New Tests for Identifying Harmful and Potentially Deadly Adulterants in Pharmaceutical Ingredients: The Role of USP-NF in Setting Revised Standards

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Director, Excipients
United States Pharmacopeia

Outline
- USP overview
- USP Standards Setting Process - Accelerated Revisions (Revision Bulletin)
- History of adulteration with diethylene glycol
- FDA request to USP to strengthen USP-NF monographs
- FDA/USP/Stakeholder collaboration in development of new tests
- Conclusions
- How stakeholders can get involved in USP
- References
USP Overview

- Nonprofit international public health organization
- Private, independent, and self-funded
- Global activities and impact
- Establishes quality standards (USP, NF, FCC)
- Expert volunteers are scientific decision-makers
- ISO-9001 and ISO-17025
- Locations
  - Rockville, MD (headquarters)
  - Basel, Switzerland
  - Hyderabad, India
  - Shanghai, China
  - Sao Paulo, Brazil
USP Mission Statement

USP mission is to improve public health of people around the world through public standards and related programs that help ensure the quality, safety and benefit of medicines and foods.

USP’s Legal Recognition

- **Federal Law**
  - 1938 - Federal Food, Drug & Cosmetic Act (FD&C Act)
    - USP and NF standards enforceable by FDA
  - intended to provide diagnosis, cure, mitigation, treatment, or prevention of disease
  - intended to affect the structure or any function of the body
  - intended for use as a COMPONENT of any article meeting the above criteria
- Excipients are *components* of the drug
USP’s Legal Recognition

FD&C Act SEC. 501. [21 USC §351] Adulterated Drugs and Devices

Section 501(b) - A drug or device shall be deemed adulterated - if it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standard set forth in such compendium...

USP’s Legal Recognition

BUT, Section 501(b) says that:

• A drug will not be deemed adulterated for failing to meet the compendial standard of strength, quality, or purity if the difference from the standards is plainly stated on the label.
• To avoid being adulterated, drugs must comply with compendial standards for strength, quality, or purity, unless labeled to show all differences.

However, Section 501(b) & 502(e)(3)(B) also says

• Drug with name recognized in USP must comply with compendial identity standards, or be deemed adulterated, misbranded, or both. Cannot label away from identity!
• USP does not enforce its standards
• FDA enforces USP standards
USP Standards Setting Process

Scientific Liaison performs technical review and drafts the monograph

Monograph is received/development initiated

Monograph is published for public review and comment

Scientific Liaison reviews comments; submits comments to Expert Committee

Expert Committee ballots

Not approved  Approved

Monograph is published in official publication (USP-NF, FCC)

Expert Committees

Staff Liaison

Industry  Other Pharmacopeias

Government
Pharmacopeial Forum

- Your voice in standards development
- Working arm of the Council of Experts
- Bimonthly journal with
  - Proposed revisions to USP-NF standards for your comments
  - Official revisions to standards
  - Updates on international harmonization
  - Stimuli articles

Web Postings

History of adulteration with Diethylene Glycol

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Incident</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>1937</td>
<td>“Elixir sulfanilamide” – 107 deaths</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resulted in the implementation of the 1938 Amendment to the FFD&amp;C Act</td>
</tr>
<tr>
<td>South Africa</td>
<td>1969</td>
<td>Sedative formulated with DEG – 7 deaths</td>
</tr>
<tr>
<td>Italy</td>
<td>1985</td>
<td>DEG in wines from Austria – no known deaths</td>
</tr>
<tr>
<td>India</td>
<td>1986</td>
<td>Medicinal glycerin laced with DEG – 14 deaths</td>
</tr>
<tr>
<td>Nigeria</td>
<td>1990</td>
<td>Acetaminophen syrup containing DEG – 40 deaths (some sources say 200 deaths)</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>1990-2</td>
<td>Acetaminophen syrup containing DEG – 339 deaths</td>
</tr>
<tr>
<td>Haiti</td>
<td>1995/6</td>
<td>Cough medicine containing DEG – 85 deaths</td>
</tr>
<tr>
<td>Panama</td>
<td>2006</td>
<td>Cough and anti-allergy syrup containing DEG – 46 deaths (116 or 365 according to other sources)</td>
</tr>
<tr>
<td>USA</td>
<td>2006/7</td>
<td>Toothpaste containing DEG – no deaths</td>
</tr>
<tr>
<td>Panama</td>
<td>2007</td>
<td>Toothpaste containing DEG – no deaths reported</td>
</tr>
<tr>
<td>Nigeria</td>
<td>2008/9</td>
<td>Teething formula contaminated with DEG from propylene glycol – 84 deaths</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>2009</td>
<td>Paracetamol syrup to children adulterated with diethylene glycol. Twenty-four children reported dead</td>
</tr>
</tbody>
</table>

Glycerin and Diethylene Glycol

- Diethylene glycol (DEG), a known nephrotoxin and hepatotoxin, is used as an industrial solvent and antifreeze.
- Glycerin, DEG, and ethylene glycol (EG) share many physical properties, including a natural sweet taste, color and viscosity.
- Inexpensive!
- This facilitates the adulteration of glycerin or other inactive ingredients with less expensive, more toxic DEG.

Diethylene Glycol (‘‘Antifreeze’’)
POISON!

Ethylene Glycol (‘‘Antifreeze’’)
POISON!
The Problem: Even to the Trained Professional...

Ethylene Glycol ("Antifreeze")
POISON!

- Light colored
- Slightly viscous liquid at room temp.
- Sweet taste

Propylene Glycol
Edible and GRAS

- Light colored
- Slightly viscous liquid at room temp.
- Sweet taste

Glycerin (Glycerol)
Edible and GRAS

- Light colored
- Slightly viscous liquid at room temp.
- Sweet taste

Diethylene Glycol ("Antifreeze")
POISON!

- Light colored
- Slightly viscous liquid at room temp.
- Sweet taste

Albinus D’Sa, Ph.D., FDA, 2008 ASM Kansas

USP Response to Haiti incident for USP Glycerin Monograph

In the late 1990s, in response to the Haiti incident, USP revised the Glycerin monograph to include:

- Identification section: Addition of “Identification Test B”. Glycerin Identification by retention time

- Impurities section: Addition of the “Limit of DEG and Related Compounds” Test
  A capillary gas-chromatographic (GC) method with flame ionization detection (FID)
  NMT 0.1% DEG
Request for USP-NF Monograph (April 2007)

- **Request from FDA:** USP to strengthen the USP Glycerin Identification section to include the identification and quantitation of DEG in glycerin.

- **Rationale:** GMPs allow the use of Identification testing alone, by dosage form manufacturers, for raw material(s) qualification
  - manufacturers could therefore not deviate from the DEG limit since this would be an aspect of identity.

- **Challenge:** Complex issue relating to ‘requirement’ that contaminant/adulterant be considered part of an article’s Identification

FDA’s May 2007 Guidance Regarding DEG Contamination of Glycerin

Reiterates §211.84(d)(2) requirement for specific ID testing when not performing full USP testing

- Requires intimate knowledge of the supply chain
- Testing has to be capable of detecting DEG
- Applies to all recipients of Glycerin USP, not only those who formulate or compound

Traceability
21 CFR Part 211 - CGMP Requirements for Drug Manufacturers (relating to Glycerin)

- Control of Components… (Subpart E)
- 21 C.F.R. § 211.84(d)(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.”
- 21 C.F.R. § 211.84(d)(1)
  - requires that manufacturers of drug products detect and quantify any DEG present both at the time of manufacture and upon receipt at the point of transfer to another party.
  - manufacturers cannot deviate from the DEG limit since this is an aspect of identity. **Cannot label away from identity!**
  - In contrast, if DEG detection and quantification is solely part of a purity (impurity) test, a manufacturer need not include as part of its identity testing *(the only test required to accept the material)*

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21 C.F.R. § 211.84(d)(1) and (2)

- 21 C.F.R. § 211.84(d)(1)
  - places burden on drug manufacturers to prevent the use of adulterated ingredients
    - Representative samples
    - Appropriate testing or examination
    - Appropriate written specifications
      - Verification of identity
      - ID testing of excipients must be specific (or must perform additional tests that support unequivocal ID)
- 21 C.F.R. § 211.84(d)(2)
  - Allows use of CoA data for conformance to other specifications provided data is verified periodically for accuracy
  - Use of the vendor CoA applies only if ongoing verification of data and the absence of adulteration exists
  - “provided that at least one specific identity test is conducted on such component by the manufacturer”
**FDA/USP/Stakeholder collaboration in method development - Glycerin**

**Jun 07:** USP Lab tested the TLC method referenced in the FDA 2007 Glycerin guidance document, Kenyon et al. published in the *Journal of AOAC International*

- Journal: Iodine and potassium permanganate staining, the lowest detected DEG levels were 1% and 0.5% level, respectively
- Modified method: chloroform, acetone, and 5 M ammonium hydroxide (10:80:10, v/v/v): the 0.1% and 0.05% DEG spots clearly visible in Standard preparations but extremely difficult to detect the same levels of DEG in spiked Glycerin samples with any degree of certainty
- The USP lab conclusions:
  - Spot intensity dependent on staining and exposure time - can lead to false conclusions, DEG and EG not separated
  - The method was not suitable as a compendia test
- USP concentrated on existing USP Glycerin GC impurities method improvement

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**Glycerin Activities contd.**

**Jun 08**
- Stakeholders request a collaborative study on GC method limit
- USP worked closely with industry groups and FDA to establish a limit that would provide adequate protection from adulteration provide industry with a compendial standard that could be met with common analytical technology

**Sep 08**
- Shared results of TLC study with FDA and Stakeholders
  - 2 web meetings (Sept 18 and 19, 2008), posted on the USP Hot Topics web page
  - 2008 USP Annual Science Meeting (Sept 24, 2008)

**Nov 08**
- PNP Stakeholder Forum (21 Nov 08). Announced the proposed limit to be not more than 0.10% each for DEG and EG.

**Feb. 09**
- Revision bulletin posted on USP website, Feb. 4, 2009, Official May 1, 2009
A Typical Chromatogram of a **Standard Solution** (2 mg/mL of glycerin, 0.050 mg/mL each of EG and DEG and 0.10 mg/mL of internal standard)

Ethylene glycol 2,2,2-Trichloroethanol Diethylene glycol Glycerin

* solvent peaks

### Parameter Settings

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detector</td>
<td>FID</td>
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<tr>
<td>Column</td>
<td>0.53 mm x 30 m fused-silica, 3.5 μm G43 stationary phase having an inverted cup or spiral liner</td>
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<tr>
<td>Injection port</td>
<td>Temperature</td>
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<tr>
<td>Detector</td>
<td>250°C</td>
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<tr>
<td>Column</td>
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<tr>
<td>Temperature</td>
<td>180°C</td>
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<tr>
<td>Carrier Gas</td>
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<td>Injection Type</td>
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<td>Oven Temperature</td>
<td>Program</td>
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<tr>
<td>Hold at 100°C</td>
<td>for 4 minutes</td>
</tr>
<tr>
<td>50°C/min to 120°C</td>
<td></td>
</tr>
<tr>
<td>Hold at 120°C</td>
<td>for 10 minutes</td>
</tr>
<tr>
<td>50°C/min to 220°C</td>
<td></td>
</tr>
<tr>
<td>Hold at 220°C</td>
<td>for 6 minutes</td>
</tr>
<tr>
<td>Injection Volume</td>
<td>1 μL</td>
</tr>
</tbody>
</table>

### USP Lab. Results for EG and DEG in Glycerin

#### Accuracy and Method Precision

Recovery of EG and DEG from Glycerin calculated against the Standard solution (2 mg/mL of Glycerin, 0.050 mg/mL each of EG and DEG, and 0.10 mg/mL of internal standard).

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>% Recovery</th>
<th>%RSD (n=6)</th>
<th>% Recovery</th>
<th>%RSD (n=6)</th>
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<tr>
<td>Spiked test solution 1</td>
<td>95.7</td>
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<td>97.2</td>
<td></td>
</tr>
<tr>
<td>Spiked test solution 2</td>
<td>95.6</td>
<td></td>
<td>97.0</td>
<td></td>
</tr>
<tr>
<td>Spiked test solution 3</td>
<td>97.2</td>
<td>1.1</td>
<td>96.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Spiked test solution 4</td>
<td>98.2</td>
<td></td>
<td>96.9</td>
<td></td>
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<tr>
<td>Spiked test solution 5</td>
<td>97.2</td>
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<td>97.0</td>
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</tr>
<tr>
<td>Spiked test solution 6</td>
<td>97.4</td>
<td></td>
<td>97.7</td>
<td></td>
</tr>
</tbody>
</table>

* % Recovery = (Conc. Found/Conc. Added) x 100- average of two injections

Acceptance criteria = 90.0%-110.0%
FDA Second Letter Jan 14, 2009

- FDA letter requested a revision to both Sorbitol Solution and Propylene Glycol consistent with the update to the USP Glycerin Monograph
  - Include a Limit test for Diethylene Glycol (DEG) contamination in the Identification section

- Both Sorbitol Solution and Propylene Glycol were categorized by FDA as "high-priority" monographs for this type of revision.

USP-NF Articles Identified as ‘High-Priority’ for Adulteration with DEG and EG by FDA

<table>
<thead>
<tr>
<th>Article</th>
<th>Category</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maltitol Solution (1) (H)</td>
<td></td>
<td>H</td>
</tr>
<tr>
<td>Sorbitol Solution (1) (H)</td>
<td></td>
<td>H</td>
</tr>
<tr>
<td>Sorbitol sorbitan solution (1) (H)</td>
<td></td>
<td>H</td>
</tr>
<tr>
<td>Noncrystallizing sorbitol solution (1) (H)</td>
<td></td>
<td>H</td>
</tr>
<tr>
<td>Propylene glycol (2) (H)</td>
<td></td>
<td>H</td>
</tr>
<tr>
<td>Propylene glycol dilaurate (4) (M)</td>
<td></td>
<td>M</td>
</tr>
<tr>
<td>Polyethylene glycol (3) (M)</td>
<td></td>
<td>M</td>
</tr>
<tr>
<td>Lactitol (1) (L)</td>
<td></td>
<td>L</td>
</tr>
<tr>
<td>Maltitol (1) (L)</td>
<td></td>
<td>L</td>
</tr>
<tr>
<td>Sorbitol (1) (L)</td>
<td></td>
<td>L</td>
</tr>
<tr>
<td>Polyethylene glycol monomethyl ether (4) (L)</td>
<td></td>
<td>L</td>
</tr>
<tr>
<td>Diethylene glycol monoethyl ether (4) (L)</td>
<td></td>
<td>L</td>
</tr>
<tr>
<td>Diethylene glycol stearates (4) (L)</td>
<td></td>
<td>L</td>
</tr>
</tbody>
</table>

1- Sugar alcohols
2- Propane diols and triols
3- Polyols (polyethylene glycol)
4- Derivatives of categories 1-3

The risk levels for undetectable contamination are categorized as:
- H – high
- M – medium
- L – low
Comments from CDER Office of Compliance on the USP List

- **Highest risk ingredients**
  - aqueous solutions or liquids that can be readily spiked with DEG or EG
  - similar physical properties in terms of viscosity
  - may be sweet tasting and thus make their way into solutions, syrups and elixirs at relatively high levels of use

- **IIG search for ingredients deemed high-risk**, revealed that they are in fact used at very large amounts such that toxic levels are readily achieved.
  - The ingredients synthesized from DEG already have a limit test, and are only used in non-oral applications per a USP labeling requirement.

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**USP-NF Articles Identified as ‘High-Priority’ for Adulteration with DEG and EG**

<table>
<thead>
<tr>
<th>USP-NF Monograph</th>
<th>Proposed text</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maltitol Solution (1) (H)</td>
<td>No DEG or EG test</td>
</tr>
<tr>
<td>Sorbitol Solution (1) (H)</td>
<td>No DEG or EG test</td>
</tr>
<tr>
<td>Sorbitol sorbitan solution (1) (H)</td>
<td>No DEG or EG test</td>
</tr>
<tr>
<td>Noncrystallizing sorbitol solution (1) (H)</td>
<td>No DEG or EG test</td>
</tr>
<tr>
<td>Propylene glycol (2) (H)</td>
<td>No DEG or EG test</td>
</tr>
<tr>
<td>Propylene glycol dilaurate (4) (M)</td>
<td>No DEG or EG test</td>
</tr>
<tr>
<td>Polyethylene glycol (3) (M)</td>
<td>Limit of ethylene glycol and diethylene glycol (MW 450 or less, MW 450 or above but &lt;1000) — 0.25% of combined ethylene glycol and diethylene glycol.</td>
</tr>
<tr>
<td>Lactitol (1) (L)</td>
<td>No DEG or EG test</td>
</tr>
<tr>
<td>Maltitol (1) (L)</td>
<td>Related compounds test -NMT 1.5%</td>
</tr>
<tr>
<td>Sorbitol (1) (L)</td>
<td>No DEG or EG test</td>
</tr>
<tr>
<td>Polyethylene glycol monomethyl ether (4) (L)</td>
<td>Limit of ethylene glycol and diethylene glycol — 500 — 0.25% of combined ethylene glycol and diethylene glycol. Limit of ethylene glycol and diethylene glycol 800 or above but &lt;1500 — 0.25% of combined ethylene glycol and diethylene glycol.</td>
</tr>
<tr>
<td>Diethylene glycol monoethyl ether (4) (L)</td>
<td>Limit of free diethylene glycol — NMT 1 µg per g Limit of 2-methoxyethanol, 2-ethoxyethanol, ethylene glycol, and diethylene glycol — NMT 50, 160, 620, 150 µg per g</td>
</tr>
<tr>
<td>Diethylene glycol stearates (4) (L)</td>
<td>Limit of free diethylene glycol — NMT 8.0%</td>
</tr>
</tbody>
</table>
‘High-Priority’ Monographs

- A total of five excipient monographs were categorized as ‘high-priority’ for update of Identification test:
  - Sorbitol Solution
  - Sorbitol Sorbitan Solution
  - Noncrystallizing Sorbitol Solution
  - Maltitol Solution
  - Propylene Glycol

- Monographs were prioritized as:
  - high (H)
  - medium (M)
  - low (L)

- Except for Propylene Glycol, the other four excipients are traditionally called sugar alcohols or polyols.

USP/Stakeholder DEG and EG Method Development

Sugar Alcohol monographs

- USP evaluated a total of 4 methods as part of their collaborative efforts with stakeholders for the following sugar alcohol monographs:
  - Sorbitol Solution
  - Sorbitol Sorbitan Solution
  - Noncrystallizing Sorbitol Solution
  - Maltitol Solution

- Concurrently, industry submitted a GC method to detect EG in a request for revision to USP-NF sugar alcohol monographs.
  - This request arose because Residual Solvents <467> does not have a test method for EG.
  - The manufacturer submitting the request for revision indicated that EG is a process impurity.
USP/Stakeholder DEG and EG Method Development

- The USP Lab did observe the presence of an EG peak in the chromatograms obtained using manufacturer provided samples for the four sugar alcohols at levels around 50–200 PPM.

- While FDA’s original request to USP did not include controlling EG in the Identification test, questions arose about also including a test for EG, given its toxicity levels, which appear to be even greater than DEG toxicity levels.

- At a May 8, 2009 meeting FDA agreed to the inclusion of EG in the Identification Test.

Method Development for EG and DEG in sugar alcohols

- TLC method was reviewed by the lab and by sugar alcohol manufacturers. (Method I - unsuitable)
  - Method unsuitable for these type of sugar alcohols

- The HPLC Assay in the current Sorbitol Solution monograph was found unsuitable for detection of EG and DEG in sorbitol containing sugar alcohols (Method II - unsuitable)

- A GC method provided by a sponsor company exhibited carry over and interference of the sample matrix peaks with DEG. (Method III - unsuitable)

- A modified method III developed by the USP lab introduced a new sample solution using a mixture of acetone: water (96:4, v/v) as diluent.
  - GC method was validated for specificity, accuracy, method precision, and LOD. (Method IV)
Method Development for EG and DEG in sugar alcohols (sponsor company method III)

Chromatograms of a Standard solution obtained using the sponsor company’s GC method

Figure 1. A chromatogram of a Standard solution prior to injection of a Sample solution
Figure 2. A chromatogram of a Standard solution after injection of a Sample solution

USP Lab Results for EG and DEG in Sorbitol solution (Method IV, Acetone: Water Mixture (96:4,v/v) )

A chromatogram of a Sample solution (80 mg/mL sorbitol solution)

A chromatogram of a Spiked sample solution containing 0.10% each of EG and DEG

* solvent peak
USP Lab Results for EG and DEG in sugar alcohols (Method IV, Acetone: Water Mixture (96:4,v/v))

A chromatogram of a Standard solution (0.08mg/mL each of EG and DEG)

* solvent peak

Results for EG and DEG in Sugar alcohols

Final GC Method Conditions:

- Column: DB-1701, 15-m x 0.32-mm, 0.25-µm fused silica
- Detector: 300° (FID)
- Injector: 240°
- Constant flow: 3.0 mL/min
- Injection volume: 1 µL
- Split ratio: 10:1
- Oven program: 70° for 2 minutes, increase to 300° at a rate of 50°/min, for 5 minutes
- Liner: Agilent low pressure, deactivated split liner with glass wool
- Solvent: 96:4 v/v (acetone and water)
- Internal Standard: None
- Run time: 13 min
A capillary gas-chromatographic (GC) method with flame ionization detection (FID) originally developed for detection of EG and DEG in glycerin was validated for detection of both analytes in propylene glycol.

Due to EG and DEG exhibiting higher area count responses in the presence of propylene glycol, an internal standard was used to avoid false positives (2,2,2-trichloroethanol).

--The method was validated for specificity, accuracy, method precision, and LOD
Propylene Glycol Analytical Research and Development Laboratory Results

A chromatogram of a Sample solution (50 mg/mL propylene glycol and 0.1 mg/mL of internal standard in methanol)

Instrument Conditions
Column: DB-624, 30-m x 0.53-mm
Helium flow: 4.5 mL/min
FID detector: 250º
Injector: 220º
Injection volume: 1 μL,
Split: 10:1
Oven: 100º for 4 min, ramp to 120º at 50º per min, hold 10 min, ramp to 220º at 50º per min, hold 220º for 6 minutes

Propylene Glycol Analytical Research and Development Laboratory Results

A chromatogram of a Spiked sample solution (50 mg/mL propylene glycol, 0.050 mg/mL each of EG and DEG and 0.1 mg/mL of internal standard in methanol)

LOD
EG: 0.001 mg/mL (0.006%)
DEG: 0.009 mg/mL (0.018%)
USP Lab. Results for EG and DEG in Propylene Glycol

Accuracy and Method Precision

Recovery of EG and DEG from Propylene Glycol calculated against the Standard solution (2 mg/mL of propylene glycol, 0.050 mg/mL each of EG and DEG, and 0.10 mg/mL of internal standard).

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>% Recovery</th>
<th>% RSD (n=6)</th>
<th>% Recovery</th>
<th>% RSD (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiked test solution 1</td>
<td>104.2</td>
<td>2.1</td>
<td>107.1</td>
<td>1.4</td>
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<tr>
<td>Spiked test solution 2</td>
<td>101.7</td>
<td></td>
<td>103.1</td>
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<tr>
<td>Spiked test solution 3</td>
<td>101.6</td>
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<td>Spiked test solution 4</td>
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<td>Spiked test solution 6</td>
<td>98.2</td>
<td></td>
<td>103.6</td>
<td></td>
</tr>
</tbody>
</table>

\* % Recovery = (Conc. Found/Conc. Added) x 100 - average of two injections

Acceptance criteria ~ 90.0%-110.0%

Monographs OFFICIAL via Revision Bulletin

- **Glycerin**
  - Official date **May 1, 2009**

- **Sorbitol Solution**

- **Sorbitol sorbitan solution**

- **Noncrystallizing sorbitol solution**

- **Propylene glycol**
  - Official date **February 1, 2010** (same DEG and EG limits)

Questions:
- Bob Lafaver, M.S., e-mail RHL@usp.org
- Kevin Moore, Ph.D., (harmonization Propylene Glycol and Glycerin), e-mail KTM@usp.org
Maltitol Solution

- USP lab developed and validated a capillary GC method with FID
  - Suitable solvent for sample preparation was identified to achieve recoveries for both analytes in the range of 90.0%-110.0%
  - Diluent: Acetone: Water (96:4,v/v)
  - 1,3-butanediol used as Internal standard

Revisions Bulletins

- **Maltitol Solution**
  - **Targeted Revision Bulletin Posting**: April 30, 2010
  - **Targeted Revision Bulletin Official date Posting**: August 1, 2010 (same DEG and EG limits)

- Official Monograph and Reference standard information posted on the USP website under the Hot Topics links:
  - [http://www.usp.org/hottopics/propyleneGlycolSorbitolInformation.html](http://www.usp.org/hottopics/propyleneGlycolSorbitolInformation.html)
Look for Revision Bulletins and other information under Hot Topics

Conclusions

GC procedure developed for the Identification test and official via Revision Bulletin is:

- Simple and easy-to-operate
- Employs a basic GC instrument with direct injection
- GC run time is short
- Sample preparation is quick and easy
- Robust and rugged
- A limit that would provide adequate protection from adulteration
- Provide industry with a compendial standard that could be met with common analytical technology

Close collaboration among USP, FDA, and USP’s Stakeholders in the RB development process resulted in these critical RBs that promote public health
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> www.usp.org/goto/nominate

Deadlines:
• December 18, 2009: Chair applications
• May 15, 2010: Expert Committee Member applications
• Starting in July 2010: Expert Panel recruitment
References


- Development of New Compendial Identification Tests for Determination of the Limit of Diethylene Glycol and Ethylene Glycol in Sugar Alcohols, Hong Wang et al., Excipient Fest Poster exhibition, May 2010

Thank You!