A Regulatory Perspective on the Use of Prior Knowledge

Cristina Ausin, Ph.D.
Office of Biotechnology Products
OPQ, CDER, FDA
CMC Strategy Forum
January 29th, 2018
Disclaimer

The views and opinions expressed should not be used in place of regulations, published FDA guidances, or discussions with the Agency.
Outline

• What is prior knowledge?

• Areas where prior knowledge is applicable

• Limitations of the use of prior knowledge
What is Prior Knowledge?

• ICH Q11:
  “Prior knowledge can include established biological, chemical, and engineering principles, technical literature, and applied manufacturing experience.”

• ICH Quality Implementation Working Group on Q8, Q9, and Q10 Questions and Answers (R4):
  Knowledge Sources:
  “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)”
What is Prior Knowledge?


“Prior knowledge in the QbD framework generally refers to knowledge that stems from previous experience that is not in publically available literature”
Areas where prior knowledge is applicable
ICH Q11

• “Identify the **material attributes** and **process parameters** likely to have the greatest **impact on drug substance quality**. This can be based on **prior knowledge** and risk assessment tools.”

• “**Knowledge management** can also facilitate **manufacturing process development**. In this context, potential sources of information can include **prior knowledge** and development studies.”

• “**Platform Manufacturing:** The approach of **developing a production strategy** for a new drug **starting from manufacturing processes similar** to those used by the same applicant to the manufacture of other drugs of the same type (e.g. as in the production of monoclonal antibodies using predefined host cell, cell culture, and purification processes, for which there already exists considerable experience).”
Areas where prior knowledge is applicable

ICH Q11

• "Design space can be developed based on a combination of prior knowledge, first principles, and/or empirical understanding of the process."

• Identification of CQAs:
  
  “Prior knowledge can be used at the beginning of development and assessments can be iteratively updated with development data (including data from nonclinical and clinical studies) during the lifecycle.”

• “Where development refers to specific prior knowledge, the relevant information and data should be provided, and where appropriate, the relevance to the particular drug substance should be justified.”
Areas where prior knowledge is applicable
ICH Q8

• ICH Q8 (R2) – Pharmaceutical Development
  – A systematic approach to development (also defined as QbD) can include, for example, incorporation of prior knowledge.

  – **Risk assessment** tools can be used to identify and rank parameters with potential to have an impact on product quality, based on prior knowledge and initial experimental data.
Areas where prior knowledge is applicable

- Manufacturing Process
- Control Strategy (QTPP and CQAs)
- Risk Assessments
- QbD and DoE
Areas where prior knowledge is applicable

• Manufacturing Process
• Control Strategy (QTPP and CQAs)
• Risk Assessments
• QbD and DoE
Prior Knowledge – Formulation and CCS

• Selection of initial formulation and CCS are informed by prior knowledge, molecule characteristics, disease (route of administration, patient population...)

• Agency’s experience:
  – Limited prior knowledge information in submissions
  – Formulation and CCS suitability supported by stability and leachables data
Prior Knowledge: Manufacturing Process Design

• Classification of Process Parameters and In-Process Controls as critical or key:
  – Initial classification based on platform (prior) knowledge
  – Confirmed based on product’s development data

• Proven Acceptable Ranges (PAR) can be supported by:
  – Validation data
  – Development data (full- and small-scale lots)
  – Prior knowledge
Prior Knowledge: Manufacturing Process Design

• Information to be included in the submission for prior knowledge:
  – Source of prior knowledge
  – Relevant data
  – Justification of its relevance/applicability

• eCTD section:
  – 3.2.S.2.6 and 3.2.P.2
  – Links from 3.2.S.2.2, 3.2.S.2.4, 3.2.P.3.3, and 3.2.P.3.4
Prior Knowledge: Process Validation

  – Process Design includes building and capturing process knowledge and understanding
  – PPQ: “Previous credible experience with sufficiently similar products and processes can also be helpful.”
  – “Decisions and justification of the controls should be sufficiently documented”
Prior Knowledge Limitations: Process Validation

• A risk of over-reliance on prior knowledge are manufacturing steps not properly controlled
  – UF/DF example 1: differences in excipient concentration between diafiltration buffer and final product formulation
  – UF/DF example 2: number of diavolumes not adequate → metal impurities present in the final product

• Validation studies expected to be performed with the actual product
Prior Knowledge: Viral Clearance Studies

Points to Consider in the Manufacture and Testing of MAb Products for Human Use (1997):

- **Generic Clearance Study**: virus removal and inactivation is demonstrated for several steps of the purification process of a *model antibody*

- **Modular Clearance Study**: demonstrates virus removal or inactivation of individual steps with *model antibodies*

- **Applicability Criteria**: extrapolation supported by information about product and process characteristics (species, class, subclass, source, cell substrate, elution buffers, elution conditions...)

www.fda.gov
Areas where prior knowledge is applicable

- Manufacturing Process
- Control Strategy (QTPP and CQAs)
- Risk Assessments
- QbD and DoE
Prior Knowledge: Control Strategy

- QTPP and CQAs:
  - Product specific: each product has unique properties that should be understood to establish proper controls
  - Defined prospectively based on prior knowledge
  - Re-defined based on development data
  - Examples of MAb QA with minimal or no known impact on safety or efficacy:
    - C-terminal lysine
    - C-terminal proline amidation
    - Some process-related impurities below a well defined limit (e.g. DNA, elemental impurities)
    - Others known for a specific product class
Prior Knowledge: Control Strategy

• Information to be included in the submission for prior knowledge:
  – Source of prior knowledge
  – Relevant data
  – Justification of its relevance/applicability

• eCTD section:
  – 3.2.S.3, 3.2.S.4.5, and 3.2.P.5.6
Prior Knowledge: Analytical Assays

FDA Guidance – Analytical Procedures and Methods Validation for Drugs and Biologics (2015):

• “Analytical procedures in early stages of development are initially developed based on a combination of mechanistic understanding of the basic methodology and prior experience.”  
  → **Development based on assay platform (prior) knowledge**

• “To apply an analytical method to a different drug product, appropriate validation or verification studies for compendial procedures with the matrix of the new product should be considered.”  
  → **Validation with the actual product**
Areas where prior knowledge is applicable

• Manufacturing Process
• Control Strategy (QTPP and CQAs)
• Risk Assessments
• QbD and DoE
Prior Knowledge – Risk Assessments

• ICH Q9:
  – “The degree of rigor and formality of quality risk management should reflect available knowledge”
  – “The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.”

• Risk assessments leverage knowledge gained during development and **prior knowledge** including understanding of the process, and experience gained from processing similar types of products in the past.

• **Prior knowledge** can be used to lower the uncertainty score in risk assessments
Areas where prior knowledge is applicable

• Manufacturing Process
• Control Strategy (QTPP and CQAs)
• Risk Assessments
• QbD and DoE
• **Prior knowledge** is a source of information for DoE, QbD, and modeling

• **Prior knowledge** can be used to determine factors for DoE studies and selection of variables for models

• FDA Emergent Technology Program was created to promote adoption of innovative approaches to product design and manufacturing

• Emergent Technology Team has cross-functional expertise to evaluate novel approaches
ICH Q10: “Knowledge management is a systematic approach to acquiring, analyzing, storing and disseminating information related to products, processes and components.”

Knowledge is updated constantly to incorporate new lessons learned

Knowledge from each new product becomes prior knowledge to be evaluated in the development of future products and improvement of existing products
Take Home Messages

• Objectives of the use of prior knowledge are faster drug development and enhanced manufacturing efficiency
• Prior knowledge is leveraged and used to confirm data rather than building data/process from scratch
• Critical: Understanding that each product has unique properties that should be understood in order to establish appropriate IPC, controls of input materials, DS and DP specs
• Main concern: risks associated with over-reliance on prior knowledge

• Use of prior knowledge to support applications should not change the expectations of assurance of quality
Take Home Messages

• Optimal use of prior knowledge in applications requires:

  – Clear distinction of what is prior knowledge and what is product specific knowledge

  – Information to be placed in supportive eCTD sections with links to facilitate navigation

  – Justification and demonstration of the relevance and applicability of prior knowledge to the new product
Acknowledgements

Chana Fuchs
Joel Welch
Leslie Rivera-Rosado
Joslyn Brunelle
Other OBP colleagues