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September 23, 2010

Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

RE: Draft Guidance for Industry: *CMC Postapproval Manufacturing Changes Reportable in Annual Reports,* Docket No. FDA-2010-D-0283

Dear Sir/Madam:

PDA is pleased to offer comments on the Draft Guidance for Industry *CMC Postapproval Manufacturing Changes Reportable in Annual Reports*. PDA is a non-profit international professional association of nearly 10,000 individual members having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in regulatory submissions management and determining reporting categories for postapproval changes, including members representing our Regulatory Affairs Interest Group and our Regulatory Affairs and Quality Committee. PDA appreciates the opportunity to offer comments on this draft guidance and wishes to thank FDA for the opportunity to do so.

PDA is pleased that FDA has chosen to provide additional clarification and guidance regarding CMC postapproval manufacturing changes for NDA and ANDA products that FDA has determined will likely present minimal potential to have adverse effects on product quality and, therefore, may be reported by applicants in an annual report. Upon finalization of the Guidance, we believe that this document will provide the appropriate guidance necessary for sponsors to accurately categorize and report relevant CMC postapproval manufacturing changes, thereby supporting FDA's implementation of a cooperative, risk-based approach for regulating pharmaceutical manufacturing.

With regard to the Draft Guidance for Industry *CMC Postapproval Manufacturing Changes Reportable in Annual Reports*, we have provided detailed comments that we believe will strengthen the utility of this Guidance for both FDA and industry. Our comments are identified by section along with a supporting rationale in the accompanying table.

Again, PDA appreciates the opportunity to comment on this draft guidance and provides these recommendations for your consideration. We suggest that the Agency look to consolidate the contents of this guidance with other existing FDA guidance and strive for consistency with other regulatory bodies from a global perspective. PDA believes that these comments will clarify and strengthen the final guidance to better serve the needs of both regulators and industry.

We would be pleased to offer our expertise in a public discussion and/or meeting with FDA to provide clarification of our comments. Should you wish to pursue that opportunity, or if there are any other questions, please do not hesitate to contact me.

Sincerely,

Richard Johnson
President, PDA

CC: Robert Dana, PDA
Rich Levy, PhD, PDA

PDA Comments; FDA Draft Guidance for Industry: CMC Postapproval Manufacturing Changes Reportable in Annual Reports

June 2010

Level: 1 (High/Significant); 2 (Medium); 3 (Low – mainly editorial)

Section	Proposed Change	Rationale	Level
III Discussion Footnote 7, Page 3	**We propose the reference include Changes Being Effected supplements in addition to Prior Approval Supplements:** ***Under 21 CFR 314.70(a)(3), an applicant is required to make a change in accordance with a regulation or guidance that provides for a less burdensome notification of the change, but in this guidance we are asking sponsors to use judgment in determining which changes should be submitted in a prior approval supplement*** **or changes being effected (CBE-0 or CBE-30) supplement.**	**The addition of changes being effected (CBE-0 or CBE-30) supplements should be included for completeness.**	**2**
III Discussion Lines 119-122	**Recommend including guidance on appropriate mechanisms for contacting FDA regarding requests for submission classification and provide estimated response timeframes.**	**To provide transparency in the mechanism for contacting FDA to ensure consistency across OPS. Having informal mechanisms to solicit this feedback is strongly recommended to enable obtaining Agency guidance in a timely manner.**	**2**

Section	Proposed Change	Rationale	Level
IV Contents of Annual Report Notification Lines 129-132	**We propose deleting the references to validation protocols and standard operating procedures and policies and clarifying which drug products be reported to the NDA or ANDA as follows:** ***This description should include a (1) list of each change by the date the change was made; (2) relevant summary of data from studies and tests performed to evaluate the effects of the change~~, including cross references to validation protocols and standard operating procedures and policies~~; and (3) list of all drug products*** **or presentations covered under the NDA or ANDA which are** ***involved*****.**	**Submission of references to validation protocols, standard operating procedures and policies should not be routinely required to be submitted unless such references or documents are necessary to describe and qualify the change. These documents would be included on a case-by-case basis in instances where they are required to support the change, as consistent with the current regulation at 21CFR § 314.70(d)(3)(v).** **The guidance is unclear whether "list of drug products" refers to multiple products covered under the same NDA or ANDA *or* to products covered under a different NDA or ANDA. The additional wording clarifies the requirements for identifying the change in the annual report.**	**2**
Appendix A Components and Composition 1.3 Lines 151-153	**We propose adding reference to excipients and reference to tightening or adding acceptance criteria:** ***1.3. New supplier of inactive ingredients*** **or excipients** ***that have a minimal effect on product performance in the drug product, providing that acceptance criteria remain unchanged,*** **or have been tightened, or added*****.***	**Excipients are generally considered inactive ingredients, as such including a new supplier of an excipient that has a minimal effect on product performance should be considered a CMC postapproval manufacturing change reportable in an annual report.** **Tightening of an existing acceptance criterion is allowed via annual report per FDA Guidance for Industry: *Changes to an Approved NDA or ANDA* (April 2004). Section 4.11 of the draft guidance also specifies this as an annually reportable change. The additional proposed wording provides further clarification and consistency with other Agency guidance.**	**2**

Section	Proposed Change	Rationale	Level
Appendix A Manufacturing Sites 2.3.3 Lines 171-176	**Delete the following from Section 2.3.3: *or a product for adults added to a line manufacturing pediatric products."***	**A product for adults added to a line manufacturing pediatric products does not represent an additional level of risk commensurate with the risk of highly toxic or potent, highly immunogenic or allergenic products, or products that can accelerate the degradation of another. Those risks relate to the potential of contamination of one product by another during manufacture when such a product is added to a multiple-product area. Products for adults which do not vary in concentration should be able to be added to a line manufacturing pediatric products without requiring reporting to FDA, as long as cGMPs are in place to prevent product mix-up or contamination.**	**2**
Appendix A Specifications 4.2	**Revise section to include specific details on which changes to relax or delete a test to comply with the official compendia (e.g., excipient monographs and general chapters) can also be reported in an annual report.**	**Additional clarity is needed for which changes to relax or delete a test to comply with the official compendia (e.g., excipient monographs and general chapters) can also be reported in an annual report as discussed in FDA Guidance for Industry: *Changes to an Approved NDA or ANDA; Specifications – Use of Enforcement Discretion for Compendial Changes* (Nov. 2004). This guidance as written could be interpreted that a Changes Being Effected supplement is required for changes to relax or delete tests in order to comply with compendial changes.**	**2**
Appendix A Miscellaneous Changes 6.4 Lines 293-296	**Revise section to delete reference to bundled supplements: *For changes in an application that are fully consistent in scope and requirements with changes previously approved in a ~~bundled~~ supplement, the same applicant can add similar drug products. (See MAPP 5015.6, "Review of the Same Supplemental Change to More than One NDA or ANDA in More Than One Review Division.")***	**It is not necessary to specify whether the change was previously approved in a single application or in multiple "bundled" applications. Once approved, the applicant should be able to add similar drug products and report the change in an annual report.**	**2**