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# What you need to know about process characterization and validation for biologic processes

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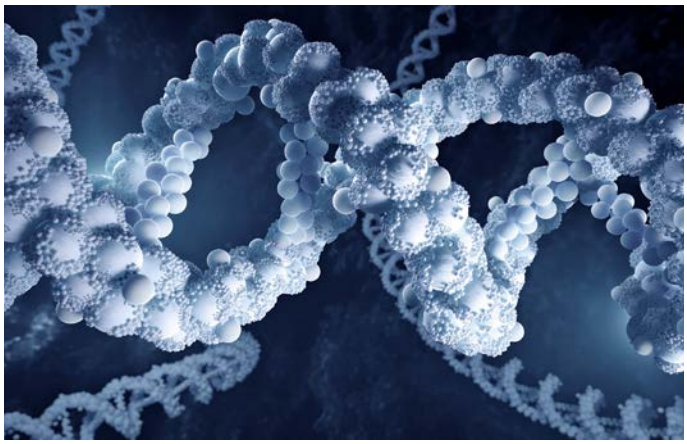
# Abstract

A major factor in the growth of the biopharmaceutical industry over the last 20 years has been continuous innovation with monoclonal antibodies (mAbs), which now make up more than 50% of the overall biotherapeutic market[1]. A significant driver for success with these therapeutic modalities has been the ability to use templated process and analytical platforms in process development and manufacturing in order to reduce timelines and facilitate robust scale-up[2]. The ubiquity of mAbs has resulted in a strong body of knowledge across the industry that can be leveraged to support critical risk-mitigation activities during the life cycle of biopharmaceutical drug management. These include the vital steps of process characterization and validation required for commercialization of your biologic molecule, where process control strategies are developed and implemented to minimize risk and control quality.

However, the recent paradigm shift in the industry toward next-generation therapeutics has resulted in increasingly complex manufacturing processes that are no longer "plug and play."[3, 4, 5] The lack of familiarity with these new non-mAb molecules has led to increased attention to their specific risks. Now, a more comprehensive understanding of how to design processes is required to ensure a molecule is developed with the appropriate quality attributes and safety profile. It is therefore imperative to carefully and skillfully evaluate the structural liabilities, key product quality attributes, and process risks associated with your molecule. Insufficient evaluation and understanding of these risks may result in a late-stage strategy that does not lay out a successful path to market.

## Getting started: Understanding process risks

Even during the early drug discovery process, there are valuable opportunities to simplify the path to commercialization. At this stage, multiple candidate molecules may be screened for their ability to bind a specific biological target and demonstrate the desired clinical effect. Often, there are multiple candidates that meet these criteria. When selecting a candidate to advance into development, it can be valuable to understand the unique properties impacting its binding affinity, activity, manufacturability, and safety that will need to be managed during commercial manufacturing.



Beginning in the early stages of development, and continuing through commercialization and beyond, Quality by Design (QbD) concepts should be applied. QbD is a systematic approach, applied throughout the entire drug development process, linking process design and control to critical product quality attributes. QbD leverages the accumulated knowledge gained throughout the drug discovery and development lifecycle to characterize risks to process performance and their potential impact on the product[6]. Preferably, QbD principles are applied to the initial design of processes and methods for production and purification of the target molecule, along with the analytical methods required to measure concentration, purity, and activity of the product[3]. However, timeline and funding constraints may limit characterization and knowledge in early phases of development.

As the molecule advances towards commercialization, regulators expect a comprehensive understanding and control of potential risks to the product due to process variability[7]. This is accomplished through characterization of process parameters and method robustness during late stage development. In order to determine which studies are needed to ensure process robustness and product safety, an initial risk assessment must be completed to capture what is known about the process based on the development work to date as well as experience with similar molecules.

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Process parameters are evaluated during process development, with respect to their effect on important product quality attributes. Out of this evaluation, key process parameters (KPPs) and critical process parameters (CPPs) are identified, as well as their effects on critical quality attributes (CQAs). Regulatory guidance from the International Council for Harmonization (ICH) define critical quality attributes (CQAs) as “physical, chemical, biological, or microbiological propert(ies) or characteristic(s) that should be within an appropriate limit, range, or distribution to ensure the desired product quality.”

ICH defines CPPs as parameters “whose variability (have) an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.”[2]

KPPs are not specifically defined in the ICH guidance, as these are process parameters which need to be monitored to ensure consistent process performance, but do not directly or significantly impact CQAs.

When approaching the initial risk assessment, it is immensely valuable to have a team with strong experience and expertise that has worked with a diverse set of molecule types at different phases of development from clinical through commercialization. An experienced team can combine their knowledge from past projects with preexisting knowledge about your molecule to confidently predict potential risks that may affect your process and product quality. This knowledge creates a strong foundation upon which to build your assessment and enables you and your team to foresee and adapt to the challenges that will inevitably occur. Experiments that are well executed and performed by a skilled and experienced team will result in a reliable dataset with the appropriate amount of information to create a control strategy for manufacturing and process validation.

Once the initial risk assessment is complete, the team will begin process characterization studies. Process characterization is a thorough, experimental and statistical evaluation of a manufacturing process. This evaluation defines and confirms process parameters and ranges that can be controlled to assure product quality, safety, and efficacy. The scope of process characterization work needed is informed by an understanding of the risks present.

If a molecule has already been demonstrated to possess fewer liabilities during process development or in early stage clinical studies, fewer studies maybe required to ensure manufacturing robustness.

The amount of characterization needed is also dependent on the type of designation and patient need. For breakthrough therapies, risk assessments are essential for prioritizing the most critical activities for completion on an accelerated timeline to start process performance qualification (PPQ).

An important element of process characterization is the development and qualification of a scale down model, which is used to represent and model the manufacturing process at a small scale. This enables the typically large number of experiments required to fully characterize a process to be executed at bench scale, rather than at manufacturing scale, which would be prohibitively demanding in terms of time and resources.

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Larger biopharmaceutical companies may have the capabilities to develop a scale-down model and perform a thorough process characterization in-house, resulting in a detailed understanding of the risks and liabilities of the process and the molecule. However, other companies may need to work with a third party to ensure a thorough and accurate assessment is completed.

In addition to design and execution of the process characterization experiments, it's critical that the quality systems used at the third party are able to provide guidance and support in order to successfully complete the study. For this reason, data integrity and quality assurance are critical to the process and must be taken into consideration when evaluating and comparing potential outsourcing partners.

A valuable tool in process development, and especially in process characterization, is the use of design-of-experiment (DoE) statistical methodologies with high-through process and analytical methods. This approach allows for multiple process parameters to be studied in parallel in order to rapidly identify their effects on product CQAs. Depending on the specific design used, these studies can screen for the parameters that have the greatest impact on CQAs, provide insights on multivariate interactions between parameters, and even identify optimal process set-points. For process characterization, DoE is well suited for defining the Proven Acceptable Ranges (PAR) for process parameters as part of the commercial process control strategy. Increasingly, these studies are being included in clinical-phase process development activities to limit the process changes needed for commercial readiness. These study results can then be leveraged to eliminate low-risk parameters from in-depth process characterization studies and greatly reduce the timelines and resources needed for process characterization studies.

After the process characterization studies are completed, the team will conduct a Failure Mode and Effects Analysis (FMEA). The FMEA is a risk assessment that reviews the entire product and process history of a molecule, including data from early development, manufacturing, and process characterization. The FMEA is used to assess each process parameter and their impact on product quality attributes critical for product safety and efficacy and to decide what process, facility, equipment, and testing mitigations are available to de-risk CPPs. This assessment is ultimately used to determine a robust in-process control (IPC) strategy that will be used to validate an at scale manufacturing process.

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## Evaluating andcontrolling product quality

The results of process characterization are used to develop the final risk assessment and an in-process control (IPC) strategy. The IPC strategy is generated following the FMEA assessment, and serves as the controlling document for the manufacturing process. These efforts determine which parameters pose the most risks to process performance and to the critical quality attributes of the molecule. For example, if the team determined in the FMEA that cell culture pH is a process parameter that might have a critical impact on product quality, process characterization results will be used to determine what pH range the bioreactor must operate within during manufacturing to safely maintain product quality.

Operating ranges are then defined for all KPPs and CPPs and built into the control strategy. This IPC strategy thereby establishes guidelines and limits for process parameters and operation. Deviation from the defined limits may result in a compromised or failed batch[8].

Following development of the IPC strategy, process validation is executed in the form of process performance qualification (PPQ) runs to validate the process and confirm adequate control. The process is run multiple times at manufacturing scale using the IPC strategy to confirm robust and reproducible performance resulting in consistently acceptable product quality. It is important to note here that process validation is not the same for all biologic molecules.

Although the industry has traditionally relied on using three batches during the PPQ phase for mAbs, this is not always the case for today's new drugs. The number of batches used for validation should depend on the complexity of the molecule and the process, the risks anticipated in manufacturing, and any potential impacts on the safety and efficacy of the product. If a large number of risks are identified, or if the risks that do exist are high, more than three batches may be required to ensure that the process is well controlled.

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Even in cases of breakthrough therapy designations and accelerated pathways to market, process characterization and validation remain critical steps in the biomanufacturing process. While accelerated approval may expedite the regulatory filing process, getting a product approved for commercial release always requires a deep understanding of any potential risks to your process and your molecule.

## Filing your process with regulatory agencies

Once process characterization is complete, a control strategy is confirmed, and the process is validated with a sufficient number of PPQ runs, your team is ready to file for regulatory approval of its manufacturing process. The data from process characterization and validation, along with the control strategy, are presented to regulatory agencies within filing documents, such as the biological licensing application (BLA).

The regulatory agencies will use this information to determine whether the process is appropriately and sufficiently controlled. If the process is deemed to have been incompletely characterized during process characterization or insufficiently validated with too few PPQ runs, the manufacturing strategy might not be accepted, potentially delaying the commercial release of the biopharmaceutical product at a significant cost to the company.

Overall, the mission of regulatory agencies, such as the FDA, is to ensure that biomanufacturers have adequate understanding and control built into each step of their manufacturing process, leading to a product with the highest level of safety, quality, and efficacy. And while process characterization and validation can be challenging, using a risk-based approach to generate an appropriate control strategy will help assure that your product meets these requirements, enabling timely approval and launch to market.

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Frank Ritacco has a PhD in Microbiology and Molecular Genetics from Rutgers University, and over 20 years of experience in the pharmaceutical industry. Prior to joining Thermo Fisher Scientific, Frank has worked at Bristol-Myers Squibb, Unigene Laboratories and Wyeth Research. His areas of expertise include mammalian cell culture, microbial fermentation, cell line development, media development and optimization, process development, scale-up, tech transfer, and clinical manufacturing. In his current role at Thermo Fisher, Frank oversees new technology development in the Bioprocess and manufacturing sciences, driving scientific innovation and collaboration between internal and external partners, and also serves as a technical subject matter expert and point of contact, interfacing with customers and the biopharmaceutical community.

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Daniel Baskind is a manager in the Scientific & Technical Affairs group in the Biologics Drug Substance division of Thermo Fisher Scientific. In this role, Daniel is responsible for driving technology development for the division, fostering technical collaborations, as well as providing technical oversight and CMC support for critical customer programs. Throughout his career, Daniel has been responsible for biologics process development, scale-up, manufacturing, and process validation specializing in downstream processes for a variety of molecule classes. Before joining Scientific & Technical Affairs in 2019, Daniel led a team responsible for the development and technology transfer of multiple early and late-stage programs at Thermo Fisher. Prior to joining the Company, Daniel focused on novel vaccine development at Novavax, with time spent in both the downstream process development and manufacturing operations. He received his bachelor's and master's degrees at Cornell University.



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