Quality By Design for Monoclonal Antibodies, Part 1
Establishing the Foundations for Process Development

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The quality by design (QbD) modernized approach to pharmaceutical development is intended to provide regulatory flexibility, increased development and manufacturing efficiency, and greater room to innovate as well as improve manufacturing processes within defined ranges without obtaining regulatory approval first. QbD is a systematic developmental approach that starts with a clear goal in mind and emphasizes understanding of how variability in both process and materials affects a final product (1).

Historically, product quality has been assured either with end-product testing (drug products) or with strict and narrow control of manufacturing processes without a comprehensive understanding of how process parameters link to product quality attributes (biologics). According to a 2011 US FDA guidance, product quality cannot be assured by testing alone (2). In the QbD paradigm, quality is built into the process rather than being “tested into” a drug product. Part 1 of this two-part article will address the early steps in process development, including defining a target product profile (TPP), a quality target product profile (QTPP), and critical quality attributes (CQAs). Part 2 (scheduled for September) will conclude this discussion by focusing on establishing a design space and optimizing process characterization through risk assessment and well-defined control strategy.

The goal of pharmaceutical development is to design a drug manufacturing process that consistently yields a high-quality, safe, and effective product (3). Before 2000, monoclonal antibody (MAb) development and manufacturing tended to be plagued by inefficiencies that resulted in limited innovation throughout a product’s life cycle and significant product waste from lost batches. Some biomanufacturers were unable to connect product attributes to manufacturing processes despite the high risk for waste generated by mistakes. FDA’s 2002 initiative Pharmaceutical CGMP for the 21st Century: A Risk-Based Approach sought to improve interactions between pharmaceutical manufacturers and regulators by focusing on science- and risk-based approaches to development (4). This document states the following:

Continuous improvement is an essential element in a modern quality system, and it aims at improving efficiency by optimizing a process and eliminating wasted efforts in production. In the current system continuous improvement is difficult, if not impossible. Reducing variability provides a win–win opportunity from both public health and industry perspectives; therefore, continuous improvement needs to be facilitated.

The shift toward risk-based development has led to use of iterative...
**ICH Guidelines Related to Quality by Design**

**ICH Q8(R2) Pharmaceutical Development** provides guidelines for drug product development. ICH Q8 defines QbD as “a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management” (5). This guideline outlines the principles for potentially achieving increased regulatory flexibility.

**ICH Q9 Quality Risk Management** provides principles and examples of tools for quality risk management that can be applied to all aspects of pharmaceutical quality, including development, manufacturing, distribution, and inspection and submission/review. This document states that risk assessment should be based on sound scientific knowledge and that the level of risk assessment activities should be a function of the level of risk (6, 7).

**ICH Q10 Pharmaceutical Quality System** applies to pharmaceutical drug substances and drug products throughout their lifecycles and provides a comprehensive model for pharmaceutical quality based on ISO standards. It is intended to promote innovation and continual improvement in pharmaceutical manufacturing (7). It outlines a pharmaceutical company’s responsibilities and ICH expectations (8). This guideline introduces the concept of “phase-appropriate” development.

**ICH Q11 Development and Manufacture of Drug Substances** covers the development and manufacturing process of drug substances (9). It provides an explanation of what should be included in the common technical document submission.

Risk assessments and QbD methodologies that help improve product and process understanding and increase innovative solutions to manage risk associated with variability inherent in pharmaceutical manufacturing.

The QbD approach provides a set of tools that support both developmental and manufacturing activities. It aligns with the phases of clinical development, enhancing pharmaceutical development processes. ICH guidelines Q8(R2), Q9, Q10, and Q11 provide the framework for QbD (see “ICH” box).

For MAbs, a QbD approach includes identifying critical process steps and parameters and designing the operation of those steps to reduce risk and increase quality. Because biopharmaceutical manufacturing involves producing a desired product in a living host organism, attention should be focused on development and characterization of a production host cell line. Product is then purified from host- and culture-related impurities using a series of orthogonal unit operations. At each step of cell culture and purification, operators should identify materials or operations that can affect product quality and safety. Well-established knowledge about MAb processes and relationships between specific process parameters and product quality is available. So implementation of QbD into a new antibody manufacturing process is more straightforward than it is for other biopharmaceuticals.

**Life-Cycle Approach to Pharmaceutical Development**

QbD is a life-cycle approach to product development that encompasses development, optimization, and validation of a manufacturing process. This strategy is part of all stages — from initial identification of a potential new product through all phases of clinical development and commercialization until withdrawal of a product from the marketplace. QbD focuses heavily on leveraging prior knowledge and experience to both improve a process and reduce overall risk. Janet Woodcock (director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA)) is credited with saying that QbD derives from a combination of prior knowledge, experimental assessment, and a cause-and-effect model that links critical process parameters (CPPs) and critical quality attributes (CQAs) (5).

The overall goal of QbD is to maintain a state of control for biopharmaceutical products and their manufacturing processes over their life cycles through design, definition, and implementation of proper control strategies. ICH Q10 defines control strategy as

a planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (8)

Figure 1 outlines a QbD approach. This strategy is aligned with the phases of clinical development and product/process development (10).

Effective product life cycle management requires engagement of cross-functional teams for all QbD steps. The development team should include a diverse group of subject-matter experts from multiple disciplines working toward successful product realization. Such experts can provide different perspectives and opinions.

**Quality By Design in Industry**

Genentech’s Gazyva (obinutuzumab) is the first MAb to be approved by FDA using a full QbD filing (11). Many key lessons can be learned from the company’s experience, not only with the approval of Gazyva, but also with the nonapproval by the FDA and European Medicines Agency (EMA) of the company’s QbD filing for Perjeta (pertuzumab). According to Lynne Krummen (the company’s vice president and global head for biologics, technical regulatory, and global lead for quality by design), every bit of flexibility that QbD potentially offers must be earned, and everything must be justified (12).

Many steps can be taken to improve a manufacturing process over a product’s life cycle. Research and process performance information as
well as internal polices and practices must be readily available and well documented to take full advantage of knowledge available and to meet relevant regulatory standards. Using risk-management tools and iterative risk assessments is essential for developing a control strategy and design space that global regulatory agencies will accept. According to Krummen, engaging those agencies early and being upfront about knowledge gaps are keys to a successful QbD filing.

Although a full QbD filing can increase flexibility in commercial MAb manufacturing, expenses associated with completing all necessary work for it makes the cost of filing for new-product approval significantly higher than a filing without QbD. In Genentech’s Gazyva filing, extensive documentation and testing associated with the QbD-related work led to a much larger chemistry, manufacturing, and controls (CMC) section of the company’s biologics license application (BLA) than for other MAb product filings. That may have added as much as US$1 million to the overall product costs (7). For smaller sponsor organizations, CMC work can be contracted to a service provider.

**Target Product Profile, Quality Target Product Profile, and CQAs**

In the QbD paradigm, development starts with a target product profile (TPP). This dynamic summary of desired product attributes is used to enhance dialogue between a sponsor and regulatory agencies. It establishes the foundation for a quality target product profile (QTPP), which is a summary of a product’s quality characteristics. Following the development of a QTPP, CQAs are proposed through risk assessment. CQAs are characteristics or properties that must be maintained within a specific range to ensure high quality.

A TPP is usually defined by the discovery functions within a company and later transferred to process development. It is the foundation of product development and can serve multiple purposes, depending on the needs of a company. A TPP is meant to facilitate interactions with global regulatory authorities. According to the FDA’s draft guidance *Guidance for Industry and Review Staff Target Product Profile — A Strategic Development Process Tool*, “the TPP embodies the notion of beginning with the goal in mind. That is, the sponsor specifies the labeling concepts that are the goals of the drug development program, documents the specific studies intended to support the labeling concepts, and then uses the TPP to assist in a constructive dialogue with FDA” (13).

A TPP states the intent of a product and can provide a snapshot of a prospective drug at a given moment in time. It includes information about the drug and its desired features. A TPP includes a drug’s description, indication, desired efficacy, safety claims, desired drug product format, and container closure design (e.g., liquid prefilled syringe or lyophilized vial), route of administration (e.g., subcutaneous or intravenous), and other desired attributes of a product (14).

The FDA currently does not require use of a TPP, and the overall interpretation of the draft guidance is left to an applicant’s judgment. Because a TPP is not a required element of filing, it does not represent a commitment to follow all stated product goals. Submitting a TPP does not represent an obligation by a sponsor to submit draft labeling in a new drug application (NDA) or BLA that is identical to that in a TPP. However, any endorsement of a TPP by the FDA during the dialogue process does not necessarily represent intent of approval of a final label (13). The TPP is not meant to constrain a company or impose restrictions, but rather to provide a useful tool to facilitate discussions between a sponsor and the FDA. In cases for which a TPP is not used, similar documentation should be used that state the overall intent of a drug, which will be used to inform a QTPP.

A QTPP is based on the foundation laid by a TPP or similar documentation. A QTPP is a prospective summary of a biopharmaceutical product’s quality characteristics that will be ideally achieved to ensure a desired quality. It takes into account both safety and efficacy. Attributes represented in a QTPP relate to a drug product’s intended use and are those that can affect patients. Considerations for the QTPP should include route of administration, dosage form, bioavailability, strength, and stability (5). Although a TPP indicates what a drug will do, a QTPP indicates the quality targets necessary to do it.

A QTPP serves as a guide for future product and process development activities. It should be defined when a drug candidate has been identified as viable for development. Because of the iterative nature of QbD, a QTPP should be revisited and updated as necessary at phase-appropriate intervals over the course of a product’s life cycle (13, 15).
The long history and abundant data available for therapeutic MAbs provide a good template for the initial definition of the QTPP for a new antibody product. Correlation between specific functions of antibodies and quality attributes that contribute to those functions are well understood for this class of molecule. So designing a QTPP in advance of clinical trials is less challenging than it is for other types of biopharmaceuticals. For example, ADCC (the mechanism by which antibodies recruit other immune system components to kill target cells) is enhanced by lower fucose levels, higher galactose content, reduced sialylated glycan content, and/or a bisecting GlcNac on the single glycan structure on each heavy chain (16–18). Cell lines and cell culture conditions can be developed to increase or decrease levels of quality attributes, depending on the desired function of an antibody product. That process directly applies a QTPP to process development activities.

A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure that a product has the desired safety and efficacy in a patient, as defined by the QTPP (5). CQAs are selected from all of a product’s quality attributes though risk assessment, as outlined in ICH Q9. Figure 2 shows the inputs to a CQA risk assessment.

CQA risk assessment considers prior knowledge about a target molecule, toxicology studies, and available clinical or nonclinical studies. The assessment takes into account two factors: the severity of something going wrong and the level of certainty of the chances of it going wrong. Those factors are scored using a severity score and an uncertainty score. A severity score measures the impact of a failure, and the uncertainty score measures the level of confidence in the information used to determine the severity score. CQAs should be sorted using a criticality matrix, with attributes having the most impact on safety and efficacy given the highest priority.

Prior knowledge is used to score a CQA risk assessment and can include molecule design, nonclinical studies, in vivo and cell-based assays, relevant platform products or quality attributes, and relevant published literature (1, 15). Prior knowledge elements are weighted differently in determining the uncertainty score (Figure 3) (19). CQAs for a new MAb product are based on extensive literature and knowledge regarding how a given type of molecule interacts with a patient’s immune system and the therapeutic target (antigen). As product knowledge evolves throughout clinical development, criticality of certain attributes may change, and a CQA criticality assessment should be repeated at phase-appropriate intervals.

Although many biopharmaceutical companies are implementing QbD methodologies as standard business practice, they have not been applied routinely early in product development. That is partly due to the lack of sufficient process data to adequately provide a correlation between process steps and product quality attributes as well as a lack of analytical data to identify a product and its process CQAs. Production of clinical trial material is always on the critical path in early development, and the initial steps of biopharmaceutical production includes generating a production cell line and cell culture/fermentation process.

Most cell line development technologies focus on obtaining high titers quickly, with little to no attention paid to posttranslational modifications and potential product heterogeneity. A more effective approach would be to use cells specifically engineered to produce desired posttranslational modifications and achieve high titers. Early development activities reflect the goals of QbD by enabling a rational approach to manufacturing products with desired quality attributes.

**QbD Knowledge Is Key**

QbD is a highly iterative life-cycle–based approach to pharmaceutical development. To complete a full QbD filing, a process must be started early and updated often. Proper documentation is essential to a QbD development effort, but it can add significantly to overall costs.

**References**


