U.S. FOOD & DRUG ADMINISTRATION

Keeping Products Safe for Consumers

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Learning Objective

- Describe how science drives regulatory actions to protect consumers from unsafe products utilizing the quality assessment of hand sanitizers as a case study

Overview:

- Importance of hand hygiene
- Agency temporary guidance used to influence laboratory testing
- Development/implementation of analytical methods for quality assessment of hand sanitizers
- Laboratory results used as evidence in enforcement actions

Background

- Hand hygiene important to mitigate spread of COVID-19, CDC recommends use of ***alcohol-based hand sanitizers*** (ABHS) when soap and water not available

- Hand sanitizers with benzalkonium chloride as active ingredient also available. ***Presentation will only focus on ABHS***

- Hand sanitizers are over-the-counter drug products frequently used by consumers

- Difficulty in accessing ABHS products due to increased demand

Background

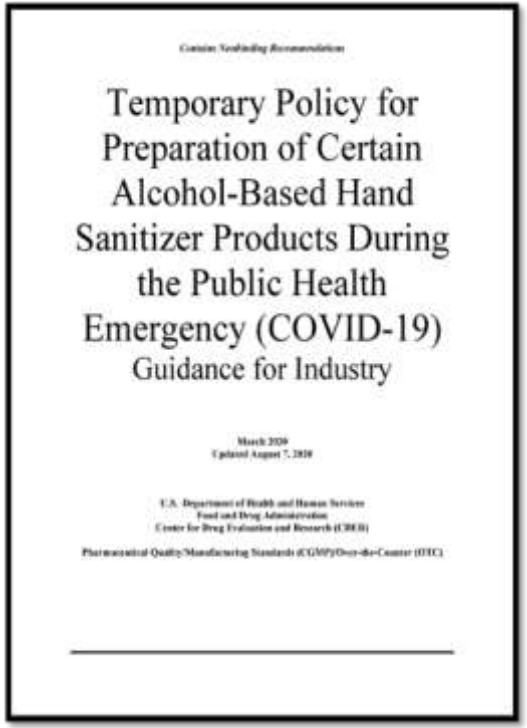
- In response, FDA issued a policy for testing alcohol for methanol and a guidance to communicate its temporary policy for preparation of ABHS

- Intended for entities not previously licensed or registered drug manufacturers

- CDC recommends ABHS contain at least 60% ethanol to be efficacious

Considerations for Ingredients:

- Alcohol meets USP or FCC grade
- Alcohol screened for potential harmful impurities (methanol substitution)



Temporary Policy for Preparation of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19)

Guidance for Industry

FRN recently announced withdrawal of temporary policies on ABHS

Laboratory Assessment

Goal: Develop testing protocol to evaluate quality of ABHS products based on temporary policy

Method Requirements:

- Identification
  - ❖Ethanol
  - ❖Isopropanol
  - ❖Alcohol substitution
- Assay - % alcohol content
- Impurities

Impurity	Interim Limit Under CDER Temporary Guidance for Hand Sanitizer Products (ppm)
Methanol	NMT 630
Benzene	NMT 2
Acetaldehyde	NMT 50
Acetal	NMT 50
Acetone	NMT 4400
1-Propanol	NMT 1000
Ethyl Acetate	NMT 2200
2-Butanol	NMT 6200
Isobutanol	NMT 21700
1-Butanol	NMT 1000
3-Methyl-1-Butanol	NMT 4100
Amyl Alcohol	NMT 4100

Rapid Screening of ABHS

Spatially Offset Raman Spectroscopy (SORS)

Through-Container Method

Advantage:

- Quickly screen ABHS products for alcohol substitution or subpotency
- Increase throughput and prioritize samples for additional testing
- Up-to-date public notices, prompt regulatory actions and remove harmful products from marketplace

Rapid Screening of ABHS

SORS ABHS Method:

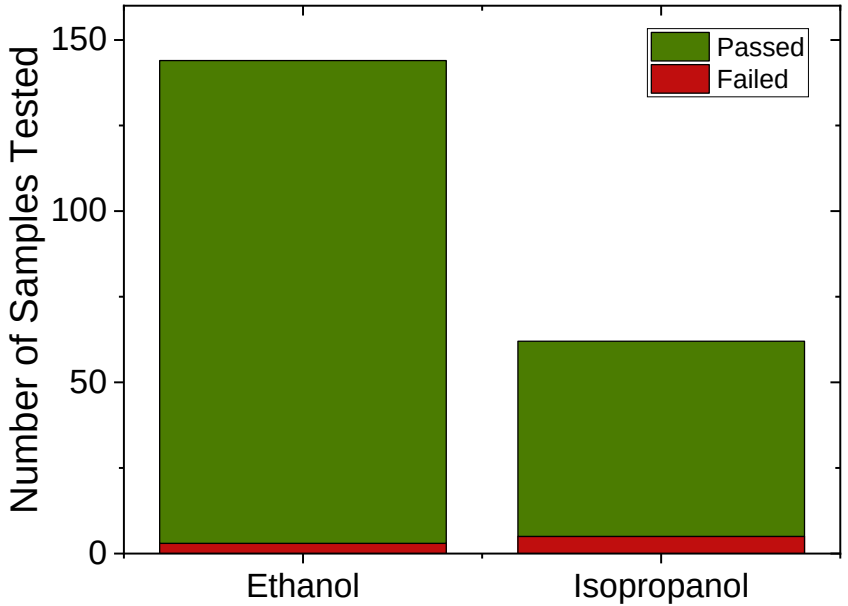
- Built custom hand sanitizer libraries for alcohol substitution and assay
- Sample analysis time 25 seconds
- Pass/Fail Results
- Method lacks sensitivity to detect impurities at levels specified in guidance

Limit of Detection (LOD)	Methanol in Ethanol-Based Hand Sanitizer	3.1 %v/v
	1-propanol in Ethanol-Based Hand Sanitizer	1.9 % v/v
	Methanol in 2-propanol-Based Hand Sanitizer	3.9 % v/v
	1-propanol in 2-propanol-Based Hand Sanitizer	2.6 % v/v
	Methanol in Water	0.49 % v/v
	1-propanol in Water	0.23 % v/v

Rapid Screening Results of ABHS

SORS ABHS Results:

- Alcohol identified in product differs from label claim ingredient
- Identified subpotent products
- Requires confirmatory testing, SORS method does not address all quality concerns outlined in temporary policy



Challenge Question #1

What alcohol has been found in alcohol-based hand sanitizers that has caused a significant number of adverse events including death after ingesting?

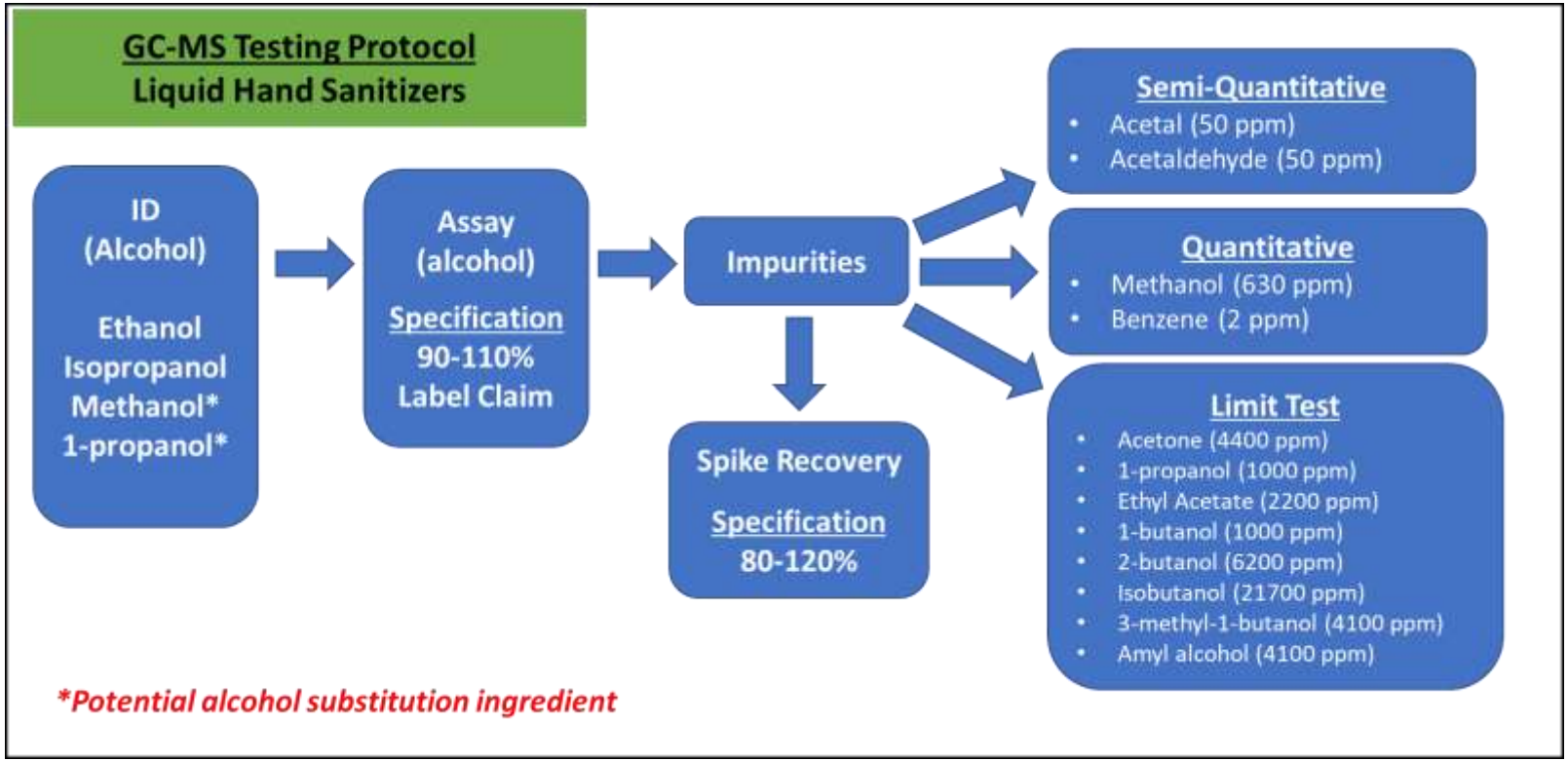
A. Ethanol
B. Isopropanol
C. Methanol
D. 1-Propanol

Gas Chromatography-Mass Spectrometry (GC-MS)

Advantage:

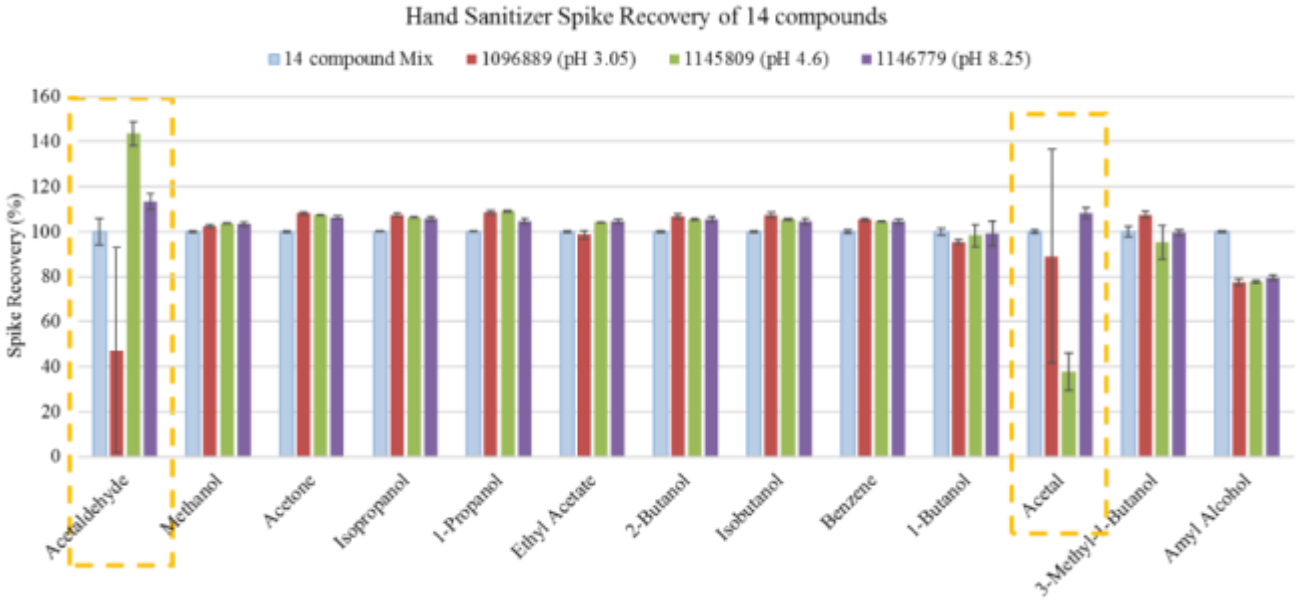
- Single method for assay and impurities determination
- Acceptable specificity and sensitivity for all active ingredients and impurities identified in guidance
- Method can be applied to all formulations of ABHS, including **liquids**, gels, foams and wipes

GC-MS Testing Protocol



Analysis of Ethanol-Based Hand Sanitizers

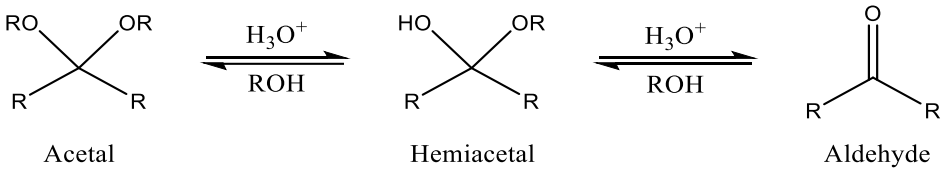
- Irregularities in spiked recoveries of acetal and acetaldehyde observed during analysis of several ethanol-based hand sanitizers



Acceptable range for spike recovery is 80-120%

Analysis of Ethanol-Based Hand Sanitizers

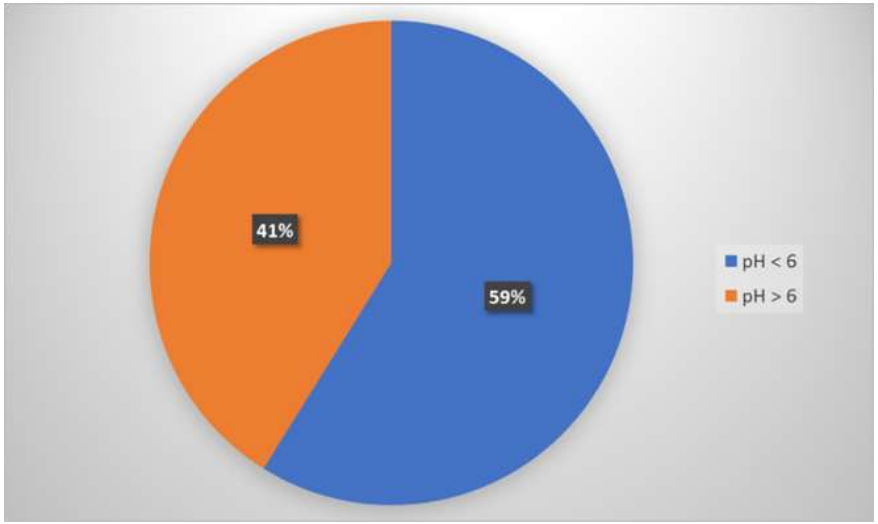
- In neutral and basic conditions, acetal is chemically stable; but in acidic conditions, acetal hydrolyzes into acetaldehyde and ethanol.



Results of pH Studies:

- 265 ethanol ABHS evaluated
- pH values ranged 3.4 to 9.4
- Nearly 60% of samples had pH< 6

Results of pH of Ethanol ABHS



Case Study – ABHS 1099537

Sample Information	
Sample #	1099537
Active Ingredient	80% v/v Ethanol
pH	4.5
Test Results	
Assay (% v/v ethanol)	82.2%
% Label Claim (LC)	102.7%
% LC Specification	90.0-110.0%

Sample

- *Sample has acidic pH*
- *Sample fails for high levels of impurities*

GC-MS Results - Sample 1099537			
	(41x) Diluted		Interim Limit Under Guidance (ppm)
Compound	Recovery (%)	Amount of Impurity (ppm)	
Acetaldehyde	99	283	NMT 50
Methanol	101	ND	NMT 630
Acetone	100	ND	NMT 4400
1-propanol	100	ND	NMT 1000
Ethyl acetate	99	185	NMT 2200
2-butanol	100	ND	NMT 6200
Isobutanol	99	ND	NMT 21700
Benzene	100	ND	NMT 2
1-butanol	100	ND	NMT 1000
Acetal	103	1953	NMT 50
3-methyl-1-butanol	100	ND	NMT 4100
Amyl alcohol	100	ND	NMT 4100

Challenge Question #2

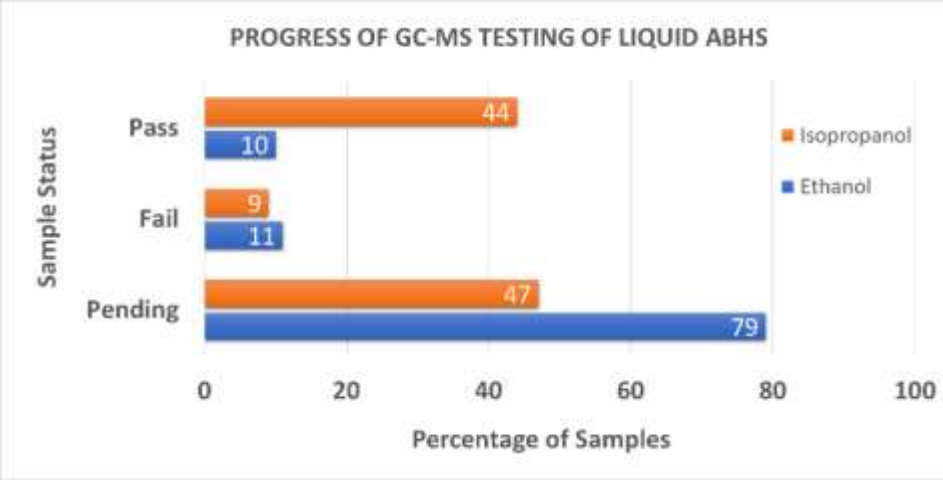
What impurities are difficult to quantitate in ABHS products with acidic pH (pH < 6.0)?

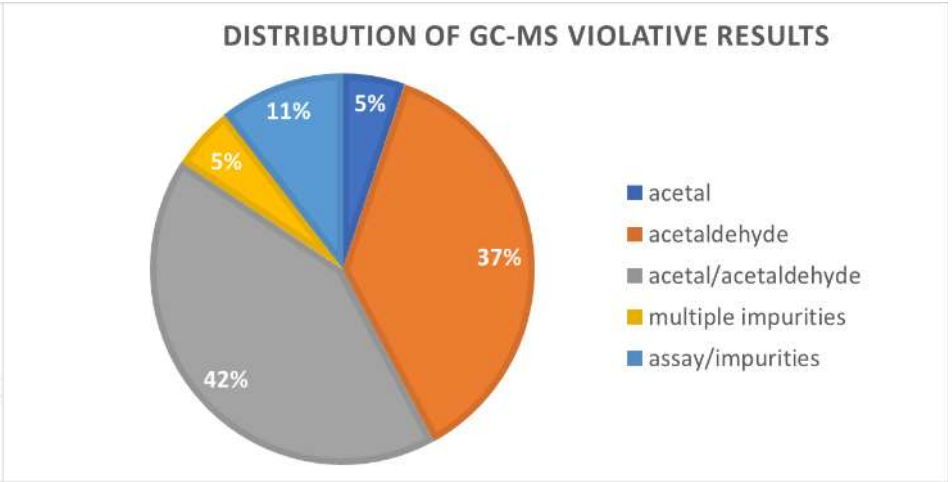
A. Methanol and Acetal
B. Acetal and Acetaldehyde
C. Methanol and Benzene
D. Acetal and Acetone

GC-MS Test Results of Liquid ABHS

GC-MS Liquid ABHS Results:

- ~ 75% of the 325 ABHS samples collected contain ethanol as the active ingredient





FDA Response to Poor Quality ABHS Products

- Refuse Admittance (imports)

- Internet and Social Media Warnings
  - ➢ Public Notifications
  - ➢ Enforcement and Recall Information

- Some firms have recalled ABHS products and more than 250 products FDA recommends consumers not use (Do Not Use List)

Summary

- FDA tested ABHS products for quality because it's a product under its regulation
- FDA laboratories developed and validated analytical methods to assess the quality of ABHS products (SORS, GC-MS)
- Serious safety concerns were discovered for some ABHS as a result of laboratory testing, including
  - Contamination with potentially toxic types of alcohol (methanol, 1-propanol)
  - Impurities listed in the guidance detected in ABHS above the specified limits
  - Not enough active ingredient (ethanol or isopropanol)
  - Labels with false, misleading or unproven claims

Resources

- Temporary Policy for Preparation of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19) Guidance for Industry
- Policy for Testing of Alcohol (Ethanol) and Isopropyl Alcohol for Methanol, Including During the Public Health Emergency (COVID-19)
- Alcohol-Based Hand Sanitizer Products; Withdrawal of Three Temporary Guidance Documents Issued During the Public Health Emergency of the Coronavirus Disease 2019
- Coronavirus (COVID-19) Update: FDA Takes Action to Warn, Protect Consumers from Dangerous Alcohol-Based Hand Sanitizers Containing Methanol
- Through-container quantitative analysis of hand sanitizers using spatially offset Raman spectroscopy
- Hand Sanitizers Consumers Should Not Use

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SORS Method:

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Questions?

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Closing Thought

Laboratory science drives regulatory action to protect consumers from unsafe products. Even over-the-counter products, like hand sanitizers, can be susceptible to quality deficiencies.