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# Ensuring Quality Hand Sanitizer Production During COVID-19 Seminar

## Formulating Quality Hand Sanitizers: The Value of USP-NF Standards

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## What we will talk about:

- ▶ What are USP Standards?
  - Introduction to USP Public standards
- ▶ What is an Excipient
  - Definition
- ▶ Importance of Up-to-date Excipient Standards
  - Identification and Assay testing
  - Recent updates to Alcohol monographs to include a test for methanol in the Identification section
- ▶ Summary and Conclusions



- ▶ USP Excipient Monographs
  - Public Standards
  - Define what “good” looks like for an article
  - Define requirements for Assay, Purity, Contaminants and Specific Tests for Performance and other Quality Attributes
  - Continuously modernized to incorporate new technologies for testing and new data



## ▶ USP Excipient Monographs

— Compliance with Monograph is based on:

- Testing the Article and meeting limits in the monograph
- Manufacture of the Article under appropriate Good Manufacturing Practices (USP General Notices, Section 3.10 states in part, “Official products are prepared according to recognized principles of good manufacturing practice and from ingredients that meet USP or NF standards, where standards for such ingredients exist”



- ▶ USP Excipient GMP General Information Chapters
  - Public Standards
  - Support Monographs
  - Define requirements for Manufacturing Quality Systems and Supporting Functions
  - Continuously updated to incorporate best industry practices
- ▶ USP General Chapters
  - numbered below 1000 contain requirements applicable to monographs, when cited
  - numbered 1000 to 1999: for informational purposes only

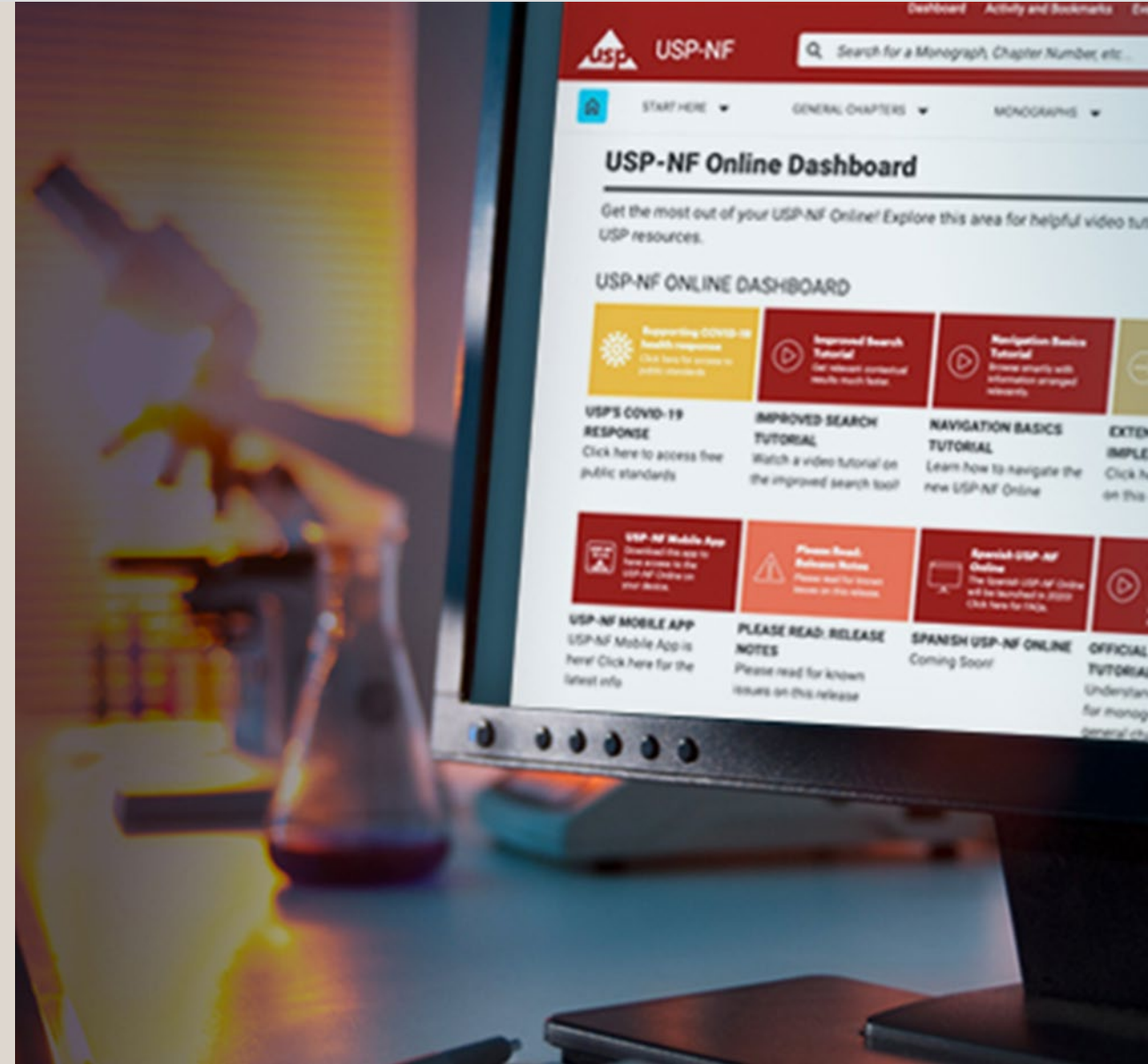
## Excipient GMP related Information Chapters and NF Functional Category Listing

- ▶ *<1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients*
- ▶ *<1080> Bulk Pharmaceutical Excipients—Certificate of Analysis*
- ▶ *<1195> Significant Change Guide for Bulk Pharmaceutical Excipients*
- ▶ *<1197> Good Distribution Practices for Bulk Pharmaceutical Excipients*
- ▶ *<1059> Excipient Performance*
- ▶ *<1074> Excipient Biological Safety Evaluation Guidelines*
- ▶ *Excipients - USP and NF Excipients, Listed by Functional Category*

# What is an Excipient?

## Excipient Definition

- ▶ “Excipients are substances other than the API that have been appropriately evaluated for safety and are intentionally included in a drug delivery system.” (USP 42/NF 37 General Information Chapter GMP <1078>)
- ▶ FD&C Act [21 U.S.C. 321] Section 201(g)(1). Term “drug” includes articles intended for use as a COMPONENT of any article meeting the drug definition
- ▶ 21 CFR 210.3(b)(8): an inactive ingredient is any component of a drug other than the active ingredient



# Raw Materials/Components Can Cause Quality Concerns

- ▶ Specifications during the product lifecycle are heavily focused on active ingredient and the final product
- ▶ However, failures of products can be caused by non-active raw materials (components)
- ▶ Raw material quality concerns have been amplified by materials supply issues over the decades (Glycerin, Heparin, Melamine, most recently with Alcohols)
- ▶ Some components are more critical than others, so risk assessment strategies are required to ensure quality

“The 2010 Task Group’s aim was to identify USP/NF monographs in need of modernization and is especially focused on monographs with outdated analytical methods that may make the drug or excipient **vulnerable to economically-motivated adulteration (EMA) or that have inadequate tests.**”

*[Emphasis added]*

Source: November 16, 2010 Letter from FDA Task Group to USP

History of USP/FDA correspondence on monograph modernization available here:  
<https://www.usp.org/get-involved/partner/monograph-modernization-history>



# FDA encourages USP to update monographs

## ▶ *The following is part of the 2010-10-12 Letter from FDA to USP:*

We believe that USP's current monograph modernization program is a good start toward achieving our objective. However, it is important that the initiative be completed with urgency and that USP's efforts focus on drug products and ingredients that have the most potential for problems. In addition to the currently identified "top 200 small molecules monographs and 96 excipient monographs," we encourage USP to update all monographs that include non-specific assay or identification tests, and to re-evaluate antiquated methodologies in general. FDA strongly believes that monographs utilizing outdated analytical procedures are vulnerable to economically motivated adulteration (EMA), and current advancements in science and technology can help to fill the void. We are similarly concerned about outdated OTC monographs, and will be sending you our expert input on OTC monographs that need to be revised.

FDA has established a new task group in CDER to focus on the USP monograph modernization initiative. This group is responsible for developing a strategy to identify priority products for monograph modernization to provide requested FDA assistance to USP in your modernization efforts.

USP/FDA correspondence is available here:

<https://www.usp.org/get-involved/partner/monograph-modernization-history>

- ▶ **USP continues its focus on updating *USP-NF* excipient monograph standards that lack the following:**
  - Specific Identification (ID) tests.
  - Adequate assay procedures.
  - Impurity specifications
  - Better characterization and composition tests for polymers/mixtures.

# Methodologies Used in Excipient Monographs Up-to-date

Test	Up-to-date methods	Examples
Identification (ID)	Orthogonal approach – spectroscopic methodology and separation science used together	IR and Chromatographic Identity
	Utilization of chemical composition profile	Fatty Acid Composition by GC Glyceride Composition by HPTLC or HPLC Aromatic compound profile by GC
	Other advanced technologies	X-Ray Diffraction and Optical Microscopy for mineral based excipients SDS-Polyacrylate Gel Electrophoresis (PAGE) and size exclusion chromatography (SEC)) for protein based excipients
Assay and Impurities	stability-indicating HPLC or GC procedures	Replacement of non-specific titrimetric procedures in many simple molecular excipient monographs HPLC procedures for some oil monographs
	size exclusion chromatography (SEC)	Introduction of SEC in polymeric and protein based excipients

- ▶ **Orthogonal approach – spectroscopic methodology and separation science used together provide greater assurance of uniquely identifying an excipient**
  - Infrared (IR) spectroscopy – fingerprinting identity
  - Chromatographic Identity (retention time against that of USP Reference Standard)
  
  - Examples:
    - Small molecules
      - Hexylene glycol
      - Ethyl maltol
      - Asparagine
    - Monodispersed synthetic polymeric based excipients
      - Polyethylene Glycol 3350

## ▶ Added and replaced non-specific assays with stability-indicating LC or GC procedures

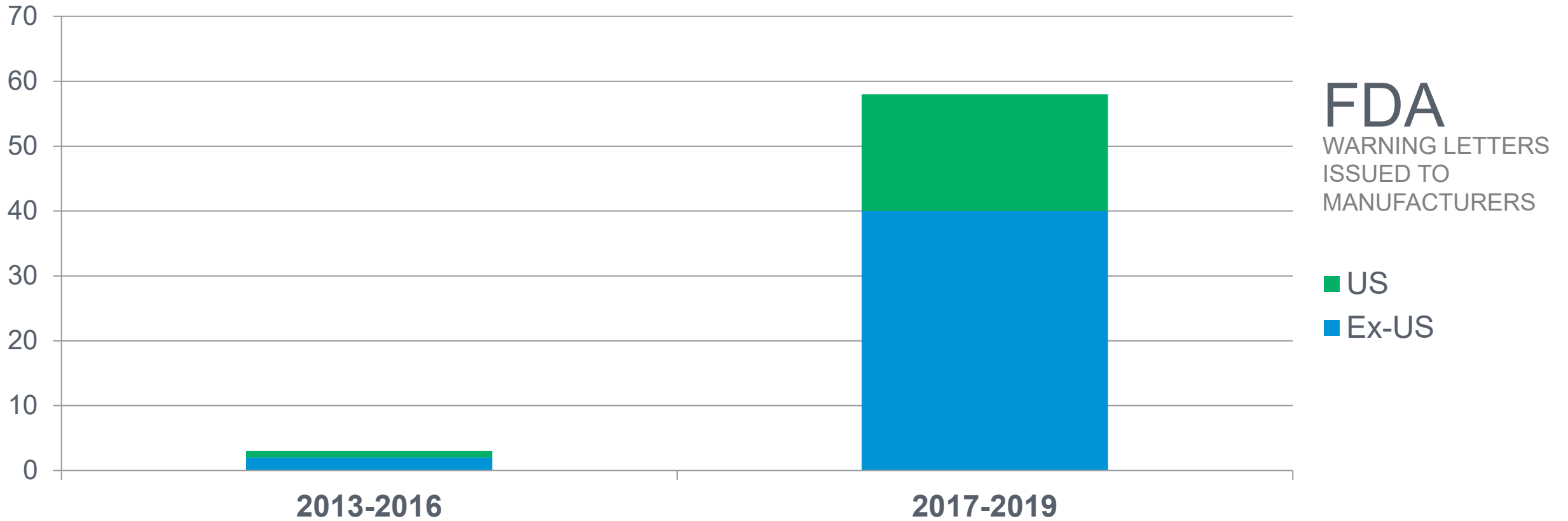
### — Examples:

- Introduced GC methods for both assay and impurity tests
  - Hexylene Glycol
    - same GC conditions for both assay and impurity tests
  
- Replaced non-specific procedures
  - Asparagine
    - replaced titrimetry-based assay with HPLC assay
    - Replaced TLC-based impurity test with HPLC method
    - Assay and impurity HPLC methods shared the same chromatographic conditions
  - Saccharin, Saccharin Calcium, and Saccharin Sodium
    - replaced titrimetry-based assay with HPLC assay

## ▶ Testing Deficiencies

- US FDA is sending deficiency letters to applicants, with respect to the functionality of the excipients, vs. quality and purity (monograph defined specifications) of excipients.
- Recently, US FDA has sent Warning letters with respect to lack of identity testing conducted on incoming excipients
- Monographs are missing tests that can discriminate (e.g., ID) and detect impurities
- Many users are not aware of deficiencies

# FDA warning letters citing excipient testing issues



## ▶ 21 C.F.R. § 211.84(d)(I) (Subpart E)

### – Control of Components...

- *“At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.”*

## ▶ 21 C.F.R. § 211.84(d)(2)

- *“Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier’s analyses through appropriate validation of the supplier’s test results at appropriate intervals.”*



# USP and FDA Updates on Methanol Testing in Alcohol, Dehydrated Alcohol Monographs



- ▶ July 30: [Letter from the U.S. Food and Drug Administration \(FDA\)](#) FDA reports increasing number of hand sanitizer products contaminated with Methanol
- ▶ FDA requests including a Limit Test for Methanol in the “Identification” section of the Alcohol and Isopropyl alcohol monographs and any related *USP-NF* monographs to help prevent Methanol contamination
- ▶ FDA recommends incorporating into the “Identification” section the Methanol **limit already required in the Organic Impurities** test of the **USP Alcohol** and **USP Dehydrated Alcohol** monographs (200 µL/L)
- ▶ If Methanol detection and quantification is part of the “Identification” test
  - CGMP regulations at 21 CFR 211.84(d)(1) would require manufacturers of drug products to detect and quantify any Methanol present for each lot of Alcohol or Dehydrated Alcohol received
- ▶ If Methanol detection and quantification is **only** part of an “Impurity” test
  - Manufacturer need not include as part of its identity testing the detection and quantification of Methanol in the Alcohol or Dehydrated Alcohol. In addition, a manufacturer could deviate from the impurity requirements established in the monograph by labeling the product to indicate that it deviates from the USP test requirements

# USP and FDA Updates on Methanol Testing in Alcohol, Dehydrated Alcohol Monographs - Stakeholder Engagement



- ▶ USP held webex meetings with FDA to discuss the impact and timeline regarding FDA's letter to revise Alcohols - July 27, 28, 31
- ▶ USP posted a Notice of Intent to Revise (NITR) on July 31, 2020 to notify stakeholders of the upcoming proposed revision of two Alcohol monographs using USP's Accelerated Revision process – Revision Bulletin,
  - NITR Posting July 31, 2020; NITR feedback end date: August 13, 2020
- ▶ USP & FDA webex stakeholder engagement: August 10, 2020 (shared draft Revision Bulletins)
- ▶ USP Alcohol and USP Dehydrated Alcohol Revision Timeline
  - Revision Bulletin Posting on USP.org website: August 17, 2020
  - Revision Bulletin Official Date: September 1, 2020
  - USP posted an FAQs on the USP website for these revisions
- ▶ USP will announce revisions to the other alcohol monographs at a future date

# According to USP General Notices

## ▶ Section 2.20. Official Articles

- An official article is an article that is recognized in *USP* or *NF*
- Official articles include both official substances and official products.
- Both a drug substance (API) and an excipient are considered an official substance

## ▶ Section 3.10. Applicability of Standards

- Official substances are prepared according to recognized principles of good manufacturing practice and from ingredients complying with specifications designed to ensure that the resultant substances meet the requirements of the compendial monographs.
- The applicable USP or NF standard applies to any article marketed in the United States that (1) is recognized in the compendium and (2) is intended or labeled for use as a drug or as an ingredient in a drug. ... The applicable standard applies to such articles whether or not the added designation “USP” or “NF” is used....
- ... any official article is expected to meet the compendial standards if tested, and any official article actually tested as directed in the relevant monograph must meet such standards to demonstrate compliance.

# Summary and Conclusions

Pharmacopeial standards can provide tools for compliance with regulatory requirements

*USP-NF* excipients standards have great value in the characterization and selection of excipients for pharmaceutical use.

- ▶ Up-to-date standards can help with controlling the quality of excipients in drug product development, e.g., through Identification, Assay, Impurity tests.
- ▶ Up-to-date standards can help with controlling the integrity of the supply chain and prevention of adulteration, e.g., Glycerin, Alcohol(s) revisions.

# Biography and Contact Information

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# Thank You

