PQRI Workshop:
Managing Excipient and API Impact on Continuous Manufacturing
May 17 – 18, 2022

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Impact of process selection on potential for failure – how to reduce the potential for failure due to special-cause variation

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Disclaimer

- The ideas and concepts discussed in this presentation are my own, and should not be construed as being the policy of any organization with which I am associated.

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Learning objectives

- On completion of this presentation, you should be able to demonstrate an understanding of:
  - Variability
  - The perils of oversimplification
  - Rational formulation and process design and development and BioRAM
  - Key questions to be answered
  - Possible solutions to allow more robust formulations and processes in continuous manufacturing

Presentation outline

- Introduction
  - Variation
  - Continuous manufacturing and trends
- Oversimplification
  - An example and the lessons learned
- Rational formulation and process design and development

What does the patient expect from their medicine?

1. Efficacy – effective treatment of the disease or condition.
2. Convenience – as convenient as possible.
3. Consistent performance – from dose to dose, and from supply to supply.
4. Continuity of supply – no disruptions in supply.

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Variation

- Common cause variation
  - Routine (random) variation in materials and processes
- Special cause variation
  - Can impact product and/or process variation in a non-random way:
    - Unanticipated!
    - Unpredictable!

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Continuous manufacturing (CM)

- System of manufacturing whereby starting components are continually fed into, and finished product is continually removed from, the manufacturing operation.
- Constraints on continuous manufacturing include:
  - No (or reduced) opportunity for operator intervention to compensate for material and process variability.
    - Requires consistent starting components (both API and excipients), or
    - Weaknesses have to be engineered out of the system.
  - Number of starting components that can be fed into the line (due to restrictions on space).
    - Favors the use of simpler formulations (fewer components).
  - Requires integration of appropriate analytical and monitoring technologies to provide for an acceptable control strategy.

Trends in continuous manufacturing of oral solid dosage forms

- Much interest in direct compression.
  - Simplest to implement (maybe).
  - Simple formulation and processing.
    - Fewer excipients.
    - Fewer unit operations.
    - Reduced inventory complexity.
- Dry granulation
  - More complex, but may be more robust.
- Wet granulation
  - Most complex.
  - Effects of long run time and the presence of water (in aqueous granulation) on microbial quality of the product may be unknown.
    - Do we need to consider including antimicrobial preservatives in the formulation?

Direct compression is not suitable for all APIs

- Digoxin example:
  - In the early 1970s, in the UK, there were problems related to the bioavailability of a leading brand of Digoxin Tablets.
    - Change in wet granulation mixer caused a ca. 3.5-fold increase in bioavailability – patients, previously stabilized, were hospitalized with symptoms of digoxin poisoning.
    - Dissolution requirement established by MCA (now MHRA) for all marketed Digoxin Tablets - ≥80% in 30 minutes.

Direct compression is not suitable for all APIs (continued)

- Comparison of three different manufacturing methods for Digoxin Tablets:
  - Direct compression – did not meet the dissolution requirements.
  - Aqueous wet granulation – met the dissolution requirements.
  - Solvent wet granulation – met the dissolution requirements within 5 – 10 minutes.

The perils of (over)simplification in CM

"Things should be kept as simple as possible – but not simpler!"

(Einstein ca. 1950 quoted in NY Times)

- If we make things too simple, are we putting the product (and the patient) at risk due a lack of robustness in the product formulation and/or process?

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Oversimplification - an example

- A formulation comprising:
  - Drug
  - Microcrystalline cellulose
  - Magnesium stearate
- Marketed for several years with no problems;
- Unanticipated change to a more stable drug polymorph.
  - Dissolution failures
  - Unable to obtain the original polymorph
- What to do?

The remedy

- There was a higher strength tablet.
- Because of the dose and potential size of tablet, this higher strength had less microcrystalline cellulose relative to the amount of API, but did include a superdisintegrant.
  - No dissolution failures with the new polymorph.

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Lessons from this example

- Oversimplification produced a formulation which was not robust enough.
- Microcrystalline cellulose does not have great disintegration properties.
- Always include a recognized disintegrant in an immediate release tablet (and powder-filled hardgel capsule).

Two questions for you!

- Can over-simplification and lack of robustness negate the benefits of continuous manufacturing for pharmaceuticals?

- Can Quality-by-Design compensate for over-simplification?

Rational formulation and process design (and development)

- Look at the properties of the API and what you want to achieve (QTPP).
  - Better understanding of the properties of the API that impact processing and finished product performance.
    - Is API stability affected by the necessary processing?
- Work out how to achieve the objective
- Carry out a risk assessment on the formulation and process.
  - e.g., using an Ishikawa diagram
- Determine the potential weak points and design them out (if possible).

Biopharmaceutics Risk Assessment Roadmap (BioRAM)

- Integrating biopharmaceutics into QbD
- Assessment and scoring
  - Box 1 – Starting point: QTPP and API properties
  - Box 2 – Formulation strategy
  - Box 3 – First feasibility assessment
  - Box 4 – Second feasibility assessment
  - Box 5 – Third feasibility assessment
  - Box 6 – Confirmatory studies and methods identified.

Dickinson PA, et al., (2016) J. Pharm Sci., 105, 3243-3255.

The key questions to be answered (1/2)

- What do I need to do with this API to get it in a form whereby it has consistent bioavailability, and is stable?
- How can I process the modified API, and maintain performance?
  - Direct compression
  - Dry granulation?
  - Wet granulation?

The key questions to be answered (2/2)

- What are the potential weaknesses in the:
  - API (before and after modification if needed)?
    - Physical form and characteristics?
    - Physical and chemical stability (degradation)?
  - Formulation?
  - Processing?
- How can we design out the weaknesses?
  - Formulation improvements?
  - Processing improvements?
  - Packaging options?

API (lack of) understanding: An example

- Poorly water soluble development candidate
- Forced degradation studies showed potential for oxidation:
  - 3 years' stability on crystalline API @ 25°C/60% RH
- Eventual formulation was an amorphous solid dispersion in a polymer.
  - After 5 days @ ambient conditions >10% degradation (oxidation).

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Investigation and remedy

- Investigated including antioxidants in the formulation
  - Sodium metabisulfite stabilized the API against oxidation
  - Unfortunately, sodium metabisulfite induced crystallization of the API.
- Adopted bottle with reduced oxygen permeability and included an oxygen scavenger sachet (together with a desiccant sachet) in the bottle.
  - Achieved acceptable stability (>2 years @ 25°C/60% RH)

Rational design vs. limited number of components

- The restriction on the number of feeders is an issue – but can we get round it?
  - Use a pre-blending arrangement (two (or more) in-line mixers in series) to allow more materials to be added?
  - Use of co-processed excipients comprising e.g. filler and superdisintegrant to reduce the number of feeders required?
- Do we need to add stabilizers to the API at the final API production stage?

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In conclusion

- Continuous manufacturing can provide significant benefits to the pharmaceutical industry, and on to the patient.
- Over-simplification has the potential to negate those benefits.
- Rational formulation and process design and development ***must*** take precedence over engineering expediency to preserve formulation and process robustness, and product availability.

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Thank you!
Any questions?