

Importance of excipient quality and development for use in medicines : USP Progress on DEG/EG ID test in Excipient Monographs

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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).

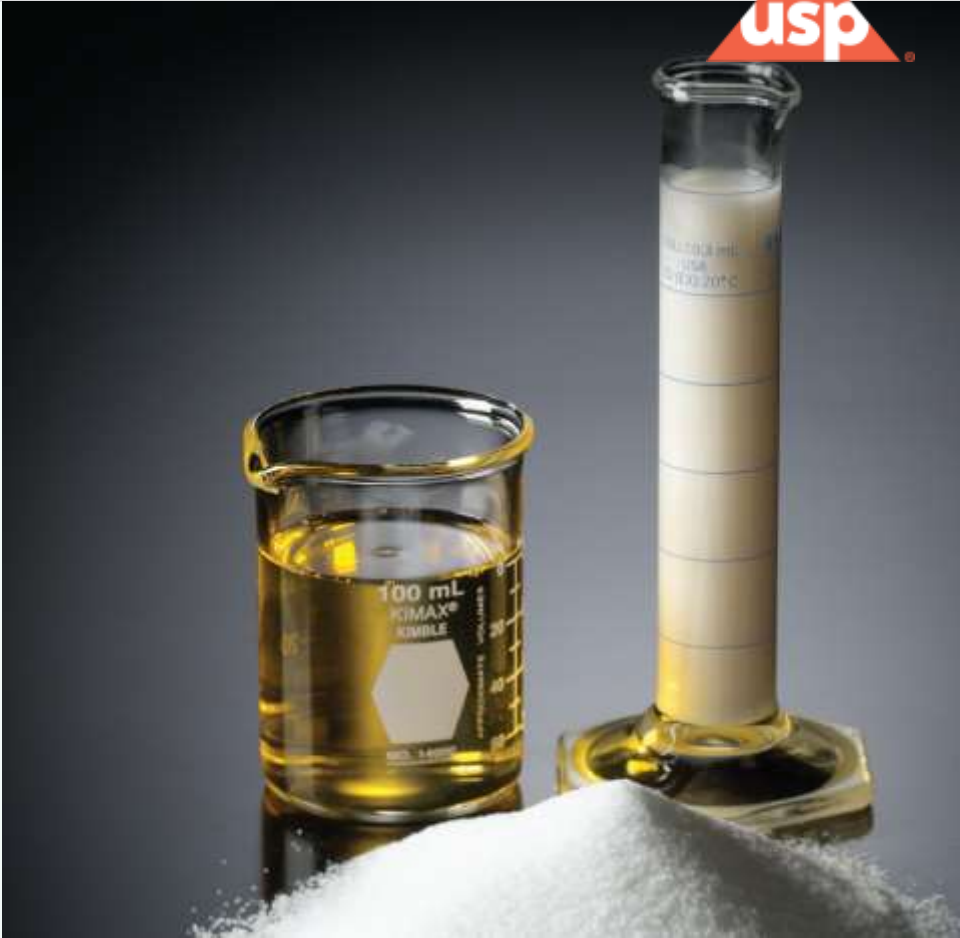
Why excipients are important !

- ▶ **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

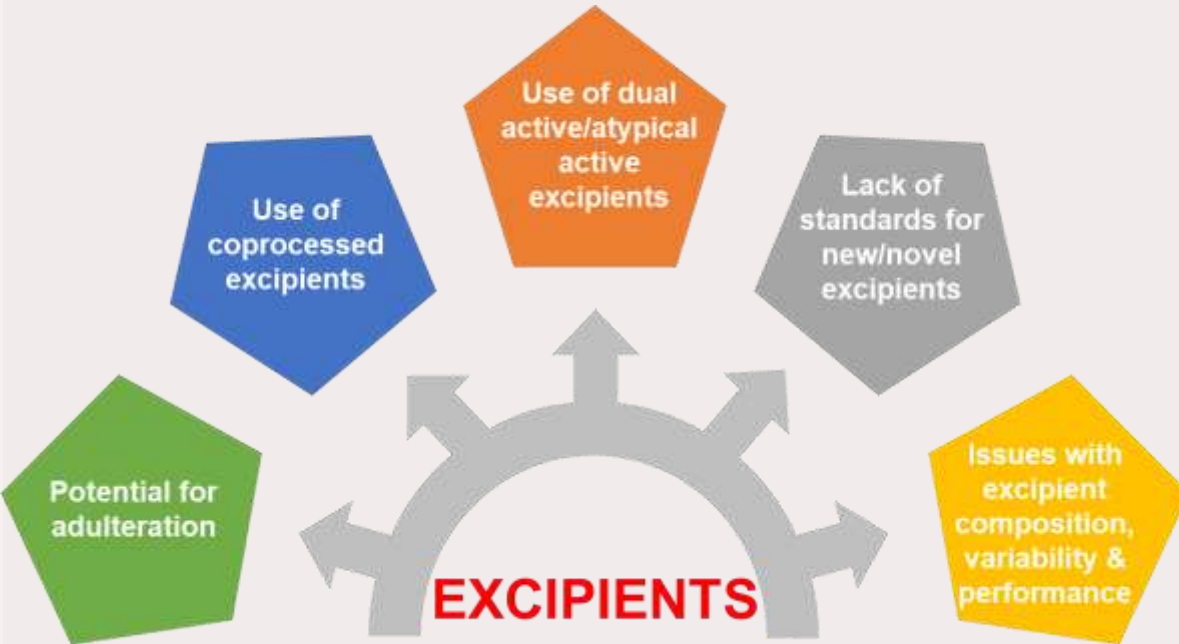
- ▶ They often help ensure the API is delivered to the site of action.
- ▶ Complex non-transparent supply chains can lead to economically motivated or accidental adulteration.



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.

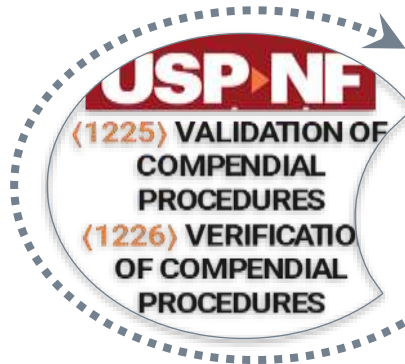
Understanding the interplay between USP-NF standards and GMPs for excipients



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

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](https://www.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,

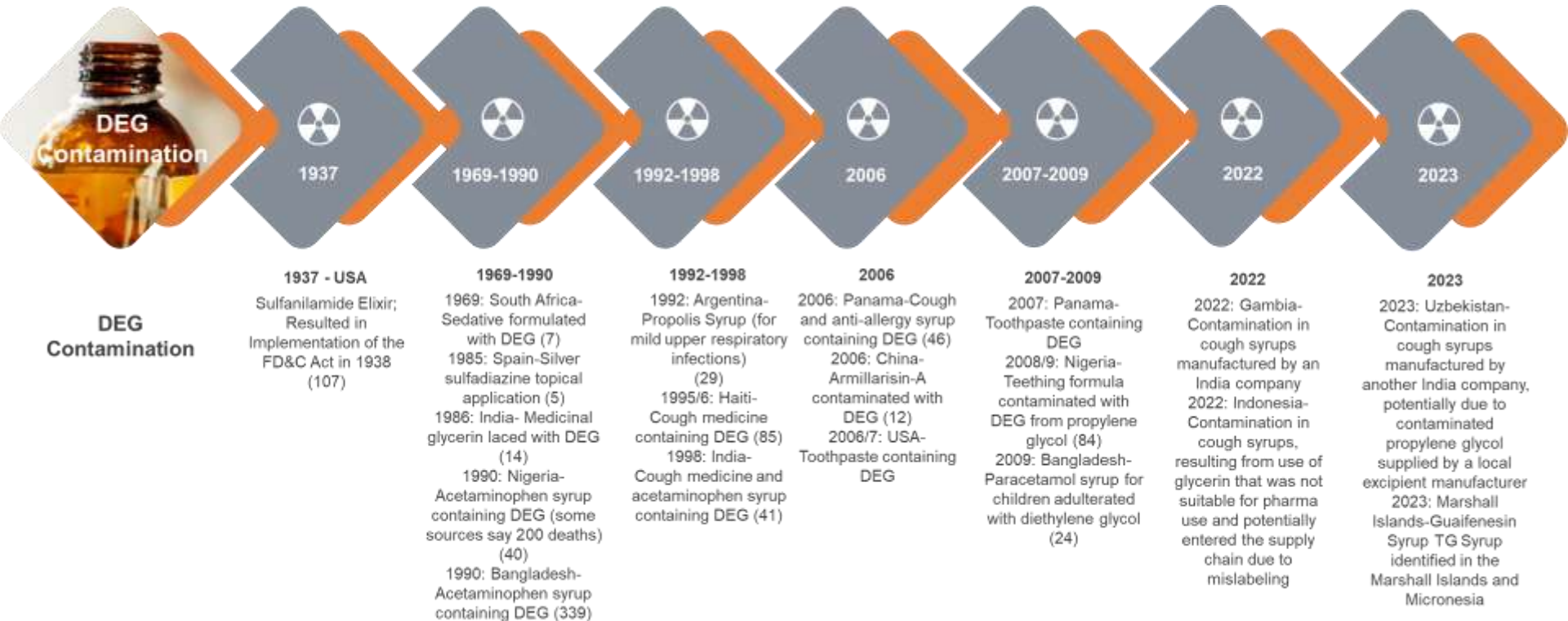
<1197> Good Distribution Practices for bulk pharmaceutical excipients

{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

Collaborative Efforts on Addressing Adulterants and Contaminants



2007-2010: DEG/EG ID tests were included in the following SIX monographs:

- Glycerin
- Propylene Glycol
- Sorbitol Solution
- Non crystallizing Sorbitol Solution
- Sorbitol Sorbitan Solution
- Maltitol Solution

Hydrogenated Starch Hydrolysate revision proposal in PF 37(1) [Jan.– Feb. 2011] and official from August 2013

**USP
DEG/EG
Tool Kit**

USP is collaborating with sponsors and the FDA lab to develop appropriate DEG/EG ID tests for different PEG types.

2007

2009

2010

2011-2013

2023/2

2023/5

2007/04/25
FDA letter: Add DEG/EG test to the ID section of **Glycerin** monograph

FDA letters: Add DEG/EG ID test 2009/01/19: **Propylene Glycol, 3 Sorbitol Solutions and Maltitol Solution**

Stakeholder submitted the DEG/EG ID test method for HSH monograph

2023/02/10
FDA letter: Add DEG/EG ID test to
1) **Polyethylene Glycol**
2) **Polyethylene Glycol 40 Castor Oil**

FDA Guidance May 2023
Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol



- ▶ 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 0.10 % 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 - 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.

Adulterants/Contaminants vs Process Impurities



- ▶ FDA and USP agreement: DEG/EG tests in USP-NF monographs should be able to monitor adulterants/contaminants from EMA and/or process impurities from manufacturing process. Example of each scenario:
 - Propylene Glycol: DEG and EG are not by-products or process impurities from manufacturing process. Purely to prevent economically motivated adulteration or contamination.
 - Four Sugar Alcohols (three Sorbitol Solutions and Maltitol Solution): trace levels of EG may be produced during the hydrogenation process, and DEG is the dimer of EG. --- Process impurities.

Polyethylene Glycol NF – Current Status



Identification

No Identification test

Assay

Average Molecular Weight

Impurities

2 DEG/EG test methods for $MW \leq 1000$

- 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

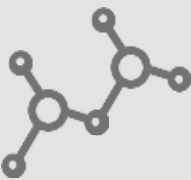


Polyethylene Glycol



DEG/EG test

A packed gas-chromatography (GC) method for impurity analysis



MW 450 -1000



An ultra-violet (UV) method for impurity analysis



MW > 1000

FDA requests to include a DEG/EG test

Issues

Packed GC columns are difficult to purchase



Tedious, less accuracy, lack of capable analyst to perform the test, etc.



No DEG/EG method in the current monograph

Solution



Collaborate with stakeholders to develop a new capillary GC based ID test

New gel permeation chromatography (GPC) method for PEG MW > 1000

Currently, the lab studies focus on liquid/Semi-solid PEGs:
Polyethylene Glycol 200, 300, 400, 600, and 1000.

Collaboration with Global pharmacopeias

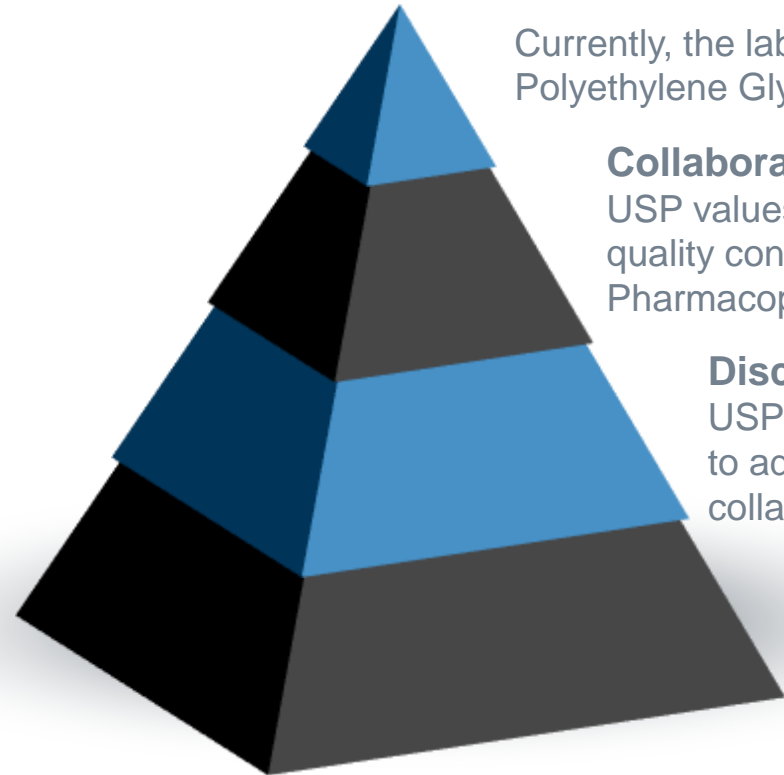
USP values the opportunity to update compendial standards to enhance quality control of critical excipients and facilitate global harmonization through Pharmacopeial Collaborations (PDG, ICH, WHO, IMWP, etc.)

Discussions with multiple PEG manufacturers

USP is engaging with stakeholders to determine a path forward to address FDA's request and to ensure transparency as USP collaborates to update the standards.

Collaboration with FDA

Collaboration with the FDA laboratory on DEG/EG, GC method evaluation and validation



Summary



Collaboration, 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>

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Thank You



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