Application of ICH Q2/Q14 to Procedure Development and Changes for Monoclonal Antibodies and Gene Therapy Products

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CASSS

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Inspired by **patients.**
Driven by **science.**

1. Method replacement: framework
2. Example 1: generic method, residual Protein A ELISA
3. Example 2: from ELISA to mass spectrometry for host cell proteins
4. Example 3: gene therapy

Guidelines on method development, replacement and validation

Analytical method/procedure lifecycle, from craddle to grave:

- ICH
  - Q14 Analytical Procedure Development
  - Q2(R2) Validation of Analytical Procedure

- PDA:
  - Technical report 57, to be replaced by:
  - BSR-PDA Standard 07 - Analytical Method Qualification-Validation for Biologic__V22 05-01-2024 | PDA

- Note:

The strategy around method replacement is sometimes called « bridging »

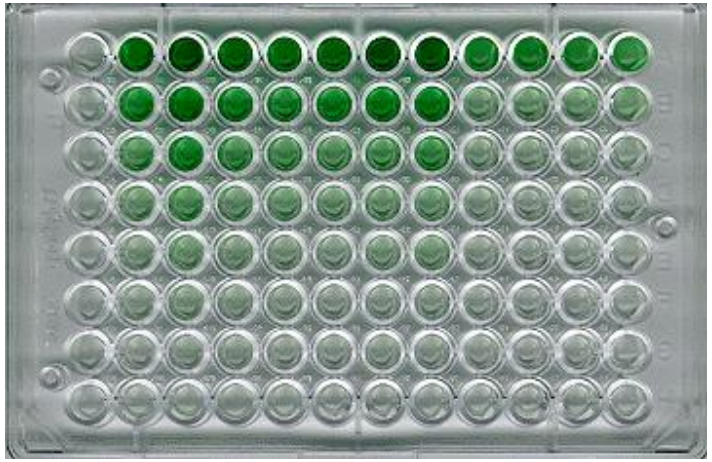
One of Rotterdam iconic bridges, Erasmusbrug:

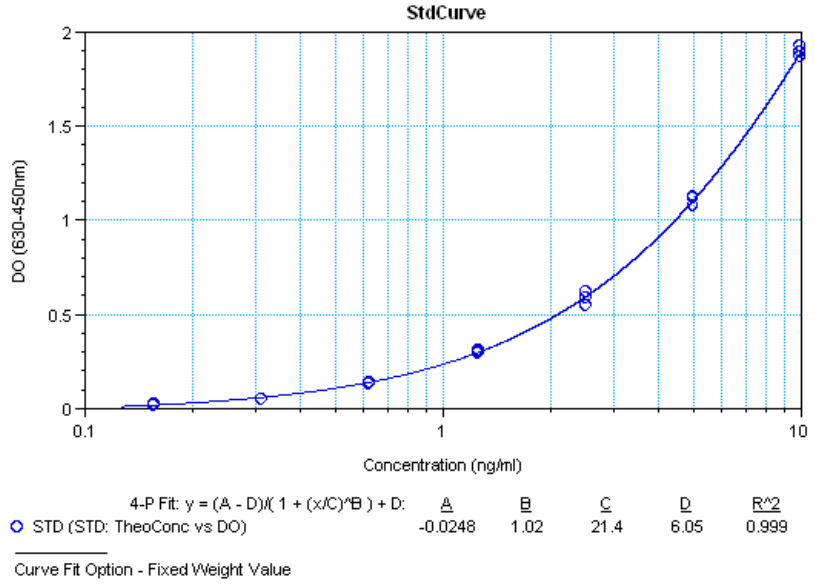
Application of ICH Q2(R2)/Q14 to an ELISA procedure

Change to an analytical procedure or change of analytical procedure?

From an ELISA to an ELISA procedure

- Protein A is a ligand used in certain downstream processes to capture the active (=an antibody)
- This ligand might leach into the drug substance
- ELISA is routinely used to quantify residual protein A



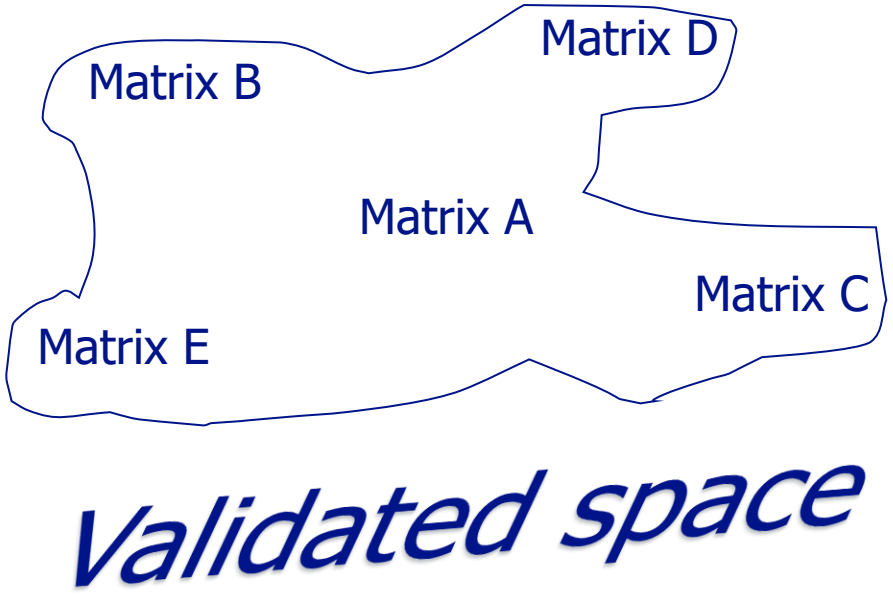


- Analytical target profile:
  - Quantification limit = 240 ng/mL drug substance
  - Maximum allowable variability = 60% total error on reportable result

Change to an analytical procedure or change of analytical procedure?

From an ELISA to an ELISA procedure

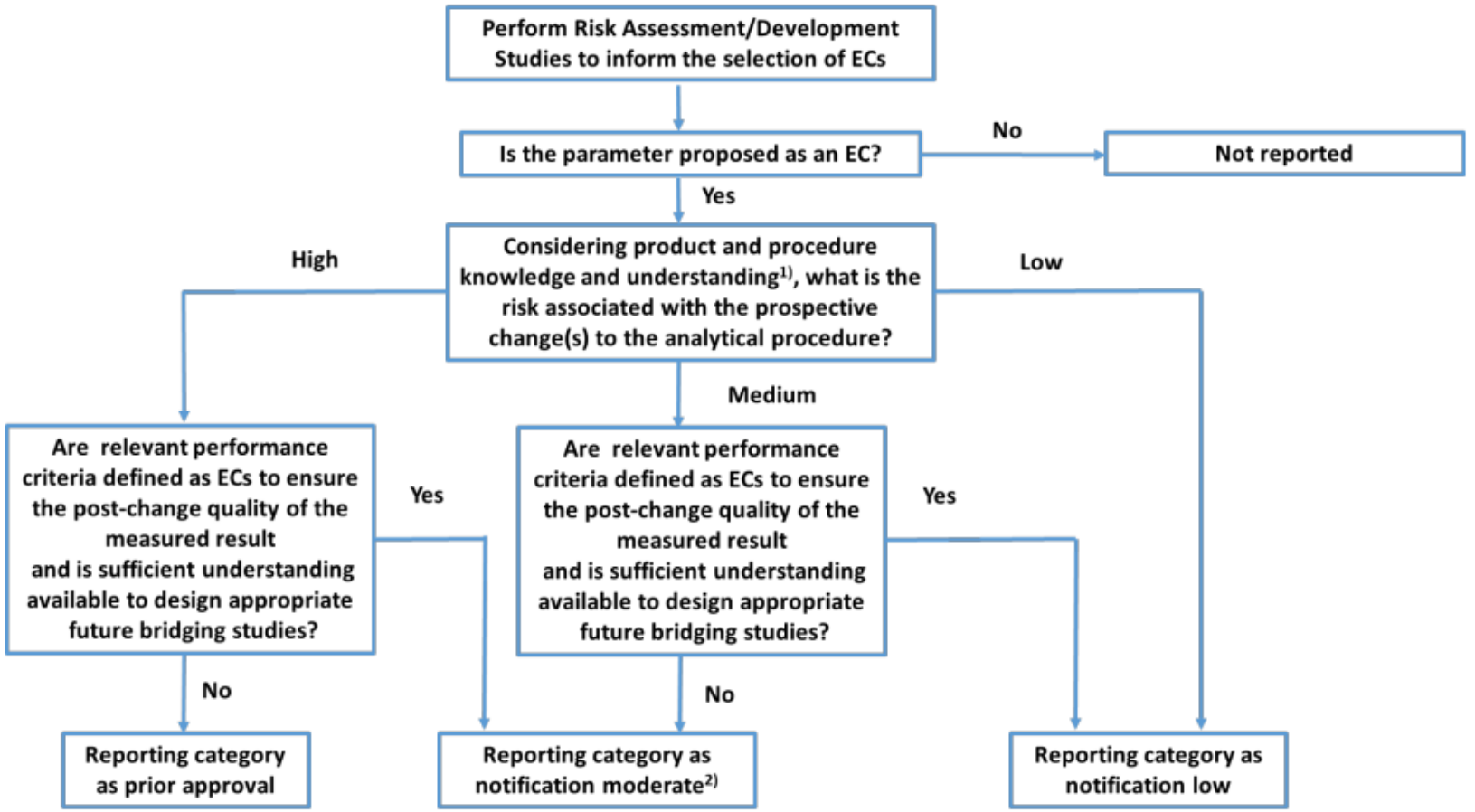
- 5 validations exercises demonstrate that for a variety of antibodies and formulations (="Matrices"), the method is fit
- Applying the method for a new antibody is, analytically speaking, a change to the method, ie, a change in sample
- How should we formulate the question of the validity of the method to a new type of sample?



+ Matrix E = ? Valid or Not ?

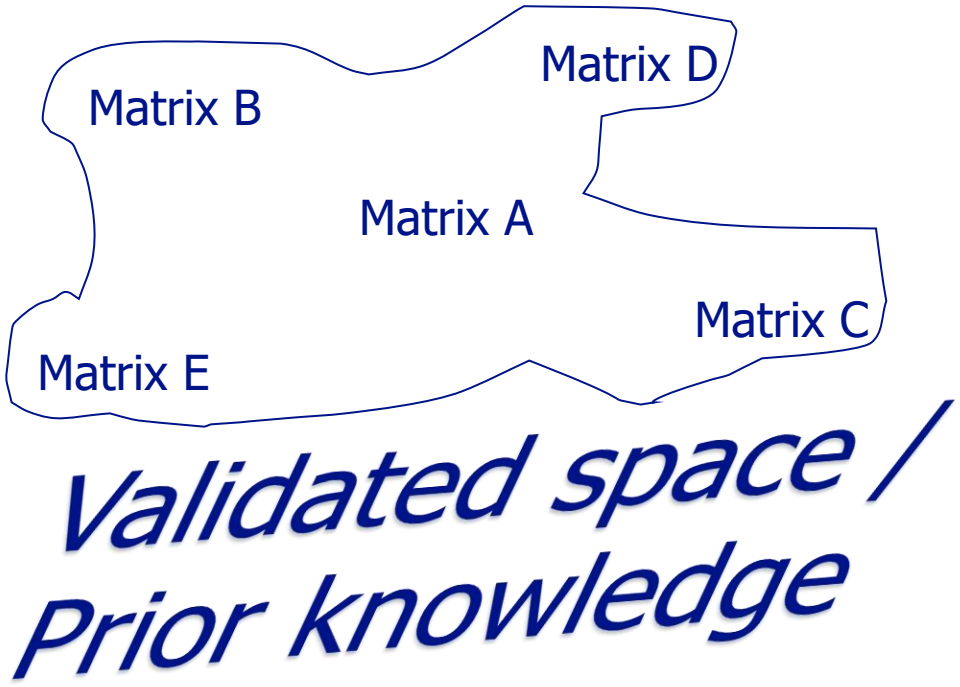
Is it a change within a method, as per ICH Q14?

Figure 2: Risk-based approach for identification of ECs and reporting categories for associated changes in the enhanced approach



Is it the use of prior knowledge within ICH Q2(R2)?

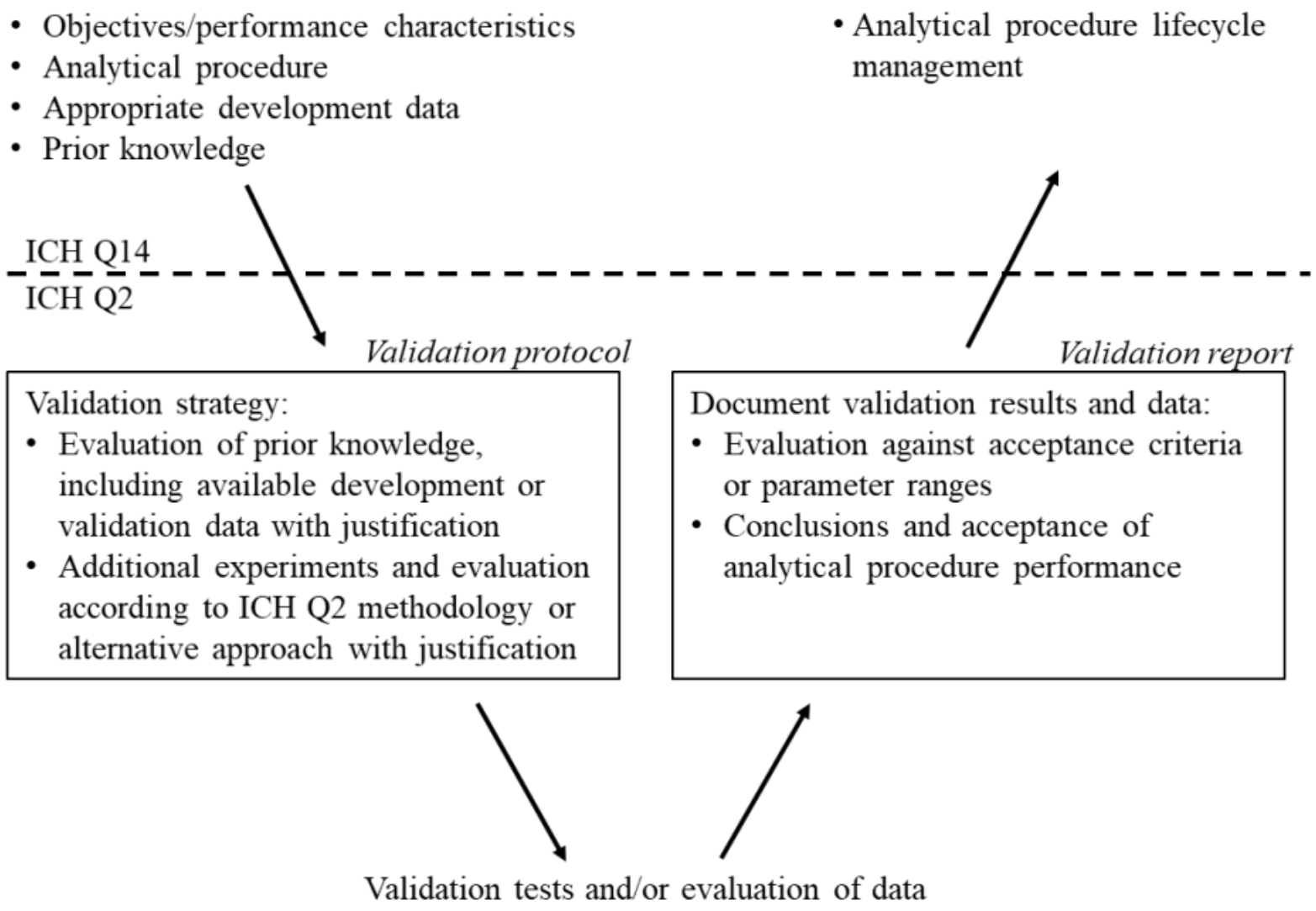
- 5 validations exercises demonstrate that for a variety of antibodies and formulations (="Matrices"), the method is fit
- The validity of the method for a new antibody is, by applying ICH Q2(R2), an evaluation of prior knowledge, if justified



+ Matrix E = ? Valid or Not ?

ICH Q2(R2) Guideline

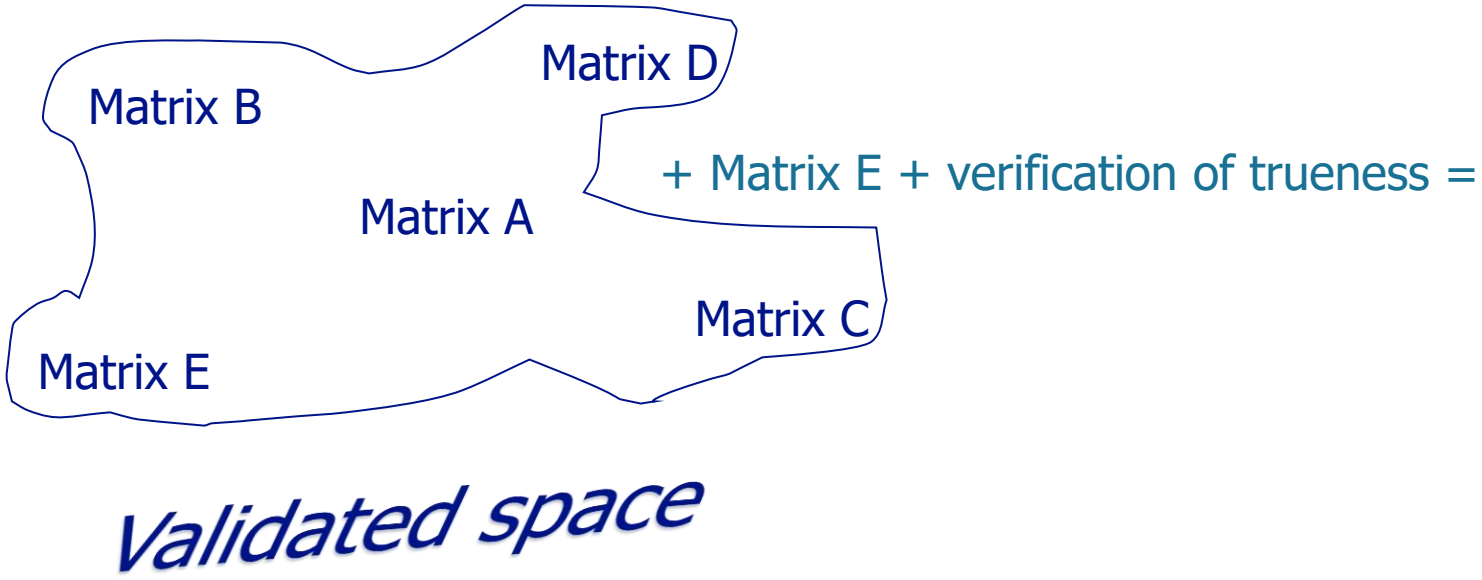
Figure 1: Validation study design and evaluation



Change to an analytical procedure or change of analytical procedure

From ELISA to ELISA

- Considering the procedure knowledge, the risk linked to the prospective change (ie, analyzing in Matrix E) is considered low
- The only risk is an interference of the matrix, eg, aspecific interaction between the antibody and protein A
  - Trueness is therefore verified by spiking one sample of antibody and protein A

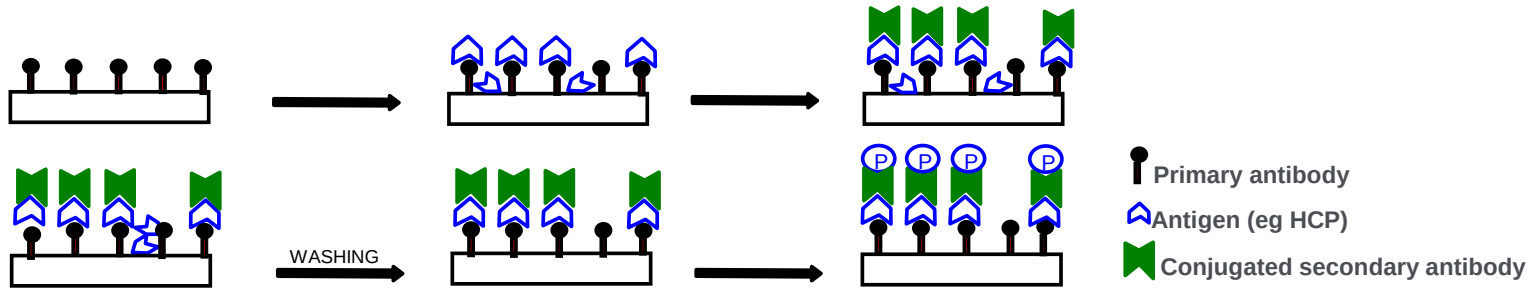


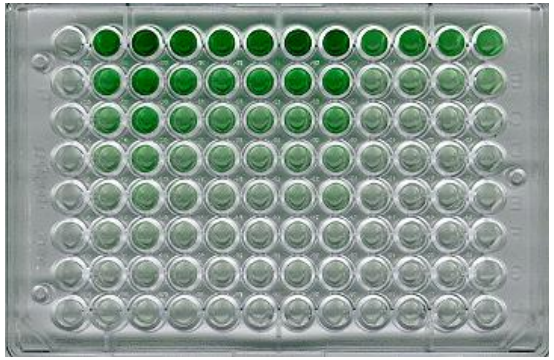
Change from an ELISA to a mass spectrometry procedure

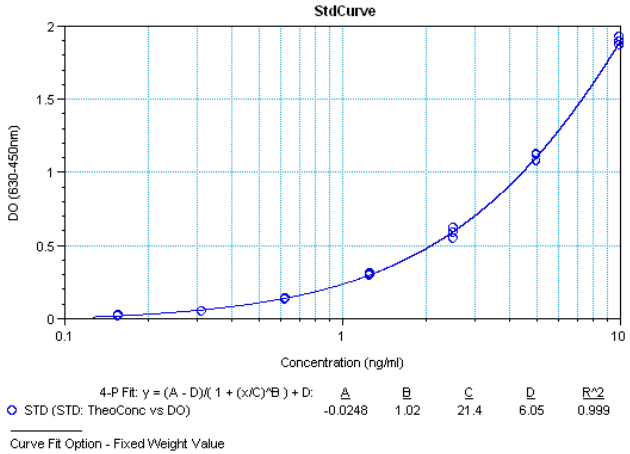
A more drastic change:
From ELISA to mass spectrometry for the quantification of HCP

- Host cell proteins: process-related impurities, produced by the CHO or *Escherichia coli* cells
- Residual quantity of host cell proteins has to be controlled at, eg, DS level
- Current gold standard for the quantification of the host cell proteins: ELISA

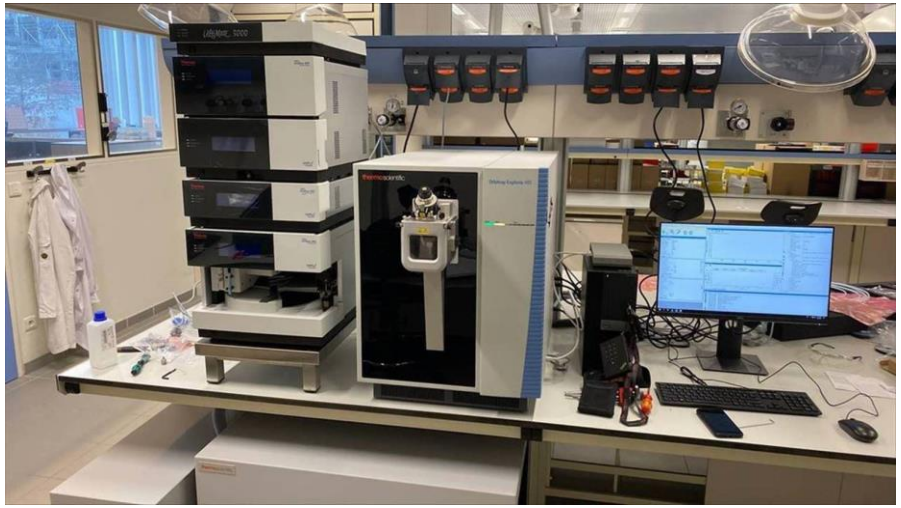
From: ELISA







To: Mass spectrometry



Change to an analytical procedure or change of analytical procedure?

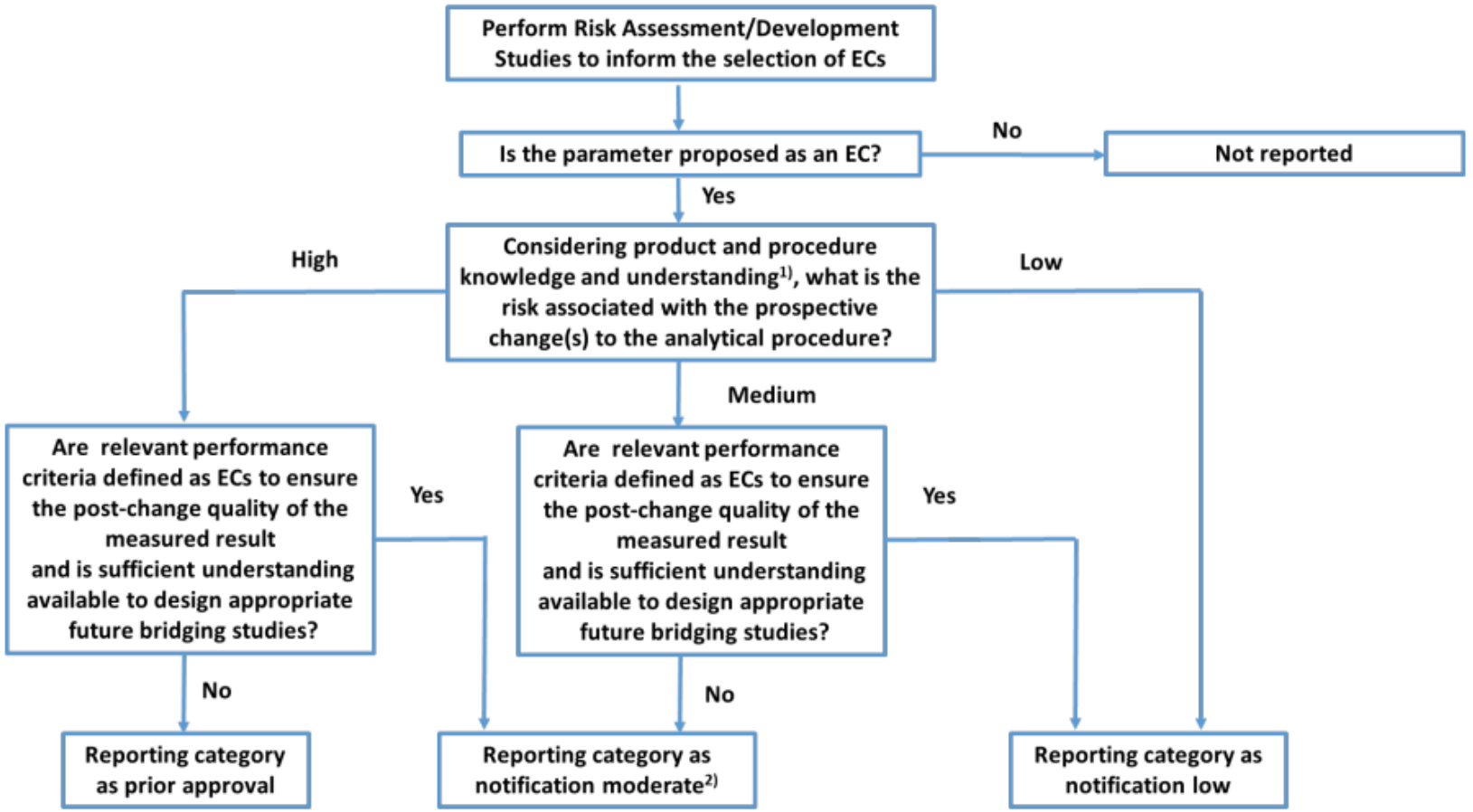
From ELISA to… mass spectrometry

- ELISA is routinely used to quantify host cell proteins
- Mass spectrometry is being validated for the same goal, same ATP
- Analytical target profile:
  - Quantification limit = ng/mL drug substance
  - Maximum allowable variability = 60% total error on reportable result

- How can the enhanced approach facilitate switching from ELISA to MS?
- "Changes to analytical procedures can occur throughout the product lifecycle and could involve modification of existing procedures *or a complete replacement including introduction of a new technology*." (ICH Q14, chapter 7)

Is it a change between methods, as per ICH Q14?

Figure 2: Risk-based approach for identification of ECs and reporting categories for associated changes in the enhanced approach



Change to an analytical procedure or change of analytical procedure

From ELISA to… mass spectrometry

- Mass spectrometry has several advantages to control the quality of the product
  - It does not rely on recognition of HCP by antibodies
  - It is a physicochemical method rather than immunochemical method
  - It allows the identification of individual HCPs

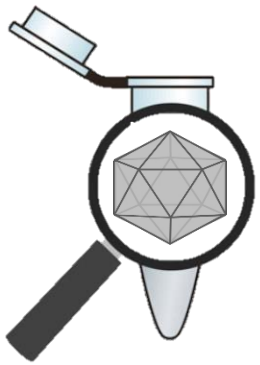
- But the change is very drastic:
  - Established Conditions helps changes within one technology (from ELISA to ELISA, eg, dilutions of samples)
  - Could the thinking of EC help if we change from ELISA to MS? The set conditions themselves drastically change
- Are we doomed to bridge the two methods although the scientific expectation is that it will be a comparison between apples and pears?

Q1A(R2) Guideline.pdf (ich.org)
Q6B Guideline.pdf (ich.org)

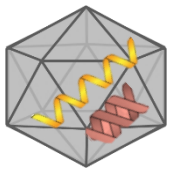
Enhanced approach for rAAV capsid content variants by SEC-MALS

Michel Degueldre

rAAV capsid content variants in CMC

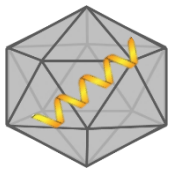


DNA containing Capsids



Overpacked Capsids

Encapsidated DNA is larger than 1 copy of the correct transgene

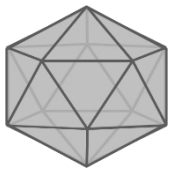


Full Capsids

Intended product

Partially-filled Capsids

Packaging of partial transgene or unwanted packaged DNA
(host cells, plasmids, …)

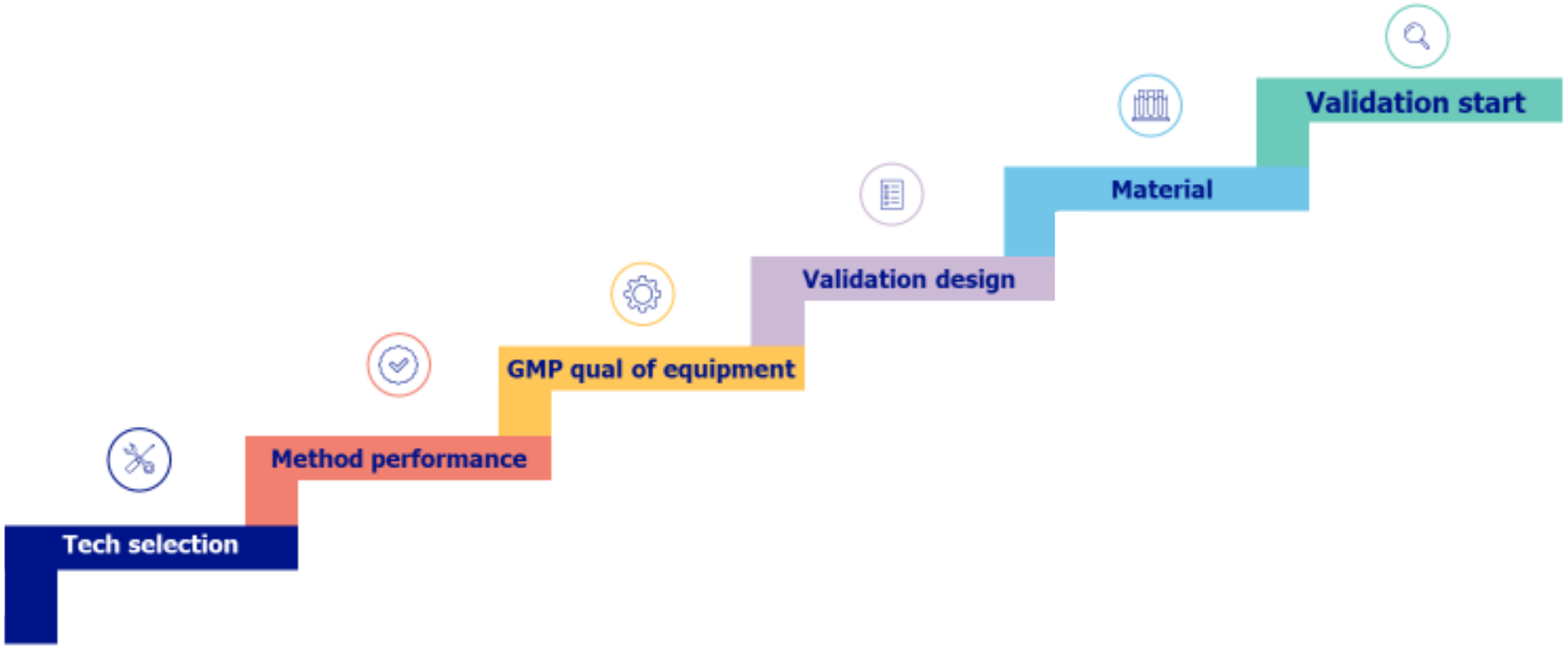


Empty Capsids

No DNA packaging

AAV Empty Capsids: For Better or for Worse?, Molecular Therapy, 2014
Gimpel et al. Molecular Therapy, Methods and Clinical Development, Vol 20, March 2021
DHC White Paper i(Jan 2023) n public consultation untill April 2023
British Pharmacopoeia: Advanced Therapy Medicinal Products Guidance Characterisation of the Capsid Particle Population in rAAV Products. https://www.pharmacopoeia.com/download/document/atmpguidance.
Optimizing AAV analytics to improve the safety, efficacy, and yield of AAV-based gene therapies. In: Alliance for Regenerative Medicine. https://alliancerm.org/indication-data/optimizing-aav-analytics/.

The GMP journey



Analytical tools in the GT landscape

DS/DP release and stab testing – Top most used techniques

Vg/capsid titer ratio (PCR/ELISA)

SEC-MALS

AUC

AEX-Fluo

Compliance

- AUC has software that is not 21CFR Part 11 compliant – "Workarounds" are required to meet health authorities' expectations.

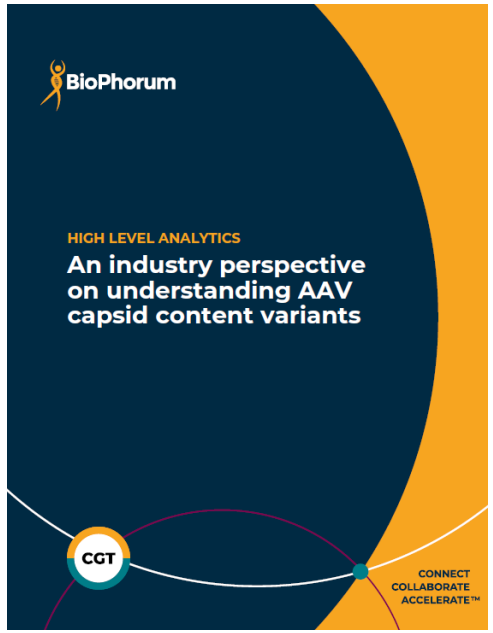
Performance

- PCR/ELISA approach relies on two different methods to get a ratio eventually
  - Inherent variability of each method
  - It might not suit its intended use; lack of precision.

Agility

- AEX separation is sensitive to the change of negative charge state of the sample ➔ re-development might be necessary for any transgene and/or serotype changes.

➔ SEC-MALS was selected
✓ E2E vision pre-tox up to clinic
✓ CMC Acceleration



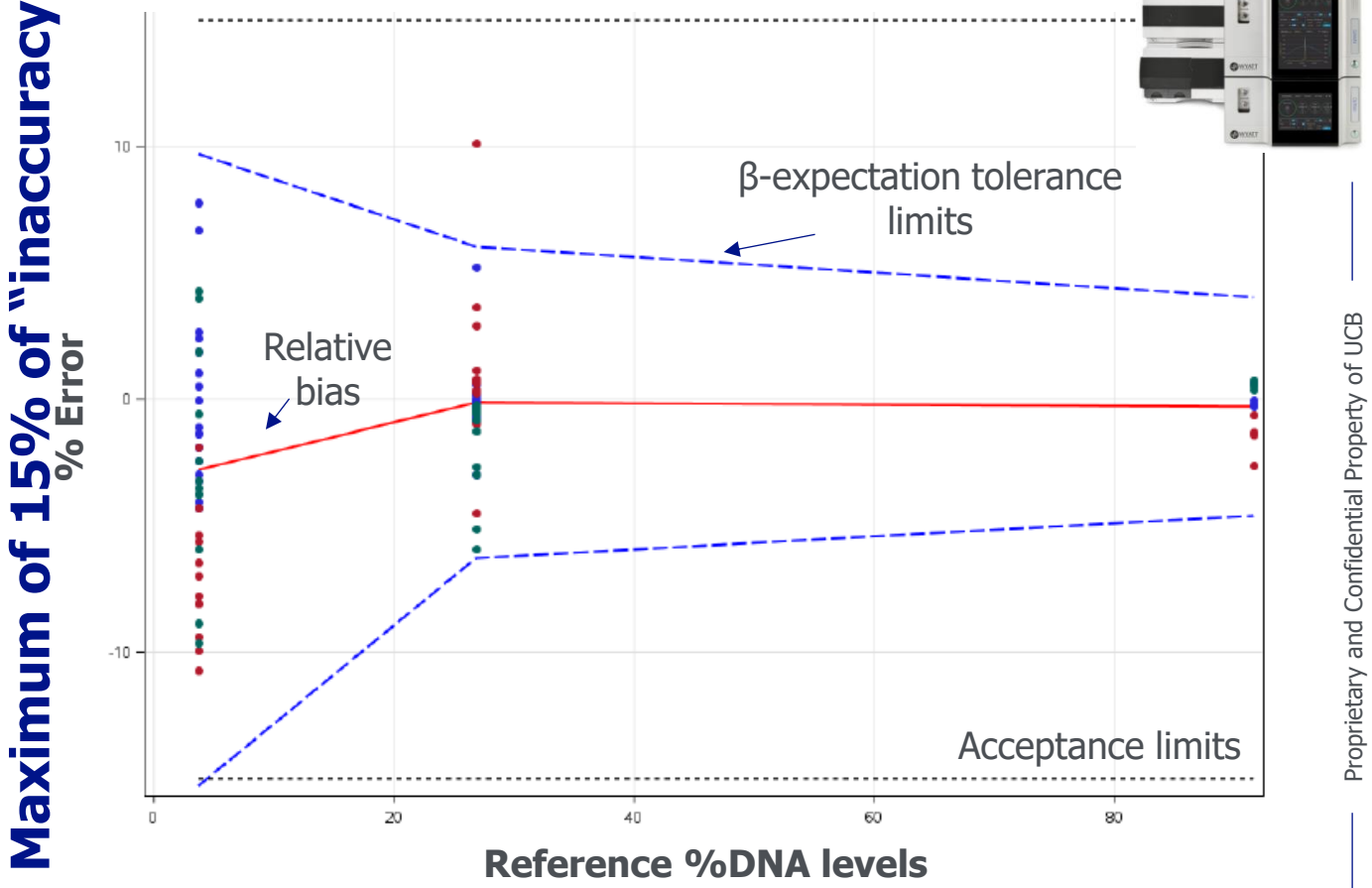
An industry perspective on understanding AAV capsid content variants. In: BioPhorum Operations Group. https://www.biophorum.com/download/an-industry-perspective-on-understanding-aav-capsid-content-variants
Control of empty, full & partially filled capsids (biophorum.com)

Method prevalidation – TAE in practice

SEC-MALS

- 3 levels of %DNA containing capsid

- Linearity / precision / trueness assessment assessed based on TAE profile



across the range
[4;92]% of DNA containing capsid

GMP qualification of HPLC-MALS system

- Validation summary report of the HPLC-MALS approved since Q4 last year
- SOPs, logbook in place

Tech selection

Technology assessment
➔ SEC-MALS

Method performance

Total analytical error

GMP qual of equipment

Equipment lifecycle management

ICH Q2(R2)
ICH Q14

Material representativity

Link with specifications

GMP

GMP validation design

Validation design

ICH Q2(R2)
ICH Q14

GMP qual of equipment

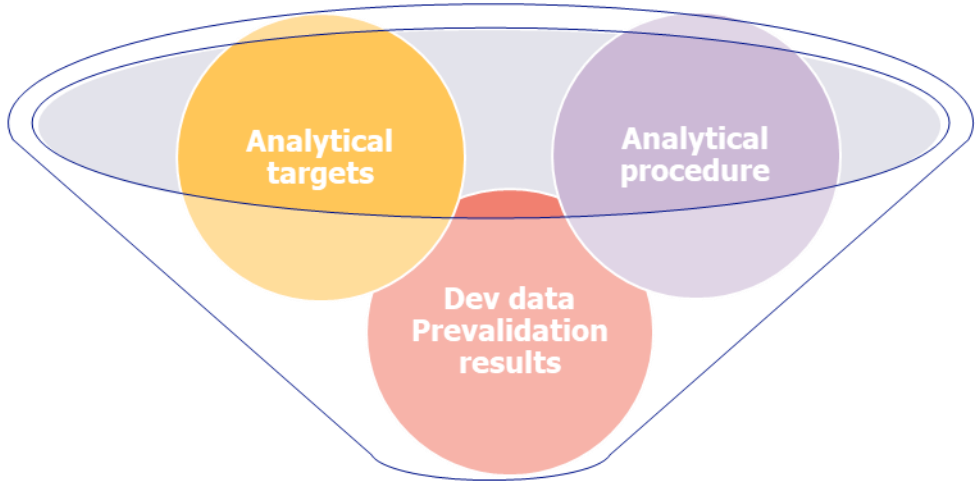
Equipment lifecycle management

Method performance

Total analytical error

Tech selection

Technology assessment
➔ SEC-MALS



Validation protocol

Validation tests

Validation report

Evaluation versus acceptance criteria
Conclusions and acceptance of the analytical procedure

Lifecycle management

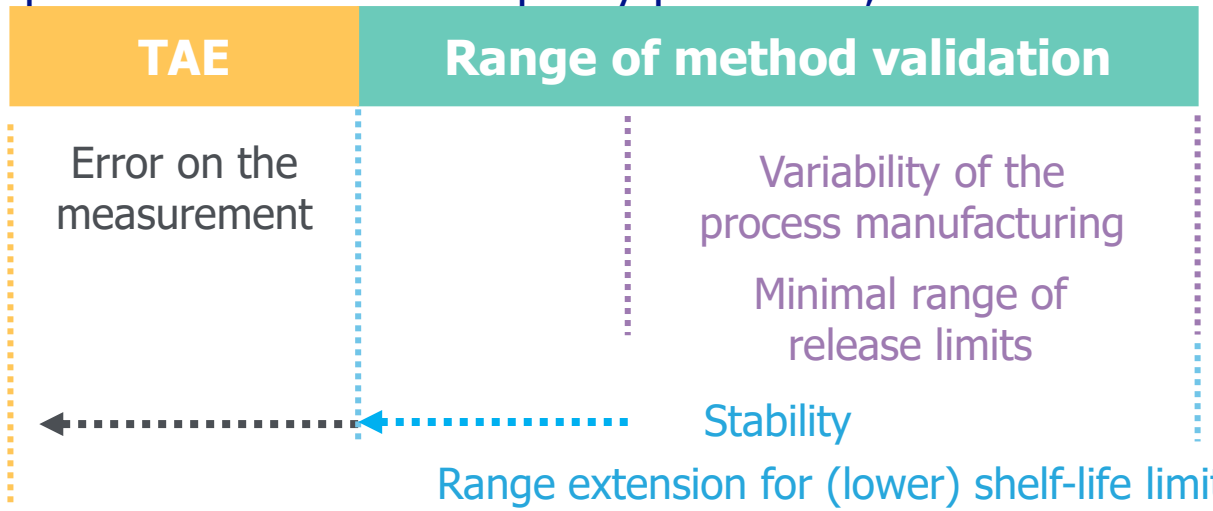
The specification range

A question of quality (and variability) – DS/DP – Product variant species

Release limits are expected to be tighter than the shelf-life limits as the proportion of full capsid species might decrease in stability study

The method still needs to be proved to be stability-indicating

%DNA containing capsid is considered as a purity parameter, therefore:



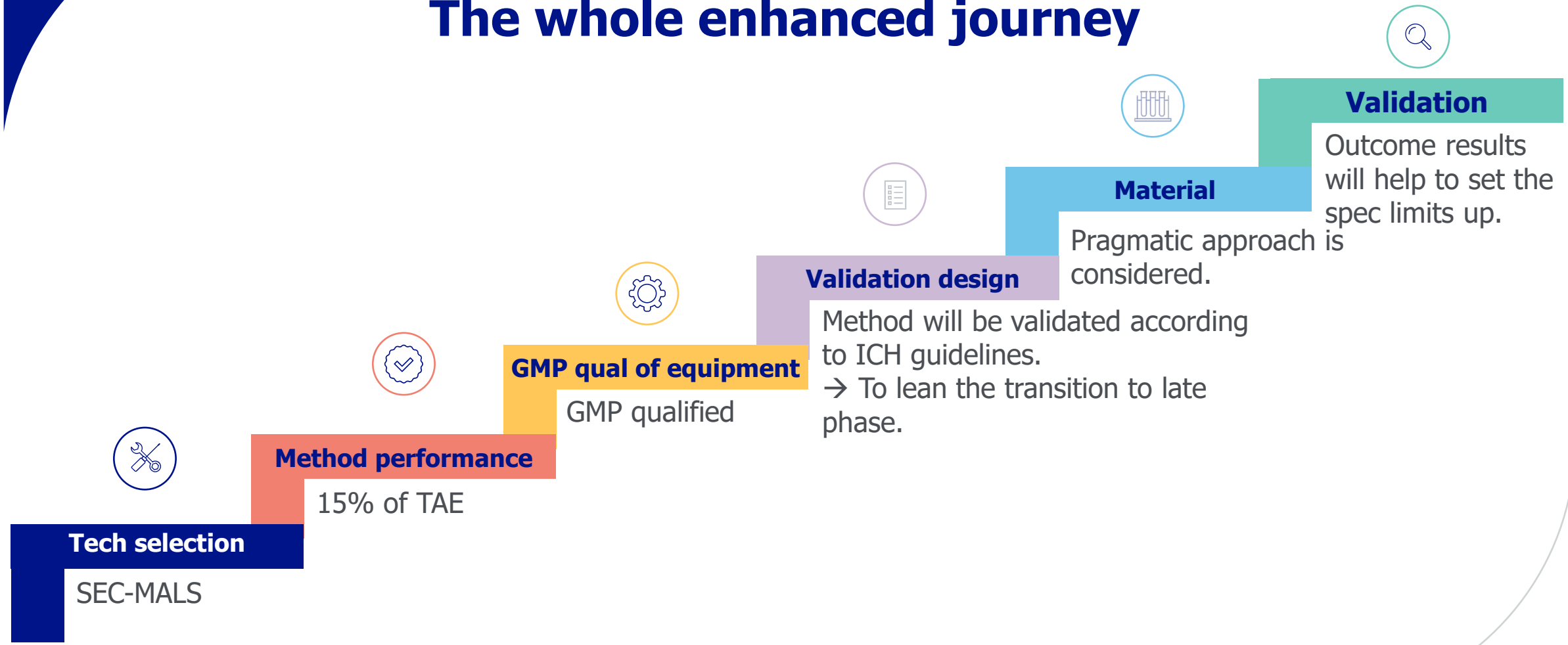
Limits setting of the attribute "%DNA containing capsid by SEC-MALS" is challenging in early phase because of limited knowledge of the product/platform

Specifications and limits are chosen to confirm product quality, here drug efficacy

→ Notion of stability-indicating profile to be built through product lifecycle/development

Q1A(R2) Guideline.pdf (ich.org)
Q6B Guideline.pdf (ich.org)

The whole enhanced journey



Conclusions

- ICH Q2**(R2)** and Q14 give a reasonable frame to method development and validation
- Use of prior knowledge for development and validation is a huge advantage to get more robust methods
- Method replacement, ie, replacing one technology by another for a certain quality attribute, is still seeking its way…

Acknowledgments

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- **Biological Method Development**
- **Physico-Chemical Analytics**

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