

ICH Q14: Analytical Procedure Development

Training Module 4: ICH Q14 General Considerations

Part A: Minimal and Enhanced Approach

Part B: Analytical Procedure Lifecycle

Part C: Analytical Target Profile (ATP)

Part D: Risk Assessment in Analytical Procedure Development

Part E: Robustness and Parameter Ranges

Part F: Analytical Procedure Control Strategy

Publication Date: 08 July, 2025

Legal Notice

This presentation is protected by copyright and may, with the exception of the ICH logo, be used, reproduced, incorporated into other works, adapted, modified, translated or distributed under a public license provided that ICH's copyright in the presentation is acknowledged at all times. In case of any adaption, modification or translation of the presentation, reasonable steps must be taken to clearly label, demarcate or otherwise identify that changes were made to or based on the original presentation. Any impression that the adaption, modification or translation of the original presentation is endorsed or sponsored by the ICH must be avoided.

The presentation is provided "as is" without warranty of any kind. In no event shall the ICH or the authors of the original presentation be liable for any claim, damages or other liability arising from the use of the presentation.

The above-mentioned permissions do not apply to content supplied by third parties. Therefore, for documents where the copyright vests in a third party, permission for reproduction must be obtained from this copyright holder.

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 guideline) 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.

Module 4 – Fundamental Principles of ICH Q14

Part A: Minimal and Enhanced Approach

Minimal and Enhanced Approach

Elements of the Minimal Approach

- Identifying attributes that need to be tested.
- Selecting an appropriate technology and related instruments or suitable apparatus.
- Conducting studies to evaluate analytical procedure performance characteristics such as specificity, accuracy and precision over the reportable range and robustness.
- Documenting the analytical procedure including the analytical procedure control strategy.

While the minimal approach remains a valid approach, the use of different elements of the enhanced approach can facilitate management and regulatory communication of post-approval changes.

Minimal and Enhanced Approach

Elements of the Enhanced Approach

In addition to the elements of the minimal approach, an enhanced approach may include the following elements as appropriate:

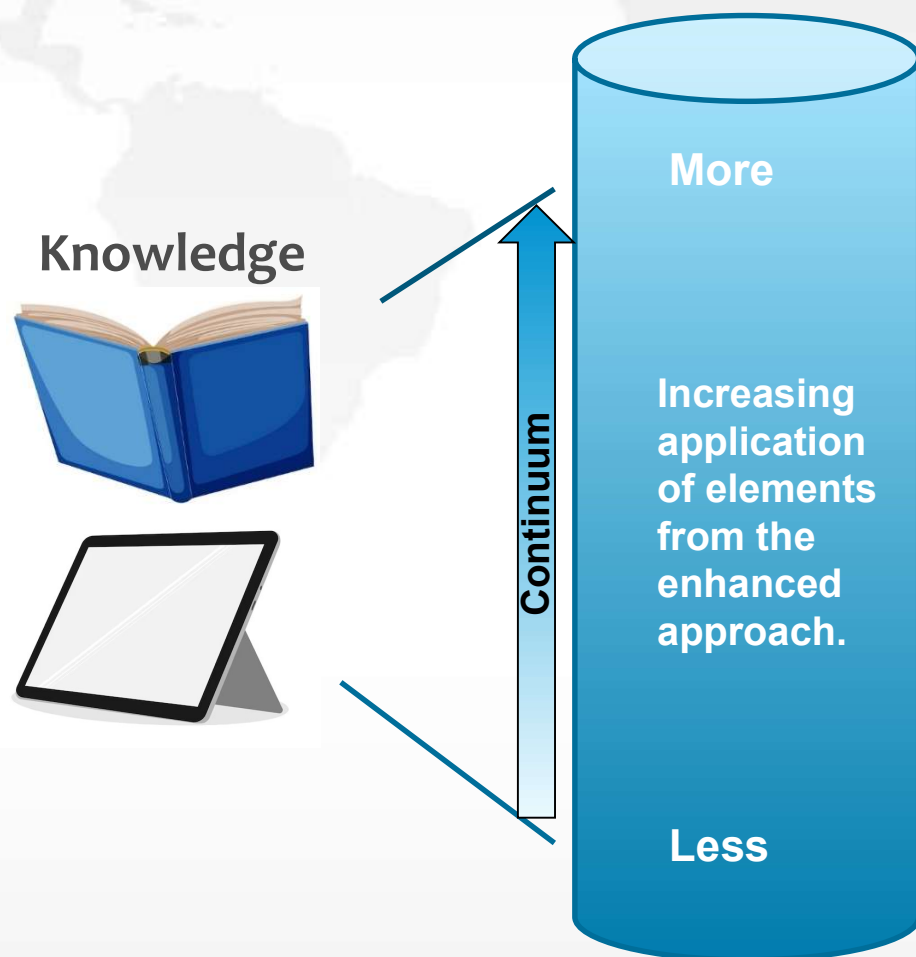
- Anticipated performance criteria for relevant performance characteristics should be documented in an Analytical Target Profile (ATP).
- Conducting risk assessment and evaluating prior knowledge to identify the analytical procedure parameters that can impact performance of the procedure.
- Conducting uni- or multi-variate experiments and/or modelling to explore ranges and interactions between identified analytical procedure parameters.
- Defining an analytical procedure control strategy including set-points and/or ranges for relevant analytical procedure parameters. These could include Proven Acceptable Ranges for Analytical Procedures (PARs) and/or Method Operable Design Regions (MODRs)

Minimal and Enhanced Approach

Benefits of the Enhanced Approach

- Represents a systematic way of developing and refining knowledge of an analytical procedure and demonstrating procedure understanding.
- Understanding of which analytical procedure attributes are essential to procedure performance (i.e., Established Conditions (ECs)).
- Employing predefined performance characteristics (e.g., in the ATP) linked to Critical Quality Attributes (CQAs) and their acceptance criteria to provide purpose driven protocols for validation of analytical procedures and for future comparisons between current and new analytical procedures/technologies.
- Improving analytical procedure control resulting in more reliable operation.
- Enabling preventative measures and facilitating continual improvement by using more analytical procedure knowledge.
- Reducing the amount of effort across the analytical procedure lifecycle. 7

Minimal and Enhanced Approach



Enhanced Approach:

Increasing understanding of the relationship between procedure parameters (input) and analytical procedure performance.

Minimal Approach:

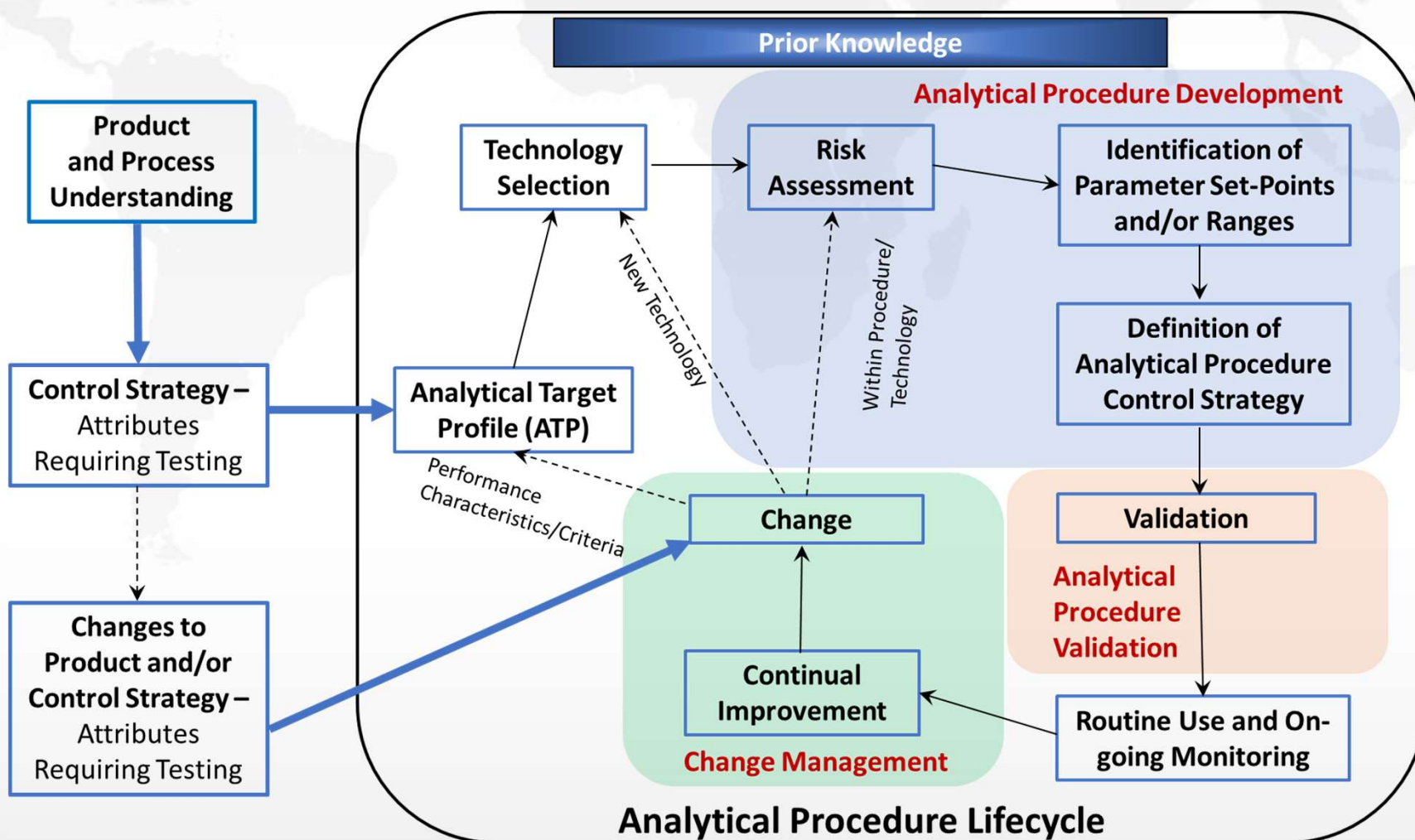
Basic understanding of the relationship between procedure parameters (input) and analytical procedure performance.

Some or all elements of the enhanced approach might be used to support development and lifecycle management of analytical procedures.

Module 4 – Fundamental Principles of ICH Q14

Part B: Analytical Procedure Lifecycle

Analytical Procedure Lifecycle



Analytical Procedure Lifecycle

- Analytical procedure development, as shown in the figure, begins with the drafting of the ATP, which is linked to the Quality Target Product Profile (QTPP).
- The ATP can be a first step in the development process and facilitates the technology selection (Chapter 3).
- Analytical procedure development is supported by risk assessment (Chapter 4) and aided by prior knowledge (product, process, technology).
- During development, evaluation of robustness and parameter ranges (Chapter 5) and establishment of the *analytical procedure control strategy* (Chapter 6) are needed.
- The analytical procedure is validated as per ICH Q2 prior to routine use.
- During routine use, ongoing analytical procedure monitoring is performed to ensure that the quality of the measured results remains as expected.
- Analytical procedures should be continually evaluated against the performance characteristics and criteria in the ATP.

Analytical Procedure Lifecycle (cont'd)

- As part of continual improvement, a new analytical procedure or adjustments to an existing analytical procedure may be implemented.
- Prior to implementation, a risk assessment of the intended change, validation and/or revalidation as needed, and fulfilment of the appropriate regulatory reporting requirements (Chapter 7) are needed.
- Major changes in the performance characteristics or additional information on attributes could lead to re-evaluation of the ATP and/or a new procedure.
- Analytical procedure modifications would generally require a risk assessment followed by appropriate adjustment of the analytical procedure control strategy and subsequent validation of applicable parameters as needed to adequately address the changes and ensure that the analytical procedure remains fit for its intended purpose.

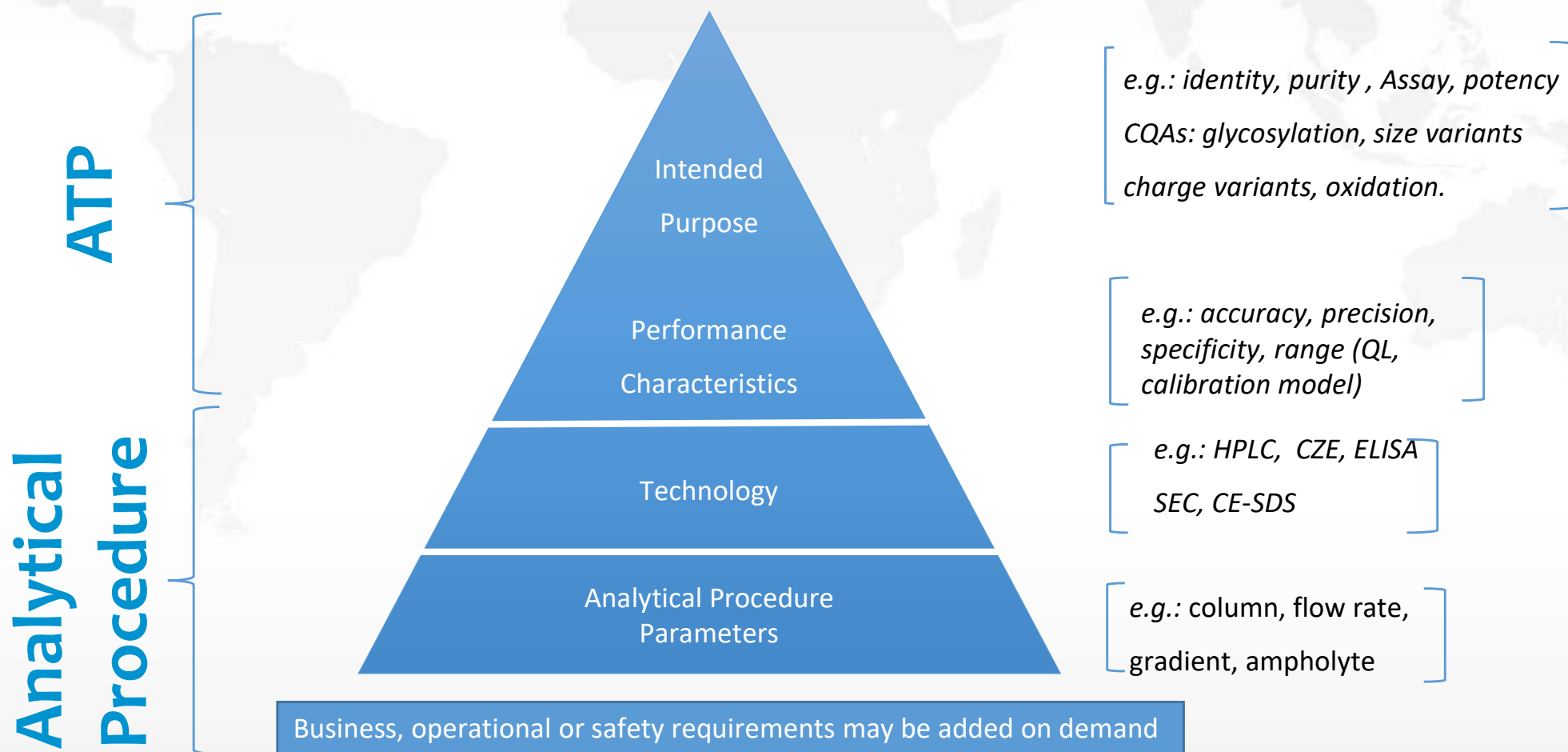
Module 4 – Fundamental Principles of ICH Q14

Part C: Analytical Target Profile (ATP)

Analytical Target Profile (ATP)

- A prospective summary of the performance characteristics describing the intended purpose and the anticipated performance criteria of an analytical measurement.
- The intended purpose should be sufficiently descriptive for the measurement of the attribute and the use of that result.
- 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.
 - An ATP could also be retrospectively established.

Analytical Target Profile (ATP)



Analytical Target Profile (ATP)

The ATP focuses on the properties of analytical procedures that impact quality decisions (e.g., batch disposition)

- The performance criteria should ensure that the measurement of a quality attribute is fit for the intended purpose and produces data that can be used with the required confidence to support specification pass/fail decisions.

Analytical Target Profile (ATP)

Example: Impurity Determination for a Synthetic Drug Substance

Intended Purpose		
Quantitation of the impurities A-D and determination of purity in Exemplix DS for release testing		
Link to CQA (impurity testing)		
The analytical procedure should allow for the quantitation of the individual known impurities A-D and should also determination of the total sum to verify the Exemplix DS purity $\geq 99.0\%$		
Characteristics of the Reportable Results		
Characteristic	Acceptance Criteria	Rationale
Performance Characteristics		
Accuracy	80–120% average recovery of spiked DS with Impurities A-C (specified at NMT 0.1% each) 90–110% average recovery of spiked DS with Impurity D (specified at NMT 0.5%)	For example, at a specification level of 0.1%, 20% bias would lead to a variation of the analytical result of 0.02%, which was found acceptable for a release decision. In a similar fashion, values for precision were derived. The recovery criteria for accuracy were set with respect to the reported result and taking into consideration any correction or response factors
Precision	Intermediate Precision RSD: Impurities A–C $\leq 15\%$ Impurity D $\leq 10\%$	
Specificity	Analytical procedure should be able to quantitate impurities A–D in presence of other likely process related substances or DS degradation products with an acceptable bias of not more than 0.02%	Potential interference with quantitation of specified impurities by other regular components in the sample
Reportable Range	Impurities A–C: at least 0.05–0.12% Impurity D: at least 0.05–0.6%	Reporting threshold to 120% of specification limit

Analytical Target Profile (ATP)

Example: Protein Content Determination for a Monoclonal Antibody Drug

Intended Purpose		
Measurement of the protein content of a therapeutic protein in drug product at release and for stability testing.		
Link to CQA (protein content)		
Protein content is a CQA as it relates to the correct dose and hence is key to ensure safety and efficacy of the drug. Specification acceptance criteria for protein content: target value of X.Y mg/ml \pm 10 %		
Characteristics of the reportable result		
Performance Characteristic	Acceptance criteria	Rationale
Accuracy	Mean recovery at each level covering the range of the reportable result, are e.g. within 97 % and 103 %, considering the intended purpose of the measurement.	Selected performance characteristic ensures that the intended method delivers the quality reportable result.
Precision	The precision (RSD) of the protein content measurement is not more than e.g. 4%, considering the intended purpose of the measurement.	
Specificity	No interference from matrix components.	Confirmation of the capability to measure protein content in the presence of the components expected to be present (formulation buffer).
Reportable Range	The range of the measurement covers at least 80% to 120% of the specified range	Range for which the required accuracy and precision characteristics are demonstrated.

Analytical Target Profile (ATP)

From QTPP to ATP

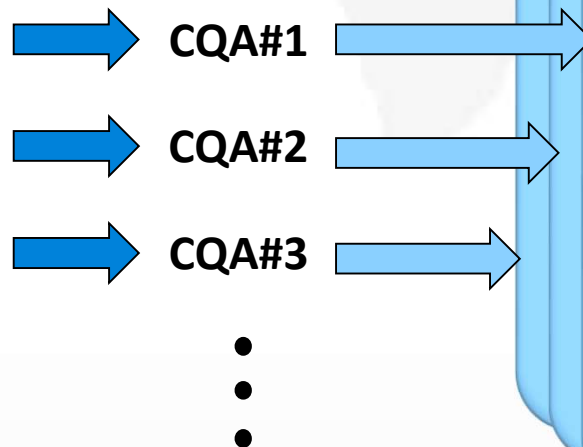
CMC
Development



QTPP*

- Quality characteristics to ensure safety and efficacy.

Identification
of CQAs

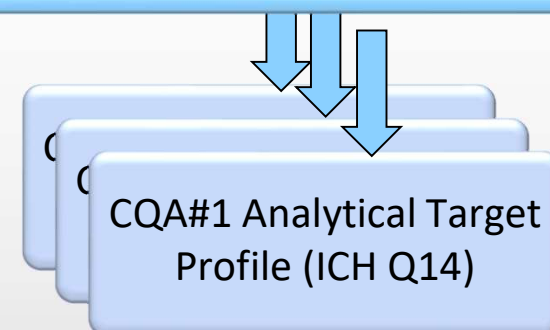


Control Strategy
(ICH Q10)

Control of CQA#1

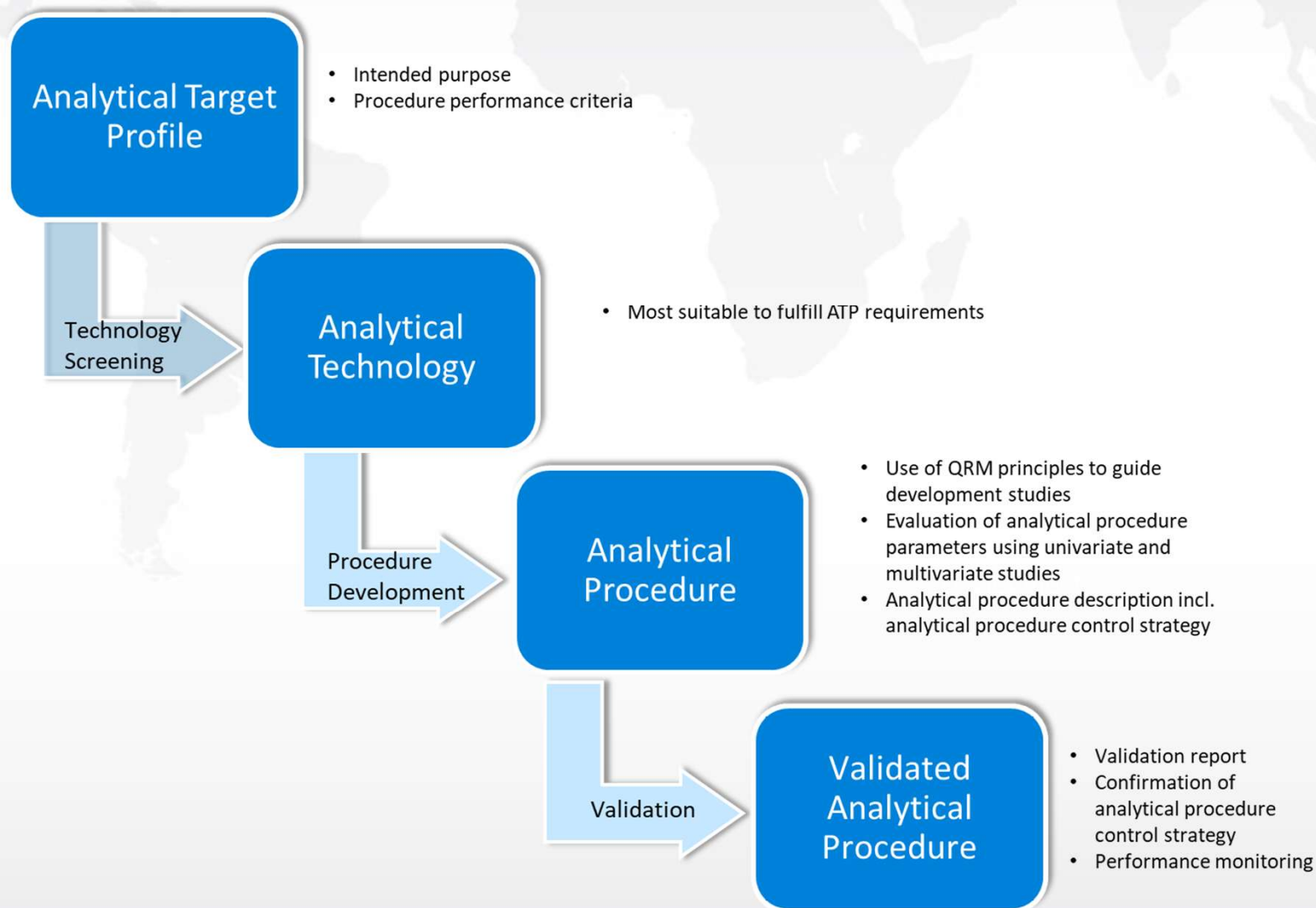
Requirements of the reportable result, based on:

- Product understanding (CQA impact on safety/efficacy).
- Process understanding/capability.
- Specification limits/ranges (linked to patient exposure).
- Regulatory or compendial requirements.



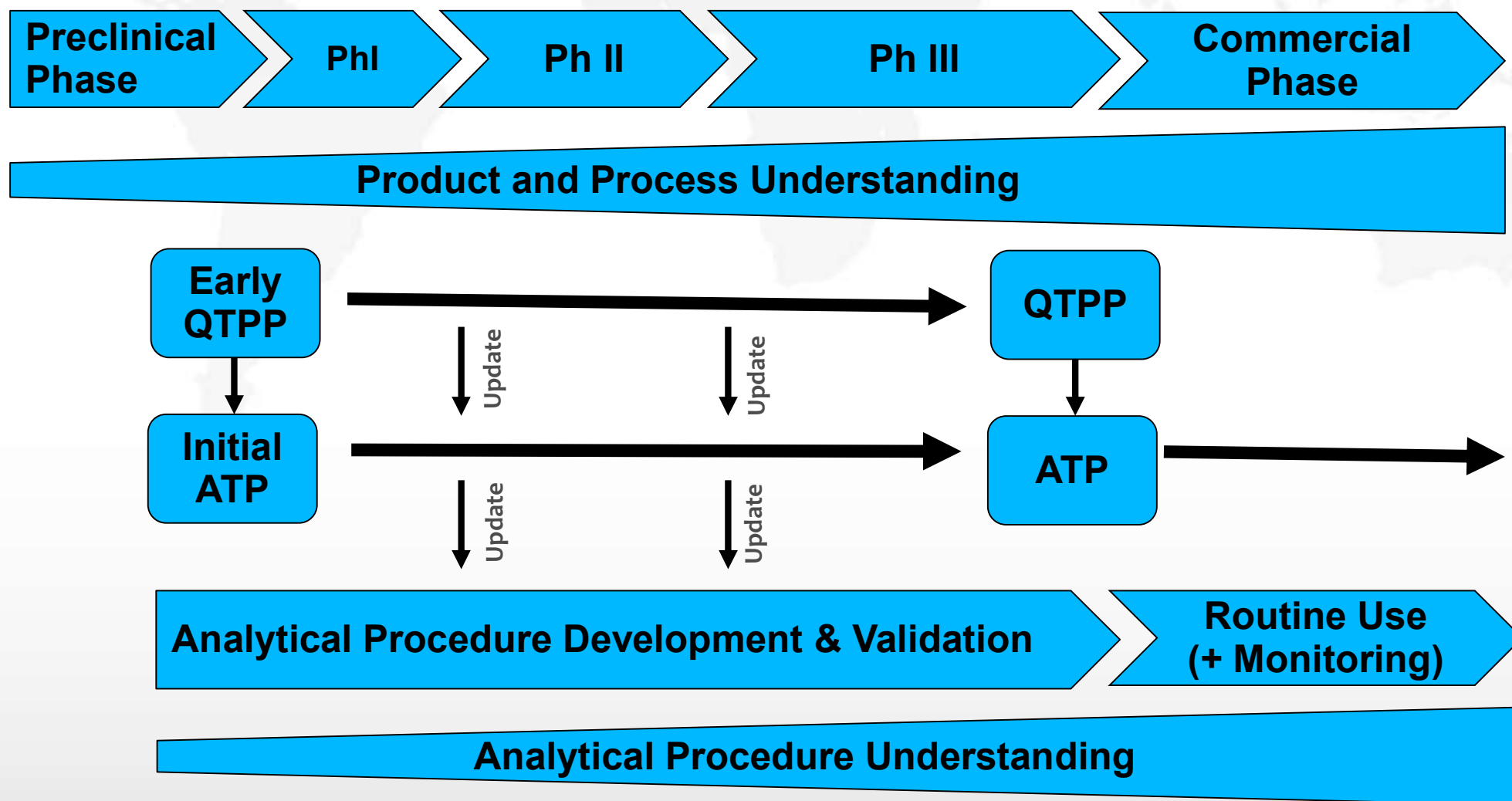
* QTPP: Quality Target Product Profile (ICH Q8)

Analytical Target Profile (ATP)



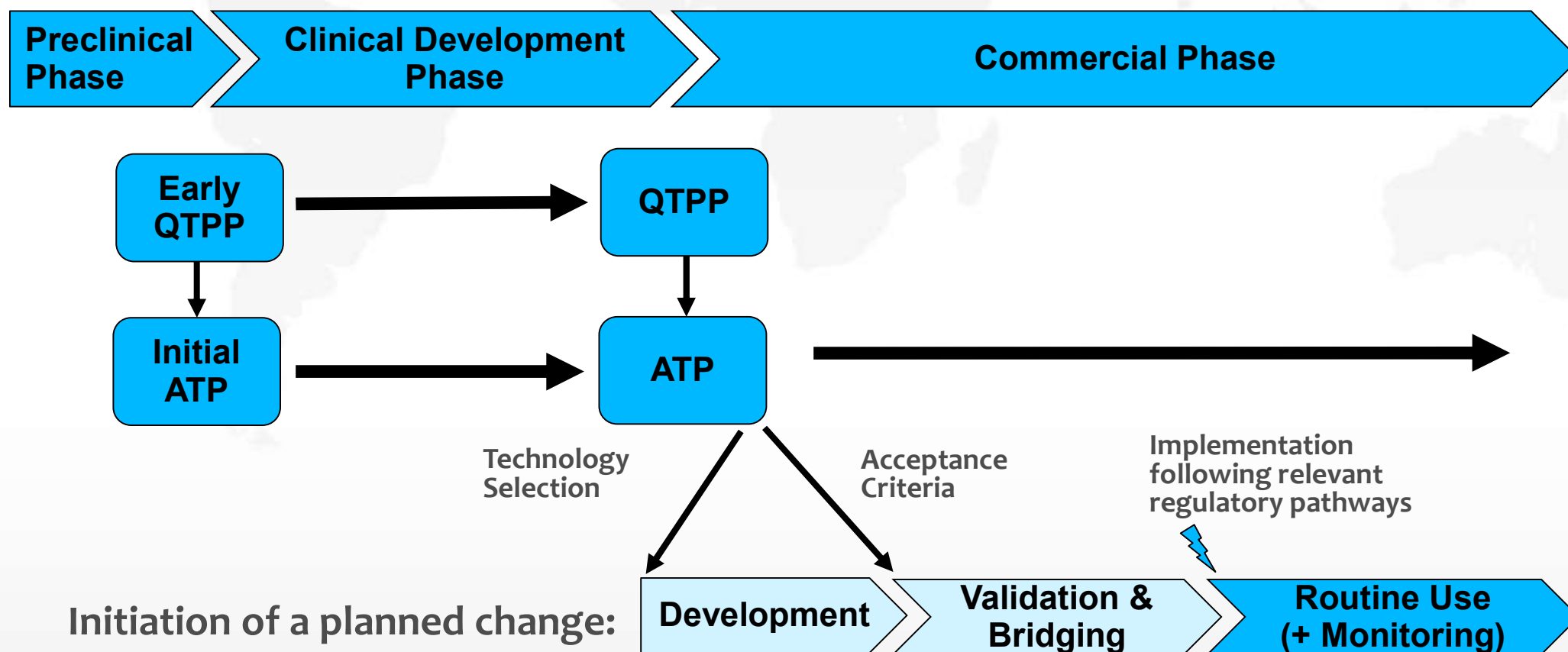
Analytical Target Profile (ATP)

ATP lifecycle



Analytical Target Profile (ATP)

Post Approval Change of Analytical Procedure



Module 4 – Fundamental Principles of ICH Q14

Part D: Risk Assessment in Analytical Procedure Development

Risk Assessment in Analytical Procedure Development

- Risk assessment tools as described in ICH Q9 Annex 1 can be used to:
 - Identify analytical procedure parameters (factors and operational steps) with potential impact on its performance, e.g., Ishikawa diagram.
 - Assess the potential impact of analytical procedure parameters on the analytical procedure performance.
 - Identify and prioritise analytical procedure parameters to be investigated experimentally.
 - Inform the need and the extent of ongoing monitoring as part of risk review.
- Risk assessment can be formal or informal and can be supported by prior knowledge. ICH Q9(R1) includes guidance on factors to consider when determining level of formality in Quality Risk Management (QRM).
- Use of risk assessment is exemplified in some of the case studies in Module 7 for analytical procedure development (and in the context of changes to analytical procedures, see Module 5).
- Additional information is available in ICH Q8/ ICH Q9/ ICH Q10 implementation documents.

Module 4 – Fundamental Principles of ICH Q14

Part E: Robustness and Parameter Ranges

Robustness and Parameter Ranges

Robustness

- Is a measure of the capacity of an analytical procedure to meet the expected performance criteria during normal use.
- Is tested by deliberate variations of analytical procedure parameters and should consider the duration of the analysis (including stability of sample preparations and reagents).
- Robustness evaluation is typically conducted during development.
- If the evaluation of robustness was already conducted during development, it does not necessarily need to be repeated during validation (as discussed in ICH Q2).
- Data from validation studies (e.g., intermediate precision) can complement robustness evaluation.
- The outcome of the evaluation of robustness should be documented and also reflected in the analytical procedure control strategy.
- As per ICH Q2, robustness evaluation can be submitted as part of development data for an analytical procedures on a case-by-case basis or should be made available upon request.

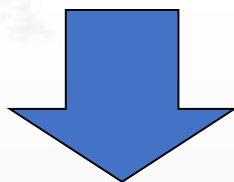
Robustness and Parameter Ranges

Controlled (C)

Procedure factors which can be fixed or controlled.

Stationary phase

Can be controlled via the analytical procedure or other GMP documents.



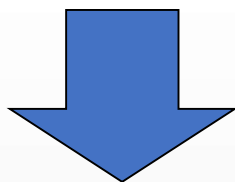
Control Plan

Noise (N)

Factors which are hard to control or are uncontrolled and contribute to inherent variability/error.

HPLC Equipment

Can be studied within intermediate precision/reproducibility.



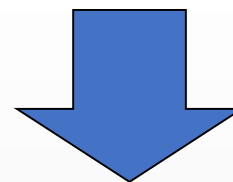
Intermediate Precision and Robustness

Experimental (X)

Procedure factors which can be varied across a limited range.

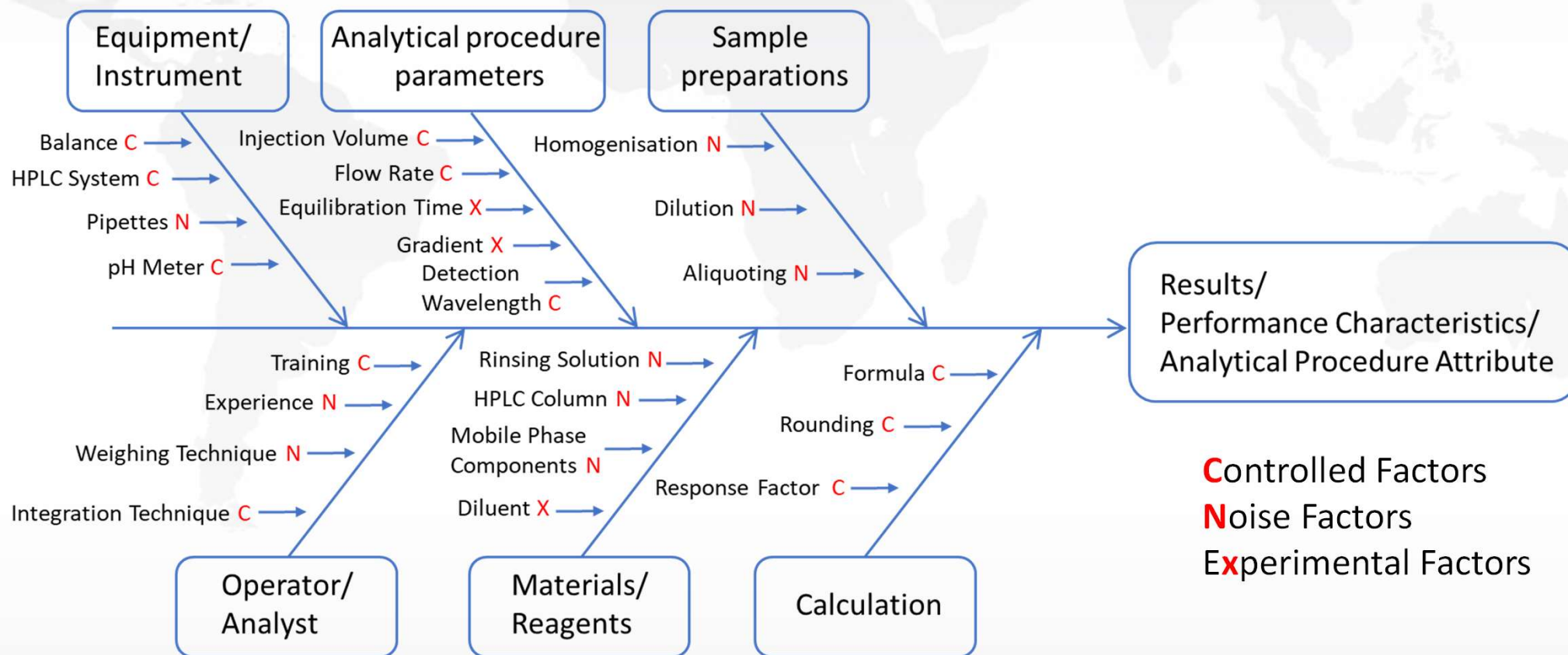
Gradient slope

Can be studied in a Design of Experiments (DoE) to assess control range and any interactions investigated.



Classification of factors is one approach; other approaches are also available.

Robustness and Parameter Ranges



Risk assessment can inform the selection of parameters to investigate during the robustness study.

Robustness and Parameter Ranges

Parameter Ranges

- Experiments to investigate parameter ranges can provide additional knowledge about the analytical procedure performance.
- Univariate examination of a single parameter can establish a Proven Acceptable Range (PAR) for the analytical procedure.
- In an enhanced approach, the ranges for the relevant parameters and their interactions can be investigated in design of experiments approaches (DoE).
- Based on the results, fixed set-points may be defined for some parameters. For others, PARs could be defined while still others could be included into an MODR.
- An MODR consists of combined ranges for two or more analytical procedure parameters within which the analytical procedure is shown to be fit for the intended purpose.
- Set-points, PARs and/or MODRs of an analytical procedure are proposed by the applicant based on development and validation data and are subject to regulatory approval.
- The part of a PAR or an MODR intended for routine use (typically the intended operational conditions or the set point) in the analytical procedure must be covered by validation data. The extent of validation tests should be justified on a case-by-case basis.

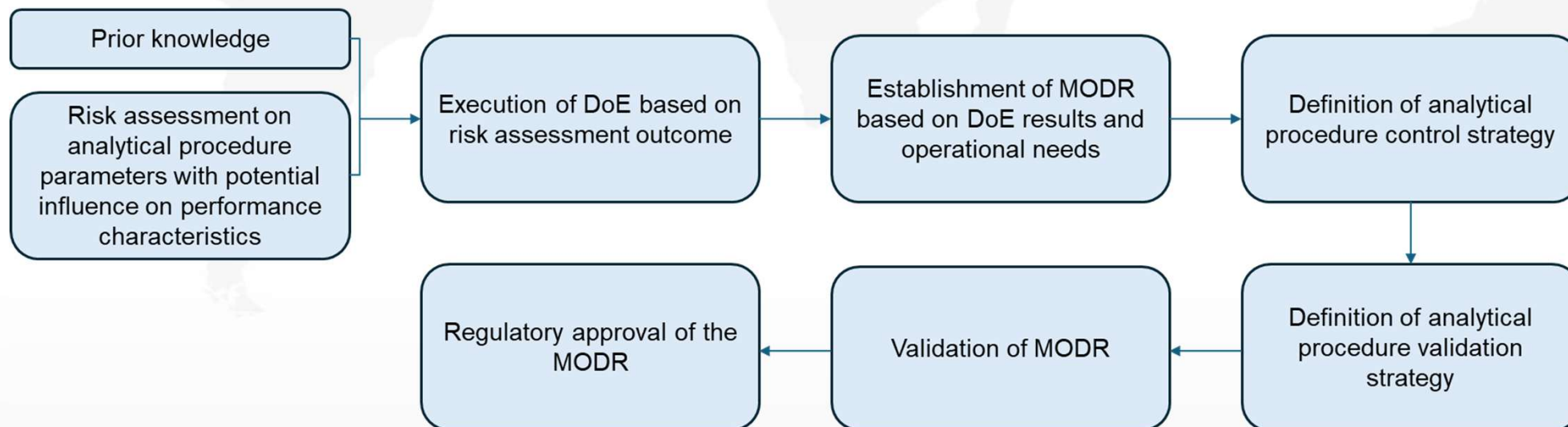
For further information see Module 2 Part A and Module 7

Robustness and Parameter Ranges

MODR - Method Operable Design Region optional element of an enhanced approach

Definition:

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.



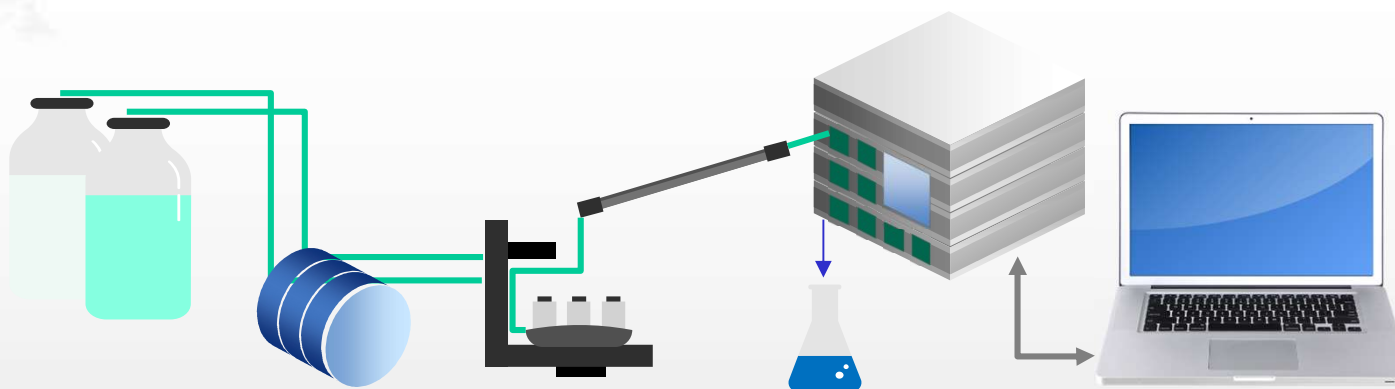
Operational usage of an MODR:

- supports the establishment of the analytical procedure validation strategy
e.g., (partial) coverage of robustness, specificity/selectivity, range
- analytical procedure parameter changes within the approved MODR without regulatory communication

Robustness and Parameter Ranges

Case Study: Liquid Chromatography (LC) Procedure for Impurity Analysis

- Analytical procedure designed to effectively separate and quantify specified impurities in the drug substance.
- Standard LC procedure using reversed phase column with gradient elution and ultraviolet detection.
- Enhanced development utilised throughout the process.
- ECs and reporting categories proposed focused on performance.



Robustness and Parameter Ranges

The workflow below and following slides provide an example of an enhanced approach for development of a chromatographic impurity procedure. Following these steps, validation is completed per ICH Q2(R2).

Define ATP

- Serves as a foundation to derive the analytical procedure attributes and performance criteria for analytical procedure validation.

Key Sample Set

- Minimally specified impurities and known degradation products.
- Understanding sample and physicochemical attributes.

Parameter Screen

- Screen various columns, pH and mobile phases to select column, pH, and organic modifier to proceed.

Model Development

- Build model for separation which is used to identify optimal center point conditions.

Perform Risk Assessment

- Determine procedure parameters likely to impact performance characteristics.

Robustness

- Based on the model and risk assessment, can vary aqueous modifier, gradient, column temp, flowrate, etc., in silico robustness studies.

Confirmation

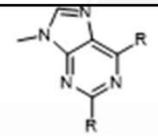
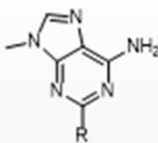
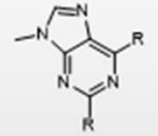
- Perform confirmation at center point, lowest resolution, high and low retention time.
- Assess results against performance characteristics.

Robustness and Parameter Ranges

Key Sample Set

- Lists all known impurities.
- Key sample set is maintained during development.
- Understanding sample and physicochemical attributes.

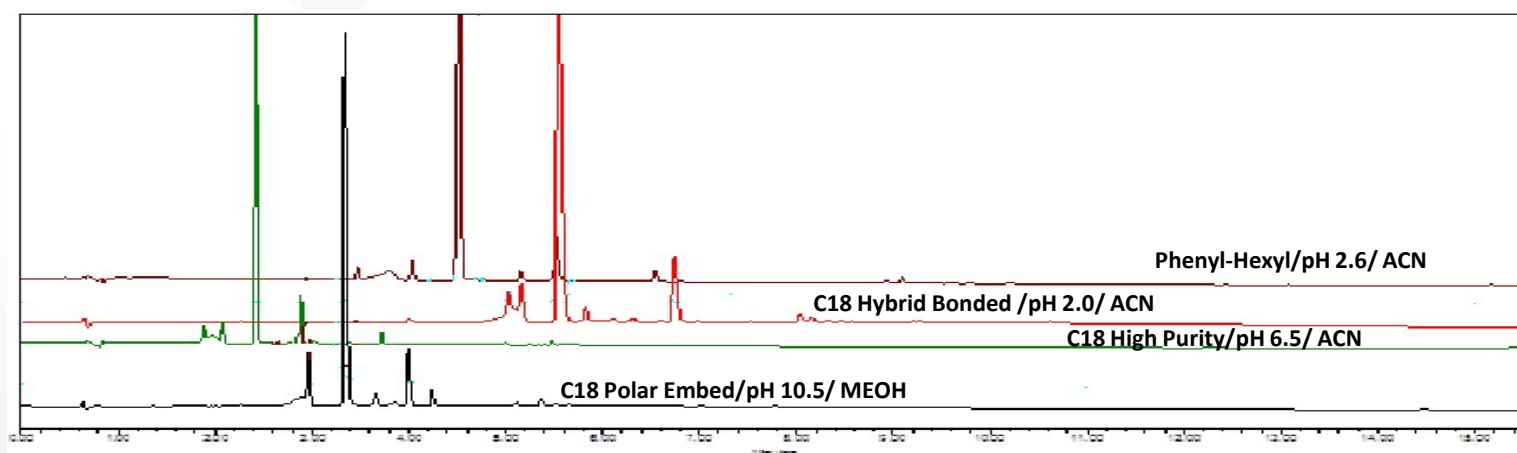
The following table lists example compounds from the Key Sample Set.
For Rating: 1=need, 2=want, 3=historical

Structure	Description	Source	Sample	Notes	Rating
<i>Structure</i>	<i>Impurity description (Drug Substance, Process Related Impurity, Degradant, Excipient Related)</i>	<i>Impurity origination in synthesis (Raw Material, Step X, forced deg...)</i>	<i>Sample lot where impurity can be found</i>	<i>Additional information (Specification/qualification , how impurity is formed...)</i>	<i>1-3</i>
	Drug Substance	N/A	Reference Standard	DS Needs to be resolved from impurities with rating of 1 or 2	1
	Specified Impurity (Hydrolysis product)	Step D PRI Degradant	Reference Material	Specified process related impurity needs to be resolved from DS and impurities with rating of 1 or 2 Acceptance criteria $\leq 0.5\%$	1
	Potential Degradation Product from acid forced degradation study	Observed in forced degradation; not observed on stability	Degraded drug substance sample with 0.1% HCl	Unspecified impurity needs to be resolved from DS and impurities with rating of 1	2

Robustness and Parameter Ranges

Parameter Screen

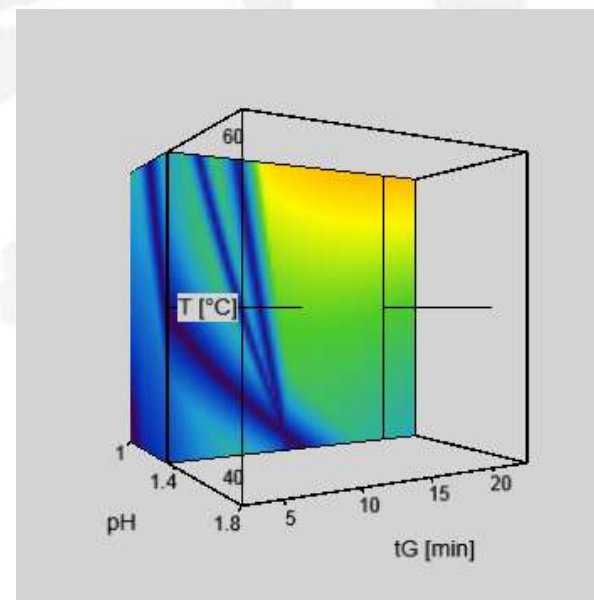
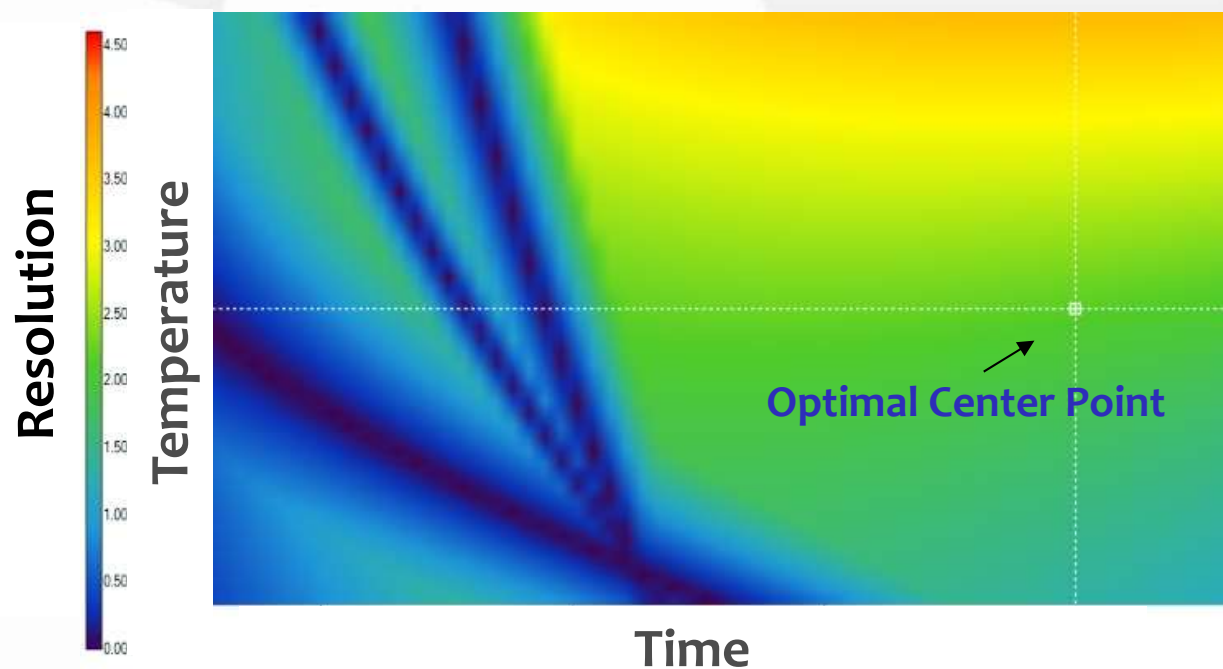
	pH 2.0		pH 2.6		pH 6.5		pH 10.5	
Mobile Phase A	0.1% TFA		0.1% HCOOH		10 mM NH ₄ OAc		0.1% NH ₄ OH	
Mobile Phase B	ACN	MeOH	ACN	MeOH	ACN	MeOH	ACN	MeOH
C18 Hybrid Bonded 1.7 µm	X	X	X	X	X	X	X	X
Phenyl Hexyl 1.7 µm	X	X	X	X	X	X	X	X
C18 High Purity 1.7 µm	X		X		X		X	
C18 Polar Embed 1.7 µm	X		X		X			



- Screen chosen that resolves most components with best peak shape.
- Parameters studied were those that typically impact separation capability.
- Evaluated columns have orthogonal retention capability.
- Design not run at every point due to pH/column instability
- Solvent gradient run from 5 % to 95 % at each condition.
- Red box represents conditions selected e.g., green chromatogram.

Model Development

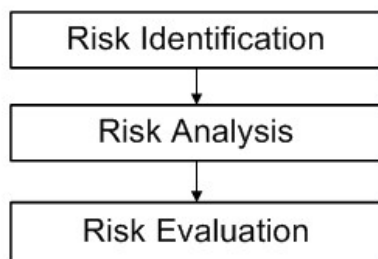
Optimised Conditions: 10 to 60 % ACN in 20 min 50 °C Buffer Ratio 1.33



- DoE optimisation study considered narrow pH range, gradient steepness and temperature.
- Results from the study were input into software to create a model.
- Objective was to find an optimal center point with sufficient robustness (best resolution between closely eluting components) and ruggedness, e.g., column longevity based on temperature.

Perform Risk Assessment

Risk Assessment



Risk Identification

List parameters that could potentially affect analytical procedure performance

Examples:

Material Properties: Formulation composition, Solubility, Tablet hardness

Extraction: Diluent, Extraction type, Shaker speed

Mobile Phase: Reagent purity, solvent grade

Injector: Strong/weak needle wash, Volume

Separation: Column temperature, Flow rate, Ionic strength, pH

Detector Wavelength, Data rate, Band width

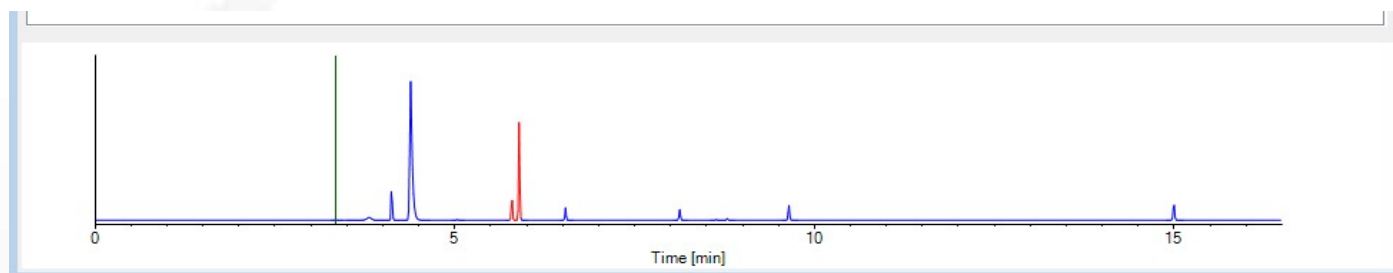
Risk assessment identified parameters that are further evaluated in DoE robustness study, ruggedness study through intermediate precision or controlled through procedure e.g., reagent quality.

Robustness

In silico DoE Study Design

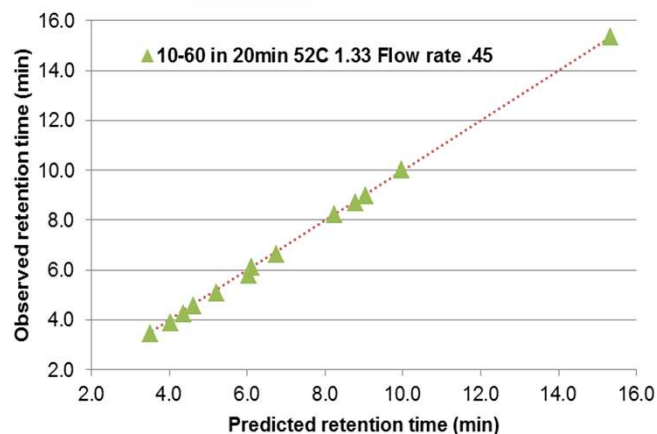
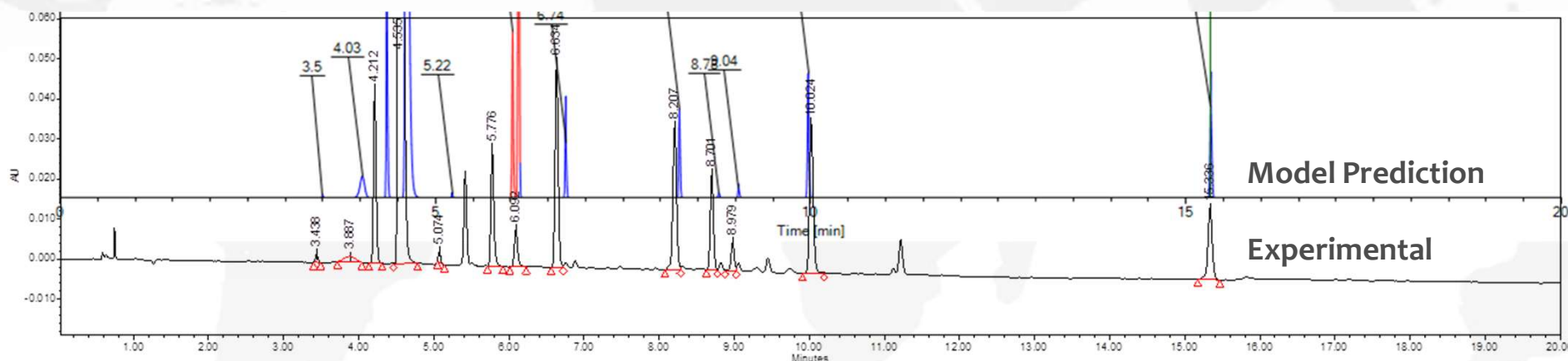
Model Parameter	Temp	Buffer Ratio	Flow Rate	Gradient Start	Gradient End	Gradient Time	Dwell Volume
Center Point	52°C	1.33	0.45 mL/min	10%	60%	20 min	0.35 mL
Vary +/-	3°C	0.1	0.05 mL/min	2%	2%	2 min	0.1 mL

Model Prediction



- *In silico* robustness study predicted acceptable multi-dimensional space with respect to pre-defined resolution criteria.
- Design should cover expected day to day variability; analyst may choose to evaluate more extensively.

Confirmation



- Confirmation study performed experimentally at edges and center point defined by the model (used for in-silico prediction).
- Confirmed retention time, resolution as predicted by model.
- Based on risk assessment suitable accuracy and precision at these points were confirmed.
- Validation studies were subsequently completed; results from the development studies could be used as part of validation.

Module 4 – Fundamental Principles of ICH Q14

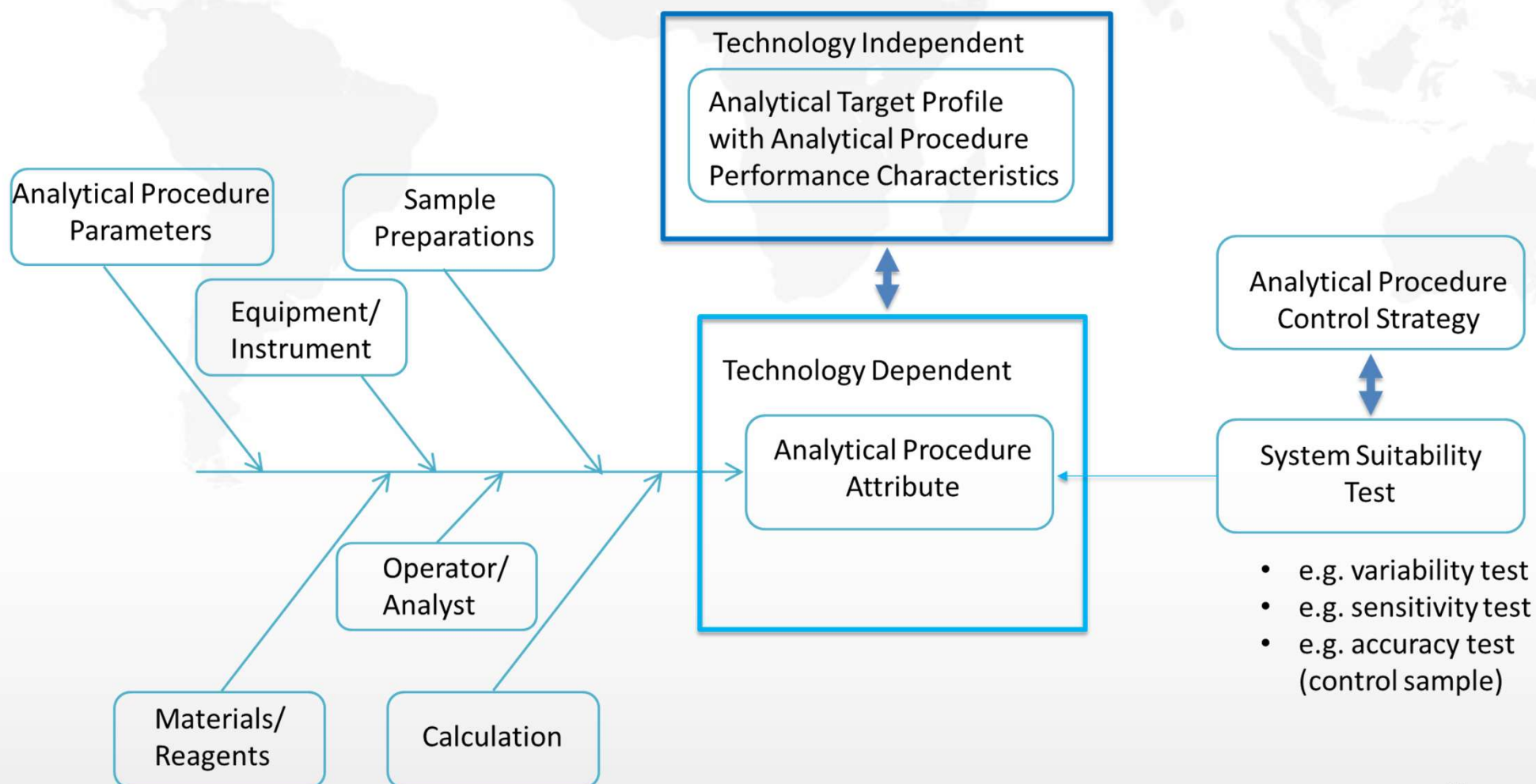
Part F: Analytical Procedure Control Strategy

Analytical Procedure Control Strategy

- An analytical procedure control strategy should ensure that the analytical procedure is fit for the intended purpose during routine use.
- The analytical procedure control strategy includes analytical procedure parameters needing control and the system suitability test (SST).
- The analytical procedure should describe the steps necessary to perform each analytical test. The level of detail should enable a skilled analyst to perform the analysis and interpret the results.
- The analytical procedure control strategy should be derived from understanding of the analytical procedure from prior knowledge, risk assessment and development data (incl. robustness).
- SST with relevant criteria could represent an important part of risk mitigation.
- For some analytical procedures, the SST should be accompanied by sample suitability assessment (e.g., some analytical procedures for biological products).
- The analytical procedure control strategy is developed before validation and confirmed after validation.

Analytical Procedure Control Strategy

Risk Assessment, ATP and Analytical Procedure Control Strategy



Analytical Procedure Control Strategy

System Suitability Test

- System suitability tests are developed and used to verify that the measurement system and the analytical operations associated with the analytical procedure are fit for the intended purpose and increase the detectability of unacceptable performance.
- The components of the SST should be selected using risk assessment as well as knowledge and understanding from development data.
- The SST is designed to verify selected analytical procedure attributes and the acceptance criteria should be based on performance characteristics and criteria. For example:
 - Specificity: e.g., critical peak pair resolution
 - Accuracy: e.g., analysis of a standard or control sample
 - Precision: e.g., relative standard deviation of the analytical system
- As part of a procedure change, the SST should be reassessed to ensure performance.

Analytical Procedure Control Strategy

Sample Suitability Assessment

- In addition to SST, sample suitability assessment may be required to ensure acceptable sample response.
- A sample and/or sample preparation is considered suitable if the measurement response of the sample satisfies pre-defined acceptance criteria for the analytical procedure attributes that have been developed for the validated analytical procedure.
- In these cases, sample suitability is a prerequisite for the validity of the result along with a satisfactory outcome of the SST.
 - For assays used for biologics, sample suitability assessment generally consists of the assessment of the similarity of the response between a reference material and the test sample and may include a requirement for acceptable levels of interfering signals arising from the sample matrix (see Module 7 Potency Example).
 - For analytical procedures relying on multivariate models, sample suitability assessment can be verified using suitable software tools which check if the sample fits within the model space. This is commonly called data quality check.

Analytical Procedure Control Strategy

Ongoing Monitoring

How can we monitor the **PERFORMANCE**?

Monitor the **INPUT*** and **OUTPUT** of analytical procedure

INPUT

- Sample weight
- Operation time
- Amount of solution
- ...

OUTPUT

- SST result
- pH of the media
- Testing result
- ...

*Some INPUT is made according to the analytical procedure and recorded as GMP documentation

Close link
to
analytical procedure
control strategy



Monitor the
performance of
analytical procedure



Detect any low
performance trend and
potential risk of
unacceptable performance



Maintain the
performance of
analytical procedure

Monitoring parameters should be decided based on risk assessment.

Example of performance monitoring: Assay of tablet

Category	Parameter	GMP Record	Analytical Procedure Monitoring	Way of Recording*
Preparation of Sample Solution	Number of tablets	√		Weight measurement
	Composition of extract liquid (water / MeCN etc.)	√		Weight measurement
	Volume of extract liquid	√		Weight measurement or image analysis
	Shaking duration for extraction	√		Time measurement
	Elapsed time after preparation	√		Confirmation of timestamp of operation
System Suitability Testing	Peak elution order (Peak A, B then C)	√	√	According to the SST
	Theoretical plate number (NLT** 20000)	√	√	
	Resolution (NLT** 1.5 between peaks A and B)	√	√	
	System repeatability (NMT*** 2.0%, n=6)	√	√	

*Some INPUT is made according to the analytical procedure and recorded as GMP documentation

**NLT: Not Less Than

***NMT: Not More Than

Step 1: Include parameters which have impact on the analytical results.

Step 2: Decide the way of monitoring (depends on the lab system and analytical procedure).

Step 3: Accumulate the monitoring data / information for real-time or retrospective performance analysis.

Contact

- For any questions please contact the ICH Secretariat:

admin@ich.org