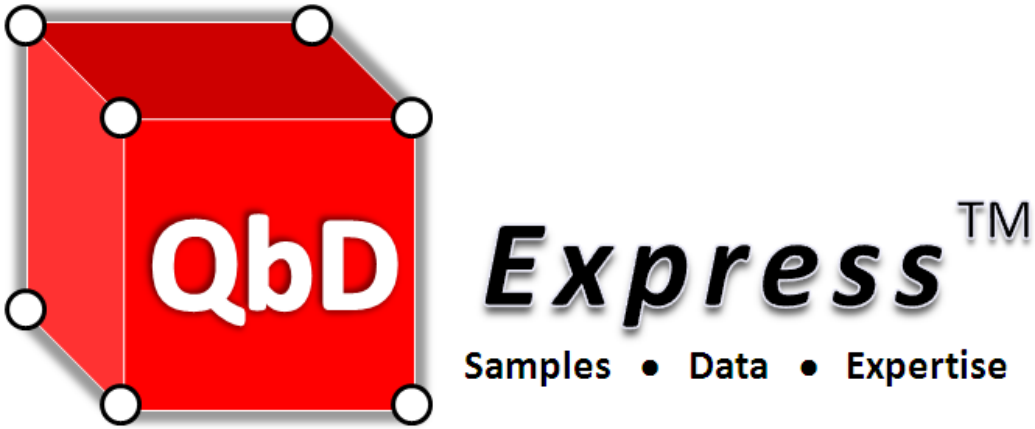

The role of the excipient supplier in supporting QbD in the pharmaceutical industry

Quality is evolving…

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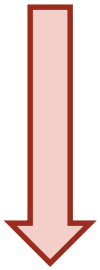
Pharmaceutical Excipients



FDA/Industry

Reactive

Quality by Inspection

Statistical Process Control

Proactive

Quality by Design

First Generation Quality Management Tool (QMT)
Inspect, reject, or accept

Second Generation QMT
Examines historical output of a process to identify the limits of a stable process and sources of error

Third Generation QMT
Prevents problems or defects from occurring. Continuous real time quality assurance

SOURCE: The Pathways to Operational Excellence in Pharmaceutical Industry – Overcoming the Internal Inertia

Goal of QbD

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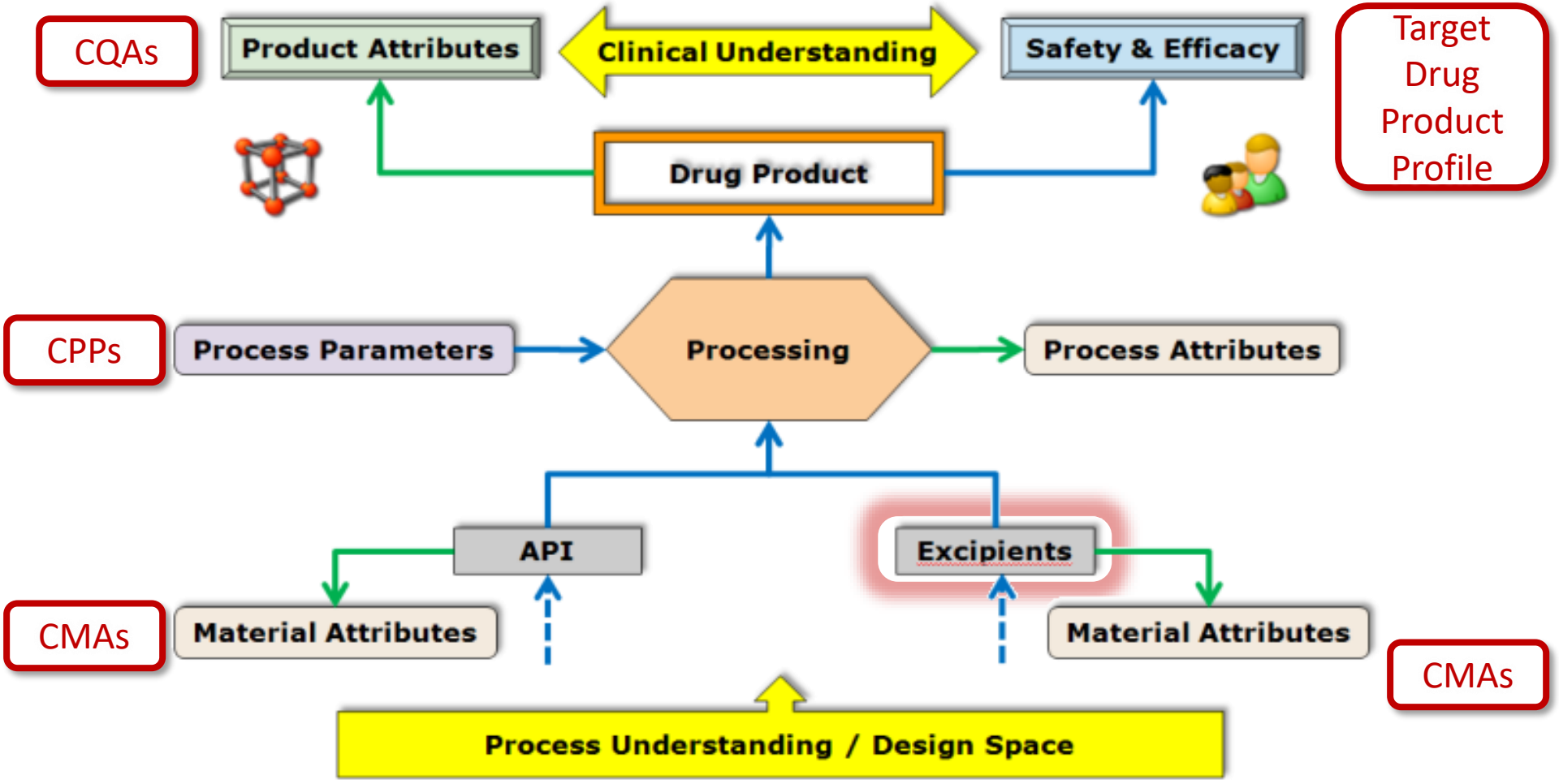

Target Drug Product Profile ⟶ CQA = f(CPP, CMA)

SOURCE:
http://inferenceforqbd.com/QbDViewpoint/default.aspx

Understanding impact of raw material variability on CQAs

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- **Formulation & process design must accommodate raw material variability (robustness)**
- **Design space (beyond experience space) must "demonstrate" absence of raw material impact on CQAs**
- **Critical material attributes and DOE**
  - Good design minimizes impact of known material attributes
  - Design around known attributes (e.g.: appropriate sourcing and grade selection)
  - More to CMAs than just specifications
    - Unspecified attributes (beyond CofA/Pharmacopoeiae)
    - Potential issue when raw material attribute interacts with unknown criticality in design (formula and/or process)

Application criticalities?

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- **Situations that can trigger failure**
- **Criticalities are not designed**
  - Unanticipated, interactions
  - Variable (scale-dependent?)
  - Not always intrinsic to an excipient

Significant impact if minor raw material variability interacts with a criticality!

- **Potential MCC-related failures:**
  - Overgranulation leading to API entrapment in coarser and denser granules
  - Drug release rate is dependent on tablet hardness/density if insufficient amount of disintegrant is used

Knowledge sharing

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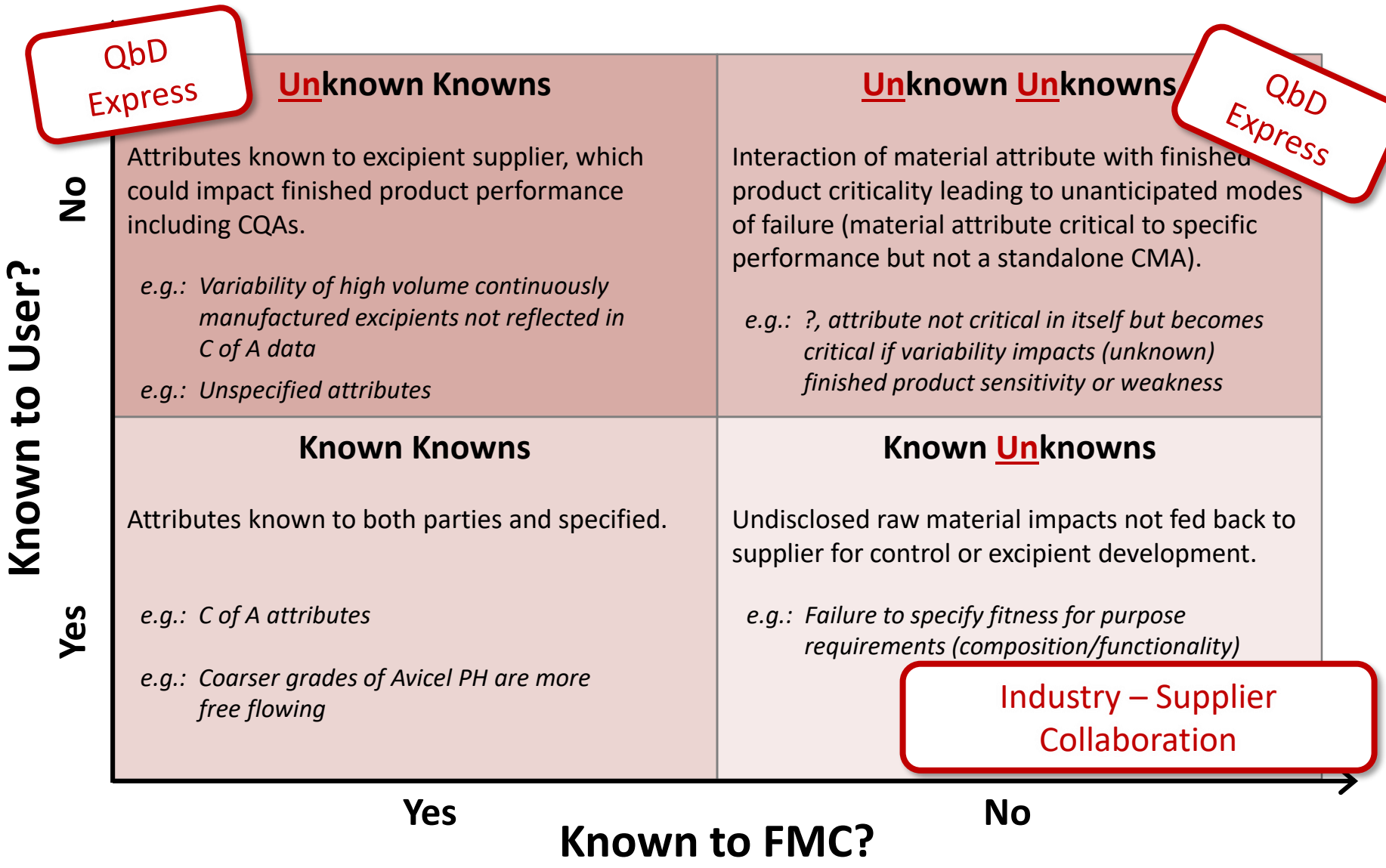

Importance of collaboration

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Supplier Knowledge

Shared Understanding

Industry Knowledge

Collaboration is crucial to identify:

impact of variability from previously unspecified raw material attributes in development and existing products

and

existence of criticalities and their potential relationship to MCC – elimination of failures

QbD Express™
Samples • Data • Expertise

aims to bridge the knowledge gap

FMC's offering in QbD

FMC BioPolymer
Pharmaceutical Excipients

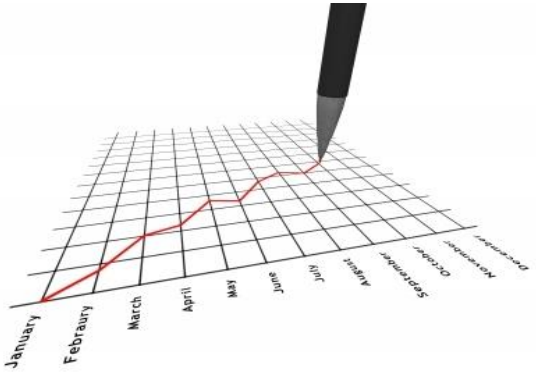
QbD Express™

Samples • Data • Expertise

Samples

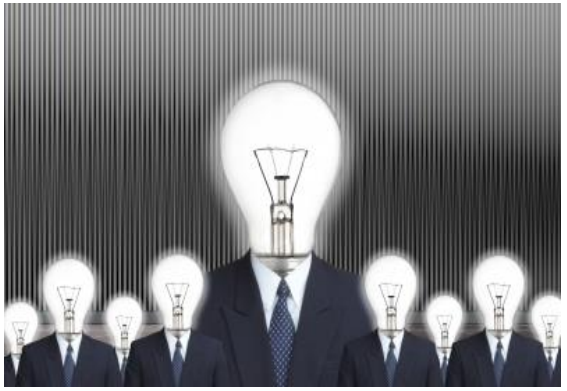
- Representing FMC's operating space

Data



- Physical and functional attributes

Expertise



- Formulation science
- OSDF process technology
- Process control
- Regulatory implications

On-time, every time!

Sample library

Differentiation of PH-101
by manufacturing site, pulp mix, and particle size

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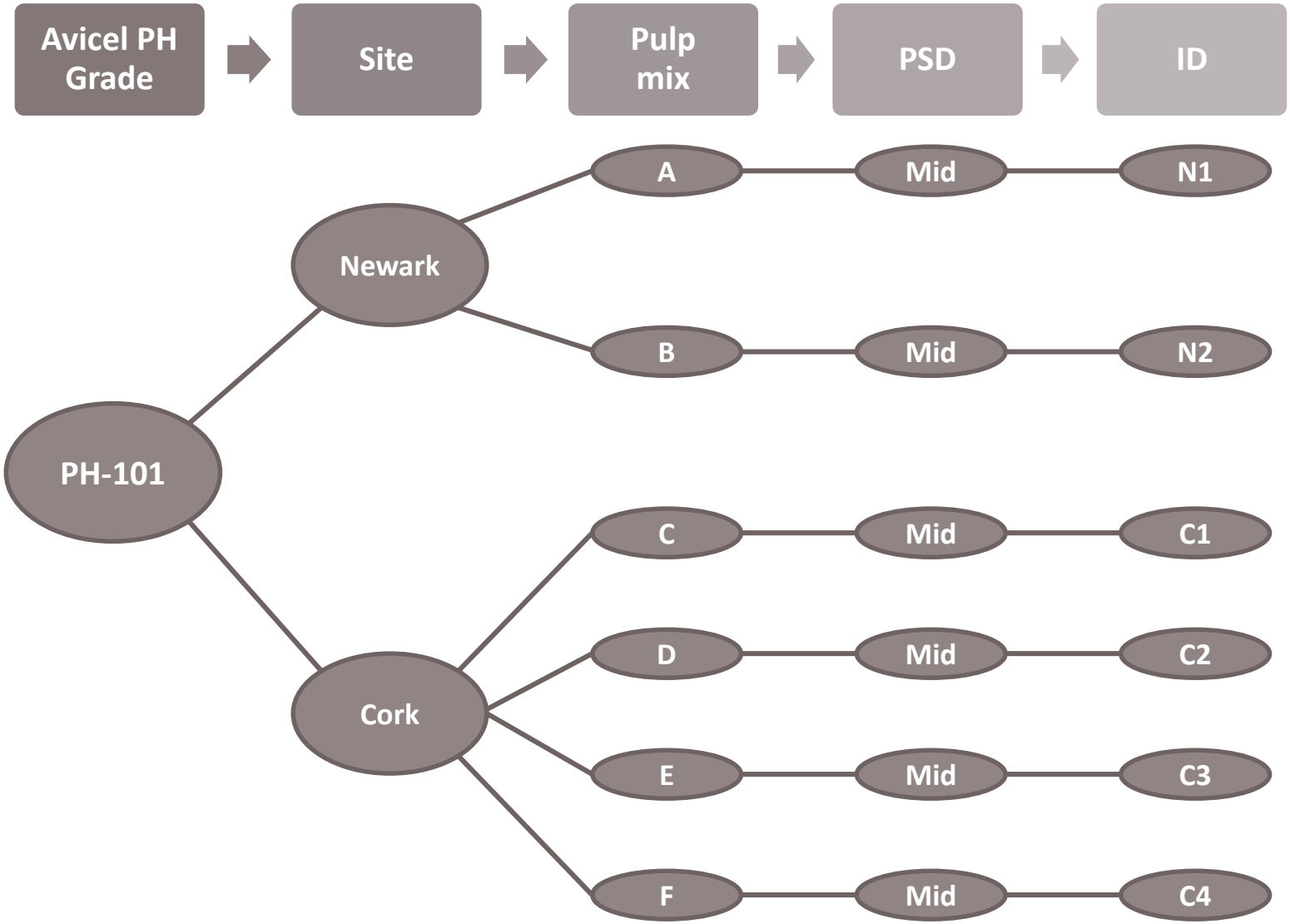

MCC-water interaction (WBC) is not consistent or controlled commercially

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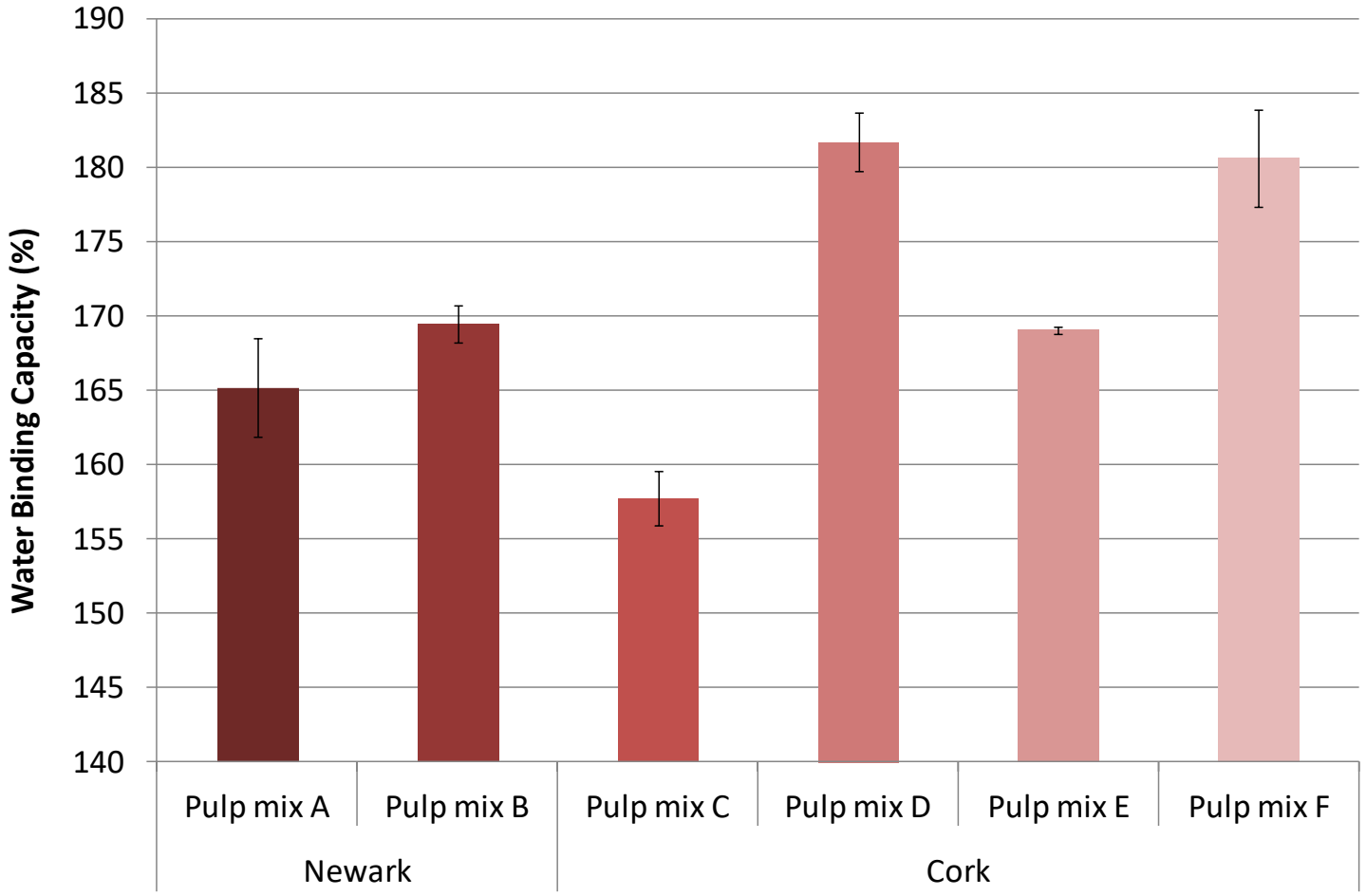

The foregoing test results relate to the specific procedure and formulation used and may vary depending on the procedure and formulation. As a result, one should not rely on the test results herein as an indicator of how a given pulp will perform in other processes and formulations.

Case Study: Critical role of MCC in extrusion/spheronization

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Avicel PH importance

- PH-101 pulp combination impact pellet properties

Formulation

Ingredient	Weight (%)
Theophylline	15.8
PH101	36.8
Wetting agent (H_2O)	47.4

Equipment

Make: Fuji
Model: MG 55

Make: Fuji
Model: QJ 230T

Variables

Avicel	Pulp mix
PH101	C
PH101	D
PH101	E

Target pellet size

- 710-1000µm (#25-#18)

Response

- Pellet size & distribution
- Yield (Desired Pellets / Total pellets)

Case Study: Results

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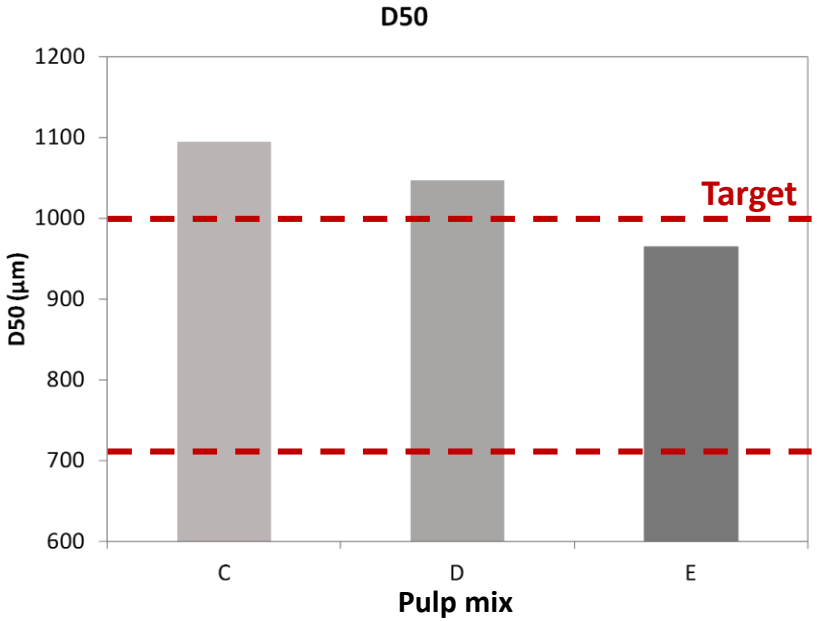
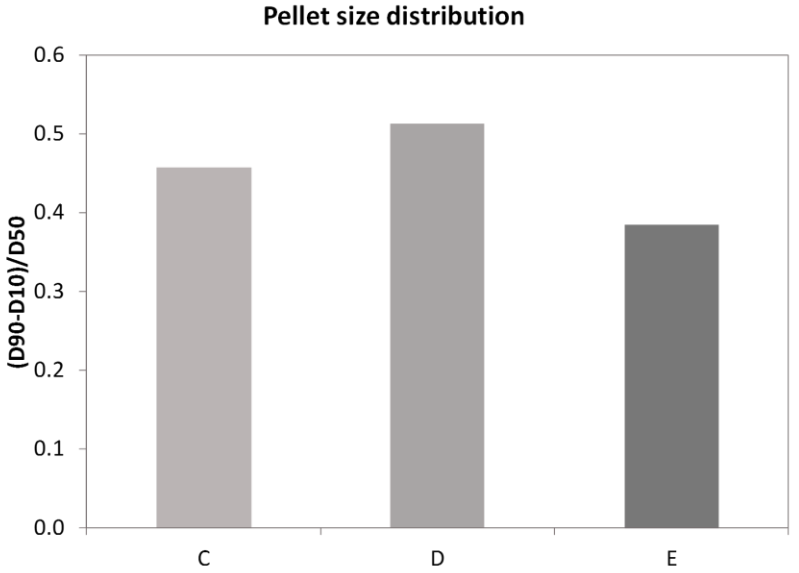
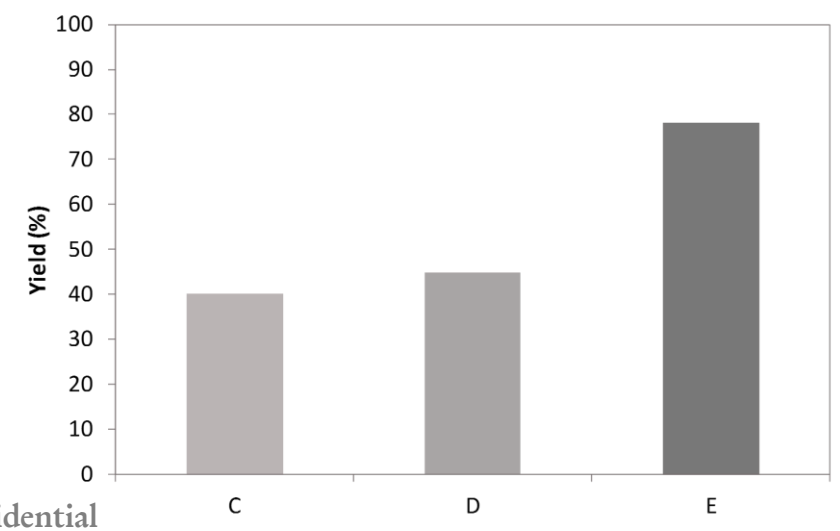




- Within the chosen formulation and under identical process parameters, different versions of Avicel PH-101 produced variance in pellet size, pellet size distribution, and to pellet yield
- Significance of impact increased as target range of pellet size got tighter

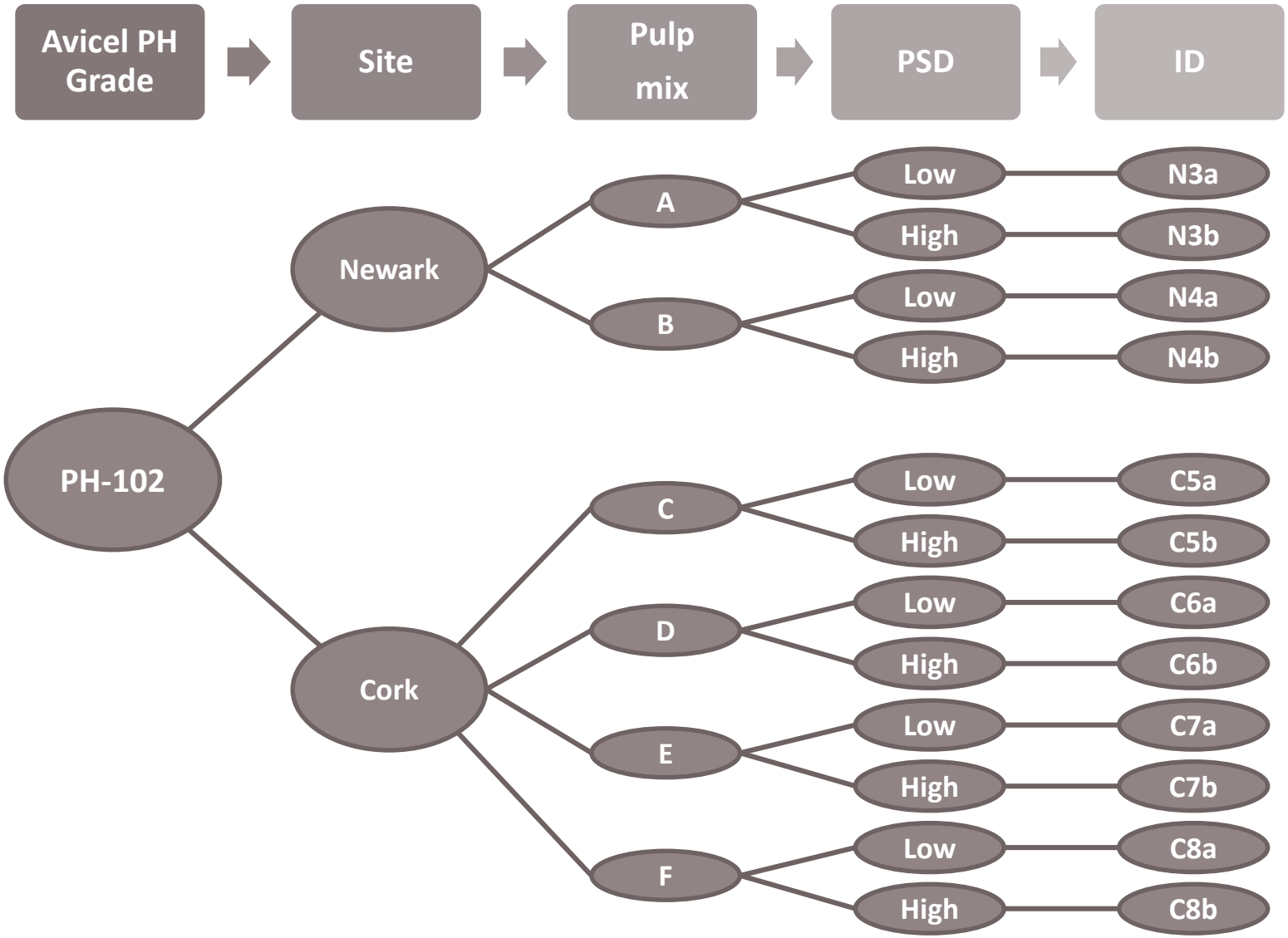


The foregoing test results relate to the specific procedure and formulation used and may vary depending on the procedure and formulation. As a result, one should not rely on the test results herein as an indicator of how a given pulp will perform in other extrusion/spheronization processes and formulations.

Sample library

Differentiation of PH-102
by manufacturing site, pulp mix, and particle size

FMC BioPolymer
Pharmaceutical Excipients



MCC compactibility may vary slightly but is not controlled commercially

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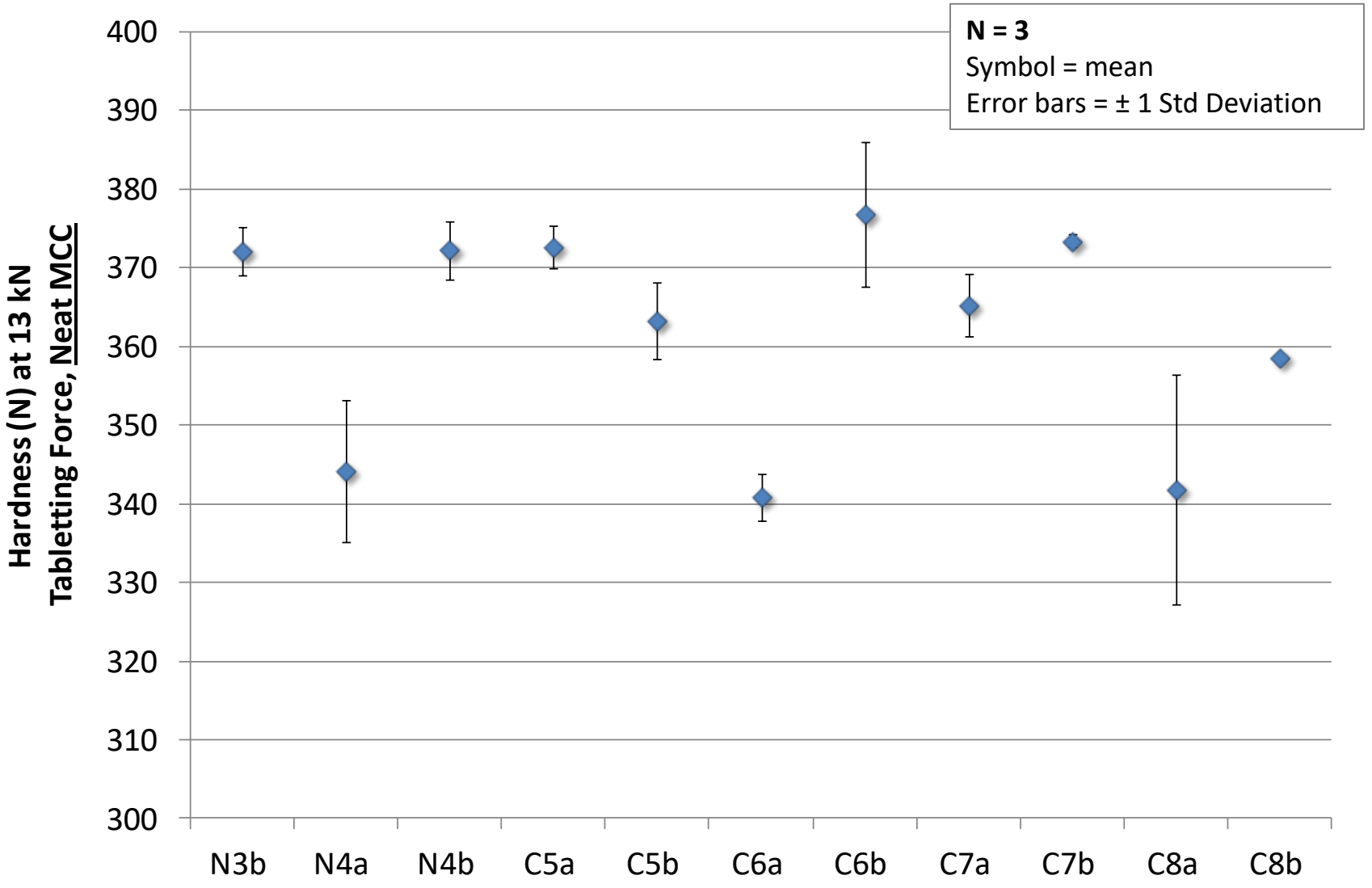
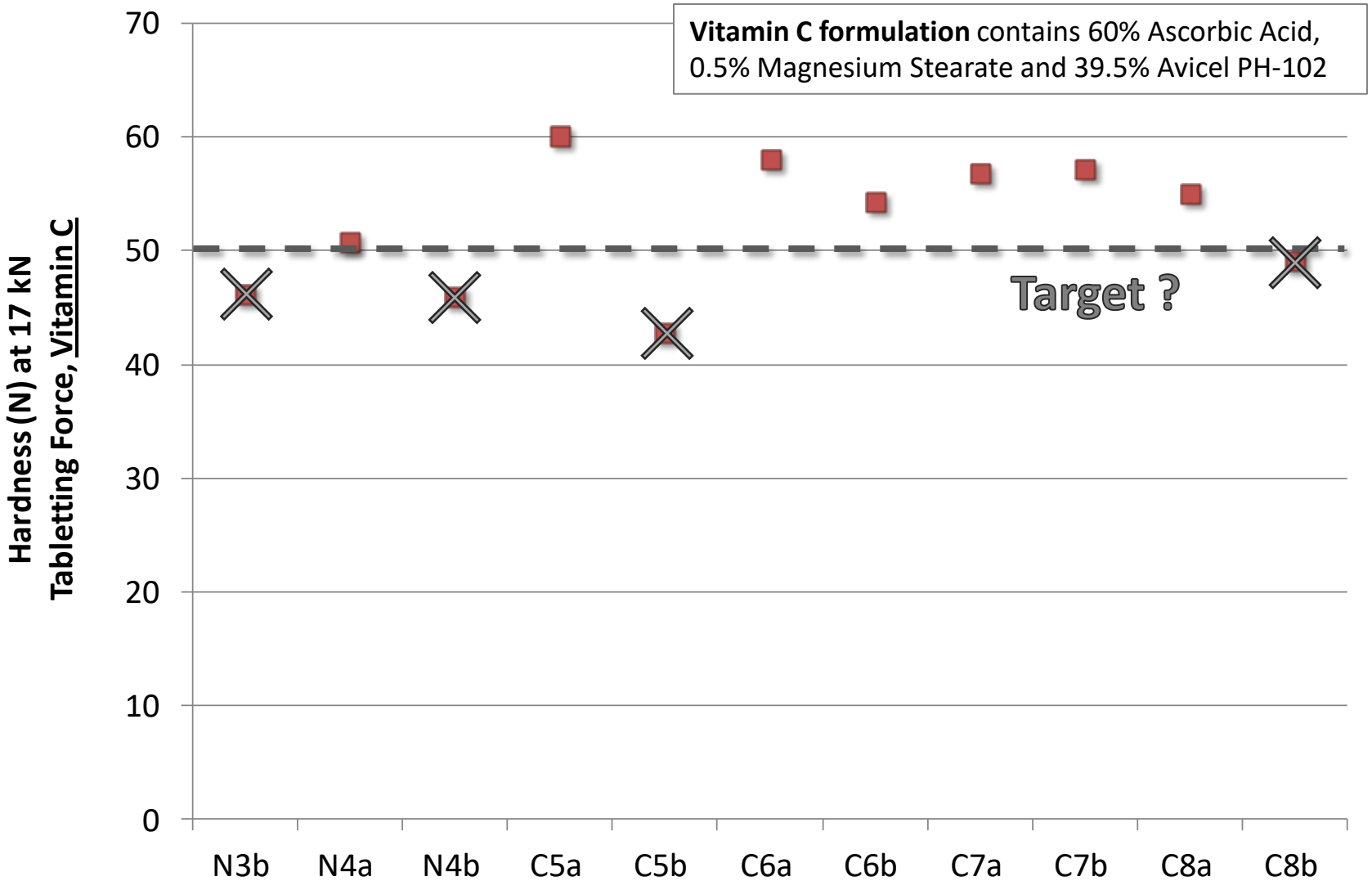
Pharmaceutical Excipients



Could MCC variability impact your minimum compactibility requirements?

FMC BioPolymer
Pharmaceutical Excipients



Benefits of QbD Express™

FMC BioPolymer
Pharmaceutical Excipients

1 Understand variability in FMC's operating space

- New Drug Development
  - Maximize robustness and reduce impact of MCC and XL-CMC variability
- Existing Products
  - Benchmarking of QbD Express
  - Identify MCC and XL-CMC based quality enhancement **with no regulatory barriers**
  - Eliminate marginal performance and optimize yields
- Supplier Benchmarking

QbD

OE

Supplier Mgmt

2 Access tailored solutions to optimize outcomes

- New specifications
  - Within current FMC operating space and no need for regulatory approval
- New grades
  - Within FMC Process Capabilities

QbD Express™ – Fulfillment

FMC BioPolymer
Pharmaceutical Excipients