February 25, 2021

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

REF: 02-25-001-N

Dear Mr. Sindaco,

This letter pertains to the modernization of the USP/NF Isopropyl Alcohol monograph and to a recent meeting between FDA and USP regarding the topic. This is a follow-up to our communication sent to USP on July 30, 2020 recommending the addition of a Limit Test for Methanol in the Identification section of Alcohol monograph, please see REF: 07-20-037-N. We thank USP for expeditiously revising the Alcohol and Dehydrated Alcohol monographs and educating stakeholders on meeting the new requirements. As requested by USP, we are providing written comments on the Isopropyl Alcohol monograph for consideration by USP and the Excipient Monographs Expert Committee.

FDA continues to see an increasing number of hand sanitizer products contaminated with methanol; updated information on this issue is available on our public website https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-methanol. Ingesting hand sanitizer products contaminated with methanol has led to recent adverse events, including blindness, hospitalizations and death. Isopropyl Alcohol is a widely used pharmaceutical ingredient in hand-sanitizer and other antiseptic products and presence of methanol is a critical contamination risk to consumers.

It is noted that the current USP Isopropyl Alcohol monograph does not list methanol as a specified impurity, and the analytical method based on area normalization lacks specificity for quantitation of specified impurities listed in the current monograph. Therefore, we have the following recommendations for the revision of Isopropyl Alcohol monograph:

- Add methanol as a specified impurity to the *'Limit of Volatile Impurities'* section with acceptance limit of NMT 200 ppm consistent with the Alcohol monograph.
- Change the method in the *'Limit of Volatile Impurities'* section from the area normalization approach for quantitative analysis to using external reference standards to quantify the impurities.
- Include a test for "Limit of Methanol" test in the *"Identification"* section of the monograph.

Similar revisions are recommended for the USP Azeotropic Isopropyl Alcohol monograph.

From a regulatory standpoint, it would be beneficial if methanol detection and quantification is part of the Identification test in addition to the Limit of Volatile Impurities test, as the CGMP regulations at 21 CFR 211.84(d)(l) would require that manufacturers of drug products detect and quantify any methanol present for each lot of isopropyl alcohol received. Furthermore, manufacturers of Isopropyl Alcohol could not deviate from the methanol limit since this would be an aspect of identity. In contrast, if methanol detection and quantification is only part of an impurity test, a manufacturer need not include as part of its identity testing the detection and quantification of methanol in the isopropyl alcohol. In addition, a manufacturer could deviate from the impurity requirements established in the monograph by labeling the product to indicate that it deviates from the USP test requirements in this regard. The agency may, however, consider isopropyl alcohol with methanol above the limit to render the drug adulterated under the Federal Food, Drug, and Cosmetic Act.

FDA intends to refer manufacturers to the updated Limit of Volatile Impurities and Identification tests in the USP Isopropyl Alcohol monograph.

Manufacturers should evaluate their supply chain for this product and contact CDER Drug Shortage Staff at drugshortages@fda.hhs.gov if any access or potential drug shortage issues arise. Contacting the Drug Shortages Staff also allows manufacturers to meet any obligations to report discontinuances or interruptions in drug manufacture under 21 U.S.C. § 356C(b) and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on the products.

Because this is a current COVID-19 related patient safety issue, we are requesting that this issue be discussed and addressed with urgency. We hope these comments will be helpful to USP and the Excipient Monographs Expert Committee. 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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Pallavi Nithyanandan, Ph.D.
Director
Compendial Operations and Standards Staff
Office of Pharmaceutical Quality
Center for Drug Evaluation & Research