ICH Q2 / Q14

From good to great

CASSS CMC Summer Forum

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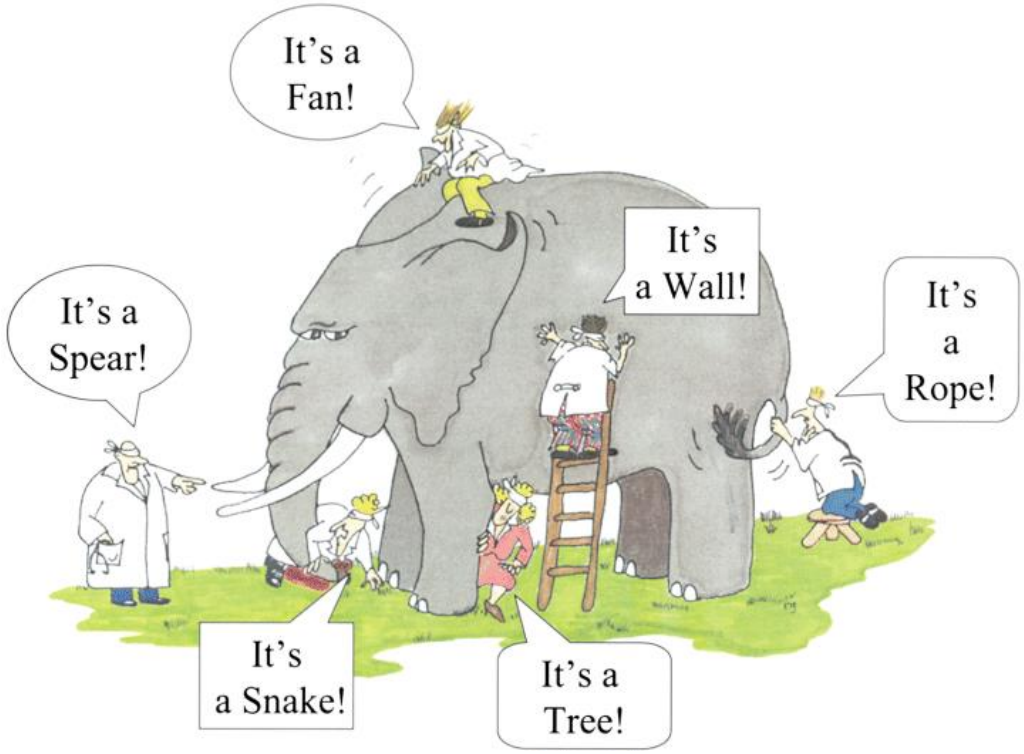
The importance of analytical procedures (AP)



- Our materials, processes and products are all characterized by analytical procedures
- The property / quality of a material appears only as good as perceived through the analytical procedure

How big is the elephant? An estimation…

Starting and raw materials:

4 Procedures x 5 Materials =20 Procedures

In process controls (API):

2 Procedures x 5 Materials =10 Procedures

API Precursors:

4 Procedures x 5 GMP Steps =20 Procedures

API:

10 Procedures =10 Procedures

Excipients:

5 Procedures x 5 Excipients =25 Procedures

In process controls (Drug product):

3 Procedures x 5 Materials =15 Procedures

Drug Product:

6 Procedures x 2 Strengths =12 Procedures

Sum = 112 Procedures

1 Manufacturing Process but easily > 100 Analytical Procedures !

ICH Q2 – A good guideline …

Q2(R1)
Document History

First Codification	History	Date	New Codification **November 2005**
Parent Guideline: Text on Validation of Analytical Procedures			
Q2	Approval by the Steering Committee under *Step 2* and release for public consultation.	26 October 1993	Q2
Q2A	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	27 October 1994	Q2
Guideline on Validation of Analytical Procedures: Methodology developed to complement the Parent Guideline			
Q2B	Approval by the Steering Committee under *Step 2* and release for public consultation.	29 November 1995	in Q2(R1)
Q2B	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	6 November 1996	in Q2(R1)
Current *Step 4* version			
Q2A and Q2B	The parent guideline is now renamed Q2(R1) as the guideline Q2B on methology has been incorporated to the parent guideline. The new title is "Validation of Analytical Procedures: Text and Methodology".	November 2005	Q2(R1)

- Step 2 in 1993 and 1995
- Q2R1 with minimal changes in 2005
- 2021 and still a good guideline!

Then in 1995…

Now…

Mobile phones

HPLC with Diode-Array detection was a Luxury!

Analytical Technology

Hyphenated techniques like HPLC-MS are standard

4%

BLA approvals for new biological drugs*

25% (in 2020)

… and new vaccines too!

*https://www.fda.gov/drugs/nda-and-bla-approvals/nda-and-bla-calendar-year-approvals

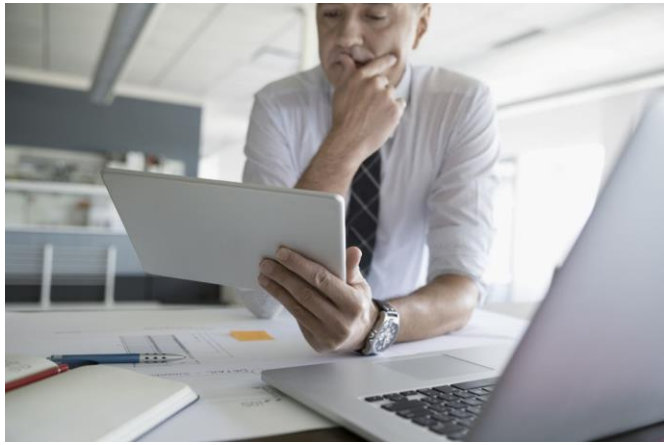
Why change?

- Evolution of new analytical technologies and multivariate analysis
- ICH Q8-Q10 guidelines were created
- Methodology for analytical procedures development has evolved in the same direction (analytical QbD, enhanced approaches)
- Increased importance of biopharmaceuticals and related analytical procedures
- More widespread use of design of experiments and CMC statistical tools
- New harmonized principles on post-approval changes in ICH Q12

A day in the lab with Maria*…

(*Maria is a fictional character)

Maria’s first challenge of the day – Cross-validation



Maria’s supervisor asked her to establish thermogravimetry as alternative technique to water (Karl-Fischer) and demonstrate that both procedures can be used to determine the water in the API

How to cross-validate and compare procedures if they are so different in technology?

From Validation Characteristics …

Validation Characteristic	Karl-Fischer Titration	Thermogravimetry
Accuracy	Absolute measurement, amounts titrant used is proportional to amounts of water by principle	Secondary procedure comparison (with KF titration)
Precision	Repetitive analysis of sample preparations	Repetitive analysis of sample preparations
Specificity	Specific for water, some side reactions may occur with other components	Not specific for water only, other volatile components may also be detected
Linearity	Titration levels of water	By principle (weighing) linear, why need to demonstrate?
Range	Better at lower water levels	Better at higher water levels

- Validation experiments may look very different depending on the technical principles used
- Not all ICHQ2 characteristics make sense to be experimentally verified

…to Performance Characteristics

Intended Purpose:	**Determination of water content in API (Specification NMT 2.0 %)**	
Performance Characteristic	**Criteria**	
Accuracy…	Max 10% rel. bias from theoretical water content	… over the range of at least 0.2-2.4 % of specified water level
Precision…	max. 5 % RSD for n=6 samples	
Specificity…	No interference by other components resulting in a bias of greater than 10% rel.	

- Driven by product requirements
- Technology independent
- Focus on the required performance of the analytical procedure
- Defines the suitability for its intended purpose
- Common denominator

From good to great when

- Performance characteristics drive the validation methodology
- Performance characteristics drive the bridging strategies
- Analytical procedure performance is defined based on product needs and knowledge

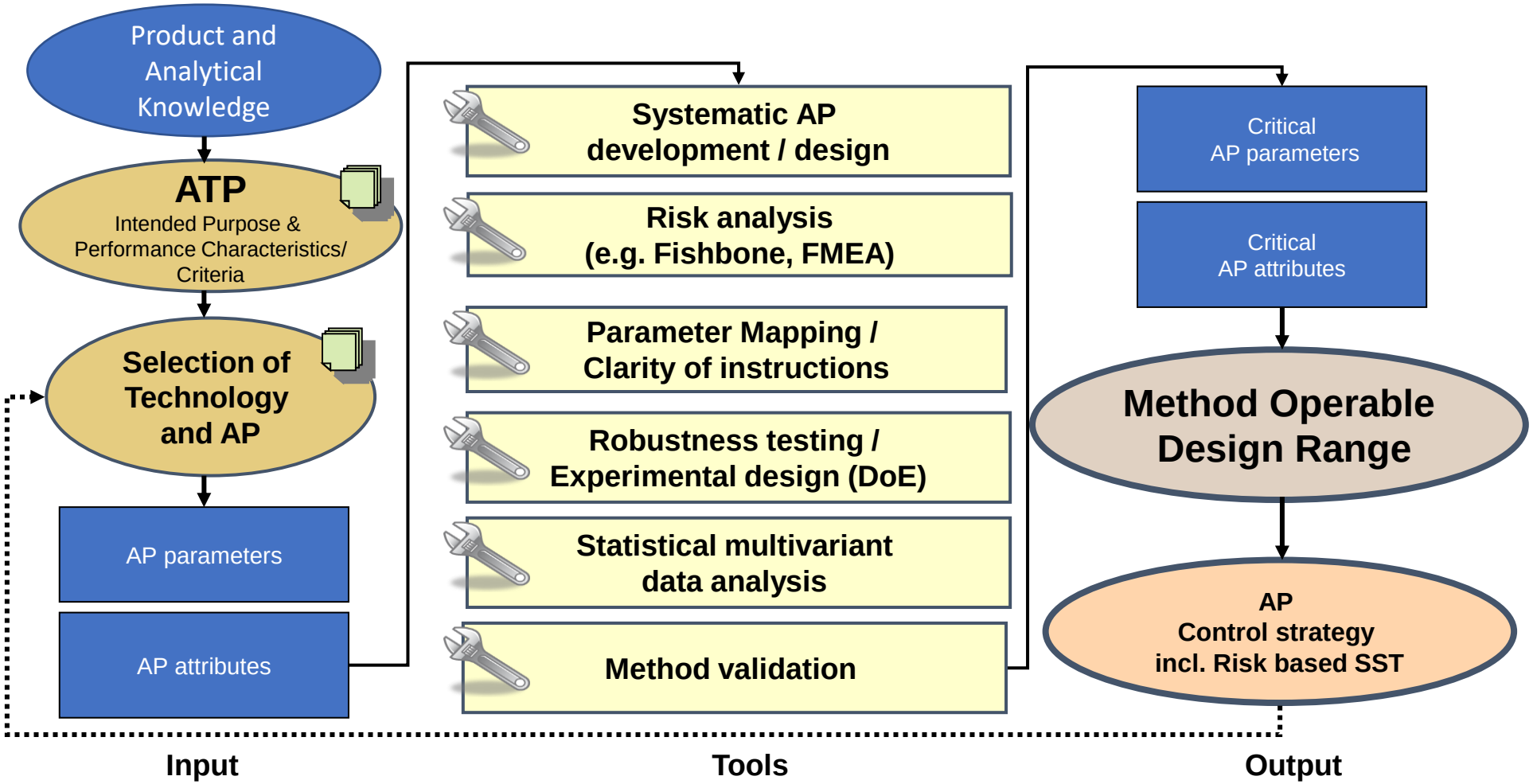
Next challenge of the day – Maria's discussion with QA

Maria has developed a new UPLC procedure for a new oncology product. She has created a comprehensive dataset to understand the procedure's performance. She has therefore proposed to include relevant development data into her validation dataset rather than repeating the experiments again for the validation. QA fears a compliance issue and insists on re-creating data once a validation protocol has been signed off.

Is validation a checkbox exercise?

How to reduce experimental efforts, unnecessary costs and accelerate drug availability?

Key Elements of Quality by Design (QbD) for Analytical Procedures



Not all elements may exist or are meaningful to be used!

From good to great when

- Pre-existing knowledge can be used
- Development data can be used in lieu of validation data
- Individual enhanced tools and elements (including MODR) are used only when meaningful
- Supportive information from an analytical development can be submitted
- A new eCTD module in ICH M4Q is in place

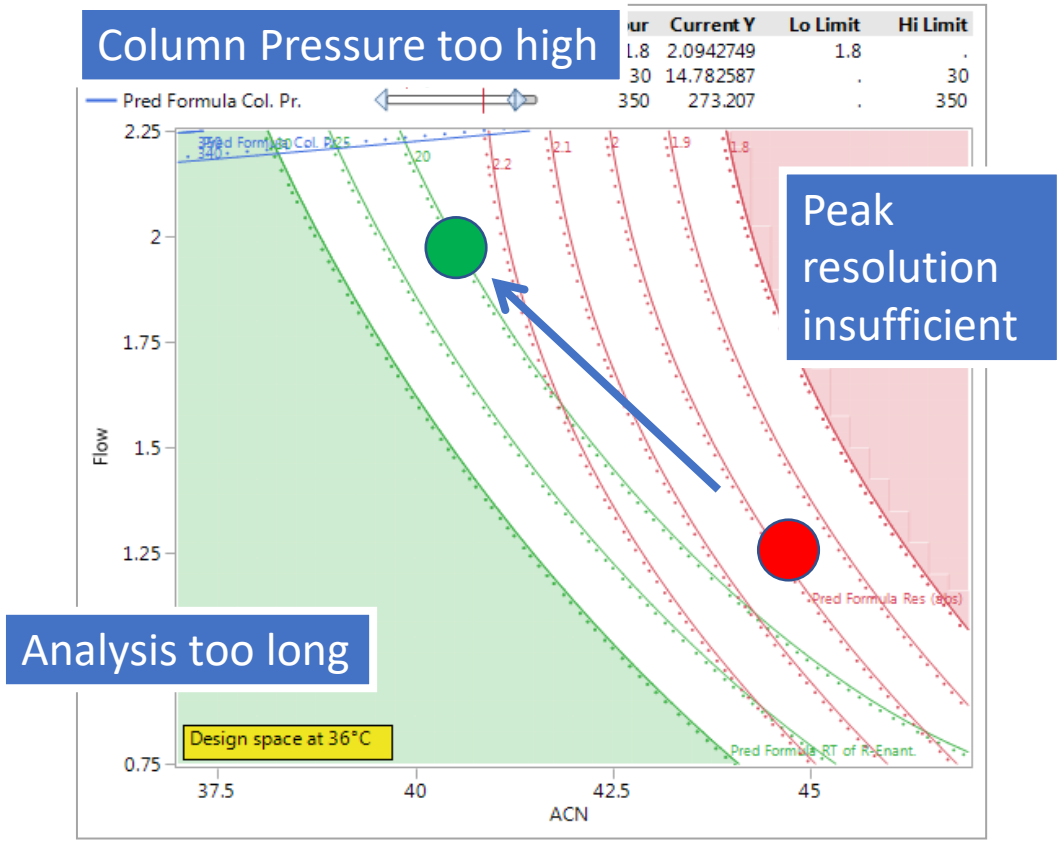
Unexpected challenge – The dying chiral column

A call came in from a partner laboratory. The lab wants to increase the costs per analysis as the SST for enantiomer resolution fails after approx. 200 runs. The laboratory has worked on proposals for adjustments to maintain column performance for longer… but that would require the change of the parameters of the analytical procedure.

Are the adjustments worth the effort for changing the procedure.

Shall we just accept the additional financial burden of replacing columns often instead?

Adjustment of analytical procedures to increase performance



- The column costs are 20kUSD/year
- The cost of changing the procedure internationally is 250 k in registration fees and internal costs for preparation

→Maria decides not to change and accepts the additional costs and work with buying frequently new columns, contributing to the product costs

Source: C. Chevreau, Elanco Animal Health, with permission

From good to great when

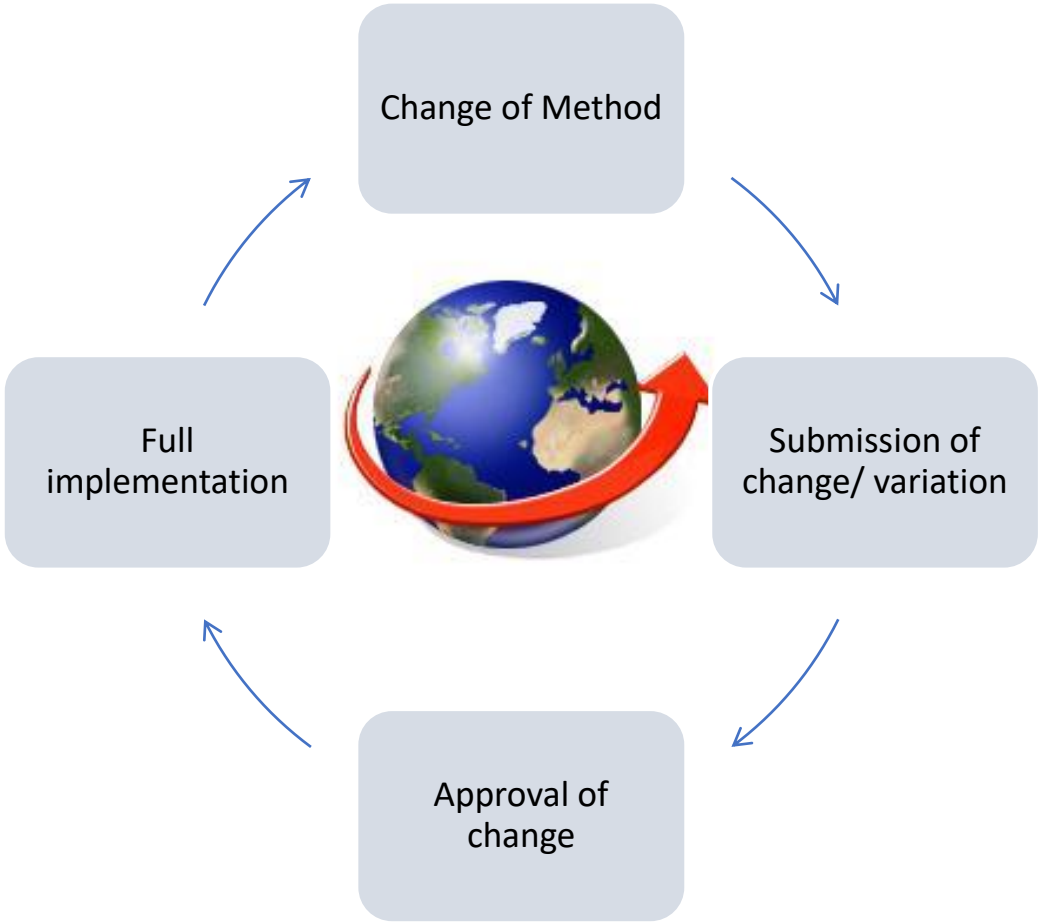
- Minor adjustments increasing the analytical procedure performance or reliability should be
  - Easy
  - Immediate
  - Within the Company’s PQS

The last challenge of the day– The “one-fits-all procedure”

Maria is attending the presentation of the company’s summer intern. The student has successfully developed a new uHPLC procedure which can monitor the degradation products of 5 different marketed products with the same analytical procedure. He also achieves a better resolution of individual degradation products. Applying the procedure would save more than 30% of resources by pooling stability samples of multiple products in one analysis. Additionally, the organic solvent waste was reduced by 50%.

What would it take to change the analytical procedures for all the products.
How and when could that harmonized status be reached?

Dimension 1: Change Procedure



Triggers:

- Increased knowledge & Innovation
- Changes in Regulations & Compendia
- Health Authority Requests

Dimension 2: non-consistent change classification on a global level

Example	US	Europe (centralized)	Japan
Change of Water determination (KF to Coulometric)	Minor	Type Ib	Notification
Replacement TLC by HPLC for (purity)	Moderate	Type Ib	Partial Change Application
Alternative analytical method: conventional HPLC and uHPLC	Minor	Type Ib	Partial Change Application
Change in a Biological Assay Technique	Major	Type II	Partial Change Application

Non-consistent classification of changes leads to different implementation timelines

Common understanding of AP change risk

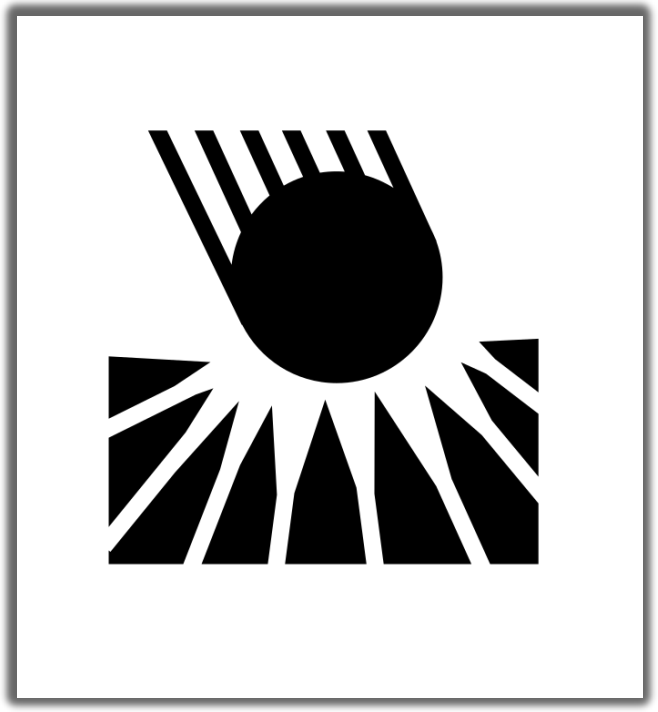
Impact on product attribute tested

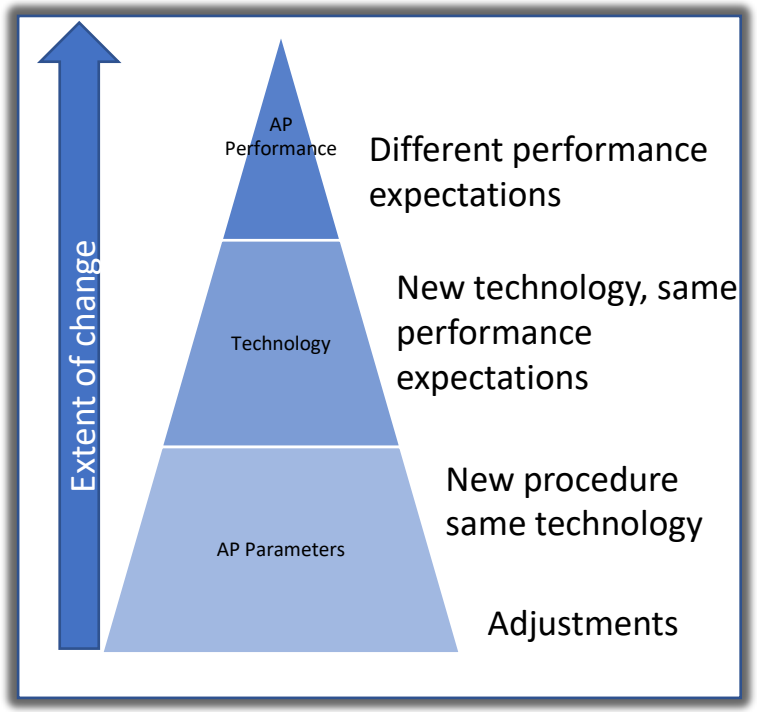
+

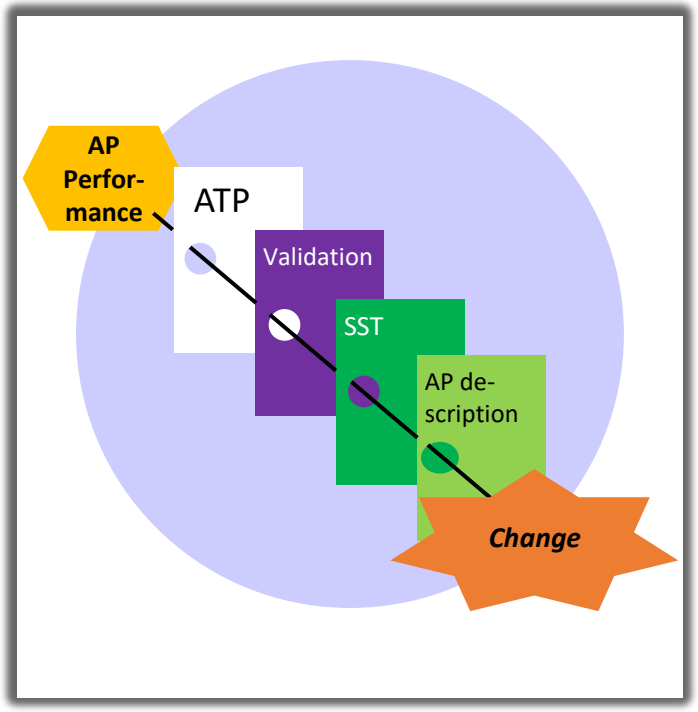
Extent of Change

+

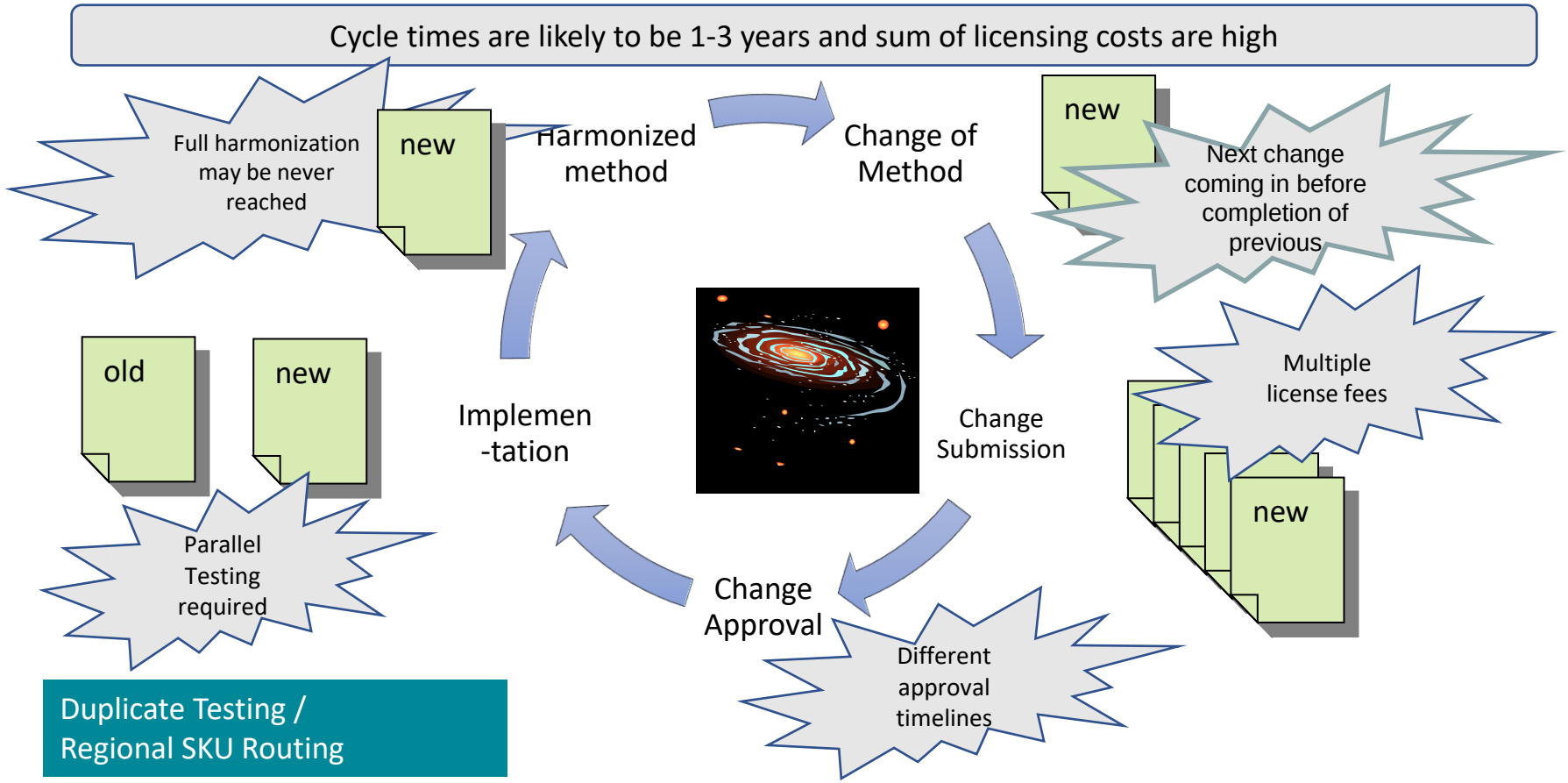
Levels of control







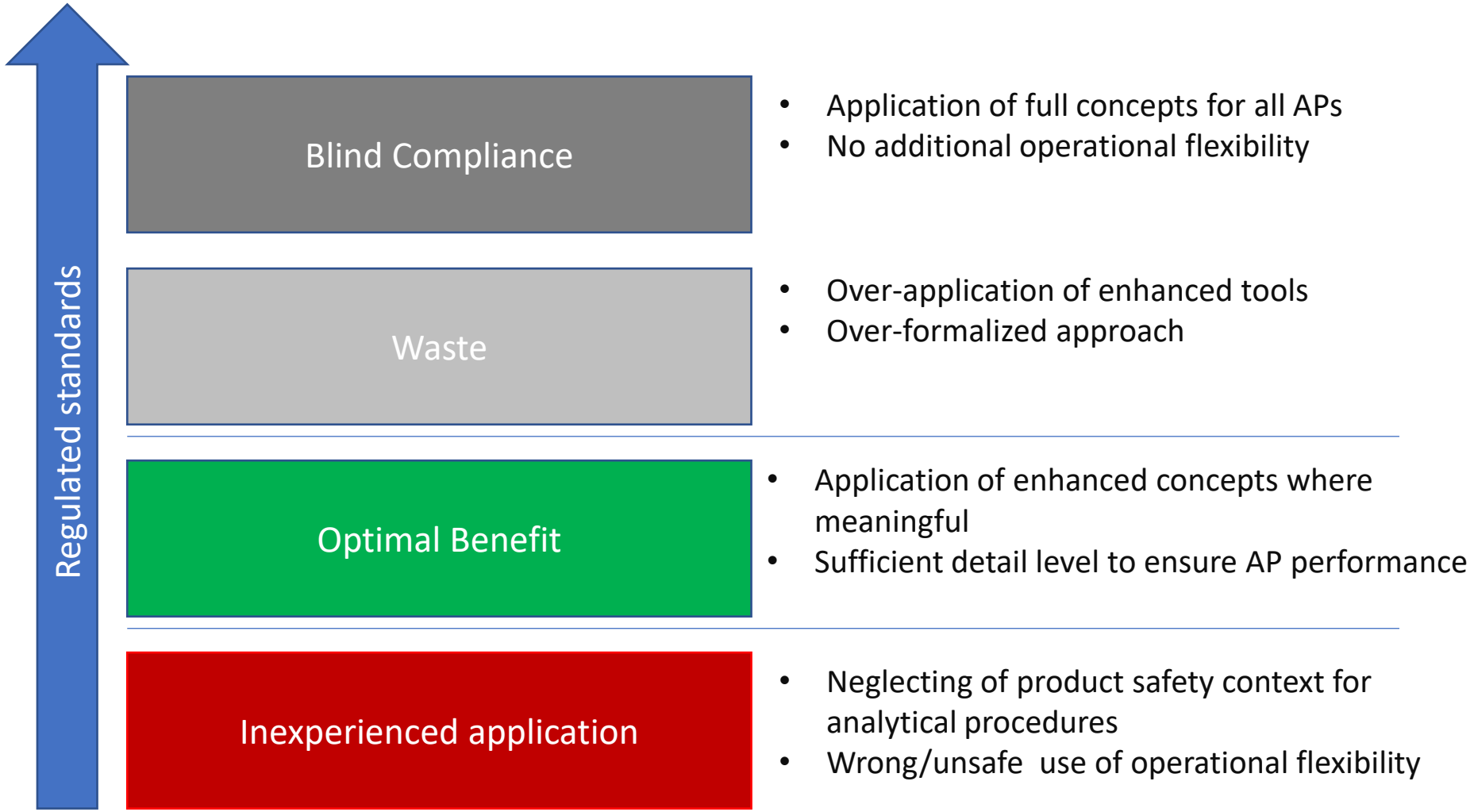
Dimension 3: Time (and Costs)



From Good to great when

- Risk evaluation for AP changes is harmonized globally
- Additional control elements from the enhanced approach can be used to lower the risk category of change
- Changes can be implemented globally at the same time

Level of detail in Q2 and Q14 guidelines



Conclusions – Q2 and Q14 will be great if…

- Analytical performance characteristics and criteria are used to their full potential
- Pre-existing knowledge can be used
- Relevant development data can be used in lieu of validation data
- Individual enhanced tools and elements can be used as meaningful
- Supportive information from an analytical development can be submitted → new eCTD module in ICH M4Q
- Risk evaluation for AP changes is harmonized globally
- Additional control elements can be used to lower the risk category of change
- Changes can be implemented globally at the same time
- Level of detail in Q2 / Q14 is appropriate to maximize benefits for safety, availability and cost of medicines

Thank you!

- Industry colleagues from Bio, Efpia, PhRMA, Elanco, Seagen
- ICH Q2/Q14 EWG