Excipient Categorization and Risk Mitigation in Continuous Manufacturing

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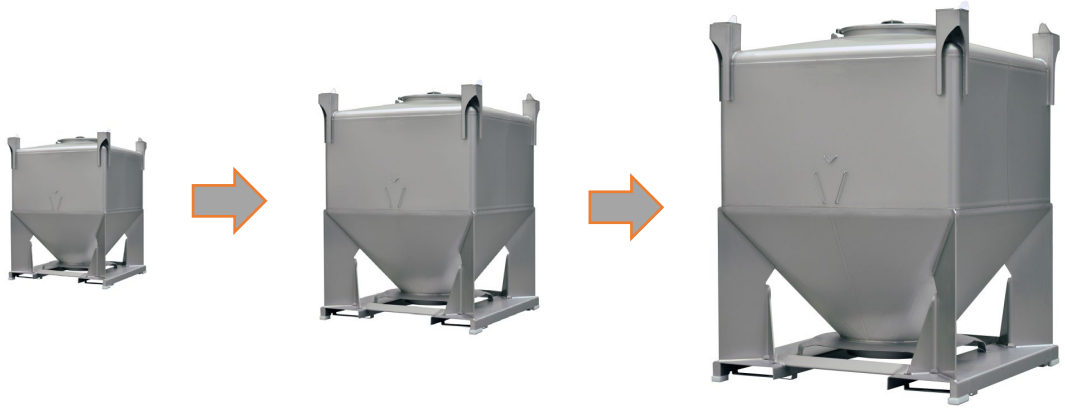
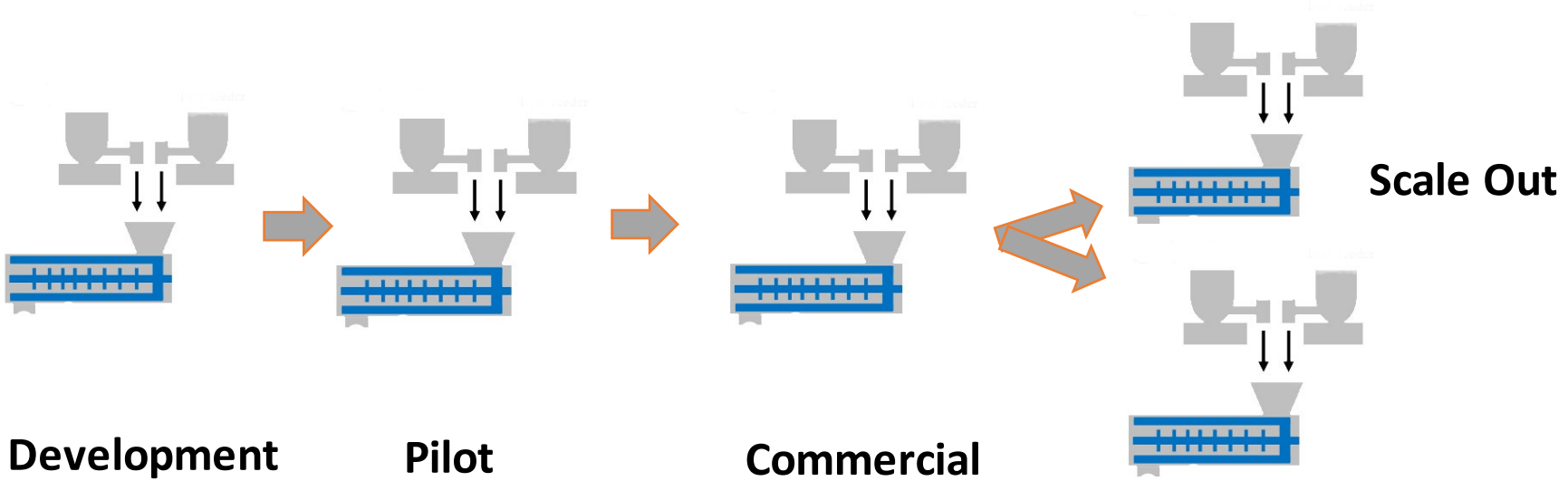
Overview

- CM mitigates Process Risk
- CM does not mitigate Raw Material Risk
- How to mitigate Raw Material Risk?

Batch vs CM: No Scale-up in CM





3.2. Changes in Production Output*

- Change in run time with no change to mass flow rates and equipment:
- Increase mass flow rates with no change to overall run time and equipment:
- Increase output through duplication of equipment (i.e., scale-out):
- Scale up by increasing equipment size/capacity:

"The continuous process verification approach, coupled with appropriate regulatory action for reporting manufacturing changes, was used to validate run time extensions beyond current experience"*

* ICH Q13 draft guidelines 2021

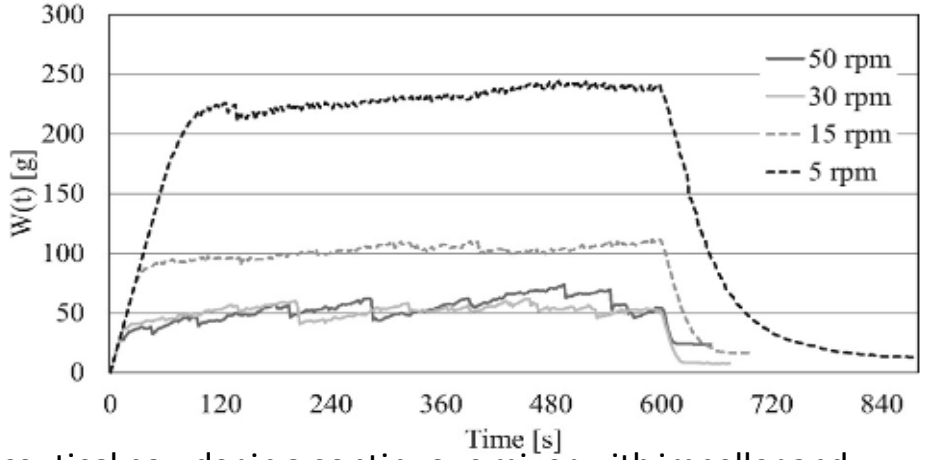
What is a CM batch size?

Batch means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture. CFR 210.3 (b) (2)

10kg/hr = 10kg at 1hr, 240kg/day, 1.7MT/week, 85MT/year

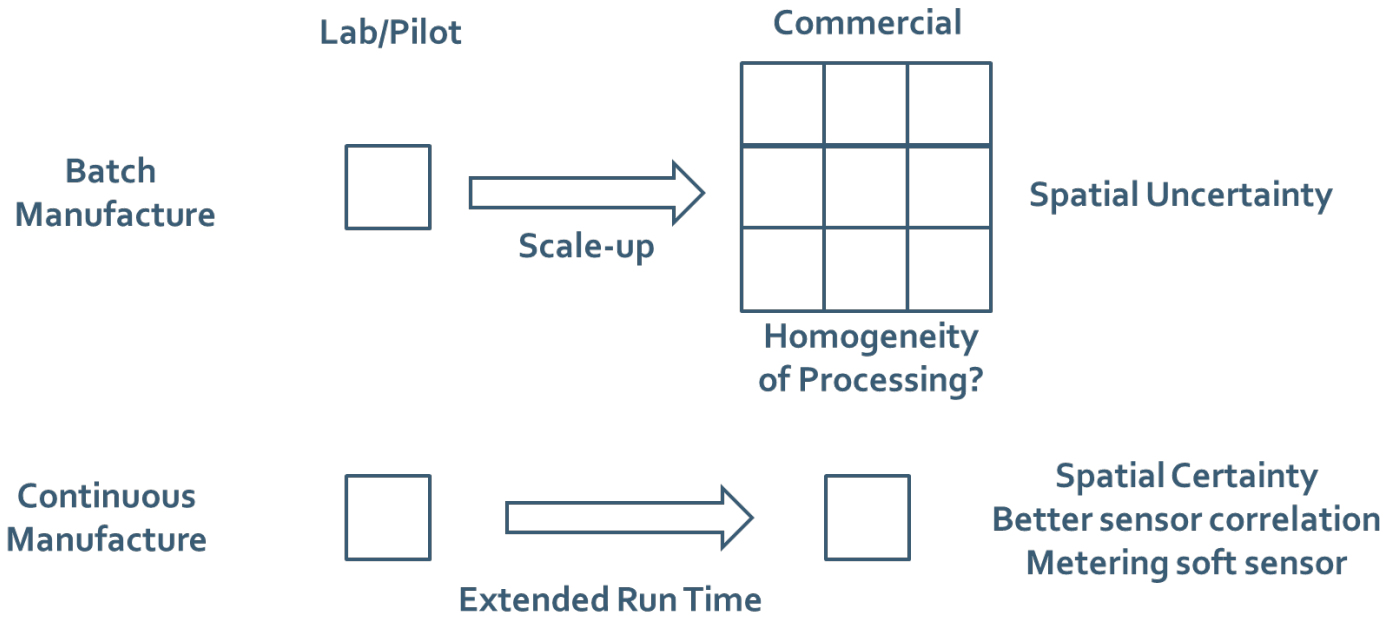
10kg/hr @ 1min mean residence time = 167 g in blender (hold-up weight, work in process)

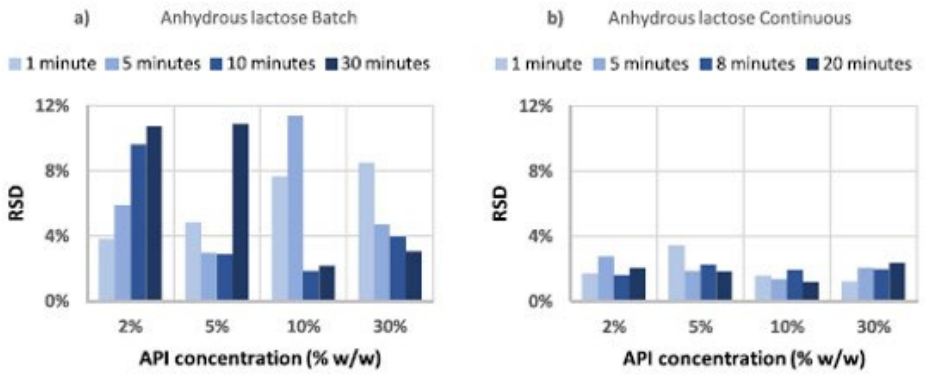
PAT Sensors: High spatial certainty, instantaneous read on process evolution



Tomita Y et al "Control of residence time of pharmaceutical powder in a continuous mixer with impeller and scraper" Int J Pharmaceutics 586 (2020) 119520

Continuous vs Batch: Fewer Degrees of Freedom





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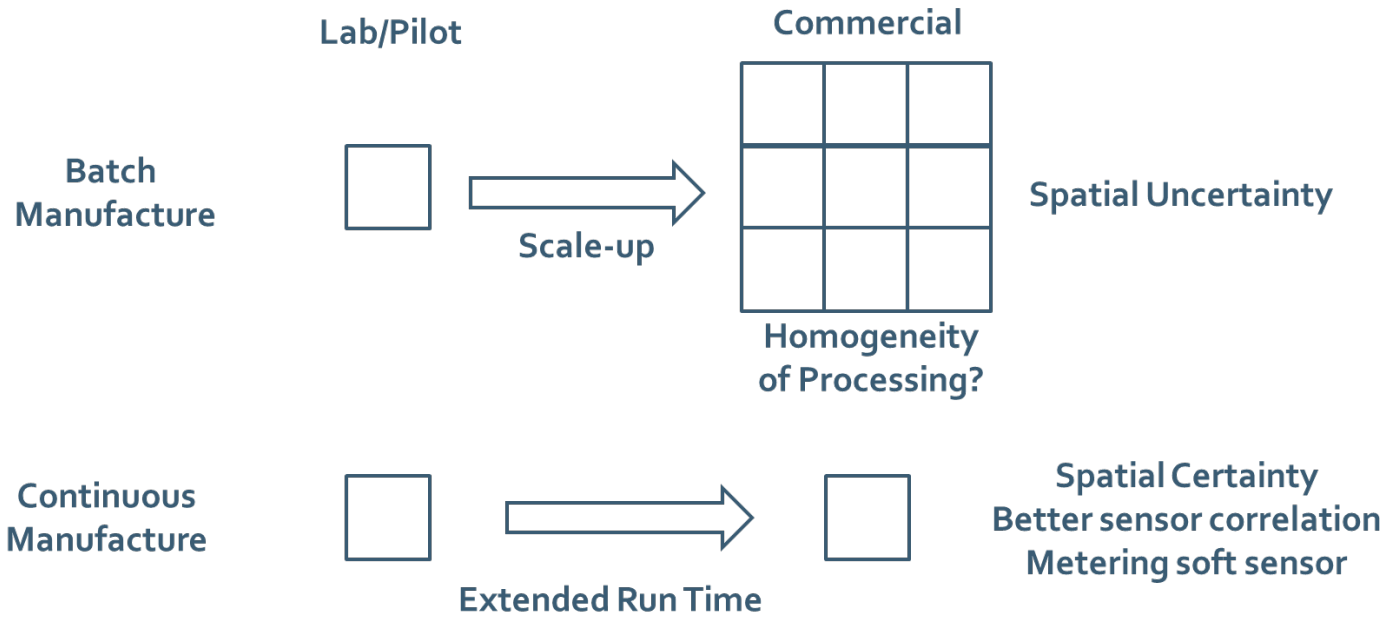

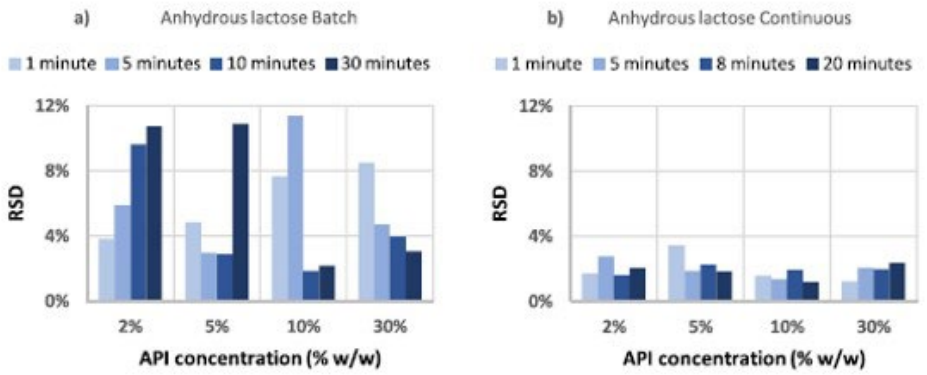

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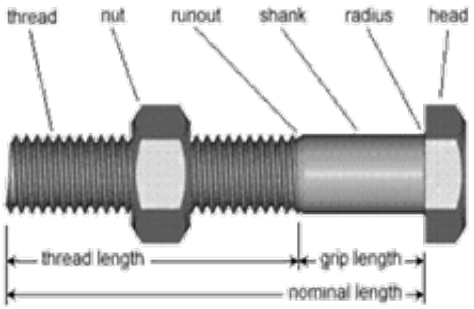
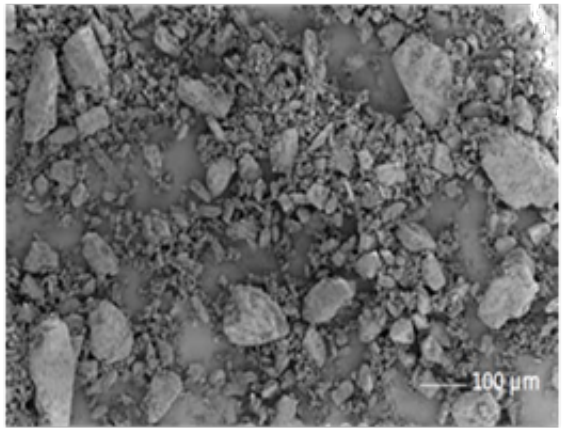
Excipient Degrees of Freedom (no control at component level?)

Polydispersity

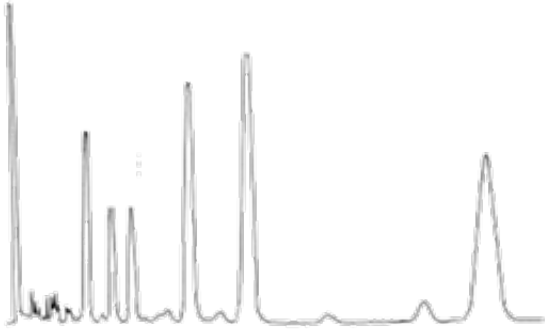
- Particle Size
- Composition
- Molecular Weight



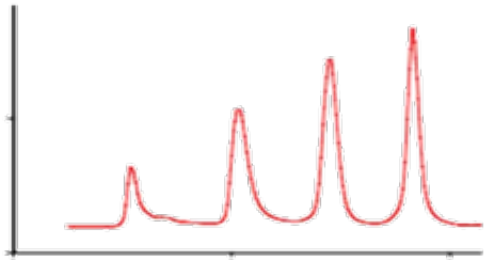
Known Composition and Tolerances: Function follows



Particle Size Distribution?



Chemical Composition?



Mol. Weight Distribution?

Pharmacopoeial/Supplier Specifications do not determine Fitness for Purpose!

Excipient Selection

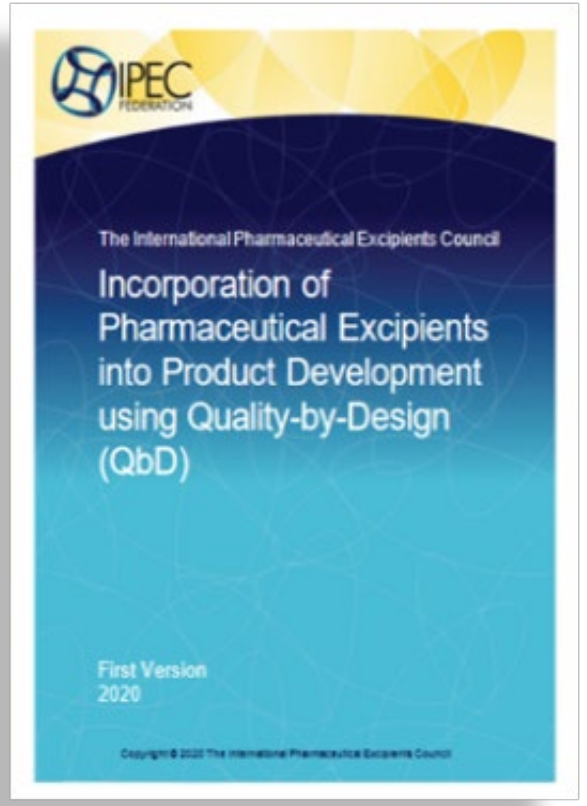
- Nominal functionality guides selection but determining performance in product requires experiment.
- A robust formulation of a medicinal product is able to accommodate the typical variability seen in:
    - API
    - Excipients
    - Processes

…without compromising the manufacture, stability, performance or any other attribute of the product critical to the patient's care or well-being.

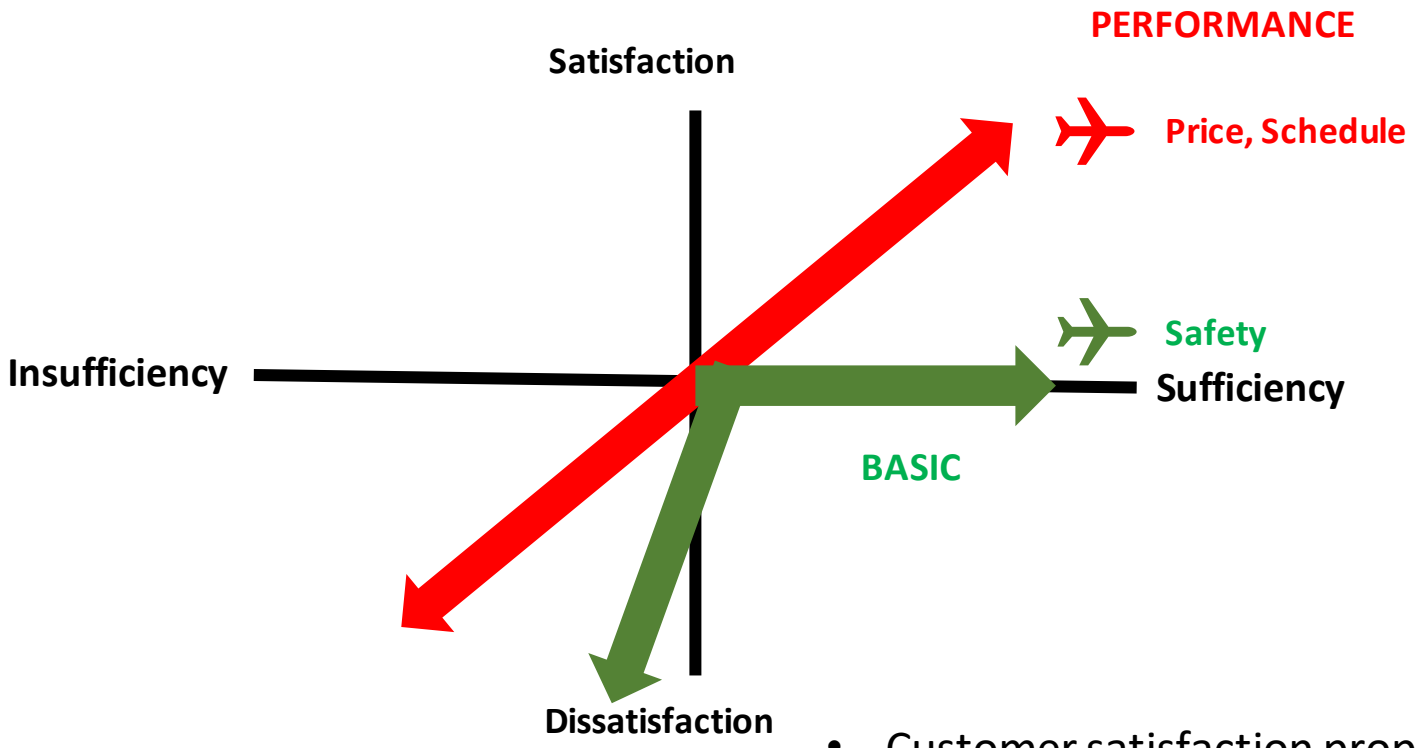
- Batch to batch/supplier to supplier variability
- Do not reply on CoA/specification

Excipient Categorisation and perceived risk

- Critical vs Non-critical
  - Criticals dominate experimental results and product performance
  - Non-criticals, low impact, therefore erroneously seen as low risk
- Functional vs Non-functional
  - Formulation design built around one or more dominant functionalities
    - Eg HPMC extended release matrix
  - Non-functional(?) covers other functionalities seen as lesser risk
- KANO used in IPEC QbD Guide

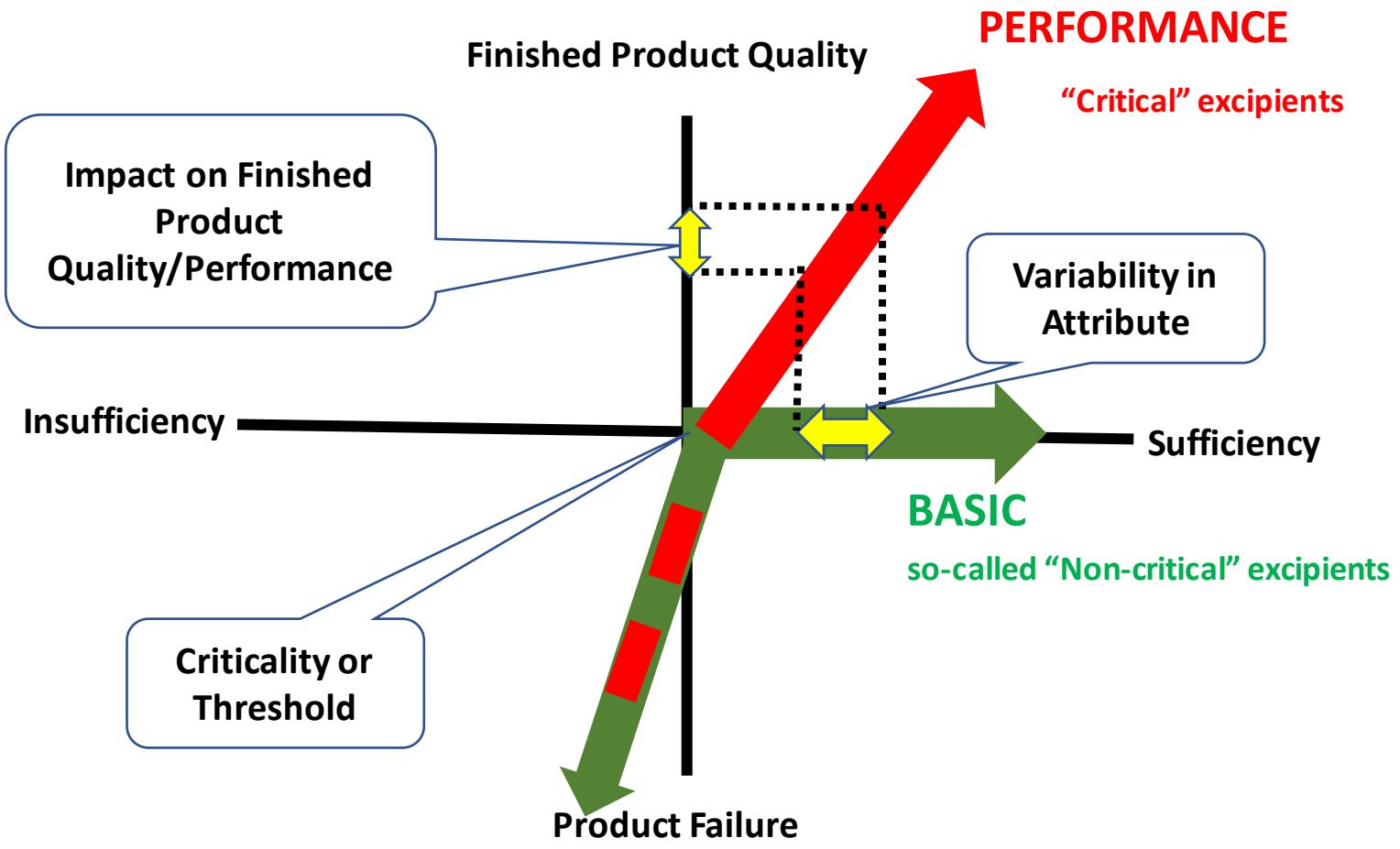


Kano Analysis Guides Investment in Design Attributes



- Customer satisfaction proportional to Performance attributes
- Basic attributes taken for granted but extreme dissatisfaction if deficient

Kano Analysis of Excipient Performance



Performance vs Basic Excipients

- Performance
  - Titrate functionality/performance into product
  - Functionality = Amount X Degree of attribute expression
    - Constant functionality vs constant amount?
    - Process control?
- Basic
  - No immediate impact to titrate
  - Impact of ranging amount down
    - Small decrement/large impact suggests higher susceptibility to excipient variation (closer to threshold).
- Automate ranging studies in CM?

Specification of Excipients

- Mandatory standards as specified in monograph
  - Methods and acceptance criteria
- Optional monograph requirements
  - Additional Requirements/Labelling
    - No acceptance criteria specified
  - PRPs (NF <1059>)/FRCs (Ph Eur)
  - Specific to application
- Critical Material Attributes (CMAs)
  - Tighter limits or alternative attributes/methods
  - Specific to a finished product
- In absence of CMA default to mandatory monograph requirements.

Critical Material Attributes

An excipient physical, chemical, or microbiological attribute (defined by an excipient User, not necessarily reflected in supplier specifications or monographs), that must be within appropriate limits, ranges, or distributions, to ensure that critical quality attributes (CQAs) for a particular drug product are maintained throughout the product life cycle.

- User-defined CPP?
- Lifecycle management as well as development

Excipient CQAs vs CMAs