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October 11, 2007

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. 2007D-0266, International Conference on Harmonisation; Draft Guidance on Q10 Pharmaceutical Quality System

Dear Sir or Madam:

The following comments are provided by the Biotechnology Industry Organization (BIO). BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 U.S. states and 33 other nations. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products. BIO appreciates the opportunity to comment on the International Conference on Harmonisation (ICH); Draft Consensus Guideline: Q10 Pharmaceutical Quality System.

General Comments

The draft guideline provides a valuable guide for setting up and maintaining an effective Quality System. However, it is critical that regulatory expectations for the pharmaceutical quality system are Good Manufacturing Practice (GMP) based, and not focused on business strategies and objectives which may impact maintenance and improvement of the quality system. It is very important that the focus of this guideline be on GMP and not on financial, environmental or safety and efficacy issues. Otherwise, the guideline is likely to come into conflict with other regulatory requirements, and confuse understanding of GMP.

We also have some concern that sliding scales for change management during development may be subject to a wide range of interpretation by inspectors regarding what is an appropriate "increase" of change control as a dynamic process, and we request that FDA take steps to make interpretation consistent (for example, during training of inspectors).

Specific Comments

Section 1.1, 1st paragraph: We suggest further clarification to the guideline by describing a model for both the pharmaceutical industry and the regulators. Thus, for consistency with the last paragraph of Section 1.1, we suggest adding the phrase "and regulatory authorities" after "pharmaceutical industry."

Section 1.1, 2nd paragraph: It is critical that the business type of elements described in this guideline do not extend GMPs into areas which are outside compliance and used to improve the quality system. As stated above under general comments, the content of ICH Q10 that is additional to current GMP requirements should be optional, and not subject to regulatory inspections or submitted to the regulatory agencies. We request these additional requirements only be included to guide manufacturers in improving the quality system, not for improved compliance.

Section 1.2, Pharmaceutical Development: In view of European Union (EU) Annex 13, and current Food and Drug Administration (FDA) activity with respect to a new GMP Guidance for Investigational Products, it is strongly recommended that Q10 acknowledges these rather than remaining silent. Therefore, we suggest the addition of a new bullet under Pharmaceutical Development, "Aspects of the Pharmaceutical Quality System may be applied incrementally to Investigational Medicinal Products appropriate to the phase of development."

Section 1.2, Manufacturing: "Procurement of materials" is outside the scope of GMP. We suggest the alternate wording, "Procurement is defined as receipt and testing of raw materials including vendor audits and technical agreements which is indeed part of the scope of GMP." We suggest adding a new bullet under Manufacturing to include "Surveillance" as an additional activity.

Section 1.3, Relationship of ICH Q10 to Regional GMP Requirements, ISO Standards and ICH Q7: It is not clear how ICH Q10 in its current form serves as a bridge between regional requirements when the GMPs differ as much as they do between the EU, US and Japan. We suggest clarification of how Q10 serves as a bridge with the following wording, "Q10 provides a harmonized understanding of a pharmaceutical quality system under which regional GMP requirements may operate throughout the lifecycle of the product."

Section 1.4, Relationship of ICH Q10 to Regulatory Approaches: We suggest deleting reference to Annex 1 because it is redundant with what has already been explained in the narrative and the examples provided in Annex 1 may not apply across all regions.

Section 1.5, ICH Q10 Objectives: ICH Q10 objectives are not as stated, but rather ICH Q10 describes systems that would facilitate meeting these objectives. We suggest adding a sentence before 1.5 i) stating that "It is the objective of ICH Q10 to describe a system that will facilitate meeting the following objectives:"…

Section 1.5, i) Achieve Product Realization: Please be consistent regarding the use of the word "processes" throughout the document. In many cases, "processes" refers to manufacturing processes. We suggest a better alternative would be "quality processes and systems that provide…"

Section 1.6, ii) Quality Risk Management: The statement "Quality risk management can provide a proactive approach to identifying and controlling potential risks to quality throughout the product lifecycle" is not accurate. Risk assessment does not control risks, it focuses attention on risks. We suggest adding the following sentence "Quality risk management can provide a proactive approach to focus attention on risk to quality areas throughout the product lifecycle. Quality risk management should not be used as a reactive approach to justify inappropriate decisions."

Section 1.7, i): Under Design and Content Considerations, the first bullet point is unnecessary and does not add value. We suggest deleting this comment since it is important that quality systems be written with enough clarity and simplicity to allow full understanding and global implementability.

Section 1.7, ii): We suggest changing the word "should" to "may", as some firms may choose to use the same pharmaceutical quality system regardless of the product's stage of development.

Section 1.7, vi): We suggest bullet point "vi" under Design and Content Considerations be the first bullet, because it describes what should be included.

Section 1.8, iv), Quality Manual: It is important to emphasize Quality is not solely the responsibility of Management alone but is dependent on staff as well. We suggest the alternate wording, "Management and staff responsibilities…"

Section 2.1, ii), (1): Under Management Commitment, we suggest adding "improvement" as a management responsibility so that ii), (1) states, "Participate in the design, implementation, monitoring and improvement of the pharmaceutical quality system;"

Section 2.1, ii), (4): It is difficult to capture all possible interactions. If responsibilities and roles are clear, the latter part of the sentence is not needed. We suggest deleting the following: ", and ensure interactions are defined and understood." from first sentence in ii), (4).

Section 2.2, i), Quality Policy: We suggest revising this to add "philosophy" so that 2.2, i) reads: "…describes the overall philosophy, intentions and directions…"

Section 2.6, Management Review: We suggest the alternate wording to the first sentence to read, "Senior management should assess the pharmaceutical quality system on a regular basis to ensure its suitability and effectiveness."

Section 2.6, Management Review: We suggest the alternate wording to the second sentence to read, "Management should assess the conclusions of periodic reviews of process performance and product quality and of the pharmaceutical quality system, as described in Sections 3 and 4, and strive to improve its effectiveness."

Section 2.7, Oversight of Outsourced Activities: The expectation for monitoring outsourced operations should be more explicit.

Section 3, Continual Improvement of Process Performance and Product Quality: We suggest deleting the first paragraph and rewriting section 3 to be more understandable. In addition, the description of the foundation of ICH Q10 is not consistent with the same statement in Section 1.3, because ISO QMS guidelines are not included. We also suggest adding training system as a fifth element.

Section 3.1: The information in the section is obvious and unnecessary. We suggest deleting this section or moving the information in it to the appendix.

Section 3.1, i), Lifecycle Stage Goals: Under Pharmaceutical Development we suggest adding the following text to include Investigational Medicinal Products so that it reads, "Pharmaceutical development may include the preparation of Investigational Medicinal Product, and elements of the pharmaceutical quality system may be applied to ensure they are of appropriate quality to support the clinical studies."

Section 3.2, i) Process Performance and Quality Monitoring System: The formula is also an important element in the Process Performance and Product Quality Monitoring System. We are pleased that "controls" has been added as these are also important. We suggest the alternate wording, "An effective monitoring system provides assurance of the continued capability of the formula, processes and controls…" We also suggest that allowance for the use of Design Space in the monitoring and control of process parameters be included here.

Section 3.2, i), Process Performance and Quality Monitoring System: Under item (3), we suggest focus on critical attributes and revising to state, "Analyze parameters and critical quality attributes…"

Section 3.2, Tables I-IV, it would be helpful to clarify that the column titled "Manufacturing" is referring to commercial manufacturing since manufacturing also occurs during development phases.

Section 3.2, ii), Corrective Action and Preventive Action System: It is important to define better how CAPA is applied to development and IMP. We suggest adding the following to the end of the paragraph: "CAPA may be a useful tool for managing non-technical exceptions (complaints, rejections, non-conformances, facility issues, audits, regulatory inspections and findings) related to the preparation of Investigational Medicinal Products. It is not appropriate to apply CAPA to the development process until the later stages, after the basic formula, manufacturing process, and control strategy

have been defined." Also, it may be useful to add a sentence that says "The development of a CAPA effectiveness monitoring system is encouraged."

Section 3.2, ii), Corrective Action and Preventive Action System: To better define how CAPA is applied during development we recommend the following changes to Table II: "Product or process variability is explored. CAPA methodology may be useful in the later stages of development where corrective actions and preventive actions can be incorporated into the iterative design and development process. CAPA may be a useful tool for managing non-technical exceptions for Investigational Medicinal Products."

Section 3.2, iii), Change Management System: In the 2nd paragraph, we suggest adding, "and that equipment and processes are maintained in a validated state," to the end of the sentence.

Section 3.2, iii), (2), Change Management System: Under item (2), All changes should be properly evaluated. ICH Q8 does not use the word "movement" but rather uses "working within the design space". We suggest using the word "working" rather than "movement" for consistency with ICH Q8.

Section 3.2, iii), Change Management System: In Table III, under the Development column, the statement that the "… formality of the change management process should increase as the product moves through development in accordance to regional GMP requirement", raises many concerns because of the wide range of interpretation by inspectors regarding what is an appropriate "increase" of change control. Please see General Comments. At a minimum, we recommend changing the word "should" to "may".

Section 3.2, iii) Change Management system: Item (4), we recommend revising the beginning of the sentence to read, "Where relevant, after implementation, an evaluation of the change…"

Section 3.2, iv), Management Review of Process Performance and Product Quality: In Table IV, under the Development column, the Pharmaceutical Quality System will require more than Management Review in Development to ensure the adequacy of product and process design. It has more application to review of the overall development Quality System. We recommend replacing text under Development with the following: "Aspects of Management Review are performed to ensure the effective application of the Pharmaceutical Quality System to Pharmaceutical Development and, where applicable, the appropriateness of the product and process design."

Section 3.2, iv), Management Review of Process Performance and Product Quality: In Table IV, under the Tech transfer column the scope should be expanded to ensure that "…the developed product and process can be manufactured at commercial scale and or at the new site."

Section 3.2, iv), Management Review of Process Performance and Product Quality: It is confusing how the management review of process performance and product quality is described and the split in subjects between this review and the management review of the pharmaceutical quality system. We suggest reconsidering these reviews and aligning them with the 21 CFR 820 requirements for management reviews of devices and with the requirements to product quality reviews in Eudralex vol 4, 1.5.

Section 4.1, Management Review of the Pharmaceutical Quality System: We suggest adding the following points to the management review of the PQS: (1) Impact of new guidelines/regulations on the quality system training metrics and effectiveness, and (2) CMO performance against Quality Agreements.

Section 5, Glossary: For "Change Management", we suggest using the agreed wording in ICH Q9 for change management and state, "Change Management: A systematic approach to identify, analyze, evaluate, approve, implement and review changes."

Section 5, Glossary: For "Corrective Action", we suggest adding the clarifying note from ISO9000:2005 as well to assure consistent understanding as there may be readers not completely familiar with the concept of CAPA as described in ISO 9000:2005. We suggest the following for inclusion: "Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence."

Section 5, Glossary: For "Preventive Action", we suggest adding the clarifying note from ISO9000:2005 as well to assure consistent understanding as there may be readers not completely familiar with the concept of CAPA as described in ISO 9000:2005. We suggest the following for inclusion: "Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence."

Annex I: We suggest Annex I be deleted as it does not add useful information to the guideline, and is likely to cause confusion.

Conclusion

Thank you for providing us with the opportunity to begin the dialogue by commenting on this Draft Consensus Guideline. We look forward to additional opportunities to discuss the matters outlined above.

Sincerely,

/s/

Sara Radcliffe
Vice President
Science and Regulatory Affairs