



ICH Q14: ANALYTICAL PROCEDURE DEVELOPMENT

Training Module 5: Further Concepts in ICH Q14

Part A - Established Conditions and the Link to ICH Q12

Part B - Change Management: Identification of ECs/Reporting Categories and the Use of the Decision Tree

Part C - Knowledge and Risk-Based Change Management

Part D - Explanation of ICH Q14 Tables 1 and 2, Implementation of Changes, and Bridging Studies

Part E - Submission Requirements in ICH Q14 Chapter 10

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Disclaimer

The materials presented in this ICH Q2(R2)/Q14 module are example approaches relating to selected aspects of analytical procedure development, validation and lifecycle. The approaches presented have been constructed to illustrate potential applications of the principles contained within the ICH Q2(R2)/Q14 guidelines and are not considered to be exhaustive. The examples are not intended to be mandatory, and alternative approaches (fulfilling the intent of the guidelines) may also be acceptable.

In some cases, additional elucidation of specific approaches is provided to aid in general understanding of a concept. This is not intended to be a promotion of the elucidated approach, nor indicate a preference for a specific approach.

Provision of acceptance criteria has been deliberately limited within this training material.

In practice, scientific rigor must be applied on a case-by-case basis when determining an appropriate approach or criterion.

Training Module 5: Further Concepts in ICH Q14

Part A - Established Conditions and the Link to ICH Q12

Analytical Procedure Control Strategy: Established Conditions (ECs) for Analytical Procedures

- In line with ICH Q12, ECs are legally binding information considered necessary to assure product quality.
 - Any change to ECs necessitates a submission to the regulatory authority.
 - ECs are proposed and justified by the applicant and approved by the regulatory authority.
 - They can be identified using tools in Chapter 2 including risk assessment, prior knowledge, and learnings from uni- and multi-variate experimentation.
- The nature and extent of ECs depends on the development approach, complexity of the analytical procedure and demonstrated understanding.

Analytical Procedure Control Strategy: Established Conditions for Analytical Procedures

ECs could consist of:

- Performance characteristics and associated criteria (e.g., included in an Analytical Target Profile (ATP)).
- Analytical procedure principle (*i.e.*, the physicochemical basis or specific technology).
- System Suitability Test (SST) and sample suitability assessment criteria.
- Set points and/or ranges for one or more analytical procedure parameters.

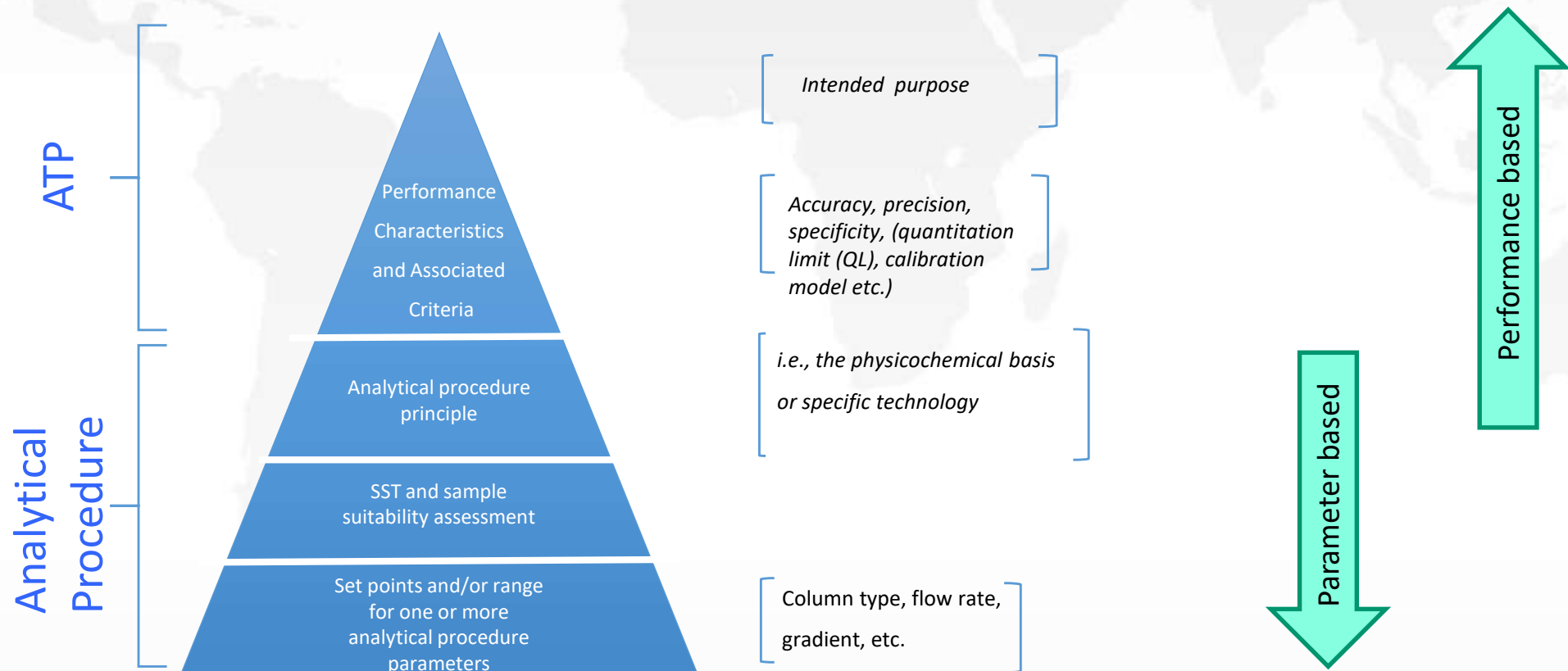
Using the minimal approach:

- The number of ECs may be extensive with fixed analytical procedure parameters and set points.

Using the enhanced approach:

- Knowledge gained facilitates the identification of an appropriate set of ECs and related reporting categories.
- The ECs can be reduced and focused on analytical procedure performance when justified by analytical procedure understanding, prior knowledge, and risk management.

ECs for Analytical Procedures Could be Output- or Input-Related



ECs towards the upper part of the triangle focus on the performance of the analytical procedure (ECs related to output) whereas ECs towards the lower part of the triangle focus on parameters (ECs related to input)

Analytical Procedure Control Strategy: Established Conditions for Analytical Procedures

- Analytical procedure parameters which need to be controlled to ensure the performance and those where the need for control cannot reasonably be excluded should be identified as ECs.
- If a specific parameter is controlled by the performance criteria and/or the SST, that parameter or parameter value may not necessarily need to be defined as an EC or may be assigned a lower reporting category, as appropriate.
- A suitably detailed description of the analytical procedures in the Common Technical Document (CTD) is expected to provide a clear understanding regardless of the approach used to identify ECs for analytical procedures.
 - Description of analytical procedures includes supportive information as well as identified ECs.

Illustrative Example: Product Lifecycle Change Management (PLCM) Document for a Chromatography Procedure with ECs Focused on Method Performance

Information Classification	Information Submitted	Reporting Category
Information considered <u>Established Conditions</u>	<ul style="list-style-type: none"> - ATP performance characteristics and criteria - Analytical procedure principle - System suitability test (risk-based) - Subset of parameters (risk-based) e.g., detection wavelength, column type including stationary phase particle size, mobile phase components 	PA or NM or NL
Information considered <u>Supportive</u> <u>(with appropriate justification as part of an enhanced approach and subject to approval by regulatory agencies)</u>	<p>Some analytical procedure parameters which are considered to be controlled by performance characteristics and/or SST, e.g.,</p> <ul style="list-style-type: none"> - Column dimensions - Column temperature - Flow rate - Injection volume - Mobile phase composition 	NR

Training Module 5: Further Concepts in ICH Q14

Part B - Change Management: Identification of ECs/Reporting Categories and the Use of the Decision Tree



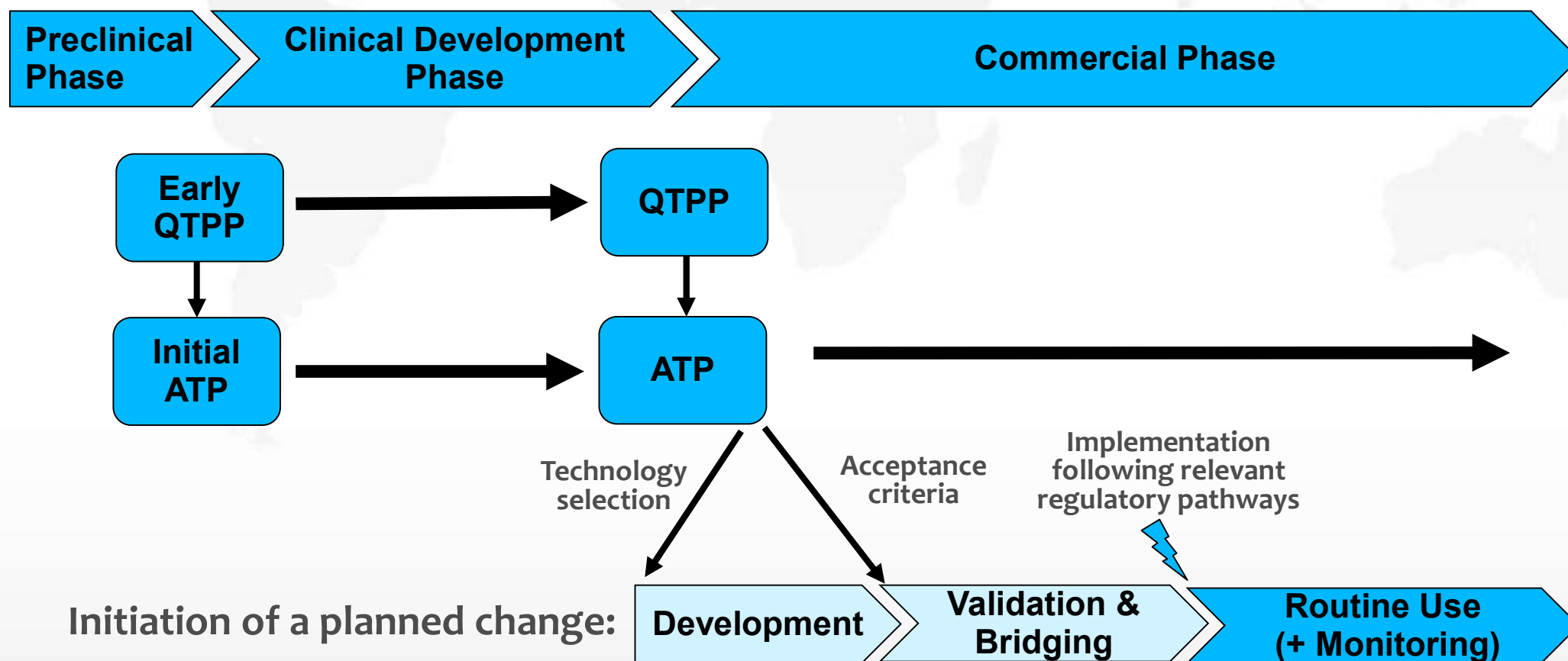
Changes to Analytical Procedures Can Occur Throughout the Product Lifecycle

- Reasons for change:
 - Accommodate process and product changes throughout the product lifecycle.
 - Incorporate advances in process knowledge, analytical procedure knowledge and continual improvement.
 - In line with best practices for current technology and instrumentation.
- The change could involve modification of existing procedures or a complete replacement including introduction of a new technology.
 - Major changes in the performance characteristics or additional information on attributes could lead to re-evaluation of the ATP and/or a new procedure.

The ICH Q12 Tools and Enablers are Applicable to Analytical Procedures

- Risk-based categorisation of post-approval changes to analytical procedures (ICH Q12 Chapter 2)
- Established conditions for analytical procedures (ICH Q12 Chapter 3)
- Post-Approval Change Management Protocols (PACMPs) which provide a detailed explanation of how future changes will be managed and provide the marketing authorisation holder with certainty about the acceptability of future changes and an associated reduced reporting category (ICH Q12 Chapter 4)
- The Product Lifecycle Change Management (PLCM) document which can facilitate regulatory communication about likely post-approval changes (ICH Q12 Chapter 5)
- The Pharmaceutical Quality System (PQS) (documentation of all changes including those not requiring regulatory submission, e.g., within a Method Operable Design Region (MODR) or for parameters deemed not to have an impact on the method performance) (ICH Q12 Chapter 6)
- The structured approach to frequent Chemistry, Manufacturing, and Controls (CMC) changes (ICH Q12 Chapter 8 and Annex II)

Analytical Target Profile (ATP) in Post-Approval Changes



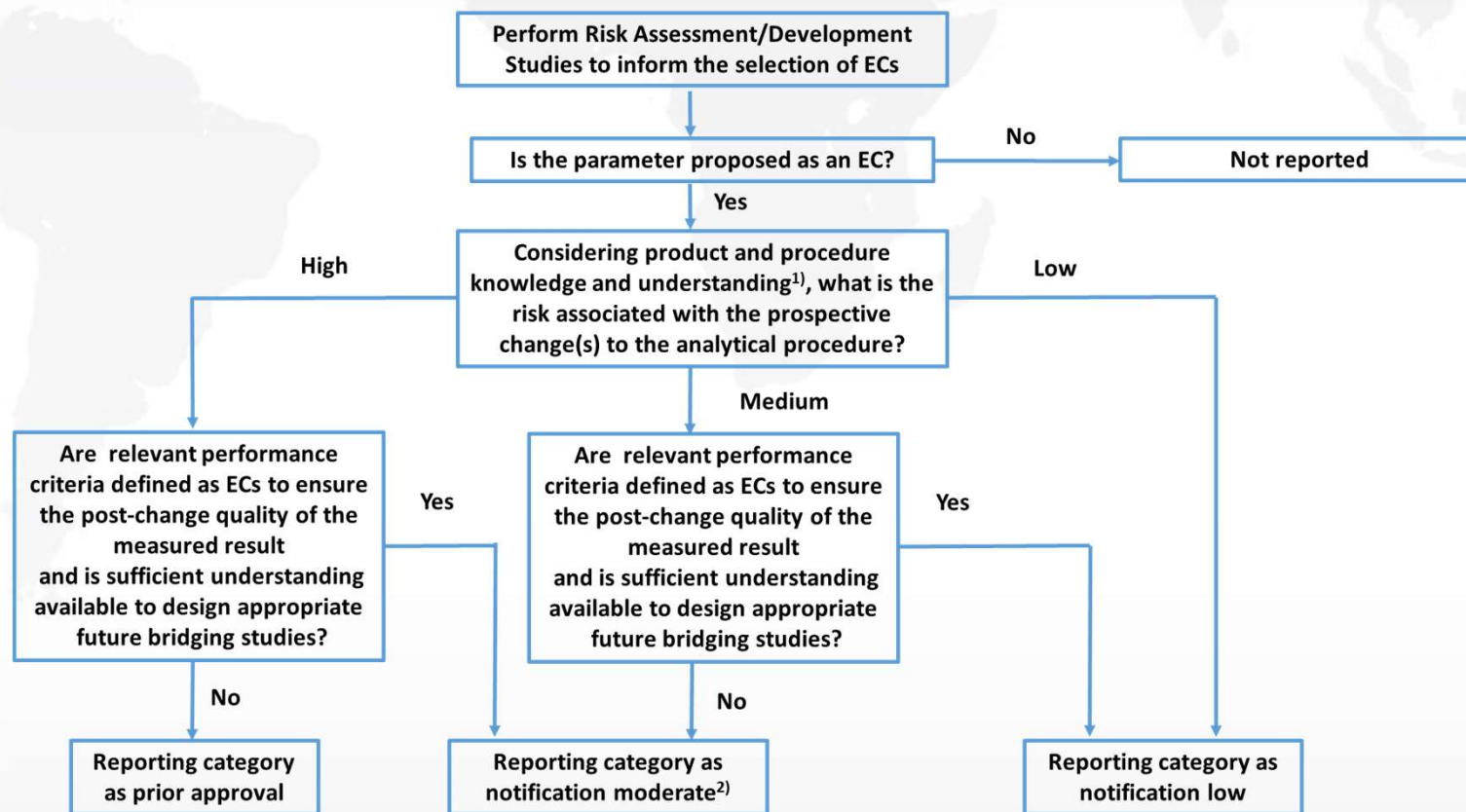
Lifecycle Management and Post-Approval Changes of Analytical Procedures

- If ECs are not proposed in the dossier, any changes should be reported according to regional reporting requirements.
- The use of different elements of the enhanced approach can facilitate management and regulatory communication of post-approval changes.
- In cases where ECs are proposed, the risk associated with prospective changes should be assessed upfront to define the appropriate reporting category. The reporting category should be commensurate with the risk.
- During implementation, Quality Risk Management (QRM) can be used to reconfirm that the originally agreed reporting category is still appropriate. The outcome of this risk assessment informs the design and extent of the studies needed to support the change, including an appropriate bridging strategy.

Risk-based Approach for Identification of ECs and Reporting Categories for Associated Changes in the Enhanced Approach

- Risk assessment, development studies, and other risk reduction measures are performed to inform the selection of ECs and to propose appropriate reporting categories.
- Risk associated with changes can also be reduced by defining relevant performance criteria that have been identified as ECs (in the ATP).
- Risk reduction is possible when sufficient understanding is available to design future bridging studies.
- Adherence to the performance characteristics and associated criteria (as defined in an ATP) and an analytical procedure control strategy ensures that the analytical procedure remains fit for the intended purpose after a change to the EC.

Lifecycle Management and Post-Approval Changes of Analytical Procedures (ICH Q14 Figure 2)



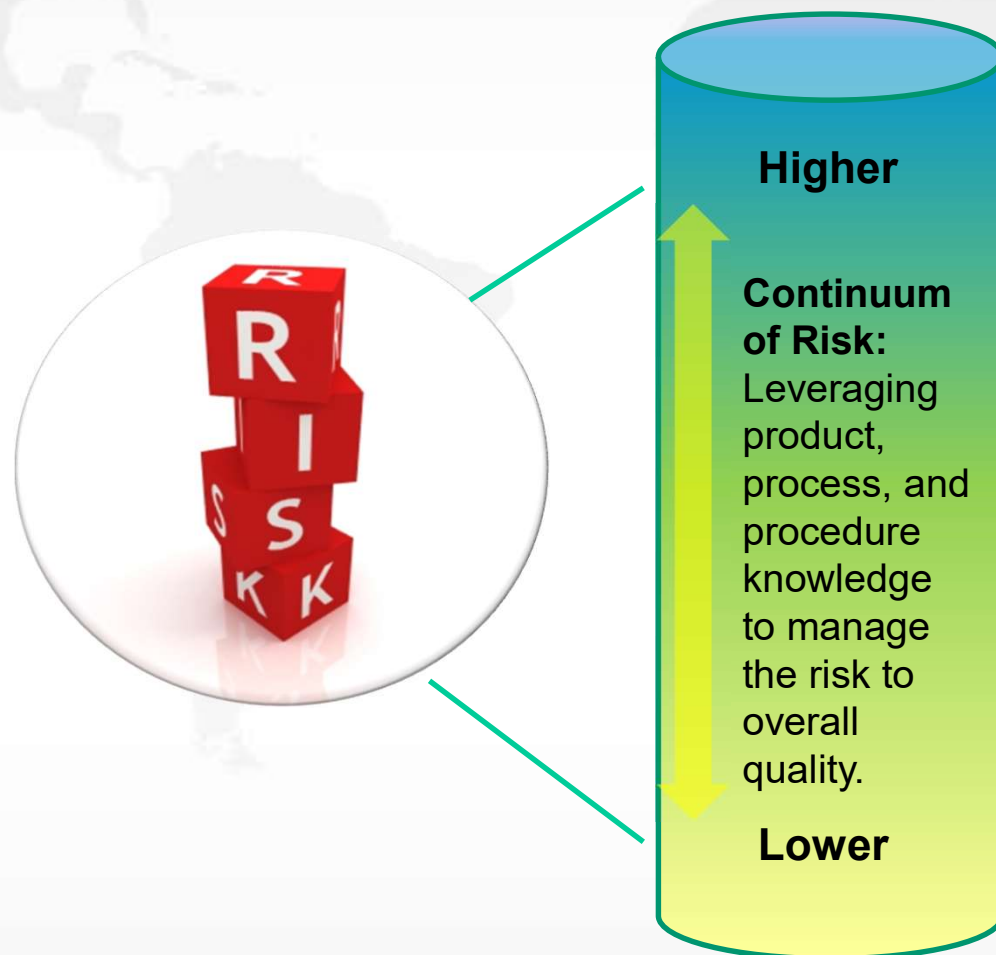
1) Including analytical procedure control strategy.

2) In some cases, moderate risk changes proposed by the company may require prior approval based on health authority feedback.

Risk-based Approach for Identification of ECs and Reporting Categories for Associated Changes in the Enhanced Approach (ICH Q14 Figure 2)

- If the factor is not proposed as an EC, a change does not need to be reported.
 - All changes should be documented in the PQS regardless of reporting category.
- If the risk associated with the prospective change is high, see if relevant performance criteria are defined in the ATP to ensure the post-change quality of the measured result with sufficient understanding available to design appropriate future bridging studies.
 - If yes, the reporting category can be defined as “notification moderate”.
 - If no, the reporting category should be “prior approval”.
- If the risk associated with the prospective change is medium, see if relevant performance criteria are defined in the ATP to ensure the post-change quality of the measured result with sufficient understanding available to design appropriate future bridging studies.
 - If yes, the reporting category can be defined as “notification low”.
 - If no, the reporting category should be “notification moderate”.
- If the risk associated with the prospective change is low, the reporting category should be “notification low”.

Defining Risk and Identifying ECs



Minimal Approach: With a minimal approach, the manufacturer may have a limited understanding of the relationship between inputs and resulting quality attributes.

The number of ECs may be extensive with fixed parameters and set points.

Enhanced Approach: With an enhanced approach the manufacturer will have an increased understanding of interaction between inputs and product quality attributes and the corresponding control strategy.

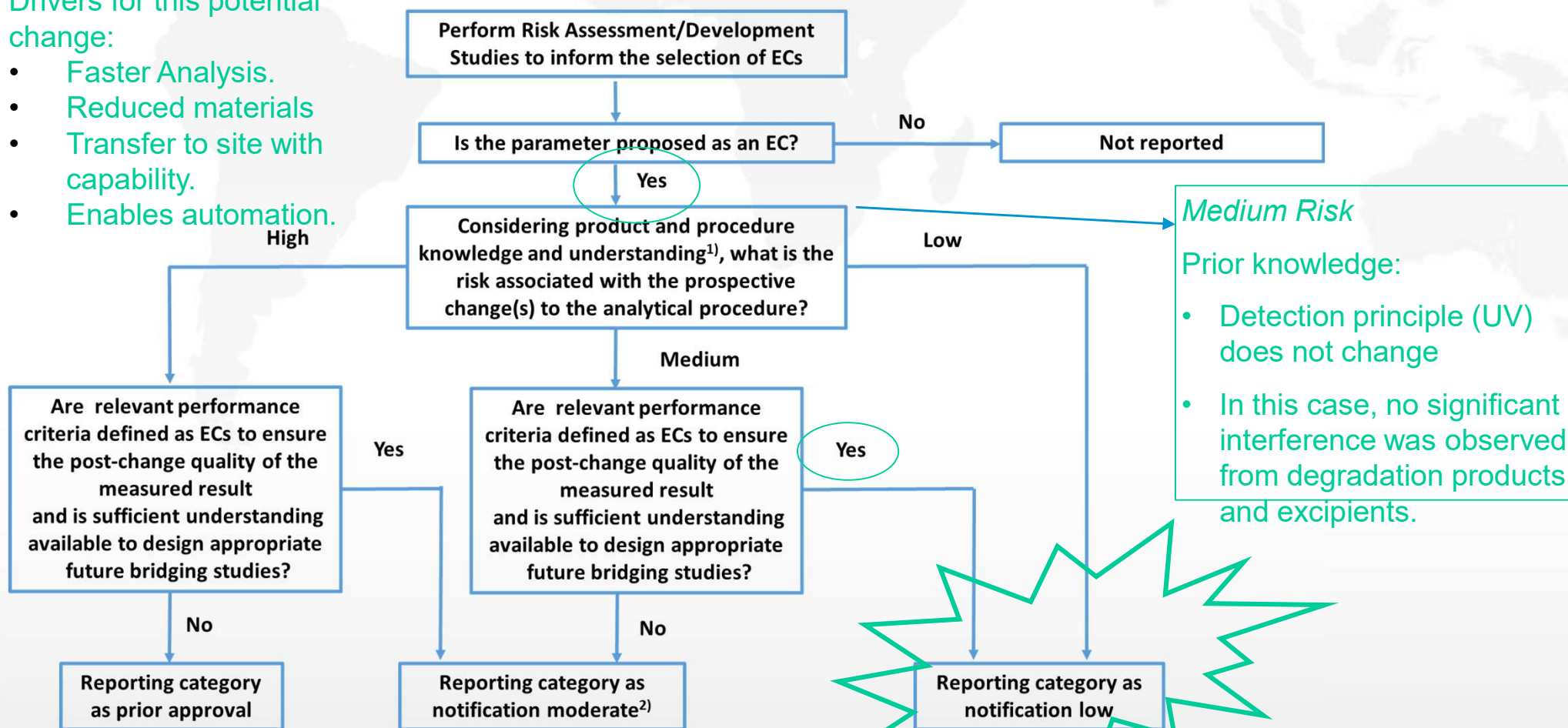
Parameters may not need to be defined as an EC or may be assigned a lower reporting categories.

Risk-Based Approach for Identification of ECs

Illustrative Example - Dissolution End Analysis Technique: Change from LC-UV to UV Spectroscopy

Drivers for this potential change:

- Faster Analysis.
- Reduced materials
- Transfer to site with capability.
- Enables automation.



Note - Performance characteristics and criteria are in the ATP and are defined as ECs.

Approach to Identify ECs for Analytical Procedures Focused on Performance

- The purpose of development is to ascertain analytical procedure parameters such that the criteria for the performance characteristics can be met.

Performance characteristic:

A technology independent description of a characteristic that ensures the quality of the measured result. Typically, accuracy, precision, specificity/selectivity and range may be considered.

Performance criterion:

An acceptance criterion describing a numerical range, limit or desired state to ensure the quality of the measured result for a given performance characteristic.

- ECs can be reduced and focused on analytical procedure performance (e.g., acceptable ranges for analytical procedure parameters, performance characteristics with associated criteria) when justified by analytical procedure understanding (including prior knowledge and product/process knowledge) and risk management.

Justification of Approach to Identify ECs Focused on Performance



With an enhanced approach, there is an increased understanding of the measurement requirements, the suitability of available technologies and the relationship between analytical procedure parameters and performance. This knowledge facilitates the identification of an appropriate set of ECs and related reporting categories.

Use of PACMPs and PLCMs

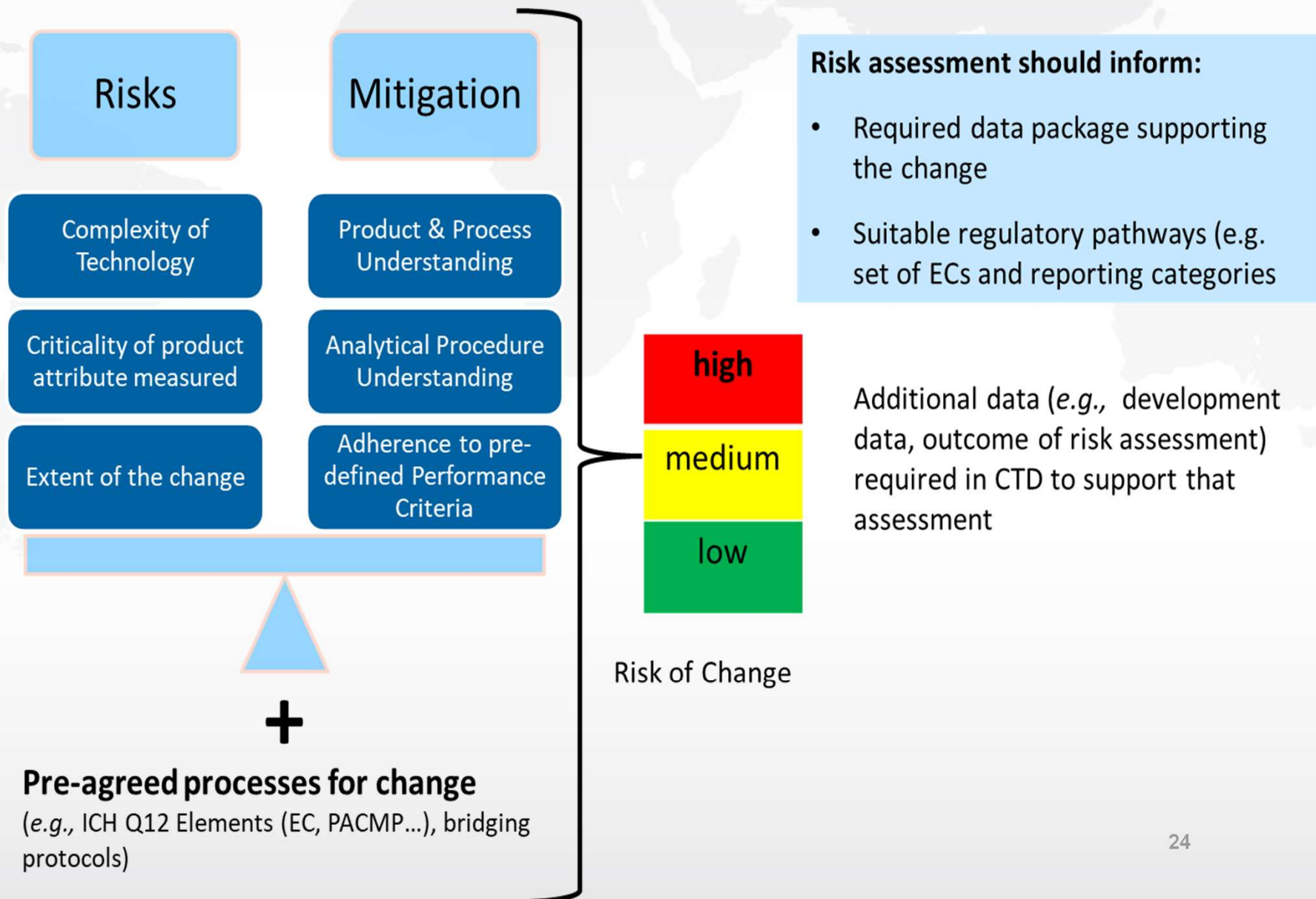
- As described in ICH Q12, PACMPs and PLCMs are tools to manage post-approval changes.
- A PACMP can be an effective tool when there is an expected change to an analytical procedure (e.g., a planned transition from HPLC to UHPLC)
- The examples in ICH Q14 Annex A (and the ICH Q2(R2) / Q14 training module 7 case studies) are presented as ECs within a PLCM because the details of the changes were not known at the time of the submission.



Training Module 5: Further Concepts in ICH Q14

Part C - Knowledge and Risk-Based Change Management

Knowledge and Risk Management



Risk Assessment for Future Changes to Analytical Procedures

- If an applicant proposes a new analytical procedure, a comprehensive risk assessment and evaluation should be conducted to determine any impact on the performance. The analytical procedure control strategy for the new procedure should be established. Any ECs associated with the new procedure should be justified when communicating the change.
- QRM can be used to evaluate the impact of future changes for analytical procedures. The subsequent list describes examples of risk factors and risk reduction measures to identify the risks associated with changes to an analytical procedure. The outcome of the risk assessment (risk level: high, medium or low) feeds into the design and extent of the studies needed to support the change.

Knowledge and Risk Management: Risk/ Risk Factors (1/2)

Relevance of the test

- Potential clinical impact of the measured attribute (efficacy, safety), e.g., controlling CQA vs. non-CQA.
- Extent of knowledge of the attribute.
- Attribute ensured by other elements of the control strategy (testing or process control).

Complexity of the technology

- Platform technologies.
- Novel versus established technology (e.g., in pharmacopoeias).
- Several attributes reported as a sum (e.g., charge variants for large molecules).
- Biological assays (e.g., cell-based assays, immunochemical assays).
- Multi-attribute analytical procedure.
- Multivariate analytical procedure.

Knowledge and Risk Management: Risk/ Risk Factors (2/2)

Extent of the change

- Change of one or several parameters outside the already proven acceptable ranges.
- Change of the analytical procedure within existing analytical procedure performance characteristics and associated criteria.
- Change to analytical procedure performance criteria (e.g., due to tightening a specification limit).
- Change to a new analytical procedure using a different technology.

Knowledge and Risk Management: Risk Reduction (1/3)

Risk reduction is defined in ICH Q9 as actions taken to lessen the probability of occurrence of harm and the severity of that harm. Different kinds of knowledge can lead to reduction of risk. Examples of relevant knowledge include:

Product and process knowledge

- Knowledge about quality attributes of the drug substance/drug product and acceptable ranges of CQAs.
- Well justified analytical procedure performance criteria that link to the CQAs and their acceptable ranges.
- Evidence to control the CQAs through the process parameter settings.
- Knowledge of the degradation pathways demonstrated by the analysis of relevant stressed samples and/or theoretical prediction.
- Other product knowledge (e.g., impurity profile, particle size and distribution).

Knowledge and Risk Management: Risk Reduction (2/3)

Analytical procedure understanding and analytical procedure control strategy (changes within the analytical procedure)

- Knowledge about analytical procedure parameters and their impact on measurement performance.
- Proven analytical procedure robustness.
- Enhanced analytical procedure understanding (e.g., Design of Experiments (DOE) studies). supporting justification of acceptable ranges.
- Other knowledge from development of analytical procedure.
- System suitability test ensures relevant analytical procedure attributes.
- Ongoing monitoring of analytical procedure output including reference material results if available.
- Clear link between signal and CQA to be measured (e.g., peak characterisation available, specificity).

Knowledge and Risk Management: Risk Reduction (3/3)

Bridging strategy for changes to analytical procedures

When considering a bridging strategy, a greater understanding of the analytical procedure can enable a reduced study design whereas a higher risk change may need a more in-depth study

- Availability of reference material, relevant historical samples and/or stressed samples to support analytical procedure output assessment against performance criteria (demonstrated ability to control the CQA).
- Comparison to output of previous analytical procedure.
- Demonstrated understanding of risks associated with parameter changes and potential interactions with other parameters.
- Prior experience with similar changes, analytes or technologies including platform analytical procedures.

In general, an understanding of the analytical procedure robustness and/or prior knowledge can be used to support risk mitigation associated with future changes. Submitting the outcomes of the risk assessments to regulatory authorities when ECs are proposed can help to justify reporting categories for future changes to analytical procedures.

Training Module 5: Further Concepts in ICH Q14

Part D - Explanation of ICH Q14 Tables 1 and 2, Implementation of Changes, and Bridging Studies

Changing an Analytical Procedure: General Principles



ICH Q2(R2) / Q14 Training Module 5

Proposal for a change

e.g., from separation technique A to separation technique B.



Step 1 of Q14 Guideline Figure 2

Re-assessment of the risk of the change considering the following points:

- *Relevance of the test, complexity of the test and extent of the change.*

Conclude on estimated risk: *high, medium or low*



Step 2 of Q14 Guideline Figure 2

Re-confirmation of the following points:

- Adherence to criteria for relevant performance characteristics: *are these defined as ECs?*
- Sufficient information or prior knowledge to design appropriate bridging studies: *Yes or No*

Risk assessment result before bridging study

Conclusion on overall risk category: *High, medium or low*



Regulatory reporting

Report the change according to the appropriate reporting category and submit suitable documents.



Conclusions

Determining the impact of the change based on validation and bridging study result

- Impact on the test performance: *Assessment if relevant performance characteristics and the analytical procedure attributes met their criteria.*
- Impact on the ECs: *Evaluation if the change affects other factors defined as ECs in the analytical procedure.*



Execution of Analytical Procedure Development and Validation

- *Describe elements used to generate analytical procedure knowledge: e.g., elements of the enhanced approach, prior knowledge.*
- *Finalisation of analytical procedure description (including analytical procedure control strategy (SST)).*

Risk Reduction for Changes (ICH Q14 Table 1)

ICH Q14 Table 1 illustrates the relationship between risk and prior knowledge when designing studies in support of a proposed change.

Lower risk enables confirmatory studies to support the change.

Increased risk drives the need for more in-depth studies to support the change.

Prior knowledge can be utilised to inform study design.

Reduced prior knowledge requires comprehensive study.

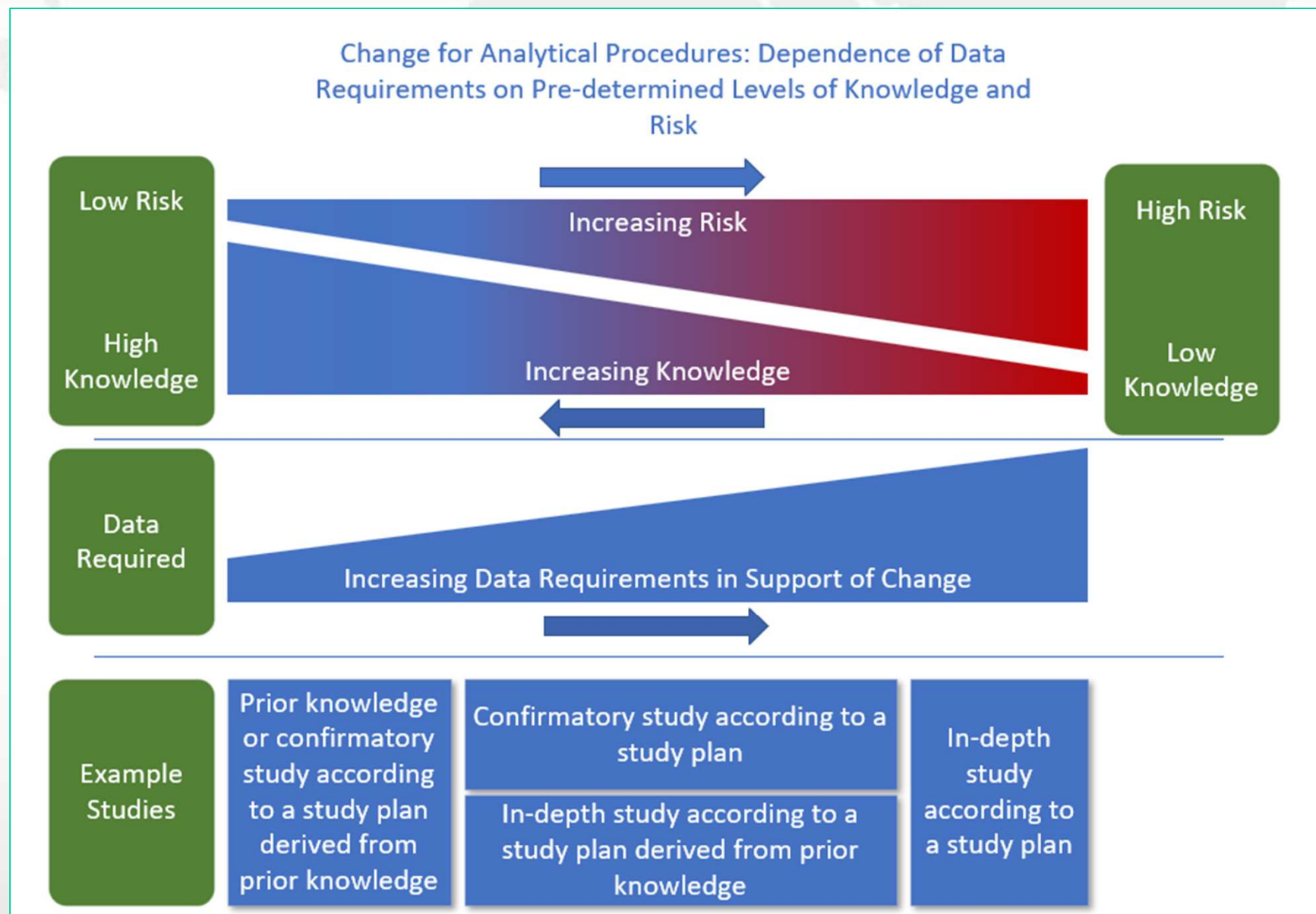
Table 1: Relationship between knowledge (understanding), risk and extent of studies for changes to analytical procedures

		Risk associated with the change	
		Low	High
Knowledge ¹⁾	High	Prior knowledge or confirmatory study according to a study plan derived from prior knowledge	In depth study according to a study plan derived from prior knowledge
	Low	Confirmatory study according to a study plan	In depth study according to a study plan


1) As described in ICH Q10

Risk Reduction for Changes (ICH Q14 Table 1)

Additional representation of the relationship between risk, prior knowledge and data requirements in support of a change.



ICH Q14 Table 2: Examples of Analytical Procedure Change Evaluation

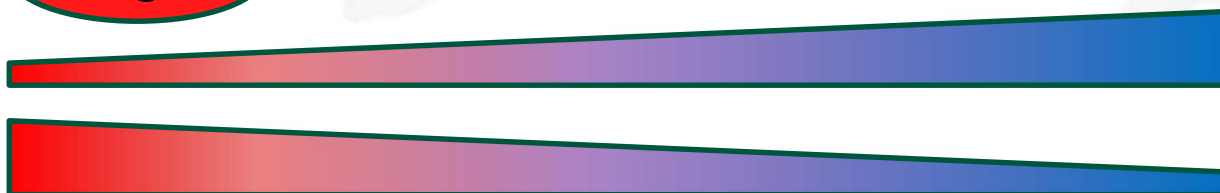
Risk Factor: Extent of change	Bridging strategy	Evidence of the suitability of a new procedure
Change of analytical procedure principle (physicochemical/biochemical basis) 	Full validation of new procedure And Comparative analysis of representative samples and reference materials. And/or Demonstration that the analytical procedure's ability to discriminate between acceptable and non-acceptable results remains comparable	Analytical procedure performance characteristics are evaluated and criteria are met after the change And Results are comparable after change or differences are acceptable and potential impact on specification evaluated

Associated risk*

Prior knowledge

Data required as part of bridging strategy

High

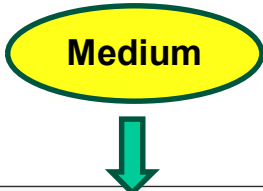


*In addition to extent of change, other factors such as criticality of the quality attributes being measured, complexity of the technology should be considered in risk assessment.

- Full validation of new procedure
- Comparative analysis of representative samples and reference materials.
- Demonstration that the analytical procedure's ability to discriminate between acceptable and non-acceptable results remains comparable.

- Full validation of new procedure.
- Comparative analysis of representative samples and reference materials.

ICH Q14 Table 2: Examples of Analytical Procedure Change Evaluation

Risk Factor: Extent of change	Bridging strategy	Evidence of the suitability of a new procedure
Change within same analytical procedure principle 	Partial or full <i>revalidation</i> of the analytical procedure performance characteristics affected by the <u>change</u> And, as appropriate Comparative analysis of representative samples and reference materials And/or Demonstration that the analytical procedure's ability to discriminate between acceptable and non-acceptable results remains comparable	Analytical procedure attributes are evaluated and criteria are met after change And, as appropriate Results are comparable after change or differences are acceptable and potential impact on specification evaluated

Associated risk*

Prior knowledge

Data required as part of bridging strategy

Medium

*In addition to extent of change, other factors such as criticality of the quality attributes being measured, complexity of the technology should be considered in risk assessment.

- Full revalidation of the analytical procedure.
- Comparative analysis of representative samples and reference materials.
- Demonstration that the analytical procedure's ability to discriminate between acceptable and non-acceptable results remains comparable.

- Partial revalidation of the analytical procedure performance characteristics affected by the change.
- Comparative analysis of representative samples and reference materials.

ICH Q14 Table 2: Examples of Analytical Procedure Change Evaluation

Risk Factor: Extent of change	Bridging strategy	Evidence of the suitability of a new procedure
Transfer of analytical procedure to a different site with no change in procedure itself	Partial or full revalidation of the analytical procedure performance characteristics And/or Comparative analysis of representative samples and reference materials Or Justification for not performing additional transfer experiments	Analytical procedure attributes are evaluated and criteria are met after change And/or Results are comparable

Low

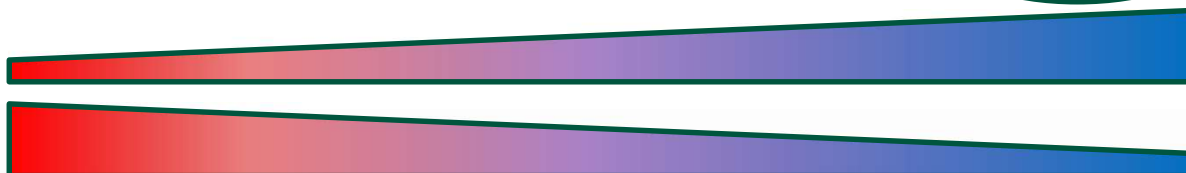


Associated risk*

Prior knowledge

Data required as part of bridging strategy

Low



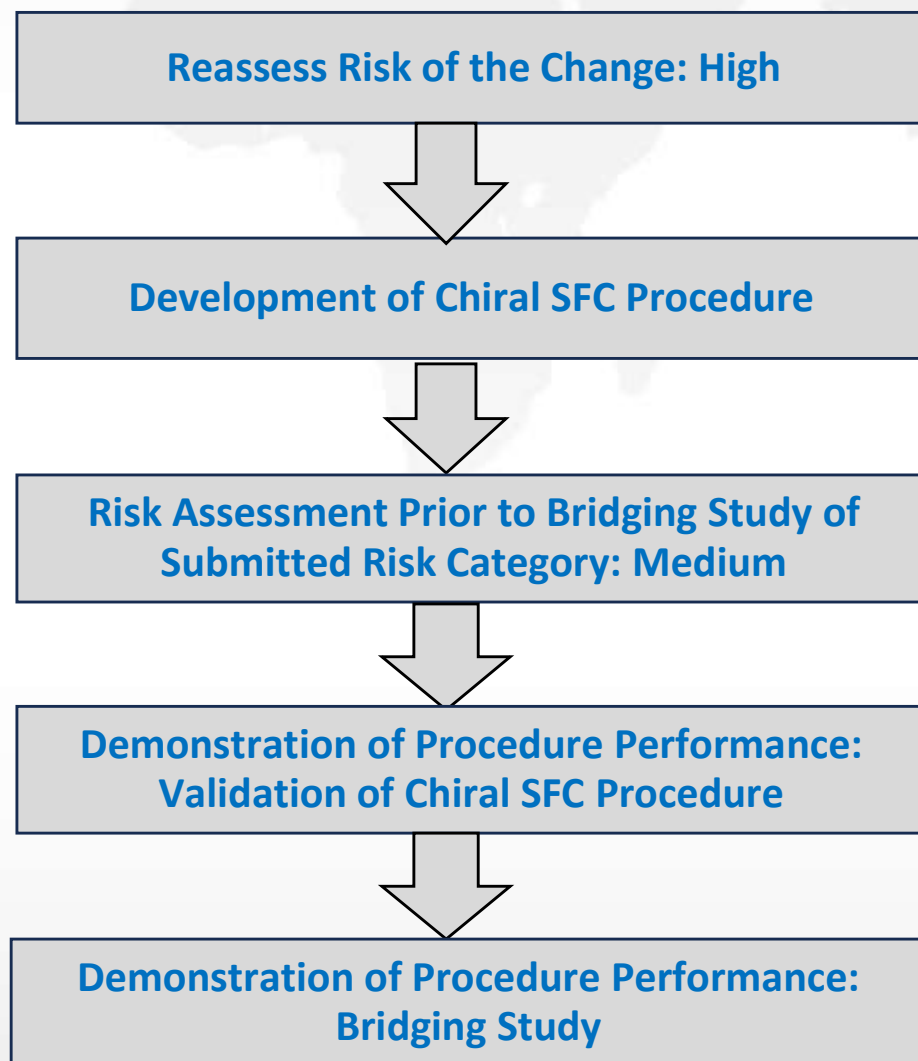
*In addition to extent of change, other factors such as criticality of the quality attributes being measured, complexity of the technology should be considered in risk assessment.

- Full revalidation of the analytical procedure performance characteristics.
- Comparative analysis of representative samples and reference materials.

- Partial revalidation of the analytical procedure performance characteristics.
- Comparative analysis of representative samples and reference materials.

- Justification for not performing additional transfer experiments.
- e.g., co-validation employed during development and validation.

Bridging Strategy Example: HPLC to SFC



Bridging Strategy Example: HPLC to SFC

Validation of New Procedure

- With the technique change from HPLC to SFC, a full validation was required.
- SFC procedure was developed with enhanced development principles.
- Validation protocol developed specific to technique and to ensure that the performance characteristics within the ATP are met.

Comparative Analysis

- Drug substance standard lot spiked with 0.1% of Impurities A-E was analyzed by new procedure (SFC) and previous (HPLC).
- Impurity F was not spiked in as standard lot contains ~0.3%.
- Acceptance criteria:

Impurity level in study (based on initial procedure)	Maximum difference between procedures (Mean)	Precision of each procedure
$\leq 1.0\%$	$\pm 10\%$ of expected result	RSD $\leq 10\%$
$\leq 0.10\%$	$\pm 25\%$ of expected result	RSD $\leq 10\%$

Bridging Strategy Example - Bioassay

Background of Change

Cell-Based Bioassay for the Determination of Potency for an Anti-TNF-alpha Monoclonal Antibody

Change was from continuous cell culture to ready to use cells for cell-based potency assay.

Impacted only the cell preparation step.

Freeze / thaw conditions for cells are critical parameters to control.

The analytical procedure remained unchanged with the exception of cell preparation.

The change was within the same technology with no impact on specification acceptance criteria.

Structured Risk Assessment

Relevance of the test was classified as **high** due to direct link to the CQA (potency).

Cell-based bioassay represents a **complex technology** as such assays have multiple sources of variability.

Factors contributing to variability were well understood and addressed in the analytical procedure control strategy.

Extent of the change was restricted to the preparation of the cells, with potential impact on only one analytical procedure attribute (cell metabolism).

Factors contributing to the cell performance were understood and monitored by the SST.

Overall risk for change: Moderate

Based on ICH Q14 Annex A

Adherence to Criteria for Relevant Performance Characteristics

Understanding of the analytical procedure and the link to the CQA allowed the definition of criteria for relevant performance characteristics to ensure the post-change quality of the measured result.

The change could potentially have affected cell metabolism, and hence potentially impacted the analytical procedure performance characteristics of accuracy and precision.

Therefore, adherence to these performance characteristics was demonstrated.

The change did not impact the performance characteristics of specificity and reportable range, as the same cell line was used and the potency was measured against the same reference standard.

Bridging Strategy Example - Bioassay

Based on ICH Q14 Annex A

Demonstration of Analytical Procedure Performance After Change

- The SST of the analytical procedure covers the suitability of the cell preparation (e.g., confluency, cell density, cell viability, signal amplitude, shape of the response curve).
- Partial revalidation of the analytical procedure was performed to demonstrate the affected analytical procedure attributes were met after the change.
 - Accuracy and precision of the analytical procedure continued to meet the predefined acceptance criteria as detailed in the ATP (see ICH Q14 Annex A, Table 4).
- Comparative analysis of a set of representative samples with the pre- and post-change analytical procedure was performed to ensure that the achieved results were comparable, or that observed differences were acceptable and did not impact the established specification.
 - Acceptance criteria were statistically determined based on maximum allowable difference between pre-change and post-change results.

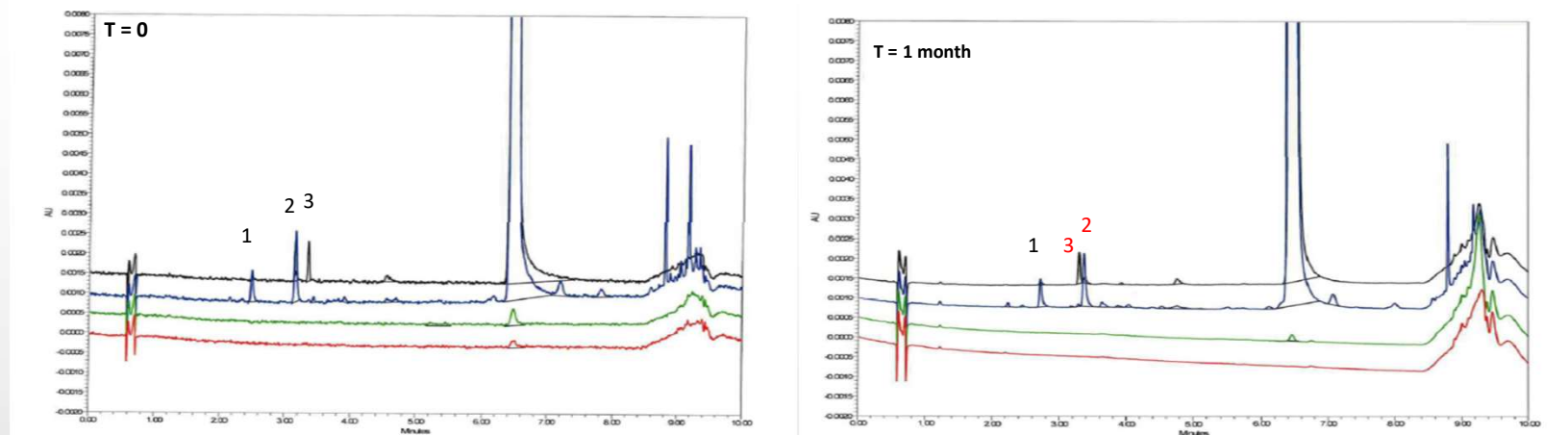
Illustrative Example - Using PACMP to Enable Analytical Procedure Change

Background: Rapid drug development in areas of unmet medical need can result in reduced prior knowledge in relation to the control strategy.

Situation:

- A small molecule, solid oral product with expedited development pathway.
- Challenges with chromatographic analytical procedure: robustness issues including short column lifetime (~100 – 150 injections) and impurity peak elution order changing/peak shifting.
- Additional analytical control strategy elements were established to manage initial robustness concerns (i.e., system suitability with unique substances to confirm specificity).

Example stability data (Impurities) – demonstrating robustness challenges – elution order shift





Illustrative Example - Using PACMP to Enable Analytical Procedure Change

PACMP was established as part of the marketing authorisation application:

- Analytical target profile (ATP)
- Defined expectations:
 - Availability of well characterised sample(s).
 - Commitment to follow enhanced approaches to analytical procedure development.
 - Commitment to analytical procedure validation (under protocol – in agreement with ATP expectations).
 - Commitment to analytical procedure bridging (under protocol).
- Reporting category of notification low (regulatory authority agreement).

ATP:

Intended Purpose: Quantification of the degradation products in drug product for release and stability.	
Link to CQA (Degradation Products)	
Analytical procedure should quantitate individual degradation products (not more than (NMT) 0.2%) and total degradation products (NMT 0.5%)	
Characteristics of the Reportable Results (performance characteristics)	
Characteristic	Acceptance Criteria*
Accuracy	Recovery 80.0 – 120.0% for $\geq 0.2\%$ of nominal Recovery 50.0 – 150.0% for $< 0.2\%$ of nominal <i>Filtered vs centrifuged, results NMT $\pm 20\%$ for impurities $\geq 0.1\%$</i>
Precision	%RSD of impurities $\leq 0.10\%$ NMT 15%; %RSD of impurities $> 0.10\%$ NMT 10% - for each analyst %RSD of impurities $\leq 0.10\%$ NMT 20%; %RSD of impurities $> 0.10\%$ NMT 15% - for both analysts combined
Specificity	Analytical procedure is capable of separating impurities (process impurities and degradation products) from drug substance Any interference from placebo components is $< 0.1\%$ of the nominal concentration of the drug substance
Reportable Range	High level: 70 – 130% of nominal Low level: 0.05 – 0.3% of nominal
QL/DL	Quantitation Limit (QL): S/N NLT 10, %RSD NMT 20%, Recovery 50.0 – 150.0% ; Detection Limit (DL): S/N NLT 3



Illustrative Example - Using PACMP to Enable Analytical Procedure Change

- Well-characterised samples available to enable analytical procedure development.
- Development following enhanced approach.
- Robustness confirmed through DOE studies.
- Risk assessment.
- Validation in alignment with ATP expectations.
- Bridging, under protocol.

Analytical procedure bridging:

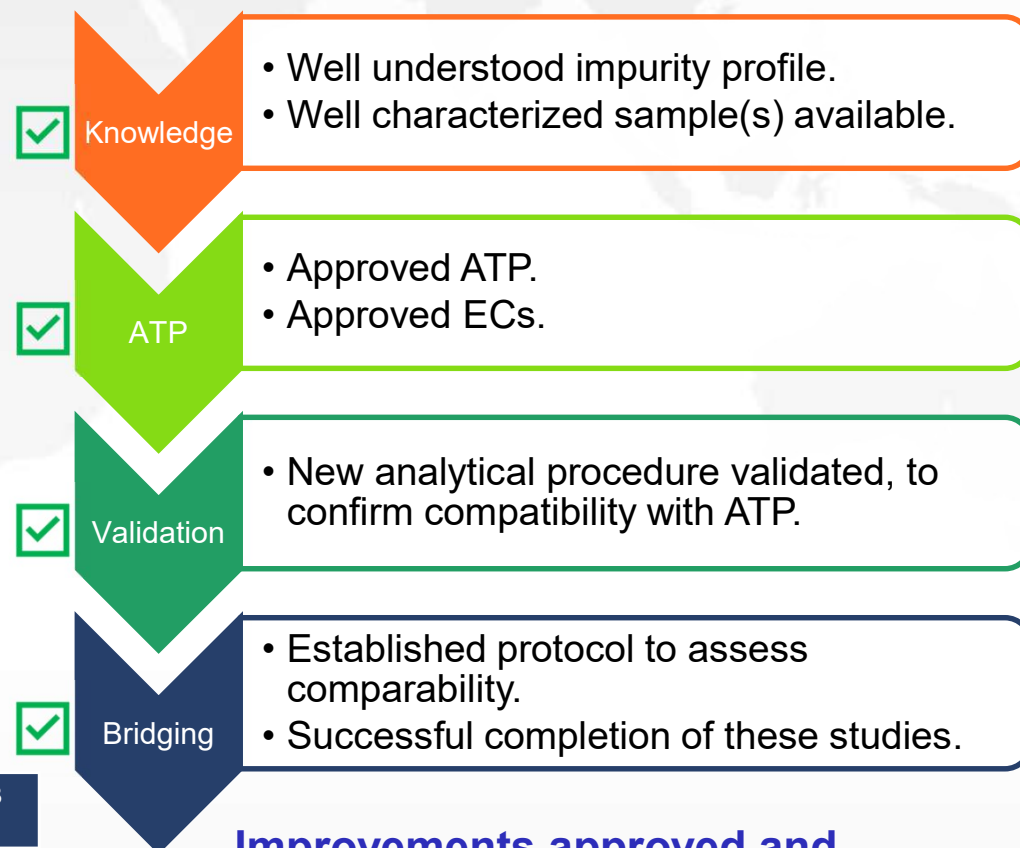
Experimental Design:

Setup	Day	Analyst	HPLC	Batch Number
1	1	A	1	1
2		B	2	2
3	2	A	2	2
4		B	1	1
5	3	A	1	2
6		B	2	1

Results:

Analytical Procedure	Impurity 2 (%)	Impurity 1 (%)	Largest Other (%)	Impurity 3 (%)
Current	0.1385	0.0345	0.0591	0.0293
New	0.1374	0.0509	0.0598	0.0261
Absolute Difference	0.0011	0.0164	0.0007	0.0032
Acceptance Criteria	NMT 0.0226%	NMT 0.0226%	NMT 0.0226%	NMT 0.0226%
Result	Pass	Pass	Pass	Pass

Conclusion: Acceptance criteria were met and analytical procedures produce comparable results.



Improvements approved and implemented via PQS. Notification low process followed (with prior agreement from regulatory authority and in accordance with regional guidance).

Training Module 5: Further Concepts in ICH Q14

Part E: Submission Requirements in ICH Q14 Chapter 10

Submission of Analytical Procedure Related Information

- Information to be included in the CTD sections 3.2.S.4.2 or 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.
 - For multivariate analytical procedures: description of any analytical procedures that are part of the registered alternative control strategy to Real Time Release Testing (RTRT).
- 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).
- When proposed, ECs and the associated reporting category for changes should be described in PLCM document according to ICH Q12.

Note - All submission requirements described are in accordance with ICH M4Q(R1)

Submission of Analytical Procedure Related Information

Regardless of the development approach used, the analytical procedure description included in CTD submissions should be sufficiently detailed to enable a skilled analyst to perform the analysis and interpret the results, and may include the following:

- Information on sample, reference materials, controls, and reagents (description and preparation).
- System suitability test.
- Where applicable, sample suitability assessment.
- Test conditions and instrumentation.
- Calibration approach.
- Number of replicates.
- Formulae for calculation of the reportable results.

Submission of Analytical Procedure Related Information

For multivariate analytical procedures and RTRT, the analytical procedure description included in CTD submissions typically includes the following:

- The property or attribute of interest to be determined by the multivariate analytical procedure and the desired quantitative ranges or limits.
- A description of the measurement principle and instrument operating parameters (e.g., sample presentation, sample interrogation time and measurement frequency).
- An overview of how the multivariate model calibration data are obtained (e.g., sample preparation approach, reference analytical procedure).
- The type of multivariate model.
- A description of reference analytical procedure or high-level description of prepared reference samples.
- Any calculations needed to adjust the model output into the reported value.

Submission of Analytical Procedure Related Information

- Summaries of validation studies to support the proposed analytical procedures and additional information needed to justify ECs and their associated reporting categories, if proposed, should be included in the CTD sections 3.2.S.4.3 or 3.2.P.5.3.
- These could include data obtained from:
 - Validation tests,
 - Prior knowledge, or
 - Analytical procedure development studies
- For dissolution procedures, information on development is generally provided in section 3.2.P.2.

Submission of Analytical Procedure Related Information

For multivariate analytical procedures and RTRT:

- Development information should be provided commensurate with the level of impact of the model.
- Information on model development is generally provided in either the validation sections 3.2.S.4.3 or 3.2.P.5.3 for multivariate models as part of drug substance or drug product specification including RTRT, or the process development sections 3.2.S.2.6 or 3.2.P.2 for multivariate models used as part of manufacturing studies or for in-process controls and tests.
- These sections should include validation information on analytical procedures used as reference analytical procedures.
- The model development, calibration and validation can be directly included or in an appended document.

Submission of Analytical Procedure Related Information

For multivariate analytical procedures, the validation approach and results should include:

- Description of the validation set with independent samples.
- The performance criteria to be met during validation of the multivariate model and the evaluation of the model validation results against these.
- Discussion of the relationship between the model performance criteria and the attribute specification limits.
- High level overview of the PQS elements for model monitoring and maintenance, such as diagnostic tools for determining the appropriateness of the sample data for the model and approach taken when outliers are identified.

Dissolution Test Development: Case Study of Typical Submission Elements

- Dissolution parameters were selected where an appropriate profile was reached (85% drug release) for an immediate release product.
- Information submitted included:
 - pH solubility data of the drug substance and relevant polymorphs.
 - Understanding of critical material attributes and critical process parameters affecting dissolution.
 - Justification of selected dissolution parameters:
 - Choice of apparatus including any details (e.g., basket mesh size, sinker type, peak vessels).
 - Media including pH, surfactant (if needed) and concentration.
 - Agitation rate.

Dissolution Test Development Case Study: Discriminatory Power of the Dissolution Step

- The capability of the dissolution step to differentiate between batches manufactured with different critical process parameters and/or critical material attributes which may have an impact on drug release and bioavailability was demonstrated.
- Variant batches were determined based on risk analysis driven by understanding of drug substance properties, formulation and process understanding, biopharmaceutics, as well as product control strategy.
- Examples of variant batches that were considered:
 - The influence of drug substance attributes (e.g., drug substance particle size).
 - The influence of a formulation component (e.g., disintegrant level).
 - The influence of a process parameter (e.g., compression force).

Dissolution Test Development Case Study: Robustness of the Dissolution Step

Effects of small deliberate changes of dissolution parameters on dissolution profiles were evaluated, for example (note - the parameters and studied ranges in the robustness exercise are procedure specific and should be selected on a case-by-case basis):

- Effect of temperature: dissolution testing below and above the target temperature (e.g., 37.0 ± 0.5 °C)
- Effect of agitation (or stirring) speed: dissolution testing below and above agitation speed (e.g., $75 \text{ rpm} \pm 3 \text{ rpm}$).
- Effect of pH-changes within a small range: dissolution testing below and above the target pH of the dissolution medium (e.g., ± 0.1 pH units).
- Effect of buffer concentration: dissolution testing below and above the target concentration in dissolution medium (e.g., ± 5 mM).
- Effect of surfactant concentration: dissolution testing below and above the target concentration in the dissolution medium (e.g., $\pm 0.1\%$).
- Effect of deaeration: air bubbles on the surface of the tablets could slow down dissolution; performed comparative study using degassed and non-degassed medium.

Tablet NIR RTRT Assay: Case Study for Typical Submission Elements (see module 7, NIR, for more details)

Development information in the dossier (3.2.P.5.3)

- 30 tablets/hour were diverted from the outlet of the tablet press to a Fourier Transform Near-Infrared (FT-NIR) instrument to perform a transmission measurement. The other tablets were collected in discrete bins.
- Tablets at 5 different concentration levels (70%, 85%, 100%, 115%, 130%) were manufactured on the commercial continuous manufacturing (CM) line for calibration and validation purpose.
- Sources of variation included: drug substance lot, drug substance particle size, excipients lot, sample age (tablet relaxation), moisture content, hardness, thickness, humidity and temperature of the environment, instrument and sample interface.
- Tablet composition details and ranges of sources of variation.
- 71 spectra were used in the calibration model.
- A leave-5 out internal test set was applied.
- The liquid chromatography analytical procedure developed and validated for assay was used as the reference analytical procedure.
- Wavelength range was justified.
- Normalisation and 1st derivative with Savitsky-Golay smoothing of 17 points combined with standard-normal variate algorithm were deployed as spectra pre-treatment and justified.
- 3 partial least squares (PLS) factors were used and justified with Prediction Error Sum of Squares (PRESS) plots.
- Handling of outliers was described (Weibull distribution of Mahalanobis distance and residuals and justified thresholds).

Tablet NIR RTRT Assay: Case Study for Typical Submission Elements (see module 7, NIR, for more details)

Validation information in the dossier (3.2.P.5.3)

Independent samples were chosen from the same batches deployed as the calibration batches (including different concentration levels) and extended with 3 other batches at target (i.e., 100%) at commercial scale. The validation summary is below: see Table 3 of module 7 NIR example for details.

Performance characteristic	Validation results
Specificity/ Selectivity	An overlay of spectra of drug substance, a core tablet and a placebo tablet are made. Furthermore, plots of the regression coefficients and the relevant PLS components as a function of wavenumbers are reported. Out-of-scope samples are challenged and rejected by the model. Specificity/selectivity was adequate.
Precision	Relative standard deviation (RSD) of 1.6% at target level (100%). Repeatability was adequate.
Accuracy	RMSEP of 2.3%. Accuracy was adequate.
Reportable Range	69.3%-132.9%. A linear response, with a correlation coefficient r of 0.998 is obtained. A plot of the residuals of the model prediction versus the actual data was provided. The response was found to be linear across the reportable range.
Robustness and other considerations (performed as part of analytical procedure development as per ICH Q14)	Variability within and between instruments, tablet hardness and thickness variability, moisture content of tablets, batch-to-batch variability, drug substance particle size variability, tablet relaxation, sample position variability, tablet composition, and environmental conditions of temperature and humidity were successfully demonstrated.

NIR RTRT Assay: Case Study

NIR Analytical Procedure Parameter		Value
NIR Instrument	Spectrometer	A FT-NIR with a transmission unit
	Spectral collection range	12500-5800 cm ⁻¹
	Spectral collection mode	Transmission
Data Acquisition	Number of scans	32
	Resolution	16 cm ⁻¹
Sample interface	Sample presentation	30 tablets/hour are diverted from the outlet of the tablet press to an at-line NIR spectrometer while the other tablets from the outlet of the tablet press are collected in discrete bins. The tablets are presented to the spectrometer in a specific sample holder, ensuring a representative and precise positioning of the tablet in the NIR radiation.
Software	Model development, spectral recording and analysis software	Software name + version
	Tablet press interface	Software name + version
Calculation	Chemometrics algorithm	Partial Least Squares (PLS) model
Analytical procedure range	% Intent	70.0 – 130.0
Reference analytical procedure	Off-line HPLC	Reversed Phase Liquid Chromatography method X
PLS Model	Spectral Pre-processing	Standard Normal Variate (SNV) followed by 17 points Savitzky-Golay 1st derivative
	PLS model spectral range	12000-8950 cm ⁻¹
	Number of latent variables	3
Data quality checks		Mahalanobis distance ≤ 0.74
		Residuals ≤ 0.078

The HPLC reference analytical procedure is used as the alternative procedure to the NIR RTRT procedure. The alternative procedure may be used only when the NIR RTRT instrument shows obvious failure, breakdown, or the multivariate model needs a major update requiring health authority approval.

NIR RTRT Assay : Case Study

Model maintenance (PQS) information in the dossier:

- Periodic model maintenance occurs at justified time intervals.
- One commercial batch per year is analysed with the NIR analytical procedure as well as the reference analytical procedure. The results need to comply with the root mean square error of prediction (RMSEP) set forth in the original validation.
- Additionally, event driven model maintenance and recalibration can also be triggered upon changes, e.g., new known process variability, unexpected process event, or scheduled instrument maintenance.
- If the evaluation fails, model development and revalidation may be needed, e.g., to add samples in the calibration set and remove those that are no longer relevant.

Contact

- **For any questions please contact the ICH Secretariat:**

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