POLITECNICO DI MILANO

School of Industrial and Information Engineering

Course 096125 (095857)

Introduction to Green and Sustainable Chemistry





Process Analytical Technology (PAT) and Quality by Design (QbD).

Prof. Attilio Citterio

Dipartimento CMIC “Giulio Natta”

https://iscamapweb.chem.polimi.it/citterio/it/education/course-topics/

Advanced Tools in Development and Manufacturing.

DEVELOPMENT

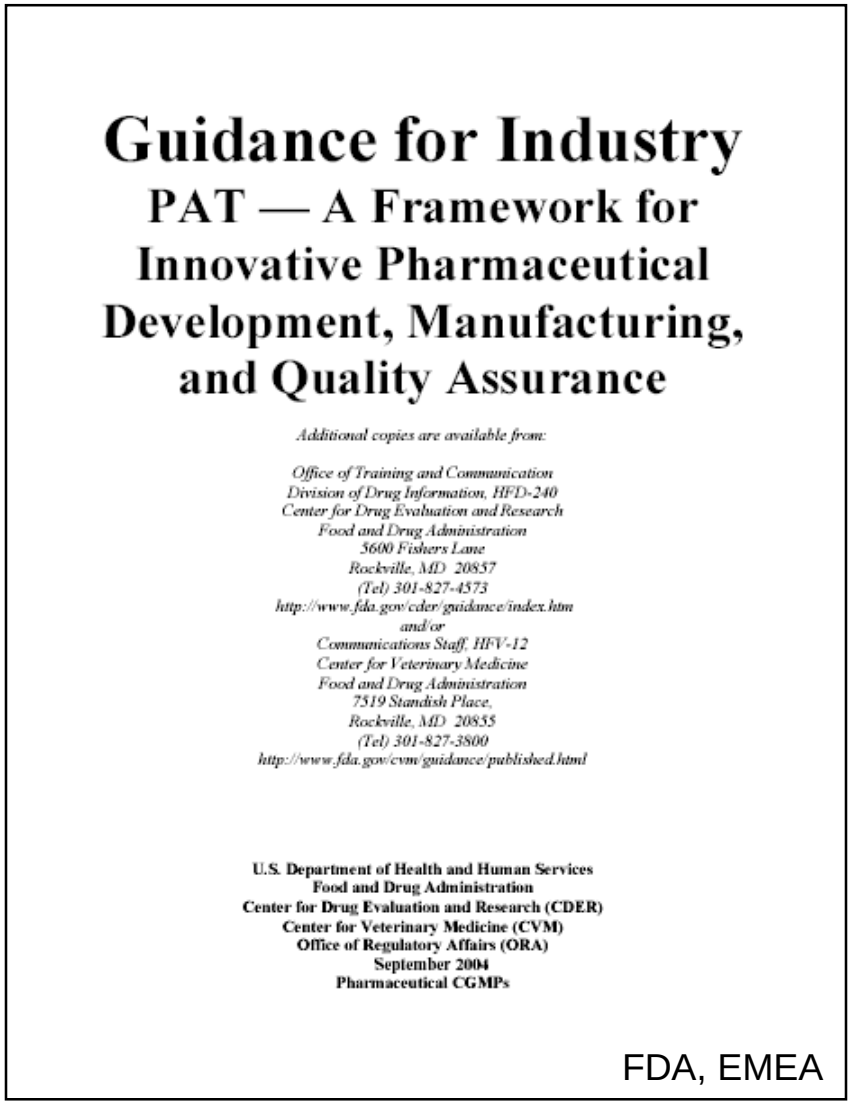
- Risk Assessment
- Design of Experiments
- Modeling Tools
- Scale-Up Methods
- Scale-Down/Miniaturization
- Process Analytical Technology

MANUFACTURING

- Lean 6 Sigma
- Visual Stream Mapping
- Failure Mode and Effect Analysis (FMEA)
- Multivariate Analysis
- 8D
- Quality by Design
- OEE

Guidance to Process Analytical Technology (PAT).

- Released September 2004 - **Process control through new technologies, focus on <u>manufacturing science</u>**
- Scientific principles and tools supporting innovation
  - PAT Tools
  - Process Understanding
  - Risk-Based Approach
  - Integrated Approach
- Regulatory Strategy accommodating *innovation*
  - PAT Team approach to Review *and* Inspection
  - Joint training and certification of staff



Guidance for Industry

PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm
and/or
Communications Staff, HFV-12
Center for Veterinary Medicine
Food and Drug Administration
7519 Standish Place,
Rockville, MD 20855
(Tel) 301-827-3800
http://www.fda.gov/cvm/guidance/published.html

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)
September 2004
Pharmaceutical CGMPs

FDA, EMEA

What is PAT?

A system for:

- **designing**, **analyzing**, and **controlling** manufacturing processes, based on timely measurements (i.e., during processing) of **critical quality and performance** attributes of raw materials and processes with the goal of ensuring final Product Quality.

"Analytical" includes:

- chemical, physical, microbiological, mathematical, and risk analysis
- conducted in an integrated manner

Quality by Design, QbD: Design to assure acceptable end-product Quality at the completion of the process.

http://www.fda.gov/cder/OPS/PAT.htm#scienceboard
http://www.fda.gov/cder/OPS/PAT.htm

Quality by Design (QbD).

- "Quality can not be tested into products; it has to be built in by design".
- Product quality and performance requires efficient design of manufacturing processes.

- Product specifications based on deep understanding of how formulation and process factors impact product performance.
- It provides a framework for continuous "real time" assurance of quality and continuous Improvement.

QbD & PAT.

- **Process Development**
  - Process monitoring to develop mechanistic understanding
  - Model building and correlations to enhance process understanding
  - Establishment of design space.
- **Manufacturing**
  - Process control to ensure robust and reproducible operations
  - Flexible operation through process controls
  - Real-time release.
- **Continual improvement**
  - Historical data tracking and trending
  - Statistical process control for early identification of potential problems.

Why PAT e QbD?
FDA – EMEA and Public Health Perspective.

- An increasing burden on FDA resources:
  - ~ 4,000 manufacturing supplements annually
  - Unable to meet statutory biennial GMP inspection requirement
  - Lower scrutiny of non-domestic industry.
- Cost implications for the industry from:
  - Low manufacturing and QA efficiency.

Drug products are of high quality, BUT:

- Increasing trend toward manufacturing-related problems
- Recalls - 176 in 1998 rising to 900 in 2010
- Loss of availability of essential drugs
- Disruption of manufacturing operations
- Negative impact on new drug approvals.

Efficient pharmaceutical development and manufacturing are vital components of the "Critical Path" leading to an effective health care system.

PAT = Process Understanding.

- The goal of PAT is to enhance understanding and controlling the manufacturing process:
  Quality cannot be tested into products; it should be built-in or should be by design.

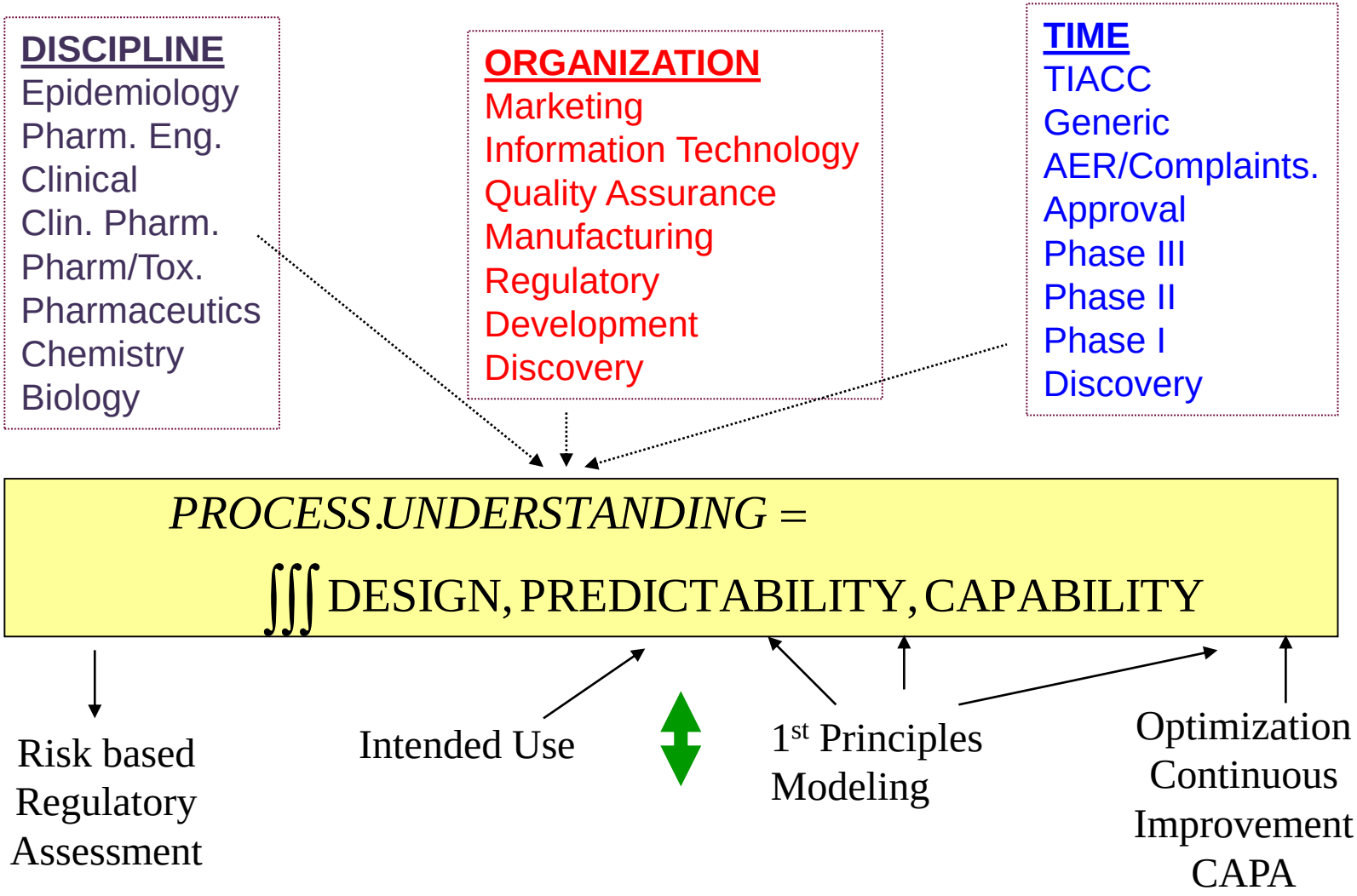
- A process is well understood when:
  - all critical sources of variability are identified and explained
  - variability is managed by the process
  - product quality attributes can be accurately and reliably predicted.
- Accurate and Reliable predictions reflect process understanding.
- Process Understanding inversely proportional to risk.

PAT Framework: Process Understanding.

- **A focus on process understanding can reduce validation burden**
  - providing more options for justifying and qualifying systems intended to monitor and control biological, physical, and/or chemical attributes of materials and processes
    - Time to market
    - Supply chain improvement.

- **Transfer of laboratory methods to on-, in-, or at-line methods may not necessarily be PAT**
  - Existing regulatory guidance documents and compendial approaches on analytical method validation should be considered.

Process Understanding.



Process Analyzers for PAT Applications: In line / On line / At line / Off line.

Spectroscopic Toolbox

- IR (infrared)
- NIR (Near Infra-red)
- Raman
- UV/Vis (Ultraviolet/visible)
- Active acoustics
- NMR (Nuclear Magnetic Resonance)
- EPR (Electro Paramagnetic Resonance)
- Colorimetry
- Fluorescence
- MS (Mass Spectrometry)
- XRF (X-ray Fluorescence)

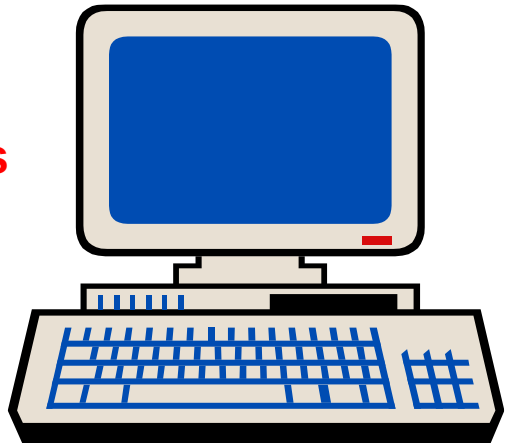
Alternative Toolbox

- TE (Thermal effusivity)
- Conductance/Resistance
- Passive Acoustics
- TOC (Total Organic Carbon)
- Vision/Imaging
- RMM (Rapid Microbiological Methods)

Hyphenated Toolbox

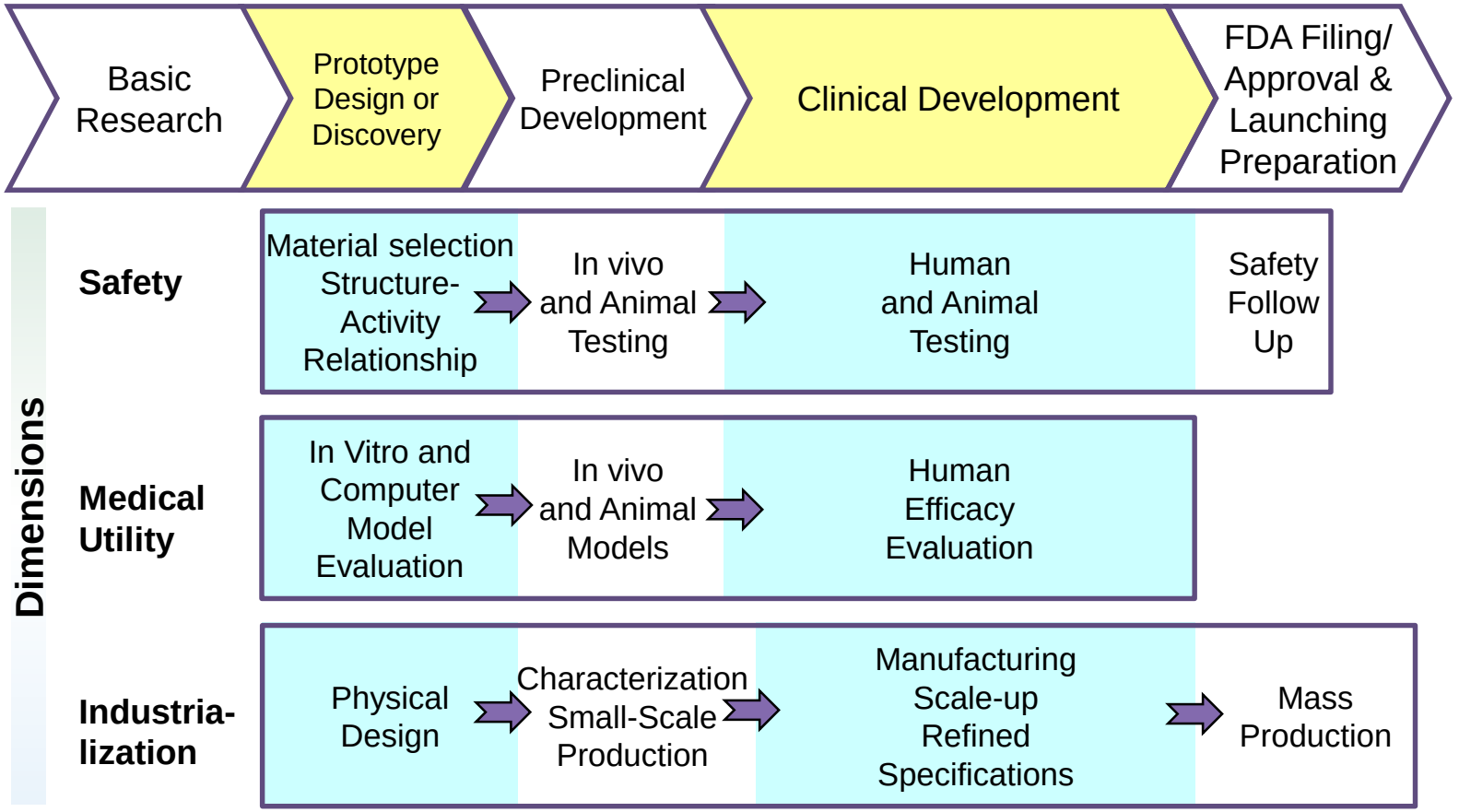
- GC (Gas Chromatography)
- IC (Ion Chromatography)
- HPLC (High Performance Liquid Chromatography)
- FIA (Flow Injection Analysis)

Applying **chemometrics** for the design and the analysis of data sets.



PAT and The “Critical Path” of Pharma.

Working in Three Dimensions on the Critical Path



“PATable” Processes and Decision Points.

Raw materials

Fermentation

Ultrafiltration/Diafiltration

Chromatography

Proteolytic processing

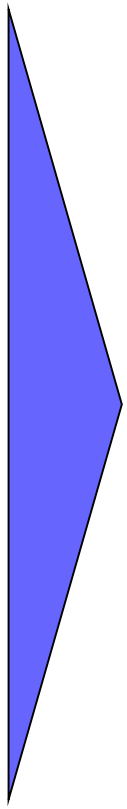
Conjugation reactions

Formulation

Lyophilization

Mixing, blending

Tableting



Acceptance controls

Fermenter feed

Fermenter harvest

When to stop diafiltration

Column equilibration

Start/stop collecting fractions

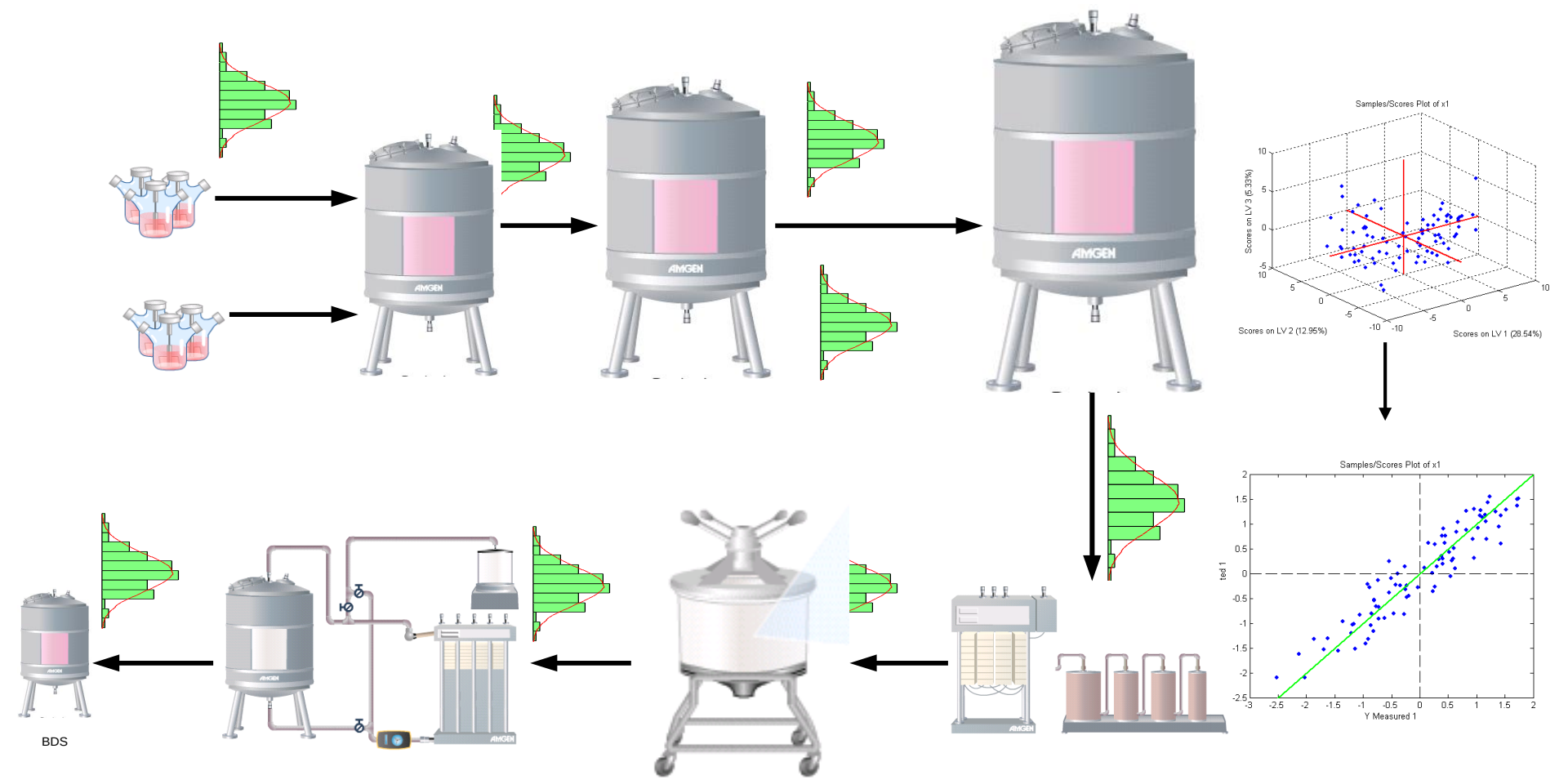
Reaction end point

Lyophilization end point

Mixing end point

Coating thickness

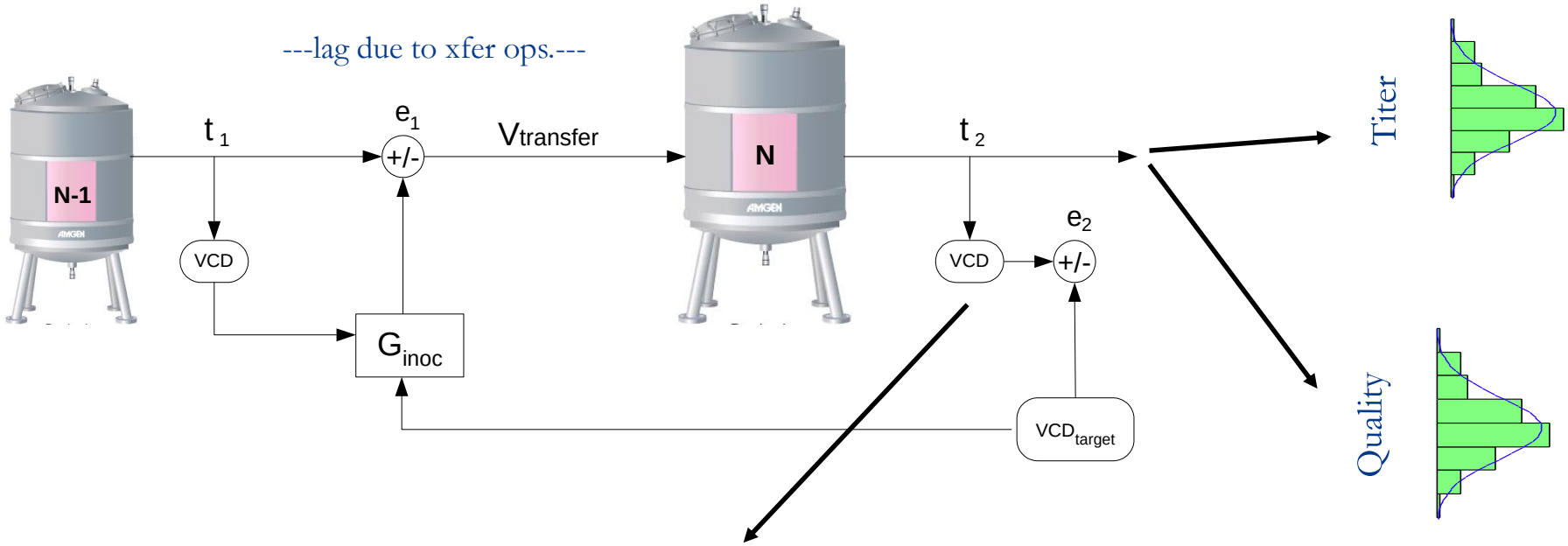
Biotechnological Processes Comprised of Consecutive Unit Procedures with Constrained Hold Steps.



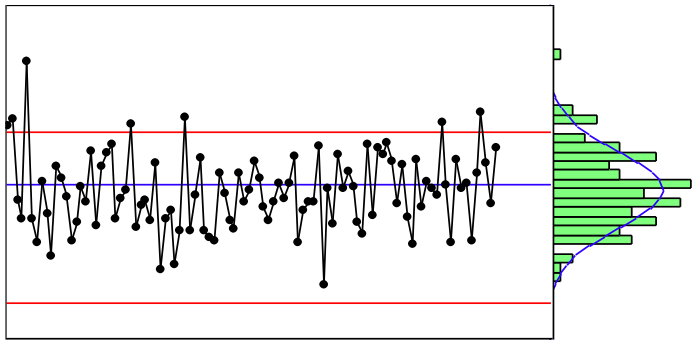
Fermentation Control Parameters.

- O_2, CO_2, pH, temperature
- Nutrient composition, feed schedule, basal media versus additives
- Cell mass, cell number
- Product titer
  - Secreted or not!!
  - from Industrial Biotechnology (IB's)
- Depletion of nutrients, accumulation of waste products, general bioburden
- Contaminants, sterility
  - Microbial, viral.

Current Seeding Density Procedures Result in Variability and Potential Process Deviations.



Current State*

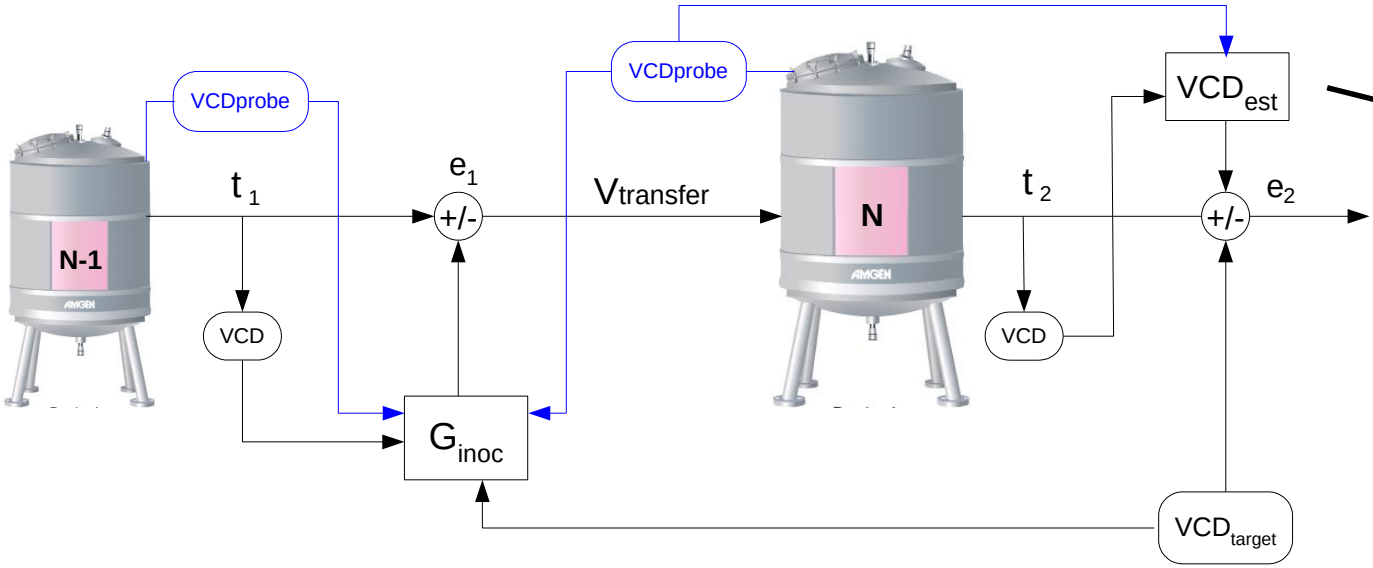


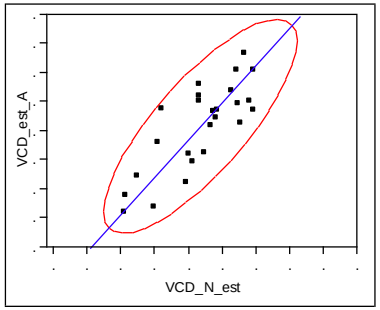
* Simulated data

PAT Strategy for Seeding Density Optimization.

- Use cell density probe technology to measure cell density in N-1 and N bioreactors.
- Use probe to measure production cell density, hitting target density confirmed by on-line cell density reading (Need robust technique).
- Compare probe results with estimated (via empirical models) cell densities at N-1 and N and with offline counts.
- Build a prediction model to give best cell density estimate, for comparison with cell density probe value. Use estimate if model predicts bad probe reading.

PAT Framework is Being Developed to Better Control Seeding Density: Option 1.

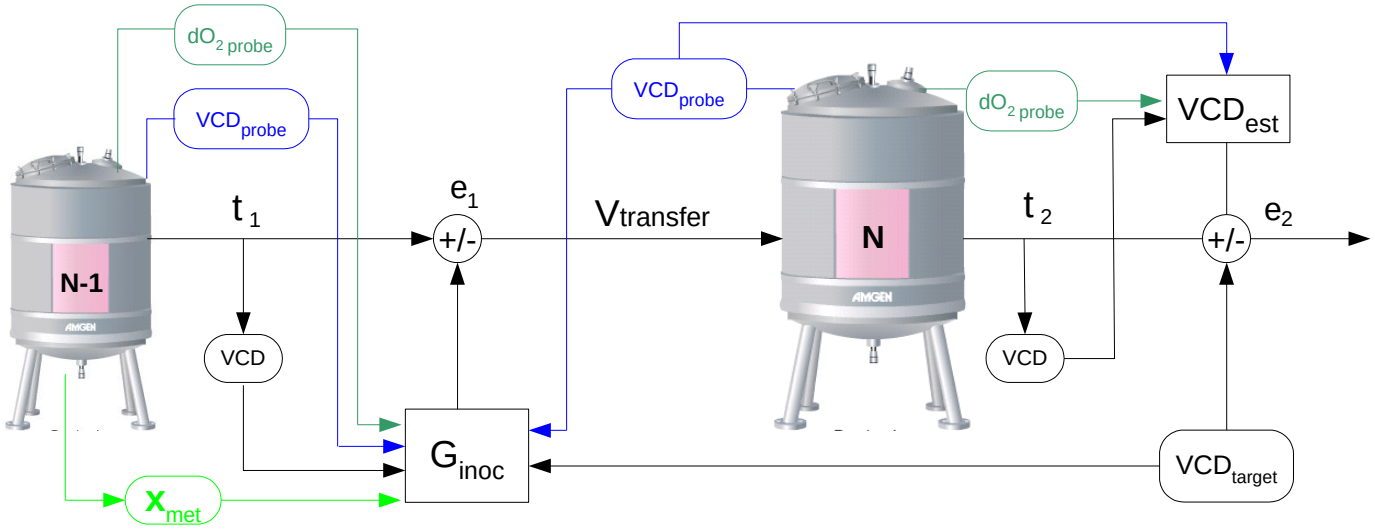


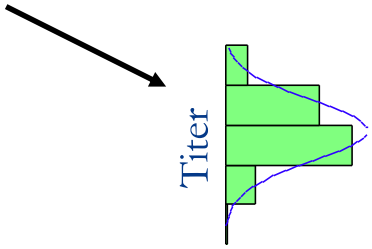


$$\min_{VCD_{est}} e_2$$

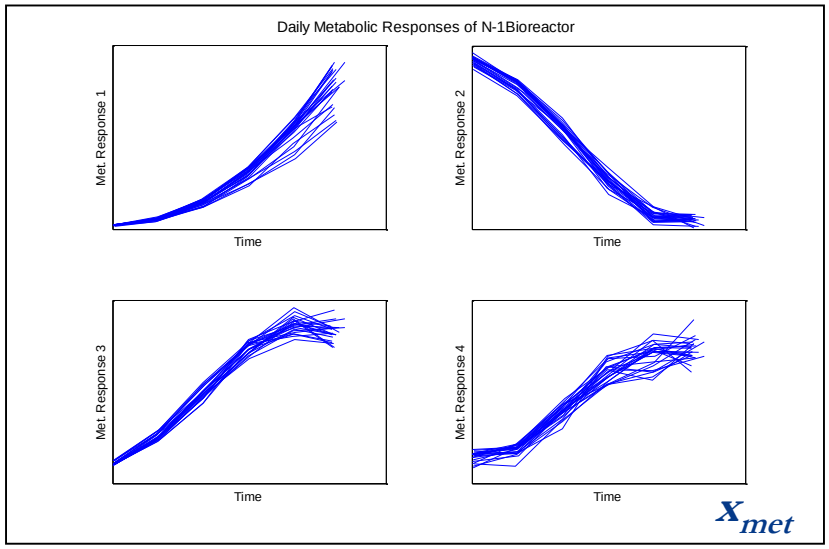
$$VCD_{est} = f(VCD_{probeN1}, VCD[t_{1N1}], V_{N-1}, V_{Nmed}, VCD_{probeN}) + \varepsilon$$

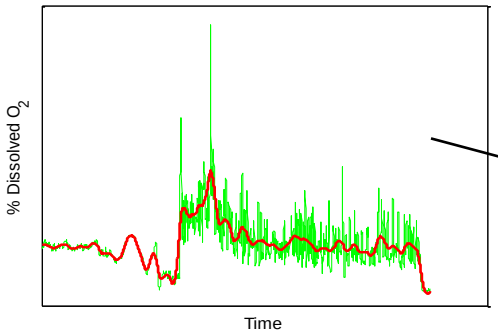
PAT Framework is Being Developed to Better Control Seeding Density: Option 2.

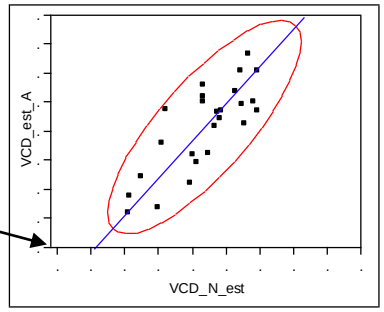




$$\min_{VCD_{est}} e_2$$

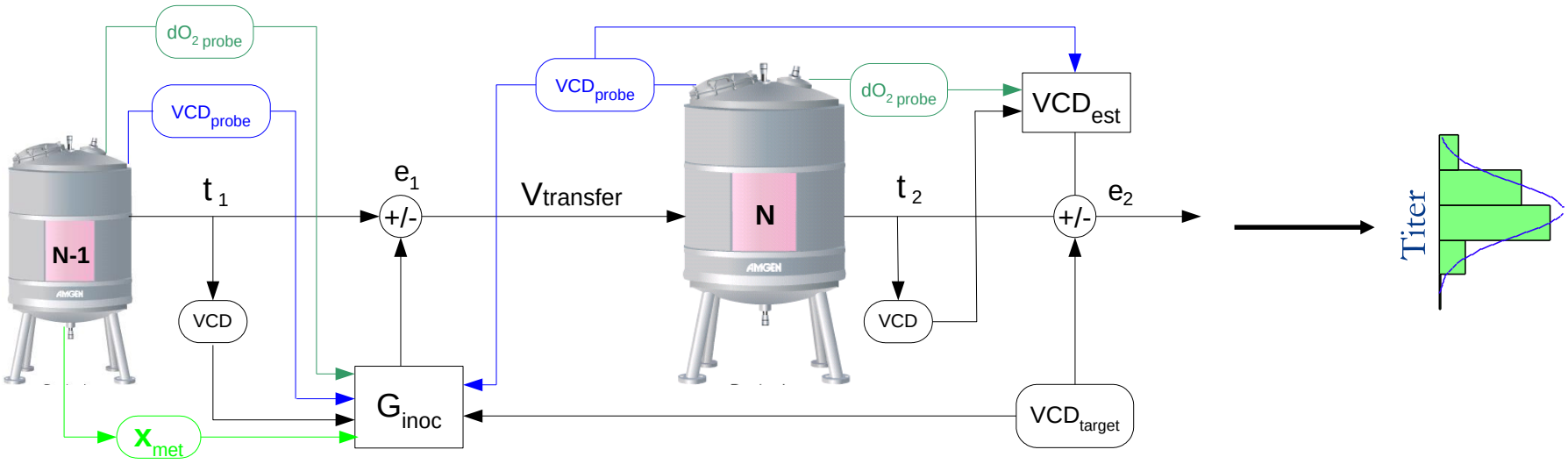






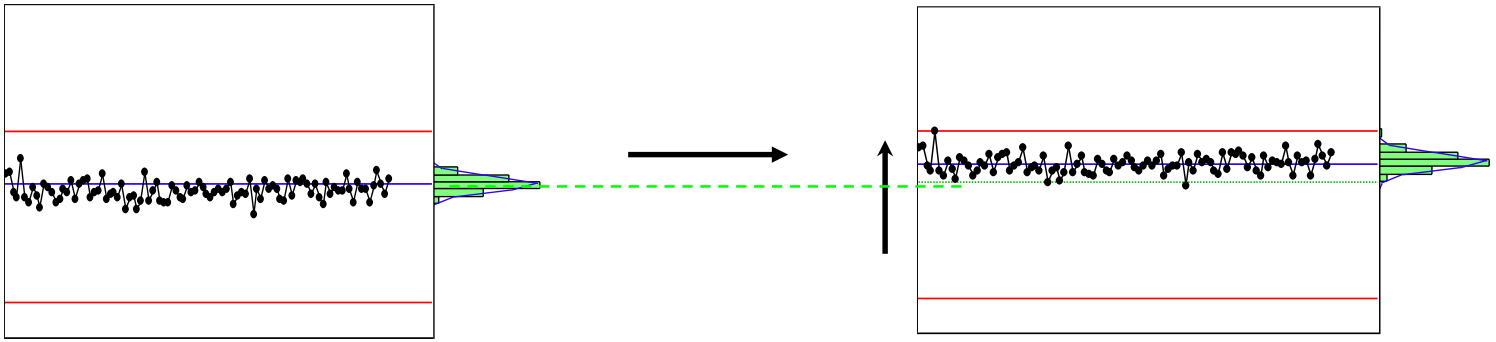
$$VCD_{est} = f(VCD_{probeN1}, VCD[t_{1N1}], DO_{N1}, V_{N1}, x_{met}, V_{Nmed}, VCD_{probeN}, DO_N) + \varepsilon$$

Control of Seeding Density Reduces Titer Variability and Process Deviations.



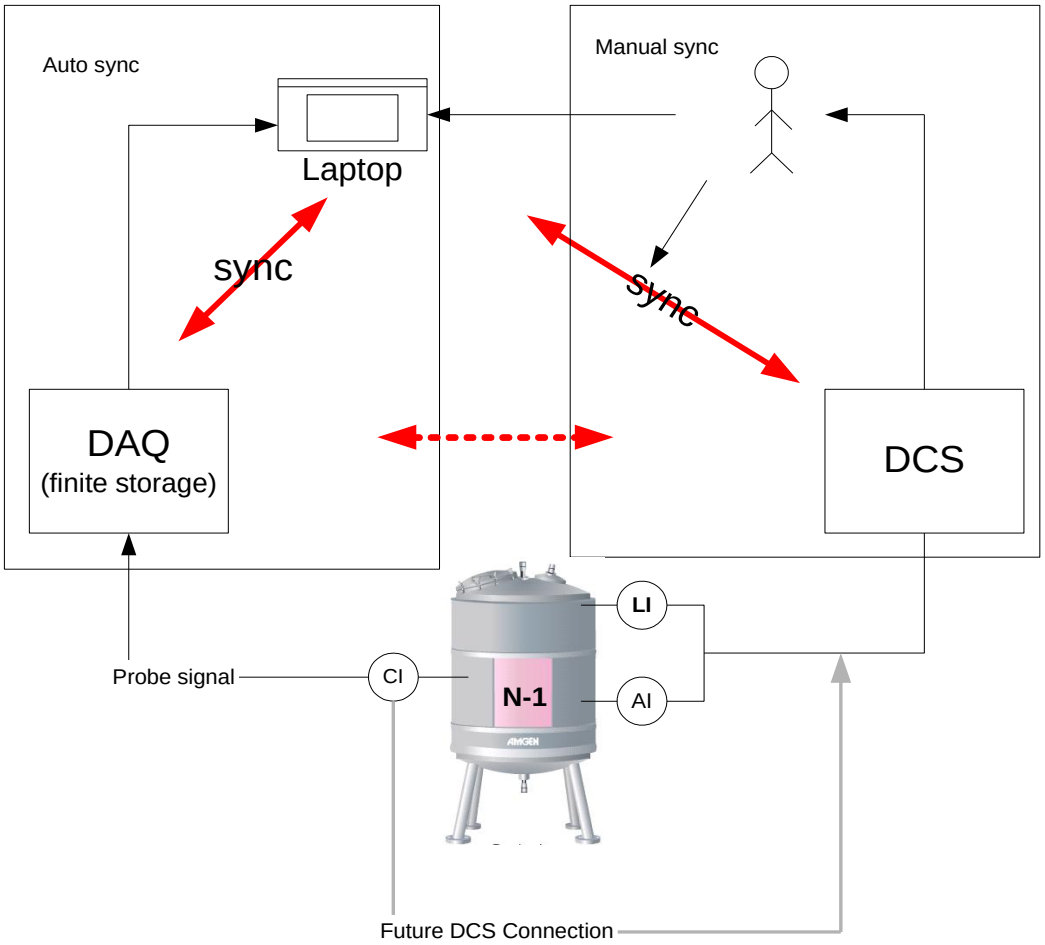
PAT State 1*: Reduced Variance

PAT State 2*: Controlled & Increased Target



* Simulated data

Considerations for Density Probe Include Robust Data Acquisition and DCS Synchronization.

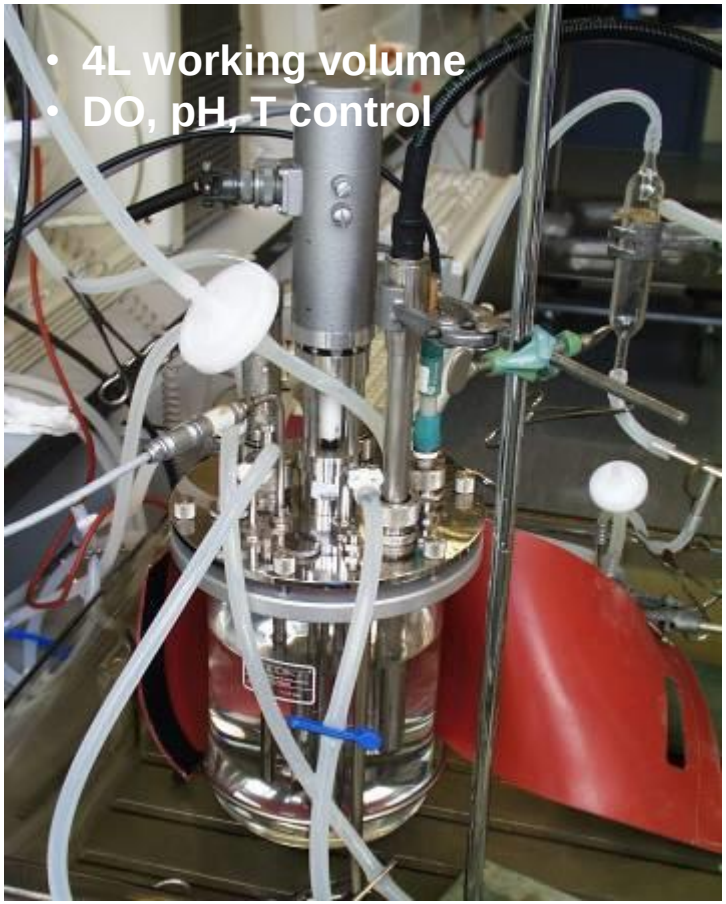


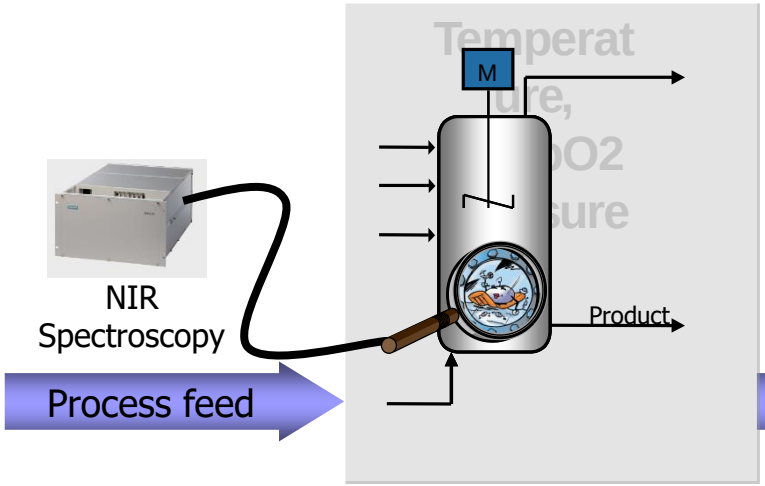
- Manual data upload and synchronization during Engineering Test Runs.
- Signal-to-Noise ratio and dampening needs are tested.
- DAQ box has finite storage capacity requires periodic data upload.
- DCS connection will be established following the test runs.

On-line Cell Density Probes are tested for Robustness, Sensitivity and Sterility.

- Bench-scale studies performed during initial testing.
- Manufacturing-scale testing was performed in the expansion train.
- Results from both studies very promising and helped probe type and technology selection.

Process NIR Spectroscopy (as a PAT tool).





Source: SIEMENS

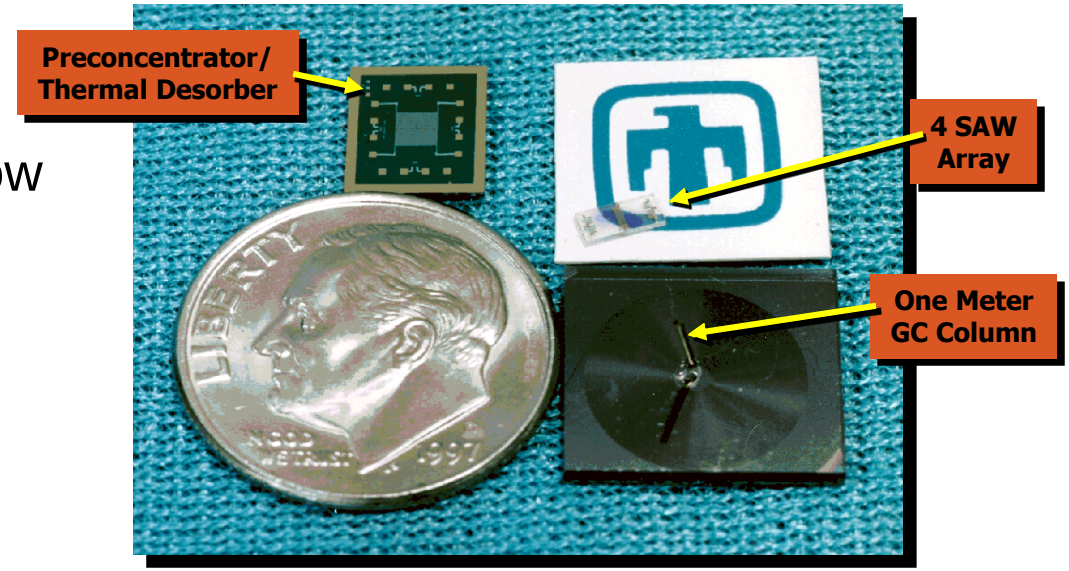
Micro Gas Chromatograph.

The C2V-200 micro GC is built for fast reliable gas analysis, in the lab or on-line.

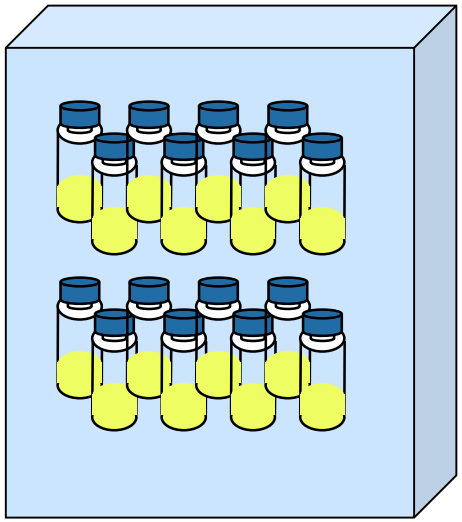
The integrated micro chip technology combined with narrow bore capillary GC columns result in a higher performance for lower costs.

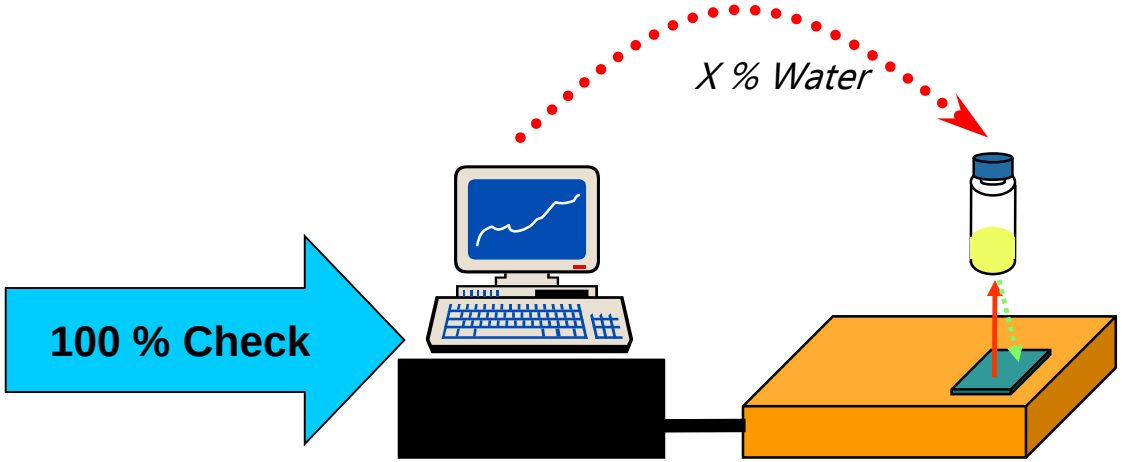
The C2V-200 micro GC is designed for ease of use, reduced maintenance, and low gas consumption.

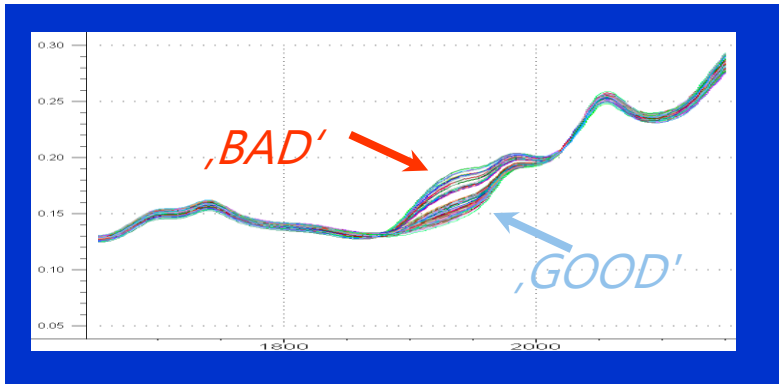
The exchangeable column cartridges, with integrated heating zones, can easily be installed.

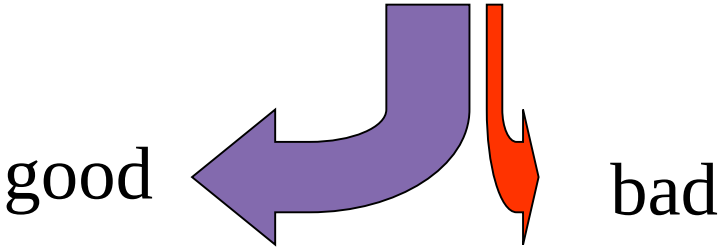


Determination of Water Content.

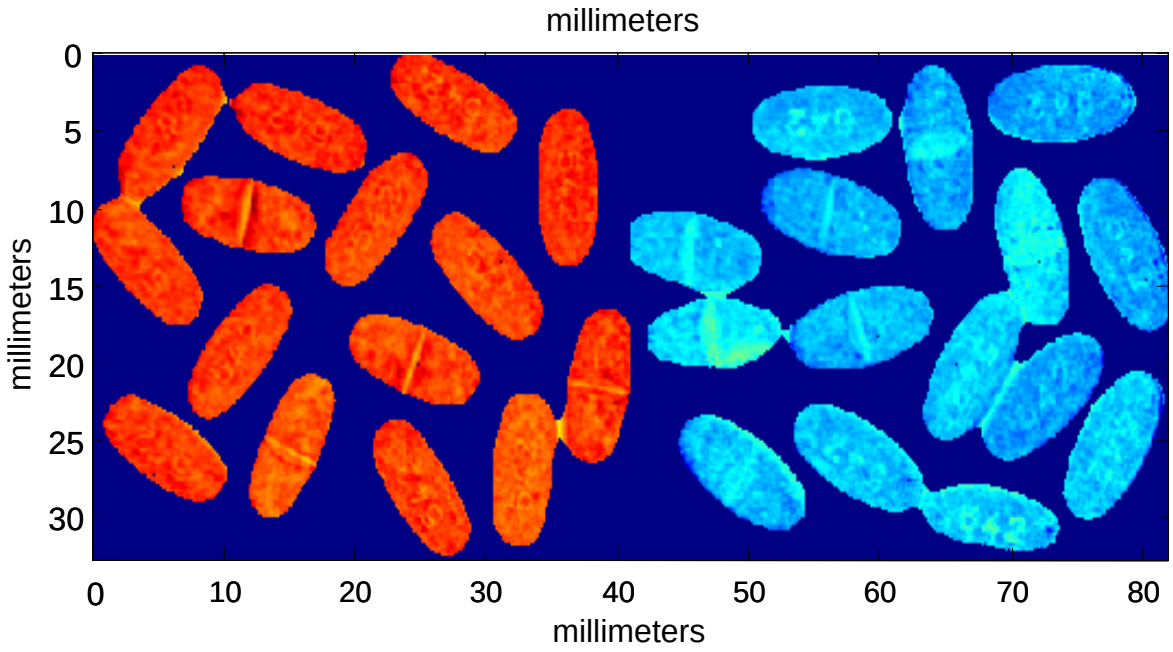








Chemical Imaging by NIR: *Fast and non destructive detection of counterfeits.*



Original

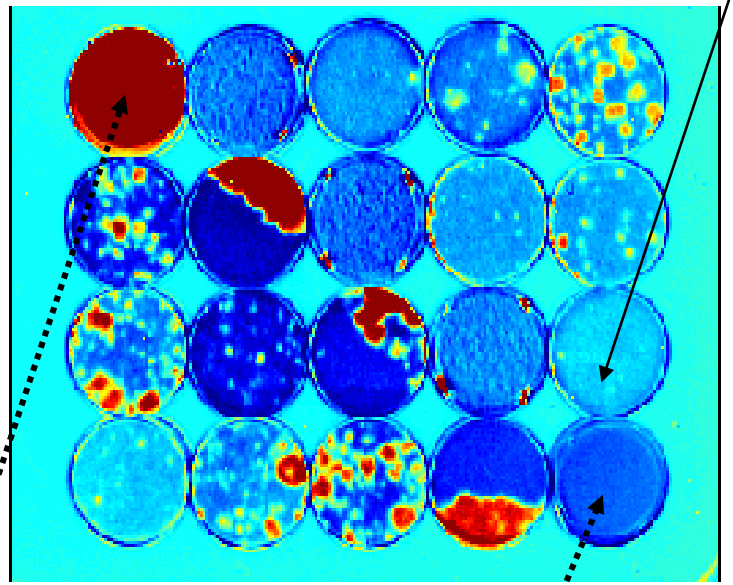
Counterfeit

NIR image of counterfeit tablets

One “Innovative” Approach.

Visible Image

NIR Image

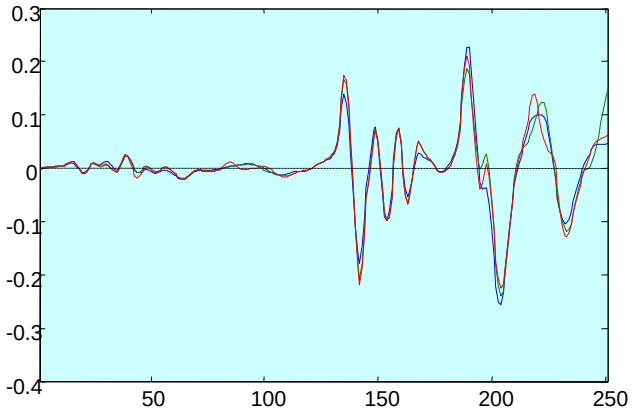


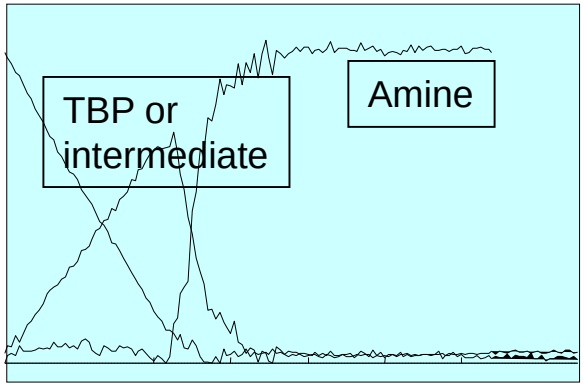
- “New Technology” in Manufacturing Process
- Analyze every tablet

Controlling a Chemical Reaction by NIR: Triple savings by online analytics.

- Reduce lab presence at night and at weekends
- Shorten cycle time by online analytics (no time loss until result is available)
- Process understanding (shortening of reaction and/ or distillation times)

Take NIR spectra online in the reaction mixture; compute the spectra with multivariate curve resolution; plot the control chart

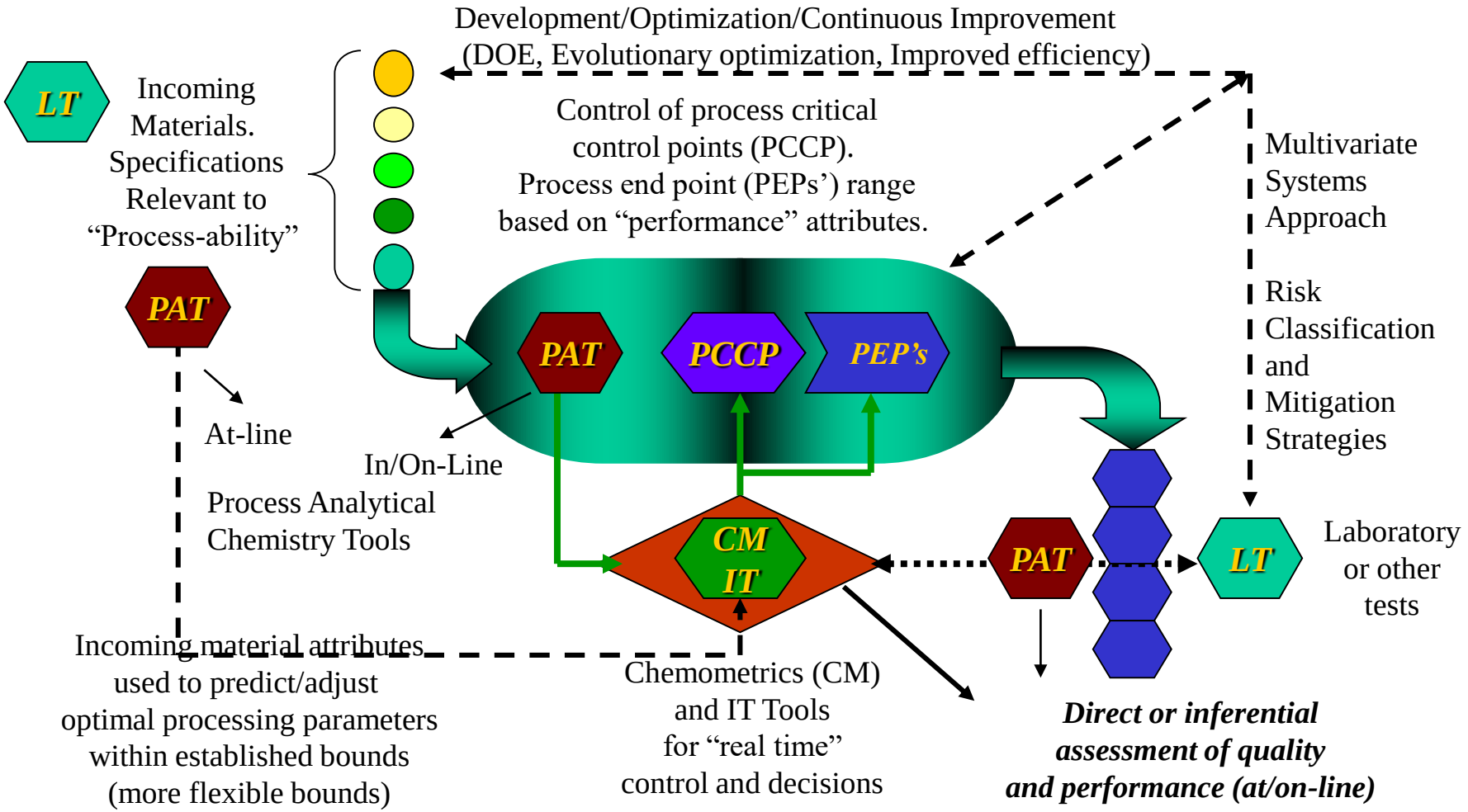




Data Mining in Practice. What is required?

- Available historical data or data warehouse
- Well formulated questions by process experts
- Data Mining tools
- Team effort involving Production / QC / QA / Development / …
- Support from management
- Well reliable software for data mining.

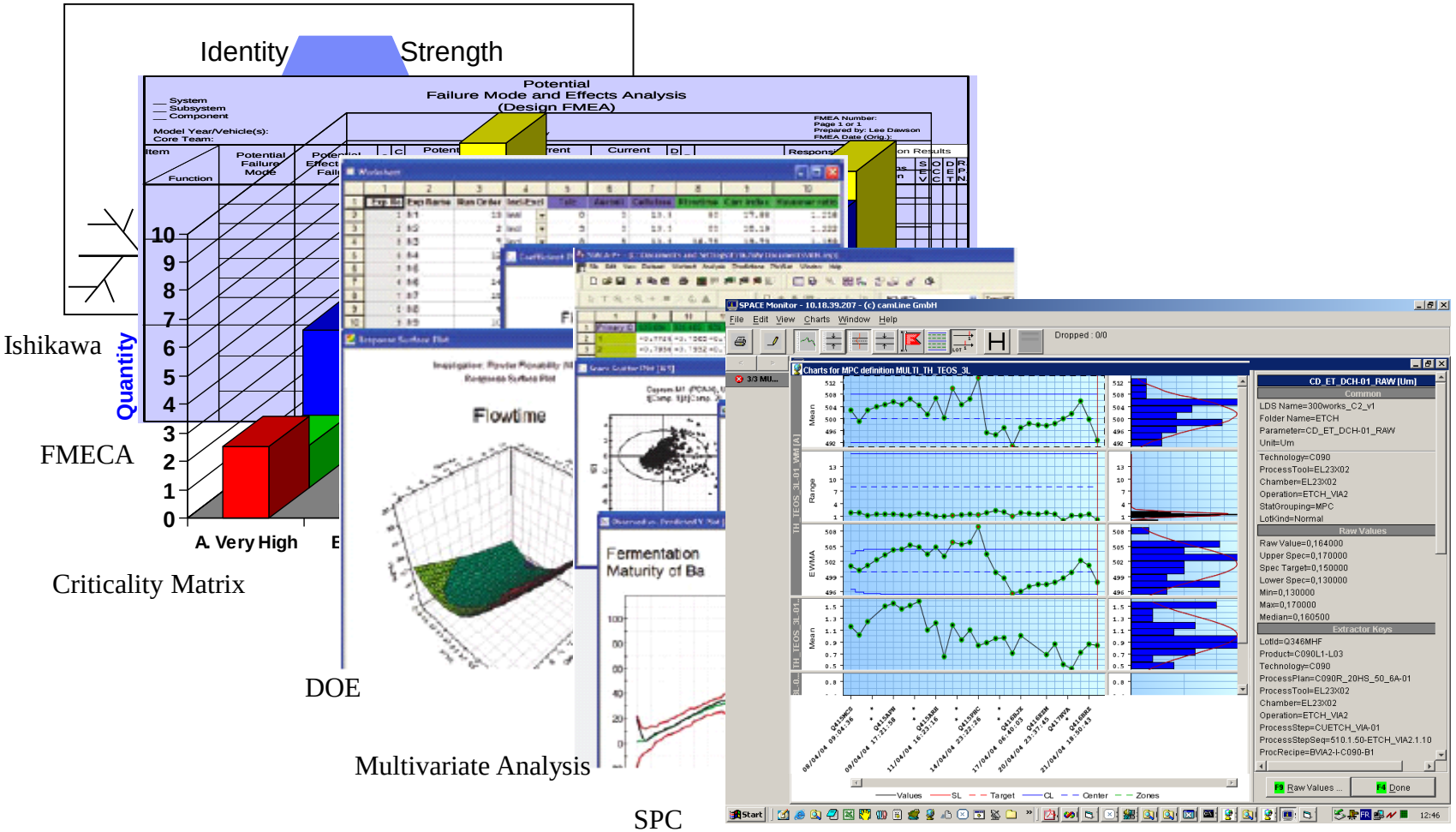
PAT Conceptual Framework.



Source: ACPS, Process Analytical Technologies (PAT) Sub-Committee Report: T. Layloff, Ph.D

PAT Example.

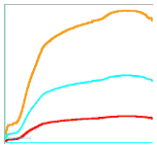
Raw Material → Dispensing → Granulation → Drying → Milling → Mixing → Tabletting → Coating



Source: ISPE-Boston, Feb. 2005

Process Analytical Technology - Chemical Processes.

Handheld NIR

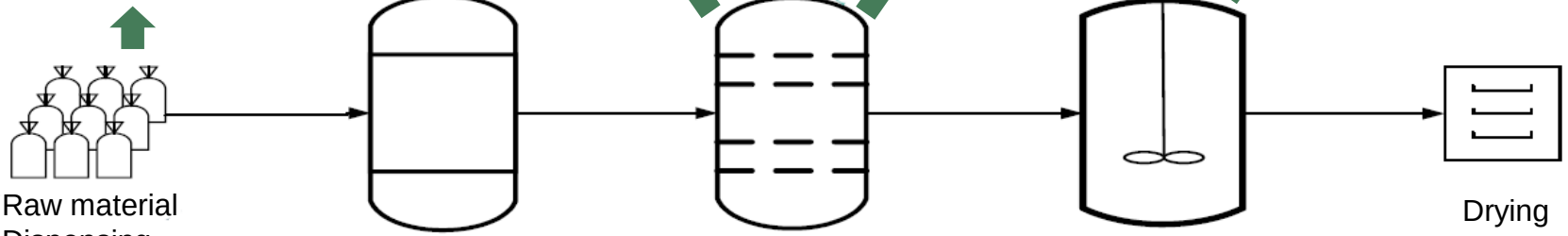


UV photometry
Concentration and end-point determination

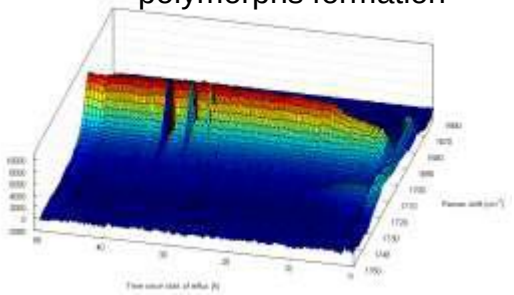
Refractometry

Raw materials identification and qualification

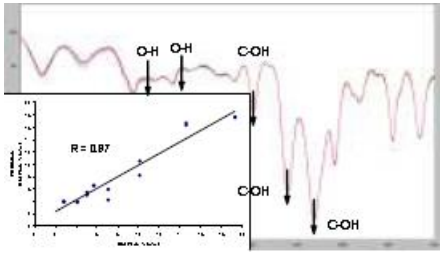
Crystals growth dynamics



Raman spectroscopy
Reaction conversion and polymorphs formation



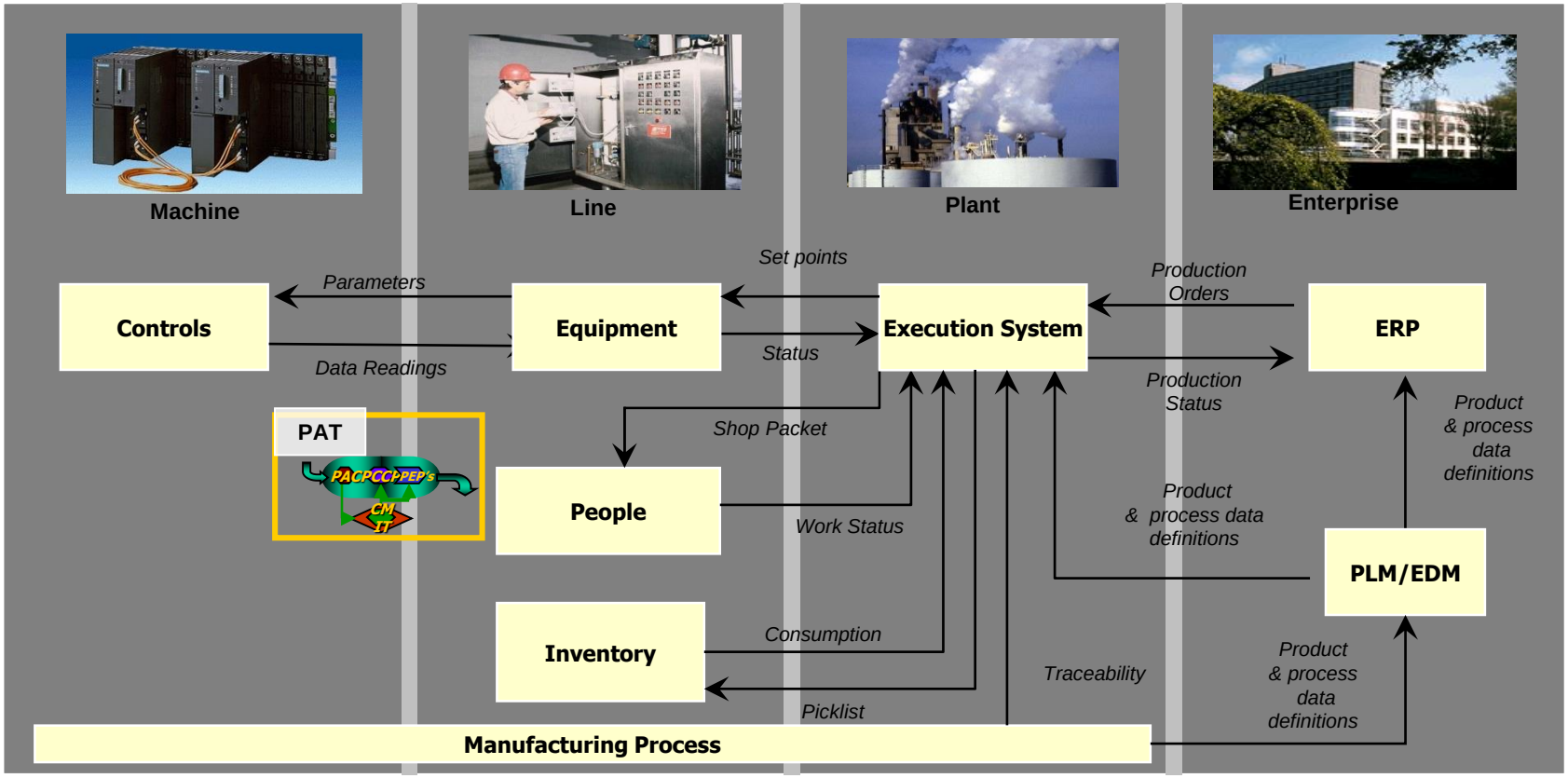
FT-IR spectroscopy
Reaction conversion and polymorphs formation



Raman and FT-IR spectroscopy
Concentration and polymorph conversion

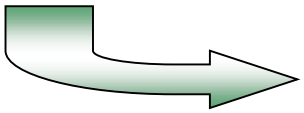
NIR spectroscopy
Drying end-point and solid state characterization

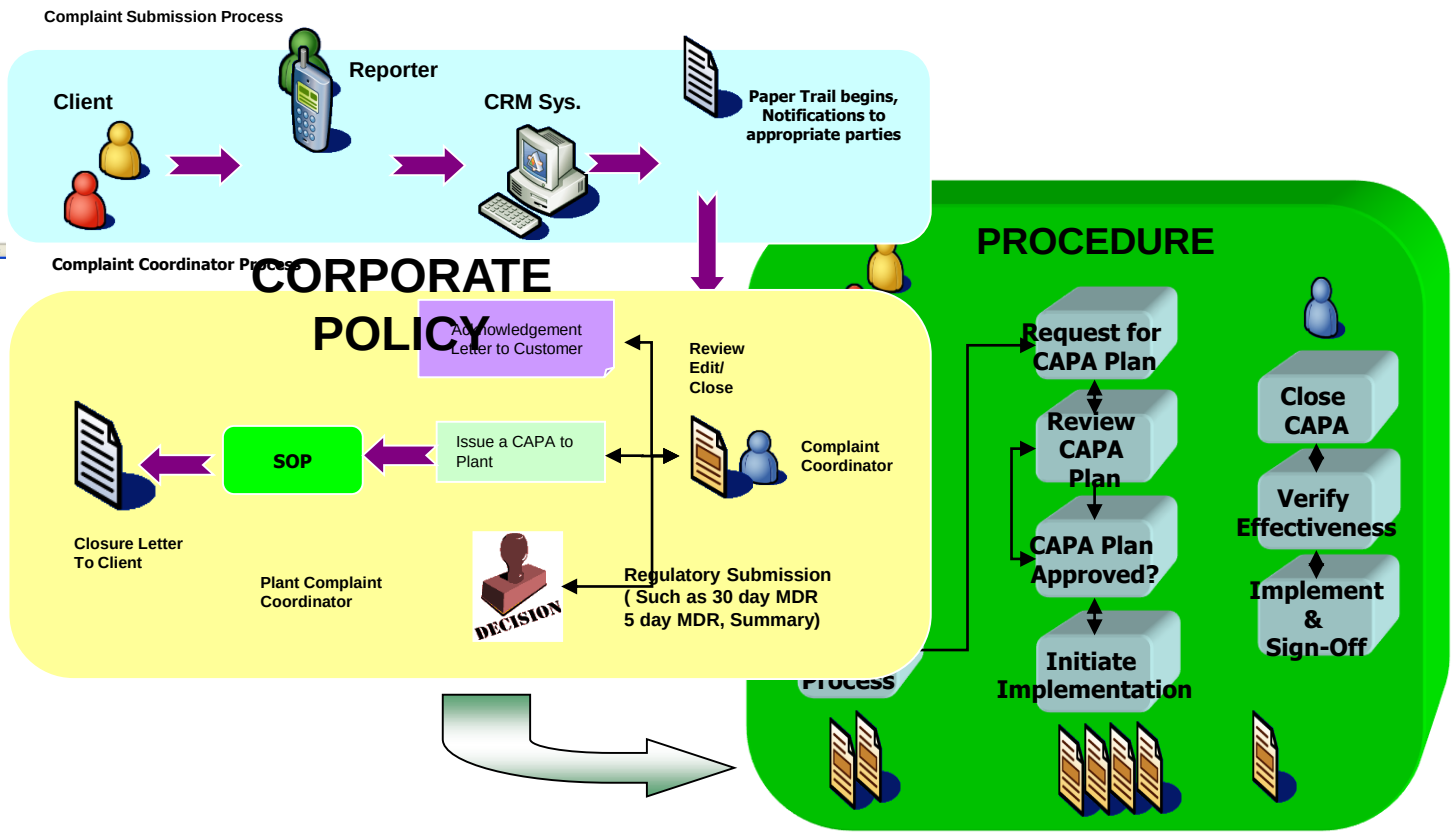
Execution Systems Orchestrate Production.



Source: IBM Life Sciences, James Bradburn

Existing Regulatory Process Control.





POLITECNICO DI MILANO

School of Industrial and Information Engineering

Course 096125 (095857)

Introduction to Green and Sustainable Chemistry





Quality by Design (QbD).

Prof. Attilio Citterio

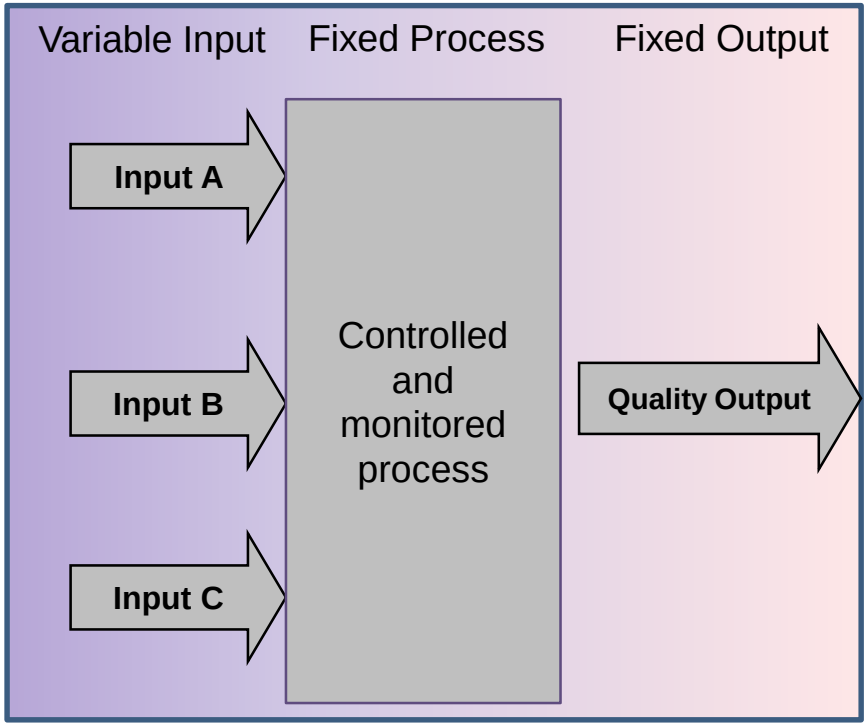
Dipartimento CMIC “Giulio Natta”

/https://iscamapweb.chem.polimi.it/citterio/it/education/course-topics/

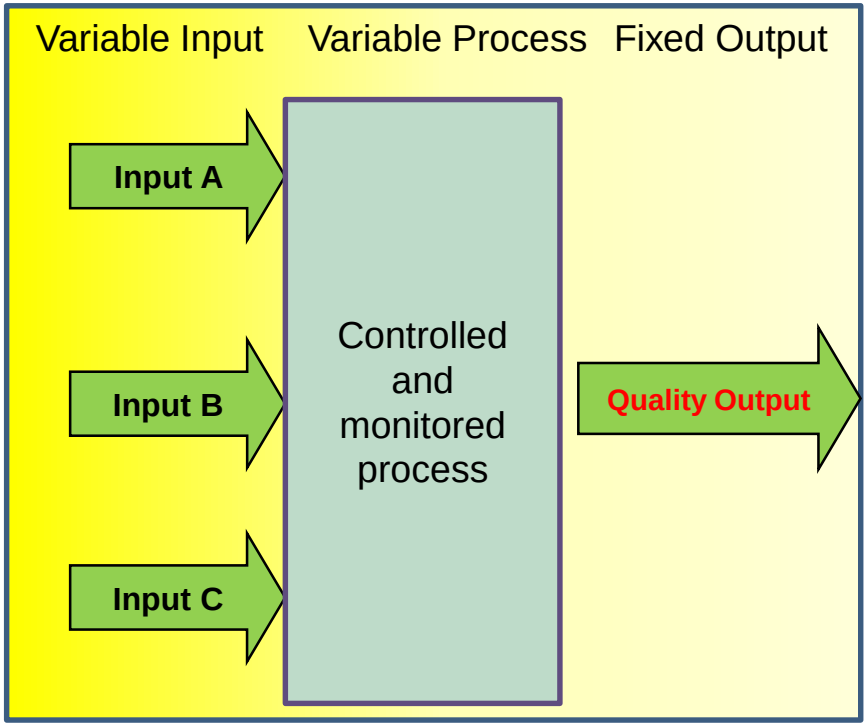
The Importance of Design.

- Multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide an assurance of quality.
- Operating within design parameters will produce a product meeting designed quality attributes.
- Working within the design parameters is not considered a reportable change.
- Movement outside of design space is considered a change – subject to regulatory approval.

Today's Validated Process and Tomorrow's Controlled and Monitored Process.

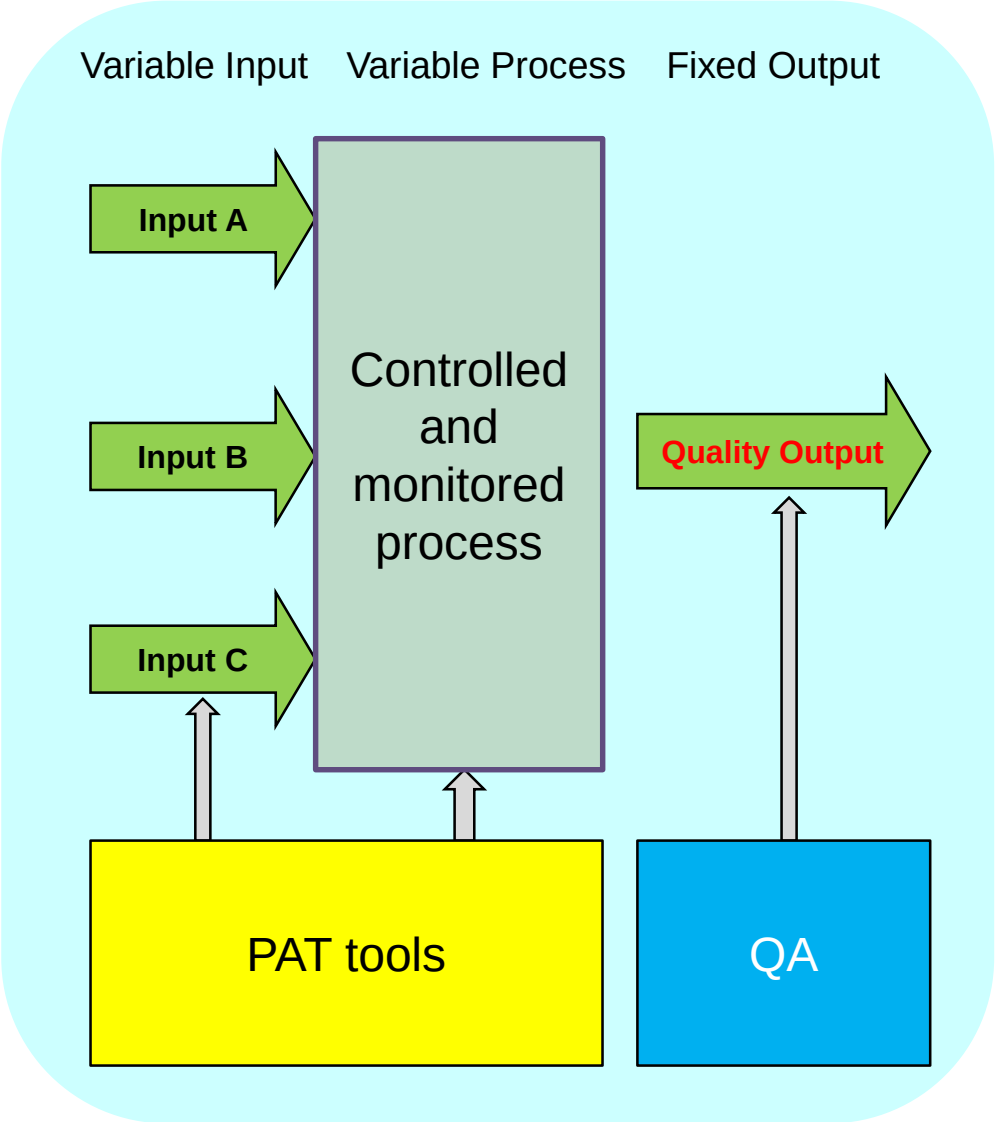


Today



Tomorrow

PAT and Process Monitoring and Control.

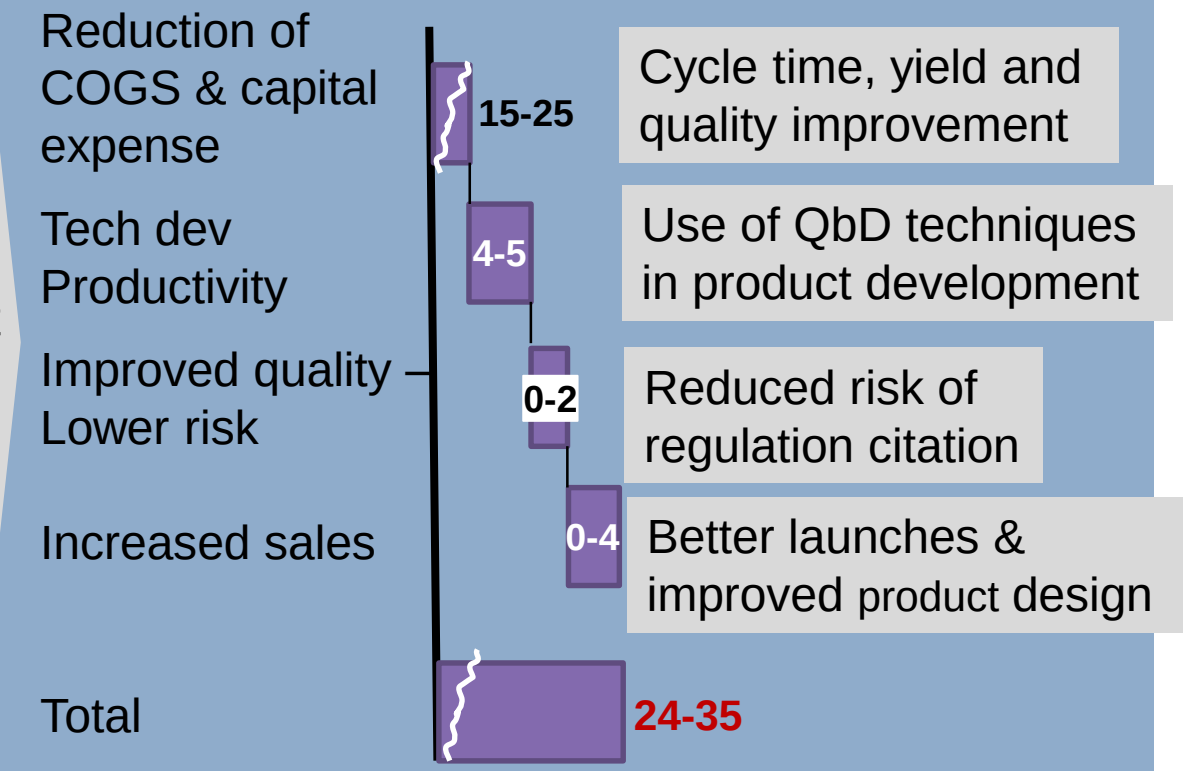


The QbD Promise ….

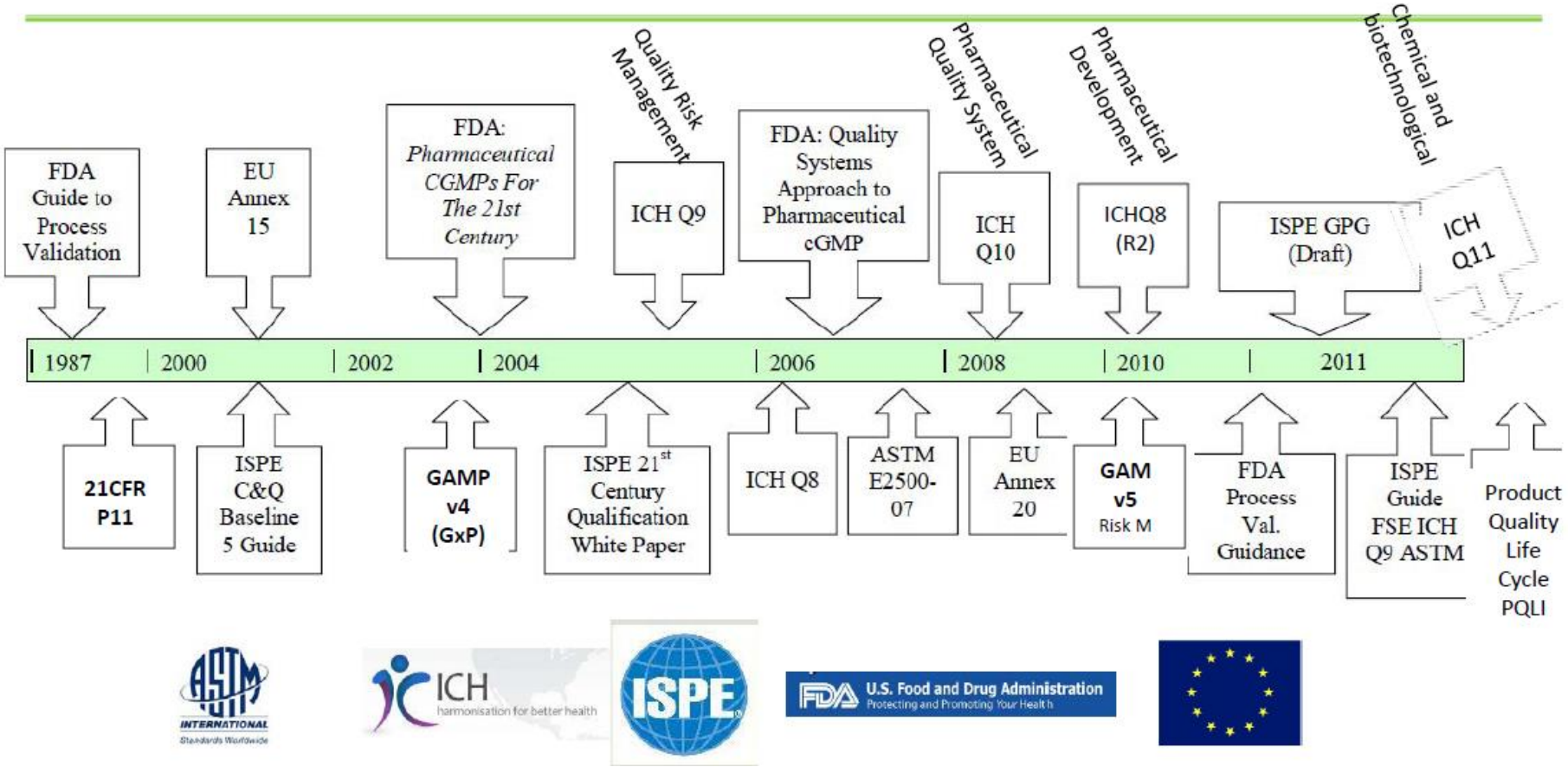
Benefits from QbD

- «Lower COGS through…. grater supply chain reliability and processability
- «Reduced development cost per program by 25% through QbD»
- Manufacturing site with QbD products has 30% lower quality staffing and cost»

Potential sources of incremental profit from QbD
USD billions



Evolution of Guidelines…



ICH Guidelines Overview.

- **ICH Q8(R2) Pharmaceutical Development**
  - Provides information on how to present knowledge gained when applying scientific approaches and quality risk management for developing and manufacturing a product.
- **ICH Q9 Quality Risk Management**
  - Provides information regarding systematic approaches to quality risk management.
- **ICH Q10 Pharmaceutical Quality System**
  - Establishes a new ICH tripartite model for an effective quality management system for the pharmaceutical industry. The model is referred to as the pharmaceutical quality system (PQS).
- **ICH Q11 Development and Manufacture of Drug Substance**
  - Apply for small and large. Is focused on risk analysis and design space for reliable drug quality.

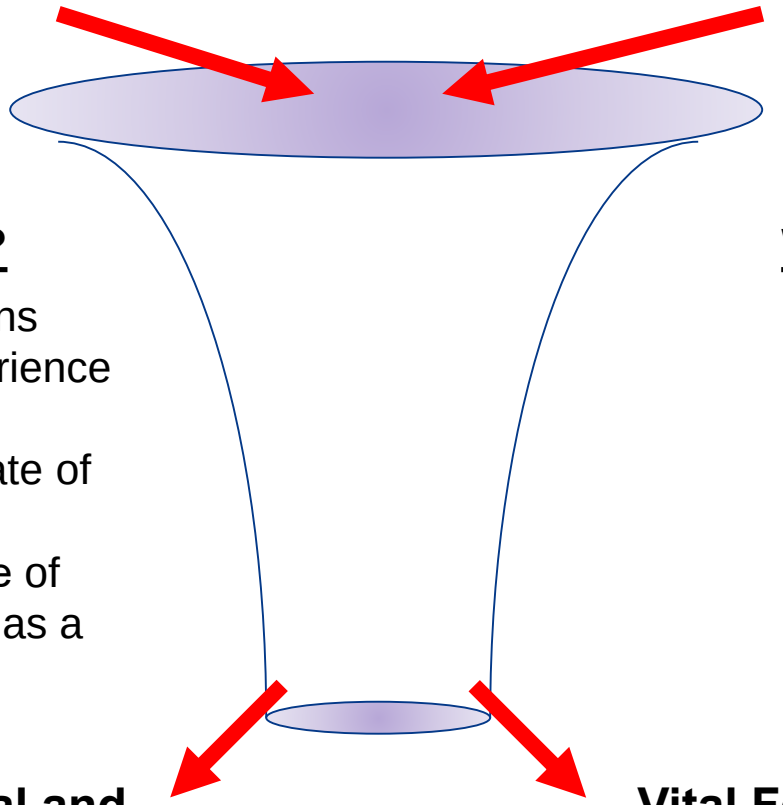
QbD Approach.

Quality Attributes

Many Y's

Process Parameters

Many X's



Which Attributes?

- Consensus decisions
- Draw on prior experience with unit operation
- Draw on current state of knowledge
- Focus on the "Voice of The Customer" DP as a customer of API

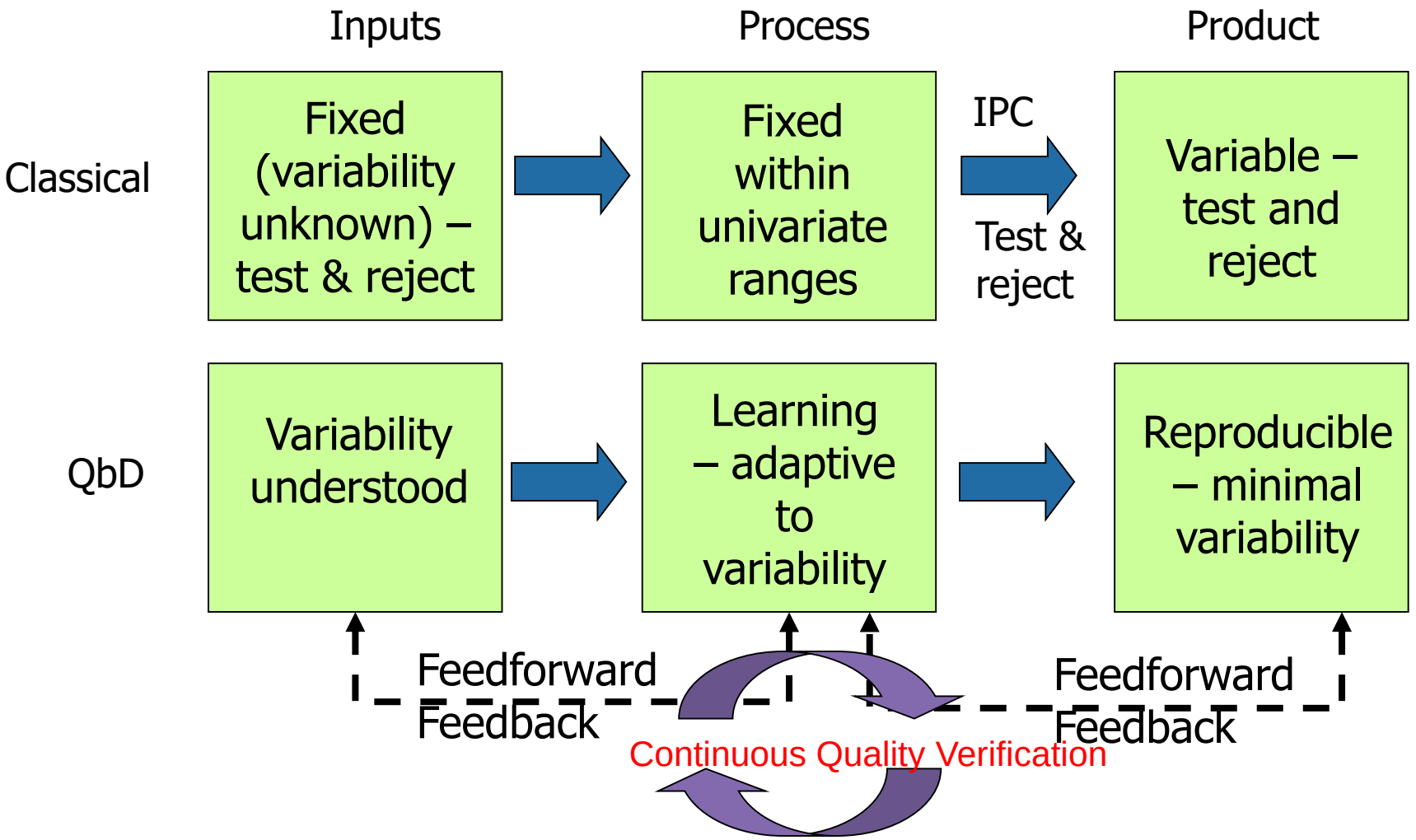
Which Parameters?

- Cause and Effect Matrix with "Effects" focused on KQAs
- Draw on prior experience with unit operation
- Draw on current state of knowledge

Vital Few Y's: Critical and Key Quality Attributes

Vital Few X's: Critical and Key Process Parameters

QbD Process can be more Flexible and Capitalise on Different Control Strategy.



Adaptive, learning processes only work with in-depth process understanding and a flexible environment: Design Space

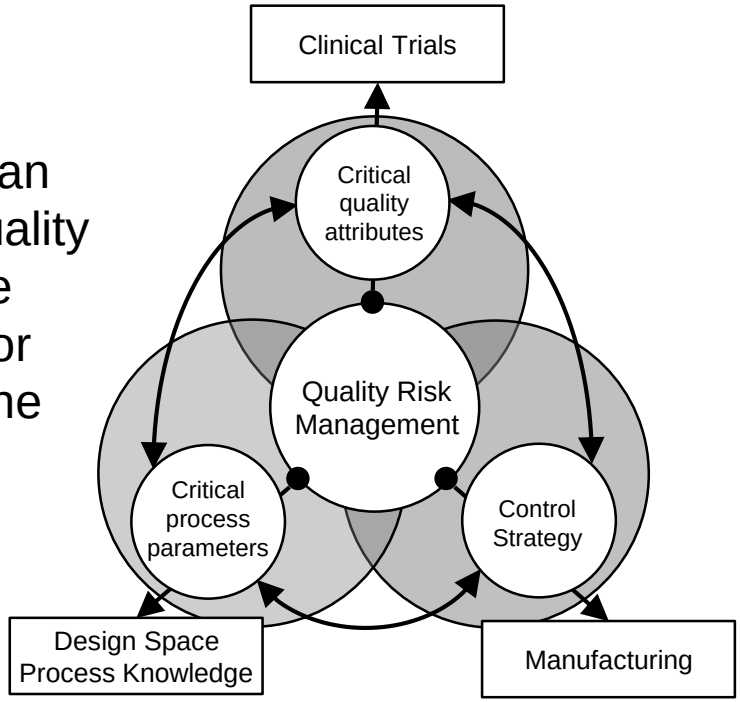
QbD Approach.

Quality Target Product Profile (QTPP)

A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.

Critical Process Parameter (CPP)

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.



Critical Quality Attribute (CQA)

A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Rouiller Y. et al., EJPB 2012

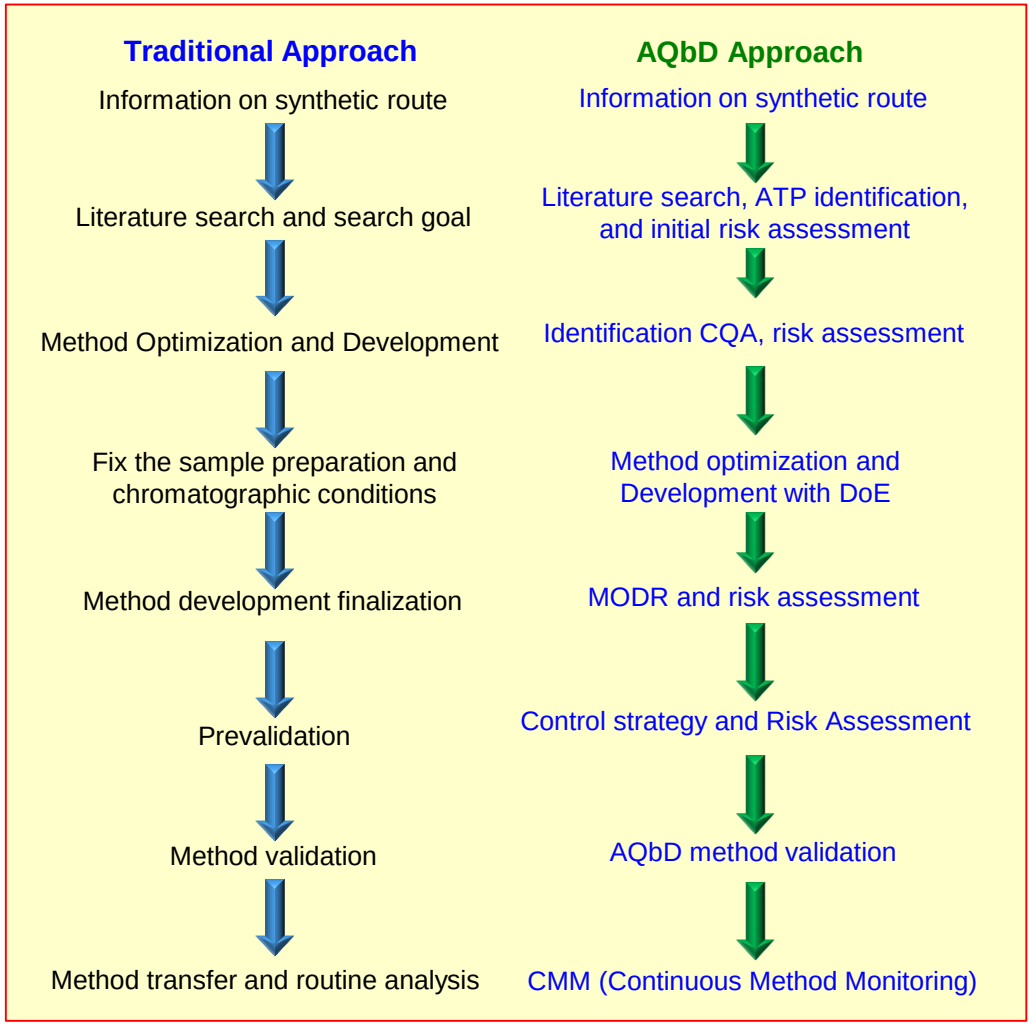
QbD Tools for Synthetic Development and Analytical Development of Drug Products.

Steps	Synthetic development (QbD)	Analytical development (AQbD)
1	QTPP identification	ATP identification
2	CQA/CMA identification, Risk Assessment	CQA identification, Initial Risk Assessment
3	Define product design space Define process design space	Method Optimization and development with DoE
4	Refine product design space	MODR
5	Control Strategy with Risk Assessment	Control Strategy with Risk assessment
6	Process validation	AQbD Method Validation
7	Continuous process monitoring	Continuous Method Monitoring

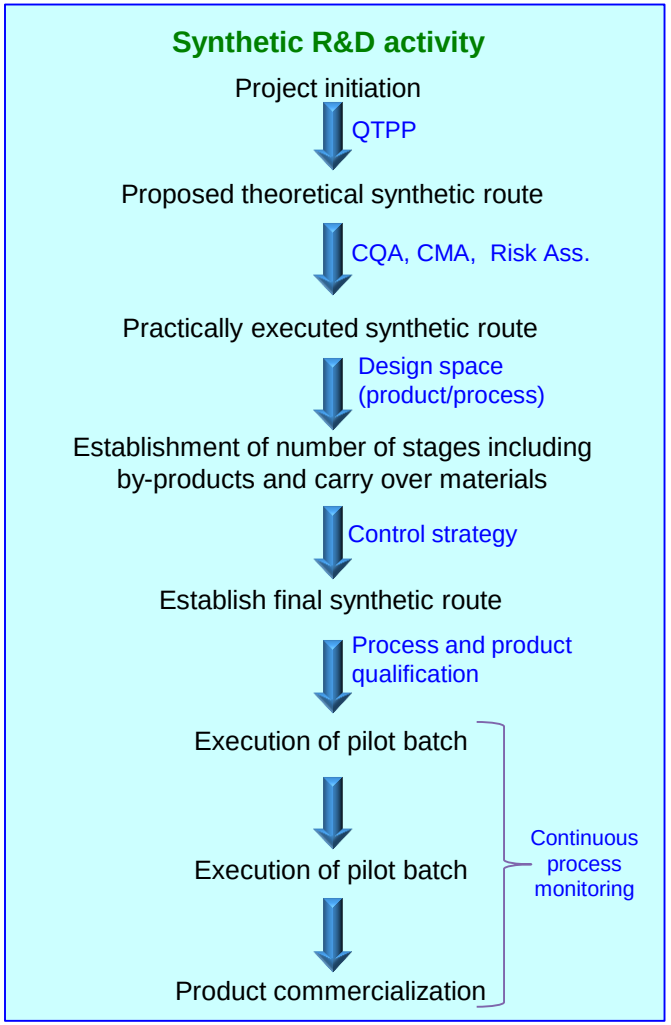
Acronyms:
QbD (Quality by Design)
QTPP (Quality Target Product Profile)
AQbD (Assessment Quality by Design)
ATP (Analytical Target Profile)
CQA (Critical Quality Attribute)
CMA (Critical Material Attributes)
MODR (Method Operable Design Region)
DoE (Design of Experiments)

API Synthetic and Analytical Methods Development under QbD Approach.

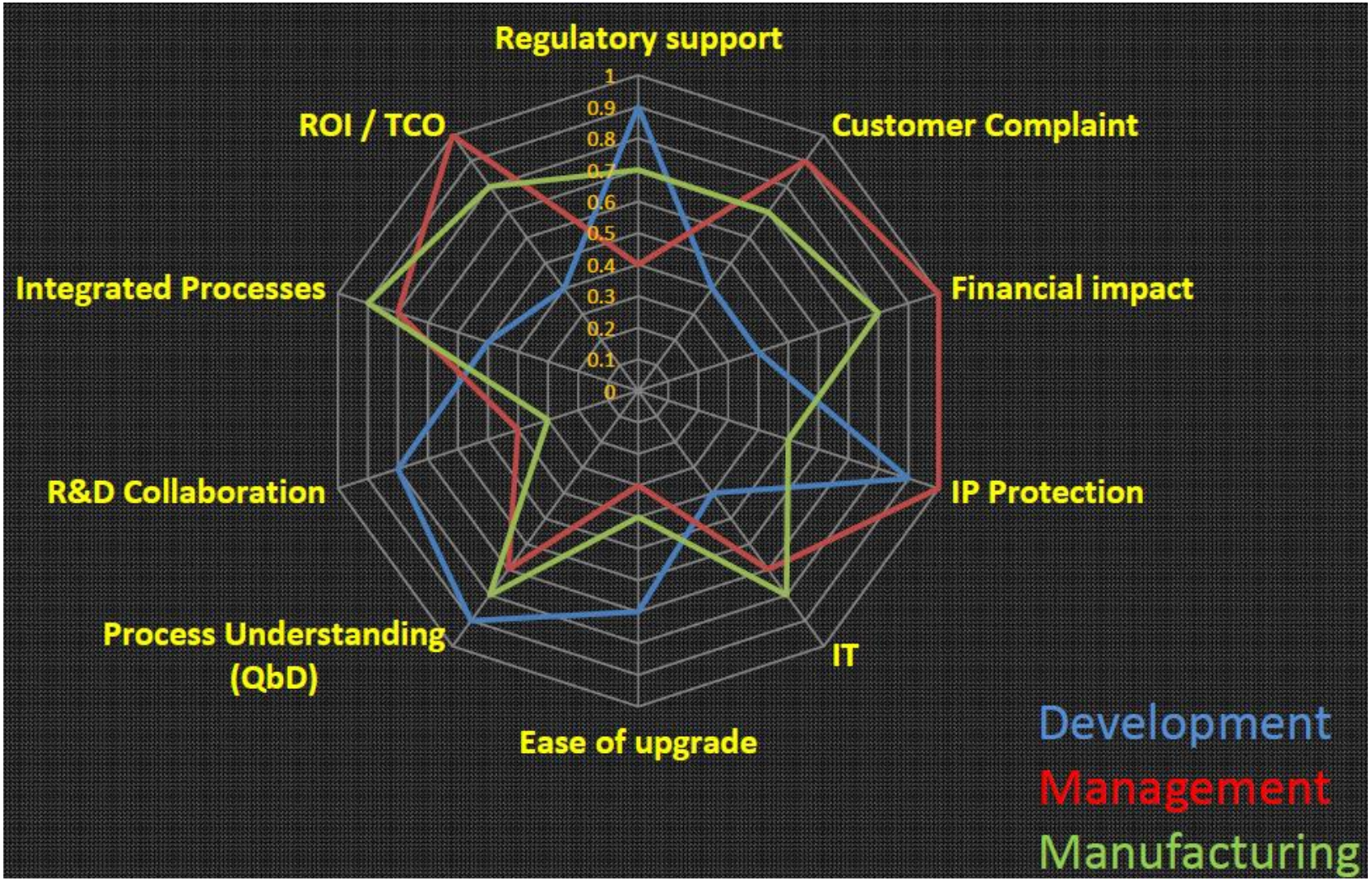
Traditional and AQbD approach for analytical method development



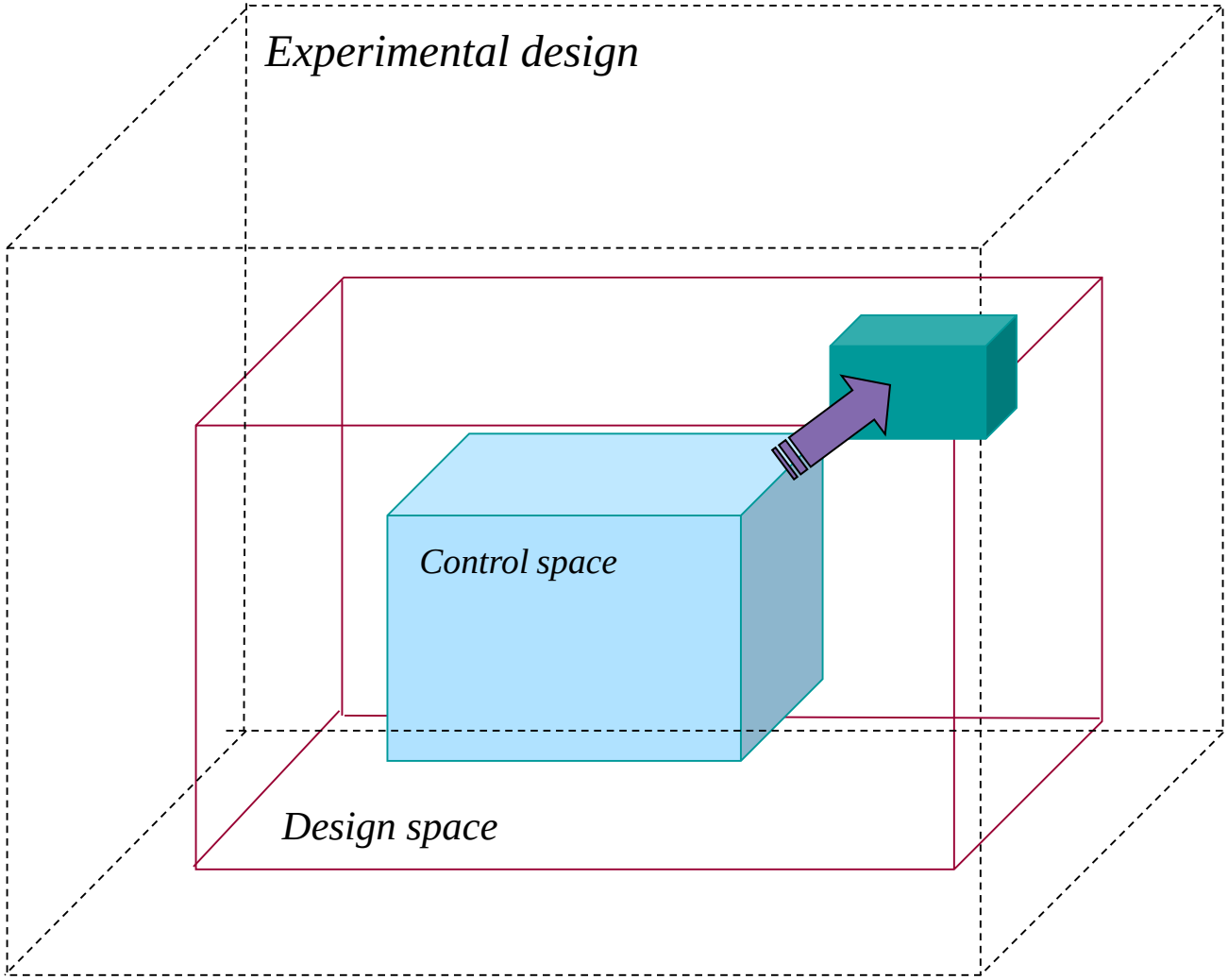
API synthetic development and ADbD approach.



Overview.


Regulatory support
Customer Complaint
Financial impact
IP Protection
IT
Ease of upgrade
Process Understanding (QbD)
R&D Collaboration
Integrated Processes
ROI / TCO
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Development
Management
Manufacturing

QbD, DoE and Continuous Improvement.



Quality by Design.

Conventional PD	Quality by Design (ideal)
Mainly empirical approach	A systematic approach
Quality assured by end-product testing and inspection	Quality assured by well understood product and process, moving controls upstream without relying on end-product testing as much as possible
Process is fixed, disallowing changes	Flexible process within design space, allowing continuous improvement
Focus on process reproducibility – often avoiding or ignoring variability	Focus on formulation and process robustness – understanding and controlling variability
Limited and simple IPC	Extended PAT tools replacing the need for end product testing

Corrective and Preventive Actions (CAPA).

- **Corrective = correct existing nonconformity**
- **Prevention = potential recurrence of nonconformity**

***Regulatory expectations*:**

- **Identify sources of problems/nonconformities**
  - **Unfavorable trends**
- **Prioritize based on risk**
- **Defined action plans**
- **Timely implementation**
- **Measure and document effectiveness**
- **Reviewed by Management**

Design Space.

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

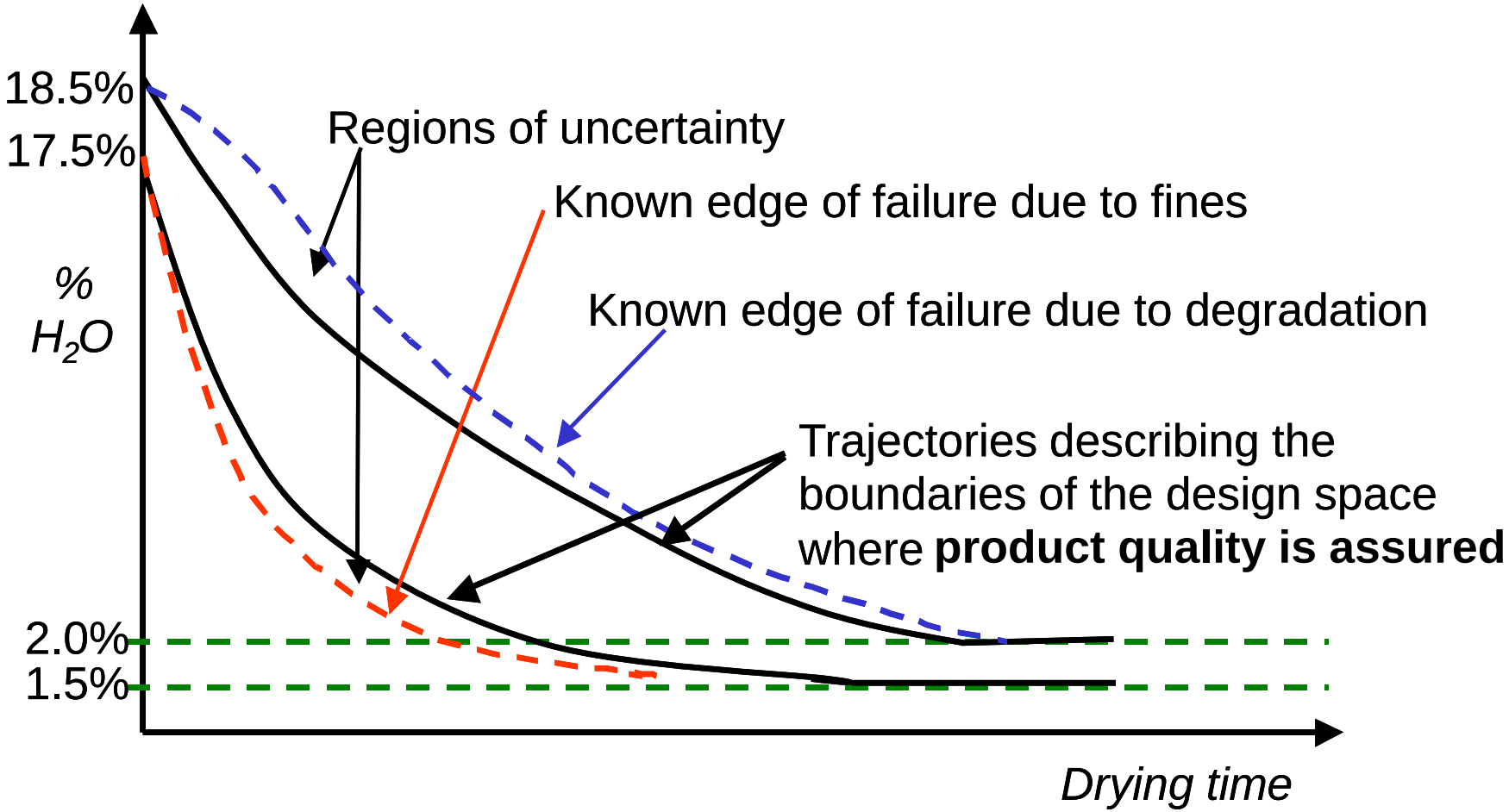
Working within the design space is not considered as a change.

Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.

Design space is proposed by the applicant and is subject to regulatory assessment and approval.

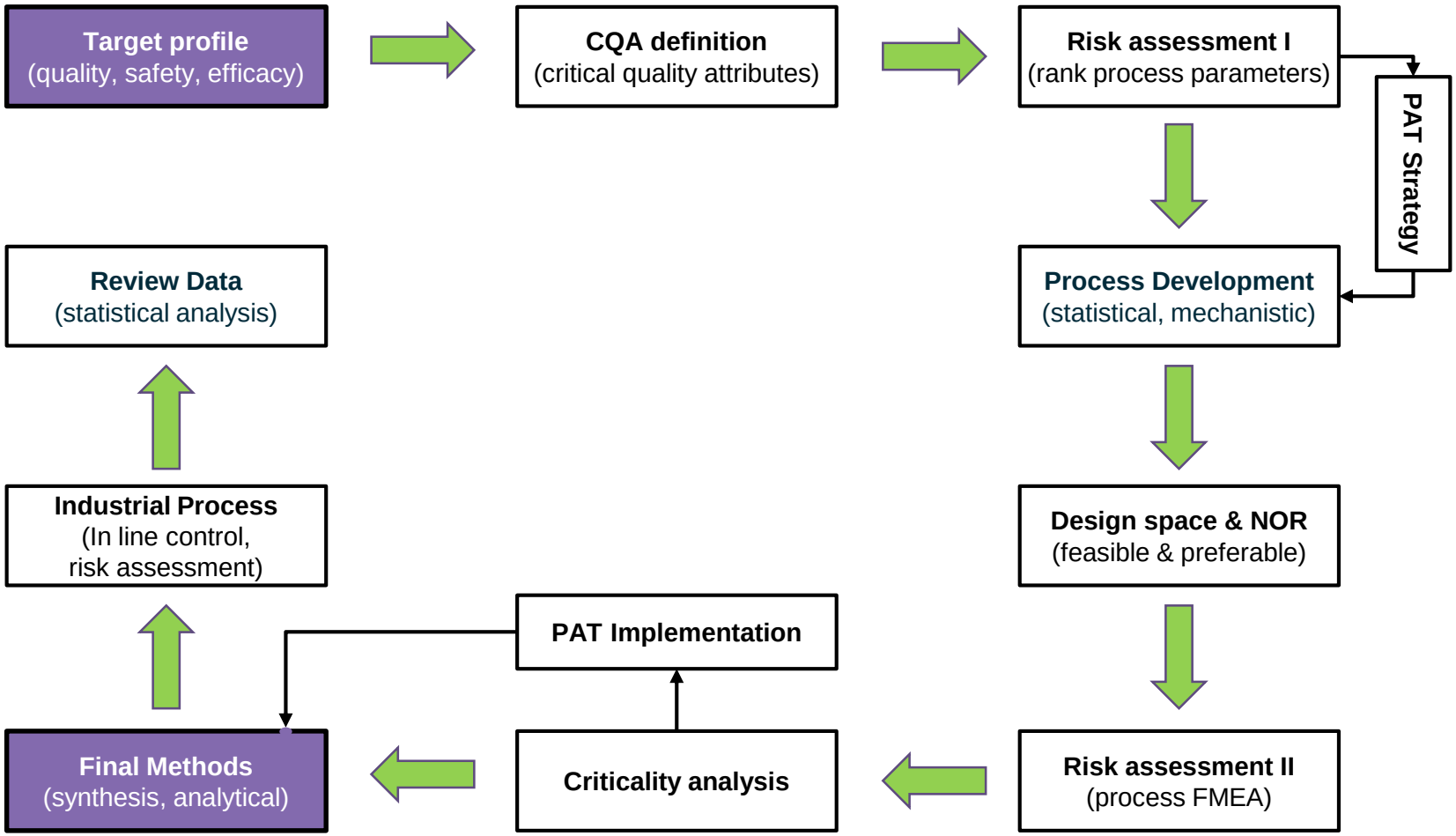
- Design Space is Key for claiming Process Understanding
- Process understanding is Key for Quality Risk Management
- QRM is the base for any Control Strategy.

Example in Design Space – Graphical Description.

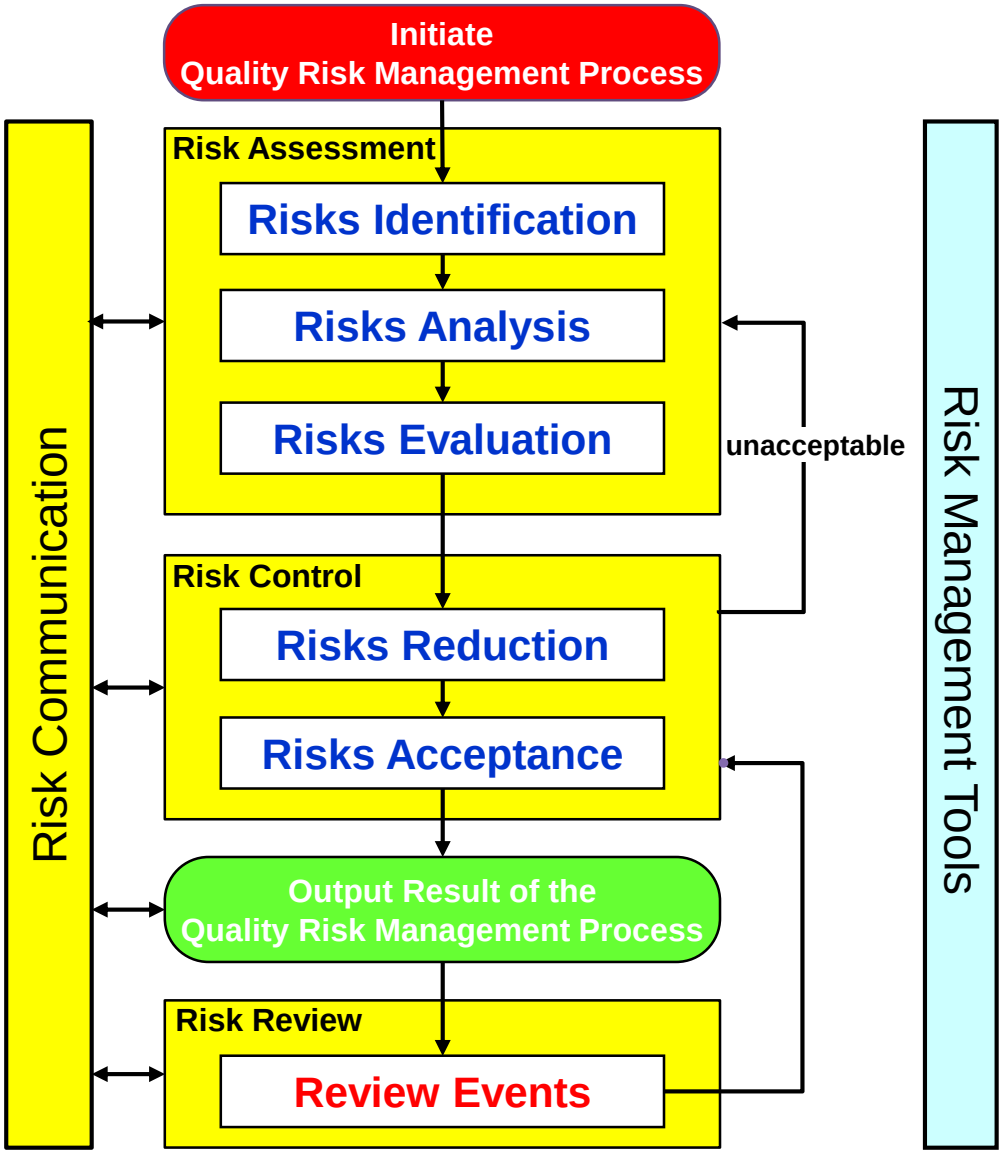


"Graphical description of the design space for the drying operation for example in hydrochloride tablet manufacture"

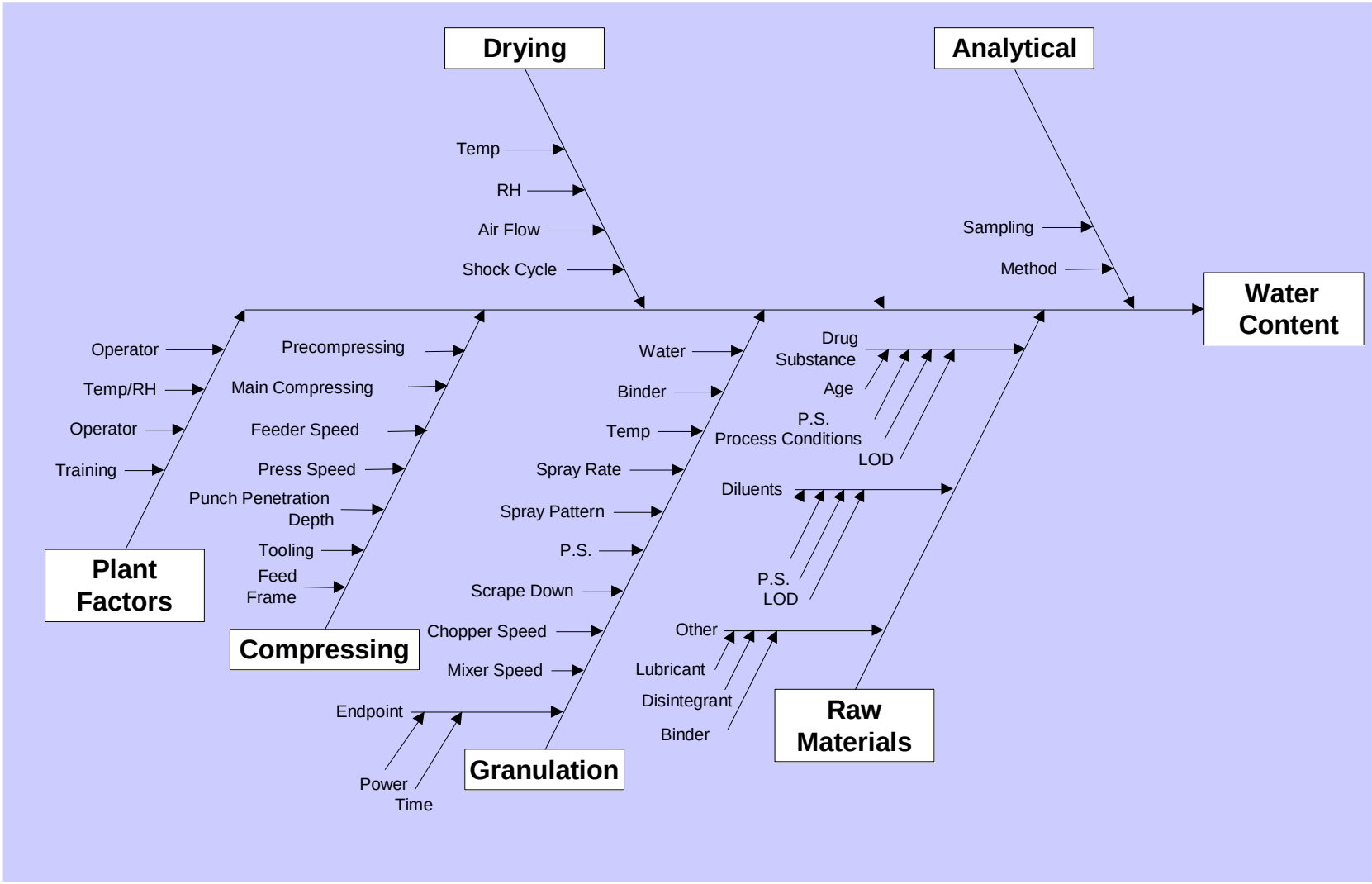
QbD Based on Science and Risk.



The Quality Risk Management Process.



Cause and Effect Process.

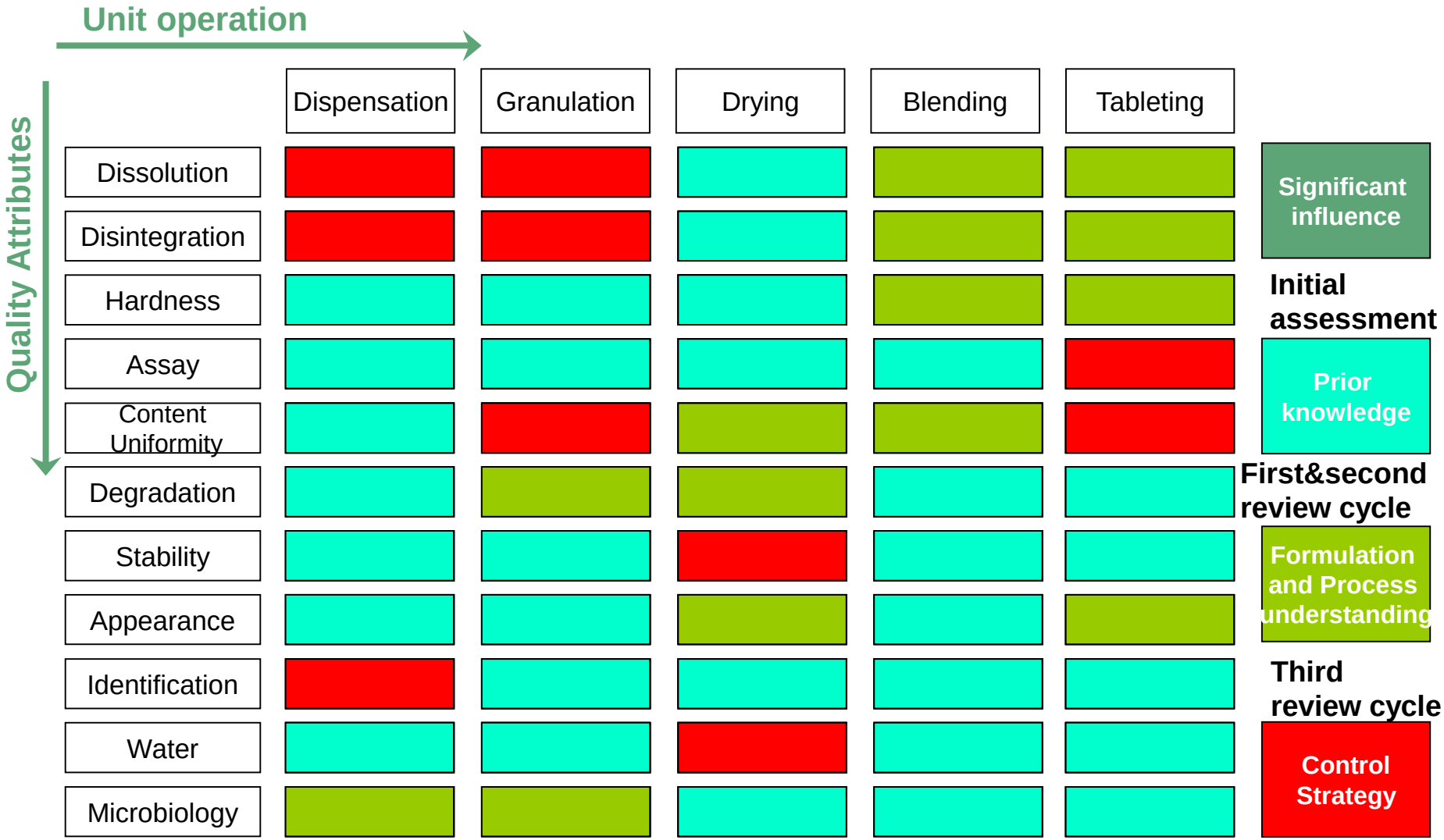


QRM Tools:
Failure Mode Effects Analysis (FMEA).

Risk Assessment						
Sub-Step	**Event (Failure mode)**	**Effect**	**Severity (S) [1<2<3]**	**Probability (P) [1<2<3<4]**	**Detectability (D) [1<2<3]**	**Risk factor (S*P*D)**
Granulation Drying	water content	not meet specification of degradation	2	3	1	6

Risk Reduction						
Actions: Risk reduction strategy	**Severity (S) [1<2<3]**	**Probability (P) [1<2<3<4]**	**Detectability (D) [1<2<3]**	**Risk factor (S*P*D)**	**Risk reduction**	**Comments**
introduce online NIR	2	1	1	2	4	indirect measurment
introduce IPC analytic	2	2	1	4	2	direct measurement; time consuming
humidity measurement in the exausting air	2	1	2	4	2	indirect measurment; unspecifoc

Risk Management Process.



Control Strategy.

- Justification of necessary controls
- Raw Materials Control
- In-Process Controls
- End Product Controls (if necessary)
- Based on Process and Formulation Understanding
- Drives the Process in the Design Space
- Based on Quality Risk Management
- To ensure conforming Quality according Specifications.

References for QbD.

1. ICH Q8(R2) Quality guidance: Pharmaceutical Development".
2. ICH Q9 Quality guidance: Quality Risk Management
3. ICH Q10 Quality guidance: Pharmaceutical Quality System
4. ICH Q11 Quality guidance: Development and Manufacture of Drug Substance
5. Guidance for Industry PAT: A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance
6. Quality by Design for ANDAs: An Example for Modified Release Dosage Forms
7. Quality by Design for ANDAs: An Example for Immediate Release Dosage Forms
8. GPhA presentations
9. Draft QbR updated.