

USP Seminar: Ensuring Quality Hand Sanitizer Production During COVID-19 For Healthcare Professionals in the United States

Executive Summary

Alcohol-based hand sanitizer is an important element in infection prevention, especially during the COVID-19 pandemic. However, when quality is compromised, it can be less effective against infection transmission and can also lead to user harm.

COVID-19-related supply chain pressures have created global shortages that led to new vendors, materials, and production pathways to meet demand. These fast-paced changes have caused an emergence of quality incidents both regionally and globally. Globally, over 200 alcohol-based hand sanitizer quality incidents have been reported in 2020ⁱ. Specifically, in the United States, approximately 80 alcohol-based hand sanitizer quality incidents were reported in 2020ⁱⁱ.

To help ensure quality alcohol-based hand sanitizer production and support the safe use of alcohol-based hand sanitizer, USP hosted a day-long seminar for manufacturers in the United States. Around 190 individuals registered to participate in USP's Seminar on February 24, 2021, including healthcare professionals who compound alcohol-based hand sanitizer, representatives from regulatory agencies, and others from interested industry groups.

Presenters from USP, U.S. Food and Drug Administration (FDA), Preston Road Pharmacy, and Banner Poison & Drug Information Center discussed the global and regional quality risks and solutions when producing alcohol-based hand sanitizer.

The following are key takeaways from the presentations and responses to the questions posed by participants during the seminar.

Key Takeaways

Quality Challenges and Public Health Impact

- When producing alcohol-based hand sanitizers, there are potential quality risks to the product and its ingredients, including contamination.
- An alcohol-based hand sanitizer product can be subpotent, meaning it has less than the required amount of an alcohol ingredient.
- If quality specifications for alcohol-based hand sanitizer products and its ingredients are not met, contamination or impurities could be introduced. Additionally, quality specifications help ensure the correct potency, so the product is not subpotent or super-potent.
- Globally, over 200 alcohol-based hand sanitizer quality incidents have been reported in 2020ⁱⁱⁱ. Specifically, in the United States, approximately 80 alcohol-based hand sanitizer quality incidents were reported in 2020^{iv}.
- In the United States, one batch of contaminated alcohol-based hand sanitizer caused 15 cases of hospitalized methanol poisoning, which led to four patient deaths and three with visual impairments^v.
- More than 20,000 calls were made to the Poison Control Center in 2020 related to alcohol-based hand sanitizers.
- Misuse of alcohol-based hand sanitizers that are contaminated with methanol can cause brain and ocular toxicity, metabolic acidosis, and stroke. Many of the cases seen in hospitals

are intentional misuse of alcohol-based hand sanitizer, as a cheaper and more accessible alternative to alcohol. Most people are not aware of the potential for methanol contamination when misusing.

- Proper labeling and packaging can mitigate potential inadvertent ingestion by consumers, especially children who may unintentionally swallow these products.
 - In March 2020, calls to Poison Control related to alcohol-based hand sanitizer increased by 79% compared to March of 2019. The majority of these calls were for unintentional exposures in children 5 years of age and younger^{vi}.
- The final product packaging system should contain, preserve, protect, and deliver. There are product risks from improperly stored and shipped products.
 - If not stored in the proper container or package, alcohol-based hand sanitizer products can also experience increased evaporative loss that may decrease its effectiveness^{vii}.
 - Temperature and light variations may impact alcohol-based hand sanitizer quality^{viii}. Additionally, alcohol-based hand sanitizer can become a fire safety hazard as its base chemicals are flammable^{ix}.
 - Ingestion by children can be avoided by properly storing alcohol-based hand sanitizer.

Regulatory and Public Health Strategies to Increase Trust

- With the rapid increase in alcohol-based hand sanitizer production and supply, new and increasing quality and safety issues have been identified.
 - The contamination and/or substitution of methanol for ethanol and 1-propanol for 2-propanol have both been linked to quality and safety issues associated with alcohol-based hand sanitizers.
- The U.S. FDA has identified adverse events including accidental ingestion, ocular injuries, and burns, as well as quality issues such as contamination and sub-potency, mislabeling of products, and packaging in food and drink containers.
 - U.S. FDA monograph for “topical consumer antiseptic rub products” (such as hand sanitizers) set certain requirements for safety and efficacy. Similarly, USP standards for identity, strength, and purity help ensure product quality and therefore contribute to patient and consumer safety.
 - To address the dramatic increase in demand and the flood of new products due to COVID-19, the U.S. FDA [issued](#) four guidance documents and a “do-not-use” list of hand sanitizer products for consumers.
 - There is a new identity testing [requirement](#) to test for methanol that is included in the USP Alcohol and Dehydrated monographs, and the FDA worked with USP to update these monographs.
 - 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);
 - 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); and
 - If Methanol detection and quantification is part of the Identification test, the CGMP regulations at 21 CFR 211.84(d)(l) would require that manufacturers of drug products detect and quantify any Methanol present for each lot of Alcohol received.
 - Furthermore, manufacturers of Alcohol could not deviate from the Methanol limit since this would be an aspect of identity. In contrast, if

Methanol detection and quantification is part of an impurity test, a manufacturer need not include as part of its identity testing the detection and quantification of Methanol in the Alcohol.

Standards, Current Good Manufacturing Practices (CGMP), and Mitigation Strategies

- Compliance with USP's science-based standards, which constantly evolve through public input, help companies in this growing market segment detect adulteration.
 - Using USP standards helps to ensure that patients receive quality alcohol-based hand sanitizers and other drug products.
 - USP has revised its alcohol monographs to address methanol contamination. The USP identity test for alcohol now includes a specific identity test for methanol content.
- Labels are essential for product identification. They must be clear, easy to read, and unable to be smudged.
 - Labels of hand sanitizer ingredients should align with FDA guidance detailed in the *Temporary Policy for Preparation of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19) Guidance for Industry*
 - Additionally, specific details such as concentration and grade (e.g., USP, FCC) should be clearly stated on the label and should be confirmed upon receipt
 - USP designation indicates that the product complies with a specific USP-NF monograph
 - If the drug complies with a USP monograph, it must have: 1) The specific monograph name on label; and 2) any additional labeling requirements described in the specific monograph.

Quality in Action

- Tracy Acosta, Pharm.D., BCSCP, shared key considerations for compounding alcohol-based hand sanitizer safely, including:
 - the formulation recommendations for compounding hand sanitizer;
 - labeling requirements for patients and healthcare providers;
 - distribution to patients, at risk individuals and frontline workers within the community; and
 - storage requirements of compounded hand sanitizer.

Q&A Responses

1. What are the specifics for healthcare professionals regarding the general use of sanitizers or disinfectants?

The U.S. CDC recommends hand washing with soap and water or using hand sanitizer to help avoid getting sick and spreading germs to others. Laboratory data demonstrates that 60% ethanol or 70% isopropyl alcohol inactivates viruses that are genetically related to, and with similar physical properties as, the SARS-CoV-2. The final concentration of 80% ethanol or 75% isopropyl alcohol recommended in the USP compounding hand sanitizer resource document is aligned with recommendations from the U.S. FDA, WHO, and U.S. CDC. The higher concentrations help ensure the final concentration of the preparation will exceed those needed to inactivate viruses. These formulas with higher final alcohol concentrations account for the potential for sub-potent ingredients, evaporative loss, and margin of error. Please consider consulting with the regulators in your area to inquire whether they have approved any other formulations or products for hand hygiene during the COVID-19 pandemic.

2. How can a regulator judge the manufacturer's reputation when a non-pharmacopeial ingredient was used?

USP, NF, or FCC grade ingredients should be used in hand sanitizers and must comply with the requirements specified in the applicable monograph. Relevant USP standards for ingredients used to prepare hand sanitizers are included within the USP hand sanitizer toolkit, accessible free of charge on the USP website.

3. Is it mandatory to use hydrogen peroxide 3%? If the manufacturer uses, for example, 4% hydrogen peroxide, will the sanitizer not meet certain requirements or specifications?

Alcohol-based hand sanitizers must be properly formulated in order to protect the health of the skin and reduce microorganisms on the hands. The USP hand sanitizer toolkit recommends hydrogen peroxide 3% and includes recommended substitutions. Other substitutions are not recommended by the USP Compounding Expert Committee at this time. USP is aware of ingredient shortages and is working with the Expert Committee on an ongoing basis to discuss alternative ingredients and formulas to meet public health needs.

4. The final concentration of an antiseptic is 75% or 80% depending on the ethanol used. My understanding is that this should be "self-preserved" at this concentration. Thus, why is a 30-day BUD assigned?

The 30-day BUD for the compounded formulation is assigned based on USP General Chapter <795> Pharmaceutical Compounding – Nonsterile Preparations defaults for Water-Containing Topical/Dermal and Mucosal Liquid and Semisolid Formulations. Also, please note that the high concentrations of alcohol used in the hand sanitizers may not inactivate all microorganisms, such as spore forming microorganisms. The hand sanitizers should therefore be formulated in order to avoid inadvertent contamination by microorganisms not killed by alcohol.

5. Can you clarify if isopropyl alcohol (IPA) should be labeled as USP?

The only name that can be used is the specific title of the monograph, Isopropyl Alcohol. If the tests from the monograph have been performed, then the title of the product should be "Isopropyl Alcohol, USP." Other synonyms or chemical names cannot be used.

6. What is the difference between healthcare personnel label and consumer label?

Per the [FDA Guidance: Policy for Temporary Compounding of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency Immediately in Effect](#), the Drug Facts Label contains specific language for consumer under the Use(s) section (See Appendices A and B) and for healthcare personnel under the Use(s) section (See Appendices C and D).

7. How can healthcare professionals ensure the correct potency of alcohol-based hand sanitizers when degradation may happen due to temperature or evaporation?

The final concentration of 80% ethanol or 75% isopropyl alcohol recommended in the USP compounding hand sanitizer resource document is aligned with recommendations from the FDA, WHO, and CDC. The higher concentrations help ensure the final concentration of the preparation will exceed those needed to inactivate viruses. These formulas with higher final alcohol concentrations account for the potential for sub-potent ingredients, evaporative loss, and margin of error.

8. When it comes to assigning best before date, are there guidelines on how this must be done or are compounders expected to base their decision on stability studies?

The 30-day beyond-use date in the USP compounding hand sanitizer resource document is based on USP General Chapter <795> *Pharmaceutical Compounding – Nonsterile Preparations* defaults for Water-Containing Topical/Dermal and Mucosal Liquid and Semisolid Formulations. Please see <795> for more details on how to assign beyond-use dates for compounded nonsterile preparations.

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- i CDSCO (11 Jan 2021). “Alerts.” <https://cdsco.gov.in/opencms/opencms/en/Notifications/Alerts/>
 - ii IDDO Medicine Quality Monitoring Globe Index (2020)
 - iii CDSCO (11 Jan 2021). “Alerts.” <https://cdsco.gov.in/opencms/opencms/en/Notifications/Alerts/>
 - iv IDDO Medicine Quality Monitoring Globe Index (2020)
 - v <https://www.cdc.gov/mmwr/volumes/69/wr/mm6932e1.htm>
 - vi <https://www.fda.gov/drugs/information-drug-class/ga-consumers-hand-sanitizers-and-covid-19>
 - vii USP Chapter <659> Packaging and Storage Requirements
 - viii USP Chapter <671> Containers—Performance Testing
 - ix <https://www.fire.tc.faa.gov/pdf/TN10-19.pdf>