Qualification of Excipients:

A key to Product Quality & Patient Safety

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Drug Regulatory Alerts!!! Quality a key concern

FY22 Drug Recalls Highest In Five Years: FDA Report

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Along with this growth in manufacturing sites, the FDA reported a drastic increase in surveillance inspection, conducting 328 of these operations in 2022. This is "nearly triple the amount" of inspections during the year prior, indicating that the regulator is starting to regain its pre-pandemic activity levels.

The FDA also issued 28 import alerts and 72 warning letters in FY22. Import alerts allow the regulator's field staff to detain products coming from certain importers even without a physical examination at the time of entry. These alerts are issued after the FDA has gathered enough evidence to show that the product, its manufacturer or shipper could be in violation of regulatory laws or policies.

Drug Alert: 53 Drug Samples Fail To Qualify CDSCO Test, 3 Declared Spurious

Metformin had the largest number of recalls throughout 2020 and at the start of 2021 with FDA citing nitrosamine contamination as the primary cause of the recalls. Nearly every month, starting in May 2020, drugmakers were announcing/reporting product recalls. In May 2020,

Indonesia court hearing into children killed by toxic cough syrup

Some 200 children have died of acute kidney injury in Indonesia since last year and dozens of cases linked to cough syrup have been reported in The Gambia and Uzbekistan.

Core Trends in Drug recalls: An analysis of 2022 and Q1 2023

- **Contamination- Microbial & Chemical**
- **cGMP deviations and sterility concerns**
- **Failed specs another driver or quality control issues**
- **Undeclared ingredients: An ongoing cause of drug recalls**

Increased recognition!
Excipients are more than just an inactive ingredients

What differentiates Excipients from APIs?

- **Does not treat the disease or the condition**
  - Without excipients, the therapeutic revolution of the last 100 years would not have been possible!
  - They are (should be) pharmacologically inactive; but they may not be physiologically inactive
- **Different sources of materials**
  - Harvested(Agriculture)
  - Mined
  - Synthetic
- **Scale of manufacture**
  - Excipient production may be measured as thousands of tons per annum
  - APIs are usually manufactured in small batches
- For many chemicals, **production of excipient grades for pharmaceutical usage is only a small fraction** of the total production
- **Many excipients are not simple 'pure' chemicals** and their composition may not be well-defined

How does one define quality to be applied for excipients?

Regulatory framework for APIs

- Extremely **well defined regulations**
- GMP production, Compendial compliance and consistency in testing results

Regulatory framework for Excipients

- No well defined regulations
- Regulators recognize that excipients CANNOT be regulated the same as APIs
- Additional flexibility is needed due to the diversity of raw material sourcing, manufacturing processes and facilities
- Although regulators recognize the importance of excipients, ***They place responsibility for excipient quality on the drug product manufacturer***

Making Adequate Supplier Qualification one of the key to Product Quality & Patient Safety

Key Qualification requirements

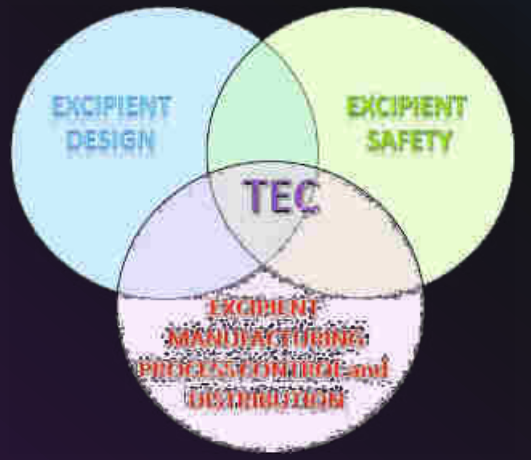
- Differentiation of excipient manufacturer & supply to pharmaceutical
- Excipient functionality and selection of right excipient grade also depends on:
  - Intended uses / claims- Is it a Drug or a Cosmetic Product?
  - Efficacy (dose)
- Regulatory Assessment
  - Safety, Toxicological and Legislation in the respective country
  - Excipient master file and other filing information like CEP
- Consistency of specification
  - Compendial compliance or Manufacturer's specification
- Validated manufacturing, composition and content including packaging
- Compliance to ICH requirements like
  - stability, impurity, residual solvent, elemental impurities

Key Qualification requirements contd..

- Information and transparency of:
  - Testing method and validation
  - Batch records
- Supply consideration
  - Identity of Source and manufacturing location
  - Commercial availability of the materials to ensure supply and business continuity
  - Evaluate a distributor's conformance to good distribution practices
  - Establish supply and quality agreement
- Manufacturer qualification
  - Audit and audit history
  - Production experience and capabilities
  - Compliance history
  - Sample and commercial consistency
  - Technical competency and support availability
  - Technological advancement and support including digitalization
- Cost

IPEC Guidelines & White Papers

- International Pharmaceutical Excipients Council (IPEC) has been developing many guidelines, programs and proposals on various aspects of Total Excipient Control (TEC) over the last 20+ years.
- Each guideline fills a specific need related to an area of excipient control.
- These Guidelines and White Papers have been used by many companies and regulators to establish appropriate standards for excipient control throughout the world.
- **TEC** covers the controls needed from the time an excipient manufacturer thinks of marketing a chemical as an excipient for the pharmaceutical industry to the time the patient takes the drug product containing the excipient.



https://www.ipec-europe.org/uploads/publications/20201026-eq-guide-revision-final-1615800052.pdf

IPEC Guidelines & White Papers

- IPEC-PQG Excipient Good Manufacturing Practices Guide
- IPEC Excipient Good Distribution Practices Guide
- IPEC-PQG Excipient Good Manufacturing Practices Audit Guide
- IPEC Excipient Good Distribution Practices Audit Guide (US & EU)
- IPEC White Paper on Excipient Pedigree
- IPEC Excipient Qualification Guide
- IPEC Excipient Information Protocol Guide
- IPEC Excipient Quality Agreement Guide
- IPEC Excipient Certificate of Analysis Guide
- IPEC Excipient Stability Guide
- IPEC Position Paper on Accelerated Stability
- IPEC Excipient Composition Guide
- IPEC Excipient Significant Change Guide
- IPEC Excipient Master File Guide (US)
- IPEC Risk Assessment Guide (US & EU)
- IPEC Co-Processed Excipients Guide
- IPEC Quality by Design Sampling Guide
- IPEC Technically Unavoidable Particles Profile Guide

All guidelines and white papers can be downloaded for FREE at: www.ipecamericas.org

IPEC Guidelines & White Papers

The IPEC-PQG Excipient GMP Guideline is accepted as the basis of cGMPs for excipients, internationally

- U.S. - FDA – actively involved with IPEC GMP initiatives
- Europe - EMA - used as the basis for Excipient GMP discussions under Falsified Medicines Directive (formalized GMP risk assessments)
- Japan – IPEC Japan translation used as industry standard
- China - CFDA – used as the basis for draft Excipient GMP regulations
- Argentina - INAME – meetings in 2012, 2013 to discuss.
- Brazil - ANVISA – IPEC GMP translated into Portuguese and provided to ANVISA for consideration in drafting Excipient GMPs – Excipient GMP Regulation was published in 2015
- India – NO specific or separate regulations for Excipients but generally GMPs - Schedule M of Drugs & Cosmetic Act 1940 and Rule 1945 are followed. However these are not fully workable for excipients.

Global Collaboration

- We need truly collaborative approaches both within and between
  - Industry and trade associations
  - Ingredients suppliers
  - Distributors
  - Regulators and Lawmakers
  - Criminal/Enforcement agencies
- IPEC is working globally to make this happen!!
- IPEC India would be able to offer its assistance to Indian regulators in developing norms for excipients or harmonising excipient standards with international standards

Thank You!

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