

Excipient Sourcing in a Global Market: How to avoid another Panama

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Presentation Outline

- **Introduction**
 - Objectives
 - History
- **What has been done/is being done**
 - FDA
 - IPEC
 - EU
 - Interagency Working Group on Import Safety
- **What the Companies can do**
- **Excipient integrity through the supply chain**
- **Conclusions**

The Objective

- **To provide/obtain acceptable, unadulterated ingredients (APIs and excipients) for the nutritional, nutraceutical, pharmaceutical and biotech industries that meet the appropriate specifications and are manufactured using appropriate GMPs.**

USP-NF Designation

- **In order to claim USP or NF compliance, the material must:**
 - a. **Conform to specification**
 - (exception for materials that do not fully conform – the exception must be included on the label)
 - b. **Be manufactured according to the appropriate standards of Good Manufacturing Practices**

(USP-NF General Notices)

What is the problem?

Country	Year	Incident
Spain	1981	Deaths due to industrial oil sold as cooking oil
India	1986	Deaths due to glycerin adulterated with diethylene glycol
Nigeria	1990	Deaths due to diethylene glycol
Bangladesh	1990-2	Deaths due to diethylene glycol in acetaminophen elixir
Haiti	1995/6	Deaths due to glycerin adulterated with diethylene glycol
India	1998	Deaths due to diethylene glycol in cough expectorant
Panama	2006	Deaths due to glycerin adulterated with diethylene glycol
USA	2006	Toothpaste adulterated with diethylene glycol found in Georgia

Common factors in adulteration

- **Fraud!**
 - Industrial grade materials deliberately mislabeled as pharmaceutical grade.
- **Sales appeared to have been targeted at less wealthy countries and/or consumers:**
 - Georgia incident is an exception; but is it? Or is it the start of a new trend?
- **Commodity items**
 - Traded without adequate quality controls in place.
- **Pharmaceutical materials probably all had CoAs:**
 - CoAs were not questioned.
- **No ID testing carried out**
 - But would the ID test of the day have picked up the adulteration?
- **A general assumption that the ‘other’ party is honest – Dangerous; can land you in court.**

Caveat emptor!

- **For any system to succeed it has to have global application and acceptance.**
- **High tech solutions/over-reliance on technology are not necessarily the best way in the global arena.**
 - **In many countries the key will be the human element**
- **If it works for Panama, Haiti, Bangladesh, etc., it will probably work in the US**
 - **But we may want to adapt it to a more hi-tech environment for the US.**

What has been/is being done to prevent similar future incidents?

- **FDA expectations:**
 - **21CFR §211.84**
 - **Auditing of suppliers**
 - **Testing of all Glycerin shipments and lots for the absence of Diethylene Glycol**
- **IPEC-Americas (with IPEC Europe and JPEC) has published a series of voluntary Guidelines.**
- **WHO has published standards for excipient distribution.**
- **European Commission has published proposals for excipient GMPs; final decision awaited.**
- **Interagency Task Force on Import Safety set up**
 - **Recommendations and action items**

FDA Expectations

- **21 CFR §211.84; mandates testing of all incoming shipments of each lot;**
 - a. **Each lot shall be withheld from use until examined and released by the quality control unit**
 - b. **Representative samples of each shipment of each lot**
 - c. **Written sampling protocols and procedures**
 - d. **Samples tested:**
 - 1) **At least one identity test to be performed on the sample**
 - 2) **Testing for conformance to written specifications. CofA may be accepted if an identity test is performed and the reliability of the suppliers testing is established**
 - e. **Lots meeting specification may be released; lots not meeting specification shall be rejected.**

FDA Expectations

- **Supplier Audits**
 - Applies to excipients
 - The FDA have already said that supplier issues will have higher priority during their audits of pharmaceutical product manufacturers in future
 - Need to confirm that supplier is following the agreed procedures
 - Need to audit the supply chain
- **Glycerin**
 - All shipments of each lot need to be tested to confirm the absence of diethylene glycol:
 - USP monograph has been amended to include this requirement

IPEC-Americas Initiatives

- **IPEC-Americas has published the following Guidelines:**
 - **Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients (with IPEC Europe and PQG)**
 - **Good Manufacturing Practices Audit Guide for Pharmaceutical Excipients (with IPEC Europe and PQG)**
 - **Good Distribution Practices for Pharmaceutical Excipients (with IPEC Europe)**
 - **Significant Change Guide for Bulk Pharmaceutical Excipients**
 - **Certificate of Analysis Guide for Bulk Pharmaceutical Excipients**
 - **Excipient Master File Guide**
 - **Excipient Information Protocol Guide**
 - **Qualification of Excipients for Use in Pharmaceuticals (Phase 1)**
- **Other initiatives include:**
 - **Revisions to some of the published Guides**
 - **Excipient Composition**
 - **Quality by Design**
 - **Quality Agreements**
 - **Excipient Pedigree**
 - **Validation as it applies to Excipient manufacture**

European Commission Initiatives

- **Draft document issued:**
 - **Specific Conditions of the Application of the Principles and Guidelines of Good Manufacturing Practices for Certain Excipients**
(Version 21, December 2006)
 - Excipients prepared from materials derived from TSE relevant species
 - Excipients derived from human/animal material with potential for viral contamination risk
 - Excipient claimed to be sterile (sold as sterile) and used without further sterilization
 - Excipients at significant risk of endotoxin/pyrogen contamination, and which are used in products required to be endotoxin/pyrogen controlled
 - Propylene glycol
 - Glycerol
 - **On-line questionnaire – Instruction Note dated March 16, 2007** (285 responses)
 - **Impact Assessment Report issued December 19, 2007 – recommending no changes; but only an advisory report!**
 - **Final decision yet to be issued.**

Interagency Working Group on Import Safety

- **Set up by Executive Order 13439, issued by President Bush July 18, 2007**
 - **Chaired by Michael O Leavitt, Secretary Health and Human Services**
 - **Senior officials from 12 Departments and Agencies**
- **Strategic Framework Document issued by the Working Group September 19, 2007**
- **Roadmap Document issued November 2007**
 - **Based on the framework document**
 - **14 broad recommendations**
 - **50 specific action steps**
- **THIS WILL AFFECT ALL OF US IN SOME WAY!**

Interim Summary

- **Excipients are now high on the Governments' agendas**
- **We can expect much more scrutiny of how we handle our excipient business in future**
- **There are resources out there; we need to use them**

What Excipient User Companies can do!

- Stop thinking of excipients as commodities!
- There are no unimportant excipients:
 - **ALL EXCIPIENTS ARE IMPORTANT!**
- Build relationships with your suppliers
 - Be 'wary' of new suppliers for existing materials:
 - Undertake the appropriate due diligence
 - An audit every 2 – 3 years may not be sufficient
 - Intermediate 'liaison' visits should be considered
 - Have a written agreement (e.g. Quality Agreement) that requires the supplier to notify the purchaser of significant changes to:
 - Process
 - Equipment train
 - Quality management system
 - Source
- Understand the excipient supply chain
 - Inter-nodal warehousing
 - Transshipment points
 - En-route security
- Audit the manufacturing site
- Audit the supply chain
- Maintain the dialog/confirm nothing has changed
 - **COMMUNICATION!**

What Excipient Manufacturers can do!

- **Stop thinking of excipients as commodities!**
- **Work with your Customers**
- **Work with your Distributors/Agents**
- **Audit your Distributors/Agents/Supply chain**
- **Maintain the dialog/confirm nothing has changed**
 - **COMMUNICATION!**

What Excipient Distributors can do!

- **Stop thinking of excipients as commodities!**
- **Work with your Manufacturers**
- **Audit your Manufacturers/Supply chain**
- **Work with your Customers**
- **Maintain the dialog (both ways)/confirm nothing has changed**
 - **COMMUNICATION!**

What we need!

- **A plan to address the issues**
 - A list of sites, etc. to be audited
 - A timeline for completion
 - The top 10% of suppliers is no longer adequate
 - No excipient is unimportant!
- **Deadline for the plan**
 - Within 6 months or by the time your next internal or FDA audit is due, whichever is sooner.
- **Resources**
 - In-house auditors vs. 3rd party auditors
 - In-house staff to follow through vs. contracted support
 - This type of program is not something every Company can do on their own!

3rd Party Audits

- **Pros**

- No increase in permanent head count
- Used only as needed
- Straightforward communication
- Not a payroll expense
- Travel expenses may be reduced
- May be able to offset some cost by sharing audits with other customers

- **Cons**

- Difficult to build supplier relationships
- More complex lines of communication
- External services expense
- Need to verify training standards at audit provider
- In-house staff do not gain experience at the site of the audit

Ways to maintain Excipient Integrity through the Supply Chain

- **No one measure is going to work in isolation; we will require a series of measures that can be implemented, and that are cost effective.**
- **Such measures could include but are not limited to:**
 - **Tamper-evident seals and packaging**
 - **Excipient pedigree documents**
 - **More effective targeting of inspections**
 - **Auditing of manufacturing site and supply chain**
 - **Using designated carriers**
 - **RFID, Bar codes**

Excipient Pedigree

- **What extra safeguards can we achieve using existing shipping documentation?**
- **Pre-requisite information:**
 - **Verified identification of site of manufacture**
 - **Audited site of manufacture and supply chain**
 - **Probably requires that carriers be approved**
- **Have traceable documented confirmation of supply chain:**
 - **All manufacturers have manufacturing records and dispatch records**
 - **All carriers have some form of documentation**
 - **All warehouses have goods receipts and dispatch documents**
 - **Customs require pro-forma invoices and notification of arrival in the country**
 - **Customs will also approve importation and release of the shipment**
- **Combining all these different documents creates a documented pedigree for the excipient shipment/lot**

Conclusions

- **THERE ARE NO UNIMPORTANT EXCIPIENTS!**
- **Excipients are now in the limelight, and are likely to stay there.**
- **We need to change our thinking about excipients, and treat them as vital components of drug products.**
- **The industry (all sides) needs to be proactive in implementing adequate excipient control strategies.**
- **WE CANNOT PREVENT FRAUD AND ADULTERATION!**
 - **We need to make it a lot more difficult for fraud to succeed!**
- **NO ONE SECURITY MEASURE WILL BE EFFECTIVE IN ISOLATION!**
 - **A series of measures that reinforce each other will be necessary!**
 - **Audits, liaison visits, testing, excipient pedigree, etc.**
- **There are documents available that can establish the excipient's pedigree:**
 - **We need to use them!**
- **There will be changes in the coming months from the FDA and Interagency Working Group on Import Safety**
- **Carpe diem!**
 - **WE DO NOT NEED ANOTHER GEORGIA INCIDENT!**