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

Docket # 03D0571

Dear Madam or Sir:

Attached are two copies of comments and suggestions regarding the draft guidance "**Drug Substance Chemistry, Manufacturing and Controls Information**" dated January, 2004.

It is obvious from reading this document that the team that put it together made a considerable effort of time and know how in formulating it. It also seems that they tried to tease out as much as possible from the subject but that effort has made the document too complex.

Some of the good points, not all of which are new in this document (this is NOT a complete catalogue of them), which will help reduce the regulatory burden are:

1. Supporting Stability Studies, page 42.
2. Periodic Quality Indicator Tests, page 32
3. Diluents, page 20
4. Characterization (S.3), page 7

The following are my general observations and recommendations about the draft guidance, especially critical are items 1. and 2., followed by an analysis of each point:

1. It is too long, especially Attachment 1 and should be shortened.
2. The definition of starting material is too complex and should be simplified. The selection principles are too cumbersome.
3. Reference to future FDA guidance documents should be eliminated and the document should stand on its own.

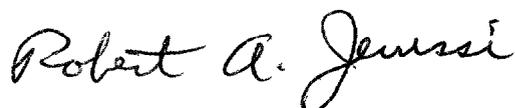
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4. Do not substitute MF for DMF.
5. Explain how a DMF that is in a non-CTD format can harmonize with a drug application which is in the CTD format.
6. Remove the word "propinquity".

I also find this guidance somewhat difficult to envision fitting into a Certificate of Suitability for an API. Some of FDA's partners in ICH accept a COS and perhaps FDA ought to begin thinking about it. What better group than the unit that wrote this guidance to look into COSs for APIs.

Sincerely,

A handwritten signature in black ink that reads "Robert A. Jerussi". The signature is written in a cursive, flowing style.

Robert A. Jerussi, Ph.D.
President

COMMENTS
FDA's Drug Substance Draft Guidance, Chemistry, Manufacturing and Controls

by Robert A. Jerussi, Ph.D.
Jerussi Consulting, Inc.

April 26, 2004

II. BACKGROUND, page 3

D. References to Other Applications or Master Files (MF), page 5

I recommend that Drug Master Files (DMFs) be used and not MF. Why the change? The letters DMF are well known not just in the USA but internationally. Additionally, the letters MF have another meaning in certain quarters of American society referring to an incestuous act! For the latter reason alone it should not be used. And if anyone reading doubts this just listen to some rap music.

Recommendation: Leave DMF as is.

1. Other Applications

Although Section A. under Background is devoted to the Common Technical Document (CTD) an area not touched is how can a DMF not in the CTD format be used or properly referenced in a drug application which is in the CTD format? Most of the DMFs residing at FDA today are not in the CTD format. How may an owner of a current DMF, not in the CTD format, convert it to the CTD format without submitting for review an entire new DMF?

2. Drug Master Files (DMFs)

This section contains 10 parts re what a DMF should hold and how the drug application applicant should reference this information. In several places things the applicant may further do that the DMF holder may not do are spelled out such as polymorph identification, micronization and studies to characterize impurities. However, FDA should not negotiate with the drug application applicant as to impurity levels or specifications when these are part of a DMF. In the latter case, FDA should be discussing these with the DMF holder if the latter is different from the applicant since it is not unusual for FDA to specify exact limits for an impurity or residual solvent that it would accept. Too often a DMF holder hears from its customer that FDA and the customer have negotiated a different specification without the holder's knowledge or agreement that the negotiated specification can be met!

III. GENERAL INFORMATION (S.1), page 8.

The Introduction indicates that the guidance does not cover peptides but this section covers protein drug substances. What is the difference? Isn't a peptide a smaller but better

characterized protein? Why and how the distinction in this guidance?

IV. MANUFACTURE (S.2), page 10.

B. Description of Manufacturing Process and Process Controls (S.2.2)

1. Flow Diagram

The amount of information that is recommended to go into a flow diagram is more than I have ever seen in an actual drug application! I believe this not to be needed and is another example of escalation of requirements as presented in this guidance.

2. Description of the Manufacturing Process and Process Controls

There are 13 bullets describing the large volume of information that should be included in this section of a drug application. From the NDA standpoint it seems like much more than that which would have previously been acceptable. If all this information is really needed why not just have the firm submit a batch record as is done in the Office of Generic Drugs?

- Process Controls, page 13.

This is now described in broadening fashion as "an all-inclusive term" to include operating parameters, environmental controls, process tests and in-process material tests. This broadening is confusing rather than helpful. The term "process control", the measurement of the process parameters and their adjustment when required to keep the process under control, should be used to replace all of the four listed terms.

3. Reprocessing, Reworking, Recycling, Regeneration, and Other Operations, page 15.

a. Reprocessing

Although a good three paragraph discussion appears under this heading, I disagree with the final sentence which states "(2) incorporated into the existing manufacturing process and performed on each batch when reprocessing occurs for the MAJORITY of batches." (emphasis added) When reprocessing occurs on a majority of batches the process may be out of control and allowing the reprocessing to continue on a MAJORITY of the batches may just be a head-in-the-sand response to the issue. In the Barr case for a drug product, the Agency didn't care for batches that reworking or reprocessing was done 20-25% of the time.

IV. MANUFACTURE (S.2), page 10

C. Control of Materials (S.2.3)

1. Starting Materials, page 18

The description of a starting material as possibly being one of two things is overly complex where "The starting material for application purposes can differ from the *active pharmaceutical Ingredient (API) starting material* -----." There should be only one starting material for any synthesis and that should be defined. Thus the additional statement on page 18 that "The recommendations for starting materials provided in this guidance are for application purposes." sounds as though FDA wants to go back as far as possible in detecting what it considers the actual starting material no matter how well known the designated starting material is! For a starting material; derived from petrochemicals one could go back to oil! This definition also completely overrides the definition in the starting material in the February, 1987 guideline for the manufacture of drug substances. The 1987 definition concentrated on the chemical nature of the starting material and how well known it is. Because this draft guidance contains a new definition of the starting material, the new definition should not be used until the guidance is finalized if the new definition is still contained in it. Yet it has already been used on one of my clients.

The guidance in this section does recognize that "In general, the starting material and API starting material should be the same for a synthetic drug substance." However, it further states that for a drug substance derived from a biological source, "the starting material (e.g. plant) and API starting material (e.g. extract) can be different." This is a contradiction since, as previously mentioned, a petrochemical designated as a starting material should not be acceptable, rather the oil should be the designated starting material and the process of distillation, cracking, reforming, etc. should be described!

I agree that a drug substance used to prepare another drug substance is not a good candidate for a starting material but should it be completely eliminated if it is well controlled and fit to be given to patients? However, there are times when starting with a relatively unknown drug substance should not be acceptable, particularly an experimental drug. This was recognized by the first drug substance and synthesis committee in the late 1970s. The latter was trying to set the stage to get more information about the preparations of APIs that appeared in INDs especially those from the NIH and other research institutions. Often FDA would get a one step synthesis in these INDs, for example involving placing a 17 acetate group on the 17 hydroxyl group of a rather complex steroid.

D. Controls of Critical Steps and Intermediates (S.2.4), page 20.

- Postsynthesis Materials - this is an unfortunate name. The synthesis is finished with the production of the API. The term postsynthesis really means something occurring after the completion of the synthesis, not before as the listed definition states. This term should be changed. If it doesn't meet the definition of an intermediate, then change the latter definition.
- Unfinished Drug Substance - this term also seems odd. Isn't this a "postsynthesis material"? One could imagine that it means a drug substance whose synthesis is unfinished. Or if this term is used for a technical grade which is further purified, then wouldn't the purified material be called a Finished Drug Substance? I recommend leaving the term drug substance to describe only the actual drug substance that is designated by the firm which includes its tests and specifications and using some other term such as crude material etc. to designate a yet to be

completed drug substance.

In all my years as a student and practicing organic chemist, I have never heard of these terms.

F. Manufacturing Process Development (S.2.6), page 23.

Why would the Agency, or for that matter any reviewer, want to see "the relationship between changes in the manufacturing process or manufacturing site and any associated changes in the chemical or physical properties of the drug substance." when all of this is in the past and really doesn't affect the present drug substance. Site changes for intermediates may be reported in annual reports according to BACPAC I and thus may never get reviewed by FDA. Manufacturing changes for intermediates are also in the annual reporting category according to BACPAC I. So why does FDA want to see how the process was developed, if such BACPAC I changes may never be reviewed in an annual report?

Part of this, e.g. the potential change in impurity profiles when a manufacturing process change is made, perhaps should go into the stability and/or tox sections.

Recommendation: This section be left up to the firm submitting the application to fill out as it sees fit.

V. CHARACTERIZATION (S.3), PAGE 24

A. Elucidation of Structure and Other Characteristics (S.3.1)

1. Elucidation of Structure

This section lists a number of physical and chemical techniques that are to be used to "confirm" the chemical structure of the drug substance. However, in section I. INTRODUCTION, it is made clear that this guidance is for drug substances that appear in NDAs, ANDAs, NADAs and ANADAs. Therefore, many of the drug substances in these applications are not NMEs and do not need the array of tests delineated in the first paragraph on page 25. Nothing in this section indicates that for well known drug substances all this testing and structural affirmation is not necessary. Some firms perform extraordinary testing for this affirmation thinking that is what FDA wants for a well known drug substance. Also why would FDA want reviewers spending time on all this unnecessary testing?

Recommendation: Rewrite this section listing the minimum number of confirmatory tests needed to "confirm" the structure of well known drug substances. For instance an IR spectrum and melting point may be all that's needed or showing sameness with a USP reference standard. Does a firm need an X-ray pattern for ibuprofen?

VII. REFERENCE STANDARDS OR MATERIALS (S.5), PAGE 40

Punting to a forthcoming guidance document is simply dead wrong in this short paragraph.

Recommendation: Replace this entire paragraph with one that describes what is needed for a reference standard which the firm must generate because there is no other source.

XI. REGIONAL INFORMATION (R), PAGE 46

A. Executed Production Records (R.1.S)

Although not required, firms should be given the option of submitting a batch record instead of all the information required under IV. B. 2.

Attachment 1: Starting Materials for Synthetic Drug Substances (page 48).

The definition given in the first sentence of this Attachment is fine and one that has been used by the Agency for at least 15 years "A starting material for synthetic drug substance is a chemical compound of defined molecular structure that contributes to the structure of the drug substance." However, dividing starting materials into two groups such as 1) starting materials with a significant nonpharmaceutical market and 2) starting materials without a significant nonpharmaceutical market seems contrived, artificial and non scientific. A synthetic drug substance is made via a synthetic scheme and is chemical in nature. Therefore the starting material is a chemical and what else it might be used for is really irrelevant

The recommendation to discuss the choice of starting materials at the end-of-phase 2 meeting is much too late for firms and should be discussed as early as possible but no later than the beginning of Phase 2..

I. Selection Principles for Starting Materials Without a Significant Nonpharmaceutical Market (page 49): These should be used to "justify" the proposed starting material!

A. Propinquity - this word should be eliminated from this guidance (Place dictionary definition at end under references). It is a word that an English major would use, not a science major. However, on first reading, its meaning in this draft guidance "A chemical proposed as a starting material should be separated from the final intermediate by several reaction steps that result in isolated and purified intermediates " is actually opposite from the dictionary definition of the word. However, what the writers were trying to get at is understandable. The question that must be asked is whether or not that requirement covers all the synthetically produced drugs currently approved by FDA? Does it even cover just New Molecular Entities (NMEs) approved by FDA? How many drug substances approved by FDA had several isolated and purified intermediates between their starting material(s) and their final intermediates? There are likely a number of them that have not. Nitroglycerin is one even if you go back to the preparation of glycerin. Additionally, this requirement does not seem to meet that of an isolated impurity in BACPAC I which does not require purification but obviously does require isolation. Thus, the purposed definition of a starting material is more stringent than in the past and an escalation of current requirements without adding value to the API.

Recommendation: Change this definition to eliminate the need for a starting material to be

separated from the API by the number of isolated and purified intermediates. After all if we separate the starting material from the API by enough intermediates, it may no longer contribute a structural feature to the API!

B. Isolated and Purified - If the starting material must be isolated and purified it will eliminate a crude substance. Starting materials that are isolated from nature may be designated as crude, that is not having had a separate purification step performed in their isolation, but still be of good quality. This requirement is unnecessarily restrictive.

Recommendation: Eliminate the "purified" portion of this requirement.

C. Carryover of Impurities - this section states that "a starting material should not be the source of significant levels of impurities in the drug substance." A significant level is further defined as greater than 0.10 percent. Well that's more restrictive than a "normal" identified impurity in a drug substance whose level above 0.10 percent depends on its tox profile! Isn't the starting material itself considered a source of an impurity in the drug substance? If so, it is not unreasonable that the actual starting material may end up as a presence in the drug substance at a level above 0.10%. What's so bad about having a starting material in the API at a level above 0.10% if its non toxic?

Recommendation: Increase the limit of significant level to above 0.10% or eliminate a percentage statement completely.

D. Complexity of Structure - this subject just goes too far. So what if an advanced technique is needed to distinguish a starting material from potential isomers or analogues. As long as it can be done what's the difference. And since when is elemental analysis an "advanced technique"? Or for that matter mass spec., H-NMR or chiral HPLC? These are all simply tools available to a chemist and have been for a long time, most for decades.

Recommendation: Eliminate this selection principle.

Attachment 2: Starting Materials of Plant or Animal Origin, page 56.

This attachment begins with the following quote: "The FDA considers (1) cells; (2) plants, plant parts, macroscopic fungi, or algae; or (3) animal tissues, organs, or body fluid from which the drug substance is derived to be the starting material for a drug substance derived from a biological source." There is merit in this statement except for plants and the guidance is correct in excluding some, but not all, starting materials that are highly purified materials obtained from plants such as sucrose and tartaric acid. However, if a PLANT is going to be considered a starting materials so should OIL and COAL (coal tar). When a chemical from oil or coal is either a starting material or the starting material for the API starting material, at least for consistency's sake, oil and coal should be considered starting materials. Of course the same exclusion can be given for a highly purified material coming from oil or coal as is given for sucrose, etc. from plants. After all both oil and coal contain polynuclear aromatics which are

carcinogenic and which are more significant than residual pesticides mentioned in the guidance for plants.

Several examples of drugs which start with an oil or coal tar derivative or whose starting material came from an oil or coal tar product can be given. Naproxan contains a naphthylene ring which is a starting material for one of its starting materials. Nabumetone contains a naphthylene group also as does nadoxolol and naphazoline. Flornoxyne contains a polynuclear aromatic ring system and halofantrine contains a phenanthrene ring system. These are just a few examples of drug substances containing ring systems coming from petroleum or coal tar.

Recommendation: Exclude plants as starting materials or add oil and coal tar as starting materials.