Overview of ICH Q2(R2)/Q14: Development and Validation of Analytical Procedures

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*based on the ICH Step 2 documents

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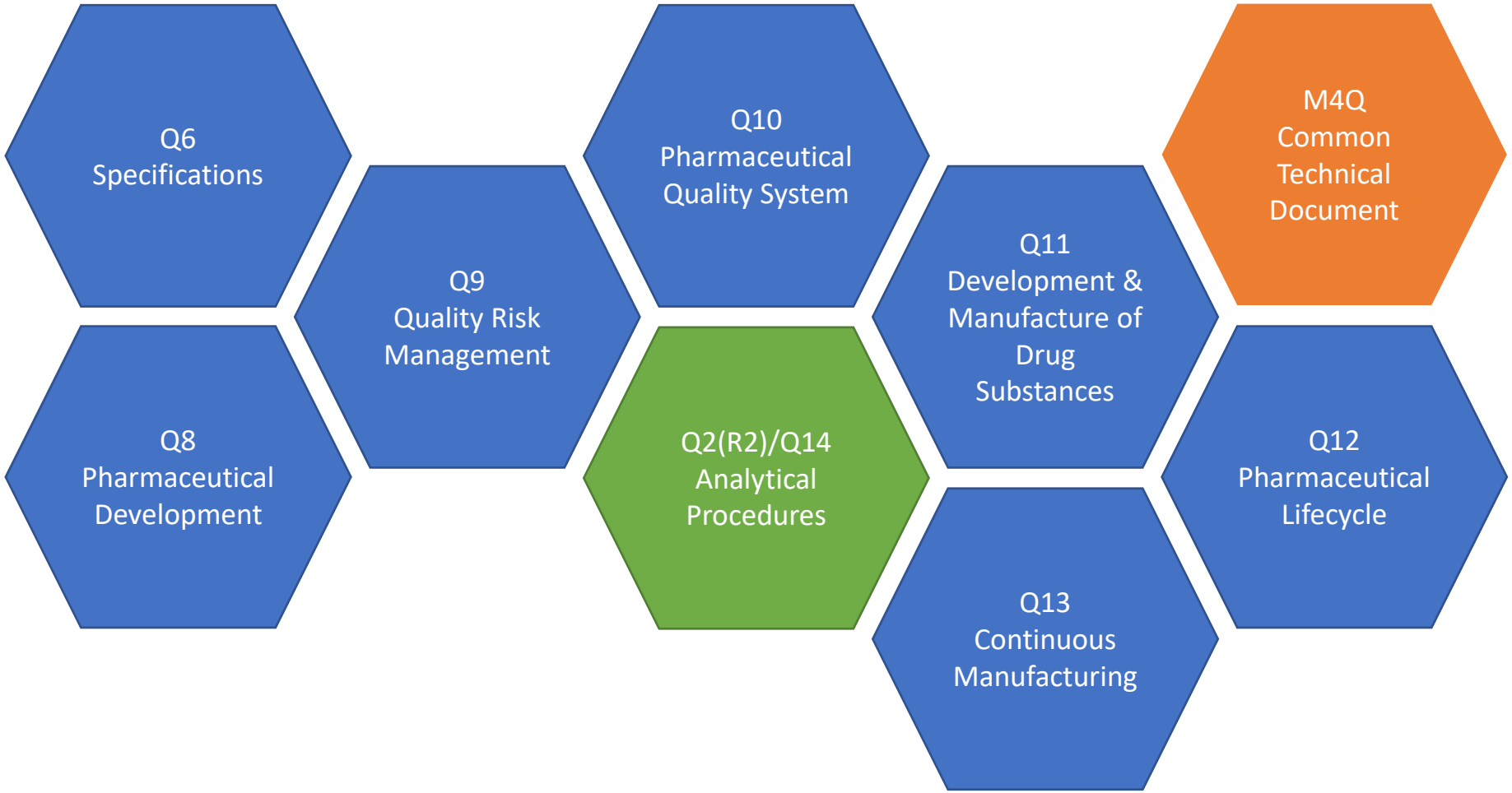
Drivers for Q2 Revision and Q14 Development

PMDA and FDA joint proposal in 2017

- “Currently there is a lack of Analytical Development guideline which should complement with Product Development guideline Q8(R2) and Q11. Although Analytical Development activities are systematically conducted in industry, **the outcome of the development activities is rarely described in detail in the market application**. Only results of Analytical Validation with implicit performance standards of Analytical Procedure are usually presented. The **situation presents challenges for regulatory communication when changes are made in analytical procedures** (Change control/Change management)”

- “to **provide an opportunity to present the knowledge** obtained through applying the enhanced approaches to analytical procedures, to provide the guidance on how to apply, and to **indicate a policy for more flexible regulatory approaches**. The proposed guideline will facilitate selecting or identifying development approaches that will reduce risk of post-approval change to procedures discussed in Q12, and enable more efficient and science-based change management. Applying the enhanced approach for analytical procedures will contribute to the resource-efficient drug development and post-approval CMC changes.”

Q2 and Q14 sit in the context of the existing and *evolving* ICH Q Guidelines and M4Q



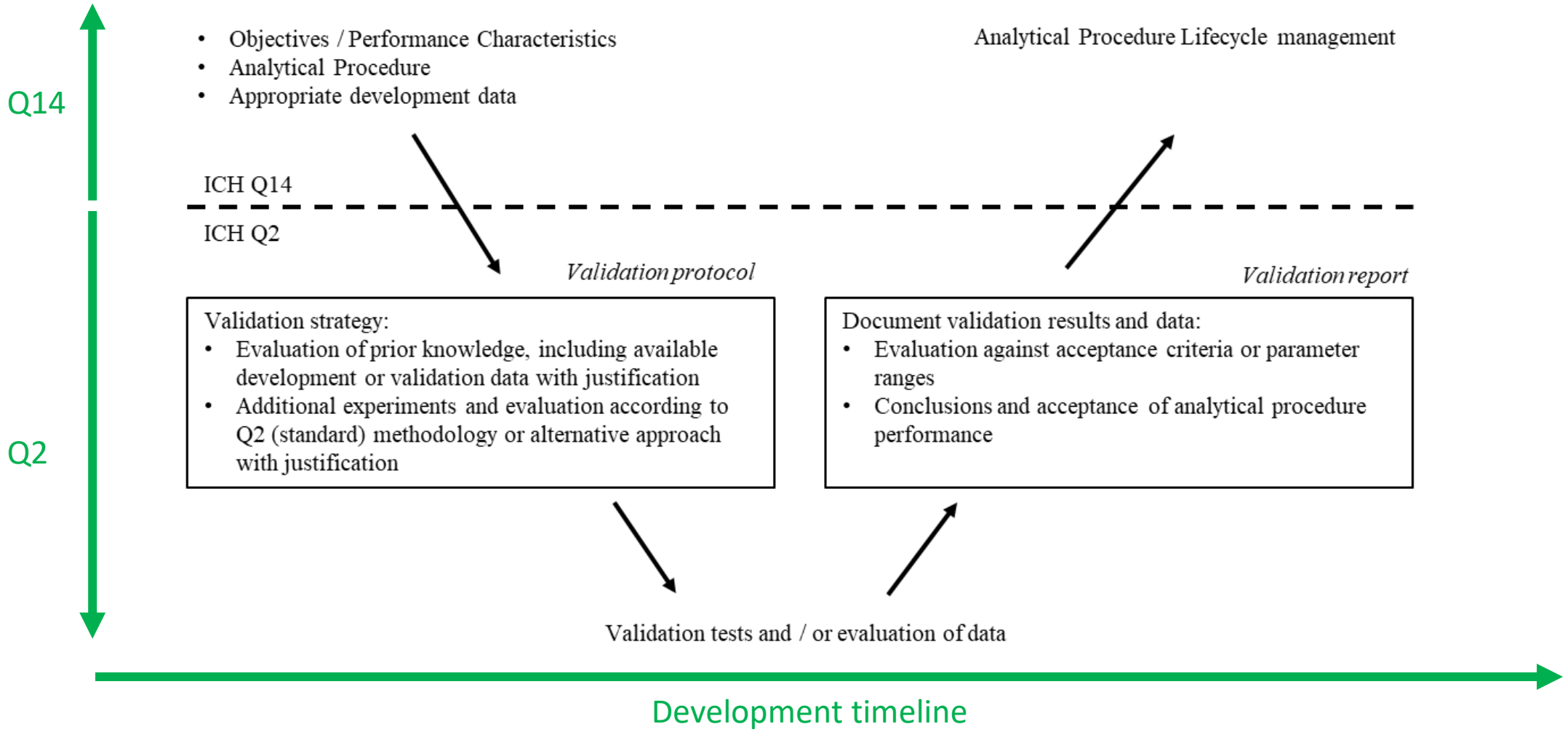
Common scope of Q2(R2) and Q14

- New or revised analytical procedures
- Release and stability testing
- Chemical and biological/biotechnological products
- Drug substance and drug product
- Commercial products

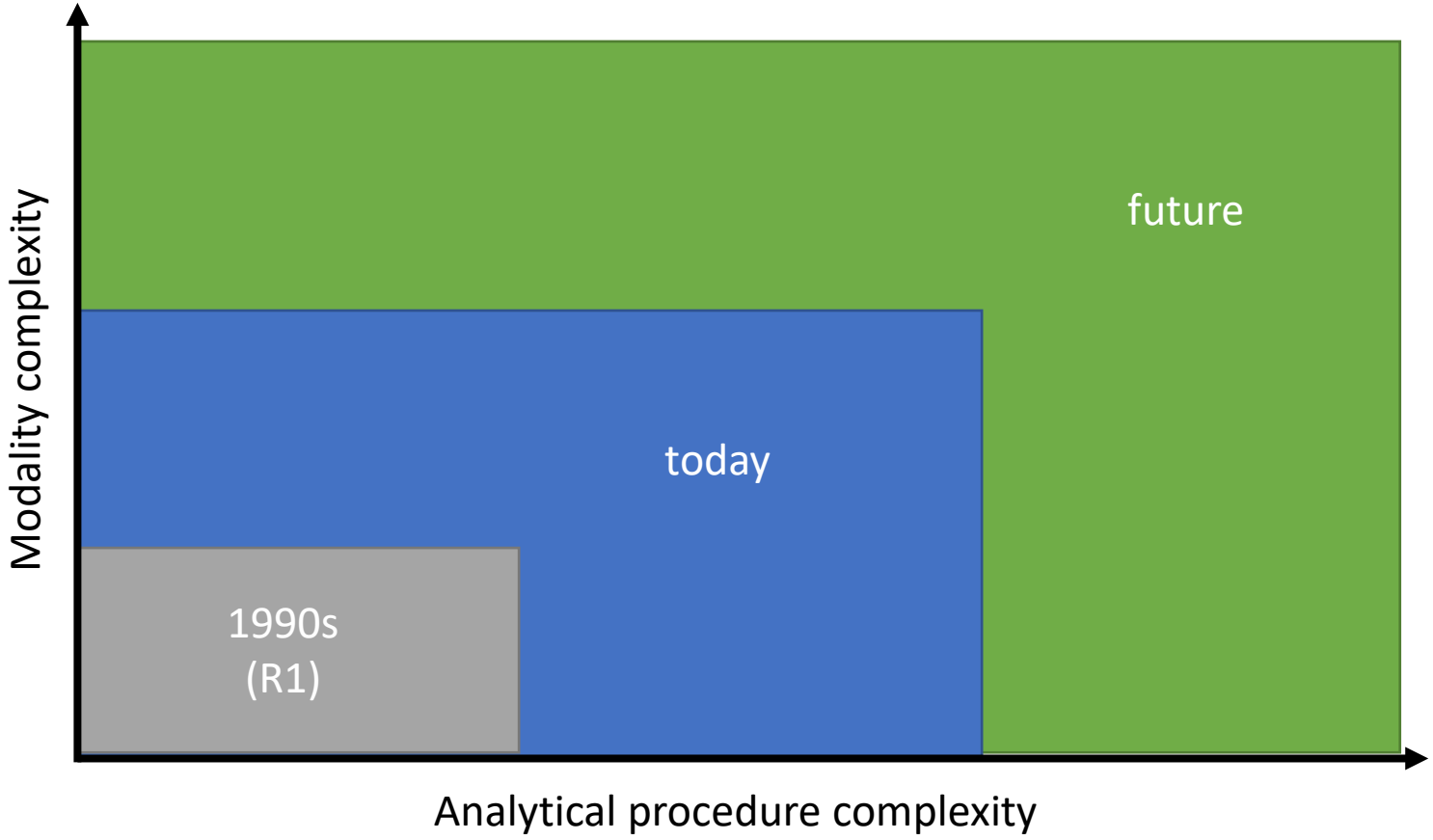
- *May* be applied…
  - To other analytical procedures used as part of the control strategy following a risk-based approach
  - In a phase-appropriate manner during clinical development
  - To other types of products, as appropriate

→ **No new regulatory requirements***

Q2 and Q14 Operate in a Continuum



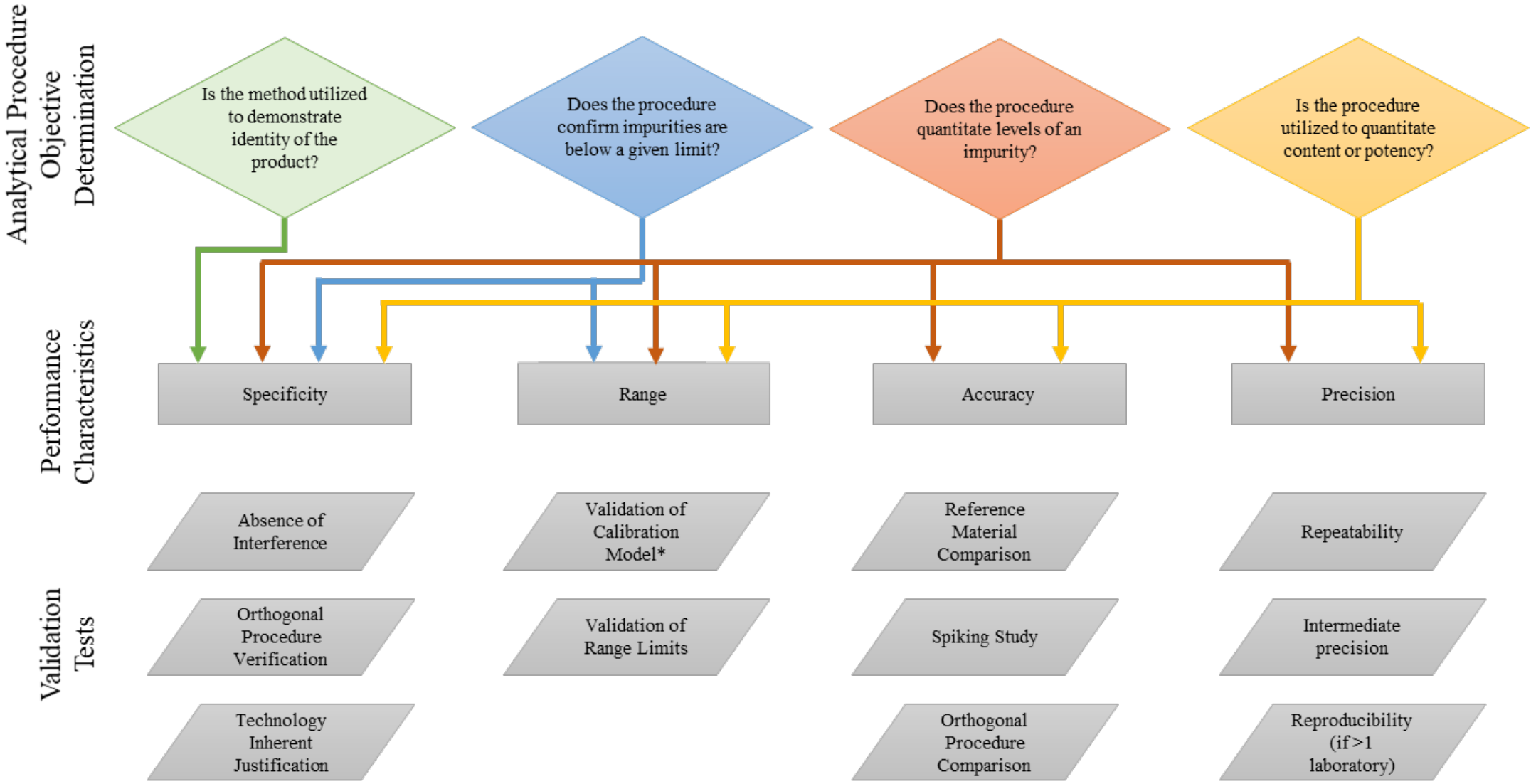
But wasn’t Q2(R1) working just fine?



ICH Q2(R2): What can you expect?

- Q2(R1) part 1 and part 2 text combined into Q2(R2)
- Generalized Q2(R1) framework to be more broadly applicable
    - e.g., multivariate methods, complex (bio)molecules
- Performance characteristics table from Q2(R1) retained but updated
- Validation performance characteristics rearranged under four major topics
    - Specificity
    - Range
    - Accuracy
    - Precision
- Robustness and system suitability concepts moved to Q14
- Examples of applications for specific technologies compiled into Annex 2

Appropriate selection of validation tests is based on the objective of the analytical procedure



Q2 Annex 1

Q2(R2) defines new concepts relevant to validation used through a procedure's lifecycle

- **Revalidation** – after a change to an analytical procedure
- **Co-validation** – validation leveraging data from more than 1 laboratory site
- **Platform analytical procedure** – a multi-product method suitable to test quality attributes of different products without significant change to its operational conditions, system suitability and reporting structure
- **Reference material** – a suitably characterized material, sufficiently homogeneous and stable with regard to one or more defined attributes, which has been established to be fit for the intended purpose. Reference materials may include national/international reference standards, pharmacopeial reference standards, or in-house primary/secondary reference materials.

Q2(R2) Annex 2 provides examples of how performance characteristics could be tested across a variety of technology and analyte types

- Quantitative separation techniques
  - Separation techniques (HPLC, GC, CE) for impurities or assay
  - Separation techniques with Relative Area Quantitation, e.g., product-related substances such as charge variants
- Elemental Impurities by ICP-OES or ICP-MS as purity test
- Dissolution with HPLC as product performance test for an immediate release dosage form
- Quantitative ^{1}H-NMR for the Assay of an API
- Binding assay (e.g., ELISA, SPR) or Cell-based assay for determination of potency relative to a reference
- Quantitative PCR (quantitative analysis of impurities in drug substances or products)
- Particle size measurement
- NIR method validation example for core tablet assay
- Quantitative LC/MS (quantitative analysis of impurities (e.g., genotoxic impurities) in drug substances or products)

Q2(R2) – where we need to think differently

- **Range** is discussed in 2 different types
  - The **reportable range** of an analytical procedure
    - Includes all values from the lowest to the highest reportable result for which there is a suitable level of precision and accuracy.
    - Typically is in the same unit as the specification
  - The **working range** of an analytical procedure
    - the lowest and the highest concentration that the analytical procedure provides meaningful results.
    - may be different before sample preparation (sample working range) and when presented to the analytical instrument (instrument working range). Mathematical calculations are typically required to generate reportable results.
  - Reportable range and working range can be identical!
- Assessment of **accuracy** and **precision** against validation acceptance criteria should include appropriate confidence intervals
  - Q2(R1) only required reporting of confidence intervals
- **Reference Materials** are defined inclusively for use in validation studies

Examples of ICH Q14 Key Points/Messages

The goal of analytical procedure development is to design an analytical procedure to be fit for its intended purpose. The guideline provides guidance on science and risk-based approaches for developing analytical procedures to ensure the quality of marketed drug substances and drug products

Developing analytical procedures is closely linked with product/process development and the guideline describes the Analytical Procedure Lifecycle including the postapproval stage

Analytical procedures could be developed by applying an enhanced approach or a minimal (traditional) approach

The guideline will provide an opportunity to present the knowledge obtained by applying an enhanced approach

The guideline describes how a comprehensive understanding based on risk assessment can support continual improvement of analytical procedures through the procedure's lifecycle and provide assurance of the quality of analytical data

ICHQ14: Analytical Procedure Development Chapter 2.2: Minimal versus Enhanced Approaches to Analytical Procedure Development

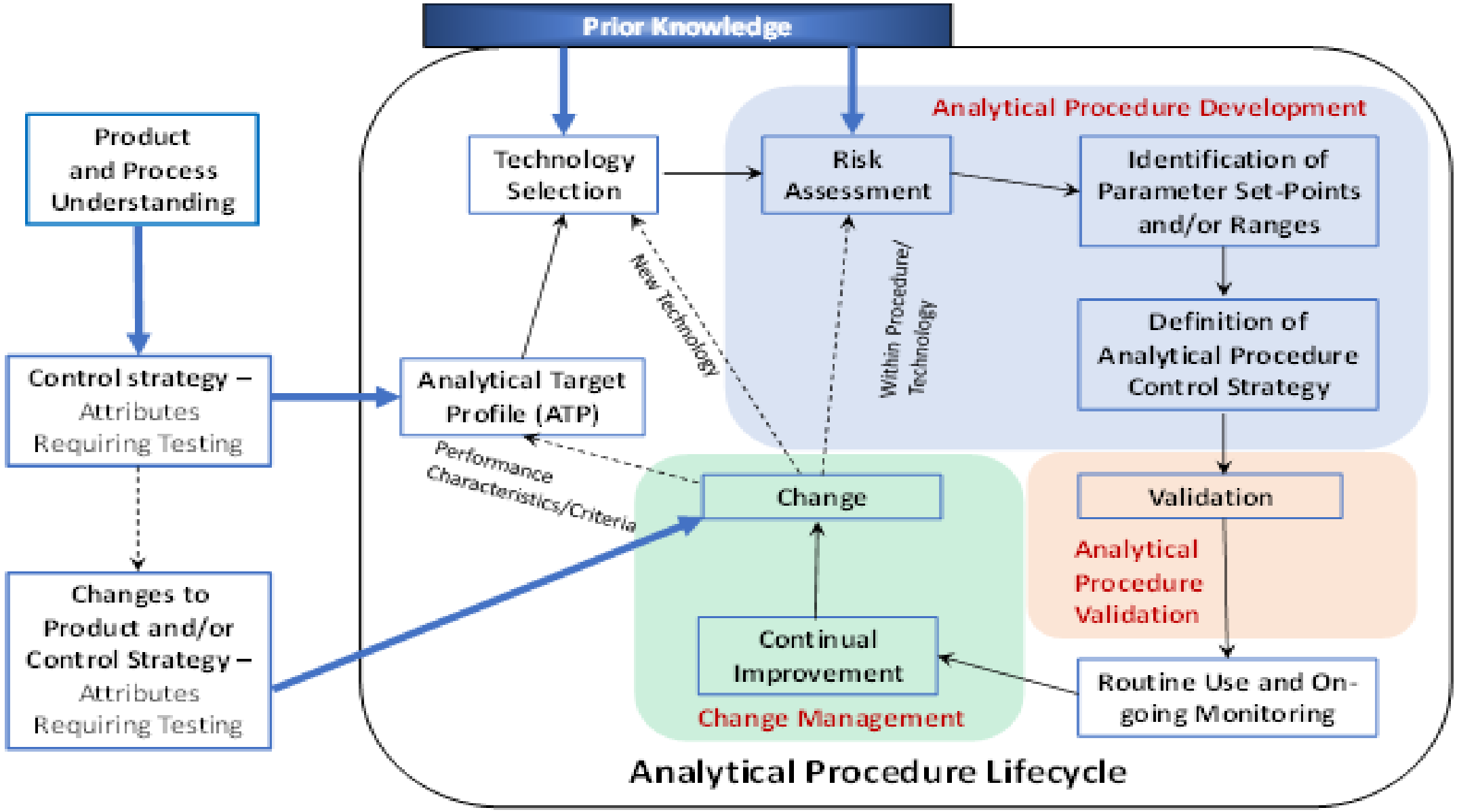
Minimal approach

- Identifying attributes need to be tested
- Selecting appropriate technology and related instruments
- Conducting appropriate development studies
- Defining analytical procedure description

Enhanced approach

- Evaluation of the sample properties
- Defining the analytical target profile (ATP)
- Conducting risk assessment and evaluating prior knowledge
- Conducting uni- or multi-variate experiments
- Defining an analytical procedure control strategy
- Defining a lifecycle change management plan

Analytical Procedure Lifecycle



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Concepts: QTTP versus ATP

Quality Target Product Profile (QTPP):

A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. (ICH Q8)

Analytical Target Profile (ATP):

- A prospective summary of the performance characteristics describing the intended purpose and the anticipated performance criteria of an analytical measurement.
- Facilitates the selection of the technology, the procedure design and development as well as the subsequent performance monitoring and continual improvement of the analytical procedure.
- Multiple available analytical techniques may meet the performance requirements.
- Maintained over the lifecycle and can be used as basis for lifecycle management

Enhanced understanding enables the definition of conditions that provide a high degree of confidence that the procedure will consistently generate results that meet the requirements of the ATP

ICH Q14: Analytical Target Profile

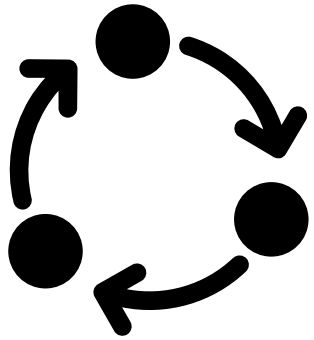
ATP

Intended purpose	**Description and context of CQA to be measured**: - Identity, purity, potency, etc. - Release, stability, in-process, etc.
Required characteristics of the reportable result	**Performance Characteristics**: accuracy, precision, range, specificity, etc.

Analytical Procedure

Technology selection	**Technology best suited to deliver ATP:** SEC, icIEF, CE-SDS, etc.
Supporting parameters	- Calibration model, specificity/selectivity, DL/QL to support the required accuracy/precision and range, etc.
Enhanced method understanding and validation	- Method understanding and SST - Clear link between validation acceptance criteria and ATP

Continual Improvement of Analytical Procedures



In order to provide continued assurance of product quality over the entire lifecycle, the analytical procedure should remain fit for purpose and needs to

- Keep up with process and product changes throughout the product lifecycle
- Be compliant with new and emerging regulatory requirements
- Employ current technology and instrumentation and avoid obsoletion

Harmonization of global regulatory requirements for various types of analytical method changes is therefore desirable

Reporting of Changes to Analytical Procedures in ICH Q14 is Based on ICH Q12 Tools (ECs, PLCM, PACMP)

Follows ICH Q12 approach - categorization of change reporting category for established conditions (ECs) is dependent on the risk associated with the change for the analytical procedure

The outcome of the risk assessment is used to justify the respective reporting category, and is also used during implementation to design the extent of the studies required to support the change

Factors to be considered in risk assessment include:

- Relevance of the test to product quality
- The complexity of the technology
- Extent of the change.

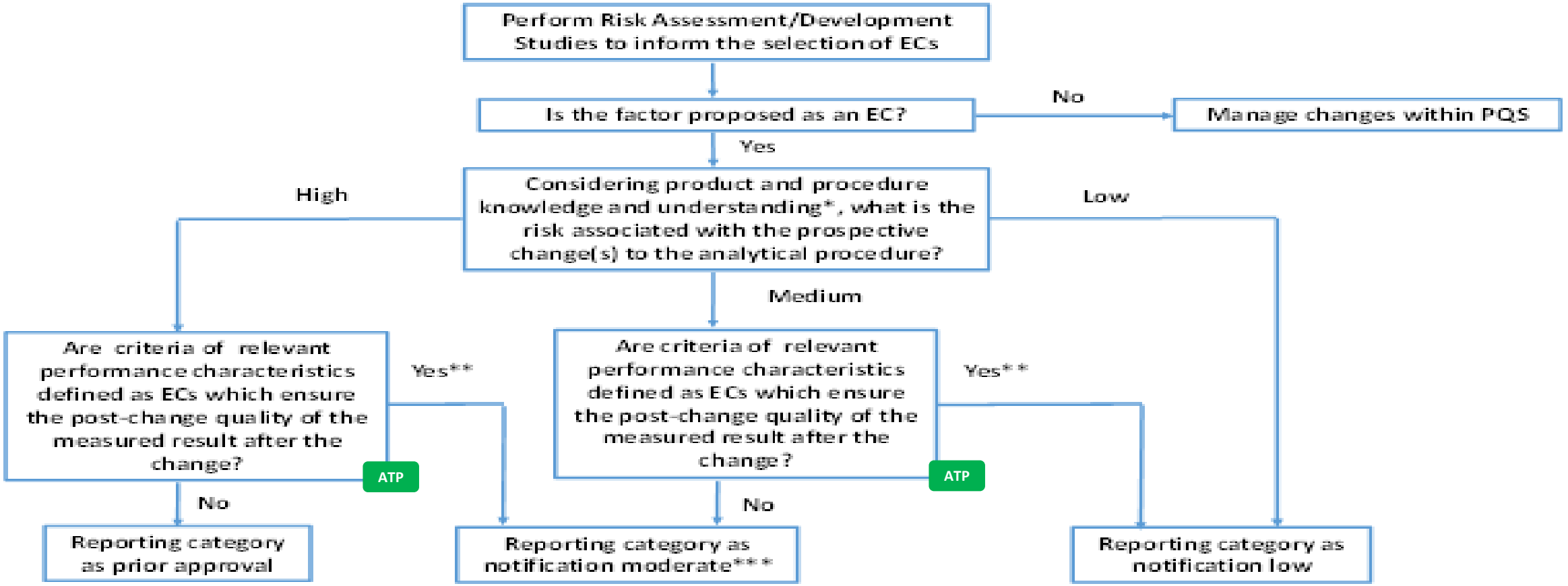
Relevant risk reduction measures should be identified based on

- Product and process knowledge
- Analytical procedure understanding
- Proposed control strategy.

ICH Q14: Lifecycle Management and Post-Approval Changes of Analytical Procedures

If a minimal approach to development is taken, then any changes should be reported according to existing regional reporting requirements.

The use of different elements of the enhanced approach can facilitate management and regulatory communication of post-approval changes.



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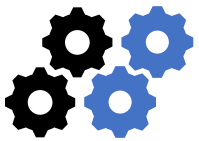
Change Management of Analytical Procedures



When implementing changes to analytical procedures, Quality Risk Management can be used to evaluate impact and re-confirm the originally agreed reporting category	Outcome informs the design and extent of the studies required to support the change Appropriate bridging strategy is needed to demonstrate that the revised or new procedure is fit for purpose
For changes related to product and process modifications	Re-assessment of the suitability of the analytical procedure may be necessary, including a re-assessment and potential adaptation of the ATP, if used.
For introduction of a new analytical procedure post-approval	Thorough risk assessment and evaluation should be conducted The respective analytical procedure control strategy for the new procedure needs to be established and ECs associated with the new procedure should be justified

Change management process in PQS should be effective and in line with recommendations described in ICH Q12

ICH Q14 Chapter 10: Submission of Analytical Procedure Related Information

Information to be included in the CTD section 3.2.S.4.2 and 3.2.P.5.2.

- The analytical procedure description
- In the enhanced approach: performance characteristics and acceptance criteria and other elements of the enhanced approach (e.g. MODRs, PARs)

Other analytical procedures used as part of the control strategy can be included in relevant CTD sections (e.g., 3.2.S.2, 3.2.P.3 and 3.2.P.4).

Information to be included in the CTD section 3.2.S.4.3 and section 3.2.P.5.3

- Validation data
- Additional development and additional information needed to justify control strategy, ECs and their reporting categories to support the proposed lifecycle management strategy

Specific guidance for submission of multivariate procedures and their validation is provided

ICH Q14 Annex A: Analytical Procedure Lifecycle Management

Provides examples describing how

- analytical procedure performance characteristics derived from the product context and knowledge could be summarized in an ATP
- ECs for analytical procedures can be identified (enhanced approach)
- QRM and the adherence to associated criteria for relevant performance characteristics can
  - help to justify the respective reporting categories for ECs
  - ensure the post-change quality of the measured result during post approval change management of analytical procedures

Example 1: Measurement of Stereoisomers as Specific Process Related Impurities in a Small Molecule Drug Substance (DS)

Example 2: Measurement of Potency for an anti-TNF-alpha Monoclonal Antibody

Overall Considerations

The ICH Q14 and ICH Q2(R2) guidelines should be applied in conjunction with other existing and prospective ICH “Q” guidelines, including Q8–Q13.

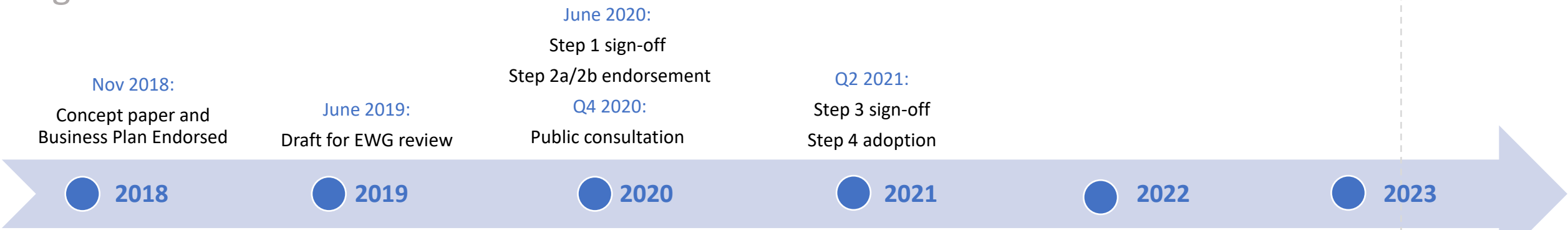
Analytical procedure development can be performed following a minimal or enhanced approach. Though not mandatory, the use of individual elements of the enhanced approach is encouraged to be applied on an as-needed basis.

Tools and enablers discussed in ICH Q12 are applicable to analytical procedures, irrespective of the development approach.

Examples in ICH Q2 Annex 2 describe common analytical technologies. The principles, however, can be applied in a similar fashion to other analytical technologies.

Q2(R2)/Q14 milestones and work plan

Original timeline



Actual timeline

Nov 2018:

- ✓ Concept paper and Business Plan Endorsed

- ✓ Drafting

- ✓ Intra-party high level review
- ✓ EWG virtual face-to-face comment review
- ✓ Document revision
- ✓ EWG (virtual) face-to-face meeting

- ✓ Document revision
- ✓ 2nd Intra-party high level review
- ✓ Comment incorporation & further revision

Feb 2022:

- ✓ Step 1 sign-off

March 2022:

- ✓ Step 2 sign-off

Q2-Q3 2022:

- ✓ Public consultation

Q4 2021:

- ✓ Begin comment incorporation

Q1-Q3 2023:

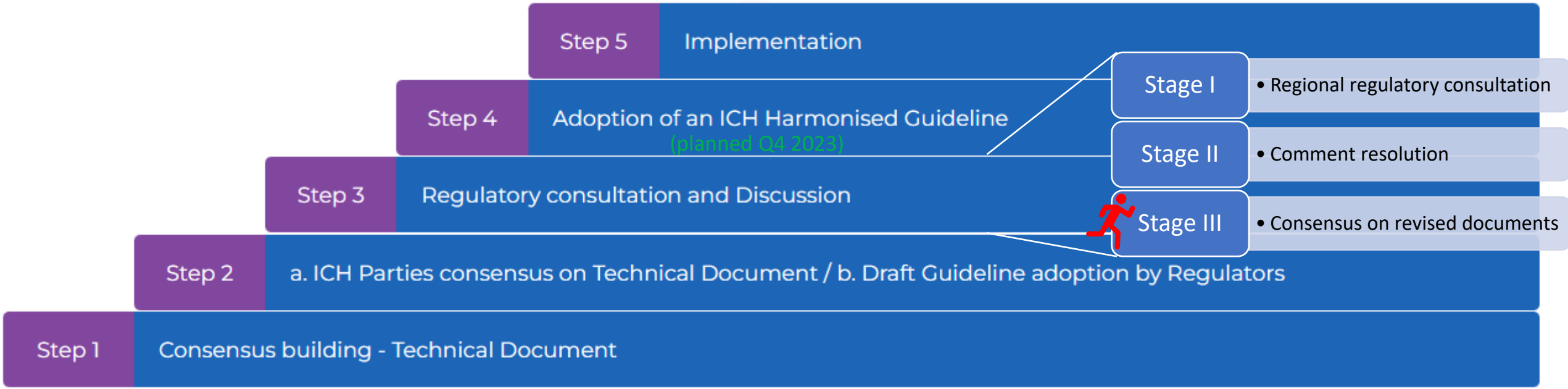
- ✓ Comment incorporation & revision

Q4 2023:

- ○ Step 3 sign-off
- ○ Step 4 adoption
- ○ Initiation of Implementation Working Group

Coming Soon!

You are here!



https://www.ich.org/page/formal-ich-procedure

Thank you!

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Q&A