U.S. Pharmacopeia
The Standard of Quality℠

September 24, 2010

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Subject: Comments of USP on "Draft Guidance for Industry on Chemistry, Manufacturing, and Controls, Postapproval Manufacturing Changes Reportable in Annual Reports"
Docket No. FDA-2010-D-0283, 75 Fed. Reg. 36421 (June 25, 2010)

Dear Sir/Madam:

The following are comments of the United States Pharmacopeial Convention (USP) in response to the above-referenced draft Guidance for Industry on postapproval manufacturing changes reportable in annual reports under 21 CFR §314.70. USP is a scientific, nonprofit, standards-setting organization that advances public health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods. USP's United States Pharmacopeia and the National Formulary (USP-NF) are "official compendia" referenced in the Federal Food, Drug, and Cosmetic Act (FDCA §201(j)), as well as in the Food and Drug Administration's (FDA) regulations on "Supplements and other changes to an approved application" (21 CFR §314.70; e.g. 314.70(c)(2)(iii), 314.70(d)(2)(i), and 314.70(d)(2)(v)) and at various points in the draft Guidance.

Enforcement of USP standards is the responsibility of FDA and other government authorities in the U.S. and elsewhere; USP has no role in enforcement. Accordingly, it is to be expected that FDA, and manufacturers subject to the full array of CMC regulations and other legal requirements, would have the most direct interest in this draft Guidance, which pertains specifically to what kind of "minor" postapproval manufacturing changes under §314.70(d) may be reportable in annual reports (as distinguished from "major changes" under §314.70(b) requiring FDA approval of a supplement prior to distribution, or "moderate changes" under §314.70(c) requiring supplement submission at least 30 days prior to distribution).

Nevertheless, as contemplated in both the law and regulations, USP compendial requirements can occasion manufacturing changes, and USP has an interest in assuring that there are no undue barriers to implementation of any new or revised compendial requirements. This includes an interest in helping to assure that compendial-related manufacturing changes may be made as efficiently as possible, consistent with law and applicable regulations. USP is concerned that in certain respects, the draft Guidance may conflict with applicable regulations (21 CFR 314.70) and unduly restrict the range of compendial-related changes that should be considered "minor" and able to be described in an annual report, rather than in a prior approval supplement.

FDA regulations (§314.70(d)(2)(i)) specify that "Any change made to comply with a change to an official compendium" that is consistent with FDA statutory

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and regulatory requirements may be annual reportable. The only exception in the regulations is for the "Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium," which is considered a "moderate" change requiring supplement submission 30 days prior to distribution (§314.70(c)(2)(iii)). The draft Guidance appears to conflict with these regulations in the following respects:

- The draft Guidance would limit annual reportable compendial-related changes to those that "tighten an existing acceptance criterion" (Appendix A, §4.2.1), whereas the regulations only exclude changes that relax such a criterion, or delete a test. This is essentially the obverse of the regulatory test, and would appear to materially constrain the range of compendial annual-reportability.
- The draft Guidance would categorically exclude from annual reportability "changes to assays, impurities, product-related substances, or biological activities in approved NDAs and ANDAs" (Appendix A, §4.2.2). This appears to go far beyond what is specified or contemplated in the regulations, and threatens to exclude from annual reportability many compendial-related changes that heretofore qualified as "minor changes."

Both of these sections in the draft Guidance should be revised to conform to the regulations and avoid unduly constraining the implementation of compendial-related changes.

A further concern is with the Guidance section on "Container/Closure System," which excludes from annual reportability any labeling changes "to a crimp cap (ferrule and cap/overseal) . . ." (Appendix A, §5.5). Again, if this were interpreted to apply to changes to an official compendium, it would appear to be inconsistent with the general authority for annual reportability of compendial-related changes in FDA regulations, 21 CFR §314.70(d)(2)(i). This provision is of special interest given USP's recent revision to the Labeling of Ferrules and Cap Overseals section of General Chapter <1> Injections (the new standard is posted on the USP Web site and will be published in USP 34-NF 29 on November 1, 2010 with an official date of December 1, 2013). This revised compendial standard in <1> is designed to reduce the likelihood of death and disability from misadministration of injectable products, by making it more likely that healthcare practitioners using injectable products will be able to better see and act on labeling statements that convey important safety messages critical for the prevention of imminent life-threatening situations. The standard provides that only those cautionary statements intended to prevent an imminent life-threatening situation may appear on the top surface of the ferrule and/or cap overseal. If no cautionary statement is necessary, the top surface must remain blank. Implementation of this standard is expected to occasion the removal of a potentially large number of existing non-complying statements. Under the regulations, removal of these labeling statements would be annual-reportable, while the Guidance seems to exclude them. To avoid unduly burdening manufacturers and FDA alike as this change to General Chapter <1> is implemented, the draft Guidance should be clarified to make clear that such compendial-related labeling changes are not intended to be excluded from annual reportability.

We appreciate the opportunity to comment on the Guidance and look forward to your consideration of our comments. Please feel free to contact Mario Sindaco on my staff at 301-816-8246 or mys@usp.org if there are any questions.

Sincerely,

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