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CMC - Quality

3533 '03 JUN 11 09:57

June 4, 2003

Documents Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Land
Rockville, MD 20857

Re: Docket Number 02D-0526

Dear Sir or Madam:

Thank you for the opportunity to comment on the draft *Guidance for Industry, Drug Product, Chemistry, Manufacturing, and Controls Information*. This is an extensive document that clearly represents a considerable investment of FDA resources and contains some important considerations for presenting the drug product section of an application.

Although comments on draft guidances often focus on the parts of the guidance that the commenter would like to have changed, I would like to highlight a few important points in the guidance that that I believe are very helpful and which should be retained in the final guidance. These are the following:

Line Number	**Comment**
1457, 1480	The concepts of sunset test protocols and interim acceptance criteria are very useful. Having them in the guidance may eliminate some barriers to their implementation. In some instances, the use of sunset test protocols could streamline the regulatory processes for both FDA and industry while ensuring the delivery of quality drug products to the marketplace.
885-901	The discussion of reprocessing is clear, concise, and provides a very reasonable approach.
1793	The concept of providing EPRs for representative batches is good and should be retained. The provision of EPRs for all stability and BA/BE lots, adds bulk and complexity to the application, but may not always serve a useful purpose.

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02D-0526 C2

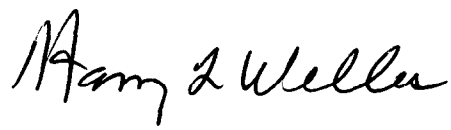
I have several general comments:

1. For consistency with ICH, replace "CMC" with "Quality" wherever possible.
2. The use of the outline numbering for the CTD headings (with CTD numbers in parenthesis) is cumbersome. If FDA needs to maintain the outline numbering system for the guidance, perhaps it could be used for Sections I and II of the guidance, then the rest of the guidance could be presented in the CTD format.
3. There are several places where this guidance calls for information that is more properly a GMP requirement. These include provision of duplicate test results (supplier and applicant) for components; in-process stability results; and stipulation of different requirements, depending on whether the applicant or the supplier performs full testing. These should continue to be GMP requirements and not be added to the application. This information should be reviewed during an inspection, rather than in a registration document.

Specific suggestions for revisions are in the attached table.

If you have questions, or if I can be of assistance in any way, please feel free to contact me at 513-831-5802 or hlwreg@fuse.net.

Sincerely,



Harry L. Welles, Ph.D.

Line Number	Proposed Revision	Rationale
65-74	Eliminate the reference to drug substance requirements.	This is a drug product guidance. Drug substance requirements should be addressed in the drug substance guidance.
320-322	Delete the sentence "Components that are used in the manufacture of the drug product and do not appear in the finished drug product ... should be identified as processing aids.".	This is very prescriptive. At times it may be useful to provide other information about these components.
362-680	Delete the pharmaceutical development section in the FDA guideline and refer to ICH.	This section in the FDA guideline is very detailed and prescriptive. My understanding is that there may be an initiative in ICH to develop a harmonized guideline on pharmaceutical development. FDA should not preempt that effort. If ICH does not develop a harmonized guideline, the CTD guidance serves as an adequate starting point for this section and the applicant should have some flexibility in presenting the data.
549	Replace "study numbers" with "appropriate cross reference identifiers".	As written, this implies that there will be stability "reports" with title pages, etc. in the Quality section, such as is done for the Clinical section. This is not necessarily the case. More general wording should be used to allow for differences in approach.
710-712	Delete this section.	Personnel information is provided in the drug establishment information attachment to Form 356H. This form is updated and submitted with every registration filed. It should not be necessary to repeat this information within the body of the Quality module. Duplication in the quality section is redundant and the information there become get outdated.

Line Number	Proposed Revision	Rationale
784-785	Delete "(e.g. weighing of components through finished product release)".	Requiring basic plant operations such as weighing and release to be shown in the flow diagram adds to the complexity of the diagram without providing useful information. The flow diagram should focus on the major manufacturing unit operations.
824-830	Move the paragraph on ruminant-derived materials to the regional information.	This is a US-specific requirement and not part of the manufacturing process description. To have the requested statement here introduces US-specific information into a document that otherwise would be suitable for use in most geographic regions. Regional requirements should be addressed in Module 1 or the Appendices to Module 3.
855-865	Delete "as illustrated in the following examples:" and the bulleted list.	The general statement that a control "may or may not be critical" is sufficient. The applicant should not have any trouble in interpreting that. If FDA thinks more detail is necessary, a discussion of the principle involved in deciding if a process is critical would be a better approach.
927-929	Add a statement such as "Although they are considered critical process controls, some tests on intermediate product may not need extensive justification if they are consistent with current industry practice or compendial standards, for example, hardness or assay of a core tablet prior to coating.".	FDA has defined tests done on intermediate products as critical process controls; however, the acceptance criteria for some of these are well established and need no further justification.
982-983	Delete "and the applicant intends to perform full testing on each batch received,".	Full or reduced testing by the applicant is a GMP issue, not a registration issue.
982	Replace "with no additional testing" with "and no additional testing is needed to ensure the suitability of the excipient in the product".	Additional testing is done from time-to-time for a variety of reasons. This section should focus on attributes of the excipient that ensure product quality.

Line Number	Proposed Revision	Rationale
989-990	Delete "The P.1.4 to P.4.4 for each individual excipient should be grouped together in the application.".	This organizational detail has some merit, but it is inconsistent with the organization of the CTD guideline and granularity document. If FDA disagrees with the organization of CTD it should work through ICH to change it.
1022-1030	Delete this paragraph.	1. Full testing must be done by either the manufacturer of the excipient or the applicant. However, the issue of whether the applicant does full testing or reduced testing is a GMP issue and should not be part of the application. 2. The statement regarding specifications and testing for polyols is important; however it should be addressed independently of the drug product guideline.
1089-1094	Delete this paragraph.	Comparison of COAs from the manufacturer and the applicant is a GMP issue. Requiring such a comparison in an application is an unjustified new regulatory requirement.
1153-1155	Reword to say "if a test that is usually performed on the finished product, is instead performed in-process, the in-process results should be provided in the batch analysis.	Clarity.
1174	Delete the reference to in-house method numbers in the table.	In-house numbers are not necessary for method identification. Alternative naming conventions could be used, for example *Reverse Phase HPLC Determination of Compound X*. With electronic cross references, this is clear and concise.
1288	Reword to say "Batch analysis data should be provided for batches used in relevant clinical efficacy and ..."	All studies and/or batches may not be relevant to the application, for example exploratory studies for other indications.

Line Number	Proposed Revision	Rationale
1286-1334	Eliminate the requirement for CofAs for all batches.	This section calls for CofAs for all batches and collated batch analysis data for some tests. Providing tabulated batch analysis data on all relevant batches would be a clearer and more practical way to present the data. The use CofAs is not a clear or efficient way to present data on multiple clinical, safety, BA/BE, and stability lots and they do not add anything useful to the application. Documentation should be checked during inspections, not as part of the review of the application.
1343-1346	Revise to say "Potential drug-product impurities should be listed. These should include degradation products of the active ingredient, and residual solvents. For some combinations of drug, dosage form, and route of administration, enantiomeric impurities, excipient degradants, and/or leachables from the container closure system may also need to be considered.	Not all of the listed sources of impurities are relevant in all cases. In general it serves little purpose to discuss well known excipient degradation products for a solid oral dosage form. Notification that the applicant should consider other sources of impurities in specific instances should be sufficient.
1346-1347	Change to read "Drug substance process impurities that carry over into the drug product should be identified here, but need not be discussed further unless they are also degradants."	Discussion in the drug substance section is sufficient.
1570 - 1571	Delete "Stability study reports should also be included.".	This assumes that freestanding stability reports are written. The guidance should describe the information needed in the application, and allow flexibility in the format.
1573-1593	Move the section on analytical procedures to line 1623, after the section on stress studies (1622).	Information on analytical procedures may apply to all three types of studies (formal, supporting, and stress studies). A stand-alone section on analytical procedures would be a more straightforward way of presenting it, rather than including it in the formal studies.

Line Number	Proposed Revision	Rationale
1580	Delete "(e.g. weight loss)".	In most instances determination of weight change of a product with a calibrated balance is a standard laboratory procedure and should not require presentation of the procedure and validation data.
1607-1613	Delete the words starting with "Stability data to support holding ..." to the end of the paragraph.	In-house holding of in-process materials should be considered a GMP requirement, not part of the application. In addition, these are not "supporting studies" as defined by ICH Q1A.
1651	Delete the footnote, or revise to say the ICH stability guidelines are the primary reference sources.	Regulators and industry have worked very hard to develop the ICH guidelines. FDA guidelines should not supercede them. FDA guidelines should only address areas not covered by ICH or that are unique to the U.S.
1793	Delete "Phase III Clinical".	The regulations require that EPRs be provided for bioavailability, bioequivalence and primary stability lots, not Phase III Clinical lots.
1817 - 1819	Delete the sentence that starts "This should include ...".	Provision of duplicate CofAs is unnecessary. Comparison of supplier and applicant data is a GMP issue and can be addressed by the inspector if appropriate.
1893	Add after included "if packaged in single unit containers.".	Uniformity of dosage unit is applicable to individual dosage units.