# A-Mab: a Case Study in Bioprocess Development

CMC Biotech Working Group















## Study Guide

Version 2.1

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### A-Mab Study Guide

#### **Study Guide Introduction and Objectives**

The Study Guide was developed as a tool to help drive discussions related to the A-Mab Case Study.

We recognize that within the Case Study itself, there are areas where the concepts behind QbD were interpreted and subsequently, implemented in ways that perhaps "pushed the envelope" related to whether or not the approach taken would be deemed appropriate. Similarly, other areas of the Case Study are based on assumptions that could be supported with more information and data.

Not surprisingly, the decision over what approach to take and how far to take it – coupled with what conclusions should be supported by data versus assumptions – generated a significant amount of interest amongst the CMC-BWG.

The Study Guide was put together to ensure these discussions were not lost. It represents a collection of additional materials, points for discussion, and questions that the CMC-BWG thinks will provide a useful substrate for discussion. In fact, many of the questions captured in the Study Guide are the same ones that came up as the group debated how best to illustrate the principles of QbD.

As you review the Case Study, you may find more issues and opportunities that could be discussed. Given the Case Study is intended to be a teaching and learning tool, our goal is to catalyse the debate and dialogue that is needed in order for industry and the regulatory agencies to overcome the challenges associated with implementing QbD. Indeed, it is our hope that these discussions will serve to provide the clarity needed for the benefits of QbD to be achieved on a global scale.

#### **Chapter 1: Introduction**

#### **Introduction and Learning Objectives**

#### Goal of the case study is to help readers understand how they can apply Qbd to achieve:

- A systematic evaluation, understanding and refining of the active ingredient manufacture, the formulation, and its manufacturing process
- Use of the enhanced product and process understanding in combination with quality risk management to establish an appropriate control strategy which, in this study,, includes a proposal for a design space(s) and/or real-time release testing.
- Development of frameworks that drive the approach illustrated within the case study; an approach that highlights and presents concepts related to how QbD can be implemented within the biotechnology arena

#### **Questions for Discussion**

The Introduction outlines the framework and approach that the case study will use to exemplify a QbD approach to product development. The framework developed is represented in the Figure 1.1 below:



Figure 1.1

The figure attempts to illustrate a sequence of activities that starts with the design (Note: molecule design not included in diagram) of the molecule and spans the development process ultimately resulting in the final process and control strategy used for commercial manufacturing.

1. Please comment on the framework established and its ability to generate the goals outlined in ICH Q8(R2)?

- 2. How does this framework compare to the current approach typically followed by the industry? How responsive would regulatory agencies be to this approach?
- 3. The diagram highlights a number of sources that influence the criticality assessment. Please comment on these sources and whether others should be considered.
  - a. Do clinical trials need to be specifically designed to understand the impact of attributes or is exposure and standard tracking of safety sufficient? Are there expectations with numbers of patients and exposure duration?
  - b. Should the levels of quality attributes be purposefully manipulated in clinical lots to gain experience with exposure?
- 4. As you read through the case study, comment on the approach taken to link the relevant product quality characteristics to the desired clinical performance of the drug.
  - a. Comment specifically on the ability to leverage prior knowledge to achieve this "cornerstone" of Quality by Design.
  - b. Comment about how uncertainty of biological effect is addressed.
  - c. Discuss the challenges (perceived or real) that industry and agencies might encounter with this approach and how could they be overcome?
- 5. The case study uses a "Continuum of Criticality" to reflect the rankings of the quality attributes that must be monitored and controlled by the manufacturing process.
  - a. Contrast this approach with the ICH recommendation of identifying those quality attributes deemed as "Critical".
  - b. Is it clear how the criticality continuum be used to drive risk adjusted understanding and control of quality attributes, i.e. higher risk vs. lower risk attributes?
  - c. Although the rankings fall along a continuum, a distinction is made between "high criticality" and "low criticality" attributes that informs the subsequent risk assessments and process development/characterization work. Is this appropriate and if so, what should be the basis for distinguishing "high" from "low" criticality?



#### Figure 1.2

- 6. Figure 1.2 illustrates how risk assessments are applied during the course of development process for A-Mab. Prior knowledge is a key component of this framework.
  - a. Please comment on how risk assessments are currently used to identify the key parameters that will impact the development process.
- 7. Please comment on the use of prior knowledge to identify critical attributes and parameters. Highlight concerns that need to be addressed.
- 8. During the development of the case study, the Team had multiple discussions related to the acceptable sources of prior knowledge and how they might be leveraged. Literature? Past experience brought over from another company? Knowledge gained from similar products developed over the past few years?
  - Please provide your understanding of what prior knowledge is, the typical and acceptable source of prior knowledge, and how and when it should be used. Highlight any limitations you see in its use.
  - b. How should this prior knowledge be documented?

#### Chapter 2: Design of Molecule and Quality Attributes Assessment

#### **Introduction and Learning Objectives**

#### After reading this section readers should be able to understand the following:

- How the Target Product Profile was used to drive the development of A-Mab
- The design strategy used for the development of the A-Mab molecule
- The use of prior knowledge to identify the criticality associated with the quality attributes
- Approaches for developing the criticality continuum that was used to assess criticality
- The approach taken to link key attributes (via prior knowledge) with clinical relevance
- The different types of information used in the criticality risk assessment

#### **Questions for Discussion**

- The case study describes how attributes may be assessed based on safety and efficacy. While it is recognized that changes in one attribute can lead to changes in others, how can multiple interactions between attributes be best addressed? How might the attributes be assessed with regard to quality (consistency)?
- 2) For the case study, a limited set of attributes was chosen to "link across" all of the sections of the case study. These attributes were selected to encompass attributes across the criticality continuum and were chosen to illustrate different types of information used in the criticality risk assessment.
  - a. Please comment about the attributes chosen to illustrate the concepts of QbDWhat would you propose as better candidates and why?
- 3) The case study presents various example "tools" for assessing criticality of quality attributes. Please comment on the "pros" and "cons" of each.
  - a. What type of justification is expected for these or other similar tools that might be proposed by sponsors?
  - b. Do you feel that a standard approach must be used or can each company chose a path with appropriate justification?
- 4) Do the risk assessment tools clearly define how attributes are positioned in the criticality continuum? Has the link between relative criticality of an attribute and the appropriate control strategy been clearly established?
- 5) Prior knowledge and platform knowledge play a significant factor in ranking the criticality of the attributes selected.
  - a. Please comment on the approach taken and whether the use of both prior knowledge and platform knowledge was sufficient to justify the rankings presented.

For example: "Literature data suggests that Fc glycans do not influence interactions with FcRn and consequently are unlikely to impact the PK of A-Mab."

6) What additional data, if any, would be needed to more clearly justify the rationale for determining whether or not an attribute is a CQA? Please comment on the level of detail that should be included in a submission.\*

\*The deamidation attribute example in the case study is defined as "moderately detailed." A "highly detailed" example would include gels, chromatograms, etc. "Summary data" would include a table(s) and some narrative).

- 7) Comment on the challenges associated with managing the prior knowledge needed to assess attribute and process criticality.
- 8) In general, regardless of the tool used, the level of criticality assigned for the attributes was consistent. A few exceptions were noted. Comment on the rationale that is provided to explain the different criticality classifications and whether these differences might impact decisions made during the development process.
- 9) The CMC-BWG had a significant amount of debate related to whether or not to include both ADCC and CDC as part of the mechanism of action. In the end, the Team went with both to help justify the criticality ranking for galactosylation. Please comment on whether you think the Team could have selected either one over the other.
- 10) The case study uses prior knowledge and molecular-specific knowledge to establish clinical relevance. Much of this prior knowledge is based on in vitro data.
  - a. What are the limitations of in vitro data?
  - b. How much in vivo data should be considered to supplement the information provided?
  - c. To what extent can animal models be used to supply supporting in vivo data?
  - d. Is it feasible to evaluate product quality attributes in human trials?

#### **Chapter 3: Upstream Section**

#### **Introduction and Learning Objectives**

The Upstream section focuses on a number of key QbD-related areas:

- Prior knowledge and platform technologies
- Risk assessments to identify the process steps (and associated parameters) that impact quality
- Use of statistical experimental designs to understand the relationships between the input parameters and quality attributes
- Development of a scale-independent design space
- Development of an engineering design space that provides the rationale to include scale in a design space
- Lifecycle Approach to Process Validation that begins during development and continues
  post-launch. Process validation encompasses cumulative knowledge that is built on
  experience gained at multiple scales. Represents a departure from the traditional 3-batch
  validation approach prior to submission, where the value of commercial-scale runs is based
  on demonstrating validity of Design Space and continued process verification.

From the information presented, the case study argues that the only step impacting on product quality is the production bioreactor. Detailed experimentation is reported that enables the derivation of a design space for this step, and that design space is represented as a mathematical model.

#### After reading this section readers should be able to understand the following:

- How platform process and prior knowledge can be used in a risk assessment approach to demonstrate that the seed expansion steps in the A-Mab process have a very low risk of impact to product quality.
- How a systematic evaluation of prior knowledge and A-Mab specific data are used to establish a scale-independent design space for the production bioreactor step.
- How to justify a scale-dependent "Engineering Design Space" based on the scientific understanding of the impact of bioreactor scale and design on culture performance and product quality.
- Use of product and process knowledge to justify scaling-up production bioreactor from 5K L to 15K L commercial scale without additional clinical studies.
- Use of a lifecycle approach to process validation to support qualification of Design Space at commercial scale, model verification and continued process verification to provide assurance of product quality throughout product lifecycle.

#### **Questions for Discussion**

#### **Overview**

1) The section starts out by listing the approaches that are taken to exemplify key QbD elements and how these approaches differ from more traditional approaches.

Table 3.1	<b>QbD</b> Compared to "Traditional"	" Approach for Upstream		
	Development			

Quality by Design Approaches Exemplified in the A-Mab Upstream Process	"Traditional" Upstream Process Development Approaches
Thorough process understanding is based on prior knowledge and product specific experience.	Process understanding is limited to product-specific empirical information
Establish predictive relationships between process parameters and product quality attributes using statistically designed experiments. Acceptable operating conditions expressed in terms of a design space	Some experiments conducted using single-variable approaches, potentially overlooking parameter interactions. Acceptable operating ranges expressed as univariate Proven Acceptable Ranges
Systematic process development based on risk management tools.	Process development based on established industry precedents.
Rational approach to establishing a control strategy supported by thorough process/product understanding.	Control Strategy based on prior experience and precedent.
Control strategy focuses on critical control points and control of critical process parameters.	Product quality controlled primarily by end-product testing
Design space applicable to multiple operational scales. Predictability and robustness of process performance at multiple scales is ensured by defining an engineering design space	Process performance at multiple scales is demonstrated through empirical experience and end-product testing.
Lifecycle approach to process validation which includes continuous process verification to demonstrate that process remains in state of control	Process validation based on limited and defined number of full-scale batches.
Continual improvement enabled Use of multivariate () approaches for process verification.	Process performance generally monitored using single variable approaches

As you read the upstream section, consider how the approaches presented in the case study contrast with the more traditional approaches.

The reader should keep in mind that the approaches presented here are intended to challenge the current paradigms by showing what QbD implementation in biotech could look like in the future- i.e. in five years or so. Based on this, consider the following as you read through the document:

- a. Are there areas and/or issues where the Team could have "pushed the envelope" further?
- b. Do you have any concerns about the proposed QbD vision and approaches? If so, what is the basis for the concerns and what additional data or information would be required to address them?
- c. What additional data and/or considerations could be added to enhance the examples given?

#### Prior Knowledge, Platform Knowledge, and Risk Assessments

- 2) The upstream process leverages extensive prior knowledge gained from development of previously licensed antibodies (X-Mab, Y-Mab, Z-Mab). This prior knowledge is used to make decisions related to:
  - Selection of unit operations for the upstream process
  - Process requirements and controls for the seed expansion steps (from frozen WCB to N-1 Bioreactor)
  - Technical risk assessments used to guide process development and process characterization studies to define a scale-independent Design Space
  - In addition, extensive prior knowledge with bioreactor engineering characterization and Mab process experience at multiple scales and configurations is leveraged to establish a scientific basis to understand the impact of scale on product quality and cell culture performance.
    - a. Do you have concerns about the approaches presented on the use of prior knowledge?
    - b. What other specific types of prior knowledge or additional data would you also like to see included to justify the decisions made?

#### Stage 1 and 2: Seed Expansion Process

Seed Culture Steps	Product Accumulation	Risk of Impact to Product Quality
Seed expansion in spinner or shake flasks	Negligible	Low
Seed expansion in wave bag bioreactor	Negligible	Low
Seed expansion in fixed bioreactor	Negligible	Low

#### Table 3.2 Risk Assessment Results

- 3) Risk analysis (See Table 3.2) based on cumulative process understanding gained from prior knowledge and process characterization studies show that the A-Mab seed expansion steps from vial thaw through N-1 seed bioreactor do not impact product quality.
  - a) The A-Mab example does not address potential risk factors associated with raw materials and medium preparation. In a real case scenario these would need to be considered. Based on your experience, what raw material considerations would need to be included in the seed-expansion risk analysis?
  - b) Do you have concerns about leveraging prior knowledge with othe Mabs that use the same host cell line/expression system, same medium composition, and process conditions to support the conclusion that the A-Mab seed expansion steps pose little risk of impact on product quality? What additional data/information would you like to see included in this risk assessment.
  - c) Do you think there are aspects of the seed expansion process that are product (or cell-line) specific and thus require process development /characterization studies?
  - d) Can you envision a future state where extensive prior /platform knowledge can provide sufficient justification to obviate the need for development studies for the seed expansion process?
- 4) Based on the risk assessment for A-Mab it was determined that seed expansion steps do not impact product quality and thus do not need to be included in the definition of design space. Assurance of process consistency is provided by operation within established process limits and controlled through batch procedures.
  - a. Does the scientific rationale and risk assessment approach presented in this section justifies the exclusion of seed expansion from the design space?
  - b. Do you have any concerns with this approach? If so, what additional information would you like to see included?

#### Stage 3: Production Bioreactor

- 5) The case study describes how prior knowledge from other Mabs, A-Mab process development data, and process characterization study results are used in sequential risk assessments to provide and enhanced process understanding.
  - a. Is the data and information presented sufficiently clear to support the conclusions e.g. risk assessment conclusions, classification of process parameters?
  - b. What additional information would you like to see included?
- 6) The definition of the "scale-independent" design space for the production bioreactor leverages data (DOEs) at the 2L scale and information from a small number of batches at large scale. The approach is based on the premise that the design space is based on scaleindependent process parameters and thus applicable to all scales of operation. Scaledependent parameters are considered through the "engineering" design space.
  - a. Are the data and approach presented sufficient to support the conclusion that the design space is scale-independent and thus valid at commercial scale? If not, what additional data and considerations should be included to support this approach?

- b. How much large scale data is required to demonstrate that the design space is valid at large scale?
- 7) The multivariate model approach used for qualification of the scale-down model is based on data from another Mab and a commitment to build a similar model with A-Mab data when sufficient large scale batch information becomes available (a minimum of approx. 40 batches is required).
  - a. Do you have any concerns about this approach?
  - b. How could the qualification of the small scale model be enhanced?
- 8) The design space is defined as a set of equations , with a graphical representation also provided.
  - a. Is this representation sufficiently clear? Is there sufficient evidence to support the validity of the equations, and if not, what would you expect to see?
  - b. Are there other more transparent approaches that could be used to communicate the design space without losing any portion of the operating space.
  - c. Would you expect to have the equations in the submission or maintained in the Quality system and available for inspection as needed?
- 9) The case study presents a high level overview of one possible approach to implement the design space into routine manufacturing.
  - a. What considerations and information would you like to see in the approach to implement/translate the design space in routine manufacturing?
  - b. What information and data would be required to provide assurance of operation within the design space and control space?
  - c. What other approaches can be used to implement design space in routine manufacturing? Is it necessary to use sophisticated computer models and controls or can you envision a simpler implementation approach?
- 10) Engineering considerations were used to justify an engineering design space based on knowledge about bioreactor performance characteristics. These considerations were used to develop an Engineering design space that would allow scale to be included in the overall design space. This approach has a strong foundation in cell culture principles, bioreactor design and engineering principles, and prior knowledge of large-scale operations.
  - a. Do the science and engineering arguments presented support the concept of engineering design space? Is this concept consistent with the definition of Design Space in ICH Q8(R2)?
  - b. How should this concept presented in a submission and how could it help to support equipment and scale changes throughout the product lifecycle?

- c. Was the data and engineering considerations presented here sufficient to define the limits of the Engineering design space? What additional data and information would you like to see included?
- d. What kind or information packages should be available by the applicant to provide a level of assurance that the Engineering design space is well characterized, robust and predictable. Should this information be included in the submission(s) or available for inspection?
- e. Would this approach minimize the requirements for product characterization/comparability studies? What concerns would you have?
- f. Is there a need for special training for the regulators to be able to evaluate this type of approach in submissions? If so, what are the training needs?
- g. Can you envision a future state where this kind of approach eliminates the need for data at commercial scale prior to file submission?

#### Life-Cycle Approach to Process Validation

- 11) Case study uses DOE and Characterization studies (see Section 3.10) to understand the impact of variation of process parameters on product quality. The authors conclude that data at the 2 L scale down model and 5K clinical manufacturing scale provided assurance that the commercial process is robust and consistently delivers product with the right quality. This conclusion is confirmed by process performance results and characterization of product made in two(2) commercial scale (15K L) batches that demonstrated process and product comparability.
  - a. Does the science and technical evidence presented support the conclusion?
  - b. What concerns do you have about this approach? What additional data and or information would you like to see included in an actual submission to support this approach?
- 12) Table 3.2 summarizes the batch history for A-Mab. As the table shows, A-Mab produced at commercial scale was not included in clinical studies. The validity of this approach generated a significant amount of debate within the CMC-BWG, and some members felt that clinical experience prior to launch should include product manufactured at commercial scale. Ultimately, the team decided that this approach is justified based on the enhanced product & process understanding available for A-Mab and the assurance of consistent product quality when the process is operated within the "scale-independent" and "engineering" design spaces for the production bioreactor.
  - a. Do you agree that the science, engineering and enhanced product & process understanding presented support this approach?
  - b. Do you have any concerns about the approach? If so, what additional data or information would you like to see included?

c. Based on your experience, what other risks and considerations should be considered in this approach?

Process	Scale	Number of Batches	Disposition		
Process 1 Steps 1 to 4: Platform Process	N-1 Seed: 100 L Prod BioRx: 500 L	2	Supply pre-clinical studies		
Process 1	N-1 Seed: 200 L Prod BioRx: 1,000 L	3	Supply clinical and pre-clinical studies and provide product/process understanding. Generate Reference Std RS-PR1		
Process 2 <u>Steps 1 and 4 :</u> Platform Process <u>Step 2:</u> Platform Process up to N-2 Optimized platform for N-1 <u>Step 3:</u> Optimized Platform	N-1 Seed: 1,000 L Prod BioRx: 5,000 L	5	Supply pivotal clinical studies and confirm end-to- end process performance. Generate Reference Std RS-PR2		
Process 2	N-1 Seed: 3,000 L Prod BioRx: 15,000 L	2	Build commercial launch supplies. Confirm design space and Control Strategy at commercial scale Generate Reference Std RS-MF1		

 Table 3.3
 A-Mab Batch History with Upstream Process Changes

- 13) The continued process validation approach presented here considers process performance qualification (PQ) separately from the validation aspects of the facility, equipment and utilities. This is based on the assumption that the commercial manufacturing facility used for A-Mab production has already been demonstrated to be capable of supporting similar Mab processes and operating in a consistent state of compliance.
  - a. Do you have any concerns about the proposed approach? What additional considerations would you like to have included to justify this proposal?
  - b. How can the envelope for this proposal be pushed even further? For example, can performance qualification information for the upstream process be limited only to the production bioreactor?
- 14) The case study moves away from the traditional (often 3-batch) process validation approach and instead proposes to use 2 initial batches at commercial scale (15K L) to confirm the design space and to layout the approach for a continued process verification approach via a multivariate statistical model.
  - a. The proposed approach is presented at a very high level. What specific information and data would you like to see included in this continued process verification approach?
  - b. Should there be specific commitments and acceptance criteria included in the submission to support the continued process verification approach?
- 15) The case study describes an anticipated change post launch that involves further scale-up from 15K-L to 25K-L bioreactors. The case study proposes that this change is supported by the following conclusion:

Operation at 25K-L is within the defined engineering and scale-independent design spaces. This is supported by science and engineering considerations that demonstrate that there is a high degree of assurance that operation at this scale would result in comparable process performance and meet expected product quality.

- a. Does the science and technical arguments presented support the conclusion?
- b. What concerns do you have about the proposed change?
- c. What additional information would you like to see in an actual submission to justify this approach?
- 16) The case study also describes how based on the engineering design space, if needed, a postlaunch change could be made to a different bioreactor (scale and design – provided assessments were conducted to confirm the new bioreactor's characteristics fell within the engineering design space.
  - a. Does the science and technical arguments presented support the conclusion?
  - b. What concerns do you have about the proposed change?
  - c. What additional information would you like to see in an actual submission to justify this approach?

#### **Statistical Analysis**

- 17) The case study includes several advanced statistical approaches that are used to establish models for the design space, define the limits of the design space, qualification of scale-down models, and continued process verification.
  - a. What additional training and outreach would need to be provided to other industry partners and regulators to adopt and implement these advanced statistical analysis approaches?
- 18) A Bayesian statistical approach is used to define the limits of the production bioreactor design space to provide a high degree of assurance that the product quality attribute limits are met.
  - a. Are there other equivalent approaches to incorporate process/assay variability in the determination of the limits of the design space?
  - b. Is it necessary to use a statistical approach to establish the limits of the design space or do you think that a simpler approach (e.g. overlapping of multiple mean responses) is sufficient?

#### Potential Post-Launch Process Changes that are not included in the case study:

19) During the course of discussions, a number of potential post-launch process changes were identified to help "test" the design space concept but ultimately where not included in the case study, mainly due to document size considerations. A summary of these potential post-launch changes is included below to provide a substrate for additional discussions:

- a. One potential change revolved around making a cell line switch. How can QbD approaches be applied to support a change in cell line without requiring additional clinical studies? What product characterization and process information would be required to support this change?
- b. Another change considered was a change in medium composition and/or feeding regime to support continuous process improvements (e.g. to increase product yields). How can QbD approaches be applied to support such changes in medium and/or feeds without requiring additional clinical studies? What product characterization and process information would be required to support these changes?

#### <u>Other</u>

- 20) The case study introduces the concepts of well controlled critical process parameters (WC-CPPs). The concept is introduced to recognize that many parameters have a low risk of falling outside the design space but that this risk depends on facility and equipment-specific control capabilities. This is particularly important since there is still a wide mis-interpretation that a variable that is well controlled is no longer critical.
  - a. Is the concept of a WC-CPP helpful? Are there other ways of addressing this issue?
  - b. Should CPPs and WCPPs treated differently in the Quality System?
- 21) Discuss what you think should be reported to an Agency versus what is not reported (but managed internally to ensure control). For example, although KPPs have acceptance limits they would be managed within the Quality System.

#### **Chapter 4: Downstream Section**

#### **Introduction and Learning Objectives**

The downstream section builds on the upstream information, and key here is the understanding and separation of the quality variables that are impacted uniquely by downstream unit operations. The downstream process illustrates and leverages prior knowledge gained from platform technologies with a proven performance history.

After reading this section, readers should understand the following:

- How the uses of prior knowledge to guide process characterization studies, removed the need for optimization studies, and helped support a proposal for a design space.
- How prior knowledge influenced the "modular approach" applied towards viral clearance
- Impact of taking a holistic approach towards development specifically, anticipating and understanding work being down by upstream counterparts and how efforts impacted the downstream development activities
- The rationale used to justify two post-launch process changes

#### **Questions for Discussion**

#### Prior Knowledge

1) The Downstream Team relied on prior knowledge to develop an initial risk assessment to identify which downstream process steps potentially impact product quality. See Table 4.1 below:

Quality Attributes	Risk of Impact to Product Quality Attribute						
	Protein A Chromatography	Low pH Treatment	Cation Exchange Chromatography	Anion Exchange Chromatography	Small Virus Retentive Filtration	Ultrafiltration and Diafiltration	Final Filtration and Bottling
Identity							
Protein Content						~	
ADCC							
Aggregate	<ul> <li>Image: A second s</li></ul>	$\checkmark$	$\checkmark$	$\checkmark$	<ul> <li>✓</li> </ul>	<ul> <li>Image: A second s</li></ul>	

## Table 4.1Quality Attributes Potentially Affected by the A-MabDownstream Unit Operations

Quality Attributes	Risk of Impact to Product Quality Attribute						
	Protein A Chromatography	Low pH Treatment	Cation Exchange Chromatography	Anion Exchange Chromatography	Small Virus Retentive Filtration	Ultrafiltration and Diafiltration	Final Filtration and Bottling
Color							
Clarity							
Oligosaccharide Profile							
Charge Variants	<ul> <li>Image: A second s</li></ul>	✓	<ul> <li>Image: A second s</li></ul>	>			
рН						<b>~</b>	
Osmolality						<b>~</b>	
Residual HCP	<ul> <li>Image: A second s</li></ul>	✓	<ul> <li>Image: A second s</li></ul>	$\checkmark$			
<b>Residual Protein A</b>	<ul> <li>Image: A second s</li></ul>	✓	<ul> <li>Image: A second s</li></ul>	$\checkmark$			
Residual DNA	<ul> <li>Image: A second s</li></ul>	✓	<ul> <li>Image: A second s</li></ul>	✓			
Residual Methotrexate	<ul> <li>✓</li> </ul>		<ul> <li>Image: A second s</li></ul>	<b>~</b>		<b>~</b>	
Bioburden							<ul> <li>Image: A second s</li></ul>
Endotoxin			<ul> <li>Image: A second s</li></ul>	$\checkmark$			
Viral Safety		$\checkmark$		$\checkmark$	<ul> <li>Image: A second s</li></ul>		

#### Table 4.1

Quality Attributes Potentially Affected by the A-Mab Downstream Unit Operations

Because prior knowledge demonstrated that glycosylation variants (e.g. galactosylation and fucosylation) are minimally impacted by downstream processing, the decision was made to not include glycosylation variants in the testing for characterization studies.

- a. Do you agree with this conclusion?
- b. What additional considerations including preceding regulatory guidances need to be considered before leveraging prior knowledge to make this claim?
- c. Are there industry challenges that also need to be considered?
- Prior knowledge is used extensively in the downstream section. One area it is used is to justify a modular approach towards viral clearance. (Contrasts with approach laid out in "FDA Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use" (1997)
  - a. Does the case study do a good job of justifying the use of prior knowledge to move forward with this approach?

- b. From a regulatory standpoint, would you be comfortable with this approach if incorporated into a submission?
- 3) Prior knowledge was heavily leveraged to assist in the risk analyses to design multifactor DoE experiments and relate process parameters to CQA. The results of the DoE were then discussed and the parameters classified as CPP, WC-CPP, KPP and GPP.
  - a. Were the risk analyses and subsequent experimental designs appropriate for the processing steps?
  - b. Was the logic used for the classification of the parameters clear?
- 4) Consider the impact of assay variability on impurity clearance. When close to safety limit, what additional studies need to be performed to address the uncertainty in the assay result?

#### Step Linkage:

- 5) A chromatography step linkage model was derived from the independent DoE studies that assumed there were no interactions of parameters from different steps.
  - a) Is the model adequately explained and is it clear how the model would be used in practice to define control ranges?
  - b) Is a 99.5% prediction interval too conservative?
  - c) Models for HCP removal in the individual steps were linked together without explicitly addressing any effect of changes in distribution of HCP species from step to step. Would additional studies need to be done to demonstrate the validity of the linkage model if making a change within the design space?

Note that we have included the embedded Excel spreadsheet for readers to explore the step linkage with focus on HCP.



#### **Design Space**

- 6) Platform knowledge is used to define the Design Space at the low pH Incubation Step. Please comment.
- 7) Do worst-case combinations of all unit operations' Design Spaces need to predict an acceptable product quality, or can setting appropriate control spaces and potentially using in-process testing be used to limit the extremes?

For example, two options are given for design spaces and control of the Protein A step. A third option (Option C) could be to use Control Space Limits plus In-Process Testing. See Figure 4.2 below:

Figure 4.2



- a. Please comment on the pros and cons of each option.
- b. Is Option C a valid approach? Discuss how it might be utilised.
- 8) The Team had a significant amount of debate over whether a model should be used to define the design space for certain parameters. In the end, the decision was made to use the model to help identify "worse case scenarios" and for potential process improvements by looking at the purification process as a whole.
  - a. Would you have used a model to design the design space?
  - b. Do you agree with the Team's decision? If not, what advice would you provide to help justify the use of a model to define the design space?
- 9) In the Case Study, a linkage model (see Section 4.2) linking all three purifications steps (AEX and CEX) is developed as an approach to develop and define the overall design space for the downstream process.
  - a. Please discuss the pros and cons of this approach and its implications for production.

#### Viral Clearance:

- 10) The viral clearance studies leveraged a significant amount of in-house data to make modular claims.
  - a) What elements in a data package for low pH inactivation are needed to make a modular claim for viral clearance with an IgG1? Can it be used for other isotypes like IgG4?
  - b) In the case of the AEX change from column to membrane, how similar does the viral clearance between the resin and the membrane have to be to claim process comparability? Within one log? Or, if the clearance by the membrane is less than that of the resin, can it be considered to be within the Design Space (from a viral clearance standpoint) if the overall process safety factor remains at 6 logs or greater?

c) In the case of small virus retentive filter validation, can an appropriately sized phage be used in place of mammalian viruses? Alternatively, could MMV studies be used without data from other viruses to claim clearance of X-MuLV and other larger viruses?

#### <u>Scale</u>

- 11) For scale down models in general, the sources of variability will differ from those in manufacturing. How should/could this be addressed?
- 12) What is an acceptable defect rate from our small-scale models to assure a robust design space at scale?

#### **Changes Proposed**

- 13) Anticipating a post-launch change between vendors of Protein A, studies were conducted to demonstrate comparability between the two sources of Protein A.
  - a. Based on the approach and data provided in the case study, do you feel this change could be made post launch? Please comment on the reporting requirements that would be needed.
  - b. If not, what is missing?
- 14) Another post launch change was the proposal to replace the anion exchange resin with a membrane format.
  - a. Was the appropriate rationale provided in the Case Study to justify this change?
  - b. If not, what regulatory implications were not addressed (or could be addressed better) to insure the change would be accepted?

#### OTHER – Testing Strategy

- 15) Case Study leveraged the extensive process characterization data with other Mabs that were developed to support elimination of AEX and CEX resin re-use studies for A-Mab.
  - a. What additional data would be needed to justify the use of this pre-existing knowledge in eliminating or reducing the amount of data for re-use studies?

#### **Chapter 5: Drug Product Section**

#### **Introduction and Learning Objectives**

Drug product section demonstrates a number of examples where the principles of QbD can be applied. This includes:

- Prior knowledge:
  - The formulation composition is based on an existing formulation that has served other antibodies and no further optimization was done for A-Mab
  - o process development is based on prior knowledge from other antibodies
- Design Space and Scale:
  - The design space for the compounding step is based on scale-independent process parameters and thus is applicable to all scales of operation
  - A risk-based approach and the use of DoE to create an engineering design space for filling pumps

#### **Questions for Discussion**

16) A subset of Table 5.1 (see below) summarizes the elements of QbD that are exemplified in this case study versus the traditional approaches to drug product development.

Quality by Design Approaches Exemplified in the A-Mab Drug Product	Traditional Drug Product Development Approaches			
Leverage of a previous formulation design space where platform composition and conditions have proven history. For A-Mab, only verification is needed through limited DoE studies	No leveraging of class knowledge or platform formulation design space. A-Mab is treated as 1 <sup>st</sup> in class. Extensive DoEs and wide ranging studies			
<b>Extensive use of prior knowledge</b> of unit operations, supported by both multi-variate or univariate risk-based verification	Prior knowledge used and both multi-variate and univariate experiments conducted, but without formal risk-based assessment			
<b>Process development leverages platform</b> <b>knowledge</b> through systematic application of risk management tools.	Process development based on established industry precedents.			

#### Table 5.1

Quality by Design Approaches Exemplified in the A-Mab Drug Product	Traditional Drug Product Development Approaches
Rational approach to establishing a control strategy supported by thorough process/product understanding.	Control Strategy based on prior experience and precedent.
Control strategy focuses on critical control points and control of critical process parameters.	Product quality controlled primarily by end- product testing

- a. Please comment on these QbD-related concepts and their discussion in this section: what are the strengths and weaknesses, the opportunities and challenges?
- b. Does the Case Study do a better job exemplifying some specific aspects over others? If so, which ones?
- c. Do you agree that the approaches taken represent processes and an approach that is much different from what is being practiced in the Industry today?
- d. From a regulatory perspective, which of these approaches present the most difficult challenges and/or greatest opportunities?
- 17) A risk analysis was used to establish which variables and unit operations were likely to have the greatest impact on product quality. This initial risk assessment is shown in the table 5.2 below:

	Variables and Unit Operations							
DP CQAs	Formulation Composition	Compounding	Sterile Filtration	Filling and stoppering				
Aggregate	High	High	High	High				
Sub-visible particles	High	High	High	High				
Visible particles	High	High	High	High				
Fucose content	Low	Low	Low	Low				
Galactosylation (%G1 + %G2)	Low	Low	Low	Low				
НСР	Low	Low	Low	Low				

#### Table 5.2

Note – while Fucose content, Galacosylation and HCP are all drug substance CQAs, they were demonstrated to be under control coming out of the drug substance manufacturing processes.

- a. Given these attributes were CQAs in the drug substance process, are you comfortable relying on prior knowledge to make the claim that these same attributes "will not affected by the drug product manufacturing process."?
- 18) Prior experience gained from the formulation and drug product process development of previous commercial monoclonal antibody products was leveraged in the case study. This was used to justify conducting only limited essential studies to verify formulation and process design space.

Using aggregation as the example CQA:

- a. Was sufficient information provided to support the use of prior knowledge from XmAb, Y-mAb and Z-mAb to allow the more limited exercise/study to identify critical formulation and process parameters for A-mAb?
- b. What other information or data, if any, would be needed to allow the knowledge and experience from the other monoclonal antibodies to be used to support only verification of formulation and process design space for A-mAb?
- c. For studies not conducted for A-mAb design space, what kind of information, and how much should be provided to justify eliminating the studies, and justify the focus of the studies executed?
- d. Is our approach to apply only a very limited set of multivariate data for design space verification based on significant experience across the previous monoclonal antibodies substantiated?
- 19) Data obtained at 50 L scale was used to predict operating conditions at 500 L and 1500 L scales.
  - a. Please comment on the manufacturing and regulatory needs that should be considered before larger-scale operating conditions are predicted based on small-scale studies.
  - b. What is an acceptable defect rate from our small-scale models to assure a robust design space at scale?
  - c. Are there weaknesses in the rationale used to justify this approach? If so, how could it be improved?
  - d. How or must we demonstrate that a model works at manufacturing scale?
- 20) The design space proposed for A-Mab was based on prior knowledge of other molecules that have been developed. In the case study, it turns out the design space defined for A-Mab is identical to the equivalent design spaces approved for X-Mab, Y-Mab and Z-Mab.

- a. What are the characteristics that would allow the use of prior knowledge to define the design space for the drug product?
- 21) In our case study, we treated sterile filtration as a standardized unit operation. A platform sterile filtration process was developed from a detailed QbD-style study using X-mAb, Y-mAb and Z-mAb. The platform was then leveraged as the basis to only conduct a limited study for A-mAb sterile filtration.
  - a. Were the data provided to establish the sterile filtration process platform the type and amount that would justify the limited study performed for A-mAb?
  - b. What is the best structure and format to submit the platform data package associated with A-mAb?

#### **Chapter 6: Control Strategy Section**

#### Learning Objective

The Control Strategy for A-Mab integrates input material controls, procedural controls, process parameter controls, in-process testing, release testing, characterization and/or comparability testing and process monitoring to provide a high degree of assurance that the acceptable ranges for the relevant CQAs are maintained.

The main learning objectives of this section are to understand:

- The overall approach towards developing a Control Strategy based on risk and process understanding.
- The decision logic used to evaluate criticality and subsequent categorization of process parameters.
- How risk is used to align the level of testing and controls that are applied to ensure the defined CQAs are being met with the current process capabilities.
- The leveraging of product and process understanding to reduce the number of tests included in the drug substance and drug product specification that would typically be included.
- The case study approach towards continuous process monitoring and how it was used to verify that the Control Strategy is performing as expected and remains appropriate.

#### **Questions for Discussion**

22) The final assessment of criticality for process parameters was performed according to the decision logic outlined in Figure 6.1 "Final Categorization of Input Process Parameters for A-Mab Control Strategy". (See below):

#### Figure 6.1



This model was used to drive the criticality for process parameters across the Case Study.

- a. Please comment on the model in general? What are the advantages and disadvantages of a "four category" model versus three or two categories?
- b. Should the ability to measure a Quality Attribute, whether real time, in-process, or lot release, influence the criticality rating for process parameters that impact that attribute?
- c. How different is this approach compared to what is typically being done in the Industry?
- d. How well does this model align with the current ICH views on categorizing process parameters?
- 23) For the purposes of this case study, the continuum of process parameter criticality was divided according to Figure 6.2 below:

#### Figure 6.2



The categorization of process parameters and their relationship to CQAs generated a significant amount of debate as the Case Study was being developed.

- a. Is the distinction between a "capable" and "non-capabable" process clear? Is is acceptable to have a "non-capable" process?
- b. Please provide your thoughts on this framework. Are there other models that would more appropriate for differentiating between CPPs, WC-CPPS, and KPPs?
- 24) Please comment on the following: KPPs and GPPs are also described for each development step but because these parameters do not result in any practical impact on the product's critical quality attributes, they are not included in the design space and not considered regulatory commitments.
  - a. Do you agree with not including KPPs and GPPs in the design space? How should these parameters be handled in the QMS?
- 25) The Case Study notes that "to properly categorize process parameters and accurately assess the significance and effect of the variability of a parameter on CQAs depends on size of the characterized process space (ie, Knowledge Space).

- a. Are you comfortable with this assertion? Are there alternative approaches?
- 26) The QbD approach provides a rational and science based approach to linking the product specification to clinical relevance. This differs greatly from the current practice of setting numerical acceptance limits based solely on clinical trial experience and/or process capability and assay performance considerations.
  - a. Agree with this approach?
  - b. Should the acceptance criteria be updated in line with process capability?
  - c. What is the impact on any design spaces if specification attributes and acceptance criteria are changed during the development lifecycle, or during the assessment phase?
- 27) Figure 6.3 (see below) provides a summary of the process control points and associated parameter categorization and testing strategy for the A-Mab drug substance and drug product. Note that only a limited number of product quality attributes were considered in the case study.



#### Figure 6.3

- a. The use of process parameter controls rather than reliance on end product testing is emphasized in the control strategy. Is the case made appropriately for the reduction of end product testing for release? What are the implications for stability?
- 28) Discuss the approach taken to link material attributes and process parameters to product CQAs. Was prior knowledge used and applied in a manner that justified the approach and subsequent conclusions that were made?
- 29) Product and process understanding was used in the case study to define the overall control strategy which is composed of several different types of control elements. The enhanced product and process understanding was further leveraged to reduce the number of tests included in the drug substance and drug product specification that would typically be included.

- a) Is it clear that all attributes are considered and become a part of the control strategy (lot release, in-process controls, parameter controls, etc.)? How might it be more clearly communicated that less critical attributes are not ignored?
- b) What concerns do you have with utilizing in-process testing versus end product testing for selected attributes? If there are no concerns with the approach, what are the compliance expectations?
- c) Is the case made appropriately for the reduction of end product testing using process parameter controls?
- 30) The case study proposes the concept of "continuous process verification". Where are the weaknesses and opportunities?
- 31) Do current quality management systems within manufacturers' operations need to evolve to enable the control strategy to be implemented?
- 32) In the case study, specification acceptance criteria are based on clinical relevance to ensure safety and efficacy (i.e, linked to design space) and not process experience (or prior precedent). Consequently, changes to specifications during the development lifecycle would reflect improved understanding of the relationship between product and clinical relevance not process capability.
  - a) What concerns do you have with this approach to managing specification acceptance criteria?
  - b) What additional data and level of detail would be required to justify the rationale?
- 33) The case study does not address 'edge of failure'. What is the value of determining an edge of failure?
  - a) For example, if it can be demonstrated that any edge of failure is well removed from the normal operating range of a process parameter, does that influence the categorization (i.e., CPP versus KPP)?
- 34) The control strategy includes the drug substance and drug product specifications.
  - a) Does the approach taken to define specifications reflect your understanding of the Q6B guidance?
  - b) What concerns do you have with utilizing in-process testing versus end product testing approaches?
- 35) How should stability be viewed in the context of developing a control strategy or should stability be considered more a component of continuous process verification?

- 36) The approach to routine stability testing leverages the enhanced product and process knowledge afforded by QbD. As implied in the specification tables, only a limited number of quality attributes would be tested as part of the stability commitment.
  - a) What concerns do you have with testing a limited number of attributes on stability?
  - b) How should stability be viewed in the context of developing a control strategy?
- 37) The concept of process monitoring is introduced in the control strategy for selected quality attributes (e.g., oligosaccharide measurement). Testing is conducted and the results compared to criteria established to demonstrate consistency. Based on data trends, testing frequency may be changed or discontinued. What concerns do you have with this testing concept?
- 38) In the context of comparability do you agree that the enhanced product and process knowledge afforded by QbD provides greater flexibility in the design and conduct of such studies (i.e., types and level of testing along with acceptance criteria).
- 39) Is the concept of "adaptive" process monitoring (i.e. changing testing frequency) based on historical results clear and justified?
- 40) Is multivariate process control a critical element of continuous verification?

#### Chapter 7: Regulatory Strategy Section

#### **Introduction and Learning Objectives**

The regulatory section is provided to stimulate discussion about how the knowledge and data exemplified in this case study can be used to create risk-based regulatory strategies for product licensure, and management of changes to the manufacturing process. Approaches are presented to demonstrate how regulatory strategies can be used to drive:

- Identifying and understanding link between CQAs, process parameters, and the associated regulatory commitments that will need to be met and maintained throughout the lifecycle of the product
- The definition of the design space using development data from small scale lots up to commercial scale lots
- The management of changes to the manufacturing process within and outside of the design space
- Understand when it is appropriate for a firm's internal Quality System to handle a change without the need for regulatory notification
- Rationale for using risk assessments in the determination of the types of data necessary to qualify a change and the proposed level of regulatory oversight.

#### **Questions for Discussion**

#### Proposition #1: Gaining an enhanced understanding of product attributes

- 1) Please comment on the following: In QbD applications, acceptance criteria for specifications are established based on a rigorous CQA analysis and should not change unless significant new data related to clinical outcomes became available.
- 2) Please comment on the case study's ability to justify tying product's specifications throughout the lifecycle to clinical relevance (using all available data). (Rather than on the traditional approach of basing adjustments on statistical analysis of manufacturing performance at target process conditions.).
  - a. What role does process capability and its assessment have in the determination of acceptance criteria?
  - b. Are there any situations where it is appropriate for criteria to change based on process capability?

#### Proposition #2: Regulatory Impact of CPPs and Design Space in Filings

- 3) Comment on the approach described where regulatory commitments are based on CPPs and WC-CPPs however; KPPs and GPPs are handled by the firm's internal Quality System.
  - a. Is this a reasonable distinction given the available data?
  - b. What are the implications for industry and regulators?
  - c. How can you present the process description and the design space and clearly establish the plans for future control of CPPs, KPPs and GPPs using the information in the case study?
  - d. Are we agreed the CPPs/W-CPPs comprise the design space?
  - e. What level of detail would be expected in a submission for KPPs and GPPs as compared to CPPs.
  - f. Has the case study clearly differentiated between types of changes and provided realistic assessment plans?
- 4) An understanding of the overall process development history incorporating risk assessments and process design decisions is important in the overall evaluation and justification of the product and process controls with regard to a regulatory submission.

To that end, an important consideration is the amount of data that is required in order to understand the process development and risk assessment summaries. This might include data to justify: logic applied, risk assessments conducted, tools used, etc.

a. The amount of data to include in the case study was a constant source of debate. What are the pros and cons of some of the data presentations in the case study with respect to the utility of the information, decision making using the data, summary information versus detailed experimental results, and data needed for submission versus inspection?

#### Proposition #3: Process Qualification and Validation

- 5) The Upstream section uses continuous process validation to monitor batches in the commercial arena and was used to justify not following a more traditional approach". The number of batches required was determined based on risk and dependent on the amount of process understanding available.
  - a. Please comment on this approach specifically, allowing commercial scale lots produced at any time during development.

6) Has the small scale data and the links to prior knowledge in the Case Study, addressed concerns that design spaces were not confirmed at scale or at the edges of the ranges?

#### Proposition #4: Quality Systems versus Regulatory Commitments

- 7) Consider case where in production there is a move within the design space to increase yield, which raises impurity levels, but still within specification acceptance criteria. How is this viewed from a quality system and regulatory notification perspective?
- 8) How should operating parameters which are not included in design space (i.e. KPPs, CPPs,) be managed in the QMS, including change control?
- 9) Consider case where in production there is a move within the design space to increase yield, which raises impurity levels, but still within specification acceptance criteria – what does this look like from a quality system and regulatory notification perspective?

#### Assessment of Risk and Continuum of Process Change

10) As with the designation of CQAs and CPPs, process change risk could also occur on a continuum, and as a result, regulatory oversight should be tied to that continuum. Risk-based change management in a systematic way is enabled by the categorization of attributes and process parameters appropriately (See Figure 7.1 below).

#### Figure 7.1



The proposed change would be evaluated for its impact on the originally defined design space, and the outputs for the specific unit operation. The assertion is made that the degree of regulatory oversight should be proportionate to the risk.

a) Are the approaches in the figure and table (below) appropriate under a QbD application?

- b) Protocols were proposed to change the Protein A resin and to change from AEX resin to an AEX membrane.
  - Are the protocols sufficient to allow change based on the in-house quality system?
  - If, as a result of the change, there were a statistically significant change to a CQA, but it was still within the specification and readily controlled, is the resulting drug substance still considered acceptably comparable?
- c) In the context of comparability and continuous improvement, do you agree that the enhanced product and process knowledge afforded by QbD provides greater flexibility in the design and conduct of such studies (i.e., types and level of testing along with acceptance criteria, expectations for reporting)? See Table 7.1 below

#### **Process Qualification and Validation**

11. Continuous process validation to monitor batches in the commercial arena was discussed in the upstream discussion. Please comment on whether there are any differences when this approach is applied downstream and/or to drug product.

#### Proposed FDA/CMC-BWG Workshop Questions DRAFT

Table 7.1 Potential Regulatory Pathways for Risk-Based Approaches to Change Management

Risk Continuum	A =Low	В	С	D	Ε	$\mathbf{F} = \mathbf{High}$	
INPUTS Raw Material/ Technology Equipment/ Site/ Scale	Like for Like	Minor Change	New Material, Technology	DS/DP Site Change	New Material, Technology, multiple changes	New Material, Technology, multiple changes	If lot release tests fail, need for non-clinical, clinical data
Process/ Engineering Fit Risk Assessment	Meets criteria	Minor Changes	Major Changes	Meets criteria	Major Changes	Major Changes	increases
CPPs/WC-CPPs	Parameters unchanged	Minor change	New Design Space	Parameters Unchanged	New Design Space	New Design Space	"Extended testing" includes
OUTPUTS Acceptable for next step	Meets Criteria	Meets Criteria	Meets Criteria	Meets Criteria	Does Not Meet Criteria	Does Not Meet Criteria	agreed upon tests beyond lot release that assure CQA
# Unit Ops Impacted	Single	Single	Single	Multiple	Multiple	Multiple	assurance of viral clearance.
Meets Lot release criteria and in process criteria	Yes	Yes	Yes	Yes	Yes	Some IPC criteria require minor modification	
Extended Comparability Required	No	No	Yes, selected testing . Results meet criteria	Yes, full testing, Results meet criteria	Yes,, full extended testing, Results meet criteria	Yes., full extended testing, some minor differences observed	Stability data would include
Additional drug substance stability	NA	NA	Yes/ (annual lot)	Yes/ (annual lot)	Yes, data provided	Yes, data provided	
Additional drug product stability	NA	NA	Yes, for DP changes only, annual lots	Yes, for DP changes only, annual lots	Yes, DP changes only	Yes, DP changer primarily	Depends on results of comparability exercise
Supportive Clinical/Non-clinical	No	No	No	No	No	Maybe	Categorization based on what we feel is justified by risk and
Example Agency Reporting Category )	Reported Upo	in Annual late	Reported prior to no approv	implementation, al required	Reported prior to implementation , expedited review timeframe	Reported prior to implementation, routine review timeframe	knowledge. Suitable reporting categories may not now be available in all regions.