U.S. FOOD & DRUG ADMINISTRATION

Quality Considerations in Managing Excipient and API Risks to CM: *Regulatory Perspective*

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Disclaimer

Opinions expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the FDA.

FDA-Approved CM Applications (Oral Tablets)

According to information available in public domain:

- Vertex: ORKAMBI (lumacaftor/ivacaftor, 2015)
- Janssen: Prezista (darunavir, 2016) – Batch to CM switch
- Eli Lilly: Verzenio (abemaciclib, 2017)
- Vertex: Symdeko (tezacaftor/ivacaftor, 2018)
- Pfizer: Daurismo (glasdegib, 2018)
- Vertex: Trikafta (elexacaftor/tezacaftor/ivacaftor, 2019)
- Pfizer: Cibinqo (abrocitinib, 2022)

Tablets are manufactured via direct compression or wet/dry granulation routes

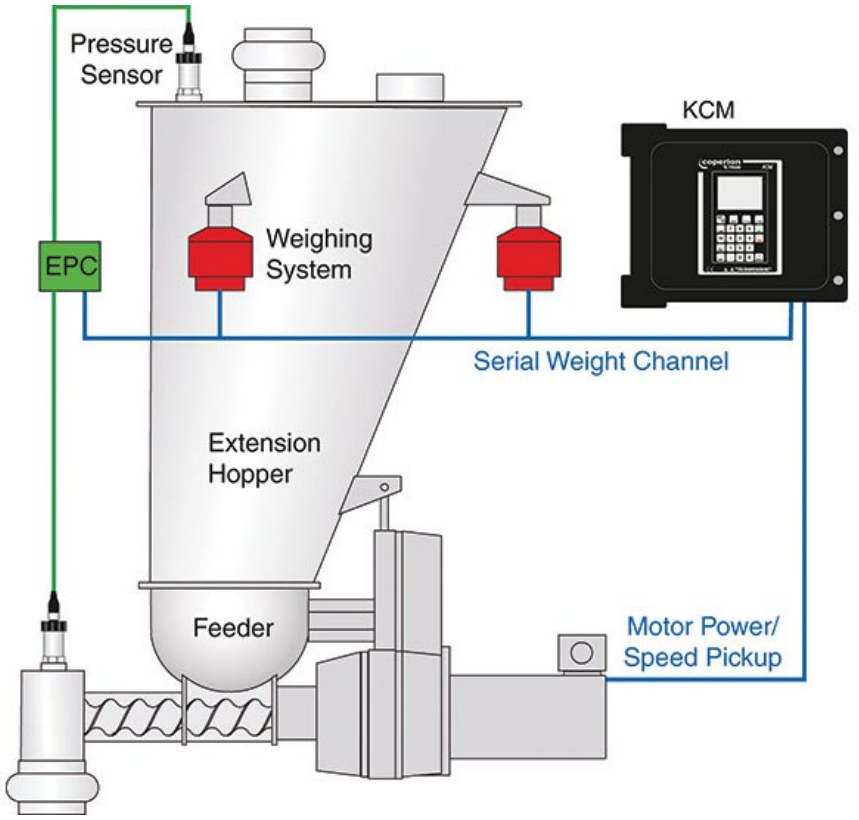
Key Enablers of CM

- Continuous feeding (e.g. LIW feeder)
- Understanding of process dynamics (e.g. residence time distribution - RTD)
  - Material traceability
- PAT (e.g. NIR)
- Diversion of non-conforming material
- Real time release testing (RTRT) if proposed

Material (API and excipients) properties can have a significant impact on all of above

Continuous Feeding

- Loss-in-Weight (LIW) feeders
  - Gravimetric mode
  - Volumetric mode (e.g. during refill)
- Control loop to adjust feed screw speed and drive feed rate to target
- Feeding of single component
- Feeding of pre-mix
  - Low dose API/excipients premix
  - Minor component excipient premix with other excipients



Material Properties and Feeding Performance

- Important to understand impact of API and excipient material properties on continuous feeding performance
  - Accuracy
  - Consistency
- Example material properties studied in applications
  - PSD, specific surface area, bulk density, flow properties, loss on drying
- Input materials for CM may require characterization and control of attributes that are typically not included in current USP monographs

Feeding Variation and Product CQAs

- Feeding variation and transit disturbances may lead to significant variability in formulation composition
- Typically, applicants study impact of various quantities or mass flow rates of API and excipients on in-process and final product CQAs
  - e.g. blend and content uniformity, dissolution, tablet hardness, disintegration
- Controls that may be implemented
  - Target and range of mass flow rate for individual materials
    - e.g. MCC 80-120% of target
  - Target and range of mass flow rate ratio
  - Target and range of % composition

Case Study: FDA's Evaluation of Feeding Rate Limits

- Applicant proposed IPC limits for feeding rates
  - Based on univariate studies
  - MCC (80-120% of target), croscarmellose sodium (80-120% of target), and Mg stearate (70.0-130.0% of target).
- Concern about the potentially cumulative effect of off-target amounts of these excipients on product CQAs (e.g. dissolution)
- Information request
  - Tighten the IPC limits based on commercial scale experience to date
- Applicant response
  - Monte Carlo simulation of feeder IPC data from 5 clinical and 3 commercial scale batches
  - Probability of more than one feeder operating off-target simultaneously is very low (< 0.001%)

Continued on next slide…

Case Study: FDA's Evaluation of Feeding Rate Limits (Cont'd)

- Simulation of Excipient Feeding Variation Dampening
  - Collaboration between FDA's review and research offices
- Simulated the impact of feeding disturbances of various magnitudes and durations utilizing residence time distribution (RTD) data provided by the applicant
  - Taylor dispersion model used to fit the experimental RTD data
  - Funnel plots: It would take
    - A feeding disturbance of ~ 240 seconds (CCS) and ~145 seconds (Mg stearate) at the bounds of the proposed IPC limits to produce tablets with the excipient contents being outside the respective acceptable limit
- Give the level of damping in downstream process, low risk of feeding variation on product composition and quality.

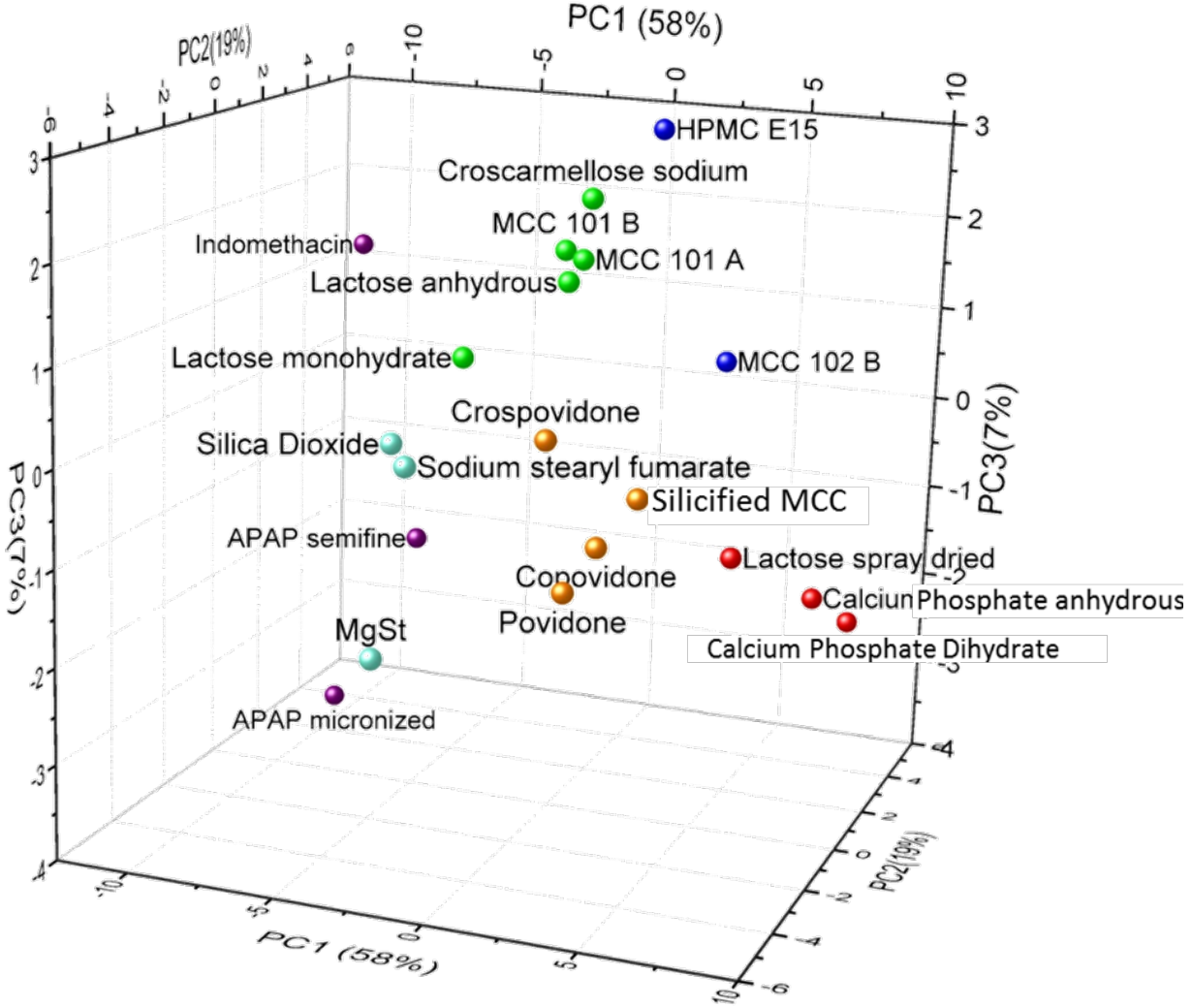
FDA Research on Material Properties and Impact on Feeding

- 20 pharmaceutical materials characterized for 44 properties for each material, capturing 880 data points.
- Multivariate Analysis
  - Principal component analysis of the established material library.
  - The first three principal components captured 84% of the overall variance in the dataset.
  - Hierarchical clustering analysis to classify materials into several clusters
  - Both PCA and clustering analysis can be appropriate tools to find materials with similar properties for, e.g.
    - Selection of surrogate materials for process development studies
      - Selection of tracers for RTD characterization

Yifan Wang, et al. International Journal of Pharmaceutics 569 (2019)

FDA Research on Material Properties and Impact on Feeding (cont'd)

- Feeding case study suggests
  - Selected materials from the same cluster show similar feeding performance (accuracy and consistency)
  - Selected materials from different clusters do not have comparable feeding performance.



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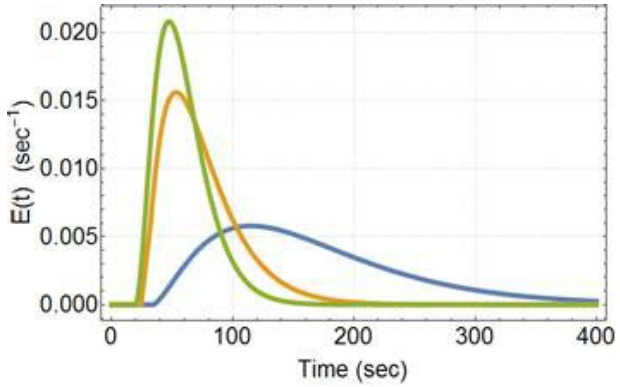
Material Properties and RTD (I)

Residence Time Distribution (RTD)

Probability distribution of time that solid or fluid materials stay inside one or more unit operations in a continuous flow system



Courtesy: Escotet-Espinoza, Rogers, Muzzio, Ierapetrirou, Engineering Research Center - Rutgers University

- RTD is a characterization tool of system dynamics and depends on:
  - Material properties
  - Process parameters (including line rate)
  - Equipment design and configuration

Material Properties and RTD (II)

- Characterization of RTD often uses a tracer to represent the API
  - ICH Q13: Selection of tracer should consider similarity of its flow properties to that of the constituent replaced
- RTD characterization and modeling should consider inclusion of material properties as input factors.
  - e.g. density, PSD, flow properties
- Lot to lot variability of material properties should be controlled, if
  - RTD is critical to the control strategy, e.g.
    - Diversion of non-conforming product from process stream
      - With RTD model
      - Without RTD model

Material Properties and PAT

- Material properties may impact spectroscopic methods and chemometric models that are often used as PAT tools in CM, e.g.
  - Changes in NIR spectra due to powder bulk density changes
  - Effects such as particle size on the intensity of scattered light
- Variation in physical characteristics of materials should be considered as a source of variability when constructing a calibration set
  - Multiple lots
  - Variation of relevant material properties
  - Different vendors, as necessary
- Model maintenance should consider input material property changes.

Case Study (2): FDA Information Request on Excipient Specs

- The specifications of excipients in P.4.1 were referenced to USP/NF, which does not address the physical criteria (e.g. PSD, density, moisture content), which may impact mass flow feeders, continuous processability, and PAT methods. Please address the following:
  - Discuss the impact of lot to lot variability of the excipients. Identify potential material attributes for excipients that may impact the proposed mode of operation and PAT method performance, and how these excipient material properties are managed within the control strategy.
  - Provide a current certificate of analysis for each excipient, as an example of the material attribute specifications for acceptability of the material beyond USP/NF.

Case Study (2): Information from Applicant

- DOE performed using different grades of MCC (major excipient) showed no significant impact of PSD on flowability of blend.
  - Minor components display reasonable flow properties and material attributes maintained by specs.
- Design and operation of the LIW feeders can correct any minor material variability due to internal feedback control loop
- Data from six formal stability batches were used to establish IPC limits for each excipient's feed rate.
- PAT chemometric models calibrated across design space using multiple lots of excipients.
- PAT method performance is controlled by model diagnostic acceptance criteria, based on multivariate statistics (Hotelling T2 and Q-residuals)
- Model Maintenance
  - Model diagnostic results trending
  - Excipient supplier change

Final Remarks

- API and excipient material properties can have an impact on continuous feeding, RTD, and PAT.
- Enhanced development approach and a good understanding of the impact will help develop risk-based control strategy for CM.
- Input material quality is a potential source of variability over lifecycle. Manufacturing issues related to material quality and the suitability of the current material specifications should be monitored over lifecycle.
  - Rich data from CM suitable for continuous process verification
  - Oversight of quality system

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  - CM application review teams

- PQRI

QUESTIONS?