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Clydewyn Anthony
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US Pharmacopeia ("USP")
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Re: Dextromethorphan **Proposals for Interim Revision Announcements *Pharmacopeial Forum*, Vol. 40(3) [May-June 2014]**

USP Correspondence Number—C109903

Dear Dr. Anthony:

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 in **Interim Revision Announcements (IRA) for Dextromethorphan published for comments in *Pharmacopeial Forum*, Vol. 40(3) [May-June 2014]**.

Because of the FDA's safety concerns regarding the control and monitoring of levomethorphan (an enantiomer of dextromethorphan), CHPA supports the control of levomethorphan as an impurity and respectfully submits the following comments regarding the proposed updates to the dextromethorphan monograph as proposed in the IRA published in PF 40(3).

Although it is unclear how USP established the toxicological basis for the limit of NMT 0.1% levomethorphan, CHPA's comments are primarily focused on the classification of this impurity reference standard as a DEA Class II controlled substance. While CHPA recognizes that USP has worked with the FDA on other cases of economically motivated adulteration with significant

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safety concerns, this is the first instance that we are aware of that USP has applied a requirement for an impurity that, depending upon the final form of the reference standard, may require manufacturers to obtain DEA site licenses. By including the acceptance criteria for levomethorphan as part of the Identification requirements of the dextromethorphan monograph, manufacturers will also be required to perform the testing regardless of how well they control the manufacturing process and/or their suppliers.

CHPA recommends that the USP work closely with the DEA to develop a reference standard that allows for an exemption under 21 CFR Part 1308. The reference sample might consist of single use ampules of a dilute solution (or a small amount of lyophilized powder) of either levomethorphan alone or in combination with dextromethorphan near acceptance limit concentrations. The stability of dilute solutions of dextromethorphan and levomethorphan is well established in slightly acidic conditions.

The use of a levomethorphan reference standard will result in significant cost and complexity for manufacturers and testing laboratories. Obtaining and operating under the appropriate DEA license requires both a state and federal review process to obtain and maintain the license. The typical time frame to obtain a DEA license to receive and handle a levomethorphan reference standard is estimated to be between 6 and 9 months. Furthermore to obtain the required DEA license, manufacturers with international manufacturing facilities would also be required to meet DEA standards outside of the US and obtain a DEA license for shipment in addition to being required to meet local regulations for receiving and handling a scheduled narcotic material.

CHPA is aware that as of July 15, 2014 the standard is not available from USP and recommends that USP consider the timing of the implementation of the monograph to coincide with the availability of the USP reference standard. At that time the dextromethorphan monograph would then be updated to reflect the final form (i.e. dilute solution) of the reference standard. CHPA recommends that USP allow adequate time after the reference standard becomes available so that manufacturers can obtain the new material and perform the appropriate method verification activities in their laboratories.

We would also like to note that if the limit of NMT 0.1% levomethorphan is not warranted by the toxicity of the compound, it should be possible to establish a higher limit and control it effectively with a stringent range for specific rotation. The specific rotation test would eliminate the need for anyone to acquire a levomethorphan standard, thus reducing complexity while still meeting the goal of increased safety and tighter control.

In summary, CHPA supports improving USP test methods and establishing specifications for levomethorphan in dextromethorphan which can provide an additional measure of safety for OTC products. CHPA supports the improvement of the dextromethorphan monographs but is concerned with the DEA licensing requirement imposed and the limit of NMT 0.1%. CHPA believes that industry will require 6 months after availability of suitable reference standards to test the methods without a clear path towards a DEA exemption. If the DEA exemption cannot be obtained additional time should be allowed.

CHPA appreciates the opportunity to comment on the proposed 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