APEC AHC – USP Center of Excellence (CoE) for Product Quality & Supply Chain
Pilot Program: “Securing Medical Product Quality Through the Supply Chain”

Incoming Materials Check

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Health Sciences Authority of Singapore
28 March 2017
Licensed & inspected for compliance to local regulation & standards

A Drug Supply Chain Example
From Supplier to Patient

Supplier(s) → Manufacturer → Wholesaler Distributor (Primary) → Pharmacy or Hospital → Patient

Licensed & inspected for compliance to local regulation & standards
# 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>Sulfanilimide</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>
</tr>
<tr>
<td>1990/2</td>
<td>Bangladesh</td>
<td>Acetaminophen Syrup</td>
<td>339</td>
</tr>
<tr>
<td>1995/6</td>
<td>Haiti</td>
<td>Cough Medicine</td>
<td>85</td>
</tr>
<tr>
<td>1998</td>
<td>India</td>
<td>Cough Medicine</td>
<td>33</td>
</tr>
<tr>
<td>2006</td>
<td>Panama</td>
<td>Cough and Anti-Allergy Syrup</td>
<td>46</td>
</tr>
<tr>
<td>2008</td>
<td>Nigeria</td>
<td>Teething Formula</td>
<td>84</td>
</tr>
<tr>
<td>2009</td>
<td>Bangladesh</td>
<td>Cough Medicine</td>
<td>26</td>
</tr>
</tbody>
</table>

US FDA presentation by Edwin Rivera-Martinez, June 2010
# Formulation of Acetaminophen cough Syrup

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>g/100 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen ((Mallinckrodt, USA))</td>
<td>5</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>0.35</td>
</tr>
<tr>
<td>Sucrose</td>
<td>23.4</td>
</tr>
<tr>
<td>Sorbitol Solution</td>
<td>20</td>
</tr>
<tr>
<td>Invert Sugar</td>
<td>27.5</td>
</tr>
<tr>
<td>Glycerin</td>
<td>5</td>
</tr>
<tr>
<td>Crospovidone (Kollidon CL-M)</td>
<td>5</td>
</tr>
<tr>
<td>Polyethylene Glycol 4000</td>
<td>0.5</td>
</tr>
<tr>
<td>Sodium Benzoate</td>
<td>0.2</td>
</tr>
<tr>
<td>Sorbitan Monolaurate</td>
<td>0.01</td>
</tr>
<tr>
<td>Disodium Edetate</td>
<td>0.2</td>
</tr>
<tr>
<td>Citric Acid</td>
<td>0.1</td>
</tr>
<tr>
<td>Sodium Citrate Dihydrate</td>
<td>0.56</td>
</tr>
<tr>
<td>FD&amp;C Yellow #6</td>
<td>0.006</td>
</tr>
<tr>
<td>Purified Water</td>
<td>q.s. to 100 mL</td>
</tr>
<tr>
<td>pH</td>
<td>5 - 6</td>
</tr>
</tbody>
</table>
If you are a Acetaminophen Syrup Manufacturer

**Source for starting materials**
- Acceptable quality attributes
- Approved supplier
- Contract agreement

**Registration of starting materials**
- Specification
- Analytical method Validation
- Approved Supplier
- Process validation
ICH Q6A Specifications: Test Procedures and Acceptance Criteria

Specification of Paracetamol EP

✓ Description
✓ Identification
✓ Test for impurities (related substances, residual solvents)
✓ Assay
If you are a Acetaminophen Syrup Manufacturer

**Source for starting materials**
- Acceptable quality attributes
- Approved supplier
- Contract agreement

**Registration of starting materials & product**
- Specification
- Analytical method validation
- Approved Supplier
- Process validation

**GMP Control**
- Correct starting materials used – Identity, Quality & Supply chain
- Appropriate handling
Management of Changes in the Starting Materials Supply Chain throughout the Product Life Cycle

- Clinical Development Strategy
- Paediatric Investigation Plan
- Orphan Designation Application
- Marketing Authorisation Application
- Advertising
  - Input into Variation and Renewal Strategy
  - Submission in Other Markets
  - Product Reclassification
- Clinical Trial Applications
- Scientific Advice
- Submission Strategy - Centralised, DCP or MRP
- eCTD, NeeS Publishing and Lifecycle Management
- Clinical Development Strategy for New Indications
- Renewal Submissions
- Variation Applications
- Submission in Other Markets
- Marketing Authorisation Application
- Orphan Designation Application
- Clinical Development Strategy
- Paediatric Investigation Plan
If you are a Acetaminophen Syrup Manufacturer

Source for excipient

- Acceptable quality attributes
- Approved supplier
- Contract agreement?

Registration of excipient

- Specification
  - Analytical method Validation?
  - Approved Supplier?
  - Process validation?

GMP Control

- Correct starting materials used
  - Identity, Quality & Supply chain
- Appropriate handling
GLYCEROL
Glycerolum

C₃H₅(OH)₂M₉2.1
[56-81-5]

DEFINITION
Propane-1,2,3-triol.
Content: 98.0 per cent m/m to 101.0 per cent m/m (anhydrous substance).

CHARACTERS
Aspect: syrupy liquid, unctuous to the touch, colourless or almost colourless, clear, very hygroscopic.
Solubility: miscible with water and with ethanol (96 per cent), slightly soluble in acetone, practically insoluble in fatty oils and in essential oils.

IDENTIFICATION
First identification: A, B.
Second identification: A, C, D.
A. Refractive index (see Tests).
B. Infrared absorption spectrophotometry (2.2.24).
Preparation: to 5 mL add 1 mL of water R and mix carefully.
Comparison: Ph. Eur. reference spectrum of glycerol (85 per cent).
C. Mix 1 mL with 0.5 mL of nitric acid R. Superimpose 0.5 mL of potassium dichromate solution R. A blue ring develops at the interface of the liquids. Within 10 min, the blue colour does not diffuse into the lower layer.
D. Heat 1 mL with 2 g of potassium hydrogen sulfate R in an evaporating dish. Vapours (acrolein) are evolved which blacken filter paper impregnated with alkaline potassium tetratodomercurate solution R.

TESTS
Solution S. Dilute 100.0 g to 200.0 mL with carbon dioxide-free water R.
Appearance of solution. Solution S is clear (2.2.1). Dilute 10 mL of solution S to 25 mL with water R. The solution is colourless (2.2.2. Method II).
Acidity or alkalinity. To 50 mL of solution S add 0.5 mL of phenolphthalein solution R. The solution is colourless. Not more than 0.2 mL of 0.1 M sodium hydroxide is required to change the colour of the indicator to pink.
Refractive index (2.2.6). 1.470 to 1.475.
Aldehydes: maximum 10 ppm.
Place 7.5 mL of solution S in a ground-glass-stoppered flask and add 7.5 mL of water R and 1.0 mL of decolourised pararosanilin solution R. Close the flask and allow to stand for 1 h at a temperature of 25 ± 1 °C. The absorbance (2.2.25) of the solution measured at 552 nm is not greater than that of a standard prepared at the same time and in the same manner using 7.5 mL of formaldehyde standard solution (5 ppm CH₂O) R and 7.5 mL of water R. The test is not valid unless the standard is pink.
Esters. Add 10.0 mL of 0.1 M sodium hydroxide to the final solution obtained in the test for acidity or alkalinity. Boil under a reflux condenser for 5 min. Cool. Add 0.5 mL of phenolphthalein solution R and titrate with 0.1 M hydrochloric acid. Not less than 8.0 mL of 0.1 M hydrochloric acid is required to change the colour of the indicator.
Impurity A and related substances. Gas chromatography (2.2.28).
Test solution. Dilute 10.0 mL of solution S to 100.0 mL with water R.
Reference solution (a). Dilute 10.0 g of glycerol R1 to 20.0 mL with water R. Dilute 10.0 mL of the solution to 100.0 mL with water R.
Reference solution (b). Dissolve 1.000 g of diethylene glycol R in water R and dilute to 100.0 mL with the same solvent.

Limits:
- Impurity A: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.1 per cent);
- any other impurity with a retention time less than the retention time of glycerol: not more than the area of the peak due to impurity A in the chromatogram obtained with reference solution (c) (0.1 per cent);
- total of all impurities with retention times greater than the retention time of glycerol: not more than 5 times the area of the peak due to impurity A in the chromatogram obtained with reference solution (c) (0.5 per cent);
- disregard limit: 0.05 times the area of the peak due to impurity A in the chromatogram obtained with reference solution (e) (0.05 per cent).

Halogenated compounds: maximum 35 ppm.
To 10 mL of solution S add 1 mL of dilute sodium hydroxide solution R, 5 mL of water R and 50 mg of halogen-free nickel-aluminium alloy R. Heat on a water-bath for 10 min, allow to cool and filter. Rinse the flask and the filter with water R until 25 mL of filtrate is obtained. To 5 mL of the filtrate add 4 mL of ethanol (96 per cent) R, 2.5 mL of water R, 0.5 mL of nitric acid R and 0.05 mL of silver nitrate solution R2 and mix. Allow to stand for 2 min. Any opalescence in the solution is not more intense than that in a standard prepared at the same time by mixing 7.0 mL of chloride standard solution (5 ppm Cl) R, 4 mL of ethanol (96 per cent) R, 0.5 mL of water R, 0.5 mL of nitric acid R and 0.05 mL of silver nitrate solution R2.

Sugars. To 10 mL of solution S add 1 mL of dilute sulphuric acid R and heat on a water-bath for 5 min. Add 3 mL of carbonate-free dilute sodium hydroxide solution R (prepared by the method described for carbonate-free 1 M sodium hydroxide), mix and add dropwise 1 mL of freshly prepared copper sulphate solution R. The solution is clear and blue. Continue heating on the water-bath for 5 min. The solution remains blue and no precipitate is formed.
• Regulatory approval is usually simplified for compendial excipients.

• For a noncompendial excipient, updates and a full description of the characterization, manufacture, control, analytical procedures, and acceptance criteria should be provided in an information amendment.
If you are a Acetaminophen Syrup Manufacturer

Source for excipient

- Acceptable quality attributes
- Approved supplier
- Contract agreement?

Registration of excipient

- Specification
  - Analytical method Validation?
  - Approved Supplier?
  - Process validation?

GMP Control

- Correct starting materials used –Identity, Quality & Supply chain
- Appropriate handling
Checking of Incoming Goods

A simplified process

1. Receipt
2. Identification
3. Quarantine
4. Sampling and Testing for Release
5. Approve for further use

Prerequisites e.g.
- Written Procedures
- Designated Areas
- Supplier Qualification, if appropriate

Checking is the last line of defense for medical product integrity
How do you verify the correct supply chain for each starting material?

- For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels.
- Approved Suppliers list

<table>
<thead>
<tr>
<th>Name of Material</th>
<th>Internal Code</th>
<th>Batch No / Receiving No.</th>
<th>Status</th>
<th>Quarantine / Release / Rejected / Hold (Use Color)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Expiry Date</td>
<td>Retest Date</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Receiving Date</td>
<td>Signature</td>
</tr>
</tbody>
</table>
How do you verify the correct supply chain for each starting material?

BB001X  
Sweetener  
GR: 01-11-2008  
SLED: 01-08-2009  
Batch/Lot: 0000078379
How do you verify the correct identity and quality of the starting materials?

There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material.

✔ Is checking the CoA given by supplier sufficient?
How do you verify the correct identity and quality of the starting materials?
How do you verify the correct identity and quality of the starting materials?

**Glycerin USP COA and Information**

**Physical Specifications: Glycerine (Glycerin) USP**
- Assay % by wt. 99.5 min.
- Color, APHA 15 Max.
- Specific Gravity 25°C 1.2607 - 1.2618
- Residue on Ignition (%) < 0.005
- Chlorides (ppm) < 10
- Sulfites (ppm) < 20
- Chlorinated Compounds (ppm) < 5
- Moisture (%) 0.5 Max.
- Fatty Acids % Esters (NMT) < 1.0 ml
- Heavy Metals (ppm) < 5
- Arsenic (ppm) < 1.5
- Ethylene Glycol & Related (%) < 0.10
- Organic Volatile Impurities (OVI) Pass
- Identification by IR Pass
- Identification by GC Pass

Vegetable Glycerin is a clear, water-white viscous liquid that is produced from select vegetable feedstocks and refined via a proprietary process. This material meets USP specifications and is produced in a FDA registered facility.

**Certificate of Analysis**

PRODUCT: KOSHER GLYCERIN 99.7
Glycerin 99.7% USP/KOSHER
LABELER: 46145

DATE OF MANUFACTURE: September 3, 2012
DATE OF EXPIRY/RE-TEST: September 2, 2013

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay % by wt.</td>
<td>99.7</td>
<td>99.5 Min. &lt; 10</td>
</tr>
<tr>
<td>Color, APHA</td>
<td>8.0</td>
<td>1.2607 - 1.2618</td>
</tr>
<tr>
<td>Specific Gravity 25°C</td>
<td>1.2612</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Residue on Ignition (%)</td>
<td>0.001</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Chlorides (ppm)</td>
<td>1.24</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Sulfates (ppm)</td>
<td>0.85</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>Chlorinated Compounds (ppm)</td>
<td>1.85</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Moisture (%)</td>
<td>0.30</td>
<td>0.50 max.</td>
</tr>
<tr>
<td>Fatty Acids &amp; Esters (NMT)</td>
<td>0.10</td>
<td>&lt; NMT 1.0 ml</td>
</tr>
<tr>
<td>Arsenic (ppm)</td>
<td>&lt; 1.0</td>
<td>&lt; 1.5</td>
</tr>
<tr>
<td>Heavy Metals (ppm)</td>
<td>&lt; 1.0</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Ethylene Glycol Content (%)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Diethylene Glycol Content (%)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Identification by IR</td>
<td>PASS</td>
<td>Match to Standard</td>
</tr>
<tr>
<td>Identification by GC</td>
<td>PASS</td>
<td>Match to Standard</td>
</tr>
</tbody>
</table>

Approved by

Customer Service Laboratory Group

Securing Medical Product Quality Through the Supply Chain

U.S. Pharmacopeial Convention | March 28–31, 2017 | USA
How do you verify the correct identity and quality of the starting materials?

- The identity of a complete batch of starting materials can normally only be ensured if individual samples are taken from all the containers and an identity test performed on each sample.
- The quality of a batch of starting materials may be assessed by taking and testing a representative sample.
The Agency recommends that:

Drug product manufacturers perform a **specific identity test that includes a limit test for DEG** on all containers of all lots of glycerin before the glycerin is used in the manufacture or preparation of drug products because of the serious hazard associated with DEG contamination.
Specific Identification Test for Glycerin

Identification of Glycerin by Infrared Absorption Spectroscopy

Figure 2. Compare result for a test sample of diethylene glycol (DEG) vs. glycerol standard

Table 1. Compare results against a glycerol standard

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>Best Hit</th>
<th>Correlation</th>
<th>Pass/Fail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerol</td>
<td>C:\pel_data\spectra\ATR\Glycerol.sp</td>
<td>0.999428</td>
<td>Pass</td>
</tr>
<tr>
<td>Diethylene Glycol</td>
<td>C:\pel_data\spectra\ATR\Glycerol.sp</td>
<td>0.307619</td>
<td>Fail</td>
</tr>
</tbody>
</table>

Specific Identification Test for Glycerin

Gas Chromatography assay method which can detect 0.1% DEG.

http://journal.scconline.org/pdf/cc2010/cc061n03/p00225-p00234.pdf
Specifications for starting and packaging materials

a) A description of the materials, including:
   - The designated name and the internal code reference;
   - The reference, if any, to a pharmacopoeial monograph;
   - The approved suppliers and, if reasonable, the original producer of the material;
   - A specimen of printed materials;

b) Directions for sampling and testing;

c) Qualitative and quantitative requirements with acceptance limits;

d) Storage conditions and precautions;

e) The maximum period of storage before re-examination.
Sampling should be conducted in such a way to prevent cross contamination.
Sampling Procedure for Starting Materials

- Method of sampling;
- Equipment to be used;
- Amount of the sample to be taken;
- Instructions for any required sub-division of the sample;
- Type and condition of the sample container to be used;
- Identification of containers sampled;
- Any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
- Storage conditions;
- Instructions for the cleaning and storage of sampling equipment.
How many containers should be sampled for identity & quality control test?

The identity of a complete batch of starting materials can normally only be ensured if individual samples are taken from all the containers and an identity test performed on each sample.

It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material will be incorrectly identified on its label.

Annex 8, clause 2
How do you verify the identity and quality of the starting materials?

Under certain arrangements, it is possible that a validated procedure exempting identity testing of each incoming container of starting material could be accepted for:

- starting materials coming from a single product manufacturer or plant;
- starting materials coming directly from a manufacturer or in the manufacturer's sealed container where there is a history of reliability and regular audits of the manufacturer's Quality Assurance system are conducted by the purchaser (the manufacturer of the medicinal products or by an officially accredited body.)
Annex 8 of the GMP provides for derogations from the requirement for identity testing of every container where there is a validated supply chain. Can I use this derogation for the glycerol I purchase?

It is improbable that a procedure could be satisfactorily validated for:

- starting materials supplied by intermediaries such as brokers where the source of manufacture is unknown or not audited;
- Starting materials for use in parenteral products.

“Glycerol is a commercial article that is widely used in the food and other industries. Generally speaking, the supply chain for glycerol tends to be complex and lengthy. The involvement of brokers is common in the supply chain.”
Evaluate the Risks in the Starting Materials Supply Chain

Starting Materials Manufacturers

Distributor

Broker

Trader

Agent

Drug Product Manufacturer

High Risk of Fraudulent practice, Repackaging, Relabeling, Mix-up

Low Risk

Direct supply
Assessment and evaluation of all the suppliers involved in the supply chain of starting materials

- Taking into consideration the nature of the starting material and the medicinal products in which it will be used
- Complexity of the supply chain
- Determine the extent of evaluation & monitoring of the suppliers (e.g., auditing, supplier quality agreements)
- Extent of QC testing
Checking of Incoming Goods

Key Messages

• Incoming Materials Checking is critical to prevent adulterated or contaminated materials from entering a pharmaceutical facility.

• Personnel need to be trained on appropriate procedures designed to prevent acceptance and use of materials lacking integrity.

• This check is meant to detect both inadvertent errors and willful adulteration of incoming materials.

• Incoming material must be verified to be the correct material of the specified quality before it can be released to be used in pharmaceutical manufacturing.

Checking is the last line of defense for medicinal product integrity
Acknowledgement

APEC GMP Workgroup Members in 2015

- David Cockburn, EMA
- Jean Poulos, Aceto
- Betsy Fritschel, J&J
- Cindy Huang, Taiwan FDA
- Stephan Rönninger, Amgen
- Rick Friedman, US-FDA
- Karen Takahashi, US-FDA
- Kang Teng Ong, HSA
Thank You
Executive Management Responsibility: Establish and Maintain a Robust Quality System

- Management commitment to continual improvement and to surfacing emerging issues
- Quality policy & planning
- Resource management
- Internal communication
- Extends in some ways beyond local site or corporation.

Also includes management review and control of:

- Outsourced activities
- Quality of incoming materials: changes in raw material and/or suppliers
All parties who manufacture (includes testing), process, pack, or hold an *ingredient or drug product* are responsible for meeting CGMPs.

Adulterated Ingredient = Adulterated Drug Product
ICH Q10 Pharmaceutical Quality System

Pharmaceutical Development → Technology Transfer → Commercial Manufacturing → Discontinuation

Investigational products

GMP

Management Responsibilities

PQS elements

Process Performance & Product Quality Monitoring System
Corrective Action / Preventive Action (CAPA) System
Change Management System
Management Review

Enablers

Knowledge Management
Quality Risk Management
Expectations and Recommendations

- QA as part of a larger outsourcing risk management plan
  - Say what you do, do what you say, prove it, improve it
  - Deming

- Tools:
  - Risk Management Strategy
  - Process Maps
  - Supplier Quality Questionnaire
  - Communications Infrastructure
  - Audit Program
  - Quality Agreements
  - Metrics/Analytics Program
  - Report cards
Industry: Traditional Quality System
Vulnerabilities (e.g.)

1. Lack of **traceability**

2. High **complexity** due to increased brokerage and trade activity
   - Many suppliers are solely distributors. To protect their enterprise, the COA is often altered to remove true identity of the manufacturer

3. Ingredient may be **repackaged** or **relabeled** multiple times

4. **COAs**: Original manufacturer COA not always obtained. Also, overreliance on COA and frequently non-specific ID test on composite sample.

5. **Supplier Management**: qualification programs, quality agreements, and lifecycle monitoring are often deficient

6. **Distant manufacturing sites** can include special risks
   - Not audited by drug product manufacturer, FDA inspection may be infrequent, and/or not subject to inspection by the regional authority
Quality System is the Backbone for Ingredient Safety and Manufacturing

Reliability

• Selecting an **Ingredient Supplier or CMO**
  
  • Is the Drug Product Manufacturer’s quality system competent to source from capable ingredient manufacturers or CMOs?
  
  • Does price often drive decisions with minimal consideration of the manufacturing & quality standards of the manufacturer of the ingredient?
  
  • Are good practices in place for identifying suppliers and monitoring them?
  
  • Are DP manufacturers vigilant to risks as they emerge throughout the lifecycle?
Quality Unit Role

Preventing DEG Contamination in Glycerin

**Drug product manufacturer Quality Unit** should ensure they *(e.g.)*:

- know the supply chain for glycerin including the component manufacturer and any distributors.

- take precautions to identify reliable suppliers and to secure shipment for components, to prevent DEG contamination

- test glycerin for DEG is performed on each batch

- make personnel are aware of the importance of testing and the potential hazards if testing is not done.

- Determine identity and suitability of any repackers, and others who distribute and prepare glycerin for their drug products, and mandate that they routinely test all glycerin lots
Quality agreements define expectations and responsibilities in a contract manufacturing arrangement up front.

Both the CMO and Product Owner are responsible to ensure safe products.