

# Supply Chain Integrity In Excipient Distribution -

## Issues and Answers

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# A Brief History of Tainted Medicines

Year	Deaths	Location/Comments
1937	107	USA / Sulfanilamide dissolved in DEG – led to FDC Act of 1938
1990	~330	Bangladesh – Paracetamol flavored with glycerin contaminated with DEG
1996	85	Haiti - Paracetamol syrup flavored with glycerin contaminated with DEG
2006	46	Panama – Expectorant syrup flavored with glycerin contaminated with DEG



# HOW COULD THIS HAPPEN?

1. Similar organoleptic properties between similar materials

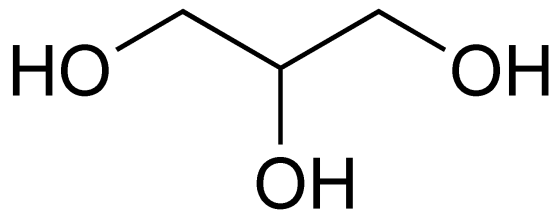
# Even to the trained professional...

Ethylene Glycol ("Antifreeze")  
**POISON!**



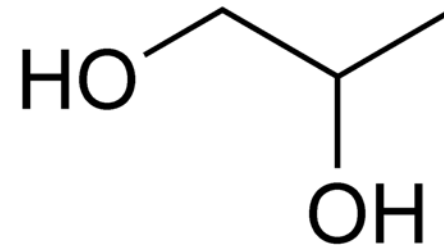
- Light colored
- Slightly viscous liquid at room temp.
- Sweet taste

**Glycerine (Glycerol)**  
**Edible and GRAS**



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

**Propylene Glycol**  
**Edible and GRAS**



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

**Diethylene Glycol ("Antifreeze")**  
**POISON!**



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



# HOW COULD THIS HAPPEN?

2. A long and questionable supply  
chain



## Taixing Glycerine Factory

Hengxiang, China

“Manufactures” glycerine

- Not certified to sell pharma Ingredients
- Substituted glycerine with cheaper DEG



## CNSC Fortune Way

Beijing, China

Trading company, brokers of glycerine and other products

- “Brokers” do NOT take title (ownership) to goods



## Rasfer International

Barcelona, Spain

Distributor of

Glycerine and other products



# 46 DEAD



## Government of Panama

Manufactures cough/cold medicine using tainted “glycerine”



## Medicom Business Group

Panama

Broker of Glycerine and other products



# HOW COULD THIS HAPPEN?

3. Alteration / adulteration of documents throughout the supply chain

Taixing Glycerine Factory  
Hengxiang, China

Product name is later deciphered  
To mean “glycerine substitute”,  
CoA reads, “99.5% pure”



CNSC Fortune Way  
Beijing, China

Removes manufacturer’s  
name from CoA and sub-  
stitutes its own, “translates”  
to English



Rasfer International  
Barcelona, Spain

Removes CNSC Fortune Way’s  
name from CoA and sub-  
stitutes its own



# 46 DEAD



Government of Panama  
Manufactures cough/cold  
medicine using tainted “glycerine”



Medicom Business Group  
Panama

Improperly changes expiration  
date of material



# HOW COULD THIS HAPPEN?

4. Lack of analytical testing /  
verification of contents



Taixing Glycerine Factory  
Hengxiang, China

Product name is later deciphered  
To mean “glycerine substitute”,  
CoA reads, “99.5% pure”



CNSC Fortune Way  
Beijing, China

No analytical testing could  
be confirmed



Rasfer International  
Barcelona, Spain

No analytical testing /  
Verification of contents  
performed



# 46 DEAD



Government of Panama  
Manufactures cough/cold  
medicine using tainted “glycerine”

**NO ANALYTICAL TESTING / VERI-  
FICATION OF CONTENTS  
PERFORMED!**



Medicom Business Group  
Panama

No analytical testing / verification  
of contents performed



# So what's being done?

## Regarding DEG in Glycerine...

- FDA Issues 2007 Guidance on DEG in Glycerine for Drug Product Manufacturers
  - ◆ Perform drug ID test including DEG limit on every container
  - ◆ Know the supply chain
  - ◆ Perform required testing properly
- Repackers (or others who do not resell in original, sealed manufacturer's packaging) should perform required testing properly
- Compounding pharmacies should either:
  - ◆ Perform required testing properly or
  - ◆ Ensure that such testing was done by a reliable supplier



# Some good news

- The principles in FDA's Guidance on DEG in glycerine are easily transferrable to other excipients

and there's more good news on ...



# The Excipient Supply Chain

- IPEC (International Pharmaceutical Excipients Council) working with:
  - Drug product manufacturers
  - Excipient manufacturers
  - Excipient distributors
  - FDA

on a white paper to determine, document, and verify the complete supply chain history of an excipient.



# Why IPEC?

- FDA does **NOT** (directly) regulate excipients\*!
- IPEC works with FDA on excipient issues. FDA is generous with input and feedback regarding IPEC initiatives

**BUT**

Excipients are covered by guidance documents,  
not regulations

\*FDA regulates excipient *users* who are held responsible for all the ingredients used in their products.



# So what?

“Guidance documents represent the Agency’s (FDA’s) current thinking on a particular subject. They do not create or confer any rights for or on any person and do NOT operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.”\*

**Result:** “possible gray areas”

\*Source: <http://www.fda.gov/cder/guidance/index.htm>



# Some Key Things to Know about the White Paper on Excipient Pedigree

- Attempts to address as many of the issues attributable to failures in the supply chain in the Panama deaths as possible.
- Supplements existing safeguards, protocols, guidances, etc.
- Removes several ambiguities which previously allowed for some “gray areas”
- Still under review as of this writing (early March 2008)



# Important Additional Information

- Excipient manufacturers are expected to follow appropriate GMP's (excipient or cGMP's). ISO:9000 or ISO:9001 certification is NOT sufficient!
- Labeling technical grade (non-GMP) excipients as compendial grade based solely upon conformance to the compendial monograph is NOT acceptable – NO “Testing up”!



# Distributor Responsibilities

- Must comply with IPEC Good Distribution Practices Guide
- Must provide chain of custody records if requested
- Must provide CoA from excipient manufacturer including the manufacturer's identity and producing location, including country\*

\*As set forth in IPEC Certificate of Analysis Guide



# Distributor Responsibilities

- If the distributor repackages from individual packages such as bags or drums
  - That distributor must sample, test, and supply all test results to the user
  - That distributor must also supply the original manufacturer's certificate of analysis
- If the distributor repackages from bulk holding tanks
  - the user should be informed of all commingled sources and lots.
  - The above sampling, testing and documentation requirements apply



# The Distributor as an Asset

- A distributor who specializes in excipients:
  - Is well-versed in supply-chain issues;
  - Stays current on IPEC and FDA guidance
  - COMPLIES with these guidances
  - Helps his/her manufacturers comply with these guidances
  - Educates his/her customers on the guidances
  - Alerts his/her customers to potential pitfalls and/or problems which might occur as a result of issues within the supply chain



# Is your Distributor an **Asset** or a Liability?

Here are some ways to determine whether your excipient distributor is an **asset** or a **liability** when it comes to supply chain integrity.

# Asset or Liability?

## Distributors who are Assets:

- Provide material in original manufacturer **FACTORY-SEALED AND LABELED** packaging if that distributor does not repackage.

## Distributors who are Liabilities:

- May provide material in packaging without seals or manufacturer labels or both

# Asset or Liability?

## Distributors who are Assets:

- Know and can trace and document the supply chain / chain of custody of the material they sell back to the original manufacturer, especially if they have not purchased the product directly from that manufacturer.

## Distributors who are Liabilities:

- Don't understand "what the big deal is about this chain of custody stuff". They may or may not be able to trace back to the original manufacturer.

# Asset or Liability?

## Distributors who are Assets:

- Provide original manufacturer CoA's with every shipment\*

\*As set forth in the IPEC  
Excipient Pedigree White  
Paper (in development)

## Distributors who are Liabilities:

- Obscure or remove the manufacturer's name on the CoA or only provide their own CoA, refusing to provide the original manufacturer CoA

# Asset or Liability?

## Distributors who are Assets:

- If asked, will reveal that they may have purchased from another distributor (NOT a problem if the product is supplied in manufacturer sealed packaging with original CoA)

## Distributors who are Liabilities:

- Do not know or will not reveal the manufacturer of the material

# Asset or Liability?

## Distributors who are Assets:

- Know which of their suppliers produce compendial materials (and thus operate under Excipient GMP's or cGMP's)

## Distributors who are Liabilities:

- Don't know, understand or care that there is a difference between GMP's, Excipient GMP's, and cGMP's

# Asset or Liability?

## Distributors who are Assets:

- Know that if a monograph for a material does not exist in the USP or NF, that material cannot be labeled “USP” or “NF”

## Distributors who are Liabilities:

- Don't know or care what a monograph is and think “USP” or “NF” is just an abbreviation for “really expensive”

# Asset or Liability?

## Distributors who are Assets:

- Work with suppliers they know and/or whose plants they have visited. (Distributors usually do not audit plants - audits are usually conducted by end users, not resellers)

## Distributors who are Liabilities:

- Love to work with cheap, off-shore companies about whom they know little and have never visited. Language and cultural misunderstandings can have deadly results.

# Asset or Liability?

## Distributors who are Assets:

- Are happy to answer customers' questions and provide documentation regarding the traceability and quality of the materials and the integrity of the suppliers they represent

## Distributors who are Liabilities:

- Either don't know or don't want YOU to know about the traceability and quality and/or the integrity (or lack thereof) of the suppliers they represent

# Asset or Liability?

## Distributors who are Assets:

- Can respond to “mock” (or real) recalls, providing you within 1 business day all manufacturer lot numbers of a given material shipped to you within a given period of time

## Distributors who are Liabilities:

- Cannot or will not provide you within even several business days manufacturer lot numbers of a given material shipped to you within a given period of time



Your most important tool in assuring  
distributor supply chain integrity...

?

Ask your distributor  
questions!



# Pharmaceutical Ingredient Supply Chain – A Shared Responsibility!

## Manufacturers and Distributors

Are responsible for assuring that ingredients they supply comply with applicable standards / specifications and are not contaminated or adulterated

## End Users

Are ultimately responsible for the use of appropriate ingredients and assuring ingredient quality at every stage of the supply chain

Courtesy of

Edwin Rivera-Martinez, Chief, Manufacturing Assessment and Preapproval  
Compliance Branch - Division of Manufacturing & Product Quality  
Office of Compliance Center for Drug Evaluation & Research



Make sure YOUR distributors are

**Assets...**

**not**

**Liabilities!**



# Special thanks to...

- Dr. Shaun Clancy, Director of Product Safety & Regulatory Services, Evonik Industries
- Dr. Arthur Falk, IPEC Americas
- Laura Horne and Dwight Mutchler, Mutchler Inc.

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