Commercial Submission Considerations for Platform Analytical Procedures

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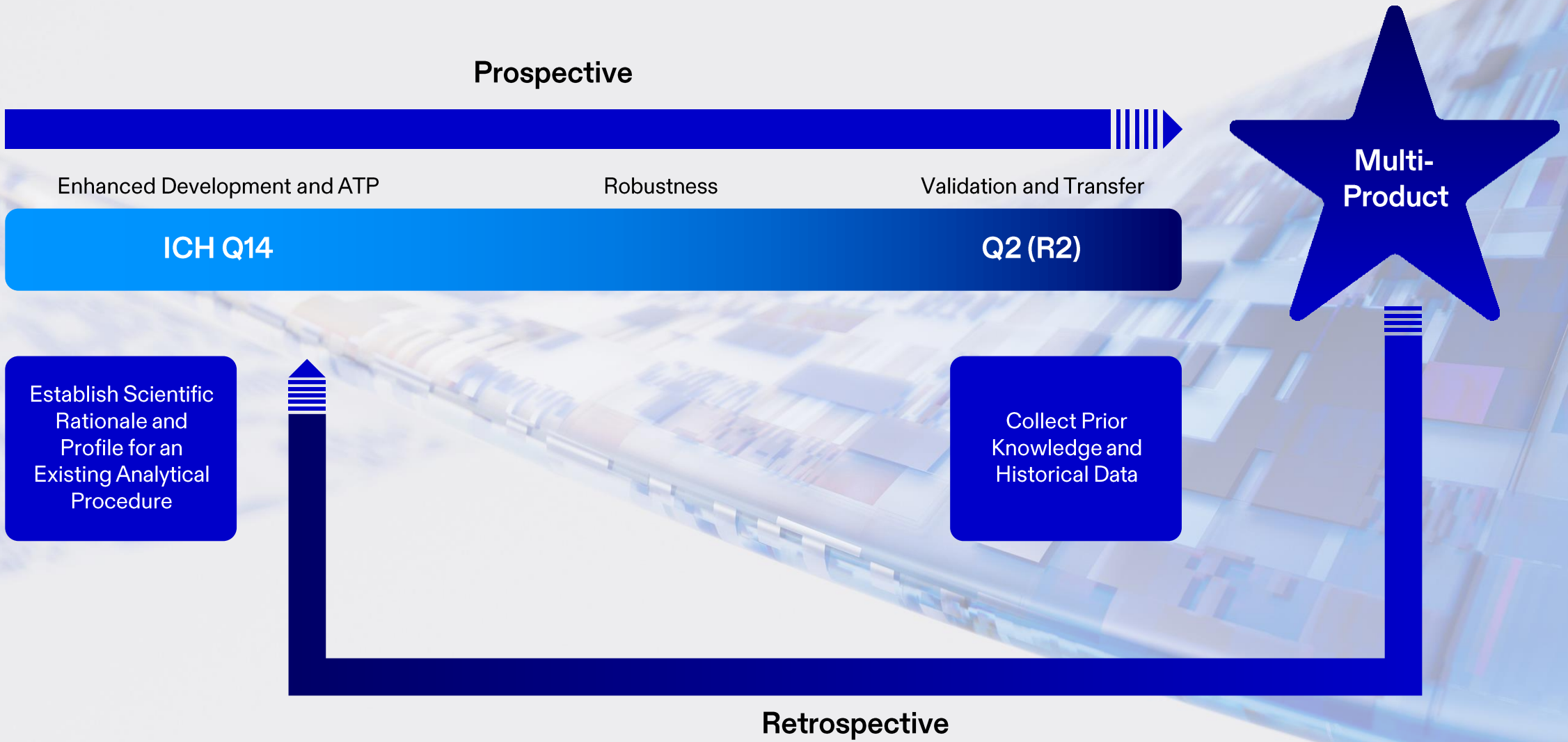
Platform Analytical Procedure Development Strategies



The Road Less Travelled...

Approval for a platform analytical procedure requires a large amount of highly subjective justifications vs the traditional approach which is well understood and readily accepted

Submission Content for Traditional Validation

Table 1: Typical Performance Characteristics and Related Validation Tests for Measured Quality Attributes

Measured Quality Attribute / Analytical Procedure Performance Characteristics to be Demonstrated (2)	Identity	Impurity (Purity) Other Quantitative Measurements (1)		Assay Content or Potency
		Quantitative Test	Limit Test	Other Quantitative Measurements (1)
Specificity (3)				
Specificity Test	+	+	+	+
Range				
Response (*Calibration Model*)	-	+	-	+
Lower Range Limit	-	QL†	DL	-
Accuracy (4)				
Accuracy Test	-	+	-	+
Precision (4)				
Repeatability Test	-	+	-	+
Intermediate Precision Test	-	+ (5)	-	+ (5)

ICH Q2(R2) Validation of Analytical Procedures Guidance for Industry; March 2024

Submission Content for Platform Analytical Procedure Validation

Retrospective

- Data
  - Historical or Prior Knowledge
  - Abbreviated Validation for new product
- Series of complicated justifications including:
  1. **Scientific rationale for why a technology is suitable for a platform**
  2. **Justification for acceptance criteria (to be used for new products) established from historical data**
  3. **Applicability assessment/Risk Assessment for application of platform to a new product**
  4. **Justification for abbreviated validation strategy**

Establishing the Platform Analytical Procedures

Analytical Procedures Targeted for Platform Strategy

Quality Attribute	Analytical Procedure
Protein Concentration	UV Spectroscopy
	Protein A HPLC (cell culture titer)
Charge Profile (Acidic, Main, and Basic Species)	Imaged Capillary Isoelectric Focusing (iCE)
Monomer and HMMS	Size Exclusion-HPLC (SE-HPLC)
Heavy Chain, Light Chain, and Fragments	Capillary Gel Electrophoresis (CGE, reducing)
Intact IgG and Fragments	Capillary Gel Electrophoresis (CGE, non-reducing)
Identity	Peptide Map
Host Cell Protein for DS testing only	HCP ELISA
N-Linked Glycan profile for DS testing only	Hydrophilic Interaction Liquid Chromatography

HMMS = high molecular mass species, **IgG** = immunoglobulin G, **UV** = ultraviolet, **HPLC** = high performance liquid chromatography; **ELISA**= enzyme-linked immunosorbent assay

Retrospective Platform Analytical Procedure Product Definition

- All products share a common immunoglobulin structure, similar absorption coefficients and formulations absent of ultraviolet (UV) interference, as well as similar molecular masses (145-149 kDa) and isoelectric points (pI 7.2-9.1), thus enabling the use of common analytical procedures for quality attribute testing
- All products have used the platform analytical procedures without significant changes to the method

Table 1. Example of a Historical Product Library Used to Establish the Analytical Platform

Product	mAb Isoform	Theoretical Mass (kDa)	Main Peak pI	DS Presentation	DP Presentation	Formulation
			Absorption Coefficient ($(mg/mL)^{-1} cm^{-1}$)	Storage Condition	Storage Condition	
Historical Products[a]						
mAb-1	IgG1	149	7.3	37.0-43.0	9.0-11.0	Platform
			1.39	-20±5 °C	5±3 °C	
mAb-2	Bispecific IgG2	148	8.4	38.4-48.0	36.0-44.0	Platform
			1.44	-20±5 °C	5±3 °C	
mAb-3	IgG4	149	7.3	142.0-180.0	135.0-165.0	Platform
			1.62	-40±10 °C	5±3 °C	
... through mAb-12						

a. mAb-1 through mAb-7 are authorized in the US and EU

UV Spectroscopy Method Established

Validation Historical Data compiled from 10 mAb's

Validation Characteristic	Historical Data Summary	Proposed Platform Validation Acceptance Criteria
System Repeatability	RSD: 0.9%	RSD ≤ 3.0%
Method Repeatability	RSD: 1.6%	RSD ≤ 3.0%
Intermediate Precision	RSD: 2.2%	RSD ≤ 5.0%
Reproducibility	RSD: 2.3%	RSD ≤ 5.0%
Accuracy	Accuracy = 102.1%	Accuracy = 100 ± 6%
Specificity	Met Criteria	No response (i.e., slope ≤ 0.1 at 280 nm) is obtained in the formulation buffer while the target sample yields a positive response (i.e., slope > 0.1 at 280 nm)
Linearity	Method is linear over the concentration range (mg/mL) aligned with the molecule's specific absorptivity coefficient $(mg/ml)^{-1} cm^{-1}$	Response factor (RF) plot shows all points within ± 5% of the average RF
		Data on the linearity plot appears linear by visual inspection
Range	The validated range of the method (mg/mL) is aligned with the molecule's specific absorptivity coefficient $(mg/ml)^{-1} cm^{-1}$	Range supports specification acceptance criteria

2

Critical Operating Parameters Established

Molecule's Specific Absorption Coefficient, Pathlength

Scientific Rationale

1

The ultraviolet absorbance of a protein solution is due to the absorption properties of the aromatic amino acid residues in the protein molecule. According to the Beer-Lambert Law, the concentration of a protein solution is calculated based on the absorbance at a given wavelength, the cuvette cell path length, and the established specific absorption coefficient. The mAb molecules developed share a narrow range of absorption coefficients and formulations absent of UV interference. Therefore, it is feasible to apply the same experimental conditions, pathlength range for variable pathlength or working protein concentration for fixed pathlength, for all the molecules of interest. As a result, the methods can be used from one molecule to another without significant changes to critical method parameters and conditions.

SE-HPLC Method Established

Validation Historical Data compiled from 10 mAb's

Validation Characteristic	Historical Data Summary	Proposed Platform Validation Acceptance Criteria
Intermediate Precision	HMMS RSD: 7.25%	HMMS RSD ≤10.0%
Reproducibility	HMMS RSD: 8.9%	HMMS RSD ≤15.0%
Accuracy	HMMS Accuracy = 106.8%	HMMS Accuracy = 100±10%
Specificity	Met Criteria	No response > 0.5% (from the reference material) is obtained in the formulation buffer
Linearity	Method is linear over the range of 0.2-12.5% HMMS	Response factor (RF) plot for HMMS shows all points within ± 20% of the average RF Data on the linearity plot appears linear by visual inspection
Detection Limit (DL)	0.2 % HMMS	The lowest sample peak area having an s/n ≥ 3
Quantitation Limit (QL)	0.2 % HMMS	The lowest sample peak area having an s/n ≥10
Range	0.2-12.5% HMMS, adjusted based on QL from verification	HMMS = 1% HMMS to approximately 120% of the upper specification limit for %HMMS

2

Critical Operating Parameters Established

Column, Mobile Phase, Flow Rate, Sample Preparation, Injection Volume, Column Temperature

Scientific Rationale

1

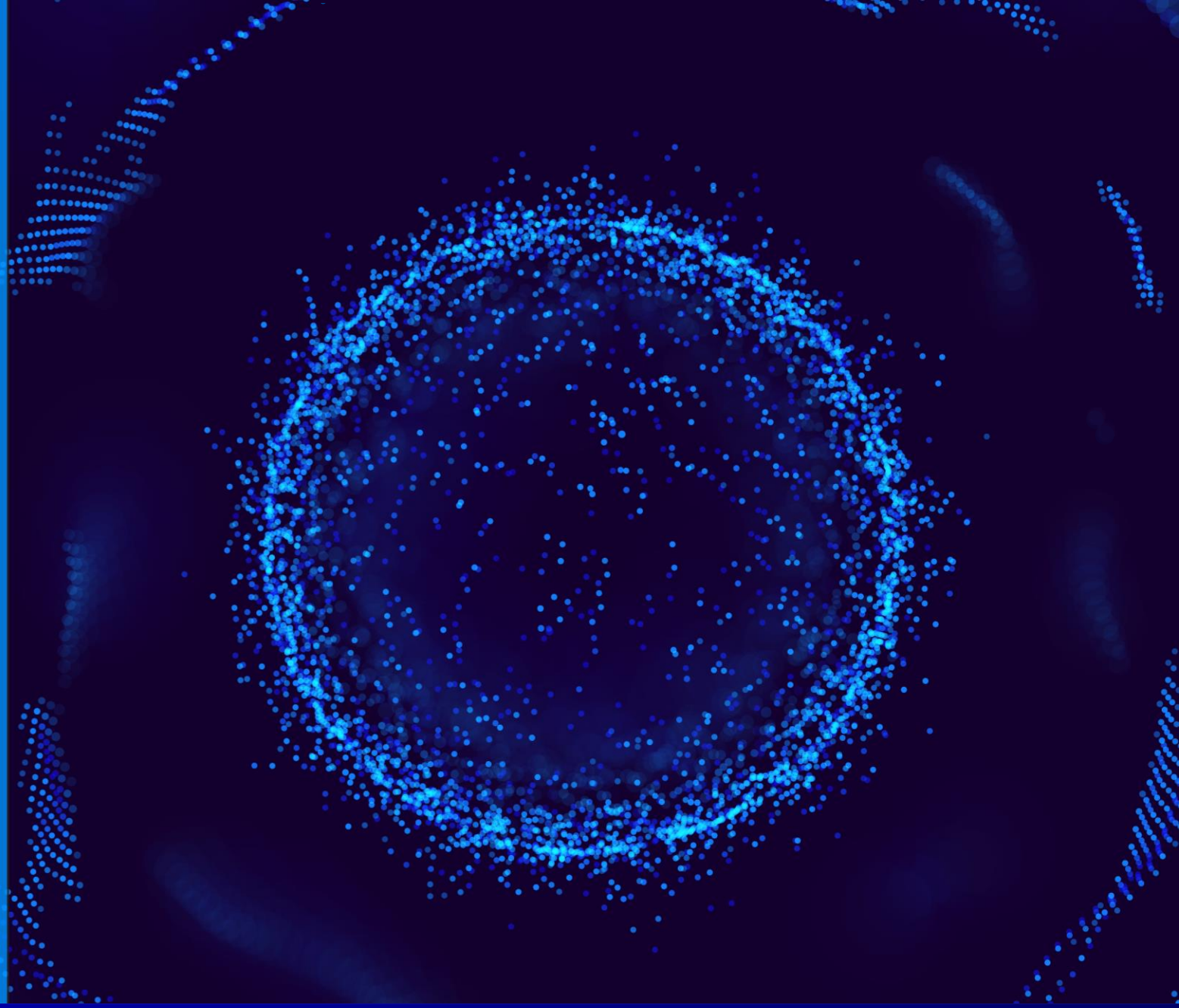
Method uses a X column designed to enable the fractionation of protein species between X,000 and X00,000 Da. Detection is based on UV absorbance at 280 nm with the working protein concentration being the same across products, the absorbances of the mAb molecules of interest are confined in a tight range resulting in consistent method sensitivity. As a result, the method can be used from one molecule to another without significant changes to critical method parameters and conditions. The capability of method to robustly resolve HMMS from monomeric species for mAbs and mAb-like products has been demonstrated through the validation data summarized.

Documentation to Establish Platform Analytical Procedures

Large investment up front to create this documentation but it is completed once and intended to support all products using the mAb platform analytical procedures

Document	Purpose	Documentation Use in Commercial Submission
White Paper	High level overarching strategic document to gain strategy alignment across stakeholders, includes the historical product library	Historical product library and overall strategy described in S.4.3 Overview
Justification/Scientific Rationale	Multi-method justification for platform use, focused from a CQA perspective	Used in summary of method establishment in S.2.6 Evolution of Methods
Technical Assessment	Contains summary and references for transfers and validations at commercial testing sites	Supportive to S.4.3 and P.5.3
Platform Validation Workbooks Method Specific	Excel workbooks with all the historical data from validations (one per method)	Submit in Regional to FDA, if asked
Platform Validation Summary Report – method specific	Summary of scientific rationale, platform validation criteria, results and qualified commercial testing sites (one per method)	Reports Submitted in S.4.3 and/or P.5.3
Method Development History	Contains summary and references for robustness and critical method operating parameters	Summary showing enhanced development needed in S.2.6 Evolution of Methods

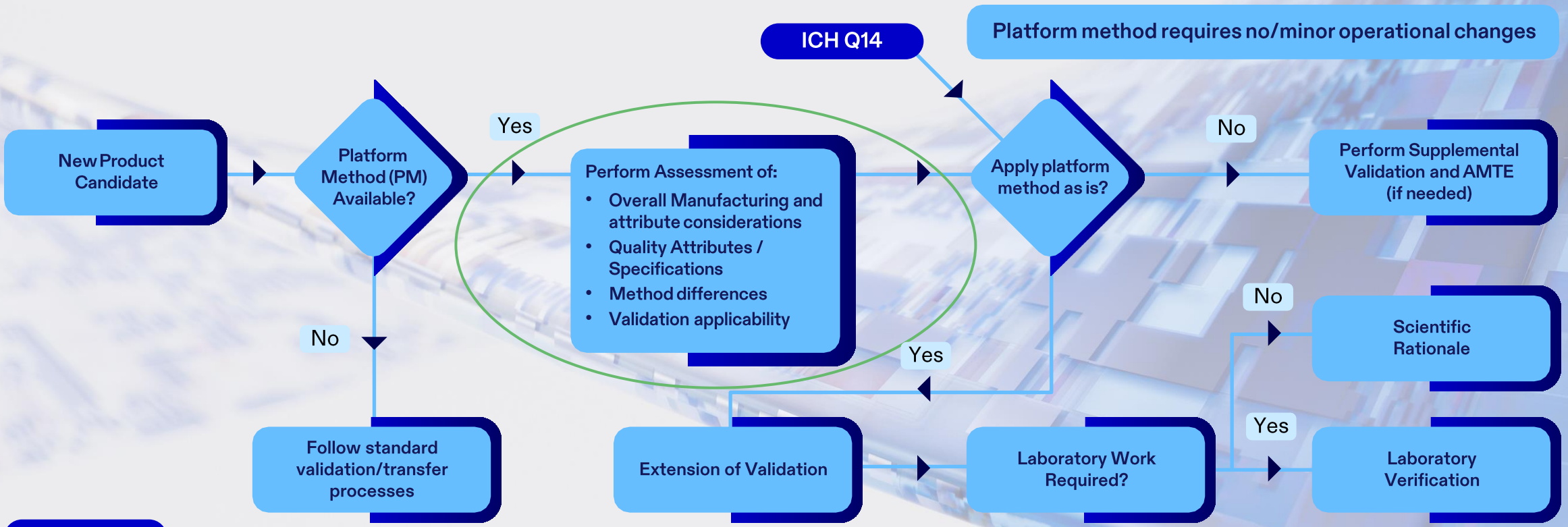
Application Of Platform to a New Product



Late-Stage Validation Strategy Flow Chart

New Term

Extension of Validation ⟷ **Extend Platform Validation to New Candidate**



ICH Q14

"Prior product knowledge plays an important role in identifying the appropriate analytical technique. Knowledge of best practices and current state-of-the-art technologies as well as current regulatory expectations contributes to the selection of the most suitable technology for a given purpose. Existing platform analytical procedures (e.g., protein content determination by UV spectroscopy for a protein drug) can be leveraged to evaluate the attributes of a specific product without conducting additional procedure development."

Industry Perspectives on Practical Application of Platform Analytical Procedures. ***Pharmaceutical Engineering, September/October 2024***, 44, Number 5

Applicability Assessment 3

- Analytical procedure has same intended purpose
- Analytical procedure used without any significant changes
- Analytical procedure evaluations during clinical development align with platform acceptance criteria
- Comparison to historical library
- Assessment of proposed commercial sites
- Formulation Buffer
- Assessment of proposed commercial specification against prior knowledge for each analytical procedure

New mAb Product

IgG1, platform formulation + new excipient,
148 kDa, pI 7.4, absorption coefficient 1.55,
DS 148-185 mg/mL, DP 139-169 mg/mL

Document in S.4.3 and P.5.3

Most complex of all justifications/risk assessment

Applicability Assessment for UV Spectroscopy

Method is Validated and Established as Platform

- √ Validation Summary
- √ Scientific Rationale
- √ Prior knowledge
- √ Critical Method Parameters
- √ Robustness

New mAb/-alike Product Applicability Assessment

- ✔ Same intended purpose to measure concentration
- ✔ Proposed commercial specification covered by historical validation
- ✔ No critical changes to the procedure

Assessment of validation applicability

Retrospective Analysis of early method evaluation

Extension of Validation – Scientific Rationale

Assess Against Product Library

- Formulation absent of UV interference
- Specific absorption coefficient determined in the range of previously validated mAbs
- Proposed commercial sites were previously qualified through co-validation or transfer

ICH Parameters Evaluated	Results	Platform Validation Acceptance Criteria Applied Retrospectively
Precision (Method)	0.8% 0.9%	Variable Pathlength RSD ≤3.0% Fixed Pathlength RSD ≤5.0%
Specificity Variable Pathlength Fixed Pathlength	0.00070 ≤0.02 at 280 nm	No response (i.e., slope ≤0.1 at 280 nm) is obtained in the formulation buffer while the target sample yields a positive response (i.e., slope > 0.1 at 280 nm)

Applicability Assessment for SE-HPLC (HMMS)

Method is Validated & Established as Platform

Validation Summary

- √ Scientific Rationale
- √ Prior knowledge
- √ Critical Method Parameters
- √ Robustness

New mAb/-alike Product Applicability Assessment

- ✔ Same intended purpose to measure HMMS
- ✔ Proposed commercial specification covered by historical validation range of 0.2 - 12.5%
- ✔ No critical changes to the procedure

Assessment of validation applicability

Retrospective Analysis of early method evaluation

4

Extension of Validation – Laboratory Verification

Conduct Precision and Accuracy at the Commercial Testing Site to Confirm Expected Results

Predefined acceptance criteria

Protocol

Report

Assess Against Product Library

- No measurable interference from the formulation
- Mass of product falls within the historical product range validated with this column
- Proposed commercial sites were previously qualified through co-validation or transfer

ICH Parameters Evaluated	Results	Platform Validation Acceptance Criteria Applied Retrospectively
Precision (Method)	0.00%	RSD ≤10.0%
Specificity	No peaks observed between 8-14.5 min	No response > 0.5% (from the reference material) is obtained in the formulation buffer
QL	Confirmed peak response above assay baseline for sample prepared at QL	The lowest sample peak area having an s/n ≥10
Prepared Sample Stability	Samples are stable for 24 hr at 2-8C	The minimum stability of the prepared sample for HMMS must be not less than (NLT) 24 hours

Summary and Conclusions

Strategy has been refined over the past year from lessons learned during implementation and from engagement with Health Authorities

Progress & Lessons Learned

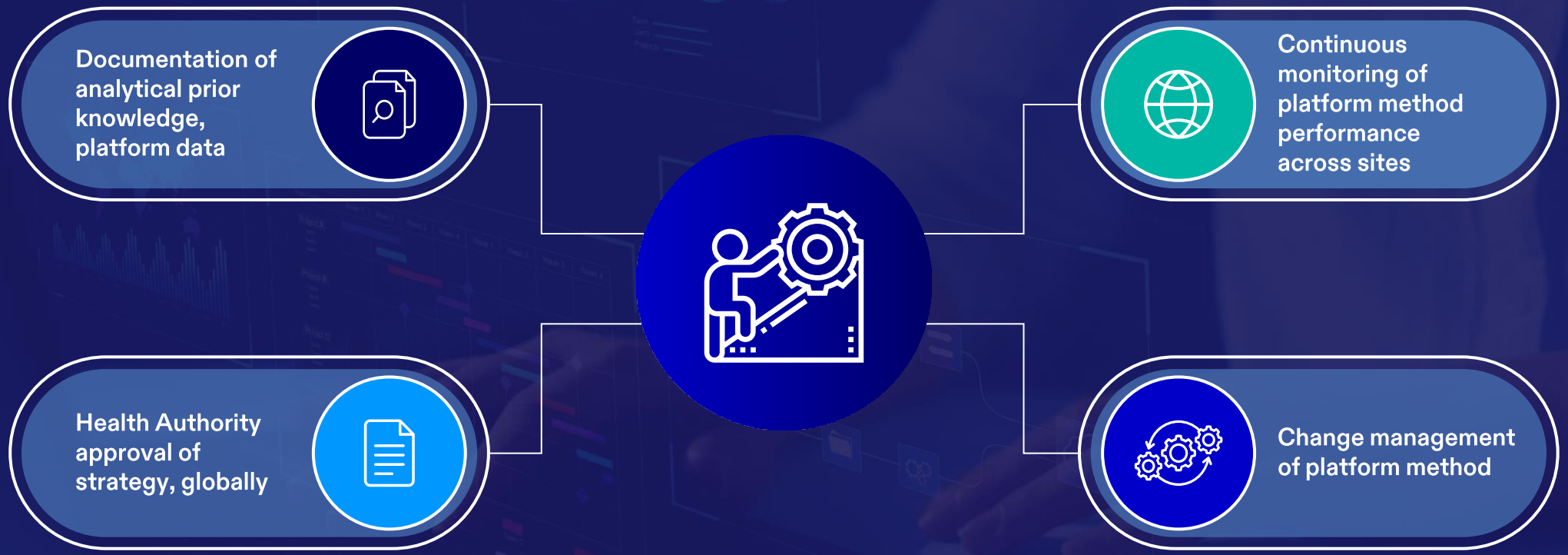
1. In Health Authority engagement the overall approach for abbreviated validation was generally acceptable
2. Accepted that protein concentration by UV spectroscopy can use extension of validation by scientific rationale
3. Historical data from reproducibility or transfers to commercial sites shows the site is qualified to test the platform analytical procedure but agreed any abbreviated validation testing should be conducted at the intended commercial test site
4. Better definition of historical mAb products required in submission

Areas for Further Discussion

1. Acceptance Criteria generated from historical data analysis
2. Justification and agreement on parameters challenged in abbreviated validation

Need continued discussions to establish a smoother, more predictable path!

Key Challenges



Thank You

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