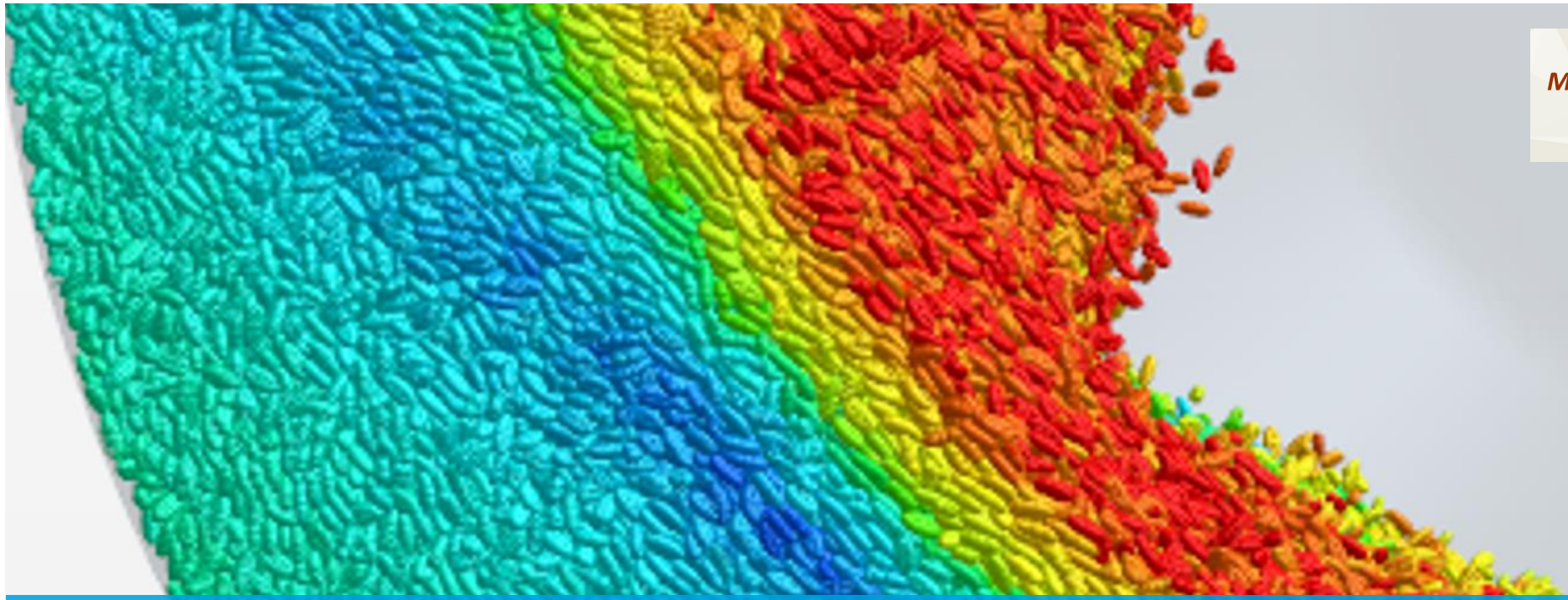

PQRI Workshop:
Managing Excipient and API Impact on Continuous Manufacturing
May 17 – 18, 2022

Understanding the difference between a marginal and robust process

The impact of excipient properties on process robustness

Bart Nitert, PhD, Mina Roudgar, PhD, Elisabeth Schäfer, PhD
Pharmaceutical Product Development & Supply, Janssen R&D, Belgium

PQRI conference, 17 May 2022

Use of discrete element modelling in a film coater to optimize the tablet film-coating process

Credit: Liang Li, Elise Vaes and Filip Willemse
Pharmaceutical Product Development & Supply, CPDS

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Outline

- Introduction Janssen
- What defines a robust process ?
- What is the role of excipient variability in building a robust process ?
- How to evaluate excipient variability during development of a continuous manufacturing process ?
- Conclusions

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Janssen in Belgium

Beerse 1

Janssen
- R&D
- Supply Chain
- Liquids & Creams
- Parenterals
- Distribution Center
- General Services

Merksem

Janssen Pharmacology Unit

Mechelen

Actelion

Beerse 2

Janssen-Cilag NV
Commercialization of all medicines in Belgium

La Louvière

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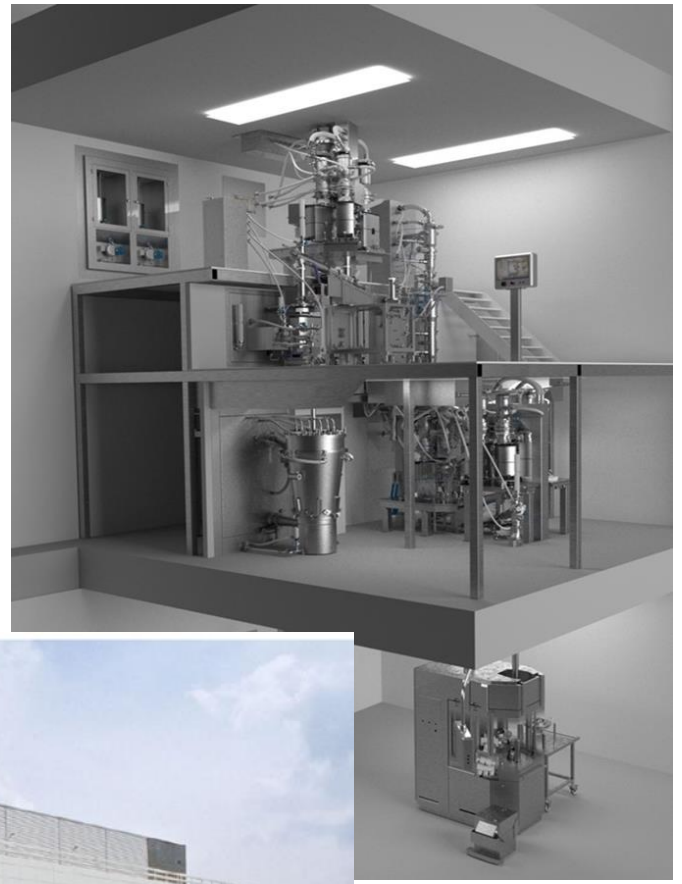
Olen

Janssen

Geel

Janssen Supply Chain
- API/Small Molecules

Beerse: CoE for Small Molecule R&D



FOYA 2020
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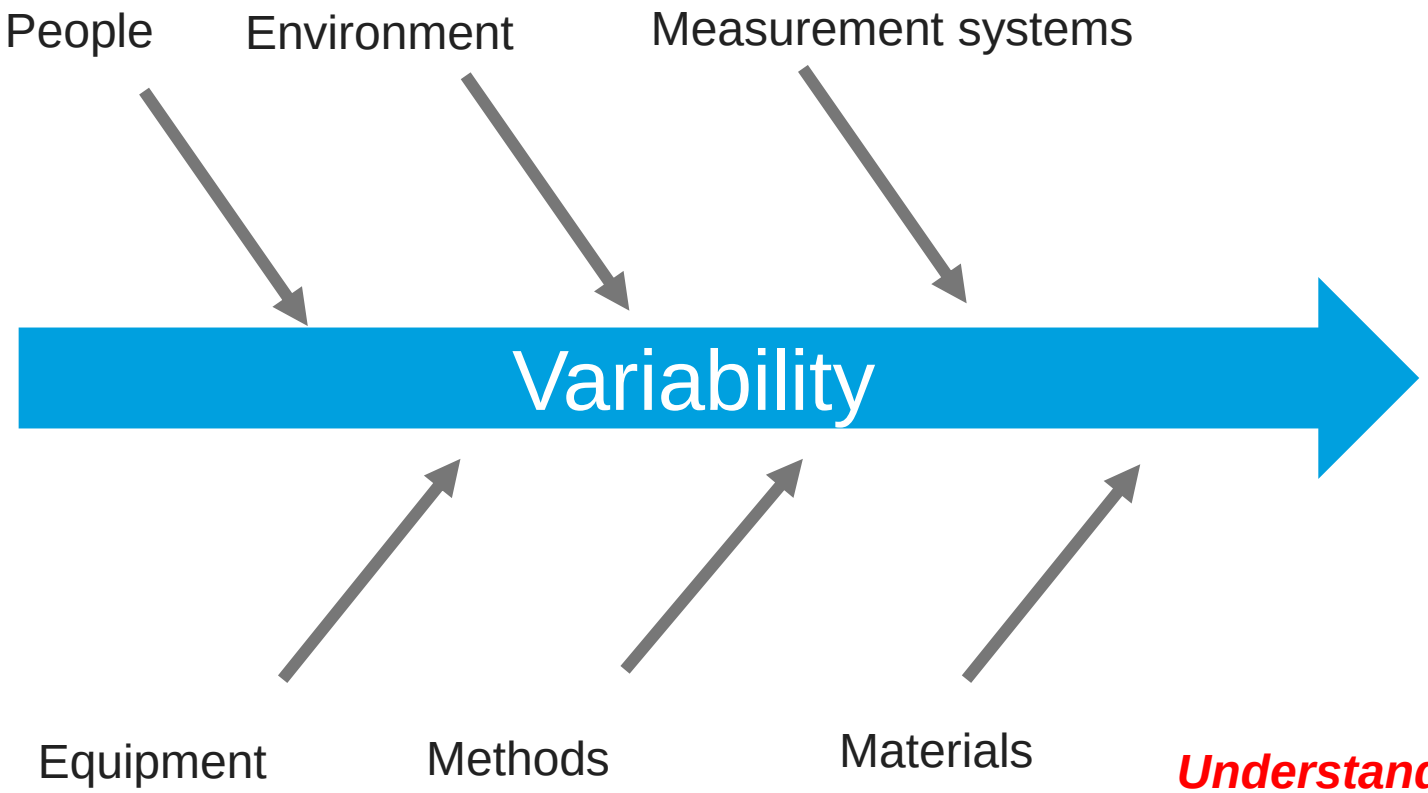
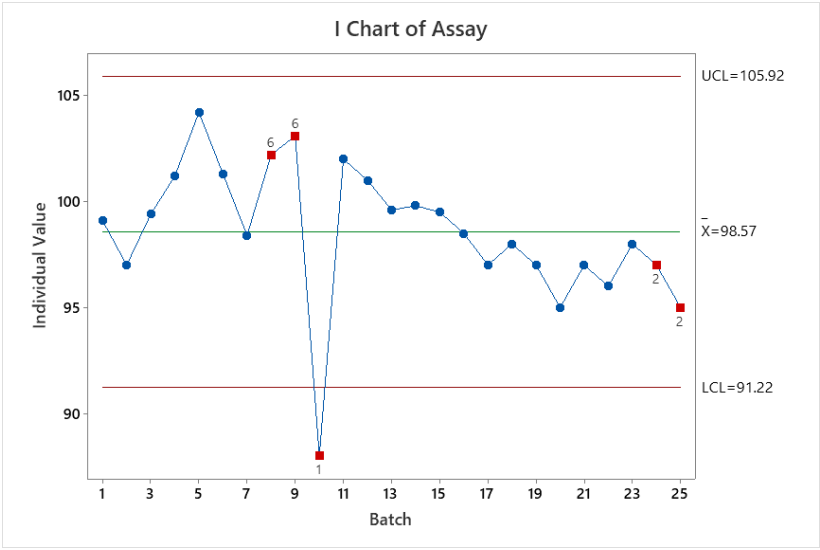
Process Innovation

What defines a robust process ?

Robustness *is the ability of a product/process to demonstrate acceptable quality and performance while tolerating variability in inputs (adopted from PQRI white paper, M. Glodek et al, 2015)*

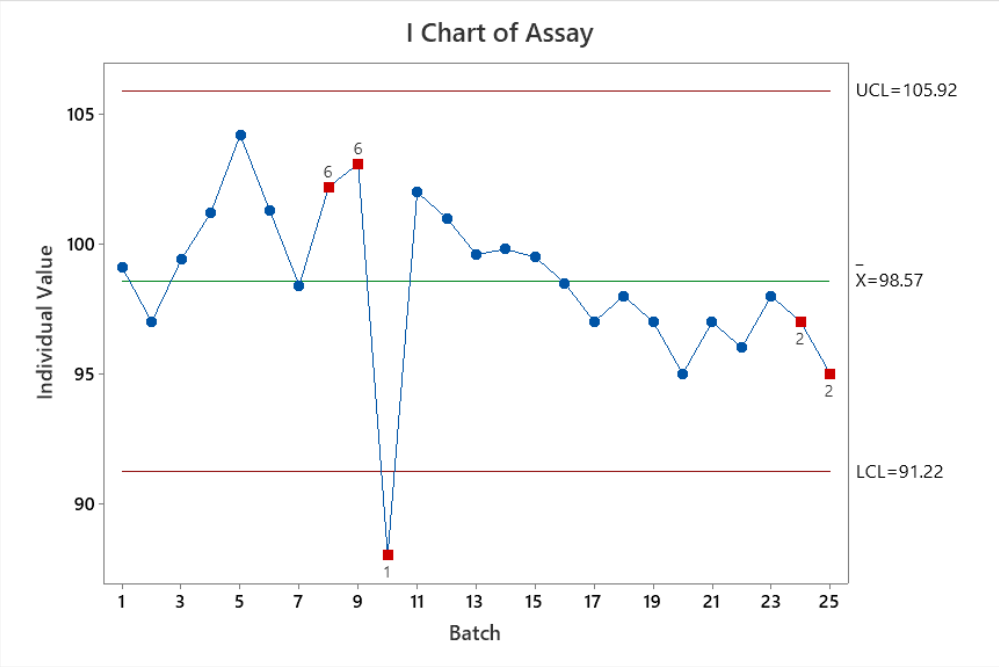




Understanding and minimizing the potential sources of common cause variability

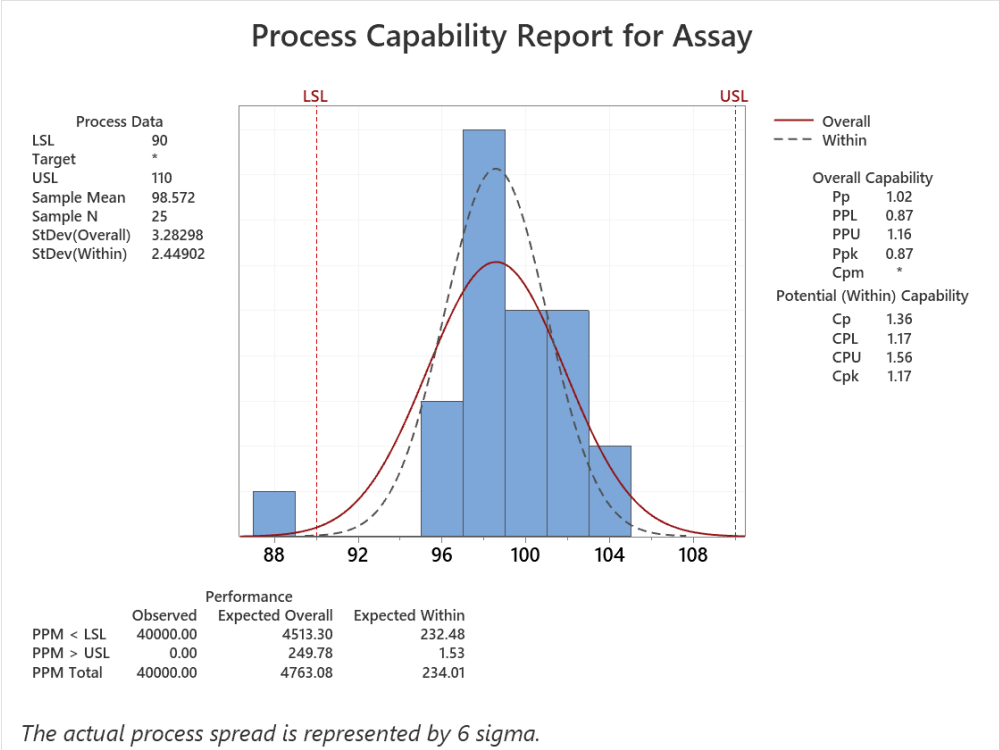
How do we measure process robustness ?

Statistical Process Control



Control charts: assessment of shifts and trends according to evaluation rules

Identify special cause events



Process capability analysis: Assessment of acceptability of CQA variability

Building robustness into drug product

ICH Q10: Pharmaceutical Quality System

Table I: Application of Process Performance and Product Quality Monitoring System throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Process and product knowledge generated and process and product monitoring conducted throughout development can be used to establish a control strategy for manufacturing.	Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Knowledge obtained during transfer and scale up activities can be useful in further developing the control strategy.	A well-defined system for process performance and product quality monitoring should be applied to assure performance within a state of control and to identify improvement areas.	Once manufacturing ceases, monitoring such as stability testing should continue to completion of the studies. Appropriate action on marketed product should continue to be executed according to regional regulations.

1. Gain knowledge during PharmDev and TT
2. Establish commercial control strategy
3. Monitor to assure performance and identify improvements

(a) Use quality risk management to establish the control strategy. This can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. The control strategy should facilitate timely *feedback / feedforward* and appropriate corrective action and preventive action;

(b) Provide the tools for measurement and analysis of parameters and attributes identified in the control strategy (e.g., data management and statistical tools);

(c) Analyse parameters and attributes identified in the control strategy to verify continued operation within a state of control;

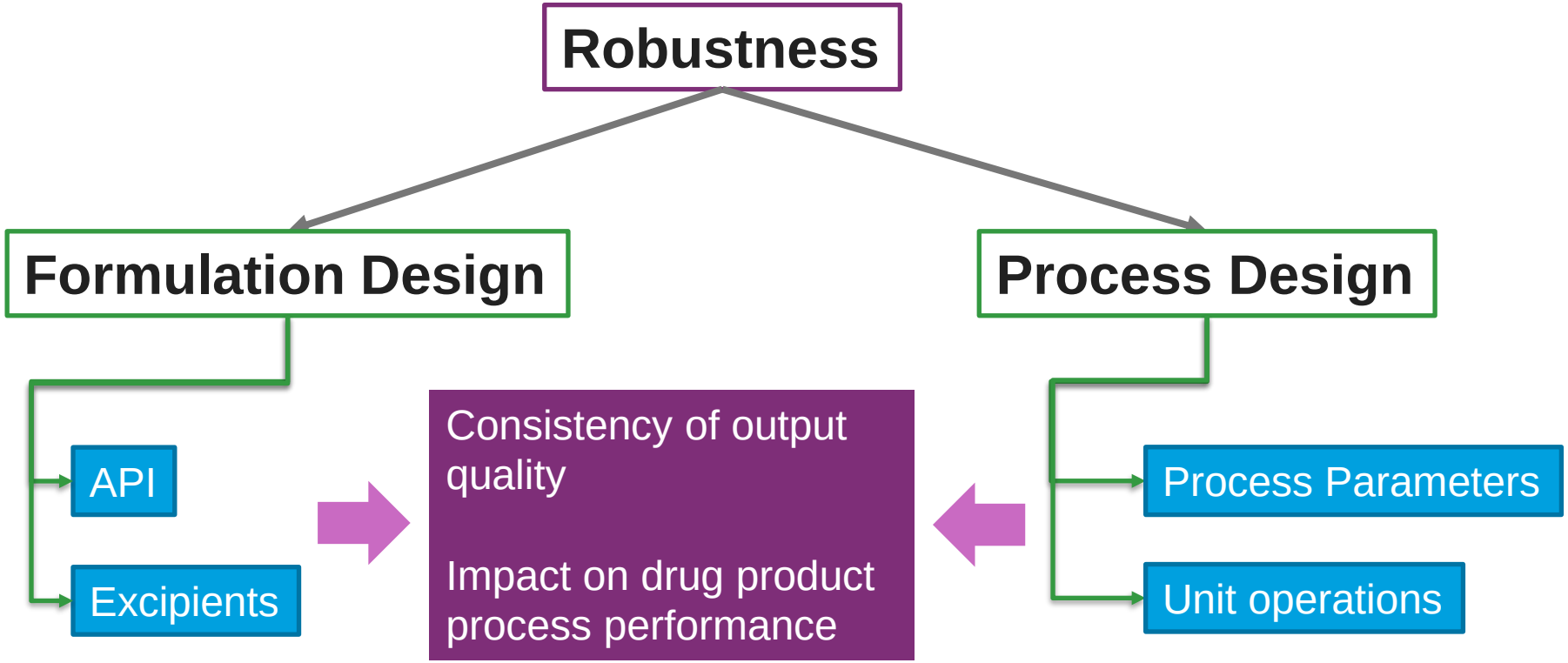
(d) Identify sources of variation affecting process performance and product quality for potential continual improvement activities to reduce or control variation;

(e) Include feedback on product quality from both internal and external sources, e.g., complaints, product rejections, non-conformances, recalls, deviations, audits and regulatory inspections and findings;

(f) Provide knowledge to enhance process understanding, enrich the *design space* (where established), and enable innovative approaches to process validation.

Building robustness into drug product

Robustness *is the ability of a product/process to demonstrate acceptable quality and performance while tolerating variability in inputs (adopted from PQRI white paper, M. Glodek et al, 2015)*



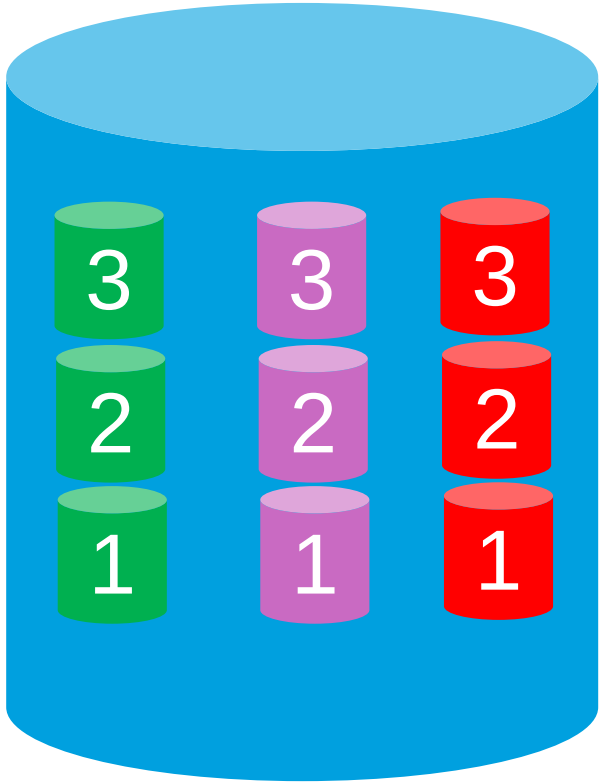
What makes excipient variability so special in CM ?

Lot-to-lot variability

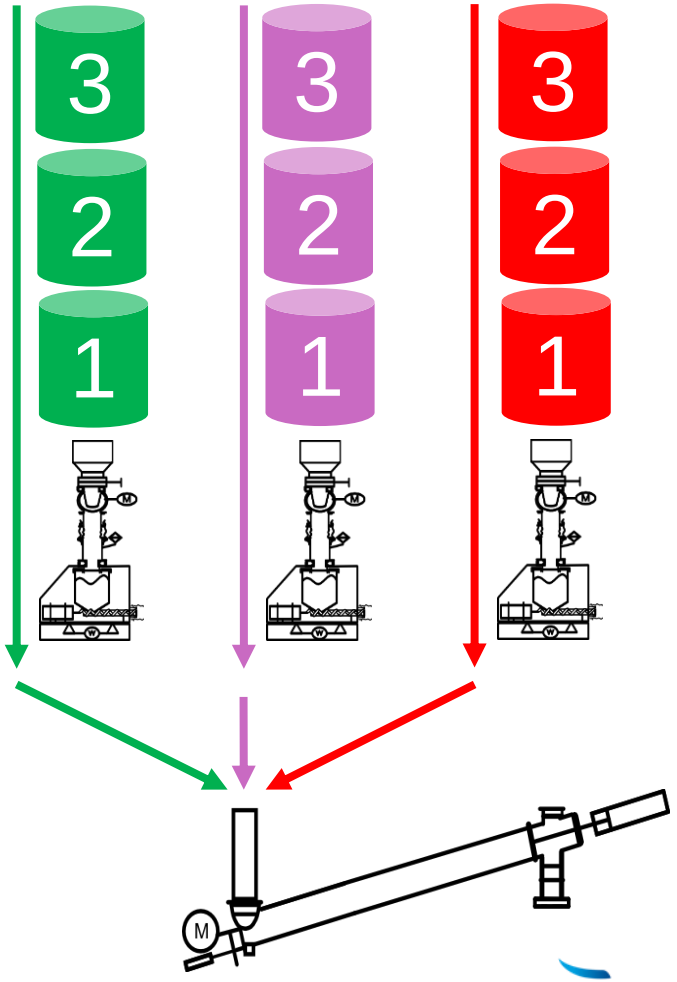
In batch blending any variability between lots is smoothened by mixing them all together.

In CM blending, the variation between lots propagates through the CM line to a tablet level.

Batch blending



Continuous Blending



Scientific understanding needed how lot-to-lot variability impacts process performance

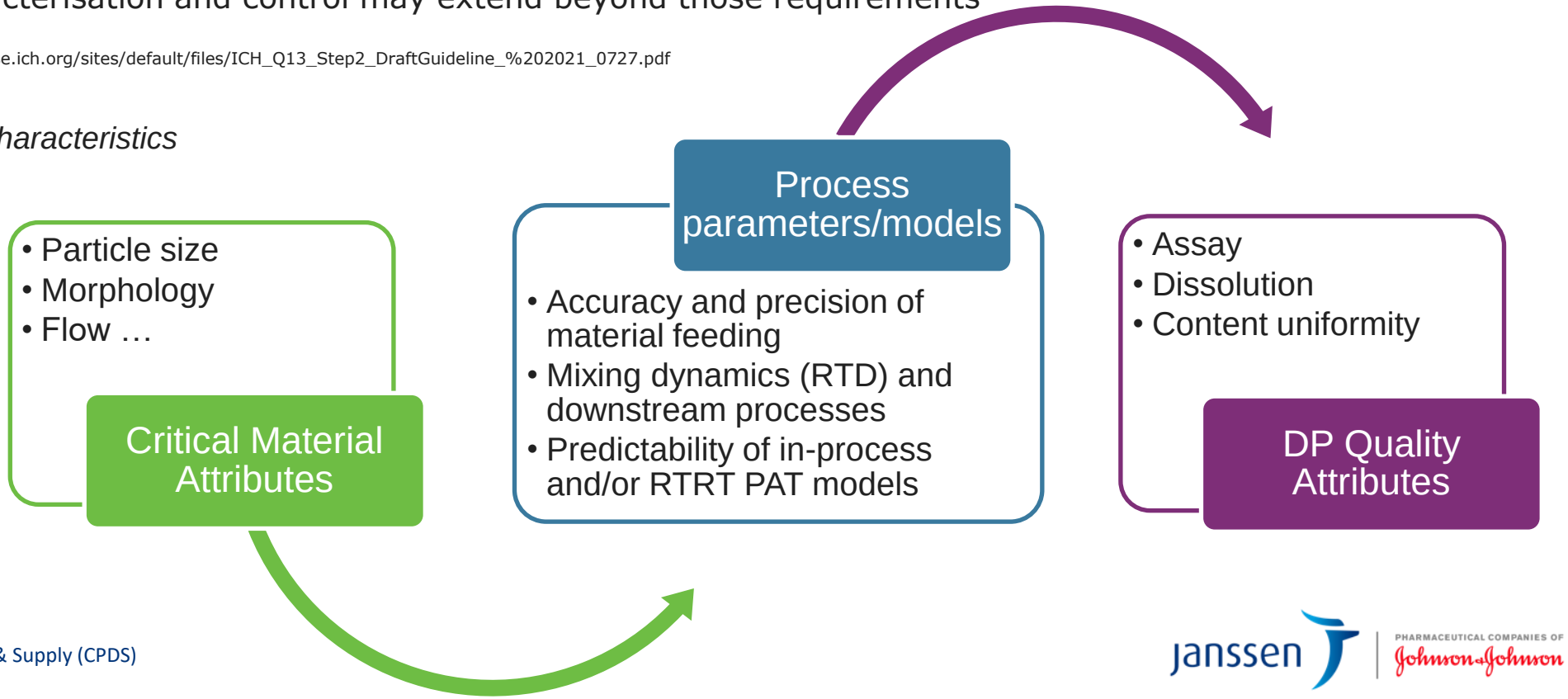
What makes excipient variability so special in CM ?

Knowledge of the relationship between raw material attributes and the impact on product quality attribute.

Input material attributes: Impact of input material attributes and their variability (e.g., intra-batch, inter-batch, different suppliers) on continuous processing should be assessed and proposed material attribute acceptable ranges should be justified when establishing the material specification. For input materials for which pharmacopoeial requirements exist, characterisation and control may extend beyond those requirements

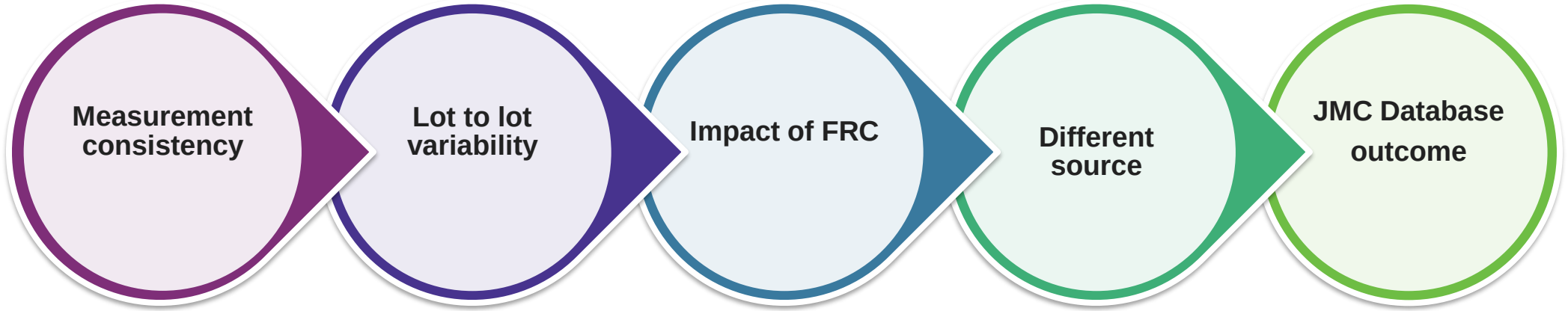
ICH Q13 – draft guidance: https://database.ich.org/sites/default/files/ICH_Q13_Step2_DraftGuideline_%202021_0727.pdf

Functionality related characteristics



Critical Material Attributes control

Material Characterization Package	
Material physical properties	**Material Flow behavior (FT4/ ring shear test)**
• Particle size distribution • Morphology • Specific surface area • Density	• **Dynamic Flow :** Basic Flowability, Aeration • **Bulk** : Compressibility, ,Permeability, Density • **Shear:** Shear Cell, Wall Friction



- ➢multiple runs/ same lot /each test
- ➢different lots of each specific grade grade/ specific supplier
- ➢Same type of excipient
- ➢Same supplier
- ➢Different grade
- ➢Same material
- ➢ Different supplier

JMC Application

JMC Application

- Identify the link between material physical properties and material flow behaviour
- Predict the impact of material variability on flow behaviour, formulation & process robustness→ reduce number of CM DOE run
- Design suitable DOE based on the high risk material attributes identified from JMC.
- Selection of suitable grade & supplier of the excipients for CM application
- Control inter/ intra lot variability of the target excipient
- Define & improve excipient CMA for desirable manufacturability (modification, new grade,..)

Control Strategy

Equipment

- Feeder alarm limits
- Feeder mass flow control
- Blender alarm limits
- Weight/hardness control tablet press
- Alarm limits process parameters compression
- Supports tablets accept/ reject decision

PAT

- Direct measurement of:
  - Blend potency
  - Content uniformity
- Supports tablets accept/ reject decision
- Works complementary with RTD

RTD

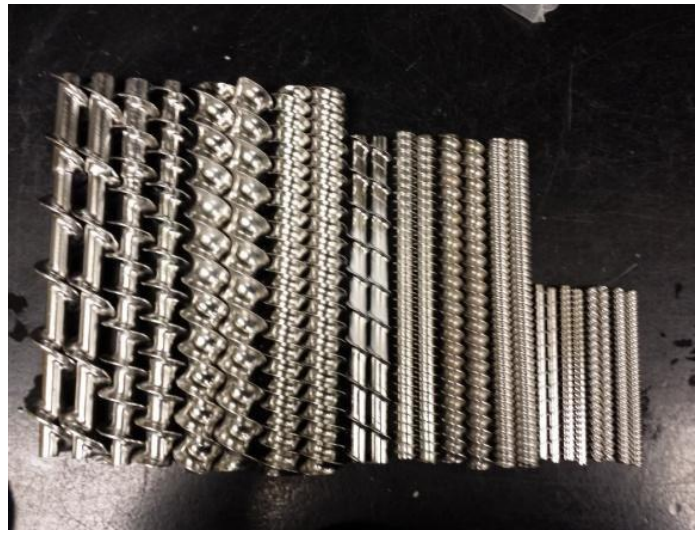
- Monitoring tool to connect feeding performance with API concentration in final product.
- Full line RTD and individual process steps RTD experiments
- Application of RTD parameters & RTD prediction uncertainty concept
- Application according to supplier software design
- Supports tablets accept/ reject decision

Criticality Analysis

All available tools work complementary to one another

Feeder mass control

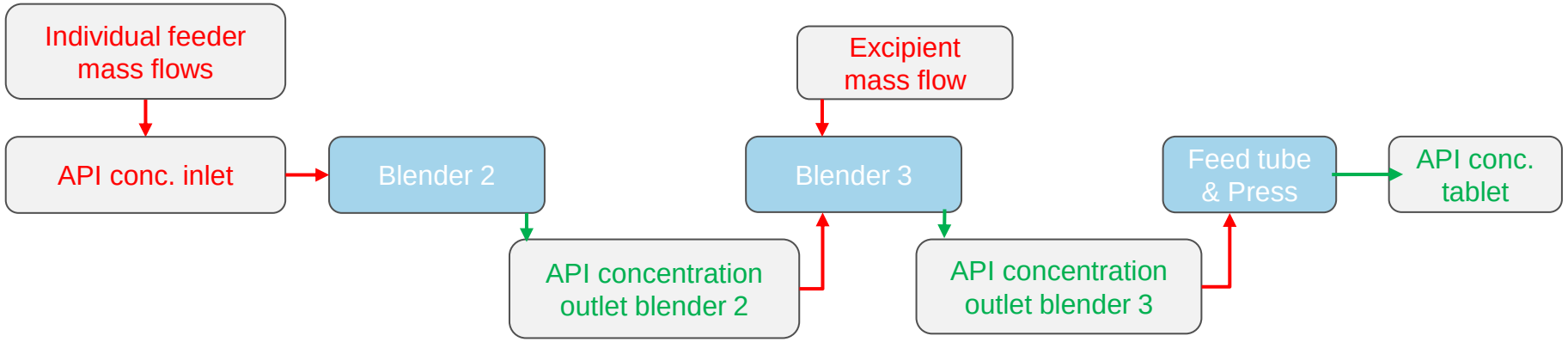
- Excipient variation is not likely to impact feeder performance within specified ranges
    1. Allow sufficient process robustness to handle CMA's of excipient over the entire range
    2. When not possible -> tighten CMA range -> not desirable
- Example: use of appropriate gearbox/screw pitch combination to allow sufficient variation (e.g. required screw speed exceeds operating range)



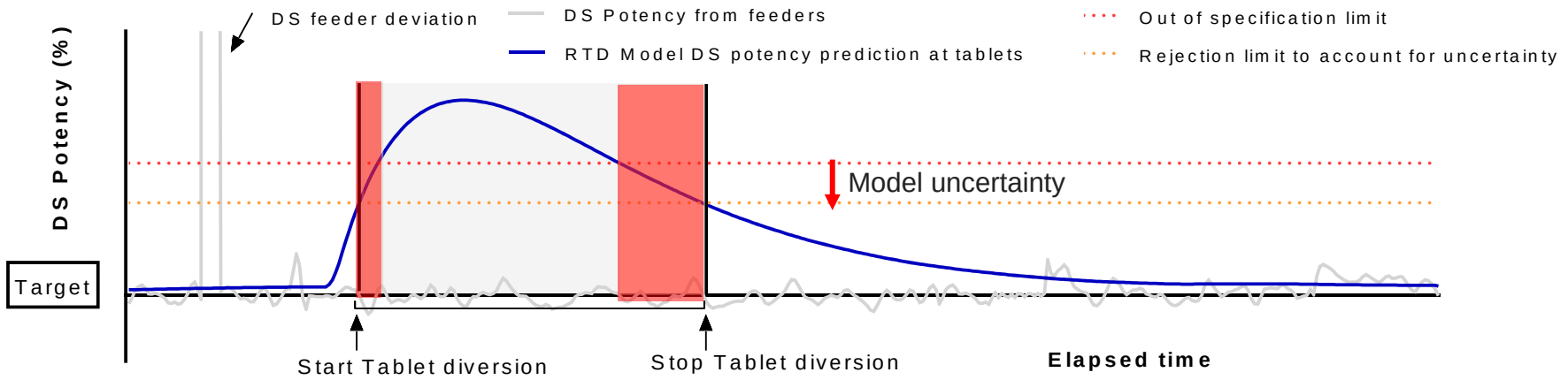
Engisch, William & Muzzio, Fernando. (2014). Loss-in-Weight Feeding Trials Case Study: Pharmaceutical Formulation. Journal of Pharmaceutical Innovation. 10. 10.1007/s12247-014-9206-1.

RTD Process Model – Control Strategy

Signal flow in the CDC process



Diversion of non-conforming material



Prediction Uncertainty

Strategy is to divert non conforming drug product in real-time based on the drug subtance potency (%) at the compression level. Discrepancies between experimental and predicted tablet potency are estimated via inverse uncertainty quantification

- Uncertainty of prediction by the RTD model is translated into prediction variance
  - **Prediction error includes all systematic error in the calculation**
  - **Error may originate from different sources of uncertainty**

Measurement uncertainty	Scenario uncertainty
- Procedural variability - Analytical variability - Variance between replicates	- Input material property variation - Process parameters variation

Integrated during development activities

Excipient variability must be factored into the overall uncertainty of the RTD model

Performing excipient variability studies contributes to increased RTD model robustness

Conclusion

Impact of excipient variability on continuous manufacturing processes

- A robust process requires a deep understanding of the impact of different sources of variability on product quality
- Lot-to-lot variability of input materials may be more pronounced in CM processes due to the sequential addition of lots. Therefore its impact must be understood.
- Input material variability needs to be investigated when developing the control strategy of a continuous manufacturing process.

Acknowledgements

Many thanks to all Janssen colleagues who are contributing to driving our continuous manufacturing platform forward !

#oneteam

Many thanks for your attention !

Questions ?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