



Informal Commentary
Limit of Ethylene Glycol (EG) and Diethylene Glycol (DEG) in Propylene Glycol
December 2009

Monograph/Section(s): Propylene Glycol/Identification B: Limit of EG and DEG
Expert Committee(s): Excipient Monographs 1
No. of Commenters: 13

Comment Summary #1: Commenter indicated that in the execution of the proposed compendial method as written, a peak was observed (originating from the USP Propylene Glycol RS source) that interferes with the Ethylene Glycol peak. Modifications were proposed to eliminate this problem.

Response: Comment not incorporated by the committee because both the comment and the proposed modifications were submitted to the Reference Standard Laboratory for evaluation. USP labs looked at overlay GC spectra for the USP Propylene Glycol RS, USP Ethylene Glycol RS, Test Solution, and Diluent. The unknown peak which was reported to co-elute with the EG peak is not present in the USP investigation.

Comment Summary #2: Commenter indicated that in a review of the proposed changes for the Propylene Glycol monograph and other sugar alcohol monographs, the acceptance criterion for diethylene glycol and ethylene glycol is recommended to be NMT 0.1% (1000ppm) for either compound. Currently USP<467> lists ethylene glycol (class 2 residual solvent) at a limit of 620ppm when present in excipient compounds. Will the monograph level of 1000ppm take precedence over the general chapter limit of 620ppm for these hazardous entities in Propylene Glycol and other sugar alcohol excipient compounds.

Response: The Expert Committee determined that the proposed test for the Limit of DEG and EG exists to require end users to perform a specific identity test that includes a limit for DEG and EG on all containers of all lots and is not related to the requirement to control EG as a residual solvent per the requirement in the General Notices.

Comment Summary #3: Commenter suggested that just like the new glycerol method, the concentration of propylene glycol in the standard and sample solutions are different, so the retention times do not match exactly. In order to run the propylene glycol retention time in standard was 4.5 min and the retention time in the sample was 4.6 min. Acceptance criterion in the proposed method states: "The retention time of the Propylene Glycol peak in the chromatogram of the Sample solution corresponds to that in the chromatogram obtained from the Standard Solution to please consider revising the language to be less restrictive.

Response: Comment incorporated. The precision for reporting retention time was reduced from 2 significant figures to 1, allowing for a less restrictive criterion.

Comment Summary #4: Commenter suggested that the System Suitability requirement for Resolution should be between Ethylene Glycol and Propylene Glycol, not Ethylene Glycol and DEG. Also, commenter suggested lowering the requirement from 6.0, as this is far greater than needed for baseline separation.

Response: Comment incorporated with the following additional changes because the Expert Committee determined that the resolution requirement to separate EG and PG should be NLT 5.0.

Comment Summary #5: Commenter suggested including one single GC test method using a capillary column and FID detector for ID, assay, and limit of EG and DEG.

Response: Comment not incorporated because Expert Committee determined that inadequate data was provided and requests validation data to consider such a request.

Comment Summary #6: Commenter questioned the requirements for use of a diluent and internal standard.

Response: Expert Committee determined that an internal standard is necessary as the instrument response for EG and DEG changes due to matrix effects. As for the use of the diluent, the Expert Committee has asked the vendor to supply validation data to support a neat material injection method.

Comment Summary #7: Commenter suggested that the proposed method should include the relative retention time for dipropylene glycol isomers

Response: Comment not incorporated because the Expert Committee determined that this information was not necessary.

Comment Summary #8: Commenter suggested that the first sentence should read: "Because of the serious hazards associated with the use of Diethylene Glycol **and Ethylene Glycol**-contaminated materials..."

Response: Comment not incorporated as this statement does not pertain to the actual monograph for Propylene Glycol. However, USP agrees with the change to the USP Website Hot topics page.

Comment Summary #9: Commenter questioned whether or not there should be some consideration of daily intake in the last sentence: "the testing of USP Propylene Glycol should demonstrate the absence at NMT 0.10%."

Response: Comment not incorporated because the Expert Committee determined that the limit of 0.10% was not made based on total intake. The understanding of the test is that it should demonstrate absence of DEG and EG and 0.10% is a practical limit that can met with routine analytical technology.

Comment Summary #10: Commenter suggested that the statement above the Relative Retention Time chart should read: "The retention time for Propylene Glycol is approximately 4 minutes" instead of "about 4.03 minutes"

Response: See response for Comment #3.

Comment Summary #11: Commenter suggested that the title for the second column in chart should read Relative Retention Time (Approximately)

Response: Comment not incorporated because the Expert Committee determined that the term "approximately" should be removed so as to not create confusion as to its meaning.

Comment Summary #12: Commenter suggested that the last sentence in the Acceptance Criterion should read “NMT 0.10% each, for diethylene glycol or ethylene glycol is found.

Response: Comment incorporated with the following additional changes because the Expert Committee determined that the acceptance criteria should be re-worded for clarity.

Comment Summary #13: Commenter reported having very different retention times for all analytes (all were eluting at about double the retention time).

Response: The Expert Committee recommends USP contact the commenter for additional information (column, possible deviations from procedure)