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

Docket No. 02D-0526

Sir/Madame:

I wish to comment on FDA's draft Guidance for Industry - Drug Product - Chemistry, Manufacturing, and Controls Information which was published on January 28, 2003 in the Federal Register with comments due by June 27, 2003. My comments are attached.

Sincerely,

Robert A. Jerussi

Robert A. Jerussi, Ph.D.

02D-0526 C4

COMMENTS ON FDA'S GUIDANCE FOR INDUSTRY DRUG PRODUCT
Chemistry, Manufacturing, and Controls Information
Issued for Comment January, 2003
by Robert A. Jerussi, Ph.D.

June 25, 2003 Docket No. 02D-0526

This document is well written and is clear and not confusing. It also makes many references to ICH and FDA guidances and to appropriate sections of the Common Technical Document (CTD) whose format is followed. However, I think that the document is too long in that it contains too much "how to" detail and can be shortened by at least one quarter. In addition, it requires firms to submit more information than currently for both NDAs and ANDAs since the CTD requires information not previously submitted in drug applications in the United States. Since the CTD format is not absolutely required in the United States (it is "highly recommended" - presentation by Justina Molzon, ICH Public Meeting at FDA, January 21, 2003) why would firms elect to submit applications in this format unless they plan to submit also in one or both of the other areas involved in the ICH process (Europe and Japan)? Additionally, since Japan's CTD effort will not cover generic products (presentation by Christelle Anquez, ICH Public Meeting at FDA, January 21, 2003) the incentive for filing in the ICH areas is reduced thus negating any advantage that the CTD format may have. Since the CTD only involves format, not data, it is also my concern that FDA will require more data in each section than its EU and Japanese partners.

Although I would prefer to see the CTD modified and changed, the comments that follow take the CTD as is with no expectation that it may be changed or shortened. Thus these comments are made in the hope of modifying FDA's interpretation of the CTD and assisting it in finding ways to shorten the guidance. Two avenues are pointed out, one is where the areas that involve an increase of requirements compared to presently submitted drug applications and the other where the document may be shortened without deleting the areas containing substantive matters.

The CTD M4Q contains a Module 2, Quality Overall Summary which is not addressed in this guidance. Yet much of the information required in Module 2, Quality Overall Summary is redundant and the document itself states that some of it may be incorporated directly from Module 3. We also believe that Module 2, Quality Overall Summary can be confusing to firms who choose to submit an application in the CTD format and no mention of it and its redundancy in this guidance is an error. It does seem that with all the information that is suggested to be submitted in Module 3 Drug Product, that Module 2, Quality Overall Summary could be eliminated. However, again, I take it as is.

Areas where more information is required then under current requirements:

1. Lines 362 - 678 IV. Pharmaceutical Development (P.2), [7.5 pages, 14% of the entire guidance].

This report has not been previously required in an NDA or ANDA. Lines 364 - 367 lists "information on the development studies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions are appropriate for the purpose specified in the application" that an application should contain. The guidance then covers 300 lines (377 - 678) to describe specifics about the information that should be included. The recommendation to submit this great amount of information, if followed, will make such a report not only large but time consuming to prepare by a firm and to review by FDA. And for what purpose?

Some general questions concerning ANDAs come immediately to mind. What kind of a report will a foreign firm submit who has had the product on the market in its own country or in Europe for ten years and has made a number of changes since the product was developed.? What kind of a report will an American firm make who has had a product on the American market but is now required by FDA to submit an abbreviated application such as recently happened with Thyroxin? Will such firms still have information on the development of their product? If not what kind of a report will they submit? And for what purpose?

Some specific comments follow:

A. Lines 394 - 399 indicate that if drug substance particle size is expected to influence dissolution, then drug product testing should be performed to test the appropriateness of acceptance criteria for the drug substance. This seems backward since the key for a generic firm is to develop a formulation with the API particle size as supplied by the vendor. The formulation developed with the particle size of the API will effect dissolution and bioavailability and if the firm can get these to come within the expected or required range using the particle size as delivered by the vendor, what testing must be performed?.

B. Lines 422 - 430 concern excipients and a discussion relative not only to the role of each excipient but to their characteristics that can influence drug product performance. What is required at present is that the role of each excipient be listed. How will a veteran formulator who has been formulating products for 20 - 30 years help his firm answer this? The role of each seems to already do that. The formulator knows how each excipient affects drug product performance and so should the FDA reviewer. The formulator's job is also how much of each excipient gets put into the formulation to give the desired formulation characteristics. The FDA reviewer probably doesn't have that type of knowledge or skill and it shouldn't be needed to review an application. What is important is that the formulation be presented and if it works, what further discussion is needed? The firm is now bound by the selected formulation.

C. Line s 492 - 493 discusses the development of the release mechanism of a modified release product. It seems that this should only be necessary when a novel or patented release system is used such as the GITS system when initially used. For other well known controlled releasing agents this should not be necessary since their mode of affecting release is well known.

D. Lines 537 - 539 states that "In general, use of an overage of a drug substance to compensate for degradation during the manufacture of a product's shelf life, or to extend the expiration period, is not appropriate." This statement is basically correct in that overages are not to be used ordinarily. However, this would be improved by adding the following statements. The word "considered" should be added before the word "appropriate". The thought should be expanded by the following sentence. "However, certain important drugs would not be marketable unless overages were used, for example epinephrin solution."

E. Lines 662 - 663 mention leachables with reference to footnote 17 which states: "The level of di-2-ethylhexyl phthalate (DEHP) leaching from polyvinyl chloride containers should be assessed, and appropriate reference to DEHP leaching should be included in the product labeling." Again, this seems to make labeling requirements more stringent than what is acceptable presently. As far as I can determine, not all drugs packaged in DEHP specifically in LVPs packaged in polyvinyl chloride containers are required to contain such a reference.

Shortening the Document

We recommend deletion of the following in the draft guidance:

1. In IV. Pharmaceutical Development (P.2) that lines 377 - 678 be deleted, about 7.5 pages. Allow firms to submit what they believe should be in such a report (section) without instructing them as to what should be therein or providing them with a "how to" guide. After all, the firms have developed the product and should know it best. Depending on the drug that was developed, there is no reason for such a report to be in the same format or cover identical areas for all drugs.

2. Delete Attachment 1, lines 1856 - 2116, about 6 pages. Leave it up to the ICH and individual firms to recommend/select specific tests for specific dosage forms such as appear in ICH guidance Q6A for solid and liquid oral drug products and parenteral drug products. As noted in the draft guidance, the universal tests have already be stated in Q6A. Allow firms the responsibility to select specific tests that best describe and control their products without too much rote instruction from FDA.

3. Delete all references that appear in a number of places in this draft guidance to additional future draft guidances. The latter have no real status at FDA or at least are not supposed to have status and therefore really cannot be factored into this particular draft guidance. This will affect perhaps 10 lines.

4. Delete Table 1: Example Target Composition Statement and Table 2: Proposed Batch Formula (no line numbers associated with these tables). Will save at a minimum of 1 page. Firms know how to prepare batch formulas and composition statements.