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MEMORANDUM

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RE: COVID-19 Update: FDA Issues Minor Updates to Guidance on Hand Sanitizer Production

In March, the Food and Drug Administration (FDA) issued guidance documents, first revised on March 27, temporarily relaxing certain regulatory requirements for the production of alcohol-based hand sanitizers, to respond to the increased demand for hand sanitizer products during the novel coronavirus crisis.[1] Yesterday, FDA issued additional minor updates to these documents.[2] Notably, FDA provides that fuel or technical grade ethanol should only be used if it meets food (or pharmaceutical) grade standards and has been screened for certain impurities. The agency invites companies wishing to use or supply fuel or technical grade ethanol that does not meet food grade requirements to submit specified data to FDA for its review. FDA also addresses several other topics, including the use of other technical grade ingredients, and the form of and packaging for the hand sanitizer. FDA maintains that ethanol used in hand sanitizers under the policy must be denatured using specified denaturants listed in the guidance, but continues to provide that companies may submit information on additional denaturants to the agency for consideration. FDA appears, however, to have ruled out acetone as a potential denaturant. This memorandum summarizes the updates to the guidance documents as of April 15.[3]

Background

The two guidance documents discussed here were first issued in March. The "Hand Sanitizer Guidance" sets out the criteria under which FDA will exercise enforcement discretion for entities that are not currently licensed or registered drug manufacturers that would like to prepare alcohol-based

[1] *See* HL Memo – COVID-19 Update: FDA and TTB Response to Increased Demand for Alcohol-Based Hand Sanitizer Production (March 30, 2020), available at https://www.hlfoodlaw.com/2020/03/covid-19-update-fda-and-ttb-response-to-increased-demand-for-alcohol-based-hand-sanitizer-production/. As the title indicates, the March 30, 2020 memorandum also addressed guidance issued by the Alcohol and Tobacco Tax and Trade Bureau ("TTB"). The updates discussed in this memorandum are only related to the FDA guidance documents.

[2] FDA also issued and updated guidance outlining the criteria under which the agency will exercise enforcement discretion for pharmacies and registered outsourcing facilities. FDA *Policy for Temporary Compounding of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency*, Immediately in Effect Guidance for Industry, March 2020, Updated April 15, 2020 https://www.fda.gov/media/136118/download. We do not discuss this guidance in this memorandum.

[3] This memorandum is offered for general information and educational purposes. It is not offered as, intended as, and does not constitute legal advice. It is not intended to create, and receipt of it does not constitute, a lawyer-client relationship.

hand sanitizers for consumer use and for use as health care personnel hand rubs.[4] Under the policy, manufacturers will need to follow a specified formulation, register with FDA as a drug manufacturer and list the product as an over-the-counter (OTC) drug, use specific labeling, and follow certain manufacturing and testing practices. The second guidance document ("Alcohol Guidance") relates to the manufacture of alcohol (ethanol) for incorporation in alcohol-based hand sanitizers.[5]

Key Changes to Guidance Documents

FDA Guidance Document #1: Preparation of Alcohol-Based Hand Sanitizer Products ("Hand Sanitizer Guidance")

Ethanol

FDA incorporates the requirements related to ethanol from the Alcohol Guidance into this Hand Sanitizer Guidance document and its appendices. Specifically, Attachment I to the updated Hand Sanitizer Guidance reproduces Appendix C from the Alcohol Guidance, addressing the specific formulas that may be used to denature ethanol. As noted above, FDA is maintaining the requirement to denature the ethanol. As before, the ethanol may be denatured either by the alcohol producer or at the point of production of the finished hand sanitizer product.

Fuel Ethanol

FDA maintains the position that ethanol used in hand sanitizers under the guidance must either be (1) derived from distillation or fermentation processes typically used for consumable goods, or (2) produced synthetically and meets United States Pharmacopeia (USP) or Food Chemical Codex (FCC) grade. FDA also adds the following:

> "Ethanol produced in facilities normally producing fuel or technical grade may be considered for use if the ethanol is produced from fermentation and distillation as would be typically used for consumable goods, and no other additives or other chemicals have been added to the ethanol. Further, special caution should be taken to ensure any other chemicals on site are not introduced into the ethanol either intentionally or via cross contamination. Because of the potential for the presence of potentially harmful impurities due to the processing approach, fuel or technical grade ethanol should only be used if it meets USP or FCC grade requirements and the ethanol has been screened for any other potentially harmful impurities not specified in the USP or FCC requirements."

FDA also notes that if a company wants to use or supply a fuel or technical grade ethanol that does not meet USP or FCC requirements, it should submit information on the ethanol with regard to the levels of impurities listed in the USP monograph as well as any other potentially harmful impurities that may be present given the manufacturing environment to COVID-19-Hand-Sanitizers@fda.hhs.gov with "ETHANOL DATA" in the subject line for FDA's assessment regarding the use of the ethanol under this policy.

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[4] *Temporary Policy for Preparation of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19), Guidance for Industry*, March 2020, Updated April 15, 2020, https://www.fda.gov/media/136289/download.

[5] *Temporary Policy for Manufacture of Alcohol for Incorporation Into Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19), Guidance for Industry*, Updated March 27, 2020, https://www.fda.gov/media/136390/download.

American Chemical Society (ACS) Grade Ingredients

FDA advises that "[i]ngredients that are described as only meeting American Chemical Society (ACS) grade standards should generally not be used in hand sanitizers. The chemical standards that have been established by ACS for reagents are not designed to determine the suitability of a chemical for human use. For example, the ACS monographs for ethanol and glycerin do not include any impurity specifications." However, where an ingredient is described as meeting both ACS grade and USP or FCC grade, use of that ingredient is consistent with the FDA policy.

If a company wants to use an ingredient described only as ACS grade (i.e., and not USP/FCC grade), the firm should submit relevant information on the ingredient's concentration and impurity profile to COVID-19-Hand-Sanitizers@fda.hhs.gov with "*name of ingredient* DATA" in the subject line for FDA's assessment regarding the use of the ingredient under this policy.

Isopropyl Alcohol

If a firm wishes to use isopropyl alcohol (IPA) as the active pharmaceutical ingredient in hand sanitizer, it must be USP grade. Alternatively, if another source of IPA is to be used, the company should provide to FDA data on the ingredient, tested against all elements of the USP monograph, including listed impurities, for FDA's assessment. The data should be sent to COVID-19-Hand-Sanitizers@fda.hhs.gov with "ISOPROPYL ALCOHOL DATA" in the subject line.

In contrast, if isopropyl alcohol is used as a denaturant, technical grade IPA that meets the requirements of the IPA regulatory specifications found at 27 CFR § 21.113 may be used.

Hydrogen Peroxide

FDA announced that technical grade hydrogen peroxide may be used as an ingredient under the policy.

Form of and Packaging for the Hand Sanitizer Product

FDA adds that the hand sanitizer product must be produced "as an aqueous solution and not as a gel, foam, or aerosol spray." Gels, foams, and aerosol sprays are outside the scope of the guidance "because different or additional ingredients may impact the quality and potency of the product" and because the propellents added to aerosol sprays "can result in altered potency of the finished hand sanitizer." Further, "[a]erosol sprays with propellent outside of the formulation (bag on valve) may have safety and potency concerns due to the increased flammability risks of ethanol in an aerosol, risk of overspraying, variability of delivery of the product, rapid evaporation of alcohol, and inhalational toxicities."

Additionally, the packaging must be appropriate for liquid drug products that will seal sufficiently to prevent evaporation of the alcohol or IPA. Manual pump sprays that seal sufficiently to prevent evaporation are consistent with the FDA policy.

Transportation of Hazardous Substances

FDA notes that hand sanitizer offered for transportation or transported in commerce may be subject to the applicable requirements of the U.S. Department of Transportation's Hazardous Materials Regulations (49 CFR Parts 171-180) or guidance issued by the U.S. Department of Transportation's Pipeline and Hazardous Materials Safety Administration (PHMSA). More information is available on PHMSA's website at: https://www.phmsa.dot.gov/news/phmsa-issues-temporary-relief-companies-transporting-hand-sanitizer-highway. These regulations include classification, packaging, marking, labeling and other requirements relevant to transportation.

Scope

FDA clarifies that the Hand Sanitizer Guidance does not apply to surgical hand rubs and patient antiseptic skin preparations. It does apply to sanitizers for use by consumers and for use as healthcare personnel hand rubs.

Data on Adverse Event Reports

Finally, FDA adds details on the adverse event reports that led the agency to take the position the ethanol must be denatured. The guidance now includes data on poison Control calls related to consumption of alcohol-based hand sanitizers. Specifically, data provided by the American Association of Poison Control Centers (AAPCC) indicated that in March 2020, calls to Poison Control centers related to hand sanitizer increased by 79% compared to March of 2019.

FDA Guidance Document #2: Manufacture of Alcohol (Ethanol) for Incorporation in Alcohol-Based Hand Sanitizer Products ("Alcohol Guidance")

Conforming Changes

The Alcohol Guidance incorporates the updates made to the Hand Sanitizer Guidance summarized above on:

- fuel grade ethanol;
- technical and ACS-grade ingredients;
- the use of technical-grade IPA; and
- data on adverse event reports.

Acetone as a Potential Denaturant

The Alcohol Guidance issued March 27 noted that FDA was evaluating acetone as a potential allowable denaturant. FDA deleted this note in the updated document, indicating the agency appears to have concluded acetone should not be used as a denaturant.

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We will continue to monitor this rapidly developing situation. If you need assistance, please don't hesitate to contact us.