Importance of excipient quality and development for use in medicines

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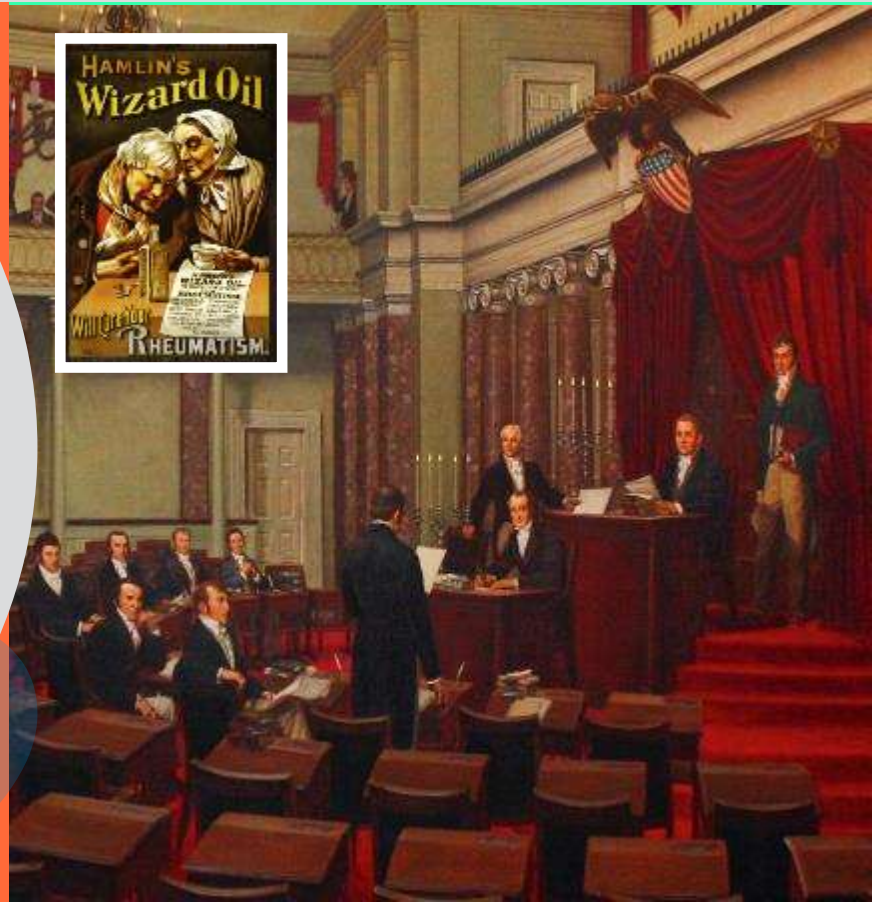
Agenda

1. Introduction
    a) USP and USP-NF: USP enduring mission, Role of USP Quality Standards
    b) Excipients: Importance of Excipients !
2. Excipients: Strategies and regulatory focus
3. USP Standard setting process
4. DEG/EG contamination
5. USP toolkit for measuring and controlling levels of DEG

USP's enduring mission

To improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods.



Role of USP Quality Standards

- In the United States under the Federal Food, Drug, and Cosmetic Act (FD&C Act), both *United States Pharmacopeia* (*USP*) and the *National Formulary* (*NF*) are recognized as official compendia for drugs marketed in the United States.

- **Section 501 - Adulterated Drugs and Devices**
  - A drug with a name recognized in *USP-NF* must comply with compendial identity or be deemed adulterated, misbranded, or both. (501(b) & 502(e)(3)(b)). …..***Cannot label away from identity*!**
  - Must also comply with compendial standards for strength, quality, and purity, unless labeled to show all differences (501(b) & 21 CFR 299.5).

Role of USP Quality Standards

- **FD&C Act [21 U.S.C. 321] Section 201(g)(1)**

The term “drug” means:

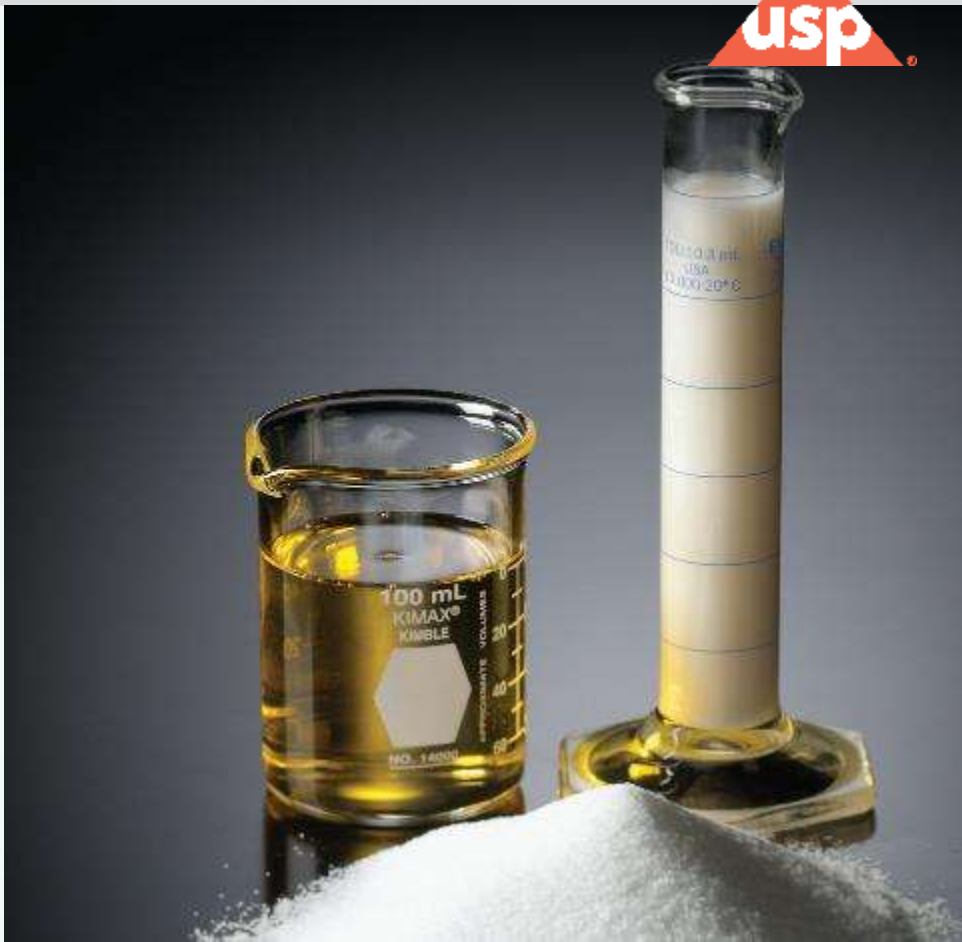
- recognized in an official US compendium: United States Pharmacopeia, Homoeopathic Pharmacopoeia, or National Formulary
- intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease
- intended to affect the structure or any function of the body
- **intended for use as a COMPONENT of any article meeting the above criteria**

Why excipients are important !

- **Excipients** can make up to about 90% of the total mass/volume of medicinal products.
- Some of functional categories include lubricant, pH Modifier, diluent etc.,

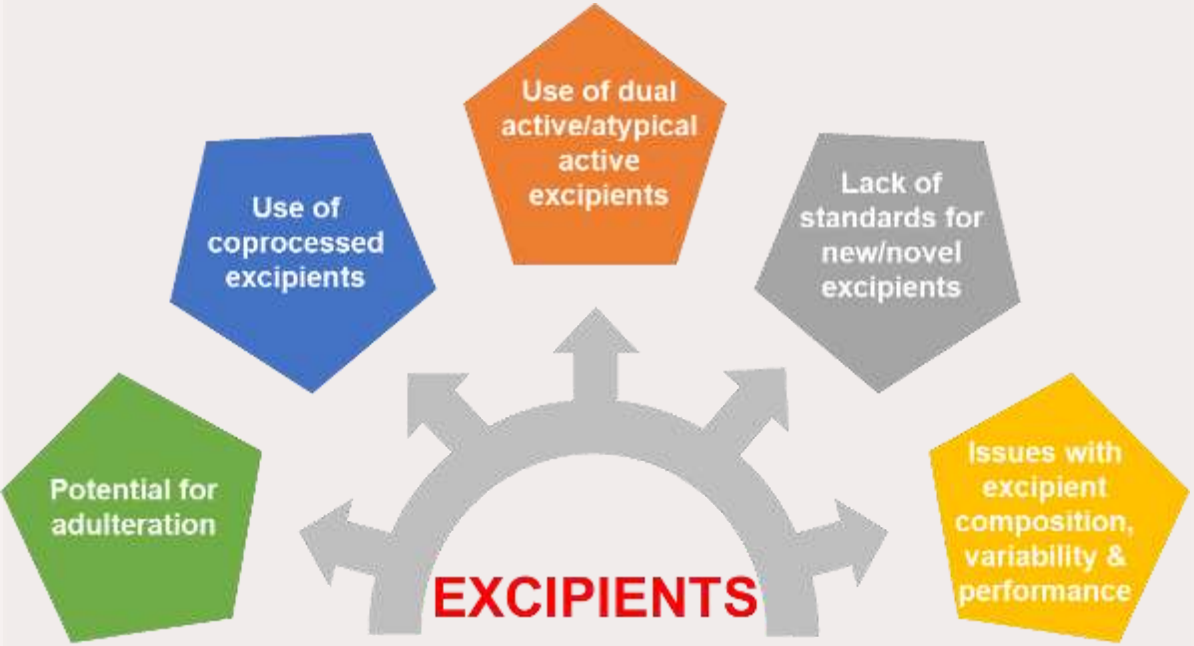
NF category listing of Excipients

- They often help ensure the API is delivered to the site of action.
- Complex non-transparent supply chains can lead to economically motivated or accidental adulteration.



Excipient Strategies for quality standards

Focus on Excipients has changed



- Traditionally, excipient specifications were established with a focus on intended use in the drug product and less on excipient composition.
- Starting from 2005-2010 revision cycle, the Expert Committee's focus on excipients has changed.

Understanding the interplay between USP-NF standards and GMPs for excipients

As per General Notice 3, Conformance to Standards (section 3.10, applicability of standards), official articles (e.g., excipients) are prepared according to recognized principles of GMP

USP chapter <1078> provides guidelines of GMP of bulk pharmaceutical excipients, covering a section on quality management system

Manufacturers should ensure that test methods are suitable for intended use, using USP chapters <1225> and <1226> on method validation and verification

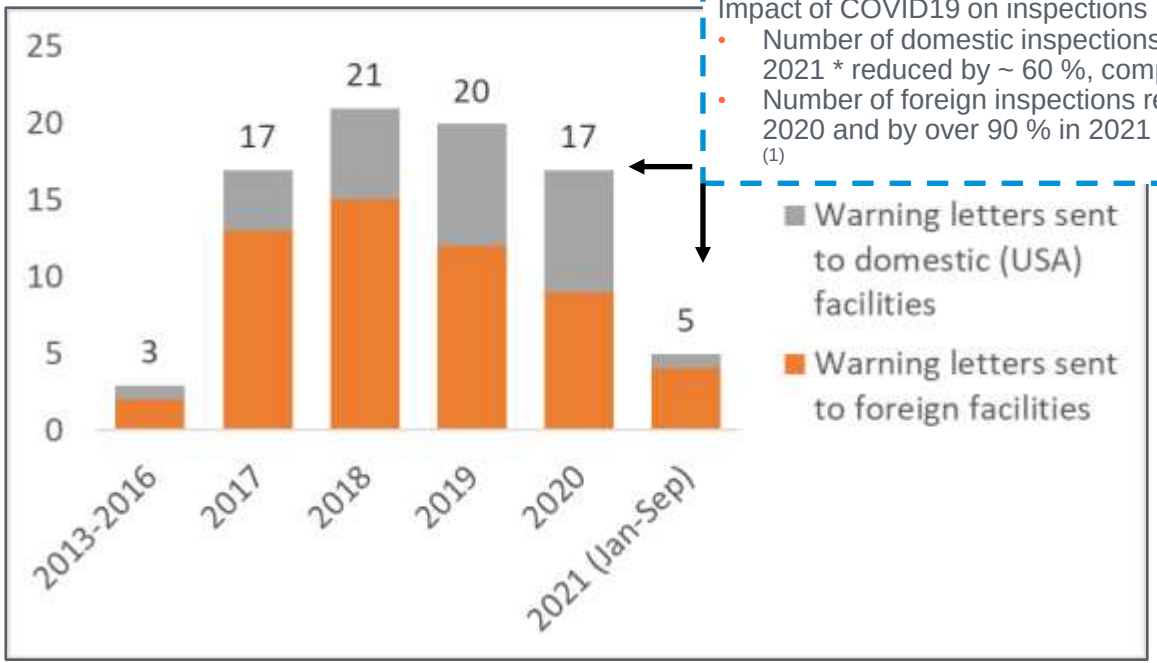
If unsuitable methods are used, it could lead to release of products with quality issues in the market, consequently, leading to time-consuming and expensive remedial actions.

In case of excipients, quality issues can be a significant patient safety issue as excipients are used in multiple drugs across dosage forms

Challenges with Pharmaceutical Excipients

- Excipients developed and manufactured specifically for pharma use sometimes have
  - Special grade or grades available (e.g., MCC, Mag. stearate)
- Multisource suppliers of the same grade
  - Lot-to-lot / batch-to-batch / supplier inequivalence or variability
  - Variability in excipient properties impacts consistent performance
  - Vast diversity of excipient applications exist in product development
- Desire to improve characterization of excipient composition
  - Use of complex excipients in highly specialized drug delivery systems
- Increasing complexity and global scope of pharmaceutical supply chains
  - Standards help to conserve the supply chain integrity

Increase in FDA warning letters citing CGMP violations related to excipients since 2016 in both domestic (USA) and Foreign drug manufacturing facilities



Impact of COVID19 on inspections

- Number of domestic inspections each in 2020 and 2021 * reduced by ~ 60 %, compared to 2019 (1)
- Number of foreign inspections reduced by ~ 80 % in 2020 and by over 90 % in 2021 *, compared to 2019 (1)

* Full year approximation based on data from Jan-Sep 2021

FDA Warning Letters citing failure to test for identity of incoming excipients and/or failure to periodically reconfirm the excipient suppliers' COA

1) https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-classification-database

The journey of a standard is not a straight path

Engagement around knowledge is an essential thread

USP standards for ensuring excipient quality

Over 530 Monograph (documentary standards) on excipients in *USP-NF*

General Notices 4. MONOGRAPHS AND GENERAL CHAPTERS
4.10. Monographs

- USP - NF provide the appropriate, validated test procedures to establish the identity, purity and quality of excipients. **Subscribe to USPNF.com**

Over 325 excipient Reference Standards (across 13 functional categories) that have been approved as suitable for use as comparison standards in USP or NF tests and assays. Visit USP store

GN 5.80. USP Reference Standards

- USP Reference Standards are authentic specimens that have been approved as suitable for use in USP or NF tests and assays (see *USP Reference Standards* ⟨11⟩)

GN 4.20. General Chapters
……(e.g., Chromatography ⟨621⟩).
General chapters may contain the following:
……Descriptions of tests and procedures for application through individual monographs….

- General information for the interpretation of the compendial requirements…….
- **General guidance to manufacturers of official substances or official products.....**
- When a general chapter is referenced in a monograph, acceptance criteria may be presented after a colon.
- Some chapters may serve as introductory overviews of a test or of analytical techniques.
- They may reference other general chapters that contain techniques, details of the procedures, and, at times, acceptance criteria.

USP Excipient GMP related General Chapters include:

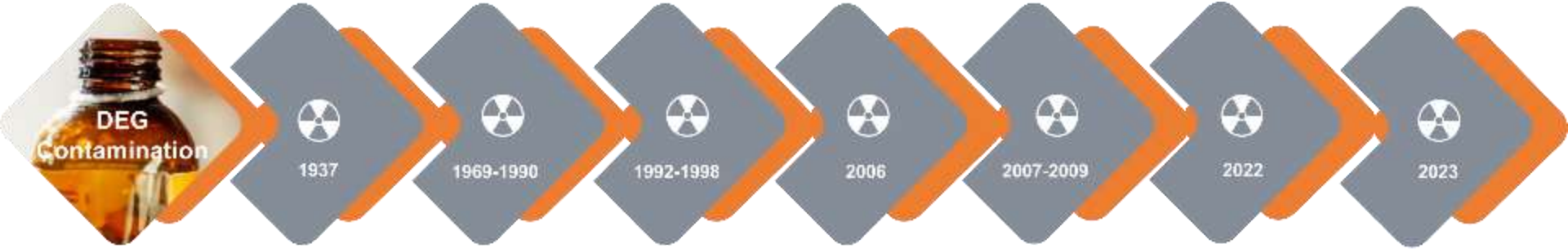
<1078> Good Manufacturing Practices for bulk pharmaceutical excipients,

<1197> Good Distribution Practices for bulk pharmaceutical excipients

⟨1080⟩ Bulk pharmaceutical excipients—certificate of analysis

⟨1195⟩ Significant change for Bulk pharmaceutical excipients

Diethylene glycol incidents and deaths
(compiled from various sources)



DEG Contamination

1937 - USA

Sulfanilamide Elixir; Resulted in Implementation of the FD&C Act in 1938 (107)

1969-1990

1969: South Africa- Sedative formulated with DEG (7)
1985: Spain-Silver sulladiazine topical application (5)
1986: India- Medicinal glycerin laced with DEG (14)
1990: Nigeria- Acetaminophen syrup containing DEG (some sources say 200 deaths) (40)
1990: Bangladesh- Acetaminophen syrup containing DEG (339)

1992-1998

1992: Argentina- Propolis Syrup (for mild upper respiratory infections) (29)
1995/6: Haiti- Cough medicine containing DEG (85)
1998: India- Cough medicine and acetaminophen syrup containing DEG (41)

2006

2006: Panama-Cough and anti-allergy syrup containing DEG (46)
2006: China- Armillarisin-A contaminated with DEG (12)
2006/7: USA- Toothpaste containing DEG

2007-2009

2007: Panama- Toothpaste containing DEG
2008/9: Nigeria- Teething formula contaminated with DEG from propylene glycol (84)
2009: Bangladesh- Paracetamol syrup for children adulterated with diethylene glycol (24)

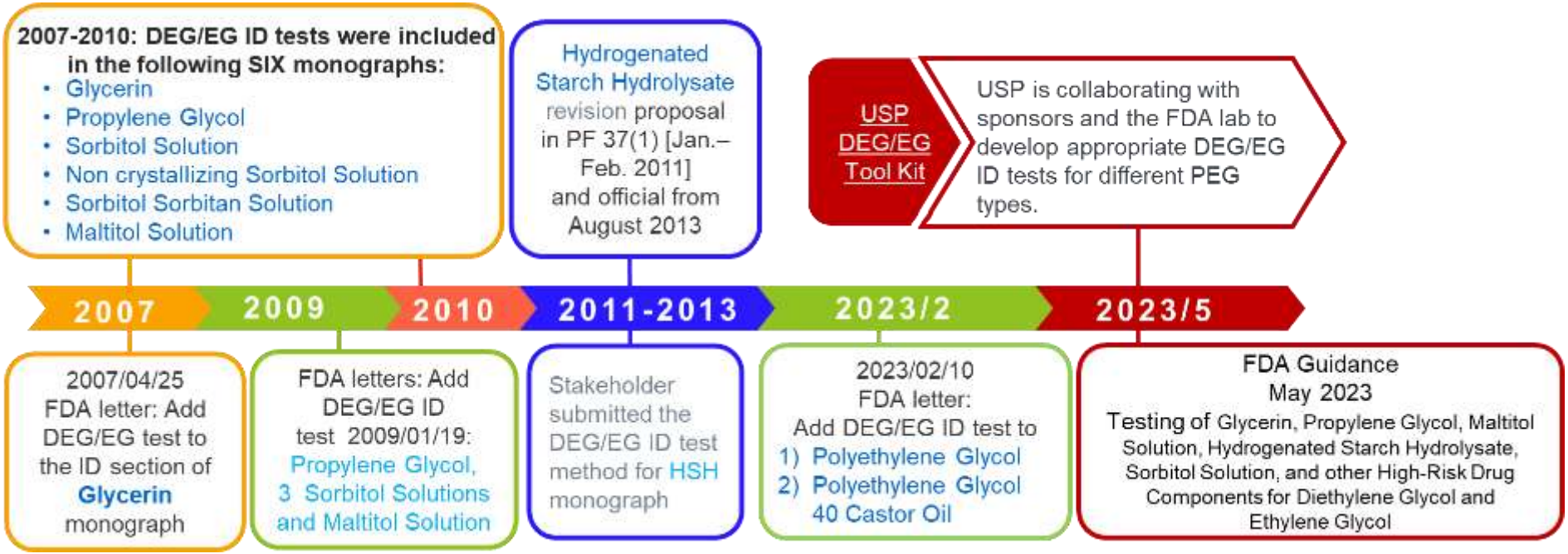
2022

2022: Gambia- Contamination in cough syrups manufactured by an India company
2022: Indonesia- Contamination in cough syrups, resulting from use of glycerin that was not suitable for pharma use and potentially entered the supply chain due to mislabeling

2023

2023: Uzbekistan- Contamination in cough syrups manufactured by another India company, potentially due to contaminated propylene glycol supplied by a local excipient manufacturer
2023: Marshall Islands Guaifenesin Syrup TG Syrup identified in the Marshall Islands and Micronesia

Collaborative Efforts on Addressing Adulterants and Contaminants



Addressing Adulterants and Contaminants for EG/DEG
Acceptance criteria for EG and DEG

- Limit of EG and DEG as part of ID tests in **seven** *USP–NF* monographs (Glycerin, Propylene Glycol, four Sugar Alcohols (three Sorbitol Solns. and Maltitol Soln.) and Liquid Hydrogenated Starch Hydrolysate (HSH), acceptance criteria: **NMT 0.10% for EG and NMT 0.10% for DEG**.

2023 FDA Guidance

- In May 2023 FDA Guidance for Industry: **Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol,** compliance to the identity standards in USP–NF monographs is required, and where the monograph (as below) has an ID test limiting EG and DEG as potential adulterants/contaminants, it is required to perform such identification test on each shipment of each lot of the component to ensure that the component contains NMT 0.1 % of EG and DEG before use in drug product manufacturing.
- USP collaborative efforts in 2007–2012 on updating the **seven** *USP–NF* monographs with DEG ID tests contributed to the above May 2023 FDA Guidance for Industry.

Collaborative Efforts to Address EG/DEG Process Impurities

Monitor Process Impurities for EG and DEG in Ethoxylated Excipients

- Several ethoxylated material manufacturers reported that the starting material, ethylene oxide, reacts with water to generate EG, and DEG (dimer of EG). Both EG and DEG are toxic.
- The manufacturers submitted to USP their in-house methodologies and validations to help establish the test for *Limit of Ethylene Glycol and Diethylene Glycol* to monitor and control EG and DEG, which are process intermediates (impurities).
- USP used the general chapter approach to address these process impurities.

2013-2022

General Chapter <469> Ethylene Glycol, Diethylene Glycol, and Triethylene Glycol in Ethoxylated Substances

The methodology in GC <469> can be used to monitor process impurities for EG and DEG in 17 polymeric excipients. GC <469> is a procedure-based chapter without acceptance criteria.

Develop and update Butylene Glycol, Polyethylene Glycol 3350, Polyoxyl 35 Castor Oil, Polyoxyl 40 Hydrogenated Castor Oil, Polyethylene Glycol 40 Castor Oil by adding the EG/DEG test.

2023 FDA Request Letter

- In February 2023, FDA submitted RFRs to **Polyethylene Glycol** and **Polyethylene Glycol 40 Castor Oil** monographs to recommend adding ID tests for limiting EG/DEG (https://www.usp.org/get-involved/partner/monograph-modernization-history)
- For other high-risk drug components that are mentioned in 2023 May FDA Guidance, USP works closely with the FDA to identify the components and searches suitable methods that can be used as ID tests for limiting EG/DEG
- **The methods to address EG/DEG process impurities in USP compendia may not be suitable for ID tests**

Polyethylene Glycol NF – Current Status

Identification

No Identification test

Assay

Average Molecular Weight

Impurities

2 DEG/EG test methods for MW ≤ 1000

- A packed GC column method for MW < 450
  (NMT 0.25% of the sum of EG/DEG)
- A UV method for MW 450 -1000
  (NMT 0.25% of the sum of EG/DEG)

MW Types

- There are 44 types in the current NF PEG monograph, covering MW up to 8000.
- There is a separate USP Polyethylene Glycol 3350 monograph. (It has a DEG/EG impurity test.)
- USP plans to develop a separate Polyethylene Glycol 20000 monograph.

Current PEG monograph: Issues and Possible Solutions

Polyethylene Glycol	DEG/EG test	Issues	Solution
MW < 450	A packed gas-chromatography (GC) method for impurity analysis	Packed GC columns are difficult to purchase	Collaborate with stakeholders to develop a new capillary GC based ID test
MW 450 -1000	An ultra-violet (UV) method for impurity analysis	Tedious, less accuracy, lack of capable analyst to perform the test, etc.	
MW > 1000	FDA requests to include a DEG/EG test	No DEG/EG method in the current monograph	New gel permeation chromatography (GPC) method for PEG MW > 1000

Challenges in developing EG/DEG ID tests

- **Challenges in developing an EG/DEG ID test for PEG MW ≤ 1000:**
  - The capillary GC method in general chapter <469> can be used for impurity analysis of DEG/EG, but not for ID testing, due to long incubation time at high temperature before and after each injection to burn off PEG polymers, resulting in short GC column lifetime.

Temperatures

Detector: 290°

Injection port: 270°

Column: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
40	10	60	5
60	10	170	0
170	15	280	0, 60[a]

[a] Hold time was 0 min for the *Standard solution* and 60 min for the *Sample solution* and *Diluent*.

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Challenges in developing EG/DEG ID tests

- **Acceptance Criteria:**
  - The current PEG monograph: NMT 0.25% of sum of EG and DEG.
  - The FDA 2023 Guidance: NMT 0.10% of DEG and NMT 0.10% of EG
- Polyethylene glycol is manufactured by addition-polymerizing ethylene oxide to ethylene glycol or diethylene glycol in the presence of an alkali catalyst with heating under elevated pressure.
- If the manufacturing process is not complete, more unreacted EG could be detected. As the PEG molecular weight increases, the amount of EG and DEG decreases.
- USP is currently working with the FDA to get clarifications and discussing about different specifications.
- In the meantime, USP is engaging stakeholders to provide batch data of EG and DEG levels in different PEG grades, especially liquid and semi-solid PEGs (MW <= 1000).

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Collaboration with FDA and Stakeholders

- **Collaboration with FDA Compendial Ops and FDA laboratory**
  - Several meetings with the FDA since February 2023
  - Collaboration with the FDA laboratory on DEG/EG GC method evaluation and validation
- **Discussions with multiple PEG manufacturers**
  - DEG/EG GC method development and validation; PEG samples
- **Discussed during Excipient Expert Committee Collaborative Group (EXC EC CG) hybrid meetings (**May 31st – June 2nd)
  - FDA OMQ presentation: *FDA strategy in controlling Excipient quality in the supply chain*
- **Currently, the lab studies focus on liquid/Semi-solid PEGs: Polyethylene Glycol 200, 300, 400, 600, and 1000**
- **USP received an alternative RFR from a stakeholder to address FDA RFR for Polyethylene Glycol 40 Castor Oil, and the proposal is being discussed with EXC-EC.**

Summary

Collaboration

-FDA, USP and Industry work together to update USP-NF standards

-Global efforts

- -Regulators to enforce regulations WHO call-to-action
- -Pharmacopeias to ensure up-to-date standards are available
- -Industry to comply with the cGMP requirements by implementing DEG/EG related compendial quality standards

USP toolkit for measuring and controlling levels of DEG

Download the toolkit here

To help the global community put an end to preventable deaths due to DEG contamination, USP is pleased to make a virtual toolkit for measuring and controlling levels of diethylene glycol available as a free resource to all interested stakeholders. The toolkit includes relevant chapters, monographs, and other resources.

Excipient Quality CANNOT be an after-thought

Stay Connected

Webpage: https://www.usp.org/excipients

Contact: excipients@usp.org

Inquiry: NFMONOGRAPHS@usp.org

Empowering a healthy tomorrow

Thank You

Empowering a healthy tomorrow