Critical Issues In The Use and Evaluation of Excipients In Dosage Forms Such As Pediatric, Geriatric and Abuse Deterrent Dosage Forms

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Outline

• Introduction to research needs for excipients
• Fundamental research needs
• Specialty excipient needs
• Continuous manufacturing
• Stream line approval for new excipients
Excipients are Key to Quality

• Excipients are added to provide:
  – Manufacturability
  – Stability
  – Patient acceptance
  – Drug delivery attributes
  – And many other properties
  – Excipients aren’t inactive ingredients
Excipient Control is Key to Quality

- Unit Operation 1: Mixing
- Unit Operation 2: Tablet Compaction
- Unit Operation 3: Tablet Coating

Material Inputs: Excipients

Process Inputs
- Process Conditions
- Unknown unknowns?

CMA

Product Quality

Excipients Control is Key to Quality
Scale Analysis

Molecular
- Physicochemical
  - e.g. - Tm, Tg,

Particulate
- Particulate
  - e.g. – size, distribution

Volume Element
- Solid - Moduli
- Powder - Flow
- Liquid - Viscosity

Unit Operation
- Mixing Patterns
- Resident Times

Manufacturing
- Process optimization

Lack of methods & Standardization

Adapted from: Perry's Chemical Engineers' Handbook 7th Ed, RH Perry DW Green, Ch20
Data Platform

HUBzero CMS

Risk Discovery

Data Platform User Interface

Decision-making

Data Load

Risk Discovery

User Interface

Data Import

Spreadsheet Upload

Risk Data Processing

Data Acquisition

Hierarchical Data Selection

Decision Support

Rules Validation

Visualization

Data View

Data Definition Language

Interactive Data Exploration

SOFTWARE COMPONENTS

DECISION VARIABLES

MASTER LISTS

RULES

VALID PATHS

FMEA STRUCTURE

RPN RISK ASSIGNMENTS

SUPPORT DATA

KNOWLEDGE BASE

hubzero web ecosystem
Specialty Applications

• Years of experience provides at least some empirical rules for tradition IR manufacturing
  – E.g., particle size and flow
  – Best practices for Mg Stearate blending
  – Etc.

• But some formulation types don’t have well established best practices and a lot of research is needed to establish best practices
  – Pediatric dosage forms – taste masking
    • Especially neonates and infants
  – Low solubility
  – Abuse deterrent Formulations (ADF)
  – Biotech products
Continuous Manufacturing

• It appears continuous manufacturing will only grow in importance

• Because knowledge of excipient performance is empirical and not fundamental in nature
  – It is unknown how the empirical experience and rules in a batch process will translate to a continuous process
    • Some will and some won’t
    • E.g., are there scale or shear differences for Mg Stearate mixing

• Need to better understand how excipients perform in continuous process and identify CMA for continues processes

• Research is needed to determine CMA and best practices for excipient use in continuous processes
Approval of New Excipients

• Currently not many new excipients are entering the market
  – Most introductions are co-processed blends of old excipients
  – Previously mentioned specialty areas would greatly benefit from new excipients with enhanced materials properties would help bring drugs to market faster and with less expense
  – Markets are small enough there is not sufficient financial incentive to develop new excipients
  – Currently new excipients are approved by piggy backing on big pharma product that needs the a certain excipient and once this product is approved the excipient is put in the inactive ingredient database (IID)
    • This approach limits and delays the introduction of new excipients into the market and underserves excipients for niche markets

• Research is needed to streamline the process for approving new excipients especially for niche markets