage 3: Continued Process Verification:**
- In the course of routine commercial manufacturing the sampling and monitoring scope can be reduced in comparison to the PPQ stage if the data status permits this
- The procedures or instructions for ongoing process monitoring should be developed on the basis of statistical considerations

**Conclusion**

The FDA Guidance for process validation has embraced the principal trends of the ICH Guides Q8-10 and thus makes scientifically-based development, risk management and quality management the cornerstones in the life cycle of product validation. However, the FDA does more than merely combine these basic thoughts by introducing a few new terms and by redefining or even no longer including established terms. It remains to be seen whether these new concepts and assignments will also be adopted in the European regulations.

**Sources / Literature:**

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**Additional links:**
- Original guideline: FDA Process Validation Guideline  
- LOGFILE No. 5/2011 - Process Validation from a FDA Perspective Part 1  
- FDA Process Validation – A Lifecycle Approach  
- Synopsis: FDA Process Validation Guideline

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