USP Seminar: Ensuring Quality Hand Sanitizer Production During COVID-19 For Manufacturers 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 2020[i]. Specifically, in the United States, approximately 80 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 in the United States. Around 183 individuals registered to participate in USP's Seminar on February 23, 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, U.S. Food and Drug Administration (FDA), Perrigo, 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-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 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.
- 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

- Manufacturer Perrigo shared a case study about their rapid response to an urgent public health request. They quickly developed, produced, tested, and donated 1 million alcohol-based hand sanitizer units by June 2020.
- As a company that was not making alcohol-based hand sanitizer before the pandemic, some of their key considerations included:
    - Adding capabilities for long-term viability,
    - Making their own gel-based formula as a New Product Development rather than as described in the FDA Guidance Formula, "Policy for Temporary Compounding of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency,"
    - Choosing three bottle options for packaging to have assurance in case of supply chain disruptions,
    - Understanding how alcohol and handling of the product will impact the printed ink on the label, and
    - Meeting the same standards as all other products.

Q&A Responses

1. **Please clarify the difference between a compounder and a manufacturer.**
   Compounding is the creation of a pharmaceutical preparation—a drug—by a licensed pharmacist to meet the unique needs of an individual patient (either human or animal) when a commercially available drug does not meet those needs. USP formally defines

compounding as “the preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug-delivery device, or device in accordance with a licensed practitioner's prescription, medication order, or initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice.” According to the FDA, “drug compounding is often regarded as the process of combining, mixing, or altering ingredients to create a medication tailored to the needs of an individual patient. Compounding includes the combining of two or more drugs. Compounded drugs are not FDA-approved."

According to the FDA, manufacturer means any legal person or entity engaged in the manufacture of a product subject to license under the act; "Manufacturer" also includes any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards. Manufacture means all steps in propagation or manufacture and preparation of products and includes but is not limited to filling, testing, labeling, packaging, and storage by the manufacturer. Domestic and foreign establishments that manufacture, repack, or re-label drug products in the United States are required to register with the FDA and list all of their commercially marketed drug products. Establishments also are subject to pre-approval inspections and must comply with CGMP.

2. **Are there a methanol limit of alcohol-based hand sanitizer?**
   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). If have additional questions, please contact U.S. FDA at COVID-19-Hand-Sanitizers@fda.hhs.gov.

   For alcohol used in hand sanitizers, the methanol limit is 200 uL/L in the USP Alcohol and Dehydrated Alcohol monographs. Find more information at: https://www.usp.org/covid-19/hand-sanitizer-information

3. **Since the FDA guidance states to use denatured alcohol, can USP methods for checking methanol content be used to test denatured alcohol? Is additional method development and validation required?**
   The USP monographs are applicable for undenatured Alcohols only. For questions related to denatured alcohol, please check with U.S. FDA at COVID-19-Hand-Sanitizers@fda.hhs.gov.

4. **Can you explain the difference between the two tests you have for purity and assay?**
   Assay and purity are two types of measurements used to determine the components of a sample. The main difference between assay and purity is that an assay is the determination of the main component in a sample, whereas purity is the determination of impurities in a sample.

5. **Approximately how many USP grade alcohol or dehydrated alcohol products have been USP Verified? Is this list publicly available through USP?**
   Some companies manufacturing alcohol or dehydrated alcohol are using the USP Verification Program. Current active pharmaceutical ingredients verification participants can be found here. Current excipients verification participants can be found here.

6. **Is there a verification process for FCC grade ingredients that is similar to the USP Verification program?**
   Not at this time.

7. **Is the USP Ingredient Verification Program conducted online?**

The USP Ingredient Verification Program is a multi-step process to help ensure that the proper quality controls are in place for active pharmaceutical ingredients, excipients, and dietary ingredients. It includes:

- An initial screening to help ensure ingredients with known safety concerns are not admitted to the program.
- A thorough audit of all manufacturing facilities, operations, records, and quality measures to help ensure that the manufacturer follows current good manufacturing practices.
- Initial testing of product samples in USP laboratories and other qualified labs to ensure that products conform to appropriate quality specifications.
- Annual testing of USP verified ingredients randomly sampled to ensure that they continue to conform to appropriate quality specifications.
- Use of the USP Verified Mark for ingredients that meet all of USP's stringent verification criteria.

Due to travel restrictions related to the COVID-19 pandemic, USP is implementing virtual audits to replace on-site audits. Virtual audits begin with providing requesting documentation for the auditor to review and request specific records to help understand how CGMP systems are implemented. Then, the auditor will conduct the "live" portion of the audit including interviews with selected staff, discussions on specific documents, and a virtual video tour.

8. **Why is glass used in packaging when it is easily broken? Why not use plastics only?**
Every packaging material, whether it is glass or plastic has its advantages and limitations. While glass has the potential for breakage, the potential for having a negative product-packaging interaction is low with glass in comparison to plastic. The choice of whether to use glass or plastic can come down to compatibility with the product.

9. **Can you share the details of data analysis in the stability testing?**
The beyond-use dates recommended for the formulas in the USP compounding hand sanitizer resource document are based on the default beyond-use states for water-containing topical compounded sterile preparations in USP General Chapter <795> *Pharmaceutical Compounding – Nonsterile Preparations*.

10. **Are the temperatures and the Relative Humidity indicated for stress stability applicable in all zones of the world or they are specific in EST?**
The recommended storage conditions for the formulas in the USP compounding hand sanitizer resource document is controlled room temperature. USP General Chapter <659> defines room temperature (also referred to as Ambient temperature) as the temperature prevailing in a working environment. Controlled room temperature is the temperature maintained thermostatically that encompasses the usual and customary working environment of 20°–25° (68°–77° F).

11. **I have observed that one of the factors that tends to decrease the quality of alcohol content of hand sanitizer is frequent opening and closing of the container due to constant usage by a patient. How can we minimize or prevent this?**
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.

12. **For answers to the following questions, please contact the U.S. FDA at COVID-19-Hand-Sanitizers@fda.hhs.gov.**
    - If using the FDA OTC monograph for active ingredients such as ethanol, does the manufacturer still have to perform effectiveness studies to make claims on the label? Is there any FDA guidance for alcohol-based hand sanitizer label claims?
    - Is an NDA required if a manufacturer produces and distributes a consumer antiseptic that is compliant with the FDA OTC monograph for consumer antiseptic, but also has a "claim statement" on the label (e.g., 99.99% effective) with applicable supporting data?
    - Is it required to submit an alcohol-based hand sanitizer that is a gel to FDA for approval as an ANDA or NDA? Or is there a specific FDA OTC monograph for these products?
    - Has FDA seen a significant amount of contamination issues with the alcohol itself as opposed to contamination of the alcohol-based hand sanitizer? It appears that the main problem is substitution of alcohol with methanol by the hand sanitizer manufacturer.
    - Since the main problem appears to be substitution, not adulteration of the alcohol itself, why does FDA think that including the methanol assay in the alcohol ID test will address the root cause of the problem, which is not the alcohol itself?
    - What is the justification for requiring testing of every container of alcohol for methanol when this will not really address the root cause risks related to substitution, and plus this will be very costly?
    - Should the CGMP requirements and inspections of alcohol-based hand sanitizer manufacturers and hand sanitizer products be increased, and the distributors (retail outlets) be required to fully qualify their suppliers and conduct testing of the hand sanitizers?
    - The import alerts and warning letters all seem to point to substitution of ethanol with methanol in the alcohol-based hand sanitizer, not adulteration of the ethanol with methanol. What evidence does FDA have that the USP monograph changes will address this root cause?
    - How many incidents of adulterated alcohol have occurred? Did the alcohol-based hand sanitizer manufacturers qualify their suppliers?
    - When the FDA temporary guidances are no longer in effect, how much notice will industry be given and what will be the expectations be for products in the pipeline?
    - Can the LPG (Liquefied Petroleum Gases like propane or butane) be poisonous once used in the alcohol-based hand sanitizer?
    - Do the suppliers of the components and the product manufacturers need to submit the analysis tests results of the components to the FDA?
    - Can you clarify whether manufacturers of ethanol and isopropyl alcohol as an excipient - given that an excipient is defined in the FDCA as a drug (FDCA 201(g)(1)(D)) - must

conform to the statutory requirements for CGMP (FDCA 501(a)(2)(B)), COVID-19 related discretion notwithstanding?

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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/qa-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