

USP Seminar: Ensuring Quality Hand Sanitizer Production During COVID-19 For Manufacturers in Africa

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 manufacturers in Africa. Around 112 individuals registered to participate in USP's Seminar on February 24, 2021, including manufacturers with alcohol-based hand sanitizers as part of their production portfolio, 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, Tanzania Medicine and Medical Devices Authority (TMDA), Aspen Sub-Saharan Africa, and the 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 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 substandard and falsified medicines.
- Countries to develop a list of notified manufacturers and respective products and communicate to the public.
- In Tanzania, TMDA developed the first edition of the guidelines for registration of Antiseptics and Disinfectants in 2015 and later revised in 2020.
 - The Guidelines for Submission of Documentation for Marketing Authorization of Biocidal (Antiseptics and Disinfectants) Products, August 2020 provides the data requirements for registration of hand sanitizers including alcohol-based hand sanitizers.
 - During the COVID-19 outbreak, an additional guidance was issued: Guidance for Production of Alcohol-based Hand Sanitizers Under Public Health Emergency Preparedness (the Emergency Guidance) to meet the increased demand and local production of hand sanitizers.
 - Since the outbreak, TMDA has expedited the review process for applications, provided technical support and expedited inspection of sites intended for production of hand sanitizers, conducted regular inspection exercises to identify substandard or falsified hand sanitizers on the market, laboratory tested all hand sanitizers in the market and recalled products as needed, and educated the community on the labeling, handing, and proper use of hand sanitizers.
- 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.
- USP's services and programs, such as the USP Ingredient Verification Program, give industry tools that help qualify their supply chain, ensure quality, and reduce risk.
 - The USP Ingredient Verification Program can help enhance a manufacturer's competitive position and brand recognition by promoting the manufacturer's commitment to produce quality products for consumers.
- 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

- Aspen Sub-Saharan Africa shared a case study on what it takes to deliver quality alcohol-based hand sanitizer from a manufacturer's perspective.
- An alcohol-based hand sanitizer manufacturer must consider formulation (composition and effect), production and storage facilities, in-process quality control, and label information.

Q&A Responses

1. **Recent studies have shown that benzalkonium chloride sanitizer products could be used as effective as alcohol-based products. This is important as this may help reduce supply shortages and is more safe, less costly particularly in schools, etc.**

Comments?

USP does not have any information on benzalkonium chloride sanitizer products' effectiveness. We recommend reaching out to the U.S. FDA for information at COVID-19-Hand-Sanitizers@fda.hhs.gov.

2. What information should be included in hand sanitizer labeling?

The following items should be present on the label of quality hand sanitizer:

- Display Panel on the front of product
 - Name of product with percentage of alcohol –
 - Example 1: Alcohol Antiseptic 80% Topical Solution
 - Example 2: Isopropyl Alcohol 75% Topical Solution
 - Volume of product in milliliters (mL)
 - Description of product
 - 1. Antiseptic Hand Rub
 - 2. Non-sterile solution
- Drug Facts Label on the back of product
 - Active ingredient, purpose of active ingredient, and percentage of active ingredient
 - Uses and Directions for Use
 - Warnings
 - Storage conditions
 - Inactive Ingredients

3. What is the limit for methanol in alcohol?

The methanol limit is 200 uL/L in the USP Alcohol and Dehydrated Alcohol monographs.

For hand sanitizer products, please refer to U.S. FDA guidance, [Policy for Testing of Alcohol \(Ethanol\) and Isopropyl Alcohol for Methanol, Including During the Public Health Emergency \(COVID-19\)](#) (January 2021). For additional questions, contact U.S. FDA at COVID-19-Hand-Sanitizers@fda.hhs.gov.

4. Which methods are manufacturers using for quality control of raw materials and alcohol-based hand sanitizer products? Is it density meters or gas chromatography (GC)? How do they use the methods for detection of adulteration/substitution?

The methods a manufacturer uses is determined by their company and what is required by local and federal health authorities for products, such as alcohol-based hand sanitizer products. For U.S. FDA guidance, see [Policy for Testing of Alcohol \(Ethanol\) and Isopropyl Alcohol for Methanol, Including During the Public Health Emergency \(COVID-19\)](#).

5. Which quality control methods is the Tanzania Medicine and Medical Devices Authority using in evaluating alcohol-based hand sanitizers for registration or market surveillance? Are the methods adequately specific for detection of adulteration/substitution? What regulatory actions are taken against errant players?

Response from the Tanzania Medicines and Medical Devices Authority:

The Tanzania Medicines and Medical Devices Authority (TMDA) uses two methods to determine alcohol (ethyl alcohol) content in the Alcohol based hand sanitizers. These are the distillation method and gas chromatography method.

In evaluating the quality of these sanitizers, additional parameters are tested including visual appearance and identification.

The GC method is validated with respect to specificity, precision, accuracy/recovery, limit of quantification (LOQ) and limit of detection (LOD).

Two solvents have been used during validation, ethyl alcohol and methanol. Thus, it is expected that chromatogram showing peaks will eventually calculate the percentage content

of the solvents in the sanitizers. If the sanitizer has an amount of methanol above the recommended limit, the product will not be registered.

TMDA instituted adequate post marketing surveillance system particularly for hand sanitizers in this material time. The samples are randomly picked from the market and tested for alcohol content and methanol residues/adulteration.

In case of defaulters, the products are confiscated and legal action is taken in accordance with the Tanzania Medicines and Medical Devices Act, Cap 219 and regulations made thereunder.

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>