Leveraging Prior Knowledge for Practical Application of Platform Analytical Procedures in Late-Stage Development of Monoclonal Antibodies

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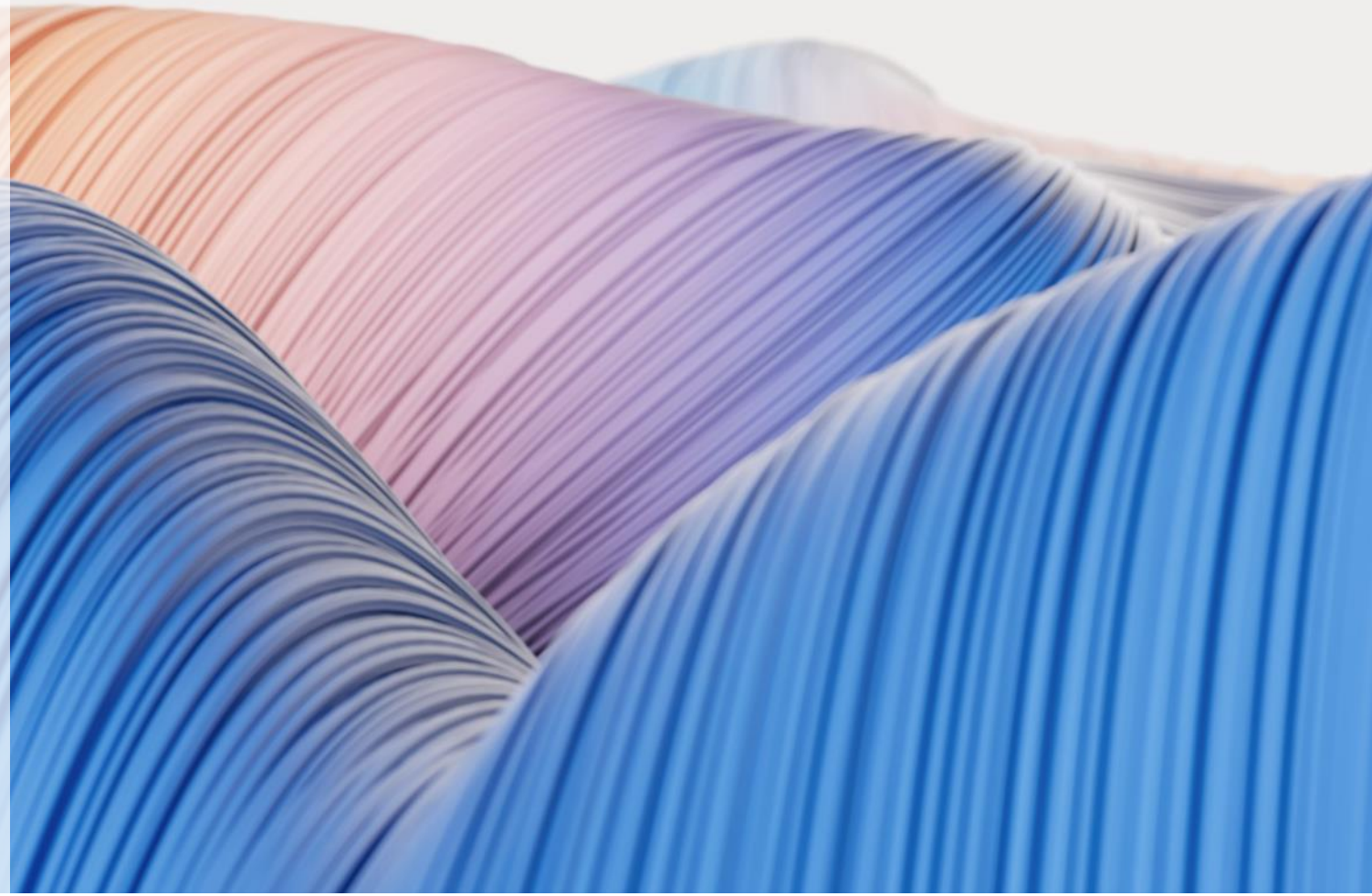
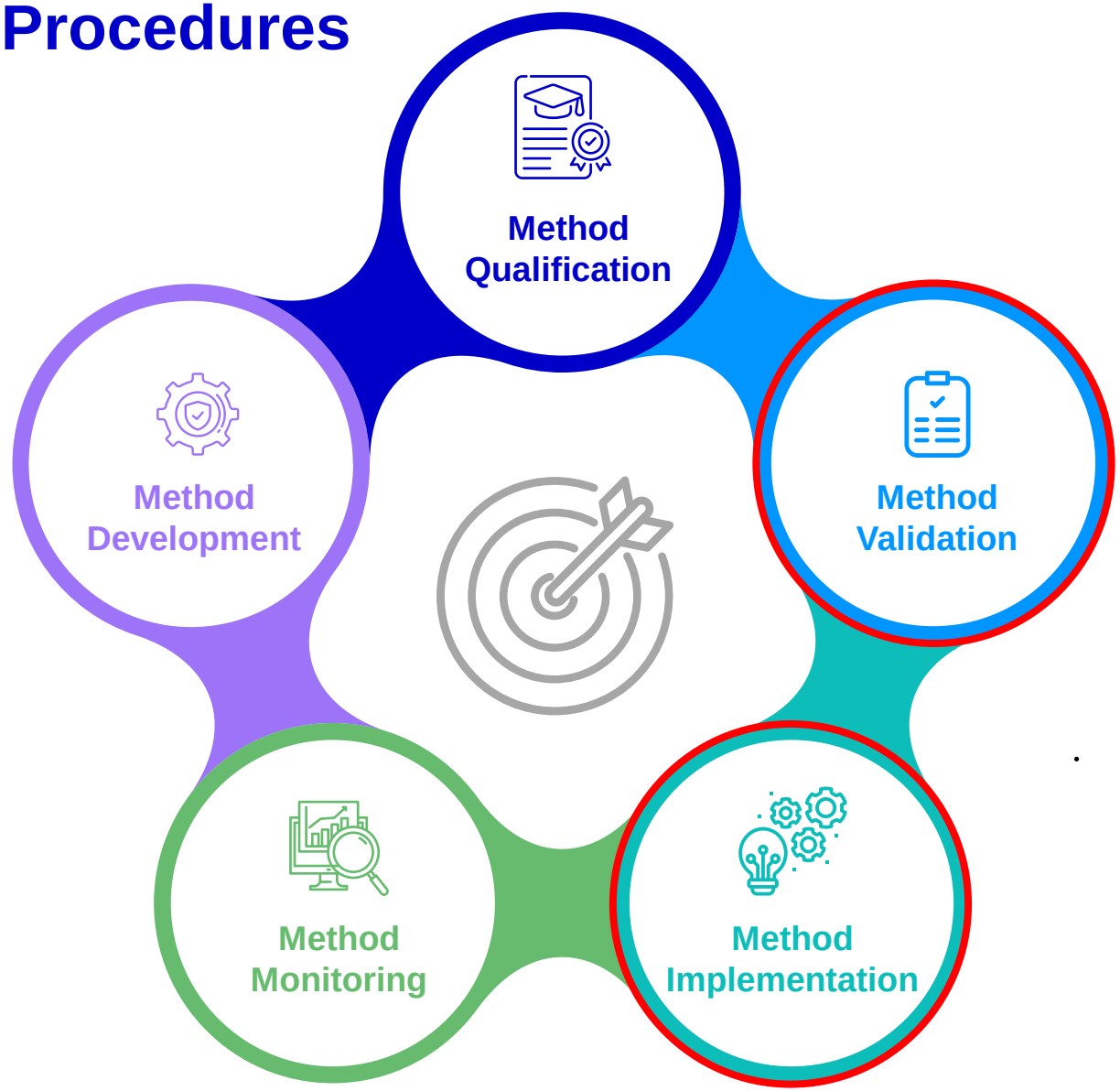


Outline

1. Platform Analytical Validation Strategy Overview
2. Practical Application to mRNA Programs
3. Expanding to mAb
4. Late-Stage Practical Applications to mAb Programs
5. Benefits & Key Challenges
6. Regulatory Strategy

Analytical Procedures Lifecycle



What is Platform Analytical Procedure?

ICH Q2 (R2) Guidance, Implementation Phase 4

From Introduction...

"When an established platform analytical procedure is used for a new purpose, validation testing can be abbreviated, if scientifically justified."

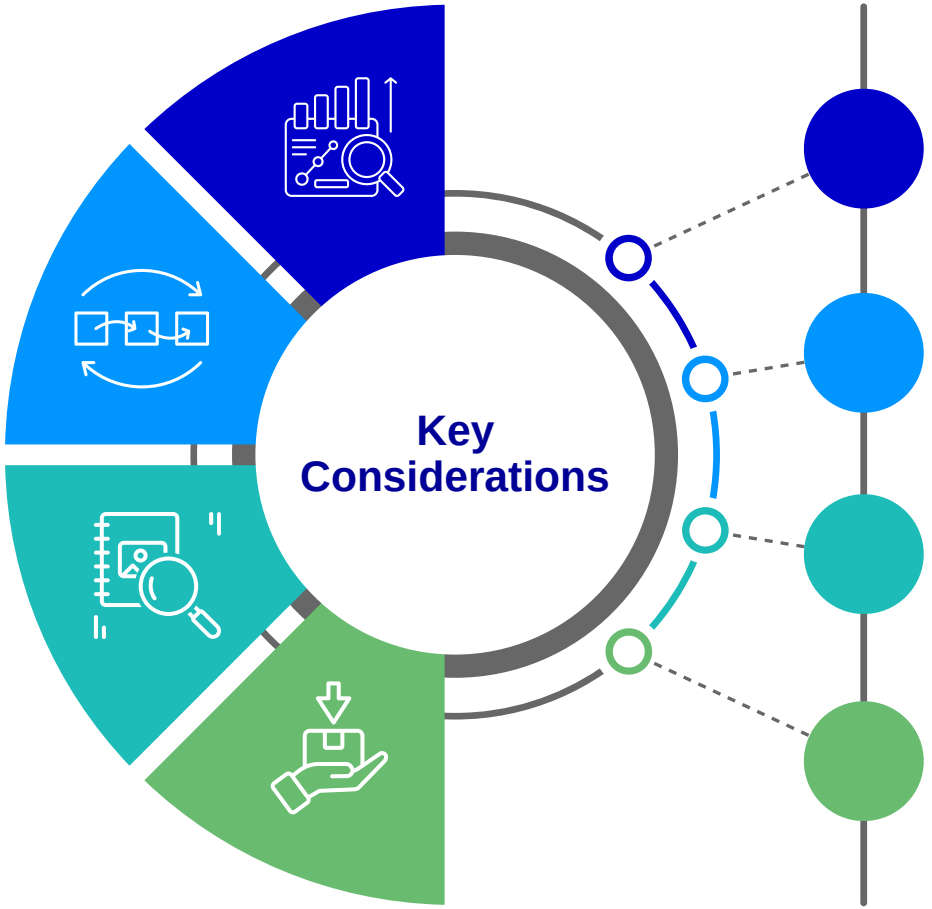
From Glossary Definitions: Platform Analytical Procedure

A platform analytical procedure can be defined as a multi-product method suitable to test quality attributes of different products without significant change to its operational conditions, system suitability, and reporting structure. This type of method would apply to molecules that are sufficiently alike with respect to the attributes that the platform method is intended to measure.

WHO/BS/2023.2442

"A platform would be considered when the elements of the manufacturing methods and/or processes, the mAb protein scaffold, and the compliance with GMP are unchanged. The experience and knowledge gained, data generated (from manufacturing, control, and stability), and the validation of unchanged methods can all be used as supportive data for the more rapid assessment and development of a new mAb product candidate that fits within the boundaries of the platform."

Late-Stage Platform Procedure Validation Primary Key Considerations



Analytical procedures must be shown to fit for its intended purpose

Establishment of platform

Prior knowledge / historical platform validation data

Receiving laboratory experience

Method Validation

Method Implementation

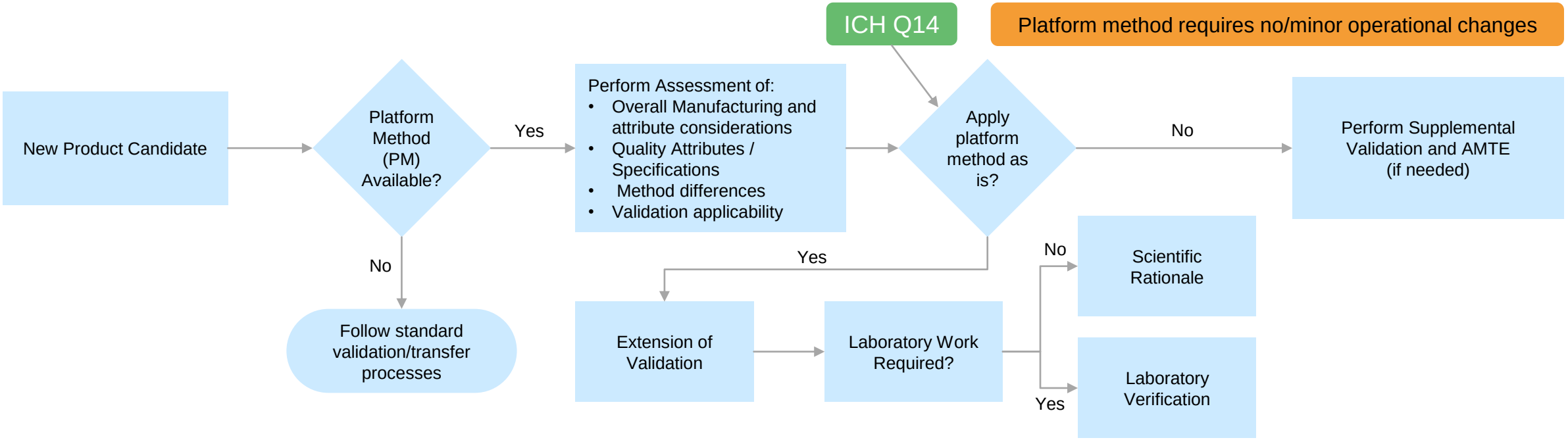
Platforming Strategy Benefits

- **Enable rapid analytical support for new products**
- **Focus on right key deliverables and avoid redundant activities**
- **Brings more consistency across modalities**
- **Cross Site rapid tech transfers**
- **Rapid commercial and BLA submission readiness**
- **Streamline regulatory agency review process**

Implementation of platforming strategy across the industry will strengthen the strategy applications across different modalities

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."

Example of Platform Application: Successfully Implemented for mRNA Vaccine

New mRNA Variant

Applicability Assessment

- Manufacturing process
- Quality attributes
- Platform method operating parameters/differences
- Validation applicability

Extension of Validation

UV Spectroscopy	Capillary Gel Electrophoresis	Critical Parameter Change (Kit, Primer / Probe)
Scientific Rationale	**Laboratory Verification**	**Supplemental Validation**
• Attribute measured unaffected by sequence change • Document scientific rationale	• Confirm expected result under real laboratory condition • Under protocol • Predefined acceptance criteria • Document scientific rationale & data	• Challenge of additional ICH Q2 • Under protocol • Predefined acceptance criteria • Document Rationale & data

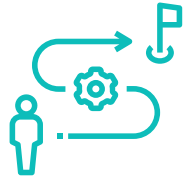
Non-platform method will require product-specific full validation

Having common structural elements with only the codon-optimized sequence encoding the target antigen being unique to each new mRNA construct/variant makes mRNA a good candidate to adopt platforming strategy

Expanding to mAbs

Many companies have extensive experience developing mAbs including a robust understanding of the key/critical steps of the platform methods, method validation, technical transfer and routine manufacturing processes

Platform procedures are established with set of conditions to measure quality attributes of mAb that are of similar size and structure



Unlike mRNA, establishment of platform in mAb space brings more challenges as it involves going through massive amount of development data, validation data from multiple mAb/-alike products to define strategy based on enhanced understanding (ICH Q14) and ICH Q2 (R2) for abbreviated validation approaches

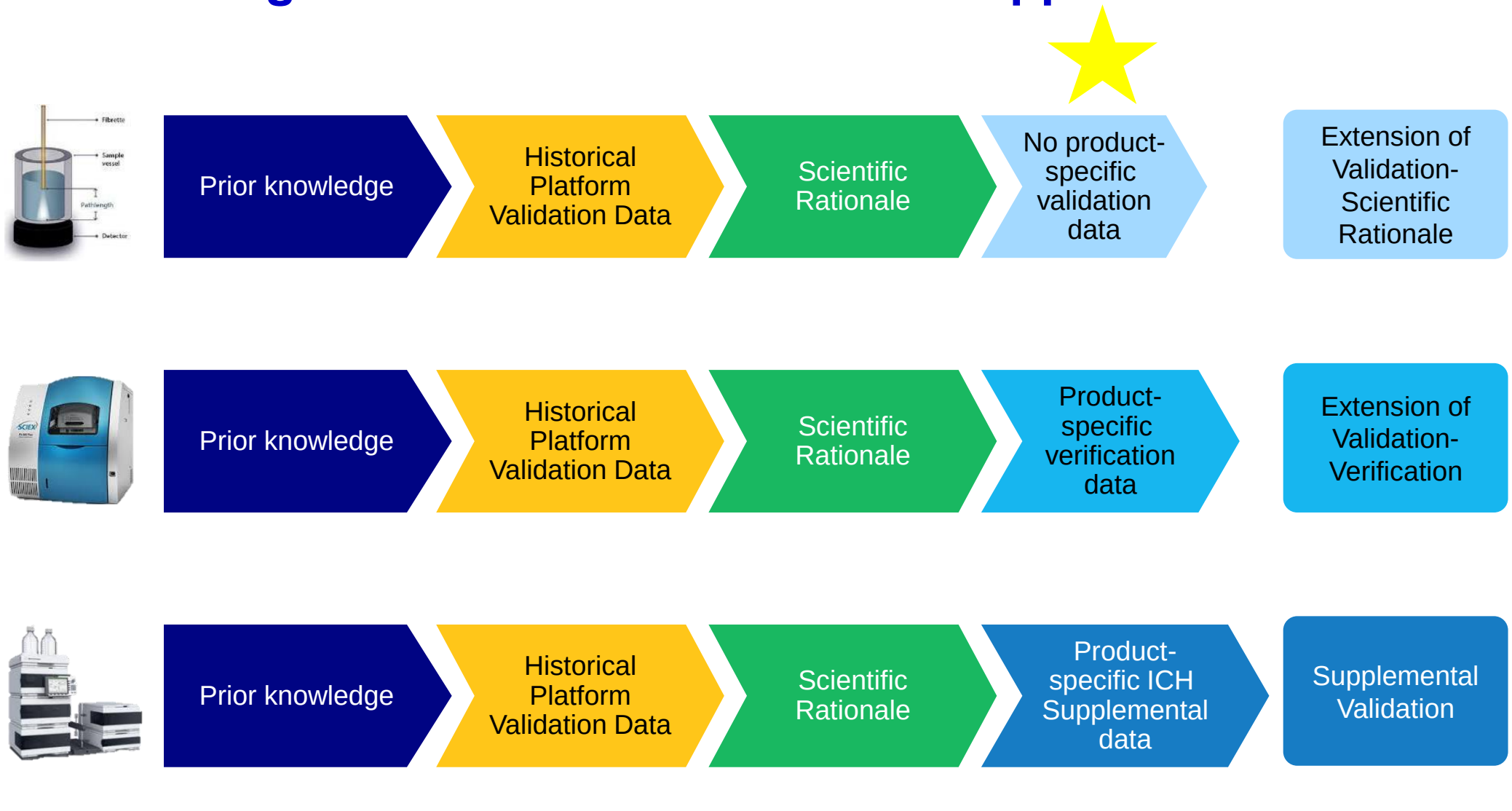
Applicability Assessment for a New Candidate

ICH Q14

ICH Q2 (R2)

Development	Early-stage	Late-stage	Transfer
"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" • Method robustness • Robust system suitability	• Analytical Target Profile • Product-specific Method Qualification/Verification	• Method Validation	• Receiving/commercial laboratory qualification to run the platform analytical procedure

Example of Late-Stage mAbs' Platform Validation Application



Example: Extension of Validation-Scientific Rationale (UV)

Validation

Method is Validated

√ Linearity
√ Precision
√ Accuracy
√ Specificity
√ Range

New mAb/-alike Product

Same intended purpose to measure concentration

Assessment of validation applicability

Document Scientific Rationale

Continuous monitoring of platform method performance in commercial laboratory

- System suitability
- Invalid Assays
- Robustness

UV Critical Method Parameters

- molecule's specific absorption Coefficient
- Path length

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 absorbance (A) of a protein solution at a fixed wavelength is related to the protein concentration (C), the cell path length (B), and the absorption coefficient (E) of the protein as follows: A = C E B. Therefore, the concentration of a protein solution can be calculated based on its absorbance at a given wavelength, the cuvette cell path length, and the known or established specific absorption coefficient value. Protein modalities include mAbs and mAb-like molecules, that, although differing in primary sequence and potentially post translational modifications, behave in accordance with the Beer-Lambert Law and thus can be tested for protein concentration as validated.

UV Example: Validation Historical Data for >10 mAbs or mAb-like Products

Validation Characteristic	Historical Data Summary	Method 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.
		Report linear regression analysis results for: slope, y-intercept, coefficient of determination (R^2), correlation coefficient (r), and residual sum of squares (RSS).
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

Example: Extension of Validation- Laboratory Verification (SEC)

Method is Validated

√ Linearity
√ Precision
√ Accuracy
√ Specificity
√ DL
√ QL
√ Range

New mAb/-alike Product

Same intended purpose to measure HMMS

SEC Critical Method Parameters

- Column
- Mobile phase
- Flow rate
- Sample preparation

Validation

- Assessment of validation applicability
- Document Scientific Rationale
- Predefined acceptance criteria
- Protocol
- Report

Continuous monitoring of platform method performance in commercial laboratory

- System suitability
- Invalid Assays
- Robustness

Method uses a X column designed to enable the fractionation of protein species between X,000 and X00,000 Da. For new mAb and mAb-like candidates that fall within this mass range, the suitability of the platform method is assessed during method evaluation and verification studies. 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.

Extension of Validation Verification

√ Precision
√ Accuracy
√ Range (if necessary)

SEC Example: Validation Historical Data for >10 mAbs or mAb-like Products

Validation Characteristic	Historical Data Summary	Method Validation Acceptance Criteria
System Repeatability	HMMS RSD: 1.61%	HMMS RSD ≤10.0%
Method Repeatability	HMMS RSD: 7.25%	HMMS RSD ≤10.0%
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. Report linear regression analysis results for HMMS: slope, y-intercept, coefficient of determination (R2), correlation coefficient (r), and residual sum of squares (RSS)
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

Example-Supplemental Validation (Critical Method Parameter Change)

Method is Validated

√ ICH Q2

New mAb/-alike Product

Same intended purpose

Critical Method Parameters

- Standard change
- Key reagent change i.e., Lys C
- Sample Preparation

Validation

- Assessment of validation applicability
- Document Scientific Rationale
- Predefined acceptance criteria
- Protocol
- Report

Continuous monitoring of platform method performance in commercial laboratory

- System suitability
- Invalid Assays
- Robustness

Supplemental Validation

√ challenge select ICH characteristics

Regulatory Submission Strategy for Analytical Procedures Following the Platform Approach

The full validation for each analytical procedure is a combination of the platform procedure validation, scientific rationale and product specific data. This will be presented in the eCTD (Common Technical Document) as follows

3.2.S.4.3/3.2.P.5.3 Validation of Analytical Procedures – Overview

- Scientific rationale and validation strategy for each analytical procedure
- Link to platform analytical procedure validation reports

3.2.S.4.3 and 3.2.P.5.3 Validation of Analytical Procedures

- Product-specific extension of validation-verification, supplemental validation data

Example of Potential Submission Content for Each Type of Platform Validation

Overview section aims to describe the full validation strategy which would also contain definitions of each validation type

Table 3.2.S.4.3-2 Validation Summary for Drug Substance Platform Analytical Procedures

Quality Attribute	Analytical Procedure	Test Site	Mode of Validation/Verification	Platform Validation Report	DS Validation / Verification Report Number or CTD Section
Protein Concentration	UV Spectroscopy	Pfizer, Andover	Platform method: Extension of validation by scientific rationale at Pfizer, Andover	VAL100220952	3.2.S.4.3 - UV Spectroscopy
HMMS	SE-HPLC	Pfizer, Andover	Platform method: Extension of validation by verification at Pfizer, Andover	VAL 100221266	3.2.S.4.3 - SE-HPLC
HCP	HCP ELISA	Pfizer, Andover	Platform method: Supplemental Validation for new critical reagent at Pfizer, Andover	VAL100222236	VAL-XXXXXXXX

Contains the scientific rationale for use of platform method

Contains the scientific rationale for use of platform method and product- specific laboratory verification results

Link to product-specific supplemental validation report

Key Challenges

- Documentation of analytical prior knowledge, platform data (submission ready and analytical)
- Common Technical Document (CTD) development & authoring
- Global Regulatory acceptance
- Change management of platform method
- Continuous monitoring of platform method performance across sites

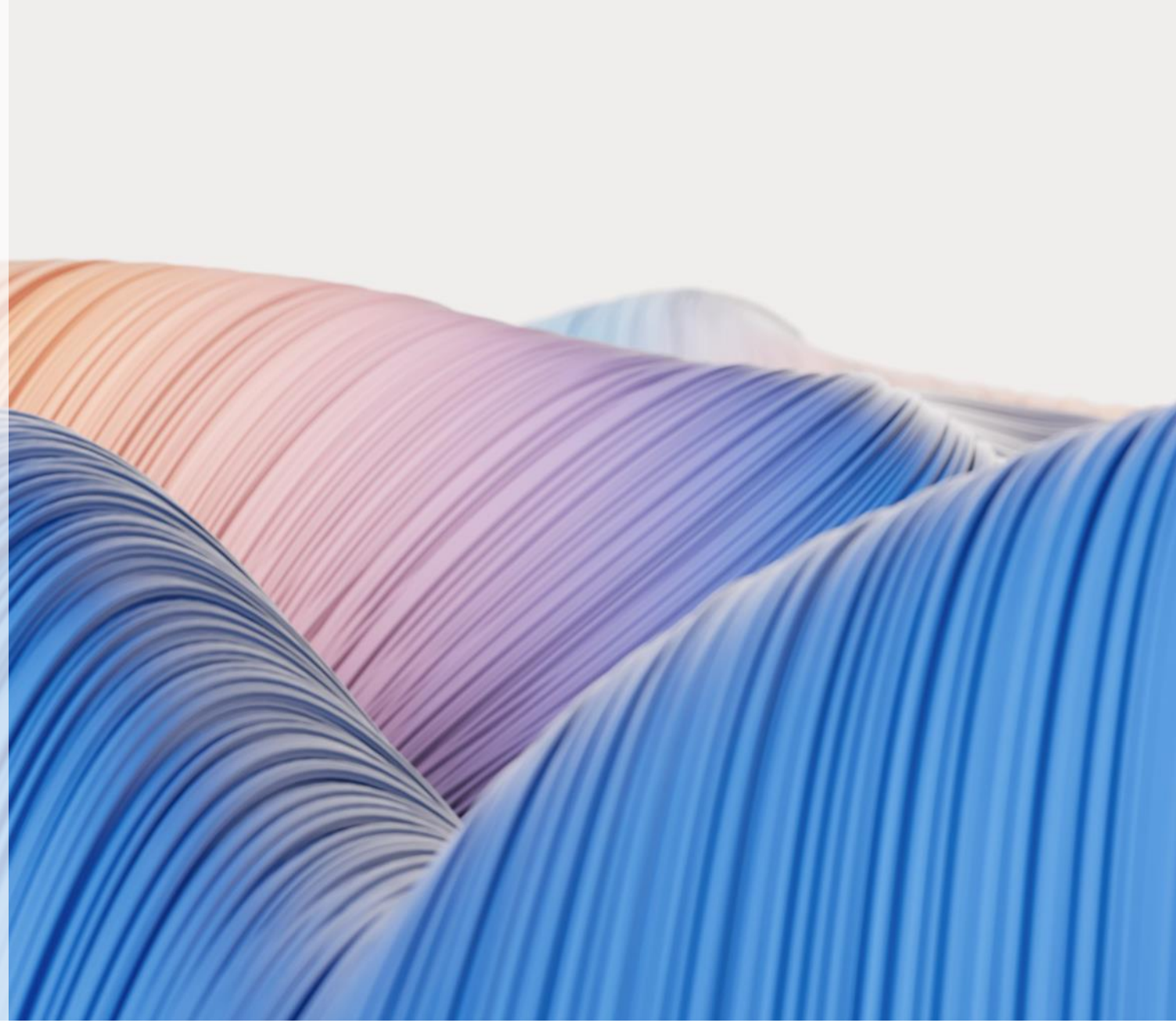
Thank You

Analytical Research & Development

Pharmaceutical Sciences, Research & Development

Pfizer Global Supply

Pfizer External Working Group



Examples of Documentation

Guidance Document

- Strategic document describing platforming approaches
- Local procedures that governs the laboratory work processes

Scientific Rationale

- Establishment of platform

Prior Knowledge

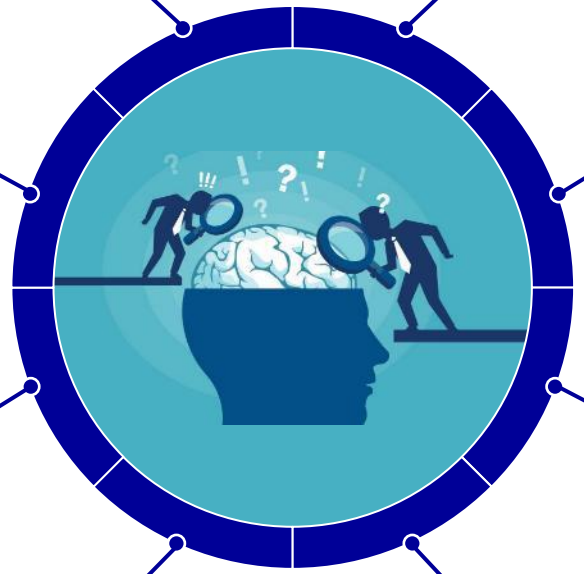
- Manufacturing platform processes
- Quality attributes
- Historical data
- Platform validations
- Sites currently using platform procedures

Product-specific

- Technical assessment
- Protocol/execution/report
- Tech Transfer

Prior Knowledge

- Technology Transfer
- Process Validation
- Technology
- Method Validation



- Development Data
- Manufacturing Process
- Critical Method Parameters
- Method Verifications