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Analytical Considerations For Biopharmaceuticals During Commercialization

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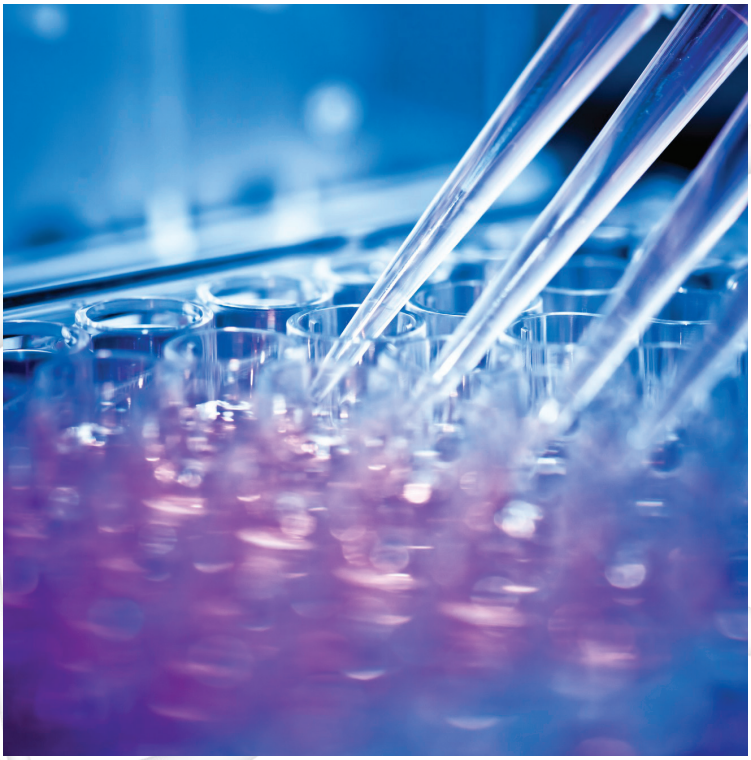
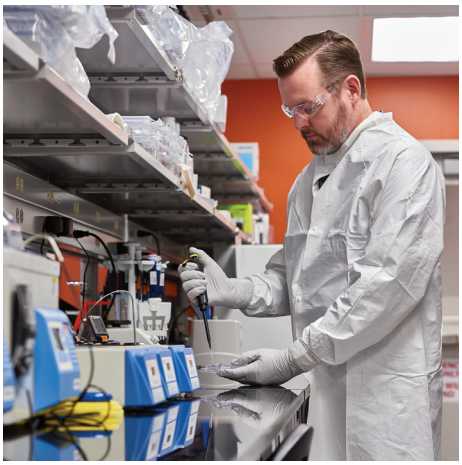


When manufacturing biologics, it is critical to validate analytical methods prior to process performance qualification (PPQ). It is an essential step in assuring the quality and safety of pharmaceutical drug products. Performing analytical method validation ensures the methods have the performance capabilities necessary to accurately monitor product quality attributes and process impurities during the production and purification of biological material. As the project approaches the PPQ phase, it is crucial to understand the expectations of regulatory agencies and identify the most efficient ways to validate the analytical methods.

Preparation of analytical methods for method validation



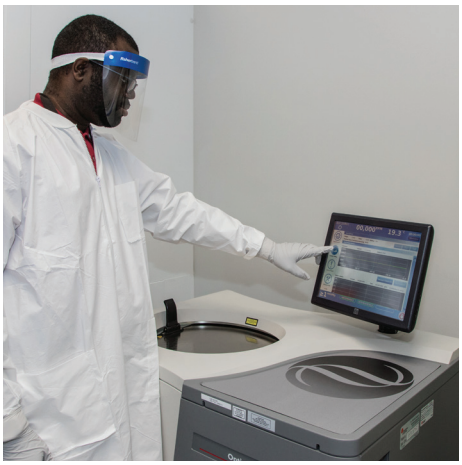
All methods used to support in-process control testing and batch release testing must be validated per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines prior to testing PPQ and subsequent commercial batches as part of the continued process verification (CPV) program. The process validation strategy dictates which methods you validate, particularly the in-process control (IPC) strategy and final, batch release specifications. A general fit-for-purpose analysis can be sufficient for methods that are not required for demonstration of in-process control after PPQ. For example, there may be areas where a robust downstream process has been adequately demonstrated to consistently clear process-related impurities, so qualification of these methods prior to PPQ testing is typically sufficient to support the PPQ activities. After PPQ, such in-process testing could be removed from the CPV testing plan if sufficient data has been accumulated to support any regulatory claim(s) related to impurity clearance.

Method robustness

It is imperative to demonstrate robustness of the analytical methods prior to method validation. Performing robustness testing early in the development lifecycle helps confirm the method will continually perform as expected throughout the life cycle of the product. If any significant adjustments are made to the method or if a product quality attribute changes dramatically after process development, additional robustness testing may be required. Therefore, before method validation begins, it is recommended that a thorough risk assessment of the method performance is completed to determine if the data obtained during method qualification is different than the data collected during Phase I and Phase II release and stability testing. If there are any gaps that were not covered during method development or method qualification, they need to be addressed before method validation to ensure the method performance characteristics are known. This improves the likelihood of successful method validation.

The difference between the method robustness studies during method development and the one completed prior to method validation is the size of the design space being assessed. Typically, the ranges evaluated are wider during method development, and the focus is to identify the edges of failure for a method. This is not the case during method validation. Rather than taking the method to its failure limits, the focus shifts instead to looking for a very tight control—generally plus or minus 10 to 20 percent of the method's major technical points—to make sure limits within the method are far enough removed from the true limits of failure, but still provide some flexibility for the routine performance of the method. If you do not assess method robustness and move too quickly into method validation, you may miss critical issues. For example, varying performance between different column lots over the course of future production lots may put you outside of the acceptance criteria set for the method. The variable of time and experience is a characteristic often undervalued when preparing for late phase programs.

The methods from the product batch release specification that can benefit the most from assessing method robustness before method validation are purity methods, such as SEC, CGE, cIEF, and CEX, as well as identity methods e.g., early phase cIEF and Binding ELISA, and late phase peptide map. Potency methods also benefit from method robustness testing, as these methods measure how effective your molecule is at eliciting its intended physiological response(s). It is also vital to have a robust reagent qualification process to identify critical equipment/reagents whose performance may change over life of use or from lot to lot e.g., biological reagents, column lots. Overall, the above-mentioned methods help identify how stable a molecule is, its critical quality attributes, and whether you have a valid drug substance or drug product. Therefore, it is critical to understand their performance before method validation.



Forced degradation study

A forced degradation study is a stand-alone study that examines multiple conditions and batches to gain a broader perspective of a molecule's degradation pathways. The process involves degradation of drug products and drug substances under a variety of conditions that are more severe than a standard stability study's stressed and accelerated conditions. Conditions for a forced degradation study are chosen based on the likelihood of a drug product being exposed to detrimental conditions during production, processing, packaging, shipping, and handling. The degradation of biologics by these factors—production, processing, packaging, etc.—are interrelated to each other and dependent on the physicochemical properties of the molecule, buffers, excipients, and operating parameters. Typical conditions assessed during a forced degradation study include high temperature, freeze/thaw, agitation, low pH, high pH, photostability, and oxidation. However, there must be careful consideration about the conditions used to degrade material. If material is degraded too harshly during this study, it may not follow the same degradation pathway as it would during natural degradation, preventing you from gathering accurate information.

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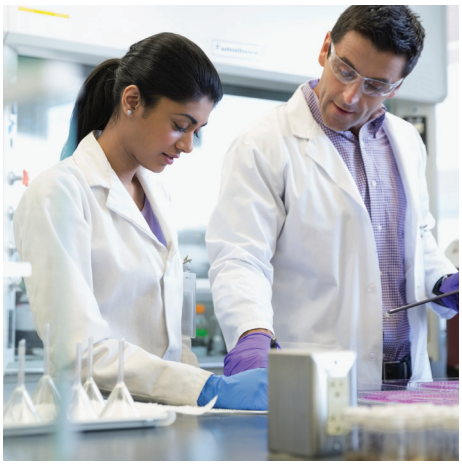
Such a study also determines which of the methods in the specification are stability indicating and the specific types of product-related impurities they detect. Examining data for conditions that arise during general handling of a product—such as oxidation or exposure to light—provides useful guidance on how to structure validation work. In addition, material from long-term thermal stability studies where it has been naturally enriched for product-related impurities, is often the best material to use for robustness studies and during method validation. Not only does a long-term, thermal stability study allow you to thoroughly evaluate the method's ability to detect and quantitate product impurities, but it also allows a more thorough evaluation of the current system's suitability criteria, such as resolution or limits of quantitation with actual product impurities.

Information gathered from a forced degradation study is also useful when there are significant changes over the course of the product lifecycle—especially right before or during Phase III clinical material production—such as changes to the cell culture media, purification strategy, or final formulation excipients. Testing the product after such process changes in a forced degradation study to assess the major degradation products of the material pre- and post-change, ensures the previous clinical results or toxicology data are not impacted by the process change. If differences are identified, the material can be further characterized to ensure the safety and efficacy is acceptable and comparable to that of the pre-change material. The extent of this work depends largely on the phase of clinical use, the extent of any changes in the product quality attributes identified in the forced degradation component of the comparability assessment, and the nature of the changes. Changing media is a much higher risk than increasing an excipient concentration in the final drug substance. Therefore, more extensive characterization and a forced degradation study would be performed.



The degradation of biologics by these factors—production, processing, packaging, etc.—are interrelated to each other and dependent on the physicochemical properties of the molecule, buffers, excipients, and operating parameters.

Method validation

Method validation can be performed in a phase-appropriate design, where limited ICH validation studies are performed during Phase I or Phase II clinical studies—often referred to as method qualification—with more extensive testing against specific criteria performed when preparing for commercialization in Phase III. To begin preparing for method validation, you must identify the critical quality attributes relevant to each method by leveraging the data gathered during routine testing, forced degradation or process characterization studies, and ICH stability studies. The approach must be tailored specifically for the molecule, using intimate knowledge of its behavior.

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Method validation can fail if you do not have a strong historical understanding of your method. Other reasons for failure are related to strategy and logistics of the validation execution. In terms of logistics, it is possible to complicate a validation run to the point where it is no longer representative of a typical assay. For example, if you are completing a linearity assessment using an intermediate precision run that takes 12 hours to execute in a single assay occasion, you may be introducing variables that would normally never be present in a quality control laboratory, such as a very high number of plates that take an extended time to process. When studies are overly detailed and lengthy, the criteria can fail due to the complexity of the work itself.

A method validation can also fail if you do not complete an analysis of previous data about your method performance to understand the limitations of your method. For example, assessing robustness elements is recommended prior to validation because you do not want to include unknowns when executing against set performance criteria. Those should be stand-alone studies performed prior to method validation. Other reasons for a failed method validation include:

- Poor analyst training
- Poor characterization of manufacturer-supplied components used during the potency assay or impurity testing kits
- Poor phase-appropriate validation—i.e., moving too quickly from the development of the method into validation without first completing method qualification

Method qualification provides a valuable early assessment of the method's performance characteristics, which is critical for setting criteria for method validation for parameters like precision, accuracy, and linearity. Ultimately, your internal risk-based approach will directly impact what is likely to pass or fail during method validation. If any aspects of a method validation study do fail, you can follow the analytical method lifecycle to determine if the method requires optimization or even redevelopment. The analytical lifecycle supports major changes to methods when needed—such as after a validation failure—by appropriately assessing a revised method using intact and degraded material, repeating robustness studies, and then reassessing method performance parameters per ICH guidelines, prior to repeating the final method validation exercise.

Method transfer

When a third party transfers a validated method to a contract development manufacturing organization (CDMO), the analytical team should review the method development and qualification/validation reports to understand what has already been done to begin evaluating the method's performance. Next, the CDMO's analytical team should execute the method for initial feasibility/shakedown, followed by several runs with all applicable sample types to ensure the performance data that the lab collects are comparable to the method performance data obtained by the transferring lab. If it is, the method can then be sent to the quality control lab for a gap analysis against ICH validation parameters. They should also verify that they can execute the method as expected, that the data is comparable based on meeting pre-set criteria in a quality-approved protocol, and that they are able to release cGMP batches using the method. It is possible that the client may choose not to transfer its method to a CDMO, however, transferring the methods to a CDMO may shorten the timeline and will ease the process of troubleshooting by having analytical support in one central location.

Some factors to consider when transferring methods to a CDMO are:

- **Potential differences in raw materials available in other regions of the world** – Critical raw materials may be not be available worldwide, particularly for biological components such as fetal bovine serum or custom synthetic peptides.
- **Equipment** – Different equipment may have been used to validate the methods originally. The CDMO will need to either adapt the method to its equipment or purchase new equipment to make sure the method can be performed comparably in the CDMO's labs. Pre-work may be required to bridge equipment prior to transfer.
- **Technical ability** – The technical fit of the analytical team for your methods and/or molecule is important, as a poor fit can create numerous problems at all stages of manufacturing.
- **Clarity of the written test method procedure** – All information coming from the transferring lab should be documented by the CDMO to not only ensure they capture any previous knowledge but also to have a resource for future analysts to refer to when they are training or if an out-of-trend result is obtained during routine testing.

Before transferring your methods to a CDMO, make sure you understand their internal policies and procedures, as this will help identify any limitations that could complicate the transfer process. Overall, establishing a strong relationship through clear and frequent communications allows you to reap the benefits that come from working with an experienced partner. They have often gathered extensive knowledge from working on a wide range of molecules and with a wide range of analytical techniques.

Conclusion

Demonstrating that a product meets the quality expectations of the regulatory bodies requires robust analytical methods that have a high degree of reproducibility and accuracy. Conducting appropriate testing to evaluate these methods before diving into the method validation will set you up for success during Phase III and commercialization stages. These studies will also give drug manufacturers the data they need to support regulatory filing per cGMP compliance expectations. Method validation ensures the necessary due diligence has been done to preserve the safety and quality of a drug product throughout late stage and commercial manufacturing. Therefore, understanding how to approach this critical activity could facilitate product approval and as a result, speed to market.

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