Applying Prior Knowledge to Accelerate CMC Development

Mini Case Studies Session 2

WCBP January 30th

10:45-11:45am

Coordinators:

Valerie Tsang, Hao Zhang, and Methal Albarghouthi

What is Prior Knowledge?

- **ICH Q11:** Prior knowledge can include established biological, chemical and engineering principles, technical literature, and applied manufacturing experience. Data derived from relevant prior knowledge, including platform manufacturing can be leveraged to support development of the commercial process and expedite scientific understanding.
- **ICH Quality Implementation Working Group on Q8, Q9, and Q10 Q&A (R4) ICH Q8(R2):** Some example of knowledge sources are: Prior knowledge based on experience obtained from similar processes (internal knowledge, industry scientific and technical publications) and published information (external knowledge: literature and peer-reviewed publications)
- **ICH Q14:** Prior knowledge is explicitly or implicitly used for informing decisions during analytical procedure development and lifecycle management.

Applications of Prior Knowledge

- Risk Assessments (CQA assessment, process impurities, E&L, etc.)
- Process development
- Formulation development
- Container closure
- Method development
- Control strategy development
- Impurity clearance
- Process validation
- Specification setting
- Stability

Knowledge Management: Knowns/Unknowns

Questions for Discussion

1. What are best practices for capturing and documenting prior knowledge?
2. What are the best practices for presenting prior knowledge to regulators or in regulatory filings?
3. How do you justify applicability of prior knowledge?
4. How do you apply prior knowledge across modalities/best practices?
5. Are there opportunities to apply prior knowledge where it is not currently applied?
6. How do you apply prior knowledge when adapting novel technologies?

Examples

Application of Prior Knowledge for Evaluation of Viral Inactivation/Clearance

Key Points from ICH Q5a(R2)

- Understanding of the mechanism underlying viral clearance
- Understanding of the process parameters affecting viral clearance
- Knowledge that product-viral interactions do not impact clearance
- Representativeness of the process intermediate matrix
- Product specific studies should be performed to address gaps

Example 1: *Application of external and internal prior knowledge*

<u>Leveraging Prior Knowledge for Viral Filtration</u>

- Phase 1 IND for monoclonal antibody (mAb) produced in Chinese Hamster Ovary (CHO) cells
- Prior knowledge is leveraged to support clearance claims for viral filtration to support opening of the IND.
  - External knowledge is leveraged to identify process parameters that can impact viral clearance.
  - Internal knowledge is leveraged to identify viral clearance claim.

Example 1: *Application of external and internal prior knowledge*

Viral Filtration

- Parameters identified as important for viral filtration (listed below)
- Leveraged results from 10 other "relevant" products[1]

Filtration Volume	Filtration Volume	Transmembrane Pressure	Pressure Release	LRV
26 - 500 L/m^2	5.0 - 57.3 L/m^2	0.69 – 0.98 bar	Variable; Worst-case included pressure pauses	**4.31 – 6.69**

- Claimed Conditions

Filtration Volume	Filtration Volume	Transmembrane Pressure	Pressure Release	LRV
45 – 60 L/m^2	≤ 4.4 L/m^2	≤ 0.98	One pause of ≤ 10 min during filtration and a ≤ 10 min pause between the end of filtration and flushing.	**4.31**

[1] Results were provided for each the listed attributes was provided in submission for each for the 10 "relevant" products. Ranges are used here to summarize the data.

Example 1: *Application of external and internal prior knowledge*

Considerations:

- The filter type was the same for all products.
- All products were mAbs or mAb fusion products.
- Representativeness of the sample matrix.
- Claimed conditions considered worst-case combination of parameters to support the selected viral clearance claim. Viral clearance claim was considered worst-case.

Example 2: *Extrapolation from similar product*

<u>Leveraging Prior Knowledge for AEX Chromatography Clearance</u>

- Phase 1 IND for cytokine produced in CHO cells.
- Prior knowledge from similar product is leveraged to support clearance claims for AEX chromatography to support opening of the IND.

Example 2: *Extrapolation from similar product*

Summary of Process Conditions

Process Conditions	Validated Product	Extrapolated Product
Column Type	GE Healthcare Capto Q (AEX)	GE Healthcare Capto Q (AEX)
Mode of Operation	Flow through	Flow through
Location in Process	2nd to last column	Last column
Flow Rate	100 cm/hr	105 cm/hr
Protein Concentration	40 g/L	35 g/L
Buffer System	50 mM NaCl, 25 mM Tris, pH 7.2	50 mM NaCl, 25 mM Tris, pH 7.2
Total Load	3 CVs	2.5 CVs
Bed Height	20 cm	19 cm

Example 2: *Extrapolation from similar product*

Considerations:

- Columns are at a different location in the process
  - There may be differences in the sample matrix that impact viral clearance. Based on the different location in the process, an addition justification would be needed to justify differences in the product matrix, including an evaluation of the product matrix. There should be equivalent or less impurities that would interfere with viral clearance.
- Justification would need to be provided to support the relevancy of the other product.
- Justification should be provided to support that differences in process parameters would not be expected to impact viral clearance claims.
- Extrapolation from a single-product may not be sufficient and would need to be considered on a case-by-case basis.

Questions for Discussion

1. What are best practices for capturing and documenting prior knowledge?
2. What are the best practices for presenting prior knowledge to regulators or in regulatory filings?
3. How do you justify applicability of prior knowledge?
4. Are there opportunities to apply prior knowledge where it is not currently applied?

Application of Prior Knowledge for Analytical Procedures

Key Concepts from ICH Q2 and Q14

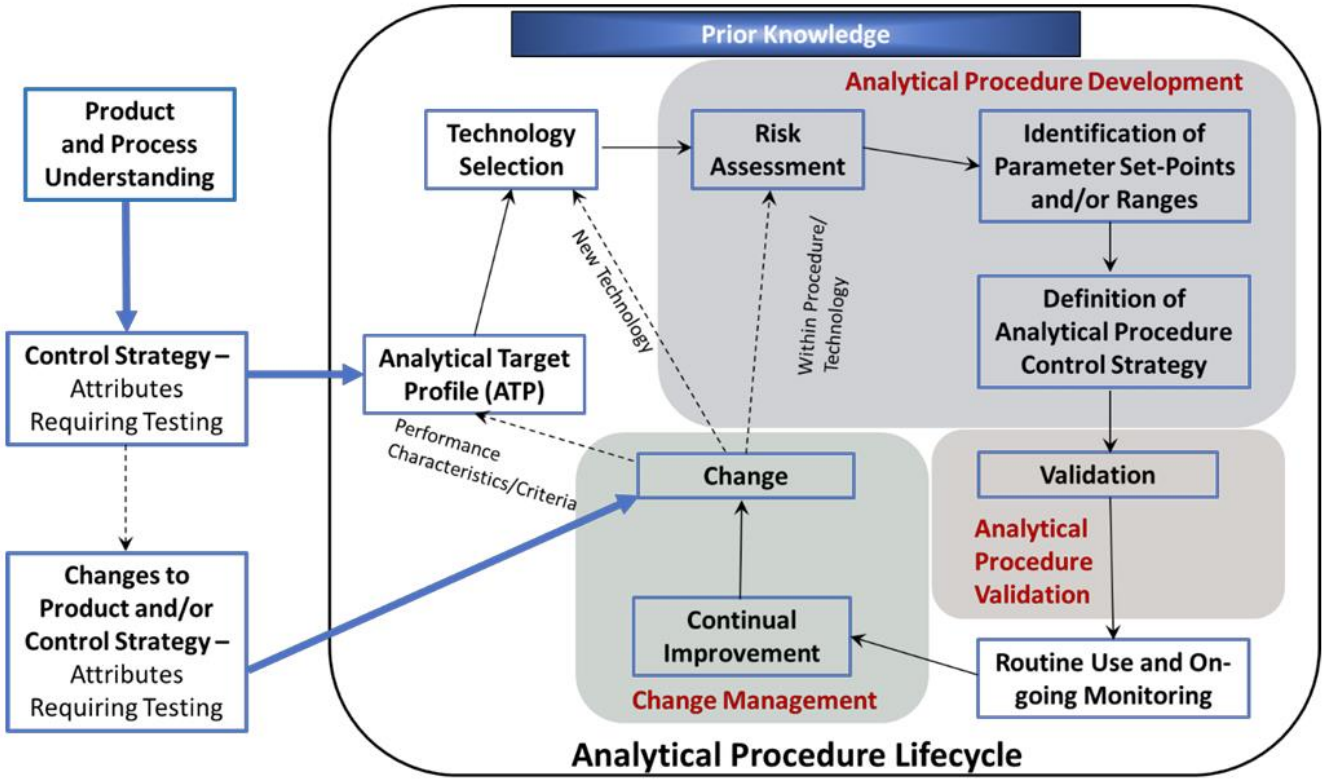
- Adaptable to technological change and allows continuous improvement
- Data acquired and analyzed over time provides knowledge to identify critical attributes to be monitored and acceptance criteria to be developed
- Sufficient information or prior knowledge should be available to design appropriate future bridging studies
- Greater level of analytical details in applications can lead to greater assessor understanding

https://www.casss.org/docs/default-source/at-europe/2022/keire-david-cder-fda 2022.pdf?sfvrsn=6f3ccc63_6
https://database.ich.org/sites/default/files/ICH_Q14_Guideline_2023_1116_1.pdf
https://database.ich.org/sites/default/files/ICH_Q2%28R2%29_Guideline_2023_1130.pdf

Case Study 3: *Application of prior knowledge for accelerated method development*

ICH Q14 Guideline

Figure 1: The analytical procedure lifecycle



Example from Capillary electrophoresis sodium dodecyl sulfate (CE-SDS)*:

- CE-SDS analytical procedures are commonly used to evaluate the size heterogeneity, purity, and manufacturing consistency of biologics.
- The conditions for analytical procedures are established by leveraging prior learnings and knowledge from previous product-specific and platform-validation studies.
- During the utilization phase, the feasibility of the analytical procedure for new mAbs is evaluated through limited assessment studies, such as precision, specificity, stability indication, and comparison of UV and fluorescence electropherograms to ensure proper dye labeling

***Published in Graul et al., Industry Perspectives on Practical Application of Platform Analytical Procedures. Pharmaceutical Engineering, September/October 2024**

Case Study 3: *Application of prior knowledge for accelerated method development*

- Considerations*

ICH Q2R2: when an established platform analytical procedure is used for a new purpose, validation testing can be abbreviated, if scientifically justified.

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

***Published in Graul et al., Industry Perspectives on Practical Application of Platform Analytical Procedures. Pharmaceutical Engineering, September/October 2024**

Questions for Discussion

1. What are best practices for capturing and documenting prior knowledge?
2. What are the best practices for presenting prior knowledge to regulators or in regulatory filings?
3. How do you justify applicability of prior knowledge?
4. How do you apply prior knowledge across modalities/best practices?
5. Are there opportunities to apply prior knowledge where it is not currently applied?
6. How do you apply prior knowledge when adapting novel technologies?

Applications of Prior Knowledge: Any Examples to Share?

- Risk Assessments (CQA assessment, process impurities, E&L, etc.)
- Process development
- Formulation development
- Container closure
- Method development
- Control strategy development
- Impurity clearance
- Process validation
- Specification setting
- Stability

Thank you for participating in the discussion!