Designing and Implementing Controllable Processes

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The content of this presentation represents the personal opinion of the author

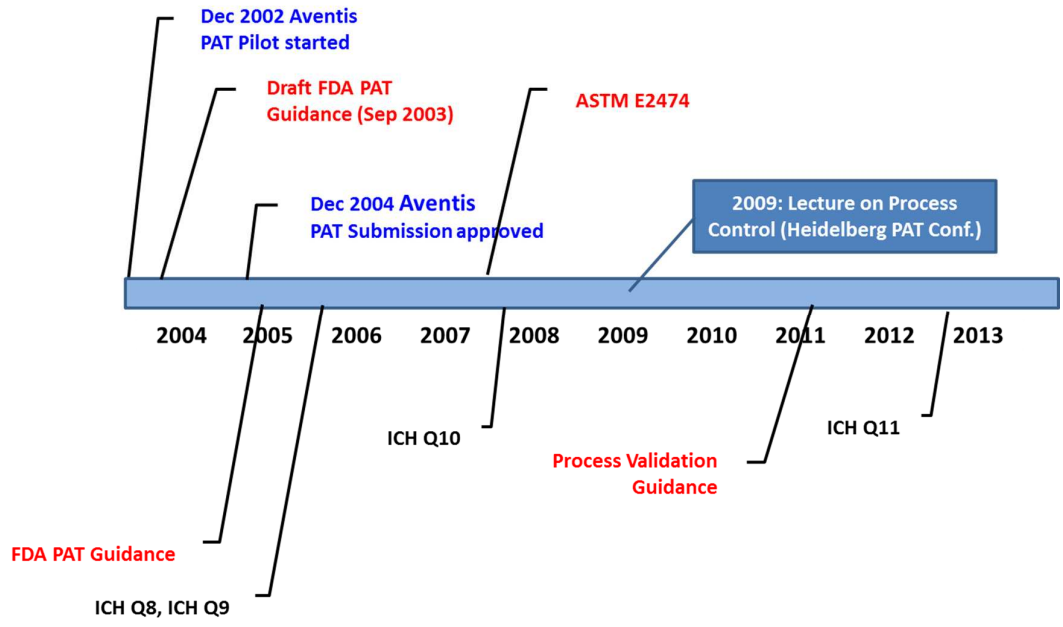
Gerd Fischer / Where I come from

- Chemist, 30 years in pharmaceutical industry
- From Hoechst to Sanofi Aventis; Boehringer Ingelheim
  Leading roles in
  - Quality Operations, API Production
  - Global Process Development Quality Management
  - Global Strategic Initiative Leader
  - Global Industrial Development Quality and Technical Expertise
  - Operations Regulatory Intelligence
- EFPIA TDOC member (incl. expert teams: PAT, ICH Q10, 'Foreign Inspections', Supply Chain Security)
- ICH Q10 Expert Working Group, ASTM Committee E55 (PAT)

Outline – Topics to be covered

- 'Controllable process' – in the context of quality systems
- Drivers for quality performance
- ASTM Standard E2474 – to design a process
- Design, validation, and control strategy
- People
- Summary or outlook

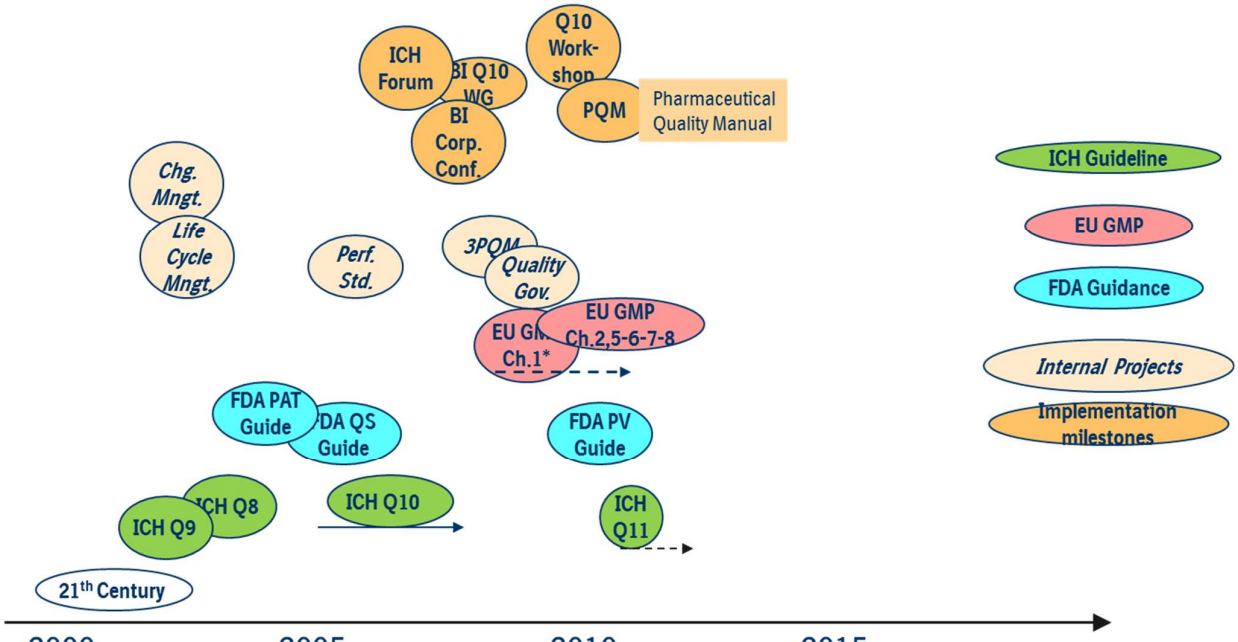
Instead of an Introduction: Where are we today



Coming back to the QbD/PAT Conference

Title of the presentation in 2009

Quality System – Continuous Adaptation (Example)



Pharma today

Not many changes ...

- 'Globalization' without global control; supply chain threats: drug shortages, criminal action
- Cost pressure (even worse), higher competition - fewer NDAs
- Same technology and methodology, no simple molecules any more
- Regulatory environment – little progress for harmonization, talk about convergence;

Generics companies are the new leaders; Big Pharma – to be minority players

- Markets – differentiation; aging population

Pharma Benchmark ?

World Class Manufacturing Comparison

Indicator	Pharm Norm	Pharm Best	World Class
Stock Turn	3 to 5	14	50
Order Time In Full Delivery	60% to 80%	97.4%	99.6%
Right First Time	85% to 95%	96.0%	99.4%
Process Capability CpK	1 to 2	3.5	3.2
Overall Equipment Efficiency	30%	74.0%	92.0%
Cycle Time in Hours	720	48	8
Safety per 100,000 Hours	0.100	0.050	0.001

ABB Eutech Process Solutions - 2003

Expectations for Quality never change

- The patients wants his drug
  - .. is safe and efficacious
  - .. is available when needed
- The patient takes for granted that his drug
  - .. has the correct identity
  - .. delivers the same performance as described on the label, and does this consistently over its shelf-life
  - .. is produced in a manner that ensures quality

What can go wrong – Industry perspective

- Interruption of market supplies
- Bad product (quality or safety)
- Bad data (process data not supporting control and compliance)
- Bad document (records not supporting compliance)

What goes wrong – Agency perspective

Significant reasons for product recalls

- Product quality (impurities, degradation)
- GMP deviations
- Lack of assurance of sterility
- Presence of particulate matter

Source: FDA statistics (2010-2013)

High Risk Areas – Inspectors' focus

- Contamination (chemical/physical)
- Process validation
- Equipment cleaning
- Method validation
- Lab records
- CAPA, Failure Investigation, Deviations, Out-of-specification (OOS)
- Stability (programs and data)

Based on FDA and MHRA public information (2010 to 2013)

What drives Quality Performance ?

1. Systems,
2. Science and technology,
3. People

Expertise
How to use systems, technology, and workflows

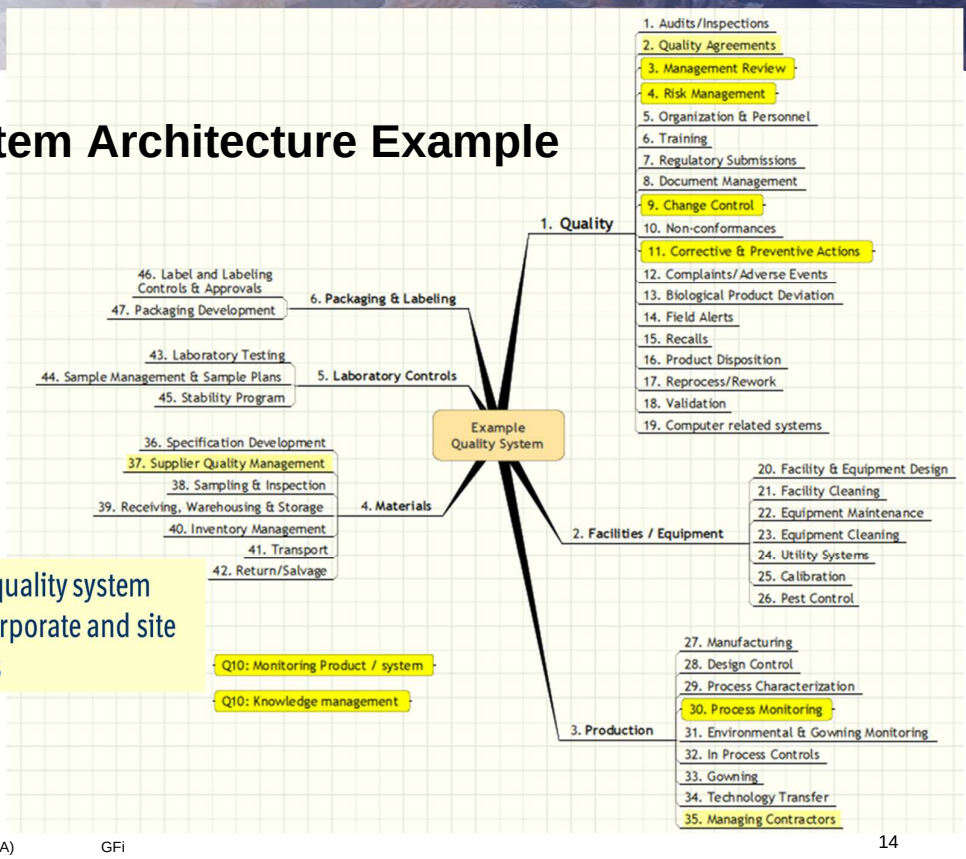
Work Flow
Organization, interaction, cooperation, projects and control

Focus
Tasks, priorities, opportunities, strategy, tactics

Science and Technology
Paradigm changes, automation, continuous improvement

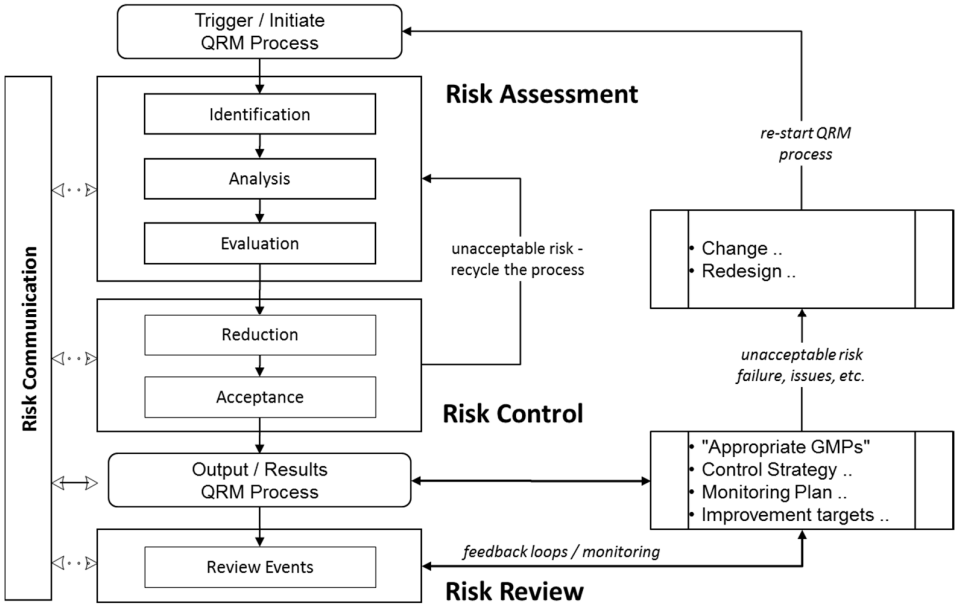
Performance

Quality System Architecture Example

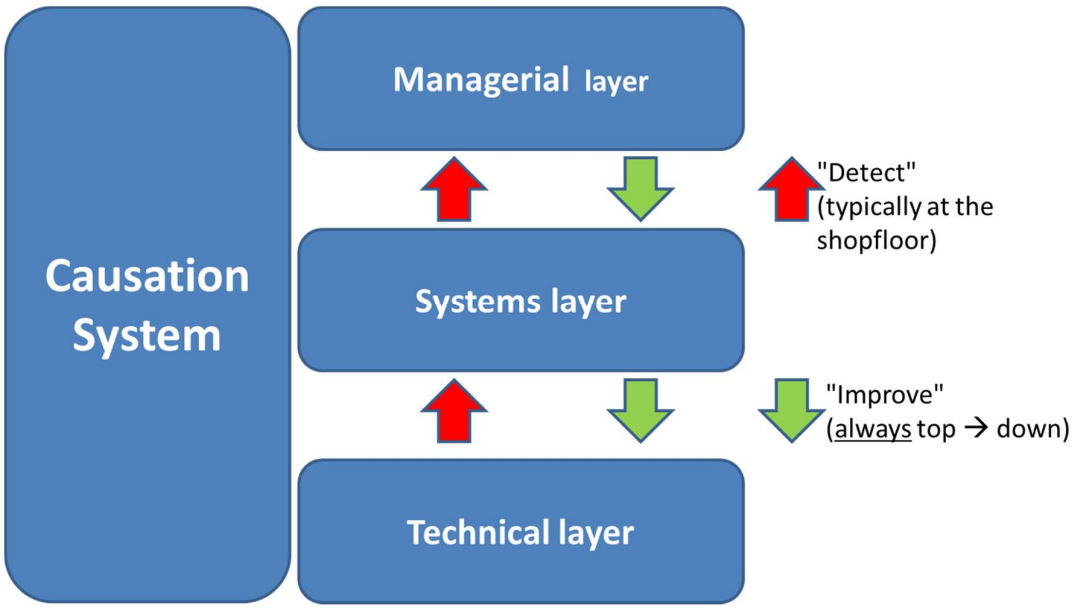


Advancing maturity of the quality system is driven by a network of corporate and site system and process owners

Prerequisite: Quality Risk Management well understood

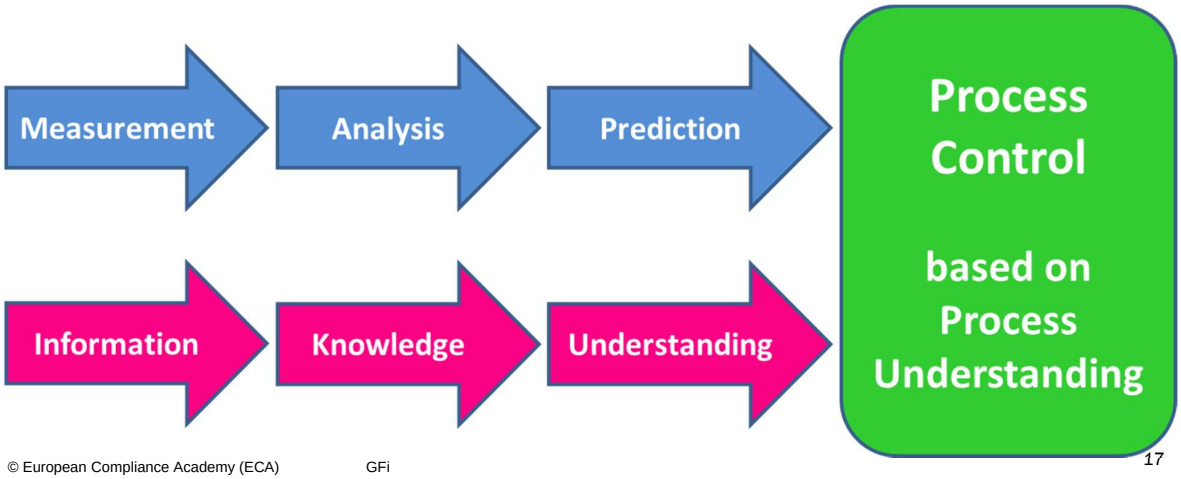


Systematic 'Learning from Failure'



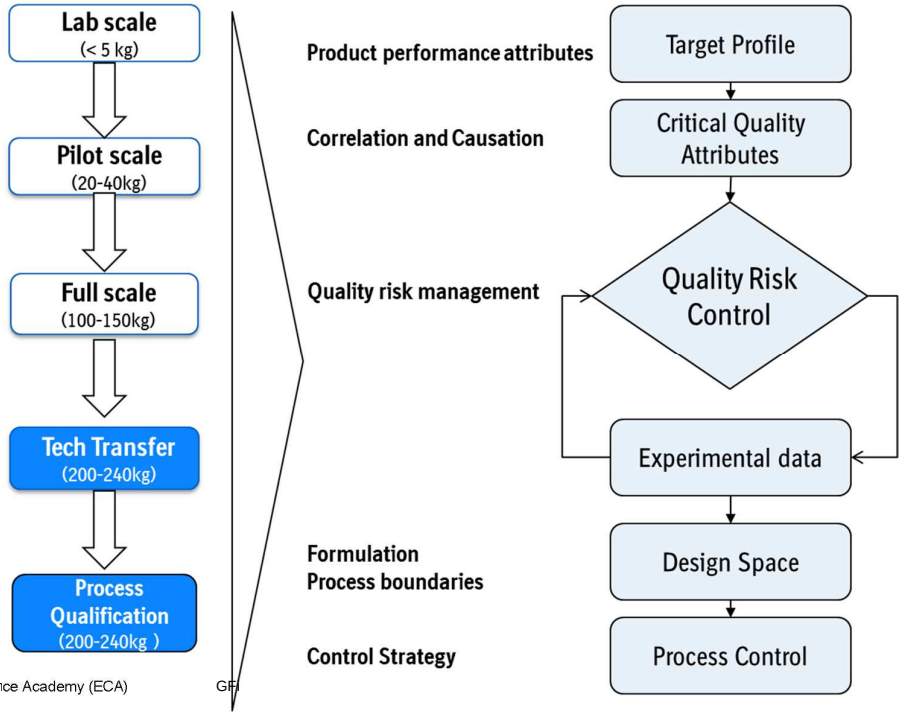
Control without Knowledge Basis is not possible

- We must understand the knowledge continuum – applying both to processes and quality systems
- Quality Metrics without quality knowledge is meaningless



 GFi

Reality Check: Today's Approaches in Development



 GFi

What do we actually need to achieve ?

- The Pharmacist says:
  "Process control is achieved when we can produce many sequential batches that readily meet specification (established post-facto)"

- The Pharmaceutical Engineer says:
  "Process control is an automated system where an artificial intelligence, developed using a process model, continuously monitors and corrects the process to keep every variable as close to its set point as possible (established in real time)"

Designation: E 2474 – 06

Standard Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology[1]

This standard is issued under the fixed designation E 2474; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

E2474 is the first industry consensus standard on PAT !

"This is the most concise description of the distinction between conventional manufacturing control and the control strategies associated with PAT." (Jon Clark, FDA)

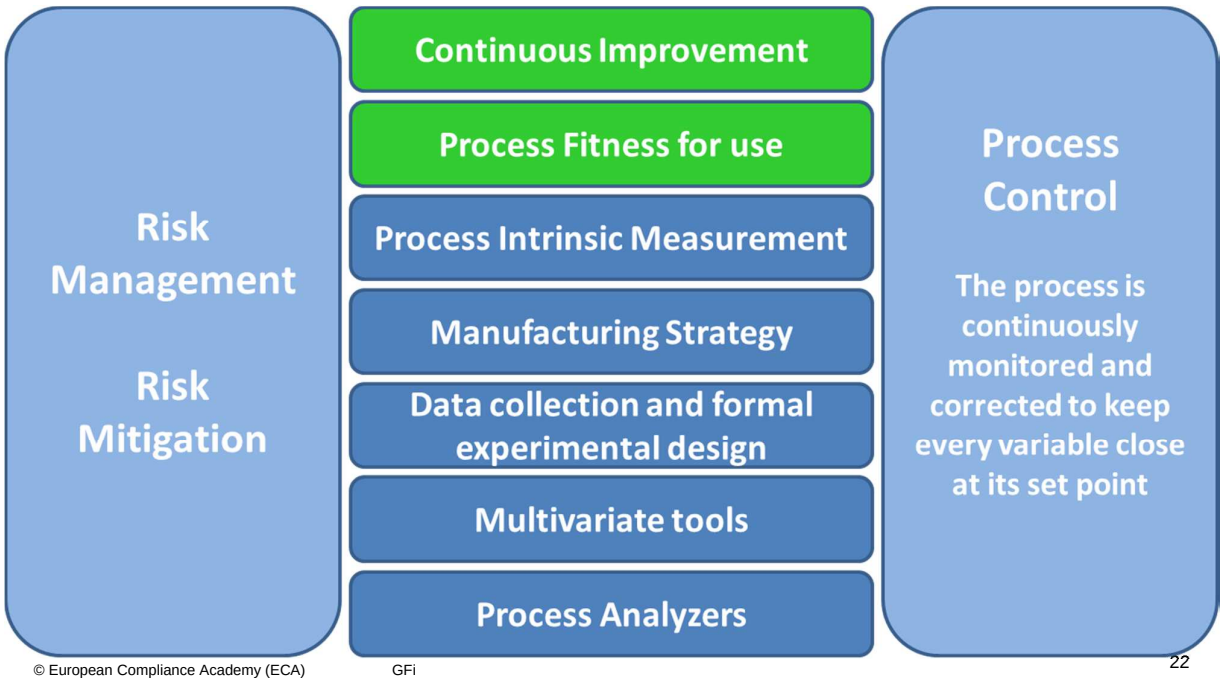
The ASTM Standard E2474 – revisited

'Standard Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology'

- Process Design definition:
  - The systematic conversion of information about needs for a product into knowledge about how to manufacture this product

How do we transform information to knowledge?

Process Design Practices (ASTM Standard E2474)



FDA View on Process Design and Development

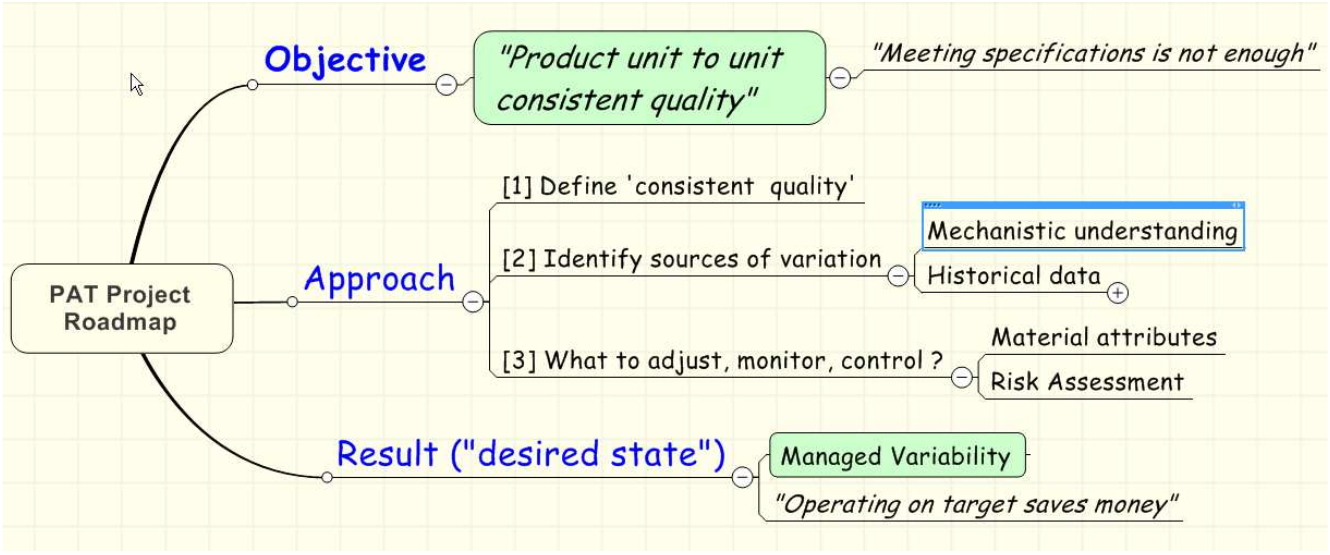
- "Good process design and development should anticipate significant sources of variability and establish appropriate detection, control, and/or mitigation strategies, as well as appropriate alert and action limits"

see: Validation Guidance and PAT Guidance

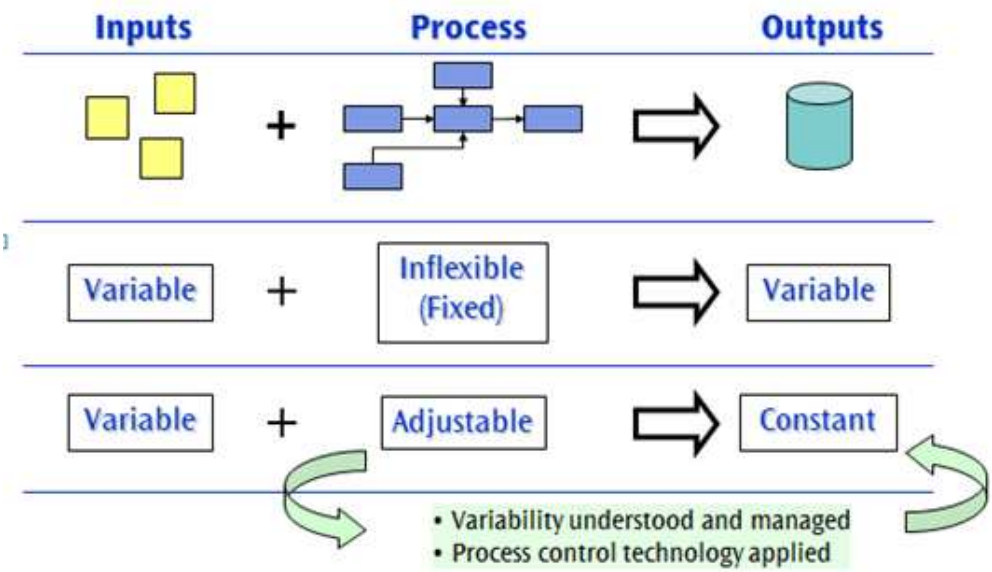
The Design Process

- Inputs: information about product structure, composition, desired quality attributes, etc.
- Initial design concepts based on institutional knowledge, intuition, experience, first principles, etc.
- Identification of feasible design options from development studies
- Detailed process development
- Design review, learning, and feedback

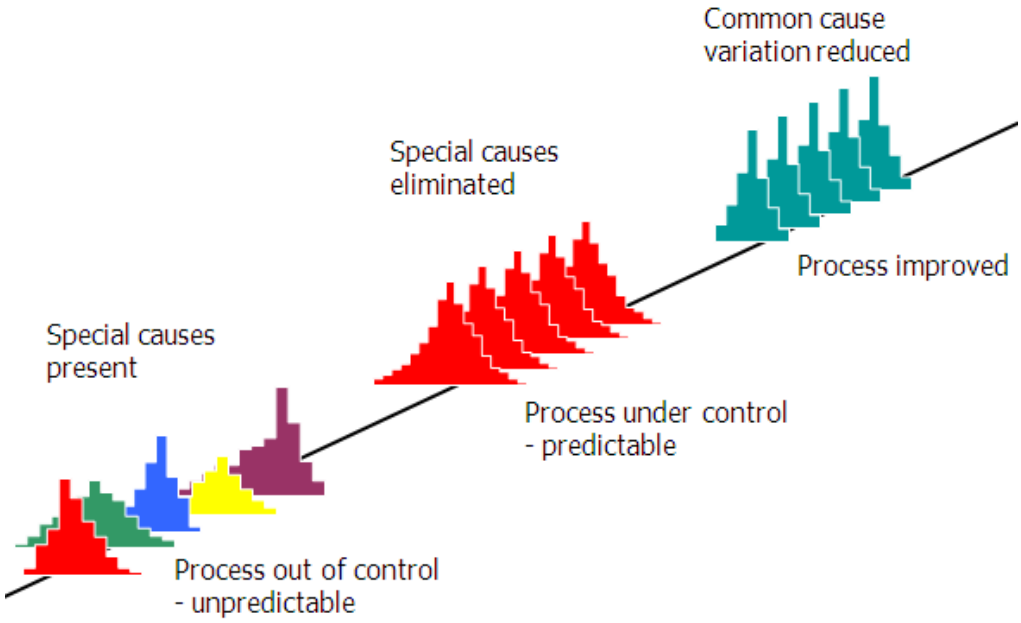
Project Roadmap (from the Aventis Project, 2004)



Managing Variation – Basics (1)



Managing Variation – Basics (2)



Managing Variation (3)

Desired State of a Manufacturing Process

- All sources of variation are defined and controlled, and end product variation is minimal
- Critical product attributes are controlled to target for all individual product units

The process should be designed to manage variation

- We cannot validate a process that was not designed in the first place

Quality Risk Management is the Act or Practice of controlling Risk

- A potential future event or condition, that results in a deviation from the expected or planned
  - It is likely, but not certain to happen – probability is > 0% and < 100%
- In process design, Quality Risk Management methodology is applied on each step
  - Information and learning is fed-back and fed-forward between all steps

What are meaningful Measurements

- Process performance:
  - Multivariate, statistically, controlled, 'real-time'
- Product quality:
  - Inferential, univariate, measurement

Intrinsic Performance Assessment

- Process assessments and control systems are integral to the process
- In-, on-, at-line process analytical tools are used for rapid measurements which can be used to evaluate material attributes and process performance and enable process control (Intrinsic Performance Measurements)
- Conventional approaches rely on separation of the 'process' from the 'process output assessment' (by sampling, averaging)
  - Testing a representative (?!) sample in a remote lab

Data and Experimental Design

- Experimental design tools are used to collect data throughout the design space
- Multivariate tools are used to generate values for
  - the critical quality attributes
  - factors linked to process condition
- Process Models are descriptive, predictive, or controlling

Manufacturing Process Design Options

- Material transitions:
  Unit-to-unit consistent quality will be achieved only if all material transitions are the same for all product units
- Scale:
  Processes should be designed for scaleability or scale-independent
  In continuous processing, scale is a function of time rather than a function of volume

Process Control

- Process Control is based on feedback / feed-forward loops
- Process endpoints are based on achieving desired critical quality attributes

Continuous Improvement

- An iterative process of design improvement
- Measured vs. 'process fitness' indicators, e.g.
  - Product characteristics
  - Process characteristics
  - Performance of process systems or system components
  - Economical parameters

Continuous improvement is often misunderstood as reaction to failure or deviations only

FDA: Process Validation Stages

- Process Design
  - Based on knowledge gained through development and scale-up activities
- Process Qualification
  - Process design is confirmed as being capable of reproducible commercial manufacturing
- Continued Process Verification
  - Ongoing assurance is gained during routine production that the process remains in a state of control

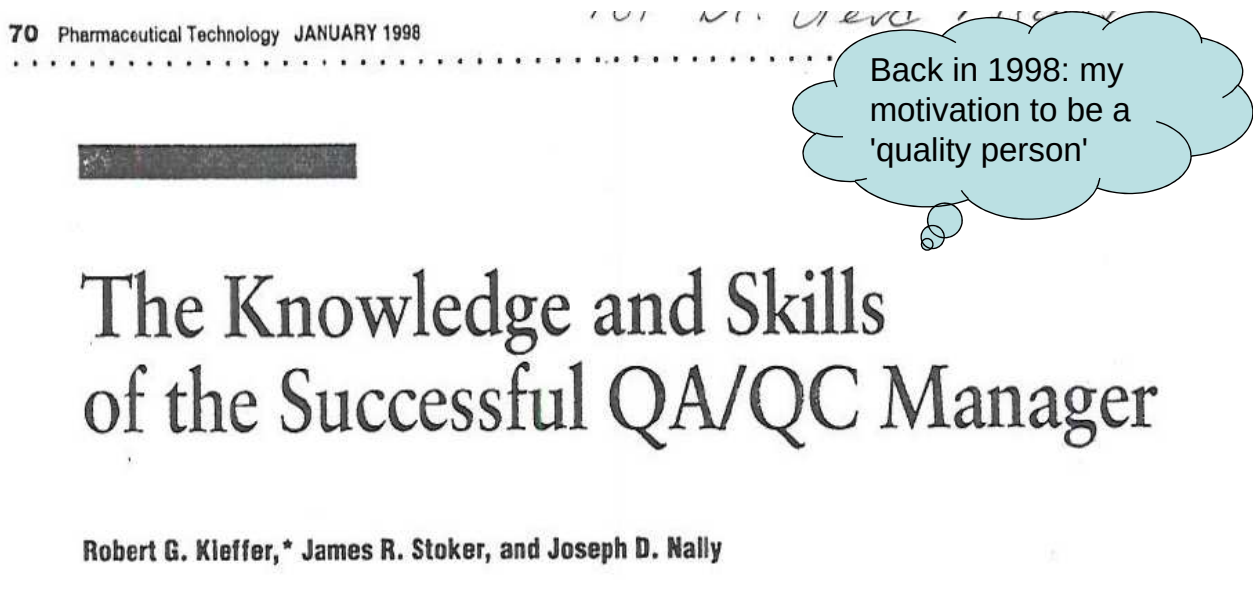
Reality Check: Control Strategy and Process Validation

I - Process Design
- Definition of commercial manufacturing process
- Establish a strategy for process control
- Develop and capture process knowledge and understanding

II - Process Qualification
- Evaluate process capability in commercial scale
- Assurance of adequate Facility Design, utilities and equipment qualification
- Process Performance Qualification (PPQ)

III - Continued Process Verification
- Continued assurance that process remains in a state of control
- Statistics-based continuous process monitoring
- Improvement and optimization of the process

"People" – The Key Factor for Quality


70 Pharmaceutical Technology JANUARY 1998

Back in 1998: my motivation to be a 'quality person'

The Knowledge and Skills of the Successful QA/QC Manager

Robert G. Kieffer,* James R. Stoker, and Joseph D. Nally

The Quality Assurance Activity Profile

- Taking proactive approaches and being co-located in manufacturing area
- Studying and building knowledge of key process parameters
- Correlating data with physics, physical chemistry and pharmaceutical formulation of the product
- Evaluating of process capability and process variability
- Studying / ensuring correlation of raw materials manufacturing processes with product manufacturing process
- Product and process improvement facilitation
- Quality systems management

Summary, Outlook, or Conclusion

'Quality Culture' or commitment to quality is demonstrated by:

- Running an effective pharmaceutical quality system
- Having process knowledge and controlled processes
- Making decisions with user / patient in mind
- Senior management presence to strengthen importance of quality compared with cost drivers
- Proactivity in maintaining products and processes 'on target' – trusting that investments in quality pay for themselves
- Seeking excellence in quality risk management

Summary, Outlook, or Conclusion

Will we overcome limitations to QbD ?

- *"It works for simple systems, not for complex systems"*
  - *fill/finish, formulation, separation process, etc., vs. catalytic processes, API physicochemistry, etc.*
- *"Add-on to conventional approaches"*
  - *Controllability does not need predictability*
  - *Validation can be based on x batches*
  - *Bio is just too complex: variability +- 30%, functional raw material testing, viral contamination, no validation on full scale, component validation (e.g. membrane fltration validated by supplier)*

Take-Home Slide

The 'State of Control' is 'a must have'. It means:

- Process performance is on target and ensures unit-for-unit consistent product quality
- "Cost of failure" is minimal through Continuous Improvement
- "Cost of detection" (inspection, review, etc.)
is well balanced and founded on process understanding and process design for quality
- "Cost of prevention" (QA systems, supplier relationships, training, etc.) is minimal and safeguarded by quality risk management