Public Health Challenges for the Quality of Human Drugs

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Overview

• Problem with quality control of drugs
• What we can do (together?) to mitigate

• Emerging guidance and regulations
  – CGMP
  – Contract manufacturing/outsourcing
Potential Gaps in Control

• The world has changed
  – Globalization in production and distribution
  – Understanding and reacting to new problems
• Outsourced production
• New distribution issues
• More to understand
  – Technology
  – Processes
Between 01 and 07, the Number of Foreign Drug Sites Doubled
Between 01 and 07, Foreign Drug Products Doubled

<table>
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<th>Calendar Year</th>
<th>Number of Active Products</th>
<th>Cumulative Listings</th>
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<td>17,558</td>
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<td>CY07</td>
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Between 01 and 07, China and India Drug Manufacturers Increased 7 and 25 Fold

[Bar chart showing comparison between China and India from 2001 to 2007]
Between 01 and 07, China and India Drug Products Increased 4 and 7 Fold
Globalization Trends

• More foreign facilities supplying the U.S.
• Increasing volume of imported products
• More outsourcing of manufacturing
• Greater complexity in manufacture and supply
• Imports involving countries with less developed regulatory systems
Related Trends

• Distribution chains are more complex
  – ‘upstream’ and ‘downstream’ of product mfg
• More attacks on distribution chains
  – Cargo theft
  – Marketing of counterfeits
• Technology is more complex
Drug Supply Chain: Complexity & Hazards

Ref.: The American Council on Science and Health, August 2006, Counterfeit Drugs

Related Compliance Needs

• Earlier Prevention – Need to move quickly to investigate and to act where there are nonconformities or signals

• Earliest Prevention -- Need for systems that safeguard against economic fraud, negligent production, theft
Strains on FDA’s Traditional Model

- Over 80% API outside U.S.
- Most drug manufacturing facilities not in U.S.
- Number of facilities is growing
- Shipments outside import system
- Rogue wholesalers / brokers
- Unregistered firms
- ‘Shadow’ firms
“Globalization has multiplied the scale of our responsibility and the challenges we face..... Although my duty as FDA Commissioner is to protect the health of the American people... public health protection is a global endeavor.”

Dr. Margaret Hamburg
FDA Commissioner
February 4th, 2010
What is to be done?

• Corporate responsibility
• Working with regulatory partners
• Information to deploy resources effectively
• Swift enforcement, if necessary
Approaches to Corporate Responsibility

Assure preventive controls
  • With suppliers and their suppliers
  • With contractors and subcontractors

Investigate and act on nonconformities
FDA’s ‘Guiding’ Role in Corporate Responsibility

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
Examples in Recent Industry Guidances

• Process validation
• ICH Q10 pharmaceutical quality system
• Identifiers for solid oral dosage form drugs
• Risks for melamine contamination
• Testing of glycerin for diethylene glycol
On-going Supply Chain Work with Industry

- eDRLS and DUNS Identifier
- Supply chain integrity programs
- Track and trace systems implementation
- Radio frequency identification technologies
- Responding to cargo thefts
FDA’s Enforcement Role in Corporate Responsibility

Ensure poor practices are not rewarded

- Increased presence through collaboration
- “Swift, aggressive, and effective” enforcement action when needed
Working with Regulatory Partners

• Increased presence for foreign offices
• More joint inspections
• Increased engagement, harmonization, and sharing
Information to Deploy Resources Effectively

- Improve manufacturing and product information
- Risk models for API surveillance and monitoring
- Risk-based site surveillance inspections
- PREDICT implementation (imports)
- Secure Supply Chain Pilot
Commissioner’s Enforcement Initiatives

• Set post-inspection deadlines
• Shift in review of warning letters
• Work more closely with regulatory partners
• Prioritize follow-up on actions
• Swift enforcement action if necessary
• Implement a warning letter close-out process
Consequences

Playing the reverse lottery

• Enforcement
• Recalls
• Lawsuits
• Damage to the brand

FDA will be looking more across the corporate family for trends
Shared Interests

• Preventive approaches and control

• Nonconformities investigated and addressed

• Secure supply chains are rewarded
Emerging guidance and regulations

- CGMP
- Contract manufacturing
Human Drug CGMP Program Priorities 2010

• Policy/Programs:
  – Compliance Program: Pre-Approval Inspection program (done!)
  – Enforcement policies (CPG Ch. 4): update

• Guidance to Industry:
  – Process validation (publish final)
  – Beta-lactam cross-sensitivity (publish draft)

• Regulations:
  – Component controls (publish draft for comment)
  – “Phase 2” changes (publish draft for comment)
**Ingredient Adulteration is a Problem**

**2008-2009** DEG contamination in glycerin used in teething gel

**2008** Melamine contamination of milk products and infant formula (in China) (low qty in foods in US)

**2008** Heparin – OSCS contaminant

**2007** DEG contamination in toothpaste

**2007** Melamine contamination in wheat gluten (pet food)

**2006** DEG contamination in ‘glycerin’ in Panama, Bangladesh

**1990-1998** Recurring incidents of DEG-contaminated ‘glycerin’ (India, Haiti, Argentina, Bangladesh, and Nigeria)
Modernize the CGMPs

• Possible **component control** improvements:
  – Know supply chain
    • Original manufacturer and subsequent handlers
    • Audit original manufacturer
  – Test each container in each shipment until...
  – Require T-E packaging and security features
  – Notify FDA of contaminated shipments/lots
  – Use only components recognized as safe for their intended use or listed in an approved application
Modernize the CGMPs

“Phase 2” CGMP proposal:

• Establish “management responsibilities”:
  – assure compliance to CGMPs; provide resources; perform periodic reviews

• Require self-inspection and response

• Enhance existing regulations defect/problem response:
  – defect investigations and follow-up
  – evaluation of data to detect a problem

• Require change control procedure

• Document training and effectiveness

• Establish Purified Water for component use; test potable

• Withdraw OTC expiration dating exemption
Contract Manufacturing: Legal Framework – Regulations

21 CFR 211.22(a)
QCU responsibilities for drug products manufactured under contract

21 CFR 211.84
Testing and approval or rejection of components, drug product containers, and closures

21 CFR Part 200.10
Contract manufacturers are an extension of the manufacturer's own facility
Warning Letters
Human Drug CGMP

FY2007 FY2010 (to June)

Contract Mfrs
Sponsors
Contract Manufacturing: Responsibilities

- Contract manufacturers are responsible for manufacturing product in conformance to CGMP.
- The firm that hires a contract manufacturer may also assume certain specified responsibilities under 211 or elsewhere.
- Sponsors and private-label distributors are also accountable under the statute.
Contract Manufacturing: Responsibilities


“Outsourcing involves hiring a second party under a contract to perform the operational processes that are part of a manufacturer’s inherent responsibilities.... Quality systems call for contracts (quality agreements) that clearly describe...”

- materials or service to be provided
- specification-setting responsibilities
- communication mechanisms
- training, qualifications, and monitoring expected
- *harmony with both parties’ quality standards*
  - i.e., they should not be in conflict
Elements of a Quality Agreement

✓ Identification of the contract site address, building, and equipment/line, and services/materials to be provided
✓ Description of the drug, its intended use: all specifications
✓ Provide for periodic audits to CGMP and contract specifics
✓ Commitment to share regulatory inspection findings
✓ Procedures for change control
  ✓ new equipment, facility modifications, change in key personnel, change in SOPs and test methods
✓ Full disclosure of all errors, deviations, changes, OOS results, investigations, as well as adverse events that did or might impact drug
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