

How Excipient GMP Certification Enhances Patient Safety

Presentation Outline

- Recent Issues with Ingredients
- Case Study of Substandard Excipients
- Current Regulatory Climate
- Assuring Conformance to GMP
- ANSI Accredited Excipient GMP Certification
- Supplier Qualification
- FDASIA and Excipients
- European Falsified Medicines Directive

FDA: Component Adulteration

- **1990-2006** DEG in 'glycerin'
 - ❖ Panama, India, Haiti, Argentina, Bangladesh, and Nigeria
- **2008-2009** DEG in glycerin in teething gel
- **2007** DEG in toothpaste
- **2007** Melamine in wheat gluten (pet food)
- **2008** Melamine in milk products and infant formula
- **2008** Heparin –OSCS contaminant

Recent Component Adulteration

- **2011** Phthalates in components
- **2011** Radiation in components
- **2012** FDA concern for glycerin derived from Jatropha
- **2012** Gelatin capsules from tanning by-product



Supplier Qualification-Case Study

- BASF & ISP concerned about excipient quality from Asian manufacturers
 - ❖ 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 Vinyl Pyrrolidone
 - Suspect carcinogens

Supplier Qualification-Case Study

- Potential Impact
 - ❖ Copovidone NF
 - Incorrect ratio of Vinyl Acetate to Vinyl Pyrrolidone
 - Performance issue
 - ❖ Crospovidone NF
 - Heavy metals in drug product

Pharmaceutical Technology October 2009, *The Case for Supplier Qualification*

Supplier Qualification-Case Study

- Conclusions
 - ❖ There has been no assessment of either Asian site for conformance to GMP
- FDA Action
 - ❖ Found Boai Cropsvidone peroxide was ~1,600ppm
 - ❖ Issued import alert in November 2010 for Boai Povidone and analogs
- Demonstrates risk in not performing site assessment of suppliers

BASF has noted that generic drugs produced in China and other countries continue to use such materials!!!

Straining FDA Resources

- Over 80% of API produced outside U.S.
 - ❖ Unknown percentage of imported excipient
- Most drug manufacturing facilities not in U.S.
 - ❖ Number of facilities is growing
 - ❖ “Shadow” firms
- Shipments outside import system
 - ❖ Rogue wholesalers / brokers
 - ❖ Unregistered firms

U.S Regulations

- Food, Drug, and Cosmetic Act
 - ❖ Components of drugs and drug products are drugs [section 201(g)(1)(d)]
 - ❖ Drugs (components and drug products) must be manufactured in conformance with current good manufacturing practice [section 501(a)(2)(B)]
 - ❖ A drug whose name appears in an official compendium, must meet the standards set forth in the official compendium [section 501(b)]

FDA 'Guiding' Role in Corporate Responsibility

FDA seeks to help industry be responsible through the development of standards and best practices

- Work with industry to set standards
- Inform industry of risks and ways to address them
- Where possible, ease the burden of responsible firms

National Technology Transfer and Advancement Act (1996)

- NIST to coordinate Federal, State and local standardization and conformity assessment activities
- Agencies adopt private sector standards, particularly those developed by standards developing organizations, wherever possible, in lieu of creating proprietary, non-consensus standards
- Goal is to reduce unnecessary government standards that create confusion and add expense for compliance

OMB Circular A119 (1993)

- “Federal Participation in the Development and Use of Voluntary Consensus Standards and in Conformity Assessment Activities”
- Establishes policies for Federal use and participation in consensus standards and on conformity assessment activities
 - ❖ Revised in 1998 to achieve consistency with NTTAA terminology

FDA “Work to Set Standards”

- NSF363
 - ❖ American National Standard: Excipient GMP
- Good Distribution Practices
- Supply Chain Security

FDA “Ease the Burden”

- Ensure poor practices are not rewarded
- Increased presence through collaboration
 - ❖ ANSI Accredited Excipient GMP Conformance Certification
- “Swift, aggressive, and effective” enforcement action when needed

FDA “Component Control Improvements”

- Known supply chain
 - ❖ Original manufacturer and subsequent handlers
 - ❖ Audit original manufacturer
- Test each container in each shipment until...
- Require Tamper-Evident packaging
- Notify FDA of contaminated shipments/lots
- Use only components recognized as safe for their intended use or listed in an approved application

Assuring Conformance to GMP

- **Expectation:** Audit all excipient suppliers
- **Impact:** Each audit cycle
 - ❖ **Pharmaceutical Manufacturer**
 - Hundreds to thousands of sites to audit globally
 - Pfizer reported 4,000 suppliers after 2003 mergers
 - ❖ **Excipient Supplier (Ashland-Texas City)**
 - Host over 300 pharmaceutical audits at facility!
 - Doesn't include purchases through distributors
 - Host audits for customers in other markets
- **Reality:** One-day Site Audit for key customers



Excipient GMP Conformance

- Certify substantial Conformance to Excipient GMP
 - ❖ IPEC-PQG Excipient GMP
 - ❖ Forthcoming ANSI Standard
- FDA urged IPEA to certify site conformance to Excipient GMP
 - ❖ Accredited by ANSI
 - Conform to ISO/IEC Guide 65



Excipient GMP Certification

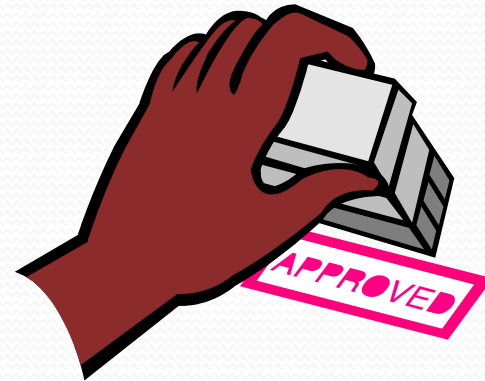
- Comprehensive Site Audit to Excipient GMPs
 - ❖ Minimum 2-days, 2 auditors, single excipient
- Auditor Training
 - ❖ Relevant education and experience
 - Excipient auditing preferred
 - API accepted
 - ❖ Excipient audit experience: 1-day workshop
 - ❖ Otherwise 3-day IPEA Excipient GMP Audit Workshop

Excipient GMP Certification

- Auditor

Qualification:

- ❖ Supervised audit
 - Observation skills
 - Report writing
- ❖ Approval by both IPEA CEO and COO



Excipient GMP Certification

- Report Review
 - ❖ Applicant for factual accuracy
 - ❖ IPEA for findings, ratings, and thoroughness
- Certification Board Review and Approval
 - ❖ 4 Independent Qualified and trained Experts review:
 - Application for scope,
 - Audit Report, and
 - CAPA plan
 - ❖ Recommendation for Certification or Recertification

Excipient GMP Certification

- Certify Conformance
 - ❖ Issue Certificate and Post to Website
 - ❖ Audit report available at nominal cost
 - Off-set cost for certification
- Post on Website Certification Status
 - ❖ Certified
 - ❖ Certification suspended
 - ❖ Certification withdrawn



Certification Program Oversight

- IPEA Management Board
 - ❖ Internal Audit
- IPEA Board of Director
 - ❖ Annual Program Review
- ANSI
 - ❖ Annual Surveillance Audit for conformance to Guide 65
- FDA
 - ❖ Invited FDA review to assure adequate cGMP compliance of certified companies

IPEA Surveillance Audit

- Annual site audit of certified facility
 - ❖ Assess ½ GMPs
 - ❖ Follow-up on corrective actions
 - ❖ Review changes to the site and above site organization
- Recertification
 - ❖ After two surveillance audits submit updated report to Certification Board
 - Affirm continuing conformance

IPEA Surveillance Audit

- One auditor for 2 Days
 - ❖ Verify completion of CAPA plan
 - ❖ Tour site operations
 - ❖ Examine additional records and reports
- Site provides CAPA plan for surveillance audit findings within 30 days
- IPEA assures significant corrections are implemented



Certification Benefits

- Certification vs. Shared Audits (Rx360)
 - ❖ Accepted by FDA
 - ❖ No cost to pharmaceutical customer
 - No FDA requirement for audit report
 - ❖ Audit report available at nominal cost
 - \$500-\$750
 - ❖ Excipient manufacturer decides scope of audit
 - Identifies excipients within scope
 - ❖ Annual surveillance audit

Supplier Qualification

- Regulatory requirement to rely on COA for incoming inspection
- Types of Assessment:
 - ❖ First Party
 - Self-audit
 - ❖ Second Party
 - Customer audit
 - ❖ Third Party
 - Regulatory audit
 - Contracted audit



Supplier Qualification

- Questionnaire

- ❖ Advantages

- Efficient
 - Low cost
 - GMP Compliant?

- ❖ Disadvantages

- Trust supplier responses
 - “One-size fits all”
 - NO ASSESSMENT OF PRODUCTION RISKS
 - NO ASSESSMENT OF LAB OPERATIONS



Supplier Qualification

- Site audit

- ❖ Advantages

- Assess production risk (excipient quality)
 - Assess laboratory operations
 - Meet the staff
 - Reliable information



Supplier Qualification

- Site Audit

- ❖ Disadvantages

- Safety

- ✓ Personal protective equipment

- Cost

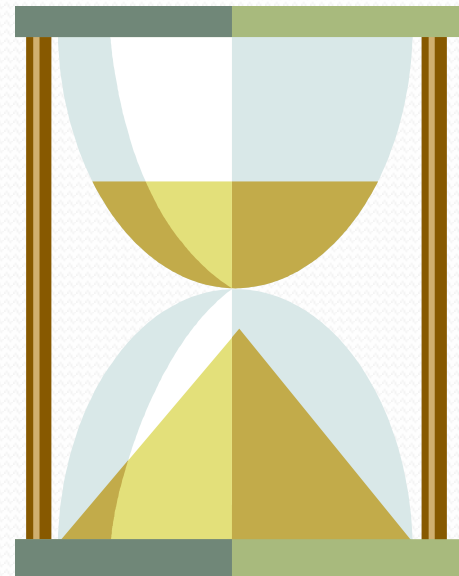
- ✓ Particularly travel

- Time

- ✓ Particularly travel

- I only have 8 hours!

- ✓ Or a group audit???



Assessing the Supply Chain

- Excipient manufacturers
 - ❖ Conformance to Excipient GMPs
 - ANSI NSF363
 - USP <1078>
 - ❖ Site audit or qualified third-party provider
- Distributor
 - ❖ IPEC Good Distribution Practices plus excipient GMP
- Broker/Trader
 - ❖ IPEC Good Distribution Practices

Excipient Supply Chain

- Distributor

- ❖ Identify manufacturer and site

- ❖ Identify role of distributor

- Warehousing

- Packaging

- Repackager

- ❖ Assess distributor through site audit

- ❖ Assess manufacturer:

- Site audit or

- Verify distributor's audit of site

Supply Chain Integrity

- Approval of Components
 - ❖ Evaluation of Packaging
 - Label matches reference label
 - Tamper-evident seal matches reference seal
 - Packaging components match reference components



FDASIA and Excipients

- FDA authority and visibility greatly expanded to include excipients and importers
 - ❖ Identification of excipient manufacturing establishments with listing of drug product
 - Must include unique facility identifier
 - ❖ Importer of drug products declare source of components
 - ❖ Provisions for third party audit and certification
 - Being implemented as part of Food Safety bill 2011

Amendments to the Act Aim to Promote Pharmaceutical Supply Chain Integrity (FDA Safety and Innovation Act)

FDASIA and Excipients

- IPEC-Americas Regulatory Affairs Committee
 - ❖ Regular meetings to identify impact on excipient makers and users
 - ❖ Identify opportunities to assist FDA in implementation relative to excipients
- In 2009, FDA stated they may ask IPEA to provide workshops to FDA
 - ❖ Approval of ANSI NSF/IPEC 363 Excipient GMP standard and FDASIA closes the loop.

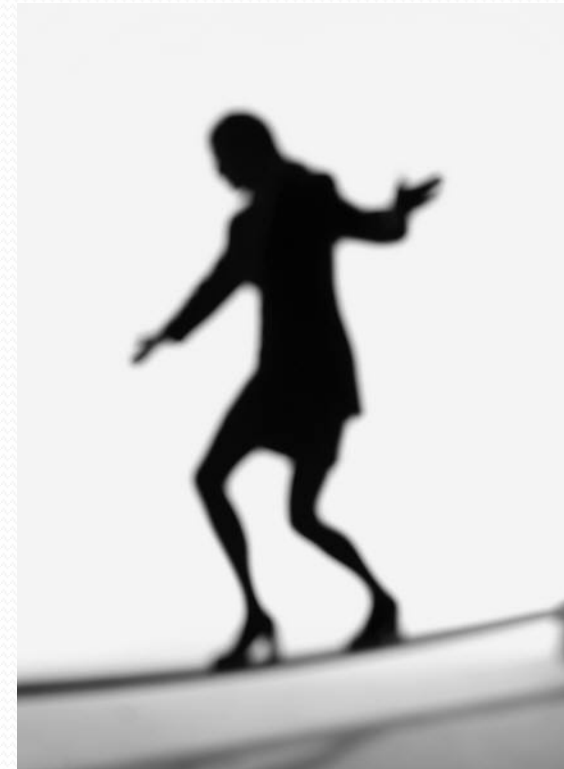
Falsified Medicines Directive:

- Manufacturing Authorization Holder (MAH) ensures excipients suitable for use by:
 - ❖ Ensuring appropriate GMP based on risk assessment of source and intended use of the excipients and previous incidents.



Three Steps of Risk Assessment

- Identification
 - ❖ Define potential for harm
- Analysis
 - ❖ Probability and Severity
- Evaluation
 - ❖ Combination of probability and severity



Potential for Harm

- Direct Hazard:

- ❖ Microbiological

- Pathogens

- ❖ Chemical

- Toxicity

- ❖ Physical

- Choking
- Irritation

- Indirect Hazard:

- ❖ Drug product manufacturing failure

- ❖ Stability failure

- ❖ Bioavailability failure

- ❖ Drug shortage

Europe: Excipient Risk Assessment

- Classify risks presented to the quality, safety and function of each excipient based on:
 - ❖ **Source:** animal, mineral, vegetable, synthetic, etc.
 - ❖ **Manufacture:** dedicated vs. non-dedicated equipment
 - ❖ **Contamination:** environmental control
 - ❖ **Stability:** storage conditions
 - ❖ **Quality concerns:** economically motivated adulteration, TSE

Guidelines on the Formalised Risk Assessment for Ascertaining the Appropriate GMP for Excipients

Europe: Excipient Risk Assessment

- Classify risks based upon application:
 - ❖ Dosage form
 - ❖ Performance or functionality
 - ❖ Quantity of excipient in dosage form
 - ❖ Expected daily intake of excipient
 - ❖ Whether the excipient is a composite
 - ❖ Potential to impact Critical Quality Attribute of drug product

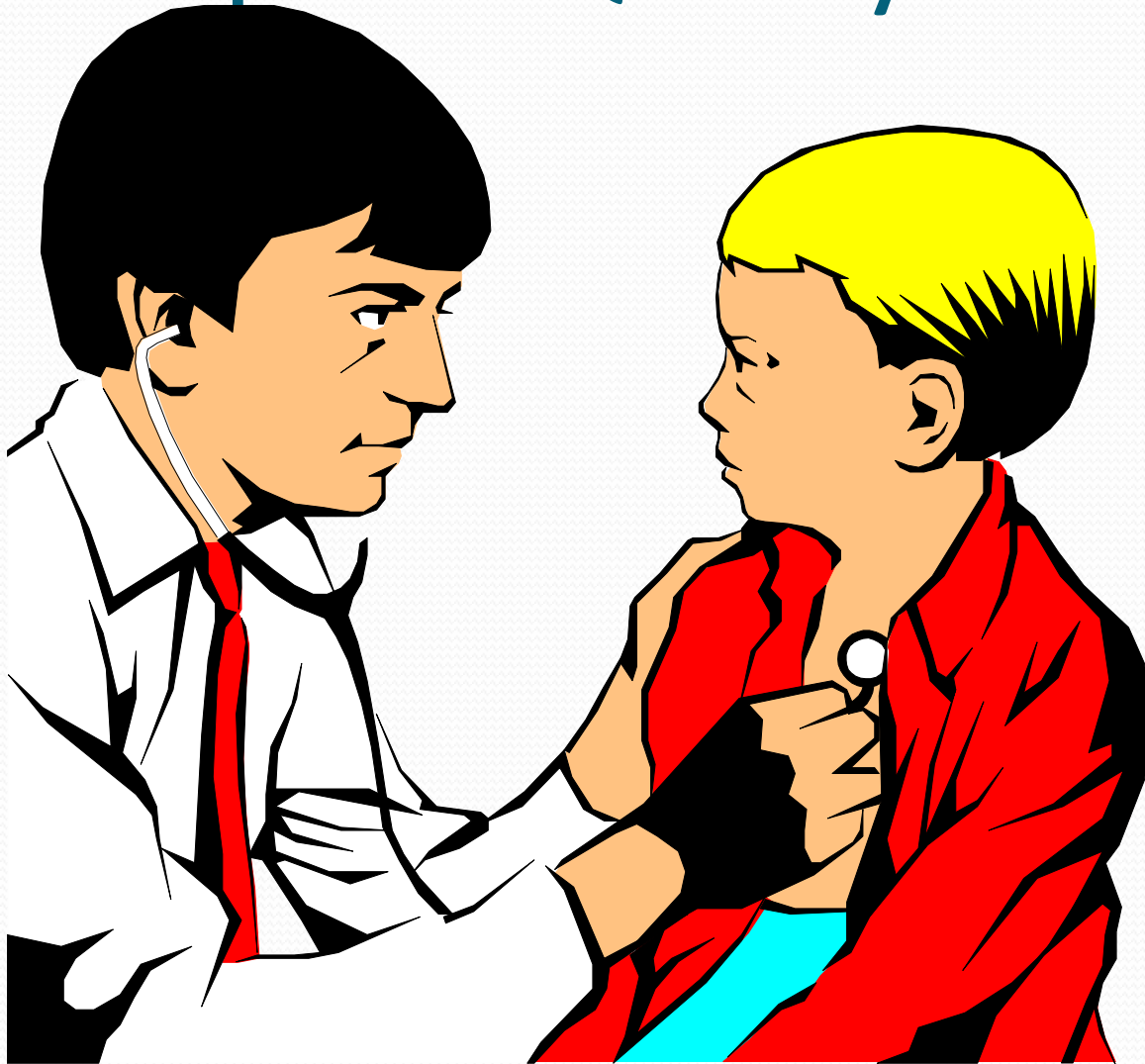
Europe: Excipient Risk Assessment

- Identify appropriate GMP implementation
 - ❖ Ranges from “acceptance through control” to “unacceptable”
- “Quality system certification or accreditation held by the excipient manufacturer and the standards against which this has been granted should be considered as this may meet the required Good Manufacturing Practices.”
 - ❖ IPEA Excipient GMP Conformance Certification
 - ❖ EXCiPACT GMP Annex

Europe: Excipient Risk Assessment

- Ongoing Assessment:
 - ❖ Number of defects on received batches of excipients
 - ❖ Type/severity of defects on excipients
 - ❖ Loss of relevant quality system accreditation by excipient manufacturer
 - ❖ Observation of trends in drug product quality attributes (this will depend on the nature and role of excipient)
 - ❖ Audit (re-audit) of excipient manufacturer.

Why Excipient Quality Matters!





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