# USP Seminar: Ensuring Quality Hand Sanitizer Production During COVID-19 For Manufacturers and Healthcare Professionals in Latin America

## 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 2020[i]. Specifically, in Mexico, approximately 35 alcohol-based hand sanitizer quality incidents were reported in 2020[ii].

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 and healthcare professionals in Latin America. Around 436 individuals registered to participate in USP's Seminar on February 25, 2021, including manufacturers with alcohol-based hand sanitizers as part of their production portfolio, healthcare professionals who compound alcohol-based hand sanitizer, representatives from regulatory agencies, and others from interested industry groups.

Presenters from USP, Mexican Pharmacopeia, COFEPRIS, ANVISA, National Institute of Quality Control in Health (INCQS), ANFARMAG, Benton Dickinson, ABIHPEC, 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-based 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 2020[iii]. Specifically, in Mexico, approximately 35 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].

    - 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[vi].
    - Temperature and light variations may impact alcohol-based hand sanitizer quality[vii]. Additionally, alcohol-based hand sanitizer can become a fire safety hazard as its base chemicals are flammable[viii].
    - 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.
- In Mexico, the problem is not limited to improper local manufacturing and consumption of hand sanitizers during the COVID-19 pandemic, but quality issues are affecting products that are exported to other countries, including the United States where the U.S. FDA has an import alert on all alcohol-based hand sanitizers from Mexico. In response, Mexican regulatory authorities have updated the applicable Monographs of the Mexican Pharmacopeia and are considering if additional changes are needed for a Mexican Official Standard of Hand Sanitizers Manufacturing.
- In Brazil, legislation was issued to define extraordinary and temporary criteria and quality control procedures for the manufacturing and commercialization of antiseptic preparations or sanitizers, without the need of obtaining prior authorization from National Health Surveillance Agency.
- 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, 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.
- 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 dug 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

- As VP of Operations Strategy of the Medical Segment of Becton Dickinson & Co (BD), Juan Pablo Solis presented the point of view of a worldwide-recognized hand sanitizers' manufacturer. His presentation showed the importance of hand sanitizing not only for COVID-19 prevention, but in several healthcare interventions, such as surgery. He talked about BD's manufacturing footprint and the regulatory compliance they need to follow. Finally, he mentioned the sanitary risks associated with emerging manufacturers.
- ANFARMAG shared the current best practices for compounding according to Brazilian regulations, from supplier qualification to pharmacovigilance, including quality control testing, packaging and labeling requirements.
- ABIHPEC commented on the ideal characteristics for an antiseptic formulation (active spectrum, toxicity, stability and user acceptance), the effectiveness of ethanol in different

concentrations for antiseptic formulations, factors that compromise the quality of antiseptics, best practices for quality assurance, and safety.

## Q&A Responses

1. **Where can I find information from the U.S. FDA on alcohol-based hand sanitizers consumers should not use?**
   It can be found published by the U.S. FDA here.

2. **Are there specifications for the additives such as carbopol, colorants, fragrances, and others that are used in hand sanitizer production and could have a negative impact in the product?**
   USP's standards and recommendations do not include quality specifications for additives.

3. **Is it allowed to use thickener in the hand sanitizer formulation?**
   No, ingredients should not be added to enhance viscosity as they may decrease the effectiveness of the final preparation.

4. **Is there a specific method to verify the antiseptic activity of hand sanitizers? What microorganisms should be evaluated?**
   There are no specific tests for antiseptic activity recommended at this time. Using a hand sanitizer with a final concentration of at least 60% ethanol or 70% isopropyl alcohol inactivates viruses that are genetically related to, and with similar physical properties as, the SARSCoV-2.2 The final concentrations in these formulations require at least 80% ethanol or 75% isopropyl alcohol due to the potential for sub-potent ingredients, evaporative loss, and to reduce the margin of error, in order to exceed the minimum concentrations for effectiveness recommended by the CDC.

5. **How can we quickly analyze the difference between ethanol and methanol, or identify the presence of them? Which is the acceptance criterion of methanol in the alcohol gel?**
   To analyze methanol in Alcohol (ethanol), refer to https://www.usp.org/sites/default/files/usp/document/health-quality-safety/usp-hand-sanitizer-ingredients.pdf.
   USP Alcohol monographs include a methanol limit of 200 uL/L. For further information, see the Alcohol FAQs at: https://www.uspnf.com/notices/alcohols-faq.
   For acceptance criteria of methanol in hand sanitizer products, 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 other question pertaining to methanol, contact U.S. FDA at COVID-19-Hand-Sanitizers@fda.hhs.gov.

6. **Can you please provide an analytical method for quality control of both active ingredient and excipients of alcohol-based hand sanitizer products?**
   For the testing of ingredients, refer to USP monographs, such as Alcohol, Dehydrated Alcohol, Isopropyl Alcohol, Glycerin, etc. at https://www.usp.org/sites/default/files/usp/document/health-quality-safety/usp-hand-sanitizer-ingredients.pdf.
   For hand sanitizer products, refer to U.S. FDA method: Direct Injection Gas Chromatography Mass Spectrometry (GC-MS) Method for the Detection of Listed Impurities in Hand Sanitizers.

7. **Are there any comments regarding the inclusion of a 70% alcohol hand sanitizer monograph in the USP-NF?**
   USP does not have a monograph of 70% alcohol hand sanitizer currently. However, in the USP Rubbing Alcohol monograph, it states that "[rubbing alcohol] contains NLT 68.5% and NMT 71.5% by volume of dehydrated alcohol, the remainder consisting of water and the denaturants, with or without color additives, and perfume oils." Check with U.S. FDA (COVID-19-Hand-Sanitizers@fda.hhs.gov) regarding the applicability of this USP Rubbing Alcohol monograph for your quality control.
   For hand sanitizer products, 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). In addition, there is U.S. FDA method: Direct Injection Gas Chromatography Mass Spectrometry (GC-MS) Method for the Detection of Listed Impurities in Hand Sanitizers.

8. **When will USP include a monograph for alcohol-based hand sanitizers?**
   The USP Expert Committee is currently deciding if a monograph will be developed for alcohol-based hand sanitizers.

   For the current time, 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) and USP's Hand Sanitizer Toolkit.

9. **Which is the test method that you recommend for the quality control of alcohol-based hand sanitizer?**
   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) and the U.S. FDA testing method for hand sanitizers: Direct Injection Gas Chromatography Mass Spectrometry (GC-MS) Method for the Detection of Listed Impurities in Hand Sanitizers.

10. **Is it necessary to consider how a container takes care of the environment since many containers will go to the water?**
    Current USP standards do not address environmental factors. It is recommended to check with local regulators on required environmental practices.

11. **What tests do you perform for extractables and leachables on primary packaging?**
    Refer to USP General Chapters <1663> *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems and* <1664> *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems*.

12. **Should packaging materials for quality control release be analyzed at the manufacturer level?**
    Product manufacturers bear the ultimate responsibility for ensuring that packaging materials and components used with the final product are suitable for their intended use. Therefore, there needs to be some control of packaging materials and components entering a facility which will involve some level of product testing.

13. **It is not clear to me how alcohol gel is categorized, e.g., a panelist mentioned hygienic product and cosmetic product.**
    Categorization depends on the particular country's regulation. It is recommended to connect with your country's regulatory authority to confirm categorization.

14. **For answers to questions regarding Brazil regulations and quality requirements, please contact the ANVISA at http://antigo.anvisa.gov.br/fale-conosco or 0800 642 9782.**

15. **For answers to questions regarding Mexico regulations and quality requirements, please contact COFEPRIS at contactociudadano@cofepris.gob.mx.**

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[i] CDSCO (11 Jan 2021). "Alerts." https://cdsco.gov.in/opencms/opencms/en/Notifications/Alerts/
[ii] CDSCO (11 Jan 2021). "Alerts." https://cdsco.gov.in/opencms/opencms/en/Notifications/Alerts/
[iii] CDSCO (11 Jan 2021). "Alerts." https://cdsco.gov.in/opencms/opencms/en/Notifications/Alerts/
[iv] CDSCO (11 Jan 2021). "Alerts." https://cdsco.gov.in/opencms/opencms/en/Notifications/Alerts/
[v] https://www.cdc.gov/mmwr/volumes/69/wr/mm6932e1.htm
[vi] USP Chapter <659> Packaging and Storage Requirements
[vii] USP Chapter <671> Containers—Performance Testing
[viii] https://www.fire.tc.faa.gov/pdf/TN10-19.pdf