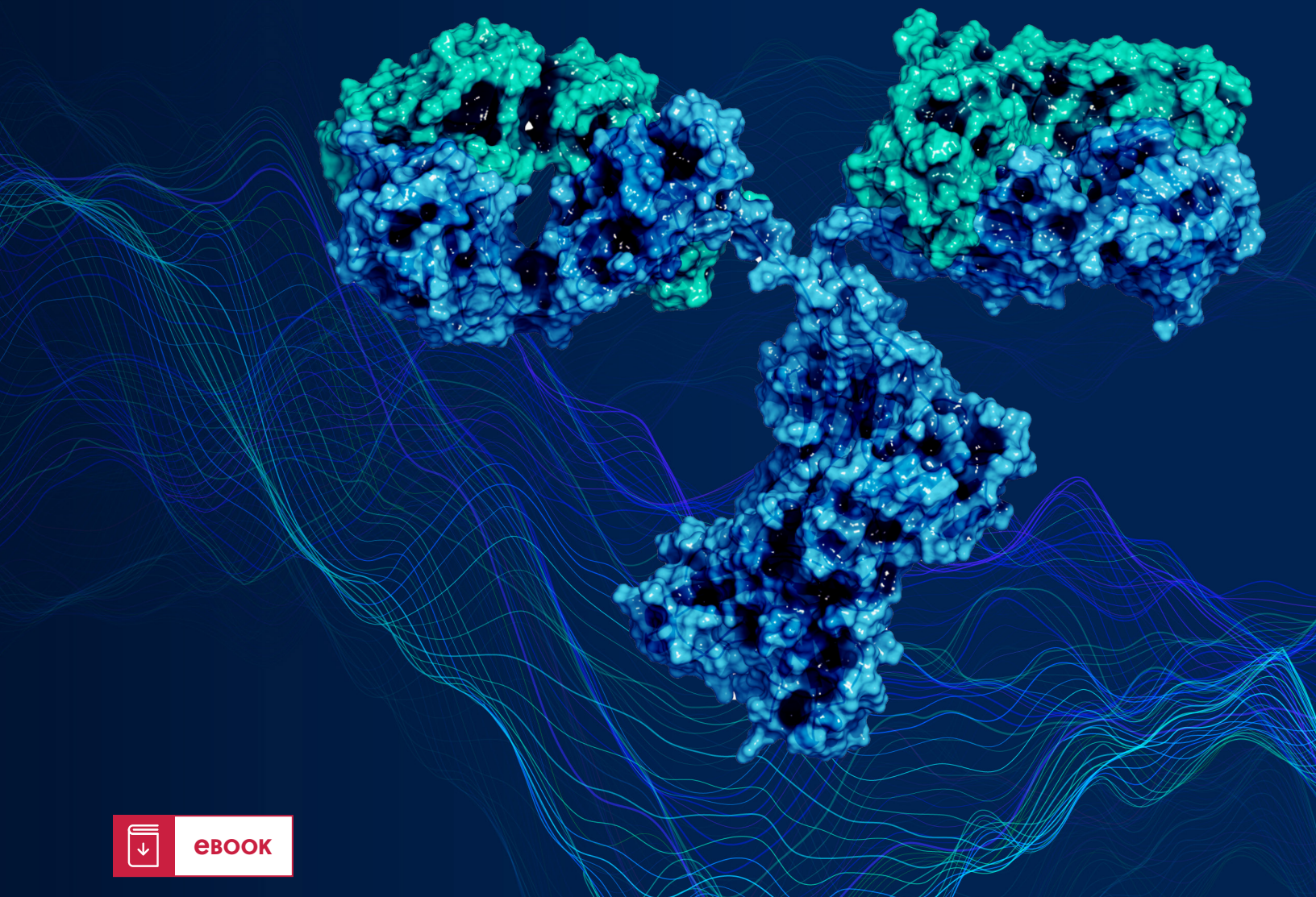
AVID BIOSERVICES



eBOOK

DEDICATED TO QUALITY:
THE CORNERSTONE OF MAMMALIAN BIOPROCESSING

Insights From 30+ Years of Experience Developing and Manufacturing Biologics

THE PURSUIT OF EXCELLENCE:
QUALITY AS THE CORNERSTONE OF BIOLOGICS DEVELOPMENT

In biologics development, it is crucial to understand that the way a therapeutic is made is as important as the final product itself, hence the industry mantra: "the process is the product." Achieving a safe, consistent, and effective drug product requires the development of robust and well-defined quality control and analysis methods both upstream and downstream.

At Avid Bioservices, we have over 30 years of biologics manufacturing experience with state-of-the-art mammalian protein biomanufacturing and purpose-built viral vector facilities. In our experience, the role of quality control and measurement is critical at every step of development. Each process from translation to final drug substance development must be carefully controlled, measured, and validated. This means that for biologics innovators seeking to bring their program successfully from discovery to clinic, finding a Contract Development and Manufacturing Organization (CDMO) that has a culture of quality is essential. Avid maintains a culture of quality — or a culture of communication and collaboration where team members are empowered to create innovative solutions with cutting-edge technologies — through continuous investment, research, and internal development. Our reputation as a CDMO partner of choice is not just built on technical prowess, but on the bedrock of an unwavering commitment to quality. In the realm of biologics, there are no shortcuts to success, and the path to excellence is paved with a dedication to meticulous processes, rigorous compliance, and uncompromising standards.

In this Ebook, we share the significant role of quality culture in biologics development at key stages through the development process. Each section explores the precise processes and rigorous compliance standards that our team builds into every client's program to ensure consistent therapy quality – standards that we feel are crucial for CDMO partners to have in place to ensure a therapeutic program's processes are as robust as their end product.

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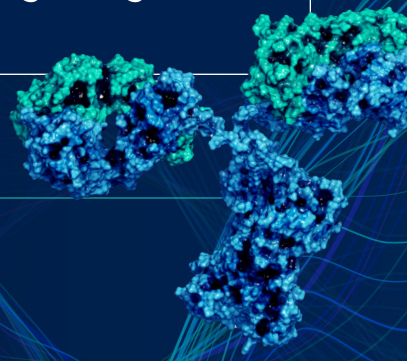


1

HOW SINGLE-USE TECHNOLOGY CHANGES THE QUALITY GAME

In the intricate realm of biotechnology, the choice of manufacturing workflows holds paramount importance, profoundly influencing the trajectory of innovation. This infographic offers a comparison of the contrasting approaches between the time-honored traditional manufacturing process for biologic therapies and the cutting-edge single-use technology-based workflow. Single-use technology (SUT), characterized by disposable components, represents a significant departure from conventional, stainless steel-based systems. Through this visual comparison, we delve into how these two methodologies impact quality outcomes and regulatory compliance. By embracing single-use technology, biotech innovators can optimize efficiency, mitigate contamination risks, and elevate product consistency, ushering in a new era of precision in biologic therapy production.

TRADITIONAL WORKFLOW	MANUFACTURING CHALLENGES	SINGLE-USE WORKFLOW
Process equipment is cleaned by **complex and labor-intensive steam sterilization, or by chemical sanitization** using hazardous chemicals.	CLEANING PROCESS	Components, equipment, and instruments arrive **pre-sterilized using gamma-irradiation** and are assembled using **aseptic tube welding or aseptic connectors.**
Product quality **investigations involving stainless-steel reactors can be very complicated** when all the equipment and systems involved need to be examined or tested.	QUALITY CONSIDERATIONS	Manufacturers can work with SUT vendors to test the materials involved and help determine the root cause of any quality concern. This simplification can enable **faster investigation turnaround times, reduce investigative costs**, and prevent extended equipment tag-outs.
Regulatory inspections and criteria are **well defined and standardized** for traditional biologics manufacturing workflows thanks to decades of use.	REGULATORY IMPLICATIONS	**SUT reduces cleaning requirements and contamination risk.** However, the regulatory criteria for SUT workflows is less well-defined due to the rapid evolution of these technologies.
Tried and true techniques and systems, with the **majority of CDMOs utilizing this approach today.**	INNOVATOR BENEFITS	SUTs offer **more flexibility and accelerated time to market** with straightforward scale-up of upstream processes, simplified investigations, and much shorter setup and changeover times.

2

ACHIEVING QUALITY IN HIGH-THROUGHPUT PROCESS DEVELOPMENT

Accelerating process development is critical to developing mammalian-based biologics, and one way that CDMOs shorten timelines is with a high-throughput (HTP) approach. While traditional process development typically involves sequential, time-intensive experiments, HTP approaches leverage advanced automation and parallelizawtion to conduct many experiments simultaneously — leading to comprehensive data sets and deeper insights in a fraction of the time.

Jeanette Doerr, Ph.D., Principal Scientist, and Haiou Yang, Ph.D., Director of Process Development at Avid joined Pharma's Almanac Editor in Chief David Alvaro, Ph.D. to discuss why a high-throughput is so important for delivering quality outsourcing solutions.

David Alvaro (DA): What are the pressures right now on CDMOs to develop robust, reproducible processes more quickly than ever before?

Jeanette Doerr (JD): During the COVID-19 Pandemic, we saw increased demand globally for therapeutics, and the timelines for their development and commercialization were extremely accelerated. This is the norm now that the industry's ability to meet those short timeframes has been established.

Haiou Yang (HY): At the same time, regulatory agencies want to see a more in-depth understanding of the process. To get all that information requires more experiments using design of experiment (DoE) and quality-by-design (QbD) approaches. HTP solutions are absolutely essential to increase the number of experiments that can be completed in shorter and shorter periods of time.

DA: How is Avid dealing with these pressures?

HY: Typically, processes have been developed at Avid in approximately six months, much shorter if a platform method can be applied. That has now shrunk to three months. The key is to cut the process development timeline in half without negatively impacting quality, which can be achieved with HTP solutions because they allow the evaluation of many ideas much more quickly.

DA: In a general sense, how are you able to increase upstream process development throughput?

JD: Upstream process development is actually really labor-intensive and time-consuming. At Avid, we have 24 benchtop bioreactors, so we can do large sets of experiments, but it is very resource-intensive. Leveraging automation, such as the Ambr® 250 system from Sartorius, we can run 24 bioreactors with a maximum working volume of 250 mL simultaneously without intense technician involvement and with reduced risk of human error. That helps us achieve our goal of generating more data with less resources in less time, leading to faster process development.

DA: How many different minibioreactor process runs are typically needed before you can advance to the next scale?

JD: It really depends on where we're starting. Pre-IND clients normally require several rounds of 10–12 bioreactors in a DOE format to really look at the design space of the process and evaluate and optimize parameter settings. For clients wanting to enter the clinic quicker, a risk-based approach might be used, in which Avid performs one set of runs and then performs a verification run and a pilot run, followed by tech transfer to manufacturing. For phase III projects, the work

often involves scale-down model qualification and process characterization which is also very intensive and involves running numerous bioreactors simultaneously.

DA: How are high-throughput approaches leveraged for downstream process development?
HY: There are several ways. One is to first understand the molecules involved in the process using commercially available modeling software. For instance, before developing a chromatography process, modeling can be used to learn about the physiological and biochemical properties of the molecules involved and thus figure out how they will interact with different types of resins.

> “I’ve been at Avid for nearly 20 years, and that creative culture has been one of the key reasons for me staying at the company. At the end of the day, we get the process and the manufacturing right, no matter what it takes.
>
> **Jeanette Doerr, Ph.D., Principal Scientist at Avid Bioservices**

Another reason is that the current approach to process development involves a significant amount of trial and error with regard to determining the optimum process equipment, materials, and conditions. When a good result is obtained, we move forward without conducting any further tests, but we do not fully understand the variability of the process. A high-throughput approach gives you the ability to fully explore the design space of processes.

DA: Does high-throughput process development make analytical development more challenging?
JD: Yes. Along with the upstream and downstream investment at Avid in high-throughput technology, we’ve also invested in the analytical development department to address these challenges with the purchase of a Sartorius Octet HTX, some Waters UPLCs, a Maurice Bi-Protein Simple, and a Hamilton Liquid Handler. Luckily, we have been able to increase throughput in the analytics group by investing in upstream and downstream process development and analytical development hand-in-hand.

DA: Has Avid invested in any other equipment for accelerating upstream or downstream process development?
JD: Upstream, we are also adopting the Sartorius Univessel® SU 2L single-use bench-scale bioreactor for transferring from the Ambr®vessels to bench scale for verification.

HY: Downstream, we’re thinking about implementing a new high-capacity membrane chromatography technology from Cytiva with the potential to speed up this important unit operation – not just for development, but in manufacturing as well. We are also considering the implementation of more inline solutions in the process development lab.

In general, we are very open-minded in terms of leveraging changes and advances in technology. Avid’s leadership generally empowers us to pursue new opportunities and transfer them to the plant where appropriate.

DA: What do you see as unique, differentiating, or intrinsic to the culture of Avid that is key to driving your success in process development?
JD: We are very creative and we always make things work. No matter what the gap is or what the issue may be, we always seem to find a solution that works. I’ve been at Avid for nearly 20 years, and that creative culture has been one of the key reasons for me staying at the company. At the end of the day, we get the process and the manufacturing right, no matter what it takes.

HY: I totally agree that creativity is our key asset, and we’re also problem solvers. Whenever we have any problem, we feel like we have a way to get there. In addition, we’re very transparent with the client. We go through every step that we have done and the thought process, how we see the problem, and what we expect the results to be. As a result, clients are informed all the time about the developments, which makes them more comfortable.

3

SIMPLIFYING SCALE-UP WITH PROCESS OPTIMIZATION AND A CULTURE OF QUALITY

Why Scale-Up Is Different for Biologics

Scale-up in bioprocess development is one of the biggest challenges faced by the biopharmaceutical industry. Developing the bioprocesses for complex molecules is a unique challenge, but developing a bioprocess that can effectively scale to every stage of production multiplies this challenge. Here are some ways to ensure smooth scale-up for your bioprocess.

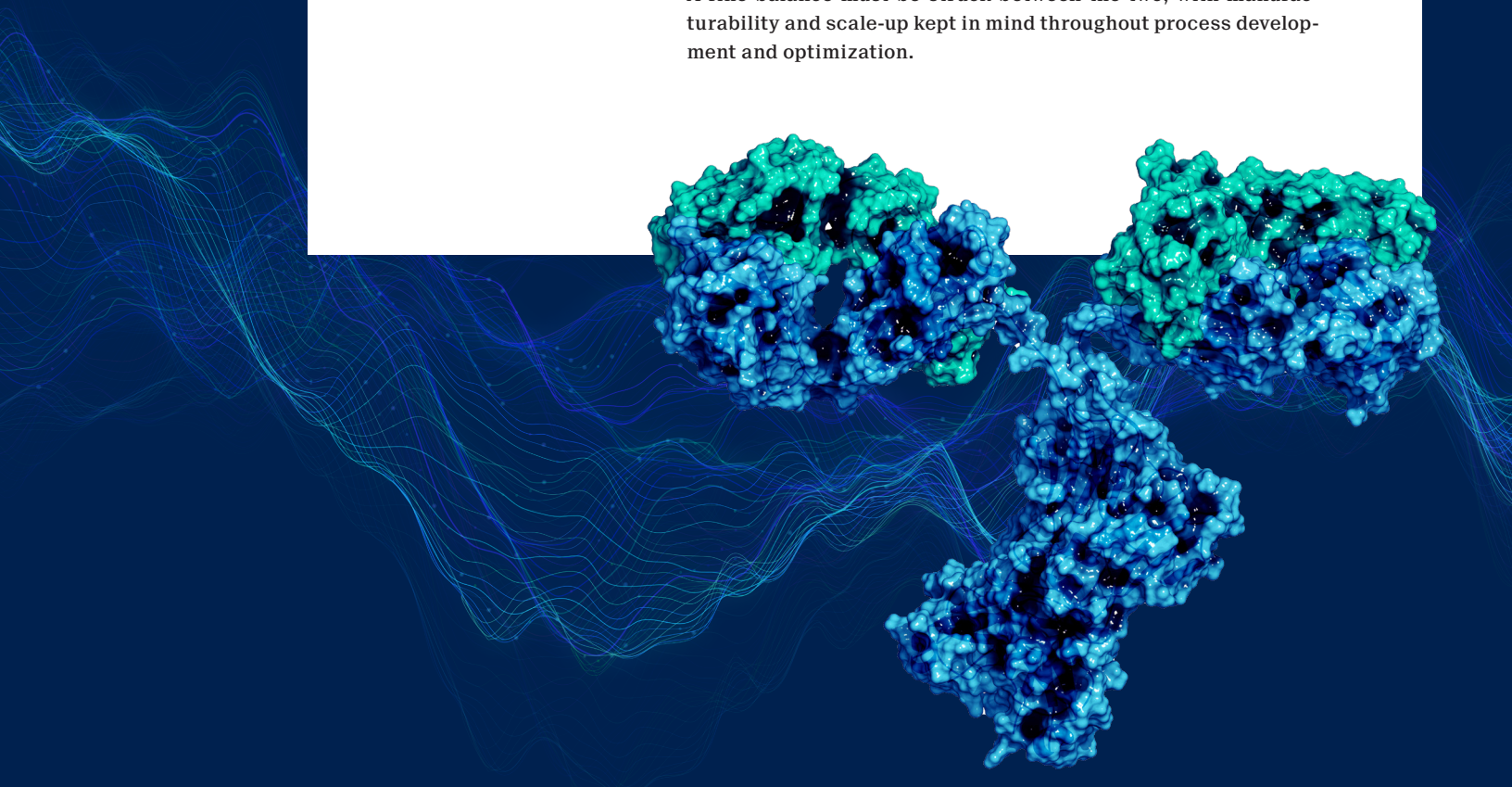
Prepare for Commercialization From the Beginning with Process Optimization

An interface between process optimization and scaling is essential. Achieving high titers at lab scale is only a first step, as high levels of expression must also be achieved at the 5,000-, 10,000-, or even 20,000-liter scale if drug candidates are to be commercialized. The ultimate goal is to reach patients – in some cases, as many as hundreds of millions of people around the world. If a drug substance cannot be produced at scale, it does not help anyone.

All aspects of bioscale-up should influence bioprocess development, and this is only possible with deep collaboration and experienced team members that understand the intricacies of the developmental process. In essence, process optimization can be looked at in two ways:

1. Increasing productivity and improving product quality.
2. Increasing manufacturability by simplifying protocols, enhancing supply chain security for critical raw materials, choosing sustainable reagents and process conditions, and so on.

The first form of process optimization can potentially reduce scalability, while the latter can contribute to greater scalability. A fine balance must be struck between the two, with manufacturability and scale-up kept in mind throughout process development and optimization.



Find the Right Team to Bring a Biologic to Market

Outsourcing partners that provide end-to-end services and have customer- and patient-centric cultures can have a direct impact on development timelines and cost. Collaborating with such partners facilitates scale-up and tech transfer because R&D and production scientists – both process and analytical – are co-located at the same site and are able to work closely together throughout the lifetime of a project.

When end-to-end CDMOs have the right combination of staff and institutional support, they can really excel at scaling up bioprocesses. Much can be lost in the translation from a process development lab to a manufacturing floor, even when scaling up within the same company. CDMOs with a collaborative environment can empower their scientists to effectively transfer process nuances at each stage of development.

Facility Design Makes All of the Difference

Effective scale-up of a bioprocess at a CDMO takes extensive collaboration both internally and externally. Having the right team ensures open conversations and innovative ideas to address roadblocks as they arise, but there is only so much that scientists can do without the right infrastructure.

A purpose-built facility – or a facility designed from the ground up for the sole purpose of biologics production – can empower CDMOs to seamlessly integrate their services. CDMOs with equipment in process development and scale-up labs that are near-identical to those on the plant floor will be able to transfer bioprocesses seamlessly. The same is true for the analytical development and quality control (QC) labs, such that an assay developed for R&D can also be conducted in a GMP environment.

The Role of Strategic Leadership at an End-to-End CDMO

How a company approaches scale-up represents one element of the organization's overall development and manufacturing philosophy. A CDMO's philosophy and culture is defined by senior leadership and directly impacts the approach, values, and solutions that they provide.

When a CDMO understands the bigger picture of the biologic lifecycle, it can be synthesized into a holistic process where all researchers, project managers, and scientists have the same objective and are rewarded for bringing products closer to commercialization. A quality of culture, where team members are encouraged to collaborate and are equipped with state-of-the-art technologies, is essential for scaling up biologics to market.

Dedicated to Quality Culture

Avid Bioservices is a CDMO up to the challenge of mammalian-based biologic scale-up, and we believe many of the core obstacles to scale-up can be addressed through maintaining a culture of quality. CDMOs must have the technology, people, and organizational structure in order to efficiently scale a biopharmaceutical process. Avid has built and maintained a culture of quality from the top-down, investing in a purpose-built facility, objective-oriented staff, and a collaborative environment.

PROBLEM SOLVING WITH EXPERIENCE

Many of the scientists at Avid have 10 or more years of experience; some over 20. We have worked on many different types of molecules at all stages of development, overcoming all sorts of challenges along the way.

PURPOSE-BUILT FOR SUCCESS

Avid keeps our process development, analytical, and manufacturing, science, and technology (MSAT) groups under one roof to cultivate collaboration and make scale-up smooth.

LEADING BY EXAMPLE

At Avid, our senior leadership always emphasizes our end goal: serving as many patients as possible at an acceptable cost of access.

4

HOW QUALITY-FOCUSED EARLY-STAGE ANALYTICAL DEVELOPMENT DRIVES LATE-STAGE SUCCESS

Analytical methods in the biologics industry are essential for quality control and product characterization. These methods must align with the drug product's life cycle, which consists of preclinical work, early clinical phases, and late clinical stages. By establishing robust and well defined analytical methods early in the product life cycle, CDMOs can establish a strong foundation for eventual commercialization activities. A quality-first mindset allows CDMOs like Avid to prioritize early analytical method development, which ultimately saves innovators time and money by avoiding costly pitfalls or stumbling blocks along the path from discovery to clinic, and then to commercialization. This article explores the goals, requirements, and documents needed for quality-driven analytical method development throughout the product life cycle.

QUALITY CONTROL METHODS

Analytical methods can be broken down into two categories: those for quality control (QC) release testing and those for product characterization. The former must be performed according to good manufacturing practice (GMP); the latter do not. Regardless, every method should be aligned with a drug product's life cycle which is comprised of three periods: preclinical work toward an investigational new drug (IND) application, early clinical phases that ensure drug safety, and late clinical work that supports a biologics license application (BLA) and launches commercial efforts. Consider the following goals, requirements, and documents during each period:

Pre-IND Submission: The initial goal is to establish a scientifically sound method that aligns with the drug's Analytical Target Profile (ATP). Good documentation practices are essential at this stage.

Phase 1-2 Clinical Trials: Focus shifts to gaining process and product knowledge. Analytical methods must be qualified according to Good Manufacturing Practice (GMP) standards, but excessive validation may not be required.

Phase 3 Trials and Commercialization: At this stage, a well-characterized method with proven performance is essential. Full validation, precision evaluation, and robustness assessment are necessary, all while adhering to GMP guidelines.

METHOD DEVELOPMENT ELEMENTS

Analytical quality by design (QbD) goes hand-in-hand with product QbD. Thus, analytical method development should begin with identification of critical product attributes and appropriate monitoring techniques. Developing a risk assessment strategy based on available clinical data will help distinguish between which methods are a "must have" and which ones are only "nice to have." Method development also requires consideration of several interconnected activities:

Analytical Quality by Design (QbD): Analytical method development should begin by identifying critical product attributes and appropriate monitoring techniques. A risk assessment strategy based on available clinical data should distinguish between essential and non-essential methods.

Understanding ATPs: Building critical quality attributes (CQAs) into the product/process helps define analytical method CQAs.

Considering Existing Methods: Modifying or replacing existing methods requires a bridging or comparability study.

Defining a Technique: Selecting the appropriate technique (e.g., HPLC, CE, or MS) and monitoring methods is crucial.

Performing "Scouting" Experiments: Evaluating different materials and parameters is necessary to develop a method suitable for the product's life cycle.

Selecting a Target: Determining where and how the method will be used in the manufacturing process.

Qualifying or Validating a Method: A risk assessment identifies method variables and parameters influencing the ATP.

Defining Controls: Setting reference and control standards ensures assay monitoring and process consistency.

UNDERSTANDING METHOD LIMITATIONS

Qualification and validation demonstrate that an analytical method is fit for purpose. Thus, it is important to understand a method's strengths and weaknesses during development. By appreciating a method's limitations, CDMOs can develop controls that ensure the reliability of past and future data.

Stability-indicating Capability: Many samples are sensitive to room temperature during method execution. By tracking this information, a product development team can minimize sample exposure to room temperature, and set appropriate controls. Adding method instructions about how, where, and when to remove samples from a freezer can aid this effort.

Intermediate Precision: Differences in equipment across sites can be resolved by selecting one instrument type from a single vendor, if possible. Variations that come fromanalysts can be eliminated with additional training.

Validation Timelines: Analytical methods are categorized by complexity into three levels. Timelines for development and validation vary accordingly. Category 3 methods, like cell-based potency assays, require the most time and effort.

CHARACTERIZATION METHODS

Orthogonal analytical approaches are used during clinical testing to demonstrate the consistency of drug products throughout their life cycle. Characterization testing helps identify molecular heterogeneity and ensures drug safety, purity, and potency. Below are some techniques for molecular characterization:

Primary Structure: Techniques such as ESI-MS, LC-MS, and CE-SDS are used for intact mass, peptide mapping, and analysis.

Secondary Structure: CD and FT-IR are employed for secondary structure analysis.

Higher-Order Structure: HDX-MS, X-ray powder diffraction, and fluorescence spectroscopy reveal higher-order structures.

Functional Assessments: Equilibrium dissociation constants, ligand-binding assays, and cell-based assays are employed to assess drug functionality.

THE EVOLUTION OF CHARACTERIZATION

Characterization efforts change throughout a product's life cycle, expanding in scope as development progresses. Early-stage characterization is essential to mitigate risks from future variations. Extractables/leachables studies become critical by phase 3.

CONSISTENCY IS KEY

Product quality depends on release testing, product/process characterization, and process control. Understanding this triad, and viewing it as an iceberg, helps in risk mitigation and ensures consistent drug manufacturing. Thorough characterization establishes a solid foundation for release testing and process control, minimizing unknowns in drug production.

5

HOW A CULTURE OF QUALITY LEADS TO PRE-LICENSE INSPECTION SUCCESS

What is a Pre-License Inspection?

Biologics License Applications (BLAs) are request forms that companies must fill out for the FDA's permission to introduce, or deliver for introduction, a biologic product into interstate commerce. Once a sponsor has filed a BLA, **Pre-License Inspections (PLIs)** are performed at facilities or sites that are responsible for the manufacture, testing, and release of the product to confirm that the development of the biologic drug product is in alignment with the information filed in the BLA.

Maintaining a CDMO's **quality culture** is essential to PLI success, which in turn leads to more successful partnerships between CDMOs and biopharmaceutical companies. Communication, experience, and a deep understanding of the industry are all critical components of passing PLIs, and all of these exist in a **culture of quality**. These are four key considerations for sponsors and CDMOs that directly lead to successful PLIs.

Having a Quality Manufacturing Process

The main objective of a PLI is for regulatory authorities to get a first-hand view of the manufacturing site, its quality systems, and the state of compliance with regulatory requirements.

In order to conform to what is claimed in the BLA filing, CDMOs must actively strive to maintain quality systems to show that they are capable of executing biological production.

Collaboration Between the Sponsor and CDMO

The primary objective of the PLI is to align roles and responsibilities between the CDMO and the sponsor. When CDMOs and clients proactively communicate about the BLA filing, it removes roadblocks for once the PLI begins. Sponsors can help their CDMOs better prepare for inspection by sharing the CMC sections of the original BLA filing.

During the PLI, a PLI committee will be formed by technical operations, quality, and project management from both the sponsor and the CDMO. The project manager plays a crucial role in facilitating discussion within the PLI committee and ensuring both the CDMO and sponsor are meeting expectations before, during, and after the PLI.

Understanding the Main Causes of Failure

Once a BLA has been submitted, both the sponsor and CDMO must conduct internal audits/mock audits as part of preparation readiness for the PLI. A poor quality system will earn a drug manufacturer a 483 citation regardless of whether the inspection is general or for a specific BLA.

Failed PLIs generally occur for two main reasons:

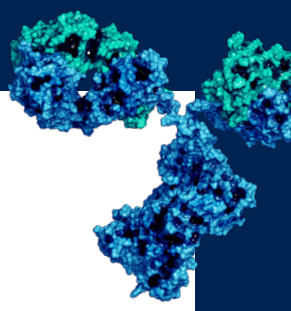
1. An inadequate quality system
2. Insufficient planning and preparation

After internal audits, CDMOs and sponsors must understand what questions will be asked and have appropriate responses ready. Avid generally develops PowerPoint storyboards to visually explain any exceptional conditions that may have occurred during the execution of the process validation activities.

Working With an Experienced CDMO

Successful CDMOs and experienced project managers will typically work on an extensive timeline building up to the PLI even before the BLA is submitted.

For sponsors that outsource development and manufacturing activities, it is essential to work with a CDMO that has experience and values excellent collaboration. Collaborative and strategic planning for tech transfer, process validation, BLA submission, and the PLI are all key to passing a PLI.



LOOKING TOWARDS THE FUTURE: A WORD FROM THE CEO

Thank you for reading Avid Bioservices' Guide to Quality in the Mammalian Biologic Lifecycle.

In the dynamic biopharmaceutical market, there are always new, creative ways to approach mammalian-based biologics manufacturing. Avid values having a quality culture, and we are committed to investing in people and technologies so we can continue to provide innovative solutions to our clients. Through all of our client partnerships, we aim to demonstrate that our quality culture, a track record of regulatory compliance, and a commitment to collaboration is imperative to outsource manufacturing.

I've always felt that to be a truly successful CDMO, companies must build a certain critical mass of business. That juncture is reached when effective quality systems are ingrained in day-to-day operations, the right engineering solutions have been implemented, and a skilled management group has been installed and operates cohesively. Certain fundamental aspects of the business culture are also essential: integrity, transparency, flexibility, and customer success.

Achieving that critical mass puts Avid in a unique and exciting position. From discovery and early process optimization to commercialization, our comprehensive solutions create peace of mind for our clients by optimizing drug development. We have been producing commercial biologics since 2005, have more than 30 years of biologics experience, and have produced over 200 commercial batches of biologics, all while maintaining regulatory excellence. This success is in large part due to our culture of quality.

As an end-to-end mammalian-based biologics CDMO, Avid offers clients cell line development expertise, upstream and downstream process development, analytical services, drug substance and drug product manufacturing, parenteral fill-finish, and regulatory support. Because of our origins as a drug development company, Avid has a great deal of insight into the consumer thought process. We maintain quality in our staff, technologies, and communication between parties to reduce the stress of entrusting your product with an outsource partner.

Over the past few years, quality culture has resonated with biopharmaceutical companies who have been bringing outsource development and manufacturing back to the United States. Avid is ideally positioned to support US-based customers with our headquarters in Tustin, California, near several biopharmaceutical innovation hubs. As the industry turns to domestic CDMOs, our goal is to extend our quality culture to your innovation and bring new, life saving mammalian-based therapeutics to market.

Nicholas Green,
CEO at Avid Bioservices