

ICH Quality Implementation Working Group

POINTS TO CONSIDER

ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation

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Document History

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Table of Content

Section 1.	INTRODUCTION	1
Section 2.	CRITICALITY OF QUALITY ATTRIBUTES AND PROCESS PARAMETERS	1
	2.1. Considerations for Establishing CQAs and CPPs	1
	2.2. Relationship of Criticality to Control Strategy.....	2
Section 3.	CONTROL STRATEGY	3
	3.1. Life-cycle of the control strategy	3
	3.2. Suitability of Control Strategy at different scales.....	4
	3.3. Specifications and Certificate of Analysis (CoA) for Real- Time Release Testing (RTRT).....	4
	3.4. Process for a batch release decision	5
Section 4.	LEVEL OF DOCUMENTATION IN ENHANCED (QBD) REGULATORY SUBMISSIONS	6
	4.1. Risk Management Methodologies	7
	4.2. Design of Experiments.....	7
	4.3. Manufacturing Process Description	8
	4.4. Models.....	8
	4.5. Design Space	8

ICH QUALITY IWG

POINTS TO CONSIDER

Guide for ICH Q8/Q9/Q10 Guidelines

Endorsed by the ICH Steering Committee on 16 June 2011

Section 1. INTRODUCTION

The ICH Quality Implementation Working Group (Q-IWG) has prepared 'Points to Consider' covering topics relevant to the implementation of ICH Q8(R2), Q9 and Q10, which supplement the existing [Questions & Answers](#) and [workshop training materials](#) already produced by this group. They should be considered all together.

The 'Points to Consider' are based on questions raised during the ICH Q-IWG training workshop sessions in the three regions. The Points to Consider are not intended to be new guidelines. They are intended to provide clarity to both industry and regulators and to facilitate the preparation, assessment and inspection related to applications filed for marketing authorizations.

The development approach should be adapted based on the complexity and specificity of product and process; therefore, applicants are encouraged to contact regulatory authorities regarding questions related to specific information to be included in their application.

Using the Quality by Design (QbD) approach does not change regional regulatory requirements but can provide opportunities for more flexible approaches to meet them. In all cases, GMP compliance is expected.

Section 2. CRITICALITY OF QUALITY ATTRIBUTES AND PROCESS PARAMETERS

Scientific rationale and Quality Risk Management (QRM) processes are used to reach a conclusion on what are Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) for a given product and process

The Quality Target Product Profile (QTPP) describes the design criteria for the product, and should therefore form the basis for development of the CQAs, CPPs, and Control Strategy.

The information developed to determine CQAs and CPPs will help to:

- Develop control strategy
- Ensure quality of the product throughout the product lifecycle
- Increase product and process knowledge
- Increase transparency and understanding for regulators and industry
- Evaluate changes

2.1. Considerations for Establishing CQAs and CPPs

The introduction of ICH Q9 states that: *"...the protection of the patient by managing the risk to quality should be considered of prime importance"*. The QTPP provides an understanding of what will ensure the quality, safety and efficacy of a specific product for the patient and is a starting point for identifying the CQAs.

As part of risk assessment, risk analysis, as defined by ICH Q9 is: *‘the qualitative or quantitative process of linking the likelihood of occurrence and **severity of harm**. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.’*

Relationship between risk and criticality:

- **Risk** includes severity of harm, probability of occurrence, and detectability, and therefore the level of risk can change as a result of risk management.
- **Quality Attribute criticality** is primarily based upon severity of harm and does not change as a result of risk management.
- **Process Parameter criticality** is linked to the parameter’s effect on any critical quality attribute. It is based on the probability of occurrence and detectability and therefore can change as a result of risk management.

Considerations for identifying and documenting CQAs can include the:

- Severity of harm (safety and efficacy) before taking into account risk control and the rationale for distinguishing CQAs from other quality attributes.
- Link to the patient as described in the QTPP.
- Basis on which the CQAs have been developed (e.g., prior knowledge, scientific first principles, and experimentation).
- Inter-dependencies of the different CQAs.

Considerations for identifying and documenting CPPs can include the:

- Risk assessment and experimentation to establish the linkage between potential CPPs and CQAs .
- Basis on which the CPPs have been identified (e.g., prior knowledge, scientific first principles, QRM, Design of Experiment (DoE), and other appropriate experimentation).
- Inter-dependencies of the different CPPs.
- Selected Control Strategy and the residual risk.

CQAs and CPPs can evolve throughout the product lifecycle, for example:

- Change of manufacturing process (e.g., change of synthetic route).
- Subsequent knowledge gained throughout the lifecycle (e.g., raw material variability, pharmacovigilance, clinical trial experience, and product complaints).

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.

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).

➤ **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.

➤ **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

maintenance and/or updates, application of design space, and control strategies incorporating real-time release testing.

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.

➤ 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

3.3. Specifications and Certificate of Analysis (CoA) for Real-Time Release Testing (RTRT)

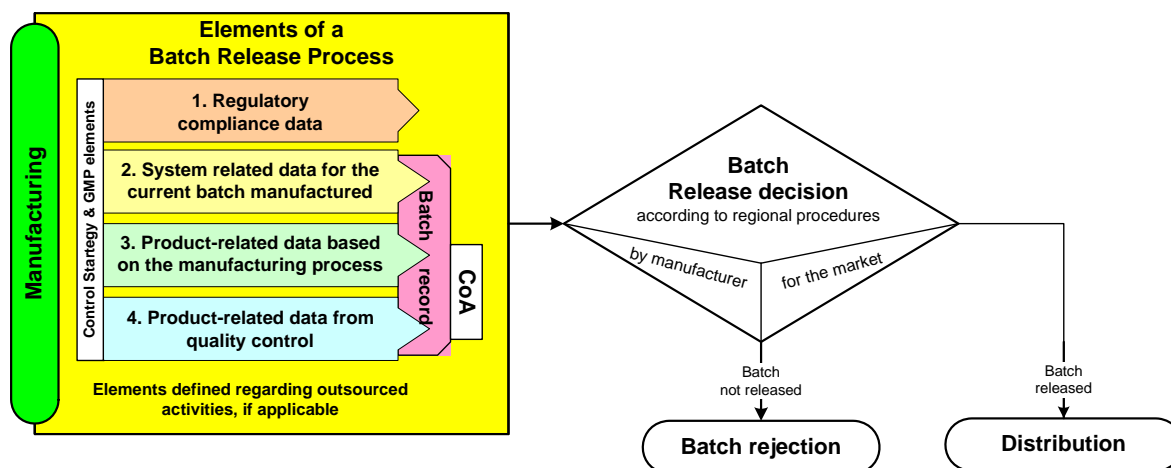
The purpose of specifications and CoAs remains the same in the case of RTRT, but the way to develop them is different. RTR tests are considered to be specification testing methods and follow the established regional regulatory requirements for release specifications (as interpreted in e.g., ICH Q6A and ICH Q6B guidelines) together with other regional regulatory requirements (e.g., formats, GMP, batch acceptance decisions).

The use of RTRT has been addressed (see ICH Q8(R2) Section 2.5.; ICH Q-IWG Q&A Chapter 2.2). The following are points to be considered when developing a specification and CoA for RTRT:

- **Quality attributes:**
 - Not all CQAs need to be included in the specification.
 - The attribute to be measured (e.g., surrogate for a CQA) can depend on the point of testing and/or control (e.g., materials, process steps, process parameters).
 - Linking of the measured attribute to CQA and QTPP.
- **Methods of control:**
 - The type of control used (e.g., models, PAT, test of isolated material, end product test, stability and regulatory test).
 - Reference to the testing method used, if relevant.
 - Validation of control method.
- **Acceptance criteria:**
 - Acceptance criteria at control point.
 - Criteria for stability and regulatory testing.
- **CoA elements:**
 - Reported results e.g., values calculated from models, established calibrations and actual test results.
 - Acceptance criteria related to the method used.
 - Method references.

3.4. Process for a batch release decision

Different development approaches lead to different control strategies. Regardless of the control strategy, the batch release process should be followed. For a batch release decision, several elements should be considered. See in the figure below an illustration of the elements of the batch release process leading to the batch release decision.



1. Regulatory compliance data:

There are regional differences in the regulation of batch release across the ICH regions [e.g., Qualified Person (EU), Good Quality Practice (Japan), Head of Quality Unit (US)] and the manufacturing licensing procedure. The PQS facilitates implementing and managing control strategy and Batch Release, notably through elements of a global approach (corporate/site/contractor). The PQS elements also facilitate regulatory

compliance (e.g., changes that call for variation of the marketing authorization), including changes at manufacturing sites (e.g., changes regarding facilities, utilities and equipment).

2. System related data for the current batch manufactured (e.g., environmental, facility, utilities and equipment):

In the enhanced approach, there is an increased focus on process monitoring, which can provide the opportunity to perform continuous process verification. Any deviation or atypical event that occurs during manufacturing (e.g., involving the manufacturing process, facility, personnel, testing) is recorded and assessed, properly handled under the PQS (including CAPA) and closed out prior to release.

3. Product-related data based on the manufacturing process:

Elements of the control strategy are defined and proposed in the marketing authorization dossier and agreed to by the regulators. Manufacturers should define, manage and monitor product-related data from batches manufactured according to the control strategy. These will be regularly assessed and reviewed during audits and inspections.

4. Product-related data from quality control:

Results from end product testing and/or RTRT provide data based on which a CoA can be issued, in compliance with the specification as part of the release decision.

The **batch release process** leading to the **batch release decision** can be performed by more than one quality individual depending on the regional regulatory requirements and company policy:

- Batch release by manufacturer or contractor for internal purposes.
- Batch release by manufacturing authorisation holder for the market.

Section 4. LEVEL OF DOCUMENTATION IN ENHANCED (QbD) REGULATORY SUBMISSIONS

This document is intended to provide suggestions on the type of information and the level of documentation that is appropriate to support a proposal for enhanced (QbD) approach. The type of information, as suggested in this document, is considered supportive and is intended to facilitate assessment and inspection without increasing the regulatory requirement. Submitted information should be organised in a clear manner and provide the regulators with sufficient understanding of the company's development approach; this information will be important to the evaluation of the proposed Control Strategy. Companies might consider, especially for QbD-containing submissions, an internal peer review process to assure quality, clarity and adequacy of the regulatory submission.

For submissions containing QbD elements (e.g., RTRT, design space), it is helpful for regulators to have a statement by the applicant describing the proposed regulatory outcome and expectations.

It is important to realize that not all the studies performed and/or data generated during product development need to be submitted. However, sufficient supporting information and data should be submitted in the application to address the following:

- The scientific justification of the proposed Control Strategy.

- The scientific rationale for the studies conducted.
- A concise description of methodologies used to conduct these studies and to analyze the generated data.
- The summary of results and conclusions drawn from these studies.

The following sections include examples of background information that can be considered by both companies and regulatory authorities to assure scientific risk-based regulatory decisions.

4.1. Risk Management Methodologies

Following determination of the Quality Target Product Profile (QTPP) of the product under development, the applicant can use Quality Risk Management (QRM, ICH Q9) tools to rank and select quality attributes (including material attributes) and/or process parameters that should be further evaluated and/or controlled within appropriate ranges to ensure the desired product quality. The applicant should consider providing information of sufficient detail to demonstrate how the conclusions were reached, which can include:

- The scientific rationale for designation of QTPP and identification of corresponding CQAs (Critical Quality Attributes).
- Material attributes, process parameters and prior knowledge that were considered during risk assessment, preferably provided in a concise/tabulated form.
- Relevant known risk factors, e.g., degradation, solubility, etc.
- The scientific rationale and basis for the risk assessment as part of risk management and experiments that determined the final criticality of quality attributes and process parameters.
- Identification of potential residual risk that might remain after the implementation of the proposed Control Strategy (e.g., movements to commercially unverified areas of design space) and discussion of approaches for managing the residual risk.
- A list of critical and other quality attributes and process parameters.
- The linkage between CPP's , CQAs and the QTPP.
- Comment on the impact of the following on risk assessment: (a) interaction of attributes and process parameters, (b) effect of equipment and scale.

4.2. Design of Experiments

The factors to be studied in a DoE could come from the risk assessment exercise or prior knowledge. Inclusion of a full statistical evaluation of the DoEs performed at early development stages (e.g., screening) is not expected. A summary table of the factors and ranges studied and the conclusions reached will be helpful. For DoEs involving single- or multiple-unit operations that are used to establish CPPs and/or to define a Design Space (DS), the inclusion of the following information in the submission will greatly facilitate assessment by the regulators:

- Rationale for selection of DoE variables (including ranges) that would be chosen by risk assessment (e.g., consideration of the potential interactions with other variables).
- Any evidence of variability in raw materials (e.g., drug substance and/or excipients) that would have an impact on predictions made from DoE studies.

- Listing of the parameters that would be kept constant during the DoEs and their respective values, including comments on the impact of scale on these parameters.
- Type of experimental design used and a justification of its appropriateness, including the power of the design.
- Factors under study and their ranges can be presented in a tabular format. Submitters should indicate if the factors are expected to be scale-dependent.
- Reference to the type of analytical methods (e.g., HPLC, NIR) used for the evaluation of the data and their suitability for their intended use (e.g., specificity, detection limit).
- Results and statistical analysis of DoE data showing the statistical significance of the factors and their interactions, including predictions made from DoE studies relevant to scale and equipment differences.

4.3. Manufacturing Process Description

While preparing regulatory submissions, applicants should consider:

- Regional regulatory requirements with regard to the level of detail in describing manufacturing processes.
- Describing the proposed design space, including critical and other parameters studied, and its role in the development of the control strategy.
- Manufacturing changes should be managed in accordance with regional regulatory requirements. Where relevant, applicants can also consider submitting post-approval change management plans or protocols to manage post-approval manufacturing changes based on regional requirements.

4.4. Models

Points to consider for the role of modelling in QbD and the associated level of documentation in the regulatory submission are being developed.

4.5. Design Space

Points to consider for the design space and the associated level of documentation in the regulatory submission are being developed.