Supply Chain Management

Supply Chain

- The network of retailers, distributors, transporters, storage facilities and suppliers beginning with the supplier of materials or components, extending through a manufacturing process to the distributor and retailer, and ultimately to the consumer
- The manufacture of a drug relies on processes that are both outside of our direct control as well as processes that we can directly control
- This presentation focuses on those activities that we cannot directly control

Concerns

- Wrong material on receipt
- Incorrect quality on receipt
- Deterioration after receipt

WRONG MATERIAL

- Deliberate fraud (intentional contamination, counterfeiting, "cutting corners")
- Mislabeling
- Wrong consignment

INCORRECT QUALITY

- Deliberate fraud
- Mislabeling
- Poor QC checking
- Misunderstanding of quality requirements
- Material deterioration during transit
- Contamination during transit

Deterioration

- Incorrect storage conditions at supplier site affecting stability
- Multiple short term exposures beyond storage limits during transit
- Undetected contamination resulting in deterioration over time

DELIBERATE FRAUD

- Economically motivated adulteration
- Fraudulent, intentional substitution or addition of a substance in a product for the purpose of increasing the apparent value of the product or reducing the cost of its production, i.e., for economic gain.
- EMA includes dilution of products with increased quantities of an already present substance (e.g., increasing inactive ingredients of a drug with a resulting reduction in strength of the finished product) to the extent that such dilution poses a known or possible health risk to consumers, as well as the addition or substitution of substances in order to mask dilution.

DELIBERATE FRAUD

- Price of a product, the availability of cheap and risky substitute ingredients, and the ease with which a test for impurities can be defeated.
  - Oversulphated Chonditin Sulphate
  - Melamine
  - Diethylene glycol

DIETHYLENE GLYCOL

- Adulteration of glycerine, an ingredient in cough syrup and other drugs, with diethylene glycol (DEG)
- 1996, contaminated acetaminophen syrup - deaths of more than 70 children in Haiti
- 2006, tainted cough syrup - dozens of deaths in Panama
- Between 2008 and 2009 contaminated teething syrup - more than 50 children died in Nigeria

MELAMINE

- Melamine and melamine-related compounds were found in products labeled as wheat gluten and rice protein concentrate
- Contaminants were added to the products to increase the apparent protein content in those products
- Formation of crystals in the kidneys, resulting in kidney damage
- 150 brands of pet food recalled

MELAMINE

- Melamine was added to diluted milk in order to increase measured nitrogen levels (indicators of protein content)
- 300,000 Chinese infants were made sick by the contaminated infant formula and it caused six infant deaths

Oversulphated Chonditin Sulphate

- Adverse reactions in paediatric dialysis patients in the U.S.
- 150 U.S. deaths occurring between January 1, 2007 and May 31,2008 in USA
- Baxter voluntarily recalled all of its heparin products
- Oversulphated Chonditin Sulphate found in Heparin API

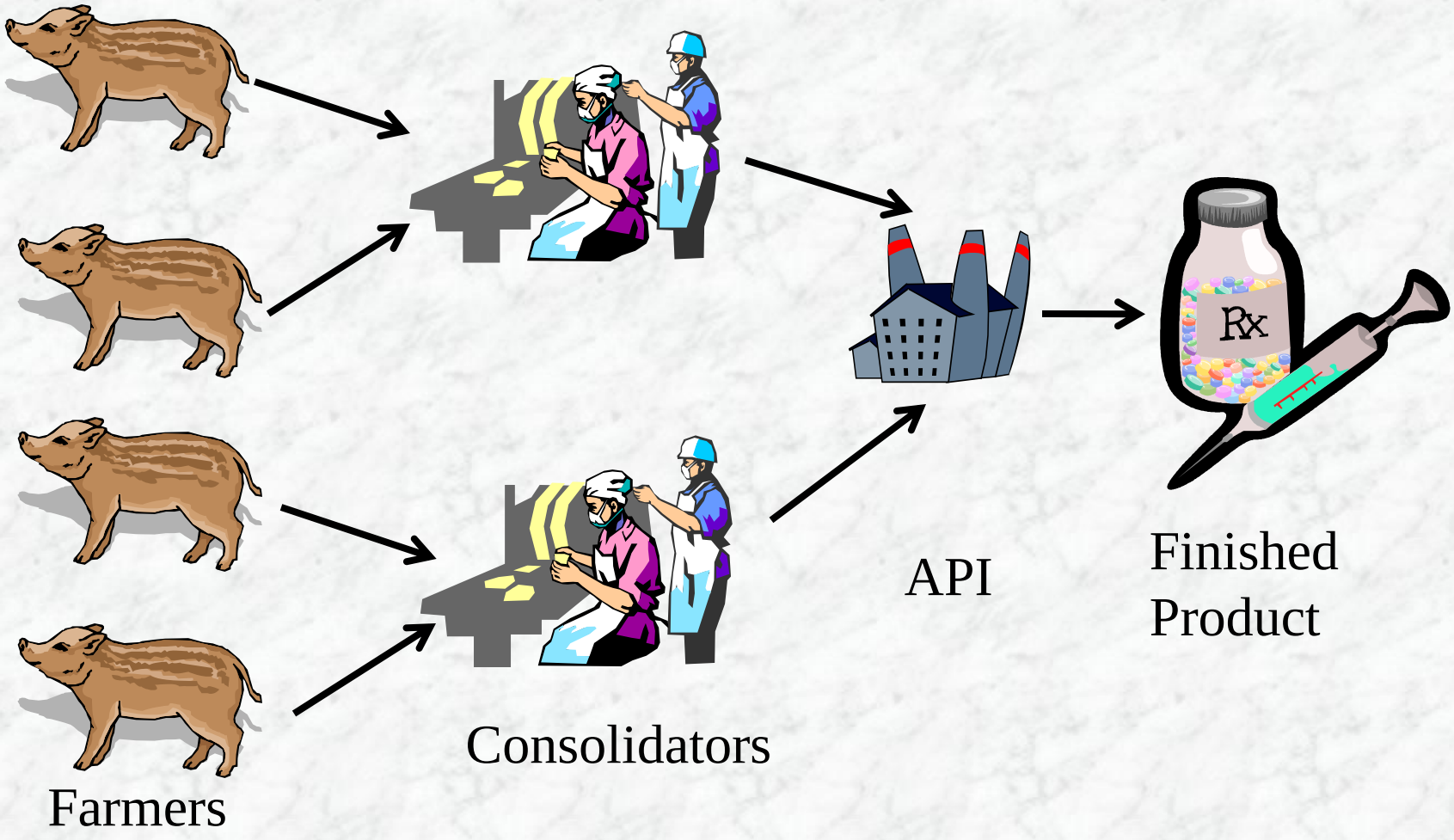
Oversulphated Chonditin Sulphate

- The raw ingredient for heparin is derived from the mucosal tissues of animals, specifically the intestines of pigs and the lungs of cattle.
  In this case, the raw ingredient came from pigs but it was doctored with chondroitin sulphate, made from animal cartilage . When chondroitin sulphate is altered, or “oversulphated,” it mimics the blood-thinning action of heparin.
  Oversulphated Chonditin Sulphate is not a naturally occurring compound

Oversulphated Chonditin Sulphate

- The contamination did not occur naturally or as a result of the manufacturing process.
  The manufacturer of the finished drug buys the API from a the API manufacturer that purchases crude heparin from brokers who buy from family farmers. The doctoring of the drug appears to have been done by brokers.
- At least 10 companies involved in upstream supply chain

OVERSULPHATED CHONDITIN SULPHATE



Oversulphated Chonditin Sulphate

- Oversulphated Chonditin Sulphate entered the supply chain during a period when pig herds were greatly diminished due to a widespread outbreak of swine virus

- To protect the supply chain, regulatory activity should occur at multiple levels:
  - Enforcement of GMP and related standards
  - Compliance reviews, including inspections of manufacturing facilities
  - Review of pharmaceutical imports at the point of entry to the importing country
  - Oversight of pharmaceutical distribution within the importing country

- Focus on prevention,
- Improve scientific and analytic capabilities,
- Expand risk based inspection

Focus on prevention

- Implement Quality Management Systems
  - A QMS approach addresses the safety, quality, and security responsibilities of all persons who manufacture products, including starting materials
  - Manufacturers are accountable for assessing the hazards introduced by operations of their suppliers and consignees
  - Monitoring for problems before they result in harm to consumers
  - Taking swift corrective actions where required

Focus on prevention

- Learn more about your suppliers
- Use third parties if required to confirm suppliers meet your requirements
- Train and educate your suppliers

Improve Scientific and Analytic capabilities

- Develop methods for tracking and tracing supplies
- Develop methods for improved testing of samples and incoming goods

Risk based inspection

- Use Quality Risk Management techniques to focus resources on highest risk areas
- US FDA now using Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting - PREDICT
- PREDICT retrieves risk information from public sources and queries FDA databases to discover patterns. It considers the likelihood that individual shipments are adulterated, misbranded, or otherwise in violation of the law and will generate a numerical, risk-based score.

COUNTERFEITING

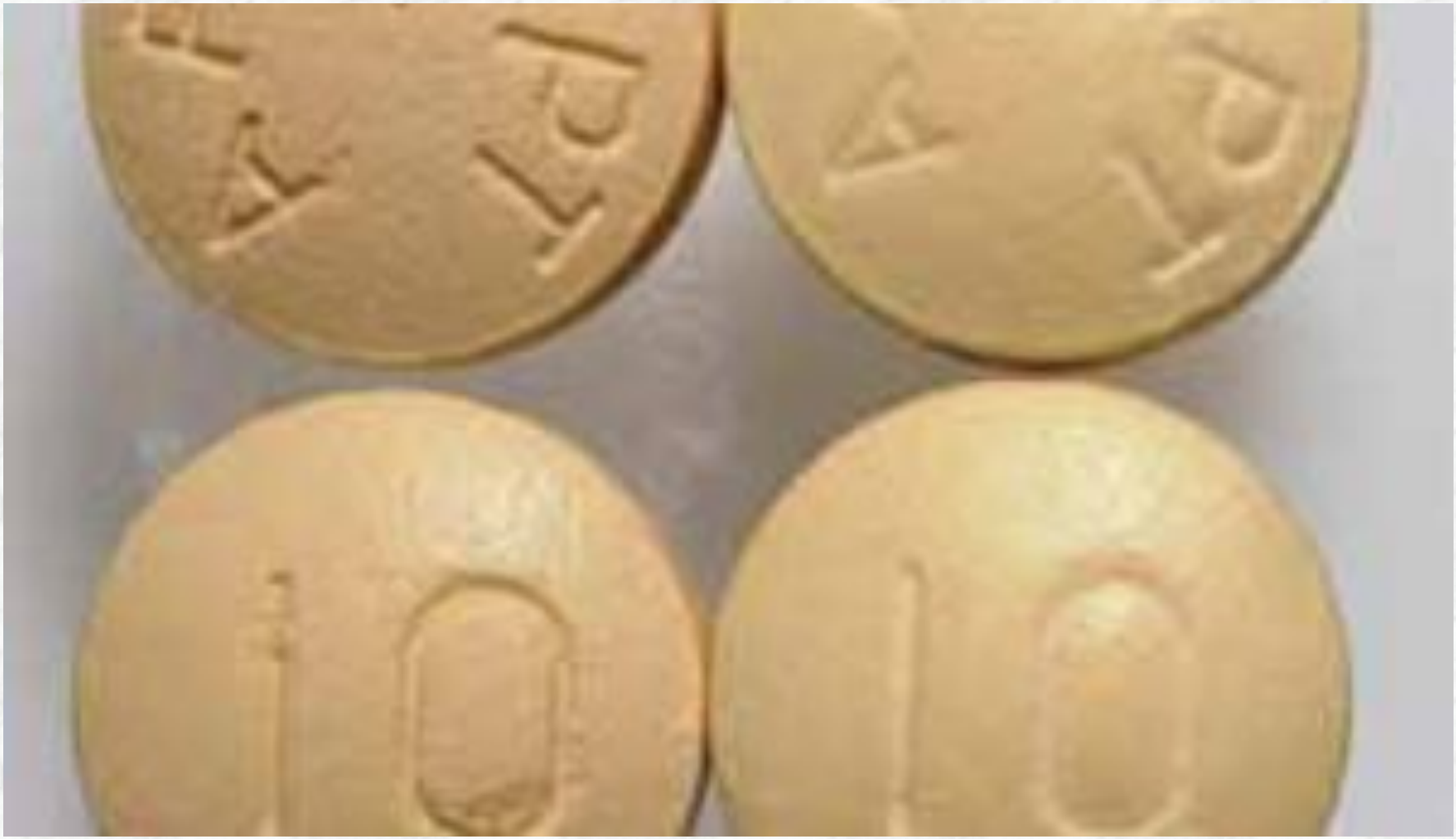
- 2006, James George (Lifeway Pharmacy) - 2 years prison
- In 2007, Mohammad Gawasmmah and Fayez Aledous (RU Sophisticated)- 20 months prison
- In 2009, Richard Fletcher (Internet site selling the drugs) - 12 months in prison
- In 2012, Luis Angel Garcia Torres - sentenced to 21 months in prison

Lu “Kevin” Xu

- 1971, born in Nanjing,
- Worked for Sinochem, then joined Everlasting Business & Industry Corporation in 2002.
- Responsible for division called Orient Pacific International
- In 2003, offered a 12-page list of generic antibiotics, cancer drugs, and biologics on the company’s website, Achpharm.com

Lu "Kevin" Xu

- In 2005, the avian flu H5N1 hit Asia and demand for Tamiflu soared
- May 2006 the Swiss regulatory agency issued a warning about counterfeit Tamiflu
- August 2006, a Turkish undercover agent who was working for Eli Lilly bought samples of a drug directly from Xu that matched some of the fake Tamiflu. She had other drugs shipped to her from Xu including Cialis, Aricept, Zyprexa, and Plavix



Lu “Kevin” Xu

- Xu received more than $1.5 million from selling counterfeit pharmaceuticals globally during 2007

Lu "Kevin" Xu

- Xu was arrested and subsequently sentenced August 2008 to 6½ years in prison for distributing counterfeit and misbranded pharmaceuticals in the United States
- In addition to his 6½-year prison term, the court ordered Xu to pay $1,286,060 in restitution ($128,363 to Pfizer Pharmaceuticals, and $1,157,697 to Eli Lilly Pharmaceutical Company)

Deterioration

- Storage – Verify that at every stage in the supply chain that:
  - Warehouses have been temperature mapped
  - Where humidity can affect the material or its packaging –humidity mapping has been perform
  - Temperature and humidity are being monitored and records kept and that there is a mechanism for alerting and managing OOS conditions
  - Equipment (cold rooms, cool rooms, freezers, refrigerators) has been qualified and is being re-qualified annually

Deterioration

- Storage – Verify that at every stage in the supply chain that:
  - Temperature and humidity monitoring and controlling instruments were calibrated at least annually
  - Records show equipment has been maintained
  - Procedures define any zones that should not be used for storage (e.g. near a blower or cooling coil)

DETERIORATION

- Shipping – Verify that at every stage in the supply chain that:
  - There are procedures for shipping and that records indicate they are followed
  - For temperature sensitive products shipping validation has been performed
  - Packaging and use of refrigerants have been evaluated for distribution systems used
  - The articles resistance to repetitive short term excursions outside defined storage limits has been tested

DETERIORATION

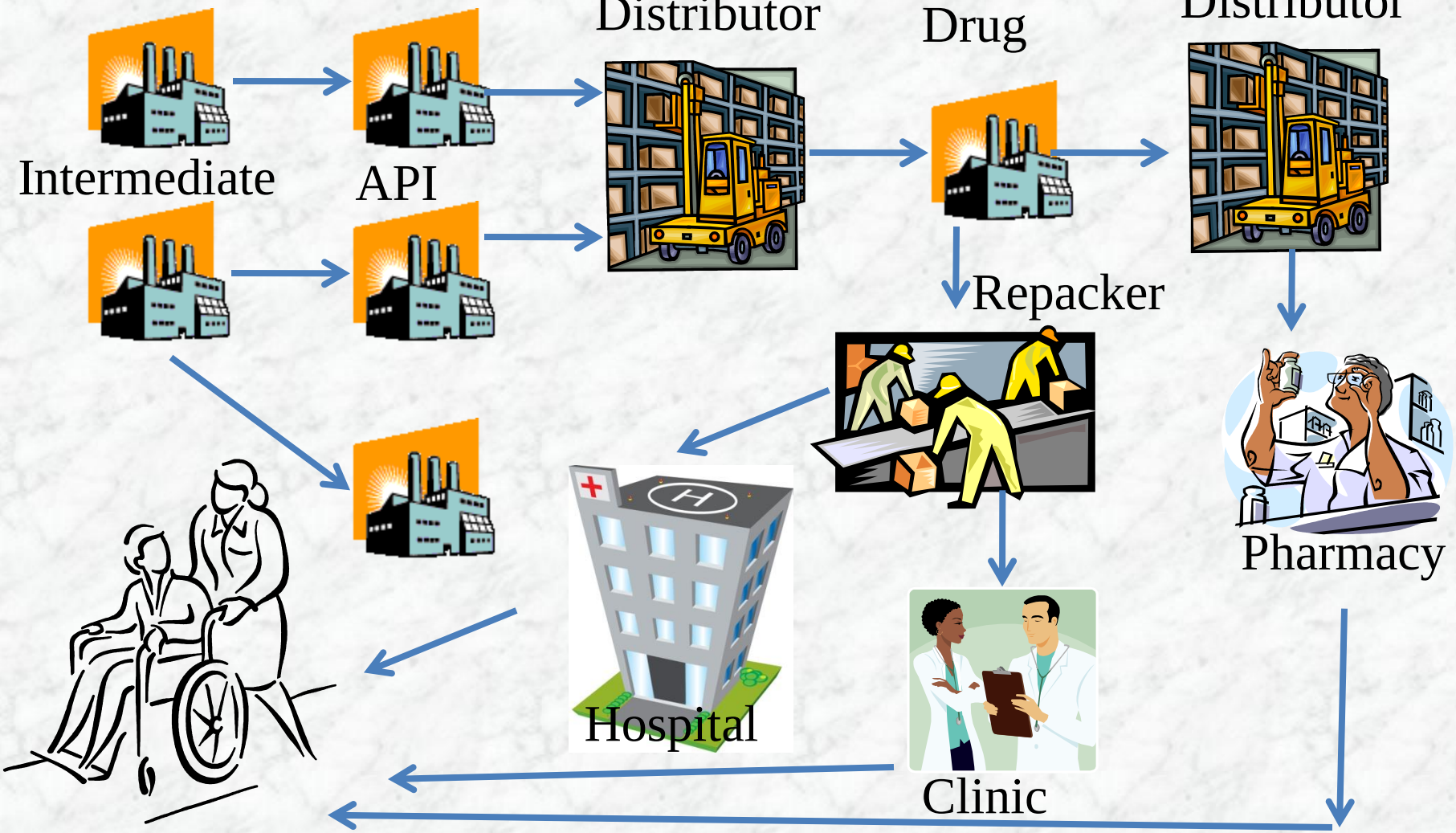
- Others – Verify that at every stage in the supply chain that:
  - There are procedures and records to show that materials upon receipt are transferred into proper storage within 2hrs.
  - Delivery document show that the Pharmacopeial articles have not been subjected to any delays during shipment that could result in exposure of the article to undesirable conditions

DETERIORATION

- Others – Verify that at every stage in the supply chain that:
  - Cold trucks if used have had storage environment qualification
  - Delivery and warehouse staff have had appropriate training
  - That there are procedures and storages defined for quarantine, reject and passed material

TRAQUE

SUPPLY CHAIN



PICs Expectations

- Approved manufacturers and supplier listings must be in place, current and readily available
- Periodic re-evaluation of each supplier's status.
- Addresses of manufacturing sites should be requested to be displayed on Certificate of Analysis and/or product containers to allow comparison to the approved list; this is particularly important where API manufacturers may have more than one API facility.

PICs Expectations

- Procurement systems must only allow purchase and receipt of APIs that are approved or undergoing controlled assessment (through change control)
- Supply with API manufacturers/suppliers must unequivocally identify the approved site(s) of manufacture.

PICs Expectations

- The entire supply chain for a supplied API must be defined and approved by the Manufacturing Authorization holder. This must include all steps from input of the starting material to the API process through intermediate stages of manufacture and any subsequent Agents, Brokers, Traders, Distributors, Repackers and Relabellers

PICs Expectations

- The precise role and responsibilities of any Agents, Brokers, Traders, Distributors, Repackers and Relabellers must be understood
- The temperature conditions during transportation must be confirmed as appropriate to the needs of the particular API or intermediate.

PICs Expectations

- It is expected that in order to approve an API source an audit(s) will have been conducted by or on behalf of the Manufacturing Authorization holder.
- All steps in the supply chain of the active substances in use by a Manufacturing Authorization holder will have been audited, including those in third countries, by or on behalf of the Manufacturing Authorization holder

PICs Expectations

- A Technical Agreement (Supply/Quality Agreement) must be in place with the API manufacturer/supplier(s).

Thank You

Questions?