Industry Case Study 5:

QbD Development (Derivation of CQAs, CPPs and Design Space using Quality Risk Assessment and Design of Experiments on a Scale-Down Model of the Manufacturing Process) of a Novel Therapeutic Protein

Graham Cook, Wyeth

Mats Welin, Medical Products Agency, Sweden

Case Study Summary - 1

- **Introduction to project**
  - QbD applied to Drug Substance
  - Monoclonal antibody in Phase 3 development
  - CHO cell manufacturing process
- **Defining the QTPP and Drug Substance CQAs**
  - Quality Risk Assessment approach to identify potential CQAs was described
  - Outline presented of Structure-Activity Relationship (SAR) studies to understand attributes with unknown impact to severity or limited knowledge
  - SAR studies ongoing

Case Study Summary - 2

- **Scale-down models**
  - Approach to development of scale-down model was described briefly
  - Data was presented to show equivalent performance across multiple scales
  - Valid scale-down model used for process characterization
- **Upstream and downstream process characterization**
  - Approach to characterization of the cell culture and purification processes was described:
    - Quality Risk Assessment and initial screening studies to identify potential CPPs
    - Multivariate DoE to develop response surfaces and design space
    - Linkage between certain unit operations explored
  - Graphical examples of response surfaces / design space presented

Case Study Summary - 3

- **Developing process understanding, design space and control strategy for the HMW CQA**
  - mAb species with potential to form HMW aggregate
  - Experimental investigation of phenomenon described, including development and use of an analytical tool
  - Process understanding used to refine scale-down model and adjust large scale process
  - Process understanding used to develop a design space for bioreactor
- **Summary - Learnings**
  - QbD principles for large and small molecules the same
  - QbD goal is product and process robustness and enhanced QA
  - Scale-down models important to develop process understanding

Main Topics Discussed - 1

Technical Discussions:

- How do you feedback large scale experience into scale-down models?
  - e.g. refinement of models based on large scale experience
- How can a company show that ‘all’ factors have been considered during development and establishment of the manufacturing process?
  - How have interactions been taken into consideration?
- How are other factors combined into the design space e.g. developing a combined design space for several CQAs?
  - Need to demonstrate the effects of the CPPs on other CQAs if a design space for a single CQA is illustrated
- How was the risk ranking process conducted - e.g. setting thresholds, and scoring?

Main Topics Discussed - 2

Preparation and Review of Dossiers and Inspections:

- In which way will the new tools will help manage changes or improvements to biologics?
- Would non-critical attributes and parameters be discussed in the submission? What commitments would be made for e.g. trending?
- Would the approach to inspections change with a biologic developed using QbD principles?

Common Understanding - 1

- Understanding of the application of QbD to biologics has advanced
- Design spaces for biologics can be registered and movement within the design space can be managed within the company's quality system
- Need for industry to continue to define, justify and focus on CQAs/CPPs AND provide rationale for non-critical attributes and parameters
- Certain non-critical attributes/parameters may be monitored without regulatory commitments e.g. fixed limits
- Data from scale-down models are important to define and understand the process
  - Needs to be predictive and applicable to large scale manufacture

Common Understanding - 2

- Data summaries for small scale characterisation studies should be presented in the dossier and at time of inspection
  - Limited time available to reviewers and inspectors means that concise, well-explained overviews are required, with enough data to support conclusions
- Approaches to inspections may not change substantially
  - Still doing a GMP inspection with similar focus on quality systems
  - Assessors may join inspectors for more complex submissions
- Design space maintenance requires knowledge management
  - Continuous feedback of experience, including iterative quality risk management, gained at both large scale and small scale
  - Maintain through robust change management process

Areas for further Discussions

- Are data coming only from scale-down models sufficient for justification of changes?
- How could different equipment be included in a design space e.g. disposable bioreactors?
- How to use prior knowledge to facilitate further planned changes?
  - e.g. inclusion of protocol describing approach in original submission (similar to approach for Stability studies)
- Presentation of design space, in a way that makes it easily understandable, where there may be >3 parameters impacting several CQAs