

# Assuring Drug Safety Thru Supply Chain Security



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# Outline

- **Adulteration Incidents**
  - ❖ **Case Study**
- **Challenges**
- **Solutions**



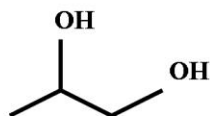
# Economic Adulterations

- **DEG in Glycerin: >788 Deaths since 1937**
  - ❖ Liquid dosage forms
  - ❖ Toothpaste
- **OSCS in Heparin**
- **Melamine Substituted for Protein**
  - ❖ Pet Food
  - ❖ Milk Products

# Adulteration of Excipients



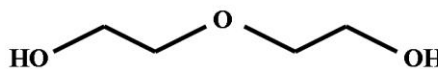
Propylene Glycol



- Light Color
- Slightly Viscous
- Sweet Taste



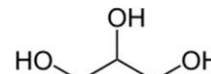
Diethylene Glycol



- Light Color
- Slightly Viscous
- Sweet Taste

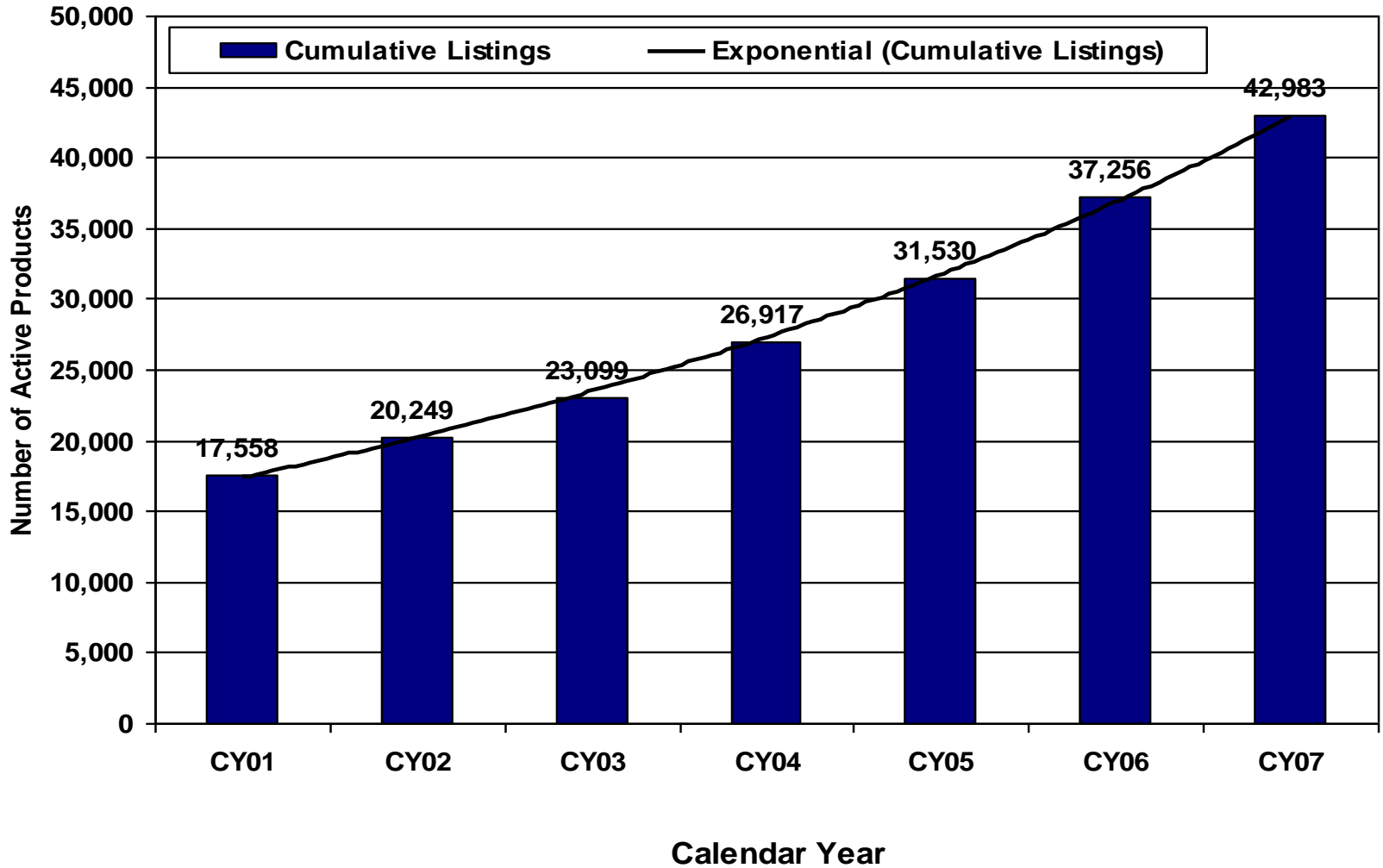


Glycerin



- Light Color
- Slightly Viscous
- Sweet Taste

# Number of Drugs\* Manufactured at Foreign Sites Has More Than Doubled Since 2001



•Finished drugs, intermediates and APIs. Snapshot of Registered Sites' Drugs obtained during 2007

•Data Source: FDA/CDER Drug Registration



# Supplier Qualification-Case Study

- **BASF & ISP concerned about excipient quality from Asian competitors**
  - ❖ Copovidone NF
  - ❖ Crospovidone NF
  - ❖ Povidone USP
- **IPEA contracted to establish testing program**
  - ❖ Commercial packages: BASF, ISP, Nanhang, Boai
  - ❖ Unopened containers sampled under supervision
  - ❖ Blind samples tested against USP by BASF & ISP



# Supplier Qualification-Case Study

- **BASF & ISP**

- ❖ All excipient lots met USP monograph

- **Asian Manufacturer's Copovidone NF**

- 1. Nanhang failed for:**

- Clarity of solution

- Limit of monomers: high

- Content of Copolymerized VA: low

- Nitrogen: high

- 2. Boai lot was good**



# Supplier Qualification-Case Study

- **Asian Manufacturer's Povidone USP**
  1. **K-12 Boai, Aldehydes: high**
  2. **K-17 Boai, K-Value, Residue on Ignition and Aldehydes: high**
  3. **K-17 Nanhang, K-Value and Hydrazine: high**
  4. **K-90 Boai, Vinylpyrrolidone: high**
  5. **K-25 Nanhang, BASF reported Hydrazine: high**
  6. **K-25 Boai met monograph**



# Supplier Qualification-Case Study

- **Asian Manufacturer's Crospovidone NF**
  - 1. BASF reported 2 grades of Boai, Heavy Metals: high**
  - 2. Nanhang met monograph**



# Supplier Qualification-Case Study

- **Potential Impact**

- **❖ Povidone USP**

- **➤ K-Value**

- – Performance issue

- **➤ Aldehydes**

- – Potential impact on API

- **➤ Hydrazine and Vinylpyrrolidone**

- – Suspect carcinogens



# Supplier Qualification-Case Study

- **Potential Impact**

- ❖ **Copovidone NF**

- **Incorrect ratio of vinyl acetate to vinylpyrrolidone**
  - Performance issue

- ❖ **Crospovidone NF**

- **Heavy metals in drug product**

**NOTE: There has been no assessment of either Asian site for conformance to GMP**



# Regulatory Oversight

- Excipients and APIs are components (ingredients) of drugs, and are “drugs” in the FD&C Act (Sec. 501)
- GMP regulations (21 CFR 210/211) apply to the **quality control and use** of components in the manufacture of drug products.
  - ❖ However, these specific regulations do not apply to the **manufacture and distribution of components.**



# Regulatory Oversight

- **Pharmaceutical manufacturer quality systems for assuring component quality are subject to inspection by FDA**
  - ❖ *Supplier selection, qualification, and monitoring*
  - ❖ *Acceptance/rejection of incoming batches*



# FDA Response to Adulteration

- **Conference on Economically Motivated Adulteration (EMA)-June 2009**
- **Enhanced Testing**
  - ❖ **Update USP Identification Tests**
  - ❖ **Require Improved ID Test for each drum of Glycerin**
  - ❖ **Require GC/MS Testing for Melamine in Ingredients**

# Challenges

- **Traceability of ingredients back to the manufacturer**

- ❖ **Distributors**

- Package from bulk
- Repackage to smaller containers
- Relabel

- ❖ **Brokers**

- Relabel

- ❖ **Traders**





# Challenge

- **Should we rely on incoming testing to identify EMA or Counterfeiting? [FDA]**
  - ❖ **Counterfeiting: Deliberately and fraudulently mislabeling (a drug) with respect to its identity or source” [WHO]**

**We always seem to be reacting to the latest incident!**

# Challenges

- Congress considered Country of Origin drug labeling.
- What is the definition of “manufacturer”?
  - ❖ Site where ingredient is produced?
  - ❖ Site where of ingredient final processing?
  - ❖ Site where ingredient is last packaged or repacked?



# Challenges

- 21CFR 211.84(c) allows ingredients from qualified suppliers to be released on COA and limited testing with:
    - ❖ At least one *specific* ID test
    - ❖ Periodic testing to confirm accuracy of COA
- But no explicit requirement to periodically confirm the authenticity of the ingredient manufacturer!

# Solutions

- **Supply Chain Security**
  1. **Qualify the supply chain**
    - A.** Ingredient manufacturer
    - B.** Distribution chain (where applicable)
  2. **Authenticate:**
    - A.** Manufacturer
    - B.** COA



# Solutions

- **Assess ingredient manufacturer using IPEC *Excipient Information Package***
  - 1. Product Regulatory Datasheet**
  - 2. Site Quality Overview**
  - 3. Site Security and Supply Chain Overview**
  - ❖ **EIP provides basic information**
    - **Additional Details Upon Request**
  - ❖ **EIP under document control**

# Solutions

- Assess ingredient manufacturer
  - ❖ Site Audit
    - 2<sup>nd</sup> Party Audit or
    - Qualified 3<sup>rd</sup> Party Audit
  - ❖ Certified to IPEC-PQG *Excipient GMP*
    - ANSI accreditation of IPEA
  - ❖ Expectations
    - Ingredient Quality meets Compendia
    - GMP conforming Quality System

# Solutions

- **Assess Distribution**
  - ❖ **Distributor Site Audit**
    - 2<sup>nd</sup> Party Audit or
    - Qualified 3<sup>rd</sup> Party Audit
    - Certification to Excipient GDP
  - ❖ **Expectations**
    - Compliant packaging and sampling
    - Proper warehouse and distribution



# Solutions

- **Assess Distribution**
  - ❖ **Broker/Trader Audit**
    - **Assure:**
      - i.** Consistent manufacturing source
      - ii.** Notification of significant change
- **Assess Manufacturer**
  - ❖ **Site Audit**
  - ❖ **Certification**



# Solutions

- **Expectation: Pharmaceutical Manufacturers audit all API suppliers**
- **Impact: Each audit cycle**
  - **Pharmaceutical Manufacturer**
    - Tens of sites to audit globally
  - **API Supplier**
    - Host ~ 1-10 site audits!



# Solutions

- **Excipient Manufacturer Assessment**
  - ❖ **Ideal: Pharmaceutical company audit all excipient suppliers**
  - ❖ **Impact: Each audit cycle**
    - **Pharmaceutical Manufacturer**
      - Pfizer reported 4,000 suppliers after '03 merger
    - **Excipient Supplier (ISP)**
      - 300+ pharmaceutical audits at ISP Texas City!
      - Other industries also audit!



# Solutions

- **Manufacturer Assessment**

- **❖ Third-Party Audit**

- **➤ IPEA**

- IPEA qualified contract auditors
- Report sharing or Certification

- **➤ R<sub>X</sub>-360**

- Sharing of reports by pharma auditors

- **➤ USP Verified**

- Certify ingredient quality

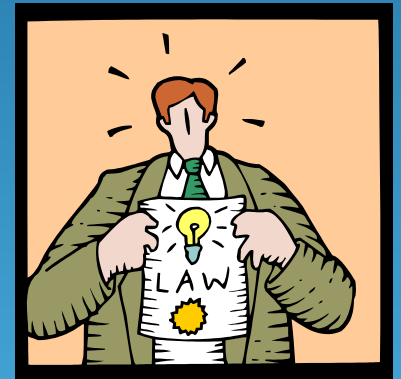
# Solution

- **FDA: Certify Conformance to Excipient GMP**
- **IPEA:**
  - ❖ Accreditation by ANSI
  - ❖ IPEC-PQG Excipient GMP
  - ❖ Comprehensive excipient site audit
- **FDA to accept certification**
  - ❖ Pending legislation may require site inspection



# Solution

- **American National Standard**
  - ❖ **NSF Joint Committee on Pharmaceutical Excipient (NSF 363)**
    - **Develop Excipient GMP Standard based on IPEC-PQG GMP guide**
  - ❖ **Certification to U.S. Standard for Excipient GMP**
  - ❖ **FDA can adopt Excipient GMP Standard as regulatory requirement**





# Solutions

- **Authenticate the Manufacturer**

- ❖ **Direct from Manufacturer**

- **Confirm through Bill of Lading**

- ❖ **Distributor, Broker, or Trader**

- **Trace paperwork back to Manufacturer**

**Periodically send Bill of Lading or COA back to manufacturer**



# Solutions

- **Authenticate COA**

- ❖ **Proper COA Content**

*IPEC-Americas Certificate of Analysis Guide*

- ❖ **Verify COA**

- **Periodically perform all specification testing**
  - Identify assignable cause for statistically significant differences
- **Return COA to Manufacturer for authentication**

# Solutions

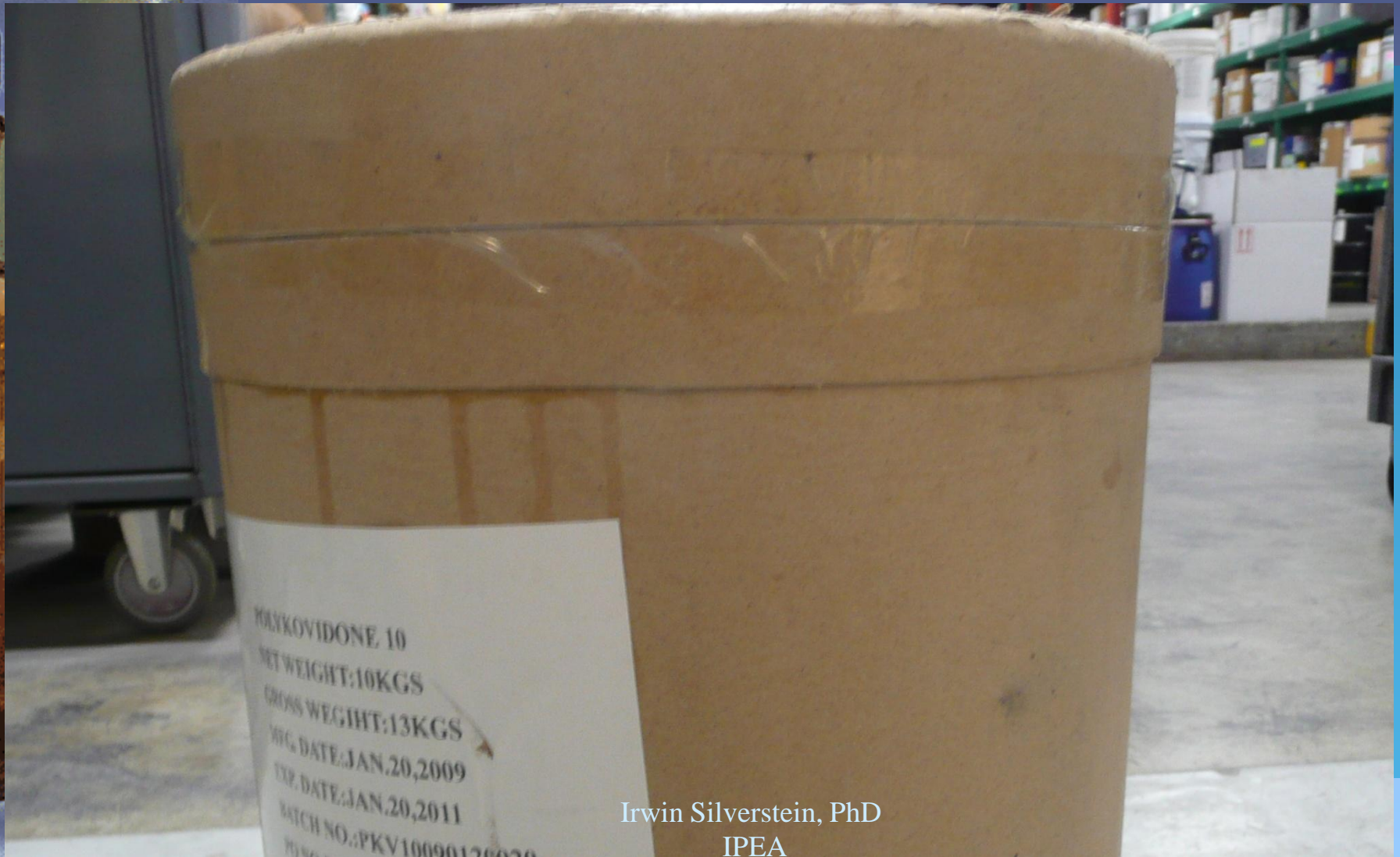
- **Supply Chain Security**
  - 3. Release of Ingredients**
    - A. Confirm Packaging**
      - i. Tamper-Evident Seal**
        - Unbroken and matches manufacturer's photograph
      - ii. Package**
        - Undamaged and matches manufacturer's photograph
      - iii. Label**
        - Matches manufacturer's photograph

# BASF Tamper-Evident Seal



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# Tamper-Evident Seal?



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# Correct Package?



# Correct Package?

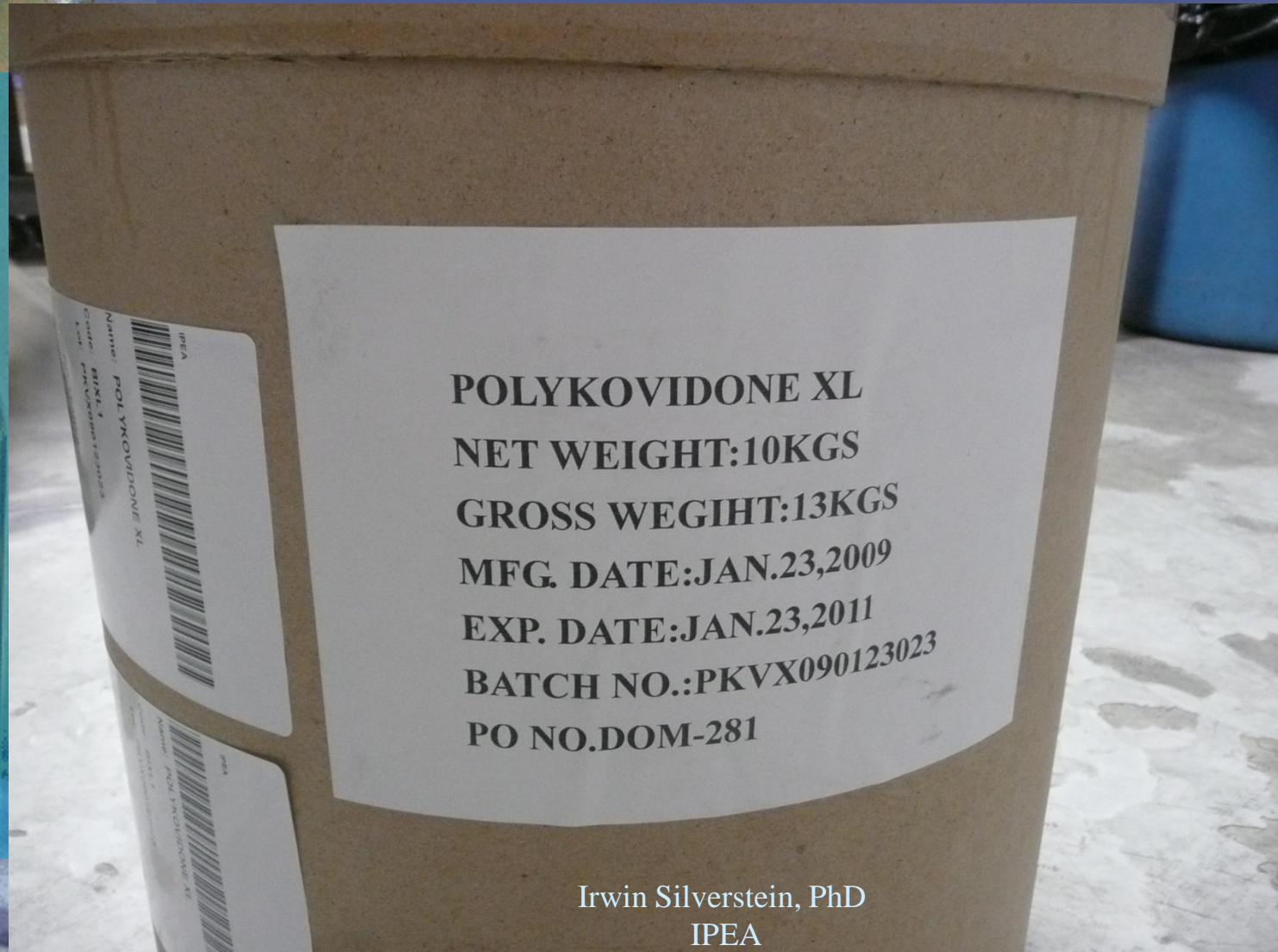


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# Correct Labeling?



# Correct Labeling?



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# Solutions

- **Supply Chain Security**

- 3. Release of Ingredients**

- B. Ingredient Identity**

- Sample each container and perform compendial identity test

- C. Ingredient Quality**

- Verify data on authenticated COA conforms to monograph/specification or
      - Perform all specification tests



# Solutions

- *IPEC Quality Agreement Guide and Template*
  - ❖ **Establish Quality responsibilities**
    - GMP conformance
    - Compendial monograph or specification
    - Change notification
    - Documentation and records
  - ❖ **Establish Quality activities**
    - Site audit
    - Complaint, deviation, and OOS handling



# IPEC Guides

- **Good Manufacturing Practices (2006)**
- **GMP Audit (2007)**
- **Good Distribution Practices (2006)**
- **GDP Audit (in progress)**
- **Certificate of Analysis (2000)**
- **Significant Change (2005)**
- **Excipient Information Package (2005)**
- **Qualification of Excipients for Use in Pharmaceuticals (2008)**



# IPEC Guides

- **Quality Agreement (2009)**
- **Excipient Composition (2009)**
- **Excipient Stability (2010)**

## **Under Development:**

- **QbD Product Development**
- **Excipient Validation**

# CONTACT ME

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