



# **Regulatory Perspectives on Supply Chain Control and Outsourcing**

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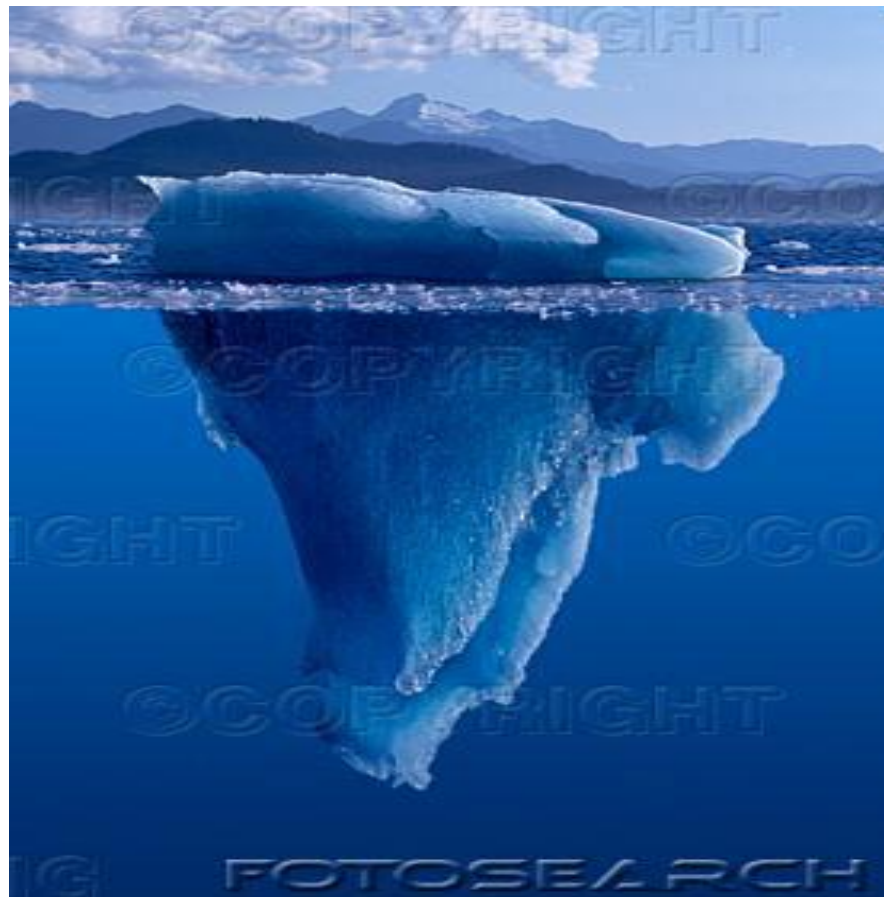
# Outline

- Supply Chains
  - Globalization
  - CMOs
  - Drug Components
- CGMP Requirements
- Management Responsibility in Quality Management
- Case Studies

## Today's Common Terminology Reflects Globalized Drug Manufacturing

- Outsourcing
- Importing
- Contracting
- Strategic Sourcing
- Supply Chain
  - Distributors
  - Traders
  - Brokers
  - Repackaging and relabeling

# What is the Magnitude of the Risk?



## Regulatory Requirements Pertaining to Contract Manufacturing Relationships

- Primary manufacturer is responsible
  - 21 CFR 200.10(b)
    - The Food and Drug Administration ..... regards extramural facilities as an extension of the manufacturer's own facility.
  - 21 CFR 211.22(a)
    - Quality Control Unit (QCU) is ultimately responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company

## Contractor and Contract Giver are Liable for Adulterated Product

- The Federal FD&C Act (the Act) states that a drug is considered to be adulterated if the drug is not manufactured in conformance with CGMP [21 U.S.C. 351(a)(2)(B) ]
  - Applies to finished drug products, drug components and all sites under contract to manufacture or supply drugs and drug components
- Manufacturer and private label distributor can both be held liable
  - Introducing or causing the introduction of adulterated drugs into interstate commerce is prohibited. [21 U.S.C. 301]

## ICH Q9 - Quality Risk Management Provides Guidance Regarding Outsourcing

- Members of the supply chain are partners
  - Play a role in determining success
- Q9 recommends a comprehensive evaluation of suppliers and contract manufacturers
  - including auditing and implementing supplier quality agreements
- A manufacturer's quality system will drive the management of outsourced processes and entities (risk and quality management)

## ICH Q9 - Application of Quality Risk Management to Making Sourcing Decisions

- How does one quantify the true cost of ownership in a sourcing relationship?
  - What are the worst case scenarios?
  - Will there be some learning curve that dictates a need to be present at contractor?
  
- How well do the supplier's quality systems assure product quality?
  - Systems often look good on paper
  - Trust and confidence are built gradually

# ICH Q10 - Pharmaceutical Quality Systems Guidance Regarding Outsourcing

- Control and review of all outsourcing activities is an element of a manufacturer's pharmaceutical quality system.
- Manufacturer is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials.
- A manufacturer should have adequate procedures for auditing and qualifying facilities prior to outsourcing and throughout the process and for contract management and supervision.

# Supplier Management

## Qualification of Suppliers

- Qualification is part of a lifecycle approach to supplier management
  - Unlikely that any one approach can possibly cover all qualification scenarios
- Lifecycle includes
  - Prospective supplier selection
  - Qualification activities\*
  - Supplier approval
  - Maintenance of qualified status of supplier

# Importance of Having Management Support

- Makes change happen
- Manages risk
- Determines resource allocation
- Develops high level plans
- Provides visionary leadership
- Reaps rewards for success
- Owns responsibility for failure

# Regulatory Requirements Pertaining to Acceptance of Incoming Drug Components

- Appropriate written specifications shall be established and each incoming batch tested accordingly to assure identity, purity, quality
- In lieu of testing vendor CoA data may be used provided
  - At least one specific ID test is performed
  - Reliability of CoA data is validated periodically
- Many weaknesses in approaches taken to “demonstrate compliance”

## Q7 - GMP Applicable to Starting Materials for API Manufacturing

- Supplier qualification
  - Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials (including maintenance of status).
- Traceability to original manufacturer
  - If the supplier (of a critical material) is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or API manufacturer.
- Use of data from supplier CoA in lieu of testing
  - If manufacturer has a system to evaluate suppliers.
    - CoA use depends on having traceability to qualified supplier

# Good Communication is Essential

- Applies to management of contractors and suppliers
- Activities involving good communication
  - Investigations of nonconformance and complaints from market
  - Change management
  - Supplies of excipients and packaging and ancillary materials coming into contact with or in the vicinity of your product or starting materials are not to be overlooked (see TBA example)
- Communication ground rules should be established in a formal quality agreement

# TBA Contamination

- Undiagnosed complaints about moldy or musty odor in products accumulated for over a year
  - Some of the complaints about odor included reports of GI disturbance
- Roughly 1 year after complaints began 2,4,6 - Tribromoanisole (TBA) was detected at ppb levels in products as the source of the odor
- Widespread, persistent contamination could not be ruled out and eventually as complaints continued to trickle in dozens of products were recalled

# What Apparently Happened

- TBA was traced to plastic bottles
  - and ultimately to treated wood used to manufacture pallets on which the bottles were stored at a contract packaging site
- The reported root cause was migration
  - after formation and within a confined headspace, TBA was able to migrate from wood, through plastic liners, and adsorb to bottles, and subsequently to tablets in the bottles

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm192869.htm>

# What Lessons Can Be Gleaned

- Who would have thought wooden pallets could contaminate drugs?
- Don't overlook
  - anything that potentially comes into contact with your product
  - any part of the supply chain!
  - asking the right questions during supplier qualification

## Numerous Deaths Have Been Traced to Contaminated Ingredients

- Glycerin/Propylene Glycol (DEG substitution)
- Heparin (OSCS substitution)
- Crude Protein (Melamine substitution)
  - Pet foods
  - Milk-derived food ingredients
    - Baby formula

# Tragedies Involving Contaminated Ingredients

## What went wrong?

- There was a complete lack of traceability for excipients
  - Cannot identify root cause
  - Cannot determine where a problem starts
  - Cannot fix and assure it won't happen again
- Acceptance was based largely upon a piece of paper purporting quality
  - Little or no testing was performed
  - Test methods that were or would have been performed were unable to detect or signal adulteration

# Globalized Supply Chains for Drug Components Tend to be Expansive and Complex

- APIs and Excipients
  - Chemical starting materials
  - Crude raw materials
- Packaging materials
- Contract manufacturers and packagers
- Storage sites
- Transportation companies
- Distributors
  - Repackaging and relabeling

## Ease With Which Bad Actors Can Infiltrate Drug Component Supply Chain

- Lack of management support
  - lack of basic knowledge about suppliers (all members) and how ingredients are derived
- Whenever shortcomings of analytical methods and lack of attention present opportunity
  - Excessive reliance on specifications employing outdated technology
    - purity testing minimally capable of signaling potential quality issues
    - ID test can give false positive
  - Excessive reliance on CoA

# Knowledge Enables Prevention

- Qualify entire supply chain
  - Audits (qualified 3<sup>rd</sup> parties are OK)
  - Certification and accreditation (accredited 3<sup>rd</sup> party)
  - Starting materials are part of supply chains
- Secure the entire supply chain
  - Tamper evident seals
  - Supply chain stewardship
- Know the distribution routes
- Know the origin of starting materials

# Detection Confirms Knowledge

- Tools to enable verification of known origin and route
  - Traceability (Pedigrees/Tracking Devices)
  - Photo libraries for incoming drug components
  - Use identity and purity testing as a means to verify quality and security
    - Purity profile of incoming batch can be related to the known purity (compositional) profile
    - Can be useful for testing compositionally diverse substances such as extracts, excipients

## As More Problems Are Traced to Management of Supply Chains What Modifications to FDA's Strategy Might Result?

- FDA recently issued a WL to a contractor in which all firms that are clients of the contractor were copied.
  - Reinforces the fact that the primary manufacturer is responsible for contractors (extramural facilities) according to 21 CFR 200.10(b)
  - Virtual companies also can cause the introduction of drugs into interstate commerce
- More recognition that quality agreements are important to establish rules for communication and each party's responsibilities

# Closing Remarks

- Knowledge is a basis toward building assurance
  - Basis for sound risk management
- Monitoring (testing, examination, auditing) is a route toward building assurance
  - Trust but verify

# Contact Information

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- Subject Contacts:

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm096102.htm>

- Questions & Answers on Drug CGMP:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124740.htm>

