

# Process characterization: Ready for the FDA?

Prior to the 2011 release of the FDA guidance on process characterization,<sup>1</sup> the pharmaceutical industry historically viewed process characterization, the validation of a manufacturing process to minimize risk and ensure consistent quality throughout a product's life cycle, as optional. As pipelines evolved to more complex molecules and manufacturing processes, though, the outlook of regulatory agencies on process characterization also changed.

Today, they see process characterization as an essential step in the commercialization of a new drug product. This is related to various benefits of process characterization, such as enhancing not only process understanding but also, and most importantly, patient safety. Realizing these benefits and more requires proper planning and application of a comprehensive process characterization strategy.

#### Why is process characterization important?

Performing a statistical evaluation of a drug's manufacturing process offers insight into the critical and non-critical parameters that have the biggest impact on the quality, safety, and efficacy of your product. Your company or CDMO can then leverage that data later to make scientific inquiries into any deviations, allowing for fewer delays and faster batch release.

Process characterization helps define process specifications and ensures you can meet them, decreasing threats to quality. It also reduces the risk of lost batches in the future as well as any risks of lost time and wasted money. Eventually, a sound characterization program enables a successful process performance qualification (PPQ) and, ultimately, the acceptance of your biologic license application.

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In order to execute a successful process characterization program, you must be able to:

- Define/characterize unit operations that impact critical quality attributes (CQAs)
- Establish Designs of Experiment (DoE), results, and statistical analyses
- Generate tubular data/attached reports
- Create a scaled-down model that accurately represents your manufacturing process
- Look at intermediate hold times and viral clearance studies that may not directly be considered characterization but are necessary for getting to PPQ
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An important factor in identifying the critical parameters of your product and creating your process characterization strategy is dependent on understanding the key attributes of your molecule. While this is a complicated activity, it is a vital element to ensuring a planned, predictable performance of CQAs as well as to developing an effective drug.

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## How to decide when and how much process characterization you do?

There are multiple ways to approach process characterization, but all include applying a risk and science-based approach. Some may take a more minimalist approach, which speeds up PPQ, potentially resulting in a shorter timeline and lower up-front costs. However, this can also lead to delayed regulatory approvals from reviewers who want more information than provided. It can also lead to an impossible set of manufacturing conditions, where you have limited knowledge about what your parameter ranges should be. If a deviation occurs, you must spend more time on scientific inquiries. A comprehensive approach creates a longer road to PPQ runs, but approvals are typically faster, and any problems are usually limited to production, not process, so they are more easily identifiable and have a definitive correction.

One of the first key steps of process characterization is an initial risk assessment, which leverages SME expertise and knowledge about the process using a preliminary or primary hazard analysis. It includes using a table with parameters listed down one side and a molecule's attributes across the top in order to quickly screen the risks based on the current strength of knowledge. Elements determined to be high risk based on either a lack of or strength of knowledge are included in the characterization package, while any that are determined to have no connection are not. Those that fall in the middle are assessed against a risk/reward profile, where patient safety is weighed against the potential risks if those elements are not included.

The result is the identification of critical process parameters (CPPs) that you will feed into your experimental design and use in the next step, which is creating a scale-down model. Next, experiments are conducted and reports for each stage of development are generated while you simultaneously run batches for clinical production. The output is a full failure mode and effects analysis that classifies all of the variables and determines what the critical rankings are for each one, so you can create an in-process control strategy for your manufacturing process, culminating in all the work completed during process characterization. When you calculate the return, in terms of reducing delays and deviations in your manufacturing process, the reward is worth the initial investment.

### Impact of process characterization on process validation

Once you create your in-process control strategy, you are ready to execute PPQ runs. The traditional approach by the industry has been to use three PPQ runs to validate the process and confirm there is adequate control over quality. However, the evolution of the industry and today's drugs have changed this mindset, and the number of batches you use should depend on the complexity of the molecule and the process, the risks anticipated in manufacturing, and how these can potentially impact the safety and efficacy of the product.<sup>1</sup> The concept of risk-based determination of the number of runs is frequently brought up by regulatory documents and industry guidance documents. If you do not complete process characterization prior to PPQ, you cannot ensure that you have a strong control strategy and a statistically valid range determination. With today's costly biologics, Thermo Fisher Scientific has found that process characterization can cost anywhere between \$7 and \$10 million. At the same time, there are risks to not having an adequately characterized process and an in-process control strategy that satisfies the regulatory bodies who are reviewing it and/or those conducting a preapproval inspection who want to understand the origin of any deviations.

In the end, the goal is to adopt and appropriately execute a scientific and risk-based approach that efficiently gathers the information you need to gain the best scientific output for patients. While far more detail is required to implement the essential steps outlined above, establishing a clear understanding of where you begin and where you end is a key piece of delivering a high-quality, effective drug in today's competitive market.

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### LEARN MORE

In the race to the clinic, we can partner with you to establish a robust and cost-effective process quickly. Contact us to find out more.





