Control Strategy and ICH Q11

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ICH Q11

Development and Manufacture of Drug Substance

- In Spring of 2008, the ICH Steering Committee agreed there was a need for Q11
  - It was understood that the concepts described in ICH guidances Q8(R2), Q9, and Q10 generally apply to Drug Substance as well as to Drug Product, but...
  - Processes for manufacture of Drug Substance are very different from Drug Product (e.g, purification)
  - Therefore, there was a perceived need for additional clarity on how the principles apply to Drug Substance, and a desire for examples

ICH Q11

<u>Development and Manufacture of Drug Substance</u>

- ICH Q11 rapporteur: Brian Withers (EFPIA)
- The ICH Q11 Expert Working Group (EWG) first met in Portland, OR in June 2008

ICH Q11

<u>Development and Manufacture of Drug Substance</u>

- EWG also met in
  - Brussels Nov 2008
  - Yokohama June 2009
  - St. Louis Nov 2009
  - Tallinn (Estonia) June 2010
  - Fukuoka (Japan) Nov 2010
- Step 2 document was published for public comment in Spring/Summer 2011
  - About 1300 comments from all three ICH regions

ICH Q11

<u>Development and Manufacture of Drug Substance</u>

- Road to Steps 4 & 5
  - Keith McDonald (EMA) became rapporteur
  - EWG met in Seville Nov 2011 to consider comments; reached agreement on a “pre-step 4” document
  - Finally reached step 4 (concurrence in all three ICH regions) in April-May 2012
- Current status
  - Published in EU (step 5)
  - Awaiting publication in USA and Japan

ICH Q11 Discusses More Than Just Control Strategy

- Manufacturing Process Development
- Description of Manufacturing Process and Process Controls
- Selection of Starting Materials and Source Materials
- Process Validation/Evaluation
- Submission of Manufacturing Process Development and Related Information In CTD Format
- Lifecycle Management

Control Strategy in ICH Q11

- A control strategy is a planned set of controls, derived from current product and process understanding, that assures process performance and product quality (ICH Q10)
  - Assures process performance, and
  - Assures “product” quality
    - “Product” here was interpreted as not necessarily meaning “drug product”; i.e., that for a drug substance manufacturing process, the drug substance is the “product”
  - Interpretation: each control strategy pertains to a manufacturing process and the “product” it creates

Control Strategy in ICH Q11

- Every drug substance manufacturing process, *whether developed through a traditional or an enhanced approach (or some combination thereof),* has an associated control strategy
- In other words:
  - The guidance does not acknowledge that there is any such thing as an “enhanced” or a “traditional” control strategy
  - A control strategy is just a control strategy, regardless of how it is developed

“Elements” of a Control Strategy

- A control strategy can include, but is not limited to, the following:
  - Controls on material attributes (e.g., of raw materials, starting materials, intermediates ...);
  - Controls implicit in the design of the manufacturing process (e.g., sequence of purification steps (Biotechnological/Biological drug substances), or order of addition of reagents (Chemical entities));
  - In-process controls (including in-process tests and process parameters);
  - Controls on drug substance (e.g., release testing).

Approaches to Developing a Control Strategy

- A control strategy can be developed through a combination of approaches
  - utilizing a traditional approach for some CQAs, steps, or unit operations, & more enhanced for others
- Traditional approach (to developing a manufacturing process and control strategy)
  - Set points and operating ranges are typically set narrowly based on the observed data to ensure consistency
  - More emphasis is placed on assessment of CQAs at the stage of the drug substance (i.e., end-product testing)
  - Limited flexibility in operating ranges to address variability

Approaches to Developing a Control Strategy

- Enhanced approach (to developing a manufacturing process and control strategy)
  - Better process and product understanding than the traditional approach, so sources of variability can be identified in a more systematic way
  - Allows for development of more meaningful and efficient parametric, attribute, and procedural controls
  - Could be developed through several iterations
  - Can provide for flexibility in operating ranges to address variability

Considerations in Developing a Control Strategy

- A control strategy should ensure that each drug substance CQA is within the appropriate range, limit, or distribution to assure drug substance quality
  - This is derived from the definition of “CQA”
  - Also based on assumption that the drug substance or drug product will always be of acceptable quality when all of the CQAs are met
    - Which is expected to be true if the material is well understood (i.e., all CQAs have been identified)
    - But how can one be sure all the CQAs have been identified?

Considerations in Developing a Control Strategy

- A control strategy should ensure that each drug substance CQA is within the appropriate range, limit, or distribution to assure drug substance quality
  - *Does not say* that the drug substance specification should ensure that each CQA is within the appropriate range, limit, or distribution
  - The drug substance specification is one part of a total control strategy and not all CQAs need to be included in the drug substance specification

Considerations in Developing a Control Strategy

- CQAs can be:
  - included on the specification and confirmed through testing the final drug substance, or
  - included on the specification and confirmed through upstream controls (e.g., as in Real Time Release Testing (RTRT)), or
  - not included on the specification but ensured through upstream controls
    - Examples of “upstream controls” include:
      - in-process testing
      - use of measurements of process parameters and/or in process material attributes that are predictive of a drug substance CQA

Considerations in Developing a Control Strategy

- Whether a traditional or enhanced process development approach is taken
  - Use of upstream controls should be based on an evaluation and understanding of the sources of variability of a CQA
  - Downstream factors that might impact the quality of the drug substance should be taken into consideration (e.g., temperature changes, oxidative conditions, light, ionic content, shear)

Considerations in Developing a Control Strategy

- A manufacturer can consider implementing controls for a specific CQA at single or multiple locations in the process
  - Depending on the risk associated with the CQA, and
  - Ability of individual controls to detect a potential problem
    - Example (for biotechnological/biological drug substances or sterilized chemical entities):
      - Ability to detect low levels of bacterial or viral contamination is inherently limited, so testing on the drug substance is considered inadequate
      - Additional controls (e.g., attribute and in-process controls) are incorporated into the control strategy

Considerations in Developing a Control Strategy

- Quality of each raw material should be appropriate for its intended use
  - Quality of input materials can depend in part on where the material is used in the process
    - Raw materials used in operations near the end of the manufacturing process have a greater potential to introduce impurities into the drug substance than raw materials used upstream
    - Manufacturers should evaluate whether the quality of such materials should be more tightly controlled than similar materials used upstream.

Submission of Control Strategy Information

- ICH Q11 quotes ICH M4Q on recommendations regarding submission of the individual elements that make up the control strategy:
  - Description of Manufacturing Process and Process Controls (3.2.S.2.2)
  - Control of Materials (3.2.S.2.3)
  - Controls of Critical Steps and Intermediates (3.2.S.2.4)
  - Control of Drug Substance (3.2.S.4)
  - Container Closure System (3.2.S.6)

Submission of Information: Control Strategy Summary

- The information provided on the control strategy should include …, *when appropriate*, a summary of the overall drug substance control strategy
  - Either a tabular format or in a diagrammatic format (to aid visualisation and understanding)
  - See Example 5
  - Ideally, the summary should explain how the individual elements of the control strategy work together to assure drug substance quality
    - I.e., the more complicated the control strategy, the more a summary would be useful and therefore “appropriate”

ICH Q11 and "Critical" Process Parameters

- What does ICH Q11 say about "critical" process parameters (with regard to the Control Strategy, or otherwise)?
  - Nothing
  - The term "critical process parameter" (either singular or plural) does not appear in ICH Q11
  - The word "critical" occurs only in reference to:
    - CQAs, and
    - ICH M4Q "Controls of Critical Steps and Intermediates"
- *The absence of the term is no accident*

Rationale for Not Discussing CPPs in ICH Q11

- CPP issues also pertain to drug product, whereas Q11 is only about drug substance
  - Discussing CPPs could be considered exceeding the bounds of the EWG's purview
- One of the most contentious issues regarding CPPs is how they relate to the reporting of postapproval changes
  - Postapproval changes were outside the scope of Q11

Conclusions

- Each drug substance manufacturing process has an associated Control Strategy
- The control strategy includes controls on input material attributes, controls on output material attributes, and controls on whatever happens in between
- The control strategy should ensure that all CQAs are within their appropriate limits, ranges, or distributions

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