Mini Case Study

Platform Analytical Procedures – Applying Concepts in ICH Q2(R2) and ICH Q14

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CASSS-WCBP 2024

25 Jan 2024

Scope of this Mini Case Study

- Generate a common understanding on what platform analytical procedures are
- Discuss development and establishment of a platform analytical procedure
- Consideration of platform analytical procedures for validations and transfers
- Consideration of documentation and change control
- Considerations for regulatory filings
- Lifecycle management, including extension for new products

ICH Q2(R2) Validation of Analytical Procedures & ICH Q14 Analytical Procedure Development

- ICH Q14 and ICH Q2(R2) to describe the development and validation activities across the lifecycle of an analytical procedures.

- ICH Q14 describes the scientific principles for development, change management and submission requirements of analytical procedures for the minimal and enhanced approach.

- ICH Q2(R2) provides guidance for establishing, submitting and maintaining evidence that an analytical procedure is fit for the intended purpose.

- Both guidelines have been adopted for step 4 in November 2023.`

Expected Benefits – ICH Q14

- Harmonizes scientific approaches and terminology for analytical procedure development (including multivariate analytical procedures and RTRT).
- Provides more reliable analytical procedures through the application of enhanced approaches.
- Improves communication between regulators and industry around analytical procedures.
- Employs predefined performance characteristics guides development and facilitates regulatory change management of analytical procedures.
- Reduces the amount of effort across the analytical procedure lifecycle.
- Enables effective analytical procedure knowledge and risk management to facilitate continual improvement.

Guideline Objectives – ICH Q2(R2)

- Encourages the use of more advanced analytical procedures leading to more robust quality oversight by pharmaceutical drug manufacturers.
- Adequate validation data, resulting in reduction of information requests and responses, which can delay application approval.
- Modernization of general methodology to include analytical procedures and data evaluation for biotechnological products, future modalities and statistical/multivariate data evaluations.
- Enables efficient use of prior knowledge to support analytical procedure validation.

Use of prior knowledge

- Prior knowledge is explicitly or implicitly used for informing decisions during analytical procedure development and lifecycle management

- Prior knowledge can be internal knowledge from a company's proprietary development and analytical experience, external knowledge such as reference to scientific and technical publications or established scientific principles

- Prior knowledge plays an important role in identifying suitable analytical techniques and in designing the development studies for an analytical procedure and can be used to demonstrate validation of analytical procedures

- ***Applying platform analytical procedures represents an efficient use of prior knowledge***

Platform Analytical Procedure

An analytical procedure that is suitable to test quality attributes of different products without significant change to its operational conditions, system suitability and reporting structure. This type of analytical procedure can be used to analyse molecules that are sufficiently alike with respect to the attributes that the platform analytical procedure is intended to measure. (ICH Q2(R2))

Source: ICH Q2 (R2) Glossary

Case study: Protein Content Determination for mAbs

- Protein content determination is an important assay as it relates to the right dose and hence efficacy of the drug
- Protein content determination is part of each release and stability specification and it is used for inprocess control testing.
- Proteins in solution absorb UV at various wavelengths and amino acids with aromatic rings are the primary reason for the absorbance
- Absorptivity (i.e., extinction coefficient) is a constant for a given protein dissolved in a given solute and measured at a given wavelength
- UV absorbance is proportional to the protein concentration
- If the extinction coefficient of the respective protein is known, Slope Spectroscopy is powerful tool to determine the protein concentration
- In a given solute the measurement is independent from other molecular attributes

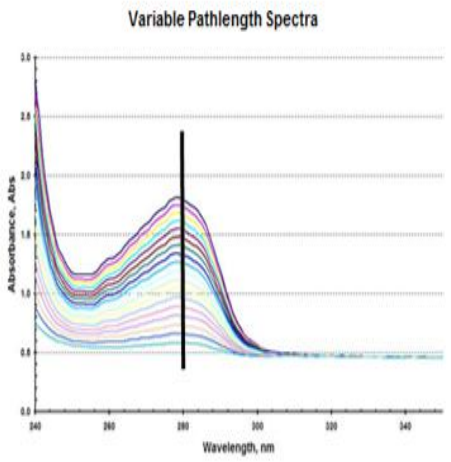
Slope Spectroscopy Overview

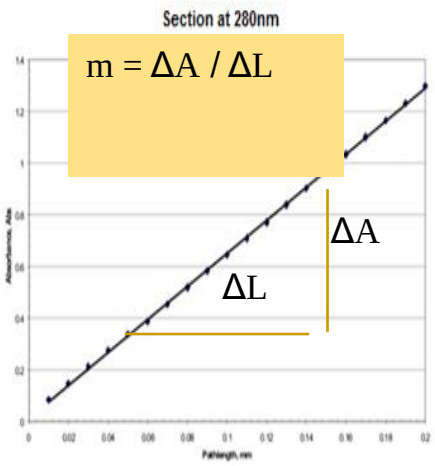
Based On Beer's Law

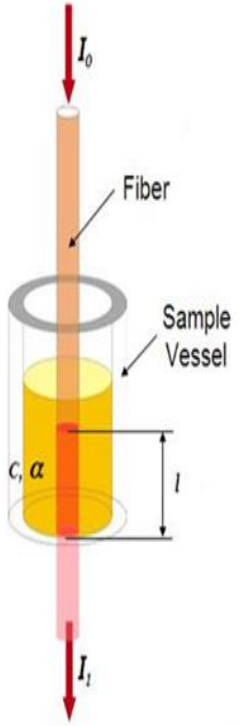
$$A = \varepsilon L c$$

Where:
A : Absorbance
ε : Molar absorptivity
L : Pathlength
C : Concentration

Variable Pathlength Spectroscopy:







Advantages of SoloVPE:

- Based on the same mechanism (Beer's Law) as UV spec scan
- **No dilution needed** as sample concentration is calculated from slope spectroscopy equation
- Wide dynamic range with high precision (RSD < 4%) and high accuracy (96-104%)
- No need for baseline correction.

Technology Selection and Analytical Procedure Development

- UV spec scan was historically used as a platform analytical procedure for protein determination during clinical development phases
- SoloVPE was chosen as platform analytical procedure candidate based on it measuement principle and prior knowledge gained form UV spec scan
- SoloVPE analytical procedure development efforts included the following aspects:
  - Sample homogenization prior to aliquoting into sample vessel
  - Establishment of analytical procedure control strategy (i.e. SST, sample acceptance criteria)
  - Influence of wavelenght reading
  - Influence of scatter correction
  - Reading time and required data points

Analytical Procedure Validation acc. ICH Q2

- Multi Product Validation approach using 5 different Mabs

Performance Characteristic	Products used	Validation Acceptance Criteria	Results
Specificity	Mab 1, Mab 2, Mab 3, Mab 4, Mab 5	Buffer slope absorbance ≤ 0.01 AU/mm	≤ 0.01 AU/mm
Linearity *	Mab 1 (high conc.), Mab 2 (high conc.)	Pearson correlation coefficient (r): ≥ 0.99 Slope - Report Y-intercept - Report	Mab 1: r=1,00; Mab 2: r=1,00 Mab 1: 0.9753; Mab 2: 1.0034 Mab 1: 0.5666; Mab 2: 0.1609
Accuracy *		96.0-104.0% (method comparison with Std UV)	Mab 1 : Pass: 2.5 mg/mL – 157.7 mg/mL Fail: 1.0 mg/mL Mab 2: Pass:1.0 mg/mL – 176.1 mg/mL
Repeatability *		RSD per level ≤ 4%	Mab 1: %RSD ≤ 1% Mab 2: %RSD ≤ 3%
Intermediate Precision	Mab 1, Mab3, Mab 4, Mab 5	RSD per level ≤ 4%	≤ RSD = 2%
Range			2.5 mg/mL – 176.1 mg/mL

* tested across the range

Analytical Procedure Transfer

- Receiving sites participated in multi product validaton (co-validation)

Reproducibility:
(Intermediate precision at each receiving lab)

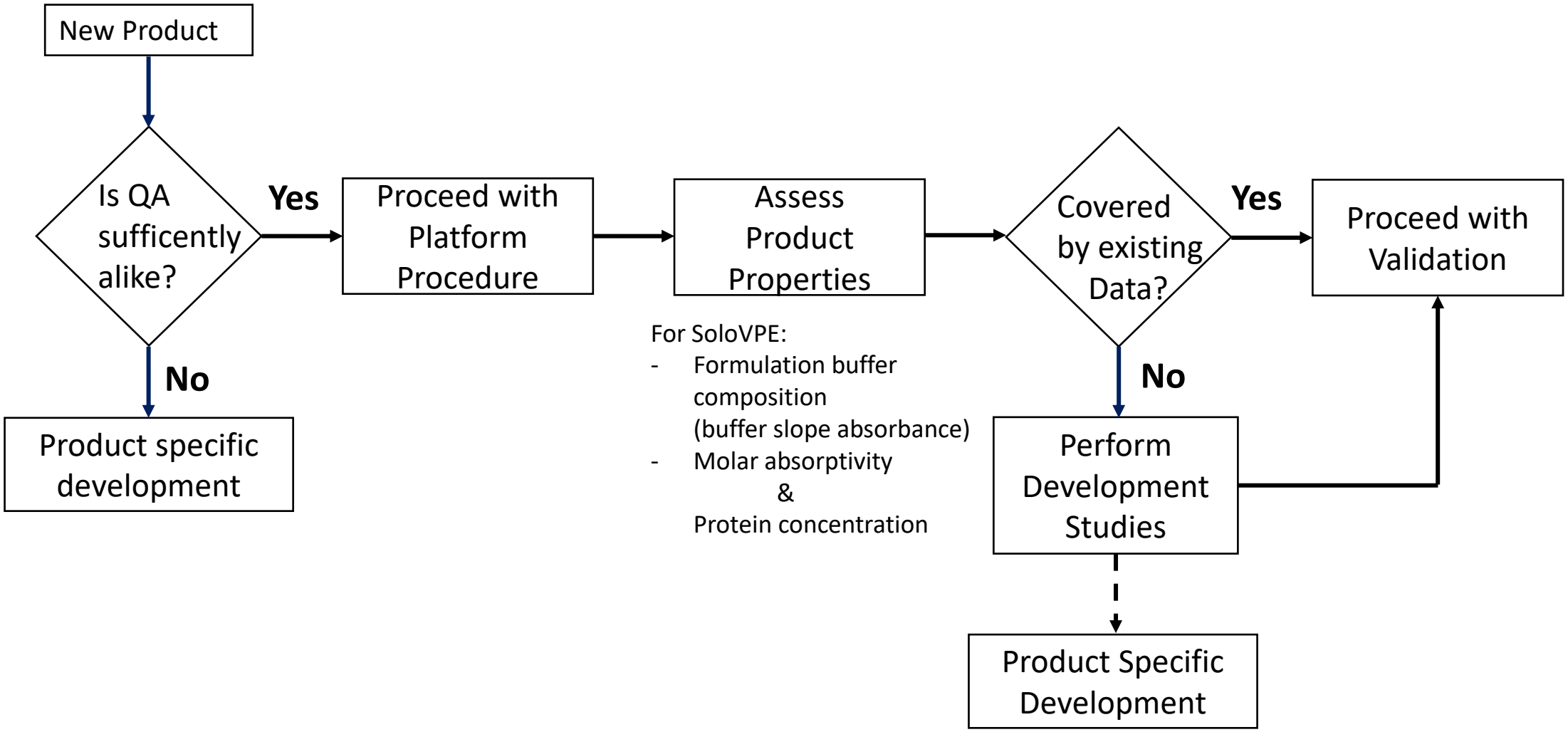
Product	Testing Site	Acceptance Critria	Results %RSD
Mab 1	Site 1	RSD ≤ 4%	2.9
	Site 2		0.6
	Site 3		1.3
Mab 2	Site 1	RSD ≤ 4%	2.4
	Site 2		1.2
	Site 3		1.7
Mab 3	Site 1	RSD ≤ 4%	2.3
	Site 2		0.9
	Site 3		0.9
Mab 4	Site 1	RSD ≤ 4%	2.0
	Site 2		0.5
	Site 3		0.5
Mab 5	Site 1	RSD ≤ 4%	1.3
	Site 2		0.6
	Site 3		1.4
Mab 6	Site 1	RSD ≤ 4%	1.3
	Site 2		1.1
	Site 3		1.7

TOST analysis and maximum allowable value of mean difference (4% of target concentration)

Comparison	Product	Mean Difference Protein Concentration (mg/mL)	90% CI for Mean Difference Results %RSD		%Max. 90% CI of Mean Difference[a]
			Lower Limit	Upper Limit	
Site 1 vs. Site 2	Mab 1	-0.2951	-0.4300	0.0367	2.6
	Mab 2	-0.5933	-3.6119	2.4252	2.4
	Mab 3	-0.0194	-0.0380	-0.0009	3.8
	Mab 4	0.0264	-0.1403	0.1932	2.0
	Mab 5	-0.1474	-0.4045	0.1097	1.6
	Mab 6	-0.1967	-0.4300	0.0367	1.7
Site 3 vs. Site 2	Mab 1	0.2492	-1.0427	1.5410	1.2
	Mab 2	-0.0971	-1.3602	1.1659	0.9
	Mab 3	-0.0048	-0.0119	0.0021	1.2
	Mab 4	0.0063	-0.0359	0.0486	0.5
	Mab 5	0.0053	-0.2876	0.2768	1.1
	Mab 6	-0.1700	-0.3762	0.0362	1.1
Site 3 vs. Site 1	Mab 1	-0.0460	-2.9152	2.8232	2.3
	Mab 2	-0.6905	-3.1598	1.7788	2.1
	Mab 3	-0.0243	-0.0423	-0.0064	4.3
	Mab 4	0.0328	-0.1347	0.2002	2.0
	Mab 5	-0.1528	-0.4939	0.1883	2.0
	Mab 6	-0.3667	-0.7041	-0.0292	2.8

[a] %Max. 90% CI of Mean Difference. = |Max. 90% CI of Mean Difference| / Target protein concentration x 100%

Extension to a new Product



In line with ICH Q14:
“Existing platform analytical procedures (*e.g.,* protein content measurement by UV spectroscopy) can be leveraged to evaluate the attributes of a specific product without conducting additional procedure development.)

Validation for a new Product

- For each new product, a validation study is performed to demontrate that the platform analytical procedure remains fit for the intented purpose

Validation Characteristics to be assessed	
Specifcity[1]	x
Linearity[2]	x
Accuracy[2]	x
Precision: Repeatability[2]	x
Precision: Intermediate Precision[2]	x
Range[2]	x
Stability of Sample Solutions	x
Robustness[2]	x

[1] Specificity data can be leveraged specificity data base if appropriate

[2] Data can be leveraged from Multi Product Validation Report

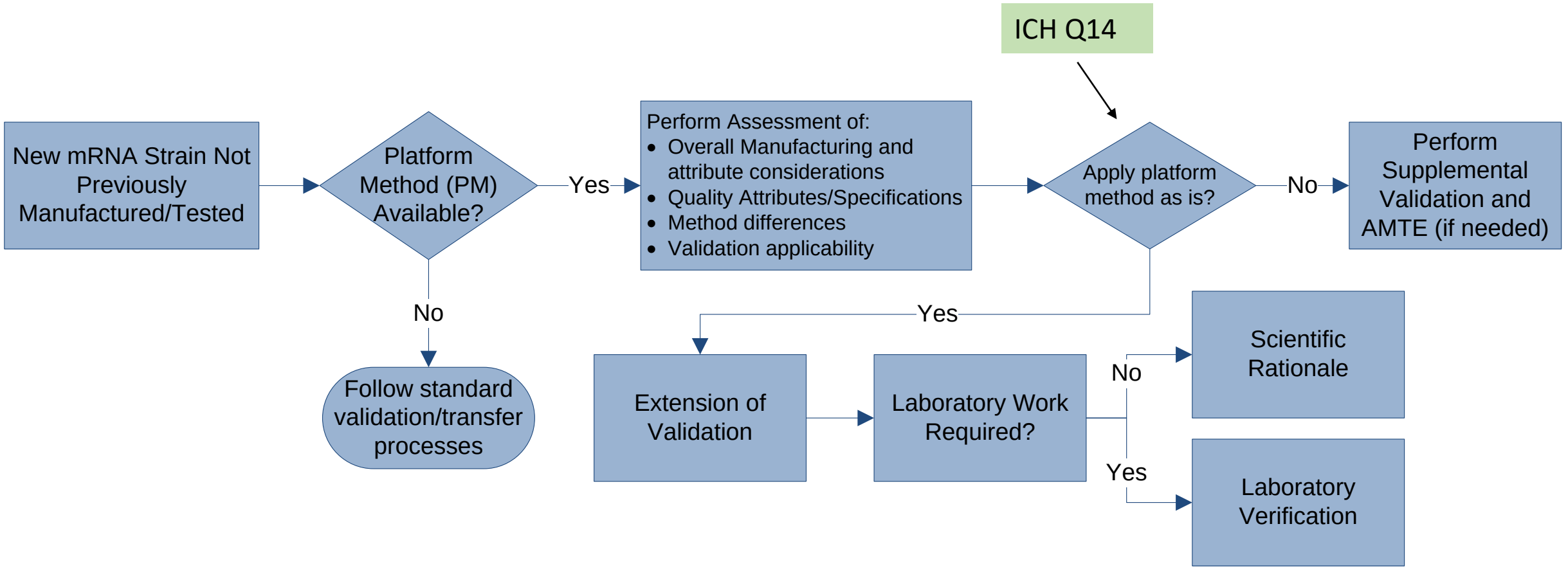
- Inline with ICHQ2(R2):
  “Suitable data derived from development studies (see ICH Q14) can be used as part of validation data. When an established *platform analytical procedure* is used for a new purpose, validation testing can be abbreviated, if scientifically justified.”

Case Study - mRNA Validation Strategy For Variants and Follow-on Constructs

- Strategic pathway to apply original mRNA validation to new mRNA strain
  - Platform method requires no/minor operational changes
  - Conditional verification activities may be required

Example of application….

mRNA Late-Stage Validation Strategy Flow Chart



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 mRNA platform application

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 (R1) • 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

Considerations for Documentation to support Platfrom Analytical Procedure Concept over Lifecycle

- Platform analytical procedure is centrally managed and valid for all sites within scope
  - Product specific additions need to be linked to global procedure under change control
- Data from previous products (e.g. on formulation buffer absorbance) can abreviate development and validation studies
- Multi Product Validation summarizes results from initial validation and can be updated to include the outcome from prodcut specific validation (e.g. expansion of range)
- Generic validation protocol describing the validation requirements and the possibility to use existing data for a new products facilitates the expansion of the platform procedure to new products
- Product specific validation reports can be used to demonstrate suitability for a given product and serve as basis for submissions

Discussion Questions

- What are strategies to establish platform analytical procedures?
- Is the concept of Platform Analytical Procedures restricted to certain product classes or can it be applied for any new modality?
  - What assessments are required?
- How to perform the assessment if a commercial site – is qualified to execute platform approach? What is the transfer approach?
  - For first transfer of platform analytical procedure
  - For subsequent transfers of platform procedure for new products
- What is the process for platform decision making and risk assessment?
- Platform experience discussion;
  - Platform method approaches across companies
  - Documentation strategies for platform analytical procedures
  - CMC – filing strategy and feedbacks for major and minor markets
  - Handling robustness in CMC filing
  - Success and Challenges
  - Handling Lifecycle / developmental work for platform procedure
  - Lifecyle Management for continuous monitoring (sites vs new products)
  - Site Specific investigations for platform procedure – who will handle it?

Thank you