A-Mab Case Study: Still A Few Challenges!!

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Goal For Today’s Presentation

- Brief recap of the A-Mab case study
- Implementation Challenges
- Current State
A-Mab: a Case Study in Bioprocess Development
To illustrate options to achieve enhanced product and process understanding
Demonstrate Industry’s vision for QbD as applied to biotech product
Creating a Biotech Case Study: “A-Mab”

- Based on a monoclonal antibody drug substance and drug product
  - “A-Mab”
  - Humanized IgG₁
  - IV Administered Drug (liquid)
  - Expressed in Cho Cells
  - Treatment of NHL
- Is freely available as a teaching tool for industry and agencies

**Why Monoclonal Antibody?**
- Represents a significant number of products approved and in development
- Good product and process experience in development and manufacture
## Outline and Intent of Case Study

### Content
- Structure
- Introduction
- Quality Attributes
- Upstream
- Downstream
- Drug Product
- Control Strategy
- Regulatory

### Intent
- Contains pieces/sections that appear realistic and represent selected QbD principles
- Illustrates the benefits of a QbD development approach
- Information represents real data or appropriate fictitious data
- Not a mock CTD
- Not a Gold Standard
What’s Next??
From Theory to Practice!

- Critical Quality Attributes
- Risk Assessment Tools
- Design Space
- Critical Parameter Designation
- Control Strategy

An evolution
Target Product Profile

Drug substance properties; prior knowledge

Proposed formulation and manufacturing process to meet desired product attributes

Determination of Cause – Effect relationships
   (Risk Identification with subsequent Risk Analysis)

Risk-based classification
   (Risk Evaluation)

Parameters to investigate (e.g. by DOE)
Road Map for Process Understanding And Characterization

Knowledge Space
- QA1 = f (PP2, PP3, PP6)
- QA2 = f (PP4)
- CQA3 = f (KPP1, CPP4, KPP5)
- QA4 = f (PP1, PP3, PP4, PP6)
- CQA5 = f (CPP2, KPP5)

Criticality Of PP
- PP1 ?→ CPP1
- PP4 ?→ CPP4
- PP5 ?→ KPP5

C&E
- QA4 associated with PP1,n
- QA3 associated with PP1,n
- QA4 associated with PP1,n
- QA5 associated with PP1,n

Risk Assessment
- QA1 associated with PP1,n
- QA2 associated with PP1,n
- QA3 associated with PP1,n
- QA4 associated with PP1,n
- QA5 associated with PP1,n

Plan Execution (DOE, Models, SOS)
- QA1 = f (PP2, PP3, PP6)
- QA2 = f (PP4)
- QA3 = f (PP1, PP4, PP5)
- QA4 = f (PP1, PP3, PP4, PP6)
- QA5 = f (PP2, KPP5)

CQA3 = f (KPP1, CPP4, KPP5)
CQA5 = f (CPP2, KPP5)

DOE/Experimental Strategy Output

Quality Attribute Criticality Assessment
- QA3 ?→ CQA1
- QA5 ?→ CQA2

FMECA

Design Space
- CQA3 = f (KPP1, CPP4, KPP5)
- CQA5 = f (CPP2, KPP5)

Describe in S2/P2 Section

Control Strategy
Align With Target Product Profile!

- Developability Assessment
  Understand Safety, Immunogenicity and CMC risks
- Aid in Molecule Selection
Quality Attributes and the Criticality Continuum

Product Understanding

Process Understanding = Design Space?

- Risk Assessment Methodologies
- Equivalence of scale down models
- Multivariate DOE studies
- CPP and non-CPP designation
- Experience from clinical batches
Comprehensive Control Strategy: Minimize Risk

Establishment of Quality Systems
Where Are We??

FDA Pilot Program

“FDA approved Gazyva (!) including the QbD based control strategy and Design Space – Nov 1, 2013”

........ Lynne Krummen, Ph.D.
    VP, Global Head Roche Technical Regulatory, Biologics
    2013  ISPE Annual Meeting

➢More to come????
A Case Study for Vaccines?

Yes, of course, we must explore QbD for vaccine development!

Look at the impact of A-mAb case study!!
CMC-Vaccine Working Group QbD Case Study
Thank you for your attention!

Questions??