



## Regulatory Expectations for Manufacturers in Assuring Quality of Components

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### Outline

- Supply chain – Why and why now?
- Supply chain challenges and recommendations – a US FDA perspective
- Excipient qualification and need for pedigree – an IPEC\*\* perspective
- Closing remarks

\* PhRMA: Pharmaceutical Research and Manufacture Association

\*\* IPEC: International Pharmaceutical Excipient Council

## Supply Chain – Why and Why Now?

- The globalization of pharmaceutical industry and the multitude of sourcing locations have brought increased complexity to ensuring the integrity and quality of pharmaceutical supply chain
- Industry and regulatory systems have not evolved in accordance with changes in the supply chain

3

## Worldwide Incidents Involving Ingredients

- 2009 – Baby teething formula contaminated with DEG (Nigeria)
- 2008 – Infant formula contaminated with melamine (China)
- 2008 – Heparin contaminated with OSCS\*
- 2007 – Toothpaste contaminated with DEG\*\*
- 2007 – Pet foods contaminated melamine
- 2006 – Glycerin contaminated with DEG (Panama)
- 1999 – Gentamicin IV contaminated with pyrogen (traced to API GMP)
- 1996 – Glycerin contaminated with glycerin (Haiti)

\* OSCS: over-sulfated chondroitin sulfate

\*\* DEG: diethylene glycol

4

## Supply Chain Challenges and Recommendations – a US FDA Perspective

Including excerpts from Steven Wolfgang, FDA, ISPE Conf, June 2008;  
Richard Friedman and Edwin Rivera, FDA, PDA/FDA Supply Chain  
Conf, Dec 2008

5

## Vulnerabilities in Industry Quality Systems

- Lack of traceability
- High complexity due to increased brokerage and trade activity
- Ingredient repackaged or relabeled multiple times
- Non-specific ID test frequently performed on composite sample
- Certificates of Analysis (CoAs)
  - Over-reliance on CoAs
  - Original manufacturer's CoA not always obtained
  - CoA often altered to remove true identity of manufacturer
  - Reported test results may be unreliable or falsified

6

## Vulnerabilities in Industry Quality Systems (cont'd)

- Supplier qualification programs, quality agreements, and lifecycle monitoring are often deficient
- Distant manufacturing sites can pose special risks
- Audits of supplier by drug product manufacturer are superficial or not conducted at all
- Over-reliance on inspections by regulatory authorities
- Counterfeiting, i.e., “deliberately and fraudulently mislabeling (a drug) with respect to its *identity or source*”
- Criminal substitution of cheaper ingredients in APIs, excipients, and drug products

7

## Vulnerability in Regulatory System

- FDA regulation, 21 CFR 211.84(d), allows ingredients from qualified suppliers to be released routinely based on CoA and limited testing
  - At least one specific ID test
  - Periodic testing to confirm accuracy of CoA
- No explicit requirement to periodically confirm the authenticity of an ingredient
- *However, it is a fundamental expectation that a firm assure identity and purity of a drug under the CGMP regulations and FD&C Act*

8

## FDA Authority and Oversight on Ingredient Sourcing under CGMP

- Drug product manufacturers are responsible for quality/safety of components used
- Quality of ingredients used cascades directly to drug product
- Quality systems for accepting/rejecting components are subject to inspection by FDA
- GMP compliance requires major effort to prevent contamination/mix-ups from the time raw materials arrive till the time consumer receives finished drug
- GMP, including documented traceability, is a cooperative effort by members of the supply chain

9

## FDA Recommendations on Securing Supply Chain Integrity

- Measures to prevent use of substandard ingredients
- Quality agreements for ingredients sourcing
  - IPEC offers templates (download for free) for Quality Agreements to use with suppliers and distributors
- Improving key elements in quality system
- Pedigree to secure movement through supply chain
  - IPEC's White Paper on Excipient Pedigree recently published in *Pharmaceutical Technology*

10

## Measures to Prevent Use of Substandard Ingredients

- Implement a comprehensive approach to monitoring ingredient supply chain integrity
  - Only do business with trustworthy sources
  - Establish a robust supplier qualification program (e.g., vendor audits, quality agreements, appropriate ongoing QC of incoming lots)
  - Verify each ingredient shipment comes from approved suppliers/manufacturers
  - Verify shipments came through expected routes and were not diverted
  - Use specially designed tamper-evident container seals
  - Thoroughly examine containers upon receipt for damage and evidence of tampering
  - Insist on original authentic CoAs

11

## Quality Agreement for Ingredient Sourcing

- FDA Guidance, “A Quality Systems Approach to Pharmaceutical CGMP Regulations,” recommends that a Quality Agreement clearly
  - describes the materials or service required
  - clarifies quality specifications and how they will be met, defining each partner company’s responsibilities in ensuring that product reflects these specs
  - establishes communication mechanisms between the sourcing company and its critical vendor partners
  - facilitates supplier qualification, maintenance of qualified status, and change management

12

## Improving Key Elements in Quality System

- Clear, thorough communication of requirements and expectations from user
- Knowledge of pedigree
- Robust supplier qualification and development programs that
  - stand the test of time
  - anticipate and mitigate risks
- Ability to detect anomalies
  - limited testing and tests have limitations

*But, will it need increased pressure from regulatory agencies?  
Are global regulatory agencies poised to cooperate?*

13

## Pedigree to Secure Movement through Supply Chain

- Pedigree – documenting each sale or transaction of the product and knowing
  - Who had the product
  - When they had the product
  - How long they had the product
  - Whom they bought it from
  - Whom they sold it to
  - Other information
- Universal and uniform pedigree – *ideal*
  - Identical format for all 50 states in U.S.
  - Passed by all supply chain stakeholders
- Electronic pedigree – *ideal*

14

## FDA Regulatory Oversight in a Global Environment

- What else can FDA do to protect consumers from drug products manufactured using substandard ingredients?
  - Promote CGMP for ingredient manufacturing
  - Promote GDP and GIP for ingredient commerce and transport
  - Strengthen border protection
  - Develop new networks for prompt communication
- Find new ways to collaborate with international counterparts

15

## Proposed FDA Globalization Act

- If passed, FDAGA will provide significant changes to current systems and FDA resources
  - Requires annual registration of all domestic & foreign firms supplying drugs or devices to U.S.
  - Generates FDA resources to support more inspections
  - Requires parity between foreign and domestic inspections
  - Restricts imports lacking documentation of safety
  - Requires verification of drug identity and purity
  - Creates strong new enforcement tools
  - Requires Country of Origin labeling for all APIs

16

## FDA “Beyond Our Borders” Initiative

- Why?
  - The number of FDA regulated products imported has doubled in the last five years
  - Many of the products are imported from regions with less sophisticated regulatory systems than in the U.S.
- What?
  - Focuses on enhancing relationships globally for the benefit of public health and patient safety
  - Opened in-country offices in China, India, Europe, and Latin America in 2008-09
  - Inspectors are asking more questions about supply chain, excipient qualification programs, vendor certification, and other items pertaining to supply chain during inspections
  - Leveraging projects, e.g., Pilots/Info sharing with EMEA

17

## FDA Guidances for Industry

- Testing of Glycerin for Diethylene Glycol (May 07)  
<http://www.fda.gov/cder/guidance/7654fnl.htm>
- Good Importer Practices (draft Jan 09)  
<http://www.fda.gov/oc/guidance/goodimportpractice.html>
- Submission of Laboratory Packages by Accredited Laboratories (draft Jan 09)  
<http://www.fda.gov/oc/guidance/labpackages.html>
- Standards for Securing the Drug Supply Chain – Standardized Numerical Identification for Prescription Drug Packages (draft Jan 09)  
<http://www.fda.gov/oc/guidance/drugsupplychain.html>
- Voluntary Third-Party Certification Programs for Foods and Feeds (draft Jan 09)  
<http://www.fda.gov/oc/guidance/thirdpartycert.html>  
(Currently not applicable to pharmaceuticals. FDA has indicated that they intend to adopt a similar program for the pharmaceutical industry.)

18

## Other Useful Information

- FDA News Page on Action Plan for Import Safety  
<http://www.fda.gov/oc/initiatives/advance/imports/news.html>
- July 08 FDA New Release: Action Plan for Import Safety  
<http://www.fda.gov/oc/initiatives/advance/imports/>
- Jan 14 09 FDA News Release: FDA Launches Pilot Program to Improve the Safety of Drugs and Active Drug Ingredients Produced Outside the United States  
<http://www.fda.gov/bbs/topics/NEWS/2009/NEW01943.html>
- Rosa Motta said (FDA Excipient Fest, May 2010)
  - If you have never been to a supplier, that supplier is NOW HIGH RISK
  - The GMPs regulations are being revised to add additional detail for Supply Chain

19

## Excipient Qualification and Pedigree – An IPEC Perspective

Excerpts from Janeen Skutnik, Pfizer, Chair, IPEC-Americas  
PDA/FDA Supply Chain Conf, Washington DC, Sep 2008; San Diego, Dec  
2008; Munich, Mar 2009; Shanghai, Jun 2009; IPEC Europe Conf, Jan 2009

20

## What is the Excipient Industry?

- *There is no real pharmaceutical excipient industry*
- Majority of pharmaceutical excipient suppliers are subsidiaries of chemical industry
  - Small fraction of main production volumes
  - Derived from diverse sources & materials
  - Varying degrees of dedicated R&D related to excipient uses
  - Specifications driven by main market (usually not Pharma)
  - Global market and manufacturing base
  - Change notification practices may be different than Pharma

21

## Current Situation

- Most excipient manufacturers still are not told how or where their customers intend to use their excipient
- This makes it difficult for the excipient manufacturer to help users select appropriate grades
- More sharing of route of administration and target market information is needed to minimize problems in registration and manufacturing

22

## Increasing Focus on Excipients

- Growing international interest in excipient supply chain issues from a regulatory, safety, and Quality by Design perspective
  - Recent issues with Chinese sourced food and drug ingredients
    - Numerous safety and GMP issues in recent years
    - Huge media exposure has created much concern
  - ICH Q8, Q9, Q10; FDA PAT initiatives
    - Understanding excipient functionality
    - Excipient variability between suppliers

23

## New Paradigm

- It is critical to use excipients in drug formulations only from high quality suppliers who have good change notification programs in place
- All alternative suppliers must be fully qualified using performance-based tests to show equivalent drug performance & stability
- *No longer is it acceptable to use excipients from suppliers simply based on specification compliance and cost!!!*

24

## IPEC Initiatives\*

- IPEC PQG GMP Guide for Pharmaceutical Excipients (USP<1078>)
- IPEC PQG GMP Audit Guide for Pharmaceutical Excipients
- IPEC Good Distribution Practices Guide
- IPEC Americas Significant Change Guide (USP<1195>)
- IPEC Americas Certificate of Analysis Guide (USP<1080>)
- IPEC Excipient Master File Guide
- IPEC **Excipient Qualification Guideline**
- IPEC Americas Standardized **Excipient Information Protocol**
- IPEC Standardized Quality Agreement Template
- IPEC **Excipient Pedigree** White Paper

\* [http://www.ipecamericas.org/public/guidance\\_documents.html](http://www.ipecamericas.org/public/guidance_documents.html)

25

## Guideline on Excipient Qualification for Use in Pharmaceuticals (2008)

- Covers all aspects of excipient qualification
- Includes both user's and supplier's perspective
- Three phases of excipient qualification process:
  - Phase 1 – Excipient development and market launch by supplier
    - Facility and equipment must be capable of producing the excipient under acceptable GMPs
  - Phase 2 – Excipient selection and overall qualification for intended use by users
  - Phase 3 – Negotiation of mutually acceptable specifications and quality agreements
    - Fully explore supplier's capability to meet any special criteria (avoid lot selection wherever possible)

26

## Excipient Information Protocol

- Developed to integrate information related to excipient qualification and sourcing into a standardized package (MSDS concept)
  - Eliminates the need for a questionnaire
- Comprised of three documents that can be used as stand-alone or together
  - Product Regulatory Datasheet
  - Site Quality Overview
  - Site Security and Supply Chain Overview

27

## Excipient Pedigree

*Based on WHO and IPEC GDPs:*

- Excipient manufacturers, users, and distributors need to cooperate to make this work
- Excipient users are obliged to know complete supply chain
- Distributors include all parties involved in trade and distribution
- Manufacturer's and distributor's original shipping papers should be received and checked by user
- Periodic site audits of manufacturers and distributors to verify paper trail
  - Can be done by user or a qualified third party, e.g., IPEA\*

\* IPEA: International Pharmaceutical Excipients Auditing, Inc., an IPEC subsidiary. IPEA is accredited by American National Standard Institute and recognized by FDA as an accredited third party

28

## Conferences and Industry Consortium

- PDA/FDA conferences on pharm. ingredient supply chain
  - Washington DC, San Diego, Munich, Shanghai (2008-2009)
  - Focus: Raising awareness, education and looking for paths forward
- Rx-360 Consortium ([www.rx-360.org](http://www.rx-360.org))
  - Formed by drug manufacturers after DC and San Diego conferences
  - Taking the lead in protecting the global pharmaceutical supply chain from threats like the heparin adulterant
  - To chart an approach that can become standard industry practice around the world to prevent similar incidents and serve as framework for emerging regional standards and regulatory requirements
  - Initial outreach was to pharmaceutical and biotech manufacturers; has now been extended to suppliers, brokers, distributors, repackagers, and relabelers
  - Mission: Create and monitor a global quality system that meets the expectations of industry and regulators that assures patient safety by enhancing product quality and authenticity throughout supply chain

29

## Rx-360 Functions

- Shared Supplier Audits
  - Sponsor audits are initiated by a single pharmaceutical firm
  - Audits led by Rx-360 are initiated by the consortium based on input from all members
  - Subscription audits are existing audits that are redacted and placed into a secure database for member access
- Adopting Standards and Best Practices
  - From existing standards (IPEC, APIC, etc.)
- Political, Macro Economic Monitoring, and Clearinghouse for Suspicious Events
- Technology Development

30

## Closing Remarks

- Inspection and testing alone are insufficient to ensure supply chain integrity in an increasingly complex global market
- All sectors of the pharmaceutical industry and global health authorities must collaborate and educate each other on risks and best practices
- FDA has enhanced its oversight by issuing new law and guidances and launching new initiatives
- IPEC has been proactively engaged in developing guidelines, collaborating with regulators, and providing training and third party audits

31