Joint EDQM-USP Webinar on Ethylene glycol and Diethylene glycol testing

18 April 2024

10:00 to 11:30 (EDT, Rockville, USA)

16:00 to 17:30 (CEST, Strasbourg, France)

Outline

- Missions and Background
- USP's role and US regulatory activities
- Ph. Eur. role and European Regulatory Requirements
- USP and Ph. Eur. perspective and efforts
- Ph. Eur. and USP current challenges and progress
- Need for stakeholder engagement

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USP and Ph. Eur. Mission
Importance of Excipient Quality
Background of DEG/EG contamination

What EDQM stands for

Mission

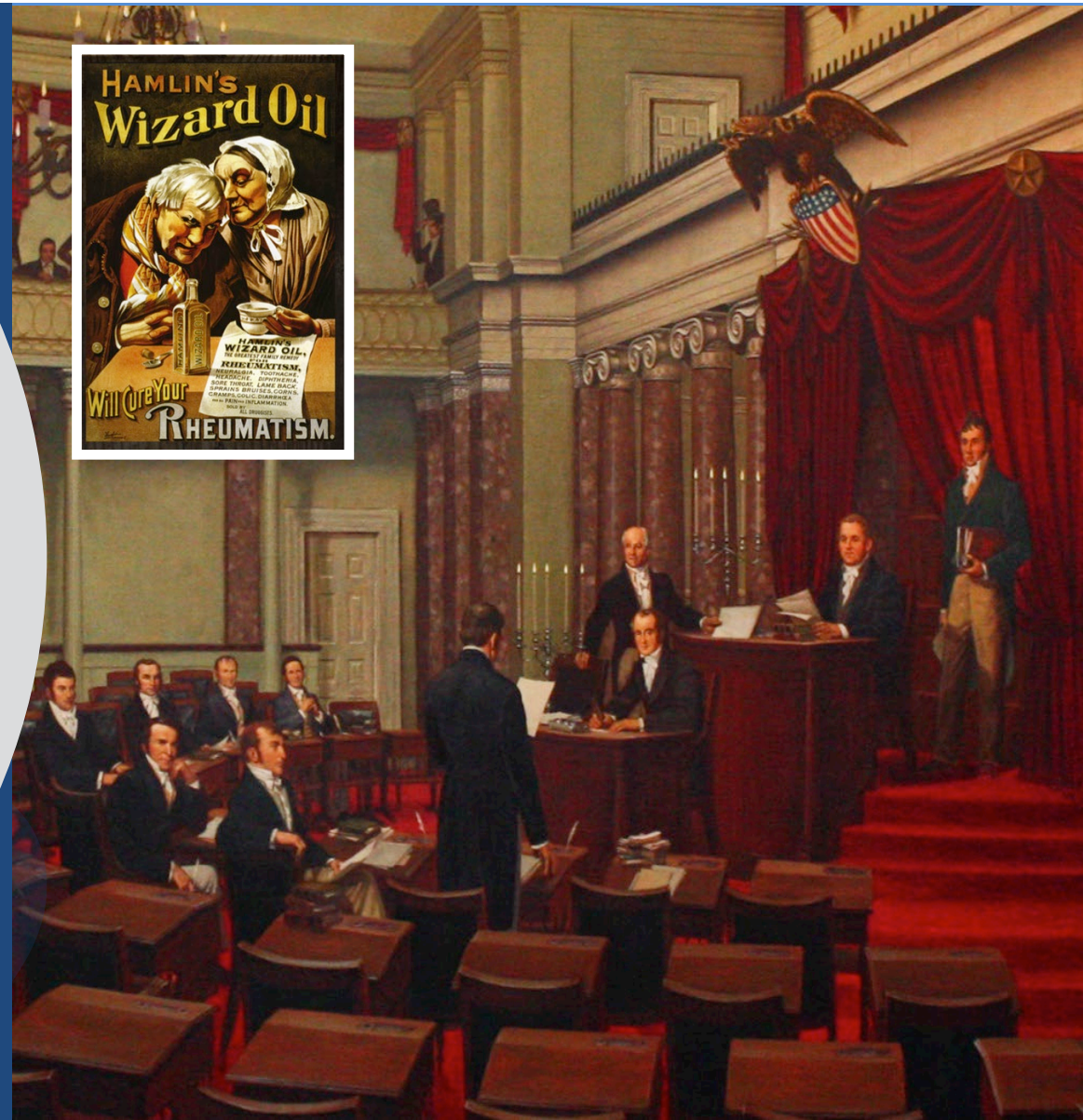
Together for better health, for all.

Vision

To contribute to public health protection by engaging with an international community of experts and stakeholders.

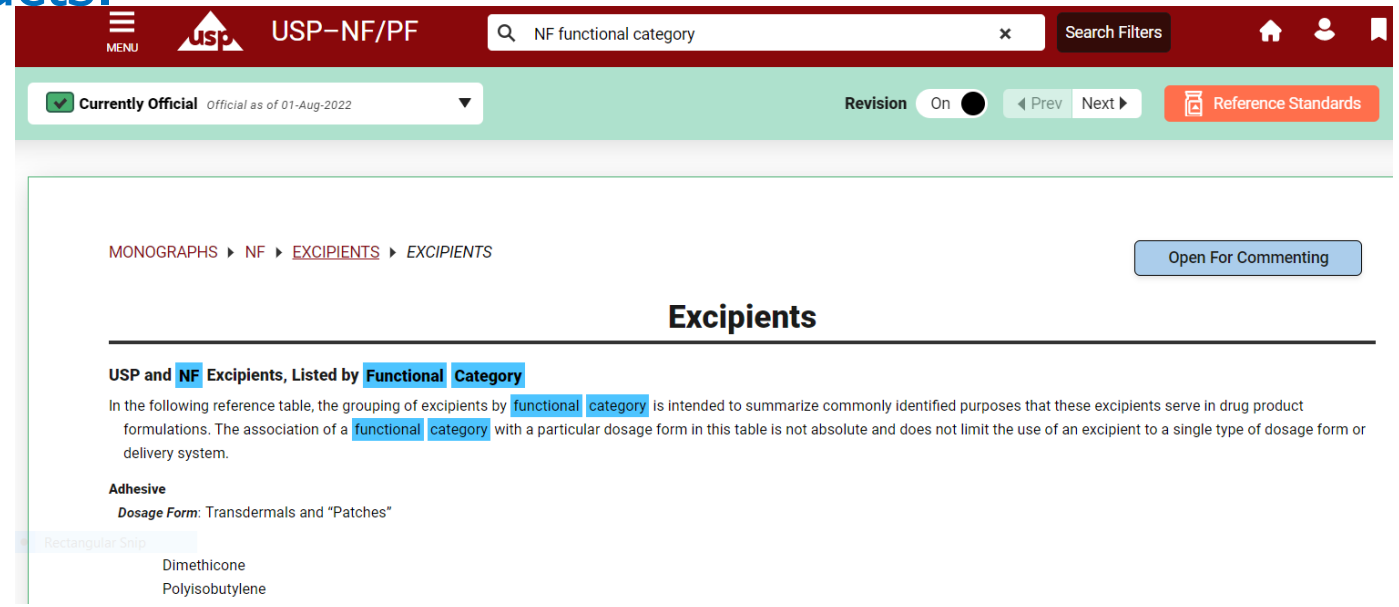
USP's enduring mission

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



Why excipients are important !

- **Excipients** can make up to about 90% of the total mass/volume of medicinal products.



- Excipients have many functions (NF Functional categories), including coating agents, diluent, emulsifying agents, flavoring, solvent, etc., and often help ensure the API is delivered to the site of action

NF category listing of Excipients

- Complex non-transparent supply chains can lead to economically motivated or accidental contamination or adulteration.

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

Diethylene glycol incidents and deaths

(compiled from various sources** – references in the last slide)

Country	Year	Number of Deaths	Incident
USA	1937	107	Sulfanilamide Elixir; Resulted in Implementation of the FD&C Act in 1938
South Africa	1969	7	Sedative formulated with DEG
Spain	1985	5	Silver sulfadiazine topical application
Italy	1985	-	DEG in wines from Austria
India	1986	14	Medicinal glycerin laced with DEG
Nigeria	1990	40 (200)*	Acetaminophen syrup containing DEG (some sources say 200 deaths)
Bangladesh	1990-2	(339)*	Acetaminophen syrup containing DEG
Argentina	1992	29	Propolis Syrup (for mild upper respiratory infections)
Haiti	1995/6	85	Cough medicine containing DEG
India	1998	41	Cough medicine and acetaminophen syrup containing DEG
Panama	2006	46 (116 or 365)*	Cough and anti-allergy syrup containing DEG
China	2006	12	Armillarisin-A contaminated with DEG
USA	2006/7	-	Toothpaste containing DEG
Panama	2007	-	Toothpaste containing DEG
Nigeria	2008/9	84	Teething formula contaminated with DEG from propylene glycol
Bangladesh	2009	24	Paracetamol syrup for children adulterated with diethylene glycol
Gambia	2022/5/10	300+ fatalities in three of seven countries (1)	Contamination in cough syrups manufactured by an India company (2)
Indonesia	2022/11/02		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 (3)
Uzbekistan	2023/1/11		Contamination in cough syrups manufactured by another India company(4), potentially due to contaminated propylene glycol supplied by a local excipient manufacturer (5)
Marshall Islands	2023/4/25		Guaifenesin Syrup TG Syrup identified in the Marshall Islands and Micronesia (6)

USP role & US Regulatory Activities

- FDA Guidance for EG/DEG Testing
- Why Identification (ID) test?

Role of USP Quality Standards in US Law

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

The term "drug" means articles:

- 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
- (other than food) intended to affect the structure or any function of the body
- **intended for use as a COMPONENT of any article meeting the above criteria**

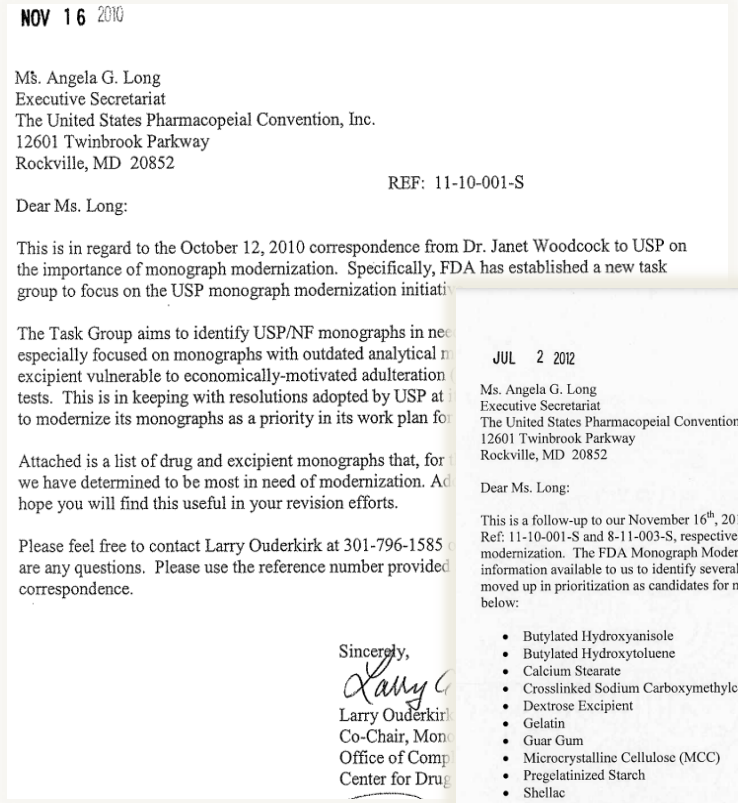
Role of USP Quality Standards in US Law & Regulations

- **US FDCA § 501(b) and 502(e)(3)(b)) - 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).
  - To avoid being deemed adulterated, such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs.
- **US FDCA § 502(g)**
  - In addition, to avoid being deemed misbranded, drugs recognized in ***USP–NF*** must also be packaged and labeled in compliance with compendial standards.

➢ Enforcement of USP standards is the responsibility of FDA and other government authorities in the U.S. and elsewhere. USP has no role in enforcement.

USP's 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.
- Used 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 initiati

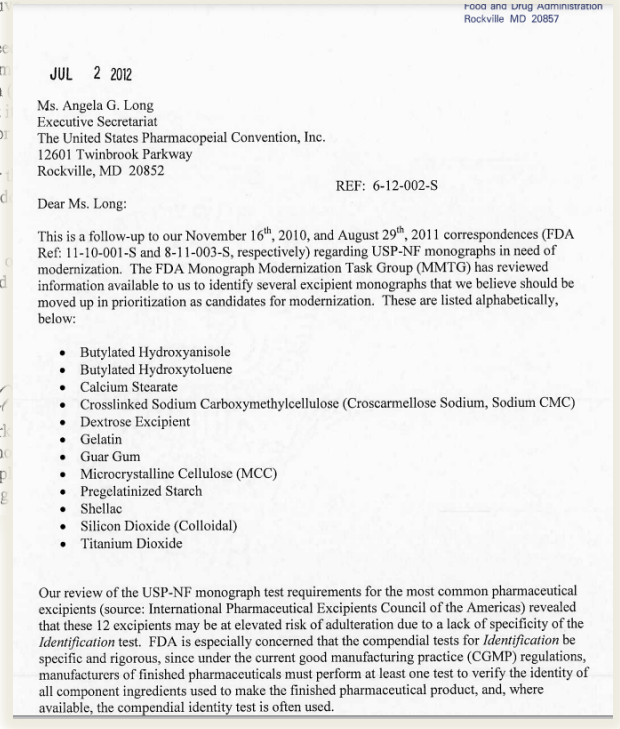
The Task Group aims to identify USP/NF monographs in ne especially focused on monographs with outdated analytical r excipient vulnerable to economically-motivated adulteration tests. This is in keeping with resolutions adopted by USP at to modernize its monographs as a priority in its work plan fo

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

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

Sincerely,

Larry Ouderkirk
Co-Chair, Mon
Office of Comp
Center for Drug



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

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)

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

Summary of FDA May 2023 Guidance

- **Similarities of cases:** DEG- and EG-contaminated components (excipients) entered the pharmaceutical raw material supply chain. However, drug manufacturers did not perform full **identity** testing and solely relied on the certificate of analysis (COA) provided by the supplier. Additionally, the COA was not from the original manufacturer, nor did it disclose the origin of the excipient.
- **Regulatory Requirements**: "Manufacturers of finished drug products must also comply with the cGMP regulations codified in 21 CFR Parts 210 and 211." "Testing bulk or repackaged high-risk components for DEG and EG content is consistent with the cGMP requirement under section 501(a)(2)(B) of the FD&C Act."
- "A drug, including a drug component, with a name recognized in the **USP-NF** must comply with compendial **identity** standards or be deemed adulterated, misbranded, or both." (emphasis added)

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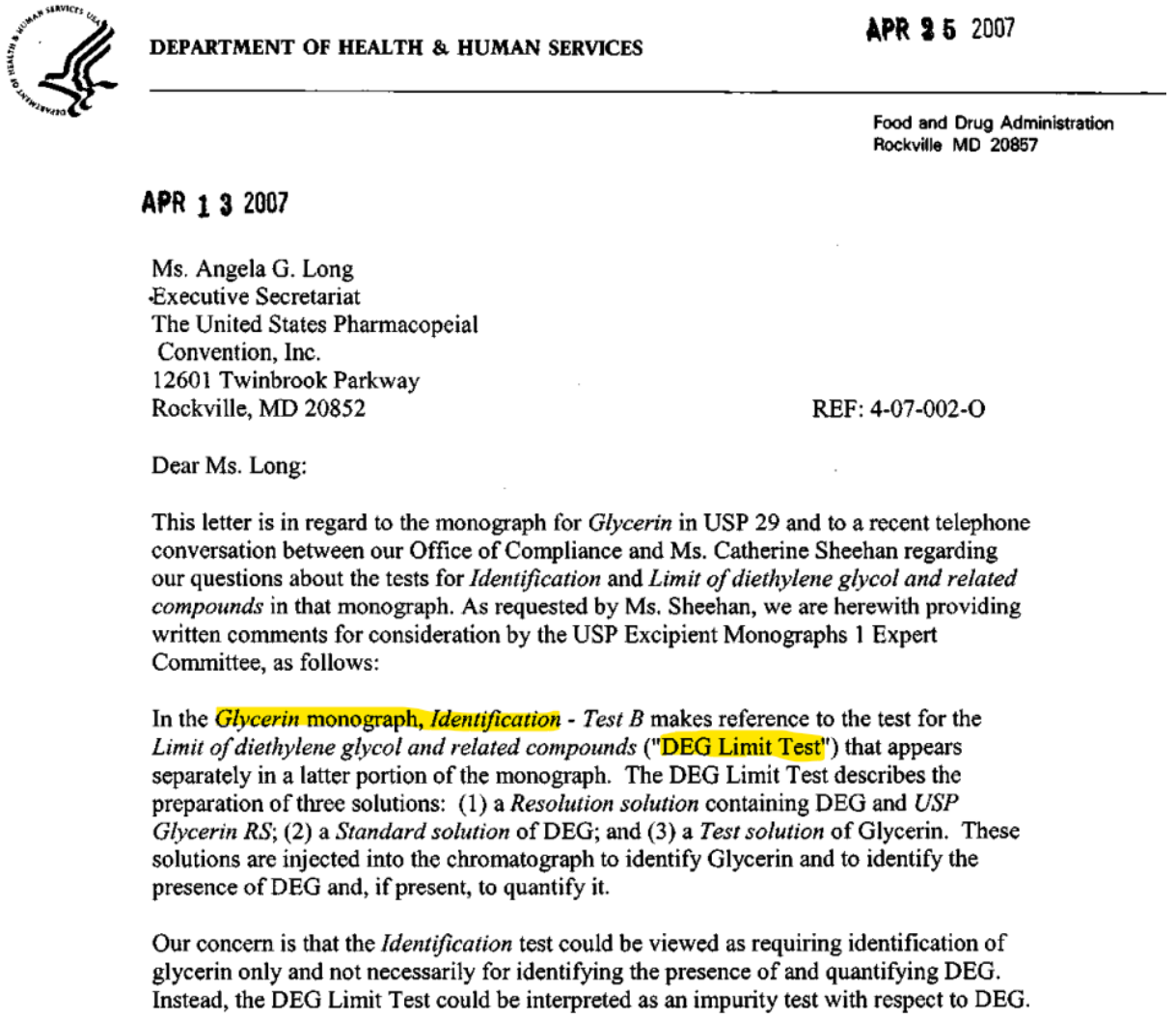
FDA letters regarding EG/DEG ID test

- 2007/04/13 FDA letter
  - Glycerin
- 2009/01/19 FDA letter
  - Propylene Glycol,
  - Three Sorbitol Solutions
  - Maltitol Solution
- 2023/02/10 FDA letter
  - Polyethylene Glycol
  - Polyethylene Glycol 40 Castor Oil



DEPARTMENT OF HEALTH & HUMAN SERVICES

APR 25 2007

Food and Drug Administration
Rockville MD 20857

APR 13 2007

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

REF: 4-07-002-O

Dear Ms. Long:

This letter is in regard to the monograph for *Glycerin* in USP 29 and to a recent telephone conversation between our Office of Compliance and Ms. Catherine Sheehan regarding our questions about the tests for *Identification* and *Limit of diethylene glycol and related compounds* in that monograph. As requested by Ms. Sheehan, we are herewith providing written comments for consideration by the USP Excipient Monographs 1 Expert Committee, as follows:

In the *Glycerin* monograph, *Identification* - *Test B* makes reference to the test for the *Limit of diethylene glycol and related compounds* ("DEG Limit Test") that appears separately in a latter portion of the monograph. The DEG Limit Test describes the preparation of three solutions: (1) a *Resolution solution* containing DEG and *USP Glycerin RS*; (2) a *Standard solution* of DEG; and (3) a *Test solution* of Glycerin. These solutions are injected into the chromatograph to identify Glycerin and to identify the presence of DEG and, if present, to quantify it.

Our concern is that the *Identification* test could be viewed as requiring identification of glycerin only and not necessarily for identifying the presence of and quantifying DEG. Instead, the DEG Limit Test could be interpreted as an impurity test with respect to DEG.

Why ID test?

- Importance of adding the *Limit of EG/DEG* test in the Identification (ID) section
  - If EG/DEG detection and quantification is part of the "Identification" section
    - cGMP regulations at **21 CFR 211.84(d)(1)** would require manufacturers of drug products to detect and quantify any EG/DEG present for each lot received for high-risk excipients (e.g., Glycerin, Propylene Glycol or PEG, etc.).
  - If EG/DEG detection and quantification is only part of "Impurity" tests
    - Manufacturers need not include, as part of its identity testing, the detection and quantification of EG/DEG for each batch of high-risk drug components (Glycerin, etc.). 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.

Excipients are Drug Components

- In FDA nomenclature, an excipient is also known as an "inactive ingredient".
  - 21 CFR 210.3 (a)(8):

    "Inactive ingredient means any component other than an active ingredient."
- However, more importantly, FDA considers both active ingredients and excipients (inactive ingredients) to be drug "components":
  - 21 CFR 210.3 (a)(3):

    "Component means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product."
- FDA May 2023 Guidance - ""high-risk drug components" are components that, through historical experience, have been found to be at higher risk of DEG or EG contamination compared to other drug components."
- "A high-risk component that is intended as an excipient or other component of a drug product is a drug as defined by section 201(g) of the FD&C Act."

21 CFR 211. 84 - cGMP Identity Requirements

Sec. 211.84 Testing and approval or rejection of components, drug product containers, and closures.

(a) Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.

(b) Representative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required by § 211.170.

Sec. 211.84 Testing and approval or rejection of components, drug product containers, and closures.

(d) Samples shall be examined and tested as follows:

(1) 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.

(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.

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Ph. Eur role &
European Regulatory Requirements

EU regulatory requirements

- EU GMP chapter 5 requires **supplier qualification and monitoring**
- **Robust supply chain knowledge** essential, e.g. about involvement of brokers or intermediates
- Principles of **quality risk management** to programmes for supply chain management is of key importance to mitigate risks of DEG/EG contamination

EU regulatory requirements

- **EU GMP Annex 8** Sampling of starting and packaging materials
  - requirement to **assess the quality of each batch** of starting materials
  - General requirement to **perform identity testing on each container**
- EMA Guidance on GMP: **Q&A for Glycerol testing** available

Starting materials

2. The identity of a complete batch of starting materials can normally only be ensured if individual samples are taken from all the containers and an identity test performed on each sample. It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly labelled.

4. The quality of a batch of starting materials may be assessed by taking and testing a representative sample. The samples taken for identity testing could be used for this purpose. The number of samples taken for the preparation of a representative sample should be determined statistically and specified in a sampling plan. The number of individual samples which may be blended to form a composite sample should also be defined, taking into account the nature of the material, knowledge of the supplier and the homogeneity of the composite sample.

The Ph. Eur. in the European regulatory system

- **European Pharmacopoeia monographs are legally binding** including both Identity and Test sections
- ensured through both
  a) convention on the European Pharmacopoeia for all 39 Ph. Eur. member states and
  b) EU directive 2001/83/EC for EU member states
- **Testing** according to relevant Ph. Eur. Monograph **compulsory independent of section** the test is included
- This covers also DEG/EG tests included in test sections
- **Ph. Eur. supports risk-based approaches:**
  - Ph. Eur. option to include Potential adulteration sections to allow risk-based approach of manufacturers or users depending e.g. on supply chain knowledge

USP's Perspective and Efforts

- ✓ EG/DEG ID tests in USP-NF
- ✓ Contaminants/Adulterants vs Process Impurities
- ✓ Identification test vs Impurity test

USP EG/DEG 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 EG/DEG Tool Kit

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

2007 | **2009** | **2010** | **2011-2013** | **2013-2014** | **2023/2** | **2023/5**

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

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

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

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

2023/02/10 FDA letter: Add EG/DEG 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

USP Efforts on Addressing Economically Motivated Adulteration (EMA)

- DEG / EG test included in Identification Section as of 2007-2013 revisions

Standard	**Revision Status: Last time revised**
Glycerin	Official May 1, 2020
Maltitol Solution	official as of May 1, 2021
Hydrogenated Starch Hydrolysate	official prior to 2013
Sorbitol Solutions • Sorbitol Solution • Sorbitol Sorbitan Solution • Noncrystallizing Sorbitol Solution	official May 1, 2021
Propylene Glycol	official as of Feb 1, 2021

FDA May 2023 Guidance

Adulterants/Contaminants vs Process Impurities

- Basically, EG/DEG tests in USP-NF monographs should be able to monitor adulterants/contaminants from EMA and process impurities from the manufacturing process. Example of each scenario:
  - Propylene Glycol: EG and DEG are not by-products or process impurities from manufacturing process. Purely to prevent economically motivated adulteration (EMA).
  - 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. (Also help prevent potential EMA.)

Adulterants/Contaminants vs Process Impurities

Methodology and Sample preparation

- Gas-chromatography (GC) methods have been developed and included in the aforementioned seven monographs as part of the ID tests.
- For Glycerin and Propylene Glycol, a direct injection of sample solution works well. However, for more complex excipients, such as sugar alcohols, a proper sample preparation (precipitation) is also needed.

Acceptance Criteria (EG/DEG limits)

- For **adulterants/contaminants:** Through collaborative studies, discussions with stakeholders, including manufacturers and regulators, EG/DEG specification limits are developed.
- For **process impurities:** Through stakeholder engagement, a better understanding on capability of manufacturing process can be considered.
- The DEG and EG limits in seven USP–NF monographs (Glycerin, Propylene Glycol, three Sorbitol Solns. and Maltitol Soln., and Liquid Hydrogenated Starch Hydrolysate (HSH): NMT 0.10% for EG and NMT 0.10% for DEG
- Note: In the general chapter <467> Residual Solvents, EG acceptance criteria is NMT 620 ppm (620 µg/g).

USP Efforts: Monitor Process Impurities – DEG/EG

- **General Chapter (GC) <469>** *ETHYLENE GLYCOL, DIETHYLENE GLYCOL, AND TRIETHYLENE GLYCOL IN ETHOXYLATED SUBSTANCES*

  - These 17 excipients are all manufactured using ethylene oxide as a starting material, which reacts with water to generate EG, while DEG is a dimer and TEG is a trimer of EG.

  - <469> is an analytical testing procedure-based chapter. It does not contain acceptance criteria.

  - The gas chromatography method in <469> helps monitor process impurities, in terms of EG, DEG and TEG.

1. Polyethylene glycol 200
2. Polyethylene glycol 300
3. Polyethylene glycol 400
4. Polyethylene glycol 600
5. Polyethylene glycol 1000
6. Polysorbate 20
7. Polysorbate 40
8. Polysorbate 60
9. Polysorbate 80
10. Polyethylene glycol monomethyl ether 350
11. Polyethylene glycol monomethyl ether 550
12. Polyoxyl 35 castor oil
13. Polyoxyl 15 hydroxystearate
14. Polyoxyl 20 cetostearyl ether
15. Polyoxyl 8 stearate
16. Octoxynol 9
17. Nonoxynol 9

Identification test vs Impurity test

Identification test

- As each batch needs to be tested for ID, more frequent testing may be required. Therefore, the method is better to have a short run time and a long column lifetime to reduce cost.

Impurity test

- Impurity tests are less frequent, so methods with longer run times and relatively shorter column lifetimes still can be tolerated.

Examples:

- The EG/DEG tests for Sugar Alcohols and Hydrogenated Starch Hydrolysate are good ID test methods because they are cost-effective based on quick and easy sample preparation procedures and short run times.
- However, the EG/DEG method described in chapter <469> has some disadvantages when used for frequent ID testing.

Ph. Eur. Perspective and Efforts

- ✓ Ph. Eur. requirements
- ✓ DEG/EG impurity origin
- ✓ Ph. Eur. control

Ph. Eur. Requirements on impurities/adulterations

Impurity Definition (chapter 5.10):

Any components of a substance for pharmaceutical use that is not the chemical entity defined as the substance

Purpose of Identification section (General Notices)

1.5.1.8 Identification

Scope. The tests given in the Identification section are not designed to give a full confirmation of the chemical structure or composition of the article; they are intended to give confirmation, with an acceptable degree of assurance, that the article conforms to the description on the label.

Applicable texts:

General Monograph Substances for Pharmaceutical Use (2034) apply to all substances including reference to

- General chapter 5.4 Residual solvents based on ICHQ3C – limit for EG ≤ 620 ppm

Individual monograph - acceptance criteria developed are based on:

- Specifications approved by European competent authorities
- batch and stability data of products on the European market

Ph. Eur. Requirements on impurities/adulterations

For adulteration – General notices "1.5.1.6 Potential adulteration"

*"Due to the rise in fraudulent activities and cases of adulteration, **information may be made available to users of the Ph. Eur.** to help them detect adulterated articles (i.e. active substances, excipients, intermediate products, bulk products and medicinal products).*

*To this end, an **analytical procedure** for the detection of potential adulterants and **relevant limits may be included** in this section of monographs on substances for which an incident has occurred or which are at risk of deliberate contamination. In such cases, a reminder that a suitable quality system is applied at all stages of production and sourcing is also provided. The **frequency of testing** by manufacturers or by users (e.g. manufacturers of intermediate products, bulk products and medicinal products) **depends on a risk assessment**, taking into account the level of knowledge of the whole supply chain and national requirements.*

The requirements listed in this section apply to the whole supply chain, from manufacturers to users. The absence of this section does not imply that attention to features such as those referred to above is not required."

DEG/EG – impurity origin

Substance	Ethylene glycol/ Diethylene glycol
Propylene glycol	Main risk is via adulteration/falsification. EG may also depend on the quality of the propylene oxide used for the synthesis
Macrogols (PEG)	Process impurities, potential adulteration Unreacted EO/EG from the manufacturing process. The amount of EG and DEG decreases as molecular weight increases. Higher amounts in lower molecular weight grades, very low level with higher MW Liquid grades (at or below Mr 1000) are susceptible to potential adulteration with liquid DEG or EG
Glycerol	Adulteration/falsification
Sorbitol	Process impurities, potential adulteration EG is trace residual from the production process. However, low levels of constantly 10 to 30 ppm (or below) reported
Maltitol	Process impurities, potential adulteration EG is trace residual from the production process. However, low levels of constantly 10 to 30 ppm (or below) reported

Controlling DEG/EG in Ph. Eur. excipient monographs – status (1/2)

Monograph	Current status in Ph.Eur.
Propylene glycol	Revised monograph to include EG/DEG test in the test section and new IR identification adopted November 2023, pre-published on EDQM website. Limit test method using GC-FID, same as USP Specification - EG: 620 ppm; DEG: 0.10%
Glycerol	EG and DEG covered under "Impurity A and related substances test" in test section. Limit test method using GC-FID Specification - EG: 0.10%; DEG: 0.10%
Macrogols (PEG)	12 grades described in the monograph EG and DEG test for liquid grades (MW < 1000) in test section. Quantitative method using GC-FID Specification - combined EG and DEG 0.4%.

Controlling EG/DEG in Ph.Eur. excipient monographs – status (2/2)

Monograph	Current status in Ph. Eur.
Other ethoxylated substances	*General chapter 2.4.30 EG and DEG in ethoxylated substances (published in 2004)* General method that may be applied but not linked to the individual monograph Quantitative method using GC-FID Analytical procedure given to mainly analyse low levels of DEG/EG process impurities
Maltitol	No test in solid and liquid Maltitol. EG is found in very low amounts only well below toxicology-derived limits
Sorbitol	No test in solid and liquid Sorbitol. EG is found in very low amounts only well below toxicology-derived limits

Ph. Eur. current challenges and progress for DEG/EG testing

Controlling EG/DEG in Ph.Eur. excipient monographs – issues/actions (1/3)

Monograph	Issue/Engagement	On-going actions
Propylene glycol	**International Harmonisation** of monograph within the PDG	PDG work ongoing, proposal to include harmonised test method for DEG/EG, method will occur in different sections of the PDG pharmacopoeias, same method to be used as Assay
Glycerol	**International Harmonisation** of monograph within the PDG	PDG work ongoing, proposal to include harmonised test method for DEG/EG, occurring in different sections of the PDG pharmacopoeias

DEG/EG in Ph.Eur. excipient monographs – issues/actions (2/3)

Monograph	Issue/Engagement	On-going actions
Macrogols (PEG)	1) **International Harmonisation** of monograph within the PDG	PDG work ongoing, but challenging, proposal to include harmonised test method for DEG/EG, occurring in different sections of the PDG pharmacopoeias
	2) liquid grades (MW < 1000) DEG/EG procedure in test section: test using packed GC column, difficult to purchase	Revision of the monograph to modernise the analytical procedure (replace packed column) – collaborating with stakeholders for new method/batch data including exchanges with USP. Challenge: Acceptance Criteria
	3) semi-solid or solid grades (MW > 1000)	No control of DEG/EG foreseen (for reasons given before).

DEG/EG in Ph. Eur. excipient monographs – issues/actions (3/3)

Monograph	Issue/Engagement	On-going actions
Sorbitol	**DEG/EG test**	To include analytical procedure in adulteration section in 3 monographs on liquid forms: 1) Sorbitol, liquid (crystallising); 2) Sorbitol, liquid (non-crystallising) and 3) Sorbitol, liquid (partially dehydrated)
Maltitol	**DEG/EG test**	To include analytical procedure in adulteration section in monograph on liquid form: Maltitol, liquid
Other ethoxylated substances	**General chapter 2.4.30 EG and DEG in ethoxylated substances**	Evaluation to include reference to this chapter in adulteration sections of the corresponding monographs: e.g. macrogolglycerol ricinoleate; macrogolglycerol hydroxystearate; macrogol 15 hydroxystearate; nonoxinol 9; macrogol cetostearyl ether

Summary ongoing Ph. Eur. actions

- **Introduction of adulteration section** for monographs (e.g. liquid Sorbitol and Maltitol)
- **Modernise analytical procedures**
  (e.g. revision of Macrogols)
- **Further analytical improvements** under discussion for methods for Glycerol or Propylene glycol (inclusion of more rapid, more robust methods)
- Ethoxylated Substances – for **method 2.4.30** for EG/DEG **evaluation to include in monographs** (e.g. in adulteration section)
- **Exchange with international partners and stakeholders like USP, WHO and PDG**

USP current challenges and progress

- Focusing on Polyethylene Glycol (PEG)

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 EG/DEG tests appear under the Impurities section and only for molecular weights (MW) up to 1000.
- FDA suggests that USP include EG/DEG 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 Monograph – Current Status

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

- 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 EG/DEG impurity test.)
- USP plans to develop a separate Polyethylene Glycol 20000 monograph.

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Challenges (1) - Methodologies

USP Polyethylene Glycol	Issues	Possible Solution
• **EG/DEG 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 EG/DEG ID test in PEG MW <= 1000
• **EG/DEG 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.	
• **EG/DEG test for PEG MW > 1000** ✓ FDA suggests to include a EG/DEG test	No EG/DEG method in the current monograph	Collaborate with stakeholders to develop a new gel permeation chromatography (GPC) method for PEG MW > 1000

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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).

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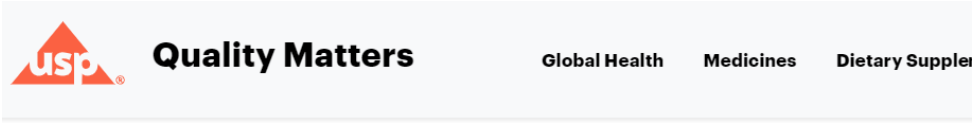
Stakeholder Engagement - Survey

- USP published a General Announcement along with a short survey regarding EG/DEG test in PEG monograph on September 29, 2023.

- Excipients Stakeholder Engagement, including presentations, blogs, and articles, etc.
  - IPEC – Americas;
  - IPEC – APV (Europe);
  - MWCDG;
  - NJPQCA;
  - AAPS – PharmSci 360;
  - Pharmexcil events (India)
  - IPEC Federation
  - Agilent Technologies Webinar



Supply Chain // September 21, 2023

Ensuring Product Safety: U.S. FDA Guidance on Testing High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol

Survey Results

- 127 stakeholders browsed the survey.
- Based on 64 responses completed for crucial questions, very useful information and feedback were received.

DEG and EG batch data for different PEG grades, including liquid, semi-solid and solid PEGs.	- Help USP setting appropriate specification limits for DEG and EG.	Several in-house EG/DEG test methods for PEG, especially MW <= 1000.	- Help USP providing available EG/DEG test methods for stakeholders to evaluate the suitability for their intended use

Stepwise Approach to address FDA's request

➢ Stepwise approach

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

- ✓ **Step 2.** Create a new general chapter to propose available EG/DEG 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)

➢ Received positive feedback and input from the FDA regarding the stepwise approach and PEG monograph revision proposal.

USP Next Steps

- PEG monograph revision proposal via interim revision announcement (IRA), targeting *PF* 50(3) [May-Jun. 2024]
  - 3-month public comment period (end on July 31, 2024), and then it will become official as soon as November 1, 2024, if *no significant comments* have been received.

  ✓ The *PF* 50 (3) monograph briefing will notify stakeholders that a new general chapter will be created to include several available EG/DEG test methods for stakeholders to evaluate the equivalency and interchangeability and use them as an alternative method according to *USP General Notices 6.30. Alternative and Harmonized Methods and Procedures,* as necessary.

- A new general chapter *<470> Determination of Ethylene Glycol, Diethylene Glycol and Triethylene Glycol in Polyethylene Glycol*, is currently under development, targeting PF 50(5) [Sep-Oct 2024].

- Collaborating with the FDA lab on evaluation of available EG/DEG test methods for PEGs.

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.

- **Stakeholder Engagement is crucial**

- **Get in touch with us !**

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

Contact: excipients@usp.org

Inquiry: NFMONOGRAPHS@usp.org

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Diethylene glycol incidents and deaths - References
(compiled from various sources**)

1. https://www.who.int/news/item/23-01-2023-who-urges-action-to-protect-children-from-contaminated-medicines
2. https://www.who.int/news/item/05-10-2022-medical-product-alert-n-6-2022-substandard-(contaminated)-paediatric-medicines;
3. https://www.who.int/news/item/02-11-2022-medical-product-alert-n-7-2022-substandard-(contaminated)-paediatric-liquid-dosage-medicines;
4. https://www.who.int/news/item/11-01-2023-medical-product-alert-n-1-2023-substandard-(contaminated)-liquid-dosage-medicines;
5. https://www.livemint.com/news/india/uzbekistan-cough-syrup-deaths-centre-alerts-pharma-companies-against-maya-chemtech-s-propylene-11678807916498.html
6. https://www.who.int/news/item/25-04-2023-medical-product-alert-n-4-2023--substandard-(contaminated)-syrup-medicines#:~:text=This%20WHO%20Medical%20Product%20Alert,and%20the%20symptoms%20of%20cough.

* Figures in parentheses indicate deaths reported from other sources which could not be confirmed officially.

** Sources include:

- Schep LJ et al. (2009) Clin. Toxicol., 47, 525-535.
- Sheehan C et al. (2010) J. Excipients and Food Chem. 1 (2), 33-39