International Pharmaceutical Excipients Council of the Americas

Janeen Skutnik-Wilkinson
Chair

April 16, 2021

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

cc: Francis Godwin, FDA, Francis.Godwin@fda.hhs.gov
Theresa Michele, FDA, Theresa.Michele@fda.hhs.gov

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

Dear Sir or Madam,

Members of the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas) have reviewed the final guidance titled, *"Policy for Testing Alcohol (Ethanol) and Isopropyl alcohol for Methanol, Including During the Public Health Emergency (COVID-19)*." IPEC-Americas provided comments to both FDA and USP on August 12, 2020 (letter attached) in response to a public meeting held August 10, 2020 hosted by both USP and FDA to provide *Updates on Methanol Testing in Alcohol, Dehydrated Alcohol Monographs - Rx/OTC manufacturers.* IPEC-Americas would like to highlight key points from the letter which are relevant to this final guidance.

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.

General IPEC-Americas Comments

Although IPEC-Americas realizes that this docket is final and not currently open for public comment, IPEC-Americas has some significant concerns that the FDA's direction on this topic does not effectively address the root cause of the problem by trying to resolve the substitution of alcohol (ethanol or isopropanol (IPA)) with methanol in hand sanitizers through compendial testing of the alcohol.

After listening to presentations and comments from the FDA during the:

- August 10, 2020 USP WebEx to provide updates from the USP and FDA on *Methanol Testing in Alcohol, Dehydrated Alcohol Monographs - Rx/OTC manufacturers*,
- January 27 & 28, 2021 USP Open Forum entitled “Manufacturing Alcohol to Combat a Public Health Emergency: Insights on Regulatory and Quality Requirements
- February 23, 2021 USP Seminar entitled “Ensuring Quality Hand Sanitizer Production During COVID-19 For Manufacturers in the United States.

IPEC-Americas would like to understand whether FDA confirmed that the methanol issues discussed resulted from adulteration of the alcohol itself (from the alcohol supplier) or from substitution of ethanol or IPA with methanol during production of hand sanitizers. Based on a detailed review of warning letters and FDA import alerts for ~ 230 hand sanitizer products recommended not for use by the FDA (https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-consumers-should-not-use#products) it appears that in most cases ethanol or isopropanol was substituted wholly or in part (by the manufacturer of the hand sanitizer) with methanol. In many of the remaining banned products it appeared that the FDA tested product(s) from the hand sanitizer manufacturer and found them to contain methanol instead of one of the approved alcohols.

IPEC-Americas is concerned that the current FDA Guidance applies to alcohol used in all drug products, not just hand sanitizers, even though the real issue appears to be substitution of the alcohol in the sanitizer formulation rather than adulteration of the alcohol used as the raw material. IPEC-Americas would like to better understand if the FDA was aware of specific cases of alcohol adulteration with methanol that was subsequently used in the manufacture of <u>any other drug products</u> prior to their awareness of this issue with hand sanitizer. IPEC-Americas believes that this issue was likely highlighted due to the recent increase in the demand for hand sanitizers, which created alcohol shortages, and is not aware of adulterated alcohol 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 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.

IPEC-Americas recognizes that some of the supply chain issues have resulted from new manufacturers producing hand sanitizer under the emergency authorization program to address the shortage due to the pandemic. However, given the lack of evidence that this issue previously existed, 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 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 (raw material) itself. The issue has not been with the alcohol, but rather with the finished product. Testing of the ethanol or IPA cannot take into account the methanol substitution that occurs after the ethanol or IPA is received and used to manufacture the OTC drug product.

Substitution of methanol for ethanol is a decades old problem due to the cheap and abundant availability of methanol. With the hand sanitizer issue, it appears there are multiple supply chain failures due to the ratio of hand sanitizer to ethanol manufacturers in the FDA recall list. If this is the case, new participants in the supply chain clearly do not know the difference between ethanol and methanol. Moving existing specifications for methanol in the alcohol monograph to a mandatory identification test and adding methanol as a specification and identification test to the isopropyl alcohol monograph will not prevent these uninformed or unprincipled companies from formulating drug products with methanol. Reputable companies that manufacture drug products containing alcohol are aware of current supply chain challenges and take appropriate steps to ensure the identity and quality of the alcohol used.

Contaminated hand sanitizers being imported into the US is an FDA enforcement issue. It is FDAs 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. The addition of mandatory identification testing for methanol in the *Alcohol and Dehydrated Alcohol USP-NF monographs* and in this Guidance 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. 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.

Historically, FDA management has routinely discussed the need for risk assessment to be the basis for appropriate controls. However, in general, this Guidance lacks requirements for a risk assessment prior to determining what level of testing is necessary. The approach being taken for routine container testing for methanol does not appear to be based on risk assessment, but rather on precautionary principles. This approach results in 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 alcohol 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. IPEC-Americas believes that root cause analysis should be used to determine the risk of potential contaminants (e.g., ethanol and/or IPA being contaminated with methanol,

benzene) in the supply chain. Risk assessment with an appropriate control strategy is better than requiring mandatory identification testing of each container to include a test for methanol.

IPEC-Americas requests access to data from the FDA that demonstrates the true risk associated with methanol is due to adulteration of the alcohol itself as opposed to methanol substitution during manufacture of the hand sanitizer. If the data is already publicly available, can FDA share where it can be found? Further, if there is adulteration of the alcohol, what are the number of incidents for foreign or domestic alcohol products? All of the publicly available data that we have found so far indicate that the contamination occurred in the hand sanitizer itself due to methanol substitution by the hand sanitizer manufacturer rather than by adulterated alcohol being used which was actually adulterated by the alcohol manufacturer. Has this substitution of alcohol with methanol been found in drugs other than hand sanitizers? If this is the case, then the actions required in this Guidance and in the USP or FCC monograph ID test for routine testing for methanol in the alcohol itself will do little to prevent this problem in the future. It does not address or mitigate the root cause.

FDA has stated that the routine ID testing requirement for methanol will be a permanent requirement even though they have recognized the temporary nature of this problem in the way they have published their other related Guidances. Why does FDA believe this testing requirement should be continued once the other temporary guidance related to alcohol is withdrawn? There does not appear to be justification for doing this since the main risks do not seem to be related to adulterated alcohol itself, but rather adulterated hand sanitizers made by substituting alcohol in the formulation with methanol by the hand sanitizer manufacturer.

Summary and Recommendation

IPEC-Americas commend the FDA for placing import restrictions on hand sanitizers manufactured in Mexico and other countries since these imports appear to be where the majority of these adulterated products have come from; however, routine ID test requirements in the USP monograph for alcohol and the FDA Guidance requiring that every container of alcohol be tested for methanol upon receipt will not resolve these types of issues since the hand sanitizer manufacturers are not utilizing appropriate GMPs. 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.

IPEC-Americas recommend the implementation of the new identification requirements for the detection of methanol in alcohol and dehydrated alcohol be aligned with the duration of the temporary FDA policy on hand sanitizers, which is expected to be withdrawn once the supply chain returns to normal demand and operation (i.e., once the COVID-19 crisis has passed). After this period, the risks of having companies adulterate drug products with methanol will go down and there will no longer be a need for these additional controls on the alcohols themselves.

With the risk management philosophy that FDA claims to ascribe to, adding mandatory ID testing for methanol for every container results in a non-value-added burden on reputable pharmaceutical companies that will simply increase the costs of drugs without any significant benefit to the patient.

Since the current alcohol monographs already contain the methanol test and limit as part of the Organic Impurities requirement, IPEC-Americas believe that it would be much better to state strongly in the FDA guidance that there is already a test and limit for methanol in these monographs and that failure to meet these requirements will result in regulatory enforcement action. The level of routine testing that is done should be determined by the drug product manufacturer based on their own risk assessment.

Thank you for your consideration in reviewing our comments. IPEC-Americas would welcome further discussion on this topic with the FDA. Should you require further clarification to our comments, please let us know.

Respectfully yours,

Janeen Skutnik-Wilkinson
Chair, IPEC-Americas

International Pharmaceutical Excipients Council of the Americas

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August 12, 2020

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Re: Notice of Intent to Revise, Alcohol, Dehydrated Alcohol

Dear USP / FDA Contacts,

IPEC-Americas understands the urgency to support public health during the ongoing COVID-19 pandemic and patient safety is a core principle of the IPEC-Americas mission and vision. IPEC-Americas appreciate the open communication and engagement the USP and FDA have demonstrated during the meeting with stakeholders on August 10th, 2020. After attending this meeting and reviewing the proposed revisions to the Alcohol and Dehydrated Alcohol monographs published in the Notice of Intent to Revise, IPEC-Americas has the following comments for consideration:

- Mandatory identification testing for methanol in the Alcohol and Dehydrated Alcohol monographs does not address the *root cause* of adulterated hand sanitizers imported into the United States. Failure to detect the importation of these adulterated hand sanitizer products at the port of entry is the primary reason they have gotten into the US supply chain. FDA and US Customs have responsibility to inspect imports and prevent adulterated products from reaching US consumers. In addition, the retail companies sourcing them are probably not qualifying the raw material manufacturers and distributors and not testing the hand sanitizer product before sale. Therefore, there are multiple supply chain

failures by the time hand sanitizer product reaches the consumer. The companies using methanol to produce hand sanitizer are likely not following USP monograph requirements and FDA regulations and guidance. Moving existing specifications for methanol in the ethanol monograph to a mandatory identification test and adding methanol as a specification and identification test to the isopropyl alcohol monograph will not prevent companies from formulating hand sanitizers with methanol which is what has caused most of the problems being observed currently. Reputable companies that manufacture hand sanitizers, particularly during the pandemic crisis, are aware of the FDA temporary policies as well as the current supply chain challenges and take appropriate steps to ensure the identity and quality of the alcohol used.

- During the question and answer session on August 10th, the FDA speaker indicated this new identification testing for methanol in alcohol would be permanent. The FDA Guidance for Industry; *Temporary Policy for Manufacture of Alcohol for Incorporation Into Alcohol Based Hand Sanitizer Products During the Public Health Emergency (COVID-19)*, is a temporary policy to increase the availability of hand sanitizers during the current pandemic. IPEC-Americas recommend the implementation of the new identification requirements for the detection of methanol in alcohol and dehydrated alcohol be aligned with the duration of the temporary FDA policy as this guidance is expected to be withdrawn once the supply chain returns to normal demand and operation once the COVID-19 crisis has passed. After this period, the risks of having companies adulterate hand sanitizers with methanol will go down and there will no longer be a need for these additional controls on the alcohols themselves.

- Further, IPEC-Americas recommend that the requirement to test these alcohols for methanol be included in the FDA guidance, not the USP monograph, as an identification test when the alcohol is being used for the temporary production of hand sanitizers. IPEC-Americas does not support making a change in the USP monograph to require mandatory identification testing for use in other drug products. As evidenced by the absence of methanol adulteration issues in other drugs prior to the pandemic and now during the pandemic, established sources and supplier qualification for ethanol and isopropyl alcohol used in these applications have not been identified as a risk nor have these been impacted by the importation of hand sanitizers adulterated by ethanol or isopropyl alcohol substitution with methanol. The pharmaceutical company's responsibility to qualify raw materials and suppliers, to ensure all ingredients meet required specifications, and to manufacture products under appropriate GMPs has not changed. The companies producing hand sanitizer with methanol are not following these mandatory requirements.

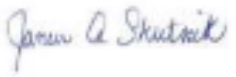
- Also during the question and answer session on August 10th, the FDA speaker indicated this new identification testing for methanol in alcohol would probably be handled in the same manner as was done for glycerin in that FDA would expect that users test every container of the product since adulteration is not always done uniformly. Clarification on this point by FDA is needed because this type of

requirement would become even a bigger burden if this identification testing for methanol were to become a permanent requirement. IPEC-Americas could support this approach during the high-risk period due to the COVID-19 crisis, but this type of control is certainly not needed long-term when risks of methanol adulteration are lower.

- Since the current ethanol monographs already contain the methanol test and limit as part of the Organic Impurities requirement, IPEC-Americas believe that it would be much better for FDA to add in any routine testing requirement for this property to the FDA guidance with strong language and refer to the test and limit for methanol that is already in these monographs without moving this requirement to the ID section. USP could then focus their resources on inclusion of these Organic Impurity requirements into the other monographs for isopropyl alcohol, etc. which currently do not contain this requirement. By handling the situation in this manner, the requirement for routine batch (and possibly container) testing would only last until FDA withdraws their temporary guidance which aligns better with the risk management philosophy that FDA claims to ascribe to without adding long-term, non-value-added burden that will simply increase the costs of drugs without any significant benefit to the patient.

Thank you for your consideration in reviewing our comments. If you have any questions or concerns, please contact IPEC-Americas for additional clarification.

Respectfully submitted,



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