



11 October 2007

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Food and Drug Administration
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Q-10 Pharmaceutical Quality System

FDA:

ISPE is pleased to provide the following comments to the Draft Guidance on Q-10 Pharmaceutical Quality System. The comments were solicited from the Regulatory Affairs Committee, which is comprised of individuals from industry.

About ISPE

ISPE is a Not-for-Profit Society comprised of 25,000 pharmaceutical manufacturing professionals from 90 countries. ISPE aims to be the catalyst for “Engineering Pharmaceutical Innovation” by providing Members with opportunities to develop technical knowledge, exchange practical experience, and collaborate with global regulatory agencies. Founded in 1980, ISPE has worldwide headquarters in Tampa, Florida, US; Brussels, Belgium, and an office in Singapore to serve Asia-Pacific. Visit www.ispe.org for additional Society news and information.

Yours sincerely,

Robert P. Best
President/CEO, ISPE

1 Appendix 2, Regulatory Comment Form

ISPE Regulatory Comment Form

Draft Regulation/Guidance Document: ICH Q10

No.	LINE NUMBER	CURRENT WORDING	PROPOSED CHANGE	RATIONALE	COMMENT LOGGED BY	COMMENT REVIEWED BY	CLASSIFICATION*
1.	Page 1, Section 1.1 Introduction 2 nd paragraph line 7	We understand that the phrase 'not intended to create any new expectations...' refers to not increasing the 'statutory' expectations of current GMP systems, but think the phrase is ambiguous and could be misunderstood since Q10 does create new expectations within a regulatory framework.	Much of the content of ICH Q10 applicable to manufacturing sites is currently specified by regional GMP requirements <i>and ICH Q10 is not intended to extend the current regulatory GMP requirements. The optional implementation of the content of ICH Q10 that is additional to current GMP requirements</i> should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.				
2.	Page 1, Section 1.1 Introduction 4th paragraph, second line	We consider that the phrase 'an effective PQS will enhance the quality ... of medicines' implies that quality is lower in the absence of a PQS.	Remove phrase or modify appropriately, e.g. to:- "assure the quality management... "	ICH Q10 demonstrates industry and regulatory authorities' support of an effective pharmaceutical quality system to enhance the <i>assurance</i> of quality and availability of medicines around the world in the interest of public health.			

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3.	Page 1, Section 1.1 Introduction 4 th para	We consider that the significant 'potential opportunities' referenced in Annex 1 should be explicitly mentioned in the introduction.	Implementation of ICH Q10, particularly together with the demonstration of product and process understanding, including effective use of quality risk management principles (e.g. ICH Q8 and ICH Q9) should create opportunities to enhanced regulatory approaches as described in Annex 1.				
4.	Page 1, Section 1.2 1 st bullet	"Novel excipient development"	Delete "Novel excipient development" or combine within the next bullet "Formulation development (e.g. including novel excipients, container closure systems) "	"Novel excipient development" is performed by excipient companies, usually not pharmaceutical companies. Use of novel excipients in pharmaceutical formulations would be covered in formulation development.			
5.	Page 3, Section 1.7 , Bullet (i)	The phrase 'well structured and clear' is rather subjective; the proposed text is clearer and more helpful in assessing the effectiveness of a PQS	The pharmaceutical quality system should be <i>designed, organized and documented</i> to facilitate common understanding and consistent application.				
6.	Page 3, Section 1.7 , Bullet (iii), Line 3	...existing one. While some aspects...	Add: "...existing one. The design of the PQS should incorporate appropriate risk management principles. While some aspects..."	Use QRM in PQS design			
7.	Page 3, Section 1.7 , Bullet (iii), Line 4	"the effectiveness of the implementation of the pharmaceutical quality system is normally demonstrated at the site level."	"the effectiveness of the implementation of the pharmaceutical quality system is normally demonstrated at the site level as applicable. "	We consider that at a particular site, the various elements of ICH Q10 may not all be applicable to all products, and conversely, that it should be possible for the quality systems for a particular product or process to be demonstrated to meet the Q10 guidance.			

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8.	Page 4, Section 2.1, Bullet (i)		Add "roles" for consistency	When responsibilities and authorities are referenced elsewhere "roles" is also included			
9.	Page 5, Section 2.3, bullet (i)		Read "Senior management should ensure that the quality objectives ..."	Reword start of sentence			
10.	Page 5, Section 2.5, Bullet (i)		Add "Communication processes regarding the PQS ..."	We propose to be more specific and clarify what is the intent of the communication.			
11.	Page 5, Section 2.5, Bullet (iii)	Communication processes should ensure the escalation of certain product quality and pharmaceutical quality system issues to appropriate levels of management in a timely manner.	The use of 'certain' is redundant, as all product quality and pharmaceutical quality system issues should be escalated to appropriate levels of management.	Communication processes should ensure the escalation of certain product quality and pharmaceutical quality system issues to appropriate levels of management in a timely manner.			
12.	Page 6, Paragraph 3, Line 1	These elements should.....	Suggest to remove the term "should" and suggest: "...companies are encouraged to evaluate opportunities...."	We question the expectation for companies to evaluate opportunities for innovative approaches to improve product quality throughout the product lifecycle, since the inference is that this is an expectation. We assert this should be <u>optional</u> .			

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13.	Page 7, Section 3.2 (i), Line 4	"An effective monitoring system provides assurance of the continued capability of processes and controls to meet product quality and to <u>identify</u> areas for continual improvement."	Suggest replacing by: "An effective monitoring system provides assurance of the continued capability of processes and controls to meet product quality and <u>identifies</u> areas for continual improvement."	Format			
14.	P 8, table I, 4. column	Once manufacturing ceases,..."	"Once manufacturing ceases, monitoring such as stability testing should continue to completion of the studies to support commercial shelf life "	If the last product batch on the market has expired, there may be no need to perform further monitoring			
15.	Page 9, Section 3.2, (iii), Paragraph 1, Line 5	There is generally a difference in formality of change management processes prior to the initial regulatory submission and after submission, where changes to the regulatory filing may be required under the regional requirements.	There is generally a difference in formality of change management processes prior to and after the initial regulatory submission and after submission of the dossier (New Drug Application (NDA) or Marketing Authorisation (MA)) , where changes to the regulatory filing may be required under the regional requirements.	It is unclear whether "initial regulatory submission" refers to an investigational or a marketing authorization submission. It is also suggested that the consistency of terminology be maintained through the document.			
16.	Page 9, Section 3.2, (iii), bullet 1	(1) Quality risk management should be utilised to evaluate proposed changes. The level of effort and formality of the evaluation should be commensurate with the level of risk. There should be an assessment to determine whether a change to the regulatory filing is required as per regional requirements	This paragraph references the assessment to determine whether a change to the regulatory filing is required. This assessment is not a part of a quality risk management, and is in any case repeated again in the next paragraph. Propose to remove from (1).	(1) Quality risk management should be utilised to evaluate proposed changes. The level of effort and formality of the evaluation should be commensurate with the level of risk. There should be an assessment to determine whether a change to the regulatory filing is required under regional requirements.			

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17.	P 9, table 2, 4. column	CAPA should continue after the product is discontinued...	If appropriate, e.g. in those cases where other products are impacted, CAPA should continue....	CAPA should continue after the product is discontinued in those cases where other products may be impacted.			
18.	Page 11 – 3.2/iv/2/d-f	Bullet items under 2 are d, e, and f	Bullet items under 2 should be a, b, c	Format			
19.	Page 12, Section 4.1, (ii), bullet 1	Complaint, deviation, CAPA and change management processes	Suggest: “complaints, product rejections, non-conformances, recalls, deviations, ...”	Data monitoring doesn't mention recall data, as key performance indicator. Section 3.2, (i),5 includes recalls. The same list should be reiterated in this section, for consistency.			
20.	Page 13	Definition of control strategy	We note that there are different definitions of Control Strategy in this Q10 guidance and in other ICH documents. We consider this to be a good definition, but would suggest that definitions are harmonised between the different ICH guidance.	'Control strategy'- In ICH Q8(R1) revision 1, the term 'Control Strategy' is defined as: “the input material controls, process controls and monitors, and finished product tests, as appropriate, that are proposed and justified in order to ensure product quality”- The team suggests using the ICH Q10 definition in both documents			
21.	General comment	Duplication of Management responsibilities in multiple sections. For eg; Pages 10, 11 and 12	It is suggested that the document is further clarified and any redundancy avoided	Format of document, clarity vs. redundancy.			
22.	General comments	Document is missing an implementation strategy.	We feel that this may be a good topic where in further clarification can be provided through the development of a white paper.				

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23.	General comment		We suggest reinstalling the original numbering system, and recommend the same system is used in the three regions for consistency.	We question why the numbering system of paragraphs in the original ICH document (ICH website) was amended in the CHMP version of the document. The original numbering system was found clearer.			
24.	General Comment	Even though the document is called Pharmaceutical Quality System, only product & process specific Quality System elements are considered (e.g. change management, process & product performance monitoring). There should be a more comprehensive view by at least referencing the more system related elements such as training, audits, facilities, equipment.	To provide a more comprehensive overview about a general Quality System, we suggest adding a reference to GMP's.				
25.		General Comment: Industry desires to have a clearer commitment on the benefits of implementation ICH Q10	There should be a clearer commitment from regulatory side as to what are the benefits of implementing Q10	The regulatory benefits of ICH Q-10 are vague and a clearer commitment on the benefits would help the embracement of ICHQ-10 principles by the Industry - This would be an ideal topic for a white paper by ISPE (similar to those currently being developed on criticality/design space/control strategy). This mechanism would facilitate input from the stakeholders, and would be an ideal way to provide some guidance regarding the implementation.			

26.	Annex 1, point 3	The opportunity to... establish real-time release mechanisms	The opportunity to... establish real-time release mechanisms (e.g.) using PAT concepts	The term 'real-time release mechanisms' may be regarded as limited to replacing release testing by in process control results. It should be clearly stated that also 'indirect proofs' , e.g. through PAT systems are also possible			
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