The New Paradigm for Excipient Qualification and Supply Chain Control – IPEC Update

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Improved Communication is Essential Today!!!!!

• Users, Makers AND Regulators MUST take more time to understand each other’s needs and controls than done in the past
• Changing World
  – Contaminated Excipients from China & Elsewhere
  – Counterfeiting of Drugs & Excipients
  – Bioterrorism
  – BSE/TSE, GMO’s, Allergens, Additives
  – Cost Reduction Goals
  – Continuous Quality Improvement – QbD/PAT
• Increased need for Supply Chain Controls and Traceability as well as Product Consistency!!

Increasing Focus on Food & Drug Components

• Recent Issues with Chinese Sourced Food & Drug Ingredients
  • Glycerin – contaminated with DEG
  • Pet Food – Wheat Gluten contaminated with Melamine
  • Tooth Paste – contaminated with DEG from Glycerin
  • Heparin – contaminated with similar but different material – still being investigated!
• However, this NOT just an issue with China!!

Increasing Focus on Excipients & APIs

• Many people have died in recent years in many countries due to contaminated Excipients, APIs and the poor distribution chain controls used by pharmaceutical companies
• The Pharmaceutical User is Ultimately RESPONSIBLE!!
• However, API and Excipient Suppliers also have responsibility if they misrepresent their products & supply to Pharma Companies

Increasing Focus on Excipients

• The days of treating excipients like commodities and buying them without FULLY qualifying the source and the ENTIRE distribution chain are OVER!!
• Some excipients are also being used as API’s by pharmaceutical companies when they were never intended by the manufacturer to be an API grade and are not made in an FDA registered facility using ICH Q7A GMPs

Increasing Focus on Excipients

• The paradigm that exists in some pharmaceutical companies today where excipients are sourced by supply chain people from distributors (based primarily on price) without knowing the actual manufacturer, manufacturing site and full distribution lifecycle chain MUST CHANGE!!
Using an excipient without knowing the manufacturing location and its path to your front door is like using a toothbrush you find laying in a public restroom.

Even if you test the toothbrush and the tests show it to be clean and free from contamination.................

Would you use it ???

U.S. Interagency Working Group On Import Safety

Action Plan for Import Safety
A roadmap for continual improvement
November 6, 2007

KEY POINT: Must control the supply chain at every step along the way!

Import Safety Action Plan - Highlights

• Creating a Stronger Certification Process
  – Mandatory Certification for high risk materials and Non-Mandatory Third Party Certification Encouraged for all other materials!
• Increasing Transparency — certified producers and importers would be made public for informed decisions.
• Enhancing Standards — Congress to provide FDA with the ability to strengthen standards based on industry best practices to leverage knowledge
• Strengthening Penalties — hold both foreign and domestic entities accountable and discourage the sale of unsafe products

Congressional Legislation & Hearings

• Dingell, Pallone & Stupak Bill – FDA Globalization Act of 2008 – provides for significant changes in current systems and FDA resources
  – Annual registration of all domestic & foreign firms supplying drugs or medical devices into the U.S.
  – Generate FDA resources to support more inspections
  – Requires party 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

Industry Initiatives

• IPEC Americas is working closely with FDA’s Pharmaceutical Ingredient Task Force to share industry best practices and guidelines to assist the FDA’s efforts to prevent these safety problems from continuing
• IPEC Europe and JPEC are coordinating similar efforts with the EMEA & MHLW
The Future

• QbD will drive pharmaceutical companies to have a much better understanding of the functional effect that excipients have on their process than they may have had in the past.
• This will create the need for even BETTER COMMUNICATION between makers, users and regulators than in the past when qualifying excipients

New Paradigm

• It is CRITICAL only to use excipients in drug formulations from high quality suppliers who meet appropriate GMPs and 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!!

Qualification of Excipient Suppliers

PREMISE: Quality cannot be tested in.

After the Haiti Glycerin incident in 1995, an IPEC White Paper was published in 1998 which addressed Excipient GMPs, Distribution Controls and the use of Certificates of Analysis (COAs).

Supplier Qualification

• ALL Suppliers of pharmaceutical excipients should be qualified by the User
  – IPEC GMP/Qualification Guidelines
  – Supplier Capability & GMP Audits of the Full Distribution Chain
  – Excipient Datasheets and Certifications
  – Initial testing of at least 3 batches for full compendial/regulatory analysis for target region
  – Routine ID tests & Periodic full testing if appropriate COAs are supplied

IPEC Initiatives

• GMP Related Guidelines
  – Excipient GMP Guideline
    • USP General Chapter <1078>
  – Excipient GMP Audit Guideline (NEW!!)
  – Excipient Good Distribution Practices (GDP) Guideline
  – Excipient GDP Audit Guideline (NEW!!)
IPEC Initiatives

- GMP Related Guidelines
  - Excipient Certificate of Analysis Guideline
    - USP General Chapter <1080>
    - Requires that Manufacturer and Mfg. Site be identified
  - Significant Change Guideline for Excipient Manufacturing Changes
    - USP General Chapter <1195> (draft)
- All completed guidelines are available for free download at: http://www.ipecamerica.org

IPEC’s Excipient Information Protocol (EIP)

- The Excipient Information Protocol (EIP) was developed to integrate information related to excipient qualification and sourcing into a standardized package (MSDS Concept)
  - Eliminates the need for a questionnaire
- The EIP is comprised of three documents that can be used as stand alone documents or together to form the EIP
  - Product Regulatory Datasheet
  - Site Quality Overview
  - Site Security and Supply Chain Overview

Excipient Qualification Process

- Manufacturer
  - Excipient Manufacturer must investigate all technical, safety and international regulatory aspects of the excipient that will be important to pharmaceutical users UP-FRONT before launching the product for a particular intended use
  - Facility and equipment must be capable of producing the excipient under acceptable GMPs

- User
  - User’s start the process when they identify a need for an excipient to solve a formulation problem during product development
  - The User’s excipient selection and qualification process should be based on the following in addition to technical performance:

User’s Excipient Selection Criteria

- Global Regulatory Acceptability
- EIP Availability
- Supplier Quality Assessment Information
- Supplier GMP Compliance (based on qualified audit information for excipient manufacturing plant and full distribution chain)
- QbD & PAT Considerations
- Change Control Agreements
- Stability
- Storage Conditions
- Bioavailability
- Availability of Supply to Intended Mfg. Site for Drug
- Labeling Concerns
- Relative Cost

Excipient Qualification Process
Excipient Qualification Process - Negotiation

- Negotiate testing responsibilities & costs
  - Additional requirements/tests normally may require premium grades w/ increased costs
  - Fully explore supplier’s capability to meet any special criteria (avoid lot selection wherever possible)
  - Avoid trying to get “something for nothing”

- Draft Standardized Quality Agreement and pursue Supplier Sign-Off (IPEC Template)
  - Must be a win-win situation

Supply Chain Controls

- Excipient Pedigree
  - Do you know where your ingredients are produced?
  - Do you know how they were distributed?
  - What evidence do you have which demonstrates this?
  - More than One Up and One Down is needed!!

IPEC DRAFT Proposal

- Radio Frequency ID
  - Cost?
  - Untested?

- Barcode
  - Equipment, Labeling?
  - Feasibility?

- Verified Paper Trail
  - Already in-use – Bills of Lading
  - All movements require transfer paperwork at each step of the way

Reality Check!!!

- How can the industry really have qualified AUDIT information for every single supplier and distributor???
  - Internal audit teams can’t do all these audits and suppliers can’t host so many audits

IPEC DRAFT Proposal

- Excipient Pedigree
  - Periodic Site audits of manufacturers and distributors to verify paper trail
  - Can be done by user’s auditors OR a qualified third party audit service
  - Original manufacturer’s and distributor’s shipping papers (BOL minus pricing info) should be received and checked by user for each lot
  - Must demonstrate that the material has gone through expected distribution channel

IPEA – Third Party Audits and Auditor Training

- IPEA can arrange audits in over 90 countries through a strong international network.
- Domestic and overseas audits are performed by IPEA trained and certified personnel who are conversant in most local languages.
- IPEC-PQG GMP & Audit Guide forms the basis for the audits (USP<1078>)
IPEA – Third Party Audits and Auditor Training

- Audit reports stored in audit report warehouse at IPEA and available to users at low cost (approx. $1000)
- IPEA audits minimize auditing costs for makers and users
  - Sponsor can be maker or user (audit cost = $5000 to $6000)
  - Cost sharing model – audit sponsor gets half of funds from audit reports sold as credit for additional audits
- IPEA also offers excipient auditor training courses and workshops

IPEA – Third Party Audits and Auditor Training

- IPEA program has been designed to provide qualified audit information on suppliers where you cannot do the audits yourselves to provide qualified audit information to the user
- IPEA – discussions occurring with ANSI about potential accreditation as official third party certifier. Meeting scheduled with FDA on May 15th to discuss program
- Do YOU have qualified audit information on EVERY supplier for EVERY excipient you use???
- For more info: http://www.ipeainc.com

IPEC China

- IPEC China is being formed to coordinate excipient regulatory activities with other IPEC groups
- New Excipient Regulations are being developed in China and there is a need for a forum to discuss excipient controls between industry and the SFDA
- All interested multinational companies who want to be a part of IPEC China should contact D. Schoneker (dschoneker@colorcon.com)

Where is this all going???

- It will be critical that User – Supplier relationships and TRUST improve to the point where each party has a much better understanding of the other’s processes, controls and problems
- This needs to be a Technical discussion, NOT just a purchasing or supply chain discussion!!!!

Discussion