IPEC Present & Future

Excipient Fest
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Chair – IPEC-Americas
IPEC Background
IPEC Activities
Potential Legislative & Regulatory Actions
Future Initiatives
**IPEC Mission**

- To collaborate with our partner regional IPEC groups to:
  - **Develop, implement, and promote voluntary guidance** and other programs for the world pharmaceutical industry that are designed to ensure continued availability of excipients and related components for finished products that meet the highest appropriate standards for quality, safety, and functionality throughout their manufacturing process and supply chain;
Encourage and assist the industry, FDA, the USP, and other public health and compendial authorities worldwide to adopt scientifically appropriate regulatory and compendial standards for pharmaceutical excipients;

Assist, educate, and cooperate with regulatory authorities, industry organizations and scientific bodies working to advance public health on matters relating to the manufacture, distribution, use, and functionality of excipients.
Several Regional/National Organisations

- IPEC Americas
- IPEC Europe
- JPEC (Japan)
- IPEC China (new 2008)
- Brasil
Excipients: Growing Interest

- Media, regulator, government, public and industry focus on Excipients has grown steadily over past 2 years
  - Quality by Design & Excipient Functionality
  - Excipient Pedigree & Supply Chain
  - GMPs
  - GDPs
IPEC Priorities

- Supply Chain: Quality, integrity
  - Supplier Quality Management
  - Pedigree
  - Transparency & Traceability
- Harmonisation
- Quality by Design
- Excipient Qualification
- Education & Training
Supply Chain

- Why SC, Why now?
  - The globalization of the pharmaceutical industry and the multitude of sourcing locations has brought increased complexity to ensuring the integrity and quality of the pharmaceutical supply chain.
  - Industry and regulators have not evolved systems in accordance with the changes in the Supply Chain.
# Supply Chain: If not now, WHEN?

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Incident</th>
</tr>
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<tbody>
<tr>
<td>USA</td>
<td>1937</td>
<td>Sulfanilamide Elixir – 107 deaths</td>
</tr>
<tr>
<td>South Africa</td>
<td>1969</td>
<td>Sedative formulated with DEG – 7 deaths</td>
</tr>
<tr>
<td>Italy</td>
<td>1985</td>
<td>DEG in wines from Austria – no known deaths</td>
</tr>
<tr>
<td>India</td>
<td>1986</td>
<td>Medicinal glycerin laced with DEG – 14 deaths</td>
</tr>
<tr>
<td>Nigeria</td>
<td>1990</td>
<td>Acetaminophen syrup containing DEG – 40 deaths (some sources say 200 deaths)</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>1990-2</td>
<td>Acetaminophen syrup containing DEG – 339 deaths</td>
</tr>
<tr>
<td>Haiti</td>
<td>1995/6</td>
<td>Cough medicine containing DEG – 85 deaths</td>
</tr>
<tr>
<td>Panama</td>
<td>2006</td>
<td>Cough and anti-allergy syrup containing DEG – 46 deaths</td>
</tr>
<tr>
<td>USA</td>
<td>2006/7</td>
<td>Toothpaste containing DEG – no deaths</td>
</tr>
<tr>
<td>Panama</td>
<td>2007</td>
<td>Toothpaste containing DEG – no deaths</td>
</tr>
<tr>
<td>Nigeria</td>
<td>2008/9</td>
<td>Teething formula contaminated with DEG – 84 deaths</td>
</tr>
</tbody>
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ALMOST 1000 Unnecessary Deaths!
Supply Chain: If not now when?

- >8,000 Pets were killed from Melamine Contaminated Pet Food
- At least 5 infants died from melamine contaminated infant formula
  - At least 50,000 Infants made ill
- At least 246 deaths from contaminated Heparin
- Almost 1,000 deaths from products contaminated with DEG
What’s next?

- Acetonitrile ??????
  - Potential vulnerability
  - Global crisis: short supply
  - Necessity for specially manufactured material
  - Prices increasing
- Could ACN be next?
Supply Chain

- Monitoring the Geo-political environment for potential vulnerabilities
- Excipient GMPs & GDPs
- Excipient Auditing & Auditor Training
- Quality Agreements
- Excipient Qualification
- EIP
- Excipient Pedigree
- IPEC Guidelines
- Looking for new partnerships
Geo-political Environmental Scanning

- What is it?
  - Keeping tabs on what is occurring globally
    - Economically
    - Politically
    - Other Industries
  - Use information to look for potential vulnerabilities
Geo-political Environmental Scanning

Why?

- Case Studies
  - Heparin Crisis
    - Heparin is sourced from Pigs
    - Majority of the world’s pig population is in China
    - It takes 50 million pigs to supply the market for a single year
    - For several years PRIOR to the incident the price of pigs was increasing
Geo-political Environmental Scanning

Why (2)?

- Global Acetonitrile Crisis
  - Slowing of Automotive industry coupled with issues at some plants created global shortage
  - Were we proactively aware and prepared for this ...............?
  - Could we have been better prepared and aware?
Excipient GMPs & GDPs

- Converting GMP & GDP Guidances into ANSI Standards (with assistance from NSF International)

- What is the benefit?
  - OMB Circular A-119
  - The circular directs government agencies to use voluntary, consensue standards in lieu of government-unique standards
Excipient GDPs

Quality Management System should:
- Include procedure to verify that any supplier of excipients has the capability to consistently meet requirements
- Should include periodic audits
  - Self or 3rd party
  - Paper audits are no longer acceptable
  - Should inquire if supplier sub-contracts out any part of the process
- Confirm that the agreed supply chain has been used
- Integrity of packaging and seals should be carried out
Excipient Auditing & Certification

- International Pharmaceutical Excipients Auditing (IPEA) Incorporated in 2001
  - Subsidiary of IPEC-Americas
- Mission: Facilitate Site Assessment for Qualification of Excipient Suppliers
- Objective: Reduce Costs for Both Makers and Users
- Approach: Sharing of Excipient Audit Reports
- Standard: Excipient GMP Guideline
- Report: Document How Site Meets GMP Expectations
IPEA’s Mission

Facilitate assessment of excipient manufacturers to appropriate GMP standards. To achieve this, IPEA provides audits of pharmaceutical and nutraceutical excipient manufacturing facilities to USP and IPEC guidelines.

Audits of manufacturing sites are performed worldwide. Audit Reports provide a basis for confirming that the quality systems used to produce the audited excipient meets appropriate cGMP.

Through audits, deficiencies in manufacturing and packaging can be identified early and potential industry tragedies can be avoided.
Excipient Certification

- Assess Conformance of Site Quality System to Excipient GMP Expectations
- Comprehensive Site Audit to Excipient GMPs
- Certify Conformance
  - Issue Certificate
  - Post to Website
    - Make audit report available
Auditor Qualification

- Education and Experience
- Training by IPEA
  - 3-Day Workshop, or
  - 1-Day Excipient GMP Expectations
Auditor Qualification

- Supervised Qualification Audit
  - On-site Performance
  - Audit Report
- Continuing Oversight
Quality Agreements

- Critical for laying out expectations
- Following may be a part of a Quality Agreement
  - Access to facilities
  - Release process
  - Change management
  - Material purchase, receipt, storage and testing
  - Specifications and Test Methods
  - Notification and approvals of deviations, out of specification results and adverse trends
  - Inspections by Regulatory Authorities
  - Handling of rejected materials and/or products
  - Product complaint handling
  - Market actions
Excipient Qualification: What’s Important?

- Use only excipient from high quality suppliers who have good change notification programs in place
- Ensure that you have a vendor/supplier qualification programme in place
- Ensure all alternative suppliers are fully qualified using performance based tests to show equivalent drug performance & stability
**EQ: What’s Important?**

- Improved communications between users, makers and regulators
- Increased understanding of systems and controls
- Increased transparency
- Increased need for Supply Chain Controls and Traceability as well as Product Consistency
- Increased testing is not a panacea and alone will not ensure patient safety
  - Focus needs to be on Quality Systems, transparency, traceability and consistency
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!!

*What is your weakest link.............?*
**Excipient Pedigree**

- **Basic Premises**
  - Based on WHO and IPEC GDPs
  - Excipient Users obliged to know complete supply chain
  - Distributors include all parties involved in trade and distribution, (re)processors, (re)packagers, transport and warehousing companies, forwarding agents, brokers, traders, and suppliers other than the original manufacturer
  - Excipient Makers, Users, and Distributors need to cooperate to make this work
Excipient Pedigree

EXCIPIENT MANUFACTURER

- Follow IPEC GMP and GDP, and provide COAs according to IPEC COA Guideline
- If a distributor is used, confirm on request, that the material was shipped to the distributor
- Periodically audit distributors used for adequate GDPs and contamination control using the IPEC GDP Guideline as the basis
- Conduct mock recalls to assure procedures
Excipient Pedigree

- DISTRIBUTOR
  - Comply with IPEC GDP
  - Provide to the USER, on request, chain of custody documentation (e.g. bills of transfer with financial data redacted)
  - Provide appropriate COA with each shipment
  - Conduct mock recalls to assure procedures
  - If a holding tank is used can only contain shipments from the same manufacturer’s site or terminal
  - have an effective change management program with customer notification
Excipient Pedigree

- **USER**
  - Bears responsibility for all excipients used
  - Performs appropriate testing
  - Audits or uses a qualified third party to audit all suppliers and distributors
  - **On a periodic basis verifies the chain of custody**
Excipient Pedigree

- No Testing Up
- Non-GMP Material must never be labeled as compendia grade based on testing
- Quality cannot be tested in, it must be manufactured in
Excipient Pedigree

- Must demonstrate that the material has gone through the expected distribution channel
- Original manufacturer’s and distributor’s shipping papers (BOL minus pricing info) 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 audit
Supply Chain Guidances / Regulations

- US recently issued “Good Importer Practices”
- FDA Pilot Program to Promote Safety of Drugs Produced Outside of U.S
- EU Pharmaceutical Package & Anti-counterfeiting initiatives
FDA Good Importer Practices

- Four Guiding Principles
  - Establishing a product safety management program
  - Knowing the product and applicable U.S. requirements
  - Verifying product and company compliance with U.S. requirements throughout the supply chain and product life cycle
  - Taking corrective and preventive action when the imported product is not in compliance with U.S. requirements
Importers should know the producer of the foreign products they purchase and any other manufacturers with which they do business,
- such as consolidators, trading companies, and distributors;

Understand the products that they import and the vulnerabilities

Understand the hazards that may arise during the product life cycle, including all stages of production; and ensure proper control and monitoring of these hazards.
Qualification of Excipient Suppliers

PREMISE: Quality cannot be tested in.
Most Excipient manufacturers still are not told how or where their customers intend to use their excipient (Excipient vs. API applications??)

This makes it difficult for the 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
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
- Excipient Qualification Guidelines
- IPEC-Americas Standardized Excipient Information Protocol
- IPEC Standardized Quality Agreement Template
- Excipient Pedigree White Paper
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 launched in Sept. 2008
- Will improve communication and understanding between makers and users
Excipient Qualification Process - Manufacturer

- 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.
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
Rx-360 Consortium: A new way?

- IPEC is exploring partnership with the newly formed consortium Rx-360
- Rx-360
  - Is an international non-profit organization
  - Biotech, pharma, device, generic, suppliers & audit firms are members while professional organizations & regulators are observers
  - Many companies and professional organizations have committed to the concept
  - The consortium is not intended to replace the regulatory system or to eliminate regulatory oversight
**Rx-360**

- **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 the supply chain

- **Goal**
  - Adopting Standards and Best Practices
  - Technology Development
  - Market Surveillance
  - Shared Supplier Audits
IPEC - Globally

- Exploring the creation of a foundation with the same mission, vision and objectives
Educational Resource

- IPEC Sponsored educational Web-based training
  - New Excipient Evaluation Procedure
  - Excipients 101
  - Food GMPs vs. Excipient GMPs
Resources

- IPEC
  - www.ipec.org
- Download IPEC Guidance documents
  - Available for free (do need to register)
THANK YOU!

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Questions & Discussion?