Testing of Ethylene Glycol and Diethylene Glycol in High-risk Excipients – A USP Perspective and Related Activities

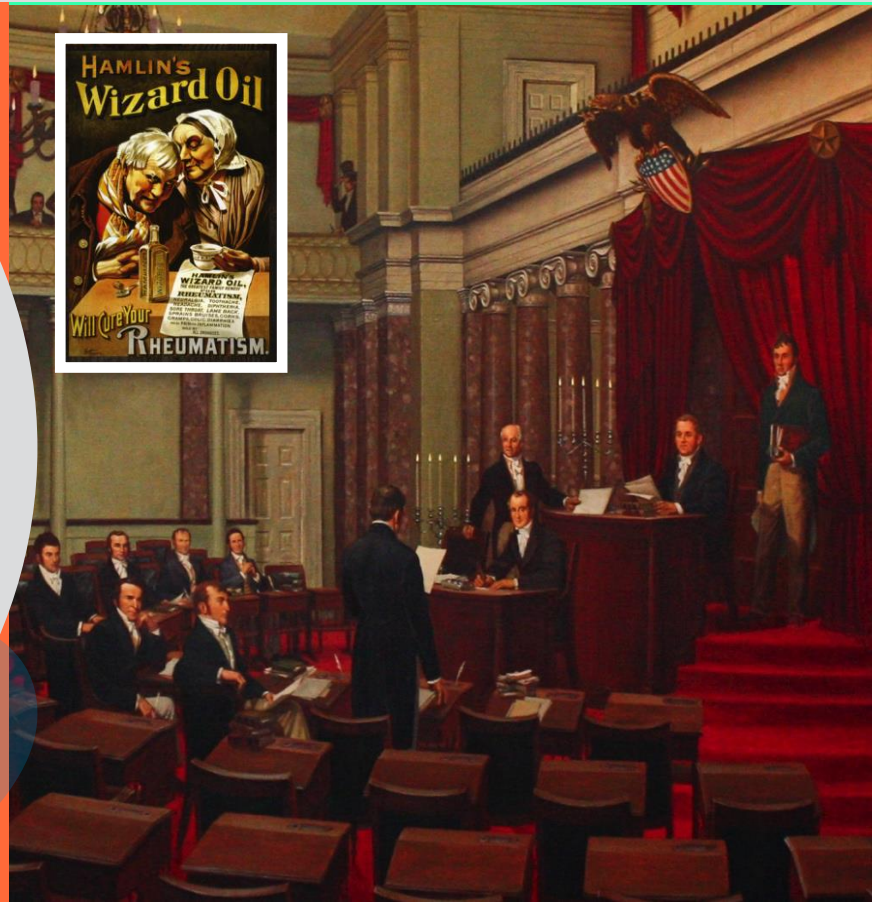
USP-PMDA Joint Workshop, Sep. 10-11, 2024
Catherine Sheehan, DRSc, MS, MS, Senior Director
Jenny Liu, Ph.D., Senior Principal Scientist
Science – Excipients, USP

Outlines

1. **Background**
   - Importance of Excipients Quality
2. **DEG/EG poisoning issues - Testing of DEG/EG for High-risk Excipients**
   - ✓ WHO Alerts, FDA Guidance, FDA letters
3. **USP Perspective and Activities**
   - ✓ Stepwise approaches
4. **PDG Harmonization**
   - ✓ Glycerin, Propylene Glycol, Polyethylene Glycol
5. **Summary**

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.



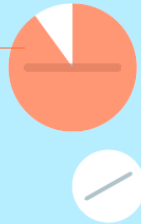
Excipients - Important Components of Medicines

go.usp.org/l/323321/2024-04-25/92v5rf

What is an excipient?

Excipients can make up to about 90% of the total mass/volume of drug products and are required for:

- Enhancing therapeutic properties
- Bulking up solid formulations
- Modifying viscosity
- Enhancing solubility
- Long-term stabilization
- Drug delivery
- Drug release



Common excipients:

Glycerin
Propylene Glycol
Microcrystalline Cellulose
Magnesium Stearate
Polysorbate 80
Sodium Chloride

Risk factors affecting excipient quality

Source

Process

Adulteration

Why excipient quality matters

Fatal consequences linked to high-risk excipients

Pharmaceutical facility closure due to excipient quality/GMP violations

Product recalls and corporate reputational damage

How to ensure the quality of excipients

Supplier qualification

Evaluations are needed to assess a supplier's facilities, personnel, documentation, and quality control procedures.

General Chapters:

<1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients

<1195> Significant Change for Bulk Pharmaceutical Excipients

<1197> Good Distribution Practices for Bulk Pharmaceutical Excipients

<1080> Bulk Pharmaceutical Excipients—Certificate of Analysis

<1083> Supplier Qualification

Excipient standards and solutions

Excipient Monographs

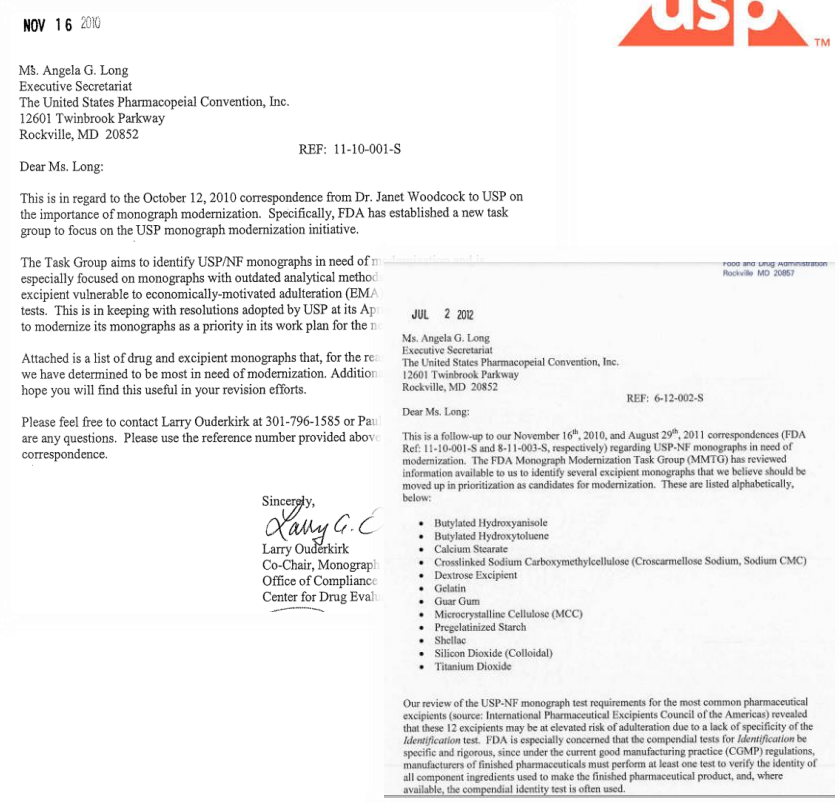
Excipient Reference Standards

Ingredient Verification Program

- Good Manufacturing Practices (CGMP)
- Ingredient testing
- GMP Facility Audit

USP Collaborative Efforts to Update Excipient Quality

- Many tests were outdated, wet chemistry or non-specific and/or not reliable in their quantitation.
  - Lack of specificity of the Identification test (s).
  - Some excipients are well characterized in traditional applications in terms of their chemistry; however, they need additional characterization in some of the newer applications.
  - Use in Complex Drug Products, e.g., excipients for Parenteral Drug Products (Long acting injectables), vaccines, advanced biologics, therapeutics, etc.



NOV 16 2010

Ms. Angela G. Long
Executive Secretariat
The United States Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway
Rockville, MD 20852

REF: 11-10-001-S

Dear Ms. Long:

This is in regard to the October 12, 2010 correspondence from Dr. Janet Woodcock to USP on the importance of monograph modernization. Specifically, FDA has established a new task group to focus on the USP monograph modernization initiative.

The Task Group aims to identify USP/NF monographs in need of
especially focused on monographs with outdated analytical metho
excipient vulnerable to economically-motivated adulteration (EMA
tests. This is in keeping with resolutions adopted by USP at its A
to modernize its monographs as a priority in its work plan for the

Attached is a list of drug and excipient monographs that, for the re
we have determined to be most in need of modernization. Additio
hope you will find this useful in your revision efforts.

Please feel free to contact Larry Ouderkirk at 301-796-1585 or Pa
are any questions. Please use the reference number provided abov
correspondence.

Sincerely,

Larry Ouderkirk
Co-Chair, Monograph
Office of Compliance
Center for Drug Evalu

Food and Drug Administration
Rockville MD 20857

JUL 2 2012

Ms. Angela G. Long
Executive Secretariat
The United States Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway
Rockville, MD 20852

REF: 6-12-002-S

Dear Ms. Long:

This is a follow-up to our November 16th, 2010, and August 29th, 2011 correspondences (FDA Ref: 11-10-001-S and 8-11-003-S, respectively) regarding USP-NF monographs in need of modernization. The FDA Monograph Modernization Task Group (MMTG) has reviewed information available to us to identify several excipient monographs that we believe should be moved up in prioritization as candidates for modernization. These are listed alphabetically, below:

- Butylated Hydroxyanisole
- Butylated Hydroxytoluene
- Calcium Stearate
- Crosslinked Sodium Carboxymethylcellulose (Croscarmellose Sodium, Sodium CMC)
- Dextrose Excipient
- Gelatin
- Guar Gum
- Microcrystalline Cellulose (MCC)
- Pregelatinized Starch
- Shellac
- Silicon Dioxide (Colloidal)
- Titanium Dioxide

Our review of the USP-NF monograph test requirements for the most common pharmaceutical excipients (source: International Pharmaceutical Excipients Council of the Americas) revealed that these 12 excipients may be at elevated risk of adulteration due to a lack of specificity of the *Identification* test. FDA is especially concerned that the compendial tests for *Identification* be specific and rigorous, since under the current good manufacturing practice (CGMP) regulations, manufacturers of finished pharmaceuticals must perform at least one test to verify the identity of all component ingredients used to make the finished pharmaceutical product, and, where available, the compendial identity test is often used.

https://www.usp.org/get-involved/partner/monograph-modernization-history; https://www.usp.org/sites/default/files/usp/document/get-involved/monograph-modernization/2010-11-16-letter-from-fda-task-group.pdf

DEG/EG Contamination/Adulteration

DEG/EG Contamination /Aduteration

1937 - USA

Sulfanilamide Elixir; DEG adulteration (107)
Resulted in the implementation of the FD&C Act in 1938

1969-1990

1969: South Africa- Sedative formulated with DEG (7)
1985: Spain-Silver sulfadiazine 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: 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

2024

2024: WHO alert regarding falsified propylene glycol found by the Drug Regulatory Authority of Pakistan.
2024: DEG contamination of cough syrups in Kenya.
2024: NAFDAC recalled cough syrups made by Johnson & Johnson in South Africa.

WHO Alert and FDA May 2023 Guidance

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

Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Comments may be submitted at any time for Agency consideration. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this document, contact (CDER) Office of Compliance, 301-796-3400.

https://www.regulations.gov/document/FDA-2023-D-1573-0001

WHO urges action to protect children from contaminated medicines

23 January 2023 | Statement | Reading time: 2 min (591 words)

WHO is releasing an urgent call to action to countries to prevent, detect and respond to incidents of substandard and falsified medical products.

Over the past four months, countries have reported on several incidents of over-the-counter cough syrups for children with confirmed or suspected contamination with high levels of diethylene glycol (DEG) and ethylene glycol (EG). The cases are from at least seven countries, associated with more than 300 fatalities in three of these countries. Most are young children under the age of five. These contaminants are toxic chemicals used as industrial solvents and antifreeze agents that can be fatal even taken in small amounts, and should never be found in medicines.

Based on country reports, WHO has issued three global medical alerts addressing these incidents. The Medical Product Alert N°6/2022 on 5 October 2022 focused on the outbreak in the Gambia, Medical Product Alert N°7/2022 on 6 November 2022 focused on Indonesia, and Medical Product Alert N°1/2023 on 11 January 2023 focused on Uzbekistan.

https://www.who.int/news/item/23-01-2023-who-urges-action-to-protect-children-from-contaminated-medicines

Recent US FDA warning letters

- Publicly available warning letters issued by US FDA recently. For example,
  - Champaklal Maganlal Homeo Pharmacy (MAY 18, 2023)
  - Lex Inc. (AUGUST 17, 2023)
  - Green Pharmaceutical Co. (AUGUST 23, 2023)
  - Dextrum Laboratories Inc. (DECEMBER 07, 2023)
  - Woorilife & Health (DECEMBER 28, 2023)
  - Prime Lab LLC (JANUARY 02, 2024)
  - Higley Industries, Inc. (FEBRUARY 22, 2024)
  - Betone S.A. de C.V. (MARCH 21, 2024)
  - Kilitch Healthcare India (MARCH 28, 2024)
  - FirstCham Co., Ltd. (APRIL 03, 2024)
  - C&T Dream Co., Ltd. (APRIL 11, 2024)

1. Your firm failed to test samples of each component for identity and conformity with all appropriate written specifications for purity, strength, and quality. Your firm also failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR 211.84(d)(1) and 211.84(d)(2)).

You failed to adequately test samples of your incoming components before using the components to manufacture your over-the-counter (OTC) drug products. You also relied on your suppliers' certificate of analyses (COA) without establishing the reliability of your component suppliers' test analyses at appropriate intervals.

Ethanol

You failed to adequately test your incoming ethanol, used as an active ingredient, for methanol. The use of ethanol contaminated with methanol has resulted in various lethal poisoning incidents in humans worldwide. See FDA's guidance document *Policy for Testing of Alcohol (Ethanol) and Isopropyl Alcohol for Methanol* to help you meet the CGMP requirements when manufacturing drugs containing ethanol at https://www.fda.gov/media/173005/download.

Glycerin

You failed to adequately test your incoming components at high-risk of diethylene glycol (DEG) or ethylene glycol (EG) contamination for identity before using them to manufacture your drug products. This includes, but is not limited to, testing of glycerin you used in manufacturing your drug products to determine its appropriate identity. Identity testing for glycerin and certain other high-risk drug components include a limit test in the United States Pharmacopeia (USP) to ensure that the component meets the relevant safety limits for levels of DEG or EG. Because you did not perform identity testing

USP DEG/EG Efforts and Progress

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

1. Glycerin
2. Propylene Glycol
3. Sorbitol Solution
4. Noncrystallizing Sorbitol Solution
5. Sorbitol Sorbitan Solution
6. Maltitol Solution

NMT 0.10% for EG and NMT 0.10% for DEG

2013
7. Hydrogenated Starch Hydrolysate
NMT 0.10% for EG and NMT 0.10% for DEG

2014
General Chapter <469> Ethylene Glycol, Diethylene Glycol, and Triethylene Glycol in Ethoxylated Substances
No acceptance criteria

USP DEG/EG Tool Kit

Ongoing USP Collaboration with sponsors/FDA lab to develop appropriate DEG/EG ID tests for different PEG types..

2007 | 200 | 2010 | 2011.-2013 | 2013-2014 | 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

Ethoxylated material manufacturers submitted the methodologies to analyze DEG/EG process impurities for 17 excipients

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

FDA Recent Letter (Feb. 10, 2023)

- On Feb. 10, 2023, USP received a letter from the US FDA that requests to include the *Limit of Ethylene Glycol (EG)/Diethylene Glycol (DEG) test* in the Identity sections of excipient monographs:
  - Polyethylene Glycol (PEG)
  - Polyethylene Glycol 40 Castor Oil
- In the current *NF* Polyethylene Glycol (PEG) monograph, the DEG/EG tests appear under the Impurities section and only for molecular weights (MW) up to 1000.
- FDA suggests that USP include DEG/EG tests for all PEG grades, including MW > 1000.
- In addition, FDA recommends that USP consider similar revisions to other USP/NF monographs that include a test for DEG and EG.

https://www.usp.org/sites/default/files/usp/document/get-involved/monograph-modernization/fda-letter_diethylene-glycol_ethylene-glycol_jenny-liu.pdf

Polyethylene Glycol NF – Current Status

Current NF Polyethylene Glycol monograph

- ✓ **No identification test**
- ✓ **Impurity section: two DEG/EG test methods for MW ≤ 1000**
  1) A packed gas-chromatography (GC) column method for MW < 450
     - **(**NMT 0.25% of the sum of DEG/EG)
  2) A UV method for MW 450 -1000
     - **(**NMT 0.25% of the sum of DEG/EG)

- ✓ **There are 44 grades 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.**

Challenges (1) - Methodologies

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

Challenges (2) – Acceptance Criteria

- **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 engaged stakeholders to provide batch data of EG and DEG levels in different PEGs, especially liquid and semi-solid PEGs (MW <= 1000).

USP Activities to address FDA's request on PEG

➢ Stepwise approach

- ✓ **Step 1.** Revise the PEG monograph to include the existing <469> DEG/EG test in the ID section via an accelerated revision process.
  - ➢ A Notice for Intent to Revise (NITR) was posted on February 23, 2024.
  - ➢ PEG monograph proposal was published in PF 50(3) [May - Jun. 2024]

- ✓ **Step 2.** Create a new general chapter to propose available DEG/EG tests.
  - ➢ A general chapter prospectus was posted on the USP website on Jan. 26th for comment.

    Determination of Diethylene Glycol and Ethylene Glycol in Polyethylene Glycol | USP-NF (uspnf.com) (Comment period ended on Feb. 29, 2024)
  - ➢ A new general chapter *<470> Determination of Ethylene Glycol, Diethylene Glycol, and Triethylene Glycol in Polyethylene Glycol* will be published in PF 50(5) [Sep-Oct 2024].

Polyethylene Glycol Proposal in PF 50(3)

- USP published the PEG monograph revision proposal via an accelerated revision process - interim revision announcement (IRA) in *PF* 50(3) [May-Jun. 2024] for a 3-month public comment period (ended on July 31, 2024). Due to comments received, an appropriate official date will be decided based on Expert Committee's discussion.

  - ✓ Methodologies
    - A validated GC method for PEG MW <= 1000 (Identification section)
    - A validated GPC method for PEG MW > 1000 (Impurity section)

  - ✓ Acceptance Criteria
    - Molecular weight 200–400: NMT 0.062% (620 µg/g) of ethylene glycol; NMT 0.25% (2500 µg/g) of the sum of ethylene glycol and diethylene glycol
    - Molecular weight >400 to 1000: NMT 0.062% (620 µg/g) of ethylene glycol; NMT 0.10% (1000 µg/g) of diethylene glycol
    - Molecular weight > 1000: Ethylene glycol: NMT 0.062% (620 µg/g); Diethylene glycol: NMT 0.10% (1000 µg/g)

<470> Determination of Ethylene Glycol, Diethylene Glycol and Triethylene Glycol in Polyethylene Glycol (upcoming)

- A new general chapter <470> Determination of Ethylene Glycol, Diethylene Glycol and Triethylene Glycol in Polyethylene Glycol will be published in *PF* 50(5) [Sep.-Oct. 2024] for a 3-month public comment.

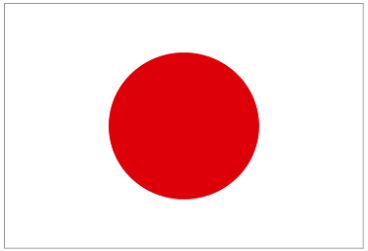
  - ✓ Methodologies
    - Four testing procedures will be proposed in addition to the existing GC-FID method in <469>
      - Backflush
      - Derivatization
      - Shorter run time
      - Lower temperature of column and detector

  - ✓ Standalone analytical testing procedure-based chapter without acceptance criteria. Stakeholders can evaluate the equivalency and interchangeability of these methods and use them as alternative methods as necessary.

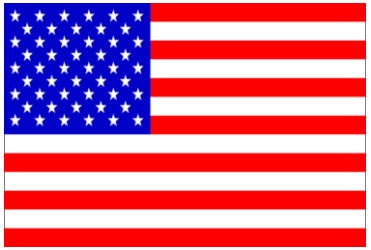
The Pharmacopeial Discussion Group (PDG)

EP
(EDQM)

IPC



JP
(MHLW/PMDA)



USP

PDG Mission

To harmonize pharmacopeial standards while maintaining a constant level of science with the shared goal of protecting public health.

Monographs under PDG Harmonization

DEG/EG tests in different PDG pharmacopeias				
Monograph	**USP**	**European Pharmacopeia (EP)**	**Japanese Pharmacopeia (JP)**	**Indian Pharmacopeia (IP)**
Glycerin	• GC-FID: Identification test • Acceptance criteria: - EG: NMT 0.10% - DEG: NMT 0.10%	• GC-FID: Impurity test • Acceptance criteria: - EG: NMT 0.10% - DEG: NMT 0.10%	• GC-FID: Impurity test • Acceptance criteria: - EG: NMT 0.10% - DEG: NMT 0.10%	• GC-FID: Impurity test • Acceptance criteria: - EG: NMT 0.10% - DEG: NMT 0.10%
Propylene Glycol	• GC-FID: Identification test • Acceptance criteria: - EG: NMT 0.10% - DEG: NMT 0.10%	• GC-FID: Impurity test • Acceptance criteria: - EG: NMT 0.062% - DEG: NMT 0.10%	• GC-FID: Impurity test • Acceptance criteria: - EG: NMT 0.10% - DEG: NMT 0.10%	• GC-FID: Impurity test • Acceptance criteria: - EG: NMT 0.10% - DEG: NMT 0.10%
Polyethylene Glycol	**PF 50(3) proposal:** • GC-FID Identification test – MW<=1000 • GPC Impurity test – MW >1000 • Acceptance criteria: MW 200–400: - EG: NMT 0.062% - Sum of EG and DEG: NMT 0.25% MW >400 to 8000: - EG: NMT 0.062% - DEG: NMT 0.10%	• GC-FID: Impurity test • Acceptance criteria: - Sum of EG and DEG: NMT 0.4%	• GC-FID: Impurity test • Acceptance criteria: - Sum of EG and DEG: NMT 0.25%	No GC-FID DEG/EG test

Summary - Collaborations

- **Global efforts**
  - ✓ - Regulators to enforce regulations
  - ✓ Pharmacopeias to ensure up-to-date standards are available
  - ✓ Industry comply with the cGMP requirements by implementing DEG/EG related compendial quality standards
- USP welcomes your suggestions, comments, methodologies and data.

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.

Stay Connected

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

Contact: excipients@usp.org

Inquiry: NFMONOGRAPHS@usp.org

Empowering a healthy tomorrow

Expert Volunteers help power USP's impact on global public health

Serving on Expert Committees, Panels and Sub-Committees, they collaborate to develop quality standards and other solutions that help build a more resilient supply of quality medicines.

Apply and amplify your impact

Thank You

Empowering a healthy tomorrow