Training / Workshops
Goals and objectives

- **Learning opportunities will be provided for participants to practice in small groups the necessary skills for the implementation of the three guidelines.**
- **The workshop deliverable will include materials to support understanding of integrated use of the concepts described in the ICH Q8, Q9 and Q10 guidelines.**
  - **These materials will be used by both regulators and industry to implement the three guidelines in their organisations.**

Training / Workshops
What is the difference?

- Only 3 workshops endorsed by the ICH Q-IWG
- Regulatory assessment and GMP inspection implementation aspects will be discussed
- The same workshop will be offered by the same faculty in each of the three ICH regions.
- All attendees to participate in the breakouts on each life cycle aspect
- Report back for future Q-IWG Q&A development
- Workshop materials can be used for internal training by competent authorities and industry

Training / Workshops
Outline of the training

- **Outline**
  - **Presentations (lecture)**
  - **Break outs / Small discussion groups**
  - **Panel Discussion Session**
- **2 days workshop before the ICH meeting**
  - **Europe: Spring 2010**
  - **US: In between in Washington D.C.**
  - **Japan: Autumn 2010**

Training / Workshops
Event in non-ICH region

- Invited to come to the arranged regional workshops
- Webcasting of regional workshops
- Provide structure and content to GCG and / or WHO sponsored training

Training / Workshops
Co-sponsorship

- Principle co-sponsor: ICH Q-IWG
- Q-IWG established criteria for co-sponsorship for logistics
- Selection of co-sponsor decided on a global or regional basis (?)

Training / Workshops
Next steps for planning

- Task force within Q-IWG
  - Develop details of the entire training program
  - Establish process and selection for training co-sponsorship
  - Recommend the program and logistics to Q-IWG
  - Q-IWG to endorse the program
- Form a workshop / training planning committee
  - Same planning committee for all regions (Q-IWG members only)
  - Including conference organiser / co-sponsor

Training / Workshops
Endorsement from ICH-SC

- Training concept
- Organisational approach
  - Timing along before ICH meetings
- Selection process of co-sponsor
- Involvement of ICH and non-ICH regions

Next steps

- Additional Q&As
- Implementation of the proposed collaboration
  - e.g. Case Studies, position paper
- Development and delivery of the training workshops
  - Development of training material
- Proposed additional activities

Proposed additional activities

- Identifying the need of revision / update of existing ICH Quality guidelines in the context of ICH Q8, Q9, Q10 and pending Q11
- Other evolving topics impacted and stimulated in the light of the new paradigm to be identified for avoiding potential dis-harmonisation
- Proposal to revise the Q-IWG mandate will be presented in ICH St. Louis

Next steps to St Louis

- Work on open Q&A
  - US: QbD; Japan: Knowledge Mgmt; EU: PQS/Inspections
  - Continue to collect additional questions through the ICH Secretariat (IFPMA)
- Q-IWG Task Team
  - Development and delivery of the training workshops
  - Implementation of the proposed collaboration

Request to ICH-SC

- Endorsement of updated Q&A
- Proposed collaboration on Case Studies (Articles / Position Papers)
- Endorsement of workshop concept
- Extend original duration beyond Nov 2009 to accommodate proposed Q-IWG workshops and training

檜山資料2

セントルイス前のプロセスバリデーションについてのQ＆Aへのコメント

Hiyama comments: I would delete Q02 and add the following QA.

This and Q02a can be combined.

Question: How can continuous process verification be introduced and employed in process validation exercises?

Answer:

Continuous process verification can be established by placing process monitor/evaluation tools at appropriate manufacturing steps based upon thorough product and process understanding. Continuous process verification can be built in process validation protocols for the initial commercial production, for manufacturing process changes and for the continual improvement throughout the product cycle.

Manufacture of conformation batch(es) may not be necessary where continuous process verification is employed because of its continuous verification feature.

Background:

There was discussion on continuous process verification relative to manufacture of (a certain number of) conformation batch(es) when Q8 approached step2. Then, the role of CPV shifted toward to lifecycle approach of process validation. There was an attempt to write a paragraph on (innovative) process validation in Q10. It, however, failed because of Q10 policy; not to repeat GMP expectations. This is a history how we get spotty mention of continuous process verification and innovative process validation approaches in Q8R2 and Q10.

From Yokohama discussion, EU and US do not have legal requirement of 3 batch conformance manufacture while Japan requires 3 batch manufacture for the for the initial commercial prospective process validation in their Process Validation Standards(2005). In all three regions, process validation is legal requirement.

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

Current version dated October 29, 2009

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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	Approved by the ICH Steering Committee under *Step 4* on newly added questions	11 June 2009
Q8/Q9/Q10 Q&As	Correction made to Question 7 of Section 2.2 "Real Time Release Testing"	23 July 2009
Q8/Q9/Q10 Q&As	Change Q8(R1) to Q8(R2) Approved by the ICH Steering Committee under *Step 4* on newly added questions	29 October 2009

TABLE OF CONTENTS

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/LOB/media/MEDIA4986.pdf*	approved Aug. 2009 *approved Nov. 10 2005* *approved Nov. 13 2008*
ICH Q9	Quality Risk Management *http://www.ich.org/LOB/media/MEDIA1957.pdf*	approved Nov. 09 2005
ICH Q10	Pharmaceutical Quality Systems *http://www.ich.org/LOB/media/MEDIA3917.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

Date of Approval		Questions	Answers
			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.

Date of Approval		Questions	Answers
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.

Date of Approval		Questions	Answers
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.

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

Date of Approval		Questions	Answers
			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.
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.

Date of Approval		Questions	Answers
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.].
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.'

Date of Approval		Questions	Answers
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.
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.

Date of Approval		Questions	Answers
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 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

Date of Approval		Questions	Answers
			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 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