



U.S. Pharmacopeia
The Standard of Quality™

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Re: Letter dated November 16, 2010

Dear Mr. Ouderkirk and Dr. Seo:

Thank you for the above-referenced letter and accompanying list of drug and excipient monographs in the *USP-NF* that the FDA Task Group has identified initially as being in need of modernization.

As promised, this letter contains USP's early thinking on how to approach modernization of monographs listed in your November 16th letter.

We offer the following general approaches for further discussion:

1. As USP envisions the general issue of monograph modernization, it is apparent that a sequential set of steps needs to be considered: 1) criteria for monographs needing modernization; 2) criteria for prioritization; 3) understanding of needed tests, new procedures and acceptance criteria on a case-by-case basis; and 4) a determination of how best to obtain needed information and materials to form the basis for a request for revision. With these steps clearly understood, work can begin by USP staff and will conclude with the scientific decision-making of the Council of Experts. Needed information can come from several sources: 1) literature; 2) manufacturers; 3) USP/FDA laboratory studies; 3) information from a regulatory filing. Materials can be obtained from manufacturers, from the market, or through synthesis. As work progress, decisions can be made as to the urgency with which the revision comes into force. Through its Accelerated Revision procedures, USP can act rapidly, but FDA's input in the decision to employ these procedures is essential.
2. Initial focus and priority should be on improving the drug substance monograph, with the drug product monographs to follow as quickly as possible.
3. USP uses ICH limits as our general default for modernizing control of impurities, with a need for an understanding of safety to justify deviations (see USP Guidelines for Submitting Requests for Revision to *USP-NF*, version 4 July 2009, General Information for All Submissions, at

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<http://www.usp.org/pdf/EN/USPNF/introduction.pdf>). FDA's input on when these deviations are needed will be important to modernization, as exemplified in the November 16 letter for acetaminophen.

4. Novel thinking is important given the magnitude of the task, e.g., development of "class chapters" that might allow us to more consistently control impurities across all products within a class; use of a performance-based approach like that we are utilizing in General Chapter <233> *Elemental Impurities—Procedures* where in addition to specifying a default procedure we can explicitly permit alternative procedures that meet the specified performance based criteria.
5. Consistent with USP's current practice for all monograph revisions, as monographs are modernized they also will be redesigned into the new format, using more modern nomenclature derived from ICH quality documents.

With these general approaches in mind, the following reflects our current proposal on how we intend to move forward with modernization of the drug and excipient monographs you identified in your November 16th letter. We have already taken steps to initiate these plans.

1. **Acetaminophen**

Drug Substance

USP's Acetaminophen monograph controls para-amino-phenol (PAP) at a limit of 0.005%. The monograph also controls p- chloroacetanilide at a level of 0.001%. We intend to revise the monograph to include an HPLC procedure and follow ICH limits for impurities, with continued control of PAP at 0.005%. USP would like to know whether p- chloroacetanilide needs such a stringent limit. To advance a monograph revision, USP will need one or more new Impurity test procedures and perhaps revisions to other tests of the monograph.

Drug Products

USP believes that the optimal way to provide better control of the quality of acetaminophen containing drug products may be through an enforceable general chapter numbered <1000 that provides a 'class' approach. This approach is currently under discussion in the OTC group recently formed between USP, FDA and CHPA representatives. To advance this approach, USP would appreciate knowing from FDA what the limit on PAP or p- chloroacetanilide in an acetaminophen containing drug product should be. Pending further consideration of a 'class' monograph chapter approach, USP has begun additional discussions with the Consumer Healthcare Products Association (CHPA) in the matter and plans a public webinar in January 2011. The input of the Task Group in this further effort will be especially beneficial.

2. **Diphenhydramine**

Drug Substance

A revision to the Diphenhydramine Hydrochloride (HCl) drug substance monograph to control impurities will appear in *Pharmacopeial Forum (PF)* 37(3) [May-June 2011]. We also are working on a monograph for the citrate form and will determine whether the HCl impurity procedure can be used in this monograph as well.

Drug Products

Work on the Diphenhydramine and Psuedoephedrine Capsules and other diphenhydramine drug product monographs will follow, using the same kind of approaches outlined above for the acetaminophen drug products.

3. Povidone, Cropsvidone, Copovidone

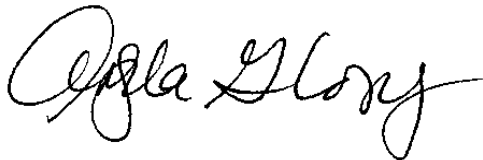
These monographs are in various stages of revision in the Pharmacopeial Discussion Group (PDG). The Povidone and Cropsvidone monographs are at Stage 6 and ready to be finalized and made official; the Povidone monograph contains harmonized limits for peroxide, aldehydes, and hydrazine, while the Cropsvidone monograph contains a harmonized limit for peroxide. Both Povidone and Cropsvidone contain a test for Heavy Metals as lead at NMT 10 ppm. A Copovidone monograph revision with harmonized limits for peroxide, aldehydes and hydrazine and the Heavy Metals test is only at Stage 4, but has already gone through the notice and comment process so it also essentially is ready to be finalized. Finally, discussions are occurring with BASF and ISP and these companies have indicated their willingness to assist with a more specific assay test that will reduce the risk of EMA as well as tests for aldehydes and hydrazine for cropsvidone.

4. Talc

Although Talc is a PDG harmonized monograph, USP will add the labeling requirements for absence of talc currently included in the FCC monograph as a non-harmonized attribute. USP also will eliminate the current two "screening" methods of IR and XRD that are part of the Absence of Asbestos test and retain the optical microscopy test as the *single* test method.

Based on this preliminary response to your November 16th letter, we would appreciate a meeting with the Monograph Modernization Task Group as soon as possible. Please note that Dr. Williams will be speaking with Dr. Woodcock on December 21, 2010 to gain her thoughts on how to move forward based on the October and November FDA letters.

Sincerely,



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Executive Secretariat
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