Hand Sanitizers and Updates on Methanol Testing

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USP Global Seminar Series:
Ensuring Quality Hand Sanitizer Production During Covid-19 for Manufacturers

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Outline

● What OMQ Does

● General Background on Hand Sanitizer

● Recent Safety Concerns and FDA Actions

● Substitution

● Methanol Testing Requirements for Drug Product Manufacturers
Office of Manufacturing Quality

What We Do
CDER/OC Mission

To shield patients from poor-quality, unsafe, and ineffective drugs through proactive compliance strategies and *risk-based* enforcement action.
What OMQ Does

• We evaluate compliance with **Current Good Manufacturing Practice (CGMP)** for drugs based on inspection reports and evidence gathered by FDA investigators.

• We develop and implement compliance policy and take regulatory actions to protect the public from **adulterated** drugs in the U.S. market.
Drug Adulteration Provisions

U.S. Federal Food, Drug, & Cosmetic Act
- 501(a)(2)(A): Insanitary conditions
- 501(a)(2)(B): Failure to conform with CGMP
- 501(b): Strength, quality, or purity differing from official compendium
- 501(c): Misrepresentation of strength, etc., where drug is unrecognized in compendium
- 501(d): Mixture with or substitution of another substance
- 501(j): Deemed adulterated if owner/operator delays, denies, refuses, or limits inspection
Section 501(a)(2)(B) requires conformity with CGMP

A drug is *adulterated* if the methods, facilities, or controls used in its manufacture, processing, packing, or holding do not conform to CGMP to assure that such drug meets purported characteristics for *safety*, *identity*, *strength*, *quality*, and *purity*.
What is CGMP?

Requirements to help ensure drugs:
• Meet quality specifications, including purity
• Are safe for use
• Have ingredients and strength they claim to have

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Enforcement and Advisory Tools

CY2020 Regulatory Actions

- Regulatory Meetings: 53
- Injunctions
- Consent Decrees
- Import Alerts: 100
- Warning Letters: 70
- Seizures
- Warning Letters
- Untitled Letters
- Administrative Detention

Excludes compounding-related actions
Actions issued January 1, 2020 to December 31, 2020
Trends in CGMP Warning Letters*

Warning Letters Issued after Initial Inspection vs. Reinspection by FY

Warning Letters Issued by Drug Type Manufactured by FY

*Warning Letters Issued 10/1/2015 to 12/31/20
General Background on Hand Sanitizers
Hand Sanitizers

CDC Recommendation for Consumers

“If soap and water are not readily available, use an alcohol-based hand sanitizer that contains at least 60% alcohol, and wash with soap and water as soon as you can.”

CDC website: https://www.cdc.gov/handwashing/hand-sanitizer-use.html

Alcohol being ethanol
Consumer Antiseptic Rub Market

Prior to COVID-19\(^1\)

- Annual dollar sales ~ $190 million
- More than 800 entities
- Most manufacturers small businesses
- Most common active ingredient ethanol (ethyl alcohol)

After COVID-19

- Dramatic increase in demand
- Degree of access problems difficult to quantitate

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\(^1\) Final Regulatory Impact Analysis, Safety and Effectiveness of Consumer Antiseptic Rub Products; Topical Antimicrobial Drug Products for Over-the-Counter Human Use, Docket No. FDA-2016-N-0124 (Apr. 12, 2019).
FDA’s Actions to Address Hand Sanitizer Access Problems

• Issued three guidance documents outlining temporary policies to provide flexibility to help meet demand during the public health emergency

• When the public health emergency is over, FDA intends to discontinue these enforcement discretion policies and withdraw the guidances

• FDA is continually assessing needs and circumstances related to the temporary policy and will update, modify, or withdraw the policy as appropriate
  – Updates issued March 27, April 15, June 1, and August 7
COVID-19 Hand Sanitizer Guidances

• Compounding Guidance
  Policy for Temporary Compounding of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency

• Manufacturing Guidance
  Temporary Policy for Preparation of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19)

• Active Ingredient Guidance
  Temporary Policy for Manufacture of Alcohol for Incorporation Into Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19)
Terms of the Manufacturing Guidance

FDA does not intend to take action against firms that prepare ABHS provided all of the conditions specified in the guidance are met.

1. Uses only specified ingredients
2. Alcohol is denatured using specified formulas
3. Finished product follows WHO formula
4. Firm does not add other active or inactive ingredients
5. Firm ensures active ingredient is correct and uses correct amount (methanol and potency tests)
6. Prepared under sanitary conditions
7. Verifies alcohol content in finished product before each batch is released
8. Dosage form is an aqueous solution (no gel, foam, or aerosol spray)
9. Labeled according to guidance
10. Facility is registered with FDA Drug Registration and Listing
11. Firm has a mechanism to accept adverse event reports

1Temporary Policy for Preparation of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19) Guidance for Industry, March 2020, Updated August 7, 2020
Finished Hand Sanitizer Formulations Under the Manufacturing Guidance

- **Alcohol (ethanol)** formulated to 80% v/v in an aqueous solution
  - Glycerin (glycerol) 1.45% v/v
  - Hydrogen peroxide 0.125% v/v
  - Sterile distilled water or boiled cold water

- **Isopropyl alcohol** formulated to 75% v/v in an aqueous solution
  - Glycerin (glycerol) 1.45% v/v
  - Hydrogen peroxide 0.125% v/v
  - Sterile distilled water or boiled cold water
Impact of Hand Sanitizer Guidances

• Thousands of new firms have registered as manufacturers of alcohol-based hand sanitizers and hand sanitizer active ingredients (ethanol and isopropyl alcohol)

• Some larger hospital systems are now able to source an adequate supply of hand sanitizers and more are available for consumer purchase

• FDA is updating the temporary guidances as needed to provide additional clarification to both increase supply and help ensure that harmful products are not on the market

• FDA appreciates the work of manufacturers, compounders, state boards of pharmacy, and the public to increase the supply of alcohol-based hand sanitizers
Recent Safety Concerns
New and Increasing Safety Issues with Hand Sanitizers

- Accidental ingestion by young children
  - Calls to National Poison Data Center increased 79% in March 2020 compared to March 2019
  - Packaging attractive to children

- Contamination
  - Methanol
  - 1-Propanol

- Subpotent and mislabeled products

See this webpage for a full list of hand sanitizers we urge consumers not to use:
Methanol Serious Adverse Events and Deaths

During May and June, 15 people in Arizona and New Mexico were hospitalized after swallowing hand sanitizer containing methanol.

METHANOL POISONING CAN CAUSE BLINDNESS AND BE FATAL

- Died
- Discharged with vision loss
- Remained hospitalized*
- Discharged with no complications

DO
- Use hand sanitizer containing ethanol or isopropanol for hand hygiene
- Check FDA’s list of hand sanitizers not to use
- Supervise children and keep hand sanitizer out of their reach

DO NOT
- Use hand sanitizer containing methanol
- Swallow any hand sanitizer

*as of July 8

Substitution
Section 501(d) requires drugs not be mixed or substituted with another substance

A drug is *adulterated* if it is a drug and any substance has been (1) mixed or packed therewith so as to reduce its quality or strength or (2) substituted wholly or in part therefor.

And yes, “therefor” is spelled correctly, this version means, “for that”
Isopropyl Alcohol vs 1-Propanol

Isopropyl Alcohol
- Acceptable Active Ingredient for hand sanitizer
- Also known as IPA, or 2-Propanol

1-Propanol
- Not an acceptable Active Ingredient for Hand Sanitizer
- Alcohol (OH) group on different carbon
Ethanol vs Methanol

Ethanol

• Acceptable Active Ingredient for hand sanitizer

Methanol

• Poison
At the Border

From Bottles

To 55 Gallon Drums
At the Border

- To jugs in the back of a truck
Methanol vs Ethanol

- Methanol toxicity concerns exist for **both ingestion and dermal exposure**

- From a recent Warning Letter:
  
  "Methanol is not an acceptable ingredient for hand sanitizers and should not be used due to its toxic effects. 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.** Although all persons using these products on their hands are at risk, young children who accidently ingest these products, and adolescents and adults who drink these products as an alcohol (ethanol) substitute, are most at risk for methanol poisoning.”

Methanol vs Ethanol

• FDA has seen test results showing various levels of methanol substitution

• From a recent WL
  – “FDA laboratory testing of batches of this product detained at the border found that the product contained an average of 39% ethanol and 28% methanol v/v. Additionally, the drug product [redacted], also labeled as manufactured at your facility, is labeled to contain 70% v/v of the active ingredient ethyl alcohol (ethanol). However, FDA laboratory testing of batches of this product detained at the border found that the product contained 0% ethanol and 83% methanol v/v. Therefore, these hand sanitizer drug products are adulterated under section 501(d)(2) of the FD&C Act in that the active ingredient of ethanol was substituted wholly or in part with methanol, a dangerous chemical when in contact with human skin or ingested.”

Substitution and CGMP

• Substitution, particularly with a poison, calls into question the entire quality unit’s ability to oversee drug manufacturing and release

• From a Recent Warning Letter
  – “The substitution and methanol contamination in hand sanitizer drug products manufactured in your facility is evidence that the quality assurance within your facility is not functioning in accordance with CGMP requirements under section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).”

Methanol vs Ethanol

• The pattern we’re seeing looks similar to other substitution cases FDA has encountered historically
  – DEG in Glycerin
  – OSCS in Heparin
• Spike in product demand/supply shortage/price increase
• Murky supply chain
• Substitution likely taking place at API/broker level
• Lacking controls at finished dosage manufacturers lets it slip through
• Then people get hurt
Actions Taken

• FDA has taken multiple actions when encountering substitution
  – Contact with firms about taking market action to limit patient exposure
  – Drugs and drug products manufactured by these firms added to import alert 66-78
  – Warning Letters issued

• Continuing heightened surveillance of hand sanitizers
  – Both imported and domestically produced

• Drugs linked to violative manufacturers are added to a Do Not Use List for consumers
Hand Sanitizer From Mexico

• On January 26, 2021, FDA Placed All Hand Sanitizer made in Mexico on Import Alert
  – [https://www.accessdata.fda.gov/CMS_IA/importalert_1171.html](https://www.accessdata.fda.gov/CMS_IA/importalert_1171.html)
  – Prevents these hand sanitizers from legally entering the United States

• Implemented due to the prevalence of methanol substitution in hand sanitizer manufactured in Mexico
  – 84% of samples were found violative.

• First time FDA has used a Country/Area import alert for drug products
  – More commonly used in foods.
A Note on the Scope of Substitution

• Only about 1% of Hand Sanitizer manufacturers are associated with substitution
• Majority of methanol contaminated Hand Sanitizers were manufactured in Mexico
• However, FDA has also taken an action against a manufacturer in Turkey and in China
• FDA has contacted regulators in other countries, and methanol substitution has been found in other countries as well
But Alcohol is Also Utilized in Other Pharmaceuticals...

• Ethanol and Isopropyl Alcohol are used in many other pharmaceutical formulations:
  – Inhalation Drug Products
  – Mouthwashes
  – Cough and Cold Products
  – Topical Drug Products

• Recently a recall for methanol substitution occurred for rubbing alcohol:
Methanol Testing Requirements for Drug Product Manufacturers
Recent Updates to Hand Sanitizer Guidances

• Temporary guidances, including for Compounding of Hand Sanitizers, updated on August 7, 2020
  – [https://www.fda.gov/media/136118/download](https://www.fda.gov/media/136118/download)

• To fall under the enforcement discretion described in the guidance
  – Hand sanitizer API (ethanol or isopropanol) procured from an outside source is tested for methanol content.
  – Testing is done prior to compounding/manufacturing
  – For OTC manufacturers
  – And for Both 503A pharmacies and 503B Outsourcing Facilities
  – Regardless of what is on the COA
Methanol Testing Exception for Alcohol produced in house for Hand Sanitizers

• Methanol testing is necessary control based on the substitution pattern observed in the alcohol distribution and supply chain.

• However, under the temporary policies, methanol substitution testing is not required for hand sanitizer manufactures who produce their own ethanol, as long as other conditions are met.

• However, this is only for alcohol made in-house by the hand sanitizer manufacturer, if a firm procures ethanol on the market, it must be tested for methanol prior to use in production of hand sanitizer.
Update to the Ethanol Monograph

• On July 30th, FDA sent a letter to the United States Pharmacopeia (USP) requesting an update to the identity section of the Alcohol monographs due to patient risk:

• The monograph was revised, and on 9/1/2020, came into effect:

• The compendial identity test for ethanol now includes a specific test for methanol content
Identity Testing and CGMP

• § 211.84 Testing and approval or rejection of components, drug product containers, and closures.

• § 211.84 (a) Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.

• § 211.84 (d) Samples shall be examined and tested as follows:
  (1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.
Alcohol Identity Testing for Drugs

• Alcohol (Ethanol) is widely used as a component of drugs.

• With the compendial revision, under CGMP, identity testing of incoming lots of ethanol must now include a test for methanol.

• This is commensurate with the patient risk for methanol toxicity.

• On January 19, 2021, FDA provided further Guidance to Industry
Policy for Testing of Alcohol (Ethanol) and Isopropyl Alcohol for Methanol, Including During the Public Health Emergency (COVID-19)

Guidance for Industry

Posted January 19, 2020

https://www.fda.gov/media/145262/download
Methanol Testing Guidance Recommendations

• Drug manufacturers know the actual manufacturer of the alcohol
• Personnel involved in drug manufacturing are made aware of the risks of methanol substitution
• The USP methanol test is suitable for both ethanol and IPA identity testing
• Testing for methanol must be performed as part of identification prior to drug product manufacturing
• Drug repackagers and distributors should also conduct methanol testing
In Summary
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• OMQ works to minimize consumer exposure to unsafe, ineffective, potentially dangerous, or poor quality drugs

• We take actions against firms with poor CGMP or when other information calls into question the quality of drugs for U.S. patients
Questions?