International Pharmaceutical Excipients Council of the Americas

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Re: Notice of Intent to revise the USP Isopropyl Alcohol monograph

To whom it may concern,

Members of the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas) have reviewed the USP Simple Excipients Expert Committee Notice of Intent to revise the *USP* Isopropyl Alcohol monograph by including a *Limit of Methanol* test in the Identification (ID) section to address the serious public health hazards associated with the use of isopropyl alcohol contaminated with or substituted with methanol. IPEC-Americas appreciates the opportunity to provide comments for the proposed revision.

IPEC-Americas Background

IPEC-Americas represents more than 50 excipient manufacturers, distributors and pharmaceutical/biopharma companies to support the safe production and use of excipients. This letter represents the IPEC-Americas membership. A complete list of IPEC-Americas member companies can be found at: https://ipecamericas.org/what-ipec-americas/member-companies. IPEC-Americas is dedicated to working closely with regulatory authorities, industry organizations and scientific bodies (globally) to advance public health on matters relating to the quality, safety, manufacture, distribution, use and functionality of excipients. IPEC is the sole association representing excipients.

IPEC-Americas Comments

IPEC-Americas has significant concerns with the proposal for implementing additional identification testing to the Isopropyl Alcohol monographs. Many of these same concerns were

shared previously with USP in our comments regarding moving methanol to an ID test for the alcohol (ethanol) monograph.[1]

More recently, IPEC-Americas also provided detailed comments to the US FDA docket which can be accessed at the following link:

Docket No. FDA-2020-D-2016: Policy for Testing Alcohol (Ethanol) and Isopropyl Alcohol for Methanol, Including During the Public Health Emergency (COVID-19).

Briefly, our concerns with changing the isopropyl alcohol (IPA) monograph to include an ID test for methanol are:

- The addition of mandatory identification testing for methanol in *monographs* does not address the *root cause* of adulterated drug products since it appears that the main problem is really the hand sanitizer manufacturers substituting methanol, in whole or in part, for the alcohol in their formulations, not that they are using adulterated alcohol as a component. Contaminated hand sanitizers being imported into the US is an FDA enforcement issue. It is FDA's responsibility to inspect imports at the port of entry to ensure that contaminated drug products do not enter the US, especially when such contamination issues have been identified. Failure to detect the importation of these adulterated drug products at the port of entry is the primary reason they enter into the US supply chain. The hand sanitizer manufacturers and retailers must also be held accountable for ensuring compliance to US regulations.

- IPEC-Americas believe that this issue was likely highlighted due to the recent increase in the demand for hand sanitizers, which created alcohol and IPA shortages, and is not aware of adulterated alcohol or IPA being used in other drug products in the past.

- FDA and US Customs have responsibility to inspect imports and prevent adulterated products from reaching US consumers. The companies using methanol to produce hand sanitizers are likely not following USP or FCC monograph requirements and FDA regulations and guidance in their operations. In many cases companies manufacturing hand sanitizers containing alcohol or IPA substituted with methanol are not following GMPs, raw material supplier qualification, FDA OTC regulations and current USP or FCC monographs. In addition, the retail companies sourcing them are probably not qualifying the hand sanitizer manufacturers and distributors and not testing the drug product before sale. If they did, the risk of substitution or adulteration of the ingredients in the product would be mitigated.

- There is a lack of evidence that substitution with methanol for other alcohols in drug formulations existed prior to the pandemic focus on hand sanitizers. It appears that historical suppliers producing under OTC monographs and GMP requirements have adequate controls and processes in-place. Supplier qualification should be a requirement to address this issue for hand sanitizer manufactures operation under the emergency use authorization. It is critical that FDA hold new drug manufacturers who make hand sanitizers or any other OTC or prescription drugs accountable for having a robust raw material supplier qualification and traceability programs, which may include

[1] IPEC-Americas' response August 12, 2020 to USP Notice of Intent to Revise, Alcohol, Dehydrated Alcohol, USP reference C287475

enhanced testing during initial raw material qualification that can be reduced and/or eliminated once the raw material/supplier relationship has been established and justified. This is a GMP requirement which will help to prevent these types of "adulteration" issues, if in fact they exist, with the alcohol or IPA (raw material) itself. The issue has not been with the alcohol or IPA, but rather with the finished product. Testing of the IPA, as related to the USP monograph, cannot take into account the methanol substitution that occurs after the IPA is received and used to manufacture the OTC drug product.

- Adding methanol as a specification and identification test to the IPA monograph will not prevent uninformed or unprincipled companies from formulating drug products with methanol. Reputable companies that manufacture drug products containing IPA are aware of current supply chain challenges and take appropriate steps to ensure the identity and quality of the IPA used.
- Addition of IPA ID testing for methanol will result in an excessive test requirement burden with little chance of preventing a significant problem related to patient safety since the main problem appears to be with the substitution of ingredients and lack of following GMPs used by hand sanitizer manufacturers, not with adulterated IPA in the supply chain.
- More recent contamination of hand sanitizers with benzene further illustrates that a reactive mode of adding additional testing to USP monographs will not address the fundamental root cause for quality issues. Risk assessment with an appropriate control strategy is better than requiring mandatory identification testing to include a test for methanol.
- Adding this type of testing to the monograph sets a dangerous precedent for future changes in USP monographs because it is not a compendial, testing or manufacturing issue, it is a supplier qualification issue! In addition, increasing required testing could also result in higher manufacturing costs which ultimately get passed on to the end-user, with no added patient safety benefit.
- USP <467> Residual solvents already has established limits for methanol in drug products; therefore, since 2008 methanol controls have already existed, which makes adding this Methanol ID test unnecessary.

IPEC-Americas recognizes the efforts of the USP and other pharmacopeias, to continually improve, harmonize, and modernize excipient monographs. We look forward to continued collaboration on the development of global standards which ensure the quality and safety of excipients.

Respectfully yours,

Janeen Skutnik-Wilkinson
Chair, IPEC-Americas