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Manufacturing Alcohol to Combat a Public Health Emergency:

Insights on Regulatory and Quality Requirements

Alcohol Requirements for Hand Sanitizer Production

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USP Open Forum, Manufacturing Alcohol to Combat a Public Health Emergency

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- DISCLAIMER: The views and opinions expressed in this presentation are those of the authors and do not necessarily represent official policy or positions of the Food & Drug Administration

Outline

- What OMQ Does
- General Background on Hand Sanitizer
- Requirements for Alcohol Manufacturing
- Impurity Controls
- 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 **C**urrent **G**ood **M**anufacturing **P**ractice (**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.

Source: FDA

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

CGMP Legal Authority

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?

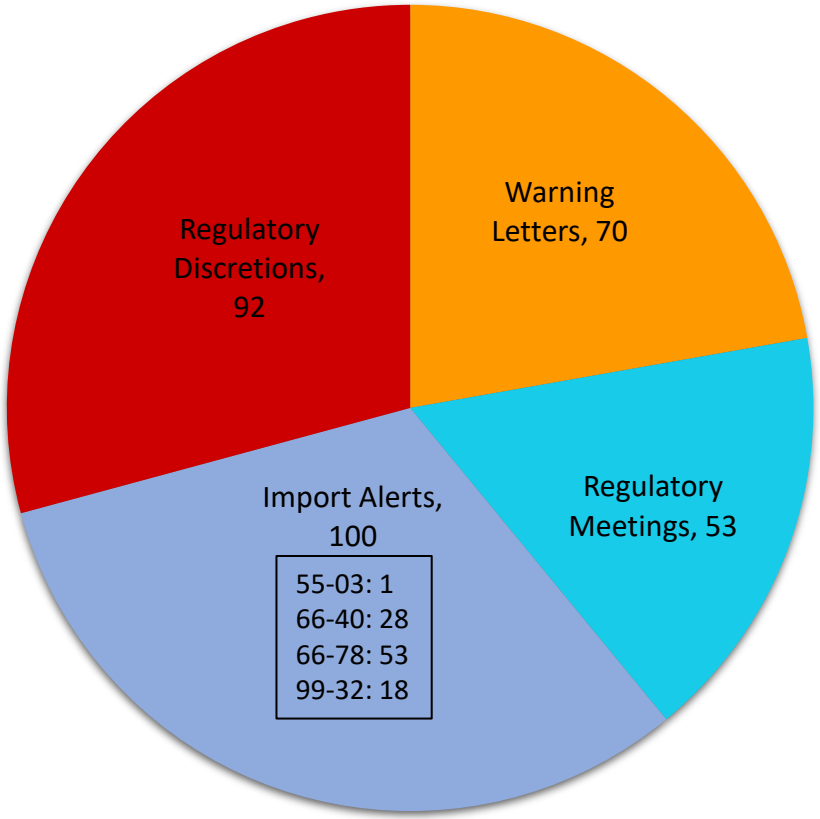
Requirements to help ensure drugs:

- Meet quality specifications, including purity
- Are safe for use
- Have ingredients and strength they claim to have

Enforcement and Advisory Tools

- Regulatory Meetings
- Injunctions
- Consent Decrees
- Import Alerts
- Seizures
- Warning Letters
- Untitled Letters
- Administrative Detention

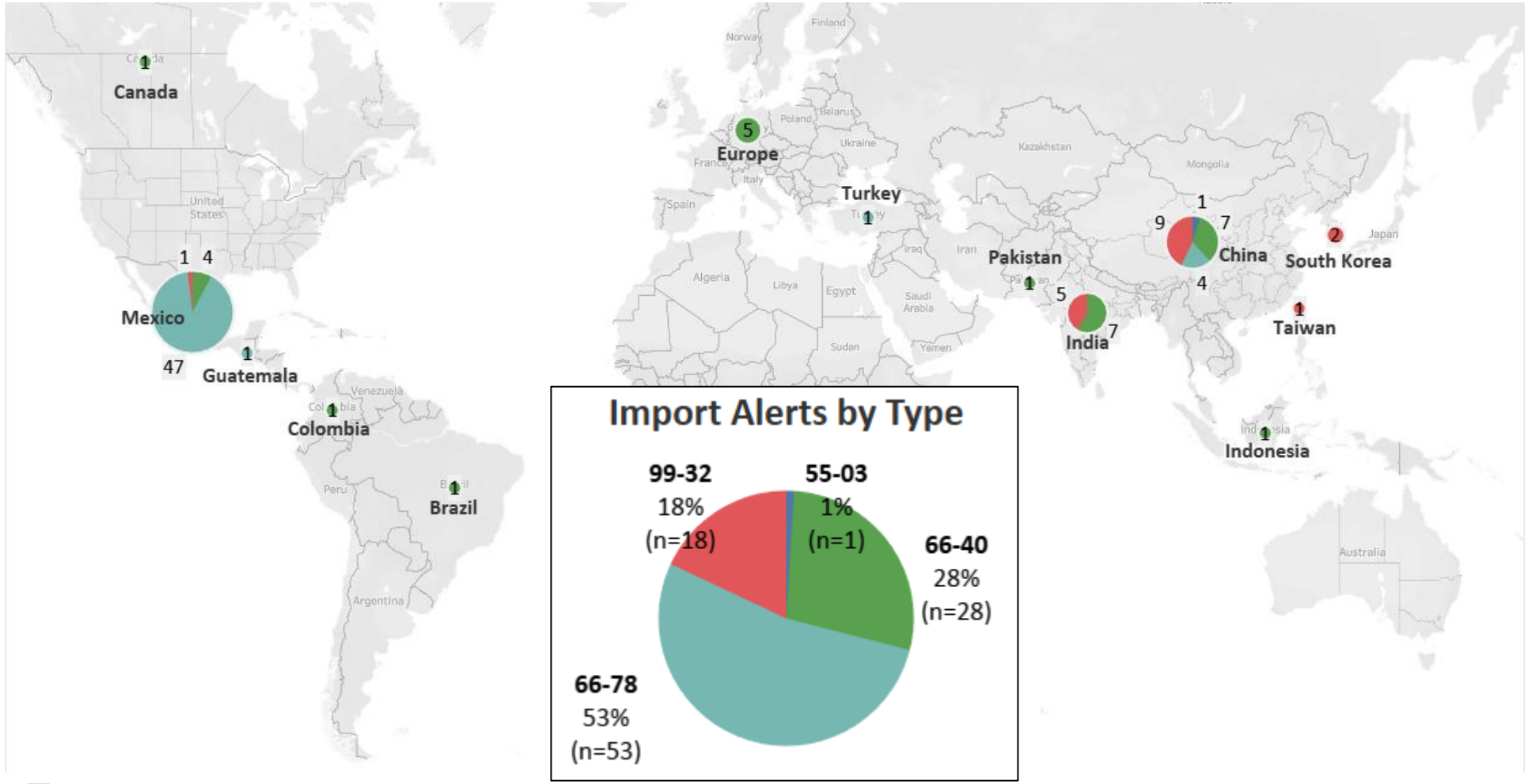
CY2020 Regulatory Actions



Excludes compounding-related actions

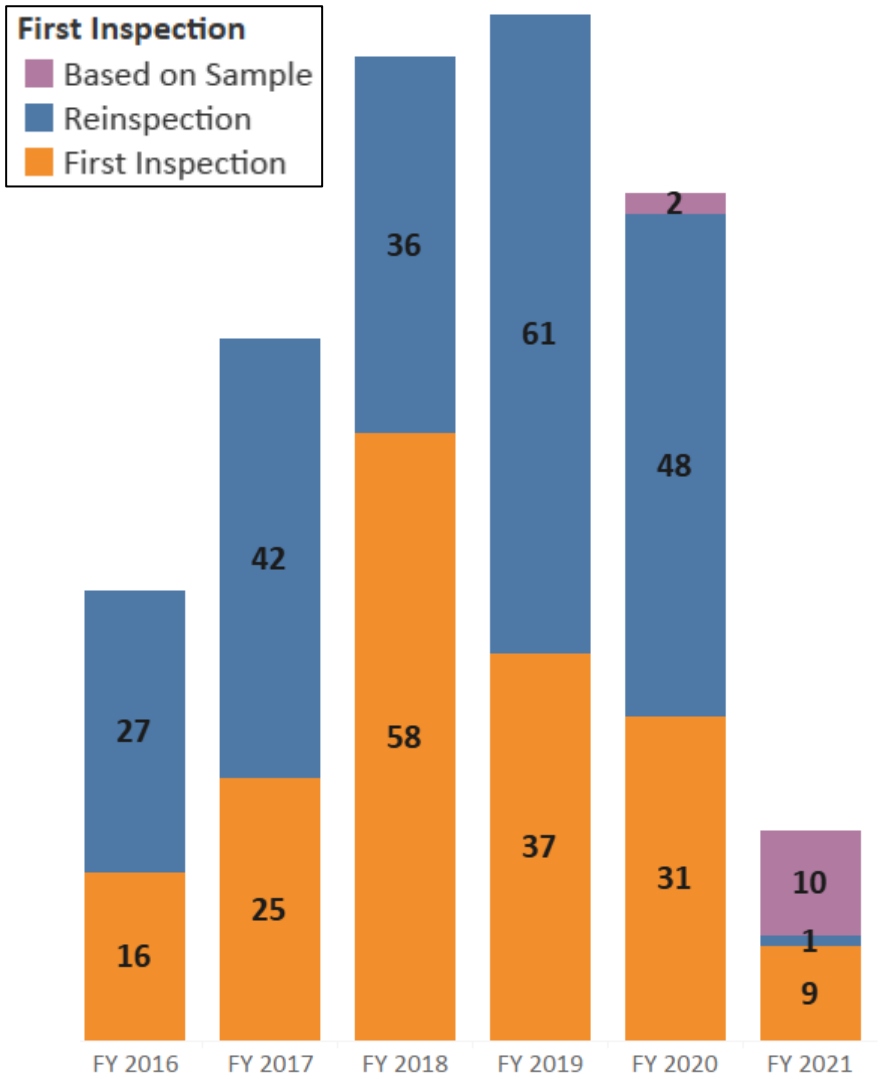
Actions issued January 1, 2020 to December 31, 2020

Import Alerts Cases CY20

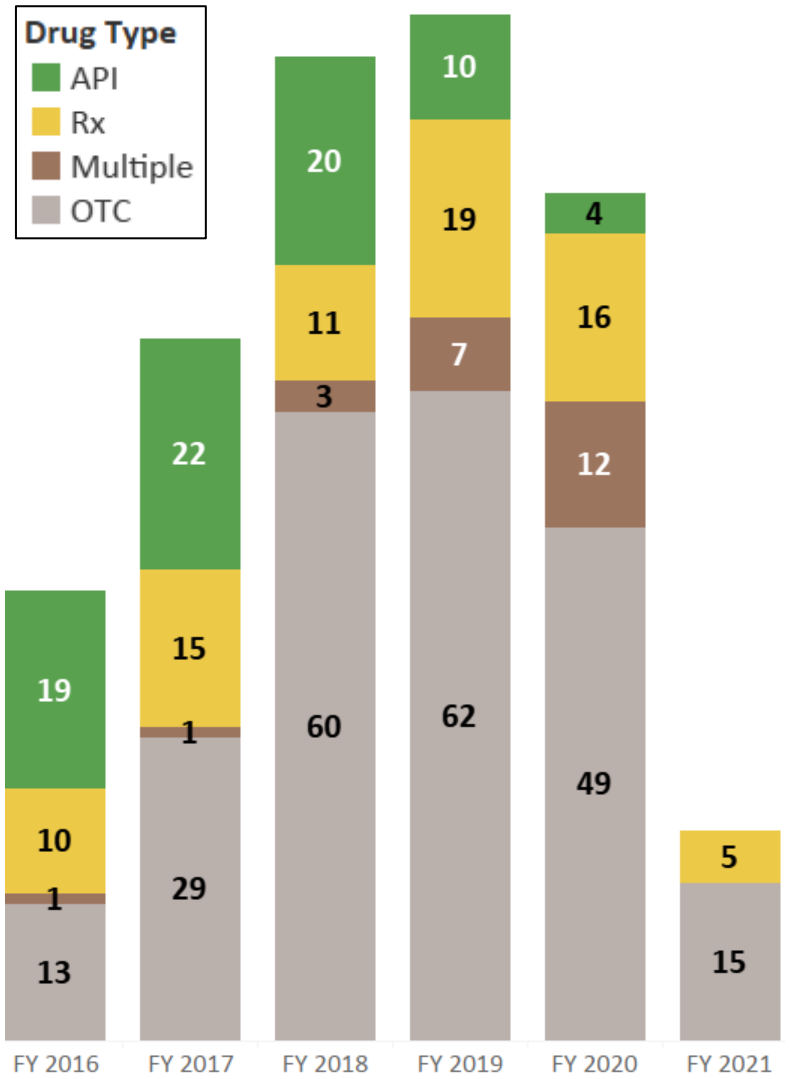


Trends in CGMP Warning Letters*

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

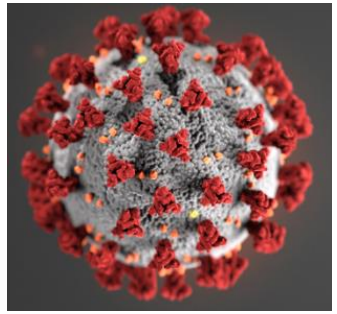
Alcohol being ethanol

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

[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 Guidance's

- 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)

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

Requirements for Alcohol Manufacturing

Temporary Policy for Alcohol Manufacturing for Incorporation into Hand Sanitizers[1]

FDA does not intend to take action against firms that manufacture alcohol for incorporation into Alcohol Based Hand Sanitizer, provided all of the circumstances specified in the guidance are present

1. The concentration of the alcohol is sufficient to enable the finished hand sanitizer to meet 80% concentration
2. Water used to adjust the finished ethanol content is sterile
3. The alcohol meets the interim impurity levels in the guidance
4. Denaturants specified in the guidance are added by the alcohol manufacturer or the hand sanitizer manufacturer
5. Alcohol is prepared under sanitary conditions and equipment used is well maintained and fit for this purpose.
6. The most accurate method of analysis at the site is used to verify ethanol content
7. If the alcohol is distributed, it is labeled consistent with labelling in the guidance
8. Facility is registered with FDA Drug Registration and Listing

[1] Temporary Policy for Manufacture of Alcohol for Incorporation Into Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19) https://www.fda.gov/media/136390/download

Facility/Process Type Considerations

- Prior to the public health emergency, different facilities were manufacturing alcohol for different purposes.

- Thus each type may have different requirements for manufacturing alcohol for hand sanitizers under the temporary policy.

Consumable Alcohol Manufacturer (e.g. distilleries) Requirements

- Alcohol is produced using fermentation and distillation processes typically used for consumable goods
- Must meet the interim impurity limits in the guidance

Alcohol Made Using Synthetic Processes Requirements

- Alcohol may be considered if alcohol meets USP or FCC grades
- FCC grade material should be tested for impurities using methods recommended in the USP, and confirms it meets interim impurity limits in the guidance

Facility/Process Type Considerations

Fuel or Technical Grade Alcohol Facility Requirements

- Alcohol is produced using fermentation and distillation processes typically used for consumable goods.
- No other additives or chemicals have been added.
- The alcohol may be considered if alcohol meets USP or FCC grade, or interim impurity limits in the guidance.
- The alcohol has been screened for any other potential harmful impurities not specified, but potentially present based on the specific manufacturing environment.
    - Note, FDA has seen proposed specification sheets with unacceptable impurities, such as gasoline and benzene (a carcinogen).

Impurity Controls

Interim Levels of Allowable Impurities in Ethanol for Hand Sanitizers

Impurity	Standard Limit	Interim Limit Under the Policy
Methanol	NMT 200 ppm (USP)	NMT 630 ppm
Benzene	NMT 2 ppm	NMT 2 ppm
Acetaldehyde	NMT 10 ppm (Sum of Acetaldehyde and Acetal; expressed as Acetaldehyde)	NMT 50 ppm
Acetal (1,1-diethoxyethane)	See above	NMT 50 ppm
Sum of all other impurities	NMT 300 ppm	NMT 300 ppm

Be Mindful of Vapor Pressures and Boiling Points

Item	Vapor Pressure	Boiling Point at 1 ATM
Methanol	16.9 kPa or 2.45 psi	64.7°C
Benzene	14 kPa or 2.03 psi	80.1°C
Acetaldehyde	120 kPa or 17.4 psi	20.2°C
Acetal (1,1-diethoxyethane)		102.2°C
Ethanol	12.4 kPa or 1.8 psi	78.4°C

Keep on an Eye on Fractions

- Batch/Pot distillation
  - Time based fractions also called foreshot/heads/hearts/tails
  - Higher vapor pressure impurities (Methanol) will be concentrated in the foreshot/heads.
  - Lower vapor pressure impurities will be concentrated in the tails.
- Recycling fractions with higher impurities may lead to excessive levels of impurities in later batches

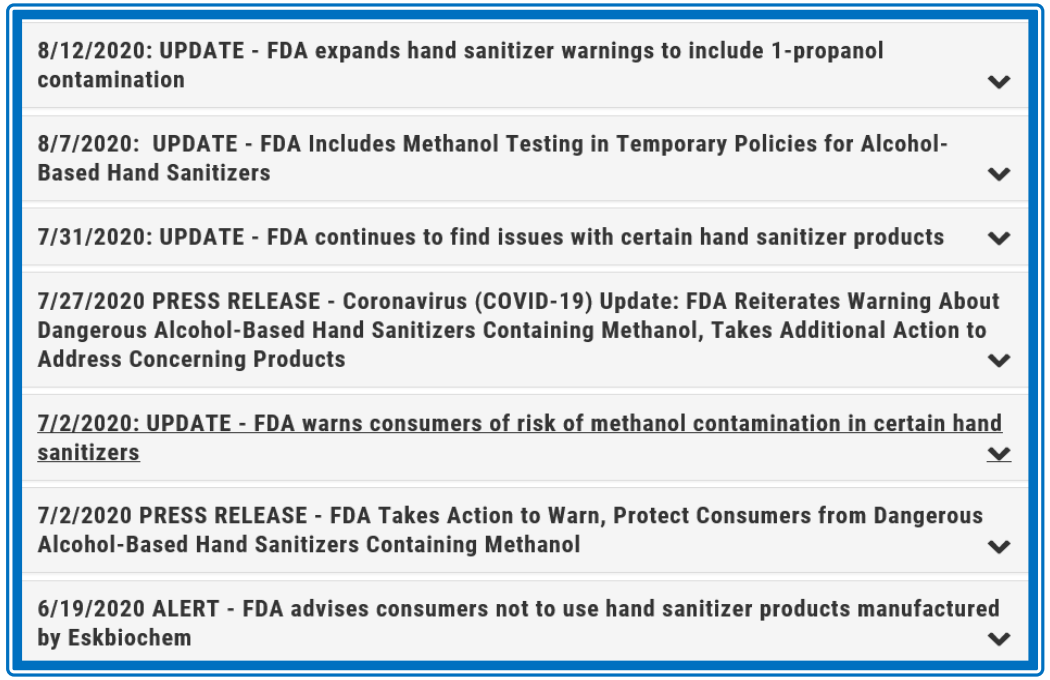
Keep on an Eye on Fractions

- Continuous distillation
  - Same fraction scenarios as with batch distillation
  - Higher vapor pressure impurities in the top fraction
  - Lower vapor pressure impurities in the bottom fraction
- Recycling fractions with higher impurities may lead to excessive levels of impurities

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: https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitzers-methanol

Methanol Serious Adverse Events and Deaths

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

Substitution

No Substitution: Legal Authority

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

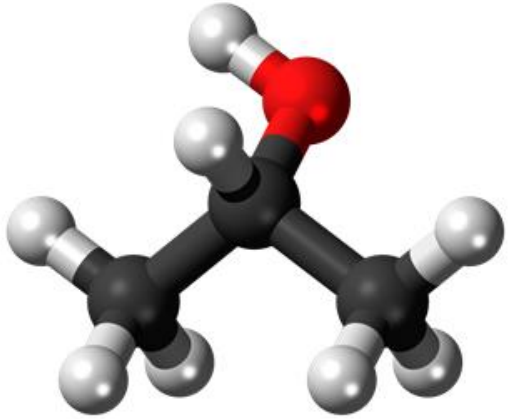
A drug is ***adulterated*** if it is a drug and any substance has been (1) mixed or packed therewith so as to reduce its quality or strength or (2) substituted wholly or in part therefor.

And yes, “therefor” is spelled correctly, this version means, “for that”

Isopropyl Alcohol vs 1-Propanol

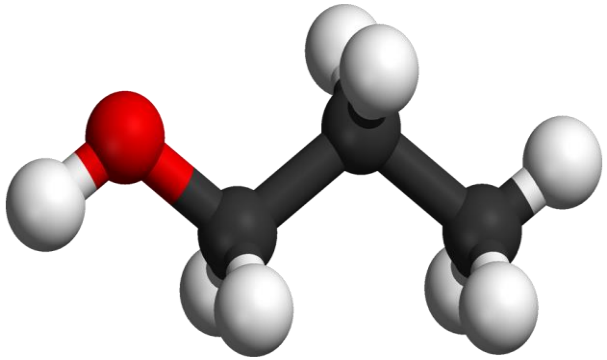
Isopropyl Alcohol

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



1-Propanol

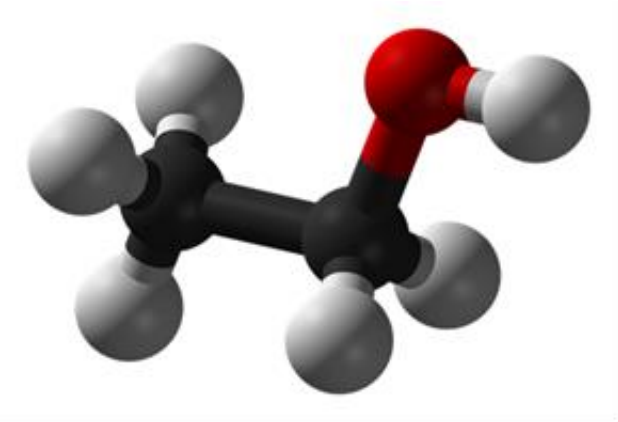
- Not an acceptable Active Ingredient for Hand Sanitizer
- Alcohol (OH) group on different carbon



Ethanol vs Methanol

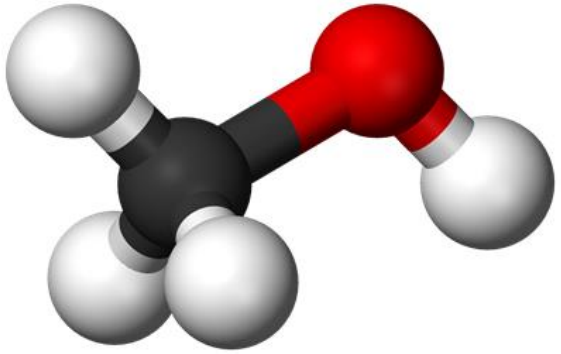
Ethanol

- 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."*

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/eskbiochem-sa-de-cv-608690-07232020

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."*
  - https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/eskbiochem-sa-de-cv-608690-07232020

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)."*

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/soluciones-cosmeticas-sa-de-cv-609057-08042020

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
  - *https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-consumers-should-not-use*

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*
  - 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:
  - *https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/essaar-inc-issues-voluntary-nationwide-recall-rubbing-alcohol-contaminated-methanol#recall-announcement*

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
- *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:
  - https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/usp-nf-notices/fda-letter-alcohols-nitr-att.pdf
- The monograph was revised, and on 9/1/2020, came into effect:
  - https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/alcohol-rb-notice-20200817.pdf
- 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

In Summary

- 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

Thank you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