Chapter 2
Lessons Learned from Monoclonal Antibody Applications to the Office of Biotechnology Products Quality by Design Pilot Program

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2.1 Introduction

Food and Drug Administration (FDA) announced the Pharmaceutical CGMPs for the twenty-first century—A risk-based approach in 2002 with the intent of ensuring that the product review and inspection programs operate in a coordinated and synergistic manner. The program was intended to encourage the adoption of modern and innovative manufacturing technologies and, as Janet Woodcock stated at the FDA-ISPE Workshop in October 2005 (AAPS 2005), to encourage the pharmaceutical industry to be "maximally efficient, agile, and flexible" and to produce high-quality drug products "without extensive regulatory oversight." The goal was to create systems where quality would be built into the product, and testing alone would not be relied upon to ensure product quality. Dr. Woodcock further indicated that in the desired state, manufacturers would have extensive knowledge on the critical

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elements of their products and processes and they would strive for continuous improvement. An important objective of the initiative was to facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance and to encourage implementation of risk-based approaches that focus on both industry and agency attention on critical areas. To achieve these objectives, the concepts of Quality by Design (QbD), risk management and the quality system approach could be utilized (Food and Drug Administration 2009a, b, c, 2012).

2.2 Quality by Design (QbD) for Biotechnology Products

ICH Q8 (R2) defines QbD as "A systematic approach to product development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" (Food and Drug Administration 2009c). QbD requires an investment of resources to develop an in-depth understanding of product quality and how the manufacturing process impacts product quality. This knowledge is then used to build product quality into the process rather than simply confirming it through testing (Rathore and Winkle 2009).

Due to the high degree of physicochemical complexity and inherent heterogeneity of biotechnology products, implementation of QbD for biotechnology products is a more difficult undertaking compared to most small molecule drugs. The molecular complexity of biotechnology products presents challenges for both the identification of product attributes that impact efficacy and safety, and the manufacturing parameters that impact product quality. Monoclonal antibody (mAb) products represent a somewhat unique biotechnology class in that most share a common structure, which has enabled the development of robust platform manufacturing processes. Platform manufacturing is defined in ICH Q11 as "the approach of developing a production strategy for a new drug starting from manufacturing processes similar to those used by the same applicant to manufacture other drugs of the same type (e.g., as in the production of monoclonal antibodies using predefined host cell, cell culture, and purification processes, for which there already exists considerable experience)." The first mAb product gained FDA marketing approval over 25 years ago and since that time there has been a significant investment in understanding the structure/functional relationships of mAb attributes. This knowledge base and the ability to leverage platform manufacturing knowledge from one mAb product to another is encouraging investment in QbD approaches for mAb products.

While the FDA is in fact seeing QbD principles applied in product characterization and process development sections of Investigation New Drug (IND) submissions and Biological License Applications (BLA), most of these submissions do not utilize all QbD concepts described in guidance (e.g., seek approval of a design space). To help facilitate more complete implementation of QbD for biotechnology

products, in July 2008 OBP initiated a QbD pilot program (Food and Drug Administration 2008). The pilot program was designed to define clinically relevant attributes for protein products regulated by OBP and link them to manufacturing processes. The program considered QbD approaches to unit operations in supplements as well as original BLAs. It was also intended to explore the use of expanded change protocols submitted under 21 CFR 314.70(e) and 601.12(e). The pilot program accepted six original BLA applications and four postapproval supplements. The program has been instrumental in helping the FDA develop an understanding of, and expectations for, how QbD will be applied to biotechnology products. In addition, CASSS and ISPE published the A-Mab case study in October 2009 (CASSS and ISPE 2009). The A-Mab case study exemplified development of drug substance and drug product design spaces for a fictitious mAb product and has been a very useful tool for discussing ways QbD concepts can be applied to biotechnology products.

While the use of advanced QbD concepts such as implementation of design space and expanded change protocols are optional approaches, the use of some QbD elements such as development of a quality target product profile (QTPP), identification and/or ranking of critical quality attributes (CQAs) and a control strategy are regulatory expectations (http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM242665.pdf). Risk assessments are important tools in identifying CQAs as well as designing a control strategy. As outlined in ICH Q8 (R2), implementation of QbD should be initiated with the development of a QTPP, which identifies the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, followed by identification of CQAs. These standard QbD concepts should be incorporated into product development regardless of whether there is intent to utilize more advanced QbD concepts.

A key lesson that came out of the A-Mab case study was that the drug product (DP) manufacturing process can be viewed as an opportunity for the development and use of advanced QbD concepts. DP processes are generally far less complex than a typical biotechnology drug substance process and consist of several operations (e.g., mixing, sterile filtration and filling) that are often highly similar or identical between products. This similarity allows knowledge of the process to be leveraged from one product to another, thus facilitating development of an enhanced control strategy that includes QbD elements. In addition, while poorly controlled DP manufacturing processes can negatively impact product quality, the DP process does not in general involve steps (other than sterility assurance steps perhaps) that increase the purity/quality of the product. Therefore, risk assessments and process characterization and design can focus almost exclusively on maintenance of product quality.

The fact that the drug product process generally does not include steps that are needed to increase product quality (e.g., steps designed to reduce impurities) does not mean that less information is required to support identification of the product's CQAs or that less rigor is applied to the identification of critical process parameters

(CPPs) and development of an appropriate control strategy. Below are some additional lessons learned in regard to application of the enhanced QbD elements to the drug product process from the A-Mab case study and, in particular, the OBP QbD pilot program.

2.3 Identification of Critical Quality Attributes (CQAs)

Development of a QTPP and CQAs assessment should be initiated early in development. A CQA is defined in ICH Q8R2 as a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. While some biotechnology products, such as monoclonal antibodies, have a wealth of publically available information that can be used to assess the likelihood a product attribute will impact safety and/or efficacy, the assessment of attribute criticality still presents a significant challenge. The simplest approach for most products may be to initially use available information to rank a product's attributes by their likelihood to impact safety and/or efficacy rather than formally identifying an attribute as critical or not. Early risk assessments (as described in ICH Q9) may draw heavily on published information when little product-specific information is available, as long as the limitations of this information source and its relevance to the molecule under consideration are kept in mind. The process of attribute ranking can help to consolidate and organize available information/data and provide a venue with which to plan and prioritize future studies. In addition to identifying attributes that are likely to be CQAs, the ranking process may illuminate areas of greater uncertainty which can help focus future investigations into attribute criticality. The initial attribute ranking profile can subsequently be updated and refined as additional product and clinical information is acquired. As described in ICH Q6B, the heterogeneity of biotechnology products defines their quality, thus the degree and profile of the heterogeneity should be characterized (Food and Drug Administration 1999). A systematic evaluation of attribute criticality will not only help identify those attributes that need to be controlled within the tightest limits, but can also be used to support other areas of product development such as demonstration of comparability after manufacturing changes (Swann et al. 2008), and support for product stability.

A common deficiency observed in the OBP QbD pilot program was the inclusion of process capability in the assessment of attribute criticality. It is the FDA's expectation that the risk ranking of product CQAs will focus on their likelihood of impacting the product's clinical activity and safety profile (e.g., severity). The CQA identification process should not include process capability or attribute detectability. It is also common that a score for uncertainty be included in the risk assessment so as to factor in the relevance of the information used to assign the impact score or rank. Experience from the OBP, QbD pilot program highlighted the importance of considering the possibility that attributes can interact and/or impact product stability in the severity assessment. For example, the level of free thiols present during

production or at release has been shown to impact both product potency and the formation of aggregates. Free thiols may therefore have a high severity due to a direct impact on product activity but also due to safety since an increase in aggregates could impact product immunogenicity.

Principles outlined in ICH Q5E may be helpful when assessing quality attribute criticality particularly for the severity assessment (Food and Drug Administration 2005). ICH Q5E states that in cases where differences are seen between products in a comparability study the "…existing knowledge [needs to be] sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety and/or efficacy." It is further stated that determination of whether the product variant affects safety and/or efficacy may require additional evidence from nonclinical or clinical studies, and that the extent and nature of those studies will be determined on a case-by-case basis. Application of these concepts to identification of CQAs suggests that assignment of a criticality designation to a quality attribute may need to be supported by nonclinical and/or clinical data in addition to a thorough in vitro assessment. There is more likely to be a need for nonclinical and/or clinical information when a significant product attribute (e.g., glycosylation, charge, etc.) is designated as noncritical and thus may not be tightly monitored and/or controlled during manufacture and in the postapproval lifecycle management process. While it is obviously not possible to clinically test purified product variants, it is sometimes possible to analyze variants from patient samples (Chen et al. 2009) or to test them in a relevant animal or in vitro model. Another approach is to use information from clinical lot extremes to support the quality attribute's criticality designation if the variant is present at high enough levels for an impact to potentially be observed in the exposed population. Such studies can also be used to justify CQA acceptance criteria both for design space development, and lot release and stability testing.

The direct assessment of some attributes (e.g., oxidation at a specific site, glycation of the antigen binding domains) may not be possible due to their low abundance. In some instances, the level of low-abundance attributes can be increased through the use of accelerated or stressed conditions, but often attempts to increase their abundance results in an increase in the level of other attributes and analysis of the impact from a specific variant is confounded. In these cases, even if the severity assessment indicates a low probability of quality impact, the uncertainty score will be high since a direct assessment of product impact was not possible. The end result may be the classification of the product attribute as critical due to high uncertainty even though at the very low levels present in the process, it is unlikely the attribute would impact product quality. Classifying the attribute as critical is important however so that the uncertainty associated with its potential to impact product quality when present at higher levels is not minimized or forgotten during the product's postlicensure lifecycle management process. For some attributes present at very low, well-controlled levels, a control strategy that only includes assessment of the attribute for comparability after relevant manufacturing changes may be justifiable.

2.4 Identification of Critical Process Parameters (CPPs)

ICH Q8 (R2) defines CPPs as those "whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality". A common deficiency noted in the pilot program was to interpret this to mean that CPPs are only those that impact CQAs if they are varied outside their acceptable range. Just as with attribute assessments, quality risk management principles can be useful in assessing the criticality of parameters. In the risk assessment and subsequent studies, it's important that parameter ranges that are explored are wider than those anticipated during routine manufacturing. Ranges may be chosen based on a combination of equipment design capability studies and previous manufacturing history. When assessing possible sources of variability, considerations should include the functionality and limitations of commercial manufacturing equipment as well as the contributions of variability by different component lots, production operators, environmental conditions, and measurement systems in the production setting. Parameters whose variation has a meaningful impact on a CQA should be classified as critical regardless of how well the parameter can be controlled and whether there is CQA impact within the proposed manufacturing range.

The ability to accurately assess the impact a parameter has on a CQA depends on the extent of process/product understanding and the size of the characterized process space (knowledge space). Narrow investigational ranges may not provide sufficient variability for a CQA impact to be detected and may result in incorrectly labeling a CPP a non-CPP. At the same time, there may be a practical and/or experimental limit to the range(s) investigated and the expectation is not to test each parameter to its limit of failure. A balance must be set between these two considerations so that the range studied is broad enough to detect CQA impact by CPPs, but is not so broad as to have no relation to the range intended to be used for manufacture. This issue was identified most often with parameters such as pH, which are generally well controlled in a narrow range, and was not generally an issue for parameters that are operated (and explored) under a wide range. QbD submissions should therefore contain robust justification for the ranges selected for the process characterization studies based on both the intended manufacturing range and the degree of variability represented by the range studied. The greater the uncertainty that the range explored was sufficient to identify whether variation of the parameter impacts a CQA, the greater the residual risk associated with that parameter. This higher residual risk may need to be taken into account in the overall control strategy.

Another common concern raised in the pilot program was whether there were sufficient data to demonstrate that the small scale models used for characterization studies were representative of the full-scale process. There are well-known cases where small scale studies have not predicted events which happened at full scale (antibody reduction case (Trexler-Schmidt et al. 2010). It is essential that applications that propose a design space address how representative small-scale models are and provide data, when appropriate, to support their linkage. If firm-specific

platform knowledge is used to support a design space, comparative information on product characteristics and process parameters should be provided so regulators can assess the appropriateness of the platform information. While verifying small-scale models of DP manufacturing unit operations may not always represent the same challenges as some drug substance unit operations (such as the production bioreactor), the importance of demonstrating representativeness of small scale models should not be minimized and should be supported by a robust statistical evaluation that supports equivalence. If sufficient full-scale data are not available at the time of submission, information should be provided on how the link between the small-scale and commercial-scale processes will be verified after approval of the design space.

Only a subset of the parameters that is monitored for each unit operation is generally included in the characterization studies performed for CPP identification. Formal risk assessments are used to prioritize parameters for inclusion or exclusion from further study and in some cases to determine which type of study (e.g., univariate or multivariate) will be used to assess the potential criticality of a parameter. QbD submissions therefore should include a list of the parameters in each unit operation, a summary of the information/data that was used in the risk assessment to determine which parameters to include in the characterization studies, and a brief summary of and justification for the final risk-assessment decision.

Formal risk assessments can also be used to determine which CQAs to monitor in the process characterization studies for a given unit operation. As stated earlier, the DP process is geared toward maintenance of product quality, and sterility assurance, and the potential to impact some CQAs is minimal. Quality attributes that are commonly impacted by the DP process are aggregates and particulates including product-related visible particles and subvisible particles. The importance of considering the possibility that attributes can interact and/or impact product stability cannot be stressed enough. As the formation of aggregates and particulates may be linked to other quality attributes such as free thiols, deamidation, oxidation, and/or leachates, the CPP identification risk assessment should consider each CQA individually for impact by the process and for linkage to other CQAs and product stability.

The potential for time and temperature dependent operations to impact CQAs should be considered in the overall framework of DP stability, including product stability over the course of the product's shelf life and possibly during shipping. For example, characterization studies to assess the acceptability of hold and processing times may need to be combined with longer term stability studies to adequately assess the impact to product stability. A common issue observed in biological license applications is the absence of data that adequately supports product quality during shipment. These studies need to include a comprehensive set of assays that are capable of sensitively detecting product degradation in addition to data demonstrating validation of the shipping container(s) and shipping conditions.

It is essential that the DP process be thoroughly assessed for its potential to impact product quality negatively, and sources of variability identified and controlled. For example, there are now multiple instances where raw materials have had an

adverse impact on drug product quality. CQAs based on variability of input materials need to be identified, with formulation of excipients of particular concern (e.g., polysorbates (Kerwin 2008)). Leachates from the container/closure system is another area that requires particular attention as evidenced by recent issues associated with glass lamellae in glass vials (Food and Drug Administration 2011), tungsten with prefilled syringes (Liu et al. 2010), and silicon from vial stoppers or prefilled syringe barrels (Thirumangalathu et al. 2009). Filters have also presented leachate issues; in one case due to incomplete washing of sterile filters by their manufacturer. An additional example is the manufacture of depth filters with the incorrect filter components which resulted in the introduction of unacceptable by-products into the finished drug product. A well-documented example of the drug product process negatively impacting product quality is the shedding of nanoparticles from a filling pump's solution-contact surfaces which may nucleate protein aggregation and/or particulate formation (Carpenter et al. 2009; Tyagi et al. 2009).

2.5 Design Space

The implementation of QbD may allow for the establishment of a manufacturing design space(s) which is defined by ICH Q8 (R2) as "…the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality" (Food and Drug Administration 2009). If approved, changes within a design space can be managed by the firm's quality management system and may provide a measure of regulatory flexibility. It should be noted that the definition of design space in ICH Q8 (R2) does not include the word "critical." A reoccurring issue in the pilot program was the definition of design space to only include parameters that had been defined as being critical. Even with robust CQA and CPP identification programs there is some level of residual risk and uncertainty associated with risk assessments and process characterization studies. This is particularly true in the absence of a large dataset that verifies the design space at full scale. The establishment of a design space should therefore focus on selecting relevant variables and ranges within which consistent quality is assured and may include parameters that have not been defined as critical using the sponsor's prespecified criteria.

The A-Mab case study (CASSS and ISPE 2009) had some interesting examples of potential drug product design spaces which focused on distinct areas of the drug product process such as formulation robustness, compounding, sterile filtration and filling. Other areas proposed for inclusion in a design space have been definition of excipient critical material attributes, and development of a product-specific control system lifecycle management protocol for periodic control system re-evaluation to allow continuous improvement in the process and testing of licensed products.

Experience from the pilot program also revealed that a firm's long-term strategy for implementing enhanced regulatory concepts could impact developmental studies (e.g., quality attribute characterization, identification of relevant process

parameters). For example, if the final control strategy will not include lot release testing for a particular CQA, it may be more important to include that CQA in process characterization studies to define the link between input material attributes, process parameters and product quality. In addition, the risk assessment of process parameters depends upon a firm's current and future manufacturing capability and plans for postmarketing management of process parameters. Therefore, expectations of the ultimate control strategy and postmarketing management plan can impact the design of QbD development/characterization studies and should be considered early in development to ensure sufficient information is available when the design space and control strategy are proposed.

2.6 Change Management

Change management is defined in ICH Q10 as a systematic approach to proposing, evaluating, approving, implementing, and reviewing changes. Successful change management should facilitate continual improvement and enabling change is a critical component of QbD. Postapproval change management is of great interest and concern for regulators since ICH Q8-11 allows for the possibility of more flexible regulatory approaches. An issue that concerns regulators is that the granting of regulatory flexibility can result in a different role for the regulator in the postapproval change management process. The Pharmaceutical Quality System (PQS) as described in ICH Q10 is an important component to an enhanced development and manufacturing approach. Therefore, if a firm proposes to use advanced QbD concepts to gain regulatory flexibility, it may be beneficial to include information in the application on the process that will be followed when the proposed changes are implemented and the criteria that will be used in the change management decision-making process.

For firms that use advanced QbD approaches and gain approval of one or more design spaces, movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process (Food and Drug Administration 2009). To facilitate the approval of a design space for a complex biotechnology product, an applicant may want to provide information on how movement within the design space will be managed post approval, particularly in the case of large or complex design spaces (Food and Drug Administration 2012). In these cases, the level of certainty in regard to design space performance may be less robust in some areas of the design space. Additional product and process monitoring may therefore be warranted if process parameters are moved to fall within areas of greater uncertainty. Movement within the design space would still be managed primarily by the firm's PQS but a commitment to perform more extended studies with specified acceptance criteria could provide regulatory agencies with a detailed understanding of how changes will be managed and a higher level of assurance that product quality will not be impacted.

Another issue that has arisen is how changes to parameters that are not included in the design space will be managed. A concept that has been proposed is to establish classifications for parameters that will dictate how changes will be managed postapproval. A quality risk assessment utilizing prior knowledge, development studies and manufacturing information can be used to categorize process parameters (e.g., high, moderate, or low-risk) based on their relative potential to impact product quality. The categorization of parameters from the quality risk assessment can be used to communicate with regulators regarding a lifecycle management approach to assure continual improvement throughout the product lifecycle. For example, high-risk parameters might be defined as those CPPs and non-CPPs included in the design space. By definition, changes to design space parameters that are within the established design space would not need prior approval from the regulator. However, changes that would extend the range beyond that established by the design space would require submission of a postapproval supplement per 21 CFR 601.12.

Definitions for moderate and low-risk parameters and their postapproval management strategy could also be proposed. For example, changes to moderate-risk parameters not included in the design space that do not exceed the knowledge space provided in the application could be managed by the firm's PQS. Changes that exceed the knowledge space would be supported by studies, tests and acceptance criteria which are outlined in the submission. If no impact to a relevant CQA is observed, the change could be reported in the annual report. If a meaningful CQA impact is observed however, the change would need to be supported by an appropriately categorized postapproval supplement. Changes to low-risk parameters would be managed by the firm's PQS. For any manufacturing change, if the evaluation of the risk is increased by new knowledge, an appropriately categorized postapproval supplement should be submitted. Where regulatory flexibility is being requested, providing information that clearly outlines how changes will be managed, including how they will be reported and additional studies that will be performed to support specific types of changes, makes the postapproval change process more transparent to regulators and will help regulators assess the acceptability of the proposed post-management lifecycle plan.

2.7 Communicating Complex QbD Concepts and Control Strategies

An issue that came up repeatedly in the pilot program was the magnitude of information that is generated in the QbD development process and the challenges associated with communicating QbD knowledge and the proposed control strategy to the FDA. While to date the Agency's experience with review of QbD BLAs is limited, several factors identified in the pilot program that may aid in our review of enhanced QbD concepts have been identified and are outlined as follows.

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