USP Excipient Initiatives: Together, How Can We Ensure the Quality of Medicines?

Danita Broyles, Senior Customer Engagement Manager and Stephen W. Andruski, Senior Manager, Verifications Program
A cautionary tale:

Incoming Material Testing and Reliance on COA of incoming excipient for receipt and release to production

Together, How Can We Ensure the Quality of Medicines?
Agenda

- History of poor excipient quality
- US Law
- Current findings
- Summary
- USP Excipient Initiatives to ensure the quality of medicines
1

History of poor excipient quality
## History of Glycerin 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>Sulfanilamide Elixir – 107 deaths Resulted in the enactment of the 1938 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>
</tbody>
</table>
## History of Glycerin adulteration with diethylene glycol

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Incident</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>2006/7</td>
<td>Toothpaste containing DEG – no deaths</td>
<td>no deaths</td>
</tr>
<tr>
<td>Panama</td>
<td>2007</td>
<td>Toothpaste containing DEG – no deaths reported</td>
<td>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>
<td>84 deaths</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>2009</td>
<td>Paracetamol syrup to children adulterated with diethylene glycol.</td>
<td>Twenty-four children reported dead</td>
</tr>
</tbody>
</table>
FDA encourages USP to update monographs

We believe that USP’s current monograph modernization program is a good start toward achieving our objective. However, it is important that the initiative be completed with urgency and that USP’s efforts focus on drug products and ingredients that have the most potential for problems. In addition to the currently identified “top 200 small molecules monographs and 96 excipient monographs,” we encourage USP to update all monographs that include non-specific assay or identification tests, and to re-evaluate antiquated methodologies in general. FDA strongly believes that monographs utilizing outdated analytical procedures are vulnerable to economically motivated adulteration (EMA), and current advancements in science and technology can help to fill the void. We are similarly concerned about outdated OTC monographs, and will be sending you our expert input on OTC monographs that need to be revised.

FDA has established a new task group in CDER to focus on the USP monograph modernization initiative. This group is responsible for developing a strategy to identify priority products for monograph modernization to provide requested FDA assistance to USP in your modernization efforts.
“The Task Group aims to identify USP/NF monographs in need of modernization and is especially focused on monographs with outdated analytical methods that may make the drug or excipient vulnerable to economically-motivated adulteration (EMA) or that have inadequate tests.”

[Emphasis added]
Source: November 16, 2010 Letter from FDA Task Group to USP

History of USP/FDA correspondence on monograph modernization available here: https://www.usp.org/get-involved/partner/monograph-modernization-history
USP Glycerin Monograph

C₃H₇O₃  92.09
1,2,3-Propanetriol;
Glycerol    [56-81-5].

**DEFINITION**
Glycerin contains NLT 99.0% and NMT 101.0% of C₃H₇O₃, calculated on the anhydrous basis.

**IDENTIFICATION**
[NOTE—Compliance is determined by meeting the requirements for Identification tests A, B, and C.]

- **A. INFRARED ABSORPTION (197F)**
- **B. LIMIT OF DIETHYLENE GLYCOL AND ETHYLENE GLYCOL**
  **Acceptance criteria:** If a peak at the retention times for the diethylene glycol or ethylene glycol is present in the Sample solution, the peak response ratio relative to 2,2,2-trichloroethanol is NMT the peak response ratio for diethylene glycol or ethylene glycol relative to 2,2,2-trichloroethanol in the Standard solution; NMT 0.10% each for diethylene glycol and ethylene glycol is found.
- **C. Examine the chromatograms obtained in Identification test B. The retention time of the glycerin peak of the Sample solution corresponds to that obtained in the Standard solution.**

**Organic Impurities**
- **PROCEDURE 1: RELATED COMPOUNDS**
  **Acceptance criteria**
  - **Individual impurities:** NMT 0.1%
  - **Total impurities:** NMT 1.0%

**ADDITIONAL REQUIREMENTS**
- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **USP REFERENCE STANDARDS (11)**
  USP Diethylene Glycol RS
  USP Ethylene Glycol RS
  USP Glycerin RS
  1,2,3-Propanetriol.
  C₃H₇O₃  92.10
USP’s Commitment to our Stakeholders

- For 200 years, USP has been dedicated to helping ensure quality medicines are available to patients throughout the world
- We have always felt a sense of responsibility to identify and communicate risks to our stakeholders in the pursuit of better global health
- *FDA has dramatically increased enforcement of excipient testing regulations for drug manufacturers worldwide*
US Law
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.
Current findings
Sharp increase in warning letters citing lack of excipient ID testing of every incoming lot and/or over-reliance on supplier COA for attribute testing
1. Your firm failed to ensure the identity of components, including your active ingredients and excipients from various suppliers (21 CFR 211.84(d)(1) and (2)).

“You failed to test incoming components you use in manufacturing drug products to determine their conformance to identity, purity, strength, and other appropriate specifications. Your firm released components for use in drug product manufacturing based on certificates of analysis (COA) from your supplier without establishing the reliability of the suppliers’ analyses through appropriate validation. For example, your firm did not test each lot of glycerin used as a component of your drugs to determine whether diethylene glycol (DEG) or ethylene glycol (EG) was present. Because you did not test each glycerin lot using the USP identification test that detects these hazardous impurities, you failed to assure the acceptability of lots used in drug product manufacture. **DEG contamination in pharmaceuticals has resulted in various lethal poisoning incidents in humans worldwide.**”

[Emphasis added]
Issue:
“Your response indicated that you will compare your laboratory results with the supplier’s COA to confirm the reliability of testing for all lots, and you provided a revised standard operating procedure (SOP) *Purchasing, Supplier Approval, Monitoring, and Risk Analysis* (SOP No. GPPL/PUR/01). The revised SOP, provided with your response as Annexure 30, also discusses adding suppliers to an “approved vendor list.”

Your response is inadequate because it is not clear whether you will indefinitely test each incoming component lot for all attributes to verify the accuracy of your suppliers’ COA, or you will instead qualify your suppliers’ test results through an initial round of testing as well as ongoing testing at appropriate intervals. Additionally, your response did not address whether your firm conducted retrospective DEG and EG testing for products distributed to the United States.”
An improved procedure that describes how you qualify your suppliers’ COA both initially and on an ongoing basis. Explain whether you intend to test each lot of incoming components for all attributes instead of relying on the suppliers’ COA. Alternatively, if you intend to rely on the supplier’s COA, provide specifics on how you will verify each supplier’s test results at regular intervals and include a commitment to test at minimum every incoming component lot for USP identity requirements.

A detailed description of how you will ensure that components (e.g., ingredients) used in the manufacture of your drug products will be withheld from use until the lot has been tested in accordance with the current United States Pharmacopoeia (USP) and released for use by the quality unit.

A detailed risk assessment for drug products that contain glycerin and are within expiry in the U.S. market. As part of your risk assessment, immediately test retained samples of all lots for DEG and EG, and take appropriate market action if the testing yields any aberrant results.

A comprehensive, independent review of your laboratory practices, methods, equipment, and analyst competencies. Based on this review, provide a detailed corrective action and preventive action (CAPA) plan to remediate your laboratory systems.”
“FDA placed your firm on Import Alert 66-40 on March 5, 2018.”
NOT Only Glycerin
ALL manufacturers are responsible!

FDA placed your firm on Import Alert 66-40 on March 8, 2018.

Note:
You and your customer, (b)(4), have a quality agreement regarding the manufacture of (b)(4) Cream. You are responsible for the quality of drugs you produce as a contract facility, regardless of agreements in place with product owners.
38 FDA Warning Letters in 2017-18 citing reliance on COA and/or lack of identity testing of incoming excipients

Over 25% of all FDA CGMP drug manufacturer warning letters cited excipient testing issues in 2017-2018.
Warning letters were issued to drug manufacturers marketing products in the United States when:

- They relied on excipient COA for release to production
- They did not perform one ID test for incoming excipients
- They did not verify COA information from their excipient supplier at regular intervals
- They did not have a written plan as to how they qualified excipient suppliers on an initial & on-going basis

Contract manufacturers are responsible for quality regardless of agreements
USP Initiatives
Ingredient Verification for Excipients (IVP-E)
USP Verification Programs

What is it?

- Comprehensive evaluation and testing program
- Voluntary participation
- Verifies quality, purity and potency
- Multi-step process
- Continuous monitoring of program participants by USP
Key Elements of the Verification Programs

1. Product appropriate for inclusion in program
2. Audit of manufacturing sites for GMP compliance
3. Review of quality control and manufacturing product documentation
4. Laboratory testing of product samples
5. Review of conformance with mark usage guidelines
6. Continuous surveillance: GMP audits, annual product reports, and product testing

Mark Approval
USP Verification – A comprehensive process
Quality systems audit

The HOW

GMPs based on regulatory status & industry best practice

- 01 Quality Management
- 02 Facilities and Equipment
- 03 Material Controls
- 04 Production
- 05 Packaging and Labeling
- 06 Laboratory Controls

- **USP General Chapter (1078)** Good Manufacturing Practices for Bulk Pharmaceutical **Excipients**
- **ANSI 363 - 2016** Good Manufacturing Practices (GMP) for Pharmaceutical **Excipients**
Supplier qualification

What it does & does not do

- Paper audit
  - Confirms they have a Quality Management System (QMS)
    - …But not how well it is implemented
    - …Also, is information trustworthy?

- On-site audit
  - Shows implementation of QMS
  - Quality of facility, general maintenance & procedures
    - …But it is only a periodic snapshot in time. Limited time means a limit to what can be reviewed (the devil is in the details)
USP Verification – A comprehensive process

An audit alone does not ensure product quality
QC & manufacturing process review

The WHY

- General information
  - Formulation; characterization; general properties

- Manufacture
  - Description of manufacturing process and process controls
  - Control of materials
  - Control of critical steps
  - Process validation and/or evaluation
  - Manufacturing process development
QC & manufacturing process review

The WHY

- Control of raw materials and finished product
  - Specifications
  - Analytical procedures
  - Validation of analytical procedures
  - Batch analysis
- Reference Standards or Materials
- Container Closure System and Labeling
QC & manufacturing process review

- Quality Control & Manufacturing (QCM) review documentation format follows:
  - ICH M4Q Common Technical Document (CTD) – Quality

- ICH and USP guidance documents referenced include:
  - ICH Q1, USP 1150 – Stability
  - ICH Q2(R1), USP 1225 and 1226 – Analytical Validation
  - ICH Q3, USP 1086 – Impurities
  - ICH Q6, USP 1080 – Specifications

Product CMC documentation review uncovers quality issues not discovered during GMP facility audits
An audit alone does not ensure product quality
Product testing

The WHAT (i.e., confirmation)

- Testing per current USP–NF and/or other compendia
- Testing using any additional tests on the manufacturer’s specifications
  - Require supportive analytical validation
  - Evaluated for their ability to control the quality of the ingredient/product
- Testing of three (3) lots per year
  - Products might be grouped based on similarities in manufacturing or other factors
For ingredients meeting program requirements, excipient manufacturers

- Receive a **Notification Letter** indicating the verification of each ingredient, per manufacturing site
- May show customers a USP Verified Certificate of Standards Compliance
- May display the **USP Verified Mark** on the ingredient’s bulk label and Certificate of Analysis
- Excipient manufacturers and their verified ingredients are posted on the USP website
PHASE II: Continuous Surveillance Monitoring

- **USP surveillance audit**
  - Performed annually for all programs
  - More frequent audits on a for-cause-basis, or in response to major change

- **Annual internal audit report**
  - Used to monitor state of operations at ingredient manufacturer’s site in between audits conducted by USP

- **Annual product review (APR) reports**
  - Lot history, List of any deviations, List of customer complaints
  - Key program feature: USP notification of changes (major or minor)
    - Type of follow-up action depends on the nature of the change (e.g., audit, documentation review, testing)

- **Product testing for conformance to specifications**
How does a Verified ingredient help?

- Provides documented evidence of ongoing product conformity to COA specifications
- Annual product testing ensures that validated analytical methods are being used and produce reliable results
- Gives you the ability to scale supplier qualification procedures and focus internal resources
- Provides a way to identify quality-conscious suppliers and for suppliers to differentiate themselves from competitors
Benefits of USP Ingredient Verification

Benefits for manufacturers of ingredients:

• Not just a US program; also can be used worldwide to verify compliance with…
  ❖ Attributes listed in USP as well as any other pharmacopoeia claimed by participant
  ❖ ANSI 363-2016 Good Manufacturing Practices (GMP) for Pharmaceutical Excipients
  ❖ USP <1078>Good Manufacturing Practices for Bulk Pharmaceutical Excipients

• Continuous surveillance monitoring

• Helps excipient manufacturers cut their audit costs
  ❖ Potentially decrease the number of customer audits/inspections

• Reduces the risk of inconsistent and substandard quality ingredients

• Gives customers assurance that comes from USP, a trusted, independent, science-based, standards setting body
Benefits of USP Ingredient Verification

Benefits for **users** of ingredients:

- Not just a US program; also can be used worldwide
- Provides strong assurance to drug manufacturers of the quality of their supplier base
- Reduces the risk of inconsistent and substandard quality ingredients
- Potentially reduce inspection costs
- Continuous surveillance monitoring
Benefits for regulatory authorities:

- Promote the public health
- Augment the resources of regulatory authorities
- Reduce the regulatory burden by creating a common review and audit function in participating countries
Items on the USP website:

- Manual for Participants
- List of manufacturing sites
- List of verified products
- Verification Summary Poster

https://www.usp.org/evp
Up To Date Monograph Initiative
Ensuring standards have impact

➢ To date, our standards impact 2 billion people globally – but our commitment to empower a healthier tomorrow doesn’t stop there.

➢ As more medicines come to market, new monographs must be created to address patient needs.

➢ Existing monographs must evolve to keep pace with industry changes.
Ensuring standards have impact

- The FDA Inactive Ingredient Database (IID)* contains ~600 listings for excipients that do not have a corresponding USP monograph.
  - ~100 are vague and need further clarification and ~100 are trade names
  * Based IID - Oct. 2018

- Obtaining monograph donations for these excipients are a key initiative to USP ensuring quality medicines.
What **can** you do to ensure the quality of medicines in the future?
Ensuring standards have impact

- **Ensure** your excipients are USP verified
  - **Contact** us to discuss the program and how you can verify your ingredients with USP

- **Collaborate** directly with USP with the up to monograph donation initiative
  - **Provide** any validated tests/methods to help us build the monograph
  - **Contact** us if your company manufactures and/or supplies items on the IID that do not have monographs
  - **Comment** on a proposed standard through the Pharmacopeial Forum.
You have the power to impact global health

➢ By **working together** we can help ensure drug quality and meet our shared goal of improving health for people around the world.

➢ You are showcasing your commitment to quality in the global market and **adding your voice in the establishment of public standards** that are used worldwide.
What **will** you do to ensure the quality of medicines in the future?
Stay Connected

(301) 412-7412 | Email - DANITA.BROYLES@USP.ORG
(301) 816-8254 | Email – SWA@USP.ORG

Empowering a healthy tomorrow
Thank You

Empowering a healthy tomorrow