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
  - Heparin – contaminated with similar but different material – still being investigated!

Increasing Focus on Excipients

- Many people have died in recent years due to contaminated excipients and poor distribution chain controls used by pharmaceutical companies

- **The Pharmaceutical User is Ultimately RESPONSIBLE!!**

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!!**

- The paradigm that exists in some pharmaceutical companies today where excipients are sourced 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

Import Safety Action Plan

- **Must control the supply chain at every step along the way!**
- Commitment to continually strengthen and improve the import safety system
- Action Plan contains 14 broad recommendations and 50 action steps that provide a road map for better protection of American Consumers
- U.S. Government has had many meetings with the Chinese Government and agreed on a number of initiatives – U.S. Stds. MUST be met for all imports into the U.S.

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!
- **Encouraging Good Importer Practices –** provide importers with best practices
- **Increasing Transparency –** certified producers and importers would be made public for informed decisions.
- **Exchanging Import Data –** exchange real-time data on each import transaction

Import Safety Action Plan - Highlights

- **Increasing U.S. Presence Overseas** – Train foreign inspection agencies, increase physical presence abroad to ensure compliance to U.S. safety standards BEFORE import into the U.S.
- **Enhancing Standards** – Congress to provide 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

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

Impact of QbD

- **The new focus on Quality by Design (QbD) will influence formulator's excipient selection choices to choose excipients which:**
  - ❑Are Well Characterized for Various Functionalities
  - ❑Are manufactured under well defined controls
  - ❑Have good batch uniformity and characterization
  - ❑Are Premium Grades designed specifically with Pharmaceutical Uses in mind
  - ❑Are supplied by manufacturers who have good change control and notification programs

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. MUST be determined EXPERIMENTALLY!!
- 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!!!***

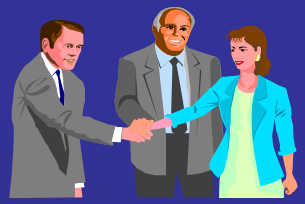
Qualification of Excipient Suppliers

PREMISE: **Quality cannot be tested in.**

IPEC White Paper was published which addressed distribution controls and the use of Certificates of Analysis (COAs).

Supplier Qualification

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



Excipient Qualification must be a Win-Win ***Negotiation***

Users and Makers must both understand how the excipient is to be used and come to a set of mutually agreed upon specifications & requirements that can routinely be met by the supplier and TRUSTED by the user

IPEC Initiatives

- **GMP Related Guidelines**
  - **Excipient GMP Guideline**
    - **USP General Chapter <1078>**
  - **Excipient GMP Audit Guideline**
  - **Excipient Good Distribution Practices (GDP) Guideline**
  - **Excipient GDP Audit Guideline**

IPEC Initiatives

- **GMP Related Guidelines**
  - **Excipient Certificate of Analysis Guideline**
    - **USP General Chapter <1080>**
  - **Significant Change Guideline for Excipient Manufacturing Changes**
    - **USP General Chapter <1195> (draft)**
  - ***All completed guidelines are available for free download at:***
    http://www.ipecamericas.org

IPEC Initiatives

- **Guidelines for Excipient Qualification**
  - ❑ Covers all aspects of Excipient Qualification
  - ❑ Includes both the User's and Maker's perspective
    - ❑ **Phase 1** -Excipient development and market launch by makers – Guide launched in Sept. 2007
    - ❑ **Phase 2** - Excipient selection and overall qualification for intended use by users – Guide under development
    - ❑ **Phase 3** - Negotiation of mutually acceptable specifications and quality agreements – Guide under development
  - ❑ Will improve communication and understanding between makers and users

Excipient Qualification Process - Manufacturer

- First Section of the guideline is completed and deals with the steps undertaken by the excipient manufacturer to assess their process, set up sales specifications for the excipient and launch the product
- The process begins when a manufacturer decides that they have a material that they would like to offer to the pharmaceutical industry
  - Can be a completely “new” excipient or a new grade of an existing excipient

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

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 - User

- User's start the process when they identify a need for an excipient to solve a formulation problem during product development
  - Existing formulary or evaluate materials or suppliers not previously used
- 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)
- 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 - Negotiation

- **Negotiate testing responsibilities & costs**
  - Additional requirements/tests normally 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

Change Notification

- In a QbD environment, the need for Notification of Significant Changes to Users becomes even more important than in the past
- User's Process Controls may be dependant on typical ranges of properties that are not fully understood
- Changes in Excipient Manufacture can impact properties outside of specifications that may be important
- IPEC's Significant Change Guideline should be used to improve communication of changes in excipient manufacture

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

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 available to users at low cost
- IPEA audits minimize auditing costs for makers and users
  - Sponsor can be maker or user
  - 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 with ANSI about potential accreditation
- U.S. FDA has stated publicly that they think this program could be a good part of an overall supplier qualification program

- **Do YOU have qualified audit information on EVERY supplier for EVERY excipient you use???**

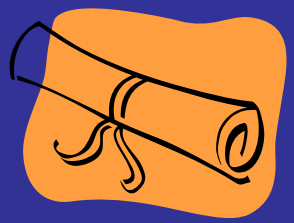
- **For more info: http://www.ipeainc.com**

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!!!!

IPEC China

- IPEC China is being formed to coordinate excipient regulatory activities with other IPEC groups
- 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)**



IPEC Foundation

- IPEC has launched the IPEC Foundation in early 2008
- The Foundation's main purpose is to promote research and education related to excipients (*i.e.* excipient characterization, performance, development of novel excipients, etc.)
- The Foundation hopes to encourage the growth of technology related to excipients for the betterment of the public and medical science.

DISCUSSION