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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
Attn: Dr. Upinder Atwal / Dr. Christopher Joneckis

June 27, 2003

Docket No: 02D-0526 CDER 1997127

Re: Draft Guidance for Industry: Drug Product - Chemistry, Manufacturing, and Controls Information

Dear Dr. Atwal and Dr. Joneckis

The above referenced FDA draft guidance entitled Drug Product – Chemistry, Manufacturing, and Controls Information, issued January 2003 has been reviewed by scientists at Johnson & Johnson Pharmaceutical Research, LLC. The following comments are provided for your consideration.

Provided in the General Discussion Section are the general impressions of our scientists including comments on issues of greatest concern to our business. Other comments, as well as those discussed in the General Discussion Section are presented in the Comments Section by section and line number. To assist you during the review, the draft guidance text appears in italics.

General Discussion:

Our scientists appreciate and commend the collaborative effort between the scientists at CBER and CDER to create this comprehensive and informative guidance. The following comments are intended to promote further discussion and ultimate creation of a scientifically-based, informative final guidance for Drug Product Chemistry, Manufacturing and Controls:

- The references to specific sections of the Common Technical Document (CTD) are particularly useful.

- This draft guidance appears to increase filing requirements in many areas and/or introduces requirements that have not been historically part of CDER filings. The collaborative work from CBER and CDER on this guidance may have precipitated these additional requirements. If so, intensive ongoing discussions between FDA and industry are recommended and non-essential requirements should be eliminated.

- Where CDER and CBER filing approaches differ, scientific requirements can be met by noting in the guidance that certain requirements pertain to specific drug product categories. Greater use of cross-referencing may be possible where new filing requirements duplicate information traditionally filed in IND Amendments. Similarly, it would be very beneficial if the draft guidance identified whether specific sections applied to NDAs, ANDAs or both. This would decrease potential confusion and filing requirements for industry. Finally, verification is requested that existing DMFs will not require reformatting into a CTD format. (Section: II.D. Line 216)

- Clarification is requested regarding FDA's position on Interim Acceptance Criteria. The draft guidance addresses the use of interim acceptance criteria when "occasional" uncertainty due to limited data and experience with the product and scale-up of manufacturing process exists. (Section VII.F. line 1480) Can FDA provide guidance on what is meant by "limited"? Can FDA clarify whether the failure to meet the interim acceptable criteria would result in batch failure on release?

- The draft guidance statement regarding inconsistencies between procedures published in the European, Japanese and United States Pharmacopoeias is incomplete. As stated in the draft guidance, "...where the texts differ or where there is a dispute, the result obtained from the USP procedure is conclusive." (Section V.I.A. line 1045) The use of the USP procedure however, may be inappropriate for any number of scientifically justified reasons. A requirement that justification be given for non-use should be added to the draft guidance statement. The statement should be revised to read "*...where the texts differ or where there is a dispute, the result obtained from the USP procedure is conclusive.* **If the USP procedure can not be used, scientific justification should be provided.**

- *"If multiple manufacturing sites are planned, it can be valuable to consider data from these sites in establishing the tests and acceptance criteria."* (Section V.II.F. line 1423) The statement regarding the use of data from planned manufacturing sites to establish tests and acceptance criteria is confusing. This statement appears to be inconsistent with FDA's position that site-specific stability data is not necessary. Further clarification would be appreciated.

- Clarification is requested on the level of testing suggested for non-novel excipients by the sponsor. The statement *"A certificate of analysis (COA) from the manufacturer and the test results from the same batch from the drug product manufacturer should be provided for the components described in P.4"* is confusing. The guidance seems to suggest that the drug product manufacturer may not utilize vendor COAs after the vendor has been qualified. Will additional testing (beyond Appearance and Identification) by the drug product manufacturer be required? (Section VI.D. line 1089) The inclusion of a complete listing of "FDA-recognized standard references (e.g. AOAC International Book of Methods...)" in the guidance would be extremely useful.

- Our scientists are concerned that this draft guidance greatly expands the requirement for identification of impurities in excipients. The draft guidance states, *"All expected drug impurities (e.g., degradation products of the active ingredient, residual solvents, enantiomeric impurities, excipient degradants, leachables from the container/closure system) should be listed in this section of the application whether or not the impurities are included in the drug product specification."* (Section VII.E.1 line 1343) This statement appears to imply that stability indicating methods should be developed by either the vendor or sponsor for vast numbers of potential excipient impurities and degradation products. Limits of detection and quantitation would potentially need to be set on a product-by-product basis. The enormous effort is scientifically difficult to justify (especially for oral or topical drug products) and is extremely burdensome for non-novel excipients. Clarification from FDA would be greatly appreciated.

- Additional clarification is needed for the following statement : *"All analytical procedures for excipients should be validated."* (Section VI.C. line 1062) Compendial procedures are well characterized, validated methods and generally should not require additional validation. Manufacturers however should ensure that these methods are appropriate for specific drug products. We propose that "All" be deleted and "appropriate" be added to the statement. The statement should be revised to read "Analytical procedures for excipients should be validated, where appropriate."

Comments Section:

Part III

IIIC - Line 265

Please change the following statement to read *"In some instances, the composition of distinct subformulations (e.g., cores, coating) of the drug product* **may be** *listed separately in the composition statement."*

IIIC – Line 269

In these cases, the composition of the immediate release and extended release portions of the drug product **may be** *listed separately.* **These changes are suggested to provide flexibility in the presentation of information. In some instances it may be more illustrative to include both subformulations in the same table.**

IIIC – Line 358 (footnote 1)

"[1]Equivalent to 50, 100 and 150 mg, respectively on the anhydrous basis" **Does this suggest that potency should be reported on an anhydrous basis? We request guidance regarding how potency should be reported, as free base/acid or salt form.**

Part IV

IVA.1a – Line 394

For example, if particle size is expected to influence the dissolution rate, drug product testing should be conducted to support the appropriateness of the test and acceptance criteria for the drug substance particle size distribution. **We recommend the following be added to the statement above "Dose Volume term > 250 mL (BCS Category 2 and 4)" The statement should be revised to read "***For example, if particle size is expected to influence the dissolution rate (***Dose Volume term > 250 mL (BCS Category 2 and 4),** *drug product testing should be conducted to support the appropriateness of the test and acceptance criteria for the drug substance particle size distribution.*

IVA.1b – Line 409

The compatibility of the drug substance with the excipients used in the drug product should be discussed if formulation stability data suggest potential incompatibility. **The statement implies that formal excipient compatibility studies are required. Because excipient compatibility is often carried out as part of formulation selection studies, compatibility studies on drug substance and individual excipient should not be performed separately.**

IVA.2 – Line 451

An applicant **may wish** *to discuss the use of noncompendial–non-novel excipients with the appropriate review division prior to submitting its application to ascertain the level of information that would be warranted to support the use of the excipient.*

IVA.2 – Line 456

See sections VI and XI.C for additional guidance on the information that should be submitted to support the use of this type of excipient. **Please define the term non-novel (e.g. used in EU, listed in Inactive Ingredient Guide, etc.).**

IVC – Line 580

"A table should be provided that compares the equipment used to produce clinical batches that support efficacy or bioequivalence and primary stability batches to the equipment proposed for production batches." **The FDA has sought to simplify equipment comparisons and has issued guidance (e.g. SUPAC Equipment Addendum) to assist industry in describing smaller scale and production equipment in a manner that allows for rapid review and approval. Clarification is requested regarding whether a list of equipment, using the table format and terminology recommended in the SUPAC guidance is satisfactory.**

IVC – Line 580

Please change the statement to read, "For equipment of different operating design or principle, *a table should be provided that compares the equipment used to produce clinical batches that support efficacy or bioequivalence and primary stability batches to the equipment proposed for production batches."*

IVC – Line 584

The table should identify (1) the identity (e.g., batch number) and use of the batches produced using the specified equipment (e.g., bioequivalence study batch # 1234), and (4) any significant equipment differences (e.g., different design, operating principle, size). **Please include in this guidance a representative table of equipment similar to that provided in SUPAC Equipment Addendum. Alternatively, a cross reference should be provided.**

IVD – Line 589

D. Container Closure System (P.2.4) **We recommend that the container-closure section be clarified and generalized into a broad outline of the information contained in FDA Guidance: Container-Closure Systems for Packaging Human Drugs and Biologics, followed by a reference to the FDA Guidance: Container-Closure Systems for Packaging Human Drugs and Biologics for more specific information.**

IVD – Line 596

For clarity, the following sentence should be revised to read, *"A brief description of the container closure systems listed in P.7* should be provided. Any special storage and transportation container closure systems that may be necessary for proteins or other environmentally sensitive drug products should also be provided."

Part V

VA – Line 695

"Addresses for foreign sites should be provided in comparable detail, and the name, address, and phone number of the U.S. agent for each foreign drug establishment, as required under 21 CFR 207.40(c), should be included." **Maintaining accurate and current information in the NDA can be problematic. Please provide guidance whether Form FDA-2857 (Drug Listing Requirement) may be used alternately to provide the detailed information requested.**

VA – Line 710

"To facilitate pre-approval inspection related activities, it is recommended that the name, telephone, fax number and e-mail address of a contact person be provided for each site listed in the application." **See comment to Line 695**

VB – Line 748

The section "*Reference to Quality Standards*" is redundant as this information is already provided in lines 304 through 315 of the draft guidance.

VC – Line 824

"A statement should be provided that ruminant-derived materials from bovine spongiform encephalopathy (BSE) countries as defined by the U.S. Department of Agriculture (9 CFR 94.11) are not used or manipulated in the same facility." **This information should be provided in Section XII, Regional Information.**

VC.2 – Line 849

"Steps in the process should have the appropriate process controls identified. Associated numeric values can be presented as an expected range. All **critical** *process controls should be included in the description of the manufacturing process (MPR or narrative)."*

Part VI

VI – Line 986

"The P.4.1 to P.4.4 information for each individual excipient should be grouped together in the application." **For greater document clarity, we propose a flexible approach that minimizes information redundancy by permitting information common to excipients to be grouped together.**

VIA – Line 1022

"In addition to listing all the tests for an excipient, the specification should identify the tests that the drug product manufacturer will routinely perform and the test results that will be accepted from the excipient manufacturer's certificate of analysis (CofA)." **We would greatly appreciate clarification regarding the impact of this statement on reduced testing/vendor qualification. Would the filing of a Supplement be required to change testing agreements between the excipient manufacturer and the drug product manufacturer?**

VIC – Line 1062
"All analytical procedures for excipients should be validated". **Please note that most compendial methods are well characterized and consequently do not require validation. We request that the statement be clarified to reemphasize this fact.**

VID – Line 1089
"A certificate of analysis (COA) from the manufacturer and the test results for the same batch from the drug product manufacturer should be provided for the components described in P.4. The information should be for the materials used to produce the batch described in the executed production record (R.1.P)". **We request that the last sentence be changed to "The information should be for a representative batch of the material showing conformance to the specification (P.4.1)." Results of tests on the components of EPRs will be included in section R.1.P, as stated in the draft guideline.**

VID – Line 1093
"Use of terms such as conforms or meets specification is discouraged." **We suggest that this paragraph be removed as it is stated in R.1.P**

Part VII
VIIA – Line 1147
The following sentence should be revised to include "and/or". The sentence should read as follows: *"If an analytical procedure will be used only to generate stability data, the analytical procedure should be described in P.8.3. Justified interim acceptance criteria* **and/or** *tests with sunset..."*

VIIA – Line 1167
"Some tests that are identified as appropriate for inclusion in the specification can be proposed as periodic quality indicator tests when there is sufficient data and justification." **Please provide further information regarding what FDA would consider sufficient data and justification to support a periodic quality indicator test.**

VII A– Line 1194
"For example, justification for a PQIT **would be more likely** *for the oral dosage form then for a biological or biotechnology-derived parenteral drug product."*

VIID – Line 1288
"Batch analysis data should be provided for all batches used for clinical efficacy and safety, bioavailability, bioequivalence, and primary stability studies." **This requirement may be redundant if certificates of analysis are provided in other sections of the NDA. The sentence should be revised to read "Batch analysis data should be provided (or cross reference provided to this data in another NDA section) for all batches used for clinical efficacy and safety, bioavailability, bioequivalence, and primary stability studies."**

VIID – Line 1289
"Batch analysis data should also be provided for any other batches that are being used to establish or justify specification and/or evaluate consistency in manufacturing." **We feel that this statement is also redundant as this is provided in Control of Drug Product, Specifications (VII. A.)**

VIID – Line 1288
"Batch analysis data **may be** *provided for all batches used for clinical efficacy and safety, bioavailability, bioequivalence, and primary stability studies."*

VIID – Line 1291
"The batch analysis reports (e.g., COAs) and collated batch analyses data should include a description of the batches." **This should not be necessary if the data is tabulated. Does this mean that COAs are required for all of the aforementioned batches?**

VIID.1 – Line 1311
"Batch Analysis Reports" **We recommend that the requirements in this section be deleted. The information requested is extensive and would typically be included in IND amendments. Only information required to support the NDA specification should be included in the NDA.**

VIID.1 – Line 1317
A summary of any change in the analytical procedures should be provided if the analytical procedure (1) change over the course of generating the batch analysis data and/or (2) are different from the analytical procedure included in P.5.2 **We believe this is also redundant as the historical information about the analytical procedures is captured in the stability section (X.C.). We feel that the requirement of a summary of changes is unduly burdensome. If the principle of the assay changes (titration versus HPLC) then this should be included, but minor changes (mobile phase and chromatographic conditions) need not be reported.**

VIID.2 – Line 1332
"However, collated data should be provided for **at least** *assay and impurities (e.g., degradation products, residual solvents) and should be considered for other tests dependent on the dosage form."*

VIIF –Line 1371
"Attempts should be made to identify all degradation products found at significant levels in the drug product." **Please provide clarification regarding what is meant by "significant levels".**

IX Line – 1539
"If an NDA is submitted for a new plastic that will be used for blood component storage, adequate information on the plastic should be submitted, including the composition of the plastic." **We recommend that specifications also be included for blood component container-closures.**

XIIIA.1 – Line 1799
"For NDA submissions, an EPR for a batch manufactured on at least a pilot scale should be submitted." **We recommend that "In cases of multiple strengths, one batch per strength should be sufficient for submission" be added to the above statement. The statement should be revised to read, "*For NDA submissions, an EPR for a batch manufactured on at least a pilot scale should be submitted.* In cases of multiple strengths, one batch per strength should be sufficient for submission."**

We greatly appreciate the opportunity to comment on this draft guidance and look forward to working closely with the FDA on future documents. If you have questions or need assistance, please contact me directly at 609/730-3425.

Sincerely,

Sue Halley
Manager
Global Chem-Pharm Regulatory Sciences
Johnson & Johnson Pharmaceutical Research and Development, LLC.