International Conference, 19-21 September 2022

Collaboration, Innovation and Scientific Excellence: the European Pharmacopoeia 11th Edition

Session 1B: Flexibility in the Ph. Eur.: a paradigm shift? Part II

Moderator: Jaana Vesterinen, FIMEA

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Analytical Quality by Design and the European Pharmacopoeia

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Collaboration, Innovation and Scientific Excellence: the European Pharmacopoeia 11th Edition
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Presentation Outline

- **General overview**
  - QbD and AQbD approaches
  - Lifecycle of (pharmacopoeial) analytical procedures
- **Use of aQbD concepts and elements in the Ph. Eur. texts**
  - Analytical target profile
  - Analytical procedure control strategy
  - Illustrative examples (performance-based standards)
- *Flexibility in the Ph. Eur.: a paradigm shift?*
  - Conclusions and outlook

(Analytical) Quality by Design

QbD Concept

"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**"

➡ QbD concepts are defined in ICH guidelines Q8 (R1): pharmaceutical development, Q9: quality risk management, and Q10: pharmaceutical quality system

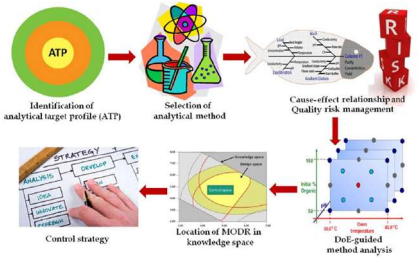
AQbD Concept

An **enhanced approach** to the development of analytical procedures, which are fit for purpose and consistently deliver results that meet predefined objectives, using QbD principles

➡ structured approach which studies multiple factors simultaneously to evaluate impact on analytical procedure performance

- **sound scientific principles** and **quality risk management** are key enablers of QbD -

Quality should be built into the product quality and most quality problems relate to the ways in which the product was designed
[QbD concept, Dr J.M. Juran, 1992]

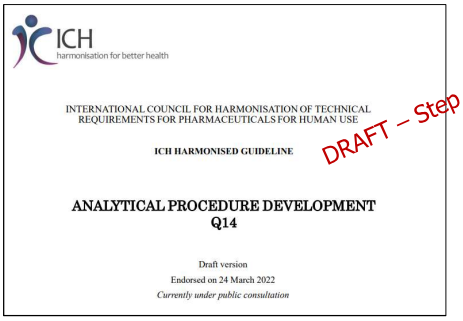


Handbook of Analytical Quality by Design, 2021

ICH Q14: Analytical Procedure Development

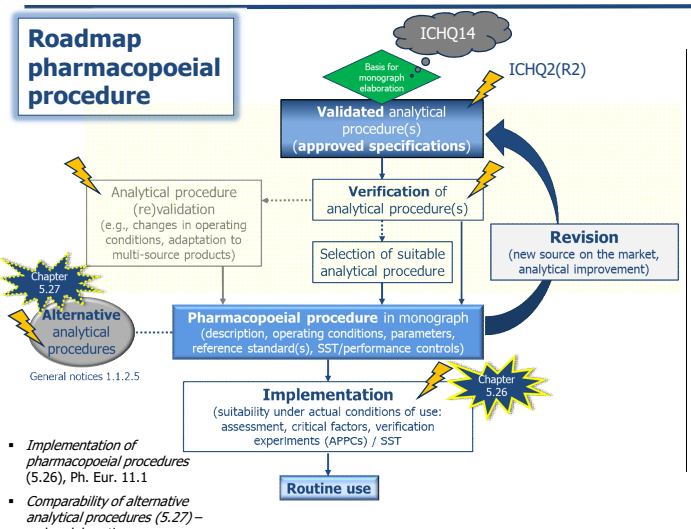
- "Describes **science and risk-based approaches** for developing and maintaining analytical procedures fit for intended use, in line with the systematic approach suggested in ICH Q8 and using principles of ICH Q9"
- "Establishes harmonised scientific and technical principles for **analytical procedures over the entire lifecycle** in conjunction with Q2(R2)"
- **Minimal** versus **enhanced approaches**

Minimal approach	Enhanced approach
• Identifying attributes need to be tested	• Evaluation of the sample properties
• Selecting appropriate technology and related instruments	• Defining the analytical target profile (ATP)
• Conducting appropriate development studies	• Conducting risk assessment and evaluating prior knowledge
• Defining analytical procedure description	• Conducting uni- or multi-variate experiments
	• Defining an analytical procedure control strategy
	• Defining a lifecycle change management plan

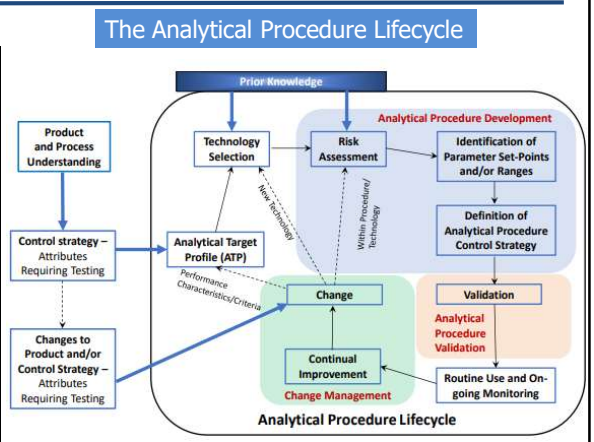


Q2(R2)/Q14 Step 2 presentation

Pharmacopoeial analytical procedures



- *Implementation of pharmacopoeial procedures* (5.26), Ph. Eur. 11.1
- *Comparability of alternative analytical procedures (5.27)* – under elaboration



ICH Q14 : Analytical Procedure Development (draft step 2)

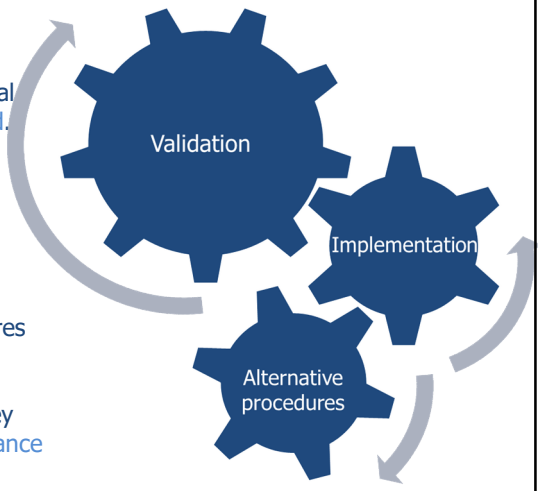
➡ *Development* of pharmacopoeial analytical procedures is out of ICHQ14 scope

Ph. Eur. Concepts Related to Analytical Procedures

- The analytical procedures given in an individual monograph have been **validated** in accordance with accepted scientific practice and recommendations on analytical validation. Unless otherwise stated in the individual monograph or in the corresponding general chapter, validation of these procedures by the user is not required.

- When **implementing** a Ph. Eur. analytical procedure, the user must assess whether and to what extent its suitability under the actual conditions of use needs to be demonstrated according to relevant monographs, general chapters and quality systems.

- The tests and assays described are the official analytical procedures upon which the standards of the Ph. Eur. are based. With the agreement of the competent authority, **alternative analytical procedures** may be used for control purposes, provided that they enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official procedures were used. In the event of doubt or dispute, the analytical procedures of the Ph. Eur. are alone authoritative.

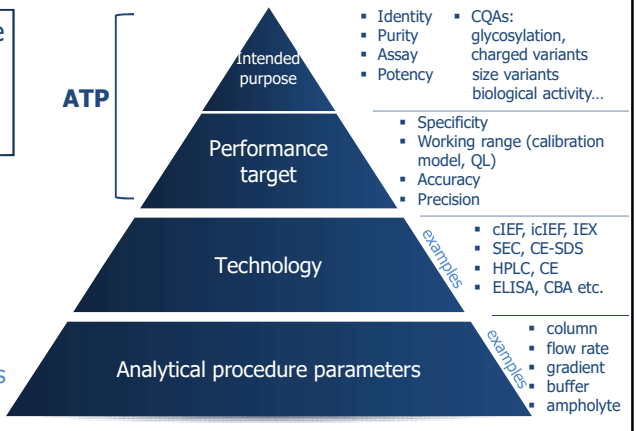


Ph. Eur. *General Notices*

AQbD: Analytical Target Profile (ATP)

- **ATP**: "A prospective summary of the performance characteristics describing the intended purpose and the anticipated performance criteria of an analytical measurement"
  (Draft ICH Q14 Glossary)

  - Element of enhanced approach
  - "Fit for purpose"
  - Multiple analytical techniques may meet the performance requirements
  - Description of intended purpose, product attributes to be measured and performance target
  - Maintained over the lifecycle and used as basis for lifecycle management

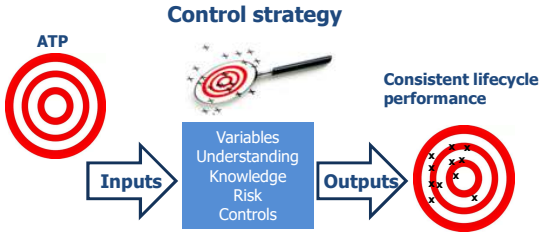


AQbD: Analytical Procedure Control Strategy (APCS)

- **APCS**: "A planned set of controls derived from current analytical procedure understanding that ensures the analytical procedure performance and the quality of the measured result."
  (Draft ICH Q14 Glossary)

  - Derived from an understanding of the analytical procedure as a process; management of risk
  - Ensures that the analytical procedure performs as expected during routine use throughout its lifecycle
  - Set of instructions that includes AP parameters or ranges requiring control
  - **System suitability test**
  - **Sample suitability assessment (where relevant)**

Ensures that ATP criteria are consistently met



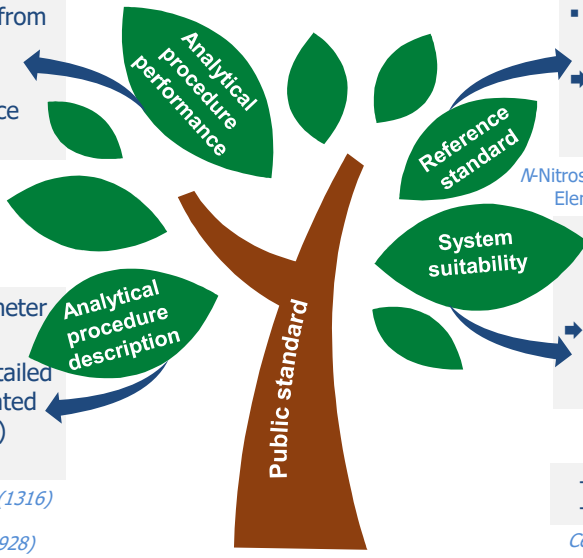
AQbD-Oriented Elements in Ph. Eur. Texts

- partially derived indirectly from SST, specifications
- ➡ **enhanced approach**: definition of AP performance standard (ATP-like)

Determination of elemental impurities (2.4.20)
Contaminant pyrrolizidine alkaloids (2.8.26)

- detailed description, parameter setting, attributes, SST
- ➡ **enhanced approach**: detailed *example procedure*, facilitated use on in-house (validated) procedure

Erythropoietin concentrated solution (1316)
Etanercept (2895)
Infliximab concentrated solution (2928)



- reference standards connected to specific analytical procedure
- ➡ **enhanced approach**: reference standards connected to ATP

N-Nitrosamines CRSs *(2.5.42)* [MS-based techniques]
Elemental impurity solutions CRS *(2.4.20)*

analytical procedure-dependent with additional tests given in general chapters

- ➡ **enhanced approach**: *overarching*, risk-based SST as part of AP control strategy

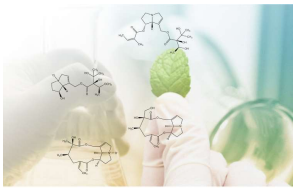
Chromatographic separation techniques (2.2.46)

- performance-based standards
- *platform* methodologies; "toolbox"

Cell-based assay for potency determination of TNF-alpha antagonists (2.7.26)

AQbD-Oriented Elements in Ph. Eur. Texts: Example

Contaminant pyrrolizidine alkaloids (2.8.26)



- Allows for use of any procedure consisting of LC-MS/MS or high resolution MS that meets the validation requirements given in the chapter

Intended purpose

Determination of 28 target PAs in herbal drugs, preparations thereof and medicinal products

Link to CQA

The analytical procedures should allow for the determination of the total sum of target PAs in the sample in a range not exceeding the max. daily intake agreed by the competent authority

Definition of AP performance standard ("ATP-like")

Validation parameter (to be assessed for each target PA in the corresponding extracted ion chromatograms)			Requirement
Identification	*MS/MS*	Position of the peaks due to at least 2 product ions acquired in SRM or MRM mode and obtained with a spiked matrix sample[4] at least at the limit of quantitation (LOQ)	fully overlap
		Difference in ion ratio[1] between a spiked matrix sample[4] and a reference solution, both at least at the LOQ	maximum ± 30 per cent
	High-resolution MS	Position of the peaks due to at least 2 ions[2] obtained with a spiked matrix sample[4] at least at the LOQ	fully overlap
		Mass accuracy[4] of each of at least 2 ions[2] obtained with a spiked matrix sample[4] at least at the LOQ	maximum 5 ppm for ions with masses ≥ 200 Da
			maximum 1 mDa for ions with masses < 200 Da
		Signal-to-noise ratio of each of at least 2 ions[2] obtained with a spiked matrix sample[4] at least at the LOQ	minimum 3[3]
Matrix effect	Difference in response between reference solutions and matrix-matched standard solutions within the working range[5], at one or more concentration points chosen by the analyst		maximum ± 20 per cent
Specificity	Difference in retention time between spiked matrix samples[4] and reference solutions within the working range[5] (applicable if the identification criteria in this table are met), at one or more concentration points chosen by the analyst		maximum ± 0.1 min
	Difference in response of each interfering peak between matrix blank solution and solvent blank[4]		maximum 30 per cent of the LOQ
Linearity	Deviation of the concentration of the calibration standards (reference solutions or matrix-matched standard solutions) calculated by the calibration function, from the true concentration, for at least 5 concentrations covering the working range[5]		maximum ± 20 per cent
Accuracy	Percentage recovery obtained with spiked matrix samples[4] for a minimum of 3 concentrations within the working range[5] (the lowest representing the LOQ) and with at least 3 determinations at each of these concentrations		70-120 per cent[6]
Repeatability	Relative standard deviation (RSD), obtained with spiked matrix samples[4], for a minimum of 3 concentrations within the working range[5] (the lowest representing the LOQ) and at least 3 determinations at each of these concentrations		maximum 20 per cent
Limit of quantitation (LOQ)[3]	Signal-to-noise ratio, obtained with a spiked matrix sample[4] at the lowest concentration in the working range[5] (applicable if the accuracy and repeatability criteria in this table are met)		minimum 10

AQbD-Oriented Elements in Ph. Eur. Texts: Example

Chromatographic separation techniques (2.2.46)

- System suitability requirements for LC and GC procedures:
  - system repeatability (assay)
  - system sensitivity (tests)
  - peak symmetry [≠ normalisation] (tests and assays)

  complementing those given in the individual monographs.
- **Describes framework for adjustments of chromatographic conditions:**
  - pharmacopoeial procedure = basis for adjustments ⇨ no further adjustments without revalidation
  - fulfilling the SST no longer the only trigger for adjustments
  - SST = bottom-line requirements but additional verification may be required
  - multiple adjustments ⇨ potential cumulative effects ⇨ proper evaluation / risk assessment by user
  - non-pharmacopoeial analytical procedures not in scope

Revised chapter (harmonised) published in Ph. Eur. 11th Edition, July 2022

Adjustments of LC chromatographic conditions*

Stationary phase		No change: identity of the substituent	Similar: chromatographic support, surface modification and extent of chemical modification	Change: TPP to SPP columns
Column dimensions	Condition: *L*/*dp* constant or within defined range	Change: length (*L*) particle size (*dp*)	Requirement: SST fulfilled + selectivity and elution order of specified impurities equivalent	
	Condition: in absence of *dp* and/or *L* change	Change: internal diameter	Requirement: SST fulfilled	
Mobile phase	isocratic elution: Condition: within defined tolerances	Change: composition pH, salt conc.	Requirement: SST fulfilled	
	gradient elution: Change: composition/ gradient	Requirement: SST fulfilled t_R principal peak within defined tolerance first peaks are sufficiently retained and last peaks are eluted		
	Condition: within defined tolerances	Change: pH, salt conc.	Requirement: SST fulfilled	

*list not exhaustive (further adjustments: flow rate, injection volume)

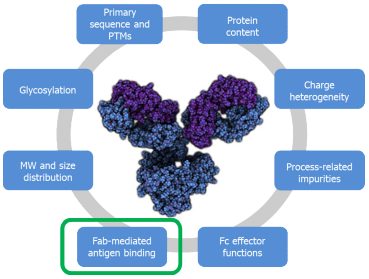
AQbD-Oriented Elements in Ph. Eur. Texts: Example

Infliximab concentrated solution (2928)

"Example procedure"

➡ in individual monographs for complex biotherapeutics*

➢ **Potency:**
- use of any suitable cell-based assay based on the inhibitory action of infliximab on the biological activity of TNF-alpha with a suitable readout [potency determination]
- use of pharmacopoeial RS (infliximab BRP) for assay performance evaluation and calibration
- **"example" procedure**



'In certain monographs [...], the terms 'suitable' and 'appropriate' are used to describe a reagent, micro-organism, test method etc.; if criteria for suitability are not described in the monograph, suitability is demonstrated to the satisfaction of the competent authority.' (Ph. Eur. *General Notices*)

'*The following procedure is given as an example*' means that the analytical procedure described has been validated and may be implemented as is or may be replaced by a suitable, validated procedure (without having to demonstrate its equivalence to the 'example' procedure), subject to approval by the competent authority. (Ph. Eur. *General Notices*)

*Buda M., Kolaj-Robin O., Charton E. *Biotherapeutic Products in the European Pharmacopoeia: Have all Challenges Been Tackled?* GaBi Journal. 2022;11(1)

AQbD-Oriented Elements in Ph. Eur. Texts: Example

Cell-based assay for potency determination of TNF-alpha antagonists (2.7.26)*

- **NEW type of general chapter** with experimentally verified specific procedures
- TNF-alpha neutralisation assays (procedures A, B, C and D):
  - ➔ different cell lines/readouts
  - ➔ validated for specific TNF-alpha antagonists
  - ➔ suitability (specificity and precision) demonstrated for each TNF-alpha antagonist substance, during verification experiments
  - ➔ procedure applied to substances outside the scope of the initial validation or not covered in an individual monograph for a TNF-alpha antagonist, require validation.
- Diversifies the choice of bioassays and facilitates migration to different assays

- Cell preparation
- TNF-alpha working solutions preparation
- Test solution preparation
- Reference solution preparation (product-specific: BRP or IHRS)
- Assay execution
- Dose-response curve construction
- Calculation of reportable result

*Ph. Eur. Supplement 11.1

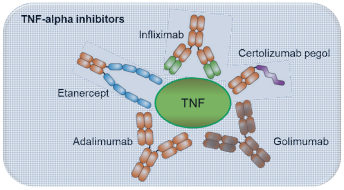
Performance-based standards

Analytical procedure control strategy
- ✓ system suitability test: quality of RS and control curves, proper functioning of the system (max to min ratio between controls)
- ✓ sample suitability assessment: compare performance of the sample to the performance of the RS (similarity/parallelism)
- ✓ **procedure-independent performance controls and one-size-fits all criteria**

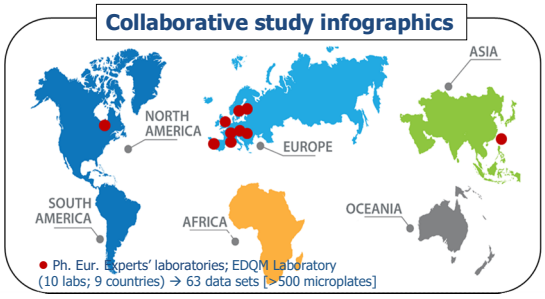
Sources of variability identified and potential mitigation strategies described:
- ✓ adjustment of assay conditions to satisfy the system suitability criteria without fundamentally modifying the procedures

TNF-alpha Bioassay Collaborative Study

Cell-based assay for potency determination of TNF-alpha antagonists (2.7.26)



Collaborative study infographics



- Laboratory-wide performance metrics (specificity, precision, recovery) -- consistent output within the performance range
- 'Real world' test data (better understanding of variability)
- Understanding of challenging aspects of the assays and how they may be addressed – foundation for refinement of assay conditions
- Platform for discussion on good practices
- Provided understanding of how analytical procedure component criticality correlates with significant sources of variability, and to determine factors that contribute most to the variability of the assay performance – basis for defining strategy for system/sample suitability (with appropriate criteria)

Ph. Eur. Texts in the Pipeline: AQbD-Considerations

- Explore **flexible concepts** and **new types of standardisation**:
  - Focus on key quality attributes and associated testing strategies
  - Establish suitable common expectations and general methodologies with broad applicability
  - Reflect robust and established practices applicable to wide range/classes of mAbs
  - Multi-laboratory collaborative studies

  - SE-HPLC, SE-UPLC, ciEF and imaged cIEF procedures, widely applicable to mAbs, given as examples (*'platform methodologies'*)
  - tools to control AP performance; common reference standard (ATP-connected, but technology-specific)
  - guidance on aspects to consider for product-specific application (validation)

Performance-based standards

Size-exclusion chromatography for recombinant therapeutic monoclonal antibodies (2.5.43)

Capillary isoelectric focusing for recombinant therapeutic monoclonal antibodies (2.5.44)

Concluding Remarks

- **The Ph. Eur. concept of flexibility has constantly evolved**:
  - continue to build further on **the science-based and flexible approach** to establish robust standards
  - nothing new – however:
    - more structured approaches
    - enhanced scientific understanding
    - more use of (A)QbD principles

- The Ph. Eur. will continue to **explore how AQbD principles may be applied to pharmacopoeial standards**, in collaboration with its experts:
  - investigate relevance and applicability to pharmacopoeial procedures
  - understand the resources required to implement various AQbD concepts against the benefits each brings

Flexibility: a real paradigm shift?!

Continuous evolution

Join the Analytical Quality by Design Working Party

… and work to shape the future of AQbD in the European Pharmacopoeia

- Assess the feasibility and impact of incorporating analytical procedures developed using the concepts of AQbD in Ph. Eur. monographs
- Advise the Commission and expert groups on appropriate elaboration/revision strategies for incorporating such analytical procedures in monographs
- Identify verification and revision approaches for analytical procedures developed using AQbD
- Co-operation and consultation with other groups of experts and working parties in charge of the elaboration and revision of monographs, where relevant

Thank you for your attention

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COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Flexible and robust monographs

R. Martijn van der Plas

CBG-MEB, NL

GOEDE MEDICIJNEN GOED GEBRUIKT

Disclaimers and the like

- Usual disclaimers apply > presentation meant to initiate further reflection
- I am a member of groups 6B, MAB, and BSP SC
- In addition, I am a member of the EMA/CHMP Biologicals Working party
- My day job is at the desk, not in the lab

Both flexible and robust

The test is the requirement (1)

- 'The test is the requirement'
  - (cf. 'the process is the product')
  - Attribute, analytical procedure, and acceptance criterion historically often conflated
- E.g. 'Differences in SE-HPLC'

- ICH Q6B:
- 'A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria (..)'
- 'Specifications are linked to analytical procedures.'

The test is the requirement (2)

- Technology driven analytical development and standardisation ('what can we actually measure with our current methods')
- Ph. Eur. monographs routinely cover all elements (attribute, method, criterion) in varying forms

Anti-A and anti-B haemagglutinins (*2.6.20, Method B*). It complies with the test for anti-A and anti-B haemagglutinins (direct method).

Anti-D antibodies (*2.6.26*). It complies with the test for anti-D antibodies in human immunoglobulin.

The test is the requirement (3)

Dimer and related substances of higher molecular mass. Size-exclusion chromatography (*2.2.30*): use the normalisation procedure.

Test solution. Dilute the solution to be examined in *0.025 M phosphate buffer solution pH 7.0 R*, so as to contain 1.0 mg/mL of somatropin.

Reference solution. Dissolve the contents of a vial of *somatropin CRS* in *0.025 M phosphate buffer solution pH 7.0 R* and dilute with the same solution to obtain a concentration of 1.0 mg/mL.

Resolution solution. Place 1 vial of *somatropin CRS* in an oven at 50 °C for a period sufficient to generate 1-2 per cent of dimer (typically 12-24 h). Dissolve its contents in *0.025 M phosphate buffer solution pH 7.0 R* and dilute with the same solution to obtain a concentration of 1.0 mg/mL.

Column:

- *size*: *l* = 0.30 m, Ø = 7.8 mm;
- *stationary phase*: *hydrophilic silica gel for chromatography R* of a grade suitable for fractionation of globular proteins in the relative molecular mass range of 5000 to 150 000.

Mobile phase: *2-propanol R, 0.063 M phosphate buffer solution pH 7.0 R* (3:97 *V/V*); filter and degas.

Flow rate: 0.6 mL/min.

Detection: spectrophotometer at 214 nm.

Injection: 20 µL.

Relative retention with reference to somatropin monomer (retention time = 12 min to 17 min): related substances of higher molecular mass = about 0.65; somatropin dimer = about 0.9.

System suitability: resolution solution:

- *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to the dimer and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to the monomer.

Limit:

- *sum of the peaks with retention times less than that of the principal peak*: maximum 4.0 per cent.

The requirement determines the test

- ICH Q14 draft:
- 'Product and process understanding (..) leads to the identification of quality attributes requiring analytical measurement for control (..)'
- Based on objective, method-independent CQAs
  - (This is actually a core pre-requisite!)
- Product or CQA-driven analytical development and standardisation ('what do we actually need to measure')

CQA-driven monographs

- What if we look to a monograph through a Q14/CQA driven lens?

- Four elements
- 1. (Critical Quality) Attribute
- 2a. Analytical Procedure (Method) Description
- 2b. Analytical Procedure (Method) Validity criteria.
- 3. Requirement/acceptance criterion

- Please note that different users may use different elements
- E.g. NCA assessors may focus on CQA and acceptance criterion

Analytical Procedure (AP) Method Description

- Traditional part
- Technical/procedural aspects of execution
- Usually stepwise and prescriptive: 'How to'

- 'Mix A with B, inject 10 µl, flow rate 1 ml/min, incubate for 1 hr at 37 C'.

Validity Criteria

- Related to ICH Q14 APCS (AP Control Strategy)
- APCS opens door to 'performance based' methods.
- Includes SST (system) and '*assay/sample suitability assessment*' (sample) criteria.
- Change within method: All kinds of variability, minor adaptations and 'tinkering' (both intended and unintended) can be accommodated.
- Change to other method: May depend, but certain general criteria may be maintained

- See e.g. MAB WP work on TNF-alfa blockers bioassay
- Common Reference Standards (may cover both system and sample suitability).

Requirement/acceptance criterion

- Draft ICH Q14 Analytical Target Profile (ATP):
- 'A prospective summary of the performance characteristics describing the intended purpose and the anticipated performance criteria of an analytical measurement' (glossary).
- '(..) description of the intended purpose, appropriate details on the product attributes to be measured and relevant performance characteristics with associated performance criteria' (section 3)
  - Reportable range is a 'performance characteristic', obvious link to (specification) acceptance criterion

All elements (attribute, method, validity, criterion) are already present!

Dimer and related substances of higher molecular mass. Size-exclusion chromatography (*2.2.30*): use the normalisation procedure.

Test solution. Dilute the solution to be examined in *0.025 M phosphate buffer solution pH 7.0 R*, so as to contain 1.0 mg/mL of somatropin.

Reference solution. Dissolve the contents of a vial of *somatropin CRS* in *0.025 M phosphate buffer solution pH 7.0 R* and dilute with the same solution to obtain a concentration of 1.0 mg/mL.

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Mobile phase: *2-propanol R, 0.063 M phosphate buffer solution pH 7.0 R* (3:97 *V/V*); filter and degas.

Flow rate: 0.6 mL/min.

Detection: spectrophotometer at 214 nm.

Injection: 20 µL.

Relative retention with reference to somatropin monomer (retention time = 12 min to 17 min): related substances of higher molecular mass = about 0.65; somatropin dimer = about 0.9.

System suitability: resolution solution:

- *peak-to-valley ratio*: minimum 2.5, where H_p = height above the baseline of the peak due to the dimer and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to the monomer.

Limit:

- *sum of the peaks with retention times less than that of the principal peak*: maximum 4.0 per cent.

Change to other method

- Change to other method foreseen in both ICH Q14 and Ph. Eur. General Notices
- General Notices state:
- (…) alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used. (..)

- Changes facilitated when method-independent acceptance criterion present!

Some pitfalls (1)

- SE-HPLC as an example (MAb experience)

- Exact chromatographic conditions could be flexible
- Flow rate, column length
- SST and assay acceptance can be well defined
- Gelfiltration standards (B12, myoglobin)
- Sample, RS, peak separation
- Main peak RT, symmetry,

Some pitfalls (2)

- SE-HPLC/MAb-example ctd.
- Which CQA is actually measured (can method be replaced by any other method)?
- Several pitfalls here, because SE-HPLC commonly optimised for monomer and certain dimers > not 'aggregates', fragments

Concluding remarks

- Monographs need some flexibility to be practical
- Four elements can be discerned: CQA, AP/Method description, Validity criteria, Acceptance criterion
- Different users may focus on different elements
- Performance based criteria in monograph (APCS) give flexibility to method description/execution
- Changes within or to other method (in line with general notices) facilitated if validity criteria and specification acceptance criterion universally defined.

Black or white – ‘nothing is always absolutely so’

COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

GOEDE MEDICIJNEN GOED GEBRUIKT

Pharmacopeial Standard Development for Biotherapeutic Products - Industry Perspective

EDQM Conference "Collaboration, Innovation and Scientific Excellence: the European Pharmacopoeia 11th Edition"
Strasbourg, France
September 20, 2022

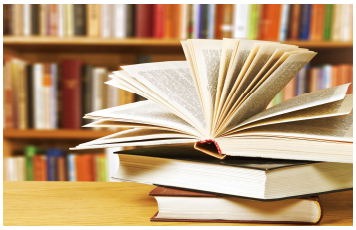
Erin Wang, Sr. Advisor, Quality - Compendial Affairs, Global Quality Laboratory
Matthew Borer, Ph.D., Executive Director, Corporate Reference Standard Organization
Jean-Bernard Graff, Ph.D., Sr. Advisor, Quality – Biomolecule Analytical, Global Quality Laboratory

Eli Lilly and Company

Overview

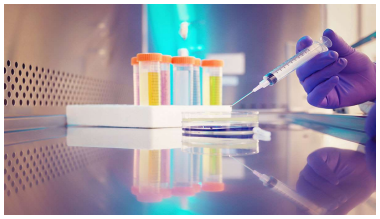
- Value of Pharmacopoeia Standards
- Manufacturers' Perspective
  - Industry Challenges
  - General Considerations
- Reference Standard for Biotherapeutic Products
  - Importance of Reference Standard
  - Industry Challenges
- Summary

Value of Pharmacopoeia Standards



- Pharmacopoeias are sources of public quality standards for pharmaceutical products, active ingredients, and components
  - Bring consistency to medicines
  - Provide common methodologies
  - Simplify and maintain registrations

- A recognized common practice
  - Contain thousands of analytical methods and specifications
  - Contain general requirements which apply to manufacturing, storage, labeling, and other aspects

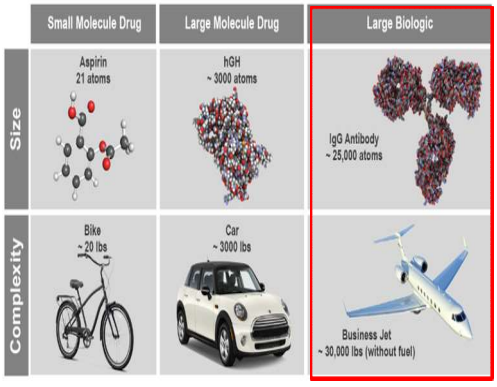


Value of Pharmacopoeia Standards

- Enforced by regulatory agencies
  - Minimum quality standard to be met by all manufacturers

- Market surveillance by health authorities

Manufacturers' Perspective
Industry Challenges



- The complexity of high-molecular-weight three-dimensional structures of biopharmaceuticals
- Manufacturing process being unique for each "similar" biotherapeutic products
- Challenges for analytical techniques
  - confirm structural equivalence with reference molecules
  - establish biopharmaceutical equivalence

Manufacturers' Perspective
Industry Challenges

- Molecular structure of a small molecule must be identical to the reference product.
- Molecular differences to the reference product for biotherapeutics are expected and add complexity for public standard.

Small Molecules	**Biotherapeutics**
CMC - standard information	CMC - standard information
	CMC - comparability
	Nonclinical data
Clinical bioequivalence	Clinical bioequivalence
	Clinical efficacy
	Clinical safety

Manufacturers' Perspective
General Considerations

- Manufacturers have expressed support for public standards for biotherapeutic products.
- Complexity of biotherapeutic products requires a certain degree of flexibility for public standard.

Manufacturers' Perspective
General Considerations

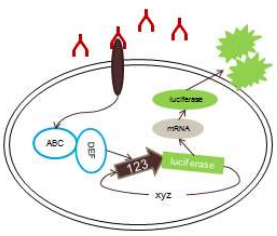
- Develop public standards within the capabilities of current science
  - meaningful harmonized general chapters for biotherapeutics resulting from industry development and scientific evolution
  - focus on setting public standards rather than writing textbooks or SOPs
- Examples:
  - Monoclonal antibodies for human use
  - Analytical procedures for recombinant therapeutic monoclonal antibodies
  - Size exclusion chromatography for recombinant therapeutic monoclonal antibodies

Manufacturers' Perspective
General Considerations

- Ensure flexibility for manufacturers and regulatory authorities
  - Standards for biosimilarity or interchangeability of biotherapeutic products are set by regulatory agencies based on additional clinical, non-clinical and quality data.
  - Determination of acceptability is made by regulatory authorities based on additional data not addressed in compendia.
- Examples:
  - Reference to limits approved by competent authority rather than including specific limits.
  - General Notices: 'The following procedure is given as an example' – allow to replace with an approved validated procedure without having to demonstrate its equivalence to the 'example' procedure.

Reference Standard for Biotherapeutic Products - *Importance*

- The basis for patient dose
  - *There is no way to correlated biological activity to physicochemical test results so the reference standard serves this purpose*
  - *Proper management of the reference is essential to prevent drift in dose from pivotal clinical studies (especially difficult in the face of variable assays for potency)*
- The basis for product identity
  - *Not only the identity of the main entity but also the fingerprint of variants and impurities*
  - *Plays a key role in monitoring the manufacturing process for consistency*



Reference Standard for Biotherapeutic Products - *Industry Challenges*

- Regulatory authorities require manufacturers to use a reference standard that is highly representative of their manufacturing process. If not, the reference standard is not suitable for potency testing and must be replaced.
  - *How can a compendial standard be useful to more than one manufacturer?*
- It is not possible to correlate potency to physicochemical tests. Instead, a two-tier reference standard system is required of manufacturers to maintain potency consistent with pivotal clinical studies.
  - *How can a compendial standard be assigned a potency without comparison to the original manufacturer's in-house standard?*
  - *Harmonization, WHO, NIBSC*
- All approaches that are scientifically sound for monitoring the stability of potency require routine execution of the potency test (e.g., cell-based assay) in an expert lab that is also releasing product.
  - *How can compendial agencies monitor potency of their reference standards?*

Summary

- COLLABORATION: Manufacturers, Regulators and Compendia should work together to find opportunities to advance pharmacopoeia standard for biotherapeutics as well as pharmacopeial processes to benefit global patients.

Summary

- HARMONIZATION:
  To promote public health by providing safe and effective biotherapeutics with consistent quality to extend and improve the lives of patients around the world.

Summary

- FUTURE:
  Scientific Advancements vs Public Standard
  - Better understanding
    - relationship between structure and potency for biotherapeutics
    - Biotherapeutic manufacturing and how process parameters affect potency
  - Improved physicochemical methods that are sensitive to properties that affect potency

Thank You


Thank
You
Merci
Gracias
Spacibo
Danke
Hvala
Arigato
TerimaKasih
KamSahHamnida
Takk
aDank
BarakAllahuFiik
Mèsi
Xièxie
Grazie
Chokrane
Kiitos
Dziakuju
GratiasAgimus
Aciu
Dankie
Tak
Motashakkeram
GratiasAgo
KopKhunKha
Gracie
CamOn
Multumesc
Saha
Salamat
Obrigado
Bayarlalaa
Nirringrazzjak
NajisTuke
Gràcies
Faleminderit
Efharisto
Dakujem
Taiku
Mercé
Malondo
Blagodaram
ThintKo
Buznyg
Rahmat
TapadhLeat
Köszönöm
Murakoze
WaadMahadsantahay
Tanemirt
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Sagolun
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Maururu
Gratzias
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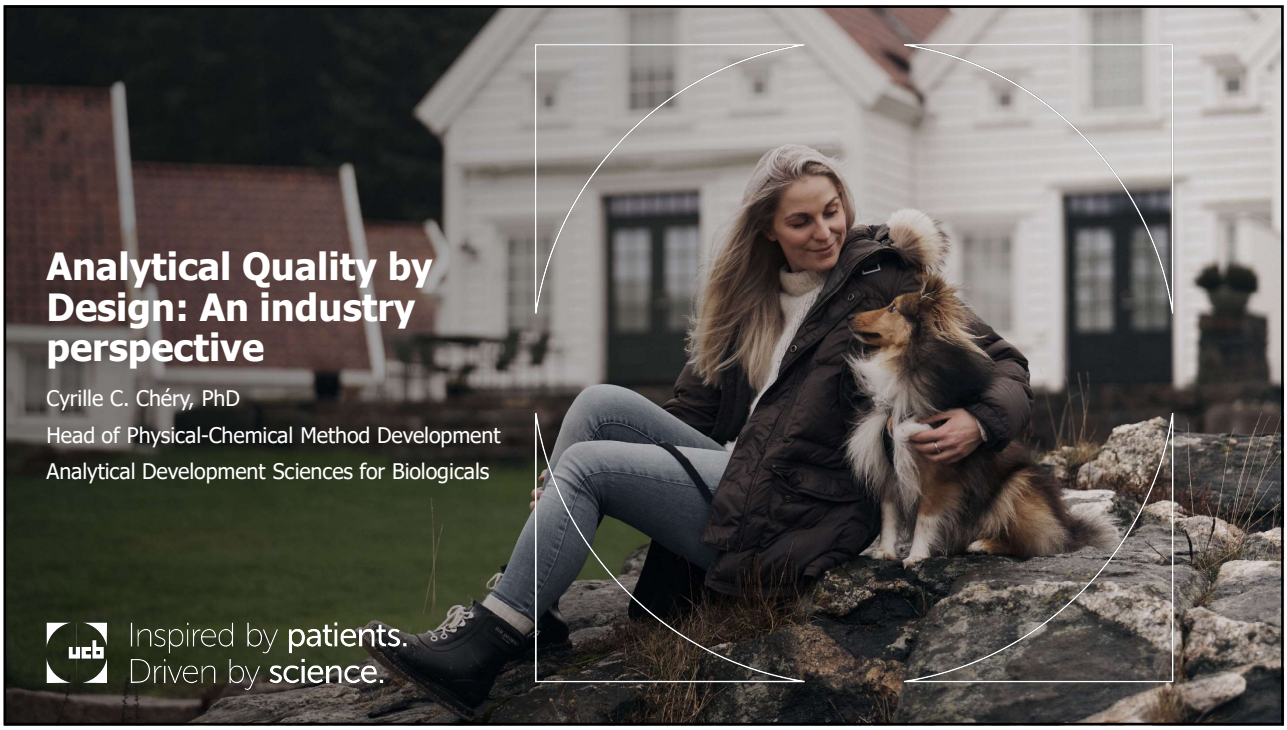


Agenda

1. Context: method development and validation are not a tick-box exercise
   ICH Q2(R2) and Q14
2. How do we apply the concepts of analytical Quality by Design?
   Potential links with pharmacopeial methods
3. Conclusion

Context

Method development and validation are not a tick-box exercise
ICH Q2(R2) and Q14

Analytical QbD: let us acknowledge the frontrunners

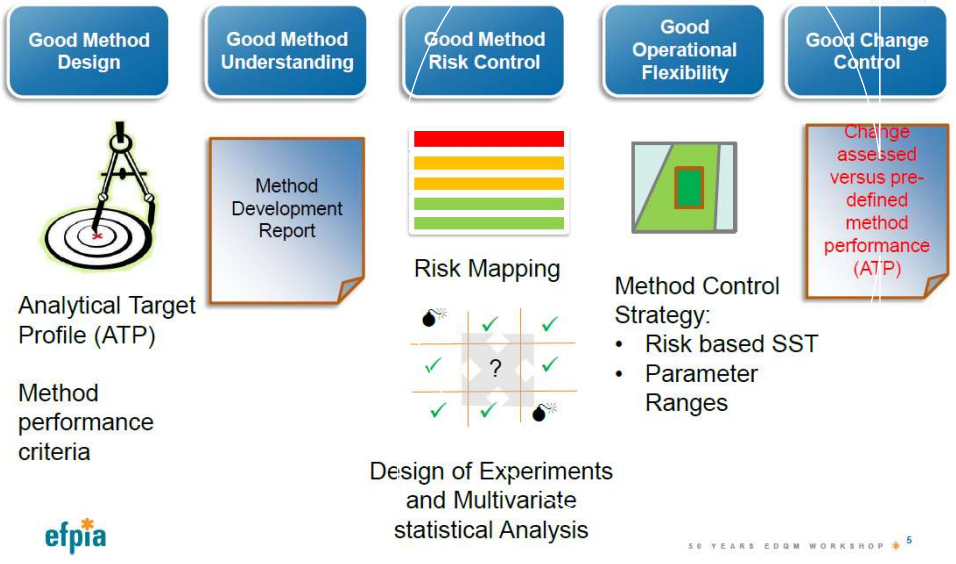
2014 EDQM Workshop

Analytical QbDv and Pharmacopoeial Monographs – a vision

Dr. Oliver Grosche

Efpia TDOC Subteam on Analytical Design Space

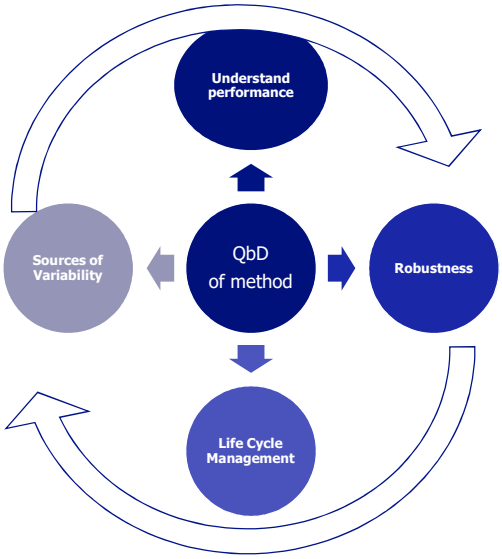
What does analytical QbD stand for?



Former situation: compliance, not science

- Procedures often driven by regulatory requirements causing analysts to respond to compliance aspects more than the science
- Often validated as a "one-off event" at the beginning of the lifecycle by the experts
- Applied in a checkbox manner without the effect of the validation parameter on the outcome of the procedure being thoroughly understood
- Prior knowledge and information from method development not leveraged for submissions

QbD brings the systematic methodology to development, validation and life-cycle: major opportunity offered by ICH Q14



aQbD: White paper by IQ with US and EU industry participants

Title:

Analytical Method Validation in the Age of QbD

Authors:

Thorsten Verch[1], Cristiana Campa[2], Cyrille C. Chéry[3], Ruth Frenkel[4], Nomalie Jaya[5], Bassam Nakhle[4], Jeremy Springall[6], Jason Starkey[7], Jette Wypych[8], Todd Ranheim[9]

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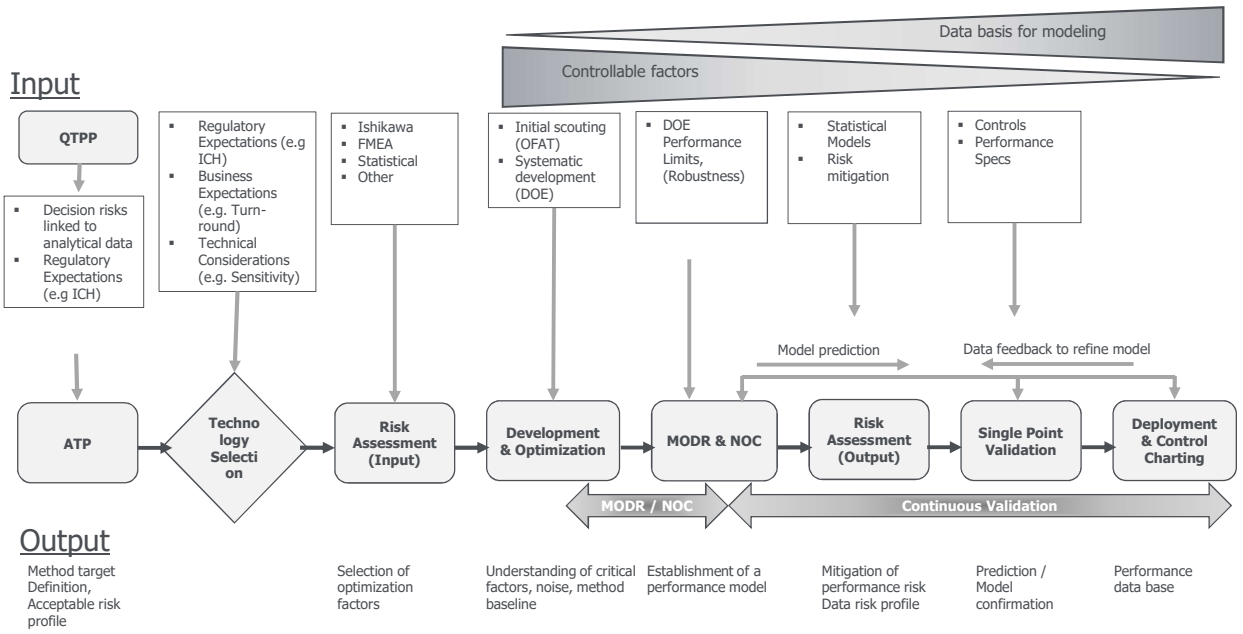
T. Verch et al., Analytical Quality by Design, Life Cycle Management and Method Control, AAPS J.. 2022 Feb 11;24(1):34. doi: 10.1208/s12248-022-00685-2.

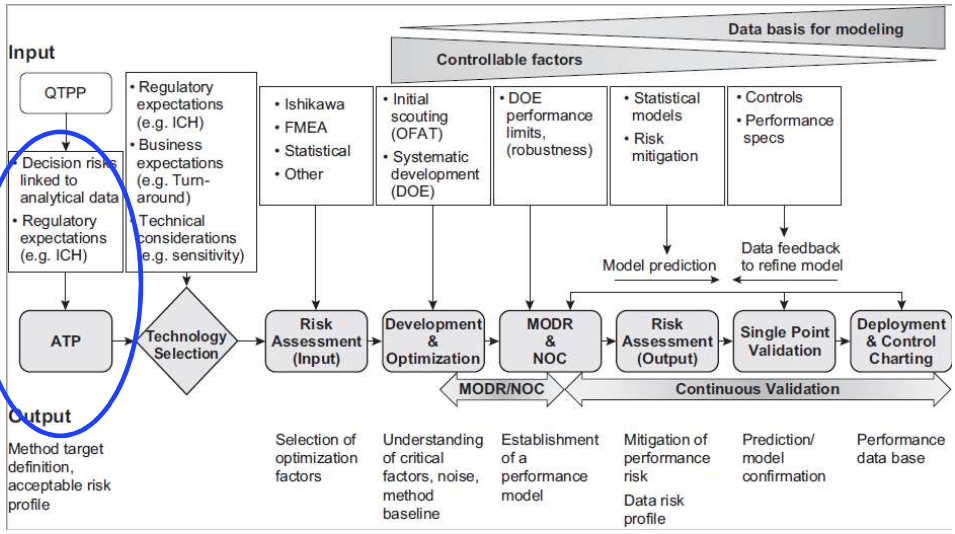
How does the industry apply the concepts for in-house methods?
Which parallels can be made with pharmacopeial methods?

"Industry" = participants to the IQ consortium



T. Verch et al., Analytical Quality by Design, Life Cycle Management and Method Control, AAPS J.. 2022 Feb 11;24(1):34. doi: 10.1208/s12248-022-00685-2.

Step by step



T. Verch et al., Analytical Quality by Design, Life Cycle Management and Method Control, AAPS J.. 2022 Feb 11;24(1):34. doi: 10.1208/s12248-022-00685-2.

Analytical Target Profile

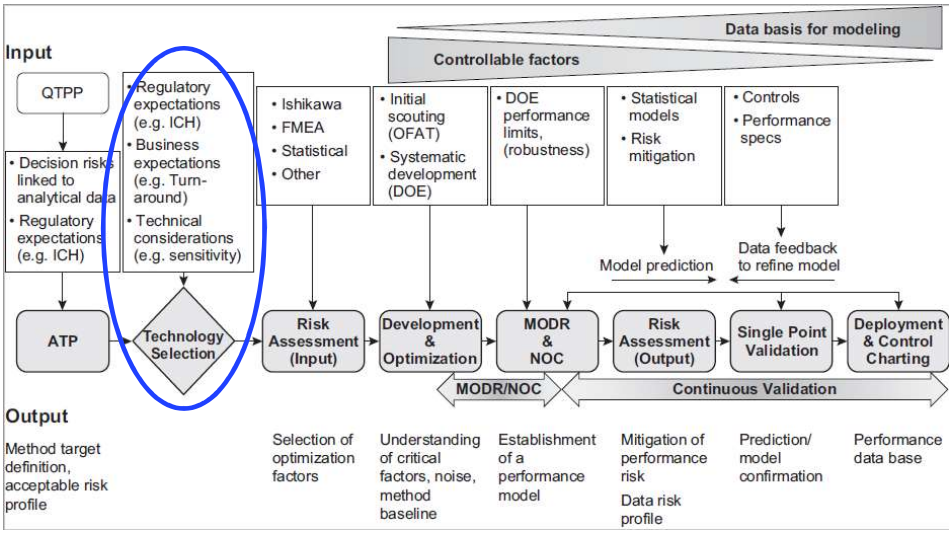
- The ATP defines the objective of the test, starting from the attribute, and quality requirements for the reportable result.
- It is a prospective summary of the required performance characteristics of the reportable result that needs to be achieved to ensure the data is fit for purpose.
- It is technology agnostic

- Example : Method for charge variants of a monoclonal antibody, drug product
- The method must be able to determine the relative quantity of monomer peak and charge variants (acidic species (APG) & basic species (BPG)) in DS and DP samples.
- The method must be:
  - Specific:
    - no interfering peak from buffers / matrix observed at the retention time of the isoforms
    - stability-indicating
  - Accuracy profile: acceptance limit 30% at 5% risk for monomer and 50% at 5% risk for APG & BPG.
  - QL of APG & BPG must be at least 5%
  - Prepared sample must be at least stable for 72 hours at 5±3°C

Analytical Target Profile and Ph. methods?

- Could the ATP be mentioned in the Ph. methods?
- Would it help to prove that a method is an alternative to the pharmacopeial method?

Step by step



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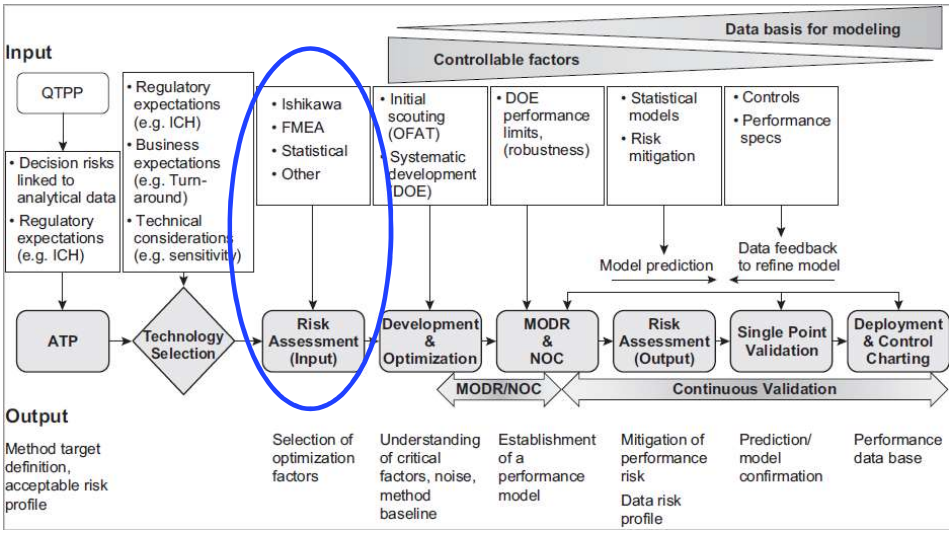
Step by step



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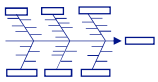
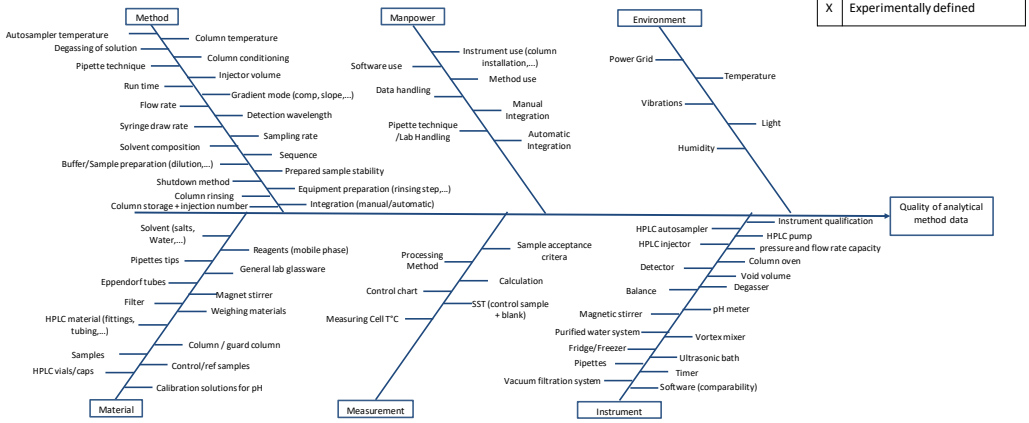
Risk Assessment: Critical Method Attributes



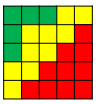
Identification of the critical method parameters:

- Start from **prior knowledge** on similar methods
- Use Ishikawa tools to classify the method parameters

Classification of Attributes	
C	can be Controlled
N	Noise cannot be controlled/ predicted
X	Experimentally defined



Risk Assessment – Quantification of risk

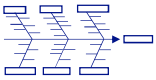


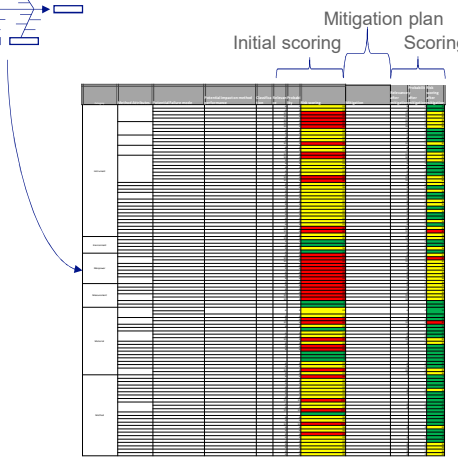
$$Risk = Relevance\ x\ Probability$$

Probability \ Relevance	2	4	6	8	10
2	4	8	12	16	20
4	8	16	24	32	40
6	12	24	36	48	60
8	16	32	48	64	80
10	20	40	60	80	100

Risk value Table (relevance x probability)			
Effect	Value	Mitigation	Color
Low	x ≤ 12	Optional	Green
Medium	12 < x < 40	Recommended to mitigate if possible	Yellow
High	≥ 40	Must mitigate	Red

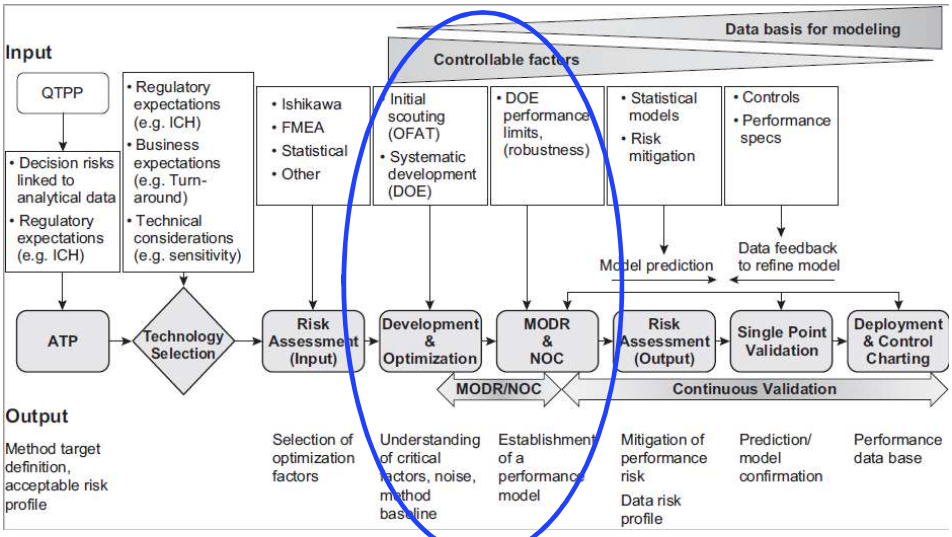
From the fish bone to the risk list





- Each line is a risk
- The systematic approach allows us to identify and mitigate risks
- Extra added value: clear identification of the critical material/reagent

Step by step



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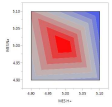
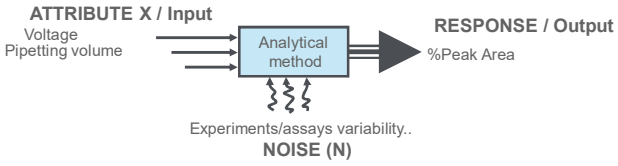
DoE for method development

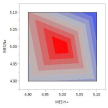


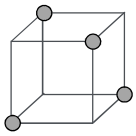
"Design of experiments (DOE) is a test or series of tests in which **purposeful changes are made to the input variables** of a process so that we may **observe and identify corresponding changes in the output response**"

from Douglas Montgomery – Introduction to statistical quality control



Critical Method Attributes

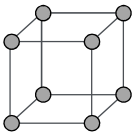




Screening designs

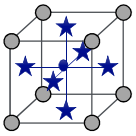
Influent factors determination/ranking

Eg – Plackett & Burman



Factorial designs

Factors effects/interaction characterization



Response surface designs

Prediction in a domain

Eg – Central Composite Design

Screening design
Main influent factors determination

↓

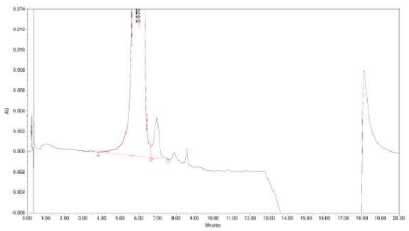
Optimisation design
Main factor & interactions

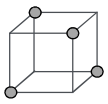
↓

Robustness design
Small variations

Screening Design

- Example of RP-HPLC method for a product related impurity





Screening Design

- Example of RP-HPLC method for a product related impurity

- Factors (chromatographic conditions):
  - %TFA in mobile phase A
  - %TFA in mobile phase B
  - % ACN in mobile phase B
  - % IPA in mobile phase B
  - Flow rate
  - Wavelength
  - Column temperature

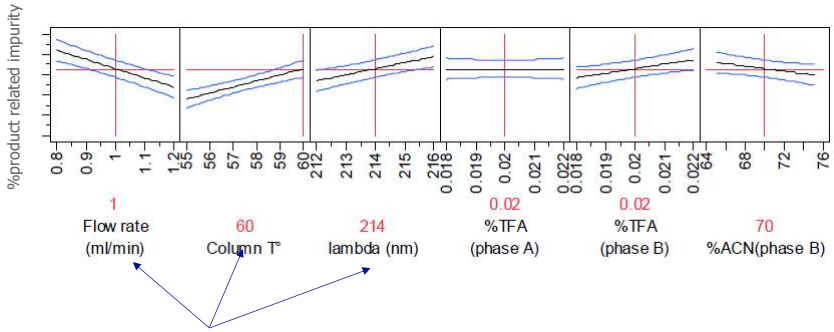
- Responses:
  - **%product related impurity**

- Model:
  - Plackett & Burman (only main effects)
  - 12 runs

Run	%TFA in A	%TFA in B	%ACN	%IPA	Flow rate	λ	Column T°
1	1	-1	-1	1	1	-1	1
2	1	1	1	-1	-1	-1	-1
3	1	1	-1	1	-1	-1	1
4	1	-1	1	-1	1	1	-1
5	-1	-1	-1	1	1	-1	-1
6	1	1	1	-1	1	1	1
7	1	-1	-1	1	-1	1	-1
8	-1	1	-1	1	-1	1	-1
9	-1	1	1	-1	1	-1	-1
10	-1	-1	1	-1	-1	-1	1
11	-1	-1	1	-1	-1	1	1
12	-1	1	-1	1	1	1	1

MODR

Prediction intervals of RP-HPLC method for a product related impurity

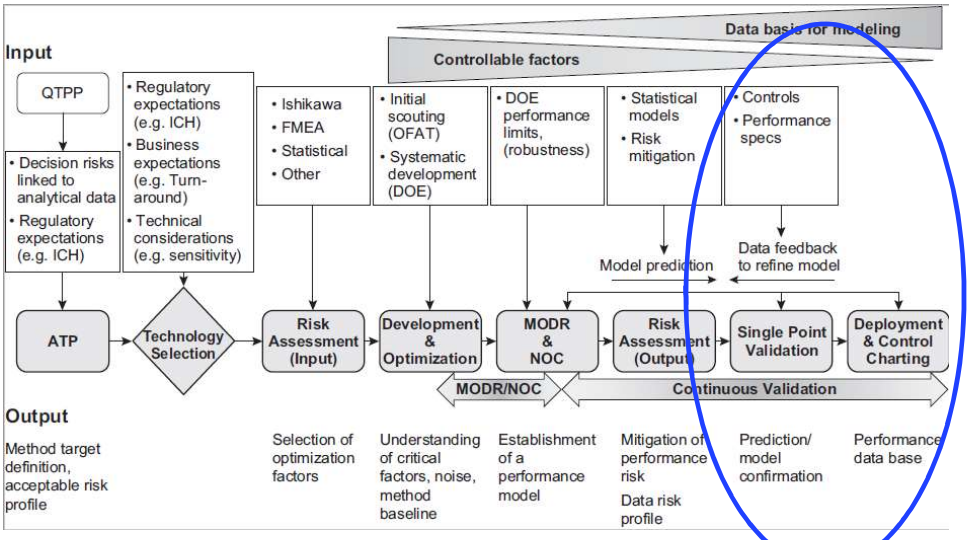


The comparison of the prediction intervals to the accepted variability allows us to identify the significant parameters

aQbD does apply to pharmacopeial methods, but needs some thoughts

- How can the analytical parameter ranges be determined / mentioned for a Ph. procedure?

Step by step



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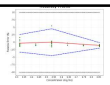
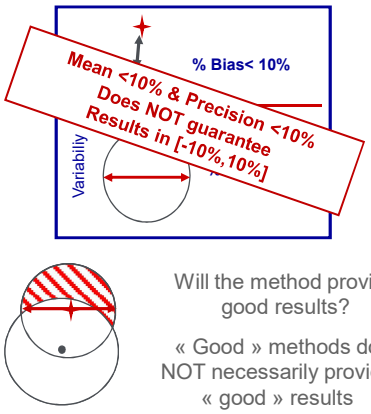
Method Validation



- From Descriptive to Predictive Approach

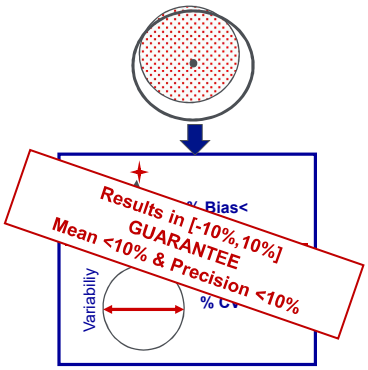
Method Driven – classical validation



Will the method provide good results?

« Good » methods do NOT necessarily provide « good » results

Data Driven – Total Error

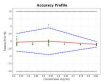


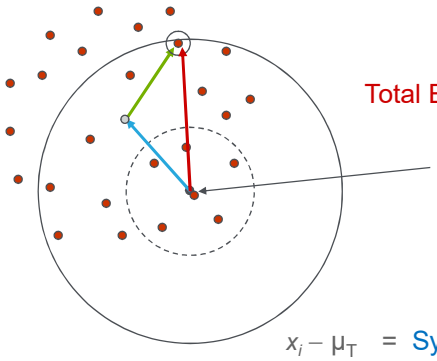
« Good » results can only be obtained by « good » methods

What is important is the result, not the assay !

Method Validation: Total Error = Measurement Uncertainty

- From Descriptive to Predictive Approach



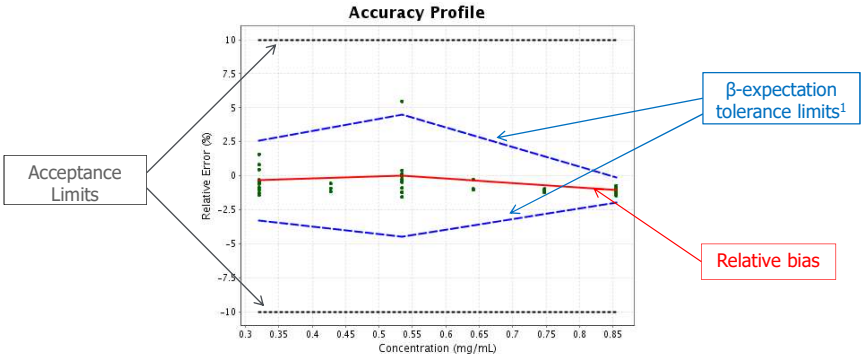


$x_i - \mu_T$ = Systematic Error + Random Error
= Bias + Standard Deviation
= Trueness + Precision
= Measurement Error / Uncertainty
= Accuracy[1]

[1] Accuracy = the closeness of agreement between an individual result found and the true value

Tolerance interval vs. Acceptance limits

- From descriptive to Predictive Approach



The method is considered accurate within the range for which the accuracy profile is within the predefined acceptance limits.

This **Total Error Approach** gives the **guarantee** that **each future measurement** of unknown samples **is included within the tolerance limits with a given risk level** (usually 5%)

[1] The β-expectation tolerance interval is the interval wherein each future measurement will fall with a defined probability β. It represents the location where β% of the future results are expected to lie.

Tolerance interval vs. Acceptance limits

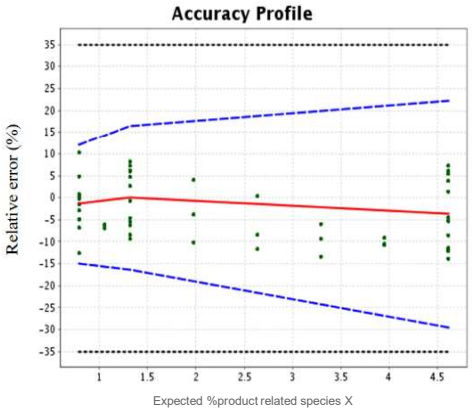
- Does the method qualification cover the whole domain?

Qualification performed at the analytical central values = at optimised parameters
No qualification at the edges of DoE

Method Validation by Total Error Approach

Validation of a RP-HPLC method for product related species

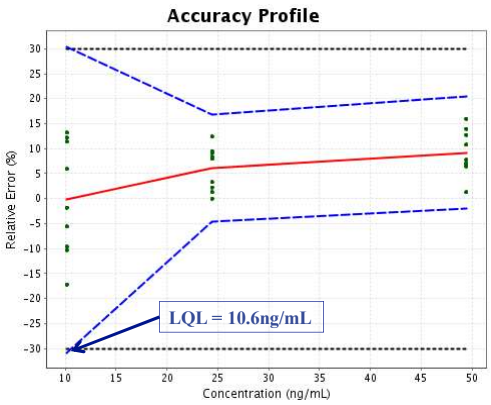
- Reportable result: %area of product related species X
- Risk = 5%, ie, the interval contains 95% of the data
- Acceptance limits = 35%



Method Validation by Total Error Approach

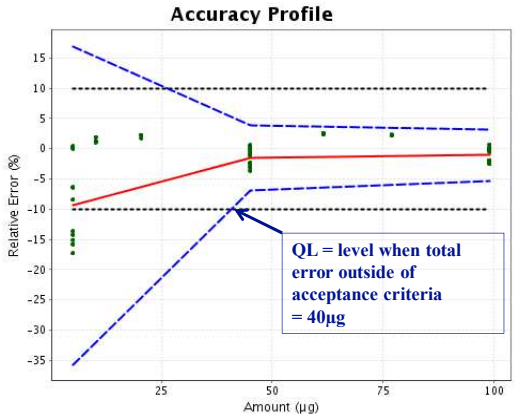
Example 2 : Validation of HCP ELISA assay

- Risk = 5%
- Acceptance limits = 30%

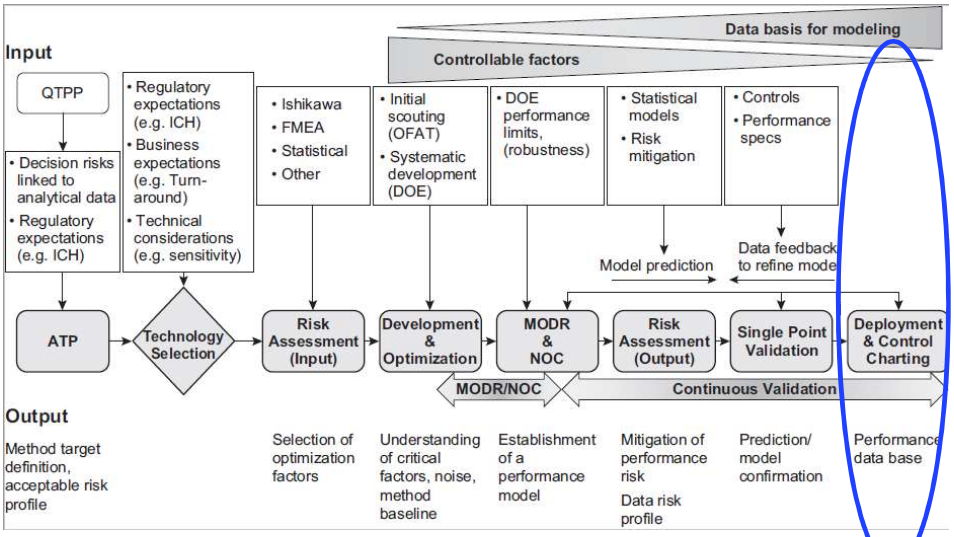


Limit of Quantitation

- Using the concept of total error, LOQ is the level (upper or lower) where the method is no longer accurate enough => fails to meet the ATP



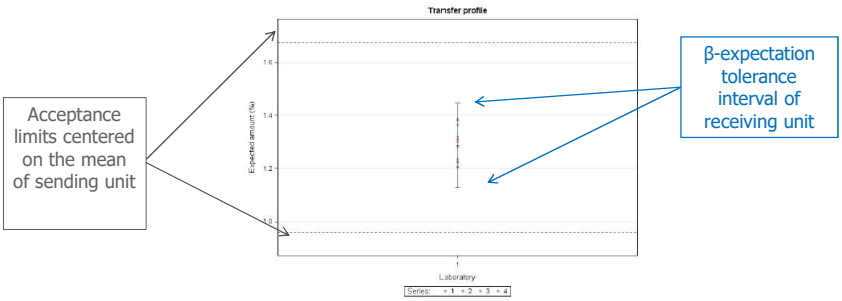
Step by step



T. Verch et al., Analytical Quality by Design, Life Cycle Management and Method Control, AAPS J.. 2022 Feb 11;24(1):34. doi: 10.1208/s12248-022-00685-2.

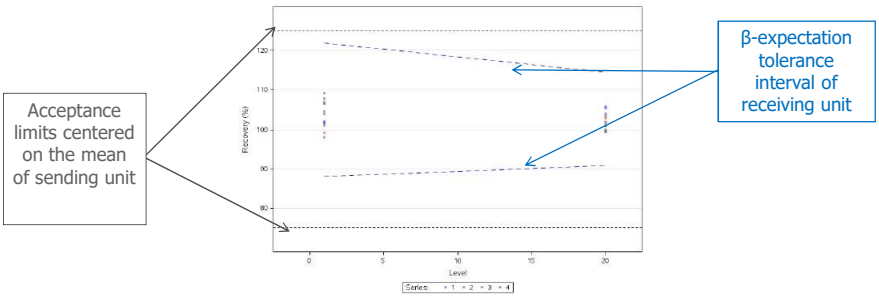
Deployment by transfer

- A transfer exercise can be performed using the same total error strategy



Transfer

- Example of a 2 levels transfer: release and stability-indicating method



Analytical Control Charts: the ultimate SST

Control strategy includes the use of control charts as follows:

- Use a control sample in each analytical run
- Report the parameters of interest measured on the control sample:
  - Reportable result from the method
  - Resolution, etc.
- Trend these parameters using control charts

Benefits of this control strategy:

- Determine if results performed on a routine basis are/remain acceptable for the intended purposes of the method.
- Allow anticipating drifts in the analytical methods.
- Allow comparing the performance of a method over time and also between laboratories/testing sites.

Control Samples for Biologicals

- Integral part of control charting

Control Samples versus Reference Standard

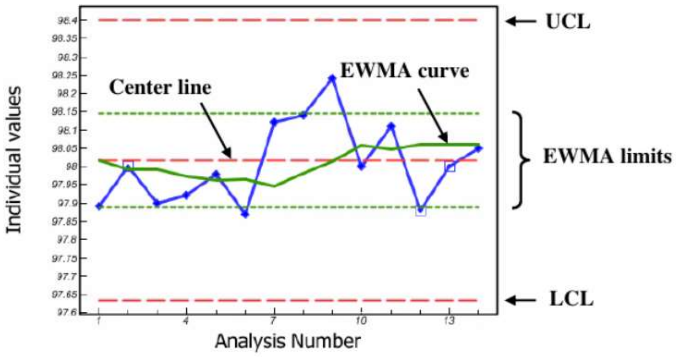
Reference standard

1. **Highly characterized material (of a "pure" batch) h**
2. **One Reference Standard by project**
3. **Used as a ref in method for release and comparability (eg pep map, potency)**

1. **Not characterized (representative material could be spiked or stressed material)**
2. **Several Control Samples by project**
3. **Used to monitor method performance through the use of control chart**

Control Sample

Analytical Control Charts



SST rules :

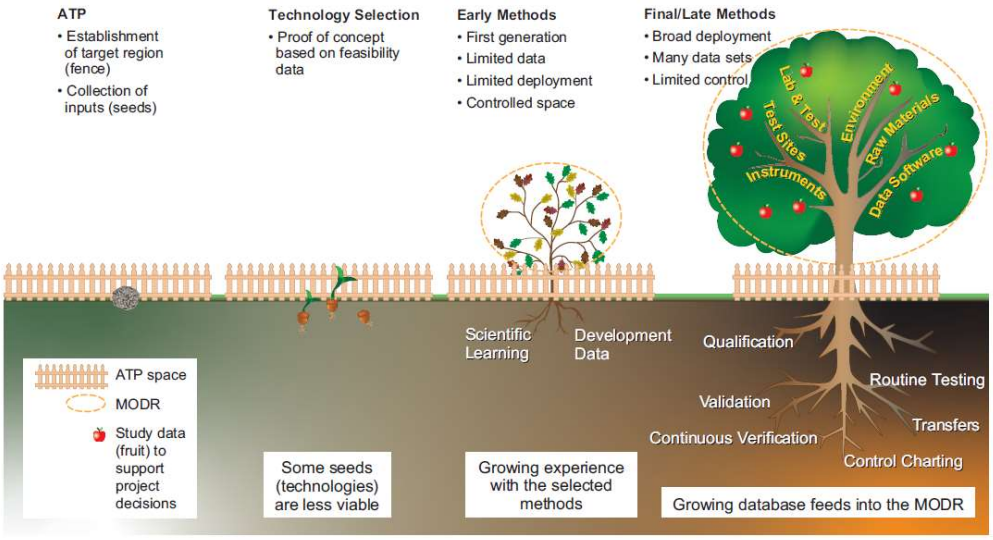
- Value outside of [LCL; UCL]: invalid analysis
- EWMA (exponentially weighted moving average) line crossing EWMA limits: out of trend

Post-approval change management: ICH Q14

- **A method could have to be replaced by a new one, still respecting the ATP**
  The ATP is technology-agnostic, therefore another technology could be selected
- **If the development followed the enhanced approach / aQbD, the higher level of knowledge**
  - should reduce the risk of changes within the method, by leveraging proper SSTs, risk understanding
  - could alleviate the reporting to the authorities in case of change to the method

Conclusion

aQbD: from the seeds to the fruit



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Conclusion

- **aQbD allows to navigate more surely within the Analytical Profile Target**
- **It makes much better use of prior knowledge**
- **Validation is then much more than a formal verification**
- **Some steps are more resource expensive:**
  - formal risk assessment
  - DoE
  - filing

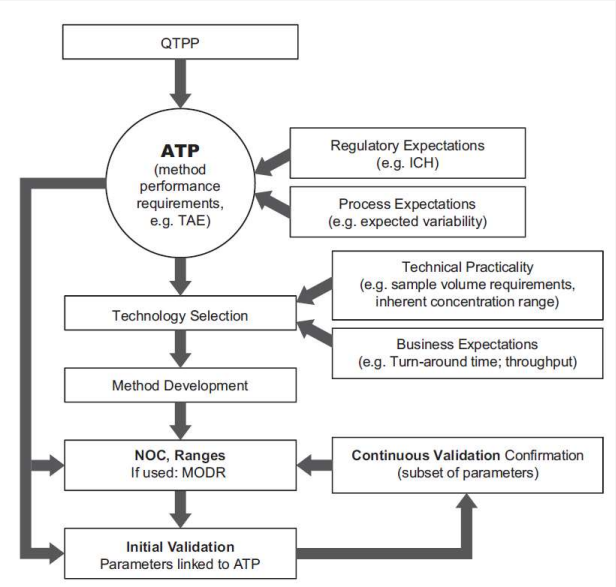
It is a plus for patient safety, with a price tag, for which the regulatory flexibility still needs to be proved

This approach could be a source of inspiration for the pharmacopeial methods

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

Thank you!

Iterative flow



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Thanks.