Howard R. Sklamberg
Director
FDA/CDER/Office of Compliance

CHPA Regulatory, Scientific & Quality Conference (RSQ)
Washington, DC
May 2013
Challenges presented by globalization

- More dispersed facilities supplying global market
- Increasing volume of imported products
- More outsourcing of manufacturing
- Greater complexity in supply chains
- Imports coming from countries with less developed regulatory systems
- Greater opportunities for economic fraud
Supply Chain for Finished Drugs

Complexity of the supply chain is increased by:

- Multiple participants
- Criminal activities (diversion, theft, counterfeiting)
- Globalization of supply chains
- Rules that vary by state
Example of threats in the supply chain:

- Counterfeit/falsified drugs sold to suppliers
- Stolen products reintroduced
- Other adulterated/misbranded drugs introduced
- Diverted drugs resold
How is FDA Addressing These Challenges?
- Partner with foreign counterparts to create global coalitions of regulators focused on ensuring and improving global product safety
- Build global data-information systems and networks and proactively share data with peers
- Expand intelligence gathering, with an increased focus on risk analytics and thoroughly modernized IT capabilities
- Effectively allocate agency resources based on risk, leveraging the combined efforts of government, industry and public and private third parties

“Today we recognize that to successfully protect U.S. public health, we must think, act, and engage globally. Our interests must be broader than simply those within our own borders.”

Margaret Hamburg, FDA Commissioner

- International Offices
- Strengthening Regulatory Capacity Building
- Harmonizing Science-based Standards
- Leveraging Knowledge and Resources
- Risk-based Monitoring and Inspection
- Advancing Regulatory Science
FDA foreign offices

- Headquarters: Silver Spring, MD
- Mexico City
- San Jose
- Santiago
- London
- Brussels
- Amman
- Beijing
- Shanghai
- New Delhi
- Mumbai
- Pretoria
- Guangzhou
Global cooperation/collaboration

- U.S. government inter-agency leveraging
- Bi-lateral/multi-lateral capacity building
- World Health Organization
  - Member State Mechanism
  - Global surveillance system
- Operation Pangea V
  - INTERPOL led global operation targeting internet websites supplying illegal and dangerous drugs;
- APEC Roadmap for Global Medical Product Quality and Supply Chain Integrity
  - Identify a path forward toward regulatory convergence of practices necessary to ensure the integrity of marketed medical products
Pharmaceutical Inspection Co-operation Scheme initiatives (PIC/S)

- CDER OC initiatives with PIC/S
  - Prior knowledge and review of revisions to EU GMP regulations and PIC/S Guidances for industry
  - Creation of common EIR Template to all PIC/S members
  - Joint Inspection Training exercises
  - Participation in “Expert Circle” groups, training, and discussions
Confidence Building to Reliance Upon

• Initiative:
  – Some GMP inspections of US and EU manufacturing sites may be deferred or waived based on inspectional findings of the other regulator.
  – FDA will exchange information as permitted under the framework of the confidentiality arrangements between EC, EMA and FDA.
  – Main objective of the initiative is to share information on inspections and GMP-related documents of common interest, and to conduct collaborative inspections when necessary.

• Benefits:
  – Reduce inspections of firms in Europe and allow FDA to shift inspection capacity to other regions
  – Provide relief to manufacturers who direct substantial resources to host inspections
  – FDA to efficiently use resources to monitor as many products as possible; wider global inspectional coverage.
Quality Focus
Commitment to quality

• Essential… from the top down and bottom up
• Cannot settle on “meeting regulators standards”
  – Must meet **YOUR** standards to reliably produce high quality products
• What Dr. Woodcock said…
  – proactively identify & promptly correct issues
  – design/qualify robust operations
  – maintain equipment and facilities
  – Implement robust quality management systems
• Significant impacts to the public’s health
  – Cost of poor quality – $$$$$$$$$$$
  – Cost to patients – shortages, adverse events, etc.
Recall definitions

• **Class I recall:** a situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death.

• **Class II recall:** a situation in which use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

• **Class III recall:** a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences
CDER total product recalls by class FY 07-13*

*1st Quarter
CDER total product recalls by type FY 08-13*

Dietary Supplements Separated

- OTC
- Rx
- DS

*1st Quarter
Major reasons for recalls FY 10-13*

2010  Impurities Degradation Products
       GMP Deviations
       Marketed Without an Approved NDA/ANDA

2011  GMP Deviations
       Marketed without an Approved NDA/ANDA
       Impurities/Degradation Products

2012  Impurities/Degradation Products
       GMP Deviations
       Lack of Assurance of Sterility

2013* Lack of Assurance of Sterility
        GMP Deviations
        Presence of Particulate Matter

*1st Quarter
Challenges of regulating OTC drugs

• Vast number and scope of OTC drug products
  - Cosmetic or device firms may not realize their products are drugs

• OTC monograph vs. OTC application (NDA/ANDA)
  – No pre-market oversight of individual drugs being brought to market
    • New dosage forms
    • Addition of unsafe inactive ingredients
    • New combination of active ingredients
    • New uses
  – Less post market control over individual products
  – Uncertainties of ongoing rulemaking

• Ensuring a consistent and level regulatory playing field
FDA’s efforts to address challenges of regulating OTC drugs

- Risk based
- Surveillance
- Making the regulatory process more accessible
- Greater transparency
- Continued support of other agency initiatives related to OTC drugs
Over-the-Counter (OTC) Drugs Branch

- About Us
- The OTC Drug Review

Enforcement Actions

- OTC Warning Letters
- All FDA Warning Letters

OTC Information for Consumers

also see Resources for You

- Antimalarials/Leg Cramps/Quinine [ARCHIVED]
- Cough/Cold
- Internal Analgesics
- Nicotine Containing Products
- Pediculicides
- Sunscreens
- OTC Consumer alerts

OTC Information for Industry

also see Resources for You

- Code of Federal Regulations Title 21
- 21 CFR Part 300
- OTC Drug Monograph Rulemakings
How can industry help?

• Keep registration and listing current and accurate

• Use the appropriate regulatory pathways for product specific innovations
  – Monograph is not a product specific review and the Agency cannot provide informal "pre-approval" for products being brought under the monograph system

• Comply with the Act, regulations, monographs, approved-applications
  – Regulation by enforcement discretion, including product specific requests, is generally not optimal
  – All non-compliant products are subject to enforcement

• Avoid using brand name extensions that will harm consumers and be mindful of marketing claims
Tainted products marketed as dietary supplements

• Challenge
  – Products marketed as dietary supplements with hidden API represent a significant public health risk

• 2010 industry letter
  – Industry responsibility as gatekeeper
  – Everyone in supply chain, from manufacturers to retailers is responsible
  – Comply with all applicable dietary supplement CGMP requirements in 21CFR 111 and 110
    • Ensure supply chain integrity
December 15, 2010

Dear Manufacturer of Dietary Supplements:

This letter addresses the significant public health problems posed by products that are marketed as dietary supplements but that contain the same active ingredients as FDA-approved drugs, analogs of the active ingredients in FDA-approved drugs, or other compounds, such as novel synthetic steroids, that do not qualify as dietary ingredients. These ingredients, generally undeclared in the labeling, can pose considerable dangers to consumers who may take these products without knowing that the ingredients are present, that the ingredients may be associated with serious side effects, or that they may interact in dangerous ways with other products consumers may be taking. FDA has received numerous reports of serious adverse events associated with consumer use of these tainted products including strokes, acute liver injury, kidney failure, pulmonary embolisms (artery blockage in the lung), and death.

Recognizing our shared interest in addressing this problem, FDA is working with the dietary supplement industry’s trade organizations to remind companies of their legal obligations and their responsibility to prevent tainted products from reaching the U.S. market.

Undeclared Active Ingredients in Products Marketed as Dietary Supplements
Tainted products marketed as dietary supplements

• Be vigilant for
  – Products in high risk categories such as weight loss, sexual enhancement, body building
  – Labeling
    • “Alternative to [approved drug product]”
    • “Do not take if you have any medical condition, if you are taking any prescription medications, or if you are pregnant”
    • “May cause positive result in performance enhancing drug test”
    • Directions and warnings that resemble FDA approved drug products
    • Primarily in a foreign language for products in high risk categories
  – Mass solicitations (e.g. emails) from suppliers and wholesalers offering products in high risk categories
OTC monograph modernization

• Challenges
  - Thousands of drug products marketed under the FDA OTC Monograph system and many OTC finished drug products lack USP monographs
  - Barriers to creating USP monographs for finished drug products
    • Large number needed
    • Various formulations used and thus challenges with associated analytical procedures
  - FDA needs solutions that have requirements/standards that are clearly enforceable

• Cooperation between FDA and industry is critical
• FDA is committed to working with USP and CHPA to develop modernized monographs and is appreciative of the efforts to offer effective solutions
New Legislation – FDASIA
Title VII – Drug Supply Chain

**Increased Risk Information**
- Registration (foreign & domestic) with UFI
- Excipient information
- Electronic system
- Information exchange
- Standards of admission for imported drugs
- Registration of commercial importers
- Notification

**Global Supply Chain**
- Risk-based inspections
- Records for inspection
- Recognizing foreign govt. inspections
- Enhancing safety and quality of drug supply / QMS

**Enhanced Tools**
- Administrative destruction
- Prohibit inspective delay, limitation, denial, refusal
- Administrative detention
- Protection against intentional adulteration
- Penalties for counterfeiting drugs
- Extraterritorial jurisdiction
What’s around the corner?

• GDUFA implementation
  – ANDA backlog
  – GMP and bioequivalence inspection and compliance program ramp up
    • Includes implementation of a surveillance inspection program in parallel with the current application-based inspection model

• Enhance collaborations with foreign regulators
  – Conducting inspections- GMP, GCP, BE, PV
  – Sharing inspectional information

• Implementation of FDASIA
• Compounding pharmacies
• Further secure drug supply chain
Thank You!

Howard R. Sklamberg
howard.sklamberg@fda.hhs.gov