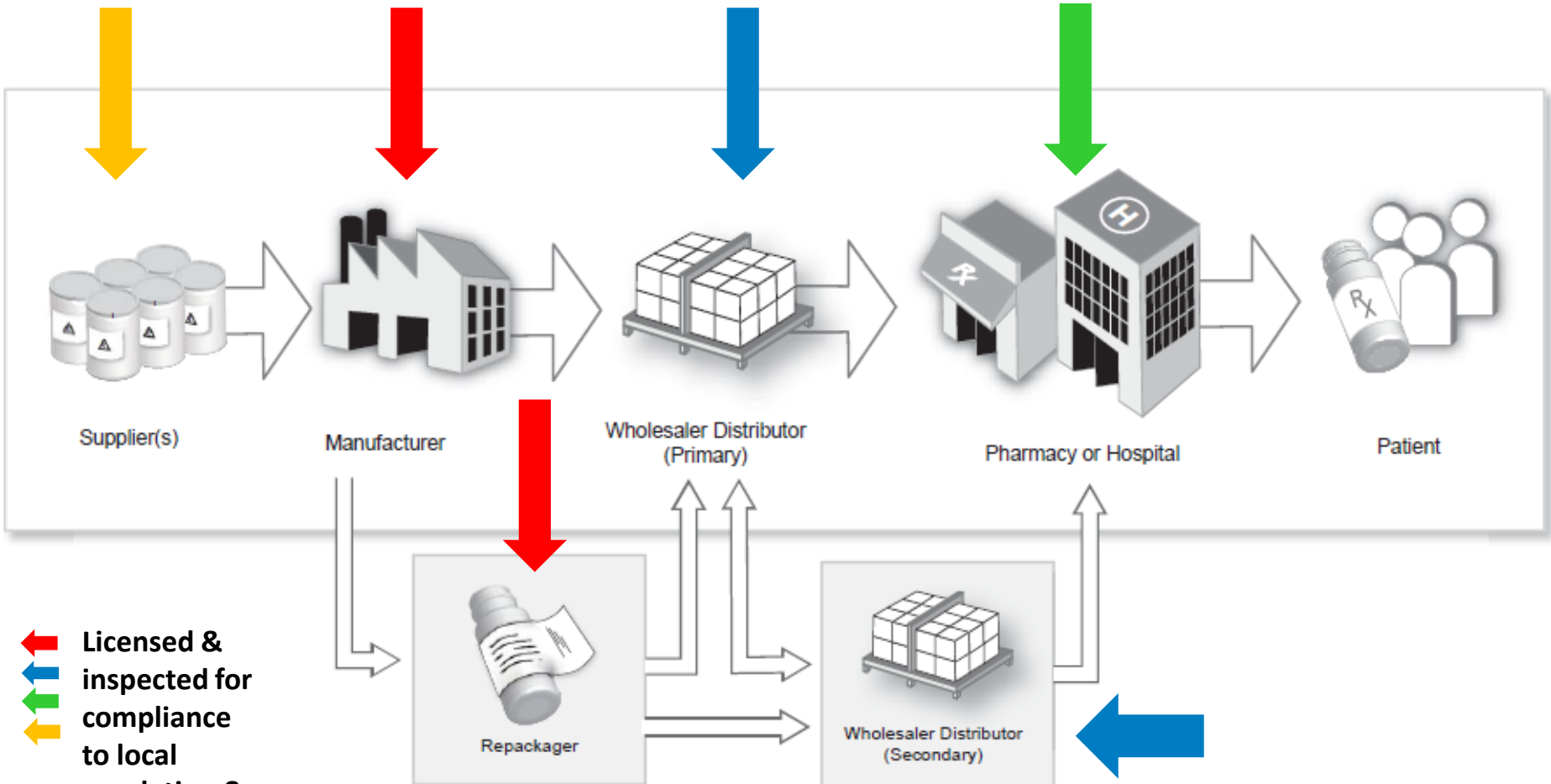
APEC AHC – USP Center of Excellence (CoE) for Product Quality & Supply Chain
Pilot Program: "Securing Medical Product Quality Through the Supply Chain"

Incoming Materials Check

Ong Kang Teng
Health Sciences Authority of Singapore
28 March 2017

A Drug Supply Chain Example

From Supplier to Patient



788 Deaths Due to DEG Contamination 1937 - 2009

Year	Country	Product	No. of Deaths
1937	USA	Sulfanilimide	107
1969	South Africa	Sedative	7
1986	India	Medicinal Glycerin	14
1990	Nigeria	Acetaminophen Syrup	47
1990/2	Bangladesh	Acetaminophen Syrup	339
1995/6	Haiti	Cough Medicine	85
1998	India	Cough Medicine	33
2006	Panama	Cough and Anti-Allergy Syrup	46
2008	Nigeria	Teething Formula	84
2009	Bangladesh	Cough Medicine	26

7

US FDA presentation by Edwin Rivera-Martinez, June 2010

Formulation of Acetaminophen cough Syrup

Ingredient	g/100 ml
Acetaminophen ((Mallinckrodt, USA)	5
Xanthan gum	0.35
Sucrose	23.4
Sorbitol Solution	20
Invert Sugar	27.5
Glycerin	5
Crospovidone (Kollidon CL-M)	5
Polyethylene Glycol 4000	0.5
Sodium Benzoate	0.2
Sorbitan Monolaurate	0.01
Disodium Edetate	0.2
Citric Acid	0.1
Sodium Citrate Dihydrate	0.56
FD&C Yellow #6	0.006
Purified Water	q.s. to 100 mL
pH	5 - 6

Active Ingredient

Excipients

If you are a Acetaminophen Syrup Manufacturer

Source for starting ma

- Acceptable quality attributes
- Approved supplier
- Contract agreement

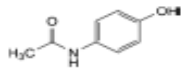
Registration of starting

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

01/2008:0049
corrected 6.0

PARACETAMOL

Paracetamolum



$C_8H_9NO_2$ [103-90-2] M_r 151.2

DEFINITION

N-(4-Hydroxyphenyl)acetamide.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: sparingly soluble in water, freely soluble in alcohol, very slightly soluble in methylene chloride.

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D, E.

A. Melting point (2.2.14): 168 °C to 172 °C.

B. Dissolve 0.1 g in *methanol R* and dilute to 100.0 mL with the same solvent. To 1.0 mL of the solution add 0.5 mL of a 10.3 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with *methanol R*. Protect the solution from bright light and immediately measure the absorbance (2.2.25) at the absorption maximum at 249 nm. The specific absorbance at the maximum is 860 to 980.

C. Infrared absorption spectrophotometry (2.2.24).
Preparation: discs.
Comparison: *paracetamol CRS*.

D. To 0.1 g add 1 mL of *hydrochloric acid R*, heat to boiling for 3 min, add 1 mL of *water R* and cool in an ice bath. No precipitate is formed. Add 0.05 mL of a 4.9 g/L solution of *potassium dichromate R*. A violet colour develops which does not change to red.

E. It gives the reaction of acetyl (2.3.1). Heat over a naked flame.

TESTS

Related substances. Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution. Dissolve 0.200 g of the substance to be examined in 2.5 mL of *methanol R* containing 4.6 g/L of a 400 g/L solution of *tetrabutylammonium hydroxide R* and dilute to 10.0 mL with a mixture of equal volumes of a 17.9 g/L solution of *disodium hydrogen phosphate R* and of a 7.8 g/L solution of *sodium dihydrogen phosphate R*.

Reference solution (a). Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b). Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Monographs P

Reference solution (c). Dissolve 5.0 mg of *4-aminophenol R*, 5 mg of *paracetamol CRS* and 5.0 mg of *chloroacetanilide R* in *methanol R* and dilute to 20.0 mL with the same solvent. Dilute 1.0 mL to 250.0 mL with the mobile phase.

Reference solution (d). Dissolve 20.0 mg of *4-nitrophenol R* in *methanol R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL to 20.0 mL with the mobile phase.

Column:
- *size*: *l* = 0.25 m, Ø = 4.6 mm,
- *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm),
- *temperature*: 35 °C.

Mobile phase: mix 375 volumes of a 17.9 g/L solution of *disodium hydrogen phosphate R*, 375 volumes of a 7.8 g/L solution of *sodium dihydrogen phosphate R* and 250 volumes of *methanol R* containing 4.6 g/L of a 400 g/L solution of *tetrabutylammonium hydroxide R*.

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 245 nm.

Injection: 20 µL.

Run time: 12 times the retention time of paracetamol.

Relative retentions with reference to paracetamol (retention time = about 4 min): impurity K = about 0.8; impurity F = about 3; impurity J = about 7.

System suitability: reference solution (c):
- *resolution*: minimum 4.0 between the peaks due to impurity K and to paracetamol,
- *signal-to-noise ratio*: minimum 50 for the peak due to impurity J.

Limits:
- *impurity J*: not more than 0.2 times the area of the corresponding peak in the chromatogram obtained with reference solution (c) (10 ppm),
- *impurity K*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (50 ppm),
- *impurity F*: not more than half the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.05 per cent),
- *any other impurity*: not more than half the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent),
- *total of other impurities*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),
- *disregard limit* for the calculation of the total of other impurities: the area of the principal peak in the chromatogram obtained with reference solution (b) (0.01 per cent).

Heavy metals (2.4.8): maximum 20 ppm.

Dissolve 1.0 g in a mixture of 15 volumes of *water R* and 85 volumes of *acetone R* and dilute to 20 mL with the same mixture of solvents. 12 mL of the solution complies with test B. Prepare the reference solution using lead standard solution (1 ppm Pb) obtained by diluting *lead standard solution (100 ppm Pb) R* with a mixture of 15 volumes of *water R* and 85 volumes of *acetone R*.

Loss on drying (2.2.32): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (2.4.14): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

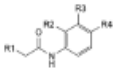
Dissolve 0.300 g in a mixture of 10 mL of *water R* and 30 mL of *dilute sulfuric acid R*. Boil under a reflux condenser for 1 h, cool and dilute to 100.0 mL with *water R*. To 20.0 mL of the solution add 40 mL of *water R*, 40 g of ice, 15 mL of *dilute hydrochloric acid R* and 0.1 mL of *ferroin R*. Titrate with *0.1 M cerium sulfate* until a greenish-yellow colour is obtained. Carry out a blank titration.

1 mL of *0.1 M cerium sulfate* is equivalent to 7.56 mg of $C_8H_9NO_2$.

STORAGE

Protected from light.

IMPURITIES



A. R1 = R3 = R4 = H, R2 = OH: *N*-(2-hydroxyphenyl)-acetamide,

B. R1 = CH_3, R2 = R3 = H, R4 = OH: *N*-(4-hydroxyphenyl)propanamide,

C. R1 = R2 = H, R3 = Cl, R4 = OH: *N*-(3-chloro-4-hydroxyphenyl)acetamide,

D. R1 = R2 = R3 = R4 = H: *N*-phenylacetamide,

H. R1 = R2 = R3 = H, R4 = O-CO-CH_3: 4-(acetylamino)phenyl acetate,

J. R1 = R2 = R3 = H, R4 = Cl: *N*-(4-chlorophenyl)acetamide (chloroacetanilide),

E. X = O, R2 = H, R4 = OH: 1-(4-hydroxyphenyl)ethanone,

G. X = N-OH, R2 = H, R4 = OH: 1-(4-hydroxyphenyl)ethanone oxime,

I. X = O, R2 = OH, R4 = H: 1-(2-hydroxyphenyl)ethanone,

F. R = NO_2: 4-nitrophenol,

K. R = NH_2: 4-aminophenol.

01/2008:1034

PARAFFIN, HARD

Paraffinum solidum

DEFINITION

A purified mixture of solid saturated hydrocarbons generally obtained from petroleum. It may contain a suitable antioxidant.

CHARACTERS

Appearance: colourless or white or almost white mass; the melted substance is free from fluorescence in daylight.

Solubility: practically insoluble in water, freely soluble in methylene chloride, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).
Comparison: *hard paraffin CRS*.

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

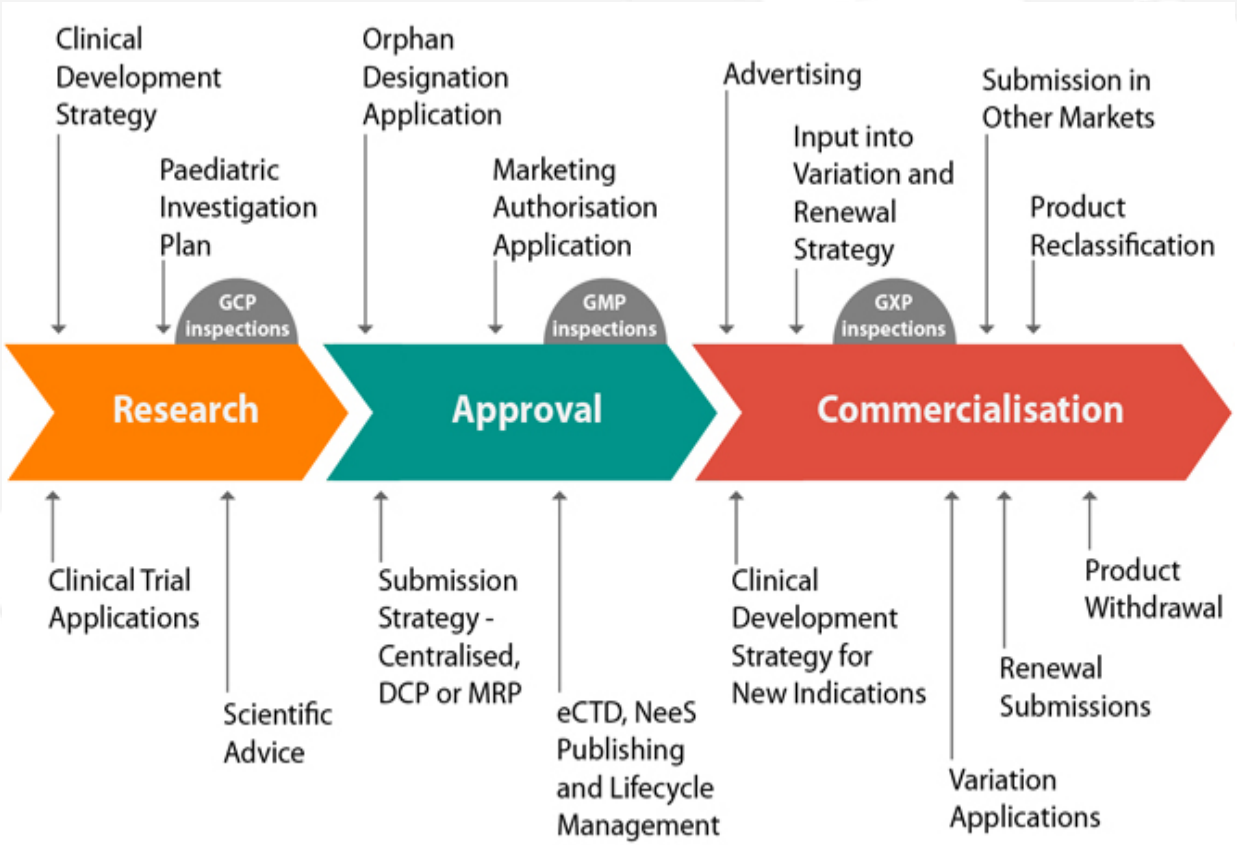
Registration of starting materials & product

- 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



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?

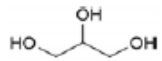
GMP Control

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

01/2008:0496

GLYCEROL

Glycerolum



$C_3H_8O_3$ M_r 92.1
[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 tetraiodomercurate 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 *decolorised pararosaniline 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 CH_2O) 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 sulfuric 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 sulfate 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.

F = relative response factor, 1.2 for glyburide related compound A, 1.0 for all other impurities

Acceptance criteria

[NOTE—Disregard any peak less than 0.05%, and disregard any peak observed in the blank.]

Glyburide related compound A: NMT 1.0%

Any other individual impurities: NMT 0.2%

Total impurities: NMT 0.50%, excluding glyburide related compound A

- **METFORMIN HYDROCHLORIDE**

Buffer, Mobile phase, Sample solution, Chromatographic system, and System suitability: Proceed as directed in the *Assay* for *Metformin Hydrochloride*.

Analysis

Sample: *Sample solution*

Calculate the percentage of each metformin impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of each metformin impurity from the *Sample solution*

r_T = sum of all the peak responses from the *Sample solution*

Acceptance criteria

[NOTE—Disregard any peak less than 0.05%, and disregard any peak observed in the blank.]

Individual metformin impurities: NMT 0.1%

Total impurities: NMT 0.5 %

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers, and store at controlled room temperature.
- **LABELING:** When more than one dissolution test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** ⟨11⟩

USP Glyburide RS

USP Glyburide Related Compound A RS
4-[2-(5-Chloro-2-methoxybenzamido) ethyl]benzenesulfonamide.
$C_{16}H_{17}ClN_2O_4S$ 368.84

USP Metformin Hydrochloride RS

USP Metformin Related Compound B RS
1-Methylbiguanide hydrochloride.
$C_3H_9N_5 \cdot HCl$ 151.60

USP Metformin Related Compound C RS
Dimethylmelamine, or *N,N*-dimethyl-[1,3,5]triazine-2,4,6-triamine.
$C_5H_{10}N_6$ 154.17

Glycerin

$C_3H_8O_3$ 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**

Standard solution: 2.0 mg/mL of USP Glycerin RS, 0.050 mg/mL of USP Ethylene Glycol RS, 0.050 mg/mL of USP Diethylene Glycol RS, and 0.10 mg/mL of 2,2,2-trichloroethanol (internal standard) in methanol

Sample solution: 50 mg/mL of Glycerin and 0.10 mg/mL of 2,2,2-trichloroethanol (internal standard) in methanol

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 0.53-mm × 30-m fused-silica analytical column coated with 3.0-µm G43 stationary phase, and a deactivated split liner with glass wool

Temperature

Injector: 220°

Detector: 250°

Column: See the temperature program table.

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
100	—	100	4
100	50	120	10
120	50	220	6

Carrier gas: Helium

Injection size: 1.0 µL

Flow rate: 4.5 mL/min

Injection type: Split ratio, about 10:1

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for ethylene glycol, 2,2,2-trichloroethanol, diethylene glycol, and glycerin are about 0.3, 0.6, 0.8 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.5 between diethylene glycol and glycerin

Analysis

Sample: *Sample solution*

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*.

ASSAY

- **PROCEDURE**

Sodium periodate solution: Dissolve 60 g of sodium metaperiodate in sufficient water containing 120 mL of 0.1 N sulfuric acid to make 1000 mL. Do not heat to dissolve the periodate. If the solution is not clear, pass through a sintered-glass filter. Store the solution in a glass-stoppered, light-resistant container. Test the suitability of this solution as follows. Pipet 10 mL into a 250-mL volumetric flask, and dilute with water to volume. To 550 mg of Glycerin dissolved in 50 mL of water, add 50 mL of the diluted periodate solution with a pipet. For a blank, pipet 50 mL of the solution into a flask containing 50 mL of water. Allow the solutions to stand for 30 min, then to each add 5 mL of hydrochloric acid and 10 mL of potassium iodide TS, and rotate to mix. Allow to stand for 5 min, add 100 mL of water, and titrate with 0.1 N sodium thiosulfate, shaking continuously and adding 3 mL of starch TS as the endpoint

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

Name of Material			
Internal Code			
Batch No.			
Status	QUARANTINE		
Expiry Date		Date Received	
Date		Signature	

Name of Material			
Internal Code			
Batch No.			
Status	RELEASED		
Expiry Date		Retest Date	
Date		Signature	

Name of Material			
Internal Code			
Batch No.			
Status	REJECTED		
Expiry Date			
Date		Signature	

Name of Material			
Internal Code			
Batch No.			
Status	HOLD		
Expiry Date		Retest Date	
Date		Signature	

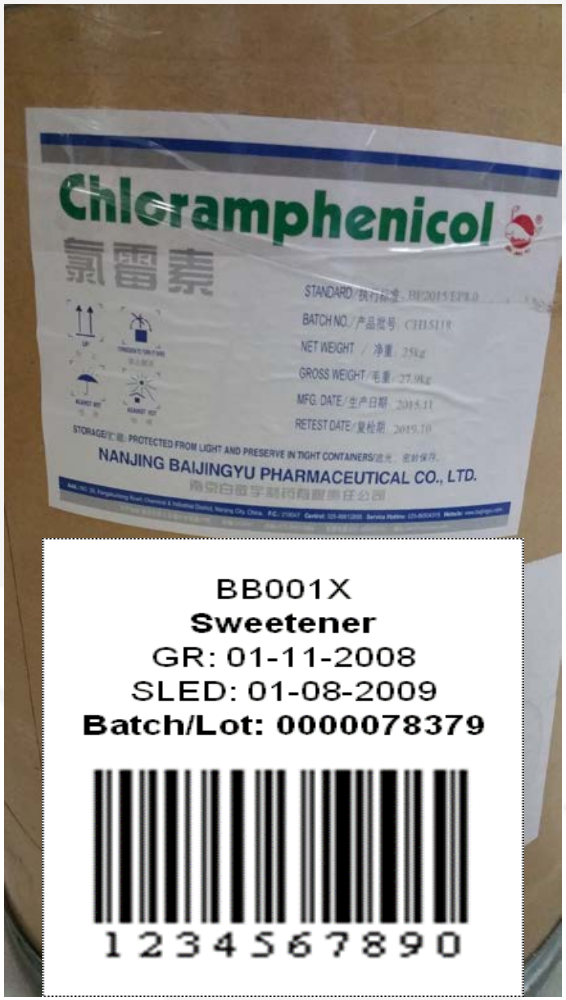
Checking is the last line of defense for medical product integrity

How do you verify the correct supply chain for each starting material?

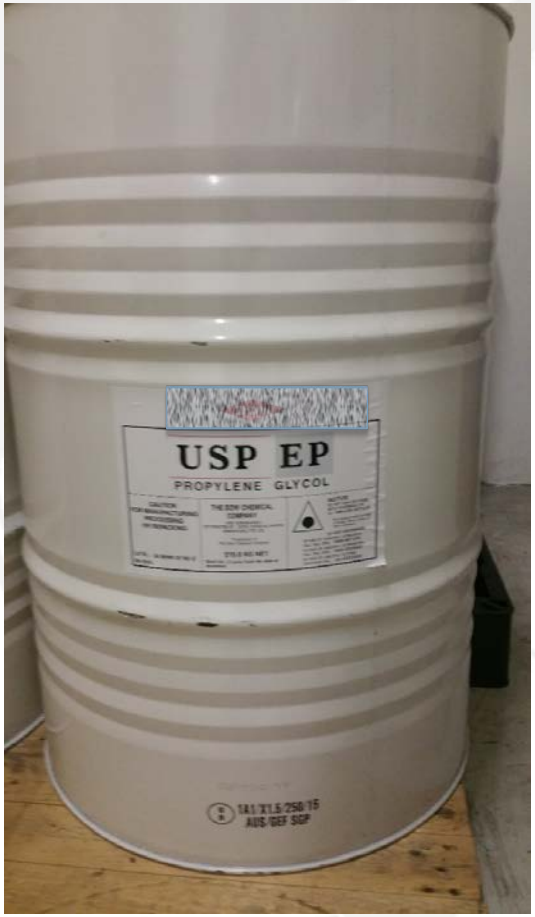
- For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels.
- Approved Suppliers list

Name of Material			
Internal Code			
Batch No / Receiving No.			
Status	**Quarantine / Release / Rejected / Hold (Use Color)**		
Expiry Date		**Retest Date**	
Receiving Date		**Signature**	

How do you verify the correct supply chain for each starting material?



How do you verify the correct identity and quality of the starting materials?



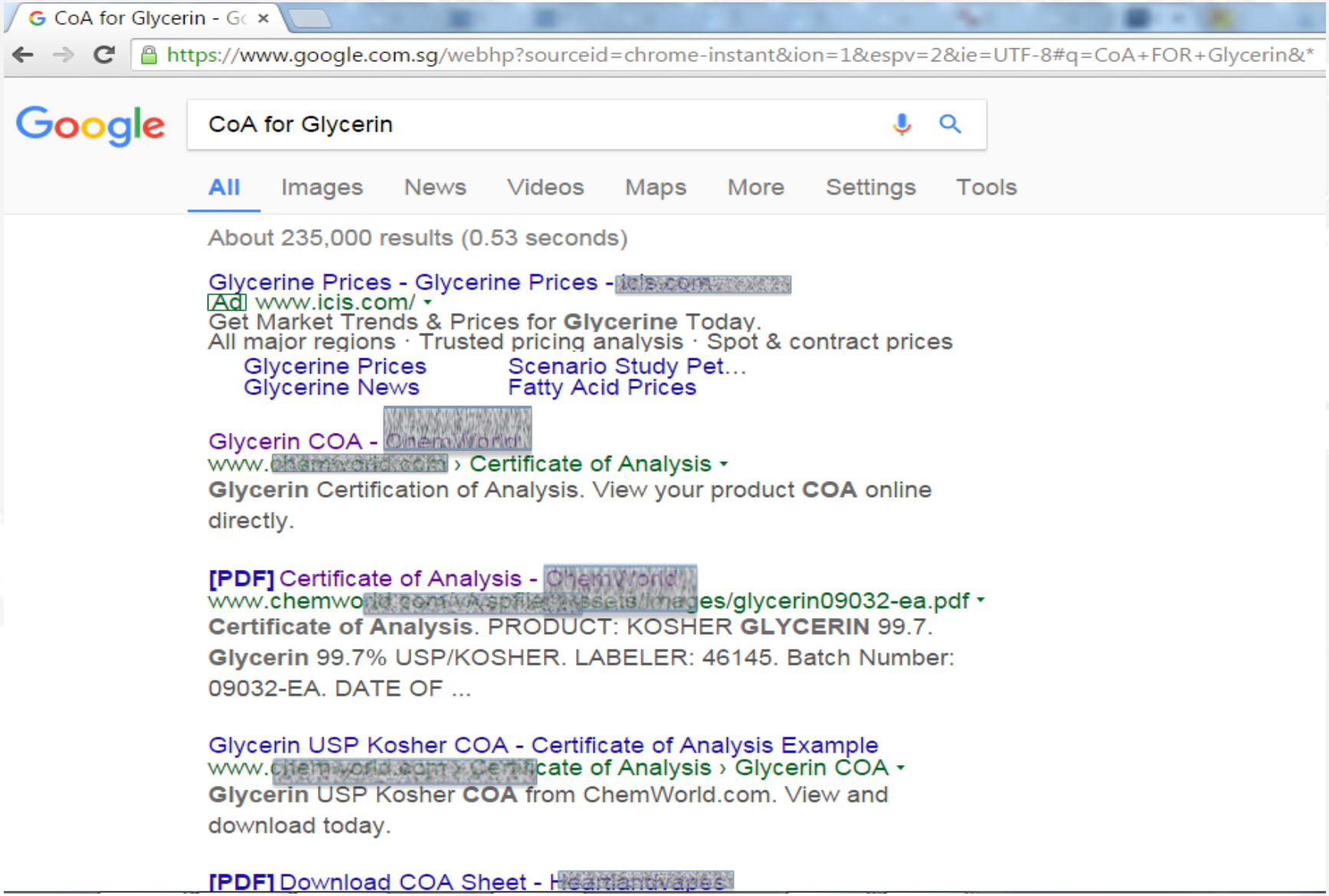
There should be

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 25C	1.2607 - 1.2618
Residue on Ignition (%)	< 0.005
Chlorides (ppm)	< 10
Sulfates (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 feed stocks 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
Batch Number: 09032-EA

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

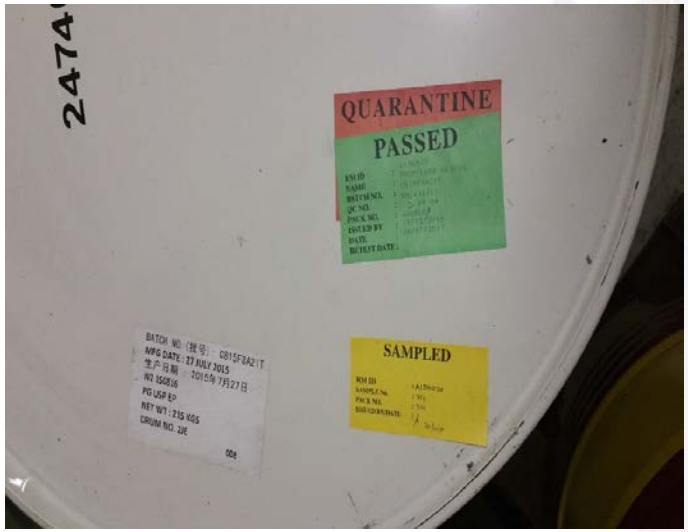
Test	Result	Specification
Assay % by wt.	99.7	99.5 Min.
Color, APHA	8.0	< 10
Specific Gravity 25°C	1.2612	1.2607-1.2618.
Residue on Ignition (%)	0.001	<0.005
Chlorides (ppm)	1.24	<10
Sulfates (ppm)	0.85	<20
Chlorinated Compounds (ppm)	1.85	<5
Moisture (%)	0.30	0.50 max.
Fatty Acids & Esters (titrant: 0.5N NaOH)	NMT 0.3	<NMT 1.0 ml
Arsenic (ppm)	<1.0	<1.5
Heavy Metals (ppm)	<1.0	<5
Ethylene Glycol Content(%)	<0.001	<0.1
Diethylene Glycol Content (%)	<0.001	<0.1
Identification By IR	PASS	Match to Standard
Identification By GC	PASS	Match to Standard

Approved by

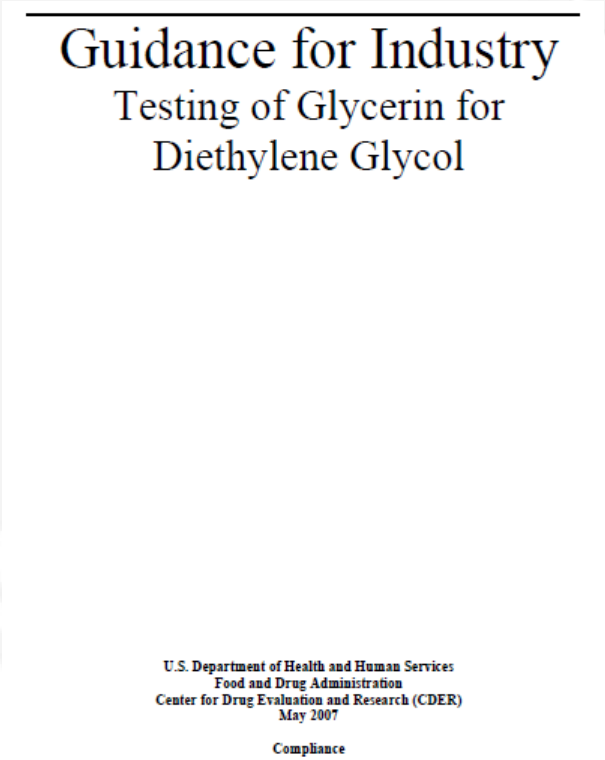
Customer Service Laboratory Group

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.



How do you verify the correct identity of Glycerin?


Guidance for Industry

Testing of Glycerin for Diethylene Glycol

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
May 2007

Compliance

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

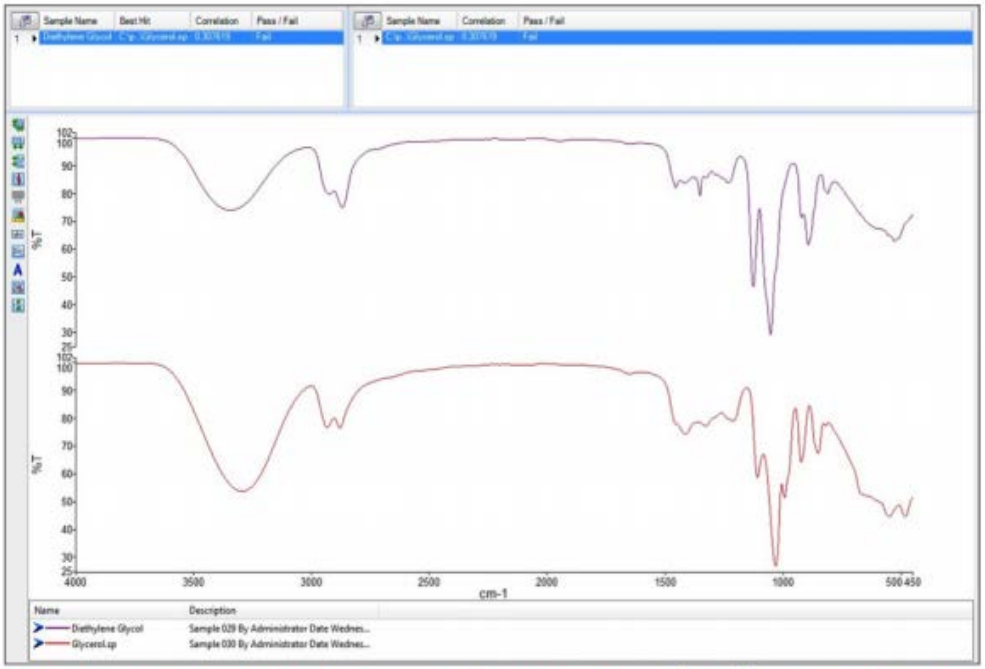


Figure 2. Compare result for a test sample of diethylene glycol (DEG) vs. glycerol standard

Identification of Glycerin by Infrared Absorption Spectroscopy

Table 1. Compare results against a glycerol standard

Sample Name	Best Hit	Correlation	Pass/Fail
Glycerol	C:\pel_data\spectra\ATR\Glycerol.sp	0.999428	Pass
Diethylene Glycol	C:\pel_data\spectra\ATR\Glycerol.sp	0.307619	Fail

https://www.perkinelmer.com/lab-solutions/resources/docs/APP_Detection_Adulteration_Glycerol_DiethyleneGlycol_IR.pdf

Specific Identification Test for Glycerin

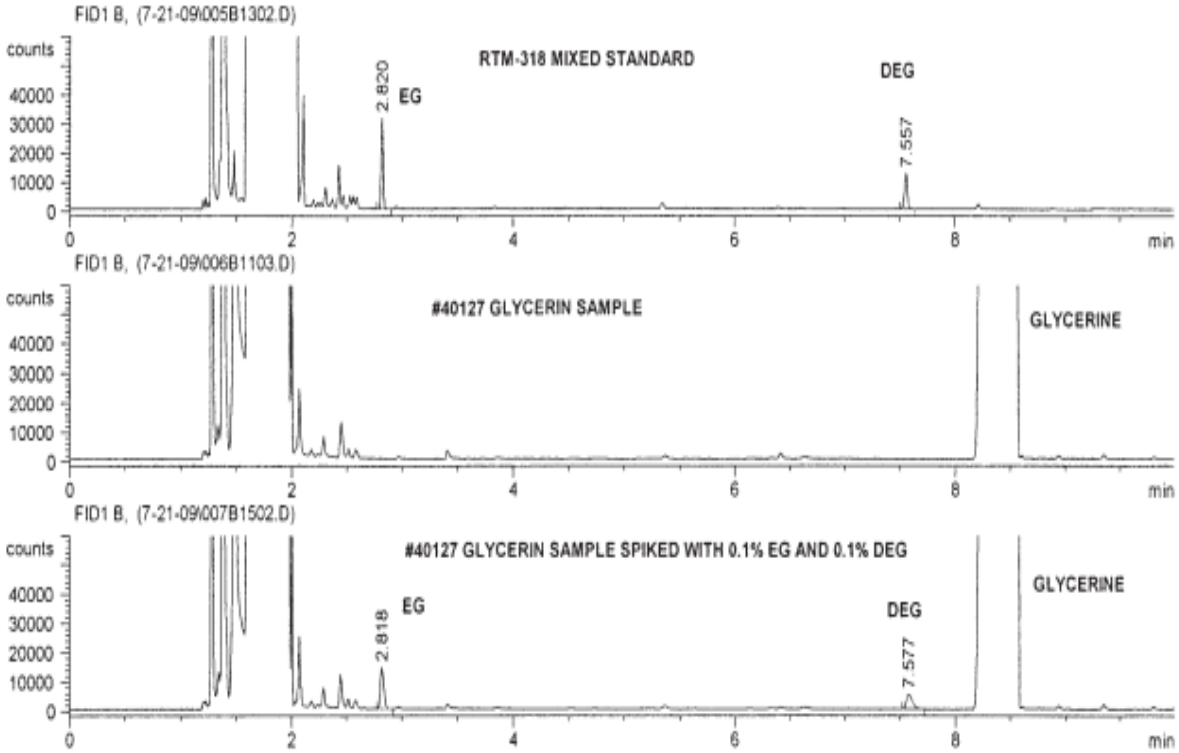


Figure 4. Typical chromatograms for standard mix (top), glycerin sample (middle), and glycerin sample spiked at USP limits of 0.10% EG and 0.10% DEG to demonstrate how sample at compliance threshold would appear (bottom).

Gas Chromatography assay method which can detect 0.1% DEG.

K. MOLEVER, J. Cosmet. Sci., 61, 225–234 (May/June 2010). Simplified assay of diethylene glycol and ethylene glycol in various raw materials by capillary gas chromatography
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;

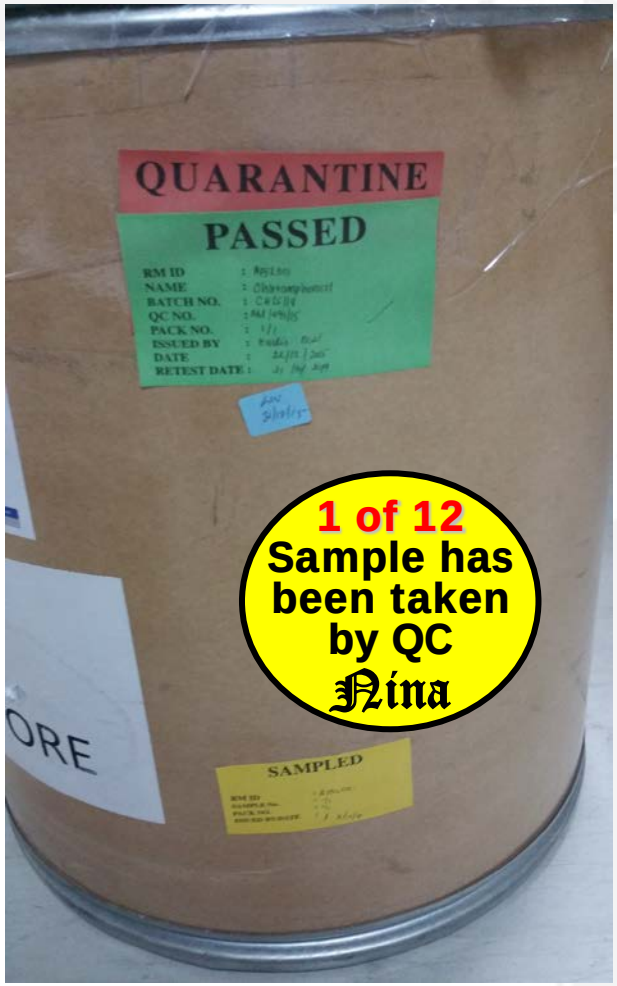
e) The maximum period of storage before re-examination.

Sampling Procedure for Starting Materials

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.

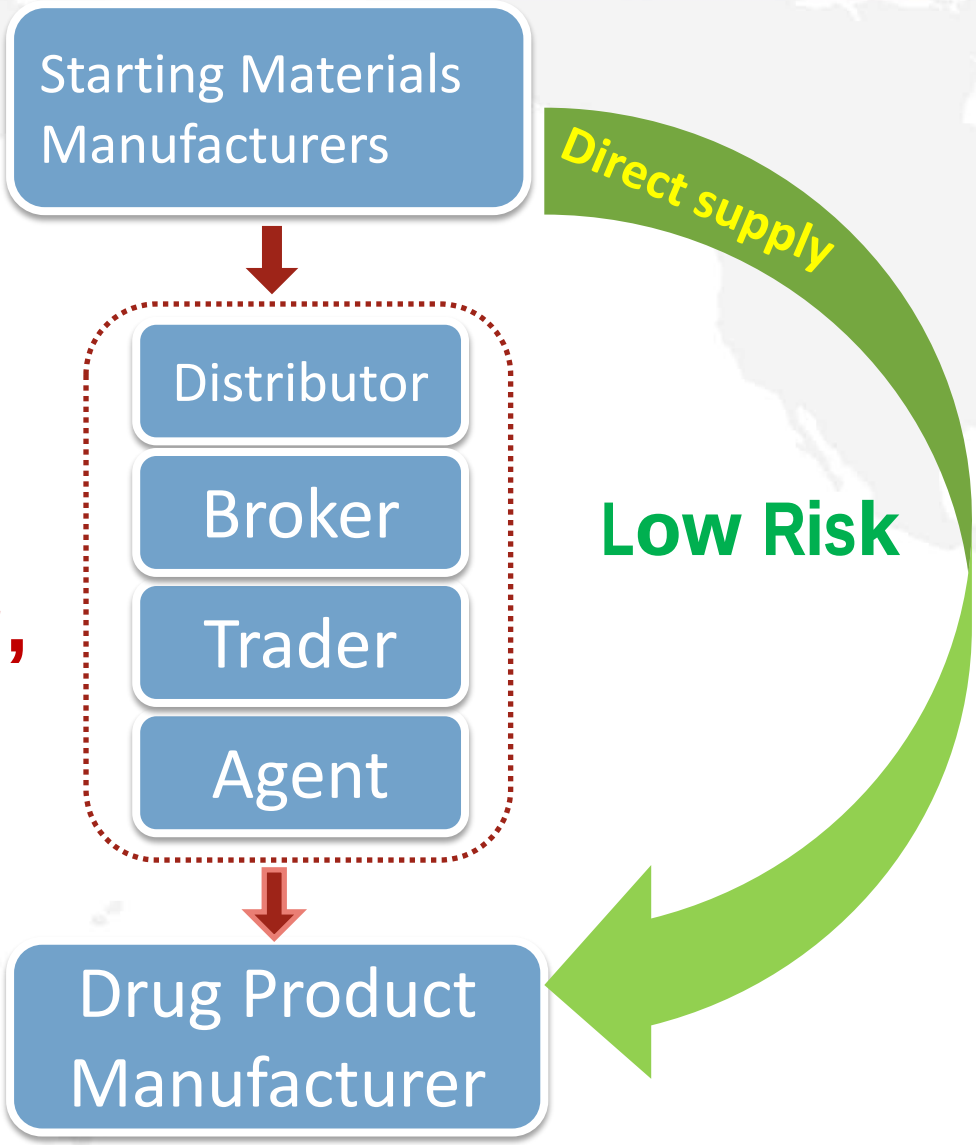
Annex 8 of the GMP provides for derogations from the requirement for identity testing of every container where there is a validated supply chain. Can I use this derogation for the glycerol I purchase?

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."

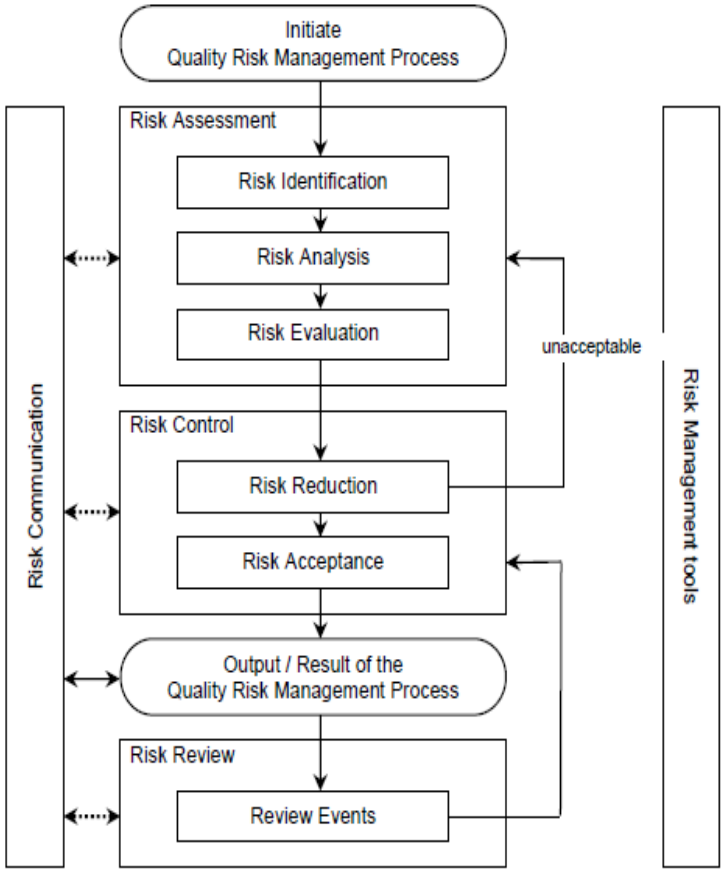
Evaluate the Risks in the Starting Materials Supply Chain



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

Application of Quality Risk Management in Materials Management

Figure 1: Overview of a typical quality risk management process



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....**

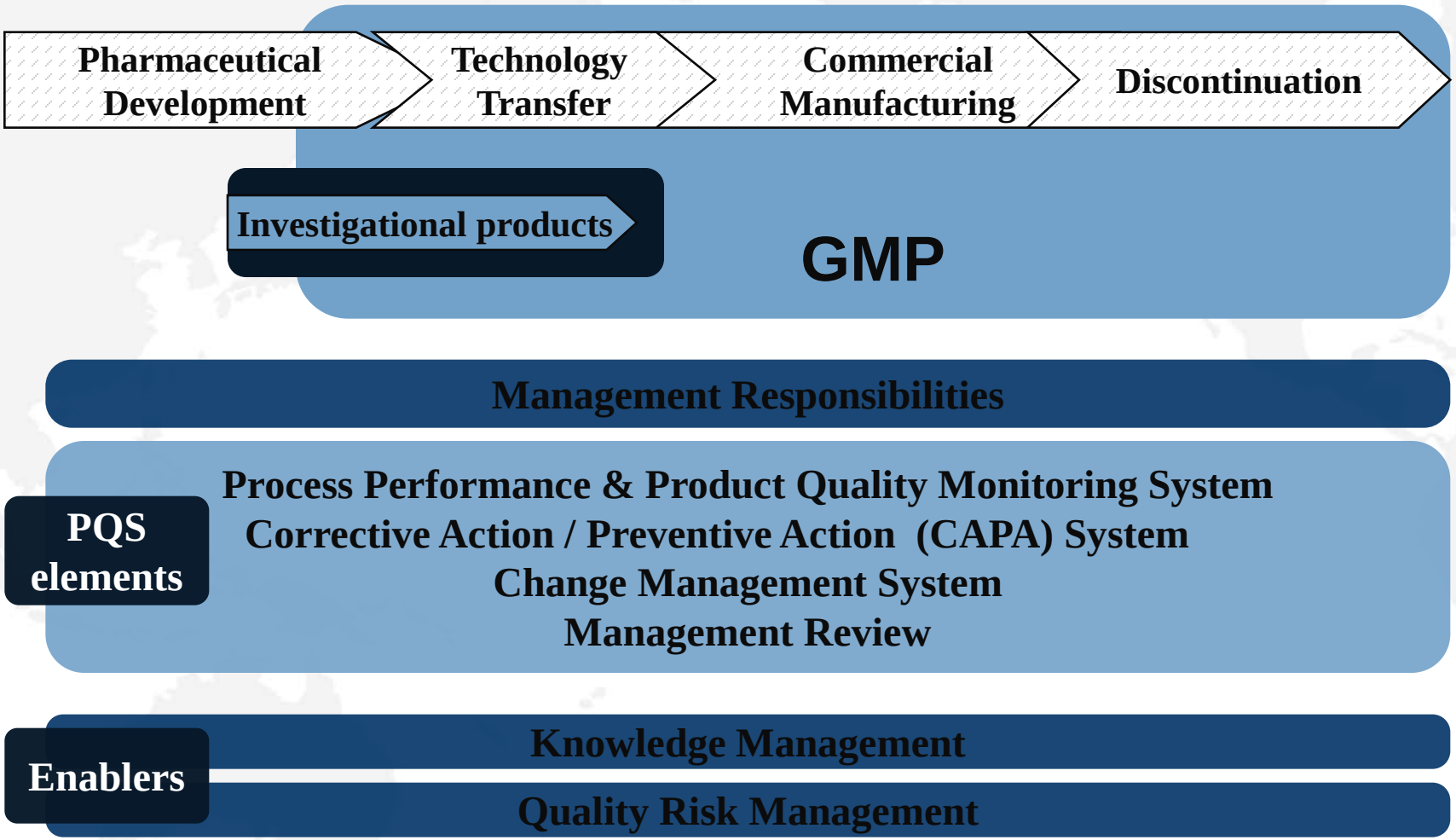
- **Outsourced activities**
- **Quality of incoming materials: changes in raw material and/or suppliers**

The Global Supply Chain: Regulatory Requirements for Chain "Links"

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



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?

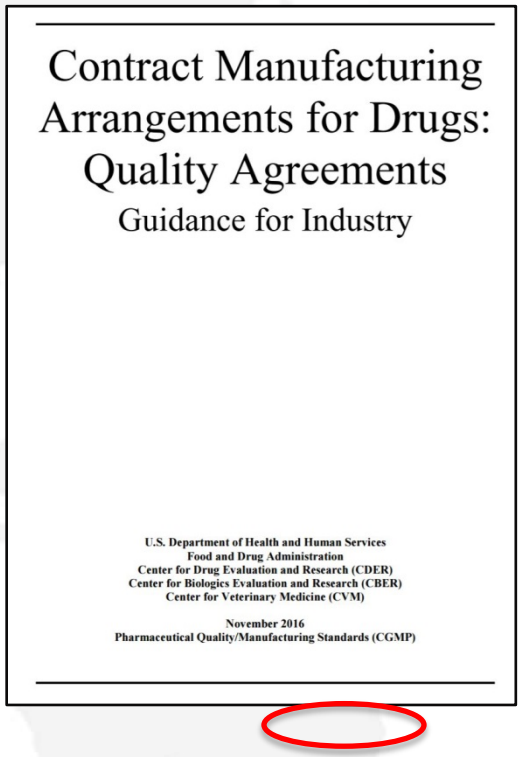
Quality Unit Role

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

Contract Manufacturing Complexities


Contract Manufacturing Arrangements for Drugs: Quality Agreements

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

November 2016
Pharmaceutical Quality/Manufacturing Standards (CGMP)

- **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**