INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

Quality Implementation Working Group on Q8, Q9 and Q10 Questions & Answers (R4)

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In order to facilitate the implementation of the Q8/Q9/Q10 guidelines, the ICH Experts have developed a series of Q&As:

Q8/Q9/Q10 Q&As
Document History

Code	History	Date
Q8/Q9/Q10 Q&As	Approval by the ICH Steering Committee under *Step 4*	15 April 2009
Q8/Q9/Q10 Q&As (R1)	Approval by the ICH Steering Committee under *Step 4* of newly added questions	11 June 2009
Q8/Q9/Q10 Q&As (R2)	Correction made to Question 7 of Section 2.2 "Real Time Release Testing"	23 July 2009
Q8/Q9/Q10 Q&As (R3)	Change Q8(R1) to Q8(R2) Approval by the ICH Steering Committee under *Step 4* of newly added questions	29 October 2009
Q8/Q9/Q10 Q&As (R4)	Approval by the ICH Steering Committee under *Step 4* of a newly added question in Section 2.1	11 November 2010

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1. INTRODUCTION

This Questions and Answers document (Q&A) refers to the current working procedure of the ICH Q-IWG on implementing the guidelines of Q8, Q9 and Q10 which have been approved by the ICH Steering Committee.

The benefits of harmonizing technical requirements across the ICH regions can only be reached if the various Q-ICH guidelines are implemented and interpreted in a consistent way across the three regions. Implementation Working Group is tasked to develop Q&As to facilitate implementation of existing guidelines.

References

ICH Q8(R2)	Pharmaceutical Development *Part I: 'Pharmaceutical Development'* *Part II: 'Annex to Pharmaceutical Development'* *http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf*	approved Aug. 2009 *approved Nov. 10, 2005* *approved Nov. 13, 2008*
ICH Q9	Quality Risk Management *http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf*	approved Nov. 09, 2005
ICH Q10	Pharmaceutical Quality Systems *http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf*	approved Jun. 04, 2008

Q8/Q9/Q10
Questions and Answers

1.1 For General Clarification

Date of Approval		Questions	Answers
1	June 2009	Is the minimal approach accepted by regulators?	Yes. The minimal approach as defined in Q8(R2) (sometime also called 'baseline' or 'traditional' approach) is the expectation which is to be achieved for a fully acceptable submission. However the 'enhanced' approach as described in ICH Q8(R2) is encouraged (Ref. Q8(R2) Appendix 1).
2	Oct. 2009	What is an appropriate approach for process validation using ICH Q8, Q9 and Q10?	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 pre-defined 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 Q8(R2) glossary] can be utilised 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.
3	Oct. 2009	How can information from risk management and continuous process verification provide for a robust continual improvement approach under ICH Q8, Q9 and Q10?	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 is needed to 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

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			consistency and provide the basis for continual improvement of the product. Quality Risk Management methodologies of ICH Q9 can be applied throughout the product lifecycle to maintain a state of process control.

2. QUALITY BY DESIGN TOPICS

Date of Approval		Questions	Answers
1	April 2009	Is it always necessary to have a Design Space (DS) or Real Time Release (RTR) testing to implement QbD?	Under Quality by Design, establishing a design space or using real time release testing is not necessarily expected [ICH Q8(R2), *Step 4*].

2.1 Design Space

Date of Approval		Questions	Answers
1	April 2009	Is it necessary to study multivariate interactions of all parameters to develop a design space?	No, the applicant will need to justify the choice of material attributes and parameters for multivariate experimentation based on risk assessment and desired operational flexibility.
2	April 2009	Can a design space be applicable to scale-up?	Yes, when appropriately justified [additional details see Q8(R2) Section 2.4.4]. An example of a scale-independent design space is provided in the EFPIA Mock P2 document [EFPIA Mock P2 submission on "Examplain": 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.

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3	April 2009	Can a design space be applicable to a site change?	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.
4	April 2009	Can a design space be developed for single and/or multiple unit operations?	Yes, it is possible to develop a design space for single unit operations or across a series of unit operations [see Q8(R2) Section 2.4.3].
5	April 2009	Is it possible to develop a design space for existing products?	Yes, it is possible. Manufacturing data and process knowledge can be used to support a design space for existing products. Relevant information should be utilised from e.g., commercial scale manufacturing, process improvement, 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 be needed 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.
6	April 2009	Is there a regulatory expectation to develop a design space for an existing product?	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.

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7	June 2009	Can a design space be applicable to formulation?	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 post approval change.
8	June 2009	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), Section 2.4.5.]. Proven acceptable ranges from only univariate experimentation 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) Section 2.4.5]. The applicant may elect to use proven acceptable ranges or design space for different aspects of the manufacturing process.
9	Nov. 2010	Should the outer limits of the Design Space be evaluated during process validation studies at the commercial scale?	No, there is no need to run the qualification batches at the outer limits of the design space during process validation studies at commercial scale. The design space must be sufficiently explored earlier during development studies (for scale up see also Chapter 2.1 Design Space Question 2; for life cycle approach see Chapter 1.1 for general clarification Question 3).

2.2 Real Time Release Testing

Date of Approval		Questions	Answers
1	April 2009	How is batch release affected by employing real time release testing?	Batch release is the final decision to release the product to the market regardless 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 GMP compliance and quality system, regardless of which approach is used.
2	April 2009	Does real time release testing mean elimination of end product testing?	Real time release testing does not necessarily eliminate all end product testing. For example, an applicant may propose RTR testing for some attributes only or not all. If all 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.
3	April 2009	Is a product specification still necessary in the case of RTR testing?	Yes, product specifications [see ICH Q6A and Q6B] still need to be established and met, when tested.
4	April 2009	When using RTR testing, is there a need for stability test methods?	Even where RTR testing is applied, a stability monitoring protocol that uses stability indicating methods is required for all products regardless of the means of release testing. [see ICH Q1A and ICH Q5C].
5	April 2009	What is the relationship between Control Strategy and RTR testing?	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.

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6	April 2009	Do traditional sampling approaches apply to RTR testing?	No, traditionally 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.
7	April 2009	If RTR testing results fail or trending toward failure, can end-product testing be used to release the batch?	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 will need to be made based on the results of the investigations. The batch release decision needs to comply with the content of the marketing authorisation and GMP compliance.
8	June 2009	What is the relationship between in-process testing and RTR testing?	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 directly impact the decision for batch release through evaluation of Critical Quality Attributes.
9	June 2009	What is the difference between 'real time release' and 'real time release testing'?	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. The term 'Real time release' in the Q8(R2), *Step 2* document was revised to 'Real time release testing' in the final Q8(R2) Part II document to fit the definition more accurately and thus avoid confusion with batch release.
10	June 2009	Can surrogate measurement be used for RTR testing?	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); Section 2.5.].

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11	Oct. 2009	What is the relationship between RTR testing and Parametric Release?	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.

2.3 Control Strategy

Refer to the definition of control strategy provided in the ICH Q10 glossary: Q10 Control Strategy definition: '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.'

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1	April 2009	What is the difference in a control strategy for products developed using the minimal approach vs. 'quality-by-design' approach?	Control strategies are expected irrespective of the development approach. Control strategy includes different types of control proposed by the applicant to assure product quality (Section 3.2.1 ICH Q10), 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.
2	April 2009	Are GMP requirements different for batch release under QbD?	No, the same GMP requirements apply for batch release under minimal and QbD approaches.
3	April 2009	What is the relationship between a Design Space and a Control Strategy?	A control strategy is required for all products. If a Design Space is developed and approved, the Control Strategy [see ICH Q8(R2), Part II, Section 4] provides the mechanism to ensure that the manufacturing process is maintained within the boundaries described by the Design Space.

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4	June 2009	What approaches can be taken in the event of on-line/in-line/at-line testing or monitoring equipment breakdown?	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 needs to be managed in the context of a deviation under the Quality System and can be covered by GMP inspection.
5	Oct. 2009	Are product specifications different for minimal versus QbD approaches?	In principle no, the same product specifications are needed for minimal and QbD approaches. For a QbD approach, the control strategy may allow achieving the end product specifications via real time release testing approaches [see ICH Q8(R2), Appendix 1]. Product must meet specification, when tested.

3. PHARMACEUTICAL QUALITY SYSTEM

Date of Approval		Questions	Answers
1	April 2009	What are the benefits of implementing a Pharmaceutical Quality System (in accordance with ICH Q10)?	The benefits are: • Facilitated robustness of the manufacturing process, through facilitation of continual improvement through science and risk-based post approval change processes; • Consistency in the global pharmaceutical environment across regions; • Enable transparency of systems, processes, organisational and management responsibility; • Clearer understanding of the application of a Quality System throughout product lifecycle; • Further reducing risk of product failure and incidence of complaints and recalls thereby providing greater

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			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.
2	April 2009	How does a company demonstrate implementation of PQS in accordance with ICH Q10?	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.
3	April 2009	Is it necessary to describe the PQS in a regulatory submission?	No, however relevant elements of the PQS, such as quality monitoring system, change control and deviation management may be referenced as part of the control strategy as supporting information.
4	April 2009	Will there be certification that the PQS is in accordance with ICH Q10?	No. There will not be a specific ICH Q10 certification programme.
5	April 2009	How should the implementation of the design space be evaluated during inspection of the manufacturing site?	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

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			manufacturing operations under the Design Space and that movement within the Design Space is managed within the company's change management system [see ICH Q10, Section 3.2. Table III].
6	April 2009	What should be done if manufacturing operations run inadvertently outside of the Design Space?	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 may contribute to the process knowledge, preventive actions and continual improvement of the product.
7	June 2009	What information and documentation of the development studies should be available at a manufacturing site?	Pharmaceutical development information (e.g., supporting information on design space, chemometric model, risk management,…) is available at the development site. Pharmaceutical development information which 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.
8	June 2009	Can process parameters be adjusted throughout the product lifecycle?	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 3.).

4. ICH NEW QUALITY GUIDELINES' IMPACT ON GMP INSPECTION PRACTICES

Date of Approval		Questions	Answers
1	April 2009	How will product-related inspections differ in an ICH Q8, Q9 and Q10 environment?	In the case of product-related inspection (in particular pre-authorisation) depending on the complexity of the product and/or process, there could be a need for greater collaboration between inspectors and assessors 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 Attribute (CQAs), Critical Process Parameters (CPPs). It will also extend into the application and implementation of quality risk management principles, as supported by the Pharmaceutical Quality System (PQS).
2	April 2009	How will system-related inspections differ in an ICH Q8, Q9 and Q10 environment?	The inspection process will remain similar. However upon the implementation of ICH Q8, Q9 and Q10, inspections will have greater focus (but not only) on how the PQS facilitates the use of e.g., Quality Risk Management methods, implementation of design space and change management [see ICH Q10].
3	Oct. 2009	How is control strategy approved in the application and evaluated during inspection?	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).

5. KNOWLEDGE MANAGEMENT

Date of Approval		Questions	Answers
1	April 2009	How has the implementation of ICH Q8, Q9, and Q10 changed the significance and use of knowledge management?	Q10 defines knowledge management as: 'Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes

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			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, PAT, real-time data generation and control monitoring systems) will need to 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.
2	April 2009	Does Q10 suggest an ideal way to manage knowledge?	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 their specific needs.
3	April 2009	What are potential sources of information for Knowledge Management?	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.:

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			- 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).
4	April 2009	Is a specific dedicated computerised information management system required for the implementation of knowledge management with respect to ICH Q8, Q9 and Q10?	No, but such computerised information management systems can be invaluable in capturing, managing, assessing and sharing complex data and information.
5	June 2009	Will regulatory agencies expect to see a formal knowledge management approach during inspections?	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 utilised. Note: 'formal' means: it is a structured approach using a recognised methodology or (IT-) tool, executing and documenting something in a transparent and detailed manner.

6. SOFTWARE SOLUTIONS

Date of Approval		Questions	Answers
1	April 2009	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 & 10 Implementation software, etc. Is it necessary for a pharmaceutical firm to purchase these products to achieve a successful implementation of these ICH guidelines within their companies?	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 guidelines, firms will need to carry out their own evaluation of these products relative to their business needs.