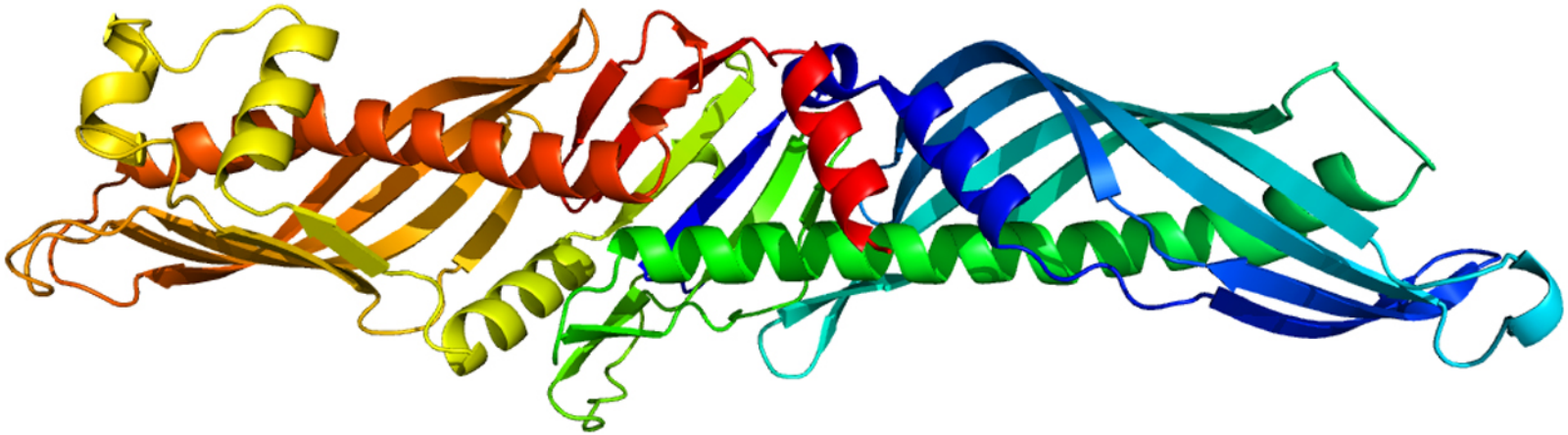
An Introduction to Quality by Design with Case Study

National Regulatory Conference 2015 (NRC 2015), Malaysia

Dr. Elisabeth Kirchisner, Roche



Outline

- What is Quality by Design (QbD) ?
- Implementation of QbD – Case Study for a monoclonal antibody
- Summary

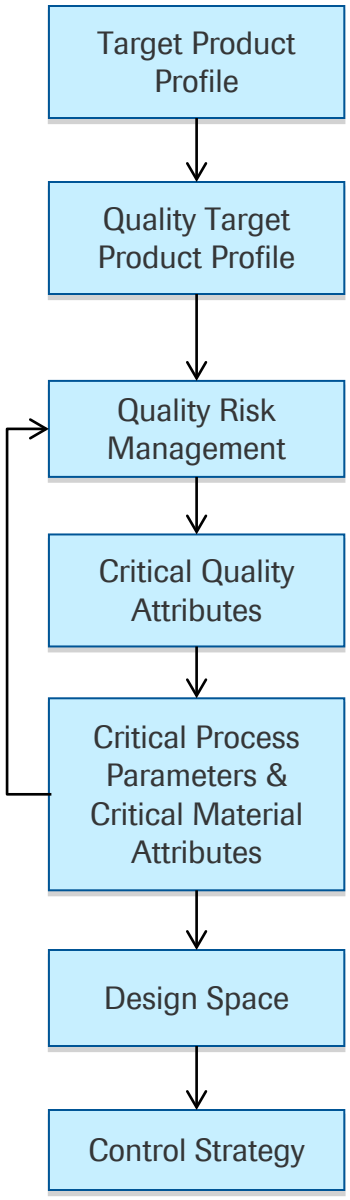
What is Quality by Design (QbD) ?

What is Quality by Design (QbD) ?

ICH Q8: 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

- Leverages knowledge of structure-function relationship to define product attributes that are important
- Uses science-based and risk-based approaches to define the commercial manufacturing process and the management of the post-approval lifecycle
- Aims at developing deeper product & process understanding throughout the lifecycle of a product
  - Ø Control system tailored to product requirements
  - Ø Process robustness enhanced
  - Ø Deviation and change assessments facilitated

QbD Approach – Beginning With the End in Mind



- **TPP** –The targeted commercial labeling claims
- **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.
- **QRM** – A systematic process of organizing information to support decision making based on identification of hazards and evaluation of risks management associated with those hazards.
- **(p)CQA** – A physical, chemical or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality (*(p) = potential*). **Considers the relevant Mechanisms of Action.**
- **(p)CPP, (p)CMA** – A process parameter or material 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 (*(p) = potential*).
- **DSp** – The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.
- **CS** – A planned set of controls, derived from current product and process understanding that ensures process performance and product quality.

Regulatory Considerations for Design Space

- **Movement within the design space is not considered as a change** (from a regulatory reporting point of view)
- **Movement out of the design space is considered to be a change** (requires regulatory reporting according to regional requirements)
- Control of all parameters including changes are managed in the Manufacturer's Quality System, regardless of whether they are reportable or require pre-approval

Roche's Design Space definition is currently the combination of all of the unit operations, their associated CPPs and non-CPPs described in the Module 3 Process Description

Implementation of QbD

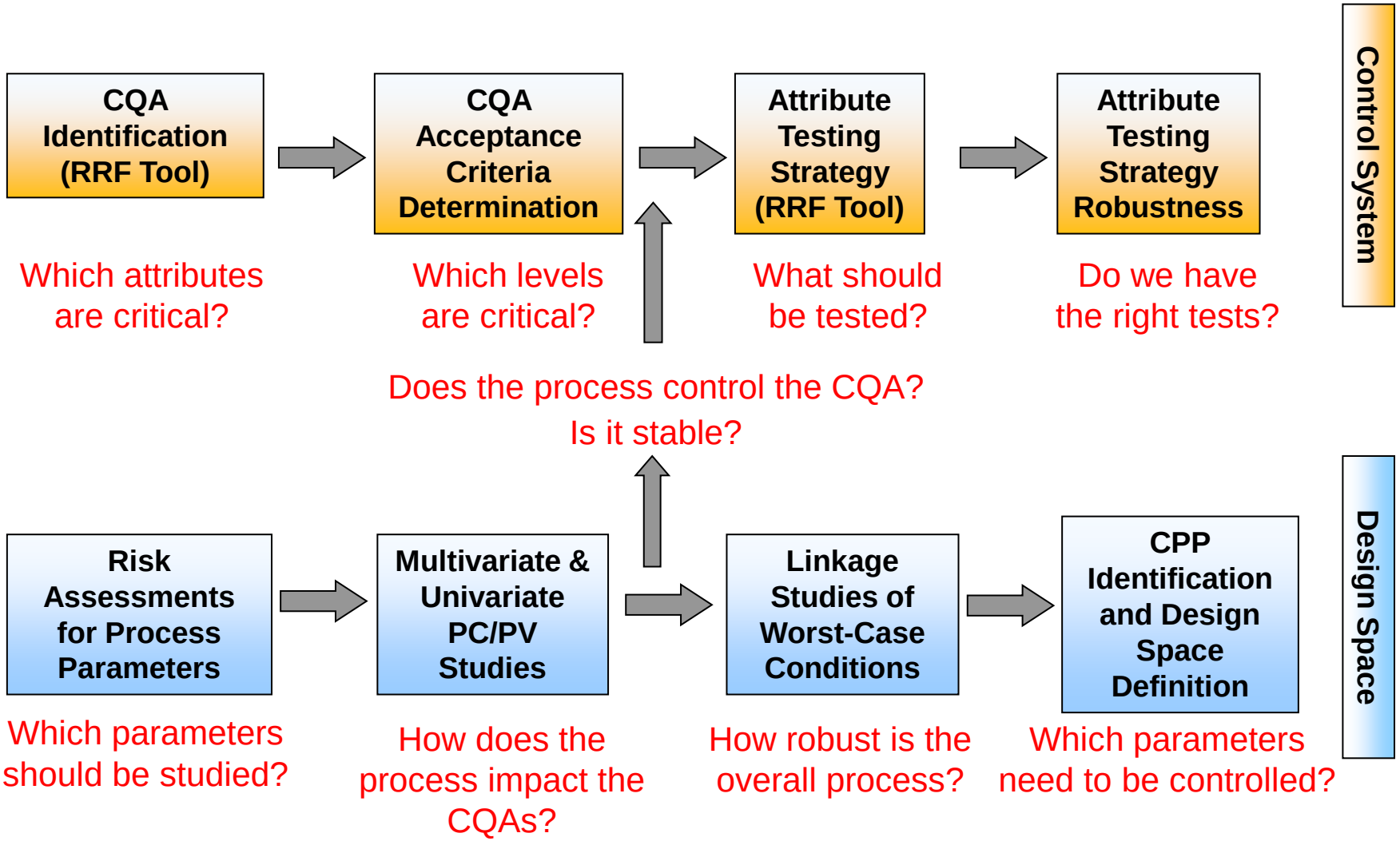
Case Study: Monoclonal Antibody

General Introduction – Monoclonal Antibody

	Monoclonal Antibody
Molecule	Recombinant, humanized, monoclonal antibody (IgG1)
Indications	Oncology
Route of administration	Intravenous (IV) infusion
Dosage form	Concentrate for solution for infusion Single 1,000 mg dose in a 50 mL glass vial containing 40 mL of liquid concentrate
Composition	25 mg/mL of antibody in 20 mM L-histidine/L-histidine hydrochloride, 240 mM trehalose, 0.02% poloxamer 188, pH 6.0
Storage conditions	2°C - 8°C, protected from light; shelf life 36 months

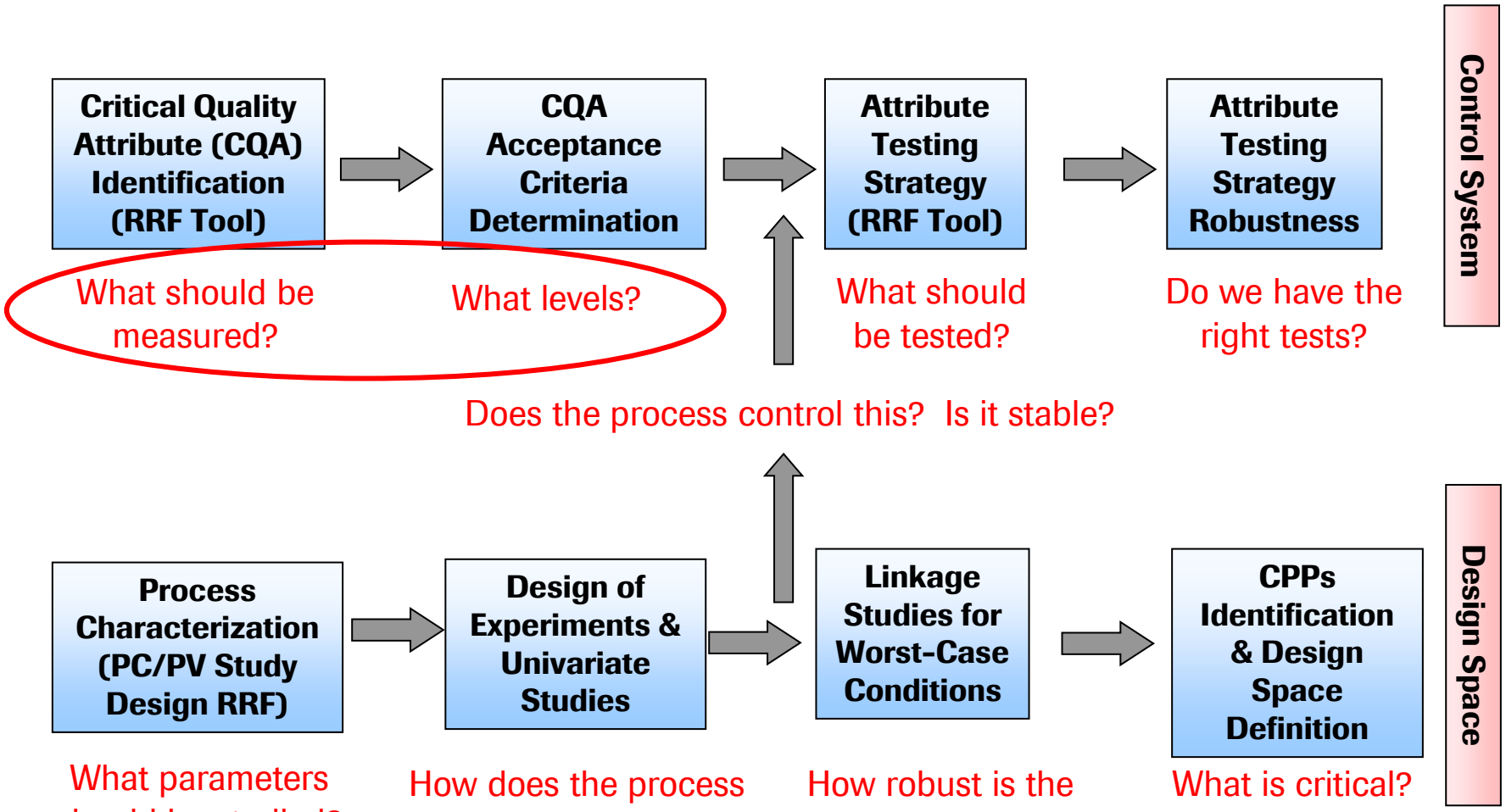
Quality by Design Tools and their Purpose

Systematic approach to Control System and Design Space



QbD provides a systematic approach to answer these questions

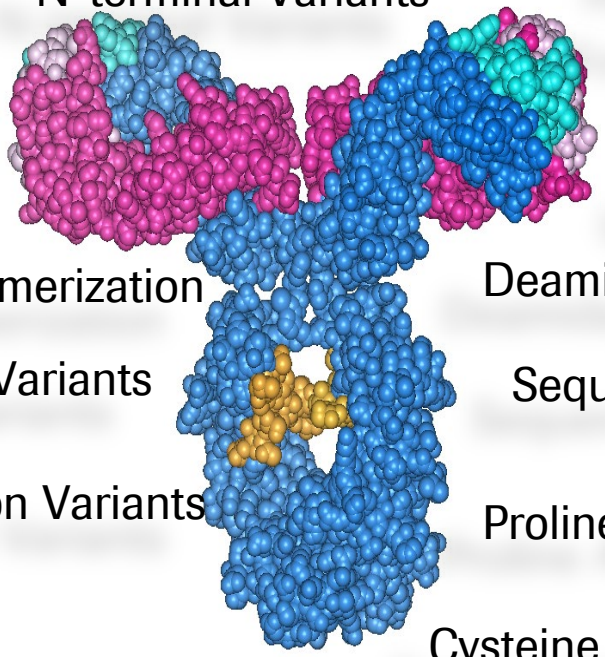
The Roche QbD Workflow



What are Potential Critical Quality Attributes for a Monoclonal Antibody?

ICH Q8 R1: Critical Quality Attributes – Link Directly to Patient Safety & Efficacy

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**.



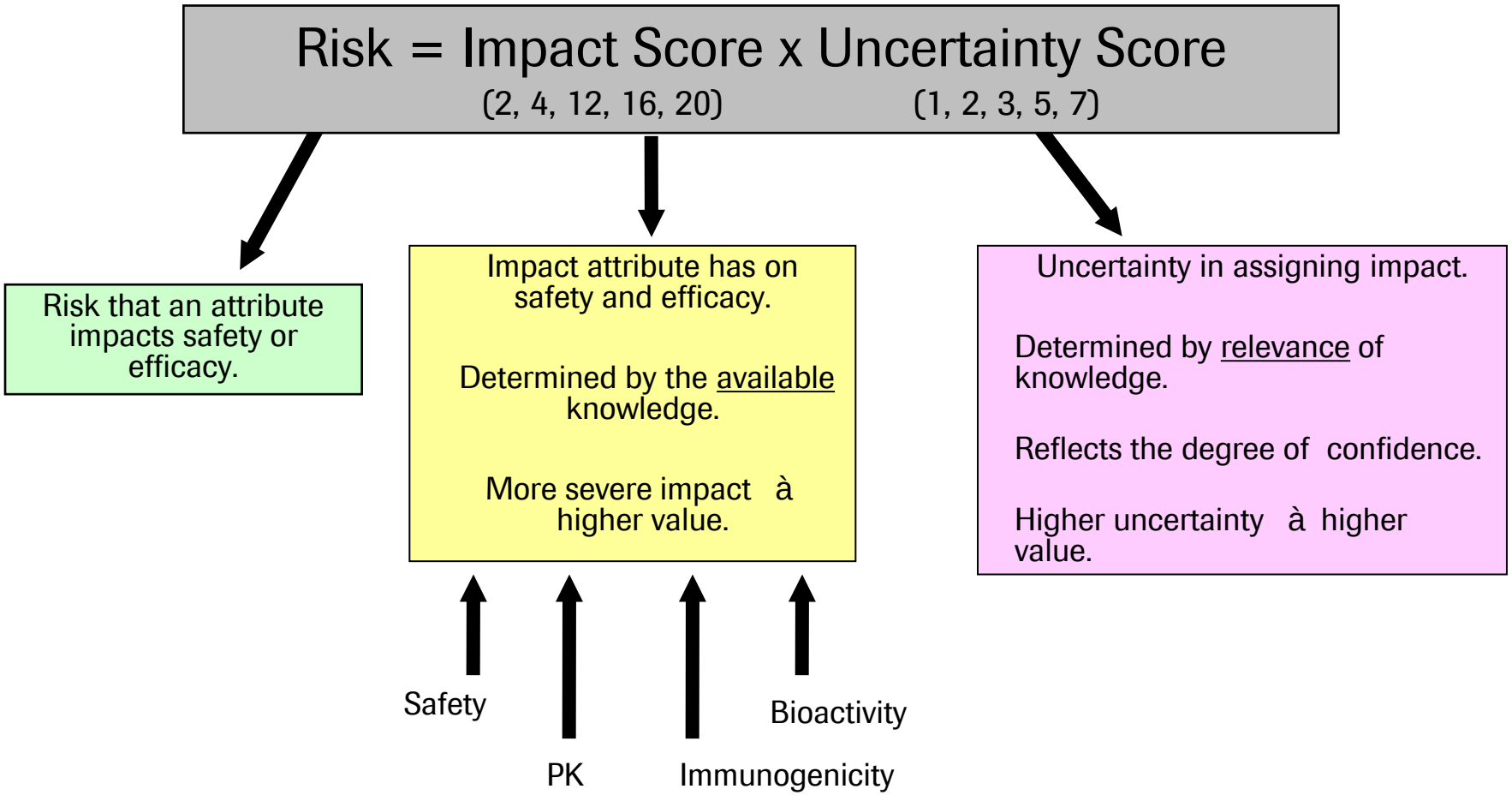
Critical Quality Attributes (CQAs)

Categorization

Category of Attribute	Assessment	Rationale for Approach
Product Variants	**Risk Ranking and Filtering**	Impact to patient safety and product efficacy is specific to variant in question, mechanisms of action, route of administration, etc.
Process-related impurities	**Risk Ranking and Filtering**	Clinical data from similar products can be used to assess safety
Composition and Strength	Obligate CQA	Potentially high impact to safety and efficacy
Adventitious Agents	Obligate CQA	Potentially high impact to safety
Raw Materials	**Compare Estimated Daily Intake and Acceptable Daily Exposure**	Extensive data available from safety and toxicity studies

Critical Quality Attributes (CQAs)

Identification: Risk Ranking & Filtering Tool



Impact and Uncertainty rankings have different scales to reflect the relative importance

Example – CQAs for Monoclonal Antibody

Product Variant CQAs

High-molecular-weight species
Low-molecular-weight species

Deamidation
Unknown acidic charge variants
Glycation

Aspartic acid isomerization

Oxidation

Afucosylation
Hybrid glycans
Mannose5
Sialylation (NANA)
Non-glycosylated Heavy Chain (NGHC)

Sequence variants
Protein structure
Cysteine forms

Product Variant Non-CQAs

C-terminal lysine
N-terminal pyroglutamic acid
C-terminal proline amidation
Galactosylation

Process-Related Impurity CQAs

Host cell proteins (HCP)
Host cell DNA
Leached protein A
Some raw materials

Obligatory CQAs

Composition and Strength
Protein Content, Osmolality, pH
Appearance (color, opalescence, clarity)
Content of: L-histidine, trehalose and poloxamer 188

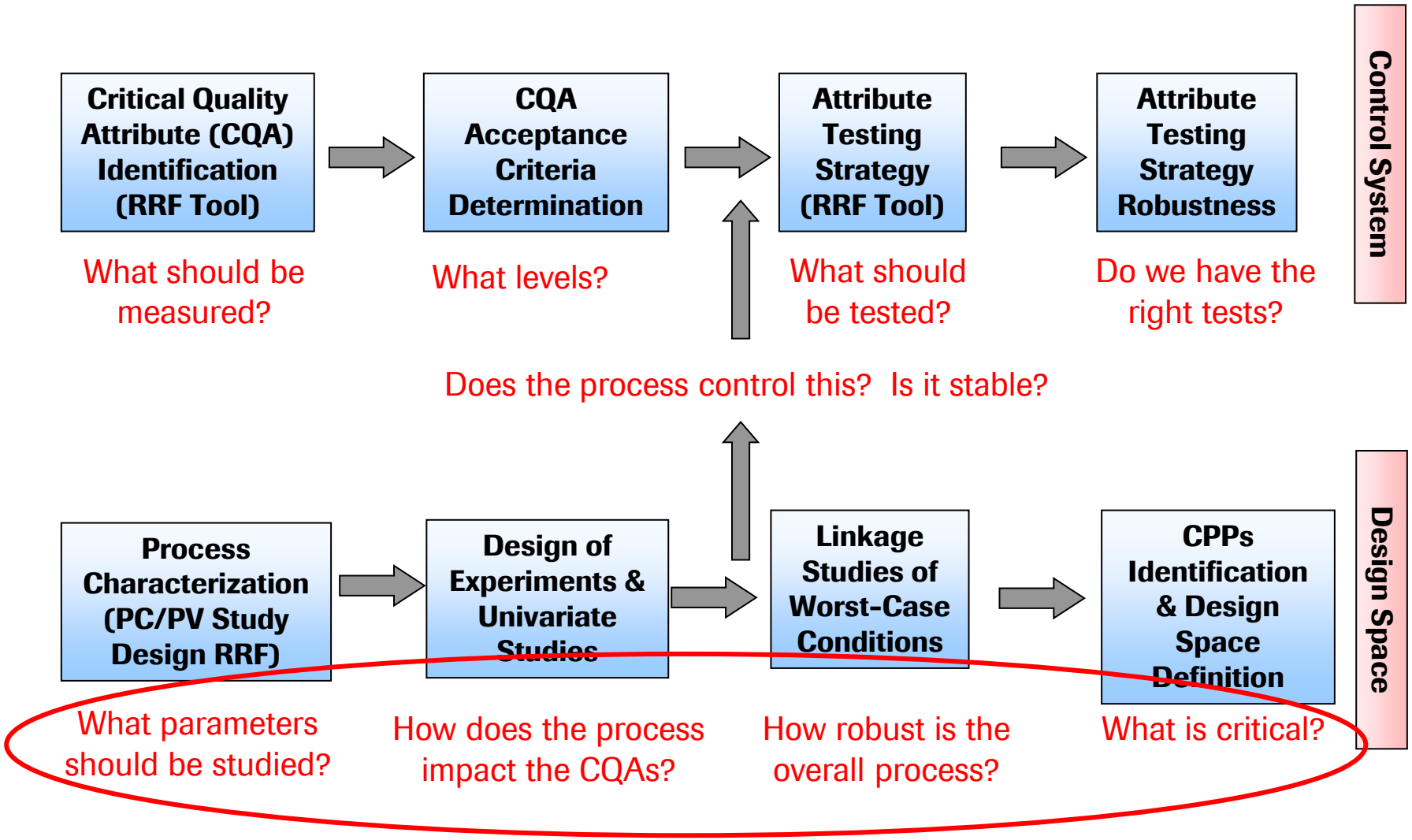
Drug Product Specific
Subvisible Particles
Visible Particles
Extractable Volume
Sterility

Most of the quality attributes are critical quality attributes or obligatory critical quality attributes

CQA Acceptance Criteria (CQA-AC)

- The CQA-AC represents a numerical limit a CQA must meet end of shelf life in order to ensure the desired quality of the product.
  - Based on patient impact, not on product-specific (clinical) manufacturing
  - Collective effect of QAs considered to ensure PK and biological activity
  - Drive CPP identification, definition of the Control Strategy and process Design Space
- CQA-AC are established based on:
  - Product-specific non-clinical and clinical experience
  - Platform knowledge and published literature
  - Process capability and testing strategy considerations
  - For CQAs that are not formed, no CQA-ACs are set
- May extend beyond product-specific clinical and non-clinical historical ranges with justification
- Not necessarily specification acceptance criteria

The Roche QbD Workflow



Knowledge of pCQAs is used to Design & Characterize Each Unit Operation – identifying CPPs & CMAs

CQAs

- Identify CQAs for the product
- Determine relevant levels for each CQA at each step

Characterize the process

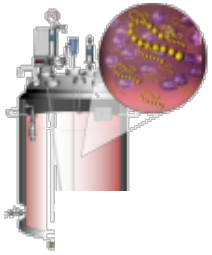
- Perform scale-down uni- and multivariate or worst-case experiments for each unit operation
- Monitor all relevant CQAs
- Defines site- and scale-independent PP impacts

Confirm a Design Space (optional)

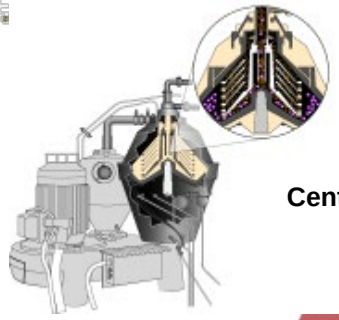
- Linkage studies for all CPPs across the whole process
- Monitor process-wide performance for relevant CQAs

Traditional at-scale Process Validation

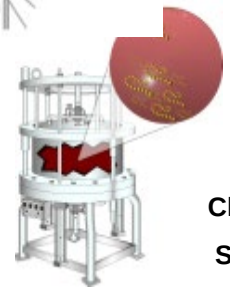
- Confirms consistency of the process at scale in the commercial manufacturing site
- Confirms site- and scale-dependent validation



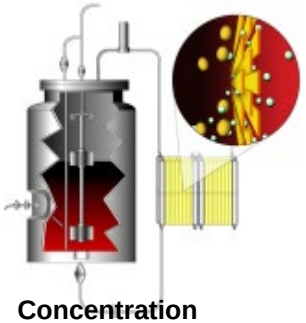
Cell Culture/ Fermentation



Centrifugation



Chromatography Steps



Concentration and Formulation

Drug Product Manufacturing

Process Characterization & Validation (Example for DS)

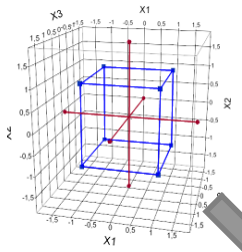
All traditional process validation is performed for along with new approaches that enhance the assurance of product quality

Validation Information	Traditional Information	Enhanced Approach
At-Scale Process Qualification Runs	- 3 consecutive runs at manufacturing scale in the commercial facility - KPIs and process-related impurity clearance - All lots meet specifications	
Scale-Down Process Parameter Studies	- Characterization of proven acceptable ranges for manufacturing parameters - Generally univariate studies. Not all CQAs studied, but specified attributes assured - Description of scale-down models	- **Greater transparency of experimental design & data analysis** - **Impact of parameter ranges on all relevant CQAs studied in multivariate studies** - **Performance of "Linkage Studies" ensures product quality within the claimed ranges** - **Statistical evaluation of scale-down models**
Scale-Down Process Performance Studies	- Process-related impurity clearance - Virus removal and refiltration - Pool hold times - Resin lifetime - Limit of in vitro cell age - Membrane carry-over - Filter leachables and extractable	

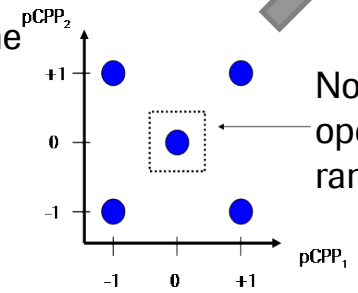
The Approach to a Process Model

- Use qualified small scale models
- Perform multivariate studies whenever possible
- Perform multiple rounds of experiments if required (e.g. screening and response surface)

Setup experimental plan



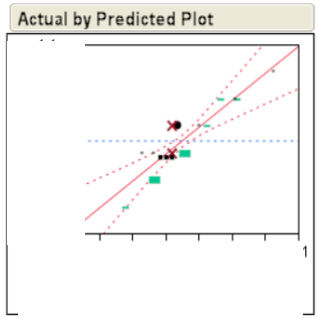
Check/redefine ranges



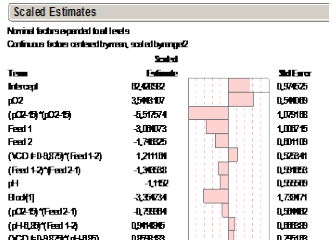
Normal operating range

Do the experiments

Check models



Evaluate the effects



Determine criticality

Identification of CPPs
Definition

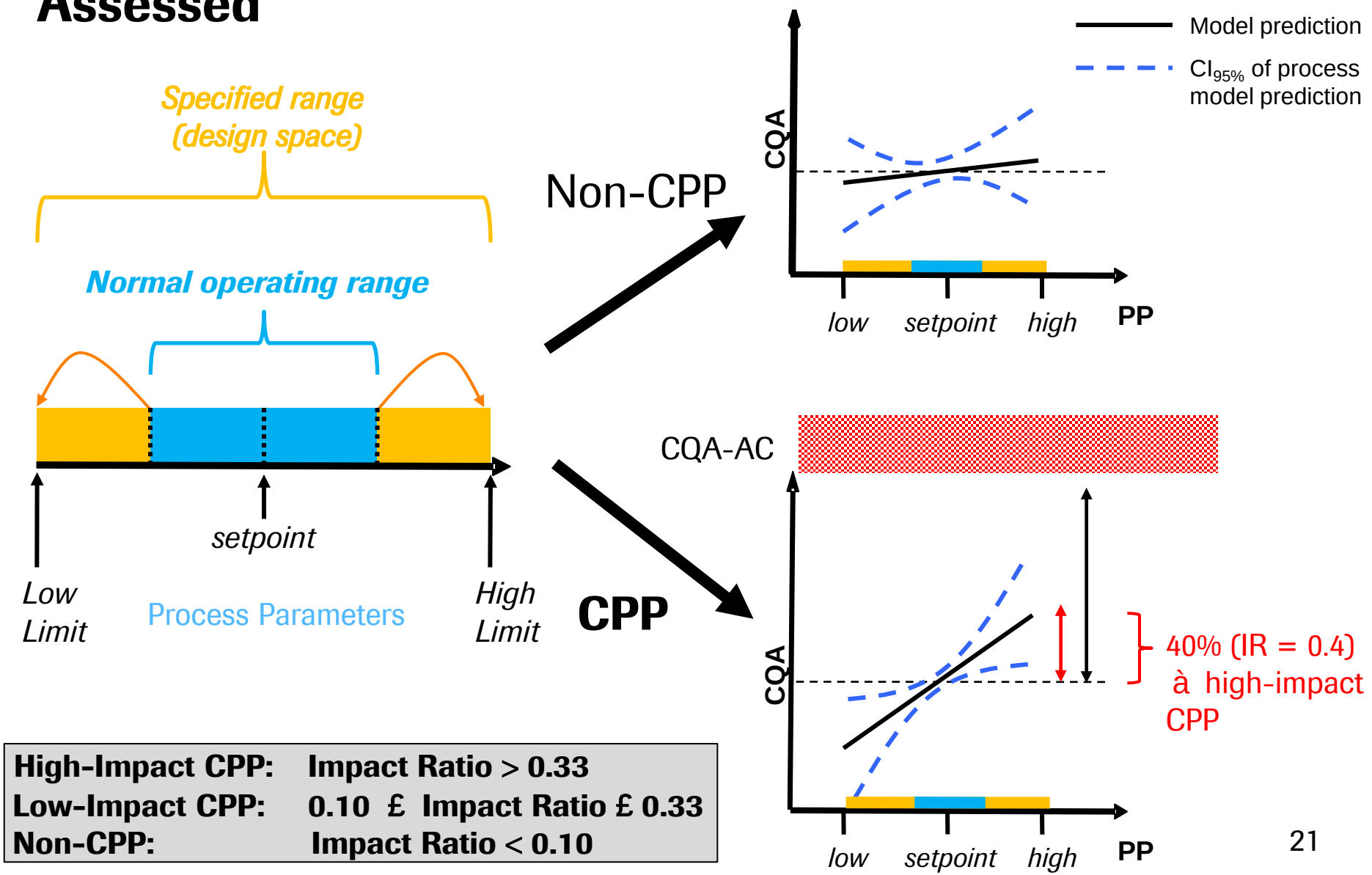
ICH Definition: *"A process parameter **whose variability has an impact on a critical quality attribute** and therefore should be monitored or controlled to ensure the process produces the desired quality"*

CPPs are all PPs that have a **meaningful impact** on CQAs (i.e. lead to a >10% CQA change relative to the allowed range).

All CPPs are controlled and maintained within ranges to guarantee CQAs remain within their acceptance criteria.

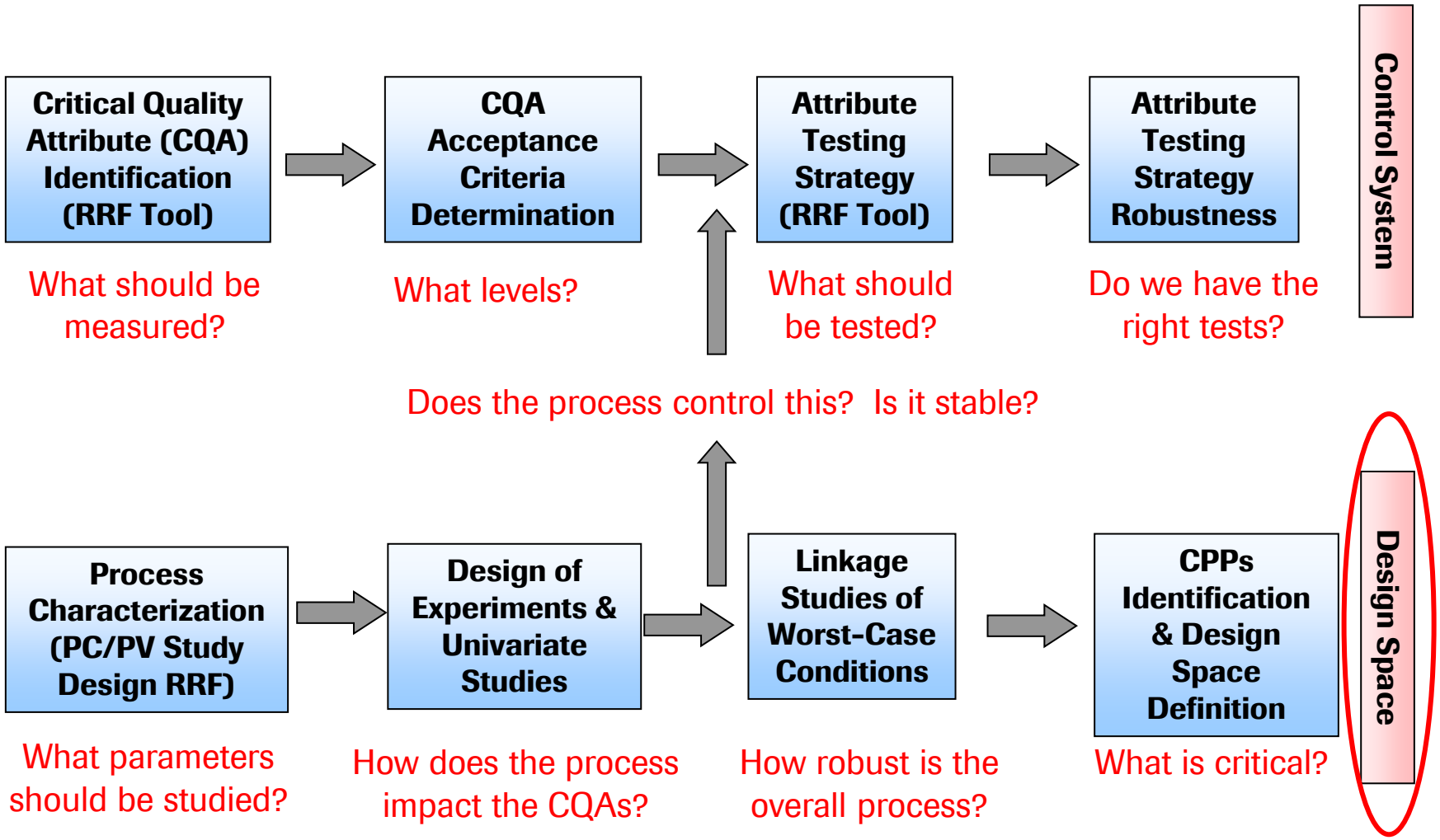
- CQA remains within its acceptance criteria when CPP is at the limit of its range
- CQA remains within its acceptance criteria considering CPP interaction at the limits of their ranges (**interaction**)
- Impact on CQA (e.g. impurity level) on a given unit operation can be managed adequately by the following unit operations (e.g. impurity removal downstream) (**linkage**)

Process Parameter Criticality is Systematically Assessed



High-Impact CPP:	**Impact Ratio > 0.33**
Low-Impact CPP:	**0.10 £ Impact Ratio £ 0.33**
Non-CPP:	**Impact Ratio < 0.10**

The Roche QbD Workflow



Roche's Design Space Definition

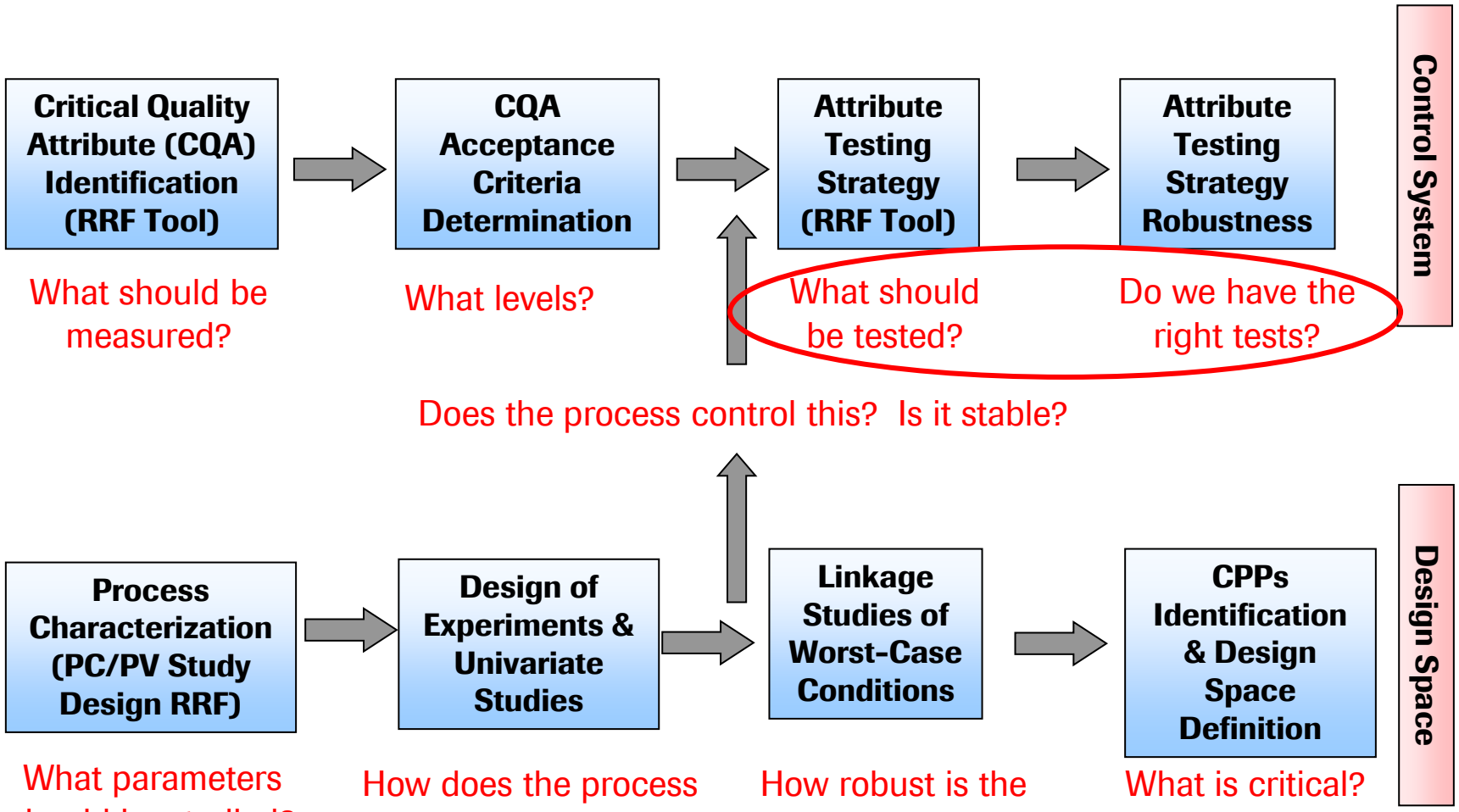
The Drug Substance and Drug Product design space includes

- All unit operations and their sequence
- All process parameters describing the operation of each of the unit operations (described in Section S.2.2 and P.3.3)
- All raw materials

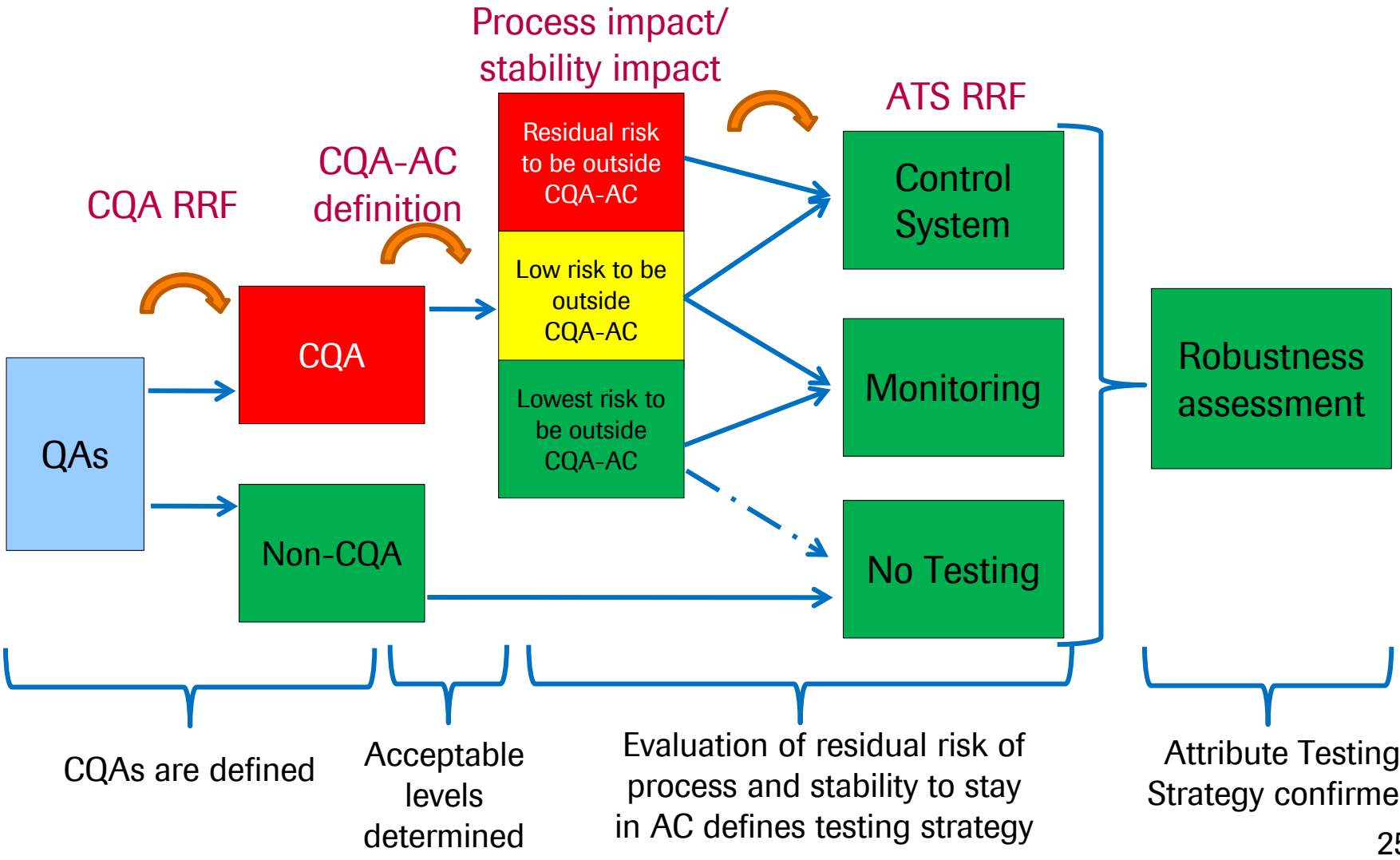
The design space is limited by the multivariate acceptable ranges for all relevant process parameters

- CPPs
- Non-CPPs

The Roche QbD Workflow



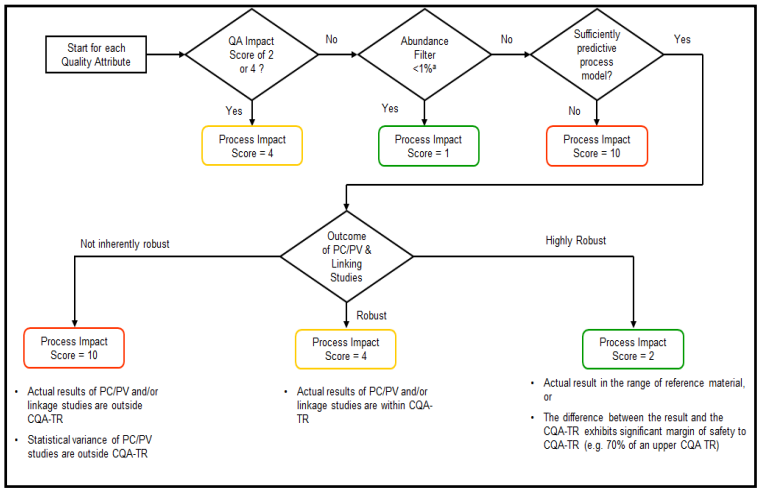
Attribute Testing Strategy (ATS) – A Major Component of the Overall Control Strategy



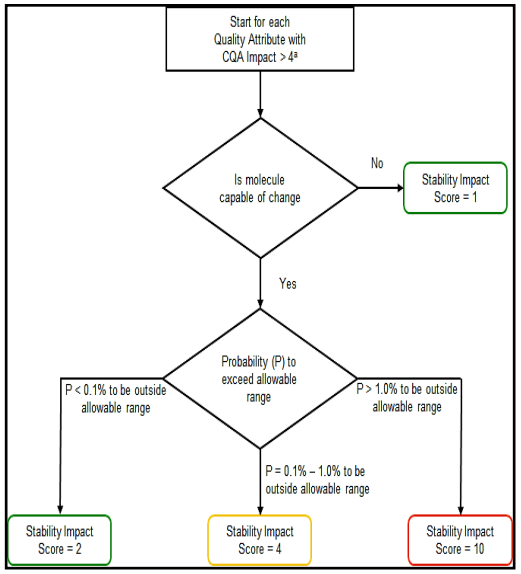
Attribute Testing Strategy Score Defines Testing Strategy

CQA Impact Score (2,4,12,16,20)	X	Process/Stability Impact Score (1, 2,4,10)	=	Attribute Testing Strategy Score

Process Impact Tree



Stability Impact Tree



Attribute Testing Strategy (ATS) Score

<21	No testing required
21-50	Monitoring required
>50	Control System testing required

ATS Robustness Assessment

- Performed by Subject Matter Experts for every Quality Attribute (QA)
- It takes the following aspects under consideration:

- **Criticality/Risk**
  The criticality is assessed as the impact of the QAs on safety, immunogenicity, and efficacy.
- **Likelihood of formation**
  Likelihood of formation of the variant during the manufacturing process and/or storage.
- **Capability of the Process**
  Ability of the process to control the attribute.
- **Capability of the analytical procedure**
- **Additional Control**
  Coverage of attribute by other analytical procedures in the ATS
- **Conclusion** Considering regulatory requirements

Assessment guides if any adaptions to the proposed testing strategy may be needed and can lead to elevating or downgrading attributes in the testing strategy categories or to redefining limits and methods. Attributes with ATS scores > 50 are not removed from the control system testing by this assessment.

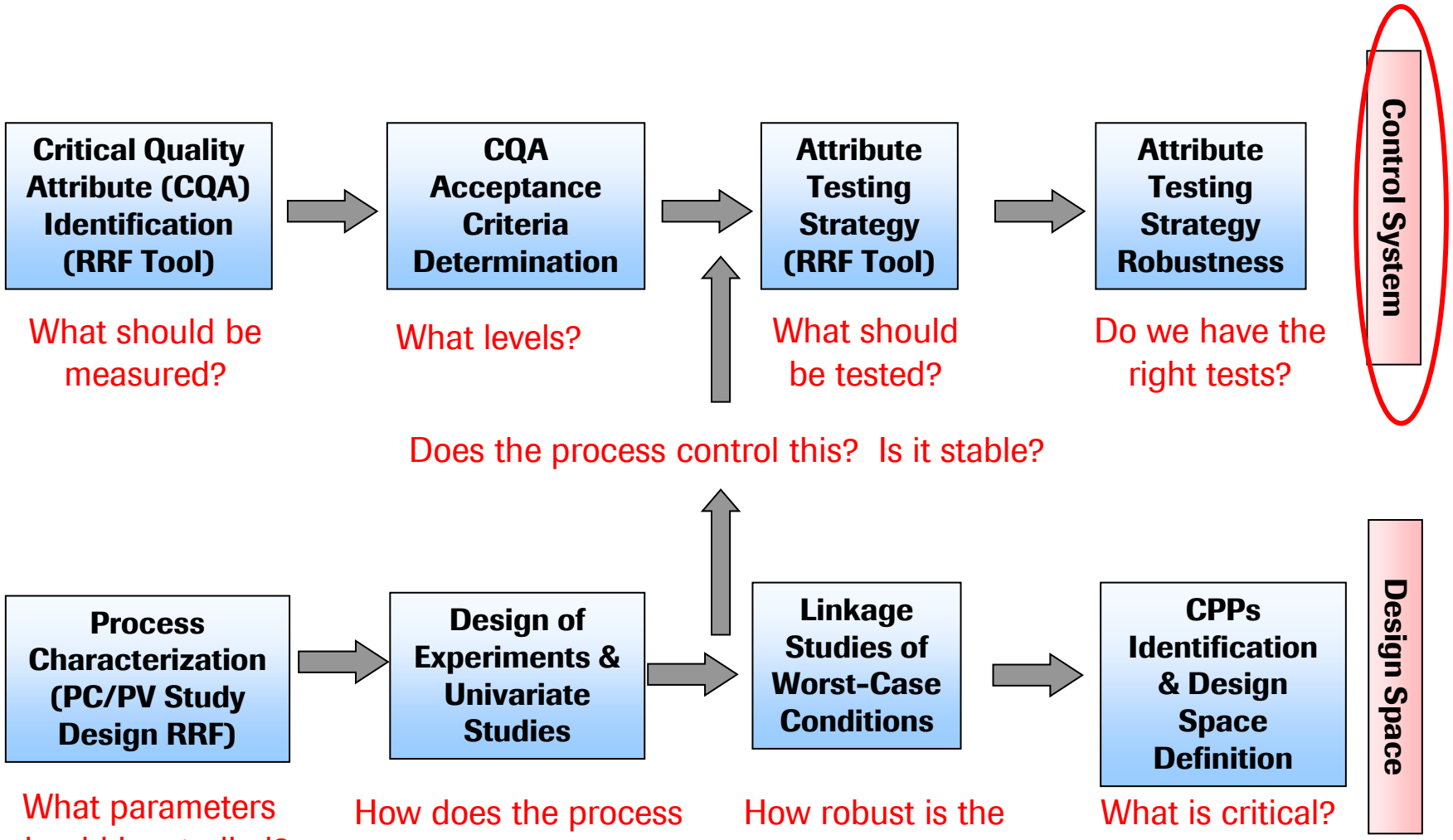
Example: Attribute Testing Strategy

CQA Category	CQA	CQA Impact Score	Drug Substance						Drug Product						
			Process Impact Score	Stability Impact Score	Control System Testing		Monitoring	Considered for Stability in Comparability Exercises	No Testing	Process Impact Score	Stability Impact Score	Control System Testing		Monitoring	Considered for Stability in Comparability Exercises	No Testing
					Batch Release[a]	Stability						Batch Release	Stability			
Size-Related Variants	HMWS	20	4	10	80	200	—	—	—	4	2	80	40	—	—	—
	LMWS	16	4	2	64	—	—	32	—	2	2	—	—	32	32	—
Charge-Related Variants: Acidic Variants	Deamidation in CDR	16	1	1	—	—	—	—	16	1	1	—	—	—	—	16
	Deamidation in non-CDR	16	1	1	—	—	—	—	16	1	1	—	—	—	—	16
	Unknown Acidic Charge Variants	12	10	2	120	—	—	24	—	2	10	—	120	24	—	—
	Glycation in CDR	16	2	1	—	—	32	—	—	1	1	—	—	—	—	16
	Glycation in non-CDR	16	2	1	—	—	32	—	—	1	1	—	—	—	—	16

Attribute Testing Strategy (ATS) Score

- <21 No testing required
- 21-50 Monitoring required
- >50 Control System testing required

The Roche QbD Workflow



Control System for Drug Substance

Testing of	
Color	Potency by Bioassay
Clarity/Opalescence	Identity
pH	Purity (e.g. by SE-HPLC, CE-SDS, IE-HPLC)
Osmolality	Glycosylation (e.g., Afucosylation)
Content of Excipients	Bioburden
Content of Protein	Bacterial Endotoxins

- Obligatory testing is implemented
- Testing is based on the residual risk of attributes to stay within acceptance criteria:
  - In case of residual risk: attribute is tested and specified
  - Testing may differ between release and stability

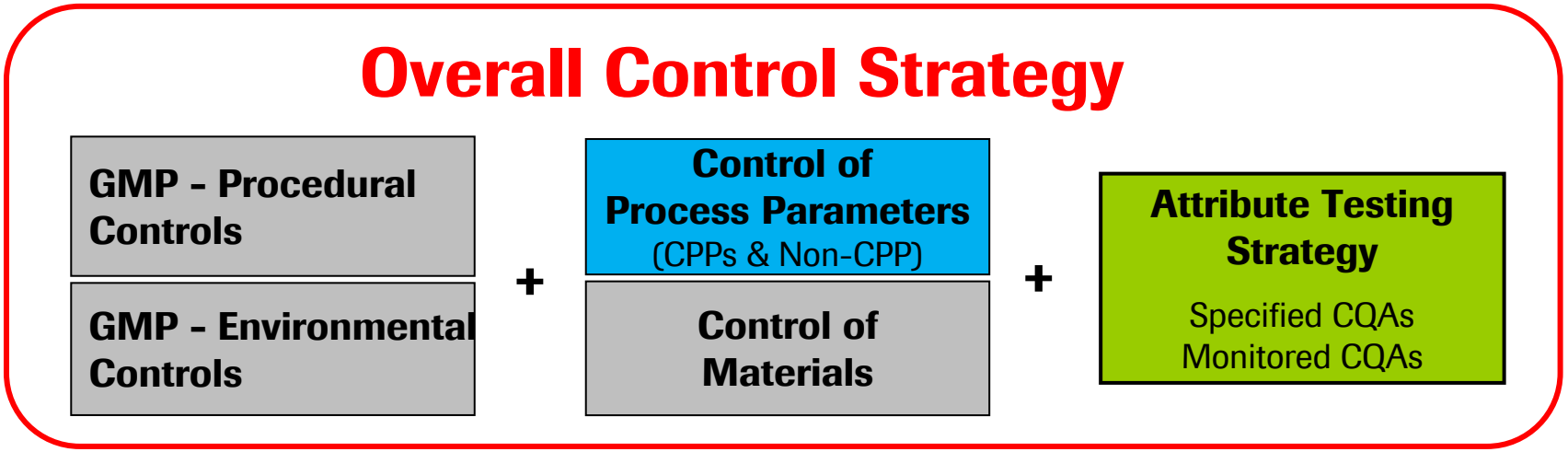
Control System for Drug Product

Testing of	
Physical State	Identity
Color	Purity (e.g. by SE-HPLC)
Clarity/Opalescence	Potency by Bioassay
Extractable Volume	Content of Protein
Particles (visible, subvisible)	Sterility
pH	Bacterial Endotoxins
Osmolality	

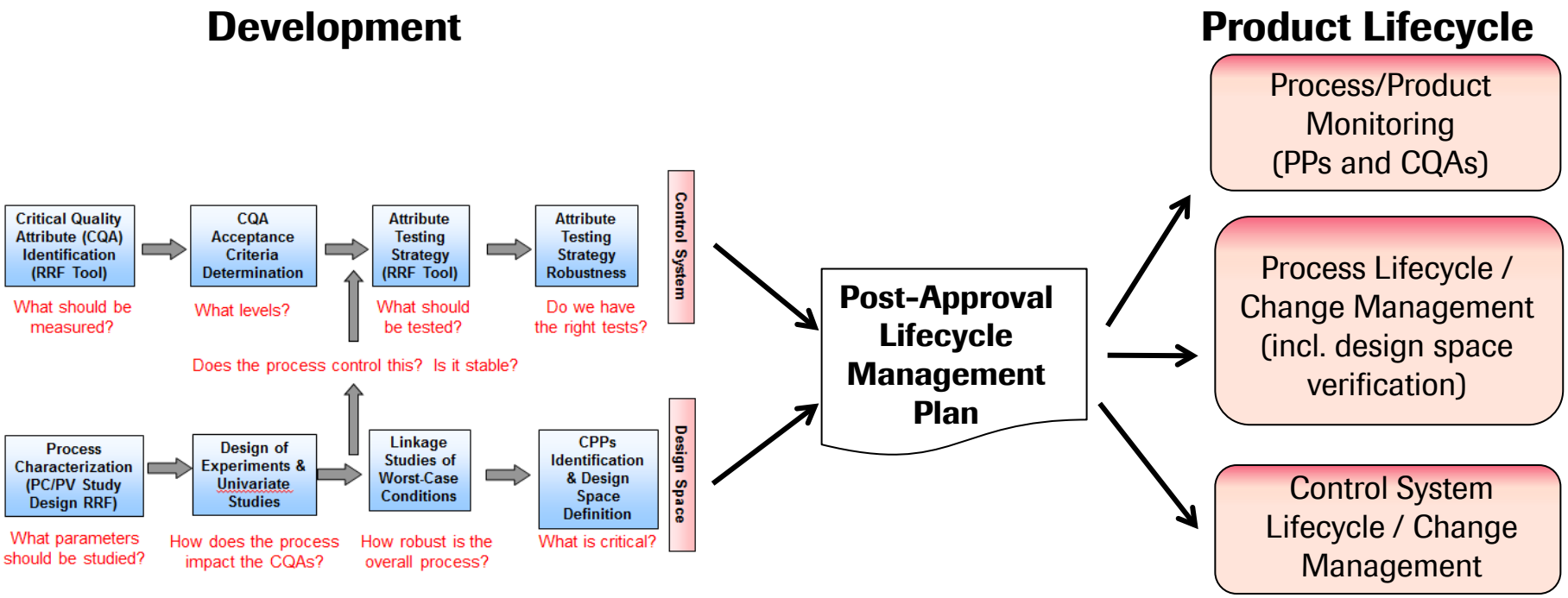
Overall Commercial Control Strategy

The overall commercial control strategy covers different aspects:

- allowed ranges for CQAs and process parameters
- control of materials
- GMP controls



Product Lifecycle
Post-Approval Lifecycle Management Plan



The PALM Plan describes how process parameters and CQAs are monitored during product lifecycle.

The PALM Plan describes how changes are managed in the Quality Management System.

Approval Status for Monoclonal Antibody

- The marketing application for the monoclonal antibody of this case study has currently been approved by approx. 60 countries
- Approved in EU, USA, Switzerland, Canada, Australia, New Zealand, Brazil, Russia, South Korea, Taiwan, many others
- Design Space and PALM plan have been approved in all countries

Summary

Bottom Line: What has changed?

- Enhanced knowledge results in more robust routine process
- Effects of process parameters on quality attributes well understood
  - Deviations and changes can be assessed more precisely
  - When moving into «unknown territory» model predictions have to be verified
- Definition of a Design Space in which we can move freely without HA approval/report
- Control system systematically covers all known risks and can be adapted during lifecycle (e.g. frequency of testing monitoring attributes)
- Process monitoring systematically adds to process understanding

Ø No fundamental changes in manufacturing rules or Quality System (new only: «monitoring attributes» according to PALM Plan)

Benefits of QbD

- QbD can be a highly effective global driver of change in the industry providing:
  - Enhanced level of product quality and process robustness
  - The foundation for continued improvement

- The work done to enable Design Space claims has clearly enhanced overall process robustness and product quality
  - More extensive evaluation of process impacts on CQAs
  - Driven DoE approaches to become “state of the art”
  - More systematic and inclusive identification of CPPs and non-CPPs
  - More rigor in developing the overall control strategies
  - More assurance that process is robust upon approval
  - More assurance of supply
  - Facilitates change - and deviation management

Acknowledgments

Thanks to:

Roche/Genentech Global QbD Large Molecule Team

Multiple Technical Development Teams

Global Health Authorities

Doing now what patients need next