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INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH Q2(R2) & Q14 Guidelines and impact on validation in OMCL Laboratories

(ISO/IEC 17025:2017)

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Who am I?

Massimiliano Conti

Head of Division Laboratory OMCL

- 19 Years of experience in the industry
- 7 Years of experience in the regulatory

Topic-Leader for ICH Q2(R2)/Q14 EWG

- Swissmedic
- ACCESS Consortium (with HSA)

Start of the EWG: November 2018

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Status and considerations of both Q2(R2) and Q14 guidelines

- ICH Guidelines are «technical documents» and NOT «regulatory» ones, which means that they define standards and common principles between regulators and industries but don't have any direct regulatory implication.
- All the following information and considerations are based on the Step-2 drafts that went out for public consultation. They are still been discussed and edited, based on the about 3'000 comments received. Therefore, slightly changes in the content, structure and terminology is still possible. The main concepts remain the same.
- The target approval of the final documents is planned at the ***ICH Meeting in Prague (CZ)*** in ***November 2023***. Only than, the document are official.
- Training documents are planned, examples will also be published as annexes to the main guidelines.

ICH Q2(R2) & Q14 Guidelines

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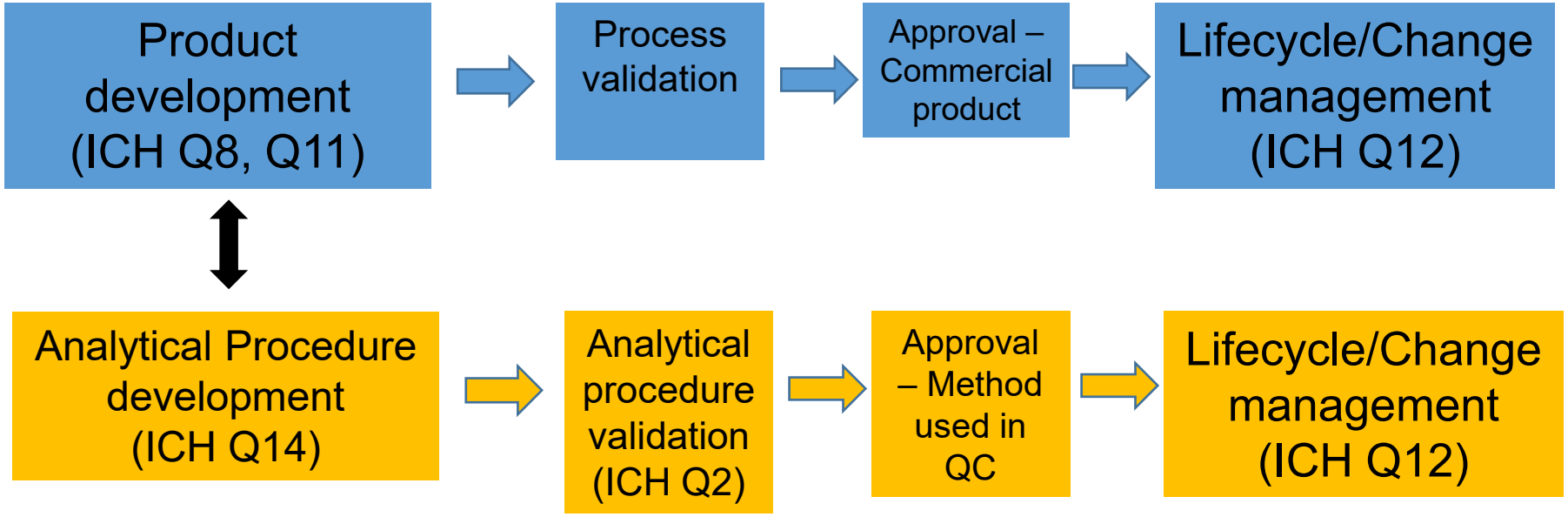
Background

- Robust and efficient analytical procedures are required to accurately measure the quality of the product.

- There is no established guidelines on analytical procedure development.

- The current Q2(R1) guideline is not directly applicable to more recent applications of analytical procedures, such as NIR, NMR.

Background



- Analytical procedure development takes place along with product development.
- The proposed guidelines Q2(R2) and Q14 are intended to complement Q8 to Q12 as well as Q13.

Key principles

- Together **ICH Q14** and **ICH Q2(R2)** describe the development and validation activities suggested during the lifecycle of an analytical procedure used for the assessment of the quality of drug substances and drug products.

- **ICH Q14** describes the scientific principles for development, change management and submission requirement of analytical procedures for the minimal and enhanced approach.

- **ICH Q2(R2)** provides guidance for establishing, submitting and maintaining evidence that an analytical procedure is fit for purpose (assuring drug quality).

Scope and details of the guidelines

ICH Q2(R2)

- Is a revision of the Q2(R1)
- Is a mandatory Guideline
- About 1’700 comments received during public consultation (mostly technical)
- Extension and revision have not introduced new regulatory requirements
- Scope of revision: *to include validation principles that cover analytical use of spectroscopic data some of which often require multivariate statistical analyses. The guideline will continue to provide a general framework applicable to products mostly in the scope of Q6A and Q6B.*

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ICH HARMONISED GUIDELINE

VALIDATION OF ANALYTICAL PROCEDURES Q2(R2)

Draft version

Endorsed on 24 March 2022

Currently under public consultation

Updates on Q2(R2)

- ***Expected benefits of the revised ICH Q2(R2) guideline***:
  - Encouragement of the use of more advanced analytical procedures leading to more robust quality oversight by pharmaceutical drug manufacturers
  - Adequate validation data, resulting in reduction of information requests and responses, which can delay application approval
  - Modernisation of general methodology to include analytical procedures and data evaluation for biotechnological products and statistical/multivariate data evaluations
  - Incorporation of the principles described in ICHQ8-Q10 which did not exist when Q2 (R1) was issued
  - Guidance and recommendations on how to derive and evaluate the various validation tests for each analytical procedure
  - Bridge the differences that often exist between various compendia and documents of the ICH member regulatory agencies

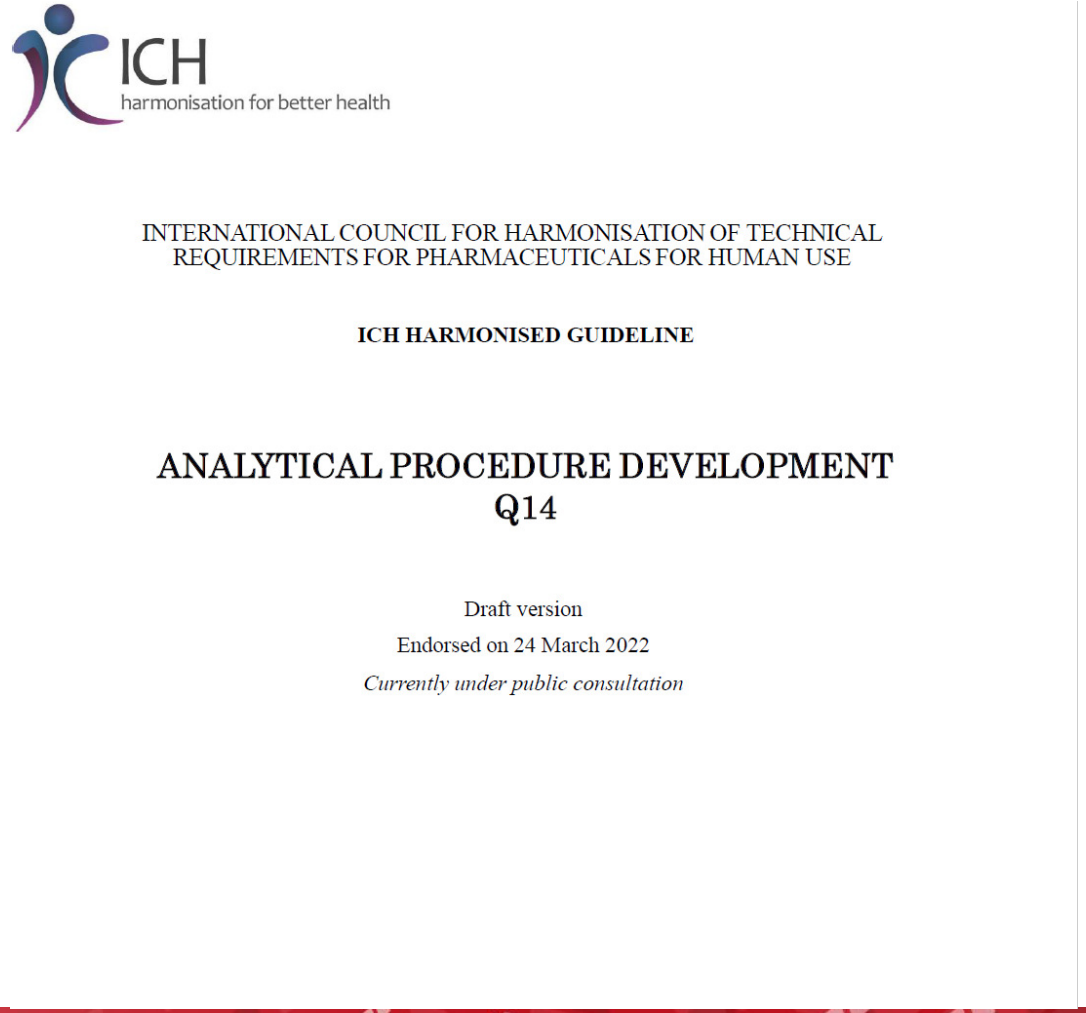
Main changes in the Q2(R2) Guideline

- Here are some new terms or definitions:
  - Introduction: The concept of providing suitable data from development (ICH Q14) to support/ complete the validation ones during submission has been added.
  - Added the concept of "*Platform analytical procedure*" and the possibility of reduced validation in case is used for new purposes.
  - To be inclusive of biological and non-linear analytical procedures, some definitions/sections have been amended, e.g. *linearity* → *Reportable range*.
  - *Performance characteristics* and *performance criteria*
  - Linearity has been replaced by "*Working range*" and consists of "*Suitability of calibration model*" (e.g. ex-Linearity) & "*Lower Range Limit verification"* (QL/DL)
  - Validation during the lifecycle, including "*Co-validation*" and "*Cross-validation*" concepts have been added.

Scope and details of the guidelines

ICH Q14

- Is a new guideline
- Is just a Guideline (NOT mandatory)
- About 1’300 comments received during public consultation (mostly conceptional)
- Scope of the new guideline: *To harmonize the scientific approaches and to provide the principles relating to the description of Analytical Procedure Development process. Applying this guideline will improve regulatory communication between industry and regulators and facilitate more efficient approval as well as post-approval change.*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ICH HARMONISED GUIDELINE

ANALYTICAL PROCEDURE DEVELOPMENT
Q14

Draft version

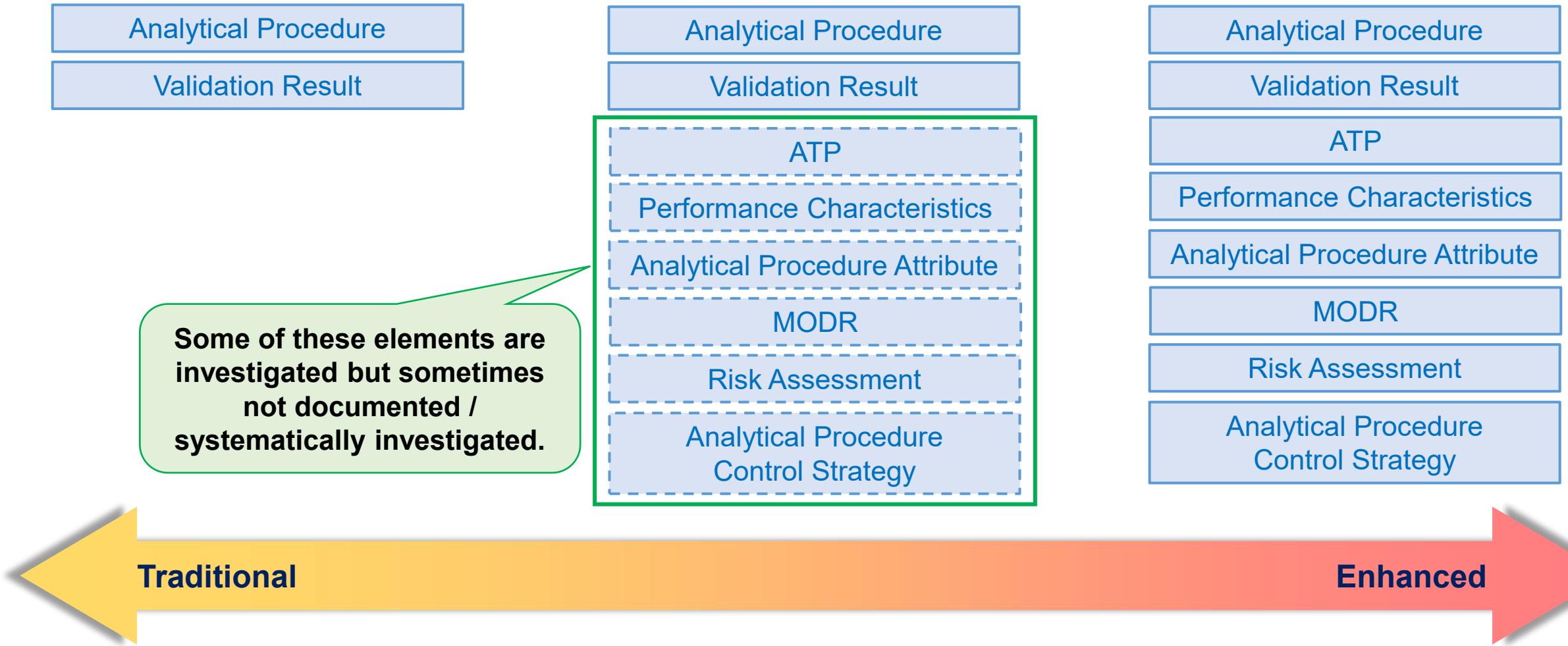
Endorsed on 24 March 2022

Currently under public consultation

The Q14 Guideline

- The ICH Q14 guideline is a guideline that aims to harmonize the scientific approaches for developing and validating analytical procedures for drug substances and drug products.
- It describes two approaches: a *minimal approach* and an *enhanced approach*.
  - The *"minimal approach"* follows the current practices and requirements for analytical procedures.
  - The *"enhanced approach"* uses an "*analytical target profile"* (ATP) to define the quality attributes and performance criteria of the analytical procedure.
- The *enhanced approach* may provide more benefits than the *minimal approach*, such as increased method understanding, improved method robustness, reduced method variability, and facilitated method lifecycle management. However, you can choose either approach depending on your product and analytical procedure characteristics and needs.
- The guideline also provides guidance on how to manage changes to analytical procedures after approval.

The Q14 Guideline

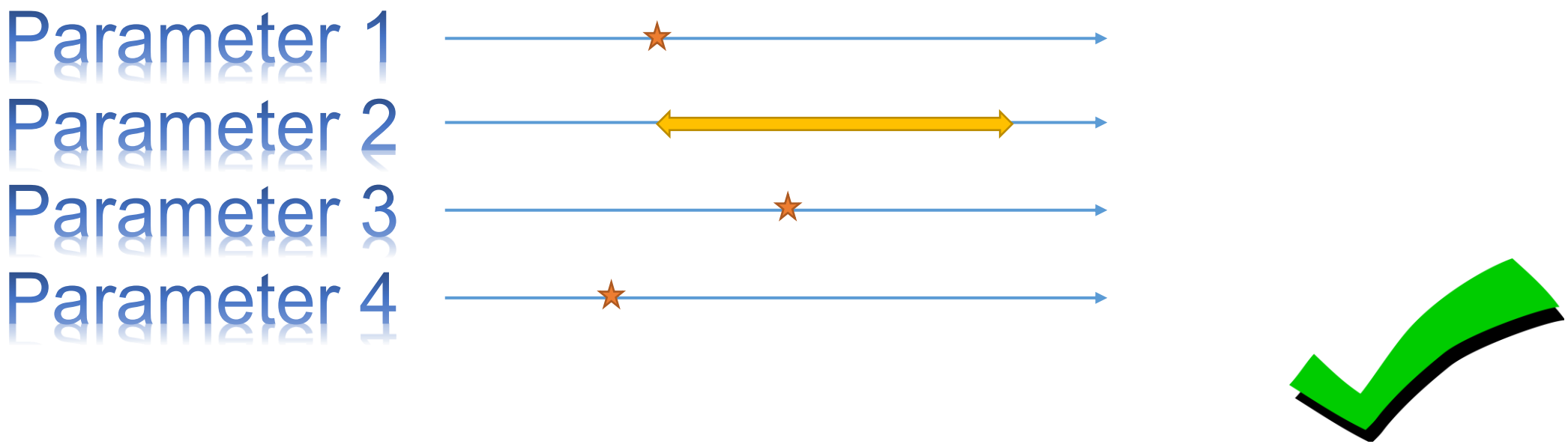


The Q14 Guideline

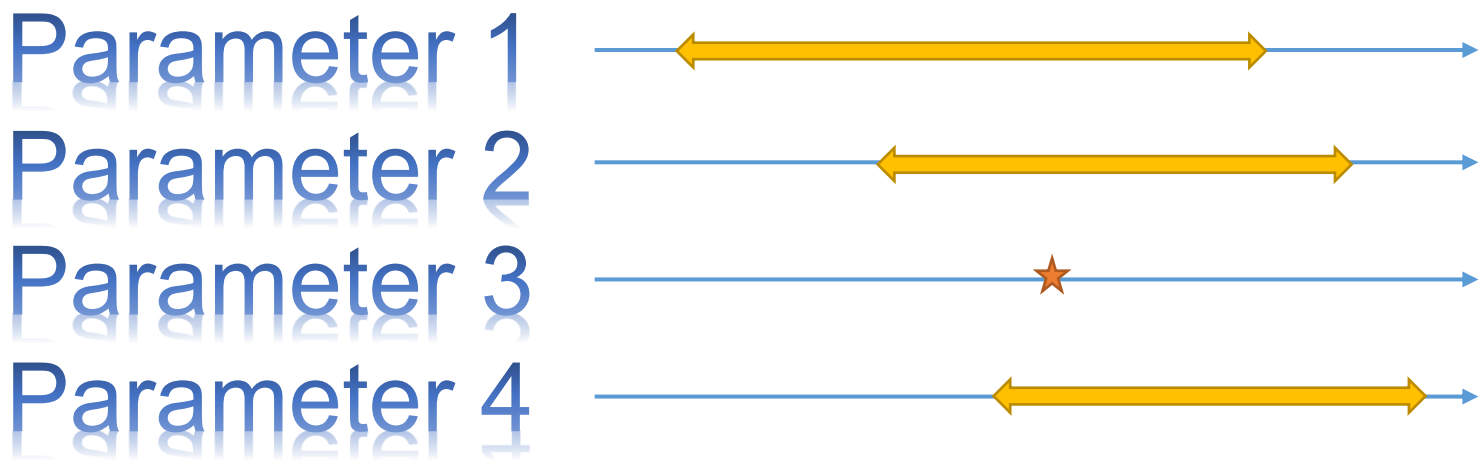
There are many new terms defined in this guideline, some are the following:

- ***Analytical Target Profile (ATP):*** A prospective summary of the performance characteristics describing the intended purpose and the anticipated performance criteria of an analytical measurement.
- ***Analytical Procedure Attribute***: A technology specific property that should be within an appropriate limit, range, or distribution to ensure the desired quality of the measured result. For example, attributes for chromatography measurements may include peak symmetry factor and resolution.
- ***Analytical Procedure Control Strategy:*** A planned set of controls derived from current analytical procedure understanding that ensures the analytical procedure performance and the quality of the measured result.
- ***Proven Acceptable Range for Analytical Procedures (PAR)***: A characterized range of an analytical procedure parameter for which operation within this range, while keeping other parameters constant, will result in an analytical measurement meeting relevant performance criteria.
- ***Method Operable Design Region (MODR):*** A combination of analytical procedure parameter ranges within which the analytical procedure performance criteria are fulfilled and the quality of the measured result is assured.

Proven Acceptable Range for Analytical Procedures (PAR)



Method Operable Design Region (MODR)



Analytical Performance Criteria (APC)

The impact for an OMCL Laboratory

- (ISO/IEC 17025:2017)

The impact for an OMCL Laboratory (ISO/IEC 17025:2017)

- OMCL (Official Medicines Control Laboratories), which are in the EDQM GEON network, must be either ISO/IEC 2017:2017 accredited or audited by GEON Members according to the MJA-Scheme and following the OMCL-Guidelines. The latter are just a harmonised way to implement the ISO rules.

- The impact on an ISO/IEC 17025:2017 accredited laboratory is evaluated based on the rules and requirements defined in the Norm itself

- OMCL are all national laboratories either used or managed by the regulator and must be totally independent and well separated from the industry (impartiality, independence). Hence the internal methods are NOT subject to regulatory filings and approval.

The impact for an OMCL Laboratory (ISO/IEC 17025:2017)

- Impact of the ICH Q2(R2):
  - Expansion of the scope to all non-linear, biological and multivariate-methods, which will help to define the extent and requirements of validation (like for the linear ones).
  - Harmonisation of these new method-type inclusion throughout the OMCL network and beyond, e.g. for pharmacopoeial methods.
  - Possibility to use development and prior-knowledge data to complement validation ones
  - Harmonisation and clarification of terminology used in validation/verification documents

The impact for an OMCL Laboratory (ISO/IEC 17025:2017)

- Impact of the ICH Q14:
  - Very limited impact, since is an informative guideline (no regulatory requirements) and because development is not mentioned in the ISO/IEC 17025:2017 norm
  - Introduction of the enhanced-approach, which can be interesting for OMCLs but way less useful (no regulatory filings)
  - Harmonisation and clarification of terminology used in development documents

Q&A

Backup slides

Updates on Q2(R2)

- ***«Working range» instead of «Linearity»***:
  - Depending on the sample preparation (e.g., dilutions) and the analytical procedure selected, the reportable range will lead to a specific working range.
  - ***Linear response*** : A linear relationship between analyte concentration and response should be evaluated across the working range of the analytical procedure
  - ***Non-linear Response***: The suitability of the model should be assessed by means of non-linear regression analysis (e.g., coefficient of determination).
  - ***Multivariate response***: Algorithms used for construction of multivariate calibration models can be linear or non-linear, as long as the model is appropriate for establishing the relationship between the signal and the quality attribute of interest
  - ***Validation of lower range limits***: Detection and Quantitation Limit can be validated through signal-to-noise, Standard Deviation of a Linear Response and a Slope or through Accuracy and Precision at lower range limits

Example of an ATP for HPLC assay of a DS

- ***Analyte(s) of interest:***
  - The drug substance (DS) with a molecular weight of 500 g/mol and a purity of 99.5%.
  - The DS may degrade under acidic or oxidative conditions and form impurities A and B.
  - The DS may also form a complex with the buffer used in the HPLC mobile phase and affect its retention time.

- ***Matrix or matrices:***
  - The DS is dissolved in water for injection (WFI) at a concentration of 1 mg/mL.
  - The WFI may contain trace amounts of metals or organic contaminants that may interfere with the DS measurement.
  - The WFI may also vary in pH or conductivity depending on the source or batch.

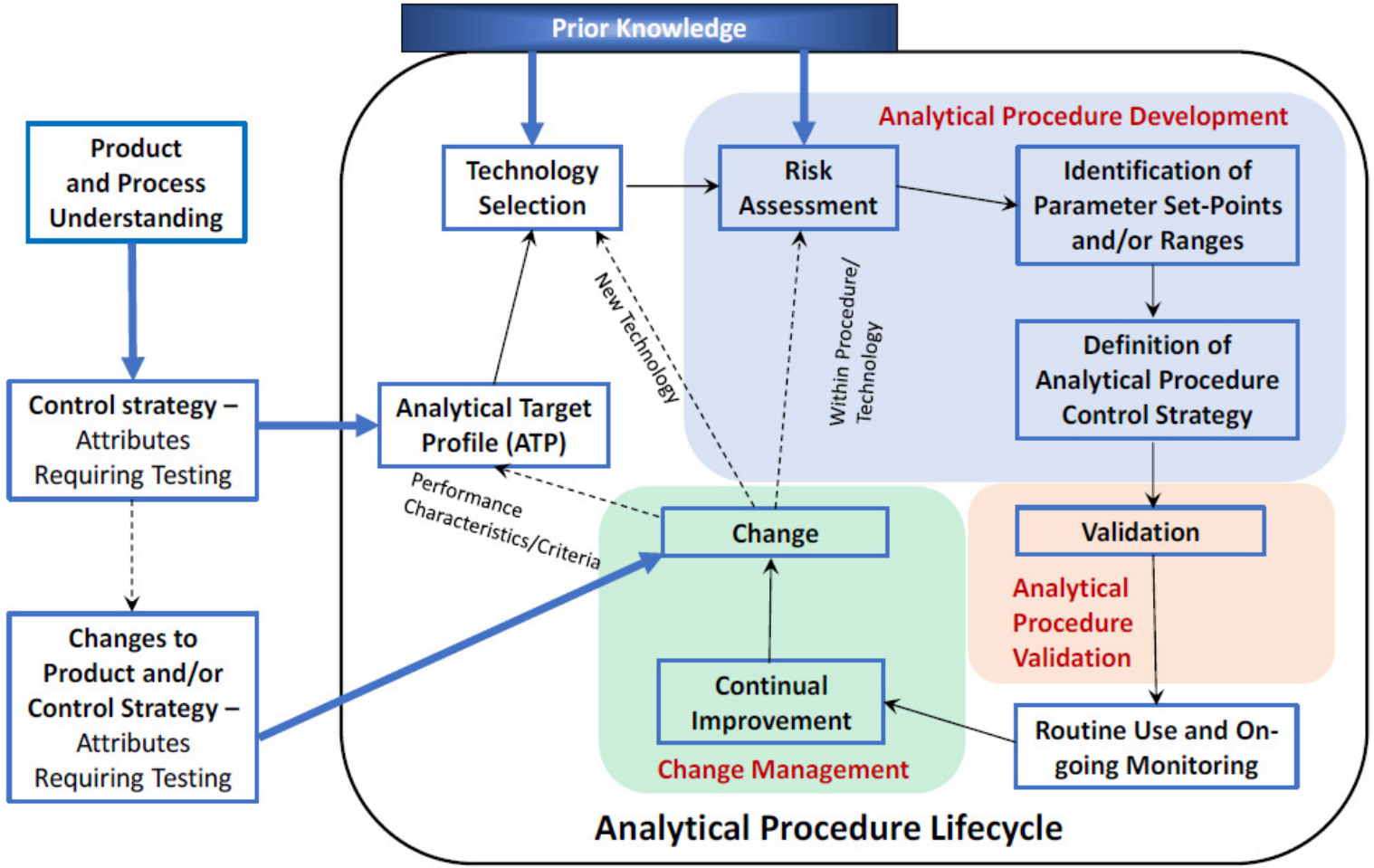
Example of an ATP for HPLC assay of a DS

- ***Intended use of the analytical procedure:***
  - The HPLC method is intended to measure the concentration and purity of the DS for release testing and stability testing.
  - The HPLC method should be able to separate and quantify the DS and its impurities A and B.
  - The HPLC method should also be compatible with the regulatory requirements and expectations for drug substance assay methods.

Example of an ATP for HPLC assay of a DS

- ***Performance criteria:*** The HPLC method should have:
  - an accuracy of ±2%
  - a precision of ≤2% relative standard deviation (RSD)
  - a specificity of ≥99%
  - a selectivity of ≥1.5 resolution factor (Rs)
  - a sensitivity of ≤0.05% limit of quantitation (LOQ)
  - a linearity of 0.8-1.2 mg/mL with a correlation coefficient ® of ≥0.999
  - a range of 80-120% of the target concentration
  - a robustness of ≤1% RSD for small changes in temperature, flow rate, wavelength, etc.
  - a ruggedness of ≤2% RSD for different instruments, operators, days, etc.

The Q14 Guideline



The Analytical Target Profile (ATP)

- To define and justify the ATP elements, a consideration of the following aspects is needed:
  - The analyte(s) of interest are the substance(s) or property(ies) that need to be measured by the analytical procedure. They should be clearly identified and described, including their chemical structure, molecular weight, purity, impurities, etc.
  - The potential interferences or matrix effects that may affect the analyte(s) measurement, including the composition and characteristics of the matrix or matrices, and how they may vary depending on the source or stage of the product lifecycle.
  - The intended use of the analytical procedure is the purpose or objective of the measurement. It may include quality control, stability testing, release testing, characterization, etc.
  - The intended use of the analytical procedure and how it relates to the quality target product profile (QTPP) and the critical quality attributes (CQAs) of the product.

The Analytical Target Profile (ATP)

- Also consider the regulatory requirements and expectations for the intended use of the analytical procedure.

- The performance criteria are the quantitative or qualitative measures that indicate how well the analytical procedure meets its intended use. They may include accuracy, precision, specificity, selectivity, sensitivity, linearity, range, robustness, ruggedness, etc.
  - Define and justify the performance criteria based on scientific knowledge and risk assessment.
  - Consider the sources of variability and uncertainty that may affect the performance criteria.

Regulatory advantages of the *enhanced approach* in post approval changes

- ***Minimal approach:***
  - Any changes to the analytical procedure should be reported according to the regional regulatory requirements. By using different elements of the *enhanced approach*, can lead to easier management and regulatory communication of said post-approval change

- ***Enhanced approach***:
  - In case a proper validated and justified MODR or PAR, a higher flexibility of changes within the approved range is available, e.g. communication trough a PQS.
  - BUT: Changes outside the approved range or extension of it, will require a regulatory reporting as per regional requirements.
  - In case ECs are proposed, which will reduce the risk of the change, a reduction of the reporting category of the post approval change is possible.

Knowledge and Risk Management in Analytical Procedure Development and Continual Improvement

- The guideline describes also how the ***prior knowledge*** is central to the analytical procedure development, since will influence and drive the decisions made during the definition, execution and evaluation of the protocol. Said knowledge can be internal (e.g. company's experience) or external (e.g. literature or established technical principles).

- Also a ***risk management*** is essential during development:
  - in order to select and define critical analytical procedure parameters and potential impact and hence identify the ones to be prioritized during the experimental investigation
  - In order to monitor the performance of the analytical procedure during the routine use and control the state of performance. It might trigger an update of the analytical procedure, if the performance is lower than expected.