

Retrospective Establishment of Platform Analytical Procedures

Considerations for Protein Content Determination by UV Spectrophotometry

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The Lilly logo, featuring the word "Lilly" in a white, cursive script font, is positioned in the bottom right corner of the slide.

ICH Q2 (R2) and ICH Q14 Changed the World for Analytical Procedures – At least a little bit...

- ICH Q2(R2) and Q14 bring development, validation and life-cycle management together, thus are closely interconnected.
- The use of prior knowledge has been enabled during analytical procedure development and validation
- Platform Analytical Procedures are “officially recognized” with a definition

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)*

ICH Q2(R2) and Q14 guideline text

From ICH Q2(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.**

From ICH Q14:

- In certain cases, an analytical procedure can be applied to multiple products with little or no modification of measurement conditions. **For a new application of such *platform analytical procedures*, the subsequent development can be abbreviated, and certain *validation tests* can be omitted based on a science- and risk-based justification.**
- Prior product knowledge plays an important role in identifying suitable analytical techniques. Knowledge of best practices, state-of-the-art technologies and regulatory expectations contribute to the selection of the most suitable technology for a given purpose. **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.**

Examples of Potential Platform Procedures

- Any procedure that works regardless of the “molecule of interest” qualifies to be a platform procedure:
 - Surfactant methods (PS80, Poloxamer, Triton)
 - Residual methods (rDNA, HCP ELISA; residual solvent methods)
 - MMV and Mycoplasma
 - Container Closure Integrity
 - Water activity
 - ...
- Any procedure/technique where the molecule properties are similar enough to allow for similar procedure conditions, thus candidates for a platform procedure:
 - UV content
 - SEC
 - CE-SDS under reducing/non reducing conditions
 - ID methods based on digestion of the analyte
 - Biophysical characterization methods (CD, DSC, FL, FTIR / MMS, AUC, DLS, SLS, NMR, mass photometry)
 - ...

Let's start simple... Protein Content by UV-Vis...

... as an example for retrospective establishment of a Platform Analytical Procedure...

Ultraviolet visible (UV-Vis) spectroscopy is an established technique for determining the protein concentration of a solution. The absorbance of a solution at a given wavelength A_λ , is a linear function of the protein concentration c , according to the Beer-Lambert law as:

$$A_\lambda = c\varepsilon_\lambda l$$

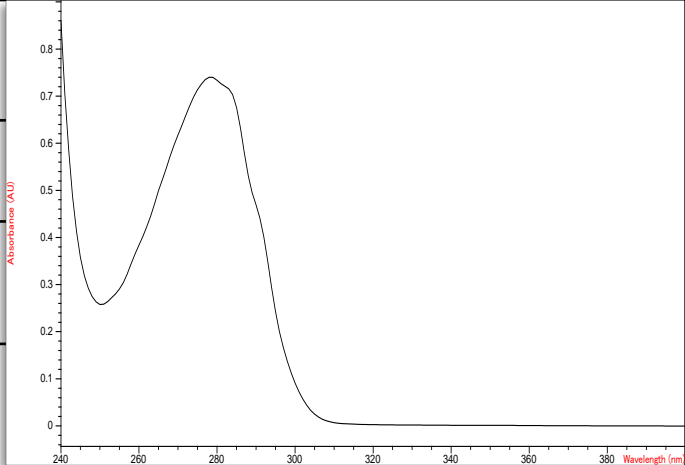
where ε_λ is the extinction coefficient at the corresponding wavelength, and l is the pathlength. Given information of the absorbance, pathlength, and extinction coefficient, the protein concentration can be calculated.

... Protein Content determination by UV-Vis Spectrophotometry with *Gravimetric* Sample Preparation...

Define the Platform Procedure

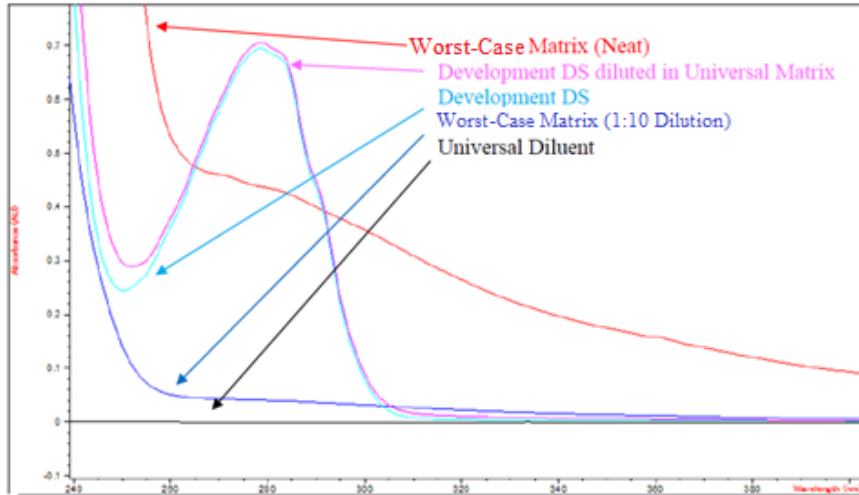
- Procedure parameters have been historically identified (prior knowledge)
 - Product specific validations across multiple molecules
 - Essentially identical procedure parameters
 - Multiple matrix backgrounds / formulations
 - Multiple target protein concentrations
- Next step is to establish those conditions as a **platform procedure**
 - Identify and justify the universal procedure parameters
 - Consolidate of performance characteristics from multiple validations (prior knowledge)
 - Generate one analytical procedure (with a unique identifier)
 - Identify any additional product specific information required

Analytical Procedure Parameter	Platform Procedure Conditions	Justification / Rationale
Wavelength Reading	400 nm to 240 nm	Molecule independent – all MAb's look the same
Temperature for Analysis	Ambient	Temp might impact A_{max} . Ambient demonstrated as OK
Scan rate of Instrument	240 nm/min - 1200 nm/min	Scan rate might impact A_{max} . Scan rate range demonstrated as OK
Analysis Volume / Cuvette	Analysis volumes may vary depending on the size of cuvette used. In all cases, a 1-cm path length quartz must be used.	Analysis volume is not impactful so long as 1-cm path length is used. Defined used of quartz (as opposed to plastic)
Diluent Composition	Predefined diluent buffer (Universal Diluent) as per Company platform	Use of a universal diluent provides consistency within the analytical procedure.
Sample Preparation Parameter	Dilute gravimetrically to target with a minimum 10-fold dilution in Diluent	Gravimetric dilution gives better precision. Minimum dilution to avoid matrix interference is based on prior knowledge.
Sample Preparation	Dilute in a defined compatible container	Some containers are incompatible due to leachates.
Minimum Sample Weight	Not less than 100 mg sample weight	Minimum weight improves precision of gravimetric dilution
Diluent Response (i.e. Blank)	The blank reading must be 0.00 ± 0.01 over the range of 240 nm to 400 nm	System suitability – molecule independent
Absorbance of Sample Preparation	The absorbance values must be in the linear range of the system	Linearity – molecule independent (Beer-Lambert)
Prepared Sample Concentration	Between x to y mg/mL (target 0.5 mg/mL)	Ensures sample preparation is within the linear range of the system. Dependent upon extinction coefficient, but typically consistent for MAbs
Calculation	...	Universal calculation can be defined
Replication	Each reportable result is an average of three independent replicate preparations	Improved precision



Support the Analytical Parameters with Data

- Specificity



- Response

- Precision, Accuracy, Linearity

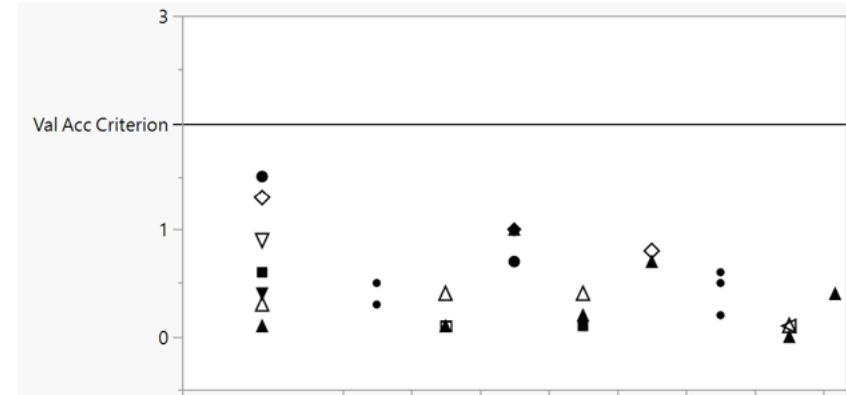
- Range

- Working range defined by absorbance linearity
- Reportable range determined by dilution factors

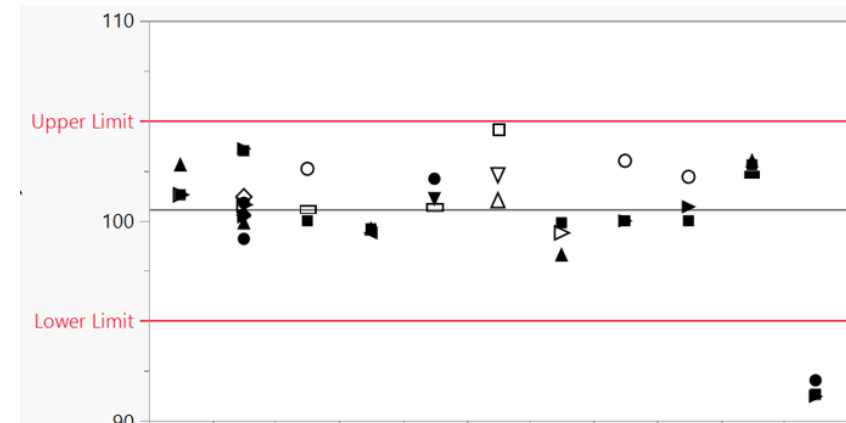
- Diluent Stability

- Determined for Universal Diluent

- Repeatability and Intermediate Precision



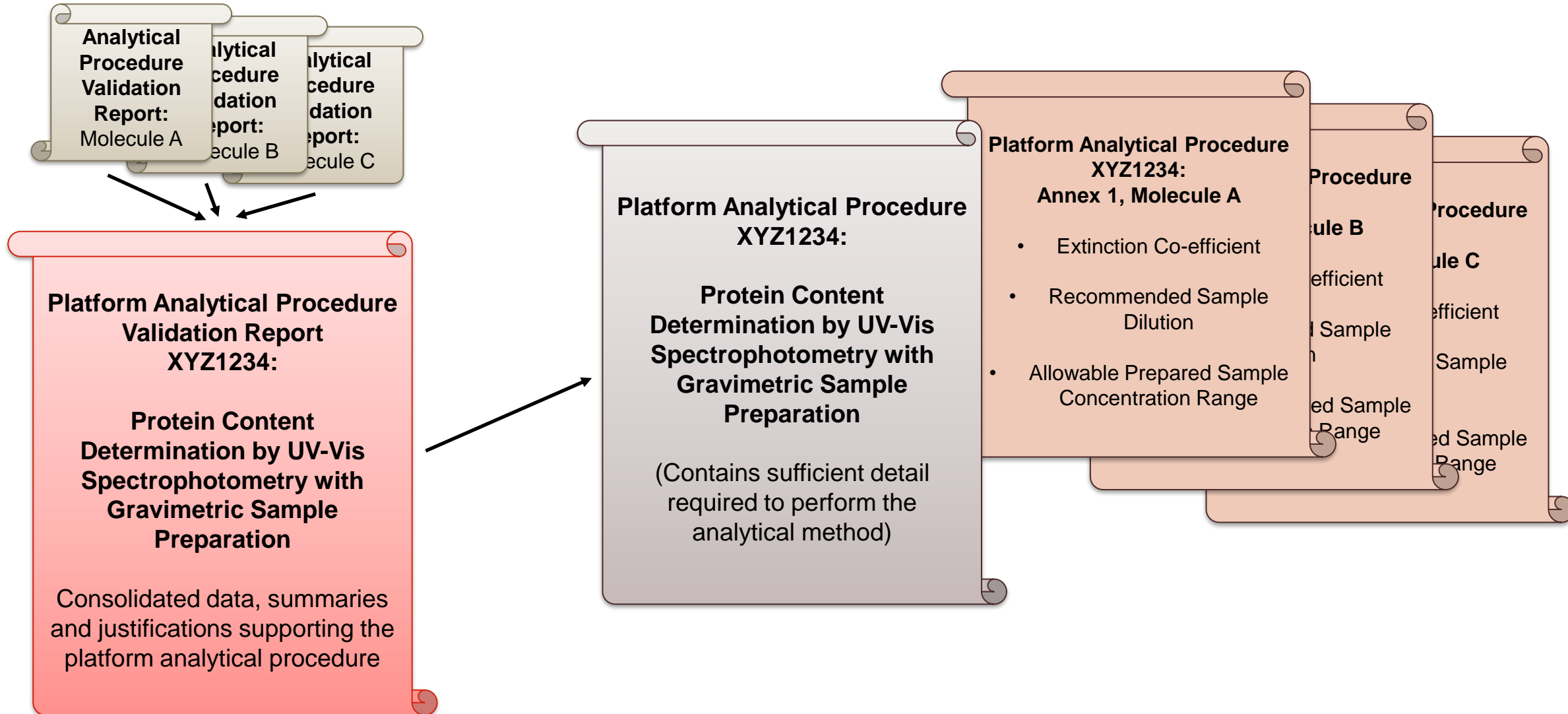
- Accuracy



Molecule Specific Activities

- Determine the Extinction Coefficient
 - Pace et al.
 - AAA
 - NMR
- Confirm specificity / lack of matrix interference
 - may be inferred from prior molecules if appropriate
- Determine prepared sample stability
- “...In certain cases, an analytical procedure can be applied to **multiple products with little or no modification of measurement conditions. For a new application of such platform analytical procedures, the subsequent development can be abbreviated, and certain validation tests can be omitted based on a science- and risk-based justification...**”

Platform Analytical Procedure Documentation



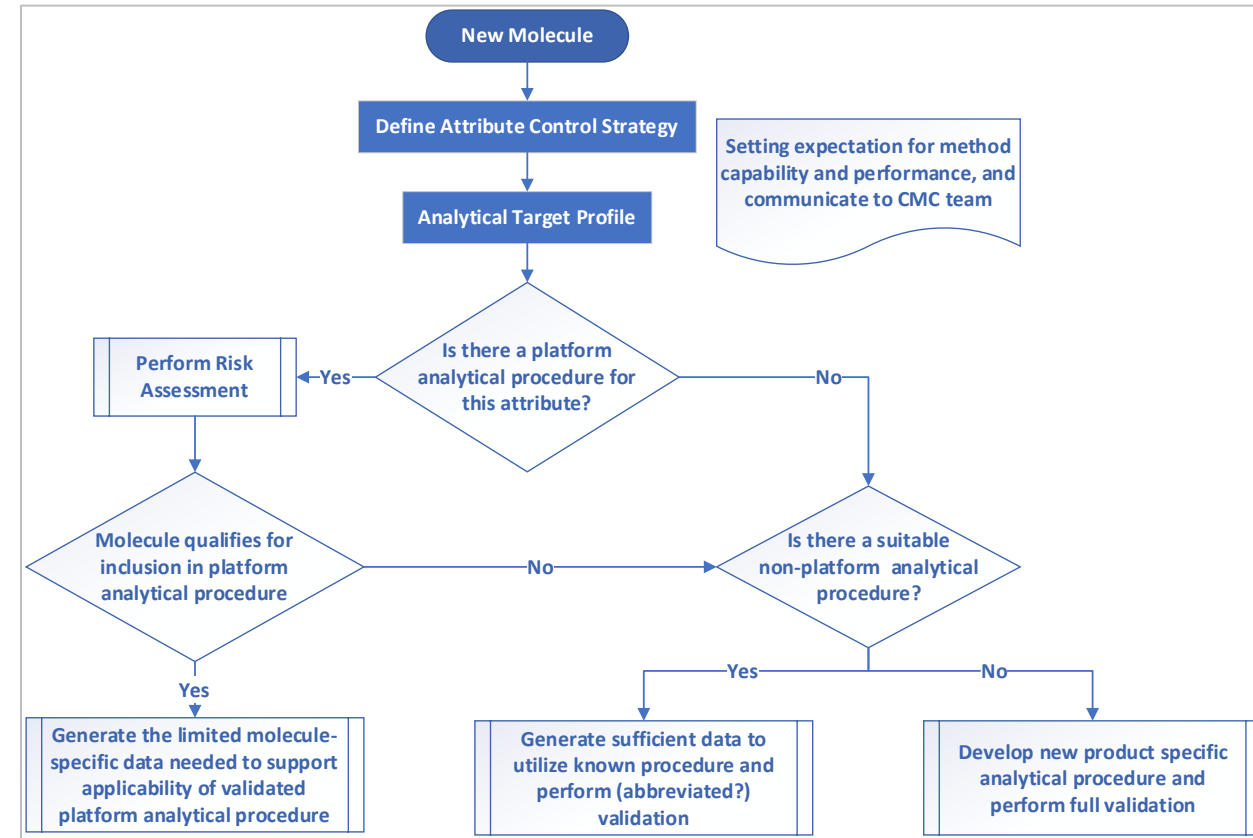
Extending to new Molecules

Early Phase Development

- Molecule specific activities:
 - Determine Extinction Co-efficient
 - Confirm Specificity
- Can I apply the procedure as written?
- Check against an independent measurement (e.g., SoloVPE)

Late Phase Development

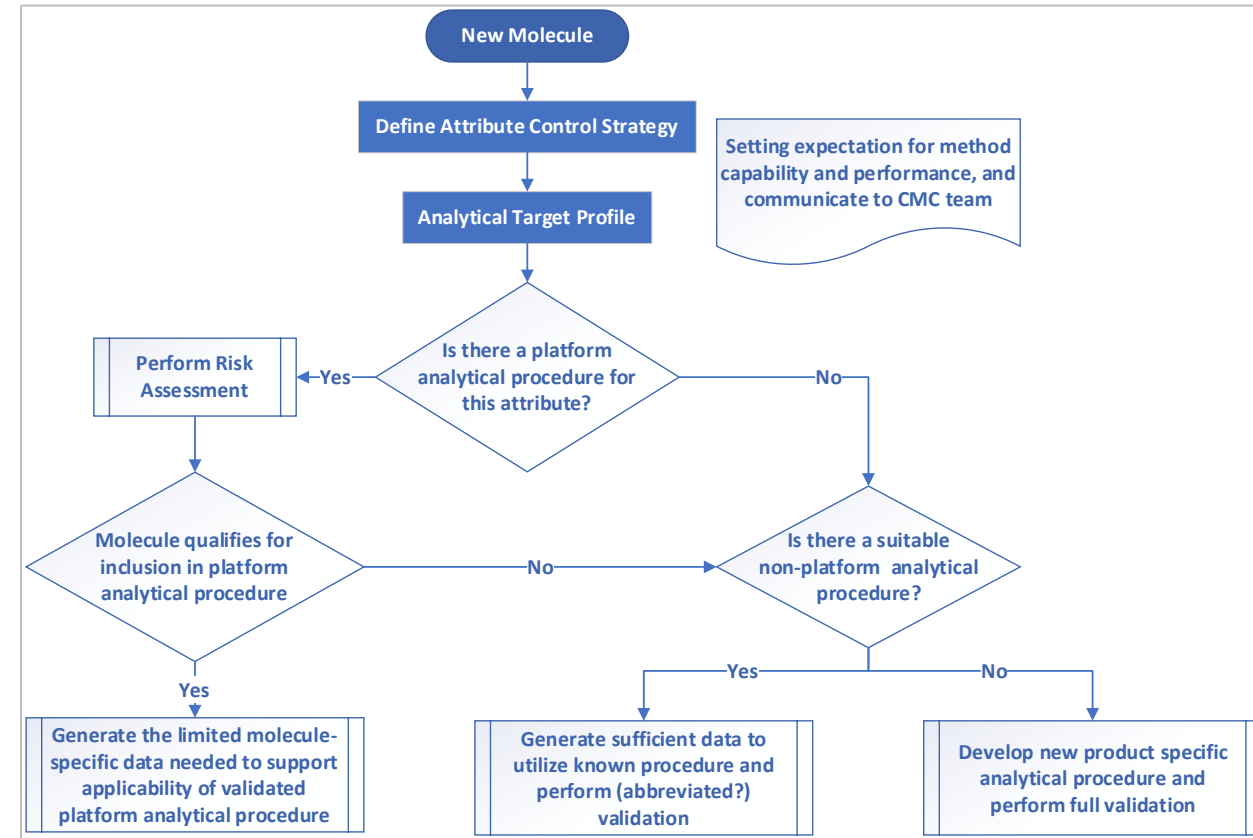
- Molecule specific activities:
 - Confirm sample stability
- Gather data supporting method performance
 - Batch release
 - Stability



Extending to new Molecules: Initial Risk Assessment

Validation Stage

- 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**



Conclusion

- The recent updates to ICH Q2 and introduction of ICH Q14 'open the door' for the development and validation of true Platform Analytical Procedures
- These offer the potential for (amongst other things):
 - Increased laboratory efficiency
 - Decreased replication of analytical procedure validation work
 - Increased consistency of analytical measurement across multiple molecules
- The example given illustrates the (relative) ease with which data could be combined across products
 - Accuracy and precision are consistent irrespective of the molecule
 - Specificity and sample stability should be demonstrated
- **Final Result:**
 - A single analytical procedure, fit for the intended purpose of quantitating multiple products

Thank you!

Mark Milford and Elisabeth Krug

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