CHPA CONSUMER HEALTHCARE PRODUCTS ASSOCIATION
founded 1881

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U.S. Pharmacopeia ("USP")
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Re: General Chapters <476> Organic Impurities in Drug Substance and Drug Products and <1086> Impurities in Drug Substances and Drug Products. *Pharmacopeial Forum*, Vol. 40(3) [May-June 2014]

USP Correspondence Numbers— C133393 and C133392

Dear Dr. Hernandez-Cardoso:

On behalf of the Consumer Healthcare Products Association (CHPA), a 133 year-old trade association representing the nation's leading over-the-counter (OTC) medicine and nutritional supplement manufacturers, I'd like to thank you for the opportunity to comment on U.S. Pharmacopeia's proposal **for General Chapters <476> Organic Impurities in Drug Substance and Drug Products and <1086> Impurities in Drug Substances and Drug Products published for comments in *Pharmacopeial Forum*, Vol. 40(3) [May-June 2014]**. CHPA strongly supports USP's efforts to address impurity control in drug substances and drug products. Guidance provided by these chapters and references therein can provide an additional measure of safety for OTC products. Overall the newly revised/created chapters provide reasonable guidance and direction for controlling organic impurities in drug substances and drug products.

CHPA respectfully submits the following comments regarding the questions USP has asked in the Pharmacopeial Forum:

1. Do the newly revised/created chapters adequately address impurity control in drug substances and drug products? If not, what needs to be changed?

- CHPA recommends that either in the General Chapter <476> or in the General Notice which is intended to implement the general chapter, USP clearly define that the scope of the General Chapter applies to drug substances and drug products that have official USP monographs.

- Chapter <476>, under the section **INTRODUCTION,** the sentence *"When a detected impurity is not described in the individual monograph, the manufacturer is responsible for developing appropriate specifications (analytical procedures and acceptance criteria)."* The above statement seems to contradict common understanding that a USP monograph will supersede a General Chapter. This above statement would make <476> the default for all monographs regardless of any impurity controls within a monograph. Clarification is needed as to the intent of this statement. We suggest for clarification: When an impurity is *detected at or above the appropriate reporting threshold the manufacturer is responsible for developing appropriate specifications (analytical procedures and acceptance criteria) unless the impurity is controlled based on monograph criteria for any other impurities."*

- General Chapter <476>, under the section **IDENTIFICATION OF IMPURITIES IN DRUG SUBSTANCE AND DRUG PRODUCTS** references are made to various stability studies at the recommended storage conditions. Clarification may be needed for accelerated stability testing (e.g 40 ^{o}C/ 75% relative humidity) which are common for many OTC drugs in pre-market studies.

- General Chapter <476>, under the section **ANALYTICAL PROCEDURES FOR IMPURITIES AND DEGRADATION PRODUCTS** *"Analytical procedures for OTC drug products may require a case-by-case approach, depending on the diversity and complexity of dosage forms."* Generally every drug product is typically taken on a case by case basis for the development of analytical procedures. CHPA recommends that USP

include language stating that alternate analytical methods may be required for OTC drug products depending on the diversity and complexity of dosage forms.

- General Chapter <476>, discussion is given to acceptance criteria and qualification limits. Several references are made to the use of available guidance that can be used for this purpose. The guidance referenced will be of limited value to OTC products as they were written for drug products that typically fall under products with an approved ANDA/NDA and not OTC drug products. CHPA recommends that the USP provide cross reference to General Chapter <1086> and include guidance or recommendations for OTC or nonprescription drug products marketed without an ANDA/NDA registration.

- General Chapter <1086> Under **DRUG PRODUCT** the sentence "*Similar principles may be applied to set thresholds and acceptance criteria for degradation products in drug products not discussed in ICH or FDA guidance [e.g., those for over-the counter (OTC) drug products].*" It is not clear from this limited text as to whether or not Table 2 above this text is applicable to OTC drugs. Table 2 (Drug Product NDA & ANDA) Degradation Product Thresholds) was developed for drugs based on having significant explicit safety data available for those drugs. Drugs marketed under the FDA OTC Monograph system will not have that same type of data. CHPA recommends that the USP provide cross reference to General Chapter <1086> and include guidance or recommendations for OTC or nonprescription drug products marketed without an ANDA/NDA registration. CHPA recommends that additional language be added that better defines the applicability of Table 2 to OTC drugs without an NDA/ANDA registration and recommends that Table 1 (Drug Substance Impurity Thresholds remain in Chapter <1086>.

2. Would it be helpful to hold a workshop to inform the user community of the upcoming changes in USP written standards for impurities and to discuss the potential impact of these changes?

Yes – CHPA believes it will be of great value to hold workshops to inform the user community of the upcoming changes in the written standards for impurities. CHPA would strongly

recommend the inclusion of FDA personnel to discuss the implementation approach for the new standards such as the internal documentation required to support products that do not fall under NDA or ANDA reporting requirements (OTC monograph products). We encourage USP to schedule the workshop prior to the time that the chapter is completed in order for the industry to understand the impact. The final chapter should be developed and documented in a manner that can be consistently interpreted and applied for the common user without a workshop.

3. What length of time would be reasonable for implementing chapter <476> in new OTC drug products, OTC products that do not have a USP monograph, and existing OTC monographs that do not refer to chapter <466>?

CHPA recommends that general chapter <476> be implanted through a General Notice 24 months after the General Chapter becomes official. The timing would allow for companies to complete the assessment of currently marketed products such as OTC products to achieve compliance to the general chapter. As with all major updates to the USP where a General Chapter is implemented via a General Notice, the changes have significant business impact to the user community and ultimately may impact product availability for the consumer. The implementation of the new General Chapter will require companies to develop new, more sensitive and specific analytical procedures for existing marketed products. As such, this may lead to additional safety and toxicological studies needing to be undertaken by the user community. Based upon the outcomes of the new analytical procedures and safety assessments, significant reformulation work may be required to come into compliance with general chapter <467>. Since this General Chapter will impact many products which currently do not have organic impurity standards, adequate time should be allowed for the user community to do a complete and thorough assessment of all products impacted.

4. Would it be useful for USP to hold pharmacopeial education classes to provide training in how to use chapter <476>?

Yes – CHPA believes it would be of great value to hold pharmacopeial education classes to provide training in how to use General Chapter <476>, CHPA would like to note however that if extensive training is necessary then documentation is deficient.

CHPA strongly supports USP's efforts to address impurity control in drug substances and products. Guidance provided by these chapters can provide an additional measure of safety for OTC products. Overall the newly revised/created chapters provide reasonable guidance and direction for controlling organic impurities in drug substances and drug products.
CHPA appreciates the opportunity to comment on the proposed monograph revision. I am happy to speak to you about this issue at greater length and detail. Feel free to contact me directly at your convenience.

Best Regards,

John S. Punzi, Ph.D
Director Quality Assurance and Technical Affairs