USP-APEC RHSC
Center of Excellence (CoE) for Product Quality & Supply Chain Pilot Program:
Securing Medical Product Quality Through the Supply Chain

U.S. Pharmacopeial Convention (USP) | March 28–31, 2017 | USA
Panama, 2006

Another tragic case of DEG poisoning!
What happened?

Courtesy of National Geographic – “Illicit – The Dark Trade”, 2008
How Did this happen?

1. Factory produced and sold a product labeled “TD Glycerin”
   - Did factory know it was not glycerin as defined by compendia?
   - Did factory know when they sold the product, it would be used for Pharmaceuticals?
   - Did factory know a license was needed to manufacture and sell for medical use?
How Did this happen?

TD Glycerin
- NOT Compendial glycerin
- NOT for Pharmaceuticals?
- NOT licensed

2. The TD Glycerin was purchased and resold by a series of distributors, agents and brokers who apparently re-labeled and changed paperwork.
   - Did the original purchaser and subsequent resellers know the history of the product?
   - Why did they change the paperwork and relabel the product as “Glycerin”?
How Did this happen?

TD Glycerin
- NOT Compendial glycerin
- NOT for Pharmaceuticals
- NOT licensed

3. The product was purchased by the Panama Government
   - Did the government make clear their requirements?
   - Did the government understand the supply chain?
How Did this happen?

TD Glycerin
- NOT Compendial glycerin
- NOT for Pharmaceuticals
- NOT licensed

Resold, relabeled and new paperwork as pharma glycerin.
- Unknown history
- Changed to "Glycerin"

Purchased by the Panama Government
- Clear requirements
- Understanding of Supply Chain

4. The product was delivered to the Panama manufacturing facility
   - Did the facility test the incoming material?
   - Were the tests sufficient to clearly identify the product?
How Did this happen?

TD Glycerin
- NOT Compendial glycerin
- NOT for Pharmaceuticals
- NOT licensed
  
  Resold, relabeled and new paperwork as pharma glycerin.
  
  Unknown history
  
  Changed to “Glycerin”

Purchased by the Panama Government
- Clear requirements
- Understanding of Supply Chain

5. The cough syrup was manufactured and released to the public
   - Did the Panama manufacturing facility test the product before release?
   - Were the tests sufficient to ensure the safety and quality of the cough syrup?
How Did this happen?

TD Glycerin
• NOT Compendial glycerin
• NOT for Pharmaceuticals
• NOT licensed

Resold, relabeled and new paperwork as pharma glycerin.
• Unknown history
• Changed to “Glycerin”

Purchased by the Panama Government
• Clear requirements
• Understanding of Supply Chain

Cough syrup manufactured and released
• Inadequate release testing
• Insufficient tests

Delivered to Panama manufacturing facility
• Test incoming material
• Insufficient testing
How Did this happen?

TD Glycerin
- NOT Compendial glycerin
- NOT for Pharmaceuticals
- NOT licensed

Resold, relabeled and new paperwork as pharma glycerin.
- Unknown history
- Changed to “Glycerin”

Purchased by the Panama Government
- Clear requirements
- Understanding of Supply Chain

Cough syrup manufactured and released
- Inadequate release testing
- Insufficient tests

Delivered to Panama manufacturing facility
- Test incoming material
- Insufficient testing
How could this have been prevented?

1. Look at the entire supply chain holistically
2. Identify likely failures and establish potential regulatory control points

Apply the appropriate APEC GMP Tool to the most critical control points, consistent with the local jurisdiction.
1. Holistic view
2. Identify failures; establish regulatory control points

Here is how!

Apply the appropriate APEC GMP Tool to the most critical control points, consistent with the local jurisdiction.
Thank You
The Impact of Good Manufacturing Practices on Ingredient Production:

The case of TD Glycerin
TD glycerin – Industrial chemical

• Chinese manufacturer, Taixing Glycerin Factory
• Chinese distributor, CNSC Fortune Way
• Spanish companies sold it to Panamanian companies.
• The product was then used to make cough syrup and other medicine.
• Chinese companies sold the industrial solvent called 'TD glycerin', to Spanish companies
• 15 percent diethylene glycol and "other substances."

Glycerin - The Problem: Even to the Trained Professional...

**Ethylene Glycol (“Antifreeze”)**
- POISON!

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

**Propylene Glycol**
- Edible and GRAS

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

**Glycerin (Glycerol)**
- Edible and GRAS

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

**Diethylene Glycol (“Antifreeze”)**
- POISON!

```
HO   O   OH
```
- Light colored
- Slightly viscous liquid at room temp.
- Sweet taste

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

Securing Medical Product Quality Through the Supply Chain

U.S. Pharmacopeial Convention | March 28–31, 2017 | USA
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.
# 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>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>
<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>
Globalization of the supply chain has a direct impact on the sourcing and qualification of quality raw materials (Excipients and APIs and regulated drug products intended for patient’s safe usage) according to cGMPs.

cGMPs Should Require ID testing of Ingredients

Component Testing Gains Prominence in Drug Product GMP Warning Letters as FDA Focus Intensifies on OTC Topicals and Upstream Supply Chain

Apr 17th, 2014

Inadequate testing of incoming components is a leading problem area being cited by FDA on finished drug product GMP warning letters and is particularly prevalent in the expanding number of those addressing compliance at topical manufacturers worldwide.

FDA is expressing concern that each component is not being tested by the dosage manufacturer for conformity with all of its specifications and/or that specific identification tests are not being conducted on components that have been accepted based on the supplier’s certificate of analysis (CoA), as required by CFR 211.84.

IPQ’s analysis of drug product GMP warning letters issued from 2012 through the first quarter of 2014 shows that over one in three of those addressing finished product manufacturing (20 of 57) have highlighted the facility’s non-compliance with 211.84. Among warning letters addressing topical manufacturing, the percentage soars to three in four (16 of 21).

[The story continues for subscribers beginning on page 2. Nonsubscribers can purchase the story for $195 by contacting Wayne Rhodes (rhodes@IPQpubs.com). For subscription/license information, click here.]

Pages: 1 2
• 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
2016 USP Glycerin Monograph (a look at Name and ID) (glis’ er in).

Official Name or Title  USP Glycerin

C₃H₈O₃  92.09
1,2,3-Propanetriol;
Glycerol   [56-81-5].

DEFINITION
Glycerin contains NLT 99.0% and NMT 101.0% of C₃H₈O₃, 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.
  C₃H₈O₃  92.10
US FDA Safety and Innovation Act (FDASIA)

- **FDA Safety and Innovation Act**
- **Statute enacted 2012**
- **Title VII: Drug Supply Chain**
  - Title VII imposes FDA registration requirements for domestic and foreign drug establishments.
  - It expands drug product listing information to include information on drug excipient establishments, including all establishments used in the production of such excipient, a unique facility identifier of such establishment, and an e-mail address for each excipient manufacturer.
  - It requires the FDA to maintain an electronic database for the purposes of risk-based inspections and to conduct risk-based inspections of registered drug establishments, including inspections for medical devices, and post a report on the FDA website on the number of domestic and foreign establishments registered in the previous fiscal year, the number of inspections of such establishments, and the percentage of the FDA budget used to fund such inspections.

- **Accomplishments:**
  - a draft guidance specifying the unique facility identifier (UFI) system for drug establishment registration. (Sections 701/702, issued 9/5/2013) This data standard will improve FDAs ability to identify drug establishments, both in US and abroad, that make products for the U.S. market.
  - the first annual report as required under section 705, outlining the number of domestic and foreign establishments registered and inspected in fiscal year 2013 and the percentage of the FDA budget used to fund such inspections. (Section 705, issued 1/31/2014. This report provides a high level overview of FDA inspection resources.

- **703 Identification of drug excipient information with product listing**
  - Drug manufacturers must provide FDA with UFI of all of their suppliers

- **704 Electronic registration and listing**
  - Ensure our drug registration and listing databases contain accurate, complete information and can interface with other relevant agency databases
Existing GMP guidances for Medicines

• What controls are in place?
  – WHO – GMP guidelines
    • GMPs for pharmaceutical products- main principles TRS, No. 961
  – ICH Quality topics
    • bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration.
  – ICH Q7 - APIs
    • Scope—“manufacturing” to include all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of APIs and the related controls.
    – However, ICH Q7 A does not cover the manufacturing of excipients of pharmaceutical grade
• Lack of clarity for industry regarding GMP excipient requirements and responsibilities.
Existing GMPs for pharmaceutical excipients

- **Amendment - March, 2015**
  - Requires a formalized risk assessment for ascertaining the appropriate GMPs for excipients of medicinal products for human use

- **South America – Brazil ANVISA**
  - GMP guideline for excipients May 2012
  - Require GMP compliance by manufacturers of pharmaceutical excipients.

- Determination of appropriate GMP based on type and use of excipient
  - The manufacturing authorization holder should take into consideration the following:
  - Potential for any impurities carried over from other processes, in absence of dedicated equipment and/or facilities;
  - Cold chain management, if appropriate;
  - Supply chain complexity;
  - Stability of excipient;
  - Packaging integrity evidence;
  - Known fraudulent adulterations related to the use and function of each single excipient;
  - Other factors identified or known to be relevant to assuring patient safety for each excipient;
  - Qualification program of suppliers;
  - Change management and deviation management system;
  - Environmental controls and storage conditions
21 CFR § 210.3 Definitions (under cGMP for Drugs; General)

a(4) **Drug product** means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an **active drug ingredient** generally, but not necessarily, in association with **inactive ingredients**. The term also includes a finished dosage form that does not contain active ingredient, but is intended to be used as a placebo.

a(3) **Component** means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such a drug product.

a(8) **Inactive ingredient** means **any component** other than an active ingredient.

21 CFR § 211 CGMPs for Finished pharmaceuticals
Subpart E - Control of Components…
21 C.F.R. § 211.84(d)(1) and (2)

• 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)*
21 C.F.R. § 211.84(d)(1) and (2) (Contd)

- **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”
Under Food Drug and Cosmetic Act (FD&C Act)

21 U.S.C. § 321 Section 201(g)(1)
- The term “drug” means:
  - 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

21 U.S.C. § 351 Section 501 - Adulterated Drugs and Devices
- A drug with a name recognized in USP-NF must comply with compendial identity or be deemed adulterated, misbranded, or both (501(b) & 502(e)(3)(b)).
  ......Cannot label away from identity!
- Must also comply with compendial standards for strength, quality, and purity, unless labeled to show all differences (501(b) & 21 CFR 299.5).
- Removing the USP-NF designation from labeling does not obviate the requirement to conform to compendial requirements.
USP General Notices-

– 2.20. Official Articles
  • The title specified in a monograph is the official title for such article. Other names considered to be synonyms of the official titles may not be used as substitutes for official titles.

– 2.30. Legal Recognition
  • A drug with a name recognized in USP–NF must comply with compendial identity standards or be deemed adulterated, misbranded, or both. See, e.g., FDCA § 501(b) and 502(e)(3)(b); also FDA regulations, 21 CFR § 299.5(a&b).
  • To avoid being deemed adulterated, such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs. See, e.g., FDCA § 501(b) and 21 CFR § 299.5(c).
  • In addition, to avoid being deemed misbranded, drugs recognized in USP–NF must also be packaged and labeled in compliance with compendial standards. See FDCA § 502(g).

– Under this provision, the established name (nonproprietary name) of a drug or component is the official title used for the drug or component in an official compendium such as USP or NF (USP-NF), unless FDA has designated another name via regulation.
USPs role in naming official articles

- USP has a statutory role in the naming of drugs, including excipients, and utilizes scientific expert committees such as the Nomenclature, Safety, and Labeling Expert Committee for this purpose. The Food and Drug Administration (FDA) is actively involved in this Committee and the overall naming system.

- When a *USP-NF* excipient standard exists, the excipient should appear under the official title set forth in the *USP-NF*.

- If there is no *USP-NF* standard, the name appearing in *The USP Dictionary of USAN and International Drug Names* should be used. FDA can cross-reference additional information to the official title thus linking related information together.

- FDA assigns UNII numbers to excipients. Helps to uniquely identify substances in the supply chain. Should consider always cross-referencing the UNII number to the *USP-NF* official title.
USP General Notices - 5.40. Identity

- A compendial test titled Identity or Identification is provided as an aid in verifying the identity of articles as they are purported to be, e.g., those taken from labeled containers, and to establish whether it is the article named in USP–NF.

- The Identity or Identification test for a particular article may consist of one or more procedures. When a compendial test for Identity or Identification is undertaken, all requirements of all specified procedures in the test must be met to satisfy the requirements of the test.

- Failure of an article to meet all the requirements of a prescribed Identity or Identification test (i.e., failure to meet the requirements of all of the specified procedures that are components of that test) indicates that the article is mislabeled and/or adulterated.
Adulterated/Contaminated pharmaceutical ingredients issue not limited to glycerin

• Any ingredient is at risk if there is a willing buyer
  – More interested in lowest cost ingredients than quality ingredients and
  – Not insuring ingredient integrity has been preserved throughout the supply chain

• Most pharmaceutical ingredient safety problems have been due to a lack of good supply chain controls

• Important to have Good Manufacturing, Distribution and Supply Chain Practices and adherence to an up to date public quality standard
Thank You
Supplier and Supply Chain Qualification and Supply Chain Verification

Roadmap for Global Medical Product Integrity and Supply Chain Security
Manufacturing Practices Work Group
Agenda

• Supplier and Supply Chain Qualification
  – Classification of Suppliers and materials
  – Quality assessment

• Supply Chain Verification
An Overview of the Supply Chain

Good Distribution Practice (GDP)

Good Manufacturing Practice (GMP)

Supply Chain Management

- **Challenges**
  - Well regulated, however complex due to domestic / regional requirements
  - Many hand overs as of different material owners
  - Demands, Safety stocks, shelf life
  - Economic and business aspects
Scope

- API
- API starting materials
- Excipients
- Intermediate and bulk products
- Primary/Secondary packaging materials

Materials

Service provider

- Wholesale distributor
- Computer system provider
- Validation and qualification specialists
- Contract laboratory
Classification of Materials

Level of regulations on GMP according to risk

- **Critical**
- **Major**
- **Moderate**
- **Minor**

- APIs
- Starting Material
- Excipients
- Primary packaging, Printed packaging materials
- Secondary Packaging materials
Classification of Suppliers (supply chain)

- Materials Manufacturers
- Distributors
- Broker
- Trader
- Agents

Low Risk

High Risk of Mix-up Repackaging Relabeling

Directly supply
Agenda

• Supplier and Supply Chain Qualification
  – Classification of Suppliers and materials
  – Quality assessment

• Supply Chain Verification
Evaluation Procedure of Suppliers

Questionnaire on GMP & Document review

Testing of sample

On-site audit

Approved

Approved with conditions

Reject

Quality agreements
• **Design of questionnaire**
  – Follow Annex II of Annex 20 of the PIC/S GMPs (Annex II in ICH Q9)

• **Documentation requirement**
  – Specifications and analytical test method (Certificate of Analysis)
  – Manufacturing/packaging/labelling details
  – Materials Safety Data Sheets (MSDS)
  – Certificates regarding Quality system, residual solvents, etc...
  – BSE/TSE evaluation, if applicable

• **Status of manufacturers**
  – Manufacturing/establishment license (where applicable), GMP Certificate, ISO Certificate
  – History of GMP compliance and inspection history (where applicable)
  – Manufacturing single product or multiple product
  – Manufacturing specific product (e.g., high sensitizing product, other products posing a high cross contamination risk)
Testing of Sample

• Materials should be tested for critical quality attributes
• Test data should be evaluated to determine if the Materials conforms to the acceptance criteria provided by the supplier as well as to USP, EP, and/ JP compendia, and the drug product manufacturer’s specifications.
• The reported result should be compared to the materials supplier’s acceptance criteria for determining compliance to the specification and or certificate of analysis claim(s).
On-Site Audit: Criteria

Quality management

- Personnel
- Facilities & Equipment
- Materials

Production & IPC

Packaging

Laboratory control

Storage & Distribution

Documentation & Records

Consider environmental, Health and safety aspects and business continuity.
Periodic Evaluation

- Regulatory or GMP/compliance issues (where appropriate)
- Conformance with respective technical/quality agreement
- Periodic full testing of material
- Assessment of changes
- Reaction on audit and remediation plan (if audit had taken place)
Agenda

• Supplier and Supply Chain Qualification
  – Classification of Suppliers and materials
  – Quality assessment

• Supply Chain Verification
Supply Chain Verification

• **Aims**
  – Ensure that each incoming delivery has been sourced from the approved manufacturer through the approved and monitored supply chain

• **Verification methods**
  – Scrutiny of all delivery: customs documentation, certificates of analysis, material itself, etc.
  – Compared to previous shipments
  – Personnel involved in goods receiving should be trained
Supply Chain Verification

• Materials obtained through agents, brokers, traders, distributors, re-packers and re-labellers should provide documentation:
  – Name and address of the original manufacturer and other parties involved in the supply chain
  – Purchase orders
  – Bills of lading and other transportation documents
  – Authentic certificates of analysis including those of the original manufacturer
Example - Double check (during receiving material)

- Purchase Order
- Approved Supplier List

Label on the container

COA from API Manufacturer
Example - Repackaging

**Critical point**
- Mix-up
- Cross contamination
- Lack of detail information for label
Conclusion: Implement GMP / GDP

- Incoming delivery has been sourced from the approved manufacturers
- Received through the approved and monitored supply chain
Acknowledgement / References

• APEC GMP Working Group
• Chi-Wen Hsieh, Chi-Hwei Chen, Rong-Ting Zou, Taiwan FDA
Re-packaging and Re-labelling

Roadmap for Global Medical Product Integrity and Supply Chain Security
Manufacturing Practices Work Group
Players of the API supply chain

Upstream Supply Chain

- Manufacturer(s) of raw materials
- Manufacturer(s) of intermediates
- Manufacturer(s) of active substance
- Service provider(s) (e.g., micronisation, sterilisation, etc.)
- Distributor(s), incl. repackers, relabellers, agents, traders, brokers, storage subcontractors

Downstream Supply Chain

- Manufacturer(s) of drug product

Distributors are ‘manufacturers’ if they perform the respective operation and need a manufacturing licence in a country (as a best practice)
Examples of Re-packaging and Re-labelling of API

- Repackaging APIs into smaller containers e.g. transferring API from storage tanks/silos into smaller containers.

In the ‘Questions & Answers document regarding Distribution Activities for Active Pharmaceutical Ingredients (APIs) by the PIC/S Expert Circle on APIs’ (PS/INF 20/2011)

Examples of Re-packaging and Re-labelling of API

• Replacing the original containers of the APIs and re-labelling of the containers

• Repackaging APIs from different primary (internal) containers into a bigger packaging

• Combining APIs in its primary containers into a bigger secondary packaging
## 788 Deaths Due to DEG Contamination
### 1937 - 2009

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Product</th>
<th>No. of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1937</td>
<td>USA</td>
<td>Sulfanilamide</td>
<td>107</td>
</tr>
<tr>
<td>1969</td>
<td>South Africa</td>
<td>Sedative</td>
<td>7</td>
</tr>
<tr>
<td>1986</td>
<td>India</td>
<td>Medicinal Glycerin</td>
<td>14</td>
</tr>
<tr>
<td>1990</td>
<td>Nigeria</td>
<td>Acetaminophen Syrup</td>
<td>47</td>
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<td>2009</td>
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<td>Cough Medicine</td>
<td>26</td>
</tr>
</tbody>
</table>
Recent Cases

• Main factors involved in these incidents:
  – Falsified / Substandard APIs
  – Complex supply chain involving:
    • Several brokers, traders and distributors in different countries
    • Alteration of traceability documents throughout the supply chain
      – Original manufacturer name removal from containers, CoA
      – Change of information change (expiry date, wrong translation)
    • Repackaging operations
    • Subcontracted manufacturing operations (e.g. micronisation)
  – Impurities not covered / not detectable with analytical methods including compendial ones
  – No, insufficient or deficient testing by parties all along the chain including the pharmaceutical manufacturer
Risks Associated

With re-packaging & re-labelling
Maintaining the quality of APIs or products

- More outsourcing of manufacturing operations
- Lack of traceability
- Risk of contamination
- Low margins
- Economically motivated adulteration
- Impact on quality/efficacy
Who is responsible for securing the global supply chain?

Authorities or industry?

Generally, as defined in the principles of GMP, it is the responsibility of all parties, and primarily finished product manufacturers, involved in procurement / sourcing, manufacturing, packaging and distribution of APIs to secure the supply chain.

Repackaging and re-labelling, whether it be drug substance or drug product, are manufacturing activities and consequently must operate in full compliance to GMP and should therefore be appropriately regulated (licensing/registration and inspection) by the authorities of the country in which they are located.

Gap assessment by Manufacturing Practices Work Group
GMP for APIs (ICH Q7)

Re-packers and re-labellers are considered as manufacturers

- Full compliance with ICH Q7 required
- Packaging requirements (9.20, 9.21, 9.46)
- Storage conditions (10.10)
- Transportation (10.21, 10.22, 10.23)
- Traceability of distributed APIs and intermediates (17.2 & 11.4)
- Quality Management (17.3 & 2)
- Repackaging, Relabeling and Holding (17.4)
- Stability (17.5)
- Transfer of Information (17.6 & 11.4)
- Complaints and Recalls (17.7 & 15)
- Returns (17.8 & 14.52)

Other relevant sections of various chapters:
- Personnel (3)
- Buildings and facilities (4)
- Documentation and records (6)
- Storage (7.4)
- Packing and identification labelling of APIs & intermediates (9)
- Storage & Distribution (10)
Re-packaging of API

Traceability of Distributed APIs and Intermediates

• Re-packers and/or re-labellers should maintain complete traceability of APIs and intermediates that they distribute. Documents that should be retained and available include:
  – Identity of original manufacturer
  – Address of original manufacturer
  – Purchase orders
  – Bills of lading (transportation documentation)
  – Receipt documents
  – Name or designation of API or intermediate
  – Manufacturer’s batch number

ICH Q7, section 17.2
Re-packaging of API

Traceability of Distributed APIs and Intermediates

• Transportation and distribution records
• All authentic Certificates of Analysis, including those of the original manufacturer
• Retest or expiry date
Re-packaging of API

Transfer of Information

• Re-packers or re-labellers should transfer **all quality or regulatory information** received from an API or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer.

• Re-packer or re-labeller who supplies the API or intermediate to the customer should provide the name of the original API or intermediate manufacturer and the batch number(s) supplied.

*ICH Q7, section 17.6*
Repackaging and Relabelling

Conclusion: Associated risks

• Maintaining the quality of APIs or products
  – Complex supply chain involving several brokers, traders and distributors in different countries
  – Outsourcing of re-packaging & re-labelling operations
  – Traceability to the ‘original manufacturer’ and all parties that are involved in the re-packaging & re-labelling activities
  – Transfer of Information (e.g., restricted release)
  – Risk of Contamination
  – Low margins → economically motivated adulteration

Who is responsible for securing the global supply chain?
Repackaging and Relabelling

Key Messages

• Repackaging & re-labelling of drug substances and/or products are manufacturing activities that should be operated in full compliance to GMP

• These manufacturers should be regulated (through licensing/registration and inspection) by the authorities of the country in which they are located.

• Issues highlighted:
  – Falsification of source & lack of traceability
  – Inadequate transfer of critical information
  – Wrong packaging & mislabelling
  – Cross-contamination & products deterioration

Both regulators & industry have roles to play
Acknowledgement / References

• APEC GMP Working Group
• Global Supply Chain Integrity – An FDA Perspective by Edwin Rivera-Martinez
• Counterfeit Drugs: Coming to a Pharmacy Near You by Wyatt Yankus, August 2006
• ICH Q7 Q&A
• 4th PIC/S Expert Circle meeting on API
• Ong Kang Teng, HSA
Asia-Pacific Economic Cooperation
5 minute break