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April 28, 2005

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Docket No. 2005D-0021

Sir/Madame:

Enclosed are two copies of my comments on FDA's draft guidance on IC11 Q8 Pharmaceutical Development. I understand that the closing date was April 11, 2005 but that comments may be accepted after that date.

Sincerely,

Robert A. Jerussi
Robert A. Jerussi, Ph.D.

2005D-0021

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Comments from Jerussi Consulting, Inc. on ICH/FDA Draft Guideline Q8
Pharmaceutical Development, Draft No. 4.3 Dated Nov. 18, 2004

By Robert A. Jerussi, Ph.D.
April 26, 2005

This draft guidance follows the CTD format re the Pharmaceutical Development as outlined in M4Q Section 3.2.P.2 Pharmaceutical Development. However, it is an odd document since it is guideline about a guidance. Since the M4Q: The CTD Quality does not reference another document in the Pharmaceutical Development section for the drug product, 3.2.P.2 and that section appears to adequately detail the information the ICH regulatory bodies desire, the need for this document is questionable (however, see next paragraph).

Objective of the Guideline:

Lines 11-13 states that the guideline “----- is first produced for the original marketing application and can be updated over the lifecycle of a product.” The last part of this statement appears nowhere in the M4Q document and should be removed from the quoted statement. Leaving it in could be interpreted to require a firm to give an updated development report each time it supplements its application for a change in manufacturing or other parts covered by Section 3.2.P.2. If that is a result of the developmental report it is making a monster out of it. As far as this commenter can determine, the development report is required for the initial review and approval of the application only. This draft guidance simply adds to what manufacturers must submit. Whatever happened to so called “regulatory relief” that FDA use to talk about? The real reason for this guideline is to make the Pharmaceutical Development section of a drug application using the CTD format a living document which will go on for the entire life of the product. For what purpose?

Recommendation: This commenter doesn't believe this guideline is needed nor does he think that the development report should be a living document. Change the quoted sentence in the paragraph immediately preceding this one to “---- is produced for the original marketing application.”

Lines 21-27 indicate that during the July, 2003 ICH meeting in Brussels “agreement was reached on a common vision and approach” for development of a guidance that would cover the life cycle of a product. The trouble with the present guideline is that it goes beyond the M4Q ICH guidance while using the elements of the latter. Thus, it is somewhat confusing and if carried to its logical conclusion will add considerable bulk to any application both pre and post approval. In the United States it will be a further incentive not to submit applications in the CTD format which are not required.

Recommendation: No matter what the “vision and approach” discussed in Brussels, remove the “lifecycle” concept from this guidance. This document should only address

the initial drug application, not what may happen post approval. A draft FDA guidance titled "Guidance for Industry Drug Product, Chemistry, Manufacturing and Controls Information", January, 2003 covers the same subsections of Section 3.2P.2 as are covered in this document but no mention of "lifecycle" was made.

Line 51 mentions "design space" with a reference to the glossary where it is supposedly defined. This commenter must confess that he considers this an odd term along with the definition given it in the glossary. From its definition, it seems to be a set of specification ranges that "Working within the design space is not generally considered as a change of the approved ranges for process parameters and formulation attributes." If that is really the case, why not simply set the specifications at the limits of the so-called "design space" and forget this term? No example is given with the definition. No such term or concept appears in either Section 3.2.P.2 of the M4Q guidance nor of the 2003 FDA guidance previously mentioned..

Recommendation: Delete the term and concept of "design space" from this document.

Lines 236-237 in Section 3.2.P.2.3 Manufacture Process Development are devoted to the development of a sterilization process, one of the more difficult manufacturing processes. The choice should be "justified". Two lines seems like an woefully inadequate amount of guidance for a drug firm to follow and this part could be greatly enhanced. The firm should be able to state why it selected a certain process versus all the other potential sterilization processes available to it and how it developed the specific process. Of course any firm involved in the sterilization of drugs knows all this and has valid reasons why it selects one process over another and the FDA microbiological reviewers know why also, which makes these two lines another example why this entire guidance is not needed.

Recommendation: If the object of this guidance is to be a how-to document, then these two lines need to be expanded. However, if my comments recorded in the previous paragraph about firms knowing what they are doing and the FDA microbiologists knowing what they are supposed to do, then the 2 lines are superfluous.

Lines 214-260 2.3 Manufacturing Process Development. This entire section seems excessive. Why does this section really have to be in this document. Have the reviewers at various regulatory agencies ever been involved in the total development of a drug product to be knowledgeable enough to review this section? Currently in the United States this is left to FDA's investigators when they visit pharmaceutical facilities. This guidance is telling firms who are in the business of drugs and who develop pharmaceutical manufacturing processes, how to do it. Additionally the ICH should consider how a firm who has developed a drug years ago and is just seeking an approval for its application would fill out this section. Would that firm be able to say we have been producing this drug for 20 years and just now have been required to submit an application (as happened with Thyroxine) and we do not have records for how we

developed the manufacturing process but we know the process is reproducible? Suppose a firm has had a drug on the European market for a number of years and now wants to submit it to Japan and the U. S. A. But it has long lost or discarded any development report it may have produced when it first developed the drug product. What does it do if it wants to submit in the CTD format?

Recommendation: Instead of telling firms what ought to be in this section, allow firms, who know most about the development of its manufacturing process, to submit the information it believes was important in the development phase. Develop some kind of a grandfather clause so that some firms would not have to submit this section of the M4Q.

In general this guidance covers the same ground as the section on Pharmaceutical Development in the draft FDA Guidance Drug Product Chemistry, Manufacturing and Controls Information, January, 2003.. In fact, in certain instances the wording is almost identical. An example of the latter is the section on Overages 2.2.2 in each document. where the wording is often identical to each other. However, there are some differences, for example, the two sections on Manufacturing Process Development which is longer and more detailed in the ICH document and the two sections on Compatibility which is longer and more detailed in the FDA document than the ICH document..

Overall Recommendation

Do away with this document - it is not needed. It is only another regulatory burden for firms with no gain for patients. Use the scientists that worked on this and other not needed guidances to review drug applications and save the time and promote the efficiency of reviewers by eliminating the need for this document.