

USP Seminar: Ensuring Quality Hand Sanitizer Production During COVID-19 For Healthcare Profession

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 Africa, approximately 20 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 healthcare professionals in Africa. Around 93 individuals registered to participate in USP's Seminar on February 25, 2021, including healthcare professionals who compound alcohol-based hand sanitizer, representatives from regulatory agencies, and others from interested industry groups.

Presenters from USP, The African Union Development Agency (AUDA-NEPAD), WHO Regional Office for Africa, Ghana Food and Drug Authority, University of Ghana School of Pharmacy, Kenya Medical Research Institute, and U.S. Food and Drug Administration (FDA) 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.
- In Africa, the COVID-19 outbreak caused a surge of demand for hand sanitizers, uncovering uninformed choices coupled with closed borders/disrupted supply and new manufacturing sites, sometimes without experience in the manufacturing of health products.
 - In Kenya, according to research from the Kenya Medical Research Institute (KEMRI), back in 2015, a study to establish the quality of the alcohol-based hand sanitizers (ABHRs) in the Kenyan market established that fifty percent (50%) of ABHRs in the Kenyan market had efficacies that were below the WHO, EN, and Health Canadian Standards.
 - Immediately, after the announcement of the first case of COVID-19 in Kenya, KEMRI became the center of activities as they were among the very few facilities that were licensed and had the stock of ABHRs.
 - Two challenges happened:

1. Low-quality counterfeits of KEMRI's ABHR products appeared in the market, where KEMRI engaged the relevant arm of the government, the Anti-Counterfeit Agency, to handle the matter; and
 2. Quality control ATTC strain of *Escherichia Coli* developed resistance to ethanol, so a research protocol was prepared to be published in a peer reviewed journal, "Assessment Of The Quality Of The Alcohol-based Hand Sanitizers And Ethanol Resistant Pattern Of *Staphylococcus Aureus* And *Escherichia Coli* Before And During Sars-cov-2 Pandemic Outbreak In Kenya."
- 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 impairmentsⁱⁱⁱ.
 - 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.
 - 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^{iv}.
 - Temperature and light variations may impact alcohol-based hand sanitizer quality^v. Additionally, alcohol-based hand sanitizer can become a fire safety hazard as its base chemicals are flammable^{vi}.
 - 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 Africa Medicines Regulatory Harmonization (AMRH) is a partnership initiative formalized in 2009 to improve the fragmented regulatory system for product registration in Africa by changing from a country-focused approach to a collaborative regional and simplified one.
 - Partnership includes African countries' regulatory authorities and regional bodies, such as NEPAD, WHO, and the World Bank.
 - Builds African regulatory capacity by region to:
 - Harmonize standards (technical requirements/guidelines) to reduce registration cycle time;
 - Conduct regional dossier assessments/GMP inspections to extend to other regulatory functions over time; and
 - Share work and pool resources to help streamline decision-making processes.
 - The African Medicines Quality Forum (AMQF) seeks to make Africa free of sub-standard and falsified medicines through capacity building of the National Quality Control Laboratories of Africa.
 - The AMQF Taskforce was formed in May 2020 to develop a strategy and guidance on supporting evaluation of the quality of medicine and medical products along the pharmaceutical value chain for the treatment of COVID-19 as well as hand sanitizers.

- In Africa, where more than 80% of the healthcare commodities are imported, a defined testing strategy is required to ensure that hand sanitizers are made available, tested, and reports provided in a timely manner. To support the approval, the following strategies should be employed:
 - Expedited sample management
 - Testing of new products using the official compendia or validated methods from manufacturers
 - Assessment of hand sanitizers for antimicrobial effectiveness and ethanol content (NLT 60% V/V alcohol –WHO)
 - Assessment of herbal products using official compendia where applicable but most importantly safety assessment which include but not limited to acute oral toxicity, microbial limit test, and absence of contaminants such as pesticide and herbicide residues, elemental metals such as Hg, Pb, Cs, Cd etc., and mycotoxins
 - The medicine samples should meet international specifications (BP, USP, Int Ph.)
 - Developing a random sampling and testing method to ensure more samples from several manufacturers are tested to ensure compliance
 - Every AMQF country member to forward to the secretariat the above samples tested that do not meet the required specifications. This data to be collected monthly and be compiled into a database to inform the countries and WHO regarding SF medicines.
 - Countries to develop a list of notified manufacturers and respective products and communicate to the public.
- In Ghana, as per the Public Health Act 2012, (Act 851) of the Food and Drugs Authority (Ghana FDA), products placed on the Ghanaian market should be registered and given market authorization by the Ghana FDA before importation or placed on the Ghanaian market.
 - Prior to the emergency of COVID-19 pandemic, there was a shortage of sanitizers on the market and therefore there was the need for local industries to produce/manufacture hand sanitizers to make it readily available on the market.
 - Regulatory processes have been reviewed to ensure that manufactured hand sanitizers are submitted to the Ghana FDA to ensure that products placed on the market are safe, of the right quality, and fit for their intended purpose.
 - Regulatory requirements and guidelines enacted included:
 - The Industrial Support Department offer technical support to stakeholders (Importers and Local Manufacturers) to ensure sanitizers are safe and of good quality.
 - Continuous Post Market Surveillance to ensure that hand sanitizers placed on the markets comply with the regulatory requirement of the Authority.
 - Conduct GMP inspections of manufacturing facilities to ensure compliance in accordance with ISO 22716
- The World Health Organization (WHO) developed a guide to local production of WHO-recommended hand rub formulations, which frames regulation from the healthcare perspective and supports local manufacturing that sustains demand for quality.
- 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)(1) 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, Good Manufacturing Practices (CGMPs), 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

- Dr. Mansa Fredeua Agyeman shared key do’s and don’ts for compounding alcohol-based hand sanitizer safely, including:
 - Fire safety signs should be available onsite, and alcohol be kept away from ignition sources (heat, spark, open flames)

- Properly label all materials and containers as flammable and use the proper type of portable container to transfer alcohol from the original container or from bulk storage, such as a drum or tank
- Store unused alcohol in a storage cabinet and do not store other types of chemicals/compressed gases in the cabinet
- Large volumes, drum quantities should be in controlled storage rooms away from heat, open flames with appropriate signage or placarding
- Production and storage rooms should have properly ventilated systems that are regularly maintained
- Unspecified ingredients should not be added to the formulations
- Personal protective equipment must be used

Q&A Responses

1. **During the seminar, in a slide it said 60% v/v alcohol, and in another slide, it said 60% ethanol and 70% IPA without v/v or w/v. In the WHO guide, it states 80% ethanol, 75% IPA. Please explain.**

The U.S. CDC recommends hand washing with soap and water or using hand sanitizer to help people 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 formulas in the USP compounding resource document were developed by the Compounding Expert Committee based on their scientific and professional expertise, and with input from regulatory agencies at the federal and state level and compounders. The final concentration of 80% ethanol v/v or 75% isopropyl alcohol v/v 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.

2. **Why is it necessary to measure microbial effectiveness?**

Alcohol-based hand sanitizers must be properly formulated in order to protect the health of the skin, reduce microorganisms on the hands, and avoid inadvertent exposure to organisms not killed by alcohol (e.g., spores).

3. **How are hand sanitizers formulated based on normal ISO standard of NLT 60% during this pandemic era (considering the recommended NLT 70% by WHO)?**

See response to question one.

4. **1-propanol is mentioned in many references that it could be used in hand sanitizers. What is the upper limit of 1-propanol?**

According to the US FDA, only ethyl alcohol and isopropyl alcohol (also known as 2-propanol) are acceptable alcohols in hand sanitizer. Other types of alcohol, including methanol and 1-propanol, are not acceptable in hand sanitizer because they can be toxic to humans.

5. **Some manufacturers use the LPG (liquefied petroleum gas: propane or butane). Can this be poisonous?**

USP does not have any safety information on these preparations. We would recommend consulting with poison control centers and regulatory agencies for further information.

6. If there is a product that is a pressurized spray of alcohol-based hand sanitizer, is it approved by U.S. FDA or is it forbidden to be in the market?

We recommend reaching out to the U.S. FDA for information on approved products at COVID-19-Hand-Sanitizers@fda.hhs.gov.

7. Is there a simple means (equipment and/or methods) of testing the presence of methanol and determination of its concentration in the alcohol-based hand sanitizers other than gas chromatography (GC) or other sophisticated methods?

The U.S. FDA guidance states that, “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.” In addition, an alternative method is also allowed as per USP [General Notices 6.30. Alternative and Harmonized Methods and Procedures](#). USP monographs use a GC method to determine methanol because it can meet the methanol specification limit (200 uL/L). We are currently not aware of other methods which can meet this requirement. For testing methanol in alcohol, please see USP monographs.

- Alcohol Revision Bulletin:
https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/alcohol-rb-notice-20200817.pdf
- Dehydrated Alcohol Revision Bulletin:
https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/dehydrated-alcohol-rb-notice-20200817.pdf

For testing methanol in hand sanitizer products, please see U.S. FDA method: Direct Injection Gas Chromatography Mass Spectrometry (GC-MS) Method for the Detection of Listed Impurities in Hand Sanitizers (<https://www.fda.gov/media/141501/download>).

8. The WHO recommended alcohol-based hand sanitizer of not less than 80% especially for in healthcare institutions. However, in Ghana, 70% alcohol-based products under 'donations' are used all over. What challenges could this bring?

The final concentration of 80% ethanol v/v or 75% isopropyl alcohol v/v 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.

9. What hazard symbols must be on the label?

Labels that indicate potential hazards of the product, such as flammability, should be included. Symbols that indicate that the sanitizer is for “external use only” could also be used if available. Warnings should also be noted in writing on the Drug Facts label of the product. It is recommended that each country follow requirements as mandated by their regulatory body.

10. Should the alcohol content in the final product be indicated on the label instead of alcohol concentration that has been used in formulation?

The alcohol concentration used in the formulation should be higher than the targeted final percentage to account for other required ingredients, as well as the potential for evaporative loss and margin of error. When the ingredients are combined, the alcohol is diluted to a lower concentration. Therefore, the label should accurately display the diluted alcohol concentration in the final volume of the product.

11. Could you elaborate more on how hand sanitizers containing alcohol are regulated in every country, and the registration or qualifications requirements in their market?

Response from the Tanzania Medicines and Medical Devices Authority:

Global approach in the regulation of alcohol-based hand sanitizers differs from country to country. Some countries opt for more stringent approach including pre-marketing authorization, facility inspection and post authorization market surveillance. Other countries have a less stringent approach in which these products are considered as general sales or cosmetics.

In Tanzania, alcohol-based hand sanitizers are regulated through mandatory marketing authorization requirement and routine surveillance in the market. Pre-marketing authorization assessment of the technical information regarding quality, safety, and efficacy is thoroughly performed including laboratory analysis of samples against specifications. After issuing marketing authorization approval, routine surveillance starts.

With regard to the other countries that may be not regulating these products, first, they should have in place a system of notification or registration that ensure that the products are assessed for their quality and safety before introducing in the market. Testing for alcohol content and adulterations is imperatively important during notification/registration and during post marketing surveillance. In addition, guidance for the preparation of alcohol-based hand sanitizers should be developed and implemented or internationally recognized guidance should be adopted.

12. Are hand sanitizers regulated as biocides or medical devices?

Response from the Tanzania Medicines and Medical Devices Authority:

Hand Sanitizers are regulated as biocides under the class of antiseptics.

ⁱ CDSCO (11 Jan 2021). "Alerts." <https://cdsco.gov.in/opencms/opencms/en/Notifications/Alerts/>

ⁱⁱ IDDO Medicine Quality Monitoring Globe Index (2020)

ⁱⁱⁱ <https://www.cdc.gov/mmwr/volumes/69/wr/mm6932e1.htm>

^{iv} USP Chapter <659> Packaging and Storage Requirements

^v USP Chapter <671> Containers—Performance Testing

^{vi} <https://www.fire.tc.faa.gov/pdf/TN10-19.pdf>