U.S. FOOD & DRUG ADMINISTRATION

October 7, 2016

Mr. Mario Sindaco
Executive Secretariat
The United States Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway
Rockville, MD 20852

REF: 10-16-001-N

Dear Mr. Sindaco,

This correspondence is a continuation of our communications regarding USP monographs in need of modernization. The FDA Monograph Modernization, and, the Over-The-Counter Drug Products Working Groups have recently identified several monographs that we believe should be high priority candidates for monograph modernization.

Based on input from across the Agency, we have identified the monographs and noted parts of the monograph in need of revision. They are listed in the table below:

Monograph or General Chapter Title	**Rationale for Inadequacy**	**Recommendations for Revision**
Benzoyl Peroxide Gel	The impurities test is inadequate. The acceptance criterion for benzoic acid poses safety concerns.	Specifications must include acceptance criterion for total impurities, including all related known impurities (e.g., benzoic acid, ethyl benzoate and benzaldehyde). The acceptance criterion for benzoic acid must be tightened.
Benzoyl Peroxide Lotion	The impurities test is inadequate. The acceptance criterion for benzoic acid poses safety concerns.	Specifications must include acceptance criterion for total impurities, including all related known impurities (e.g., benzoic acid, ethyl benzoate and benzaldehyde). The acceptance criterion for benzoic acid poses safety concerns and must be tightened.
Hydrous Benzoyl Peroxide	The impurities test is inadequate. The acceptance criterion for benzoic acid poses safety concerns.	Specifications must include acceptance criterion for total impurities, including all related known impurities (e.g., benzoic acid, ethyl benzoate and benzaldehyde). The acceptance criterion for benzoic acid poses safety concerns and must be tightened.

Monograph or General Chapter Title	Rationale for Inadequacy	Recommendations for Revision
Bromocryptine Mesylate	The Identification test and Impurities tests are inadequate.	Revise the identification, and, impurity tests.
Albuterol	Test requirements included in the monograph are non-specific (e.g. assay by titration, TLC for impurity testing, etc.)	Develop HPLC method for both assay and impurities for entire product family.
Sulfamethazine	The monograph contains no related substance test.	Revise to include related substance test.
Vancomycin	The current impurity tests are inadequate.	Impurity limits must be tightened. We recommend that this monograph be considered for harmonization with the European Pharmacopeia.
Conjugated Estrogens	The identification test is inadequate.	Update the identification test.
Nitrofurantoin	The limit for nitrofurfural by TLC method is outdated. Currently the limit is not ICH compliant (structural alert).	Replace TLC method with HPLC (or other modern method). Update impurity tests, Limit impurities with structural alerts per ICH M7.
Oxycodone Hydrochloride	The chromatographic system utlizes a packed GC column for limit of alcohol test. This is outdated and not normal for current GC technology. Note: Some other USP monographs also use a packed GC column for GC methods.	GC capillary column is readily available for use. Update to capillary column, or refer to USP General Chapter <467> for alcohol test as a general residual solvent for this particular monograph.
Paroxetine Hydrochloride	HPLC methods for related compounds use up to four separate proceudres; this seems cumbersome. The longest HPLC run time is 110 min, which may be excessive for current HPLC technology. Because of this, firms tend to develop their simplified in-house method.	Update the methods to be user-friendly and efficient.
Ritodrine Hydrochloride Tablets	Monograph lacks tests for significant impurities/related substances and total impurities.	Add analytical method for related substances and total impurities.

Monograph or General Chapter Title	Rationale for Inadequacy	Recommendations for Revision
Phenobarbital Sodium for Injection	Monograph has several problems including an inadequate 'Definition' section and no specified assay amount.	Evaluate the entire monograph and revise accordingly.
Naproxen	Monograph utilizes outdated acid/base titration method for assay and impurities determination.	Replace acid/base titration with stability- indicating HPLC method.
Naproxen Sodium	Monograph utilizes outdated acid/base titration method for assay and impurities determination.	Replace acid/base titration with stability- indicating HPLC method.
Selenium Sulfide	Identification/Assay methods are by open digestion followed by titration.	Replace outdated methods with modern analytical methods.
Selenium Sulfide Topical Suspension	Identification/Assay methods are by open digestion followed by titration.	Replace outdated methods with modern analytical methods.
Trimethoprim Tablets	Monograph contains outdated HPLC method for assay. Also, the TLC method for ID test should be replaced.	Replace outdated methods with modern analytical methods.
Trimethoprim Sulfate	Monograph contains outdated HPLC method for assay. Also, the TLC method for ID test should be replaced.	Replace outdated methods with modern analytical methods.
Trimethoprim	Monograph contains outdated HPLC method for assay. Also, the TLC method for ID test should be replaced.	Replace outdated methods with modern analytical methods.
Sodium Monoflurophosphate	Monograph uses outdated titration method for assay test.	Replace outdated methods with modern analytical methods.
Hydroquinone	Monograph uses outdated titration method for assay test.	Replace outdated methods with modern analytical methods.
Hydroquinone Cream	Monograph uses outdated titration method for assay test.	Replace outdated methods with modern analytical methods.
Hydroquinone Topical Lotion	Monograph uses outdated titration method for assay test.	Replace outdated methods with modern analytical methods.
Chlorpheniramine Maleate Oral Solution	Test requirements inlcuded in monograph are non-specific (e.g. assay by titration, TLC for impurity testing, etc.)	Replace outdated methods with modern analytical methods.

Monograph or General Chapter Title	Rationale for Inadequacy	Recommendations for Revision
Chlorpheniramine Maleate Injection	Test requirements inlcuded in monograph are non-specific (e.g. assay by titration, TLC for impurity testing, etc.)	Replace outdated methods with modern analytical methods.
Diphenhydramine HCl & Phenylephrine HCl Liquid	Test requirements inlcuded in monograph are non-specific (e.g. assay by titration, TLC for impurity testing, etc.)	Replace outdated methods with modern analytical methods.

We hope this list will be helpful to USP in modernization efforts. Please feel free to contact me at pallavi.nithyanandan@fda.hhs.gov if there are any questions. Please use the reference number provided above on any ensuing correspondence.

Sincerely yours,

Pallavi Nithyanandan -S

Digitally signed by Pallavi Nithyanandan -S
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