USP Excipients Stakeholder Forum
Wednesday, November 13, 2019

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

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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

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History of poor excipient quality

History of Glycerin adulteration with diethylene glycol

Country	Year	Incident
USA	1937	Sulfanilamide Elixir – 107 deaths *Resulted in the enactment of the1938 FFD&C Act*
South Africa	1969	Sedative formulated with DEG – 7 deaths
Italy	1985	DEG in wines from Austria – no known deaths
India	1986	Medicinal glycerin laced with DEG – 14 deaths
Nigeria	1990	Acetaminophen syrup containing DEG – 40 deaths (some sources say 200 deaths)
Bangladesh	1990-2	Acetaminophen syrup containing DEG – 339 deaths
Haiti	1995/6	Cough medicine containing DEG – 85 deaths

History of Glycerin adulteration with diethylene glycol

Country	Year	Incident
USA	2006/7	Toothpaste containing DEG – no deaths
Panama	2007	Toothpaste containing DEG – no deaths reported
Nigeria	2008/9	Teething formula contaminated with DEG from propylene glycol – 84 deaths
Bangladesh	2009	Paracetamol syrup to children adulterated with diethylene glycol. Twenty-four children reported dead

Five jailed in Panama over toxic cough syrup scandal that killed hundreds

Posted 29 Jul 2016, 10:09pm

Five people were sentenced to prison in Panama on Friday over a 2006 poison cough syrup scandal in which hundreds of people died after unwittingly ingesting a toxic compound found in antifreeze.

The verdict capped years of investigation and a convulsion of shock at the many deaths in this small Central American nation.

Officials say 400 people died when they drank the adulterated cough syrup, which had been mixed and distributed by the national health agency using an ingredient supplied by a private company, Medicom.

PHOTO: The medicine had been mixed and distributed by the national health agency. (ABC)

From China to Panama, a Trail of Poisoned Medicine

By WALT BOGDANICH and JAKE HOOKER MAY 6, 2007

FDA encourages USP to update monographs

- *The following is part of the 2010-10-12 Letter from FDA to USP:*

> 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.

FDA Task Group supporting USP-NF modernization

"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**."

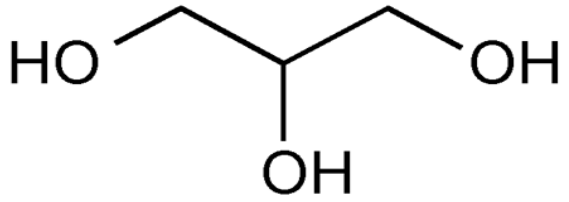
[Emphasis added]

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

$C_3H_8O_3$ 92.09
1,2,3-Propanetriol;
Glycerol [56-81-5].



DEFINITION

Glycerin contains NLT 99.0% and NMT 101.0% of $C_3H_8O_3$, 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.
  $C_3H_8O_3$ 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

US Law: 21 CFR 211.84(d)(1) & (2)

d. Samples shall be examined and tested as follows:

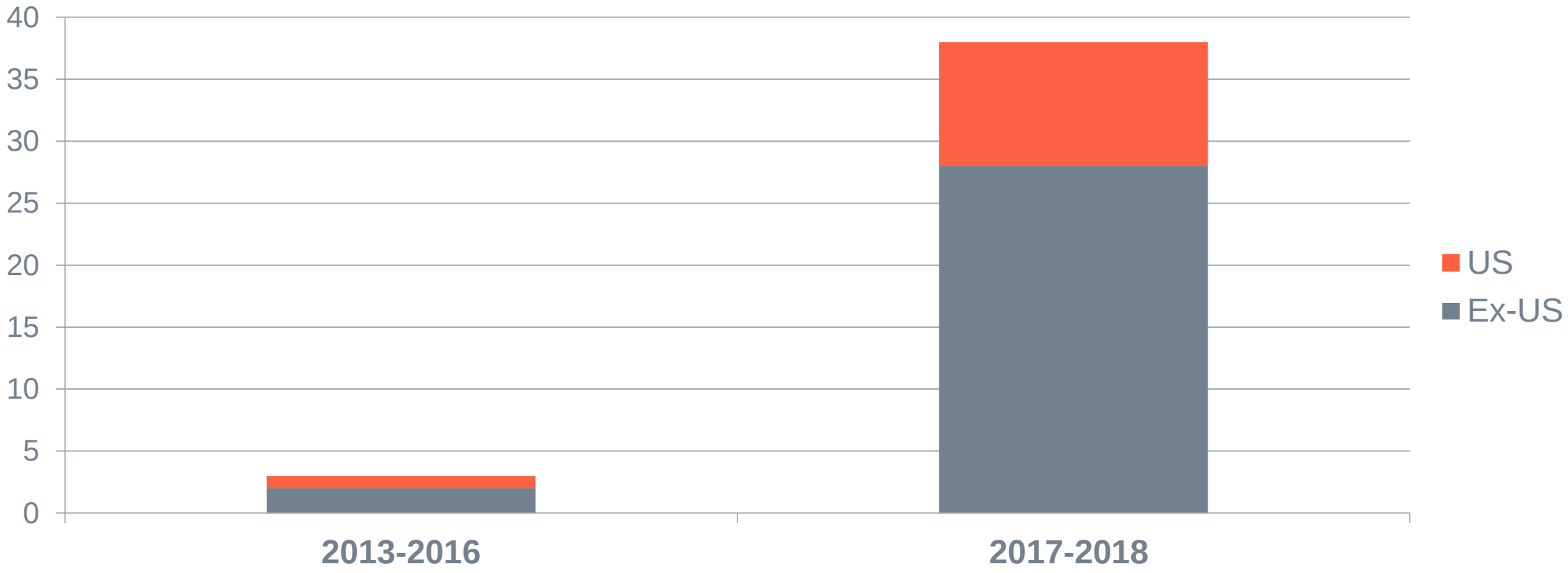
1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.

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.

3

Current findings

FDA warning letters citing excipient testing issues



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

CDER Warning Letter 320-18-48,Sihor, India, April 24/18

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]

CDER Warning Letter 320-18-48,Sihor, India, April 24/18

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."

[Emphasis added]

CDER Warning Letter 320-18-48,Sihor, India, April 24 (4/4)

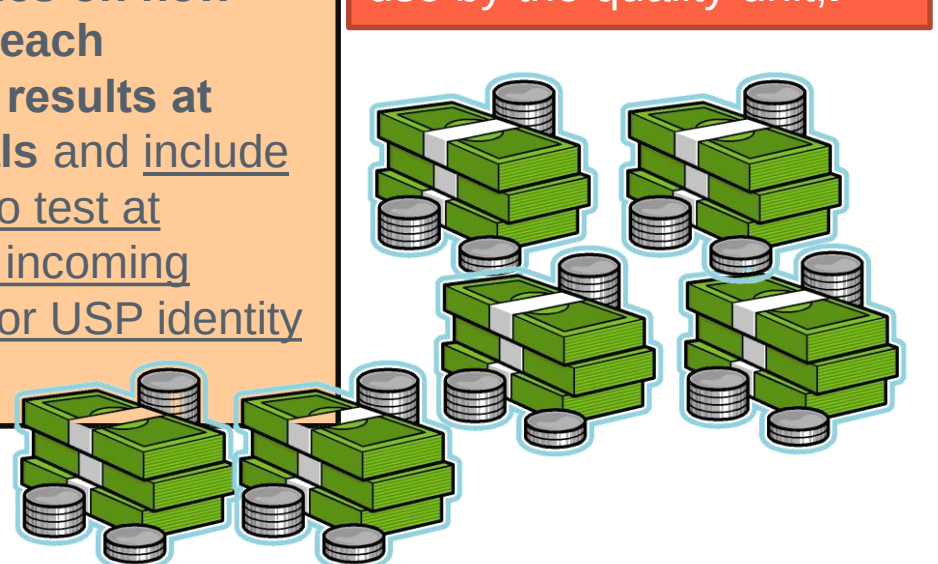
In response to the warning letter, FDA instructed the firm to:

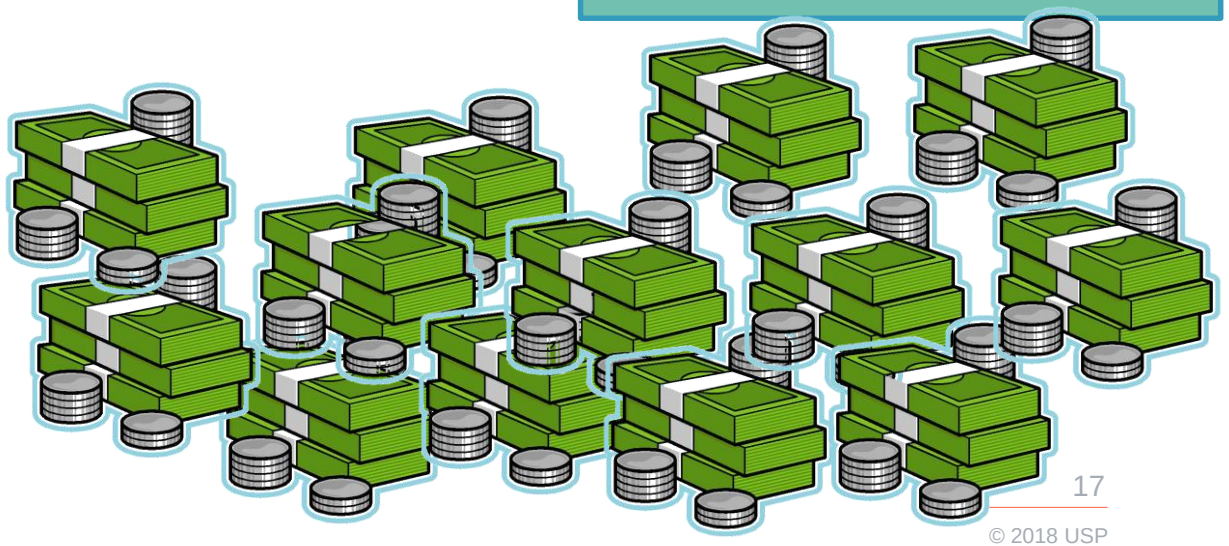
An **improved procedure** that describes how you **qualify your suppliers' COA both initially and on an ongoing basis**. Explain whether you intend to test each lot of incoming components for all attributes instead of relying on the suppliers' COA. Alternatively, if you intend to **rely on the supplier's 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."





[Emphasis added]

CDER Warning Letter 320-18-48,Sihor, India, April 24 (4/4)

"FDA placed your firm on Import Alert 66-40 on March 5, 2018."

[Emphasis added]

NOT Only Glycerin

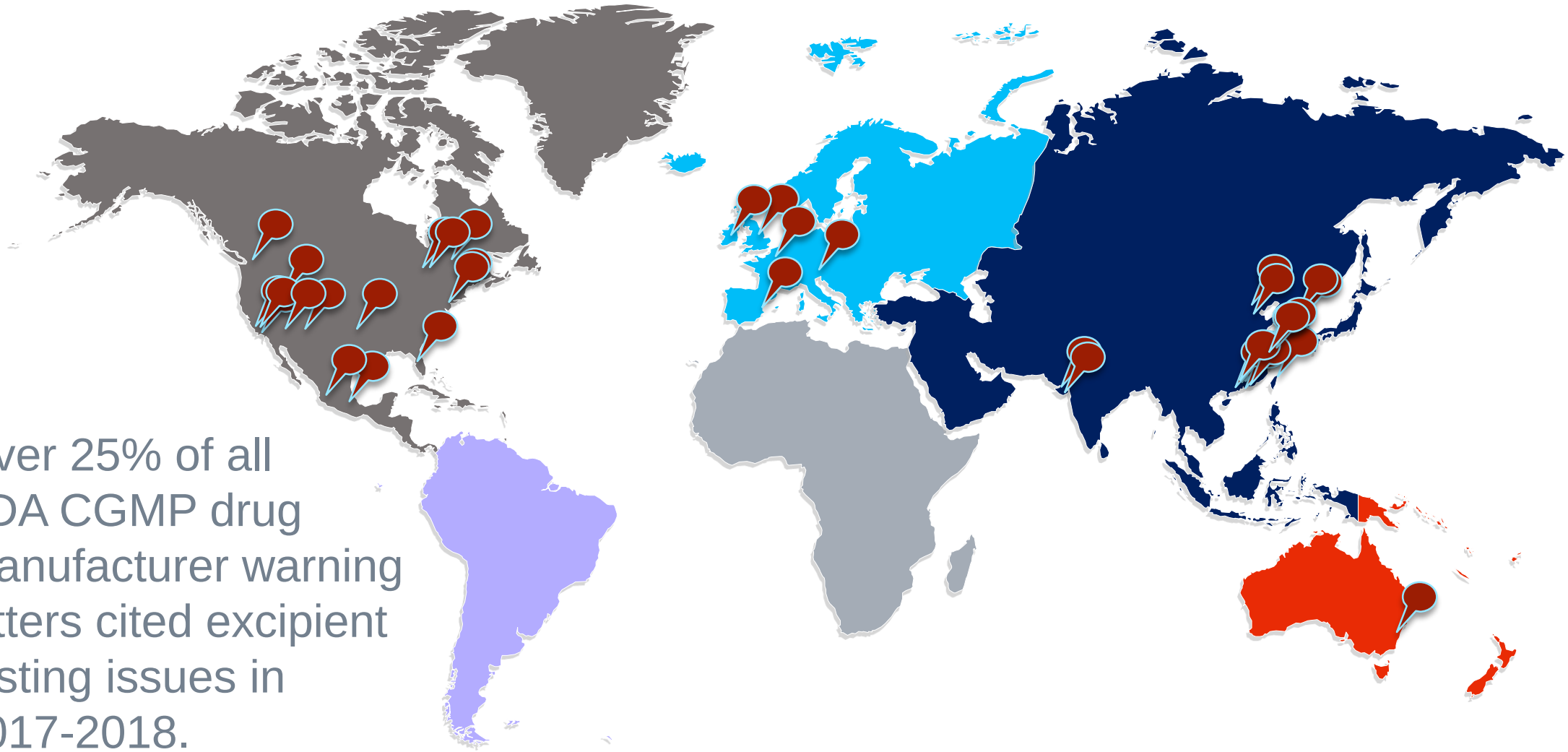
ALL manufacturers are responsible!

CDER Warning Letter 320-18-54, Silverwater, NSW, Australia, May 18 (2/2)

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**

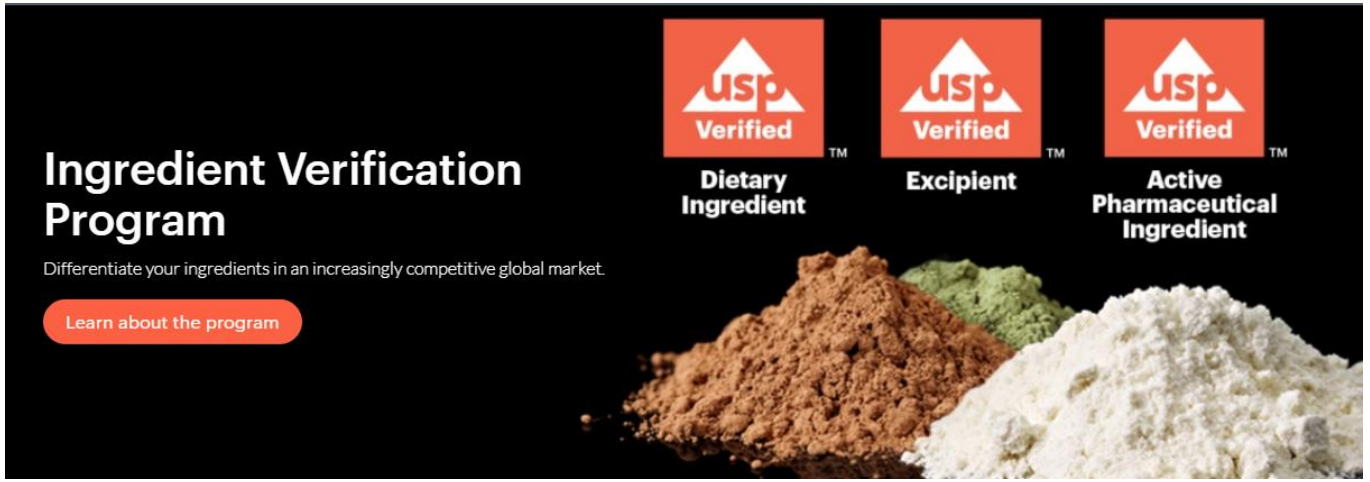
4 USP Initiatives

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

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***

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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

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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

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USP Verification Program Mark and Certificate

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

USP Verified Excipient™

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

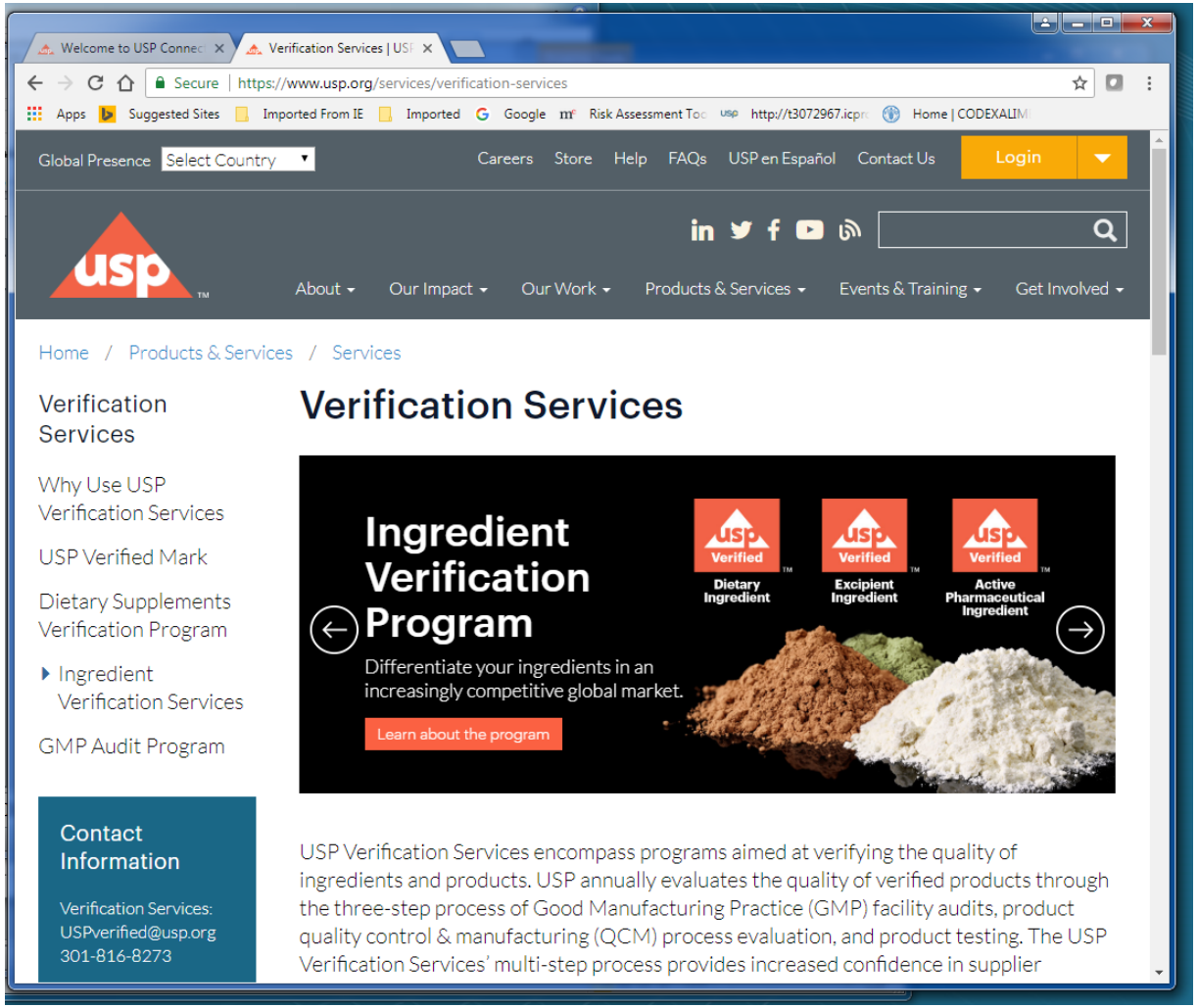
Benefits of USP Ingredient Verification

Benefits for <u>regulatory authorities</u>:

- 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

https://www.usp.org/evp

- **Items on the USP website:**
- Manual for Participants
- List of manufacturing sites
- List of verified products
- Verification Summary Poster



Up To Date Monograph Initiative

Ensuring standards have impact

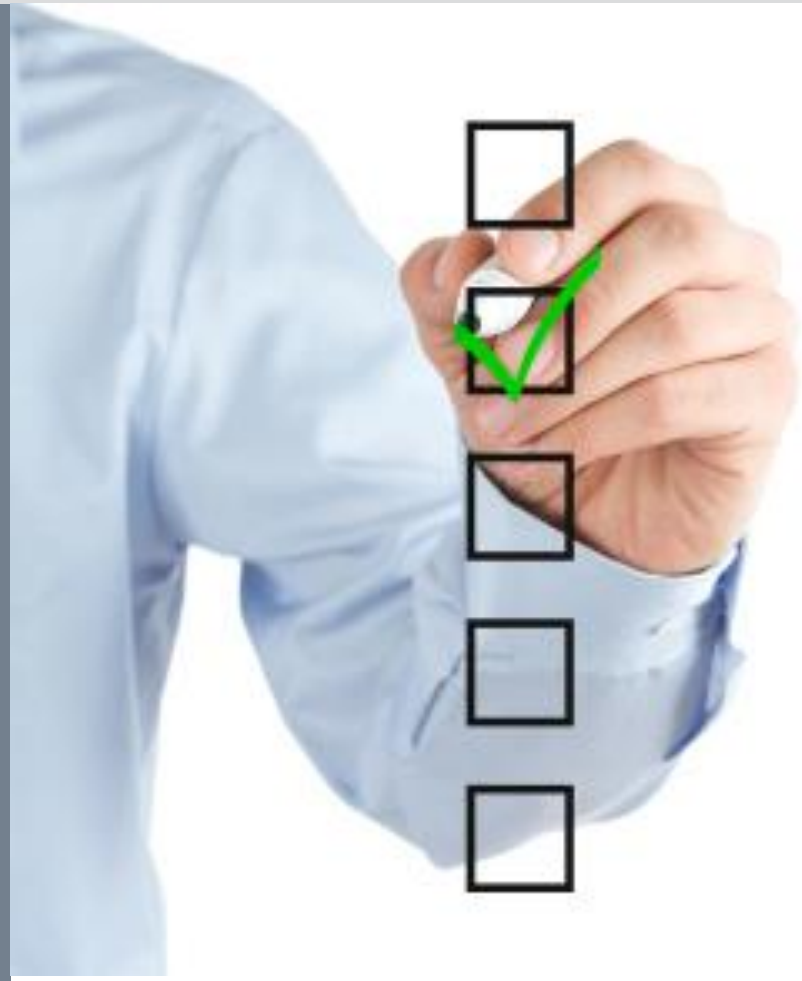
- To date, our standards impact 2 billion people globally – but our commitment to empower a healthier tomorrow doesn't stop there.
- As more medicines come to market, new monographs must be created to address patient needs.
- Existing monographs must evolve to keep pace with industry changes.

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?

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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

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Empowering a healthy tomorrow

Thank You

Empowering a healthy tomorrow