ICH Q14 Enhanced Approaches:

From ATP to Analytical Procedure Validation Using Prior Knowledge and Development Data

Dr Mark Milford

- 26 years' industrial experience in the protein analytical field
- PhD from the University of Southampton (UK)
- Analytical roles spanning development, commercialisation and routine manufacture of biopharmaceuticals
- Based at the Eli Lilly Kinsale manufacturing facility (Ireland)
- Technical oversight of analytical aspects of new product introduction and commercialisation for biopharmaceutical drug substances across the Lilly analytical network, incl. method lifecycle and analytical control strategy
- Particular interest in analytical procedure development, validation and post-approval lifecycle from a large molecule perspective
- Industry Expert on the ICH Expert Working Group for ICH Q2(R2) / ICH Q14
- Current Deputy Topic Lead for the EFPIA ICH Q2(R2) / ICH Q14 Support Group

DR MARK MILFORD

DIRECTOR - ANALYTICAL

ANALYTICAL MOLECULE DS STEWARDSHIP

Analytical Procedures in ICH

ICH Q14 & ICH Q2(R2) finalised in late 2023

- First ICH update to Analytical Procedures since 2005.

ICH Q2(R2)

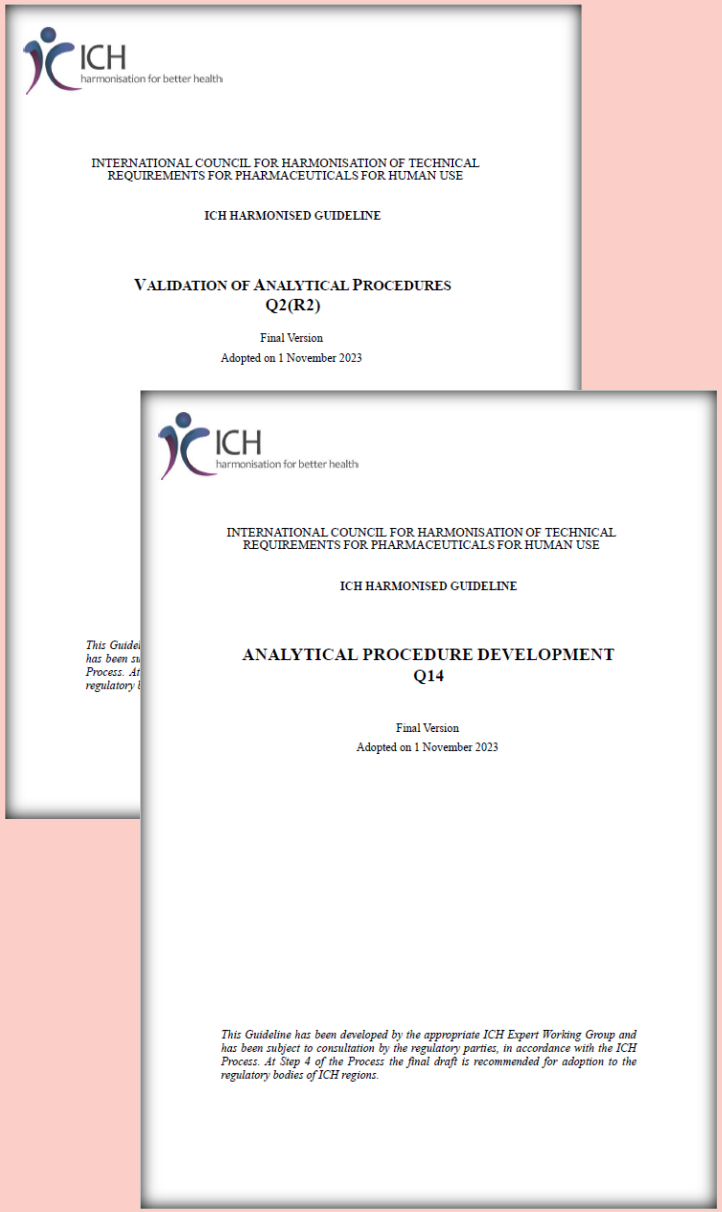
- Provides guidance for establishing evidence that an analytical procedure is fit for purpose (assuring drug quality).

ICH Q14

- Describes the scientific principles for development and change management, including concepts of minimal and enhanced approaches.

Together

- ICH Q14 and ICH Q2(R2) describe the development and validation activities suggested during the lifecycle of an analytical procedure.

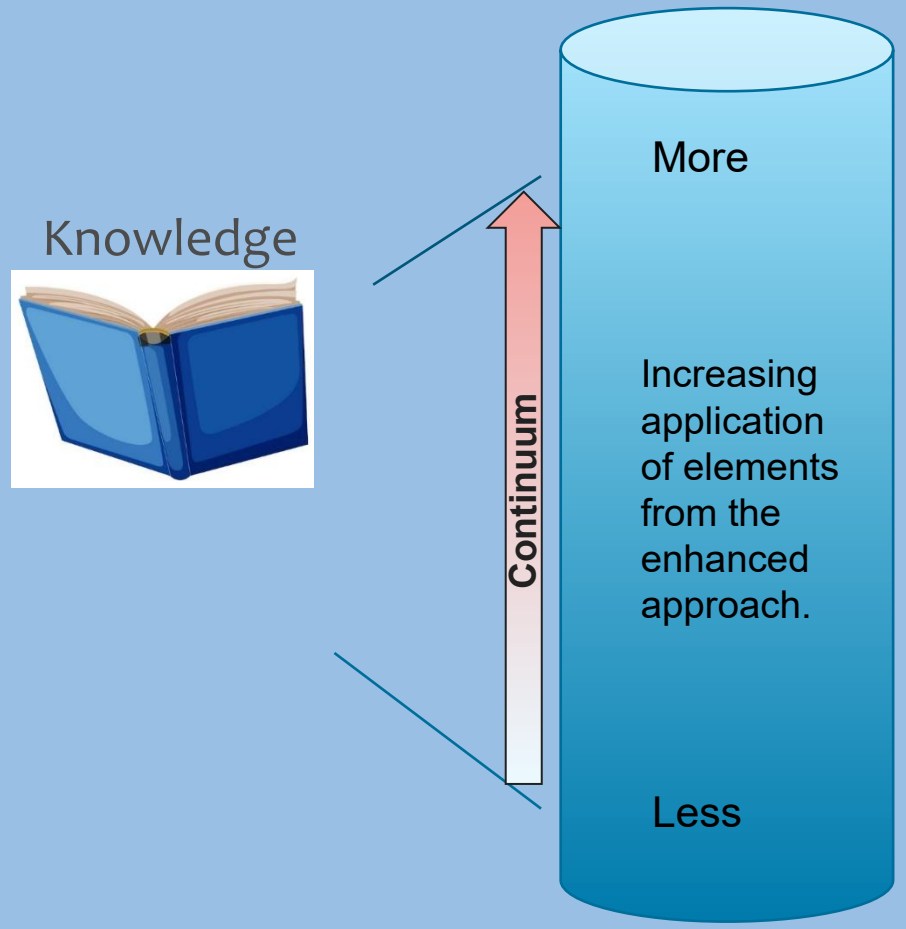


ICH Q14 - ANALYTICAL PROCEDURE DEVELOPMENT

ICH Q14 Guideline Objectives

- **Describes science and risk-based approaches for developing and maintaining analytical procedures fit for intended use**
- **Specifies minimal and enhanced approaches for analytical procedure development**
- Describes considerations for the development of multivariate analytical procedures for real time release testing (RTRT)
- Defines change management of analytical procedures based on risk management, analytical procedure understanding and predefined criteria for performance characteristics
- Includes submission considerations of analytical procedure development and related lifecycle information

Minimal vs 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.

ICH Q2(R2) / Q14 Training Module 4

Analytical Target Profile

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 ± 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.

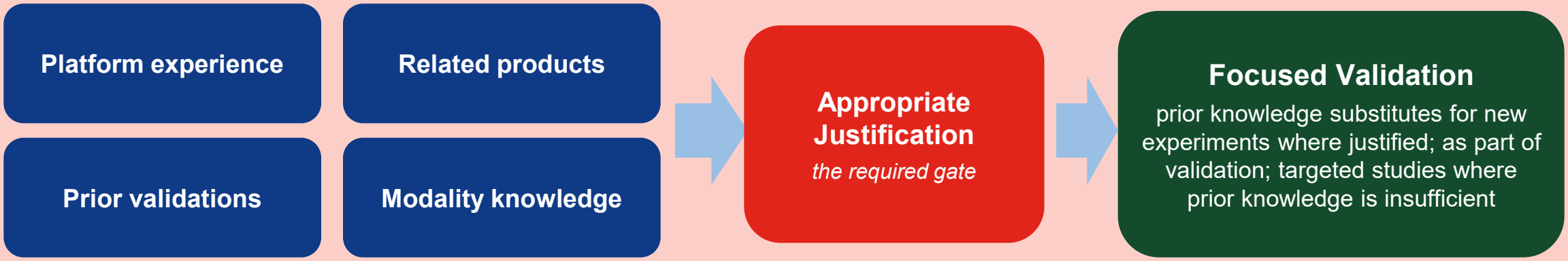
ICH Q2(R2) / Q14 Training Module 4

- *A predefined statement of what the procedure must measure and the quality required of the result — independent of the technology used.*
- *The anchor that defines the required performance*
- *Acceptance criteria for validation can be derived directly from the ATP — the same target, whatever the technology.*

Leveraging Prior Knowledge

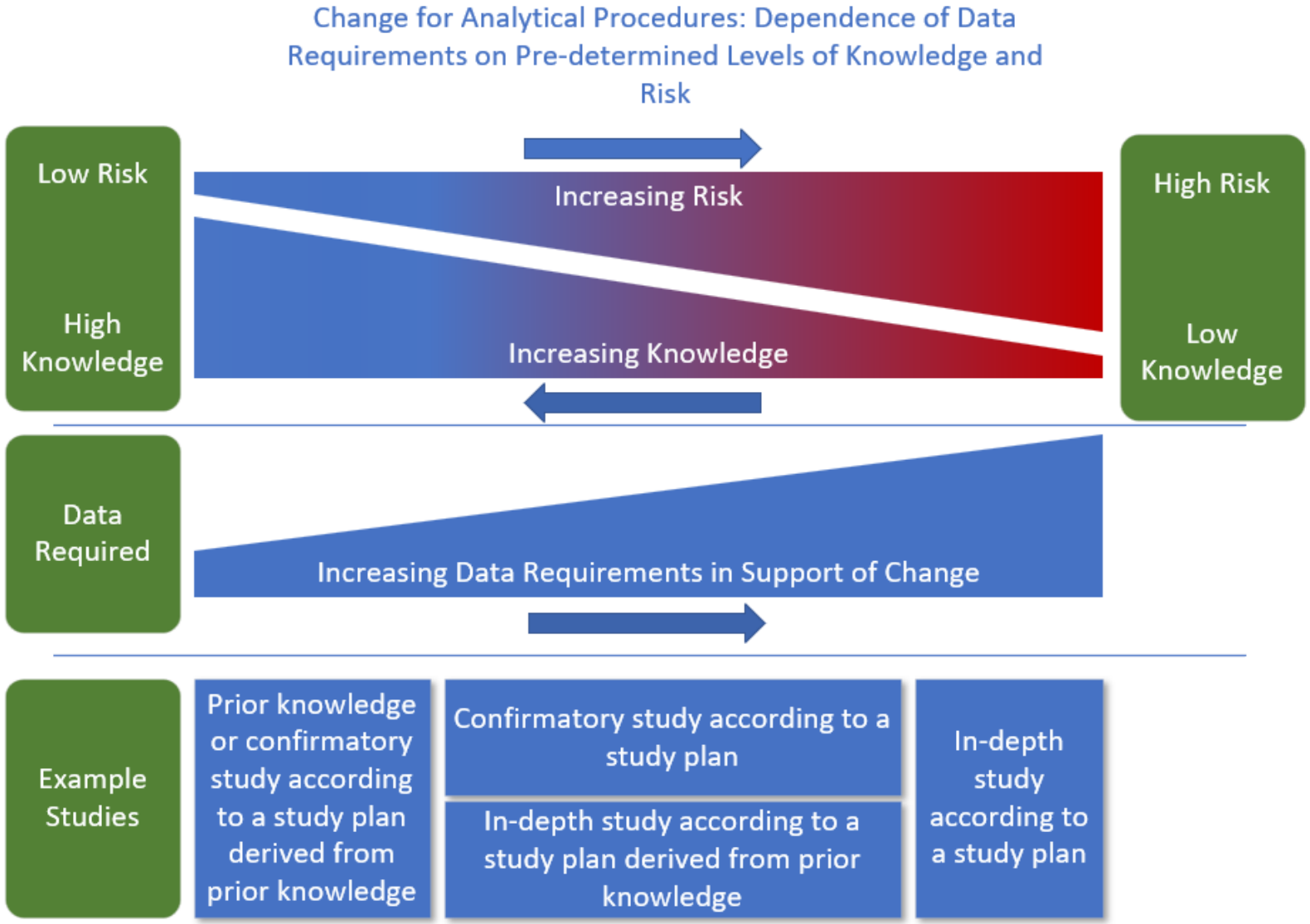
Knowledge from earlier work can reduce new experimentation — provided it is justified.

SOURCES OF PRIOR KNOWLEDGE



"Where prior knowledge is used, appropriate justification should be provided." — ICH Q14 / Q2(R2)

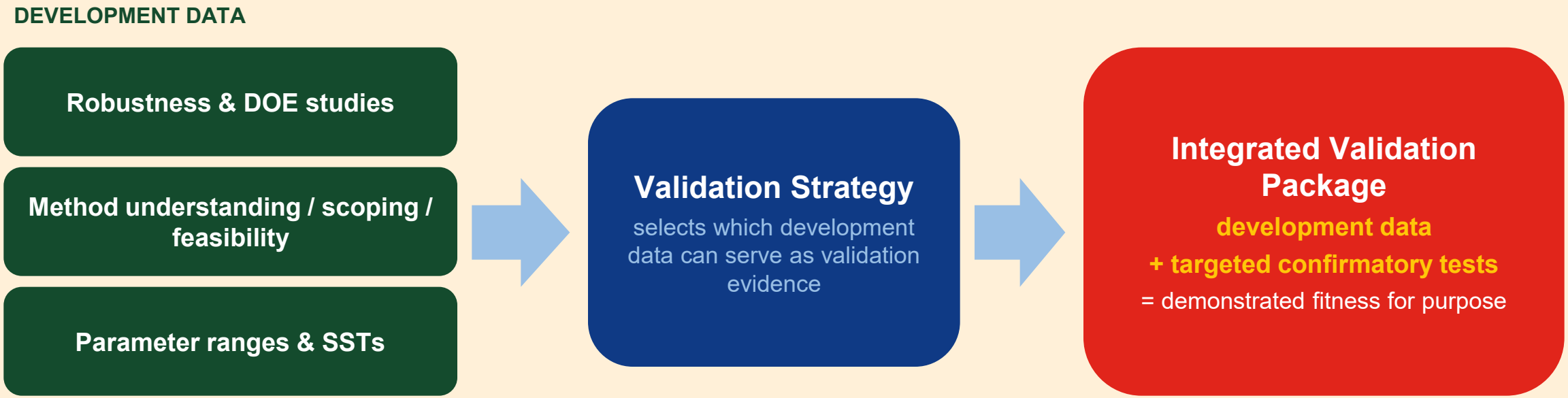
Risk Reduction with Prior Knowledge



- **Representation of the relationship between risk, prior knowledge and data requirements**
- **Exemplifies prior knowledge in support of 'change'**
- **Principle can be applied for use of prior knowledge in development / validation**

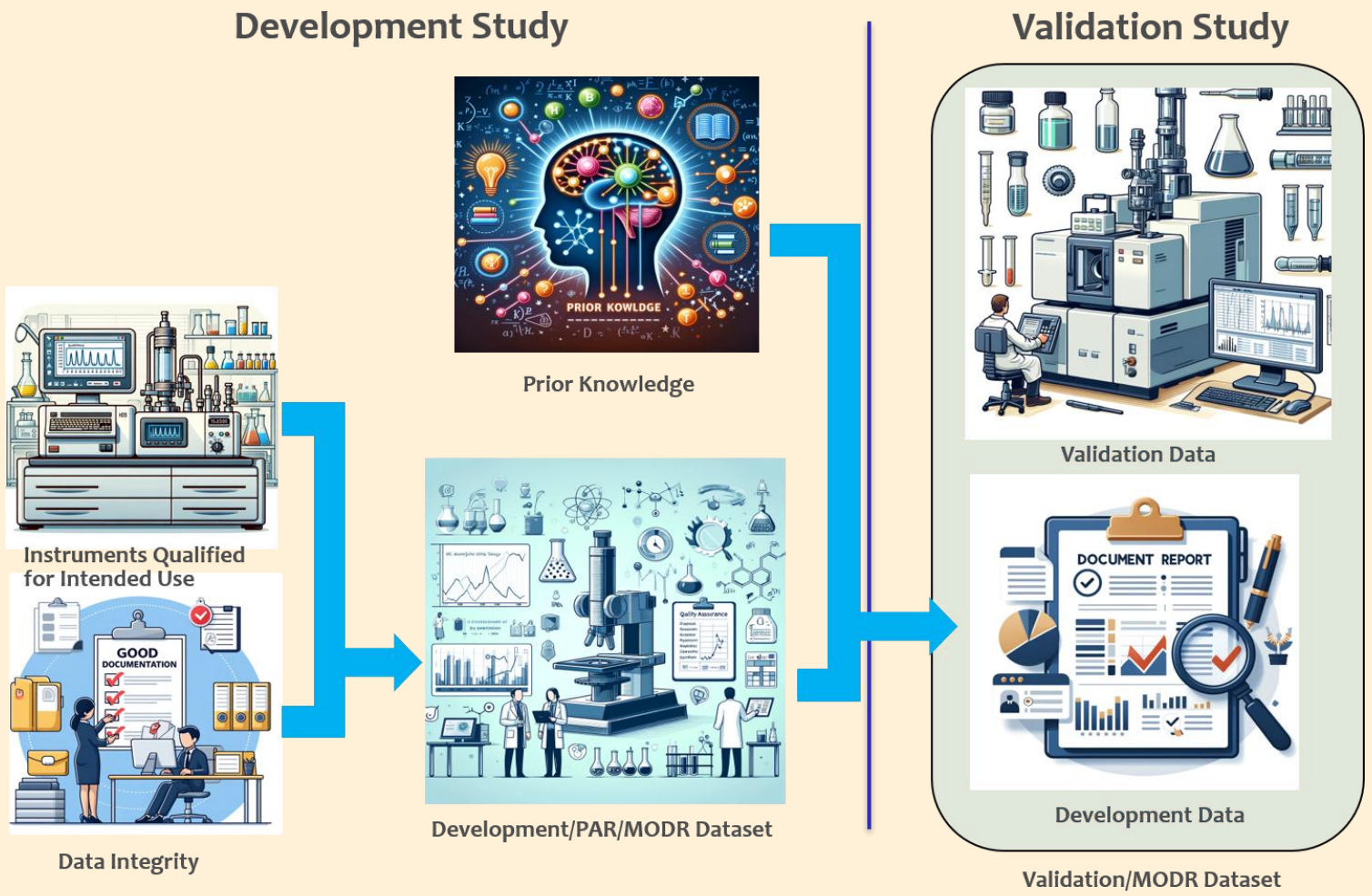
Use of Development Data in Validation

Suitable knowledge generated during development can contribute directly to the validation package.



"Suitable data derived from development studies can be used as part of validation data." — ICH Q2(R2)

Use of Development Data



Potential uses of development data :

- Selectivity and Specificity
- Linearity
- Lower Range Limit (DL/QL)
- Robustness
- Relative Response Factors
- System Suitability Testing (SST)
- Sample Stability

ICH Q2(R2) / Q14 Training Module 3

Development Data for Specificity

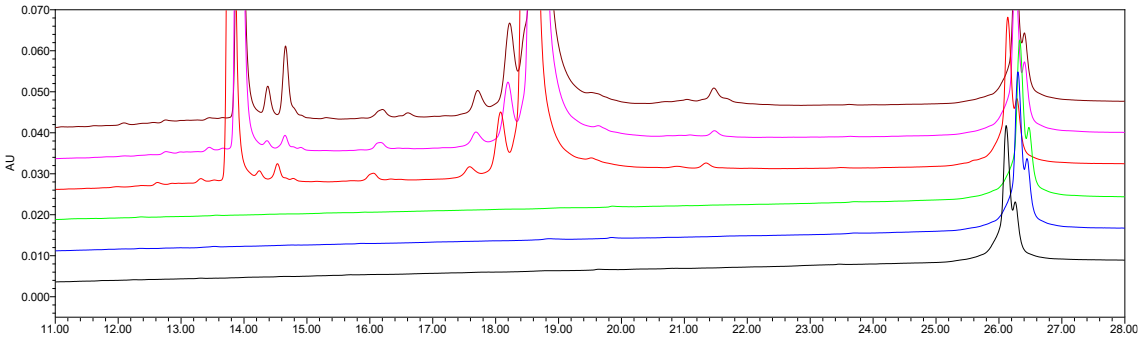
Purity and Identity by Sub-unit RP-HPLC

Validation Protocol: Specificity

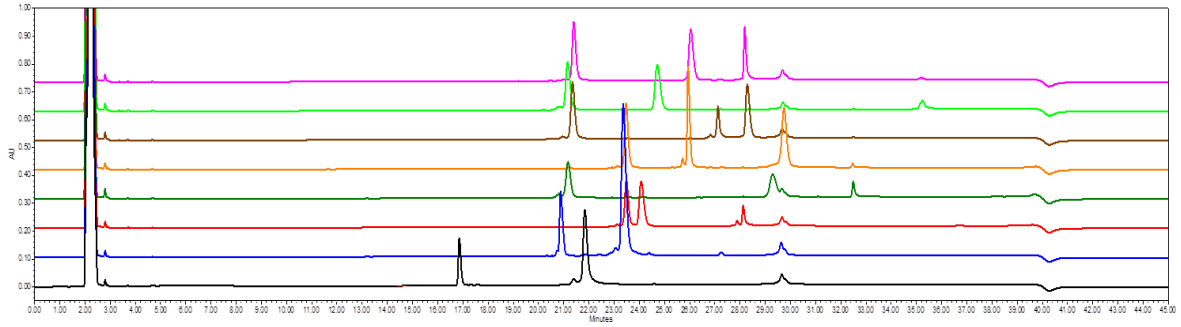
- Analyze DS & RS matrix components at their highest expected levels (no DS present; neat) and diluted similar to the DS (nominal assay concentration) or RS as appropriate.
- Analyze a DS at nominal assay concentration.
- Analyze a stressed DS at nominal assay concentration.
- Analyze reference standard at nominal assay concentration.
- Identity against portfolio molecules has been previously assessed and will be included in the final report.

Portfolio Identity:

- Analytical Development Laboratory
- Quality systems
- Qualified equipment
- Data integrity and traceability



Blank, matrix, RS, DS and stressed material analyzed as part of during validation exercise in full GMP laboratory.



Portfolio specificity previously assessed during development, included in validation report.

Development Data for Linearity

Purity by Reduced CE-SDS

Linearity across purity range:

Prepared at least five solutions in triplicate at the nominal protein concentration across the range expected. Prepared samples by co-mixing the typical (unstressed) representative (DS and/or DP) sample and a high impurity (DS and/or DP) (stressed) sample.

Linearity across the purity range has been previously evaluated in several phase appropriate qualifications. Due to the uniform charge to mass ratio of reduced and SDS-denatured Heavy chain, Light Chain, and fragmented species, sample load and separation of these species within the capillary is expected to be consistent across monoclonal antibodies. This consistency has been demonstrated through previous method phase appropriate qualification experiments by preparing at least five solutions in triplicate at the nominal protein concentration across the range expected using comixes of unstressed typical sample and a high impurities sample. Prior knowledge may be utilized as per International Council for Harmonisation (ICH) Q8, Q10, Q11, therefore, experiment execution is not required.

Linearity Acceptance Criteria:

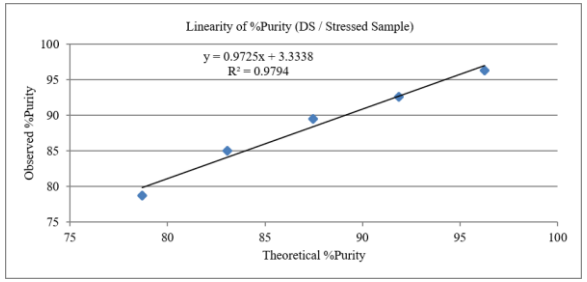
Width of Range	Criterion
6-8%	r ≥ 0.9300
8-12%	r ≥ 0.9500
12%+	r ≥ 0.9800

Qualification Data:

%Stressed	Average Observed %Purity	Theoretical %Purity	Average Observed %Total Fragments	Theoretical %Total Fragments
0%	96.2548	96.2548	1.4696	1.4696
25%	92.5641	91.8630	2.1972	2.6713
50%	89.5129	87.4712	3.0863	3.8730
75%	84.9873	83.0794	4.3033	5.0747
100%	78.6875	78.6875	6.2763	6.2763

Linear Regression:

	Drug Substance Reduced Purity	Drug Substance Total Fragments	Drug Product Reduced Purity	Drug Product Total Fragments
Range of Level (%)	(78.7% - 96.3%) Width of Range =18%	(1.5% - 6.3%) Width of Range = 5%	(77.2 – 96.1) Width of Range = 19%	(1.2% - 5.6%) Width of Range = 4%
R^2	0.9794	0.9579	0.9990	0.9970
r	0.9897	0.9787	0.9995	0.9985

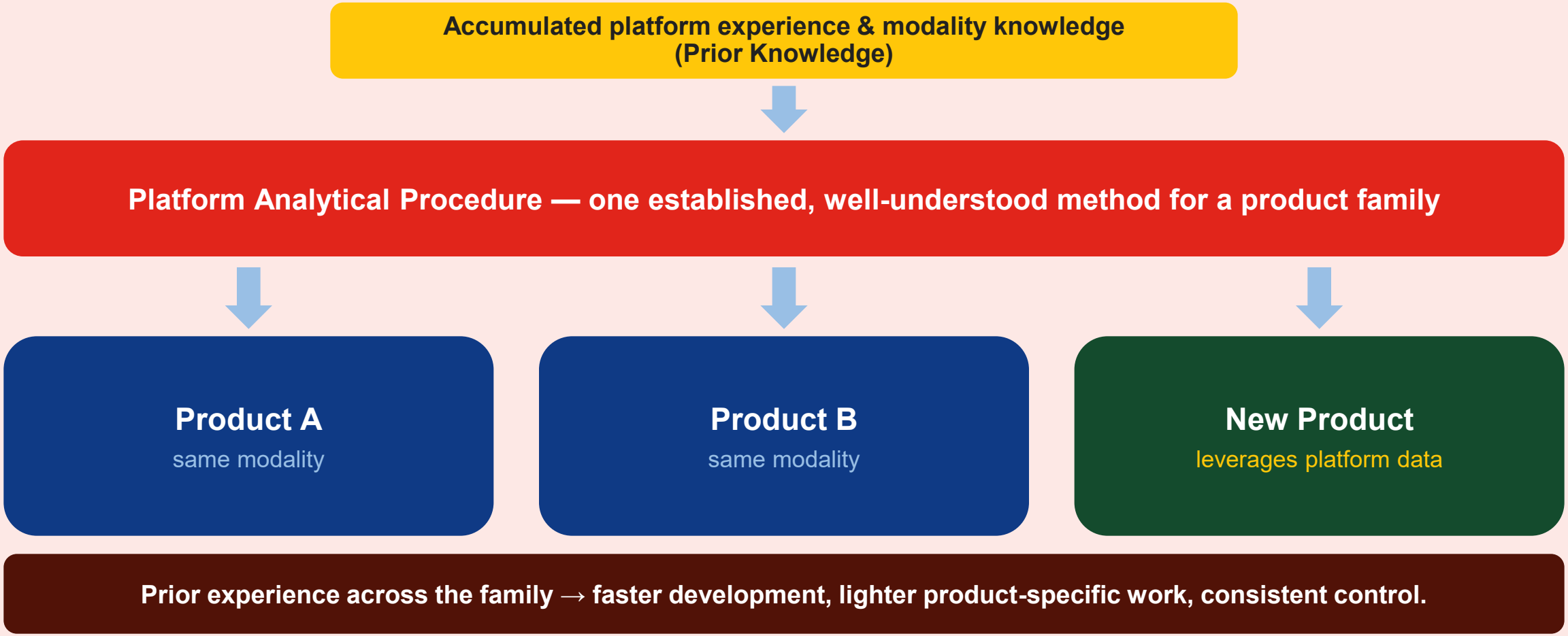


Prior knowledge:

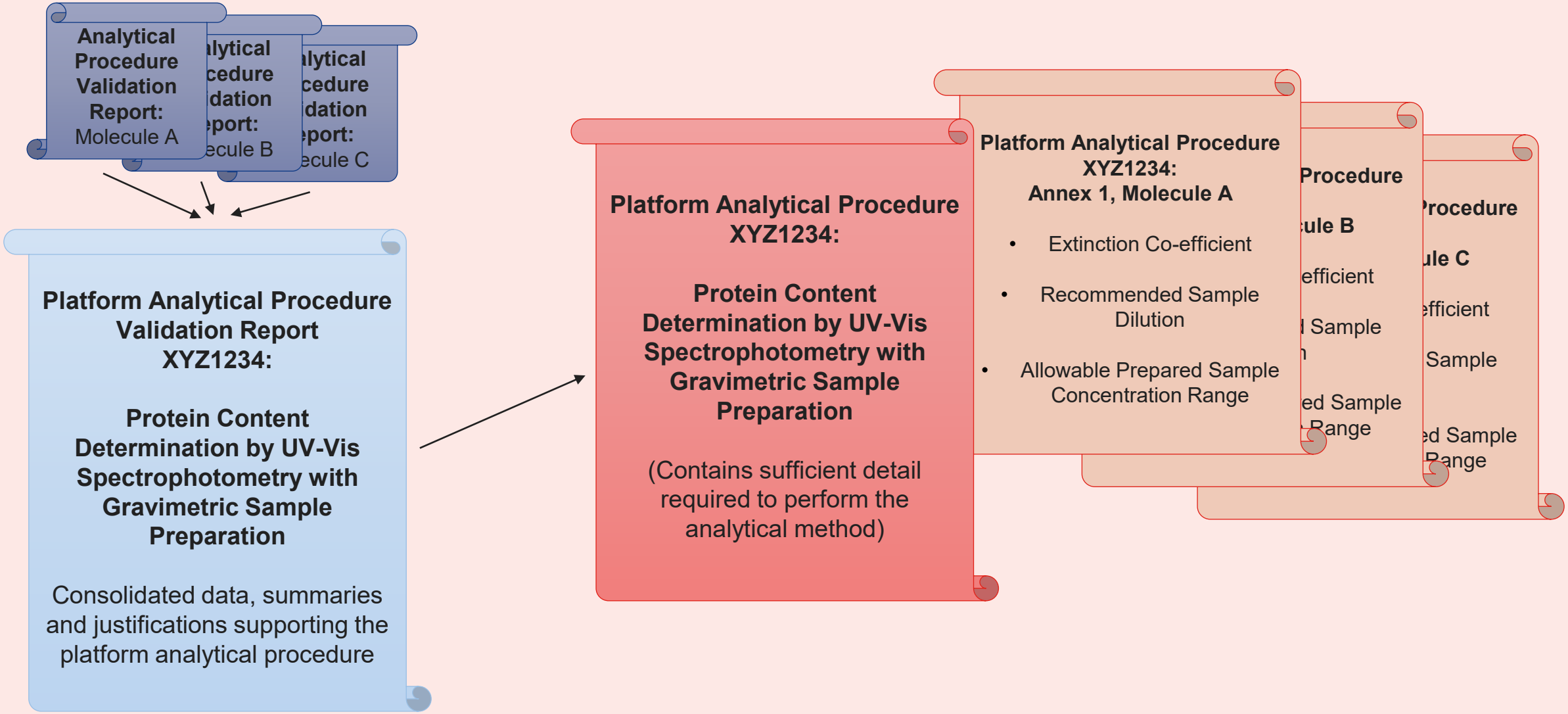
	Drug Substance Reduced Purity	Drug Substance Total Fragments	Drug Product Reduced Purity	Drug Product Total Fragments
Range of Level (%)	(77.2% -98.7%) Width of Range = 21.5%	(0.5% - 20.8%) Width of Range = 20.3%	(85.5% - 98.7%) Width of Range = 13.2%	(0.4% - 13.8%) Width of Range = 13.4%
r	0.9853 to 0.9999	0.9646 to 1.0000	0.9869 to 0.9996	0.9807 to 0.9996

Platform Analytical Procedures

An established, well-understood method applied across products of the same (or similar) modality — built on accumulated experience.

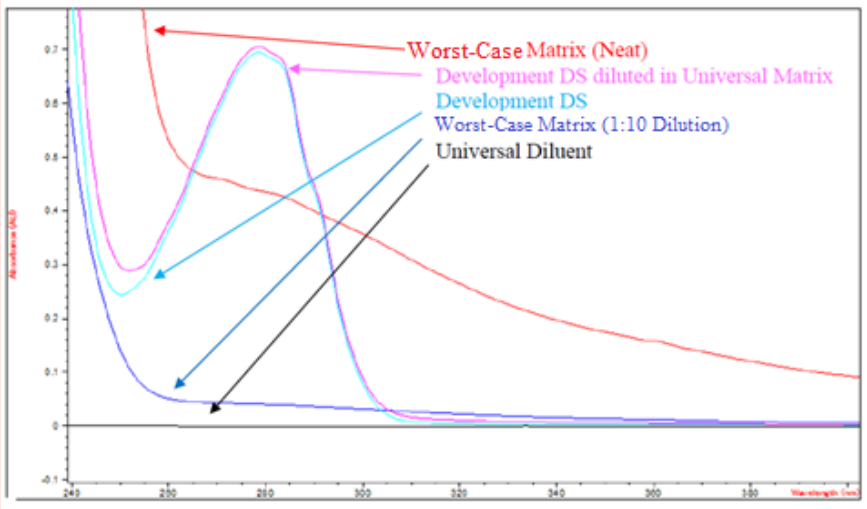


Platform Analytical Procedure Documentation



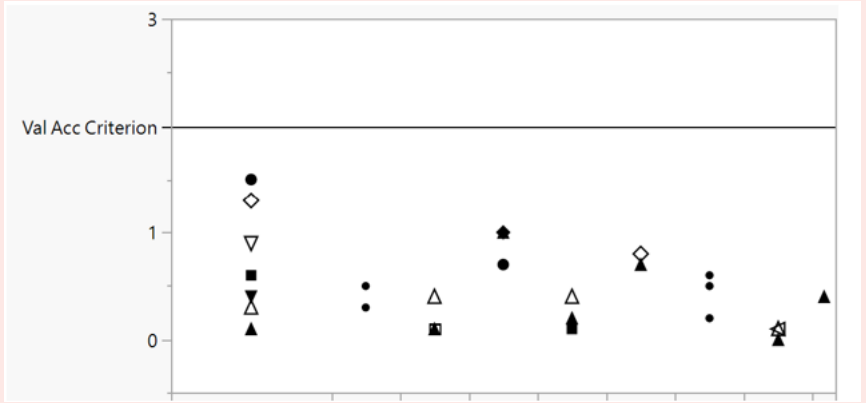
Support the Analytical Parameters with Data

- **Specificity**

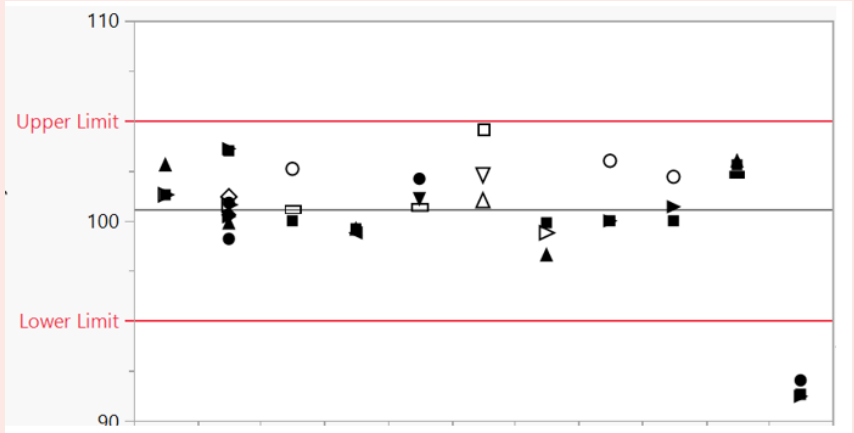


  - **Response**
    - Precision, Accuracy, Linearity
  - **Range**
    - Working range defined by absorbance linearity
    - Reportable range determined by dilution factors
  - **Diluent Stability**
    - Determined for Universal Diluent

- **Repeatability and Intermediate Precision**



- **Accuracy**



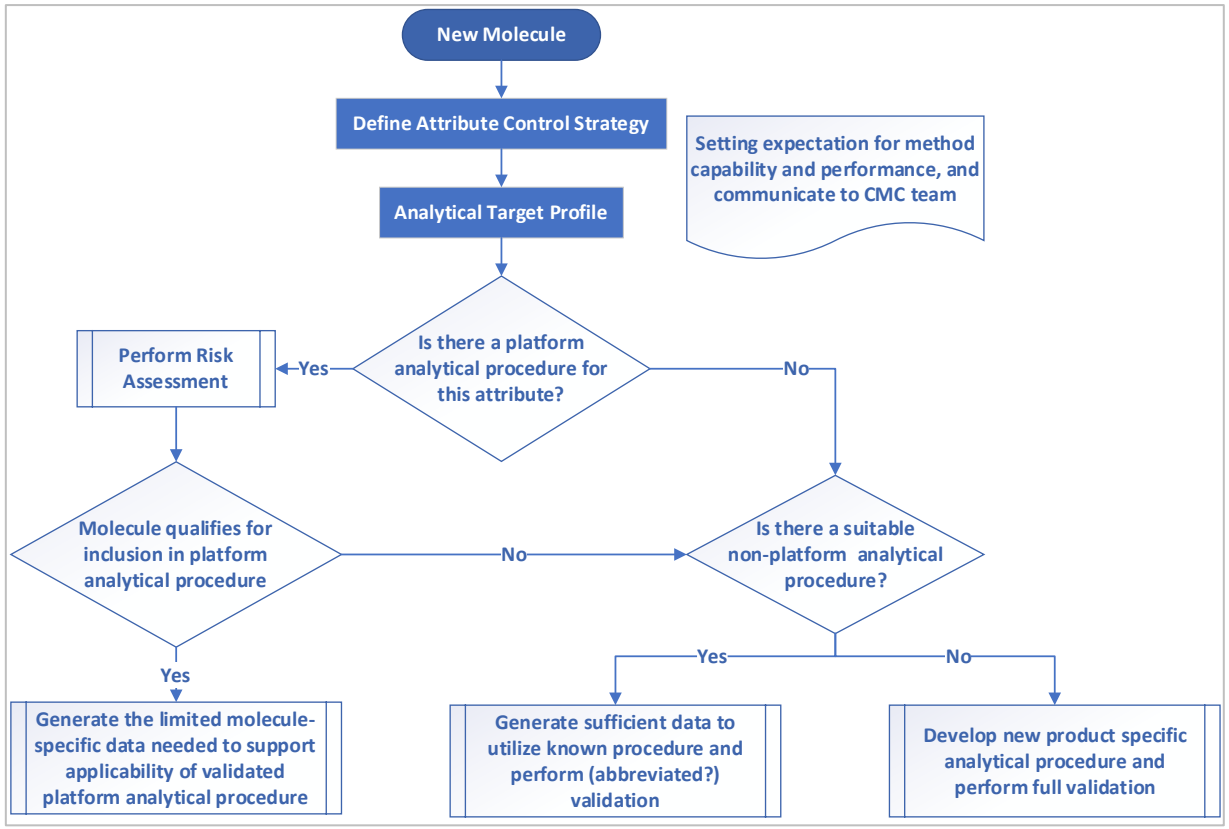
Extending to new Molecules

- Perform a risk assessment to confirm the applicability of the platform procedure conditions
  - e.g., addition of a low concentration formulation, resulting in inability to maintain minimum dilution factor→ additional specificity data needed

- Look at available data (e.g., from development) to confirm procedure performance
  - DS content at frozen conditions

- Confirm molecule specific activities
  - Extinction Co-efficient – determined in development
  - Specificity – data generated in development may be suitable
  - Sample Stability - data generated in development may be suitable

- Apply validated method to new molecule



Where Are We Now?

The possibilities are real — implementation is still being worked out.

What Q14 Enables

- Enhanced, science- and risk-based development
- Prior knowledge & development data as validation evidence
- Platform procedures across a product family

Open Questions

- How far can prior knowledge be leveraged?
- What rigour lets development data count as validation?
- Moving from guideline intent to practical use
- How will regulators respond in practice?

Greater scientific flexibility — while maintaining confidence in procedure performance, product quality, and regulatory acceptability.


Lilly