The Impact of Excipient Variability on QbD

The Need for Good Qualification Processes – IPEC America’s Perspective

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Pharmaceutical Development, Quality Risk Management and The Quality System: Foundation for Assuring Ongoing State of Control

The Materials System

• Integral to the Quality System

• Includes selection, characterizing, qualifying, and monitoring excipients and suppliers

Ref.: S. Wolfgang - FDA
QbD involves Understanding Product Variability

\[ \sigma_{\text{Product}}^2 = \sigma_{\text{API}}^2 + \sigma_{\text{Excipients}}^2 + \sigma_{\text{Process}}^2 + \sigma_{\text{Interactions}}^2 \]

Ref: C. Moreton
What is the Excipient Industry?

There is No Real Pharmaceutical Excipient Industry

Majority of Pharmaceutical Excipient Suppliers are Chemical or Food Industry subsidiaries

- Small fraction of Main Production Volumes
- Varying degrees of dedicated R&D related to excipient uses
- Specifications-driven by main market (usually not Pharma)
- Global Market and Manufacturing Base

Ref: B. Carlin (FMC)
Excipient Industry PAT & QbD Predates FDA Initiative

Many excipients manufactured by Continuous Production

Optimisation not always pharmaceutically congruent

Excipient Industry PAT & QbD may hinder or help Quality, Functionality & Safety of Medicinal Products

Ref: B. Carlin (FMC)
What is the Excipient Industry?

Diverse Materials Base

- Chemical synthesis (Polymers) (often less defined than low molecular wt. entities)
- Mining of minerals
- Harvesting of vegetation
- Formulated Products
- Biotechnology
- Genetic Modification
- Animal by-products

Ref: B. Carlin (FMC)
Cultivated Carrageenophytes

“Marine Agronomy”

- Mariculture
  - *Kappaphycus alvarezii* (cottonii = kappa)
  - *Eucheuma denticulatum* (spinosum = iota)

- Invented by Marine Colloids (FMC) and Univ of Hawaii – late 60’s in the Philippines.

Unlike Pharma, Carrageenans in the Food Industry are mainly sold to agreed customer functionalities. In Pharma., we typically have focused on compendial specifications.

Ref: B. Carlin (FMC)
Carrageenan Bearing Seaweeds

Class: Rhodophyceae (Red Algae)

Genus:
- Chondrus
- Iradaea
- Gigartina
- Hypnea
- Eucheuma

Species:
- crispus
- ocellatus
- cordata
- boryana
- undulosa
- laminarioides
- stellata
- acicularis
- pistillata
- radula
- chamissoi
- skottsbergii
- canaliculata
- cervicois
- musciformis
- spinosum
- cottonii
- edule
- serra
- gelatinae

† The most commercially important carrageenan bearing weeds
† Adopted from GH Therkelsen

Ref: B. Carlin (FMC)
Continuous Quality Improvement

• QbD/PAT involves gaining a thorough understanding of a process and the impact on that process of all the input variables and their effect on that process.
  • Manufacturing Equipment Variables
  • Variable Manufacturing Techniques
  • Manufacturing Process Conditions
  • Environmental Conditions
  • Formulation (API and EXCIPIENT) Chemical & Physical Property Variation
  • Interactions of ALL these factors
So you need an excipient…

What do you want......ideally?

– Physiologically Inactive
– *Exhibit no lot-to-lot variability in properties and functionality***
– Available worldwide meeting global requirements
– Available from multiple vendors (*who provide equivalent materials***)
– Well characterized and made under GMPs
– Compatible with other excipients
– Easy to store
– *Inexpensive!*
Impact of Variables

Input Variables
- API Physical Properties
- Excipient Physical Properties

Process Variables
- Equipment
- Process Conditions
- Process Parameters
- Process Steps

Operator Variables
- Manual Steps
- Operator Training

Product Consistency
*Variable??

Not under the control of the Pharmaceutical User

Can it be?? Adjustments are A GOOD THING!!!
Variable Raw Material + Fixed Process = Variable Product
Variable Raw Material + (Anti)variable Process = Constant Product

Raw Materials → Process → Product

Control (Anti-phase) → PAT
Formulation (API and **EXCIPIENT**)

Chemical & Physical Property Variation

• API’s typically make up a small portion of a drug formulation

• Excipient physical property variation is one of the most important input variables that can impact a pharmaceutical manufacturing process.

• **PROBLEM** – Many excipients are made in large chemical plants primarily designed for producing chemicals for other industries
Formulation (API and EXCIPIENT) Chemical & Physical Property Variation

• Excipient Manufacturer’s Process Capability is primarily focused on chemical characteristics and CERTAIN physical properties for the Excipient Manufacturer’s INTENDED MARKET

• Excipients get used by Users for many functions which may not be what the excipient was designed for
Formulation (API and **EXCIPIENT**)
Chemical & Physical Property Variation

• **QbD/PAT controls will require a better understanding of:**
  - Excipient Batch Uniformity
    - *Batch vs. Continuous processes?***?
  - Batch-to-Batch Consistency
  - Supplier-to-Supplier Variability

• This does **NOT** mean tighter specifications for existing excipients

• **QbD is about building robust formulations and processes which can adapt to normal expected excipient variation**
Impact of QbD/PAT

• The desire for QbD/PAT registrations may 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
Formulation (API and **EXCIPIENT**) Chemical & Physical Property Variation

- Performance or Functionality Related Characteristics (FRCs) identified by Users may **NOT** be properties typically controlled by the Maker’s Manufacturing Process
  - User MUST communicate special needs to the manufacturer and supplier must determine if process capability exists to meet these needs
  - FRCs are specific to a particular Drug Formulation & Process not to an Excipient alone
  - FRCs **MUST** be determined experimentally!!!
  - Cannot just use an FRC listed in a compendia
Supplier Capability

• Discuss additional performance related requirements with suppliers to determine potential for availability!!!
  – Make sure that the supplier feels that they have the process capability to supply material meeting any specific requirements
  – Do not set specifications with lot selection criteria that suppliers are concerned about or are based on testing of a limited number of batches
Lot Selection Risk

- Approx. 50% of the time the excipient can’t meet the criteria if limits are tightened!!
- Usually variability is not cyclical like this!!
Quality by Design (QbD)

• IPEC Americas has formed a QbD Product Development Committee to address the following areas:
  - Proper Selection and Use of Excipient Performance Tests (addressing functionality) – Decision Tree approach;
  - Development of robust formulations (including QbD, PAT, etc.);
  - Introduction of Co-processed Excipients with customized functionalities (removal of regulatory barriers and customer acceptance)
Robustness of Formulation

• Obtaining excipients which are consistent from lot-to-lot in desired functionality properties is often difficult

• Special grades can be expensive and lot selection can be risky!!
  – Material may not always be available to meet special requirements when needed
  – Especially for commodity type excipients
Robustness of Formulation

• Therefore, it is critical that formulators make sure that they have fully investigated excipient variation and developed the most ROBUST formula possible with excipients meeting standard sales specifications before pursuing specifications with a supplier which are tighter than sales specifications & process norms

• Otherwise, the Operations and Supply Chain people may have significant difficulties during commercial production – THIS IS THE REAL COST!!!
Robustness of Formulation

• Samples will usually NOT be available however at the low, mid and max of the ranges for any specific properties
  • Presents a key challenge to QbD
  • Excipient companies target normal production to be in the center of their sales specification ranges and typically will not have samples at limits
  • These types of samples cannot be expected by users!!!
  • Other mechanisms must be found
Robustness of Formulation

• To evaluate the design space, sometimes you need to get creative and evaluate things such as:
  – Samples of different grades with properties on either side of the target grade properties to determine if this level of variability truly affects performance
  – If this level of variability can be handled by developing a robust formulation and process, then the typical variation within a given grade should be no problem

• Can use DOE with limited samples that may not show full range but can determine interaction potential
Excipient Realities!!!

• Some desired functionalities will still require commodity type excipients that do not meet all of the users criteria

• Therefore, it is critical that users and makers frankly discuss what can be done and what cannot be done during the qualification process
The Future

• QbD/PAT 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.

• This will create the need for even BETTER COMMUNICATION between makers, users and regulators than in the past when qualifying excipients