

Contains Nonbinding Recommendations

Policy for Testing of Alcohol (Ethanol) and Isopropyl Alcohol for Methanol, Including During the Public Health Emergency (COVID-19)

Guidance for Industry

January 2021

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)**

Current Good Manufacturing Practice (CGMP)

Preface

Public Comment

This guidance is being issued to address the Coronavirus Disease 2019 (COVID-19) public health emergency. This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or the Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to <https://www.regulations.gov>. All comments should be identified with the docket number FDA-2020-D-2016 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA webpage titled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders," *available at* <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders>, and the FDA Webpage titled "Hand Sanitizers | COVID-19" *available at* <https://www.fda.gov/drugs/coronavirus-covid-19-drugs/hand-sanitizers-covid-19>, and the FDA webpage titled "Search for FDA Guidance Documents," *available at* <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>. You may also send an e-mail request to druginfo@fda.hhs.gov to receive an additional copy of the guidance. Please include the document number FDA-2020-D-2016 and complete title of the guidance in the request.

Questions

For questions regarding ethanol or isopropyl alcohol for use in hand sanitizer products, contact FDA at COVID-19-Hand-Sanitizers@fda.hhs.gov. For other questions regarding this document contact the applicable Center at: CDER (Email: CDER-OPQ-Inquiries@fda.hhs.gov), CBER (Email: ocod@fda.hhs.gov), or CVM (Email: AskCVM@fda.hhs.gov).

Contains Nonbinding Recommendations

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	BACKGROUND.....	3
III.	POLICY ON TESTING FOR METHANOL	6

**Policy for Testing of Alcohol (Ethanol) and Isopropyl Alcohol for Methanol,
Including During the Public Health Emergency
(COVID-19)
Guidance for Industry¹**

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The Food and Drug Administration (FDA or Agency) plays a critical role in protecting the United States from emerging infectious diseases, such as the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support continuity and response efforts to this pandemic.

This guidance is intended to alert pharmaceutical manufacturers² and pharmacists in State-licensed pharmacies or Federal facilities who engage in drug compounding³ to the potential public health hazard of alcohol (ethyl alcohol or ethanol) or isopropyl alcohol contaminated with or substituted with methanol. FDA is aware of reports of fatal methanol poisoning of consumers who ingested alcohol-based hand sanitizers that were manufactured with methanol or methanol-contaminated ethanol.⁴ FDA has also received numerous reports of dermal toxicity associated with such products.

¹ This guidance was developed by the Center for Drug Evaluation and Research (CDER), Food and Drug Administration, in cooperation with the Center for Biologics Evaluation and Research and the Center for Veterinary Medicine.

² For the purposes of this guidance, references to “manufacturers” include registered outsourcing facilities because outsourcing facilities are subject to current good manufacturing practice (CGMP) requirements. See section 503B(a) of the Federal, Food, Drug, and Cosmetic Act (FD&C Act); see also draft guidance for industry *Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act*. When finalized, this guidance will represent the FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>. References to “manufacturers” also include repackers, relabellers, and suppliers of alcohol.

³ See section 503A of the FD&C Act.

⁴ Yip L, Bixler D, Brooks DE, et al. Serious Adverse Health Events, Including Death, Associated with Ingesting Alcohol-Based Hand Sanitizers Containing Methanol — Arizona and New Mexico, May–June 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1070–1073. DOI: [http://dx.doi.org/10.15585/mmwr.mm6932e1external icon](http://dx.doi.org/10.15585/mmwr.mm6932e1external%20icon).

Contains Nonbinding Recommendations

FDA also is concerned that other drug products containing ethanol or isopropyl alcohol (pharmaceutical alcohol⁵), which are widely used active ingredients in a variety of drug products, could be similarly vulnerable to methanol contamination. For example, certain inhalation products, mouthwashes, cough and cold products, and many topical drug products include pharmaceutical alcohol. As the COVID-19 pandemic has increased the demand for hand sanitizer products, the demand for pharmaceutical alcohol as the active ingredient of those products has also increased. In the past, increased stress on supply chains has made ingredients more vulnerable to economically motivated adulteration.

For these reasons, the policy outlined in this guidance applies to pharmaceutical alcohol used as an active or inactive ingredient in a drug regardless of whether the drug product is a hand sanitizer. This policy will help pharmaceutical manufacturers and pharmacists who engage in drug compounding avoid using pharmaceutical alcohol contaminated with or substituted with methanol in drug products.⁶

The Agency is issuing this guidance to communicate its policy for the duration of the public health emergency declared by the Secretary of Health and Human Services (HHS) on January 31, 2020,⁴ including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Service Act (PHS Act) (42 U.S.C. 247d(a)(2)). At such time when the public health emergency is over, as declared by the Secretary, FDA intends to reassess this guidance. FDA is continually assessing the needs and circumstances related to this policy, and as relevant needs and circumstances evolve, FDA intends to update or modify this policy as appropriate. Therefore, within 60 days following the termination of the public health emergency, FDA intends to revise and replace this guidance with any appropriate changes based on comments received on this guidance and the Agency's experience with implementation.

Given this public health emergency, and as discussed in the Notice in the *Federal Register* of March 25, 2020 (85 FR 16949), titled "Process for Making Available Guidance Documents Related to Coronavirus Disease 2019," available at <https://www.govinfo.gov/content/pkg/FR-2020-03-25/pdf/2020-06222.pdf>, this guidance is being implemented without prior public comment because the FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C)(i) of the FD&C Act (21 U.S.C. 371(h)(1)(C)(i)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless

⁵ For the purposes of this guidance, we use the term *pharmaceutical alcohol* to mean either ethanol (ethyl alcohol) or isopropyl alcohol (2-propanol). Both are used as an active ingredient in alcohol-based hand sanitizers and may be used in other drug products as an active or inactive ingredient.

⁶ In this guidance, "drug" and "drug product" include both human and animal drugs and biological products.

Contains Nonbinding Recommendations

specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named “SARS-CoV-2”, and the disease it causes has been named “Coronavirus Disease 2019” (COVID-19). On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.⁷ In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.⁸

Hand hygiene is an important part of the response to COVID-19. Washing hands often with soap and water for at least 20 seconds is essential, especially after going to the bathroom, before eating, and after coughing, sneezing, or blowing one’s nose. If soap and water are not readily available, the Centers for Disease Control and Prevention (CDC) recommends consumers use an alcohol-based hand sanitizer that contains at least 60 percent alcohol.⁹ In response to the demand for alcohol-based hand sanitizers, FDA issued guidance to communicate its policies for the temporary manufacture or compounding of alcohol-based hand sanitizer products and ethanol for use in alcohol-based hand sanitizer by some companies and pharmacies during the public health emergency posed by COVID-19 (temporary policies).¹⁰

Since the beginning of the public health emergency, FDA observed an increase in reports of serious adverse events (including some associated or reported deaths) related to ingestion (both unintentional and intentional) of alcohol-based hand sanitizers. FDA also received numerous reports of dermal toxicity associated with such products. In the spring of 2020, FDA began finding numerous hand sanitizer products that were labeled to contain ethanol but tested positive for methanol contamination and drinking some of these hand sanitizer products resulted in serious adverse events consistent with methanol poisoning. In some instances, manufacturers of hand sanitizers labeled their product as containing methanol, even though methanol is not a suitable ingredient for drugs.¹¹ At the same time, methanol

⁷ Secretary of Health and Human Services Alex M. Azar II, Determination that a Public Health Emergency Exists. (originally issued January 31, 2020, and subsequently renewed), *available at* <https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>.

⁸ Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (March 13, 2020), *available at* <https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/>.

⁹ See <https://www.cdc.gov/handwashing/hand-sanitizer-use.html>.

¹⁰ See [Temporary Policy for Preparation of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency \(COVID-19\) Guidance for Industry; Policy for Temporary Compounding of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency](#); and [Temporary Policy for Manufacture of Alcohol for Incorporation Into Alcohol-Based Hand Sanitizer Products During the Public Health Emergency \(COVID-19\)](#).

¹¹ Methanol is not an acceptable ingredient in any drug product and should not be used due to its toxic effects (*infra* p. 5). See, e.g., 21 CFR 330.1(e) (requiring that inactive ingredients in OTC monograph drug products be safe and suitable); see also Centers for Disease Control and Prevention (CDC), National Institute for Occupational Safety and Health (NIOSH) website for methanol https://www.cdc.gov/niosh/ershdb/emergencyresponsecard_29750029.html.

Contains Nonbinding Recommendations

was detected in hand sanitizer drug products from multiple manufacturers through the screening and sampling of hand sanitizers being imported into the United States.¹²

FDA's ongoing investigation into methanol substitution and/or contamination cases has thus far revealed:

- Multiple manufacturers, while manufacturing hand sanitizer products, were neither complying with drug current good manufacturing practice (CGMP) requirements under section 501(a)(2)(B) of the FD&C Act,¹³ nor manufacturing their products in a manner consistent with FDA's temporary policies.
- The manufacturers of the hand sanitizers in which the ethanol was substituted with methanol or was contaminated with methanol did not perform any testing or performed inadequate testing¹⁴ on the ethanol component, including tests to verify the purity of the ethanol lots received and to quantify the amount of methanol present.
- Many of the manufacturers of the hand sanitizers failed to adequately test each incoming component lot for identity,¹⁵ as well as to properly evaluate identity testing data.
- When testing was performed by some firms on incoming lots of the ethanol active pharmaceutical ingredient (API), the test was inadequate to detect that substituted methanol (i.e., methanol at levels exceeding allowable limits)¹⁶ was present.
- Many of the manufacturers of the hand sanitizers in which the ethanol was substituted with methanol or contaminated with methanol relied on the certificate of analysis (COA) provided by the ethanol supplier, or a test result sheet provided by the supplier, without adequately validating the supplier's COA.¹⁷

¹² See <https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-methanol>.

¹³ Manufacturers of drugs, as defined in section 201(g) of the FD&C Act, must comply with drug CGMP requirements in section 501(a)(2)(B) of the FD&C Act and, for finished drug products, the regulations at 21 CFR Parts 210 and 211 as well.

¹⁴ To comply with CGMP regulations, each component of a drug product shall be tested for conformity with all appropriate written specifications for purity strength, and quality, unless the certificates of analysis provided by suppliers have been appropriately validated. See 21 CFR 211.84(d)(2).

¹⁵ To comply with CGMP regulations, identity testing must be conducted to verify each component of a drug product. See 21 CFR 211.84(d)(1). Under that provision, specific identity tests, if they exist, must be used. Identity testing confirms that the component is what it is labeled to be. A component's identity can be described as its chemical structure and its physical form (e.g., polymorph, solvate, and appearance) including, if appropriate, its stereochemistry or immunochemistry. See FDA Guidance for Industry, "Questions and Answers on Current Good Manufacturing Practices—Control of Components and Drug Product Containers and Closures," at <https://www.fda.gov/drugs/guidances-drugs/questions-and-answers-current-good-manufacturing-practices-control-components-and-drug-product>. In addition, a drug with a name recognized in the United States Pharmacopeia-National Formulary (USP-NF) must comply with compendial identity standards or be deemed adulterated, misbranded, or both. (See section 501(b) and 502(e)(3)(B) and (g) of the FD&C Act; see also 21 CFR 299.5(a) and (b).) In such cases, the identity is determined by the official tests, procedures and acceptance criteria in the applicable USP-NF monograph. See USP-NF General Notices 2.30.

¹⁶ See 21 CFR 211.160; see also footnote 19.

¹⁷ See 21 CFR 211.84(d)(2). Each component of a drug product shall be tested for conformity with all appropriate written specifications for purity, strength, and quality, unless the COAs provided by suppliers have been

Contains Nonbinding Recommendations

- The origin of the ethanol used in their products is not readily apparent to many firms manufacturing hand sanitizer. When queried about how they had qualified ethanol suppliers used in the manufacture of contaminated hand sanitizer, many hand sanitizer manufacturers could not identify the true source of the alcohol used in their hand sanitizer production.¹⁸
- Ethanol contaminated or substituted with methanol was seen in hand sanitizers imported into the United States from multiple countries. FDA is also aware of reports of methanol substitution in hand sanitizer distributed in several countries outside the U.S.

As a result of these various practices, methanol-contaminated ethanol and hand sanitizer products contaminated or substituted with methanol have entered the pharmaceutical supply chain. FDA is concerned that other drug products containing pharmaceutical alcohol could be similarly vulnerable to methanol contamination, including drugs in oral dosage form presentations. For these reasons, the policy outlined in this guidance applies to pharmaceutical alcohol used as an active or inactive ingredient of a drug regardless of whether the drug product is a hand sanitizer.

Methanol is not an acceptable ingredient in any drug product and should not be used because of its toxic effects. When methanol is present as an impurity in a component of a drug that is recognized in an official compendium, it must be below acceptable maximum levels set forth in the official compendium (e.g., in a United States Pharmacopeia monograph) in order for the drug to meet applicable quality standards and specifications.¹⁹ Skin exposure to methanol can cause dermatitis, as well as transdermal absorption with systemic toxicity. Substantial methanol exposure can result in nausea, vomiting, headache, blurred vision, permanent blindness, seizures, coma, permanent damage to the nervous system, or death.

appropriately validated.

¹⁸ In previous instances of contamination for other drug products (e.g., diethylene glycol in glycerin), a similar pattern was observed. The COA for glycerin obtained by the pharmaceutical manufacturers was often a copy of a COA on the letterhead of the distributor and not the COA provided by the manufacturer of the glycerin. The chain of custody or distribution history of the glycerin was also not readily known because the glycerin may have been sold several times between its manufacture and its use in medicinal syrup or other drug product. See FDA's guidance for industry, *Testing of Glycerin for Diethylene Glycol*, at <https://www.fda.gov/media/71029/download>.
¹⁹ See section 501(b) of the FD&C Act. The United States Pharmacopeia (USP) is an official compendium and its monographs establish identity testing for drugs listed therein in addition to tests and methods for strength, quality, and purity for those products. See FD&C Act sections 201(g)(1), (j) and 501(b). To meet the requirements of the USP Alcohol Monograph, alcohol (ethyl alcohol) for use in an application product (i.e., a new drug application (NDA), abbreviated new drug application (ANDA), biologics license application (BLA), new animal drug application (NADA), abbreviated new animal drug application (ANADA)) or a product marketed in conformity with an OTC drug monograph, must contain no more than 200 parts per million (ppm) of methanol. We recommend that isopropyl alcohol for use in such products meet the same 200 ppm limit for methanol.

For hand sanitizer products manufactured or prepared in accordance with the temporary policies, we are providing short-term flexibility during the COVID-19 public health emergency with respect to certain impurities, including methanol. See footnote 10. Based on our review of available data, we have determined that an interim impurity level of 630 ppm for methanol can be tolerated in alcohol-based hand sanitizers for a relatively short period of time, given the emphasis on hand hygiene during the COVID-19 public health emergency and to avoid exacerbating access issues for alcohol-based hand sanitizer.

Contains Nonbinding Recommendations

Although all persons using drugs contaminated with methanol via any route are at risk of methanol toxicity, oral or systemic administration of methanol may lead to death. We are aware of reports of young children who unintentionally ingest hand sanitizers and adolescents and adults who drink these products as an ethanol substitute.^{20,21} Where the pharmaceutical alcohol in hand sanitizers is contaminated or substituted with methanol, people who have ingested the hand sanitizer are most at risk for serious methanol poisoning.

III. POLICY ON TESTING FOR METHANOL

Because of the serious hazards associated with methanol, in order to prevent pharmaceutical alcohol used in drug products from being contaminated or substituted with methanol, it is critical that all pharmaceutical manufacturers, as well as pharmacists who engage in drug compounding using pharmaceutical alcohol, are aware of the importance of properly testing pharmaceutical alcohol to detect methanol contamination or substitution.

Drug Products, Generally

Manufacturers of drugs are subject to CGMP requirements pursuant to section 501(a)(2)(B) of the FD&C Act and, for finished drug products, the regulations at 21 CFR Parts 210 and 211 as well. These products include those marketed under a new drug application or abbreviated new drug application, products marketed in conformity with an over-the-counter (OTC) drug monograph²², products manufactured by outsourcing facilities,²³ and others. Compliance with drug CGMP requirements includes certain analytical testing procedures that must be performed on all lots of pharmaceutical alcohol prior to use in drug manufacturing.²⁴ As described below, manufacturers of drug products that include pharmaceutical alcohol must perform a specific identity test that includes a limit test for methanol, on each container within each shipment of each lot of pharmaceutical alcohol before the component is used in the manufacture or

²⁰ McCulley L, Cheng C, Mentari E, et al. Alcohol-based hand sanitizer exposure and effects on young children in the U.S. during the COVID-19 pandemic. *Clin Toxicol* 2020. doi: <https://doi.org/10.1080/15563650.2020.1811298>

²¹ Santos C, Kieszak S, Wang A, et al. Reported adverse health effects in children from ingestion of alcohol-based hand sanitizers—United States, 2011-2014. *MMWR* 2017; 66:223-6. Doi:

²² Certain nonprescription drug products (commonly referred to as “OTC drugs”) can be legally marketed without review and approval of a product-specific premarket application under section 505 of the FD&C Act if they satisfy applicable requirements under section 505G of the FD&C Act. The requirements in section 505G for marketing OTC monograph drugs include conformity with applicable conditions of nonprescription use for the drug or class of drug, such as specified active ingredients and dosage strengths. Such drugs also must meet the general requirements for nonprescription drugs, which include requirements that these drugs contain only safe and suitable inactive ingredients and be manufactured according to CGMP. See, e.g., 21 CFR 330.1(a).

²³ See draft guidance for industry *Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act*, available at <https://www.fda.gov/media/88905/download>.

²⁴ See 21 CFR 211.84(d).

Contains Nonbinding Recommendations

preparation of drug products.^{25,26}

The United States Pharmacopeia (USP) monograph for Alcohol (ethyl alcohol or ethanol) establishes a limit for methanol in alcohol of 200 ppm. Any ethanol found to contain more than 200 ppm methanol therefore is considered adulterated under section 501(b) of the FD&C Act because its quality or purity falls below the standards prescribed in the USP.

On July 30, 2020, FDA sent a request to the USP to include a test for methanol in the “Identification” section of the Alcohol, Isopropyl Alcohol and any related USP/National Formulary (NF) monographs to help prevent methanol contamination.²⁷ On July 31, 2020, the USP posted a “Notice of Intent to Revise the Alcohol and Dehydrated Alcohol Monographs” to include the test for Limit of Methanol as an additional Identification C test.²⁸ On September 1, 2020, the revised Alcohol Monograph and Dehydrated Alcohol Monograph became official. Therefore, manufacturers of products in which alcohol (ethyl alcohol) is used as an ingredient must test the alcohol ingredient using the limit test for methanol that appears in the Identification section of the USP Alcohol Monograph.²⁹ As a result, use of any identity test conducted for ethanol (ethyl alcohol) pursuant to 21 CFR 211.84 that does not contain a limit test for methanol using the USP method may be considered a violation under 501(a)(2)(B) and/or 501(b) of the FD&C Act.

The USP test method for methanol described in the Alcohol Monograph can also be used to test for methanol contamination in isopropyl alcohol. While USP has not yet updated the Isopropyl Alcohol Monograph to include a specific methanol limit, FDA considers the 200 ppm methanol limit for ethanol to also be suitable for isopropyl alcohol, and may consider any isopropyl alcohol with more than 200 ppm methanol to be adulterated under section 501 of the FD&C Act. Alternatively, a manufacturer may use an equivalent identification procedure that includes a test to detect and quantify methanol, provided it is validated and fit for such purpose.³⁰

²⁵ The CGMP regulations at 21 CFR 211.84(d) require that each lot of a component undergo testing to confirm its identity before use in drug product manufacturing. A specific identity test must be used. In addition, a drug with a name recognized in USP–NF, such as alcohol, must comply with compendial identity standards or be deemed adulterated, misbranded, or both. (See section 501(b) and 502(e)(3)(B) and (g) of the FD&C Act; see also 21 CFR 299.5(a) and (b)). In such cases, the identity is determined by the official tests, procedures and acceptance criteria in the applicable USP–NF monograph. See USP–NF General Notices 2.30.

²⁶ 21 CFR 211.84(b) requires that a representative sample of each shipment of each lot be collected for testing and states that the number of containers to be sampled shall be based upon appropriate criteria. Alternatively, knowledge of shipping controls can help in the determination of a representative sample. See, for example, section XVII (17) of FDA’s guidance for industry *Q7A Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* (Q7A). We update guidances periodically. To make sure you have the most recent version of a guidance, check our web site at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

²⁷ See https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/usp-nf-notices/fda-letter-alcohols-nitr-att.pdf.

²⁸ See <https://www.uspnf.com/notices/methanol-testing-nitr-20200731>.

²⁹ A drug with a name recognized in USP–NF must comply with compendial identity standards or be deemed adulterated, misbranded, or both. (See section 501(b) and 502(e)(3)(B) and (g) of the FD&C Act; see also 21 CFR 299.5(a) and (b)). In such cases, the identity is determined by the official tests, procedures and acceptance criteria in the applicable USP–NF monograph. See USP–NF General Notices 2.30.

³⁰ See 21 CFR 211.84(d); 21 CFR 211.194.

Contains Nonbinding Recommendations

Additional Considerations

- Drug product manufacturers are responsible for knowing the entities in their supply chain for pharmaceutical alcohol (i.e., knowing the identities and appropriately qualifying the manufacturer of the pharmaceutical alcohol and any subsequent distributor(s)).³¹
- Manufacturers must establish finished product test methods adequate to ensure that when testing for ethanol or isopropyl alcohol content (assay), the method also distinguishes between the active ingredient and methanol.³² CGMP requires assay testing to be conducted on all batches of finished drug products prior to release/distribution decision per 21 CFR 211.165.
- All personnel in pharmaceutical manufacturing facilities (especially personnel directly responsible for receipt, testing, and release of pharmaceutical alcohol) should be made aware of the importance of proper testing and the potential hazards if the testing is not done.
- Repackers and others who distribute and prepare ethanol or isopropyl alcohol API for use in drug products should test pharmaceutical alcohol that are used, sold for use, or intended for use in drug products.
- Bulk or repackaged ethanol or isopropyl alcohol intended as an excipient or other component of a drug product is a drug as defined by section 201(g)(1) the FD&C Act (21 U.S.C. 321(g)(1)). Section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) requires that the methods used in, or the facilities or controls used for, a drug's manufacture, processing, packing, or holding conform to CGMP. Testing bulk or repackaged ethanol or isopropyl alcohol for methanol content is consistent with CGMP required under the FD&C Act.

Compounded Drug Products, Generally

A drug product compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility consistent with the conditions in section 503A of the FD&C Act, or in an outsourcing facility consistent with section 503B of the FD&C Act,³³ can qualify for certain exemptions from the Act.³⁴ These conditions include that bulk drug substances used in

³¹ See section 501 of the FD&C Act, which states, "For purposes of paragraph (a)(2)(B), the term 'current good manufacturing practice' includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products."

³² See 21 CFR 211.160(b) and FDA's guidance for industry, "Analytical Procedures and Methods Validation for Drugs and Biologics," available at <https://www.fda.gov/media/87801/download>.

³³ Physicians compounding pursuant to 503A of the FD&C Act are also required to comply with the requirements of that section in order for the compounded drug products to qualify for the exemptions set forth therein.

³⁴ See sections 503A(a) and 503B(a) of the FD&C Act. For hand sanitizer products compounded during the COVID-19 public health emergency, FDA's guidance for industry entitled [Policy for Temporary Compounding of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency](#) states that the Agency does

Contains Nonbinding Recommendations

compounding comply with the standards of an applicable USP or NF monograph, if a monograph exists, and the USP chapter on pharmacy compounding.³⁵ Similarly, ingredients other than bulk drug substances must also comply with the standards of an applicable USP or NF monograph, if a monograph exists, and the USP chapter on pharmacy compounding.³⁶

As discussed above, the USP monograph for Alcohol (ethyl alcohol or ethanol) establishes a limit for methanol of 200 ppm. Thus, compounded drug products containing ethanol with more than 200 ppm methanol may be considered adulterated under section 501(b) of the FD&C Act and would not qualify for the relevant exemptions in section 503A(a) or 503B(a) because they do not comply with the standards in the applicable USP monograph. Pharmacists in State-licensed pharmacies, Federal facilities, or outsourcing facilities that compound products using ethanol must test the ethanol for methanol content using the test method that appears in the Identification section of the USP Alcohol Monograph or, in the case of State-licensed pharmacies and Federal facilities, ensure that such testing was properly done by a reliable supplier.³⁷ FDA recommends that the USP test method for methanol described in the Alcohol Monograph also be used to test for methanol contamination in isopropyl alcohol.

Hand Sanitizer Drug Products Marketed Consistent with FDA's Temporary Policies

In response to the demand for alcohol-based hand sanitizers during the COVID-19 public health emergency, FDA issued temporary policies for the manufacture of alcohol-based hand sanitizer products and ethanol for use in alcohol-based hand sanitizer. The temporary policies explain that FDA does not intend to take action against firms with respect to certain violations of the FD&C Act, including section 501(a)(2)(B), provided that certain conditions are present.³⁸ Use of pharmaceutical alcohol procured from another source, rather than manufactured in-house by the firm, is consistent with those policies if the firm tests, or has tested, each lot of the pharmaceutical alcohol for methanol content prior to use. For both ethanol and isopropyl alcohol, FDA recommends the test methods described in the USP Alcohol Monograph. FDA strongly recommends the test for methanol be conducted in a laboratory that has been previously inspected by FDA and found in compliance with CGMP. All personnel involved in production of hand sanitizer products (especially personnel directly responsible for receipt, testing, and release of pharmaceutical alcohol) should be made aware of the importance of proper testing and the potential hazards if the testing is not done.

not intend to take action against compounders compounding these products provided that the circumstances described in the guidance are present. Specifically, for the duration of the public health emergency, FDA does not intend to take action against pharmacists in State-licensed pharmacies or Federal facilities for violations of sections 501(a)(2)(B), 502(f)(1), and 505 of the FD&C Act, or against outsourcing facilities for violations of sections 502(f)(1), 505, or 582 of the FD&C Act.

³⁵ See sections 503A(b)(1)(A)(I) and 503B(a)(2)(B) of the FD&C Act.

³⁶ See sections 503A(b)(1)(B) and 503B(a)(3) of the FD&C Act.

³⁷ See supra note 30.

³⁸ See [Temporary Policy for Preparation of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency \(COVID-19\); Guidance for Industry; Temporary Policy for Manufacture of Alcohol for Incorporation Into Alcohol-Based Hand Sanitizer Products During the Public Health Emergency \(COVID-19\); Policy for Temporary Compounding of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency.](#)

Contains Nonbinding Recommendations

For these products, any pharmaceutical alcohol that contains more than 630 ppm methanol is not consistent with FDA's temporary policies and may be considered evidence of substitution and/or contamination. Hand sanitizers containing methanol-contaminated ethanol or isopropyl alcohol may be considered adulterated under sections 501(a)(2)(A), 501(a)(2)(B), and/or 501(d) of the FD&C Act.