P&G

P&G Pharmaceuticals, Inc.
Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040
www.pg.com

4135 '03 JUN 25 A9:25

June 19, 2003

Food and Drug Administration
Documents Management Branch (HFA-305)
5600 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket Number 02D-0526
Comments on Draft Drug Product CMC Guidance issued by FDA

Dear Sir or Madam:

Thank you for the opportunity to comment on the draft FDA Guidance *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 CMC sections of an application.

Comments to this draft Guidance, made by Procter & Gamble Pharmaceuticals Inc., Mason, Ohio, are presented in the following pages for Agency's consideration. In case there are any questions, please feel free to call me. Thank you.

Sincerely,

Ray D'Alonzo, Ph.D.
Senior Director, Regulatory Affairs CMC
U.S. Regulatory Affairs
Phone: 513 622 1977
Fax: 513 622 5365

02D-0526 C6

Procter & Gamble Pharmaceuticals, Inc. Comments on the Draft FDA Guidance
Drug Product Chemistry, Manufacturing and Controls Information Guidance issued in January 2003

Guidance Line #	Proposed Revision	Rationale
General comment	Replace reference to the term CMC with Quality wherever possible.	Consistency with ICH.
67-70	Eliminate reference to drug substance requirements.	This is a drug product guidance. Drug substance requirements should be addressed in the drug substance guidance.
249, 334, 342	It is suggested that the ICH numbering convention be adopted throughout the referenced lines (e.g., in line 249, change IV.B.1 to P.2.2.1).	Ease of use and improved clarity.
311 and 358	Delete DMF holder's standard.	Quality standards should be pertinent to acceptance criteria of the drug product manufacturer. While the DMF holder's standard could be used as a starting point for setting internal specifications, it may not be appropriate to use the DMF holder's specification as a drug product manufacturer's regulatory specification.
320-322	Delete the sentence that starts "Components ..... should be identified as processing agents".	This is very prescriptive. It may be appropriate to state "granulating agents - removed during processing, or solvent for ink / marker".
328-329	Reference to the metric system is good and should be maintained.	
362-680	Delete the pharmaceutical development section in this FDA guidance and refer to ICH's in case ICH issues one.	This section in the FDA guideline is very detailed. My understanding is that there may be an initiative in ICH to develop a harmonized guideline. FDA should not preempt that effort.

Guidance Line #	Proposed Revision	Rationale
461	Provide clarification on what is meant by tracers or markers.	These concepts may not be familiar to everyone. They could be explained briefly here or in the glossary.
495	Revise to say "A summary of formulations used in ~~all~~ relevant clinical trials should be provided".	Early clinical formulations might have no relevance to the final commercial formulation or have been applied to an indication other than that for which approval is sought. The most pertinent information is the formulations critical to supporting the suitability of the intended commercial product for the intended indication.
501	Revise to say "... that link relevant clinical formulations to ...".	For meaningful comparative in-vitro and in-vivo analysis, it is valuable to discuss phase III and proposed commercial formulations.
549	Replace "study numbers" by "appropriate cross reference" identifiers.	As written, 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. We do not present stability data as reports, and while study numbers are included in the stability information provided, they are not presented as a primary identifier (i.e., in the table title). Suggest that this be left more open to allow for variation in approach.
667-669	Revise the first sentence to say "For drug products that are intended to be mixed with diluents prior to administration (e.g., constitutable suspensions, powders for injection) compatibility studies should be performed with commonly used diluents even if they are not mentioned in the labeling".	Clarity.

Guidance Line #	Proposed Revision	Rationale
696	Delete "name address and phone number of the U.S. agent for each foreign drug establishments".	Personnel information is provided elsewhere in a registration (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. Making personnel information part of the regulatory commitment is not appropriate, as it would result in personnel changes having regulatory implications.
710-712	Delete "To facilitate preapproval inspection related activities, it is recommended that the name, telephone number, fax number and e-mail address of a contact person be provided for each site listed in the application."	Same rationale as for line 696.
756	Delete "DMF holder's standard"	Quality standards should be pertinent to acceptance criteria of the product manufacturer. While we may use the DMF holder's standard as a starting point for our internal specification, we would not consider it appropriate for the DMF holder to either dictate what should be our regulatory commitment or be responsible for changes to that regulatory commitment. To imply that for a material specification we would just refer to a material DMF is inappropriate.
769	Delete and change to "In-house standard": DMF Holder Y Standard DMF Holder Y Standard DMF Holder Z Standard	
769	Change "Proposed" to "Typical".	All commitments in an application are "proposed" until the application is approved, so use of the word proposed is unnecessary in this single case.
784-786	Delete "(e.g. weighing of components through finished product release.)" and change to "(e.g. charging of components through finished product sampling)".	Details like weighing and finished product release do not add value in many cases and will add to the complexity of the diagram without providing useful information. The flow diagram should focus on the manufacturing unit operations.

Guidance Line #	Proposed Revision	Rationale
785	Revise to say "The entire manufacturing process should be depicted, including packaging,...".	As presented it is not clear that the packaging process needs a flowchart as well. In line 800, packaging is mentioned. For consistency it should be mentioned here as well.
824-830	Move this paragraph to P.3.1 Manufacturers, or preferable the appendices.	This is 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. Additional regional requirements should be addressed in Module 1 or the Appendices to Module 3.
891-894	This is a significant improvement in documenting that no documentation is required to be able to carry out reprocessing work. No change needed.	The principle that, for most products, reprocessing need not be described in the application is important and should be retained.
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 chosen to define tests done on intermediate products as critical process controls, however, the acceptance criteria for some of these is well established and needs little further justification.
956	Remove "documentation" from "Description, documentation, and results".	Documentation is a PAI inspection item not a filing requirement.
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.

Guidance Line #	Proposed Revision	Rationale
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.
986-987 & 989-990	Delete "The P.4.1 to P.4.4 for each individual excipient should be grouped together in the application."	While this may be useful for the FDA, 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.
991	Delete the comment "Additional CMC information can be warranted..." or provide an explanation of the type of details that can be warranted.	Clarity
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 the applicant doing full testing or reduced testing is a GMP issue and shouldn't be specified in the application. 2. If FDA wants to make a policy statement of specifications and testing for polyols, it should do that independently of the drug product guideline.
1037-1038	Delete the statement "-or test results will be accepted from the excipient manufacturer's COA".	If the standard is the monograph standard, then the issue of accepting results from the supplier is a GMP issue.

Guidance Line #	Proposed Revision	Rationale
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. Such data/information can be provided upon request during a GMP audit. It should be sufficient to provide a representative COA from the drug product manufacturer which reflects data used for the purpose of establishing specification compliance.
1149	The terms "interim acceptance criteria" and "sunset provisions" should be more clearly defined either here or in the glossary.	While these terms are commonly used in some areas, they may not be familiar to all applicants. The addition of definitions would help in these cases.
1153-1155	Reword to say "if a test that is usually performed on the finished product, are instead performed in-process, the in-process results should be provided in the batch analysis, e.g. assay on a core tablet in lieu of assay on the finished coated tablet.	Clarity

Guidance Line #	Proposed Revision	Rationale
1156	General descriptor of analytical procedures. Delete rest of the statement starting from "....identifying which are regulatory ....can be used for a test".	From the example in Table 3 it appears that what is expected here is an in-house method number. The FDA almost (but not quite) appears to be asking for the in-house specification document. It should be sufficient to give the specification and a general descriptor of the technology applied e.g., Assay, HPLC or Identity, Infrared. An electronic cross reference to the specific method presentation within the submission could be included if necessary. It shouldn't be necessary to distinguish between regulatory and alternate procedures in the specification presentation. This is done as part of the method presentations.
1174	Delete reference to in-house method numbers (e.g., AP #EFG, AP #PQR, etc). Delete Regulatory and alternative method differentiation.	See comments above. Since FDA registrations are being done electronically now, a cross reference to where the method appears in the submission can be provided. In-house identifiers for methods should not be part of the regulatory commitment.
1208-1221	Delete.	This amounts to a commitment to operate in accordance with cGMP. Since our operations are fully expected to be GMP compliant, such a commitment statement should not be necessary in a regulatory submission.
1288	Change to read "Batch analysis data should be provided for all relevant batches used for...".	Need to avoid the implication that every clinical or developmental batch needs to be reported. All studies and/or batches may not be relevant to the application, for example exploratory studies on other indications.
1291-2	Change to read "The batch analysis tabulation should include a description of the batches.".	It should be more efficient for the chemical reviewer to assess data tabulation than a pile of COAs. Having both COAs and collated data is unnecessary and provides no added value to the intended purpose of batch analysis data.
1292 and 1328-1332	Delete the word "collated" and replace by "tabulated".	Clarity

Guidance Line #	Proposed Revision	Rationale
1311-15	Delete the requirement for Batch Analysis Reports.	A well designed tabulation of data should suffice.
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.
1346-1349	Delete "drug substance process impurities...".	This section should focus on impurities unique to the drug product. Since any drug substance process impurities probably also be present in the drug product, a cross reference to drug substance impurity information should suffice. It shouldn't be necessary to discuss it again as part of the drug product impurity discussion.
1362	Regarding identification of impurities, the information provided should include structural formula, empirical formula, molecular weight if not provided in S.3.2. Providing the structural elucidation for all potential impurities and degradants should not be necessary.	For those situations where there are (for example) in excess of twenty potential impurities in a drug substance, this could prove really burdensome and result in an entire volume just for impurity structural elucidation. The companies should be left to determine the best approach to providing what is most pertinent and meaningful for the submission.
1457	Sunset test protocol – provide further clarification.	This is a good approach and should stay in the Guidance. It would be helpful if the Agency can further define expectations related to this protocol.

Guidance Line #	Proposed Revision	Rationale
1480	Interim acceptance criteria – provide further clarification.	This is a good approach and should stay in the Guidance. It would be helpful if the Agency can further define expectations related to interim specifications, i.e., what type of submission would be required to finalize the specifications. Also, are these interim specifications applicable to in-process testing as well?
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 after the section on stress studies (1622).	This material applies to formal, supporting, and stress studies and would be better as a separate section.
1580	Delete "(e.g. weight loss)".	Determination of weight loss 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 material starting with "Stability data to support holding ..." to the end of the paragraph.	1. In-house holding of in-process materials should be considered a GMP requirement, not part of the application. 2. This is 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 are only appropriate to address areas not covered by ICH or unique to the U.S.
1793	Delete "Phase III Clinical" from the sentence. The concept of providing EPRs for representative batches is good and should be retained.	The regulations require that EPRs be provided for bio-availability, bioequivalence and primary stability lots. The provision of EPRs for multiple stability lots, for example, adds bulk and complexity to the application, but may not always serve a useful purpose.

Guidance Line #	Proposed Revision	Rationale
1811-1816	Delete • Name and address of DS manufacturing • Names and addresses of sources of noncompendial excipients • Names and addresses of sources of container-closure system for DP • Names and address of each contract facility	All of these pieces of information are included elsewhere in the registration and should not need to be repeated here. In the interest of facilitating any future updates, it would be important to simplify by only stating the information once in the appropriate place within the appropriate section.
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.