ICH Q8 / Q9 / Q10 / Q11

with GMP and ISO-9001 references

ICH HARMONISED TRIPARTITE GUIDELINES:

Q8 (R2) PHARMACEUTICAL DEVELOPMENT (Aug 2009)
Q9 QUALITY RISK MANAGEMENT (Nov 2005)
Q10 PHARMACEUTICAL QUALITY SYSTEM (Jun 2008)
Q11 DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES (CHEMICAL ENTITIES AND BIOTECHNOLOGICAL/BIOLOGICAL ENTITIES) (May 2012)

KEY2COMPLIANCE®

Management controls, ICH references				Other GMP references		
Q8(R2)	Q9	Q10	Q11	210/211	EU Part I	ISO9001
NA	4.1	1.3	9	210.1(b)	1.1-1.11	1
	4.4	1.7		211.22	2.1-2.9	4.1-4.4
	4.5	1.8		211.25	3 Principle	5.1-5.3
	4.6	2.1 - 2.8		Subpart C&D	4 Principle	7.1
	II.1	3.2		211.160	4.1	7.5
	Glossary	3.2.4 & Table IV		211.180(e)	4.27	8.4
		4.1		211.180(f)	4.32	9.3
		4.2		211.198		
		4.3				
		Glossary				
		Annex II				

Quality by Design, ICH references				Other GMP references		
Q8(R2)	**Q9**	**Q10**	**Q11**	**210/211**	**EU Part I**	**ISO9001**
All	1	1.1	All	NA	1.2	8.3
chapters	2	1.2	chapters		1.4	
	4.1	1.3			4.29	
	4.3	1.6.1				
	6	3.1.1				
	7	3.1.2				
	Annex I.2	3.2.1 & Table 1				
	Annex I.4	3.2.2 Table II				
	Annex I.5	3.2.3 & Table III				
	Annex I.6	3.2.4 Table IV				
	Annex I.7	Glossary				
	Annex I.9	Annex I				
	Annex II.1	Annex II				
	Annex II.2					
	Annex II.3					
	Annex II.4					
	Annex II.5					
	Annex II.6					
	Annex II.8					

Reference matrix ISO 9001 and GMP texts

In this matrix we have used the structure from ISO 9001:2015 as the base and correlated it to the corresponding requirements in the GMP's. Note that the requirements of the ISO-standard does not have the same degree of detail and not specifically require procedures and

ISO 9001	Requirement description
4.4.1; 7.5.1	Quality management system established
4.4.1 a, b	Determining processes, sequence and their interaction
4.4.1 c,d,e,f	Criteria, methods and resources for control of processe
4.4.1 f; 6.1	Risk management
4.4.1 g	Monitor, measure and analyze proc sse a act on the results.
na	Quality manual
4.4.2	Documented procedures and specifications
4.4.2	Records
5.1.1 f	Top management shall communicate the importance of quality
5.2.1 ; 5.1.1 b; 6.2.1	Quality policy and quality objectives established by management
5.2.2	Quality policy communicated and understood within the organization

records the same way as in the GMP's, but contains general principles for a complete quality management system. Requirements in the ISO standard where there is no equivalent in the GMP's have been omitted (eg requirements related to design and development).

EU GMP PART I	21CFR210/211	EU GMP PART II
Ch. 1, Principle; 1.1; 1.7	na	2.11; 2.19; 17.30
1.8(i)	na	2.12
1.4(i)&(iv)	na	2.12
Ch. 1, Principle; 1.3; 1.12-13 5.20-21; Ch. 8, Principle;	na	2.20-21
Ch. 1, Principle; 1.4(vi); 1.4(viii)&(ix); 1.10; 2.8-9; Ch. 4, Principle; 6.2; 6.9; 6.26-36; 7.7	211.100; 211.180(e); 211.192	6.60; 6.71; 11.15; 15.12
1.7; 4.32	na	na
Ch. 4, Principle;	211.22(c)&(d); 211.100(a); 211.160(a)	2.12
Ch. 4, Principle; 4.8	211.180	2.15; 6.14
1.5	na	2.11
Ch. 1, Principle; 2.4	na	2.19
Ch. 1, Principle; 1.5	na	2.10-11

PART II:

PHARMACEUTICAL DEVELOPMENT - ANNEX

ICH Harmonised Tripartite Guideline

Having reached Step 4 of the ICH Process at the ICH Steering Committee meeting on 13 November 2008, this guideline is recommended for adoption to the three regulatory parties to ICH

1. INTRODUCTION

This guideline is an annex to ICH Q8 Pharmaceutical Development and provides further clarification of key concepts outlined in the core guideline. In addition, this annex describes the principles of quality by design[1] (QbD). The annex is not intended to establish new standards or to introduce new regulatory requirements; however, it shows how concepts and tools (e.g., design space[1]) outlined in the parent Q8 document could be put into practice by the applicant for all dosage forms. Where a company chooses to apply quality by design and quality risk management (ICH Q9, Quality Risk Management) linked to an appropriate pharmaceutical quality system, opportunities arise to enhance science- and risk-based regulatory approaches (see ICH Q10, Pharmaceutical Quality System).

Approaches to Pharmaceutical Development

In all cases, the product should be designed to meet patients' needs and the intended product performance. Strategies for product development vary from company to company and from product to product. The approach to, and extent of, development studies vary and should be outlined in the submission. An applicant might choose either an empirical approach or a more systematic approach to product development, or a combination of both. An illustration of the potential contrasts of these approaches is shown in Appendix 1. A more systematic approach to development (also defined as quality by design) can include, for example, incorporation of prior knowledge, results of studies using design of experiment, use of quality risk management, and use of knowledge management (see ICH Q10) throughout the lifecycle[1] of the product. Such a systematic approach can enhance achieving the desired quality of the product and help the regulators to better understand a company's strategy. Product and process understanding can be updated with the knowledge gained over the product lifecycle.

A greater understanding of the product and its manufacturing process can create a basis for more flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided in the registration application. It is the knowledge gained and submitted to the authorities, and not the volume of data collected, that forms the basis for science- and risk-based submissions and regulatory evaluations. Nevertheless, appropriate data

[1] See Glossary

harm (detectability) also factors in the estimation of risk.

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions.

In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output. Revealing assumptions and reasonable sources of uncertainty will enhance confidence in this output and/or help identify its limitations. Uncertainty is due to combination of incomplete knowledge about a process and its expected or unexpected variability. Typical sources of uncertainty include gaps in knowledge gaps in pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a process), sources of variability), and probability of detection of problems.

The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risk. When risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as "high", "medium", or "low", which should be defined in as much detail as possible. Sometimes a "risk score" is used to further define descriptors in risk ranking. In quantitative risk assessments, a risk estimate provides the likelihood of a specific consequence, given a set of risk-generating circumstances. Thus, quantitative risk estimation is useful for one particular consequence at a time. Alternatively, some risk management tools use a relative risk measure to combine multiple levels of severity and probability into an overall estimate of relative risk. The intermediate steps within a scoring process can sometimes employ quantitative risk estimation.

4.4 Risk Control

Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.

Risk control might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level (see Fig. 1). Risk reduction might

II.6 Quality Risk Management as Part of Production

Validation

To identify the scope and extent of verification, qualification and validation activities (e.g., analytical methods, processes, equipment and cleaning methods;

To determine the extent for follow-up activities (e.g., sampling, monitoring and re-validation);

To distinguish between critical and non-critical process steps to facilitate design of a validation study.

In-process sampling & testing

To evaluate the frequency and extent of in-process control testing (e.g., to justify reduced testing under conditions of proven control);

To evaluate and justify the use of process analytical technologies (PAT) in conjunction with parametric and real time release.

Production planning

To determine appropriate production planning (e.g., dedicated, campaign and concurrent production process sequences).

II.7 Quality Risk Management as Part of Laboratory Control and Stability Studies

Out of specification results

To identify potential root causes and corrective actions during the investigation of out of specification results.

Retest period / expiration date

To evaluate adequacy of storage and testing of intermediates, excipients and starting materials.

II.8 Quality Risk Management as Part of Packaging and Labelling

Design of packages

To design the secondary package for the protection of primary packaged product (e.g., to ensure product authenticity, label legibility).

Selection of container closure system

To determine the critical parameters of the container closure system.

Label controls

To design label control procedures based on the potential for mix-ups involving different product labels, including different versions of the same label.

- Technology Transfer:
  - o New product transfers during Development through Manufacturing;
  - o Transfers within or between manufacturing and testing sites for marketed products.
- Commercial Manufacturing:
  - o Acquisition and control of materials;
  - o Provision of facilities, utilities, and equipment;
  - o Production (including packaging and labelling);
  - o Quality control and assurance;
  - o Release;
  - o Storage;
  - o Distribution (excluding wholesaler activities)
- Product Discontinuation:
  - o Retention of documentation;
  - o Sample retention;
  - o Continued product assessment and reporting.

1.3 Relationship of ICH Q10 to Regional GMP Requirements, ISO Standards and ICH Q7

Regional GMP requirements, the ICH Q7 Guideline, "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients", and ISO quality management system guidelines form the foundation for ICH Q10. To meet the objectives described below, ICH Q10 augments GMPs by describing specific quality system elements and management responsibilities. ICH Q10 provides a harmonised model for a pharmaceutical quality system throughout the lifecycle of a product and is intended to be used together with regional GMP requirements. The regional GMPs do not explicitly address all stages of the product lifecycle (e.g., Development). The quality system elements and management responsibilities described in this guideline are intended to encourage the use of science and risk based approaches at each lifecycle stage, thereby promoting continual improvement across the entire product lifecycle.

1.4 Relationship of ICH Q10 to Regulatory Approaches

Regulatory approaches for a specific product or manufacturing facility should be commensurate with the level of product and process understanding, the results of quality risk management, and the effectiveness of the pharmaceutical quality system. When implemented, the effectiveness of the pharmaceutical quality system can normally be evaluated during a regulatory inspection at the manufacturing site. Potential opportunities to enhance science and risk based regulatory approaches are identified in Annex 1. Regulatory processes will be determined by region.