Development by Design

Best Practices in Pharmaceutical Development

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Hovione

Agenda

Advanced Tools in Development and Manufacturing

Excellent Development and Manufacturing

Quality by Design at Hovione

Advanced Tools in Development and Manufacturing

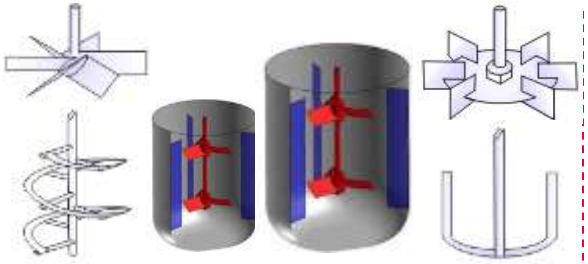
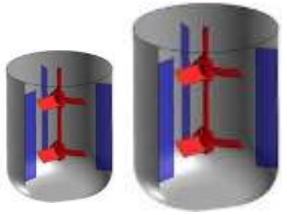
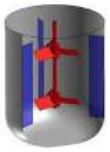
DEVELOPMENT

- Risk Assessment
- Design of Experiments
- Modeling Tools
- Scale-Up Methods
- Scale-Down / Miniaturization
- Process Analytical Technology

MANUFACTURING

- Lean 6 Sigma
- Visual Stream Mapping
- Failure Mode and Effect Analysis
- Multivariate Analysis
- 8D
- Poka-Yoke
- OEE

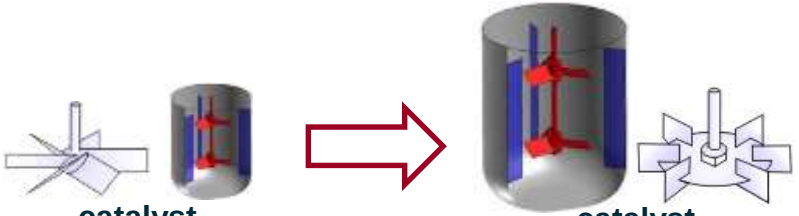
Modeling Tools
Adjust model complexity

	Concept	Development	Solution	Domain (Problem statement)
1st principles models	$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{u}) = 0$ $\frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u} \cdot \nabla)\mathbf{u} = -\frac{1}{\rho}\nabla p + \mathbf{F} + \frac{\mu}{\rho}\nabla^2 \mathbf{u}$ *Fundamentals captured*	 (months)		
Mechanistic models	$Fr' = \left(N^2 D / g\right) \cdot (\rho_L / \Delta\rho)$ $Re = N \cdot D^2 \cdot \rho_L / \mu_L$ *Main mechanisms captured*	 (weeks)		
Statistical models	$y_1 = f_1(x_1, x_2 \ldots, x_n)$ $y_2 = f_2(x_1, x_2; \ldots, x_n)$ *"Behaviour"captured*	 (days)		

Best modeling approach: considering the problem statement, "*keep things as simple as possible, but not simpler*"

Modeling Tools
Case-study: chemical synthesis

Problem statement (troubleshooting)



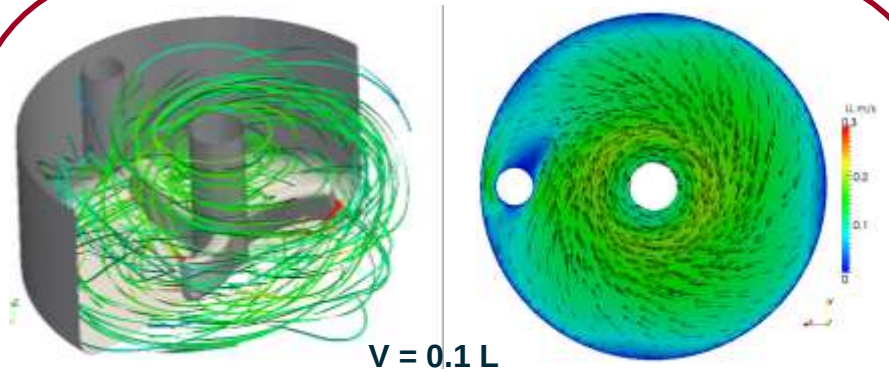
• During an alkylation reaction, the content of raw material increased after IPC (upon scale-up).

• Hypothesis: poor mixing leading to un-reacted raw material accumulation; detailed analysis needed.

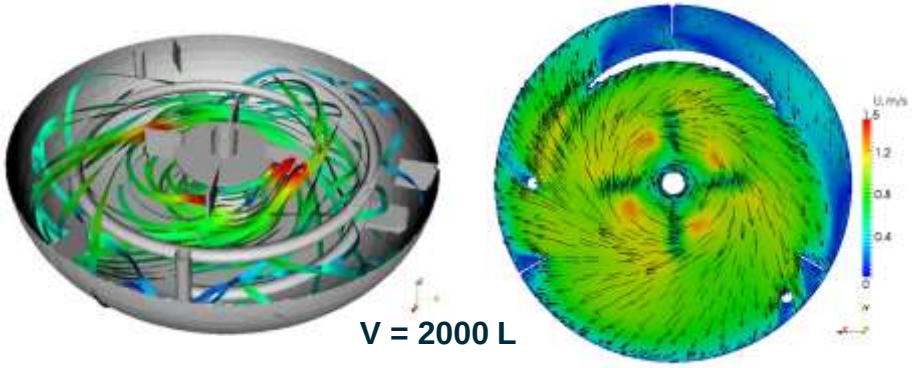
Approach

• Axial & radial mixing patterns should be compared **in detail** for the lab and commercial-scale reactors.

1st principles



V = 0.1 L

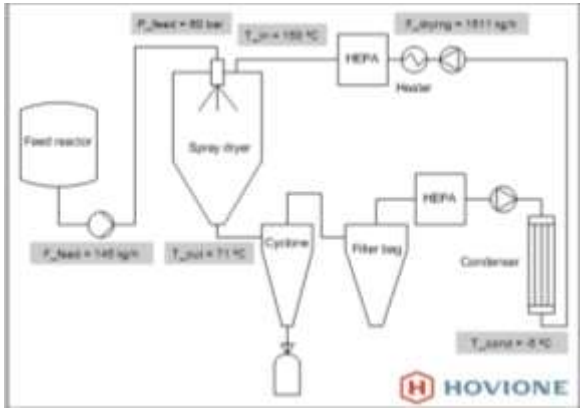


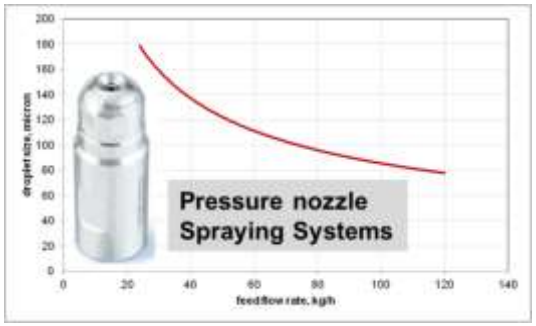
V = 2000 L

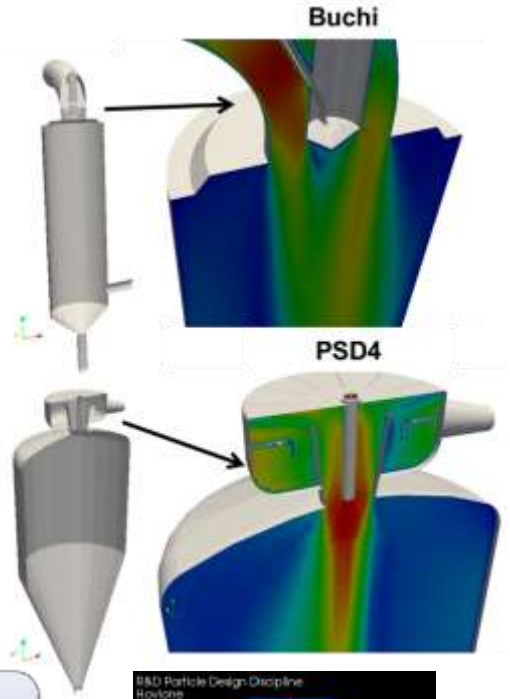
• For the 2000 L reactor, ~ zero velocity (stagnant fluid) is observed in the region below the impeller.

• Impeller was re-designed; problem was solved.

Scale-up
Case-study: spray drying







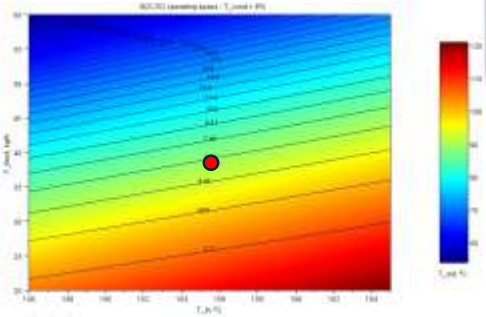
Droplet size correlations

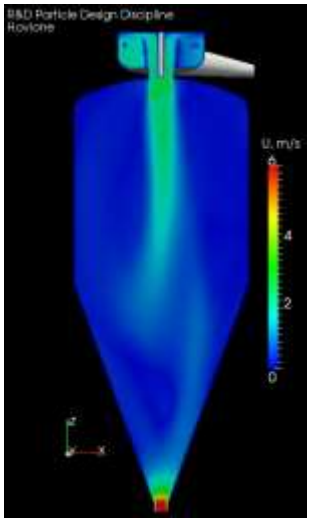
Heat and mass balance

CFD

Scale-up methodology

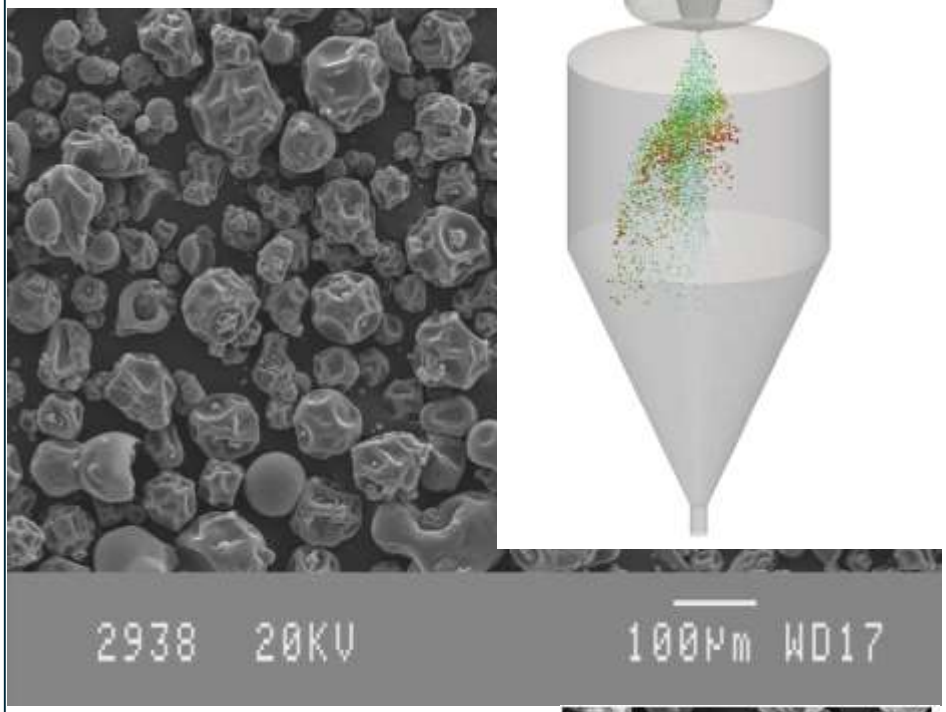
Thermodynamic space

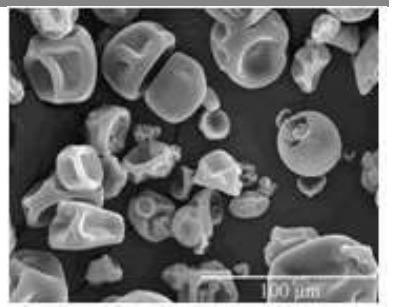




Scale-down
Case-study: spray drying

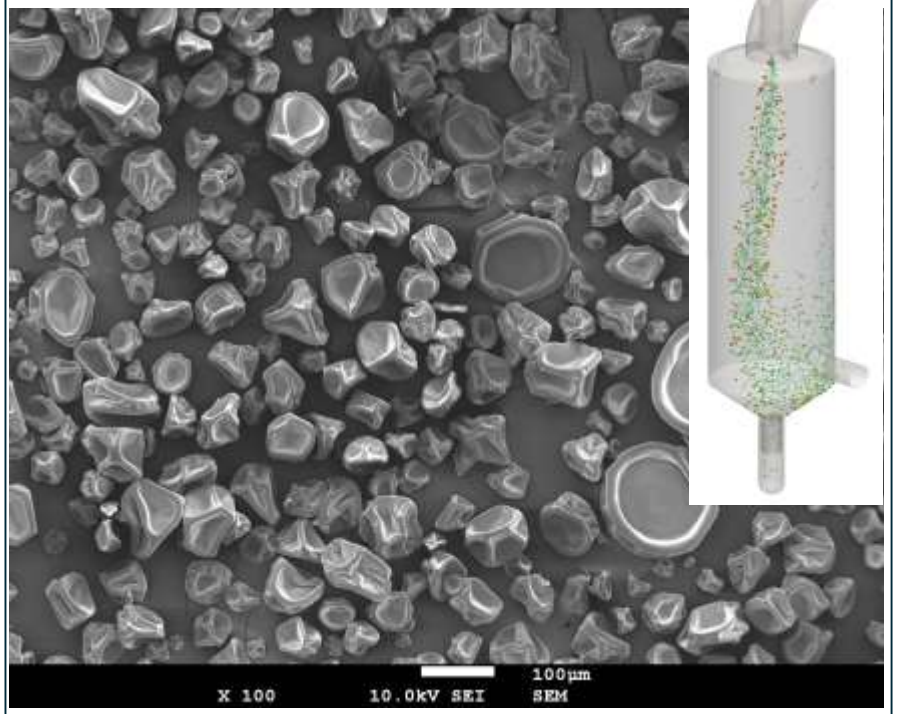
Commercial unit

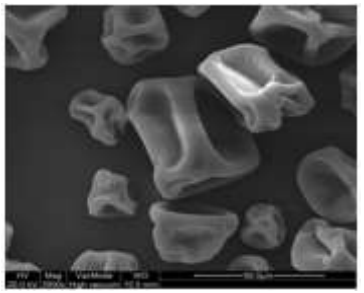




D_v50 = 82 µm
span = 1.7
bulk density = 0.29 kg/L
tap density = 0.40 kg/L
solvent = 5% w/w

Lab unit

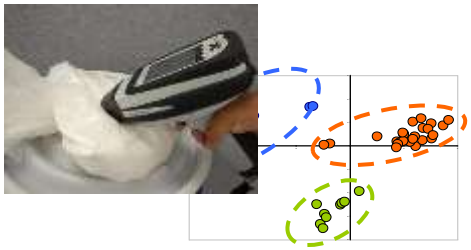




D_v50 = 83 µm
span = 1.5
bulk density = 0.34 kg/L
tap density = 0.42 kg/L
solvent = 7% w/w

Process Analytical Technology
Chemical Processes

Handheld NIR



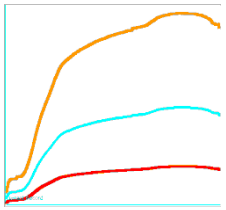
Raw materials identification and qualification

UV photometry

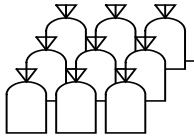
Refractometry

Concentration and end-point determination

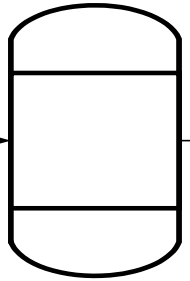
FBRM



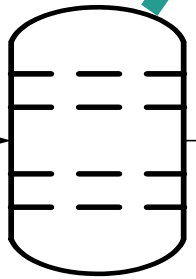
Crystals growth dynamics



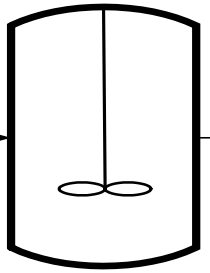
Raw material dispensing



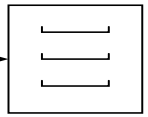
Reaction



Purification

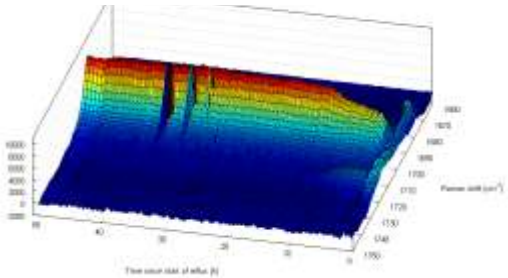


Crystallization

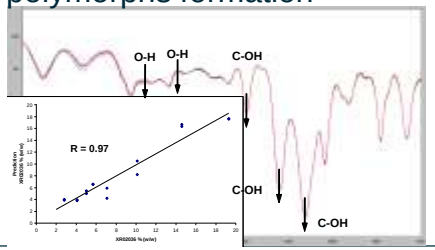


Drying

Raman spectroscopy
Reaction conversion and polymorphs formation



FT-IR spectroscopy
Reaction conversion and polymorphs formation

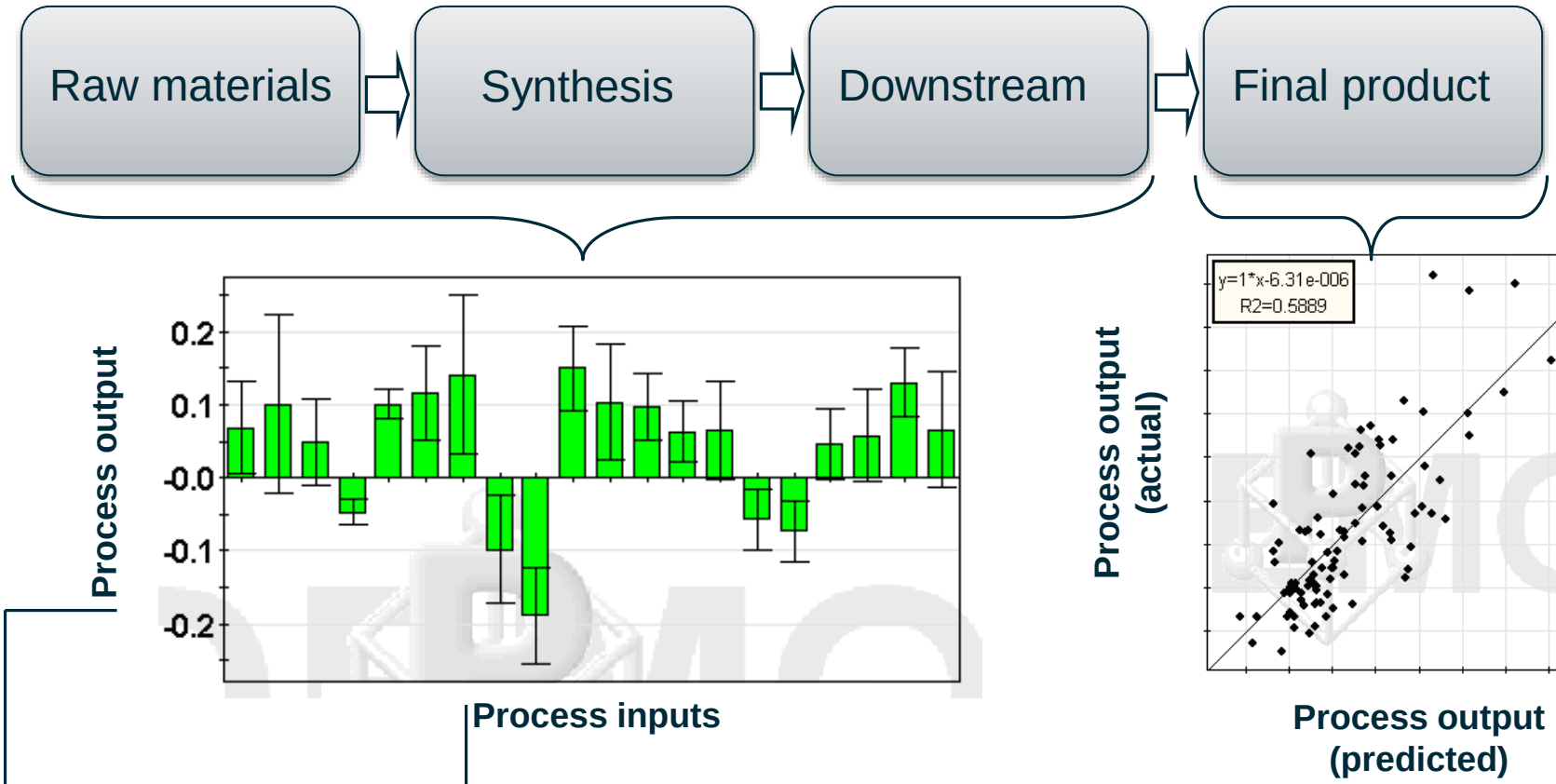


Raman and FT-IR spectroscopy
Concentration and polymorph conversion

NIR spectroscopy
Drying end-point and solid state characterization

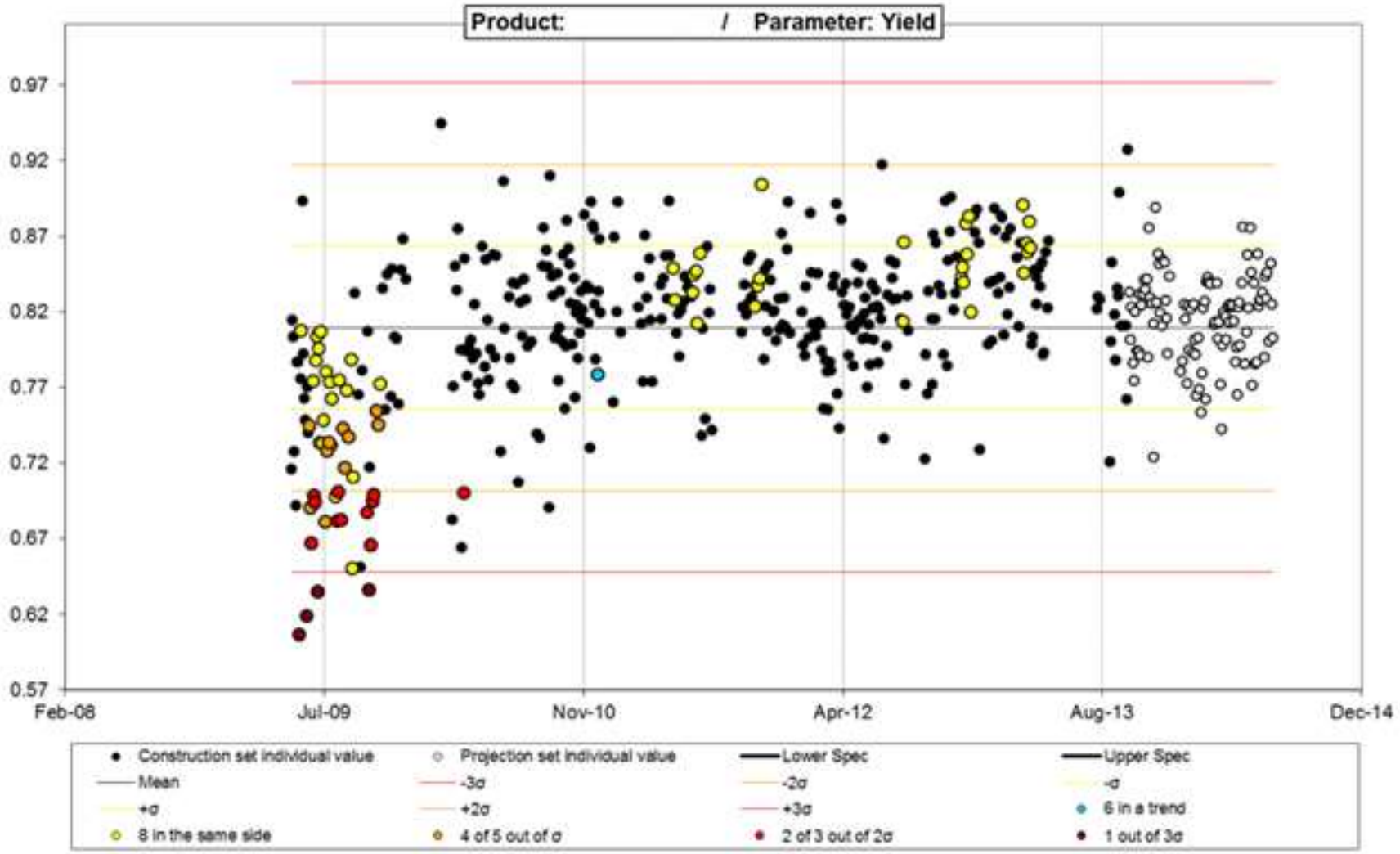
Hovione

Multivariate Analysis

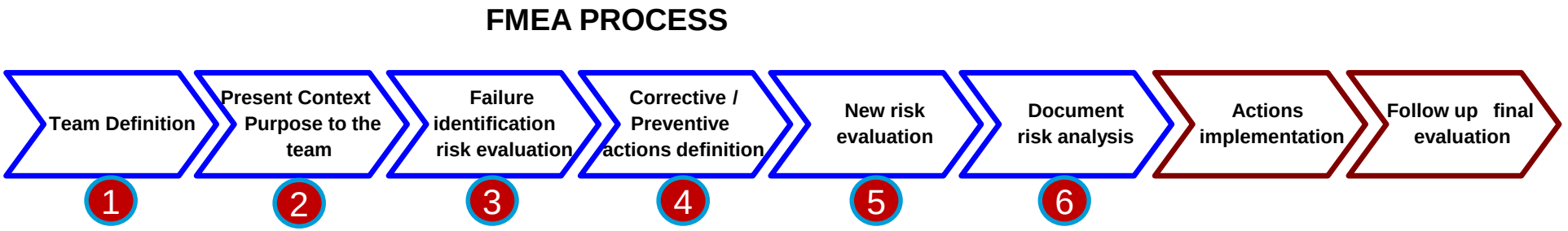


- Quality attributes (e.g.: purity) or process performance indicators (e.g.: yield)
- Impact of process inputs on a process output
- Higher the absolute value => greater impact

Statistical Process Control
Control Chart



How to use FMEA?



- List ALL possible failures
- Classification and quantification (1 to 10) of failures based on:
  - Frequency (F)/ probability of failure occurs
  - Severity (S) of the effect
  - Detection (D) of the failure (capacity to detect)
- Prioritization by calculating Risk Priority Number: **RPN = F x S x D**

Agenda

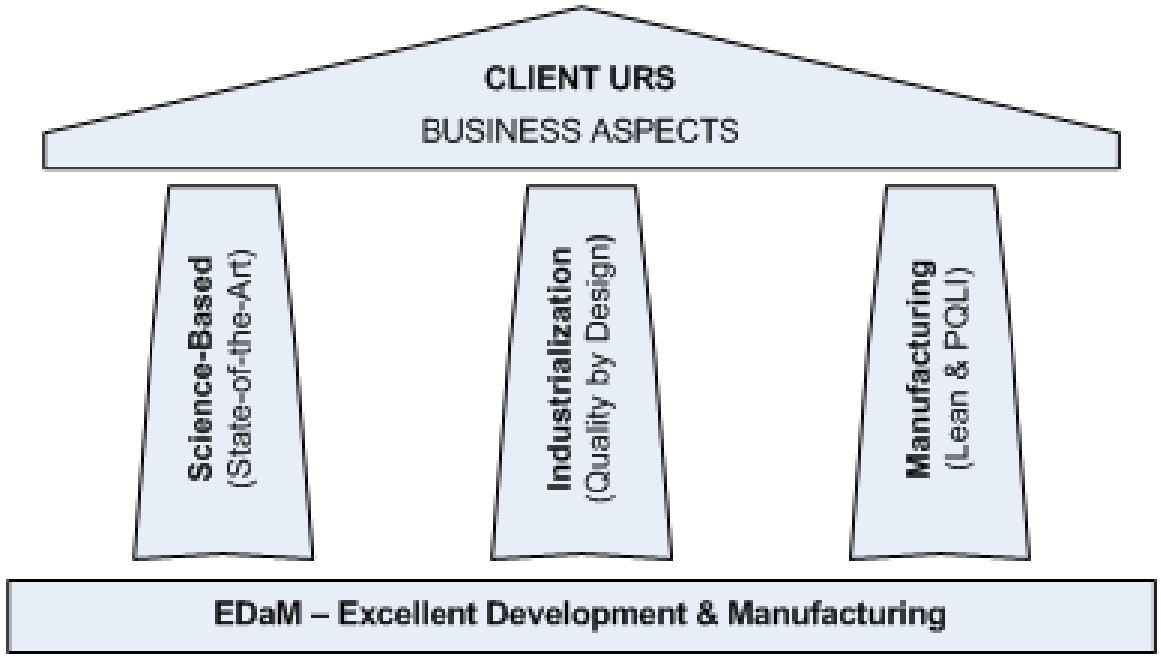
Advanced Tools in Development and Manufacturing

Excellent Development and Manufacturing

Quality by Design at Hovione

Excellent Development and Manufacturing
New approach at Hovione

- Established methodologies:
  Britest, QbD, Lean
- State-of-the-art tools
- Throughout project life-cycle
- Site independent
- Accessible by everyone
- Aligned with regulators (FDA & EMA)



Excellent Development and Manufacturing Guidelines

FAMILIARIZATION

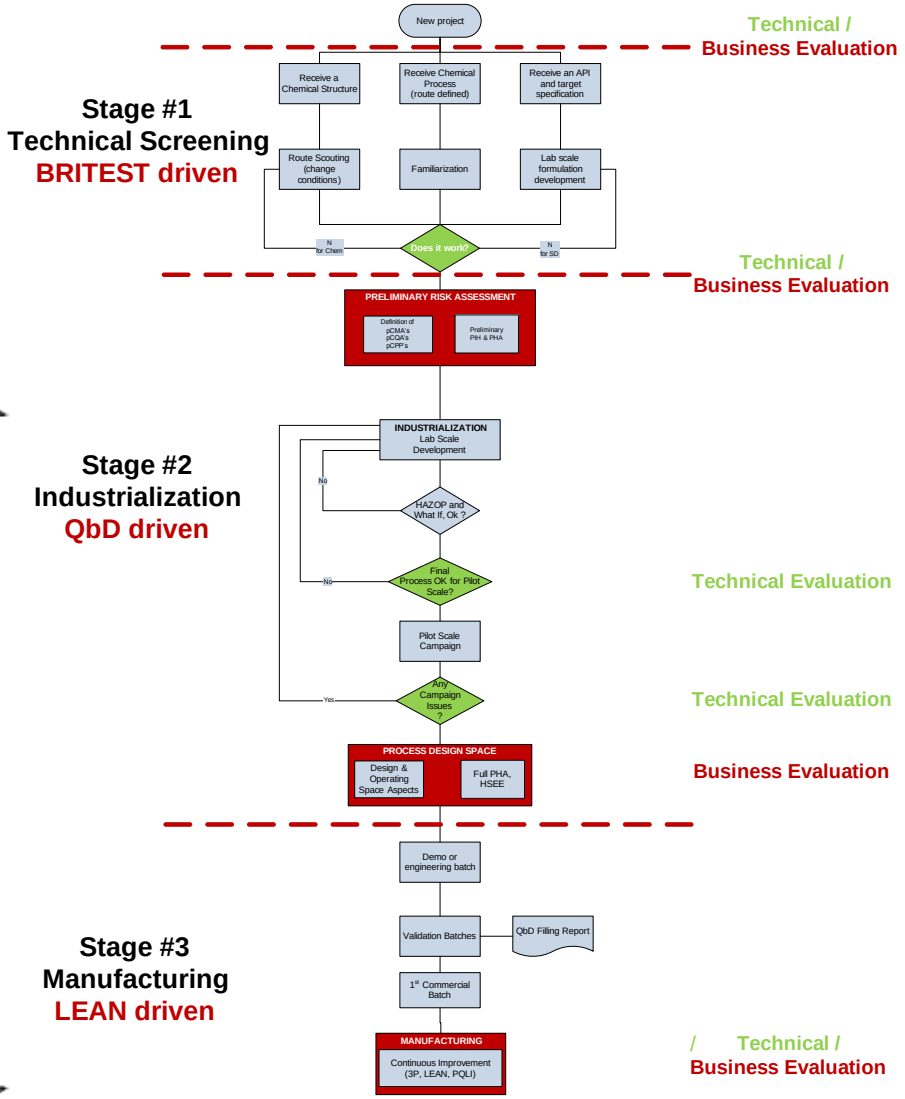
LAB SCALE DEVELOPMENT and PILOT SCALE

VALIDATION and MANUFACTURING

Technical screening (BRITEST)

Industrialization (QbD)

Manufacturing (LEAN)



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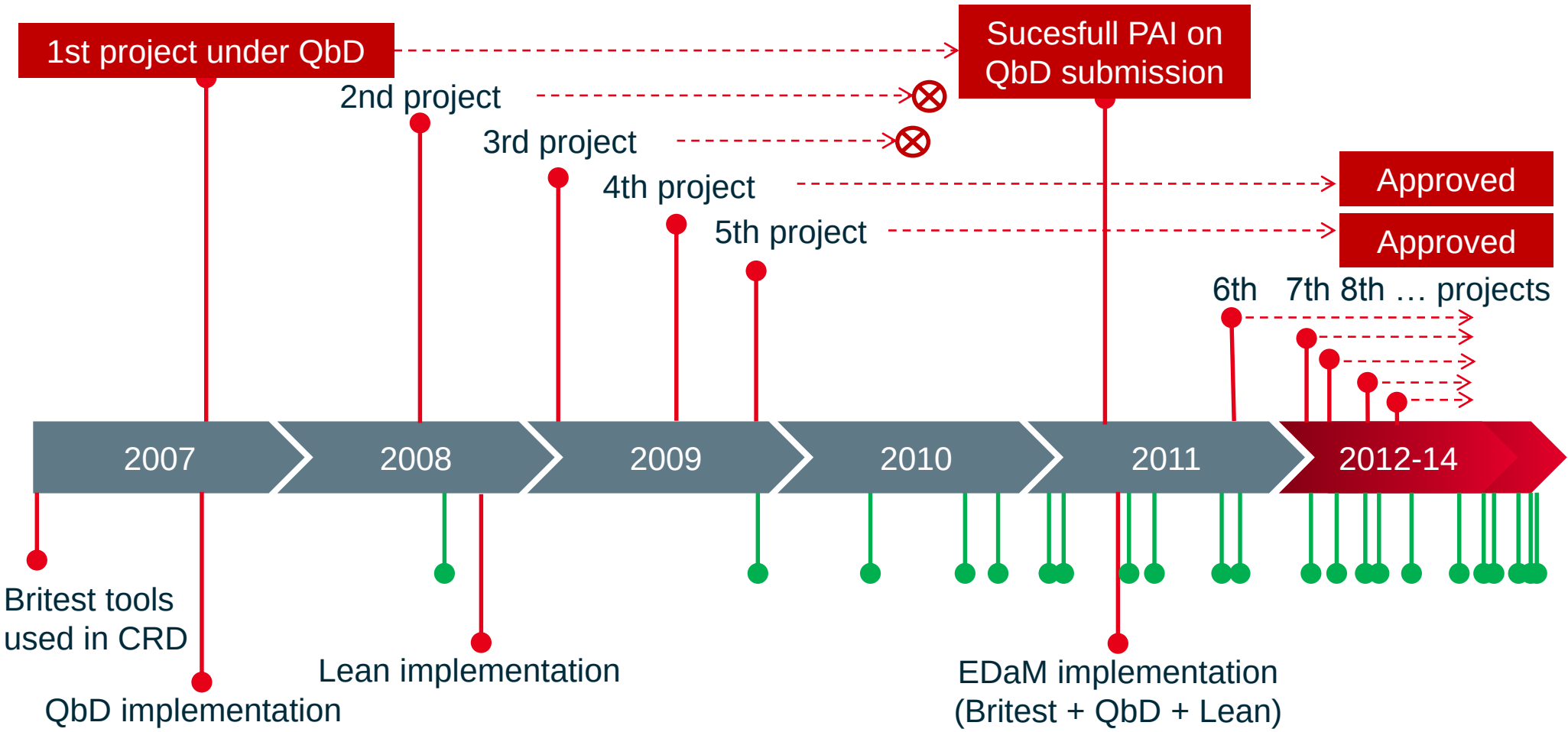
Excellent Development and Manufacturing

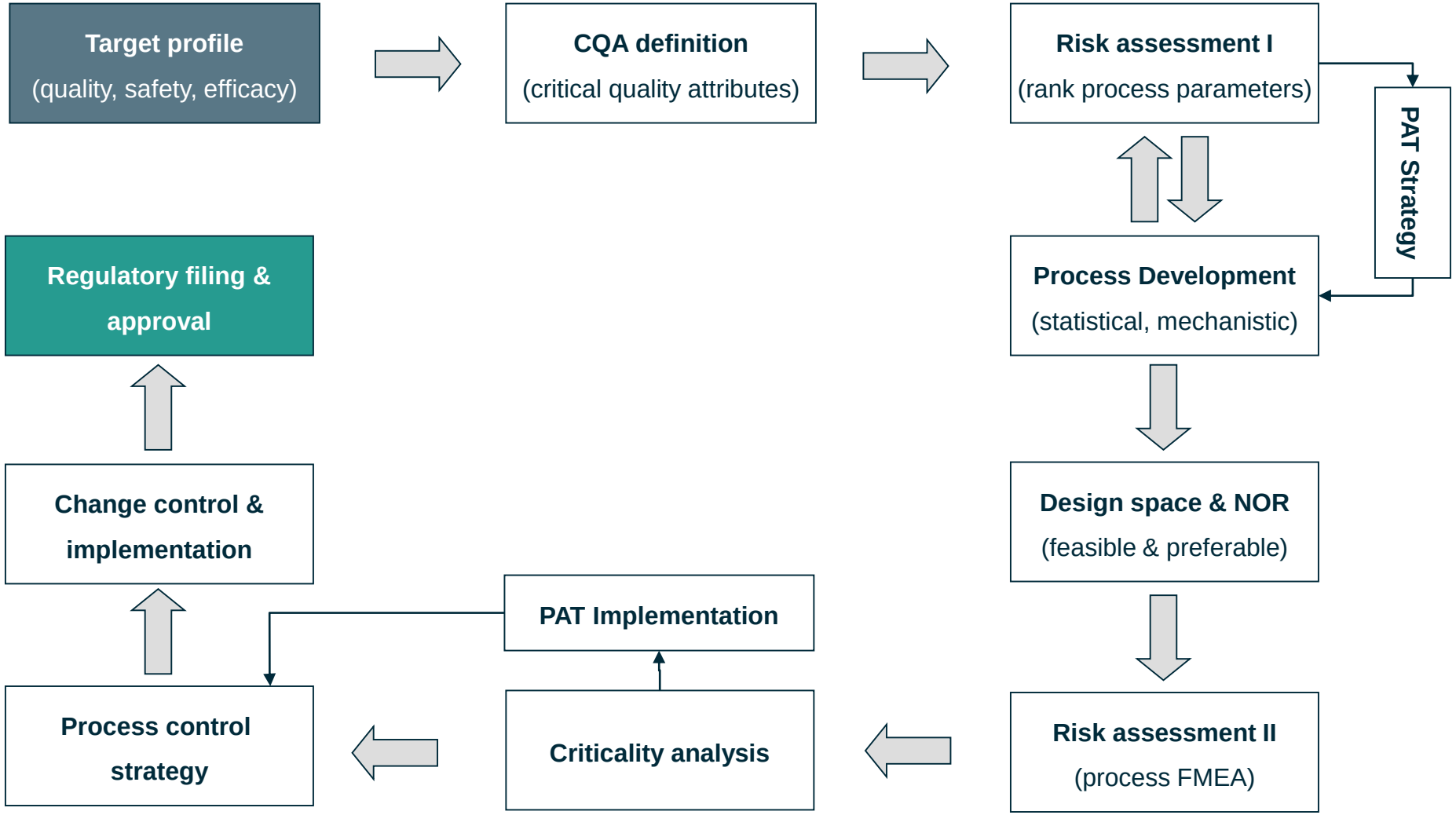
Quality by Design at Hovione

QbD at Hovione



QbD at Hovione

Science and Risk based



QbD at Hovione
Development by Design

	1st QbD filing	2nd QbD filing	Today
# Runs at full scale	~ 270	~ 60	~ 9
Material needed	~ 900 kg (~ $9 MM*)	~ 200 kg (~ $2 MM*)	~ 40 kg (~ $0.4 MM*)
Time required at full scale	~ 4 months	~ 4 weeks	~ 4 days

*** Assumed $10,000/kg of API as reference**

10 Years of Commercial Spray Drying

The most extensive commercial spray drying facilities in the world

Thank you for your attention.

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