
Guidance for Industry

Q8, Q9, and Q10 Questions and Answers

**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)**

**May 2010
ICH**

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Q8, Q9, and Q10

Questions and Answers

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Guidance for Industry¹

Q8, Q9, and Q10 Questions and Answers

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I. INTRODUCTION (1)

Since the Q8, Q9, and Q10 guidances were made final, experiences implementing the guidances in the ICH regions have given rise to requests for clarification. This question and answer (Q&A) document is intended to clarify key issues. The guidance reflects the current working procedure of the ICH Quality Implementation Working Group (Q-IWG) for implementing the Q8, Q9, and Q10 guidances.

The benefits of harmonizing technical requirements across the ICH regions can be realized only if the various quality ICH guidances are implemented and interpreted in a consistent way across the three regions. The Q-IWG is tasked to develop Q&As to facilitate implementation of existing quality guidance.

The Q&As reference the following ICH guidances available on the Internet at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> under International Conference on Harmonisation — Quality:

- *Q8 (R2) Pharmaceutical Development* (includes the Q8 parent guidance (Part I) and the annex (Part II), which provides further clarification of the Q8 parent guidance and describes the principles of quality by design)
- *Q9 Quality Risk Management*
- *Q10 Pharmaceutical Quality Systems*

¹ This guidance was developed within the Quality Implementation Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. The Q&As in this document have been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, April 2009, June 2009, and October 2009. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

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FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. QUESTIONS AND ANSWERS

A. For General Clarification (1.1)

Q1: Is the minimal approach accepted by regulators?

A1: Yes. The minimal approach as defined in Q8(R2) (sometime also called "baseline" or "traditional" approach) is the expectation that is to be achieved for a fully acceptable submission. However, the "enhanced" approach as described in ICH Q8(R2) is encouraged (Ref. Q8(R2) Annex, appendix 1). (Approved June 2009)

Q2: What is an appropriate approach for process validation using ICH Q8, Q9, and Q10?

A2: The objectives of process validation are unchanged when using ICH Q8, Q9, and Q10. The main objective of process validation remains that a process design yields a product meeting its predefined quality criteria. ICH Q8, Q9, and Q10 provide a structured way to define product critical quality attributes, design space, the manufacturing process, and the control strategy. This information can be used to identify the type and focus of studies to be performed prior to and on initial commercial production batches. As an alternative to the traditional process validation, continuous process verification (see definition in ICH Q8R(2) glossary) can be utilized in process validation protocols for the initial commercial production and for manufacturing process changes for the continual improvement throughout the remainder of the product lifecycle. (Approved October 2009)

Q3: How can information from risk management and continuous process verification provide for a robust continual improvement approach under ICH Q8, Q9 and Q10?

A: Like the product itself, process validation also has a lifecycle (process design, process qualification and ongoing process verification). A risk assessment conducted prior to initial commercial validation batches can highlight the areas where particular focus and data collection could demonstrate the desired high level of assurance of commercial process robustness. Continual monitoring (e.g., via continuous process verification) can further demonstrate the actual level of assurance of process consistency and provide the basis for continual improvement of the product. Quality Risk Management methodologies of ICH Q9 can be

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applied throughout the product lifecycle to maintain a state of process control.
(Approved October 2009)

B. Quality by Design (QbD) Topics (2)

Q1: Is it always necessary to have a design space (DS) or real-time release (RTR) testing to implement QbD?

A1: Under Quality by Design, establishing a design space or using real-time release testing is not necessarily expected (ICH Q8(R2)). (Approved April 2009)

1. Design Space (2.1)

Q1: Is it necessary to study multivariate interactions of all parameters to develop a design space?

A1: No, the applicant should justify the choice of material attributes and parameters for multivariate experimentation based on risk assessment and desired operational flexibility. (Approved April 2009)

Q2: Can a design space be applicable to scale-up?

A2: Yes, when appropriately justified (for additional details, see Q8(R2) Annex section II.D.4 (2.4.4)). An example of a scale-independent design space is provided in the European Federation of Pharmaceutical Industries and Associations (EFPIA) Mock P2 document (EFPIA Mock P2 submission on “Explain”: Chris Potter, Rafael Beerbohm, Alastair Coupe, Fritz Erni, Gerd Fischer, Staffan Folestad, Gordon Muirhead, Stephan Roenninger, Alistair Swanson, A guide to EFPIA’s “Mock P.2” Document, Pharm. Tech. (Europe), 18, December 2006, 39-44).

This example may not reflect the full regulatory requirements for a scale-up.
(Approved April 2009)

Q3: Can a design space be applicable to a site change?

A3: Yes, it is possible to justify a site change using a site independent design space based on a demonstrated understanding of the robustness of the process and an in depth consideration of site specific factors (e.g., equipment, personnel, utilities, manufacturing environment, and equipment). There are region specific regulatory requirements associated with site changes that need to be followed. (Approved April 2009)

Q4: Can a design space be developed for single and/or multiple unit operations?

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A4: Yes, it is possible to develop a design space for single unit operations or across a series of unit operations (see Q8(R2) Annex, section II.D.3 (2.4.3)). (Approved April 2009)

Q5: Is it possible to develop a design space for existing products?

A5: Yes, it is possible. Manufacturing data and process knowledge can be used to support a design space for existing products. Relevant information should be utilized from e.g., commercial scale manufacturing, process improvement, corrective and preventive action (CAPA), and development data.

For manufacturing operations run under narrow operational ranges in fixed equipment, an expanded region of operation and an understanding of multi-parameter interactions may not be achievable from existing manufacturing data alone and additional studies may provide the information to develop a design space. Sufficient knowledge should be demonstrated, and the design space should be supported experimentally to investigate interactions and establish parameter/attribute ranges. (Approved April 2009)

Q6: Is there a regulatory expectation to develop a design space for an existing product?

A6: No, development of design space for existing products is not necessary unless the applicant has a specific need and desires to use a design space as a means to achieve a higher degree of product and process understanding. This may increase manufacturing flexibility and/or robustness. (Approved April 2009)

Q7: Can a design space be applicable to formulation?

A7: Yes, it may be possible to develop formulation (not component but rather composition) design space consisting of the ranges of excipient amount and its physicochemical properties (e.g., particle size distribution, substitution degree of polymer) based on an enhanced knowledge over a wider range of material attributes. The applicant should justify the rationale for establishing the design space with respect to quality attributes such as bioequivalence, stability, manufacturing robustness etc. Formulation adjustment within the design space depending on material attributes does not need a submission in a regulatory postapproval change. (Approved June 2009)

Q8: Does a set of proven acceptable ranges alone constitute a design space?

No, a combination of proven acceptable ranges (PARs) developed from univariate experimentation does not constitute a design space (see Q8(R2) Annex, section II.D.5 (2.4.5)). Proven acceptable ranges from only univariate experimentation

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may lack an understanding of interactions between the process parameters and/or material attributes. However proven acceptable ranges continue to be acceptable from the regulatory perspective but are not considered a design space (see ICH Q8(R2) Annex, section II.D.5 (2.4.5)).

The applicant may elect to use proven acceptable ranges or design space for different aspects of the manufacturing process. (Approved June 2009)

2. *Real-Time Release Testing (2.2)*

Q1: *How is batch release affected by employing real-time release testing?*

A1: Batch release is the final decision to release the product to the market regardless of whether RTR testing or end-product testing is employed. End-product testing involves performance of specific analytical procedures on a defined sample size of the final product after completion of all processing for a given batch of that product. Results of real-time release testing are handled in the same manner as end-product testing results in the batch release decision. Batch release involves an independent review of batch conformance to predefined criteria through review of testing results and manufacturing records together with appropriate good manufacturing practice (GMP) compliance and quality system, regardless of which approach is used. (Approved April 2009)

Q2: *Does real-time release testing mean elimination of end-product testing?*

A2: Real-time release testing does not necessarily eliminate all end-product testing. For example, an applicant can propose RTR testing for some attributes only or not all. If all critical quality attributes (CQAs) (relevant for real-time release testing) are assured by in-process monitoring of parameters and/or testing of materials, then end-product testing might not be needed for batch release. Some product testing will be expected for certain regulatory processes such as stability studies or regional requirements. (Approved April 2009)

Q3: *Is a product specification still necessary in the case of RTR testing?*

A3: Yes, product specifications (see ICH Q6A and Q6B) still need to be established and met, when tested.² (Approved April 2009)

Q4: *When using RTR testing, is there a need for stability test methods?*

A4: Even where RTR testing is applied, a stability monitoring protocol that uses stability indicating methods is required³ for all products regardless of the means of release testing (see ICH Q1A and ICH Q5C). (Approved April 2009)

² See 21 CFR 314.50(d)(1) and 21 CFR 211.165.

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Q5: What is the relationship between control strategy and RTR testing?

A5: RTR testing, if utilized, is an element of the control strategy in which tests and/or monitoring can be performed as in-process testing (in-line, on-line, at-line) rather than tested on the end product. (Approved April 2009)

Q6: Do traditional sampling approaches apply to RTR testing?

A6: No, traditional sampling plans for in-process and end-product testing involve a discrete sample size that represents the minimal sampling expectations. Generally, the use of RTR testing will include more extensive on-line/in-line measurement. A scientifically sound sampling approach should be developed, justified, and implemented. (Approved April 2009)

Q7: If RTR testing results fail or trending toward failure, can end-product testing be used to release the batch?

A7: No, in principle the RTR testing results should be routinely used for the batch release decisions and not be substituted by end-product testing. Any failure should be investigated and trending should be followed up appropriately. However, batch release decisions should be made based on the results of the investigations. In the case of failure of the testing equipment, please refer to the previous question. The batch release decision should comply with the content of the marketing authorization and GMP compliance. (Approved April 2009)

Q8: What is the relationship between in-process testing and RTR testing?

A8: In-process testing includes any testing that occurs during the manufacturing process of drug substance and/or finished product. Real-time release testing includes those in-process tests that have a direct impact on the decision for batch release through evaluation of critical quality attributes. (Approved June 2009)

Q9: What is the difference between “real time release” and “real-time release testing”?

A9: The definition of *real-time release testing* in Q8(R2) is “the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data, which typically includes a valid combination of measured material attributes and process controls.”

³ 21 CFR 314.50(d)(1).

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The term *real time release* in the Q8(R2), step 2 document was revised to “real-time release testing” in the final Q8(R2) Annex to fit the definition more accurately and thus avoid confusion with batch release. (Approved June 2009)

Q10: Can surrogate measurement be used for RTR testing?

A10: Yes, RTR testing can be based on measurement of a surrogate (e.g., process parameter, material attribute) that has been demonstrated to correlate with an in-process or end-product specification (see ICH Q8(R2); Annex, section II.E (2.5)). (Approved June 2009)

Q11: What is the relationship between RTR testing and parametric release?

A11: Parametric release is one type of RTR testing. Parametric release is based on process data (e.g., temperature, pressure, time for terminal sterilization, physicochemical indicator) rather than the testing of material and/or a sample for a specific attribute. (Approved October 2009)

3. ***Control Strategy (2.3)***

Refer to the definition of *control strategy* provided in the ICH Q10 glossary:

A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

Q1: What is the difference in a control strategy for products developed using the minimal approach vs. “quality-by-design” approach?

A1: Control strategies are expected irrespective of the development approach. Control strategy includes different types of control proposed by the applicant to assure product quality (ICH Q10, section IV.B.1 (3.2.1)), such as in-process testing and end-product testing. For products developed following the minimal approach, the control strategy is usually derived empirically and typically relies more on discrete sampling and end-product testing. Under QbD, the control strategy is derived using a systematic science and risk-based approach. Testing, monitoring, or controlling is often shifted earlier into the process and conducted in-line, on-line, or at-line testing. (Approved April 2009)

Q2: Are GMP requirements different for batch release under QbD?

A2: No, the same GMP requirements apply for batch release under minimal and QbD approaches. (Approved April 2009)

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Q3: *What is the relationship between a design space and a control strategy?*

A3: A control strategy is required for all products.⁴ If a design space is developed and approved, the control strategy (see ICH Q8(R2), Annex, section IV (4)) provides the mechanism to ensure that the manufacturing process is maintained within the boundaries described by the design space. (Approved April 2009)

Q4: *What approaches can be taken in the event of on-line/in-line/at-line testing or monitoring equipment breakdown?*

A4: The control strategy provided in the application should include a proposal for use of alternative testing or monitoring approaches in cases of equipment failure. The alternative approach could involve use of end-product testing or other options, while maintaining an acceptable level of quality. Testing or monitoring equipment breakdown should be managed in the context of a deviation under the quality system and can be covered by GMP inspection. (Approved June 2009)

Q5: *Are product specifications different for minimal versus QbD approaches?*

A5: In principle no, product specifications are the same for minimal and QbD approaches. For a QbD approach, the control strategy can facilitate achieving the end product specifications via real time release testing approaches (see ICH Q8(R2) Annex, appendix 1). Product must meet specification, when tested.⁵ (Approved October 2009)

C. Pharmaceutical Quality System (3)

Q1: *What are the benefits of implementing a pharmaceutical quality system (PQS) (in accordance with ICH Q10)?*

A1: The benefits are:

- Facilitated robustness of the manufacturing process, through facilitation of continual improvement through science and risk-based postapproval change processes
- Consistency in the global pharmaceutical environment across regions
- Enable transparency of systems, processes, and organizational and management responsibility
- Clearer understanding of the application of a quality system throughout product lifecycle

⁴ 21 CFR 314.50(d)(1).

⁵ 21 CFR 211.165.

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- Further reducing risk of product failure and incidence of complaints and recalls, thereby providing greater assurance of pharmaceutical product consistency and availability (supply) to the patient
- Better process performance
- Opportunity to increase understanding between industry and regulators and more optimal use of industry and regulatory resources; enhance manufacturer's and regulators' confidence in product quality
- Increased compliance with GMPs, which builds confidence in the regulators and may result in shorter inspections

(Approved April 2009)

Q2: How does a company demonstrate implementation of PQS in accordance with ICH Q10?

A2: When implemented, a company will demonstrate the use of an effective PQS through its documentation (e.g., policies, standards), its processes, its training/qualification, its management, its continual improvement efforts, and its performance against pre-defined key performance indicators (see ICH Q10 glossary on *performance indicator*).

A mechanism should be established to demonstrate at a site how the PQS operates across the product lifecycle, in an easily understandable way for management, staff, and regulatory inspectors, e.g., a quality manual, documentation, flowcharts, procedures. Companies can implement a program in which the PQS is routinely audited in-house (i.e., internal audit program) to ensure that the system is functioning at a high level. (Approved April 2009)

Q3: Is it necessary to describe the PQS in a regulatory submission?

A3: No, however relevant elements of the PQS (such as quality monitoring system, change control, and deviation management) can be referenced as part of the control strategy as supporting information. (Approved April 2009)

Q4: Will there be certification that the PQS is in accordance with ICH Q10?

A4: No. There will not be a specific ICH Q10 certification program. (Approved April 2009)

Q5: How should the implementation of the design space be evaluated during inspection of the manufacturing site?

A5: Inspection should verify/assess that manufacturing operations are appropriately carried out within the design space. The inspector in collaboration with the assessor, where appropriate, should also verify successful manufacturing operations under the design space and that movement within the design space is

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managed within the company's change management system (see ICH Q10, section IV. B.3 (3.2), Table III). (Approved April 2009)

Q6: *What should be done if manufacturing operations run inadvertently outside of the design space?*

A6: This should be handled as a deviation under GMP. For example, unplanned "one-off" excursions occurring as a result of unexpected events, such as operator error or equipment failure, would be investigated, documented, and dealt with as a deviation in the usual way. The results of the investigation could contribute to the process knowledge, preventive actions, and continual improvement of the product. (Approved April 2009)

Q7: *What information and documentation of the development studies should be available at a manufacturing site?*

A7: Pharmaceutical development information (e.g., supporting information on design space, chemometric model, risk management) is available at the development site. Pharmaceutical development information that is useful to ensure the understanding of the basis for the manufacturing process and control strategy, including the rationale for selection of critical process parameters and critical quality attributes, should be available at the manufacturing site.

Scientific collaboration and knowledge sharing between pharmaceutical development and manufacturing is essential to ensure the successful transfer to production. (Approved June 2009)

Q8: *Can process parameters be adjusted throughout the product lifecycle?*

A8: Process parameters are studied and selected during pharmaceutical development and monitored during commercial manufacturing. Knowledge gained could be utilized for adjustment of the parameters as part of continual improvement of the process throughout the lifecycle of the drug product (see ICH Q10, section IV (3)). (Approved June 2009)

D. Impact of New ICH Quality Guidance on GMP Inspection Practices (4)

Q1: *How will product-related inspections differ in an ICH Q8, Q9 and Q10 environment?*

A1: In the case of product-related inspection (in particular, preauthorization) depending on the complexity of the product and/or process, greater collaboration between inspectors and assessors could be helpful (for example, for the assessment of development data). The inspection would normally occur at the proposed commercial manufacturing site, and there is likely to be greater focus on enhanced process understanding and understanding relationships, e.g., critical quality attributes (CQAs), critical process parameters (CPPs). The inspection might also focus on the application and implementation of quality risk

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management principles, as supported by the pharmaceutical quality system (PQS). (Approved April 2009)

Q2: *How will system-related inspections differ in an ICH Q8, Q9, and Q10 environment?*

A2: The inspection process will remain similar. However, upon the implementation of ICH Q8, Q9, and Q10, inspections will have greater focus on (but not only focus on) how the PQS facilitates the use of e.g., quality risk management methods, implementation of design space, and change management (see ICH Q10). (Approved April 2009)

Q3: *How is control strategy approved in the application and evaluated during inspection?*

A3: Elements of control strategy submitted in the application will be reviewed and approved by the regulatory agency. However, additional elements are subject to inspection (as described in Q10). (Approved October 2009)

E. Knowledge Management (5)

Q1: *How has the implementation of ICH Q8, Q9, and Q10 changed the significance and use of knowledge management?*

A1: Q10 defines *knowledge management* as: “Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes and components.”

Knowledge management is not a system; it enables the implementation of the concepts described in ICH Q8, Q9 and Q10.

Knowledge management is not a new concept. It is always important regardless of the development approach. Q10 highlights knowledge management because it is expected that more complex information generated by appropriate approaches (e.g., QbD, process analytical technology (PAT), real-time data generation, and control monitoring systems) should be better captured, managed, and shared during product life-cycle.

In conjunction with quality risk management, knowledge management can facilitate the use of concepts such as prior knowledge (including from other similar products), development of design space, control strategy, technology transfer, and continual improvement across the product life cycle. (Approved April 2009)

Q2: *Does Q10 suggest an ideal way to manage knowledge?*

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A2: No. Q10 provides a framework and does not prescribe how to implement knowledge management. Each company decides how to manage knowledge, including the depth and extent of information assessment based on its specific needs. (Approved April 2009)

Q3: What are potential sources of information for knowledge management?

A3: Some examples of knowledge sources are:

- Prior knowledge based on experience obtained from similar processes (internal knowledge, industry scientific and technical publications) and published information (external knowledge: literature and peer-reviewed publications)
- Pharmaceutical development studies
- Mechanism of action
- Structure/function relationships
- Technology transfer activities
- Process validation studies
- Manufacturing experience, e.g.,
 - Internal and vendor audits
 - Raw material testing data
- Innovation
- Continual improvement
- Change management activities
- Stability reports
- Product quality reviews/annual product reviews
- Complaint reports
- Adverse event reports (patient safety)
- Deviation reports, recall Information
- Technical investigations and/or CAPA reports
- Suppliers and contractors
- Product history and /or manufacturing history
- Ongoing manufacturing processes information (e.g., trends)

Information from the above can be sourced and shared across a site or company, between companies and suppliers/contractors, products, and across different disciplines (e.g., development, manufacturing, engineering, quality units). (Approved April 2009)

Q4: Is a specific dedicated, computerized information management system required for the implementation of knowledge management with respect to ICH Q8, Q9, and Q10?

A4: No, but such computerized information management systems can be invaluable in capturing, managing, assessing, and sharing complex data and information. (Approved April 2009)

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Q5: Will regulatory agencies expect to see a formal knowledge management approach during inspections?

A5: No. There is no added regulatory requirement for a formal knowledge management system. However, it is expected that knowledge from different processes and systems will be appropriately utilized.

Note: “formal” means: it is a structured approach using a recognized methodology or information technology (IT) tool, executing and documenting something in a transparent and detailed manner. (Approved June 2009)

F. Software Solutions (6)

Q1: With the rapid growth of the new science and risk-based quality paradigm coupled with the IWG efforts to facilitate globally consistent implementation of Q8, Q9, and Q10, a number of commercial vendors are now offering products that are being marketed as “ICH compliant solutions” or ICH Q8, 9, and 10 Implementation software, etc. Is it necessary for a pharmaceutical firm to purchase these products to achieve a successful implementation of these ICH guidances within their companies?

A1: No. The ICH Implementation Working Group has not endorsed any commercial products and does not intend to do so. ICH is not a regulatory agency with reviewing authority and thus does not have a role in determining or defining “ICH compliance” for any commercial products. While there will likely be a continuous proliferation of new products targeting the implementation of these ICH guidances, firms should carry out their own evaluation of these products relative to their business needs. (Approved April 2009)