MilliporeSigma

Optimize your Biologic's Analytical Program

for Greater Risk Reduction

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Pharma & Biopharma Manufacturing & Testing Services

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Table of Contents

Analytical methods are used throughout upstream and downstream processes to help ensure the desired molecule is being produced with the desired purity. In addition to having the right molecule, quality must be confirmed in terms of glycosylation, oxidation, aggregates, activity and concentration. The analytical package must also ensure that all impurities from the manufacturing process and environment are consistently removed.

Determining the activity and concentration of the molecule is one of the most important analytical requirements as this analysis mimics the activity of the molecule when dosed in humans. In other words, the analytical optimization process follows Critical Quality Attributes to ensure that a drug has the right quality and activity without causing adverse effects in patients.

Critical Success Factors for your Analytical Program

1. Invest time and resources from the earliest stages of product characterization to identify the critical quality attributes and establish analytical methods

2. Follow the quality attributes throughout the process to understand clearance of impurities and behavior of the molecule

3. Begin development of a cell-based assay early to ensure an activity method is available at the start of development

4. Remember that process development can be accelerated with a robust analytical panel

A Critical Balancing Act

With a long list of attributes to assess, the development and implementation of analytical methods are essential for success at all phases of a molecule's journey, from pre-clinical development, to clinical manufacturing and ultimately, commercialization. The overall strategy for establishing the program, however, varies depending on the stage of the company and requires an appropriate balance of speed, risk and cost, all while ensuring quality.

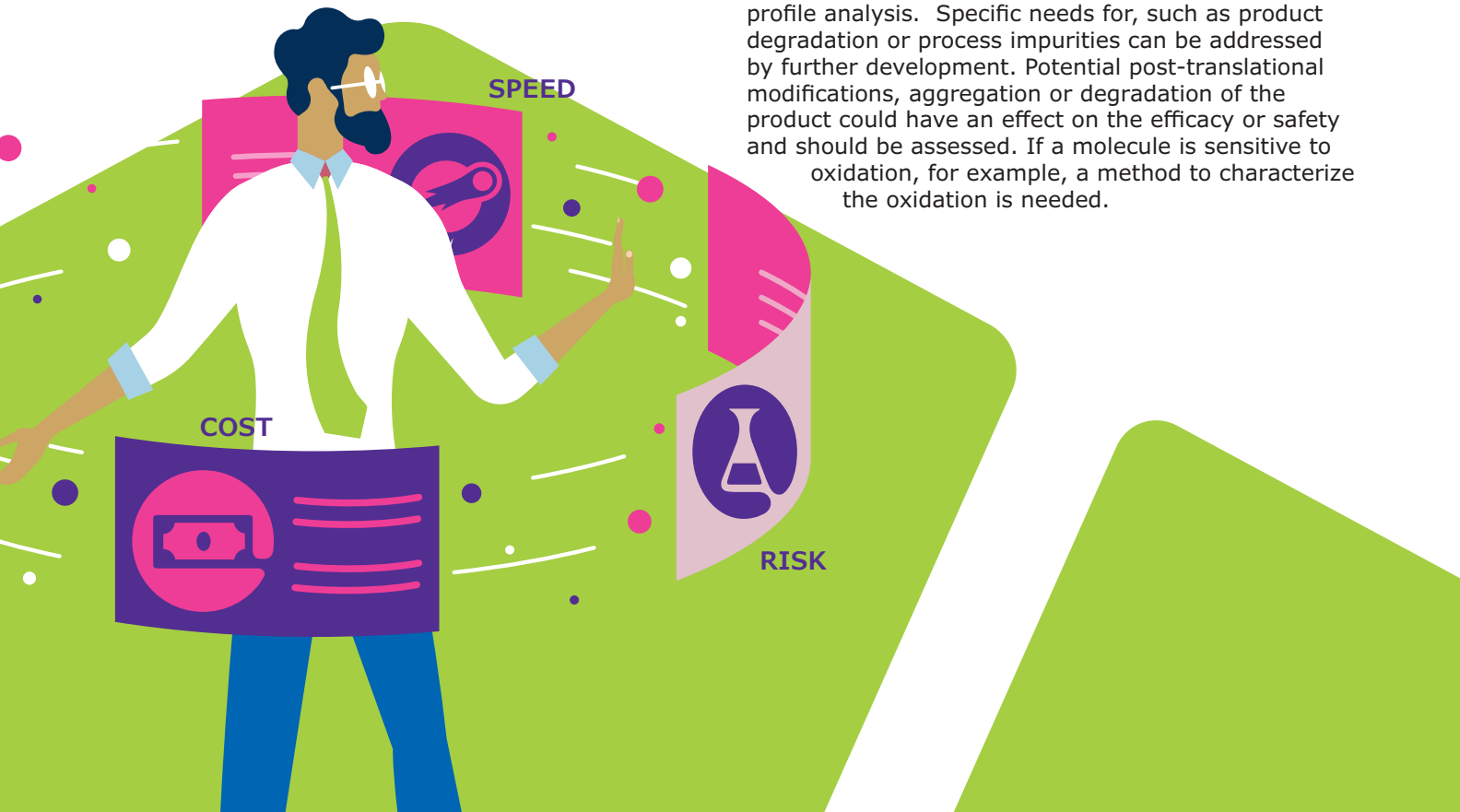
The analytical methods will be developed and implemented first for process development and clinical phase I/II manufacturing, during which a comprehensive understanding of the process will be established. The collection of data in phase I/II and process validation will be applied to trigger the method adjustment if needed prior to phase III. Following the process validation runs, the final analytical panel will be defined for commercial manufacturing support.

Without the benefit of revenue coming into the company, a start-up biotech must advance as rapidly and efficiently as possible to an investigational new drug (IND) filing or investigational medicinal product dossier (IMPD) filing.

Driven by the need for rapid advancement towards key milestones, what should an early-stage company think about when it comes to their analytical program? An optimum balance of speed and safety, while ensuring quality and gathering important information about the molecule, is essential. Ultimately, the analytical package must be designed to mitigate the risks for key milestones. Missing key milestones might result in failure at an early stage and the need for subsequent redevelopment and remanufacturing, which adds significant time and cost to the process.

Early-stage companies can, however, leverage a streamlined analytical program that focuses on what is needed for IND/IMPD filing and for Phases I and II batches. The same analytical panel can be applied in characterization and comparison of drug substances (DS) in both preclinical and GMP batches with additional necessary safety controls to ensure GMP DS as will be dosed in humans the first time. This approach is time- and cost-efficient while delivering the necessary information for the company and fulfilling requirements for regulatory agencies for IND/IMPD filing and early clinical trials.

For an early stage company, a basic analytical package should include content, purity, activity and safety controls. Establishment of analytical methods can be accelerated by starting from use of standard or platform methods, such as H/UPLC, CE-SDS and glycan profile analysis. Specific needs for, such as product degradation or process impurities can be addressed by further development. Potential post-translational modifications, aggregation or degradation of the product could have an effect on the efficacy or safety and should be assessed. If a molecule is sensitive to oxidation, for example, a method to characterize the oxidation is needed.



Purified material will be used in method validation to ensure that the analytical method is suitable, with sufficient sensitivity, for product release and stability studies. Following characterization of the first GMP batches and comprehensive understanding of the product including post-translational modifications and glycosylation, the analytical methods will be finalized. The panel will then be ready for product characterization and stability assessment of the GMP batches to ensure batch-to-batch consistency.

One of the objectives of the phase I/II studies is to collect data on the DS and in-process controls needed for phase III. During phase III, the process validation will need to have a complete and fully validated analytical package to support the process validation needed before commercial manufacturing.

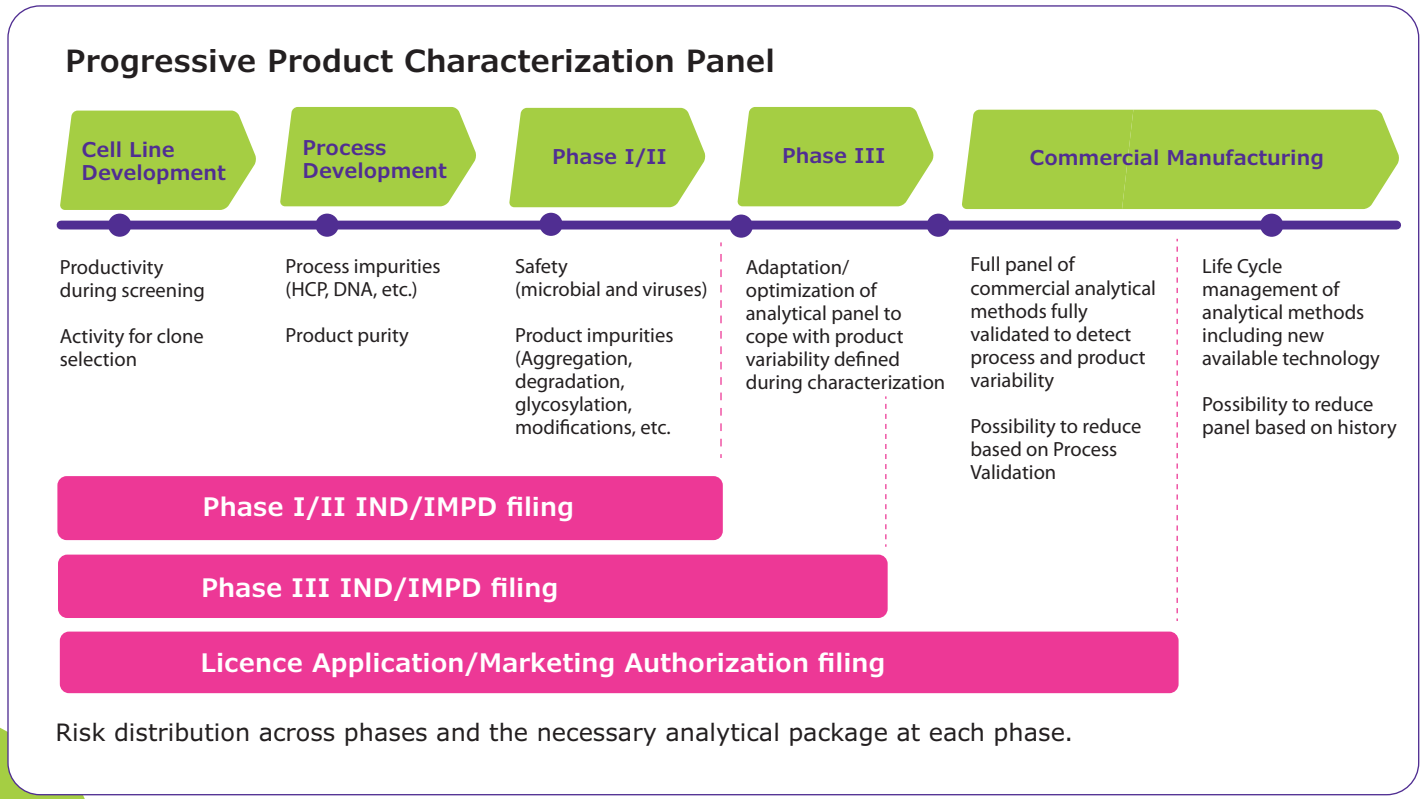
With this streamlined approach of focusing on a limited analytical panel at the outset, comprehensive knowledge about the molecule and process is established throughout the clinical phases. This phased approach allows a stepwise investment to first ensure the safety during clinical phases I and II and then progresses towards a complete knowledge of the molecule. An unanticipated issue may arise during the clinical trials, however, necessitating redevelopment of the process and analytical panels. This risk must be considered and balanced with the aggressive timelines and budget parameters.

The overall strategy for establishing the program, requires an appropriate balance of speed, risk and cost, all while ensuring quality.

The alternative to this streamlined approach is to establish a complete analytical panel prior to phase I in which a comprehensive characterization is performed along with full validation. This strategy certainly reduces risk, but it is time- and resource-intensive and typically not needed. And if the molecule fails in phase I or II, a larger investment has been wasted.

In contrast, an established company with pipeline assets in later clinical development typically requires a more robust analytical program to support Phase II and III and the transition into commercialization. Here the analytical program fulfills the needs of rapid application during earlier phases and more comprehensive characterizations in later stages.

We have experience developing analytical programs for companies of all sizes and all stages of clinical study. Our tailored approach enables a strategic balance of speed, cost and risk while maintaining quality of the therapeutic candidate.



Risk distribution across phases and the necessary analytical package at each phase.

Fundamentals of Success

While the analytical package should be customized to the stage of the biotech and effectively balance speed, risk and cost, there are fundamental principles that should always be leveraged to optimize the approach – no matter the stage of the company or asset.

Get an Early Start

During upstream processes, analytical methods are applied to samples from the bioreactor culture and harvest in order to monitor product content, quality and molecular information such as the glycosylation pattern. Samples from each downstream purification step are characterized for product purity and quality and process contaminants. Because analytical methods are so integral to the entire workflow, developing the right panel of methods and establishing the method robustness should start early, at the time of process development and in close collaboration with the process development team.

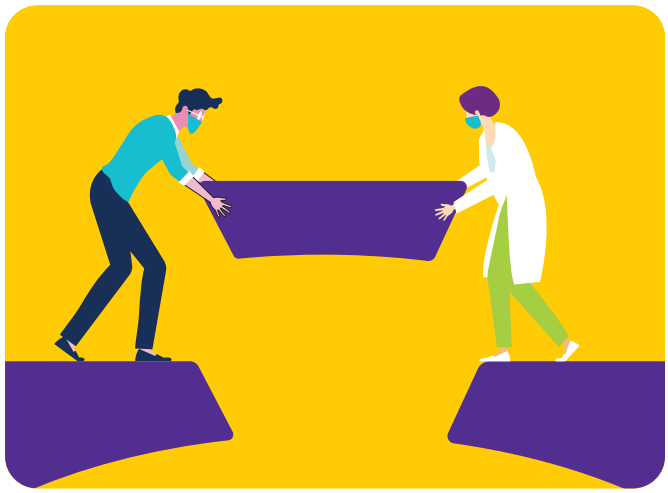
Future-Proof the Methods

While analytical methods are developed early in the process, the requirements for later stage studies should be considered in the development plan. At some point the analytical method will be used in a GMP setting or production support and likely be part of a technology transfer. A best practice is to not use unusual or exotic reagents or those which are difficult to secure from GMP qualified suppliers. An optimized method and a secure reagent supply will reduce the risk from the start and protect the process when transferring to the validation method.

Leverage a Templated Approach

Starting from scratch is not always necessary when a new method is needed. The development of analytical methods can be accelerated by use of a templated approach, starting with evaluations of robust generic/ platform methods and modifying to fit the specific molecule. Even if a specific, novel method is needed, the templated approach will save time as it starts with proven, foundational elements of the method and then integrates customized aspects tailored to each phase and project

At some point in the lifecycle of the drug, the manufacturing process and the associated analytical methods will transfer to another suite or site.



Prepare to Bridge

Considering that it can take ten years to progress from clinical phases to commercialization, changes in analytical methods should be expected across the lifecycle of a drug. These changes can be necessitated by a variety of factors including scientific, technical, operational and regulatory. The process of bridging analytical methods will demonstrate that the new method delivers suitable performance relative to the previously validated approach. Given the likelihood of changes, it is important to have a bridging strategy in place that facilitates comparisons of existing methods validated by previous batches to the new methods needed for new batches.

Anticipate a Tech Transfer

At some point in the lifecycle of the drug, the manufacturing process and the associated analytical methods will transfer to another suite or site. Once the analytical methods are transferred from the source site to the receiving site, the technical transfer is evaluated by use of a comparable data set. Without a transfer of the existing methods, the receiving site would need to redevelop and revalidate the methods, a time-consuming and costly process.

Success Driven by Experience and Flexibility

The team that delivers BioReliance® End-to-End Solutions has the expertise and flexibility to support accelerated development and commercialization of biologics. With experience developing more than 250 biologics, the team can tailor analytical packages with validated quality attributes and flexibility to support companies in the development of molecules at all stages.

The analytical development and optimization team works closely with our process development and manufacturing teams to reduce uncertainty and mitigate risk at the very early stage of development so that to ensure the success. The strength of our analytical team lies in an open mindset and expertise to tailor programs fitting needs of the company and the pipeline asset.

CASE STUDY:

The Risk of Short-cuts in Analytical Development

A critical decision must be made in terms the strategy used for development of the analytical package. The table below summarizes the options – including development of a robust package, use of a minimal package or a risk-based approach.

Each has implications in terms of the impact on speed to clinic, speed to market and risk.

Analytical Panel Development Strategy	Impact on Speed to Clinic	Impact on Speed to Market	Risk
Take time to develop a robust analytical package adapted to the molecule fully characterized	↘	↘	↘
Use minimal panel and generic methods for early phases and improve panel later	↗	↘	Possibiliy of missing important product variability and jeopardizing batch to batch consistency ↗
Risk-based approach built on experience of the type of molecule and stress studies	↗	↗	→

A risk-based approach built on experience of the type of molecule and stress studies effectively balances speed and risk.

The following example highlights the risk of using only the minimum characterization panel for a hyperglycosylated molecule. The lack of an activity-based glycosylation method led to a costly and timely redevelopment of the process.

Characterization panel

- Minimum characterization panel was developed based on a non-glycosylated molecule
- There was no analytic in place for glycosylation
- There was no activity-based analytic in place during process development

Analytical Results

First clinical batch tested for activity showed an inactive molecule

Insights for process development

- Production process yielded molecules with two different glycosylation patterns; only one of which was active
- Media selection was inducing production of mostly inactive molecule; the downstream process designed to separate the two types of molecules was removing the active version

Consequence

The process had to be redeveloped from scratch, having a significant impact on time and cost

About BioReliance® End-to-End Solutions

We are an integrated contract development and manufacturing partner, offering adaptive solutions for small and mid-sized biotechs needing to develop and commercialize biologics. We do this by balancing speed, risk and cost through custom solutions, by leveraging our bioprocessing technologies and process development expertise, and by allowing our clients to transfer their process and knowledge to their end point at any step of the way.

To learn more, please visit
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