AT Europe
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Strategies of overcoming risks of changing analytical methods

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Method changes – risks and risk mitigation

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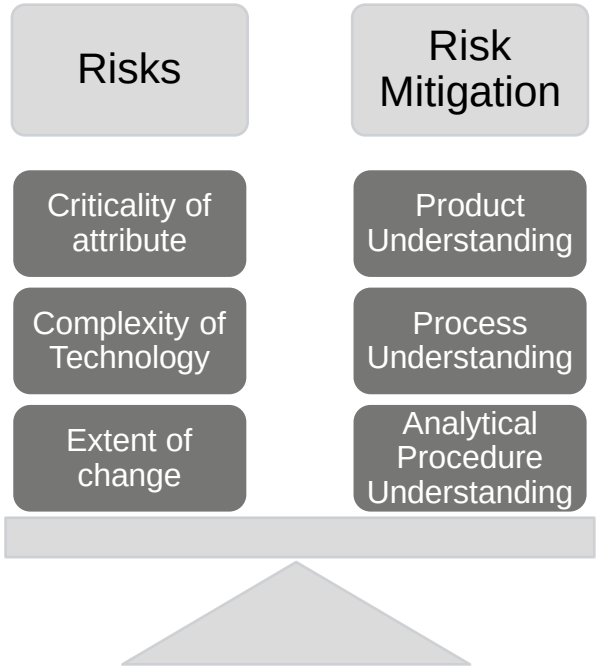
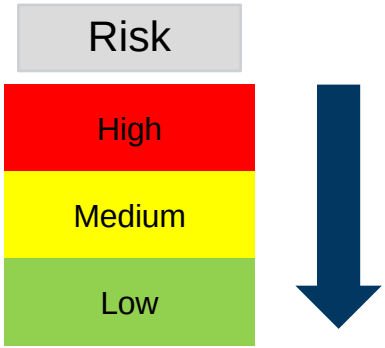




Different purposes of analytical methods

- Product understanding: Analytical methods for characterization

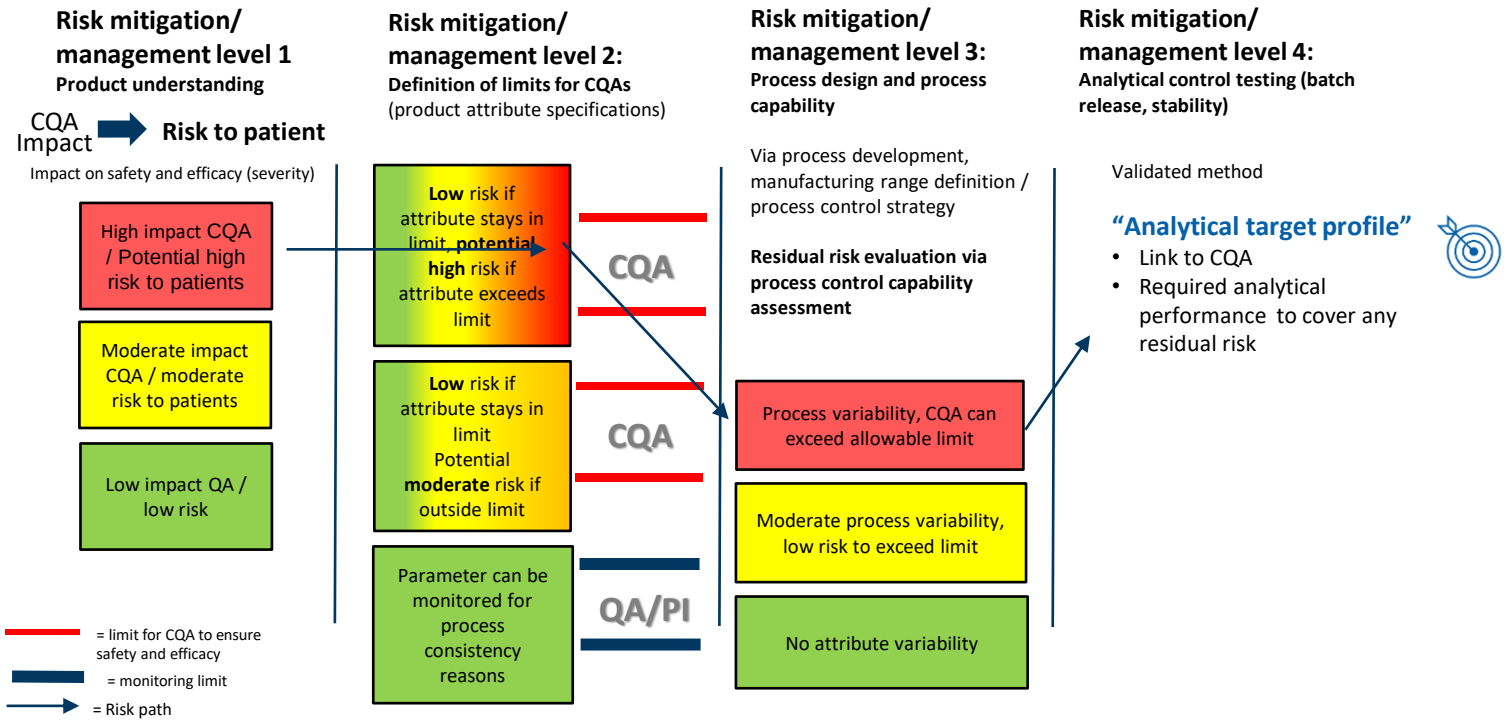
- Process understanding: Support process development

Knowledge generation

- Control system testing: Validated methods to control impact of critical quality attributes and process performance

Risk control

Risk-mitigation management in an integrated risk-based control strategy – How does it work?

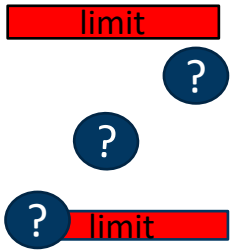


Analytical Target Profile as risk control tool

Critical risk control elements contained in an ATP:

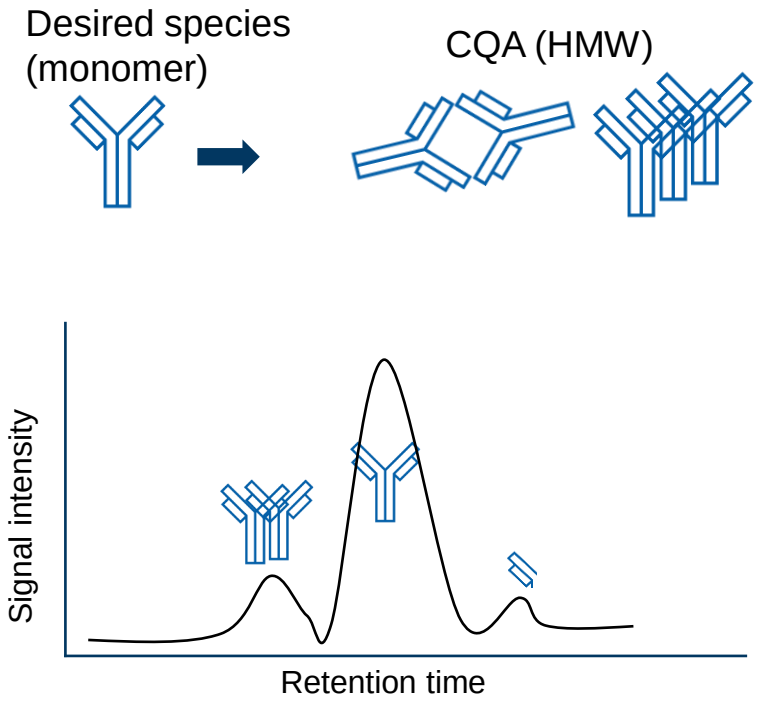
1. Link to CQA: Attributes with impact on safety and/or efficacy (potency: link to MoA; Size variants: high molecular weight species) **or** method outputs indicative for process consistency

2. Performance requirements: Avoids the risk of erroneously accepting a batch that does not meet specifications (unnoticed OOS)



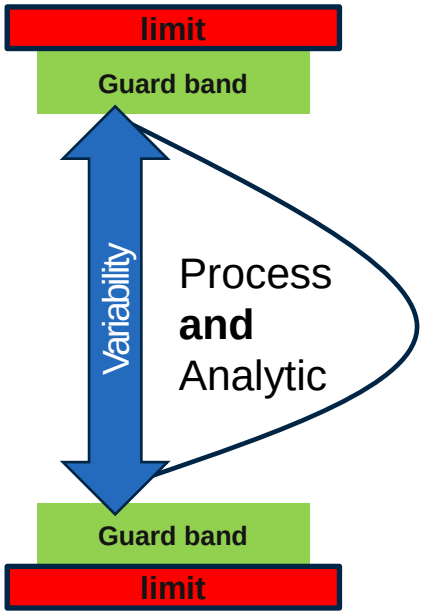
True value is influenced by method variability which is mainly driven by a combination of method **accuracy** (bias) and **precision**

1. Link to CQA: HMW vs monomer – example MAb



- Size exclusion chromatography as one of several possible methods to **relatively** quantify the amount of HMW
  - ATP can be method independent but i.e. for biologics the specifications are often not
- Method provides additional analytical information e.g. on the monomer (non-CQA), which is useful to monitor process performance consistency

2. Performance requirements: to avoid being erroneously outside specification



With the definition of **required** accuracy and precision (performance characteristics) the risk of being erroneously outside a safe and efficacy limit e.g. for HMWs can be significantly reduced

Statistical tools to define the required performance (accuracy and precisions) can be used such as:

- **Total Analytical Error**
- **Target Measurement Uncertainty**

Literature examples:

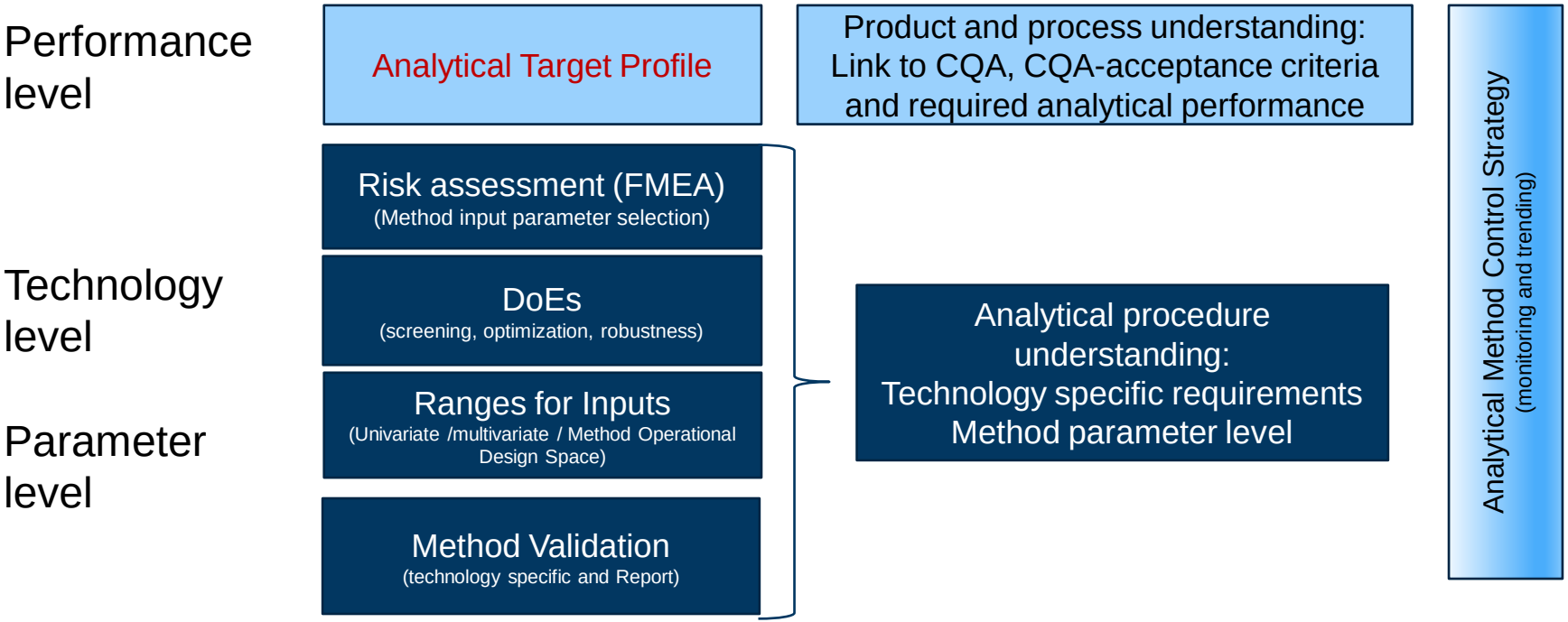
- USP<1220> - Analytical Procedure Life Cycle
- USP<1210> - Statistical tools for procedure validation
- E. Rozet, et al., *Anal. Chem.* 2012, 84, 1, 106-112
- P. Jackson, P. Borman, C. Campa, et al., *Anal. Chem.* 2019, 91, 4, 2577–2585
- R. Mayer, G. Gellermann, et al., Parenteral Drug Association, Inc.: Bethesda, Md., 2021; pp 363-95.

Risk mitigation through adherence to ATP

Adherence to ATP is

Any change to an analytical method that does not lead to a change of what is analyzed (**link to CQA**) or changes the **performance characteristics (performance requirements)** has **low impact** (risk to patient remains low)

Analytical Quality by Design – a tool box at different levels



How does it work on the different levels - example HMW

Performance level

- **Intended purpose (link to CQA)**
- **Performance requirements** (Accuracy and precision)
- **e.g.:** *Relative bias not more than 0.1 %*
- **Based on enhanced product and process understanding:**
  - considering: e.g. patient impact, acceptable abundance, relevance of test in the control system, information from characterization and forced degradation studies

Adherence to ATP on different levels – performance control

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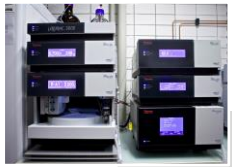

Technology level

- **Translation into method specific requirements** and controls (SSTs)
- **e.g.:** *The HMW peak needs to be separated from the monomer with a resolution factor of x*
- **Based on enhanced analytical understanding:**
  - to select best technology principle and translate ATP requirements into technology specific (measurable) performance requirements

Parameter level

- **Operator level, translation into method parameters** (PAR, MODR)
- **e.g.:** *Gradient of x % over x minutes at incubation temperature of 25 °C +/- x°C*
- **Risk assessment and experimental knowledge (FMEA, DoE):**
  - required to translate technology specific performance requirements into allowable method parameter settings

Performance Control: e.g.: **Quality control sample trending** with acceptance criteria **aligned** to ATP performance requirements

Covers ALL levels: ensures required performance on ATP level is continuously met (continuous verification/validation of result)

Enhanced understanding and performance based ECs - notification high, moderate, low

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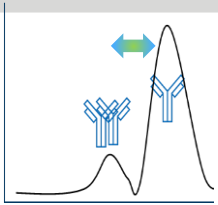

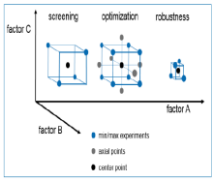

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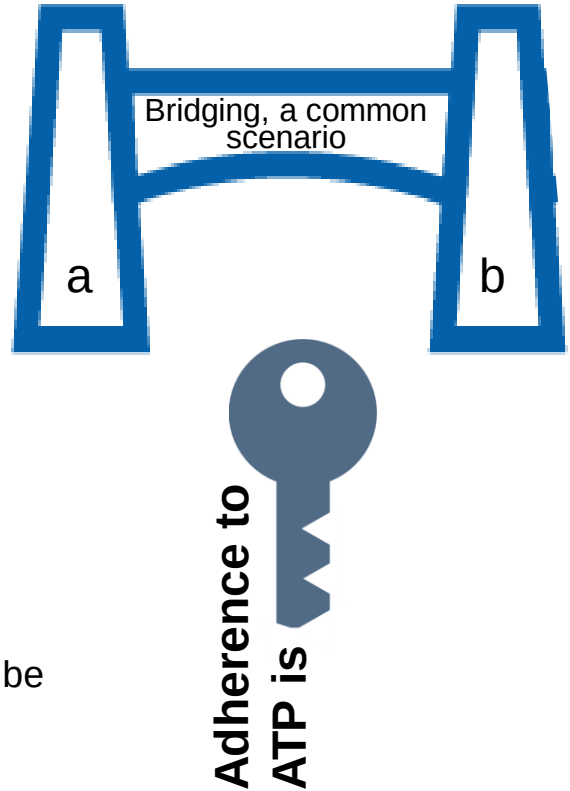
Changes and bridging – supported by performance based ECs

In a **complex** regulatory environment **the more change flexibility** a control system offers, **the more innovation and improvements** can be implemented during product life-cycle (some changes are no predictable at initial submission)



- The change evaluation should **always follow a structured approach** considering
  - Does the change impact the ability to link to CQA?
  - Does the change impact my ability to meet the performance requirements?

→ The structured bridging approach and **commitment to adhere to ATP** can be described in ICHQ12 tools such as **PLCM or "generic" PACMP**

Summary

- Changes outside ATP (performance requirements and link to CQA) could have a potential impact on safety and efficacy and require heath authority approval
- Adherence to ATP **is key** to **mitigate risk to patients**. A change implementation where adherence to ATP was demonstrated (bridging strategy and study) has consequently low risk
- Continuous performance control and pre-defined bridging strategies ensure **adherence to ATP**
- The risk control elements (ATP, performance control and bridging) that are based on enhance **understanding** are enablers for **proposing lower heath authority notification** categories on the parameter and/or technology level

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Thank you

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