PDA
An International Association For Pharmaceutical Science And Technology

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June 10, 2005

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

Dear Sir/Madam:

**Ref: INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE: DRAFT CONSENSUS GUIDELINE PHARMACEUTICAL DEVELOPMENT Q8, November 2004 [Docket No. 2005D–0021]**

PDA is pleased to provide comments to FDA on the ICH Draft Consensus Guideline Pharmaceutical Development Q8, issued in November 2004. PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological and device manufacturing and quality.

PDA commends this initiative to develop a Consensus Guideline on Pharmaceutical Development. We encourage FDA to continue to develop more harmonized Guidelines. We have also included some suggestions as to where more specific guidance is needed. PDA stands ready to participate in a process that will provide more detailed guidance in the future.

The following comments are provided for the Agency's consideration.

**Point #1 Scope (Section 1.3)**
The scope states this guideline is intended to provide guidance for drug products and may be applicable for other types of products. However, the specific case examples contained within the document provide a slant more towards small molecules. For this guideline to be applicable to protein drug products and biological products, then the guideline would benefit from including specific guidance through examples in an appendix for these types of products. This will assure manufacturers of the more complex protein products would be able to more easily apply the principles contained within the guideline.

Further, the evolution of the development of the formulation for large molecule drug products (typically protein drug products and biological products) normally takes place during the development of the drug substance. Since this document does not apply to drug substances, there is a gap in how this document can be applied for those drug products. Inclusion of drug substances in the scope would be preferred.

The guideline makes no differentiation between generic and innovative products. While the Common Technical Document is primarily for innovative products, it would be beneficial for the guideline to include some clarification on this issue.

The issue of scale-up is not addressed either in the body of the document or in the glossary. It would be beneficial for the guideline to include some clarification on this issue.

**Point #2 Design Space (Line 51), Approved Design Space (Line 77)**
The term "design space" is first used in Line 51. Understanding "design space" as a concept is crucial to a complete understanding of this guideline and the benefits contained within. It would be preferable to include the definition within the body of the text where the term is first used in addition to the definition in the glossary.

The concept of design space would also benefit from a more detailed definition and description. It is not clear if the design space refers to product specifications or to

processing parameters. Also, the intended inter-relationship between the design space, the critical processing parameters and product release specifications is not clear. PDA supports the recent discussions at the PQRI Workshop on Specifications. At that meeting, the concept of separation of release specifications based on clinical relevance (critical quality attributes) from critical processing parameters internally controlled during manufacturing was advanced.

Clarification is needed for the mechanism by which a design space becomes an approved design space by different regulatory authorities. There should be assurance across the three regions concerning consistent interpretation of the design space.

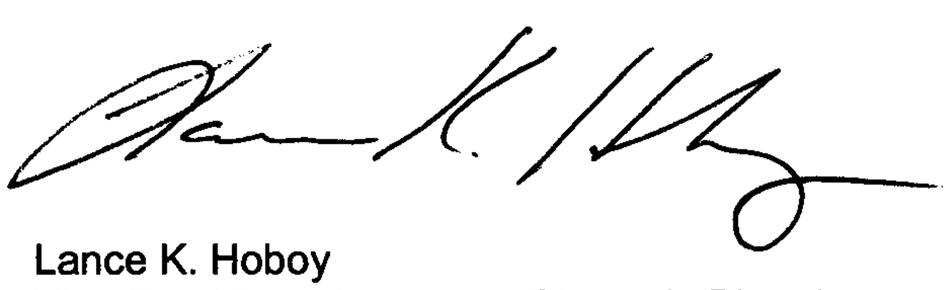
Changes outside of the design space could be implemented according to protocols demonstrating parity with original processes. Thus, regulatory flexibility would be realized. Process knowledge must be demonstrated for a firm to take advantage of this regulatory flexibility. We would suggest the addition of a fourth bullet point stating manufacturing process improvements, outside of the approved design space (described in comparability exercises) could be implemented without further regulatory review.

**Point #3 Initial Concept to Final Design (line 143)**
Line 143 states "The summary should highlight the evolution of the formulation design from initial concept up to the final design." It is unclear what is meant by the initial concept. The term "Initial concept" should be replaced by the term "initial early development" for greater clarity. The term "final design" should be replaced by the term "commercial formulation". The sentence would then read "the summary should highlight the evolution of the formulation design from the initial early development formulation up to the commercial formulation".

**Point #4: Test Methods**
The guidance is silent regarding the test methods utilized throughout pharmaceutical development. Some comments on analytical methods should be included. Those methods that support critical process parameters should be demonstrated to be reliable, accurate and robust as early as possible in the development stage.

PDA would be pleased to offer its expertise to assist in the clarification of its comments, and the continued evolution of this important Guideline. We look forward to working with FDA, industry and other professional associations to develop a world class document.

Yours sincerely,



Lance K. Hoboy
Vice President, Finance & Strategic Planning
PDA



Attachment: Comment Grid

[redacted]

# PDA Comments on ICH Q8: "Pharmaceutical Development"

| Section | Line | Suggested Change | Comment/Rationale |
|---|---|---|---|
| | General | The guidance is silent regarding the test methods utilized throughout pharmaceutical development. Some comments on analytical methods should be included. Those methods that support critical process parameters should be demonstrated to be reliable, accurate and robust as early as possible in the development stage. | See Point # 4 in the cover letter |
| | 17 | Include assessor with reviewer to read "reviewers, assessors and inspectors" | Consistency with following paragraphs, incorporates life cycle approach |
| 1.3 | 31 | The scope should be broadened as specified in the cover letter | See Point #1 in cover letter |
| 1.3 | 32 | Please add in term in italics: ...(Pharamaceutical Development) for "new and generic" drug products as defined in the scope of Module 3..... | To clarify scope. |
| | 36 | Delete the sentence "[T]this guideline might also be appropriate for other types of products". | The sentence is unclear and does not add value. |
| | 43 | Add predictable to phrase to read "in a reproducible and predictable" | The goal of defining the design space to assure a predictable outcome of the process |
| | 47 | Change "is" to "can be" to read " development studies can be a basis" | Not all studies are the basis for risk management |
| 2 | 51 | The term “design space” is first used in Line 51. Understanding “design space” as a concept is crucial to a complete understanding of this guideline and the benefits contained within. It would be preferable to include the definition within the body of the text where the term is first used in addition to the definition in the glossary.<br><br>The concept of design space would also benefit from a more detailed definition and description. It is not clear if the design space refers to product specifications or to processing parameters. Also, the intended inter-relationship between the design space, the critical processing parameters and product release specifications is not clear. PDA supports the recent discussions at the PQRI Workshop on Specifications. At that meeting, the concept of separation of release specifications based on clinical relevance (critical quality attributes) from critical processing parameters internally controlled during manufacturing was advanced. | See Point #2 in the cover letter |
| | 52 | Delete "also" | Grammatical |
| 2 | 59 | The amount and detail of information provided should depend on the drug substance used, the dosage form, the manufacturing process and the physical and chemical characteristics and stability of the final drug product. | It is advisable to provide as much data as possible without commercial scale production experience. |

# PDA Comments on ICH Q8: "Pharmaceutical Development"

| Section | Line | Suggested Change | Comment/Rationale |
|---|---|---|---|
| | 59 | Add to read "are encouraged because they add clarity and facilitate review" | Tables and graphs should be a value added activity |
| 2 | 62 | Add a definition of "significant risk" or delete its use | The term 'significant risk' is not defined in the glossary. |
| | 76 | Amend to read: "regulatory decision over the lifecycle of the product" | Clarification |
| 2 | 77 | Clarification is needed for the mechanism by which a design space becomes an approved design space by different regulatory authorities. There should be assurance across the three regions concerning consistent interpretation of the design space. | See Point #2 in the cover letter |
| | 78 | Changes outside of the design space could be implemented according to protocols demonstrating parity with original processes. Thus, regulatory flexibility would be realized. Process knowledge must be demonstrated for a firm to take advantage of this regulatory flexibility. We would suggest the addition of a fourth bullet point stating manufacturing process improvements, outside of the approved design space (described in comparability exercises) could be implemented without further regulatory review | See Point #2 in the cover letter |
| | 99 | Change "crystal engineering" to "polymorphic form" | The latter is a better example |
| | 108 | Add link for Q6a | clarity |
| 2.1.2 | 123 | All substances used in the manufacture of drug product should be discussed whether they appear in the finished product or not. | These substances can affect drug product performance/reproducibility. |
| | 143 | Line 143 states "The summary should highlight the evolution of the formulation design from initial concept up to the final design." It is unclear what is meant by the initial concept. The term "Initial concept" should be replaced by the term "initial early development" for greater clarity. The term "final design" should be replaced by the term "commercial formulation". The sentence would then read "the summary should highlight the evolution of the formulation design from the initial early development formulation up to the commercial formulation". | See Point #3 in the cover letter |
| | 149 | Please place the word "formal experimental designs" in italics to denote it is a defined word contained within the glossary | Without the demarcation, the reader can become confused as to what constitutes a formal experimental design. All development studies should have a good scientific basis with proper documentation practices. The aforementioned concept should also be included in the definition. |
| | 155 | Change to: A summary of formulations used in clinical safety and efficacy, and any relevant bioavailability or bioequivalence studies should be provided | The document implies that formulations used in all human studies associated with the development of a product should be summarized. |
| | 210 | Add link for Q6a | Clarity |

# PDA Comments on ICH Q8: "Pharmaceutical Development"

| Section | Line | Suggested Change | Comment/Rationale |
|---|---|---|---|
| | 224 | Add to read " validation, continuous quality verification (where applicable) and process control" | Continuous quality verification, where process controls and monitoring is in place, should be an alternative to traditional process validation |
| 2.3 | 250 | Please change to read "During development, if it is possible to identify those aspects of theprocess which can be measure, this identification may aid in future applications for process optimization. | The sentence as written is unclear and implies that during development, one would need to determining future proces optimization applications. |
| | 291 | Add link for Q6a | Clarity |
| | 300 | Add to read "contamination, thus assuring sterility of the product through the expriy period" | The container closure must prevent contamination in order that sterility is maintained. Manufacturers test for sterility at the end of expriy. |
| | 317 | A section 2.7 should be added to address cleaning and changeover. | Often times, manufacturing, engineering and development departments are Iface difficulty in finding pertinent information regarding toxicity of the drug substance, product and most especially excipients. Having the information regarding the least aqueous soluble, most toxic and greatest concern regarding carryover potential would certainly enhance the manufacturing knowledge especially in times where rapid changeovers are becoming more common. |