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2005 30 09 12 11 17

April 8, 2004

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

Subject: Comments to: International Conference on Harmonization; Draft Guidance on Q8 Pharmaceutical Development, [Federal Register: February 9, 2005 (Volume 70, Number 26)] [Notices] [Page 6888 – 6889] [Docket No. 2005D – 0021]

To whom it may concern:

Novartis is a world leader in the research and development of products to protect and improve health and well-being. As a global pharmaceutical corporation, Novartis is supportive of efforts to improve and to harmonize the technical requirements for registration of pharmaceutical products. We appreciate the opportunity to comment on this guidance in accordance with FDA's Good Guidance practices.

Novartis is generally in agreement with the Draft Version of Q8 Pharmaceutical Development, but would like to re-affirm the following:

This document describes the suggested contents for the Pharmaceutical Development section in the quality module of a regulatory submission in the ICH M4 Common Technical Document (CTD) format. In addition, the draft guidance is intended to assist in the development of pharmaceutical studies that provide scientific understanding to support the establishment of specifications and manufacturing controls and serve as the basis for risk management of the life cycle of the product. We feel that it is important that the FDA are fully aware that the document serves a dual purpose and in most large pharmaceutical companies it is being directed at a dual audience.

Additional comments are provided in the attached tabular format, for ease of FDA use.

These comments are being provided in duplicate in written form and electronically as directed in the Federal Register Notice.

Novartis appreciates the opportunity to submit these comments and looks forward to continuing to work collaboratively with the agency on this important initiative to finalize Q8.

2005D-0021

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Thank you for the opportunity to comment. If you have any questions, please contact me at (862) 778-7005 or at e-mail: robert.clark@novartis.com.

Sincerely,



Robert J. Clark
Director
Global Regulatory CMC

Attachment

**ICH Q8: Pharmaceutical Development
Key Items for Consideration
Step 2**

<u>Item with Reference Page, paragraph and line number</u>	<u>Key Concerns with Explanation of Position</u>	<u>Proposed change</u>
p.3, 1.1 Objective of guideline lines 11-13	We are aware that the Pharmaceutical Development section of a New Drug Application is an essential component of the CMC portion of the file. The statement that it is " <i>first produced</i> " and " <i>can be updated</i> " implies that it may or should be filed in subsequent submissions. Under what circumstances can or should this document be re-filed. Should it be filed in the absence of a post approval change (as additional data becomes available, etc.)?	Please provide clarification in the finalized guidance.
p.3, 1.2 Background, lines 25-27	EWG established to develop guidance for pharmaceutical development <i>per se</i> , or documentation to be submitted in dossier?to develop guidance on the dossier documentation of alternative approaches to pharmaceutical development, which will cover.....
p.3, 1.3 Scope, lines 33-34	Would there be an opportunity for the FDA to review a "early version" of the Pharmaceutical Development document during the development of a product. Such a review would help to assure and maintain a high level of communication between sponsors and the Agency during development?	Please provide clarification in the finalized guidance.
p.4, 2.0, Pharmaceutical Development, lines 68-74	Is there an opportunity to include lessons learned with a particular process or a particular piece of equipment into a drug master file for future reference in subsequent applications.	Opportunities should exist to create filed processes (like DMFs) which could be referenced in future applications
p.4, 2.0, Pharmaceutical Development, line 76	Wording change requested	<ul style="list-style-type: none"> ▪ "risk managed regulatory decisions
p.5, 2.1.2.Excipients, lines 125-128	Performance through shelf-life will be demonstrated by stability studies rather than during development experiments – cross-refer. should also be demonstrated, with reference to stability data in 3.2.P.8.3 where appropriate.
p.5, 2.1.2.Excipients, lines 127-128	It is unlikely that full shelf life data will be available so as to demonstrate compatibility of all dosage form components at the time of an original filing. Supportive (laboratory or accelerated) data will on the other hand be available.	The sentence could be changed to "throughout the intended drug product shelf life, should also be supported"

p.5, 2.1.2.Excipients, after line 133		Add a section on Novel Excipients
p.6 2.2.1 Formulation Development, lines 144 - 147	Is there an opportunity to include lessons learned with a particular process or a particular piece of equipment into a drug master file for future reference in subsequent applications.	Opportunities should exist to create filed processes (like DMFs) which could be referenced in future applications
p.6, 2.2.1 Formulation Development, lines 156 - 159	With respect to stability: Q1A requires that "the primary batches should be of the same formulation.....". An open invitation here to consider formulation differences (which could be considered to include qualitative change in composition) as acceptable if justified could lead applicants into a false sense of security. If assessing authorities gave greater weight to Q1A, prompt approval could be jeopardised. Suggest weakening the statement:	Change to: "proposed commercial formulation (used in the primary stability studies) and those formulations used in pivotal clinical batches should be clearly described and the rationale for the changes provided.
p.6 2.2.1 Formulation Development, lines 171-172	Scored Tablets or anti-counterfeiting measures should not be part of process development	Please remove references
p.6, 2.2.3 Physicochem and biological properties, lines 199-202	Long sentence, whole section (lines 190-212) could use some simplification	Please split and or section re-write
p.7, 2.3 Manufacturing Process Development, line 222	It needs to be clarified which level of detail is expected. E.g. is there a need to justify why a Dyosna granulator and not a Collete gral is used?	Please provide clarification in the finalized guidance.
p.8. 2.3 Manufacturing Process Development, lines 226-7	Use of updated terminology	"The knowledge gained from process development studies can be used as appropriate to justify the drug product specification" to "The knowledge gained from process development studies can be used for the selection of tests and acceptance criteria"
p.8. 2.5 Microbiological Attributes, line 290	Please change wording	The rationale for not performing microbial limits ...
p.8, 2.5 Microbiological attributes, lines 302-304	Clarification only	For products containing antimicrobial preservatives, although.....