## DEPARTMENT OF HEALTH & HUMAN SERVICES



COPY

Food and Drug Administration Rockville MD 20857

NOV 16 2010

Ms. Angela G. Long
Executive Secretariat
The United States Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway
Rockville, MD 20852

REF: 11-10-001-S

Dear Ms. Long:

This is in regard to the October 12, 2010 correspondence from Dr. Janet Woodcock to USP on the importance of monograph modernization. Specifically, FDA has established a new task group to focus on the USP monograph modernization initiative.

The Task Group aims to identify USP/NF monographs in need of modernization and is especially focused on monographs with outdated analytical methods that may make the drug or excipient vulnerable to economically-motivated adulteration (EMA) or that have inadequate tests. This is in keeping with resolutions adopted by USP at its April 2010 Convention to work to modernize its monographs as a priority in its work plan for the next five years.

Attached is a list of drug and excipient monographs that, for the reasons cited in the spreadsheet, we have determined to be most in need of modernization. Additional articles may follow. We hope you will find this useful in your revision efforts.

Please feel free to contact Larry Ouderkirk at 301-796-1585 or Paul Seo at 301-796-4874 if there are any questions. Please use the reference number provided above on any ensuing correspondence.

Sincerely,

Larry Ouderkirk

Co-Chair, Monograph Modernization Task Group

Office of Compliance

Center for Drug Evaluation & Research

Paul Seo, Ph.D.

Co-Chair, Monograph Modernization Task Group

Office of Pharmaceutical Science

Center for Drug Evaluation & Research

## Attachment: List and Rationale of Drug and Excipient Monographs Most in Need of Modernization

Modernization		
Monograph(s)	Rationale	
Acetaminophen (drug substance) Acetaminophen Oral Suspension; Acetaminophen Oral Solution; Acetaminophen for Effervescent Oral	Because products marketed under the OTC monograph system have never been subject to a pre-approval assessment of quality by FDA, these products may lag behind the quality standards that are required of drugs marketed under an approved New	Acetaminophen is known to be one of the highest volume selling drugs regulated under the OTC monograph system, and it is currently being marketed in a variety of single ingredient analgesic/antipyretic products, as well as a component in cough/cold combination products. Paraamino-phenol (PAP) is a known
Solution Oral Solution Containing at Least Three of the Following— Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine Acetaminophen,	Drug Application (NDA). In view of the history of past quality failures attributed to impurity contamination, consumer's safety expectations, consumer's quality expectations, and congressional expectations, the lack of modernized compendial monographs for these drugs is especially problematic.	degradation product of acetaminophen that should be monitored in all compendial monographs. A known nephrotoxic impurity, it has been shown to increase over shelf life in a variety of NDAs/ANDAs and its formation appears to be accelerated with decreasing pH for solution dosage forms. In addition to being a known degradation product of acetaminophen, PAP is also
Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution		known to be a process impurity and has been found to be the final intermediate in some known synthetic processes for Acetaminophen production. Finally, PAP is controlled very tightly (usually 0.1% or less) in recently approved NDAs and
Acetaminophen Tablets		ANDAs. Only 2 compendial monographs have any acceptance criteria for this known nephrotoxic impurity. Finally all of the compendial monographs need to be
Acetaminophen Capsules		modernized to include a comprehensive impurity testing protocol (e.g., other known impurities, unspecified impurities, total impurities, etc.).
Diphenhydramine		Diphenhydramine is known to be one of the highest volume selling drugs regulated
Hydrochloride  Diphenhydramine and Pseudoephedrine Capsules		under the OTC monograph system, and it is currently being marketed in a variety of single ingredient antihistamine products, as well as a component in cough/cold and nighttime sleep aid combination products. Recently approved ANDAs are following the extensive European Pharmacopeia acceptance criteria for this drug substance and have fully qualified impurity testing protocols for drug product release and stability testing. No impurity testing protocols exist for the drug substance or drug product in any of the USP compendial monographs.

Povidone; Crospovidone; Copovidone	Nitrogen assay test is nonspecific and it would be preferred to have a more specific assay due to concerns about EMA involving e.g. melamine. Monographs for 3 Povidone analogs are not consistent with respect to the impurity specifications and should be harmonized within USP and to the EP monographs (e.g. Limit of hydrazine; limit of aldehydes; limit of peroxides (estimate based on absorbance value); heavy metals (estimate using 5 ppm and 10 ppm stds) and EP monographs)	
Talc	Labeling should be revised to match the statements that are provided in the Talc FCC monograph, thereby assuring that Talc is not sourced from mines that are known to contain asbestos. Also, USP should consider revising the current tests for asbestos to ensure adequate specificity.	

.\*