Making Medicines Affordable

What to control?
CQAs and CPPs

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Agenda

- Critical Quality Attributes (CQAs)
  - Scoring Impact and Uncertainty
  - Uncertainty Dilemma
  - Continuous quality attribute critical scale
- Critical Process Parameters (CPPs)
  - Process control point analysis
    - High level overview on process – product linkage
  - FMEA risk assessment as life cycle approach
  - Considering process parameter range
- CQAs and CPPs as basis for the control strategy

Elements in Biopharmaceutical Development

- Establish Quality Target Product Profile – the QTPP forms the basis of design for development of the product
- Determine Critical Quality Attributes – linking quality attributes to clinical safety and efficacy
- Linking process parameters and critical material attributes to CQAs – Definition of critical process parameters (CPPs)
- Optional: Define the design space – (multivariate) acceptable process parameter ranges
- Design and implement control strategy using risk management e.g. by linking CQAs to process capability and detectability
- Manage product life cycle, including continuous process verification and continual improvement

Regulatory landscape for CQAs

ICH Q7	Validation: “Defining the API in terms of its critical product attributes“
ICH Q8(R2)	“At a minimum, those aspects of drug substances [...] that are critical to product quality should be determined and control strategies justified“.

Definition in ICH Q8(R2) ANNEX: 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.

ICH Q11 Step 3	“Manufacturing process development should include, at a minimum, the following elements: Identifying potential CQAs associated with the drug substance [...]”
FDA MaPP **“Applying ICH Q8, Q9, Q10 Principles to CMC Review”**	“Applications should include the following minimal element [...]: - Critical Quality Attributes (CQAs) of the drug product - CQAs of the drug substance and excipients”

CQAs are a key concept for a pharmaceutical product development

Assessing quality attribute criticality

- Start with list of all possible quality attributes
  - Consider mode of action and molecule type
- Risk-based approach to identify CQAs
  - Links quality attributes to safety and efficacy
  - Standardizes judgment and documents rationale
- Criticality reflects impact on safety and efficacy
- Keep process considerations separate from CQA assessment
  - CQA impact on safety & efficacy is independent of process capability, process changes shouldn't impact QA criticality
  - makes CQA assessment more modular

Using quality attribute criticality for:

•Prioritization in QbD cell line & process development

•clone and process selection establishing and justifying analytical program

•comparability exercises, justification of acceptance ranges and quality differences

•process characterization (linking process parameters to quality attributes)

•control strategy (process, IPCs, specifications)

•dossier (CQA as regulatory expectation)

•Knowledge management (beyond licensing)

Quality Attribute Criticality Assessment

- Risk assessment for ranking and prioritizing quality attributes
- General concept described in A-MAb case study (Tool #1)

Criticality Score = f(Impact,Uncertainty)

e.g.: Criticality Score = Impact x Uncertainty (A-MAb)

Criticality Score

Quantitative measure for an attribute‘s impact on safety and efficacy.

Using best possible surrogates for clinical safety and efficacy

Impact

Known or potential consequences on safety and efficacy, considering:
- Biological activity
- PK/PD
- Immunogenicity
- Safety (Toxicity)

Uncertainty

Relevance of information
e.g.
literature
prior knowledge
in vitro
preclinical
clinical
or combination of information

Manufacturer‘s accumulated experience, relevant information, data

e.g. literature, prior & platform knowledge, preclinical and clinical batches,*in vitro* studies, structure-function relationships

Scoring Impact – examples scales from A-Mab

Table 2.3 Impact Definition and Scale for Tool #1

Impact (Score)	Biological Activity or Efficacy[a]	PK/PD[a]	Immunogenicity	Safety
Very High (20)	Very significant change	Significant change on PK	ATA detected and confers limits on safety	Irreversible AEs
High (16)	Significant change	Moderate change with impact on PD	ATA detected and confers limits on efficacy	Reversible AEs
Moderate (12)	Moderate change	Moderate change with no impact on PD	ATA detected with in vivo effect that can be managed	Manageable AEs
Low (4)	Acceptable change	Acceptable change with no impact on PD	ATA detected with minimal in vivo effect	Minor, transient AEs
None (2)	No change	No impact on PK or PD	ATA not detected or ATA detected with no relevant in vivo effect	No AEs

AE = adverse event; ATA = anti-therapeutic antibody

[a]Quantitative criteria should be established for biological activity/efficacy and PK/PD. Significance of the change is assessed relative to assay variability.

- Scoring **Impact** on biological activity, PK/PD, immunogenicity and safety individually for all quality attributes

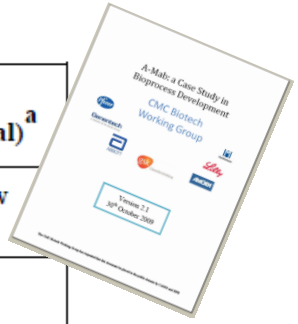
Scoring Uncertainty – example from A-Mab

Table 2.4 Uncertainty Definition and Scale for Tool #1

Uncertainty (Score)	Description (Variants and Host Related Impurities)	Description (Process Raw Material)[a]
7 (Very High)	No information (new variant)	No information (new impurity)
5 (High)	Published external literature for variant in related molecule.	---
3 (Moderate)	Nonclinical or in vitro data with this molecule. Data (nonclinical, in vitro or clinical) from a similar class of molecule.	Component used in previous processes
2 (Low)	Variant has been present in material used in clinical trials.	---
1 (Very Low)	Impact of specific variant established in Clinical Studies with this molecule.	GRAS or studied in clinical trials

GRAS = generally regarded as safe

[a] Assesses the impact of a raw material as an impurity. Impact of the raw material on the product during manufacturing is assessed during process development.



- Scoring **Uncertainty** for every scored Impact
- Criticality Scores for A-Mab calculated by Impact x Uncertainty
  - Criticality Score between 2 and 140

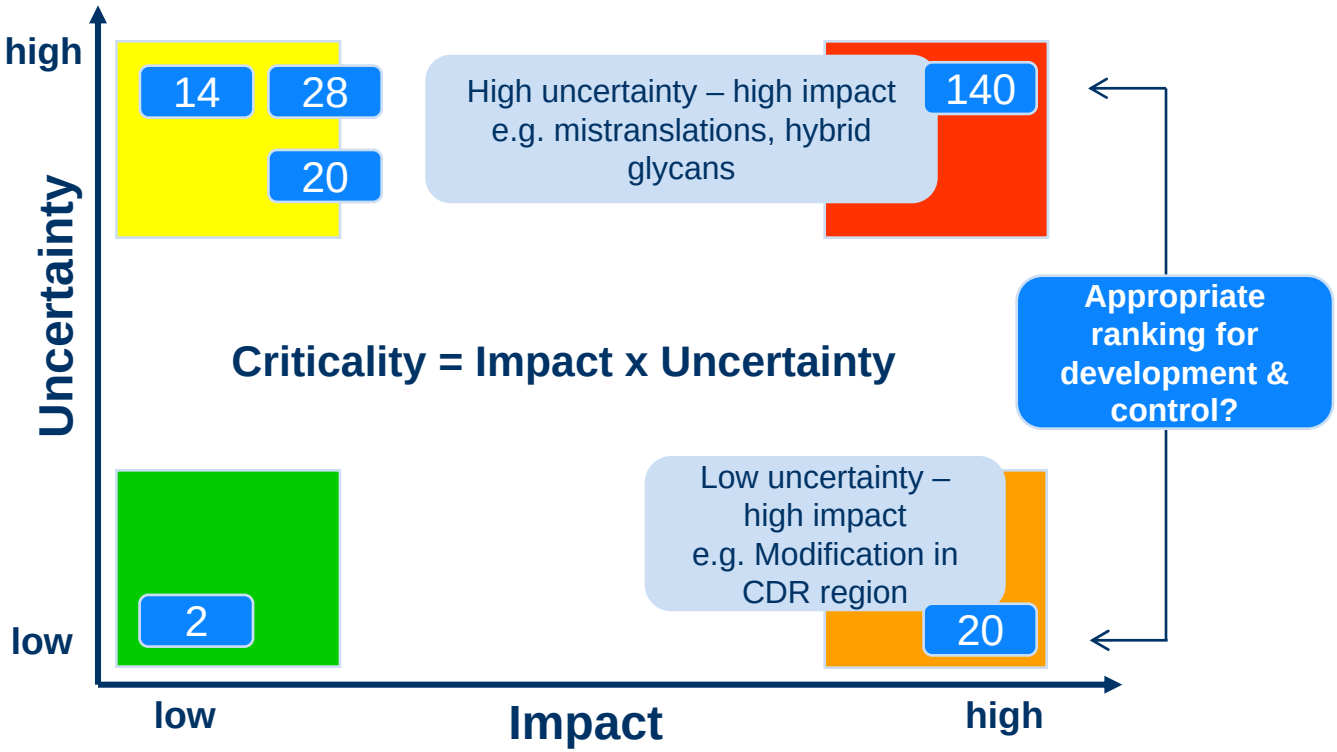
Benefits of a continuum of criticality

- FDA guidance on process validation
  - The degree of control over those attributes or parameters should be commensurate with their risk to the process and process output. In other words, a higher degree of control is appropriate for attributes or parameters that pose a higher risk.
  - **Perception of criticality as a continuum rather than a binary state is more useful.**

Source: *FDA Guidance on process validation*

Criticality Score: Dilemma of high uncertainties

- Highest scores for high impact – combined with high uncertainty
- Lower scores for high impact – combined with low uncertainty



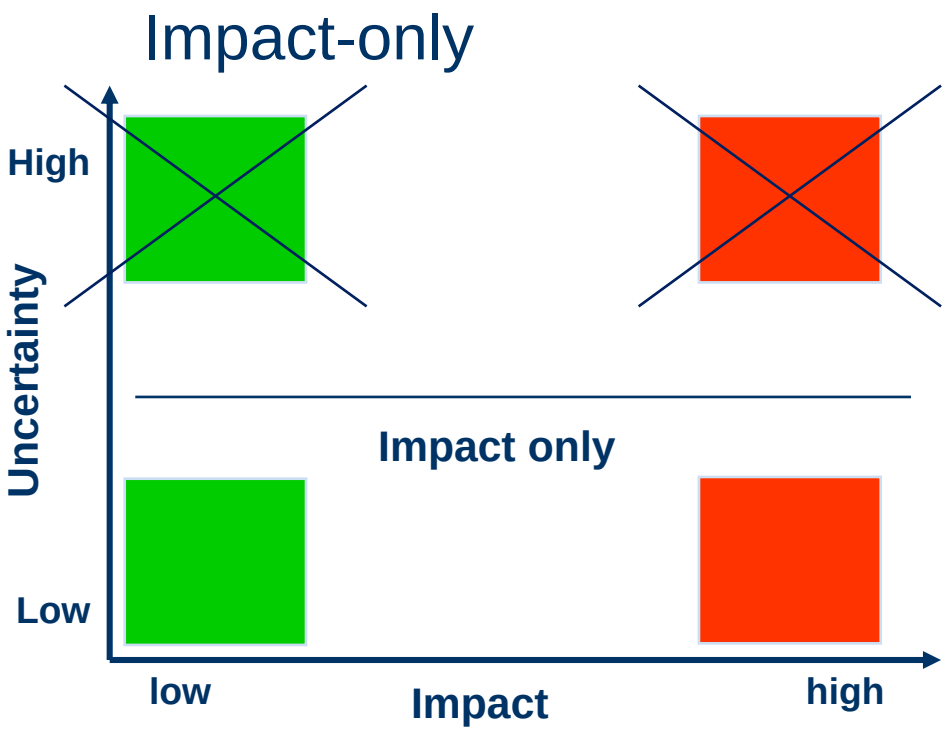
What is more critical?

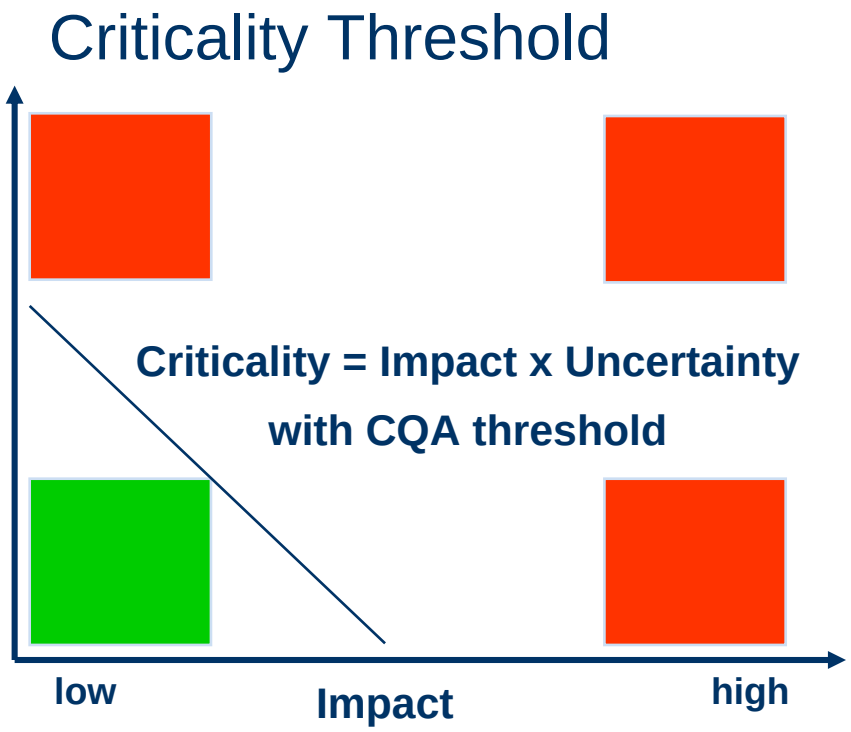
"I know it has an impact"

or

"It might have an impact"

Approaches to solve the Uncertainty dilemma



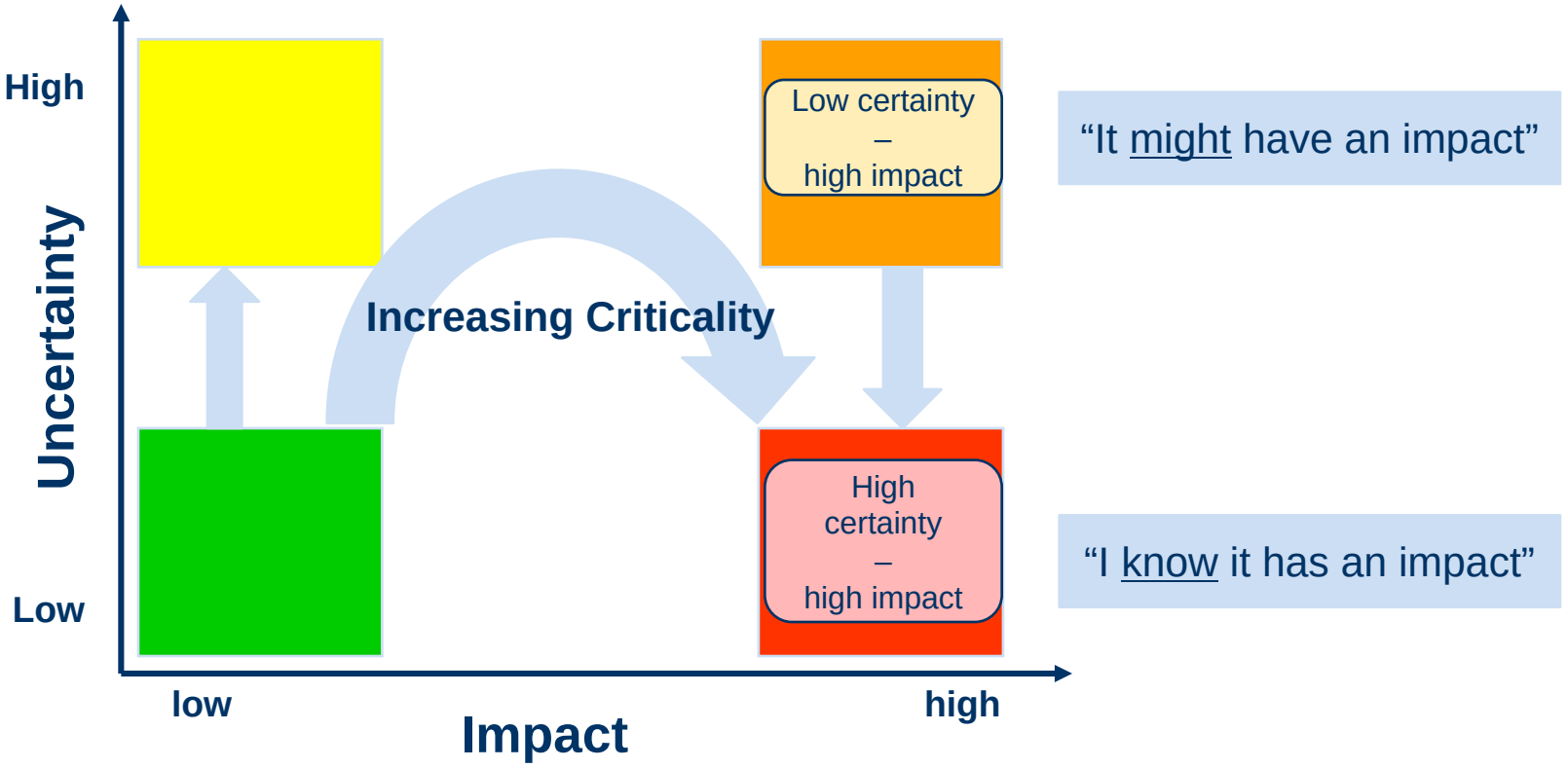


- May only be applicable very late-phase with very good product understanding
- Loosing the uncertainty information

- Low threshold necessary to avoid any false non-criticals
- Loosing continuous criticality score

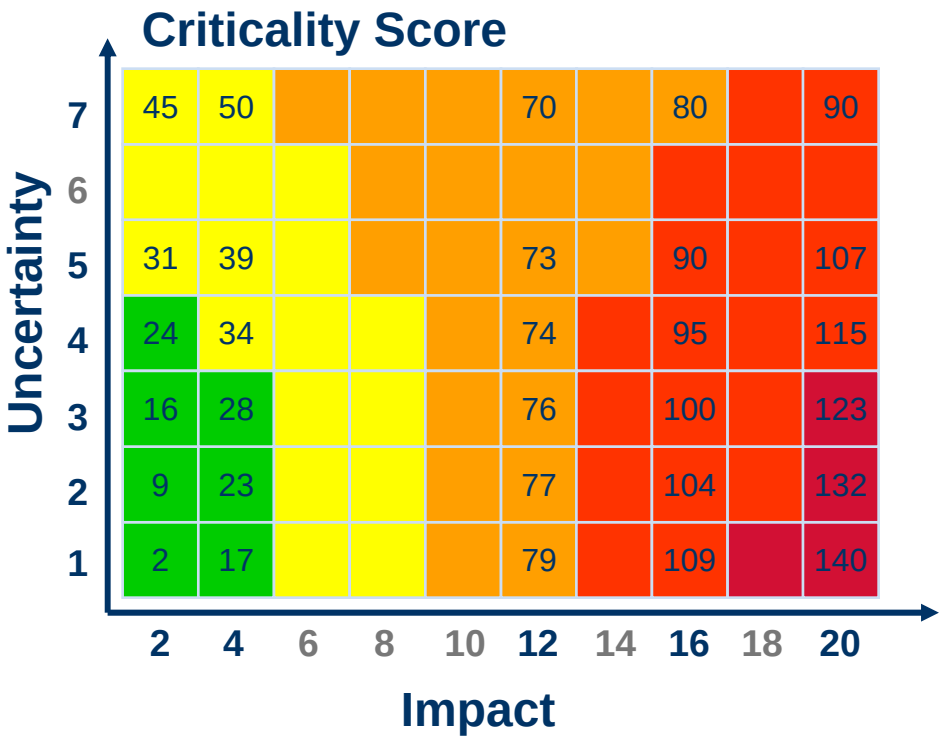
Alternative approach for the criticality score

- Putting highest criticality on high impact & low uncertainty
  - And ensure sufficient criticality for high uncertainty attributes
- Criticality as a continuum rather than a binary state



Example for a continuous criticality scoring

- Scoring of Impact & Uncertainty conceptually similar to A-Mab
- Determination of criticality score using either
  - Scoring matrix as shown (5 criticality categories or continuous score)
  - Calculation using a formula



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Process control point analysis

- Basis for a risk-based control strategy

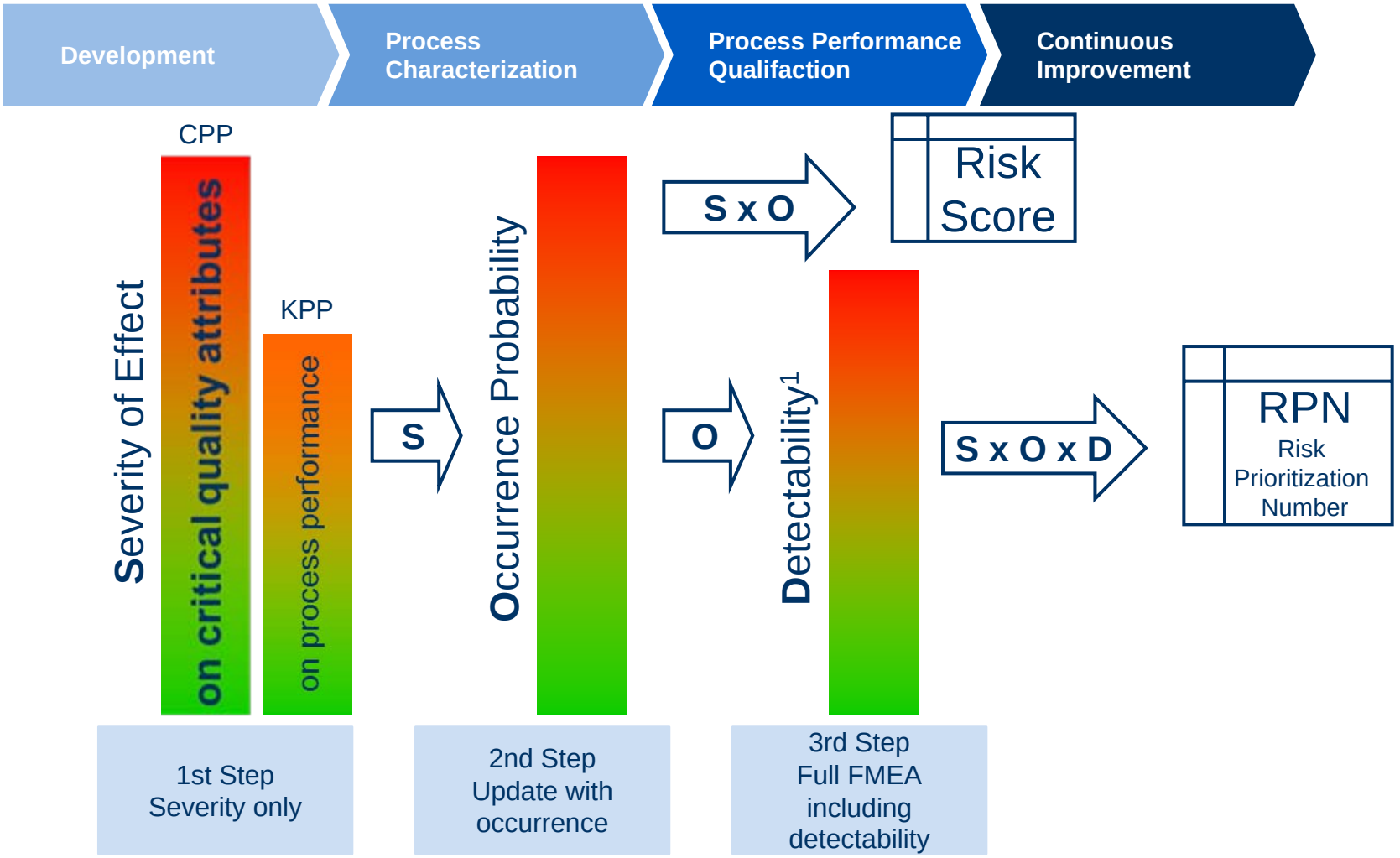
Quality Attributes vs Process Steps	Glycosylation	Aggregates	Acidic Charge Variants	HCP	DNA	Adventitious Agents	Leached Protein A	Free thiols / disulfide mismatch	Leachables / Additives
Criticality	++	++	+	++	+	++	++	++	++
Main-stage bioreactor	Form	Form	Form	Form	Form	Form		Form	Form
Primary separation				Remove	Remove			Form	Form
Capture		Form		**Remove**	**Remove**	Remove	**Form**		**Form / Remove**
Low pH treatment		Form	Form	Remove	Remove	**Remove**	Remove	Form	Remove
AEX (FT mode)		**Remove**	Remove	**Remove**	**Remove**	**Remove**	**Remove**	?	**Remove**
CEX		**Remove**		Remove	Remove	Remove	**Remove**		Remove
Nanofiltration						**Remove**			
UF/DF		Form							Form
Final Fill									

Remove: Process step removes quality attribute / impurity
Form: Process step introduces quality attribute / impurity

Stepwise FMEA for process risk assessment

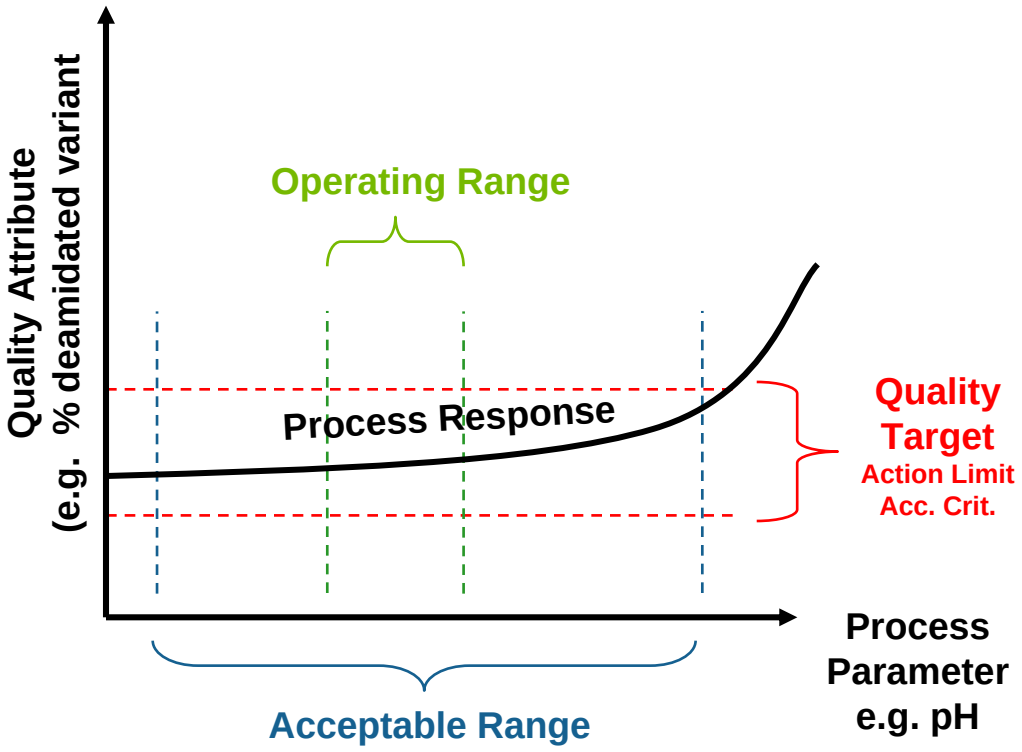
Scoring severity, occurrence and detectability for each process parameter

Life cycle approach of the process risk assessment



Process Parameter Classification & Criticality

Process parameter criticality is linked to the defined acceptable range for the process parameter



Process Parameter Classification

Critical Process Parameter (CPP)
Parameter of the process that must be maintained in a narrow range to ensure acceptable product quality

Well Controlled CPP
Although critical, the parameter is easily controlled in a meaningful range and is therefore of low risk

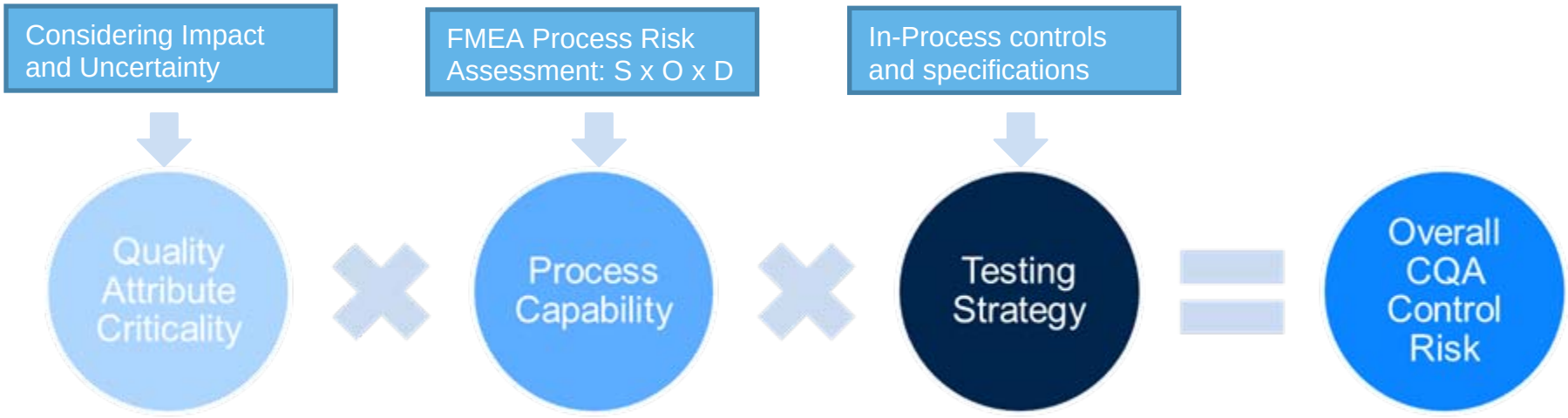
Key Process Parameter (KPP)
Parameter of the process that must be maintained in a narrow range to ensure process performance consistency and robustness

Non-key Process Parameter (NKPP)
Easily controlled process parameter with no impact in quality or performance within wide ranges

Source: PDA TR42; A-MAb Case Study

CQAs and Process Capability are the basis for establishing a Control Strategy

- Criticality of attributes and process parameters is needed for establishing, understanding and evaluating a risk-based control strategy
- Testing strategy for a certain quality attribute depends on quality attribute criticality and process capability



Conclusions

- Assessing the criticality of quality attributes is challenging but useful for the later steps in defining of what to control
- CQA risk assessment: We presented one option of implementing a continuum scoring of criticality
  - Beneficial compared to criticality scoring which simply multiplies impact with uncertainty
  - Note: other approaches are also possible
- Process control point analysis provides a good visual representation of what needs to be controlled
- A step wise FMEA to assess the process risk is an powerful tool as it reflects the project steps in the manufacturing process development
- Process parameter criticality is linked to the defined acceptable range for the process parameter