Best Practices in Pharmaceutical Technology

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October 2014

Hovione

Agenda

Technological Trends in Pharmaceutical Development and Manufacturing

Advanced Tools in Development and Manufacturing

Excellent Development and Manufacturing

Quality by Design at Hovione

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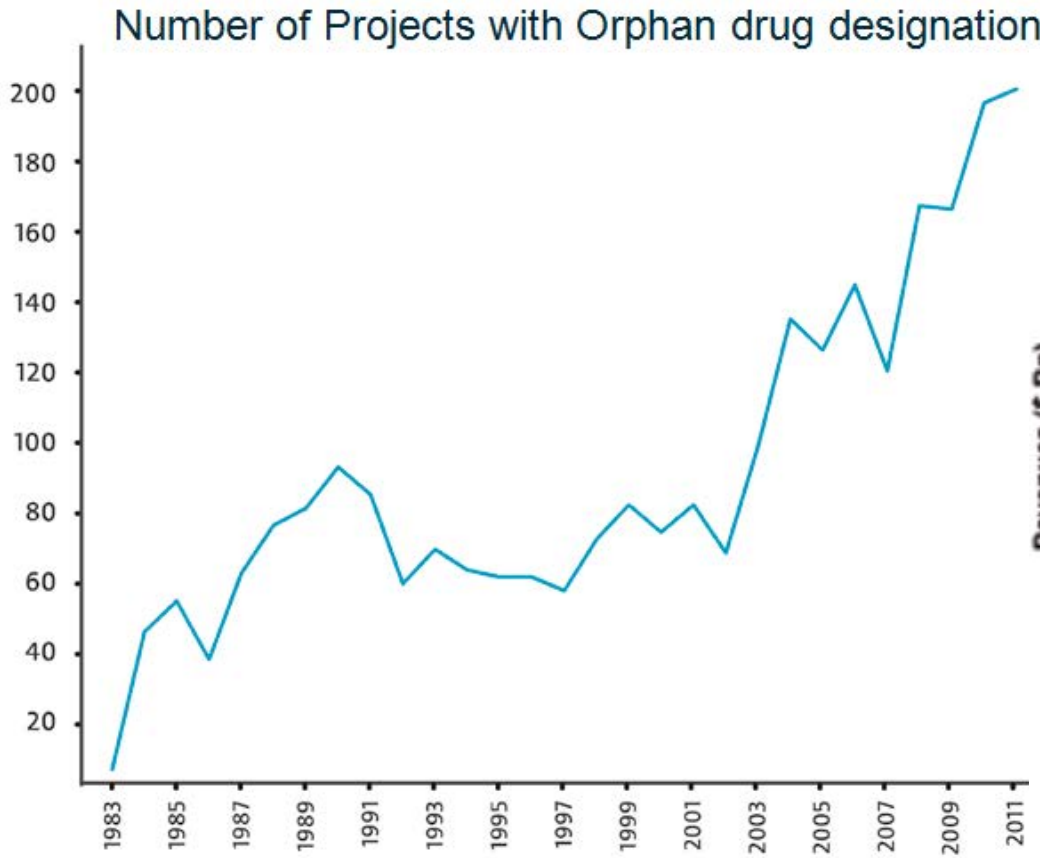
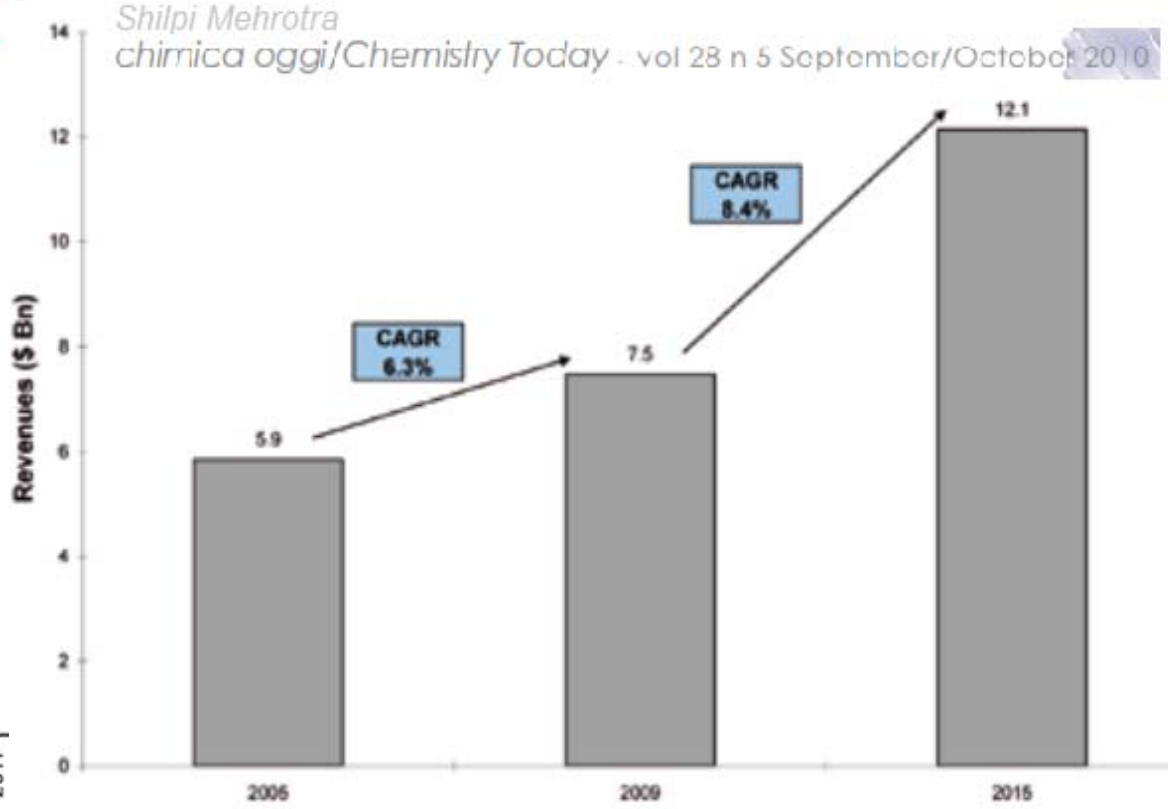
Technology Trends in Pharmaceutical Manufacturing

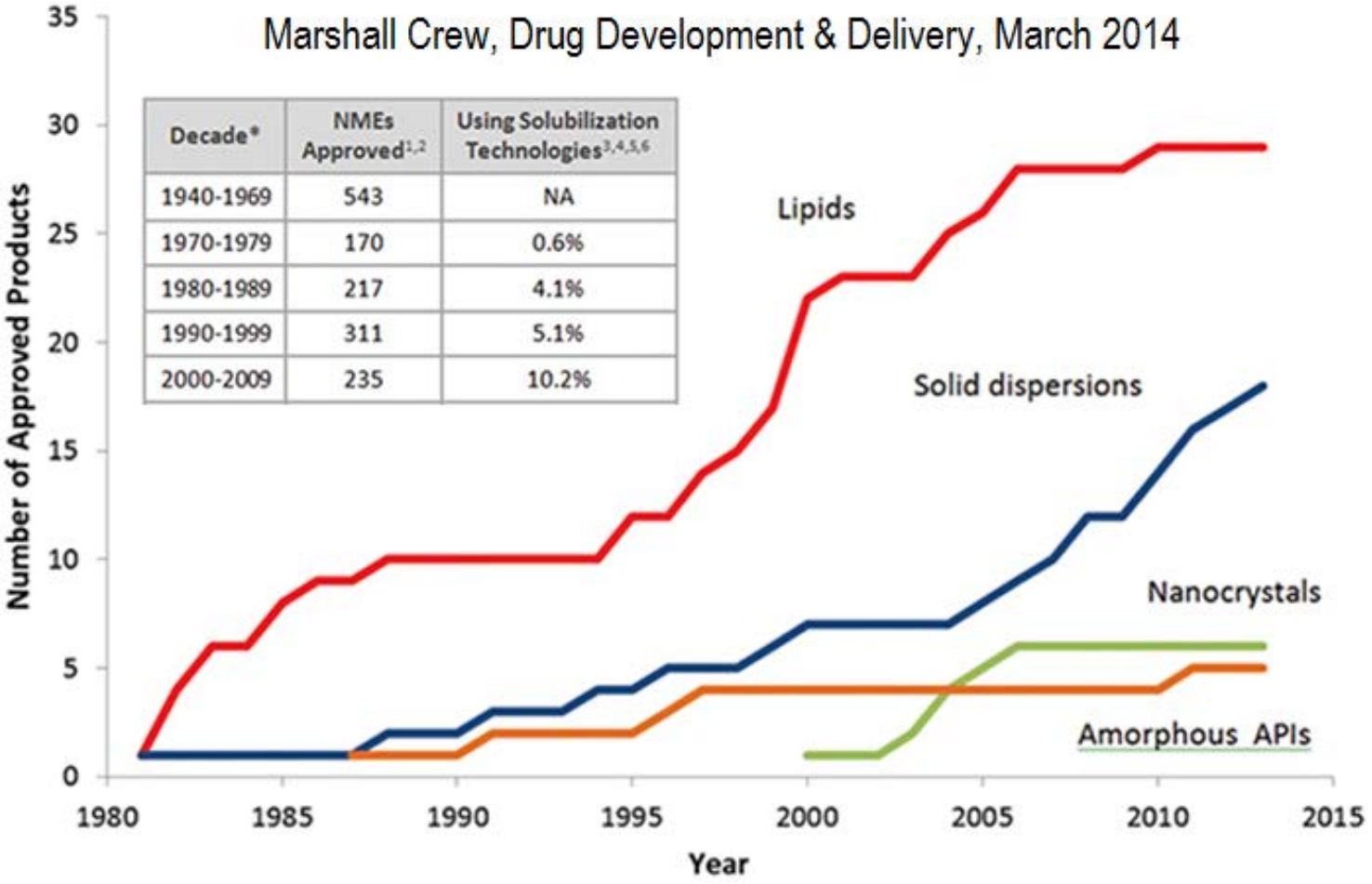
- Smaller volumes (personalized medicines, orphan drugs, niche)
- Higher potency





Technology Trends in Pharmaceutical Manufacturing

- More biopharmaceuticals and associated technology
- More complex drugs requiring more sophisticated technologies



Technology Trends in Pharmaceutical Manufacturing

- Moving into continuous processes (???)
- CROs and CMOs becoming key solution & technology providers
- Eager to introduce new technologies
- Increasing volume of real time operational data
  - generated by highly networked control and analytical technologies

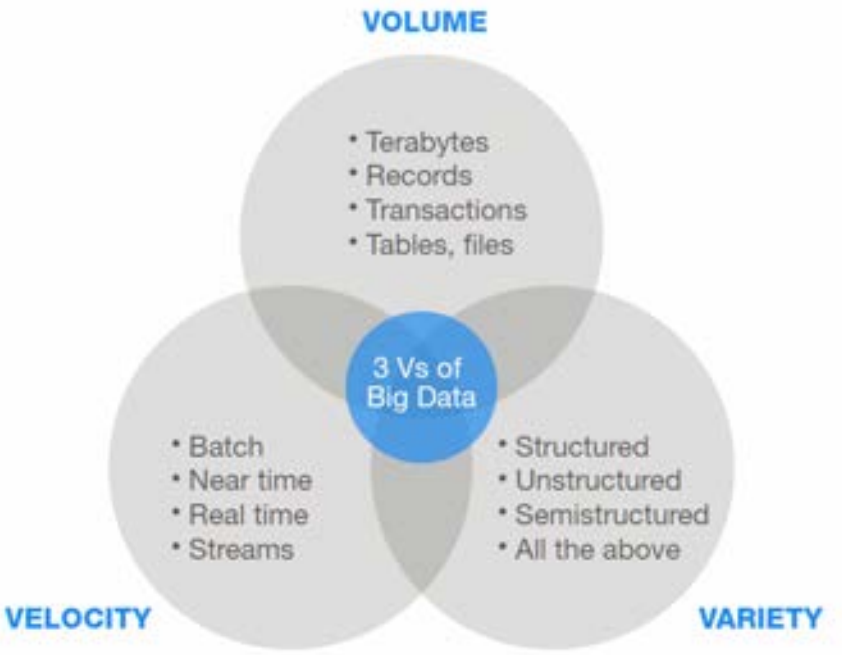
  … challenge being its consolidation in differentiating knowledge

Some Key Tools in Pharmaceutical Development and Manufacturing

- Statistical design and analysis
- Process analytical technologies
- Advanced modeling tools
- Risk assessment and management
- Lean 6-Sigma
- Quality by Design
- Big Data / Big Data Analytics

Big Data
What is it?

3 Vs: High-volume, high-velocity and high-variety information



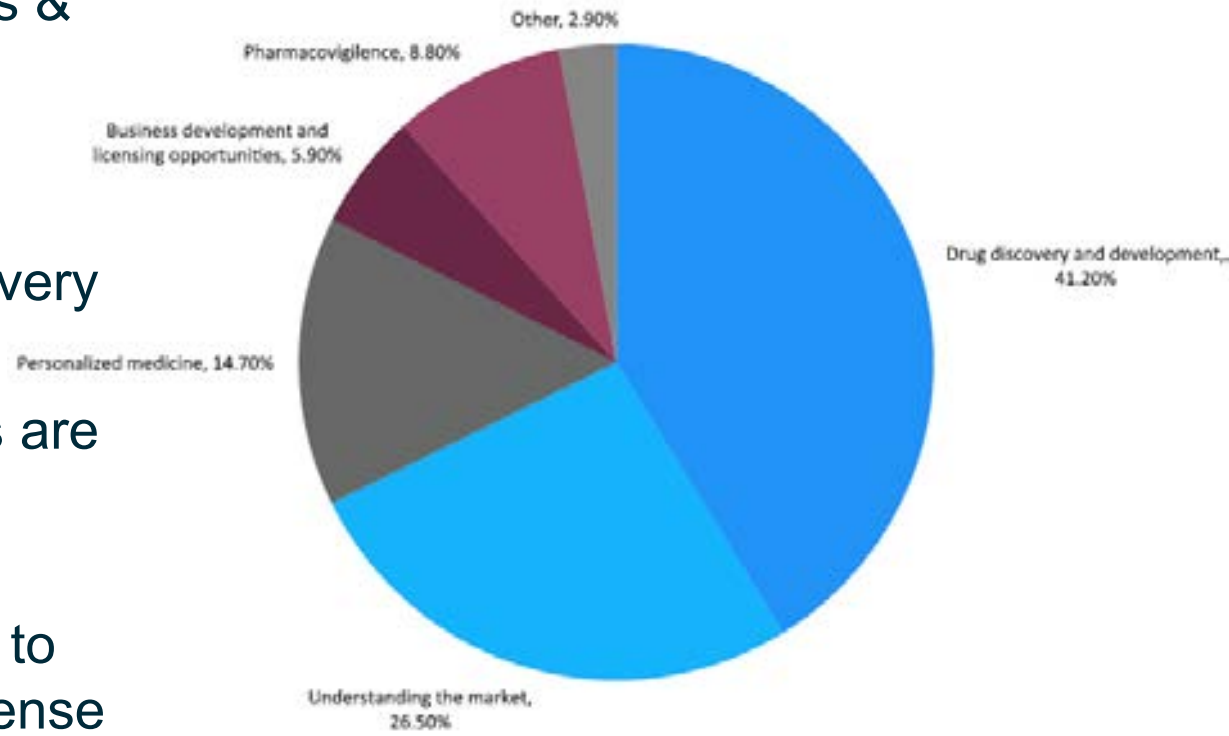
It is both a problem and an opportunity:

- The types and volumes of available data are increasing beyond the reach of human understanding
- Efficient use of the data will reduce it to human proportions, and bring an added value to those that have the right tools and techniques to shrink the data

Philip Russom, Big Data Analytics, TDWI best practices report 2011
Thomson Reuters, Big Data and the needs of the Pharma Industry, 2013

Big Data
Opportunities for Pharma Industry

- Big Data was firstly introduced in customer-facing functions eg sales & marketing
- Integration of data from R&D, retailers, patient and caregivers is expected to accelerate drug discovery and development
- Sophisticated modelling techiques are key to generate data quickly and consistently
- Driving force is often the pressure to reduce the timeline and huge expense of a typical drug development process



McKinsey, How Big Data can revolutionize pharmaceutical R&D, 2013
Dan Munro, Big Pharma Opens New Chapter On Big Data Collaboration, Forbes 2014
Thomson Reuters, Big Data and the needs of the Pharma Industry, 2013

Big Data
Challenges for Pharma Industry

- Adjust organization to enable efficient data collection
- Technology and analytics
  - Upgrade legacy systems
  - Invest in people with the right skills

- Mind-sets
  - Companies do not want to be the first mover, since there are few examples of success
  - Large companies should learn from smaller ones that are the early adopters of Big Data
  - Collaborate internally and externally, eg CROs, CMOs and academia

McKinsey, How Big Data can revolutionize pharmaceutical R&D, 2013

Agenda

Technological Trends in Pharmaceutical Development and Manufacturing

Advanced Tools in Development and Manufacturing

Excellent Development and Manufacturing

Quality by Design at Hovione

Advanced Tools at Development and Manufacturing

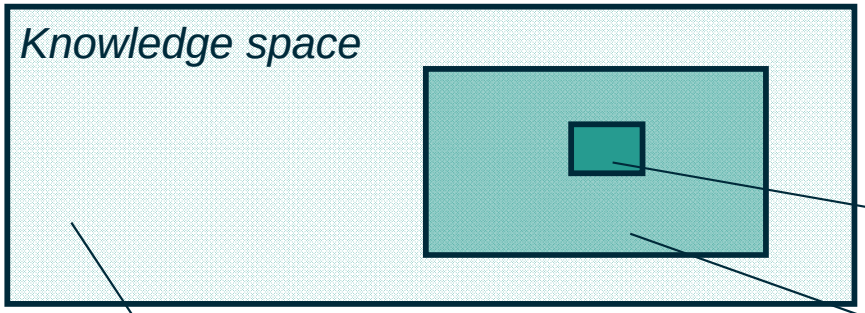
DEVELOPMENT

- Risk Assessment
- Design of Experiments
- Modeling Tools
- Scale-Up Methods
- Scale-Down / Miniaturization
- Process Analytics
- Multi Variate Analysis

MANUFACTURING

- Lean 6 Sigma
- Visual Stream Mapping
- Statistical Evaluation
- Failure Mode Effective Analysis
- 8 D
- Poka-Yoke
- 5 S, OEE

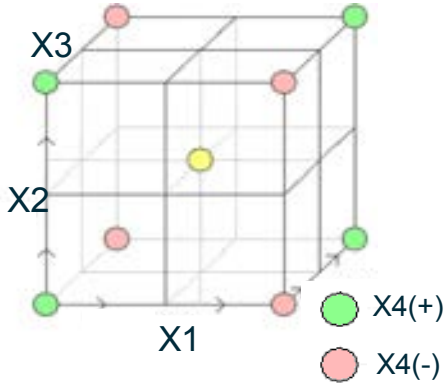
Design of Experiments



Screening stage

Control variables (initial set)

Quantify criticality
& *Check the space*

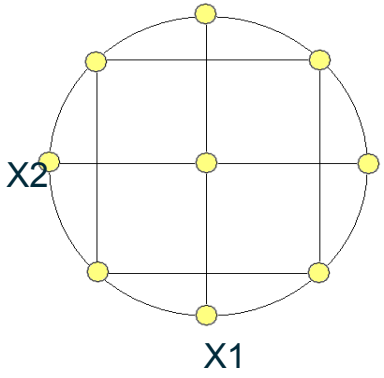


- Average resolution
- Wide space

Optimization stage

Control variables (reduced set)

Refine quantification
& *Locate optimality*

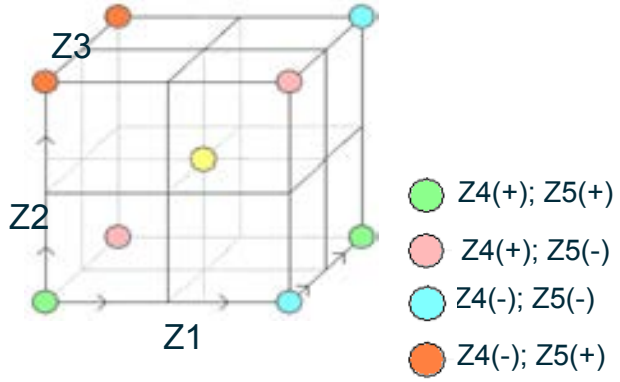


- High resolution
- Average space

Robustness stage

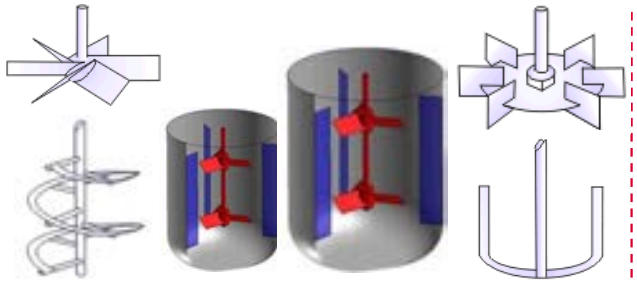
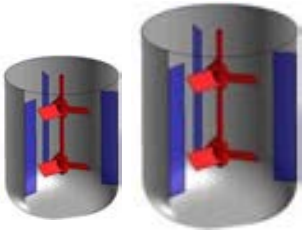
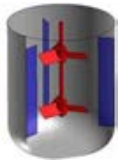
"Fixed" variables (emulate deviations)

Assume optimal point
& *Check the stability*



- Low resolution
- Narrow space

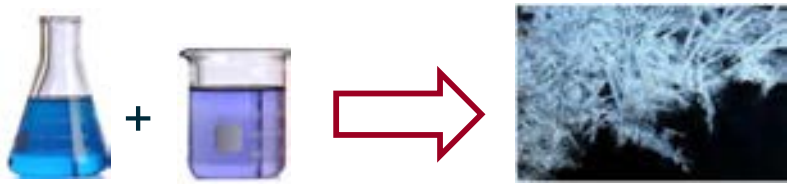
Modeling Tools
Adjust model complexity

	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-studies: Chemical synthesis

Problem statement (routine)



Solvent **Anti-solvent** ***f* (temperature)**

- Solubility curve determination is key to determine the best crystallization conditions.

- However, the procedure takes weeks of experimental work, representing a burden (time and resources).

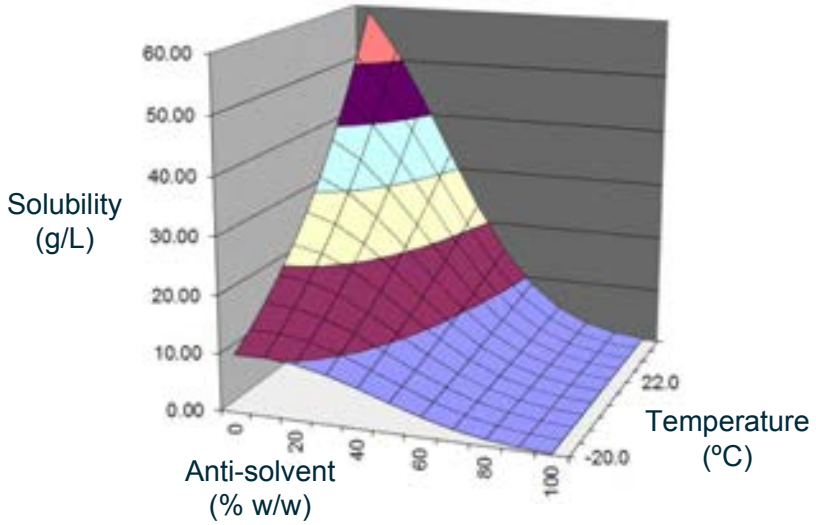
Approach

- Easy-of-use / **fast solution** tool, capable of reducing the amount of experimental work (Dynochem).

Mechanistic

- 1 solubility point for each pure solvent / anti-solvent
- 1 solubility point with a mixture of solvent / anti-solvent
- 2 different temperatures for each of the previous;

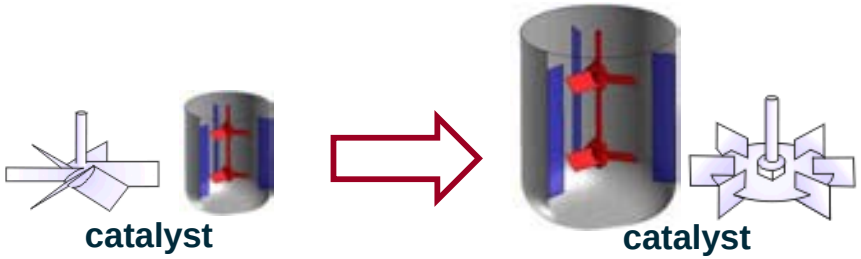
- 1 model: $\frac{d\ln(x_A)}{dT} = \frac{H_A(solid) - H_A(liquid)}{RT^2} = \frac{\Delta H_B(fusion)}{RT^2}$



- Above procedure enables calibration / extrapolation
- With only 8 experiments, full curve estimated!

Modeling Tools
Case-studies: Chemical synthesis

Problem statement (troubleshooting)



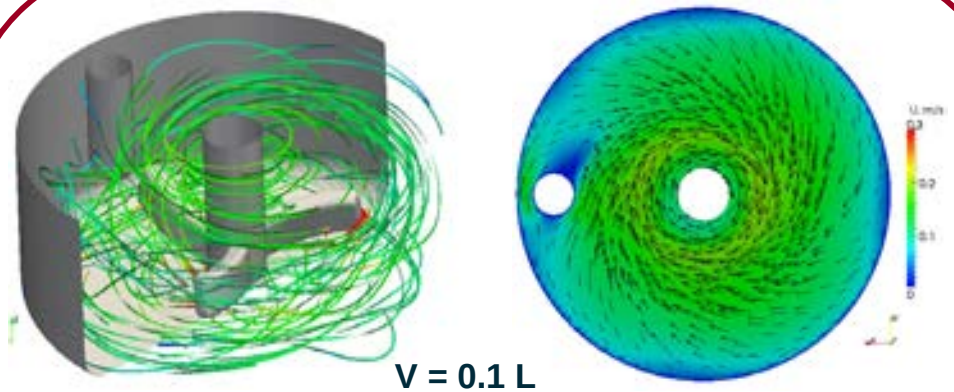
• During an alkylation reaction, the content of raw material increased after IPC (upon scale-up).

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

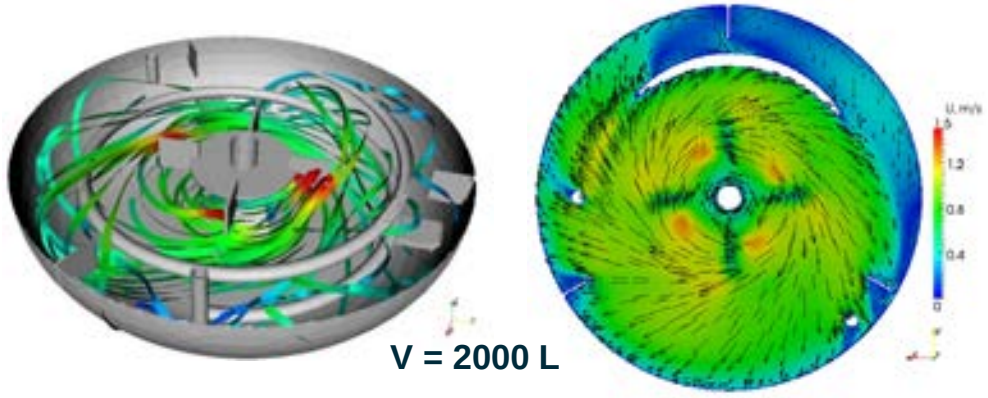
Approach

• Axial & radial mixing profiles 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.

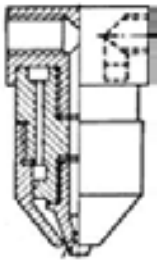
• Stirrer was re-designed; problem was solved.

Modeling Tools
Case-studies: Particle engineering

F_feed

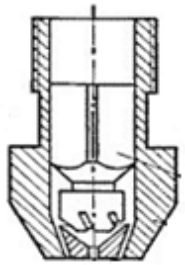
F_atom

C_feed



2-fluid nozzle

Pressure nozzle



P_feed

μ_feed

C_feed

How to predict particle size?

Modeling Tools
Case-studies: Particle engineering #1

Problem statement - Inhalation (routine)

- Performance very sensitive to particle size (±0.2 μm);
- Different “classes” of nozzles across different scales;
- Lower number of product under development.

Approach

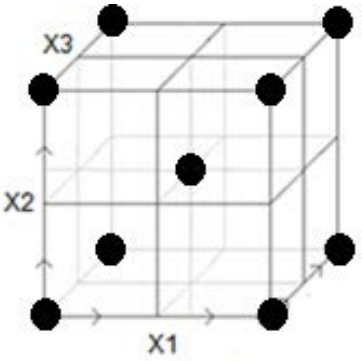
- Build an **accurate local** model for each product

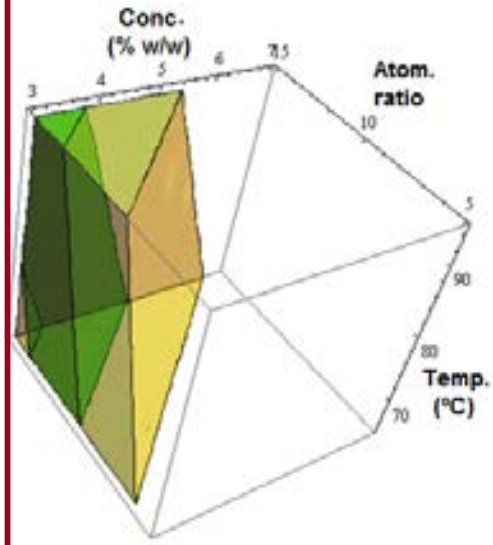
Statistical

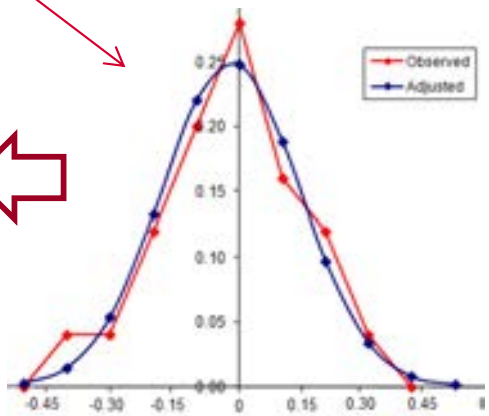
DoE

1) Experimentation / modeling

2) uncertainity evaluation







- Uncertainty evaluation is critical given the narrow ranges!
- **Scale-dependent** (local model) but very accurate.

Modeling Tools
Case-studies: Particle engineering #2

Problem statement - Oral (routine)

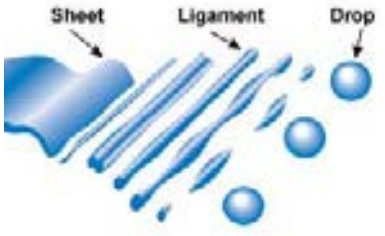
- Performance less sensitive to particle size;
- Same “class” of nozzles across different scales;
- High number of new products on a yearly basis.

Approach

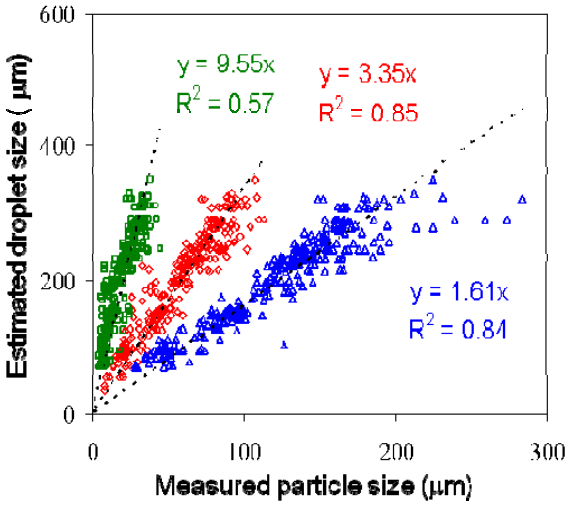
- Build a **calibrated general** model for PN systems

Mechanistic

LISA model



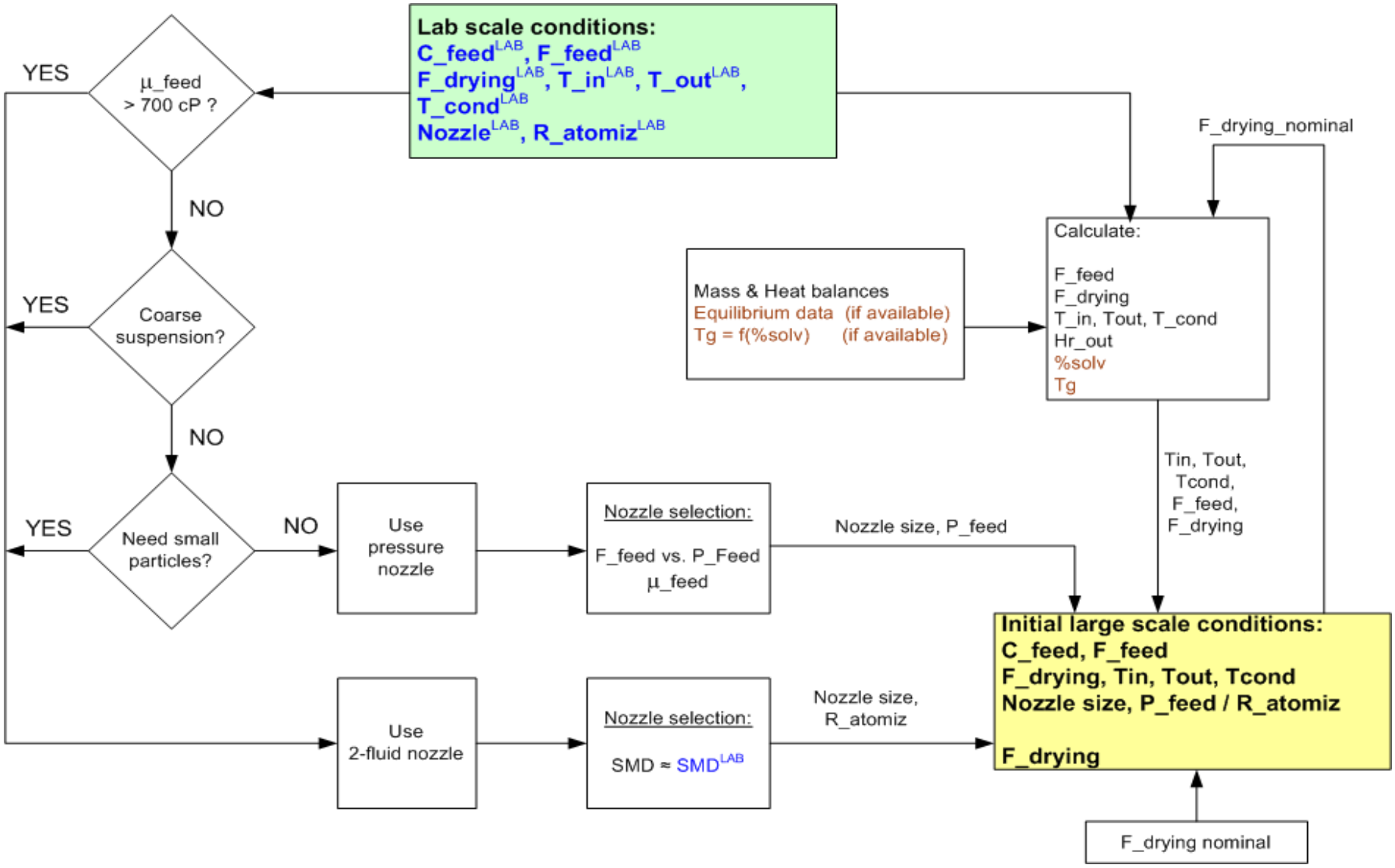
$$\omega_r = -\frac{2\nu_1 k^2 \tanh(kh)}{\tanh(kh)+Q} + \frac{\sqrt{4\nu_1^2 k^4 \tanh^2(kh) - Q^2 U^2 k^2 - F(k,h,Q,U,\sigma,\rho)}}{\tanh(kh)+Q}$$



Calibration sucessfull
(> 150 past runs used)

- Prediction error of +/- 15% is perfectly acceptable!
- **Scale-independent** model for general use.

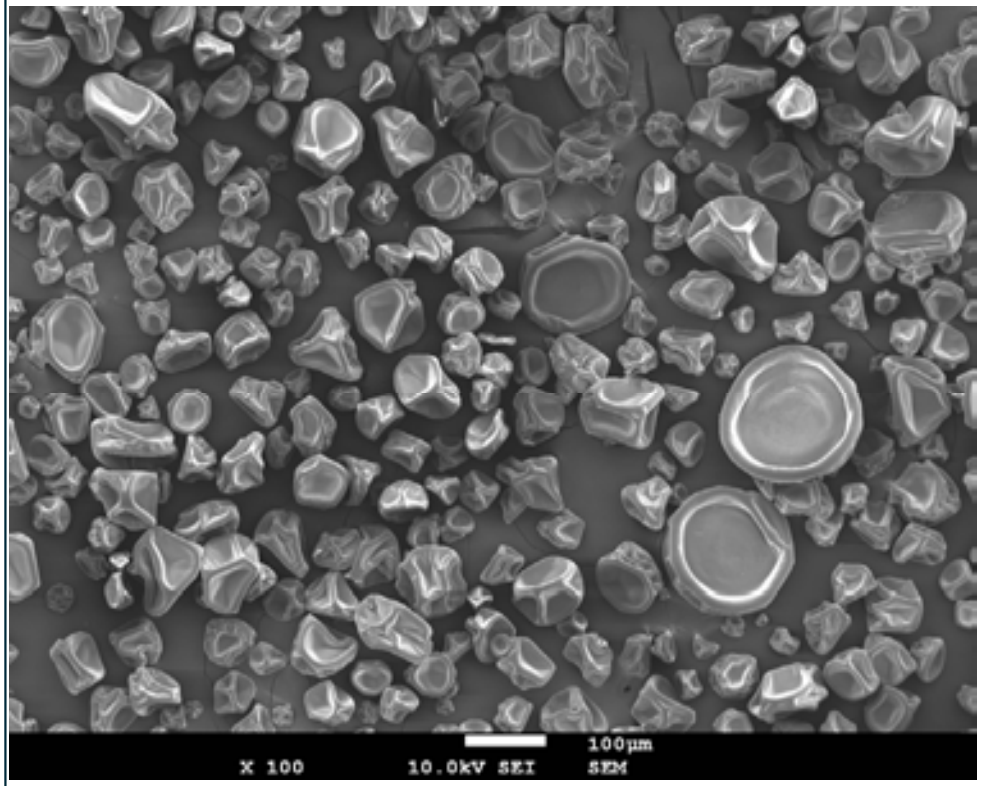
Scale-Up Method



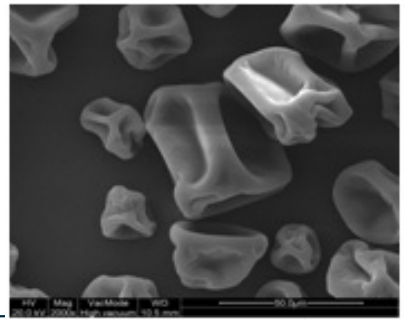
GIL M., VICENTE J., GASPAR F.; *Spray Drying in the Pharmaceutical Industry Scale-Up Methodology*; Chemistry Today, Jul/Aug 2010

Scale-Down Approach

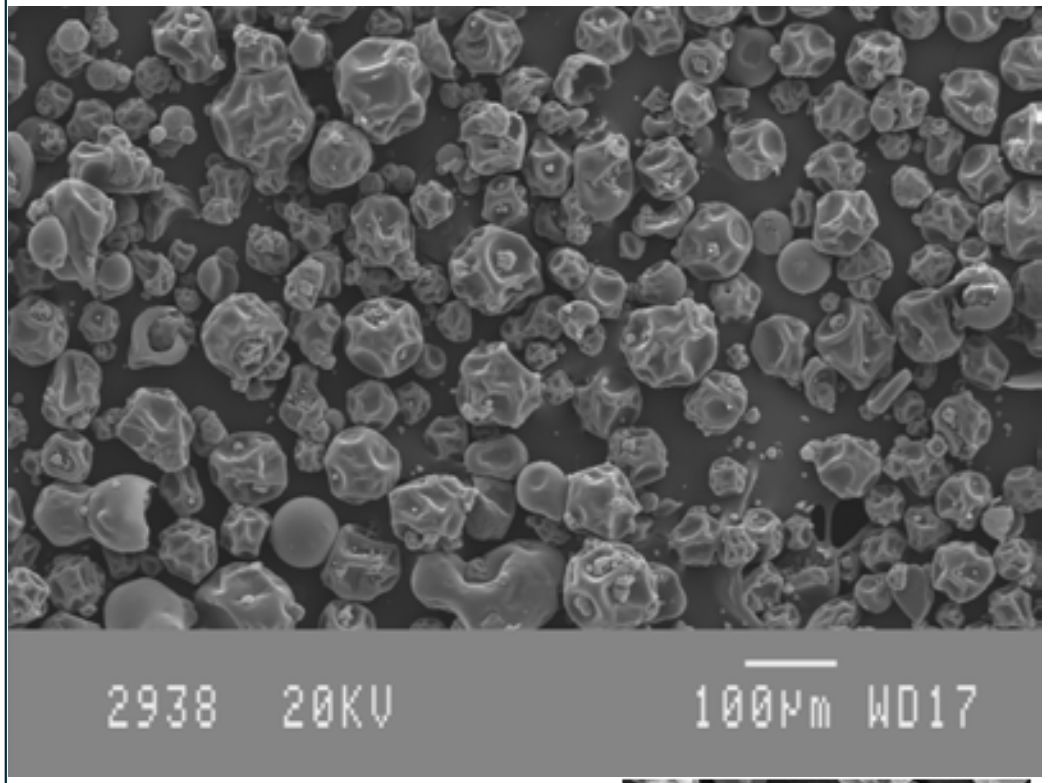
Lab unit



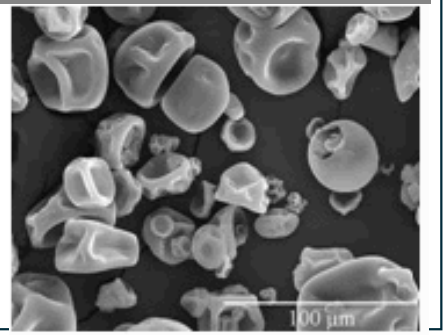
D_v50 = 83 µm
span = 1.5
bulk density = 0.34 g/ml
tap density = 0.42 g/ml
solvent = 7% w/w



Commercial unit

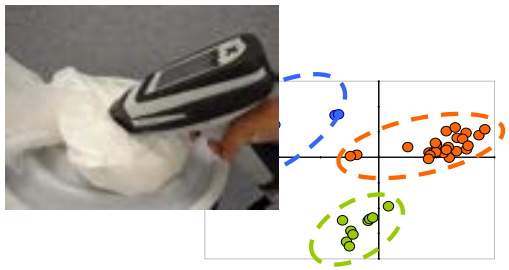


D_v50 = 82 µm;
span = 1.7
bulk density = 0.29 g/ml
tap density = 0.40 g/ml
solvent = 5% w/w



Process Analytics for Chemical Processes

Handheld NIR

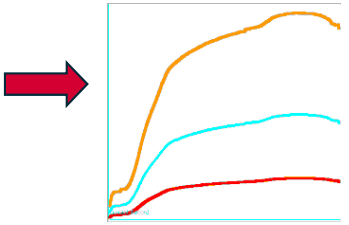


Raw materials identification and qualification

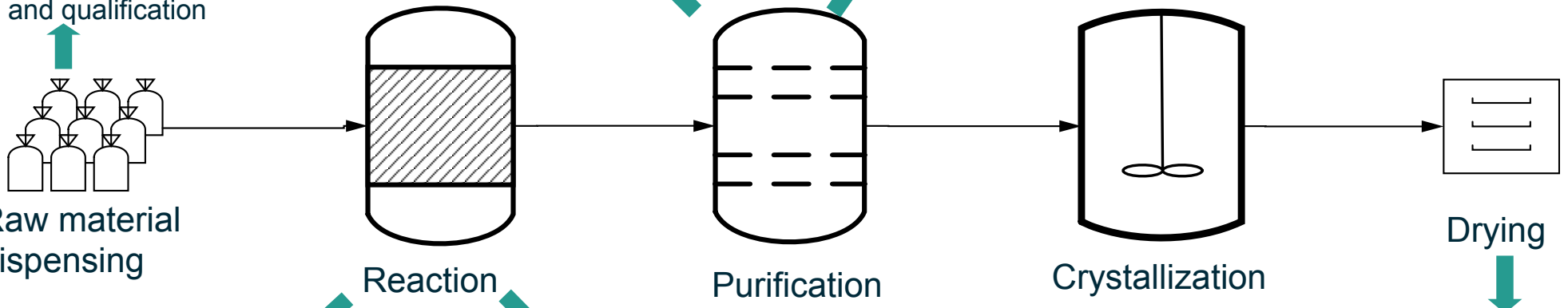
UV photometry
Concentration and end-point determination

Refractometry

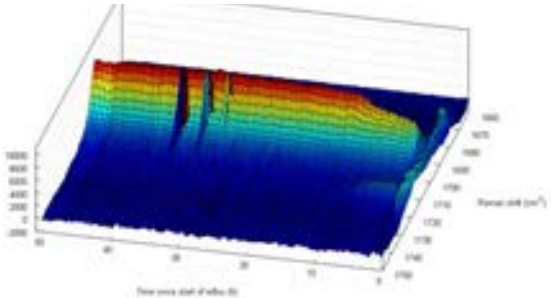
FBRM



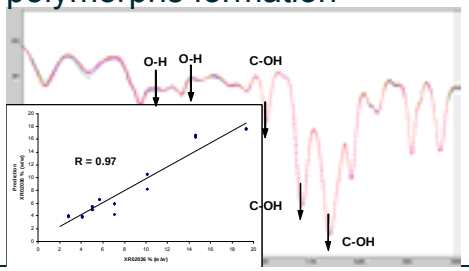
Crystals growth dynamics



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

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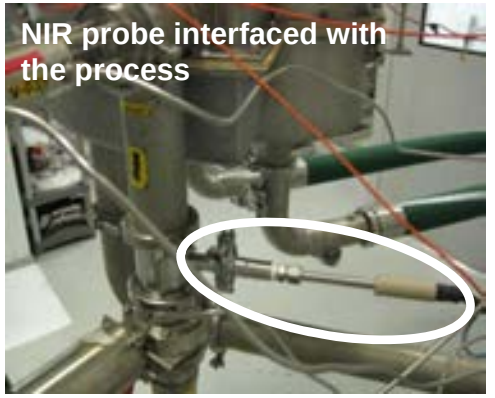
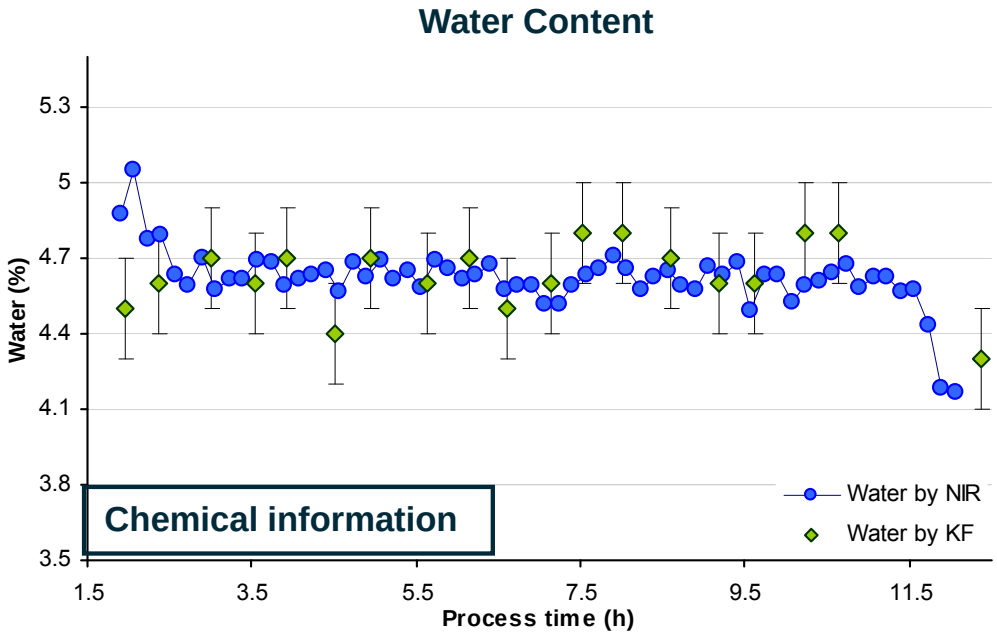
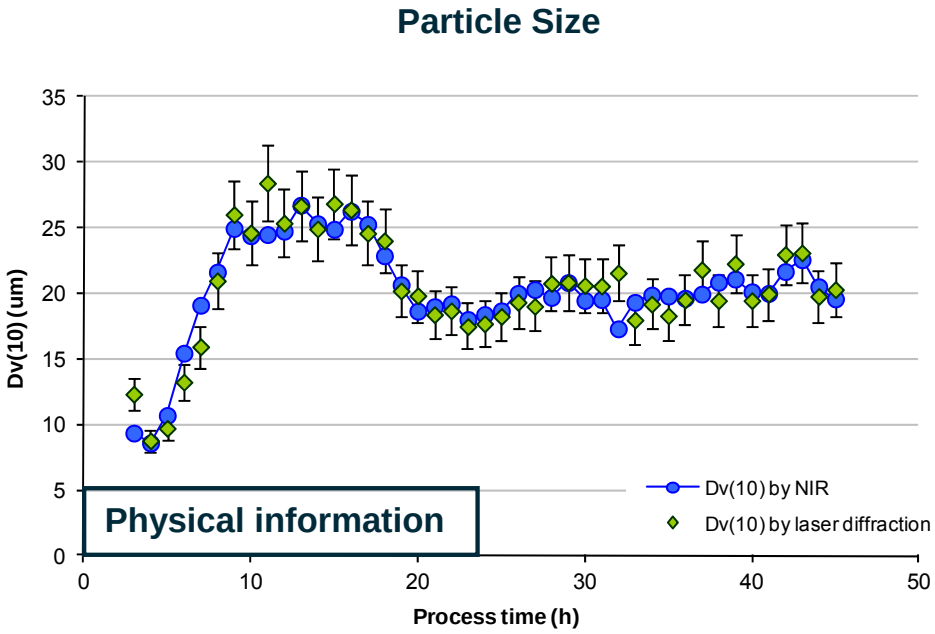
Process Analytics

A reflectance probe can be used to **characterize** the resulting material

NIR technology allows the monitoring of more than one attribute using only one sensor







Process Analytics Technologies Toolbox

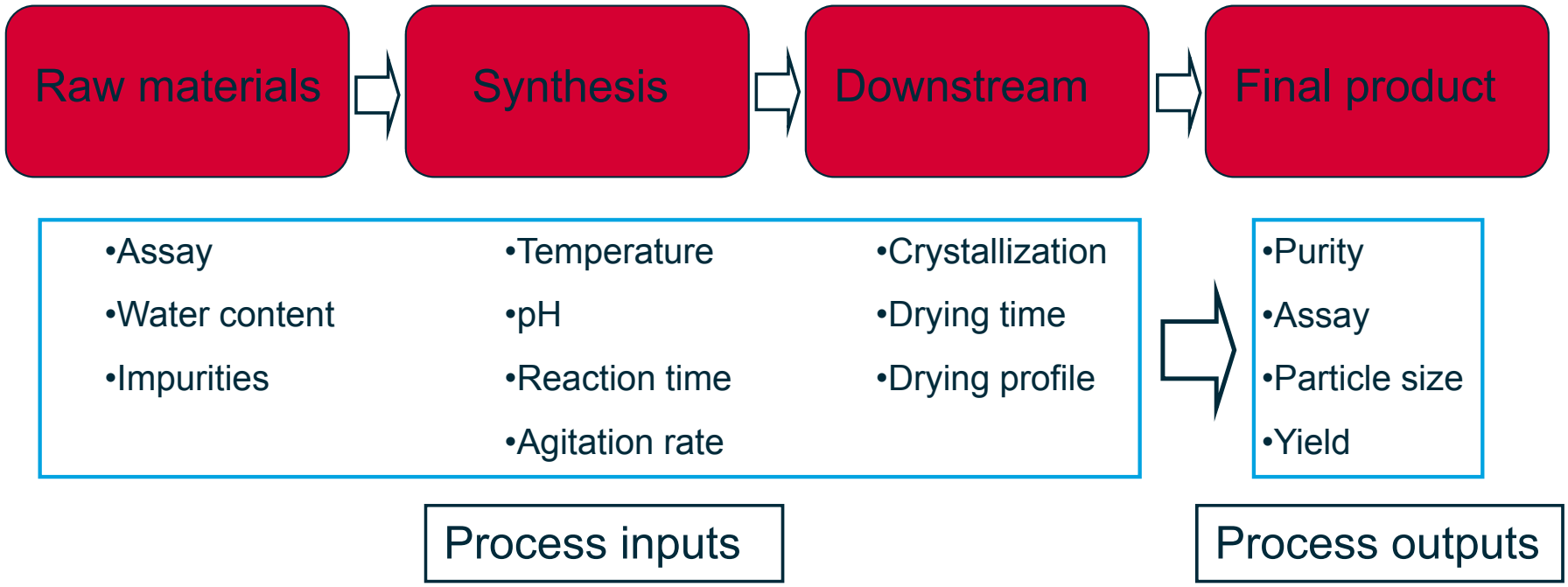
		Currently available PAT Technologies								Under development	
		Near Infrared Spectroscopy	Turbidimetry	Refractometry	Viscometry	Focused Beam Reflectance Measurement	Ultra Violet Photometry	Laser Diffraction	Mass Spectroscopy	Mid Infrared Spectroscopy	Raman Spectroscopy
Process unit operations	Dispensing	✓									✓
	Dissolution	✓	✓	✓	✓					✓	✓
	Suspension Prep.	✓	✓		✓	✓				✓	✓
	Distillation	✓		✓						✓	✓
	Reaction	✓								✓	✓
	Crystallization	✓	✓	✓	✓	✓				✓	✓
	Column Purification			✓			✓			✓	✓
	Wet-milling					✓				✓	✓
	Jet-milling							✓			✓
	Spray-Drying					✓		✓			✓
	Drying	✓							✓		✓
Process Development Steps	Familiarization									✓	✓
	Industrialization	✓	✓	✓	✓	✓		✓	✓	✓	✓
	Scale-Up	✓	✓	✓	✓	✓			✓	✓	✓
	Commercial Mnfg Start-Up	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Commercial Routine Mnfg	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Continuous Improvement	✓				✓			✓	✓	✓

Multivariate Analysis

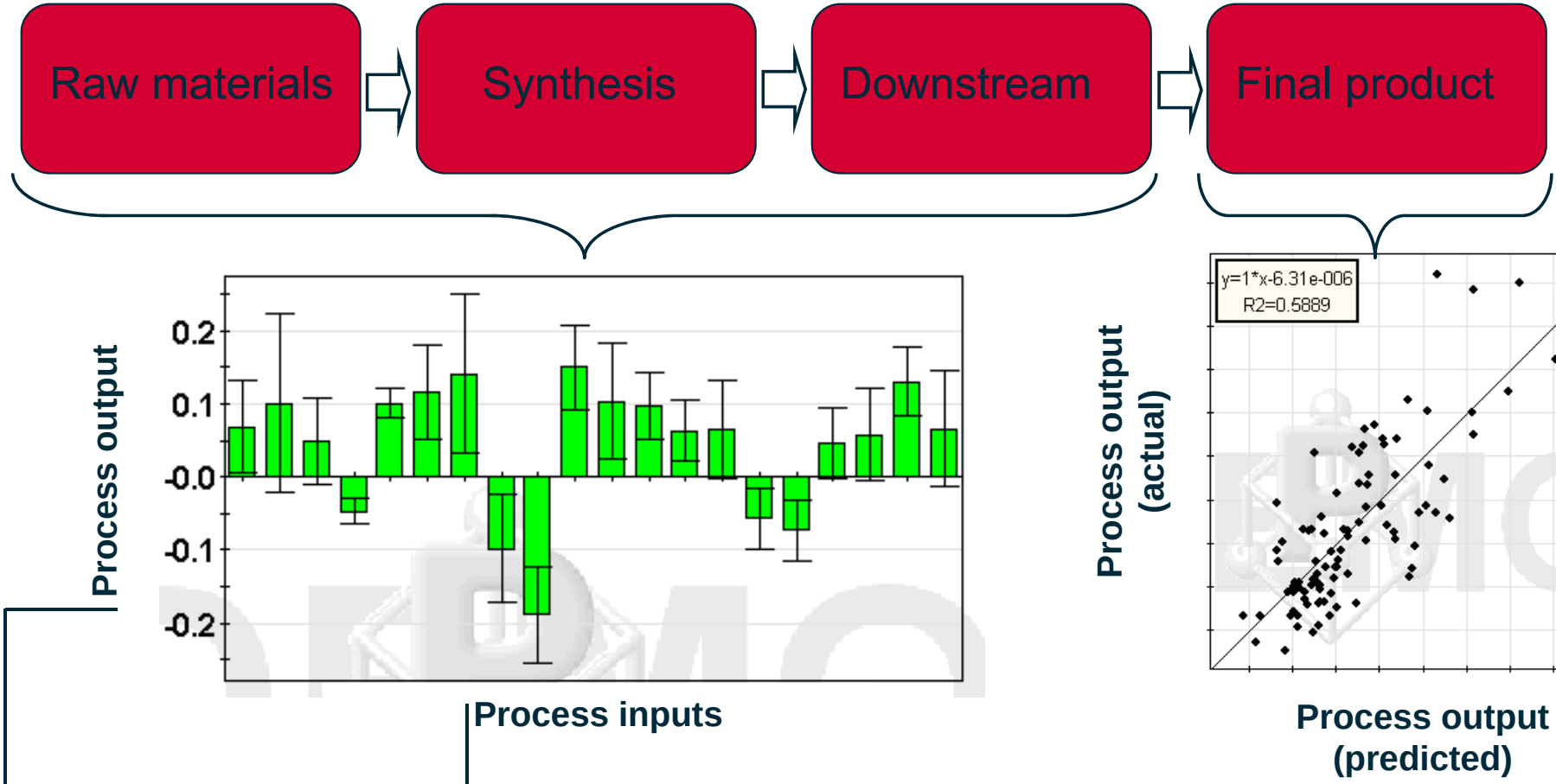
Variability in process inputs translates into variability in the final product

How are the process outputs affected by the inputs?

What variables and combination of variables affect the process outputs more significantly?



Examples: Multivariate Analysis



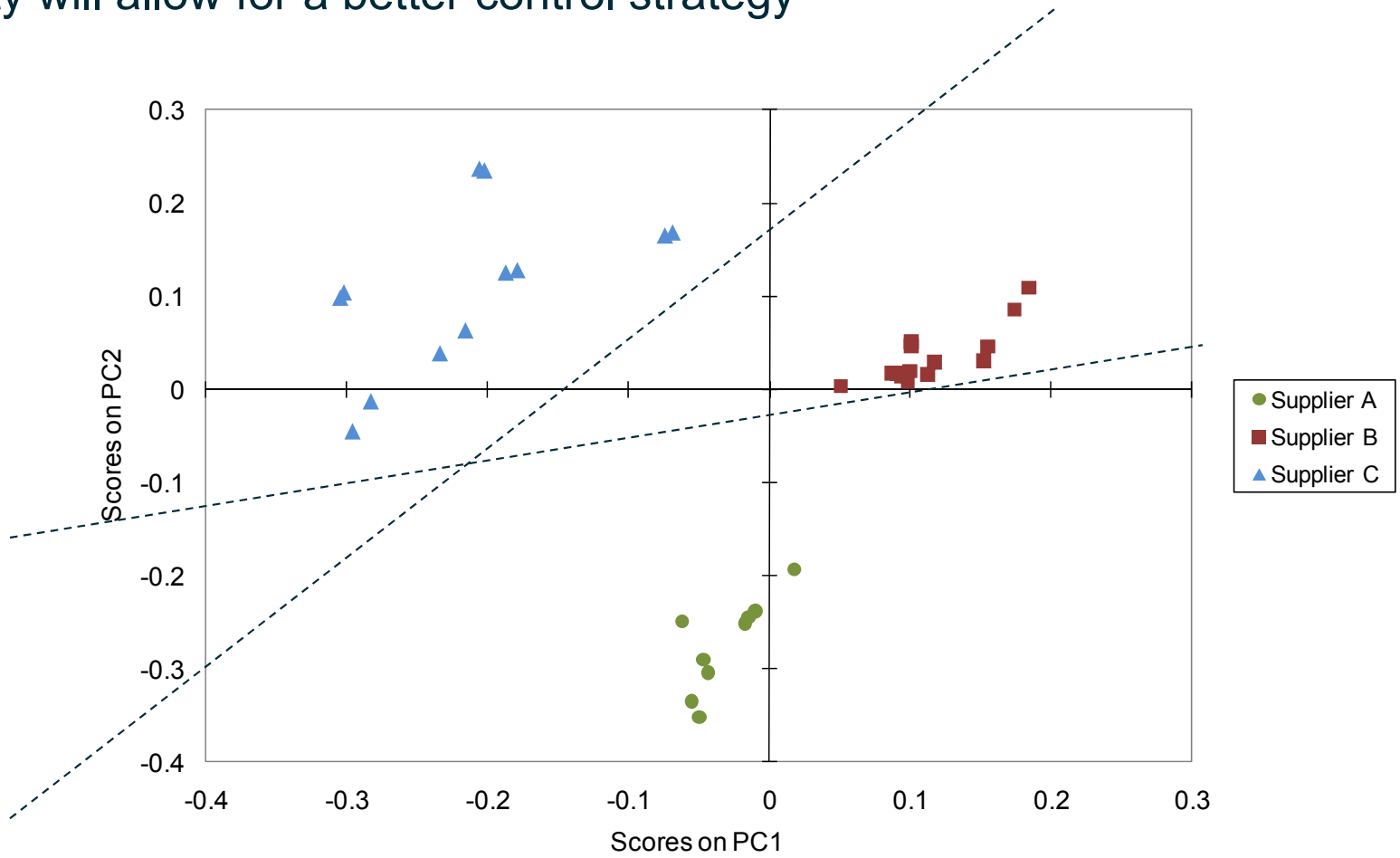
- Quality attributes (e.g.: purity) or process performance indicators (e.g.: yield)

- Impact of process inputs on a process output
- Higher the absolute value => greater impact

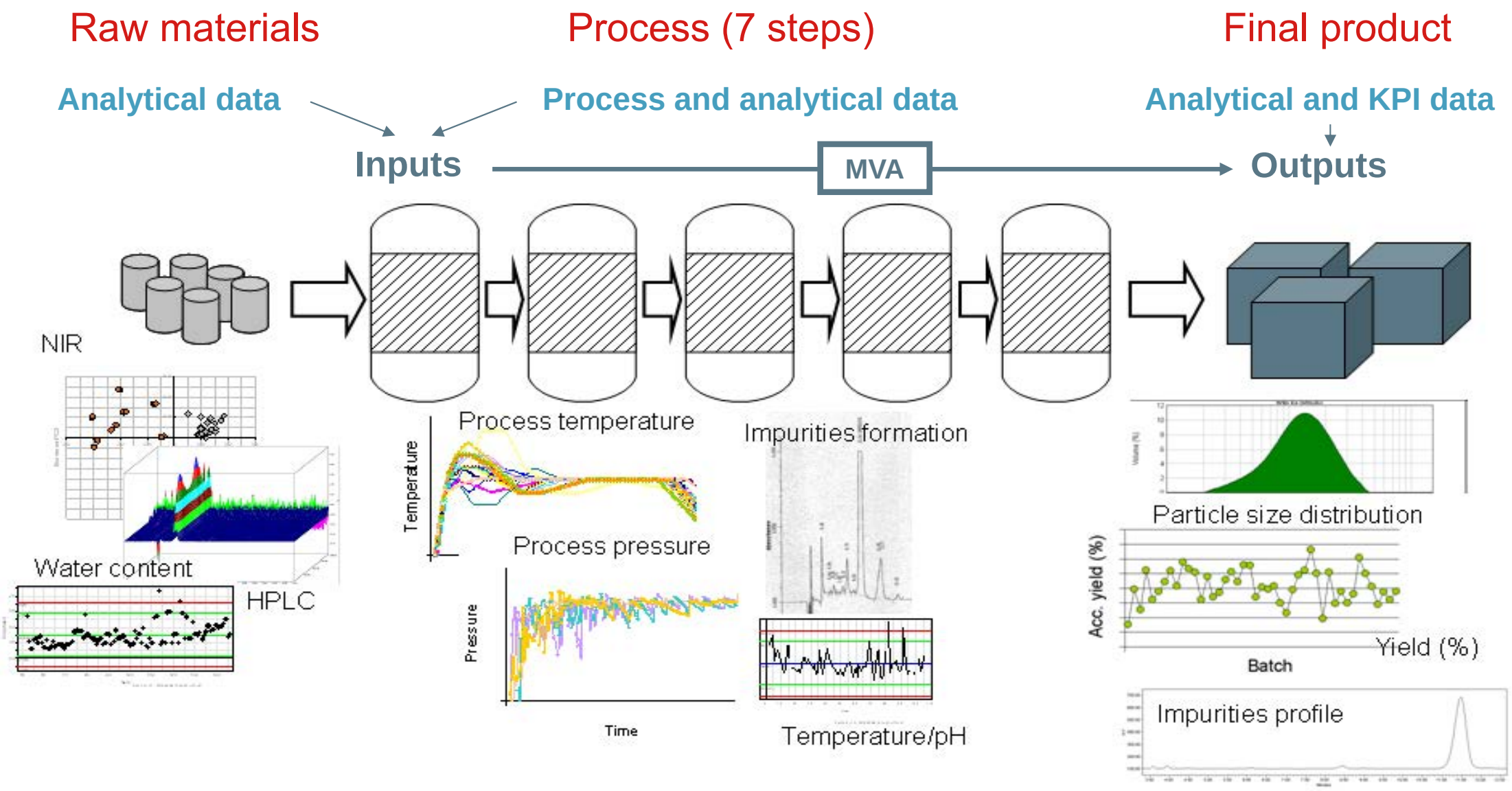
Multi Variate Analysis
PCA for Raw Material Dispensing by NIR

NIR may reveal variability between **suppliers** which may impact downstream

Accounting such variability will allow for a better control strategy



Multivariate Data Analysis
The PLS - Real Example



Multivariate Data Analysis
The PLS - Regression

Raw materials

NIR spectra; HPLC; Water content

Reactions

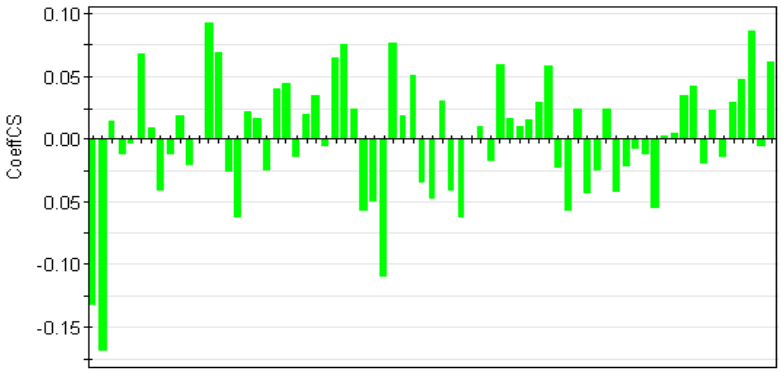
Temp./pressure profiles

Intermediates HPLC

Downstream

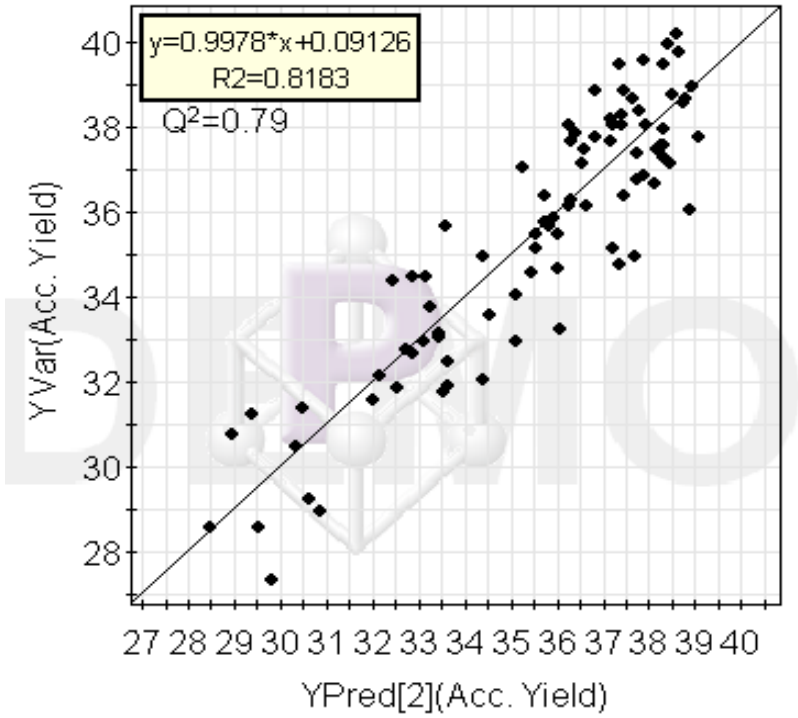
Temperatures/pH

Intermediates HPLC



Partial Least Squares Regression

- **Final product**
  - Impurities
  - Particle size distribution
  - Accumulated yield



RMSEE = 1.300

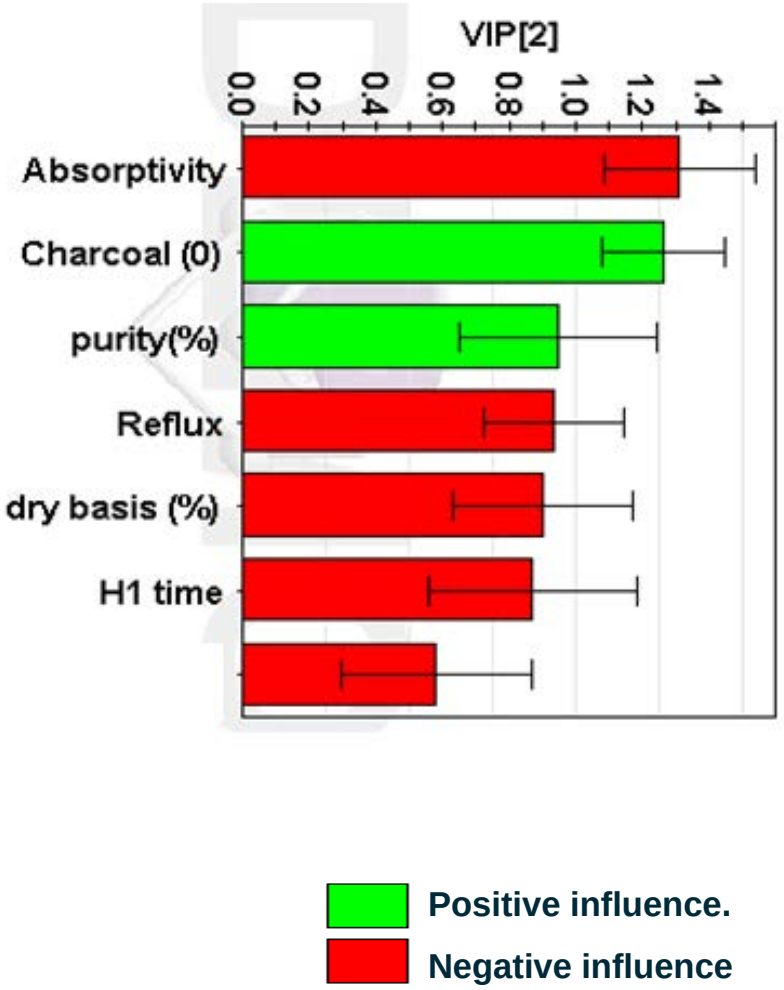
Multivariate Data Analysis
PLS - The Results

Prediction of variability leads to process knowledge

Model coefficients allows identification of critical variables and how to change them for improvement:

Amount of catalyst was changed;

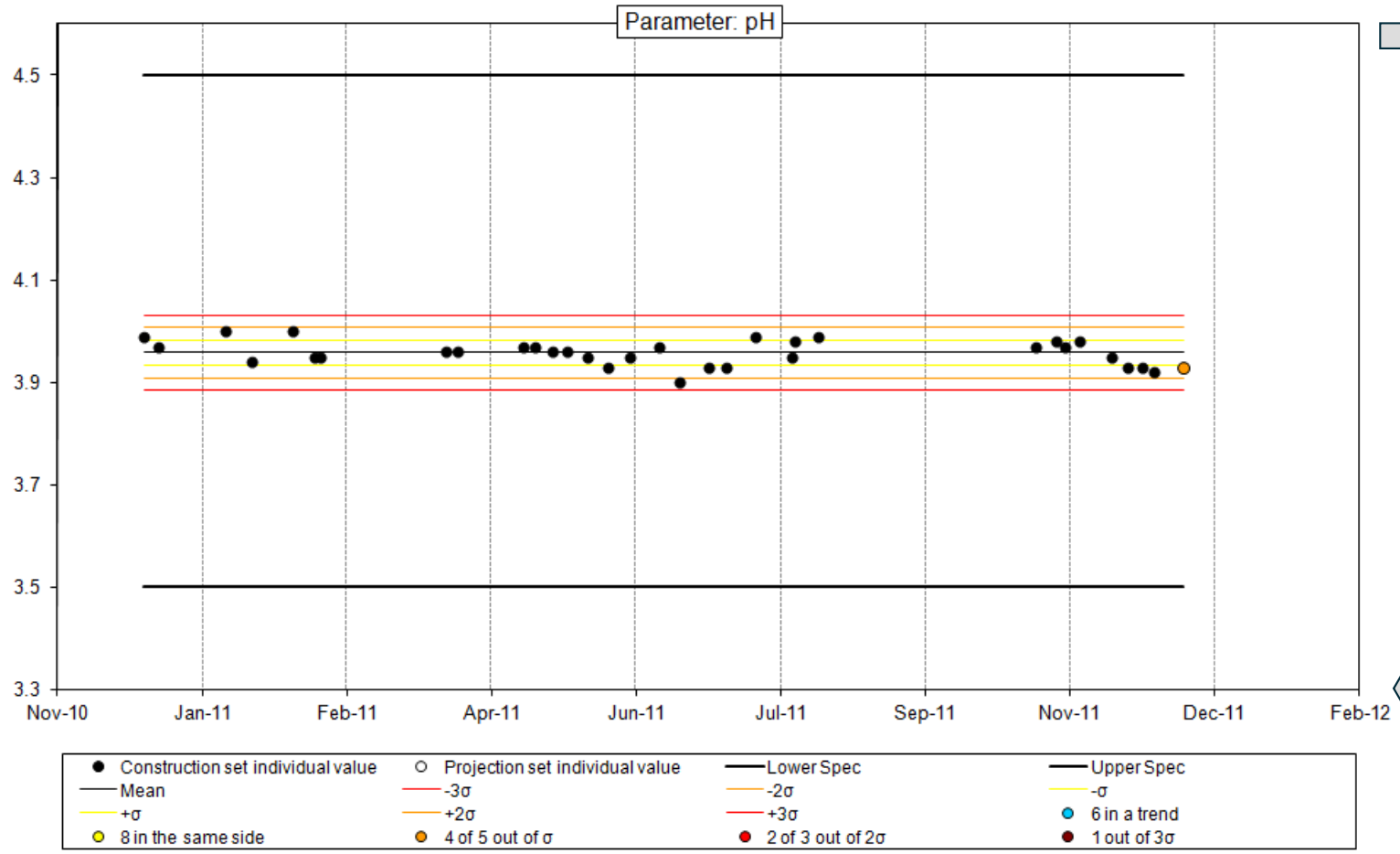
Average yield improvement of ~1.5%



Statistical Process Control

Goal: **Assure the continuous trending of the process (capability improvement)**

Example: **Control Charts**



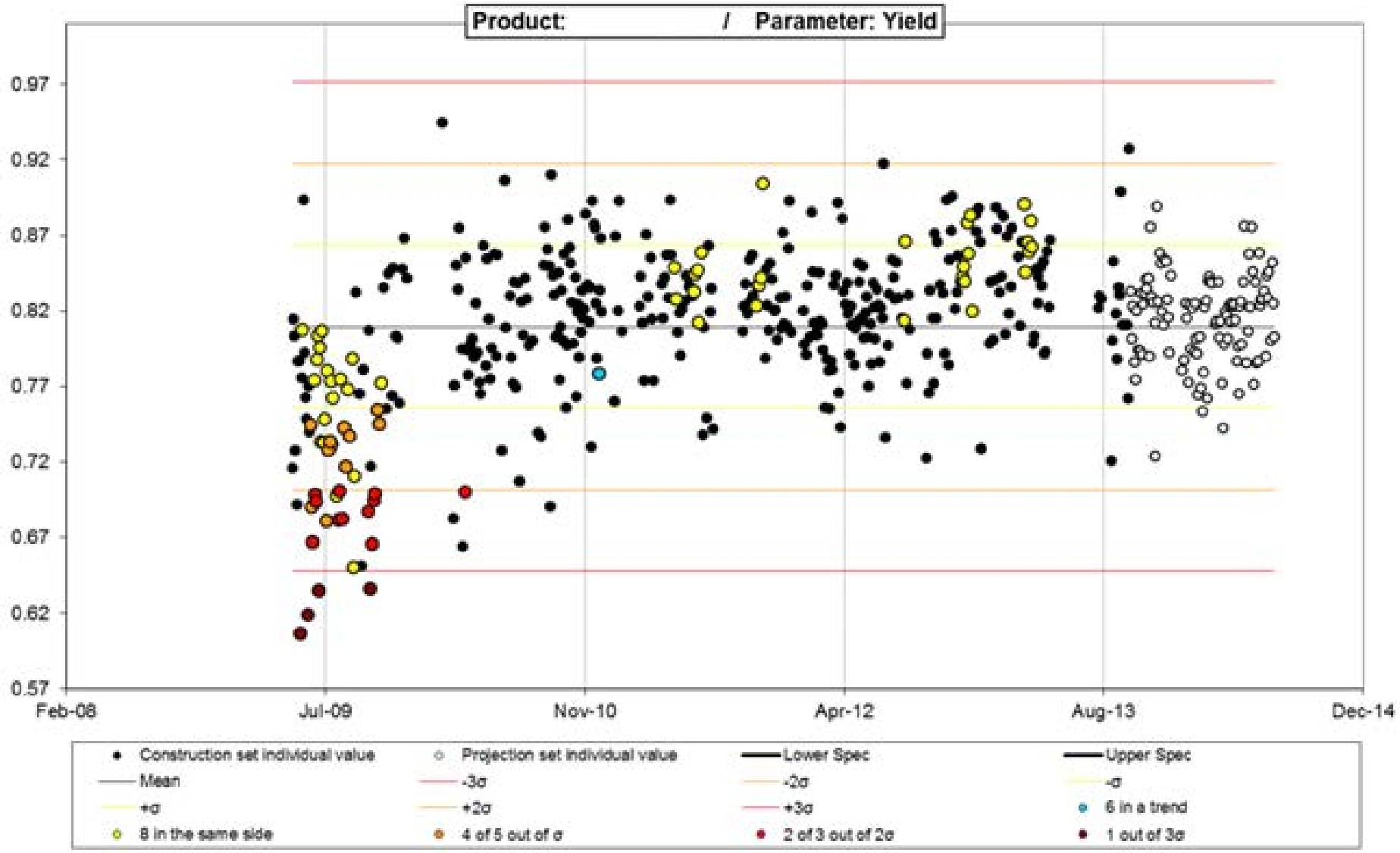
Capability is OK but space for improvement

Gathered data used for continuous analysis

Part of the variability due to the NOR of a CPP

Better control (narrower NOR) improves capability

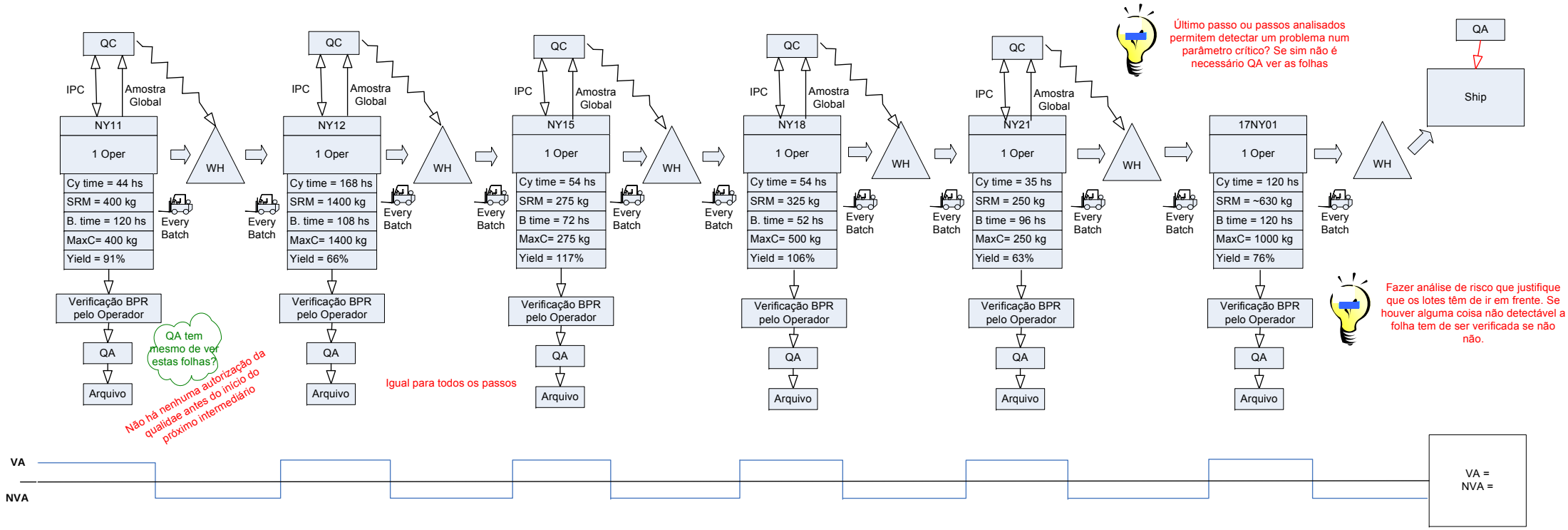
Statistical Process Control – Control Chart



VSM – Visual Stream Mapping

How to use it?

- **VSM**
  - Is a **simple** and **visually comprehensive** tool very useful for the kick off of any project (is used in every Lean 6 Sigma project)
  - It helps the team to **focus on more important** (higher return) aspects



What is FMEA?

- **FMEA is normally used during development stages to reduce risk before implementation**

- **Based on 3 important concepts**
  - **Failures**
  - **Effects**
  - **Detection**

FMEA key words

➢ **Failure**: Potential (or real) evidence of the occurrence of an anomaly in the process/ product due to one or more reasons to be identified

➢ **Effect**: Is a consequence of a failure which will be later detected (by operator, QC or Customer)

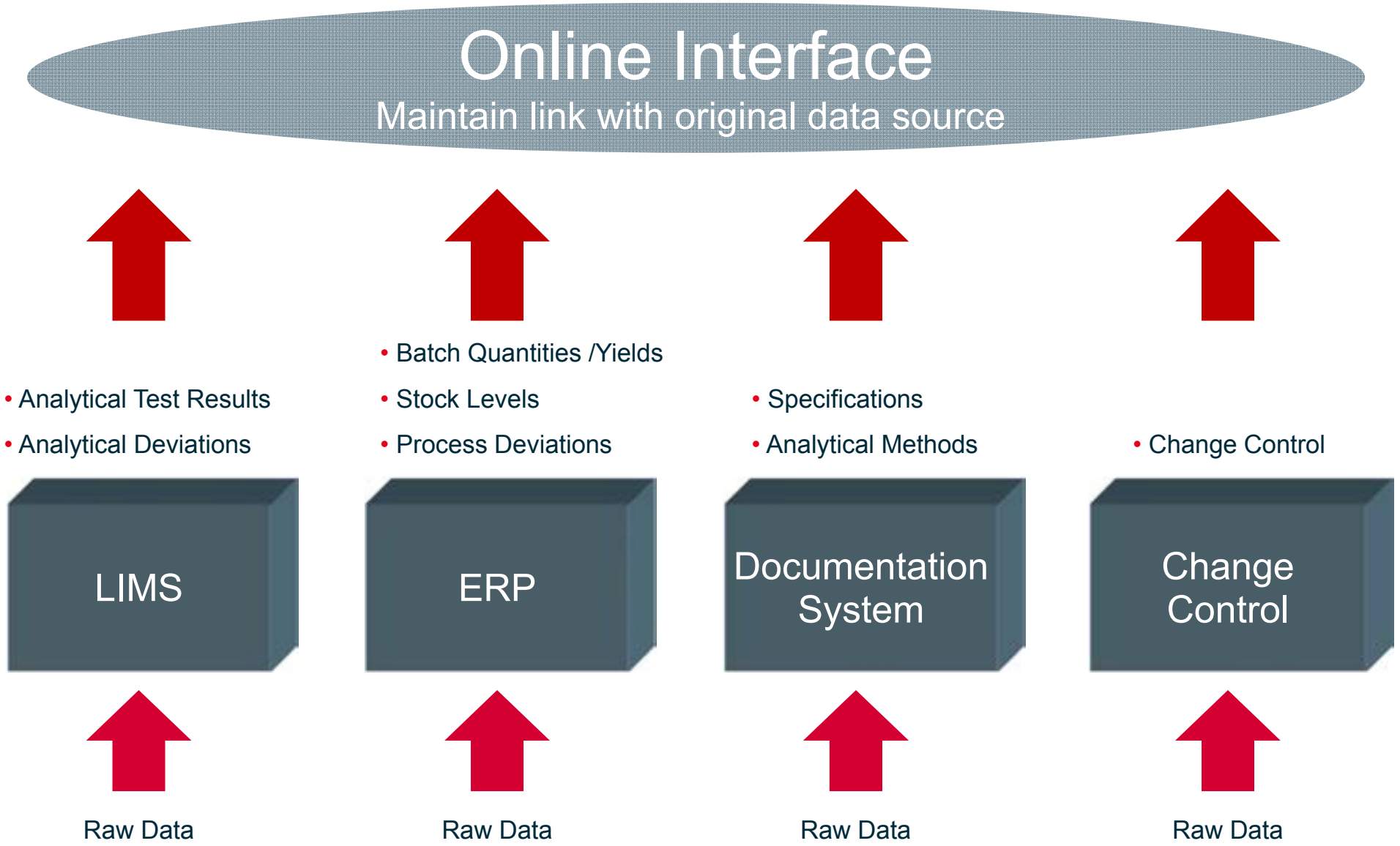
How to use FMEA?

- **FMEA Criteria table**

	Probability of occurence (P) / Frequency (F)		Severity (S)	Detection (D)	
1	> 5 years	1 in 10,000	None	Extremely likely	Detection on > 99% of cases
2	2 - 5 years	1 in 1,000	Very minor	Highly likely	Detection on > 90% of cases
3	1 - 2 years	1 in 500	Minor		Detection on > 75% of cases
4	Once a year	1 in 100	Very low		Detection on > 60% of cases
5	6 - 12 months	1 in 50	Low	Likely	Detection on > 50% of cases
6	3 - 6 months	1 in 20	Moderate		Detection on > 40% of cases
7	Once a month	1 in 10	High		Detection on > 30% of cases
8	Once a week	1 in 5	Very high	Unlikely	Detection on < 30% of cases
9	2 - 4 days	1 in 3	Extremely high		Detection on < 20% of cases
10	Every day	1 in 2	Catastrophic		Detection on < 10% of cases

Linking to Sponsor

Data/Knowledge Sharing



Advanced Tools at Development and Manufacturing

DEVELOPMENT

- Risk Assessment
- Design of Experiments
- Modeling Tools
- Scale-Up Methods
- Scale-Down / Miniaturization
- Process Analytics
- Multi Variate Analysis

MANUFACTURING

- Lean 6 Sigma
- Visual Stream Mapping
- Statistical Evaluation
- Failure Mode Effective Analysis
- 8 D
- Poka-Yoke
- 5 S, OEE

Agenda

Technological Trends in Pharmaceutical Development and Manufacturing

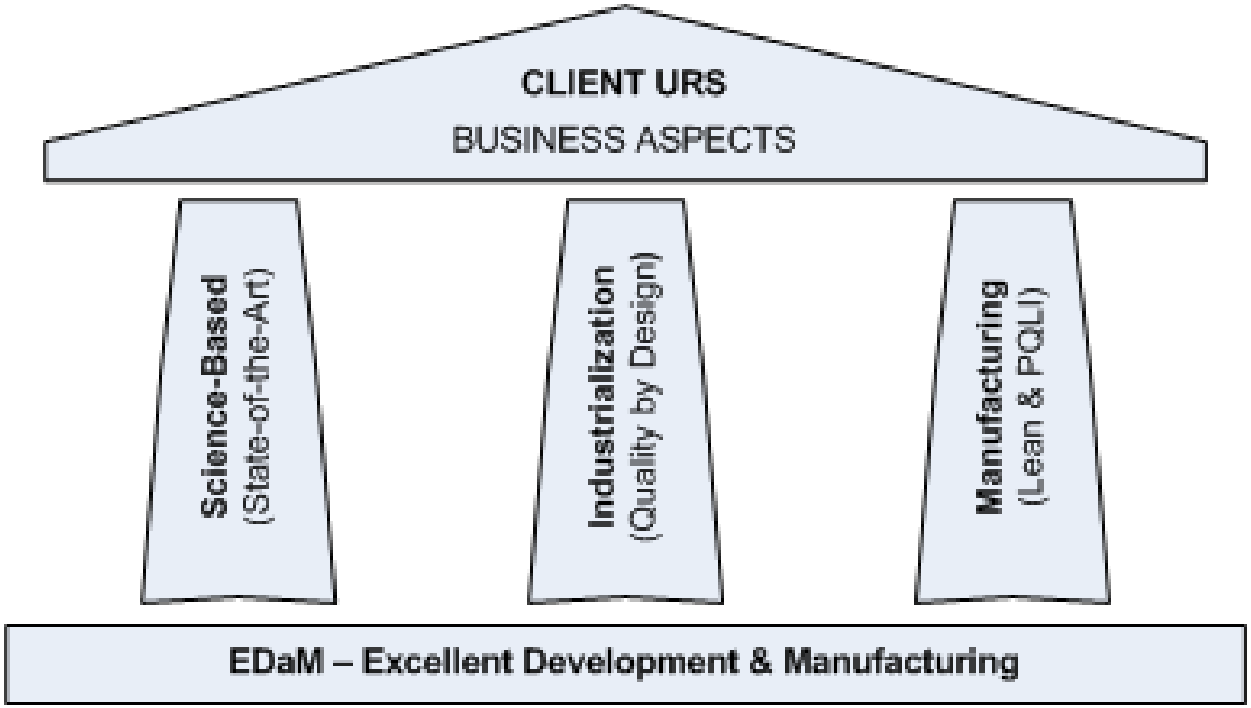
Advanced Tools in Development and Manufacturing

Excellent Development and Manufacturing

Quality by Design at Hovione

New approach at Hovione: Bridging the gap

- 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 Manufacture Guideline

FAMILIARIZATION

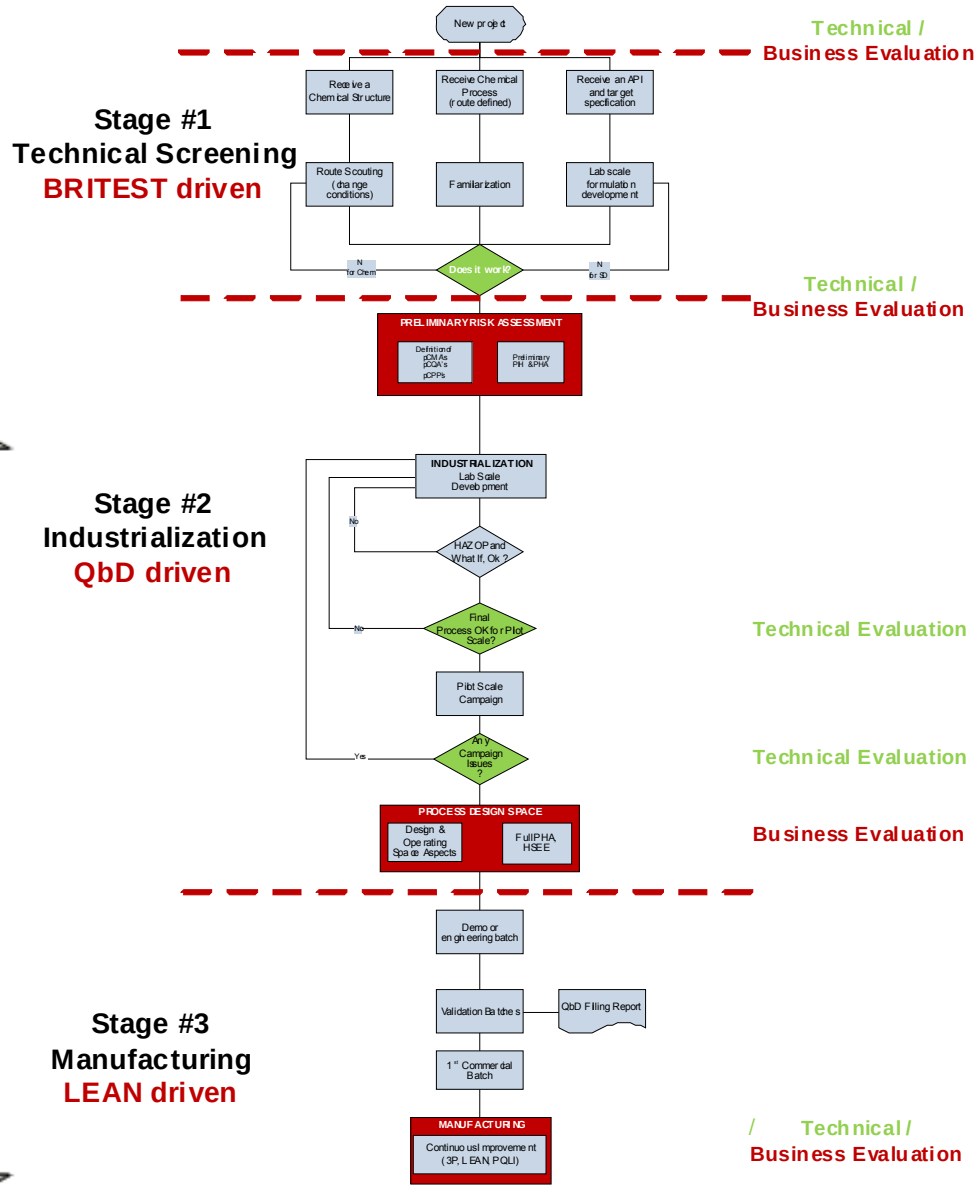
LAB SCALE DEVELOPMENT
and
PILOT SCALE

VALIDATION
and
MANUFACTURING

Technical screening (BRITEST)

Industrialization (QbD)

Manufacturing (LEAN)



Agenda

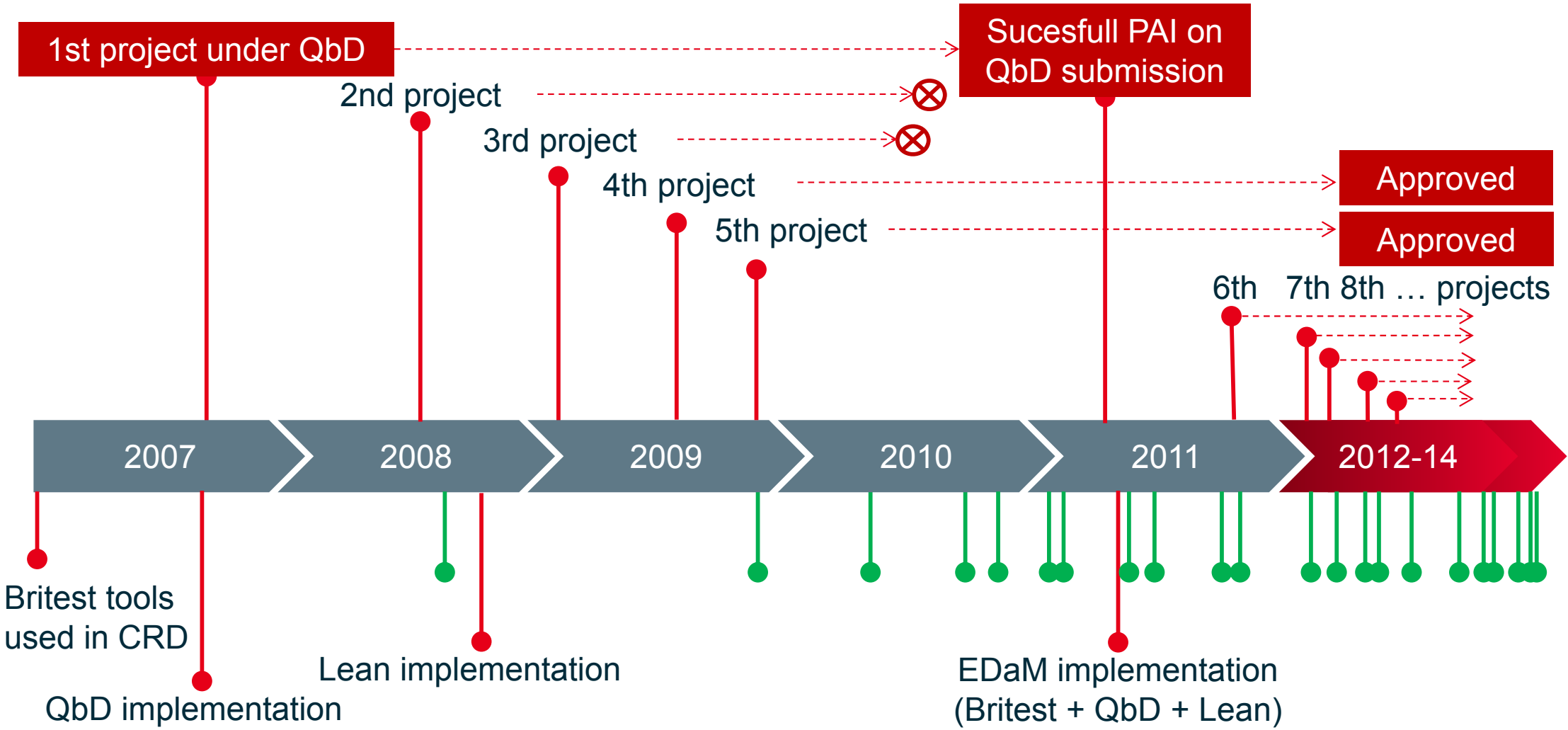
Technological Trends in Pharmaceutical Development and Manufacturing

Advanced Tools in Development and Manufacturing

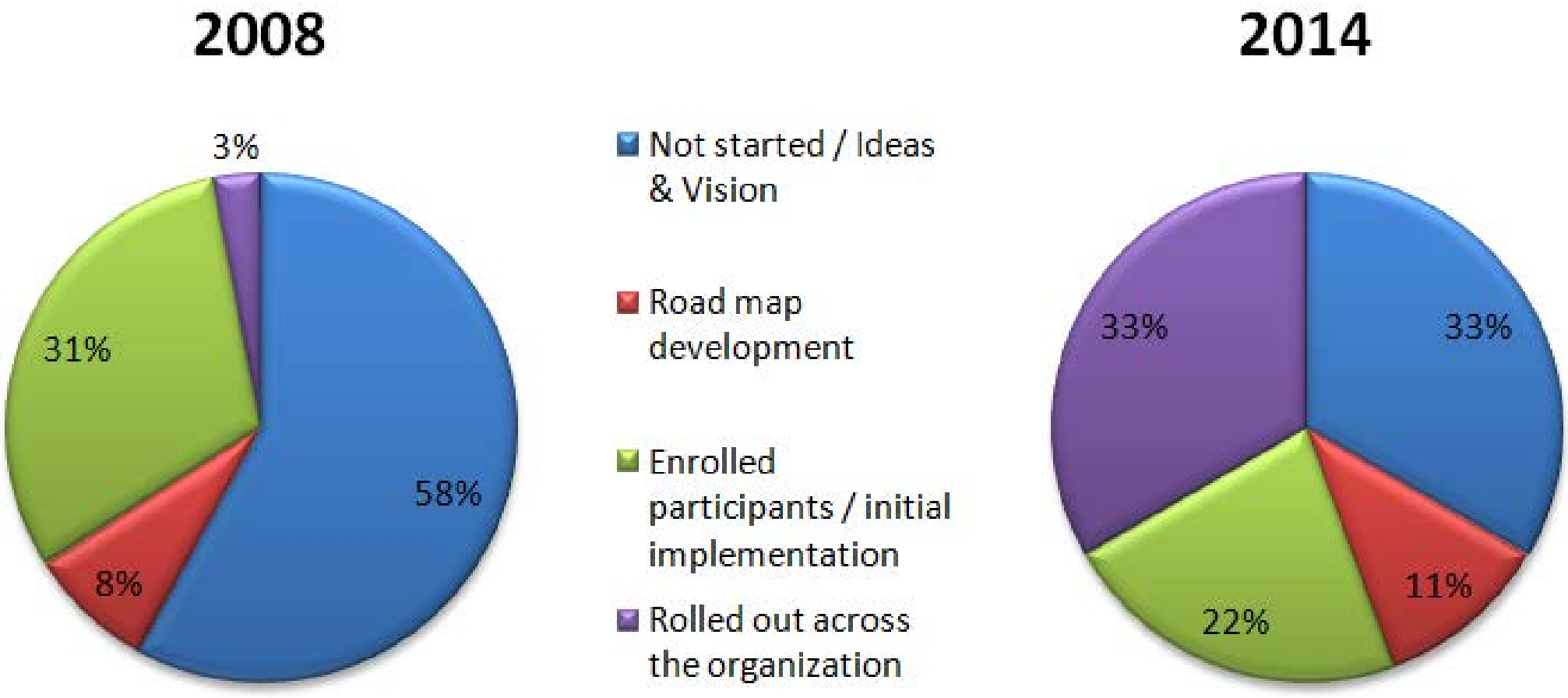
Excellent Development and Manufacturing

Quality by Design at Hovione

Hovione and Quality by Design



QbD is moving on…but slower than anticipated



Kane, *Quality by Design: A Contract Organization Perspective*, DCAT Week 14, Mar. 2014

Understanding Challenges to Quality by Design

"Achieving the 21st Century Quality vision will require a transformative journey for the industry that demands a significant shift in its development process."

"This transformation has not taken place due to challenges within companies, within the FDA, as well as the international regulatory community."

December 2009

Understanding Challenges to Quality by Design

Different implementation phases at Regulators

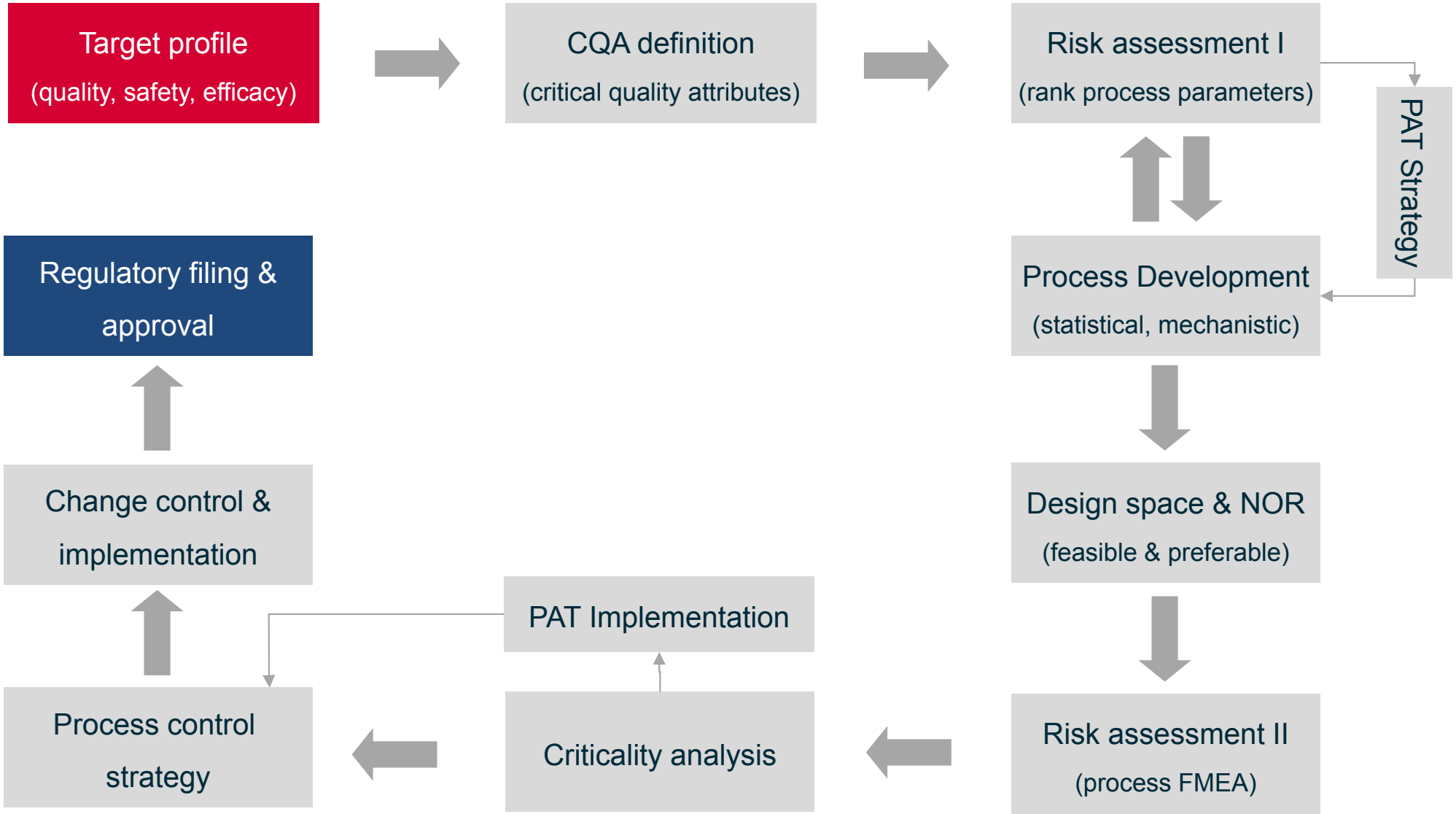
Different levels of comfort with QbD concepts

Launch of products in multiple markets

Submissions under QbD are often

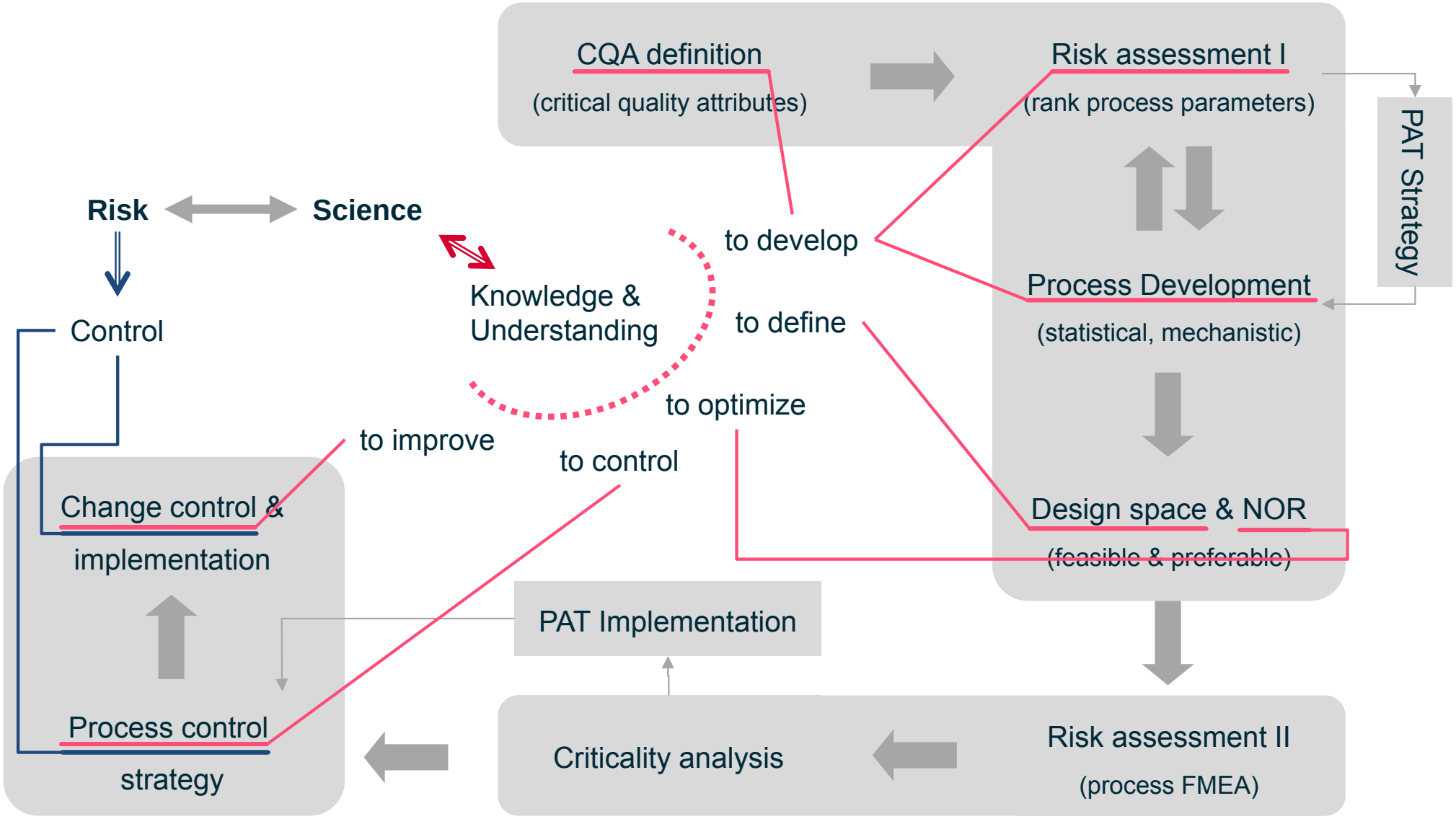
- replaced by “enhanced traditional approach” or
- complemented with “traditional” submissions/validation

QbD at Hovione
A lifecycle perspective

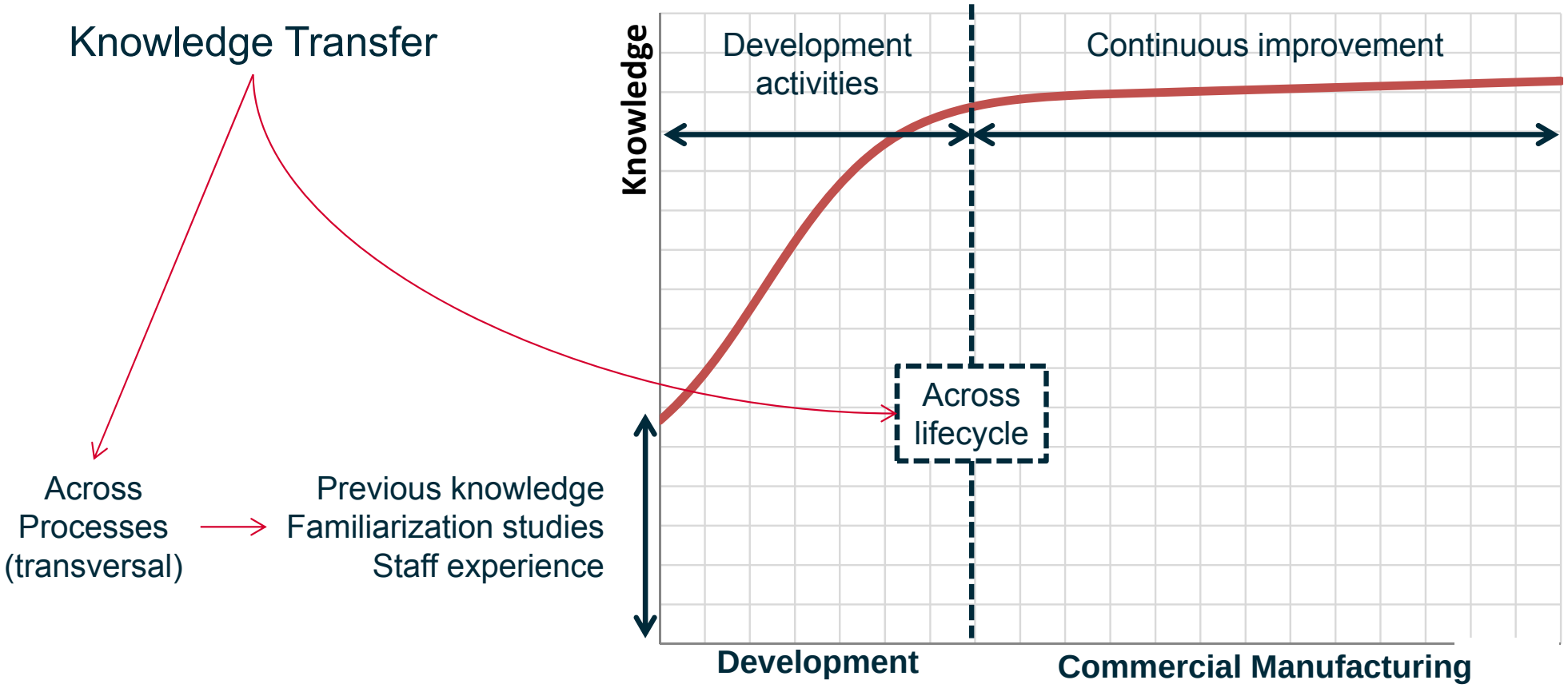


QbD at Hovione

Science and Risk based

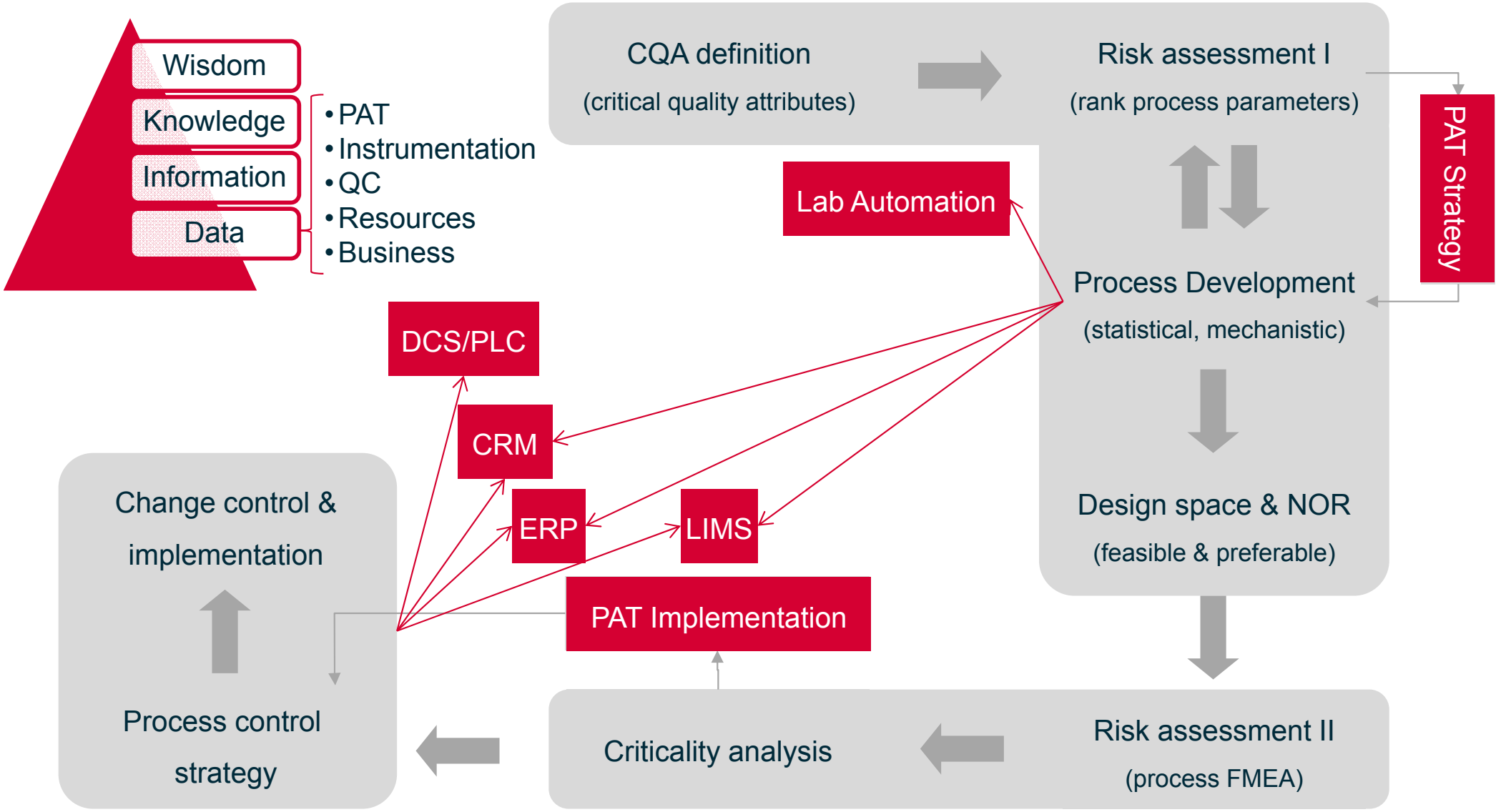


QbD at Hovione
Knowledge Management



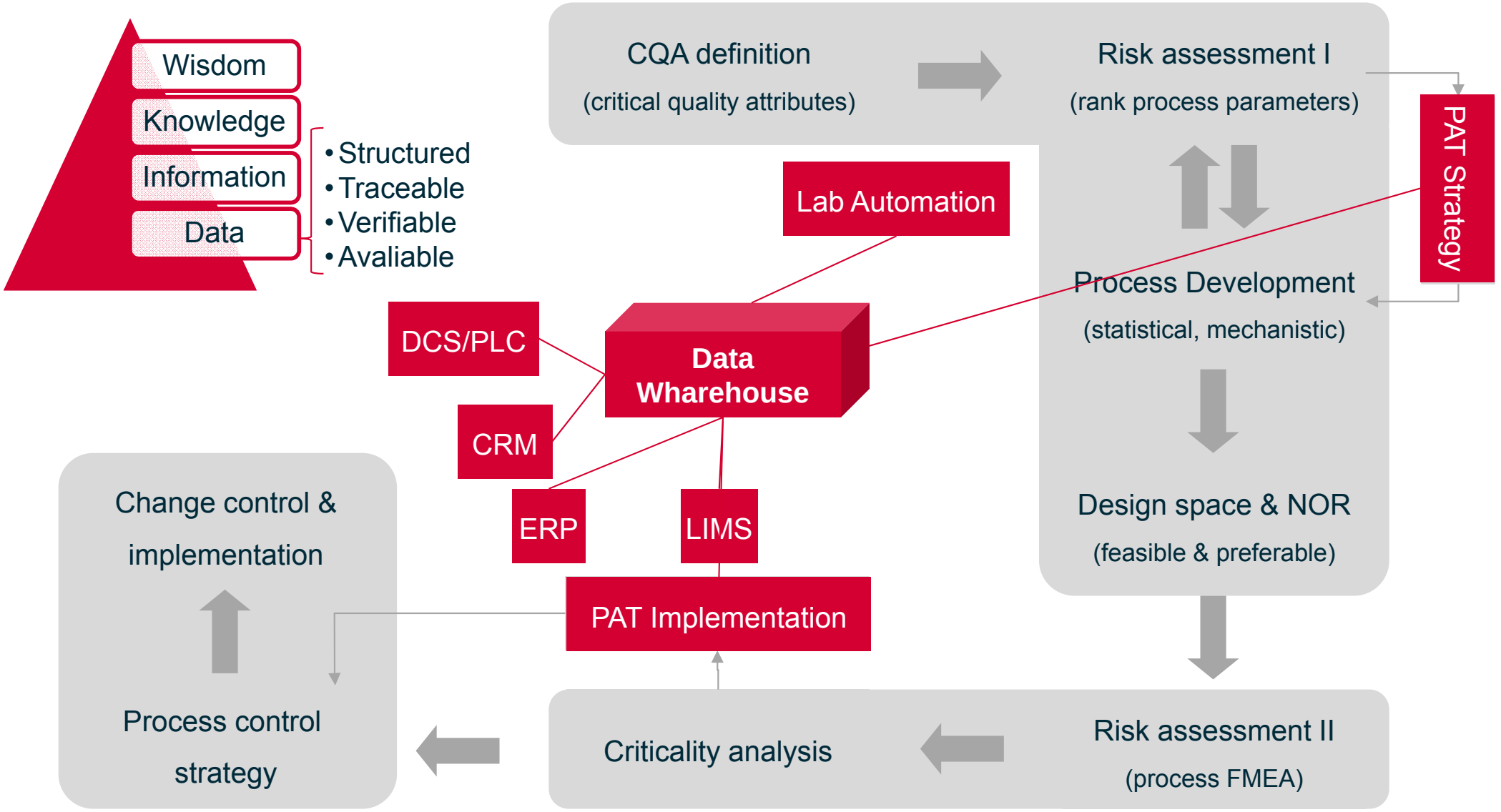
QbD at Hovione

Knowledge Management - Data



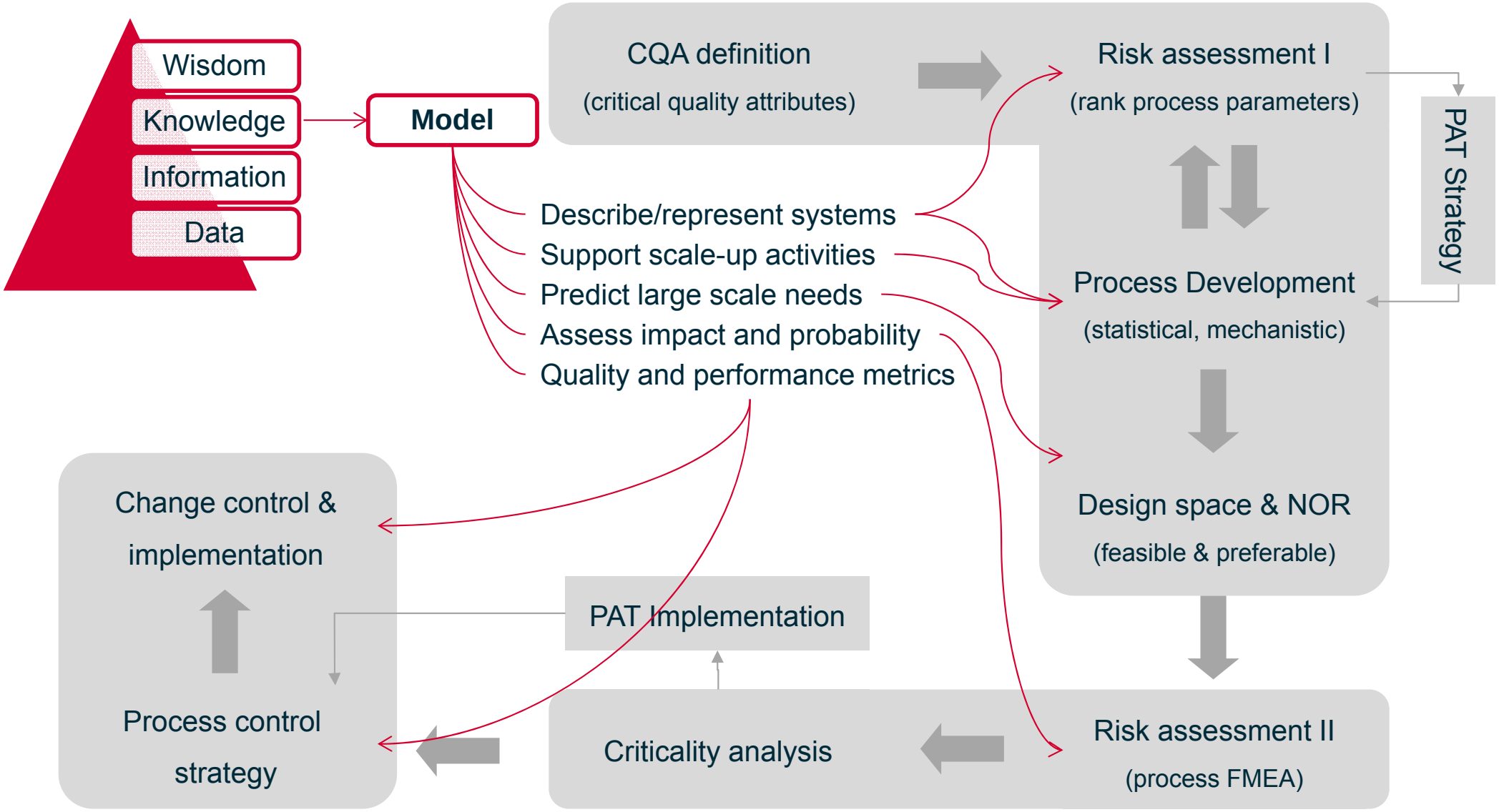
QbD at Hovione

Knowledge Management - Data



QbD at Hovione

Knowledge Management - Model



What changes did QbD bring to Hovione?

- Structured approach to process development and continuous improvement
- Stronger science & process understanding
- State-of-the-art risk evaluation and mitigation tools
- New metrics to manufacturing: process robustness, RPN
- Higher state of control => less failures
- Leaner development through effective knowledge management

Case-study: Traditional vs. Quality by Design
Introduction

From our products portfolio, two processes were chosen for **comparison**

- Both spray drying processes at the same scale and equivalent equipment trains
- Both are commercial products with more than 70 batches produced
- One followed a **traditional** approach, the other a **QbD** based approach

Restrospective analysis to evaluate the following:

- Process performance
- Quality
- Continuous improvement
- Supply chain reliability
- Cost

Benchmarking: Process Performance

Indicator: Yield percentage relative to theoretical yield

Traditional	QbD
95 ± 2 %	97 ± 1 %

Process developed under QbD shows higher and more consistent yield.

During process development, process performance as measured by yield was also targeted

Better yield in QbD based process results from a better state of control and is also an outcome of the continuous improvement program.

Benchmarking: Quality

Indicators: Number of deviations per batch, and Process Capability index for CQAs

	Traditional	QbD
# Deviations per batch	0.7	0.3
Average Cpk	1.1 (~3σ)	2.0 (6σ)
Minimum Cpk	0.7	1.2

Deviations related with process control and yield were considered

Average process capability index (Cpk) takes into account all CQAs identified for each product

Higher consistency in targeting the specification/design space, and in targeting the desired NOR

Benchmarking: Continuous Improvement

Indicator: Number of batches needed for a process improvement

Traditional	QbD
42	9

Knowledge gained during process development is the starting point for the continuous improvement; multivariate analysis may fill the gaps using commercial data.

Continuous improvement programs are part of a successful QbD approach. In their absence improvements are mainly reactive.

- Facilitated by body of knowledge and built-in regulatory flexibility.

Benchmarking: Supply Chain Reliability

Indicators: right first time, delivery against plan, risk value

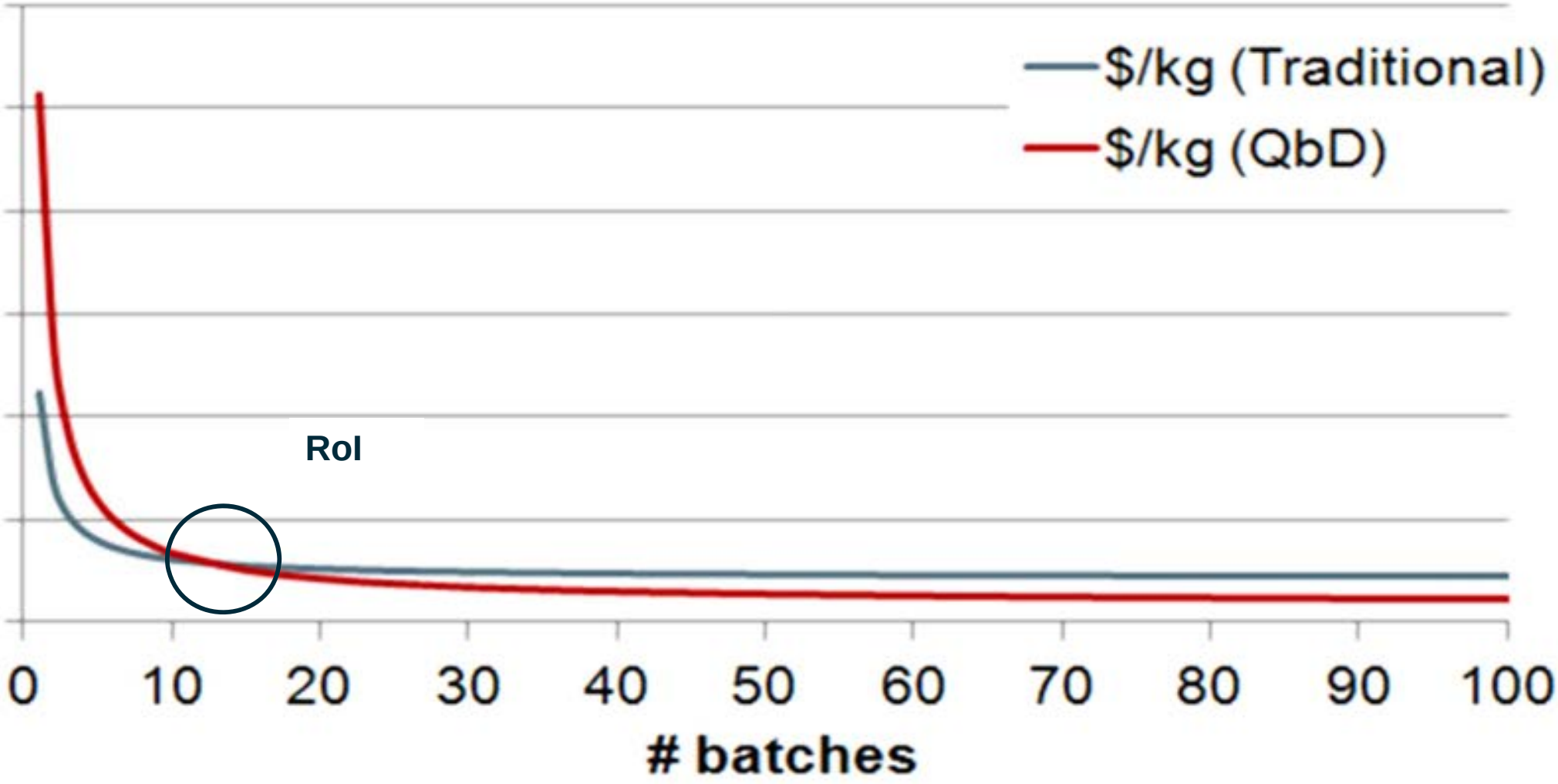
	Traditional	QbD
% batches right first time	95%	100%
% deliveries according to plan	91%	100%
Average RPN (action limit: 100)	79	48
Average # RPN above 100	22	1

Supply chain reliability can be inferred by:

- Batches produced within spec
- Batches delivered to the sponsor within the planned date.
- Average RPN and number of RPN above 100.

Higher state of control reduces failure and process cycle-time variability.

Benchmarking: Traditional vs. QbD



Effective Knowledge Management

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

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

Thank you for your attention.

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