

Shire's Strategic Decision to Implement QbD for all Drug Development and Manufacturing

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Biopharmaceutical Process and Quality Consortium
University of Massachusetts, Lowell
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Our purpose

We enable people with life-altering conditions to lead better lives

Shire's Strategic Decision to Implement QbD for all Drug Development and Manufacturing

Abstract

Shire is embarking on a comprehensive implementation of QbD principles in biopharmaceutical drug development and manufacturing. An overview of the approach that Shire is taking will be presented including an outline of new business processes and the use of quality risk management (QRM) to arrive at an integrated control strategy. This strategy will be applied to both pipeline and legacy processes to better support life-cycle management while providing a high degree of assurance that the product quality specifications are met. Initial objectives, considerations, and challenges to design and implementation will also be discussed.

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Shire's Strategic Decision to Implement QbD for all Drug Development and Manufacturing

Outline

- Biopharm paradox
- Factors for consideration
- Strategy and approach
- QbD Work Flow and Lifecycle Management
- Integrated Control Strategy



The Biopharmaceutical Paradox!!

Speed to Market

***Manufacturing Process
Performance /
Robustness***

Speed to Market

- First to market reward
- Market share
- Lower investment risks
- Investor relations
- Limited resources

VS.

Process Robustness

- Thorough product and process understanding
- Design space definition
- Less implementation risk
- Lower cost and failure rate
- Lower compliance risk



Shire's Lexington Facility: Biopharmaceuticals Manufacturing for Rare Diseases

- Three biological products approved. Legacy processes (developed before QbD)
 - *Hunter's Syndrome*
 - *Fabry's Disease*
 - *Gaucher's Disease*
- Several products in pipeline
- Some from in-house innovation
- Some from acquisition
 - Typically at earlier stages of development
- Internal manufacturing and CMO-sourced production

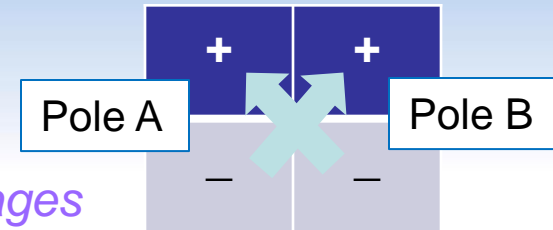


400 Shire Way, Lexington. Green-field project. Construction completed in 2010



Dilemma Management!!

Requires monitoring of leading indicators



Advantages

- Market Capture
- Potential exclusivity
- Earlier proof of concept
- Lower-risk back-end expenditures

Advantages

- Well understood process with less upsets or deviations
- Smoother tech transfer
- More complete filing and better chance of approval
- Ability to meet product demand

SPEED TO MARKET

STABLE PROCESS

Disadvantages (imbalance Indicators)

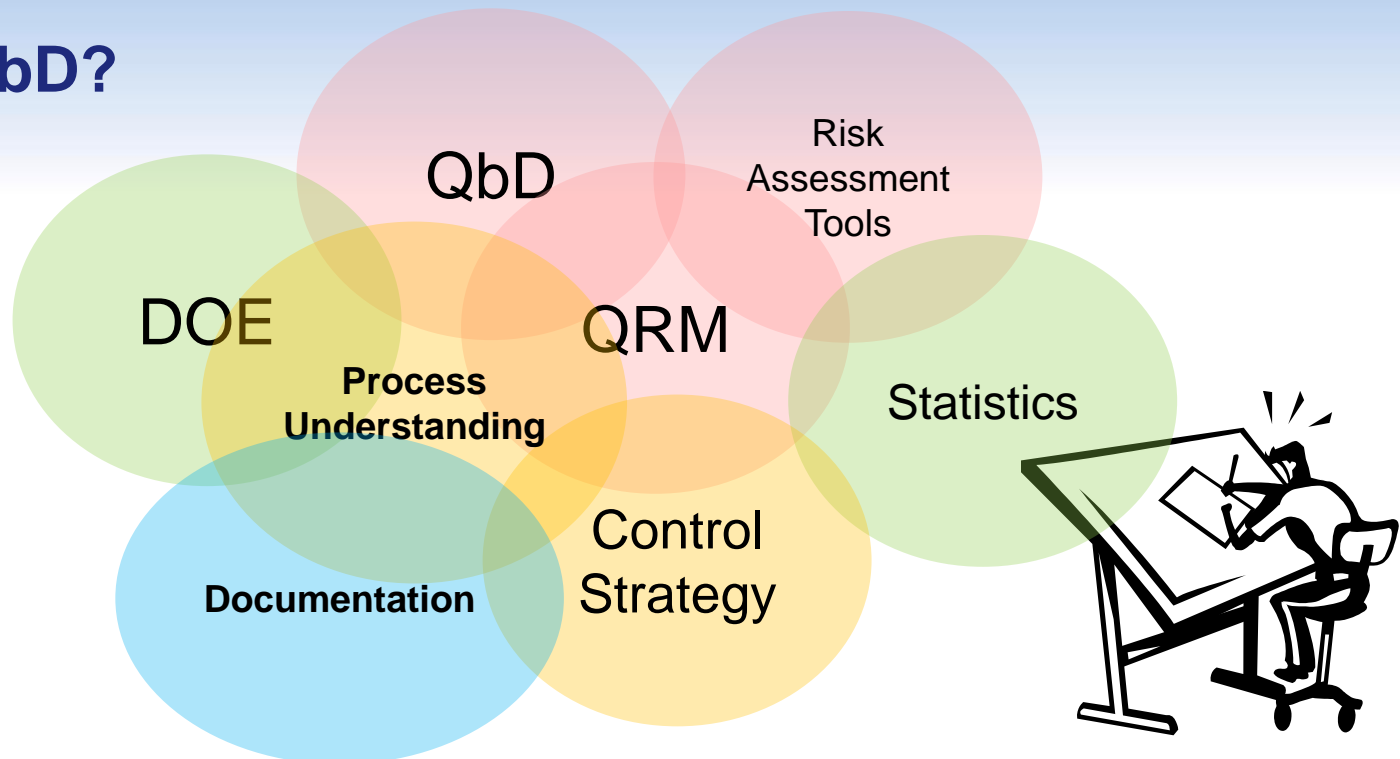
- Process failures, deviations and investigations
- Variability in product quality
- Resource drain on operations and quality personnel
- Filing rejections or delays
- Regulatory inspection observations

Disadvantages (imbalance Indicators)

- High up-front expenditures
- High resource loads
- Program delays
- Loss of market advantage

Know what you don't know!!!

What is QbD?



An approach to rational design. “Building in quality from the development phase and throughout a product’s life cycle” “Designing and developing a product and associated manufacturing processes that will be used during product development to ensure that the product consistently attains a predefined quality at the end of the manufacturing process.”

Guidance for Industry, Quality Systems Approach to Pharmaceutical CGMP Regulations ; U.S. Department of Health and Human Services, Food and Drug Administration, September 2006

Quality by Design (QbD): [ICH Q8 (R2) Definition]

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE. This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

QbD and Product / Process Lifecycle – Guiding Principles

FDA: Guidance for Industry, Quality Systems Approach to Pharmaceutical CGMP Regulations. U.S. Department of Health and Human Services, Food and Drug Administration, September 2006

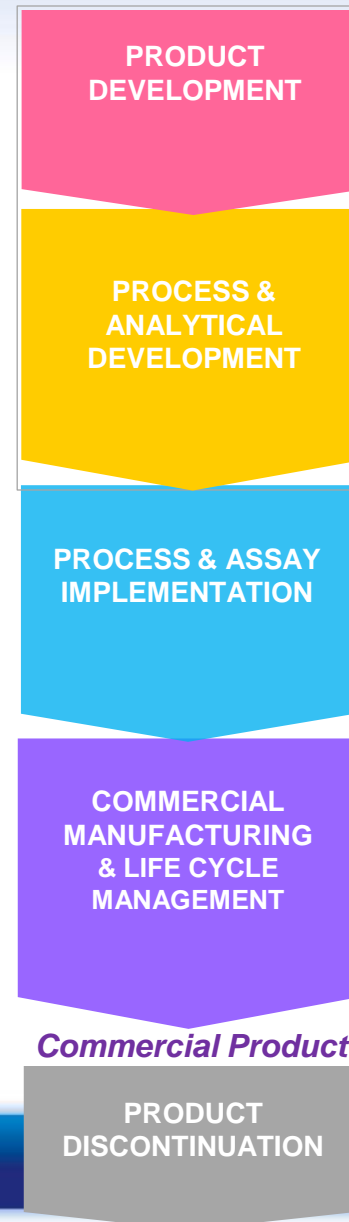
- “QbD is an approach to rational design”; “Building in quality from the development phase and throughout a product’s life cycle”
- “Designing and developing a product and associated manufacturing processes that will be used during product development to ensure that the product consistently attains a predefined quality at the end of the manufacturing process.”
- “The overarching philosophy articulated in both the CGMP regulations and in robust modern quality systems is: Quality should be built into the product, and testing alone cannot be relied on to ensure product quality.....”
- “QbD in conjunction with a quality system, provides a sound framework for the transfer of product knowledge and process understanding from drug development to the commercial manufacturing processes and for post-development changes and optimization.”
- “The CGMP regulations, when viewed in their entirety, incorporate the concept of quality by design.” (i.e. controlling all the critical inputs to a manufacturing enterprise)

ICH Q8 (R2)

- QbD “is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding, based on sound science and quality risk management.”

PDA Technical Report #56

- The goal of pharmaceutical process development is to design, develop and characterize a manufacturing process that can be transferred to a commercial environment and yield a quality product on a consistent basis



PDA Technical Report #60

- Lifecycle approach to Process Validation.....



Stage 1
Process Validation:
Process Design

Stage 2
Process Validation:
Process Performance Qualification

Stage 3
Process Validation:
Continued Process Verification

Strategic Direction

Objectives and Benefits

Mission: *Adopt Quality-by-design principles and methods that are business-appropriate for Shire biopharmaceutical process development, design, technology transfer and implementation.*

Objectives:

- *Define and establish Shire-appropriate QbD approach*
- *Clarify business process for QbD-based development and tech transfer to improve consistency of approach*
- *Standardize documentation to promote consistency between PD project teams and functions*
- *Provide means of demonstrating and documenting product and process knowledge and understanding*
- *Standardize risk assessment methods*
- *Address regulatory expectations*
- *Embrace risk management practices*
- *Extent of QbD filing? (out of scope currently – future work)*

QbD Lifecycle Approach

Organizational Commitment to Systematic Approach throughout Product Development and Commercialization

PRODUCT DEVELOPMENT:

- Key focus on product's critical quality attributes (CQA) as the primary process performance target.
- Use of structure / function and pre-formulation studies for rational development
- Use of advanced high-throughput analytical methods

PROCESS & ANALYTICAL DEVELOPEMNT:

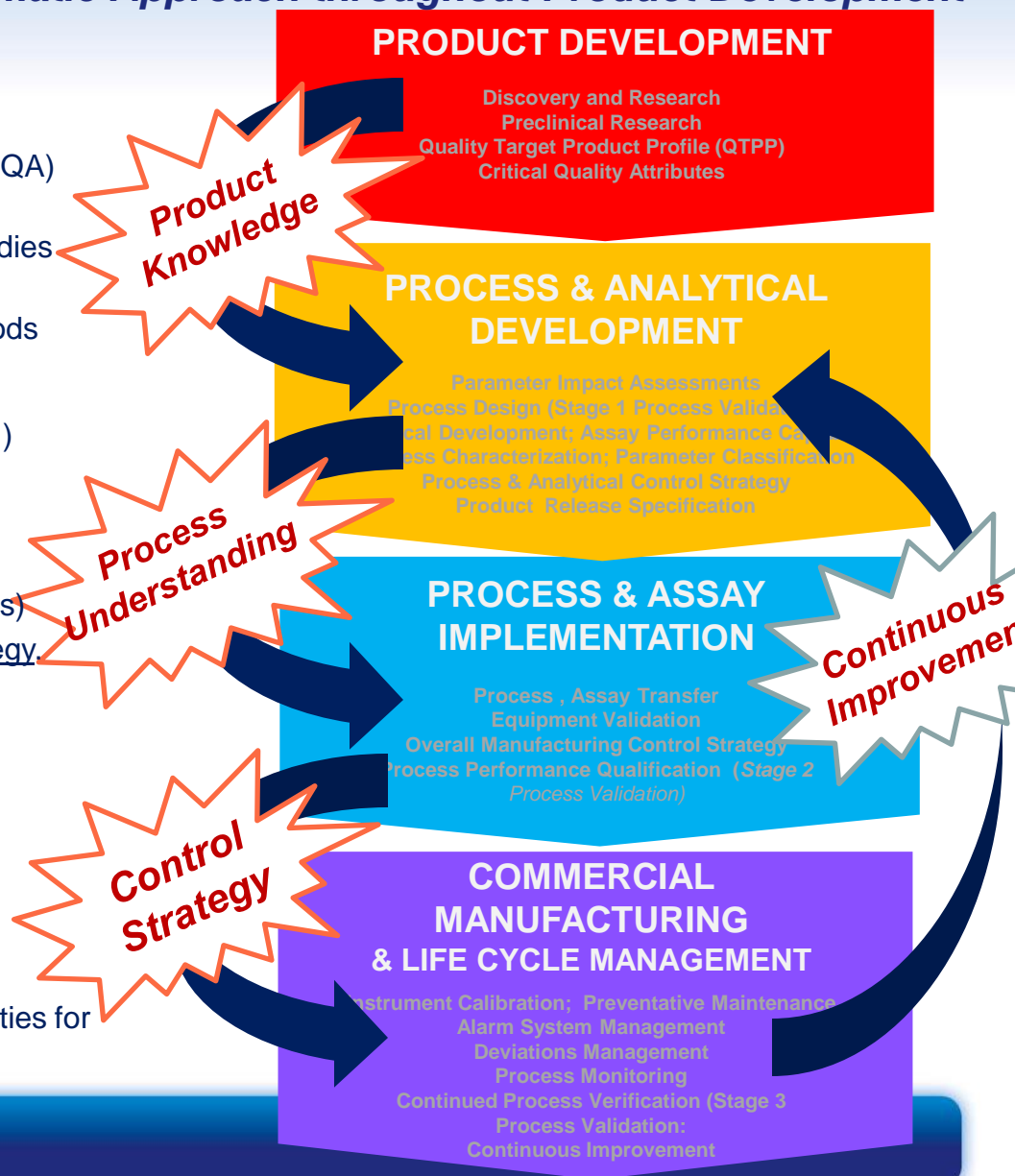
- Well documented use of risk assessments (QRM!!)
- Use of qualified Scale-down models
- Design of Experiments (DOE) and statistical data analysis
- Identification of Critical Process Parameters (CPPs)
- Process understanding used to build control strategy.

PROCESS & ASSAY IMPLEMENTATION:

- Technology Transfer and
- Integration of process-specific controls and Manufacturing and Quality Systems to create comprehensive control strategy.

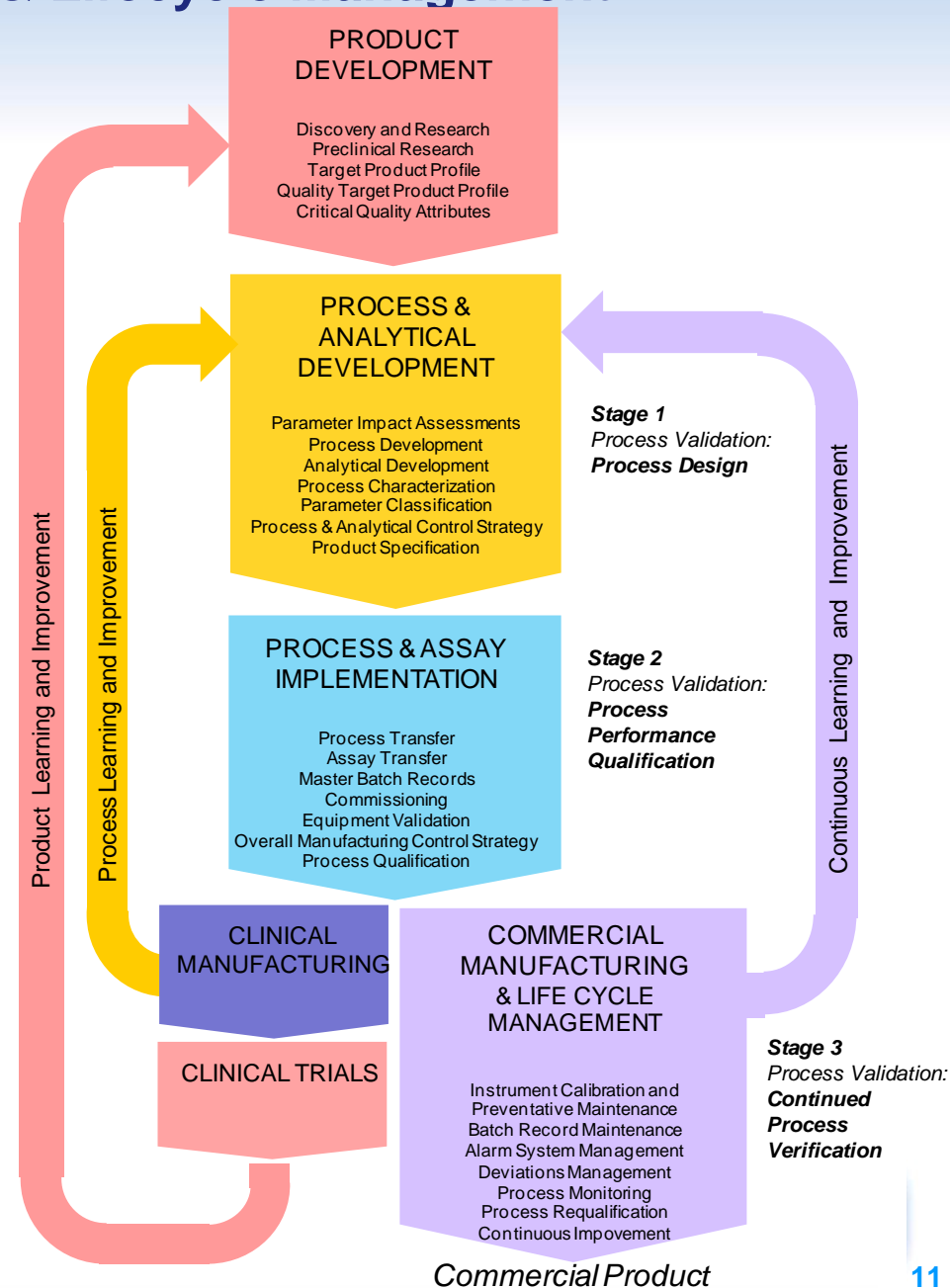
CLINICAL /COMMERCIAL MANUFACTURING:

- Continuous monitoring and process verification
- Identification of performance trends and opportunities for improvement.



Product / Process Development & Lifecycle Management is an Iterative Process!

- The development work flow is iterative by virtue of the phases of clinical development through human trials. Phase appropriateness.
- Clinical data feed back into product development and ultimate definition of product's design space
- Knowledge gained from clinical manufacturing of the clinical lots can be leveraged for subsequent rounds of process development.
- As the development progresses, the total quality risk is reduced until acceptable for commercial licensure and manufacturing.
- Continuous process monitoring and verification enables process improvement over time.



Business Process Design for Product / Process Development & Lifecycle Management

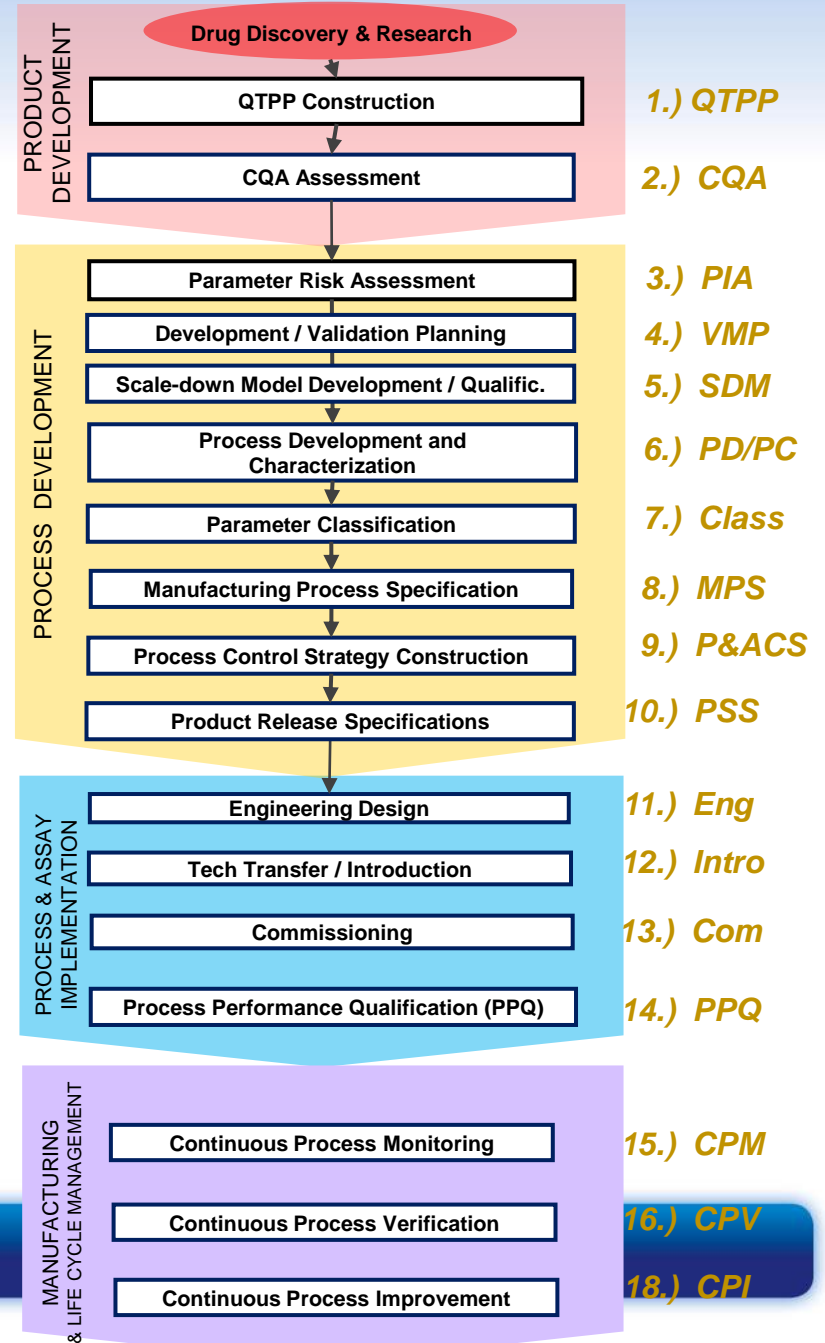
QbD Work Flow Design / Guidance:

- Product and process development work flow definition
- Creation of guidance documents for each step in the work flow
- Design of tools and templates
- Construction of process-specific portion of control strategy

Integrated Control Strategy:

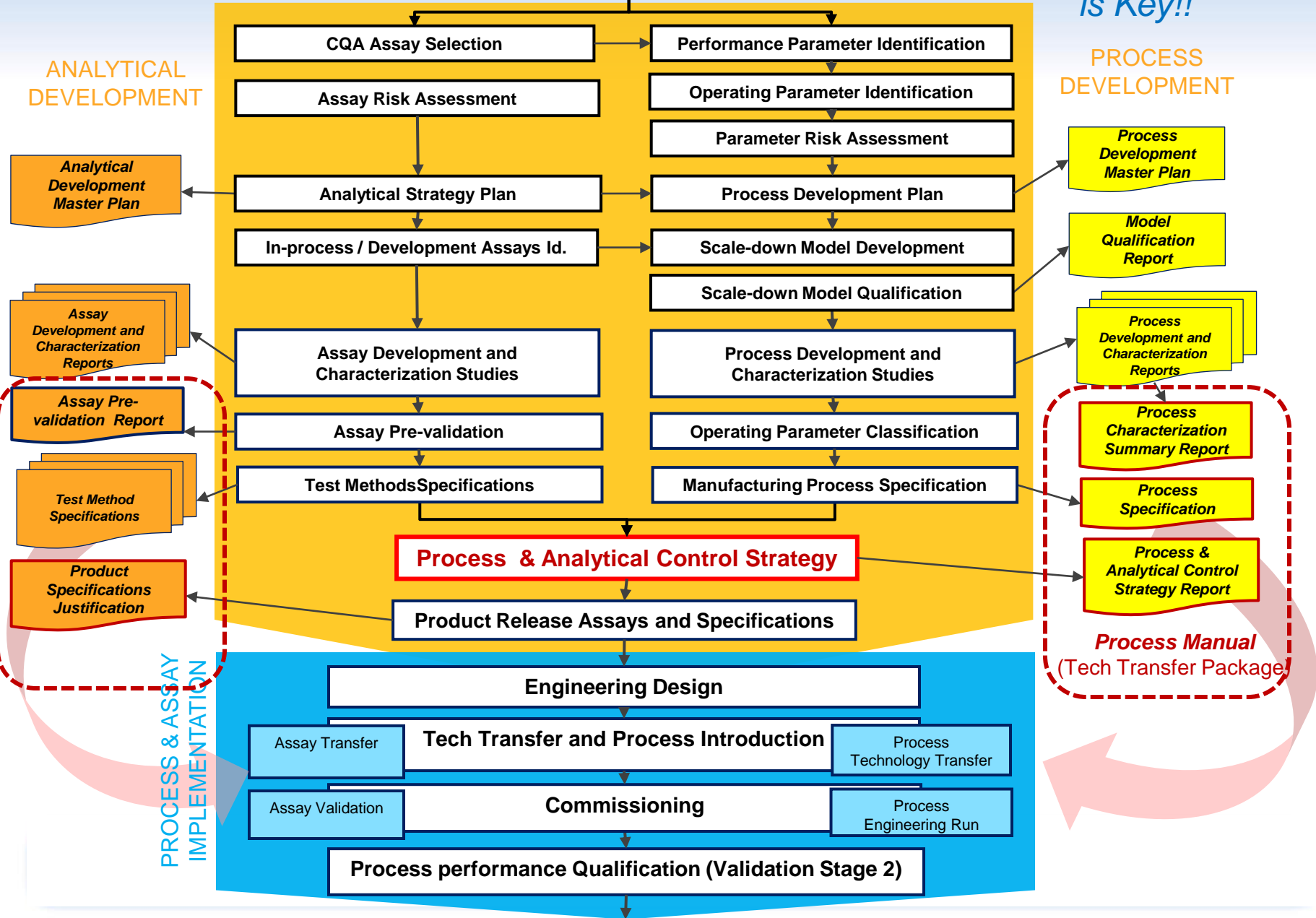
- Extension of QbD work flow into engineering design and cGMP manufacturing.
- Cross-functional integration of control elements and systems involved in direct control of product quality

Simplified Work Flow (and Abbreviations)



Knowledge Transfer with Standardized Documents

Documentation is Key!!



What is a “Control Strategy”

- **ICH Q10 Control Strategy Definition:** ‘a planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include:
 - parameters and attributes related to:
 - drug substance
 - drug product materials
 - components
 - facility and equipment operating conditions,
 - in-process controls,
 - finished product specifications, and the associated methods and
 - frequency of monitoring and control.’
- **A-Mab Definition:** “The Control Strategy for A-Mab integrates:
 - input material controls,
 - procedural controls,
 - process parameter controls,
 - in-process testing, release testing, characterization and/or comparability testing and
 - process monitoring..... to provide a high degree of assurance that the product quality specifications are met.”

Segregation of Control Elements: Process-specific vs. General

ICH Q10 'Control Strategy' Definition:

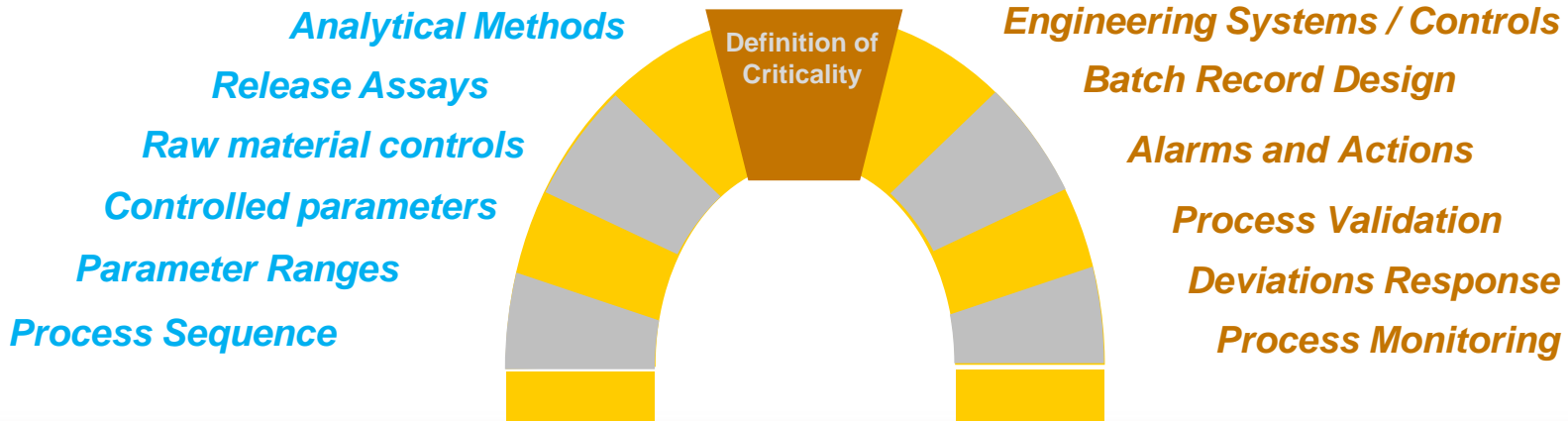
- ← Parameters and attributes related to:
 - drug substance, drug product materials, components
- ← facility and equipment operating conditions, →
- ← in-process controls, →
- ← finished product specifications, and the associated methods and frequency of monitoring and control.' →

A-Mab 'Control Strategy' Definition

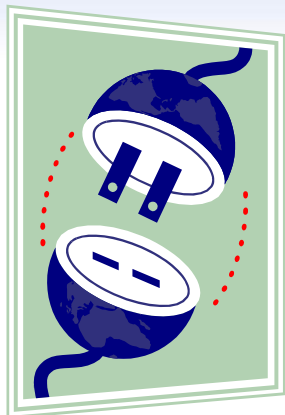
- ← material controls, procedural controls, process parameter controls, in- →
- ← process testing, release testing, characterization and/or comparability
- ← testing and process monitoring →

Process-specific Control Elements

General Control Elements



Process –specific and General Elements fit together to form Overall Control Strategy



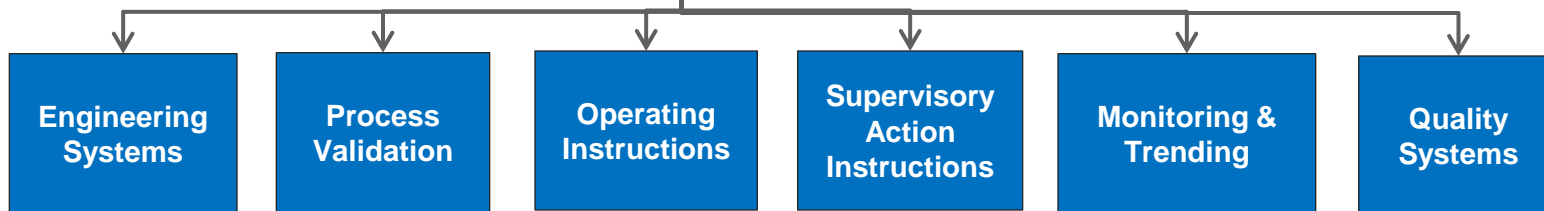
Overall Control Strategy



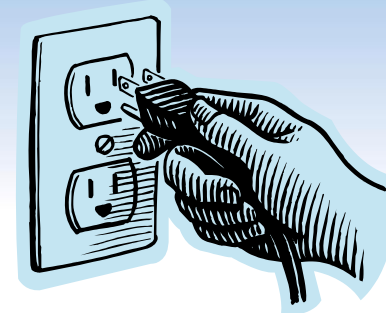
A control strategy can include, but is not limited to, the following: (ICH Q10)

- Control of input material attributes (e.g., drug substance, excipients, primary packaging materials) based on an understanding of their impact on processability or product quality;
- Product specification(s);
- Controls for unit operations that have an impact on downstream processing or product quality
- In-process or real-time release testing in lieu of end-product testing (e.g. measurement and control of CQAs during processing);
- A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.

System of controls that work together to provide a high degree of assurance that the product quality specifications are met.

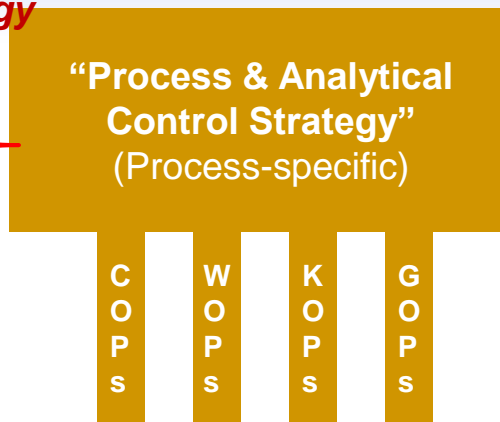


Criticality is 'Key' to Translation of Process into Manufacturing Control Strategy



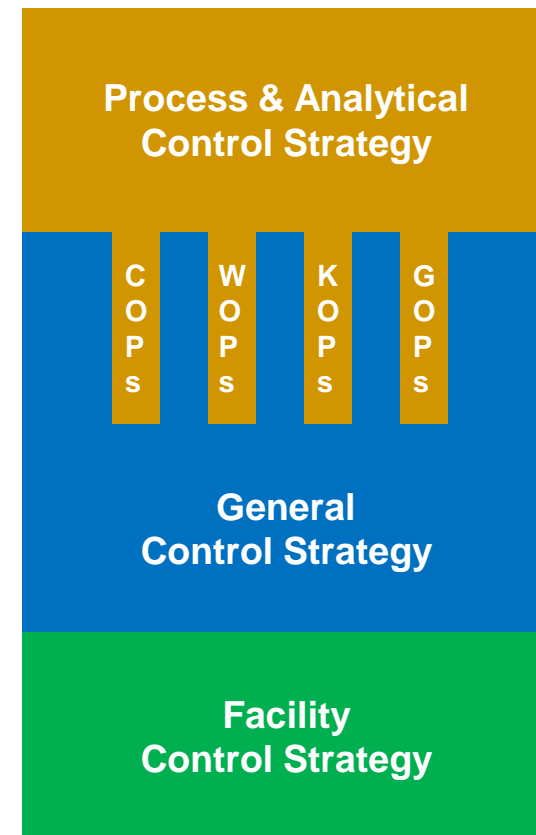
Process & Analytical Control Strategy (Process-specific)

- Critical and Non-critical Process Parameters
- Well-controlled parameters?
- Critical and Non-critical Raw Materials
- Critical and Non-critical Components and Containers



Generalized Process Control Elements Related to Parameter Criticality, Non-product Specific, Direct Product Quality Influence)

- Engineering Systems / Controls
- Batch Record Design
- Alarms and Actions
- Process Validation
- Process Monitoring
- Deviations Response

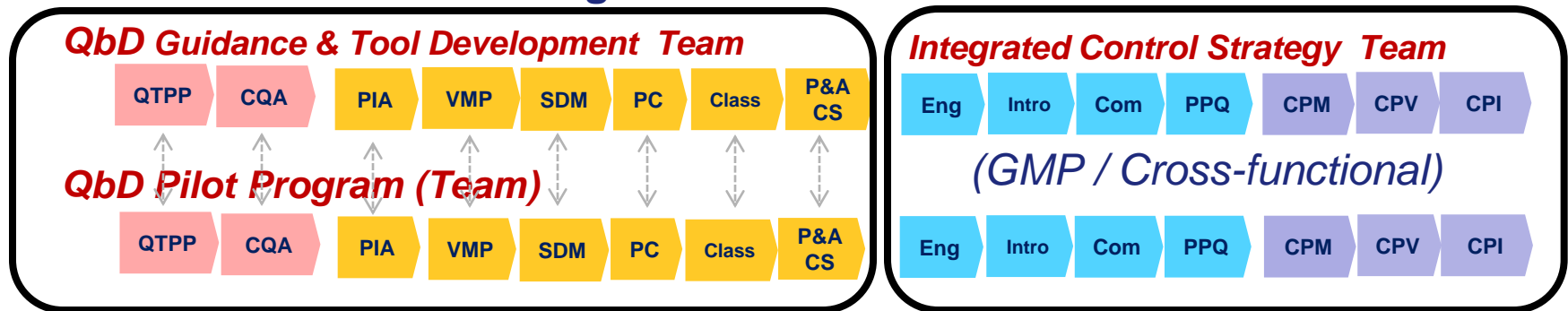


QbD Deployment Strategy

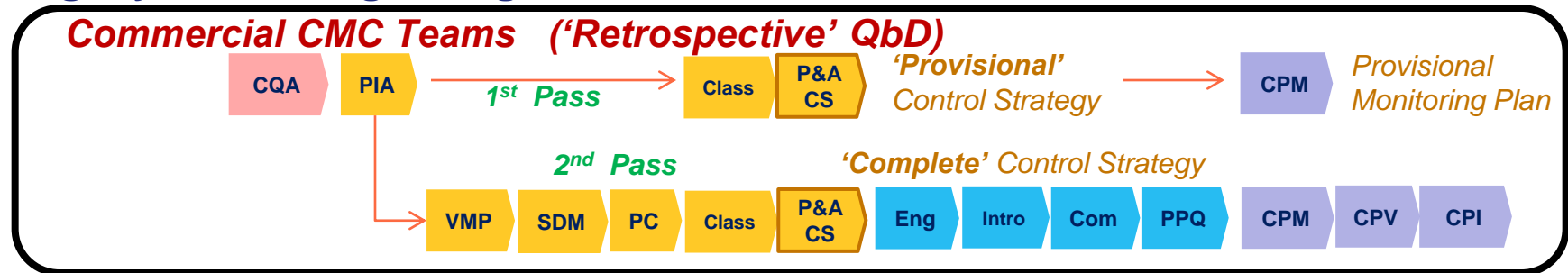
Major Phases and Steps in QbD Work flow / Lifecycle



QbD Business Process Design



Legacy / Late-stage Programs:



New / Early-stage Programs:



QbD Deployment Teams and Objectives

Major Phases and Steps in QbD Work flow / Lifecycle



QbD Business Process Design

QbD Guidance & Tool Development Team

Guidance: Develop templates and guidance around concepts, definitions of terms, methods, and work flow

Process Controls: Develop control strategy for control elements that have a direct impact on product quality and process performance and are product/process specific.

Real Example: Work through a specific and current project-relevant example to verify function and user-friendliness of the tools and guidances.

Support: Help guide other programs through QbD work flow

Training: Provide training if necessary

Integrated Control Strategy Team

Control System: To build a system of controls that work together to provide a high degree of assurance that the product quality specifications are met.

Definitions: Establish definitions for parameter ranges and criticality classes

Higher-level System: Use cross-functional expertise to set high-level structure to Manufacturing, Engineering and Quality systems that serve as control elements directly affecting product quality and process performance.

Legacy / Late-stage and New / Early-stage Programs:

Development and Commercial CMC Teams

Work Flow: Follow QbD business process

Risk Assessments: Conduct formal risk assessments and document throughout the process development lifecycle

Design Space: Define process design space through appropriate planning and design of experiments

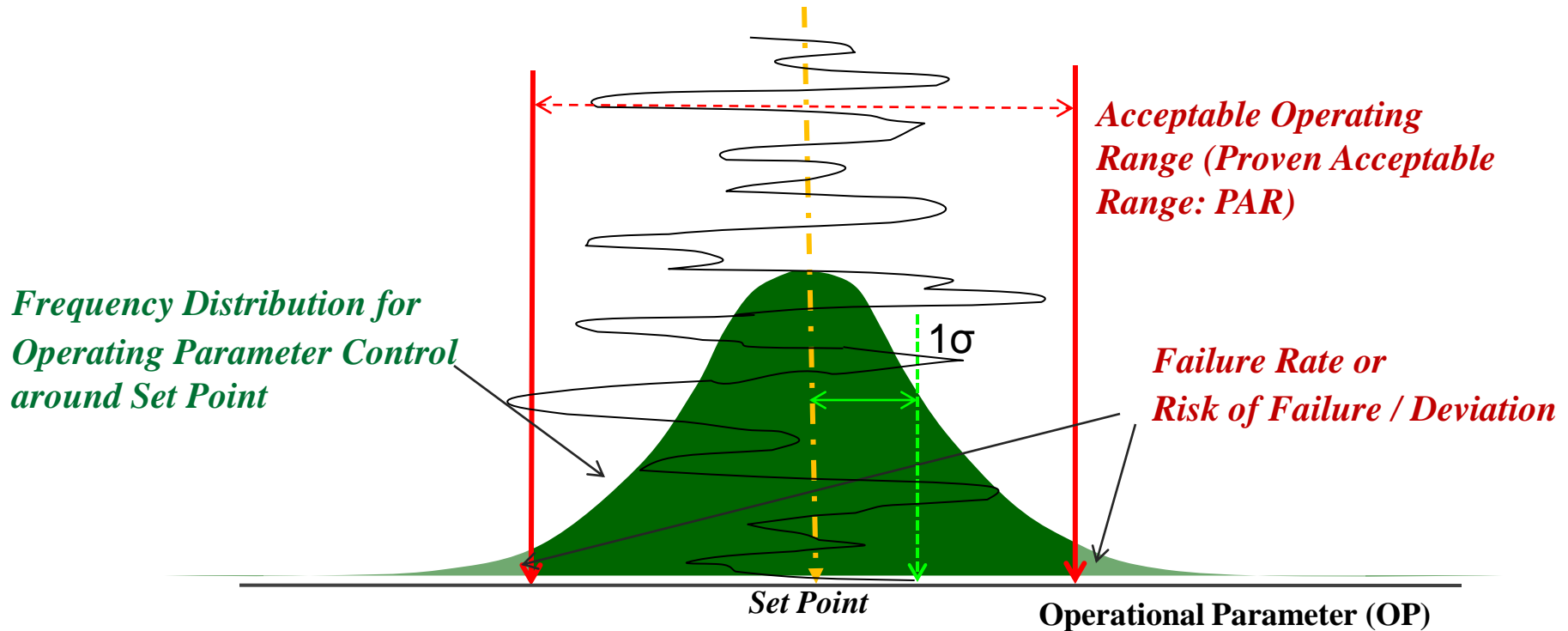
Documentation: Generate standardized documents to capture product and process understanding

Monitor: Support and improve processes throughout lifecycle

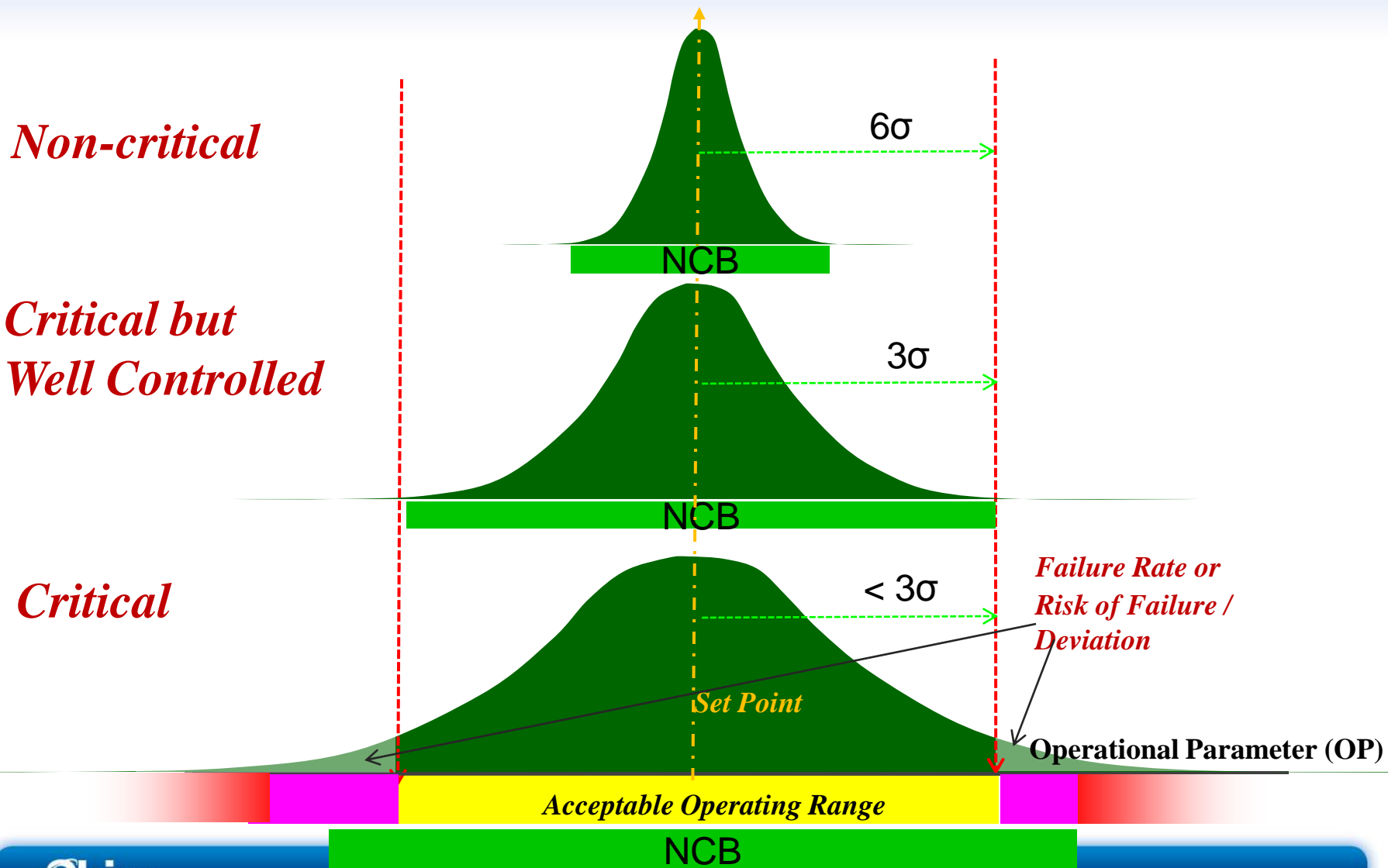
Feedback: Provide feedback on business process and Guidelines

Operating Parameter Criticality is a function of both.....

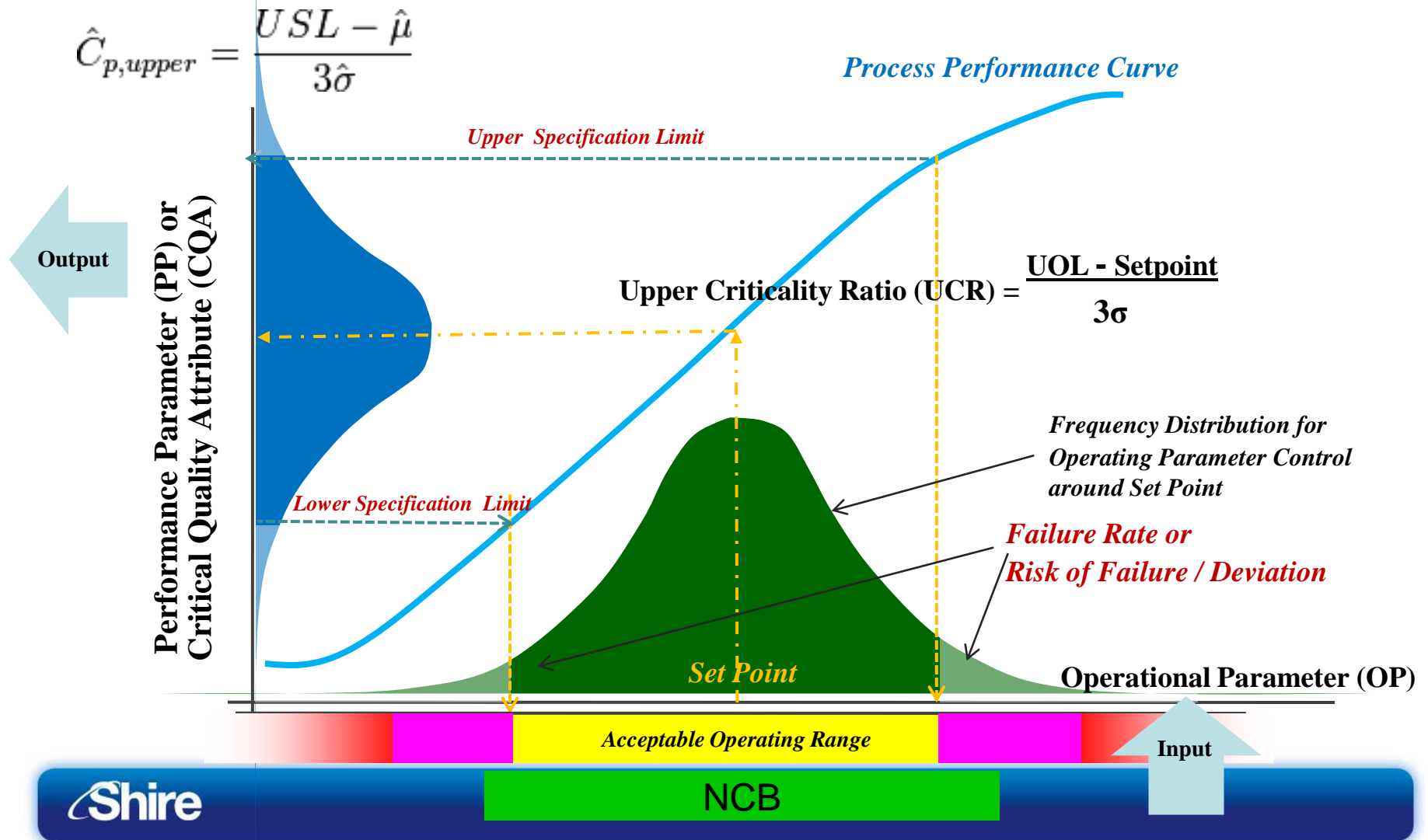
- The accuracy to which a performance parameter needs to be controlled (i.e. Acceptable Operating Range)
- The accuracy and precision that an operating parameter can practically be controlled (i.e. true equipment capability)



Criticality Ratio Could be used for Parameter Classification



Operating Parameter *Criticality Ratio* is analogous to Process (Performance) Capability Index (Cp)!



Parameter Criticality Heat Map!

Risk Analysis and Mitigation Matrix (RAMM) – A Risk Tool for Quality Management

by Chris Watts, Alex Brindle, Steve Davy, and David Tiffany. Pharmaceutical Engineering, January/February 2012, vol. 32, no. 1.

under control and well understood. The RAMM was updated accordingly to demonstrate that risk has been reduced changing the risk scores and providing a simple signal that risk had changed from reds and yellows to greens. This can be seen

first time with a team that has some knowledge of the process. This time can be significantly reduced for subsequent products especially if process steps and products are somewhat similar.

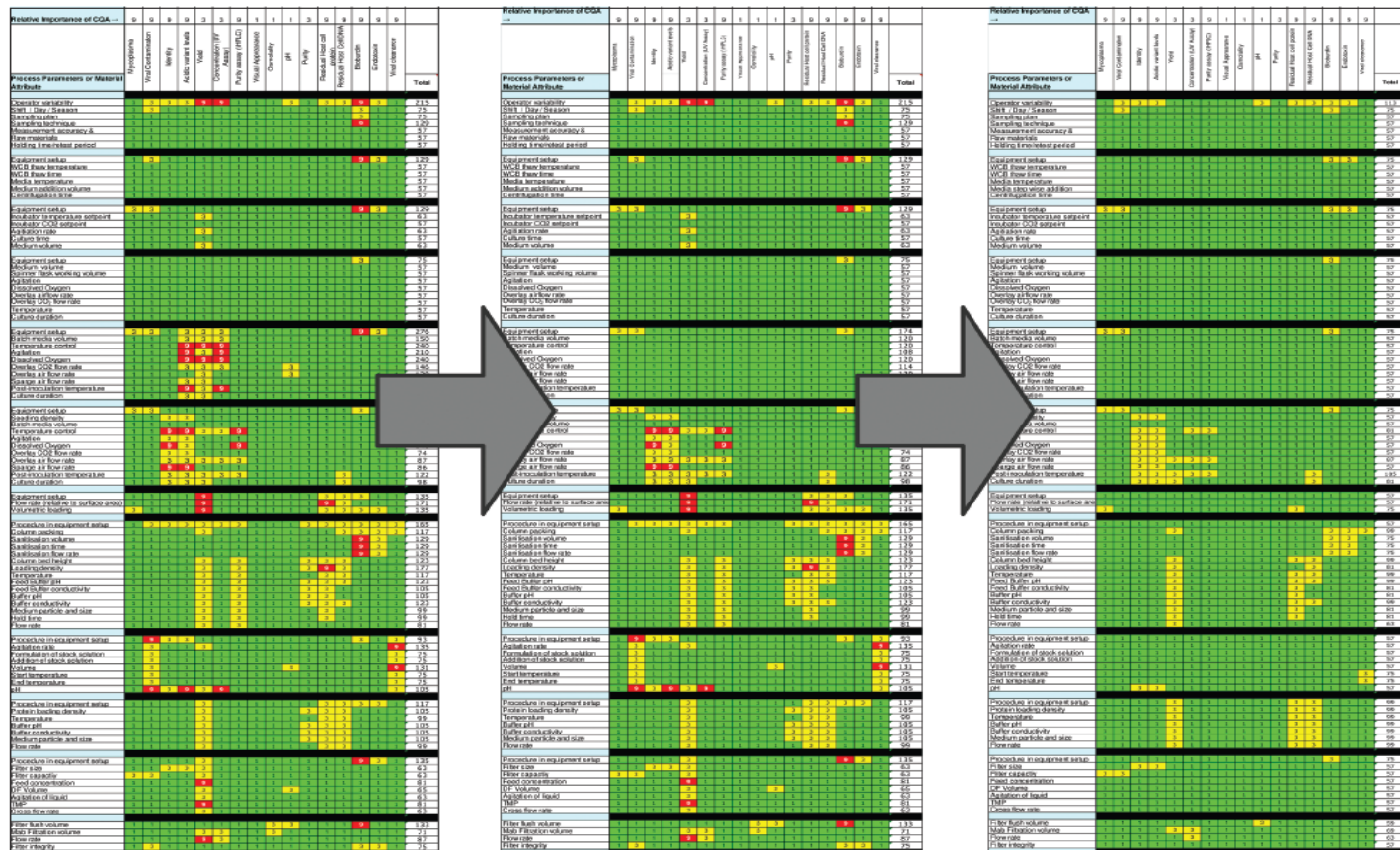
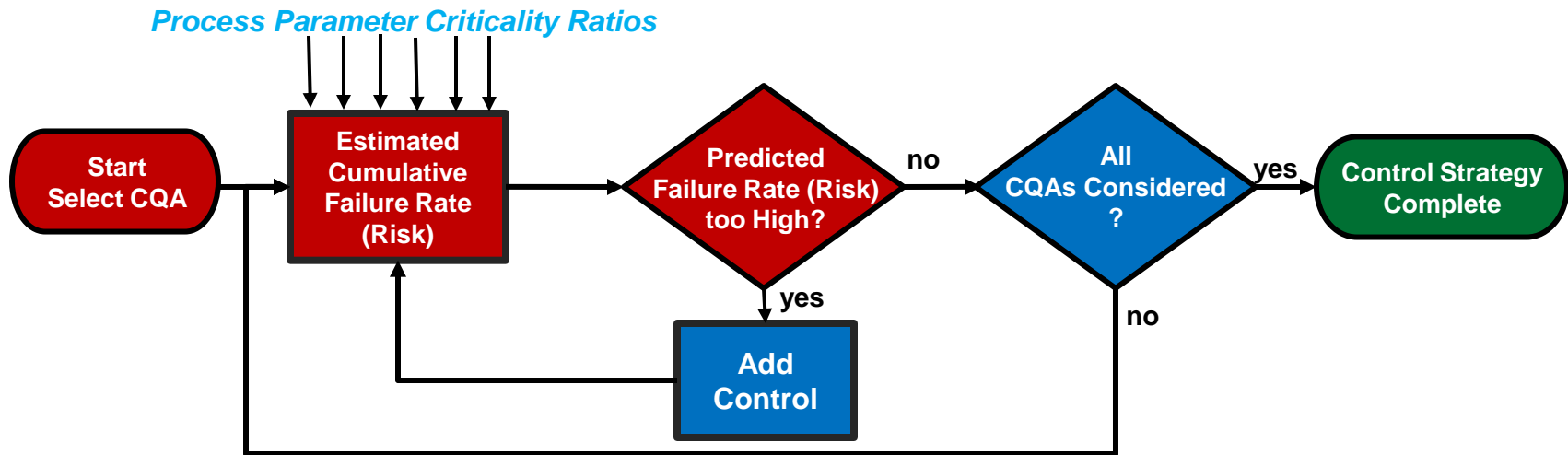


Figure 6. Impact of mitigation actions on total process and material risks. Mitigation actions change the risk flags from red to yellow or green.

Critical Steps / Parameters may Require Additional Controls to Maintain all CQAs within Specifications....

- **Construction of Risk-based Control (A-Mab)**

- The level of control for each individual quality attribute is determined on the basis of the criticality level of the attribute and a risk assessment of the capability of the process to consistently deliver product that meets the acceptance criteria for each attribute.
- Based on this risk assessment results, a rational control strategy is formulated for each quality attribute by choosing the appropriate control elements. Thus it is the sum of the individual control strategies that represent the overall strategy
- Level of testing and controls is commensurate with risk. Risk is determined by the Criticality Level of the CQA, the process capability (or probability that a CQA would fail at a given step) and the probability of detection of a CQA failure. cess control strategy for A-Mab.



'Overall' Control Strategy Design

.... a Multi-layered System Objective is to drive bulk of control to lower tiers

Quality Management Level

Enterprise policies, Change Control, Document Control

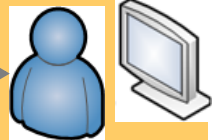
Quality Control Level

Release testing, Non-conformances, In-Process Controls



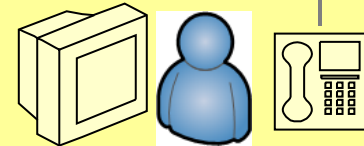
Supervisory Level

Performance Monitoring and Statistical Process Control



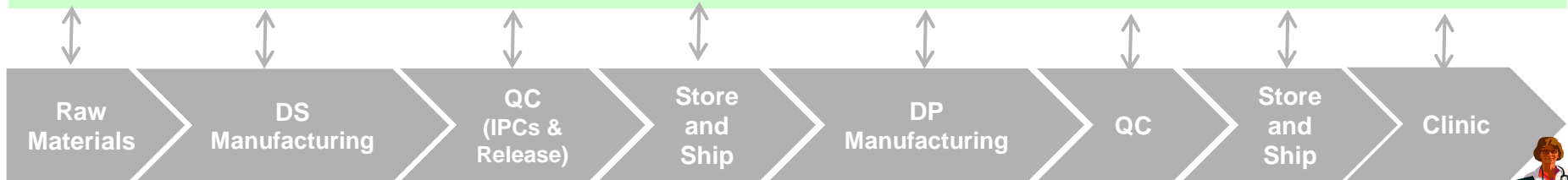
Operator Level

Batch records, Operator Alerts and Alarms



Controller Level

On-line Feedback Control, Direct Process Interface



PROCESS



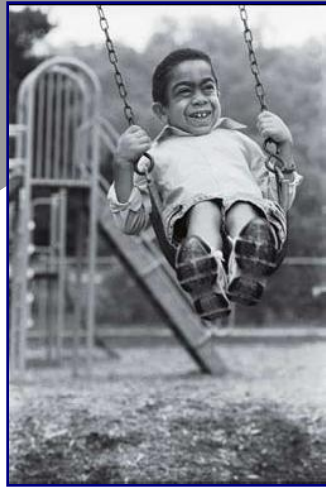
Deployment Strategy - Conclusions

- Requires critical mass of decision makers
- All functions involved
- Comprehensive strategy needed
- Requires top down coordination
- Control strategy is focal point, culmination of QbD work
- Common definitions and concepts critical
- Integrated control system requires bottom up design but is iterative
- Clear document hierarchy helpful



*the QbD
Czar!*





Shire

To be as brave as the people we help.

