Commentary

USP-NF Apr 2025

April 25, 2025

In accordance with USP's *Rules and Procedures of the Council of Experts ("Rules*"), and except as provided in Section 9.02 *Accelerated Revision Processes*, USP publishes proposed revisions to the *United States Pharmacopeia and the National Formulary* (*USP–NF*) for public review and comment in the *Pharmacopeial Forum (PF),* USP's free bimonthly journal for public notice and comment. After comments are considered and incorporated as the Expert Committee (EC) deems appropriate, the proposal may advance to official status or be re-published in *PF* for further notice and comment, in accordance with the Rules. In cases when proposals advance to official status*,* a summary of comments received and the appropriate Expert Committee's responses, as well as Expert Committee-initiated changes, are published in the Proposal Status/Commentary section of USPNF.com at the time the official revision is published.

The *Commentary* is not part of the official text and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of Expert Committees' responses to public comments on proposed revisions. If there is a difference or conflict between the contents of the *Commentary* and the official text, the official text prevails.

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Comments were received for the following when they were proposed in Pharmacopeial Forum:

Monographs
POLYETHYLENE GLYCOL
XYLAZINE HYDROCHLORIDE

No comments were received for the following proposals:

Monographs
XYLAZINE
XYLAZINE INJECTION

Monograph

Monograph/Section(s):	POLYETHYLENE GLYCOL (PEG) (66430)
Expert Committee:	Complex Excipients
No. of Commenters:	31

Ethylene Glycol (EG)_Diethylene Glycol (DEG) method (PEG MW >1000 - 8000)
Comment Summary #1: Commenters stated that they have experienced challenges with system suitability (resolution, peak tailing, negative baseline, %RSD, etc.). when evaluating the gel-permeation chromatography (GPC) method for PEG MW 1000-8000.
Response: Comment not incorporated. The proposed gel permeation chromatography (GPC) method has been an existing method in USP-NF Polyethylene Glycol 3350 monograph for many years. The Expert Committee acknowledges that while some stakeholders may encounter challenges in implementing the method, it is acceptable to most stakeholders and addresses a pressing need in the industry. A new general chapter <470> has been published in PF 50(5) [Sep. – Oct. 2024]. Several EG/DEG test methods are proposed for stakeholders to evaluate the suitability and interchangeability for their intended use. Suitable methods can be used as alternate method for testing EG/DEG in different PEGs. It will be helpful for stakeholders to provide feedback on their evaluated methods. USP may consider updating the PEG monograph using the most suitable methods for EG/DEG testing of different PEGs.

To engage stakeholders and address questions regarding this important PEG monograph revision process, USP has posted three General Announcements, as follows:

1) 1st General Announcement: Polyethylene Glycol | USP-NF (Oct. 7, 2024)
2) 2nd General Announcement: Polyethylene Glycol | USP-NF (Dec. 27, 2024)
3) 3rd General Announcement: Polyethylene Glycol | USP-NF (Feb. 28, 2025)

Harmonize EG/DEG limits with FDA Guidance
Comment Summary #2: Commenters recommended that the PEG IRA proposed limits for EG/DEG with a nominal molecular weight of 200 – 400 be aligned with the limits in the FDA guidance (not more than 0.10% for both ethylene glycol and diethylene glycol).
Response: Comment not incorporated. The specification limits for EG and DEG are proposed based on batch data and manufacturing process capabilities. Liquid PEGs (low molecular weight) tend to contain more EG and DEG and cannot meet the limit of NMT 0.10 % for DEG,

especially PEG 200, 300 and 400, based on manufacturing processes. The US FDA was consulted before the PF publication, and they agreed with the proposed limits.

EG_DEG GC method (PEG MW 200 - 1000)
Comment Summary #3: The commenters commented that they experienced challenges with system suitability (poor peak shape, precision and linearity, etc.), extended run time, and limited column durability.
Response: Comment not incorporated.
The proposed gas-chromatography method has been an existing method in USP-NF chapter <469> for many years. The Expert Committee acknowledges that while some stakeholders may encounter challenges in implementing the method, it is acceptable to most stakeholders and addresses a pressing need in the industry.

A new general chapter <470> has been published in PF 50(5) [Sep. – Oct. 2024]. Several EG/DEG test methods are proposed for stakeholders to evaluate the suitability and interchangeability for their intended use. Suitable methods can be used as alternate method for testing EG/DEG in different PEGs. It will be helpful for stakeholders to provide feedback on their evaluated methods. USP may consider updating the PEG monograph using the most suitable methods for EG/DEG testing of different PEGs. Also see the aforementioned general announcements that USP posted previously.

Column and condition
Comment Summary #4: Commenters requested clarifications of columns used in the EG/DEG testing methods.
Response: Comment partially incorporated. Clarifications were sent to the commenters via email replies.
Column information has been included in the USP Chromatographic Database.

PEG 3350
Comment Summary #5: Commenters required clarification for different specification limits of EG and DEG between PEG revision proposal and PEG 3350 monograph:
PEG PF 50(3) proposal for PEG MW >1000
- Acceptance criteria: EG - NMT 0.062%; DEG - NMT 0.10%
PEG 3350
- Acceptance criteria: EG - NMT 0.062%; Sum of EG and DEG - NMT 0.20%
Response: Comment not incorporated. The PEG IRA proposal will have no changes to the specification limits of EG and DEG. However, the Complex Excipients Expert Committee will consider revising Polyethylene Glycol 3350 monograph based on the FDA's input.

Identification (ID) Test using Infrared (IR) Spectroscopy
Comment Summary #6: Commenters provided the following comments:
1) They have observed larger peak shift or additional peaks in some positions.
2) The listing of peak maxima is over-prescriptive, causes additional work, adds potential confusion, and does not add value. They recommended cross-referencing to chapter <197> without specified peak positions, like PEG 3350 monograph.
Response: Comment partially Incorporated. The Complex Excipients Expert Committee agreed to partially incorporate the comments regarding larger peak shift or additional peaks.
1) The IR test in ID section will include a note - “Due to peak width, the peak maxima may have a larger shift compared to the listed peak positions.”. The Acceptance Criteria will be updated to reflect the USP reference standard qualification results.
2) The comment regarding only cross-referencing chapter <197> is not incorporated. The

rationale to include the peak maxima of major peaks in the PEG monograph is because the PEG monograph covers many grades. Multiple PEG grades are compared to one PEG grade reference standard (RS), so larger peak shifts may be observed, affecting sample and RS conformity. Listing peak maxima of major peaks helps lab scientists to check conformity between sample and RS. In contrast, the PEG 3350 monograph has only one grade and refers only to the general monograph <197> as the IR spectrum of the sample matches well with that of PEG 3350 RS.

Additional information – the updated Acceptance Criteria for ID by IR: (also see the 2nd General Announcement: Polyethylene Glycol | USP-NF (Dec. 27, 2024)

Acceptance Criteria:
Polyethylene Glycol 200:
Locate peak maxima of the following major peaks at about 832*, 885, 941*, 1066, 1110*, 1249, 1294, 1350, 1458, and 2870*cm−1. The test sample spectrum peak maxima differ by NMT ±10 cm−1 from the Standard.
Polyethylene Glycol 300–600: Locate peak maxima of the following major peaks at about 844, 885, 941*, 1110*, 1249, 1294, 1350, 1458, and 2869 cm−1. The test sample spectrum peak maxima differ by NMT±10 cm−1 from the Standard.
Polyethylene Glycol 1000–8000:
Locate peak maxima of the following major peaks at about 842, 947*, 1061, 1110*, 1147, 1241, 1280, 1342, 1360, 1467, and 2880 cm−1. The test sample spectrum peak maxima differ by NMT ±10 cm−1 from the Standard.
[*Note: Due to peak width, the peak maxima may have a larger shift compared to the listed peak position.]

Mobile phase/Diluent
Comment Summary #7: Commenters recommended replacing the toxic reagent and using appropriate grade of solvent in the mobile phase.
Response: Comment not incorporated. As revisions of EG/DEG methods take time and there is an urgent need for official methods to be available, the currently proposed methods in the PEG IRA will become official as planned. However, the Excipients Expert Committee will consider updating the EG/DEG testing methods in the future to adopt more user-friendly and environmentally friendly methods.

Implementation time
Comment Summary #8: Commenters recommended an extended implementation time to allow companies the opportunity to go through all these necessary steps to ensure they are able to comply with the upgraded monographs.
Response: Comment incorporated. In light of the additional time required by industry and the changes to the monograph, the Complex Excipients Expert Committee approved a new official date of August 1, 2025. (See the 3rd General Announcement: Polyethylene Glycol | USP-NF (Feb. 28, 2025). The delayed implementation is intended to provide the time needed by manufacturers and users to implement the test methods and make necessary changes.

Using Reagent Grade for Internal Standard
Comment Summary #9: The commenter recommended reagent grade of Butane-1,3-diol be used as the internal standard in Diluent.
Response: Comment not incorporated. USP recommends the use of USP 1,3-Butanediol RS in diluent to prepare appropriate standard and sample solutions because USP RS has been

qualified for use in the EG/DEG testing method in the USP-NF monograph. There is no quality guarantee for using other grades of 1,3-butanediol as the internal standard.

Monograph/Section(s):	XYLAZINE HYDROCHLORIDE (89238)
Expert Committee:	Small Molecules 3
No. of Commenters:	1

EC-Initiated change: First listed chemical name in the Chemical Information section is similar to the third listed name and therefore the duplicated text was deleted.