Hand Sanitizer Safety and Efficacy During the COVID-19 Pandemic

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Abstract

Background: A shortage of hand sanitizers during the initial COVID-19 surge led to the issuance of an FDA temporary guidance allowing non-traditional sources to manufacture and distribute alcohol-based hand sanitizers (ABHS). Since many of these manufacturers were previously unregulated, quality assessment was performed by Agency laboratories to gauge safety and efficacy of products from the new market entrants.

Purpose: To determine alcohol identity, alcohol content, and impurity quantity of ABHS. These critical quality attributes were selected to detect economically motivated adulteration via alcohol substitution, poor/inaccurate manufacturing practices, and usage of low-grade alcohol.

Methodology: The Office of Testing and Research (OTR) developed several analytical methods to perform the required testing. First, a rapid (< 30 s) spectroscopic screening method was utilized to determine alcohol identity and provide a semi-quantitative content estimate. This allowed OTR to prioritize samples that were suspected to be violative for analysis by fully quantitative, lower throughput techniques. Multiple methods were developed for gas chromatography-mass spectrometry (GC-MS) to analyze liquid and gel samples.

Results: OTR collaborated with the Office of Quality Surveillance (OQS) to analyze approximately 350 ABHS samples, and over 63% were determined to be violative. Most violations occurred due to the presence of acetal and acetaldehyde impurities detected over their combined interim specification limit of 100 ppm in ~85% of liquid ethanol-based hand sanitizer samples. The content of these impurities strongly correlated with the pH of the sample, and low pH samples (< 6) were most likely to be violative. Other violations included the presence of methanol, which was found in 5 samples above its 630 ppm specification, and benzene, which was found in a gel-based sample at 18 ppm (specification NMT 2 ppm). Finally, several samples were determined to contain alcohol content outside the efficacy ranges, which were 60-95% v/v and 70-91.3% v/v for ethanol- and isopropanol-based hand sanitizers, respectively.

Conclusion: OTR provided all testing results and data to OQS. Following review, violative products were referred to the Office of Compliance/Office of Manufacturing Quality for enforcement actions.

Introduction

FDA released a guidance in March 2020 allowing non-traditional domestic manufacturers to produce ABHS due to a shortage following onset of COVID pandemic. Product attributes and specifications included the following:

Assay:

- Alcohol (ethanol) (formulated to 80% (v/v)) in an aqueous solution, or
- Isopropyl Alcohol (formulated to 75%, v/v) in an aqueous solution.

Impurities and interim limits:

Table 1. Interim impurity limits for ABHS

Impurity	Interim Limit (ppm)
Methanol	NMT 630
Benzene	NMT 2
Acetaldehyde	NMT 50
Acetal	NMT 50
Sum of other impurities	NMT 300

Table 2. In cases where the sum of other impurities exceeds 300 ppm, these individual impurities must meet the following limits:

Impurity	Interim Limit (ppm)
Acetone	NMT 4400
1-Propanol	NMT 1000
Ethyl Acetate	NMT 2200
2-Butanol	NMT 6200
2-Methyl-1-Propanol	NMT 21700
1-Butanol	NMT 1000
3-Methyl-1-Butanol	NMT 4100
Amyl Alcohol	NMT 4100

Materials and Methods

The Office of Testing and Research (CDER/OPQ/OTR) developed several analytical methods to assist the Agency in assessing the quality of AHBS produced domestically by non-traditional sources.

Rapid Screening – Spatially Offset Raman Spectroscopy (SORS)

- Suitable for evaluating alcohol identity, detecting alcohol substitution, and determining the presence of abundant impurities (1 -5 % v/v)
- 30 sec testing time, PASS/FAIL result
- Used to prioritize suspected violative samples for lower throughput quantitative testing with ppm LOQs.

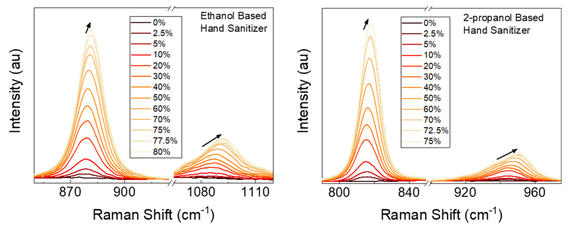


Figure 1. Raman spectra of ethanol- (left) and isopropanol (right)-based hand sanitizer solutions

Gas Chromatography with Mass Spectrometry (GC-MS)

- Two orthogonal GC-MS methods were developed by OTR to determine alcohol ID and to quantitatively determine assay and impurity content.
- Methods were validated according the ICH Q2 guidelines to facilitate analysis of ABHS

Table 3. Limits of Detection (LOD) and Quantitation (LOQ) for Headspace GC-MS method

Impurity	Interim Limit (ppm)	LOD (ppm)	LOQ (ppm)
Methanol	NMT 630	5.2	17.3
Benzene	NMT 2	0.1	0.3
Acetaldehyde	NMT 50	0.7	2.3
Acetal	NMT 50	0.8	2.8

- Due to the potential for unknown excipients interfering with low ppm impurity measurements, all samples underwent spiked recovery experiments to demonstrate the accuracy of measurements. Results were only used for reporting purposes if accuracy was demonstrated.

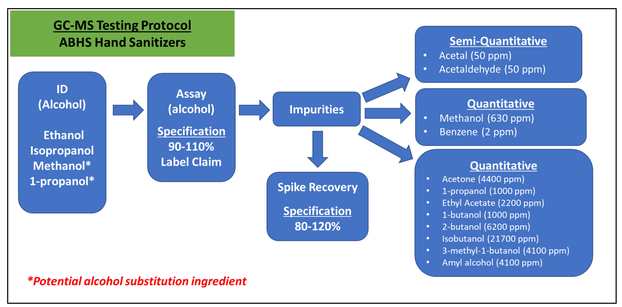


Figure 2. GC-MS testing protocol for analysis of ABHS

Results and Discussion

Rapid Screening Results

- 6% of samples FAILED screening and were prioritized for GC-MS testing
- Suspected product deficiencies included the wrong active ingredient, sub potency, and high levels of a contaminant (methanol).

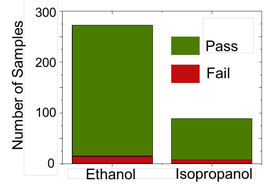


Figure 3. Summary of rapid screening results for ABHS organized by API

Assay Results (GC-MS)

- The assay specification for alcohol content in ABHS is 90-110% of the label claim. However samples were determined "acceptable" if they contained alcohol within efficacy ranges (60-95% v/v for ethanol and 70-91.3% v/v for isopropanol).

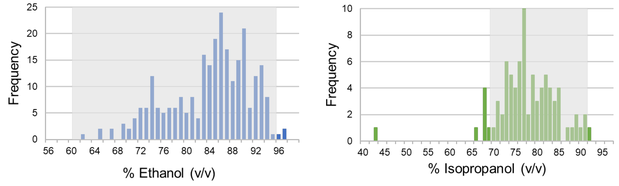
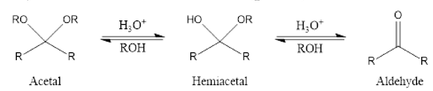


Figure 4. ABHS assay content for ethanol (left) and isopropanol (right) samples. The shaded regions represent efficacy ranges

Impurity Results (GC-MS)

- Impurity analysis was complicated by the interconversion of acetal and acetaldehyde under acidic conditions (pH<6).



- Due to the likelihood of acetal undergoing hydrolysis, acetal and acetaldehyde quantities were summed and reported as one value.

Table 4. Impurity results for ABHS samples

Sample Type	Impurity	Interim Limit (ppm)	Number of Samples	
			Liquid	Gel
Ethanol	Methanol	NMT 630	3	0
	Acetal/Acetaldehyde	NMT 100	201	5
	1-propanol	NMT 1000	1	0
	Ethyl acetate	NMT 2200	1	0
	3-methyl-1-butanol	NMT 4100	1	0
Isopropanol	Methanol	NMT 630	2	0
	Benzene	NMT 2	1	0
	Acetal/Acetaldehyde	NMT 100	0	1
	Acetone	NMT 4400	2	0

- Greater than 60% of samples tested contained violative levels of acetal and/or acetaldehyde. The FDA temporary hand sanitizer guidance labels these impurities as genotoxic and potentially carcinogenic.
- Ethanol-based samples with low pH showed the highest acetal/acetaldehyde levels, suggesting these conditions are more favorable for these impurities.

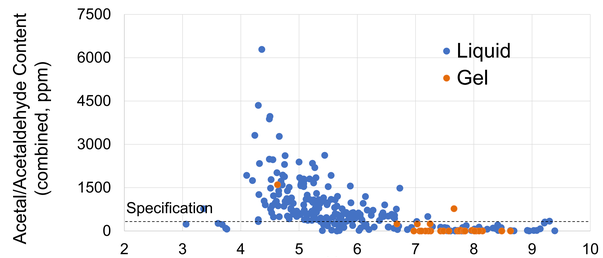


Figure 5. Acetal/acetaldehyde impurity content in ethanol ABHS samples as a function of pH.

Conclusion

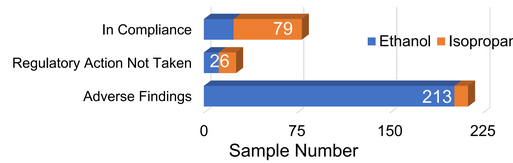


Figure 6. Lab classifications of ABHS for liquid formulations

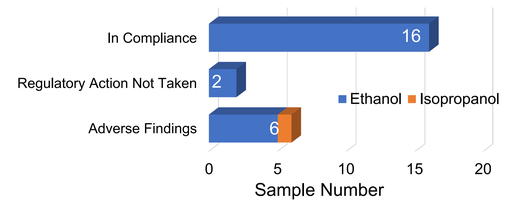


Figure 7. Lab classifications of ABHS for gel formulations

- ~85% of liquid ethanol-based samples contained violative levels of acetal and acetaldehyde impurities.
- Five samples contained methanol greater than the 630 ppm interim limit.
- One sample contained benzene at 18 ppm (interim limit NMT 2 ppm).
- Several samples contained violative amounts of level 2 impurities and are suspected of being manufactured using low grade alcohol.
- OTR provided all testing results and data to OQS. Following review, violative products were referred to the Office of Compliance/Office of Manufacturing Quality for enforcement actions including publicly identifying violative products on the "do-not-use" register.