



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Questions and Answers on Design Space Verification

In March 2011, the EMA and FDA launched a pilot program to allow joint evaluation of QbD (Quality by Design) elements. As a result of this pilot program, the EMA and FDA reached agreements on a wide range of QbD elements. A joint question and answer (Q&A) document was published on August 20, 2013 that reflects EMA and FDA harmonization on some QbD aspects.

The Q&A below is a reflection of EMA's and FDA's position on the topic of design space verification.

Design space verification is a demonstration that the proposed combination of input process parameters and material attributes are capable of manufacturing quality product at commercial scale.

This document is conceptually divided into three sections. The first section includes general question and answers that are harmonized between EMA and FDA. Appendix 1 includes EMA specific expectations and Appendix 2 includes FDA specific expectations.

1. Why would a design space be verified during the product lifecycle?

In both Agencies' experience, the design space verification at commercial scale is not necessarily complete at the time of submission of the application but should occur over the lifecycle of the product and process. Initial design space verification often occurs solely at or near the target operating ranges.

However, movements from one area to another area within the design space (e.g., re-establishing the Normal Operating Ranges (NOR)) within the approved design space in an unverified area) may pose higher or unknown risks due to potential scale –up effects and/or model assumptions. It is important that these risks are understood and evaluated utilizing an appropriate control strategy, including but not restricted to the controls submitted in the dossier. It is understood that when an applicant demonstrates that a design space is scale independent, then additional risk mitigation steps are not necessary for design space verification.

2. What is the purpose of design space verification at commercial scale?

Design space verification demonstrates that within design space boundaries scale-up effects are under control and do not adversely affect the expected product quality at commercial scale.

3. How is a design space initially developed and verified at commercial scale?

Both Agencies acknowledge that when a design space is established at early stages of product development, it is typically developed based on experiments conducted at laboratory or pilot scale. The confidence in the design space at commercial scale can vary depending on the amount and type of

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development data generated and the knowledge of the scalability (i.e., the degree of scale dependency of the design space). Design space limits at commercial scale can be based on scale-up correlations demonstrated during development studies and/or experimentation. In addition, design space limits can be challenged with computational simulations.

The Agencies further acknowledged that the commercial process is generally operated in a specific area of the design space, sometimes called the NOR (Normal Operating Range). The NOR describes a region around the target operating conditions that contains typical operational variability. Initial process verification often occurs solely within the NOR at commercial scale.

4. How can a design space be verified at commercial scale?

It is not necessary to repeat at commercial scale the experiments initially conducted to define a design space at lab or pilot scale. Furthermore, it is neither necessary to verify entire areas of design space nor to identify the edge of failure. In principle, more than one area of a design space may be verified at the time of submission but the design space can, as appropriate, also be further verified over the product lifecycle.

The approach to design space verification over the product lifecycle can be guided by the results of risk assessment on the potential effect of changes to scale dependent parameters on product quality. Depending on the specific change, the potential impact to the product quality, and the ability of the control strategy to detect product failures, the management of the risk can include additional monitoring of quality attributes and/or process parameters not included in the routine control system.

5. How should design space verification protocol be addressed in the submission?

In principle, a design space verification protocol could include the following: list of scale dependent parameters whose impact on the CQAs has not been verified at commercial scale, definition of the potential scale-up risks to the CQAs, discussion of whether the control strategy can address these risks, and description of any additional controls, as needed.

EU authorities' expectation is that a protocol for design space verification be submitted in section 3.2.R of the application. At the time of submission, a proposed design space not verified at commercial scale should be accompanied by an appropriate verification protocol. The protocol would be assessed at the time of review. Verification data are managed and documented in the site change management system.

FDA's expectation is that any plans for design space verification be available at the manufacturing site as an element of the change control, validation, and/or knowledge management strategy. Providing data for initial design space verification and a high-level overview of the plan for design space verification over the product lifecycle can be beneficial to the review of the application.

6. What if unexpected results/events are obtained during the design space verification studies?

If the verification studies prove the process does not meet the predefined product quality attributes in a new region of the approved design space, this may indicate an underlying issue with the design space or a flaw in the assessment or verification plan. Changes to the boundaries or description of the design space and any required changes to design space verification protocol should be reported to the Agencies, using appropriate notification categories, in accordance with regional requirements.

Appendix 1 and 2 address regional expectations and regulations

Appendix 1: EU's expectations

7. How can a design space be verified at commercial scale for biological products?

Principles laid down for chemical products are applicable to biological products. In addition, verification studies should provide evidence that the quality attributes of the product are comparable prior to and after the change. This could include a proposal for modular sets of tests and acceptance criteria to be deployed, taking into account the nature of the change and its associated risk.

8. What is the difference between process validation and design space verification?

Design space verification should not be confused with process validation. Both take into consideration prior knowledge and development conclusions and are conducted at commercial scale, however the scope of the studies are not the same. Whereas process validation demonstrates consistency of the process at normal operating ranges, design space verification demonstrates that scale effect and or model assumptions are under control in the new area of design space and do not affect product quality. Unlike validation which covers all the steps of the manufacturing process, verification studies refer only to those operations where a design space has been proposed.

In order to address the risks identified during the risk assessment of operating in the unverified area of the design space the verification studies may also include testing / monitoring of additional parameters or at an increased frequency as compared to the routine control strategy.

When verification data proves that the extent of movement within the design space is of high risk (e.g. critical quality attributes are met but close to edge of failure identified at laboratory/pilot scale), process validation (consistency of the process) in the new area of design space (new NOR) should also be considered.

A protocol for design space verification should be submitted in section 3.2.R. irrespective of the validation approach. When a strategy for continuous verification is envisaged, where relevant, the elements of design space verification should be included as part of the continuous verification protocol.

It is understood that when an applicant can demonstrate that the design space is scale independent then a verification protocol is not requested in the dossier.

NB: Continuous Process Verification is an alternative approach to traditional process validation in which manufacturing process performance is continuously monitored and evaluated (ICH Q8).

Appendix 2: FDA expectations

9. How should design space verification approach be addressed in the pharmaceutical quality system?

FDA recommends that firms have a written plan for when and how to evaluate the need for design space verification under their pharmaceutical quality system. FDA's expectation is that such plans for design space verification be available at the manufacturing site. Additionally, it can be beneficial to the review of the application for the applicant to include in the initial submission a high-level overview of the plan for design space verification over the product lifecycle.