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July 31, 2013

Clydewyn Anthony, Ph.D.
Scientific Liaison - New Monographs
US Pharmacopeia ("USP")
12601 Twinbrook Parkway
Rockville, MD 20852-1790

Re: 4-Aminophenol in Acetaminophen-containing Drug Products, Pharmacopeial Forum, Vol. 39(3) [May-June. 2013].

Dear Dr. Anthony:

On behalf of the Consumer Healthcare Products Association (CHPA), a 131 year-old trade association representing the nation's leading over-the-counter (OTC) medicine and nutritional supplement manufacturers, we thank you for the opportunity to comment on U.S.

Pharmacopeia's proposed new General Chapter: **〈 227 〉** 4-Aminophenol in Acetaminophen-containing Drug Products, **Pharmacopeial Forum, Vol. 39(3) [May-June. 2013]**.

CHPA supports advancing modernization of USP's quality monographs, updating and improving the compendial test methods and establishing product standards which can provide an additional measure of safety for OTC products. We support USP's mission to improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods. Since the safety limit of 4-aminophenol (PAP) has been established as 0.15 % w/w relative to acetaminophen based on a thorough toxicological evaluation¹, CHPA recommends a single specification for PAP in acetaminophen-containing drug products of 0.15%

¹ CHPA's Proposal of Limit for the Process Degradant 4-aminophenol dated July 12, 2011

w/w relative to acetaminophen in all dosage forms. This level complies with the ICH Q3B Guidance on impurities in new drug products and is on par with the limit adopted by the British Pharmacopoeia.

CHPA considers a limit of 0.15% w/w PAP to be a great example of quality by design. Mechanistically it is known how PAP forms, a safety limit has been established based on toxicological data and the ability to measure PAP is being established by this general chapter. This process illustrates the use of good science combined with risk and knowledge management to set a public standard that will result in safe high-quality, consistent drugs being available to the public. QbD is not about disallowing degradation, it is about understanding and appropriate control.

In summary, CHPA supports advancing modernization of USP's quality monographs, updating and improving the compendial test methods and establishing product standards which can provide an additional measure of safety for OTC products. CHPA supports the USP proposal to develop methods and acceptance criteria for 4-aminophenol in acetaminophen containing drug products and believes that a standard based on safe levels determined from toxicological perspectives is justified for all dosage forms. CHPA recommends a single specification for 4-aminophenol in acetaminophen-containing drug products of 0.15% w/w relative to acetaminophen is appropriate for all dosage forms.

CHPA appreciates the opportunity to comment on the general chapter. We are happy to speak to you about this issue at greater length and detail. Feel free to contact me directly at your convenience and I can arrange contact with our members.

Best Regards,



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

cc: Todd Cecil, Ph.D.