



PAT tools enabling control strategy of CQAs / Regulatory Updates

PPAR Annual Meeting 2011

ICH Q8 Control Strategy Definition (1)

2.5 Control Strategy

A control strategy is designed to ensure that a product of required quality will be produced consistently. The elements of the control strategy discussed in Section P.2 of the dossier should describe and justify how in-process controls and the controls of input materials (drug substance and excipients), intermediates (in-process materials), container closure system, and drug products contribute to the final product quality. These controls should be based on product, formulation and process understanding and should include, at a minimum, control of the critical process parameters¹ and material attributes.

ICH Q8 Control Strategy Definition (2)

A control strategy can include, but is not limited to, the following:

- Control of input material attributes (e.g., drug substance, excipients, primary packaging materials) based on an understanding of their impact on processability or product quality;
- Product specification(s);
- Controls for unit operations that have an impact on downstream processing or product quality (e.g., the impact of drying on degradation, particle size distribution of the granulate on dissolution);
- In-process or real-time release testing in lieu of end-product testing (e.g. measurement and control of CQAs during processing);
- A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.

Regulatory updates

- PAT control tools mentioned in the **new FDA Process Validation Guideline** (January 2011)
- Control Strategy section in the **ICH Points to Consider / ICH-Endorsed Guide for ICHQ9/Q9/Q10 Implementation** (June 2011)
- ASTM standards?
- EMA and PQRI working groups on **Large Sample Size statistical evaluations** -> Separate discussion
- Impact of EMA/FDA QbD Pilot Program on evaluation of PAT tools?
- Anything else?

Ref. 1: FDA Validation Guideline (Jan 2011)

■ Section B-2 (bottom page 9 / page 10)

Guidance for Industry

Process Validation: General Principles and Practices

Additional copies are available from:

Office of Communications
Division of Drug Information, W051, Room 2201
10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov

<http://www.fda.gov/Drugs/Guidance/ComplianceRegulatoryInformation/Guidance>

and/or

Office of Communication, Outreach and Development, HFM
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
(Tel) 301-835-4709 or 301-827-1800

<http://www.fda.gov/BiologicsBloodVaccines/Guidance/ComplianceRegulatoryInformation>

and/or

Communications Staff, HFV-12
Center for Veterinary Medicine
Food and Drug Administration
7519 Standish Place,
Rockville, MD 20855
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<http://www.fda.gov/AnimalVeterinary/Guidance/ComplianceRegulatoryInformation>

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

January 2011
Current Good Manufacturing Practices (CGMP)
Revision 1

More advanced strategies, which may involve the use of process analytical technology (PAT), can include timely analysis and control loops to adjust the processing conditions so that the output remains constant. Manufacturing systems of this type can provide a higher degree of

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Contains Nonbinding Recommendations

process control than non-PAT systems. In the case of a strategy using PAT, the approach to process qualification will differ from that used in other process designs. Further information on PAT processes can be found in FDA's guidance for industry on PAT — *A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*.¹⁴

Ref. 2: ICH Doc. “Points to Consider” (Jun 2011)



ICH Quality Implementation Working Group

POINTS TO CONSIDER **ICH-Endorsed Guide for** **ICH Q8/Q9/Q10 Implementation**

Document date: 16 June 2011

Discussion topics

- What is the importance of using PAT tools in developing a control strategy for a pharma process / CQAs in your company?
- Do you use PAT tools for feed-forward/-back control loops?
- What is the role of PAT tools to achieve RTRT for CQAs?
- Do you have first-hand experience with registration of PAT solution(s) for Control Strategy?
- From a regulatory point of view, are PAT control strategies treated in the same way in EU, US and Rest of World?

Back-ups

Ref. 2: ICH Doc. “Points to Consider” (Jun 2011)

2.2. Relationship of Criticality to Control Strategy

The identification and linkage of the CQAs and CPPs should be considered when designing the control strategy. A well-developed control strategy will reduce risk but does not change the criticality of attributes.

The control strategy plays a key role in ensuring that the CQAs are met, and hence that the QTPP is realised.

Ref. 2: ICH Doc. “Points to Consider” (Jun 2011)

Section 3. CONTROL STRATEGY

3.1. Life-cycle of the control strategy

The life-cycle of the control strategy is supported by Pharmaceutical Development, Quality Risk Management (QRM) and the Pharmaceutical Quality System (PQS) as described in the ICH guidelines ICH Q8, Q9, Q10.

The following points can be considered:

➤ Development of control strategy:

- The control strategy is generally developed and initially implemented for production of clinical trial materials. It can be refined for use in commercial manufacture as new knowledge is gained. Changes could include acceptance criteria, analytical methodology, or the points of control (e.g., introduction of real-time release testing).
- Additional emphasis on process controls should be considered in cases where products cannot be well-characterized and/or quality attributes might not be readily measurable due to limitations of testing or detectability (e.g., microbial load/sterility).

Ref. 2: ICH Doc. “Points to Consider” (Jun 2011)

➤ Continual improvement of the control strategy:

- Consideration should be given to improving the control strategy over the life-cycle (e.g., in response to assessment of data trends over time and other knowledge gained).
- Continuous process verification is one approach that enables a company to monitor the process and make adjustments to the process and/or the control strategy, as appropriate.
- When multivariate prediction models are used, systems that maintain and update the models help to assure the continued suitability of the model within the control strategy.

➤ Change management of the control strategy:

- Attention should be given to outsourced activities to ensure all changes are communicated and managed.
- The regulatory action appropriate for different types of changes should be handled in accordance with the regional regulatory requirements.

Ref. 2: ICH Doc. “Points to Consider” (Jun 2011)

➤ Different control strategies for the same product:

- Different control strategies could be applied at different sites or when using different technologies for the same product at the same site.
- Differences might be due to equipment, facilities, systems, business requirements (e.g., confidentiality issues, vendor capabilities at outsourced manufacturers) or as a result of regulatory assessment/inspection outcomes.
- The applicant should consider the impact of the control strategy implemented on the residual risk and the batch release process.

➤ Knowledge management:

- Knowledge management is an important factor in assuring the ongoing effectiveness of the control strategy.
- For contract manufacturing, knowledge transfer in both directions between the parties should be considered, particularly for model

Ref. 2: ICH Doc. “Points to Consider” (Jun 2011)

3.2. Suitability of Control Strategy at different scales

➤ Management of risk on scale-up:

- Risk associated with scale-up should be considered in Control Strategy development to maximize the probability of effectiveness at scale. The design and need for scale-up studies can depend on the development approach used and knowledge available.
- A risk based approach can be applied to the assessment of suitability of a Control Strategy across different scales. QRM tools can be used to guide these activities. This assessment might include risks from processing equipment, facility environmental controls, personnel capability, experiences with technologies, and historical experience (prior knowledge). See the ICH Q-IWG case study for examples.

Ref. 2: ICH Doc. “Points to Consider” (Jun 2011)

➤ Scale-up considerations for elements of Control Strategy:

- *Complexity of product and process*
- *Differences in manufacturing equipment, facilities and/or sites*
- *Raw materials:*
 - Differences in raw material quality due to source or batch to batch variability
 - Impact of such differences on process controls and quality attributes
- *Process parameters:*
 - Confirmation or optimization
 - Confirmation of the design space(s), if used
- *In-process controls:*
 - Point of control
 - Optimization of control methods
 - Optimization and/or updating of models, if used
- *Product specification:*
 - Verification of the link to QTPP
 - Confirmation of specifications i.e., methods and acceptance criteria
 - Confirmation of RTRT, if used