Utilisation of QbD Principles for the Management of Post Approval Changes for a novel recombinant monoclonal antibody:

Feedback from Case Study

Kowid Ho, AFSSaPS

Jason Hampson, Amgen UK

Case Study Background

- Fully human IgG monoclonal antibody manufactured in rDNA CHO cells
- Licensed in several territories including the EU
- Appropriate control strategy currently licensed, based on:
  - Initial product and process characterisation
  - «Traditional» process validation
  - Extensive commercial experience
- Supplemental product and process knowledge studies utilising QbD principles will:
  - Enable process improvements
  - Optimize process robustness and operational flexibility

Case Study Content

- Criticality ranking of quality attributes using risk assessment tool
  - Considering prior knowledge and extensive product characterisation
  - Criticality continuum approach
- Relative criticality ranking guides & focuses:
  - Priorities for risk assessments for Design of Experiments (DOE) for targeted unit operations
  - Confirmation of robustness of control strategy (in combination with process capability risk assessment)

Case Study Content

- **3 examples of unit operation Design Space (DSp):**
  - Simple 2-D representation, where only 1 CQA was impacted by interaction of 2 process variables
  - More complex DSp, with 2 CQAs impacted by interaction of 5 process variables
  - Upstream, cell expansion unit operation, where no CQAs were impacted across full characterised range
- **DSp is not linear, expressed as 1 or more equations (per CQA)**
  - There are several valid ways in which operating ranges within the DSp can be selected, depending on which process variable is restricted
- **Limitations of DSp defined only by impact on CQAs**
  - Other process consistency controls may be implemented to define the resulting in-house operating range
- **In post-approval setting, commercial scale batch data used to confirm and refine the DOE output (Statistical Process Model)**

Main Topics Discussed

Extent of a Design Space:

- Movement within a (unit operation) Design Space is not a change requiring regulatory oversight
- Clarity regarding more complex changes within (multiple) DSps is important
  - A complex change (e.g. covering multiple unit operations DSps, or including change of scale and site) would require:
    - Re-assessment/change in control strategy
    - A degree of regulatory oversight
  - More complex changes may be better described in a dedicated post-approval change protocol / PMP?

Main Topics Discussed

- What does S2.5 Process Validation/Evaluation look like in a post approval QbD environment?

  Options:

  – Lab scale DOE data, plus process validation protocol
  – Submit data from process qualification at pilot scale,
- Continuous process monitoring/verification at commercial scale
  – Mechanism for regulatory oversight of data generated post-implementation (explicit & descriptive FUM, provision of data?)
- Scale-Down Models
  – Lab scale
  – Pilot scale (optional)

Main Topics Discussed

- Information to be presented in the regulatory application
  - Control Strategy
  - Design Space
  - Process Validation / Evaluation
- Information to be made available during inspection
  - Quality systems
  - Other?
- For discussion:
  - Results of continuous monitoring/verification activities?
  - Submission of pilot scale model?

Common Understanding

- QbD approach is equally applicable to biotech products
- Quality Risk Management approach to identification of criticality of Quality Attributes is consistent with ICH Q9
- DOE principles valid for biological products/processes
- Change within a DSp is not a change requiring regulatory oversight

Areas For Further Work

- What information to be included in the regulatory application?
- What information will go into S2.5 Process Validation/Evaluation?
  - Qualification of scale-down models (lab & pilot) to be predictive of commercial scale
  - Process Validation protocol approach combined with continuous monitoring / verification?
- Mechanism for regulatory oversight of continuous verification/validation?
  - Agreement between Industry and Regulators (Assessor & Inspector, OMCL)
- Terminology:
  - DSp – for a unit operation or broader?
  - Validation vs qualification vs verification vs monitoring
  - DSp is independent of post approval change protocol

Closing

- Case study has been very valuable to further QbD understanding
- Continued dialogue is important to further elucidate & refine
- More understanding, consistency / consensus is highly desirable
  - Regulator-Industry
  - Regulator-Regulator
  - Industry-Industry
- Achievable via
  - Regulator-Industry collaboration, workshops
  - Scientific advice meetings, trial submissions
  - New & amended guidance, Q&A

Backups

Case Study Content

- Qualification of a pilot scale model
  - Optional, supplemental tool which may be used to understand & qualify planned changes
- Post-approval management plan (PMP) concept
  - Documented (Repository of?) product and process knowledge
  - May be used to describe future process changes and prospectively define criteria for successful implementation
  - PMP concept may enable a shift of regulatory oversight toward pre-implementation review with post-implementation data verification

Proposal: Control strategy elements that will be contained in a regulatory submission

Updated CTD Components:

- **S.2.3 Control of Materials** – risk assessment for raw materials used in the process and control of incoming materials
- **S.3.1 Elucidation of structure and other characteristics and S.3.2 Impurities** – detailed assessment of product characteristics and identification of critical product quality attributes
- **S.2.4 Control of Critical Steps and Intermediates** – procedural controls, including a list of test methods and acceptance criteria
- **S.4.1 Specification** – update to tests and controls as needed for end product testing

Information available at inspection

- Quality Systems

Information to be provided in Post Approval Management Plan

- Outline of overall control strategy
- Continuous verification
- Justification for change in control strategy

Proposal: Design Space elements that will be contained in a regulatory submission

Updated CTD Components

- **S.2.2 (Description of Manufacturing Process and Process Controls)**: Design space for each unit operation
  - Maximum acceptable ranges and description of each restriction on the design space, including quality attribute limits for parameters that impact product quality
  - Description of acceptable ranges for parameters not affecting quality attributes
- **S.2.6 (Process Development):** Supporting Information
  - Risk assessment output for each unit operation
  - Summary of DOE studies performed for screening and optimization
  - Summary of statistical analyses for relevant quality attributes (eg, Response surface model, parameter significance, estimates, ranking, interactions, equations)

Information available at inspection

- Full reports from Process Characterization
- Operational ranges for manufacturing process unit operations
- Quality Systems

Information to be provided in Post Approval Management Plan

- Unit Operation Design Space
- Plan for evaluation of specified changes

Post-Approval Management Plan (PMP)

One example of potential PMP Content:

- Product knowledge including known criticality of quality attributes
  - Identified to ensure continued safety and efficacy of product
- Defined control strategy
  - To confirm that the manufacturing process is performing as expected and that product quality remains within specified criteria
- Process knowledge, crystallised as unit operation design space
- Procedure for evaluation of future changes
  - Change qualification strategy (including use of scale-down model(s))
  - Includes assessment of appropriateness of control strategy based on the nature of the change
- Summary of Quality procedures and systems
  - To ensure that the appropriate controls, oversight, and regulatory notification are performed once a change is implemented