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Pharmaceuticals Inc.

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

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**Docket No. 2005D-0021, International Conference on Harmonization;
Draft Guidance on Q8 Pharmaceutical Development**

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Dear Sir or Madam:

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Boehringer Ingelheim Pharmaceuticals, Inc. is submitting comments on the subject draft ICH guidance "Q8 Pharmaceutical Development", per the notice published in the Federal Register of February 9, 2005 (70 FR 6888). Our comments are tabulated beginning with general strategic comments, followed by comments identified with the line number of the draft guidance.

Thank you for the opportunity to provide comments on this guideline. Please contact the undersigned with any questions or comments on this correspondence.

Sincerely,



Patricia Watson
Head Technical DRA
Drug Regulatory Affairs

Comments
ICH Q8: Pharmaceutical Development
Step 2 – Version 4.3

Key Philosophical or Strategy Issues
Clarification is needed on “flexible regulatory approaches” that pharmaceutical development can create a basis for, with an adequately supported design space. In particular, examples of “risk based regulatory decisions” in the context of application review as well as pre-approval inspection would be necessary for better understanding and adherence to the concept worldwide.
Clarifications are needed on the scope of this guideline: original marketing applications and over the life cycle of the product (post- approval submissions) as well as the type of products covered.
In order to avoid region-specific approaches to the maintenance of current pharmaceutical development information in the registration application, it is recommended that the guideline address how applicants should update the dossier with additional development information over the life cycle of the product. Furthermore, it is recommended that such updates occur on an “as needed” basis rather than according to a prescribed periodic update.
The concept of “Design Space” is a pivotal concept and should be moved from the glossary and discussed in the body of the guideline. The design space should be clearly described as those formulation attributes, manufacturing parameters, packaging systems, stability conditions, etc. within which the applicant has demonstrated the product remains a quality product. The guideline should make it clear that the “specifications” for the product reside within the established design space; they do not define the design space.
The guideline should instruct applicants to (and how to) explicitly describe the “Design Space” that has been justified by the knowledge obtained. Applicants should be instructed to propose that the Design Space be approved, and future changes within the Design Space may be implemented without prior regulatory approval.
The guideline does not clearly delineate what is the minimal amount of pharmaceutical development information that must be submitted in section 3.2.P.2.
Therefore it is not clear whether or not a “Design Space” is required for all applications. If it is considered appropriate for all applications to include a Design Space proposal, then the guideline should explain that a ”traditional” development according to the current paradigm will result in a constricted Design Space since the knowledge will be relatively limited. A more expanded

Comments
ICH Q8: Pharmaceutical Development
Step 2 – Version 4.3

Key Philosophical or Strategy Issues
Design Space may result from a development program where the body of knowledge is greater.
If the concepts of “Design Space” in this guideline are taken to their logical conclusion, the structure of Module 3 of the CTD is called into question with respect to the concepts of Critical Steps, Justification of Specifications, etc. The inter-relationship of the 3.2.P.2 section with the other parts of the dossier should be considered and guidance provided.
The definition of terms and acronyms in the glossary should be expanded to include all key terms and acronyms utilized in the development guideline. The glossary should be fully aligned and harmonized within the frame of all ICH-guidelines.
We believe a Part 2 to the existing Q8 guideline to define specific dosage form guidance would be appropriate. However, Part 2 for dosage form specific guidance should be added <u>after</u> experience is gained with this guidance and then adjust it if necessary.
Since some concepts in the existing ICH Q6A are inconsistent with certain aspects of the ICH Q8 guideline, it is recommended that Q6A be revised accordingly.
An ICH guideline which addresses the development knowledge on drug substance is not considered to be necessary at the same level as ICH Q8 Pharmaceutical Development. The attributes of the drug substance that impact product quality and performance are already captured within the ICH Q8 guideline. Other aspects of the drug substance development knowledge are located in the CTD-format in the “S” section, <i>e.g.</i> , 3.2.S.2.4 Control of Critical Steps and Intermediates 3.2.S.2.6 Manufacturing Process Development, 3.2.S.3.1 Elucidation of Structure and other Characterization, etc.
Unlike the drug product section, there is no single drug substance section where a consolidated overview of the drug substance development is located. Unless the EWG proposes to establish a new section in the CTD, or otherwise restructure the CTD Module 3 format, any new ICH guideline on drug substance development should provide guidance in the context of the existing CTD sections.

Comments
ICH Q8: Pharmaceutical Development
Step 2 – Version 4.3

<u>Item with Reference Line #</u>	<u>Relative Importance</u>	<u>Key Concerns with Explanation of Position</u>	<u>Proposed change</u>
INTRODUCTION			
Line 12	1		Please insert ..can be updated “at the applicants discretion..”
Line 13	1		Please insert after ..lifecycle of product. "In addition to the minimum information described in this guideline for the Pharmaceutical Development section, the guideline also references where the optional provision of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches."
Line 36	2	Provide an example of “other types of products” or delete this and the following sentence.	For example, combination products, devices...biotech products, well characterized biotech products to include recombinant proteins and monoclonal antibodies.
Line 38	3	We question the expectation that an applicant “should consult” with the appropriate regulatory authorities in order to determine applicability of ICH Q8 for a particular type of product.	Change “should consult” to “can”consult”.

Comments
ICH Q8: Pharmaceutical Development
Step 2 – Version 4.3

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PHARMACEUTICAL DEVELOPMENT			
Line 44	2	The document refers to pharmaceutical development studies, which implies that experience from commercial manufacture is excluded.	Change ‘from pharmaceutical development studies’ to ‘from pharmaceutical development studies and manufacturing experience provide’
Line 47	3	Not all studies are the basis for risk management	Change “is” to “can be” to read “development studies can be a basis..”
Line 50	1	Changes “should”	Please change should to “can”
Line 51	1	Move a sentence from Line 322 to Line 51	Add after Line 51 “Working within the design space is not generally considered as a change of the approved ranges for process parameters and input variables. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process”
Line 59	2	Tables and graphs should be a value added activity	Add to read “are encouraged where they add clarity and facilitate review”
Line 72-73	1	Clarify whether or not the concept of “Design Space” applies only if studies beyond the “minimum” have been conducted. We suggest that a Design Space exists, albeit more restricted, based on the “minimum” knowledge suggested in Lines	Begin a new paragraph with the amended sentence: “The level of scientific understanding establishes the design space, which can be the basis for more flexible regulatory

Comments
ICH Q8: Pharmaceutical Development
Step 2 – Version 4.3

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		61 – 66.	approaches, for example:”- and indent the bullet points
Line 88-89	3	We note reference to “the stage of the development of the product” and suggest that this could seem ambiguous versus the earlier statement (1.3 Scope) that this guideline does not apply to drug products during the clinical research stages of development.	Delete “and the stage of development of the product”.
Line 99	1	The term “e.g., crystal engineering” may not be widely understood	Reword accordingly (e.g. solid state properties)
Line 147	2	We suggest that “experiences” should more appropriately read “knowledge”	Replace “experiences” with “knowledge”
Lines 155-159	2	Give more clarity to what is meant by “pivotal clinical” batches	Change to: “A summary of formulations used in pivotal clinical safety and efficacy, and in any relevant bioavailability or bioequivalence studies should be provided.”
Line 173	2	We suggest that the final sentence is not needed, since it reiterates points already made.	Delete “Information to support.....should be provided”.
Lines 177 and 180-182	1	The first sentence of the paragraph appears too restrictive and could be more	<ul style="list-style-type: none"> • Delete first sentence in section and move a modified version to line 184 before

Comments
ICH Q8: Pharmaceutical Development
Step 2 – Version 4.3

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		explanatory. EU guidance approach describing different types of overages as examples would be welcome (differentiation between manufacturing overages and stability overages).	<p>last sentence in section. Use wording similar to: “In general, use of an overage of a drug substance to compensate for degradation during manufacture or a product’s shelf-life, or to extend the expiration dating period, is discouraged.”</p> <ul style="list-style-type: none"> • Delete last sentence of this section, but include a fragment of it in sentence before: “<i>Any overages in the manufacture of the drug product, whether they appear in the final formulated product or not, should be justified and shown in the representative batch formula. Information should be provided on...</i>”
Line 191	1	Move sentence from line 204	...and discussed. “The physiological implications of the drug substance....”
Line 223	3	Continuous quality verification, where process controls and monitoring is in place, should be an alternative to traditional process validation	Add to read “ validation, continuous quality verification (where applicable) and process control”
Line 232	3	As currently written, this sentence implies that critical process parameters will always exist. It should be acknowledged that this is not necessarily the case.	Modify sentence to read “should identify any critical process parameters”

Comments
ICH Q8: Pharmaceutical Development
Step 2 – Version 4.3

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Lines 239- 241	1	For clarity and consistency within this guideline, the discussion and rationale for manufacturing process changes should be focused on changes from <u>pivotal</u> batches to primary stability and commercial batches	Change to read: “Significant differences between the manufacturing processes used to produce batches for <u>pivotal</u> clinical use (safety, efficacy, bioavailability, and bio-equivalency), primary stability, and the process described in 3.2.P.3.3 should be discussed. Alternately insert the word “relevant” before the word bioavailability.
Line 242	1	The sentence neglects to include impact on quality.	Change to read.....”The discussion should summarise the influence of the differences on the performance, manufacturability, and quality of the product.”
Line 258		Clarity	It is suggested that the glossary include a definition and / or example of the term, “structured risk management tools”. Propose this be altered to:- Include cross-reference (and a link to) ICH Q9
Line 276	2	This section does not mention the inclusion of secondary packaging materials, if needed.	Justification for secondary packaging materials should be included, when relevant.
Lines 281-283	1	Add Dry Powder Inhaler or Metered Dose Inhaler as examples.	

Comments
ICH Q8: Pharmaceutical Development
Step 2 – Version 4.3

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Line 290 - 293	2	The rationale for whether or not a nonsterile drug product should have a microbial limits specification, should be located in 3.2.P.5.6 Justification of Specifications. This rationale will be based (at least in part) on the knowledge presented in 3.2.P.2.5. The language in these lines could create confusion on what is to be located in 3.2.P.2.5. Reword for clarify.	For nonsterile products, discuss any scientific evidence of inherent antimicrobial properties that support the conclusions on whether or not a specification for microbial limits is needed.
Line 310	2	Compatibility with dosage devices should be located in P.2.4.	Change “dosage devices” to “infusion diluents and administration sets”
GLOSSARY			
Line 318	1	Additional terms should be defined in glossary, e.g. attribute, critical, overfill, overage, process robustness, Quality by Design.	
Line 320	3	We recommend that the concept of Design Space be placed and discussed in the body of the guideline rather than as a glossary definition. The concept of 'Design Space' as an 'established range...as demonstrated' is apparently assumed to be experimentally-derived rather than allowed from prediction or other sources of knowledge. A Design	

Comments
ICH Q8: Pharmaceutical Development
Step 2 – Version 4.3

<u>Item with Reference</u> <u>Line #</u>	<u>Relative</u> <u>Importance</u>	<u>Key Concerns with Explanation of</u> <u>Position</u>	<u>Proposed change</u>
		<p>Space should be allowed to be established from prediction, use of algorithms and use of broad knowledge. Additionally it must not be defined by requiring definition of failure.</p> <p>The second two sentences of the proposed definition describe what may be inferred from consideration of design space, rather than what it is.</p>	
Line 342	2	The definition of risk as only relating to harm misses the point of the positive aspects of risk management.	Change the definition of risk to read the same as in Q9.