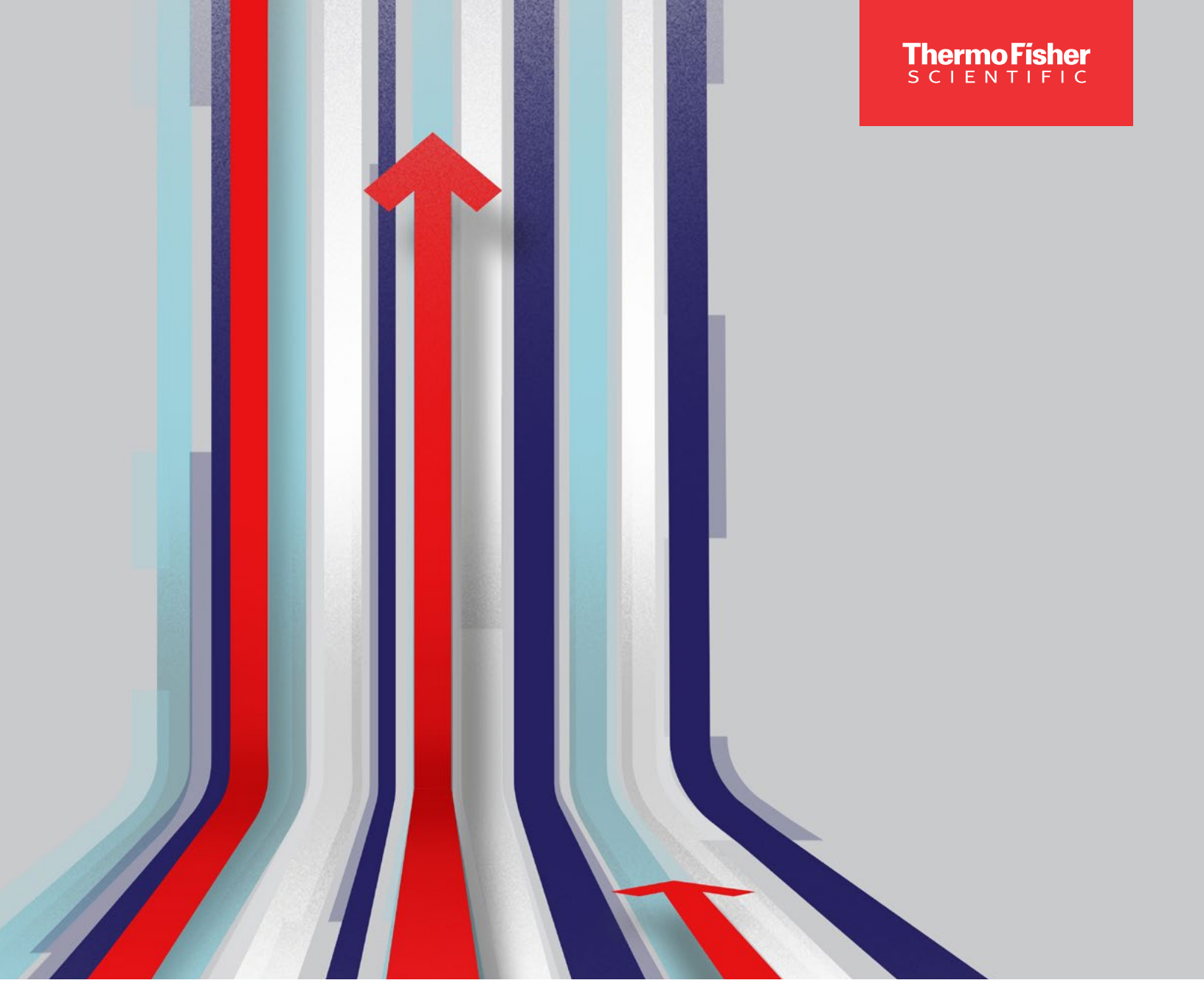
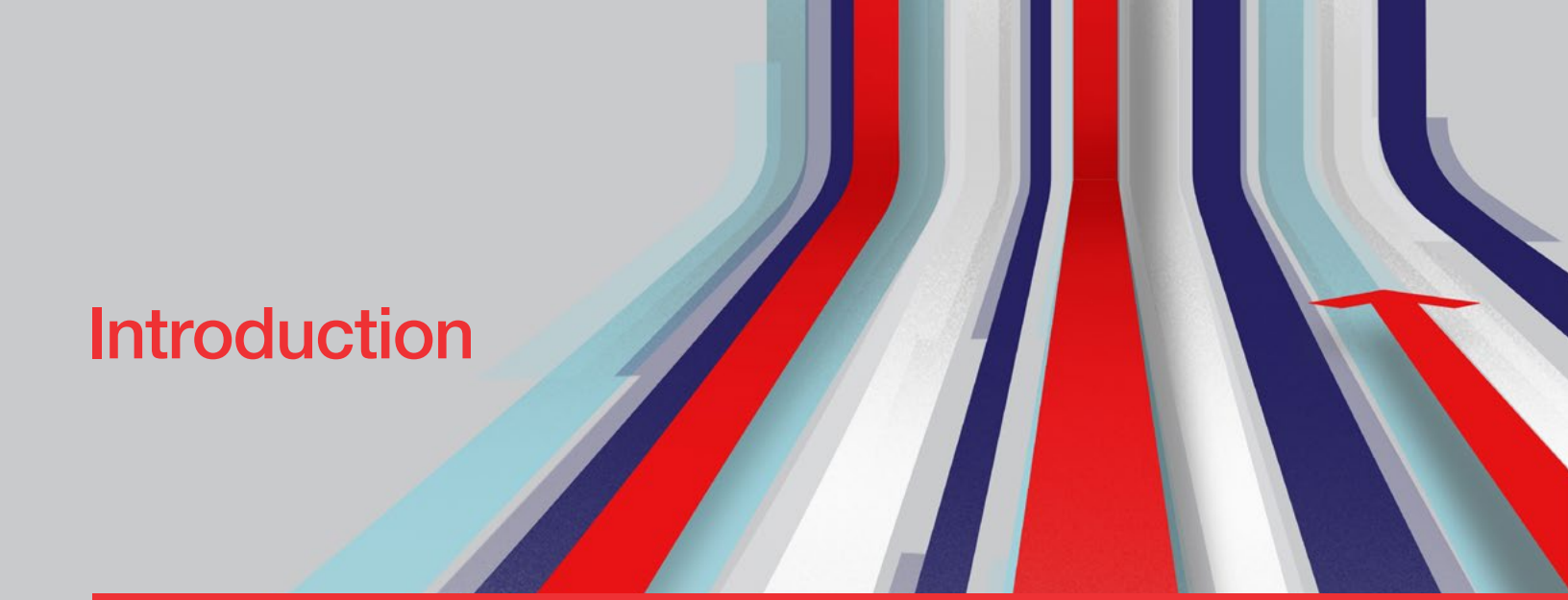


eBook

Key considerations for accelerating biologics manufacturing

Getting safe and effective therapeutics to market quickly

Introduction



Current biomanufacturing trends have placed exceptional pressure on industry leaders to innovate processes and platforms to remain competitive. In order to make life-saving therapeutics more accessible, it is essential to evaluate effective ways to minimize risk while maximizing efficiencies.

This eBook offers strategies for accelerating manufacturing processes and increasing operational flexibility. The information enclosed will help you refine your process to achieve optimal outcomes consistently, regardless of molecule. Read on to learn more about how Thermo Fisher Scientific can help you accomplish your bioprocessing goals.

Contents

Keys to consistent bioprocessing

This is a very exciting time in the biopharmaceutical industry. While we continue to see companies investing in new therapeutic proteins and biosimilars, we are also seeing an emergence of gene and cell therapy treatments. Each one of these therapeutics presents unique complexities in process development, but for all, the development of a robust and scalable bioprocess is critical to long-term manufacturing success. Ultimately, it's about developing a quality process that delivers the desired performance and product consistently.

So what are the main things to consider when developing a robust and consistent bioprocess? The first step is to define what the critical quality attributes (CQA) are for the biologic you are producing. These are typically tied directly to the safety and efficacy of that biologic. But in the case of biosimilars, they may also include other measurements necessary to demonstrate comparability to the novel molecule. Second to the CQAs are the key process attributes (KPAs). These are the measurements that will demonstrate that the process is in control, and may include cell growth and product production profiles. Once the CQAs and KPAs are defined, take a risk-based approach—based on internal experience and publically available information—to determine which process inputs are likely to impact them. In upstream process development, it's easy to first think about bioreactor parameters such as pH and temperature, but additional inputs to consider should include raw materials, cell inoculum, and processing time.

Developing and characterizing the process

Once CQAs and KPAs have been identified and an assessment has been completed to determine which process inputs may impact them—now what? It is not just important to recognize that temperature may impact cell growth (a KPA) and your raw materials may impact glycosylation (a CQA). To ensure you are developing a consistent process, it is critically important to define the operating ranges or material specifications that will achieve the defined KPA and CQA ranges for your molecule.

For your specific process, consider the following questions when preparing for development and characterization work:

- **How will I measure my CQAs?** mAbs have been around long enough that it is generally accepted that glycosylation profiles and charge variants are two CQAs. And there are reliable and high-throughput methods to measure them (including some online tools). But what about gene and cell therapies? Many scientists rely on ELISAs, which are labor-intensive and potentially variable, when there may be more manufacturing-friendly assays.
- **Which raw materials are critical?** This will vary based on the type of biologic, as well as any process or cell line sensitivities. It's easy to focus on "complex" or undefined components, including animal-derived materials or plant-based hydrolysates, but chemically defined raw materials can also pose challenges. All components could possibly bring in trace impurities that can have a big impact on the process. Understanding where the risks are early in development is key to success.
- **What is the right scale-down model?** Whether your manufacturing approach is to scale up or scale out, having a reliable and representative scale-down model is necessary for process development, as well as for future troubleshooting or process improvement activities.

Of course, a high-performing cell culture process is important, but this means more than just maximizing titer. Characterizing the critical attributes of your system leads to a process that delivers the expected product every time. Raw material control and bioreactor process conditions are clearly important here, but scientists are also beginning to utilize an omics approach to better understand intracellular pathways. This information can be leveraged to optimize the system, maximize productivity, and to identify and mitigate process risks.

Preparing for cGMP manufacturing

The complexity of transferring from a process development lab to a clinical or commercial manufacturing suite is sometimes underestimated. Frequently, processes that ran smoothly in the lab fail when operated in a cGMP environment. Many times, this failure is due to a difference in equipment.

For example, a customer developed a mAb process that worked perfectly as a CHO fed-batch process in 3 L glass benchtop bioreactors—consistently achieving 3 g/L—but when they scaled up to a 1,000 L stainless steel bioreactor to produce toxicology material, the titer fell to 1 g/L. The customer was operating this bioreactor with a backpressure of 7.5 psi, but didn't take into account that the higher pressure would result in an increase in the dissolved carbon dioxide (pCO_2) in a culture. The increase in pCO_2 resulted in an increased demand for base, which led to a corresponding increase in lactate production—ultimately resulting in the lower-than-expected titer. Bioreactor pressure, one process parameter unique to large-scale production, ultimately resulted in poor performance. Once this was understood, they implemented a specification, setting a maximum pCO_2 level prior to starting base addition, and were able to achieve 3 g/L at pilot scale. This experience highlighted how important it is in process development to collaborate with manufacturing to understand, and then account for, the differences in production equipment.

Leveraging analytics

The last few years have seen significant advances in analytical technologies used to develop and characterize a consistent bioprocess. The use of omics—specifically proteomics and metabolomics—in early-phase development can optimize cell lines and media through improved understanding of intracellular pathways. Throughout process development, identifying and using reliable assays and online tools for the measurement of CQAs is critically important to define operating ranges. And extending the use of analytical tools to measuring and controlling variability in raw materials helps to ensure a consistent supply.

A great example of this is cell culture media, which can be comprised of over 100 different components, each with the ability to introduce impurities into the process that may impact productivity or product quality. Working with a media manufacturer who has safeguards in place to prevent impurities from both off-the-shelf media and customized media can help mitigate threats to your process.

The complexities of manufacturing biologics reinforces the importance of a systematic and risk-based approach to developing a consistent process. This approach means using past experience to estimate how each variable may impact performance or product quality, and then defining operating ranges and raw materials based on how your specific process behaves. Designing the right scale-down model, leveraging analytics, and working with trusted suppliers is key to establishing a plan for long-term, consistent bioprocessing.

"For autologous cell therapies, variability in the donor material and its performance in the process is the greatest source of variation. So process characterization and the control of raw materials is even more crucial [than with mAbs]."

— VP of bioprocess development and manufacturing for a top pharmaceutical company

© Originally published in The Medicine Maker, **https://themedicinemaker.com/manufacture/keys-to-consistent-bioprocessing**

Best practices for evaluating a perfusion medium

Know your process goal

Evaluating a perfusion process and its associated medium requires numerous factors to be considered. So, how should you start?

Before you begin, you need to understand your process goal and boundaries in terms of acceptable quality and operating limits so that these factors can be approximated in each testing approach. If your product is only acceptable within a certain cell viability limit but a test model doesn't provide controls or plans to actively drive toward that target, the test may be both misleading and less useful for predicting scale-up behavior.

Consider the continuous perfusion operated at two steady states in Figure 1. For the first 19 days, the culture operation is run using a recipe generated from previous studies and achieves an excessively high percent of cell viability. Running with an unnecessarily high cell viability doesn't properly utilize the medium. For example, nutrients are less utilized before they are removed in the spent medium, thus hurting the process efficiency.

From day 20 onward, the continuous perfusion run is adjusted to actively target a slightly lower viability at about 95%. This change has a notable impact on the viable cell density (VCD) at steady state and the productivity of the process. When the process works at 95% viability, the medium is better utilized by the higher VCD. This leads to a more efficient process and achieves a steady-state cell density of about 120 x 10^6 viable cells/mL and a cell specific productivity (Qp) of about 30 pg/cell/day (approximately 1.7 g/L/day harvest titer).

How a perfusion operation is carried out has significant impact on the results. Clear operating goals and mechanisms to achieve them should be planned out so that the medium tested can be put on a level playing field that is meaningful for the process goals and effectively challenges what is being evaluated.

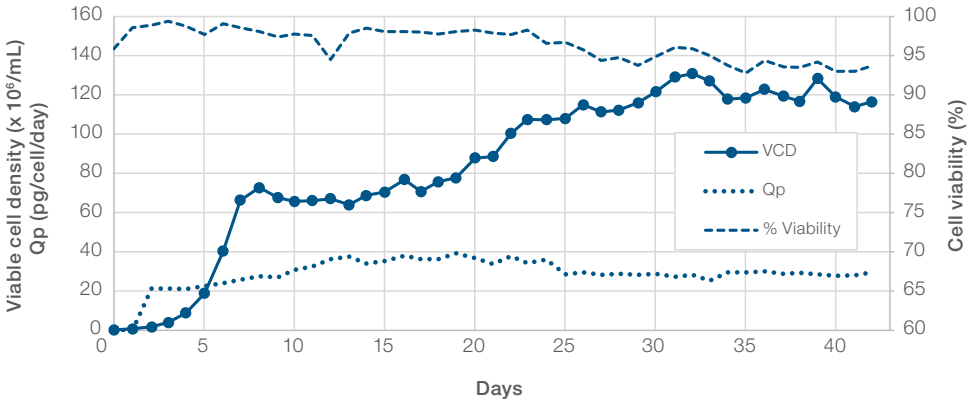


Figure 1. Continuous perfusion at steady state. 1 vessel volume per day (VVD) continuous perfusion using Gibco™ High-Intensity Perfusion (HIP) CHO Medium. At day 19, the operation was changed to better utilize the medium, resulting in a new steady state targeting a lower percent cell viability. New targets were reached around day 26.

Know your test model

Once clear design goals are established, the next step is to define a test setup. You want the testing to give you results that are meaningful to your process goals and make sure the equipment and materials used don't become accidental limiting factors. The following questions need to be considered before you run your test model:

- How long will you run your process?
- How much oxygen transfer can you support?
- What is your target scale-up and what additional restrictions will this cause, such as how much shear will be generated?

Ideally, your test setup allows the systematic evaluation of critical parameters to optimize cell viability and productivity. It will also help identify the parameters that require scaling and how much flexibility exists. For example, there are multiple approaches to scaling agitation (Table 1), so it is important to know what your process limits are. When combined with your product quality needs, these limits should establish control boundaries for your run, which are meaningful with respect to how you plan to operate the process. This will also help avoid your results being limited by an unplanned, or worse unnoticed, factor in your test model. Additionally, it will help reduce risk when scaling up the process.

Table 1. Common agitation scaling parameters in a 3 L bench-scale stirred-tank reactor at increasing rpm. Typical animal suspension cell culture agitation power (W/m^3) is highlighted in blue. Progressive comparative minimum tip speeds are highlighted in orange and red with process scale-up to 2,000 L, and Kolmogorov eddy length common targets using microcarrier beads are highlighted in green.

Agitation scaling parameters				
Reactor speed (rpm)	**Agitation power (W/m^3)**	**Tip speed (m/sec)**	**Pow num**	**Kolmogorov length (µm)**
55	0.42	0.16	1.99	91.345
75	1.02	0.22	1.89	73.326
200	14.99	0.59	1.47	37.417
239	25.26	0.70	1.45	32.841
292	45.07	0.86	1.42	28.416
348	75.22	1.02	1.40	25.001
389	105.06	1.14	1.40	22.997
443	155.17	1.30	1.40	20.861
486	204.88	1.43	1.40	19.461
555	305.11	1.63	1.40	17.617
610	405.11	1.79	1.40	16.411

Know your cell line

It is important to know the limits of your cell line. Some of this can be built into your screening test model as noted previously. Some limitations need to be evaluated and considered directly. For example, some cell clones lose productivity too quickly when selective pressure is removed to be able to support a long-term continuous perfusion process. Some cell clones do not behave well at higher VCD, which may limit perfusion benefits. Figure 2 is from a cell line stress run with ramping agitation up to 600 rpm. The cell line handled the stress run and other mechanical stress tests well, but the production stability made it a poor candidate for continuous perfusion tests.

Another limitation to cell line development could be the selection of the medium. Before you begin your test, make sure your cell line is fully adapted for any medium conditions. Keep in mind that some cell lines require complex or specialty components from the medium they were developed in. Make sure these are present in all medium conditions tested. Failure to include special components such as growth factors, peptones, and hydrolysates that a cell clone has been developed in can compromise the cell performance and make for a very difficult adaptation. If it is important to remove a specialty component, weaning it off should be considered separately after adapting to a new medium with the component present.

When adapting your cell line, make sure your growth rate and productivity are stable for two additional passages after the cells seem to have fully recovered. If a cell line adapts readily via direct adaptation, you should still run a total of six adaptation passages to ensure it is behaving well in the new medium with little to no carryover from the previous formulation.

Also remember, when operating in perfusion, medium is constantly exchanged, so supplements must be considered carefully. Some supplements that normally accumulate in fed-batch culture will be continuously removed in perfusion and may need to have concentrations increased. Some supplements that are dosed once early, such as L-glutamine, will be constantly added back in perfusion and may benefit from reduced concentration. Finally, some components accumulate in the cells themselves and should be supplemented with caution to avoid overloading the cells over time.

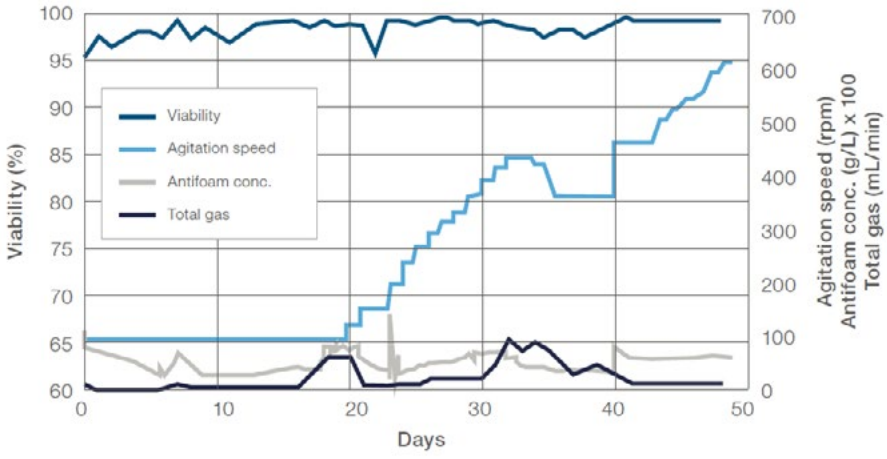


Figure 2. Chemostat operation of a CHO cell culture evaluating varying mechanical stress factors while monitoring cell health.

Know your assumptions

It is equally important to understand what you are not testing as it is to know what you are testing in your model. It is generally not practical to cover all critical process parameters in a screening model. However, anything not covered in a screening model is a risk that should be evaluated independently, or it may catch you by surprise later. For example, if you have already demonstrated that your cell clone is mechanically highly robust, it may not be important to get agitation scaling and other mechanical stress factors right in your screening model. Having a clear understanding of what risks mean for your cell clone and process goals is critical when making assumptions and conclusions about generated data. Bolus versus continuous fluid handling, using different mechanisms to retain cells, weak scaling representation, and other operating differences should all be evaluated.

For example, one of the biggest weaknesses in most screening models is time. Typical screening tests only run for about 7–15 days. This may not be enough to see limits and final behavior of a given process and medium. In Figure 3, a continuous 1 VVD perfusion run was carried out in triplicate. Bleed was employed to maintain a consistent ~97% cell viability. It was not until day 27 that this process approached a final steady state. Had it been screened in the first 10 to 15 days, the conclusions would not have given a realistic representation of the cell line and would suggest a steady state limit of ~1 g/L harvest titer, as opposed to what seems to be the cell line and medium's ultimate final behavior in a continuous process of around 1.6 g/L harvest titer.

By comparison, other media tested have demonstrated the opposite behavior—showing high early productivity on day 0 through 10 but reduced productivity over time at a faster rate of decay than what the native cell line's productivity decline looked like during passaging without selective pressure.

Some cell lines exhibit long periods of metabolic oscillations that require additional efforts to mitigate.

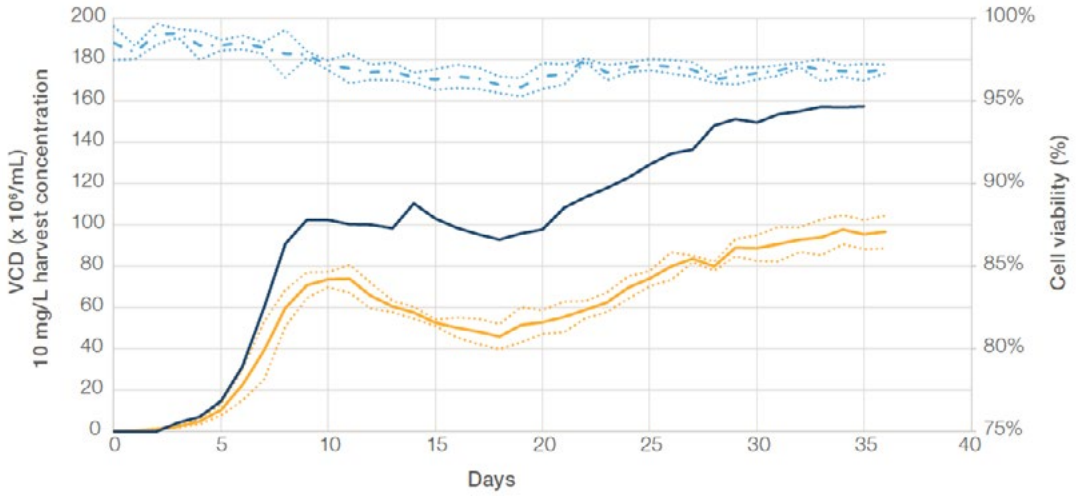


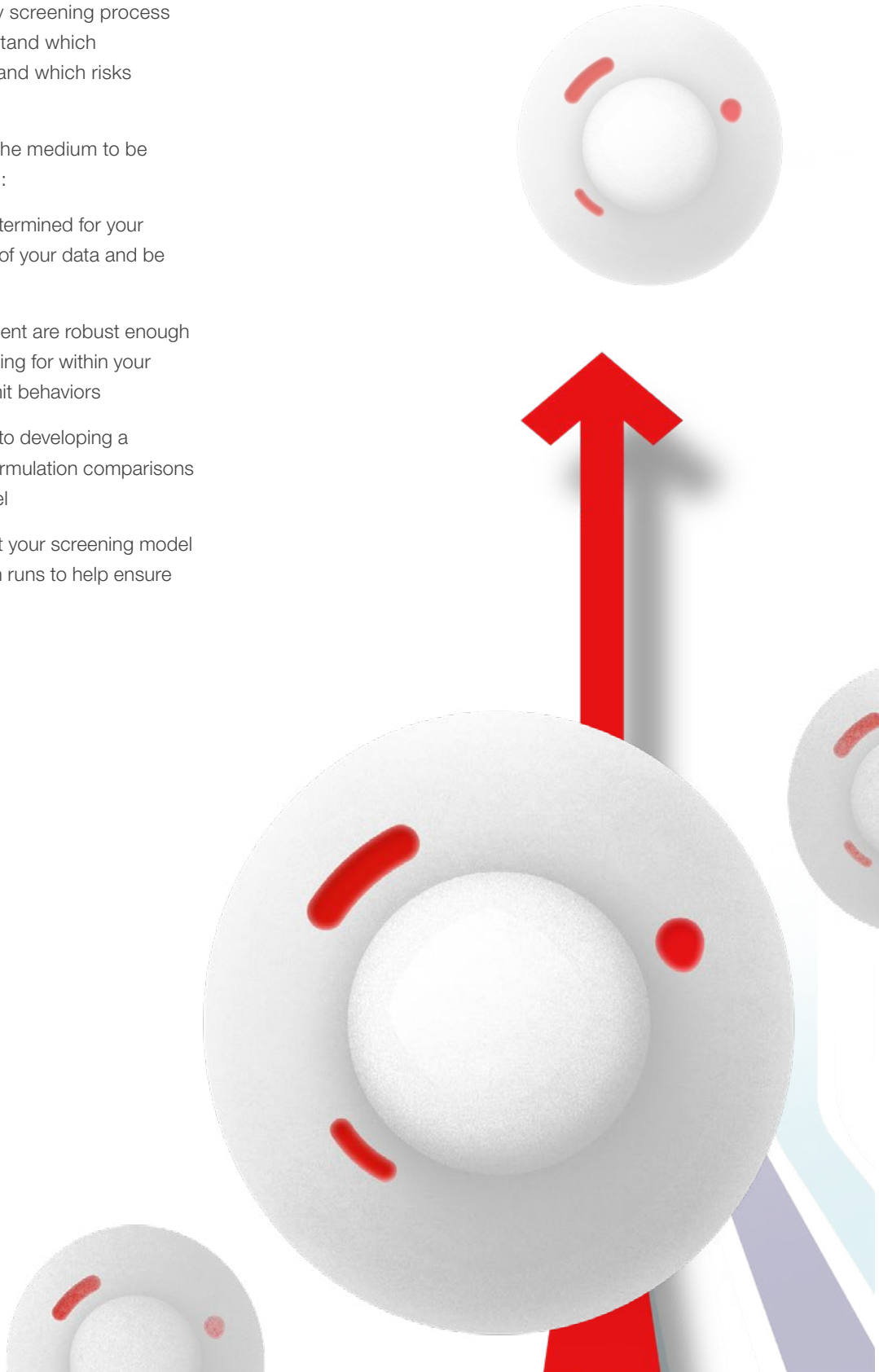
Figure 3. Continous perfusion operation at 1 VVD targeting constant cell viability, run in triplicate. Dotted lines are ±1 standard deviation. Note: harvest titer is in units of 10 mg/L.

On an even simpler level, operating perfusion screening for too short of a duration in some cases doesn't allow enough time for cells to start dying, leaving a misleading impression about what VCD can be sustained at a given target percent cell viability.

Ultimately, it is important to benchmark any screening process with an actual perfusion run to help understand which performance assumptions are reasonable and which risks are practical.

When evaluating a perfusion process and the medium to be used, keep the following key points in mind:

- Have a clear goal and design space determined for your screening so that you can build on top of your data and be confident in your comparisons
- Make sure your test model and equipment are robust enough to deliver the performance you are looking for within your design space and don't accidentally limit behaviors
- Understand your cell line's needs prior to developing a screening model, and make sure the formulation comparisons are complete before adapting the model
- Know and account for the limits in what your screening model doesn't address, and plan for validation runs to help ensure your assumptions are reasonable



A rapid alternative to culture-based mycoplasma detection

Introduction

Mycoplasma contamination represents a serious and costly problem for biomedical facilities involved in development and manufacture of cell-derived pharmaceutical products. Undetected mycoplasma contamination in pharmaceutical products has serious consequences for patient safety and product quality. Testing guidelines to ensure mycoplasma-free, cell-based biotherapeutics are provided by multiple international guidelines and regulatory agencies (e.g., United States Pharmacopeia (USP), European Pharmacopoeia (EP), Japanese Pharmacopoeia (JP), Section 21 of the Code of Federal Regulations (CFR), International Conference on Harmonisation (ICH), and Food and Drug Administration (FDA)).

Traditionally, this testing involved the culture of viable mycoplasmas in broth, agar plates, and indicator cells. While this is an efficient method of detection, it is costly and time-consuming (28 days), and requires specialized training to interpret the results. The amount of on-test time for these culture-based assays does not allow for timely decision-making during routine, in-process testing. Additionally, the emergence of single- or low-dose therapeutics with short shelf lives, such as gene and cell therapy, has made the 28-day culture test impractical and has driven the need for an accurate, sensitive, and rapid mycoplasma detection assay.

Chapters on mycoplasma testing in both the United States Pharmacopeia (USP<63>) and the European Pharmacopoeia (EP 2.6.7) allow for the use of properly validated nucleic acid amplification test (NAT) methods as an alternative to the 28-day culture-based test. Following validation, regulatory filing, and review, our customers have received regulatory acceptance to use the Applied Biosystems™ MycoSEQ™ Mycoplasma Detection Kit for lot-release testing applications across multiple therapeutic modalities (Table 2).

Here we describe the MycoSEQ assay, an accurate and sensitive real-time PCR mycoplasma detection assay that provides results in under 5 hours. Additionally, we present two case studies from users who have validated and received regulatory approval to use the assay for product lot release.

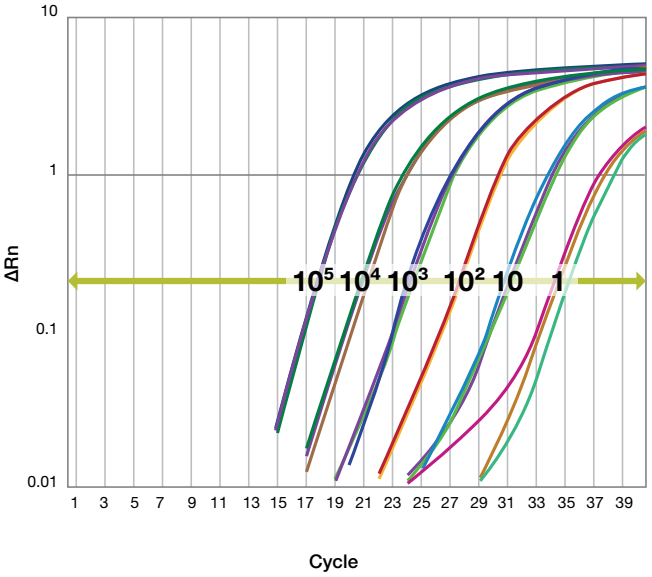
Table 2. Number of products, by therapy, using the MycoSEQ assay for rapid mycoplasma lot-release testing as of 2021.

Product category	Number of approved products	Number of products in the process of validation and approval	Regulatory agency for approval
Cell/gene therapy	22	19	EMA/FDA/PMDA/local agencies
Tissue therapy	3		EMA/FDA/local agencies
Recombinant protein	1	1	EMA/FDA
Monoclonal antibodies	5	6	EMA/FDA
Vaccines	3	4	MFDS/local agencies
Contract services/ others	8	2	Local agencies
Total	**42**	**32**	

The MycoSEQ assay

The MycoSEQ mycoplasma detection system combines sample preparation and a qPCR assay, including automation systems for sample preparation, the real-time PCR instrument, and a fully integrated software package with a module to help meet 21 CFR Part 11 compliance. The assay provides quantitative detection of more than 90 Mycoplasma species in under 5 hours with consistent and comprehensive detection down to 1 genome copy (Figure 4).

Analysis of a 10-fold dilution series of purified *Mycoplasma arginini* DNA:



Melt analysis at 1 genome copy/rxn

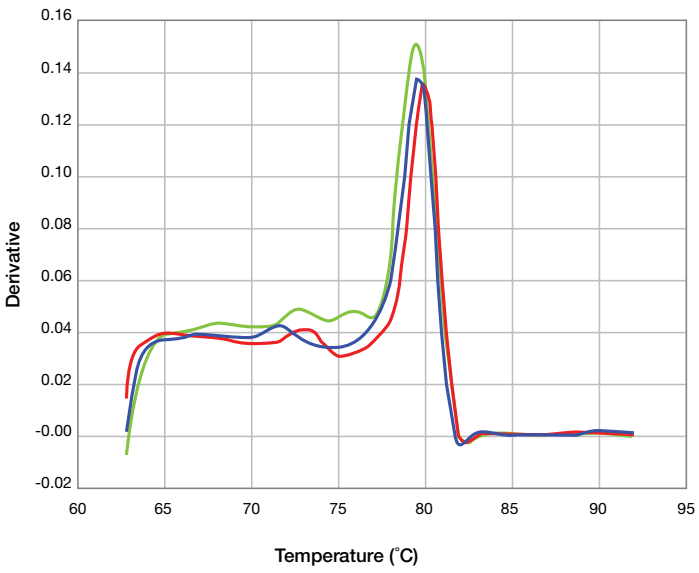


Figure 4. Assay sensitivity down to 1 genome copy.

Reference

1. **A Rapid Alternative to Culture Based Mycoplasma Detection**, Darren J. Bauer and Michael Sherriff, Thermo Fisher Scientific, 35 Wiggins Avenue, Bedford, MA 01730 USA

Case study #1

Mycoplasma lot-release testing for a cell therapy product

Background

- Vericel Corporation in Cambridge, Massachusetts produces an autologous cell therapy product with a high number of samples
- Regulatory expectations are that testing is required at various stages in the production process for advanced therapeutic medicinal products intended for human use

Scenario

- The product has a short shelf life with the expectation of same-day release; standard testing methods take at least 28 days to complete
- The main objective was to mitigate risks of mycoplasma contamination
- A risk-based approach to mitigate validation issues during implementation was adopted and is consistent with the objectives of ICH Guideline Q90

Derived value

- EMA approval was received for the cell therapy product in 2013 and FDA approval in 2016
- Mycoplasma test results are now available for same-day release of autologous cell products
- qPCR can be used to rapidly identify potential contamination, significantly reducing the risk to other processes in the facility

Key to success

Vericel discussed mycoplasma testing validation plans with the FDA before submitting the Biologics License Application (BLA), thus facilitating its use in the application. Table 3 summarizes the validation protocol and results. The validation study found the new method's specificity and limit of detection (LOD) to be equivalent to or better than the traditional culture method. The rapid PCR method detected mycoplasmas in samples spiked with 10 CFU/mL, which the culture method did not detect.

Table 3. Summary of validation protocol.

Parameter	Sample	Acceptance criteria	Results
Specificity	Unspiked	No mycoplasma detected	6/6 negative
	Mycoplasma DNA	Detection in spiked samples	6/6 positive replicates for 6 species
Detection limit	Mycoplasma DNA	Detection in spiked samples	6/6 positive replicates for 6 species
	Mycoplasma <10 CFU/mL	Detection in spiked samples	6/6 positive replicates for 6 species
Repeatability	Unspiked	All replicates negative	24/24 negative
	Mycoplasma DNA	All replicates negative	24/24 positive replicates for 6 species
Ruggedness	Analyst to analyst	Δ(Average C_t) < 3	Δ(Average C_t) < 2
	Instrument to instrument	Δ(Average C_t) < 2	Δ(Average C_t) < 2
	Reagent lot to reagent lot	Δ(Average C_t) < 3	Δ(Average C_t) < 2
	Laboratory to laboratory	Δ(Average C_t) < 4	Δ(Average *A. laidlawii* C_t) = 3.1 Δ(Average *M. arginini* C_t) = 0.2 Δ(Average *M. fermentans* C_t) = 1.2 Δ(Average *M. hyorhinis* C_t) = 3.4 Δ(Average *M. orale* C_t) = 1.4 Δ(Average *M. pneumoniae* C_t) = 3.1
Equivalence	*Mycoplasma orale* 7 CFU/mL	NAT positive ≥ PTC positive	NAT 6/6 and PTC 0/6 positive
	MACI SUMMIT clinical trial samples	NAT results = PTC positive	NAT 78/78 and PTC 78/78 negative

Watch John Duguid, Senior Director, R&D at Vericel discuss [why Vericel chose the MycoSEQ assay](#).

Case study #2

In-house alternative to outsourced culture-based testing

Background

- Octapharma AB in Stockholm, Sweden produces a human recombinant factor product in a perfusion process
- Current culture-based method was outsourced

Scenario

- A large number of samples made the outsourced testing cost-prohibitive
- The main objective was to find an in-house alternative to outsourcing
- Determined a commercially available assay provided a faster timeline to validation

Derived value

- qPCR can be used to rapidly identify potential contamination
- The MycoSEQ assay was implemented as a replacement for culture-based tests and mycoplasma testing is no longer outsourced
- After validation and filing, regulatory approvals are in process

Key to success

Due to the scope of the project, early communication with all relevant departments was critical to success. Full implementation took about four years from the point of investigating the PCR method as an alternative to the traditional method, to regulatory submission (Figure 5). Thermo Fisher Scientific technical support and assistance throughout all phases of the project was critical.

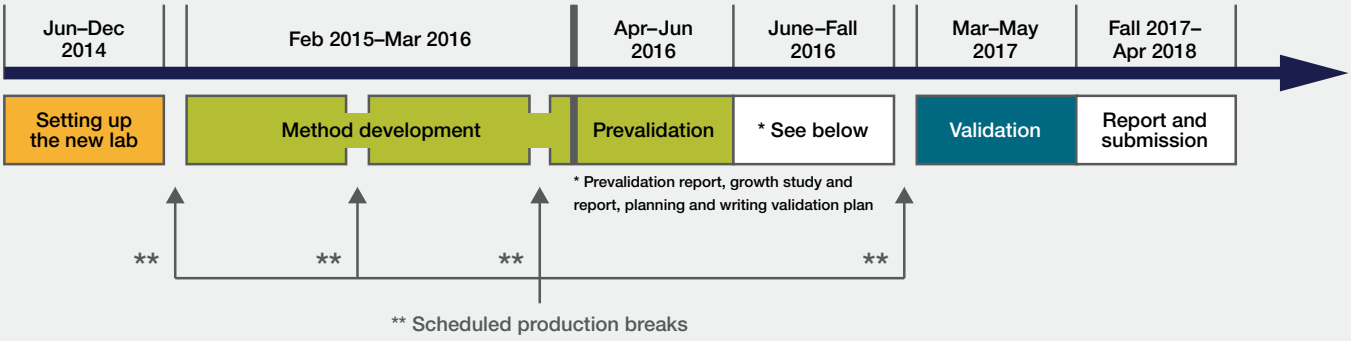


Figure 5. Project phase timeline.

For more details, read the white paper titled "Making the Switch to In-House Mycoplasma Testing".

Process intensification: getting more from less

Intensifying or simplifying your bioprocess may mean more product, shorter manufacturing times, or lower costs—understanding what matters most is key to making the right decisions.

It's no secret that the biopharmaceutical industry is under intense pressure to reduce costs—especially in manufacturing—and getting more output from a given process is a clear win. Process intensification does just that. The goal is to take an existing process and optimize it to increase output: more product in a shorter time, with fewer steps, and from a smaller working footprint. Process simplification, on the other hand, focuses on streamlining activities to increase efficiencies.

Which option is best: intensification or simplification? It ultimately depends on the type of molecule you're making, the current manufacturing challenges and bottlenecks you're facing, and the stage of development your product is in. Process changes can occur at any stage during development, even post-launch, and the better characterized your existing process and product are, the easier it will be to evaluate the impact to the critical quality attributes of your product and implement changes.

Evaluating impact

During early-stage development, there's usually pressure to quickly identify a first-generation process and get the molecule into the clinic as quickly as possible. After this point, there is typically time to consider where opportunities for process intensification and simplification exist. These pre-launch changes are driven by commercial requirements—can I effectively and efficiently manufacture enough material to meet patient demand? And manufacturing needs—is this process robust enough to run consistently for the lifetime of the product?

During late-stage development, there may be pressure to minimize changes and focus on finalizing the commercial process to prepare for launch. But while late-stage and post-launch process changes can be more difficult to implement, they should still be considered when there are opportunities to reduce risk of manufacturing failures, increase throughput, and improve the consistency of the product and process.

Regardless of where you are in the life cycle of your molecule, there will be no shortage of potential opportunities for improvement. The key is determining which ones to pursue.

Should I streamline?

To streamline a process is to reduce unnecessary steps or operations. Focusing on these areas of improvement could reduce processing time and the risk of manufacturing and contamination failures. One common area that can usually be streamlined is cell expansion. It may be possible to reduce the number of expansion steps in the process, or reduce the amount of aseptic manipulations required during cell expansion. Another area to consider would be release testing. With current advancements in analytics, it is possible to replace cell-based assays, which take weeks, with significantly shorter assays.

How do I intensify?

Process intensification helps enable you to get more out of your process. For an upstream process, you could consider transitioning from fed-batch to perfusion, or implementing a hybrid, high cell density process enabling you to increase the amount of protein produced without increasing batch size or processing time. For a downstream process, you could optimize chromatography resins to improve cycle times and increase yields. All of these changes should result in an increase in material throughput.

Could this be simplified?

Identifying tasks that are labor- or time-intensive and simplifying those operations enables you to focus resources on more critical activities. Some areas to consider are media and buffer preparation, as well as material handling and transfer. There are likely opportunities to outsource or automate these tasks.

Improving manufacturability

Overall manufacturability is a key consideration to whether or not a product will be commercialized. Process simplification or intensification could greatly improve the manufacturability of the molecule through improved robustness, increased throughout, reduced supply concerns, or reduced cost of goods. These activities have the potential to make a bad process good or a good process great.

Process intensification is used to get more out of the process, whether it's by producing more product upstream, or retaining more product downstream. Intensifying the process requires changes in manufacturing—different media or resins, new operating ranges, or even replacing specific unit ops, and therefore has the potential to have the greatest impact on the molecule. For this reason, these activities are typically done during early-phase development. They can still be pursued during late-stage development or even post-launch, but you would first need to demonstrate no adverse effect on the identity, quality, purity, and potency of the biological product.

"We are exploring opportunities to use more efficient purification technologies to reduce the number of purification operations required to generate purified drug substance. Our ability to simplify processes improves likelihood for successful validation, reduced scope of process development and characterization, reduced number of manufacturing deviations and failed manufacturing campaigns, and improved yield."

—Andrew Keefe,
Principal Development Engineer at Shire

One area where process intensification may be critical is in the rare disease space. The majority of biological products in development for the treatment of rare diseases are not the more common monoclonal antibodies, but rather are enzymes, fusion proteins, and cell therapies. These products are typically more challenging, and therefore more costly, to manufacture, which makes process intensification crucial to successfully bringing these products to market.

Process simplification can also have significant positive impacts on manufacturability; most simplifying operations are likely to have no impact on the molecule, and are therefore routinely implemented even post-launch.

Analytical testing is an area where simplification can improve the release of biological products. For all sterile products, sterility testing is required for release and may be the longest test to complete. This is a challenge for all of those molecules, but for cell therapy products it is even more of a concern. Monoclonal antibodies, for example, are targeted to specific diseases and, once purified, are typically stable for multiple years. Cell therapies, on the other hand, are live cells and may be patient-specific. Therefore, it is imperative that the material gets to the patient without delay, and identifying viable solutions to streamline analytical testing is crucial to getting those products to the patients that need them most.

Simplifying or intensifying a process may make the difference in whether or not a company can manufacture or even launch a successful biologic. Choosing what and when to intensify can be difficult. With any change, the benefits must always be carefully weighed against the potential risks. But understanding your rationale for change, conducting thorough reviews of the impact to the product and process, and leveraging the expertise of a trusted partner, can lead to tremendous success and result in more product at better costs by transitioning your bioprocess from good to great. Remember, in all situations, the patients' best interest should be top of mind when you are evaluating product and/or quality risks.

"Microbial testing is required at different points throughout a manufacturing process, but standard methods take too long to be useful for cell therapy products. USP mycoplasma testing takes 28 days; Vericel's method has reduced that to about six hours [with the] MycoSEQ mycoplasma detection assay."

—John Duguid, PhD,
Senior Director of R&D at Vericel

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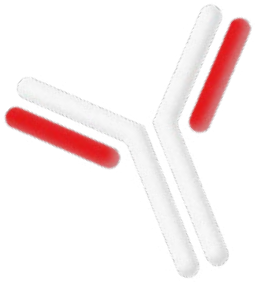
Using improved communication to overcome data management challenges in the laboratory and beyond



The process of bringing a new drug to market requires a multidisciplinary approach. It involves a wide range of expertise in science, engineering, analytics, quality, supply chain logistics, and clinical implementation across the entire product life cycle. All stakeholders work together to ensure that a potential new drug is effective and can be produced in an efficient manner, delivering a high-quality and consistent product that meets clinical quality and commercial demands.

Decisions made early in development, and even in discovery, can send the molecules down very different paths, which will challenge your team in multiple ways. Planning early for manufacturability reduces surprises, such as challenges with reproducibility and scale-up, as the molecule goes through the chemistry, manufacturing, and control (CMC) journey and, upon approval, to the patient. Drug development is rewarding, but the number of approvals each year is minimal compared to how many molecules are in development pipelines.

Many critical decisions are made in process development that can minimize obstacles as a drug is transferred and produced in manufacturing. Scaling challenges, timelines, and regulation pitfalls can be diminished when these teams are aligned with each other's capabilities. Resources, such as capital equipment, can also be conserved. There will always be challenges, but through communication, data, new technologies, and problem solving, next-generation medications can be delivered safely and in an efficient manner.

The value of process data and communication

Our drug development and manufacturing colleagues are familiar with the fallout when things happen unexpectedly, and while not all of it is within their control, it is nonetheless frustrating. Those responsible for designing and executing effective experiments and then analyzing them know they are an important piece of the journey.

Without the ability to produce material for testing in the quantity necessary to meet patient needs, though, they cannot produce a life-saving (or life-improving) treatment.

Pharmacological and biological development is an iterative process, and often the scientists do not realize there is a challenge until an issue occurs later in the process. Therefore, even in the most thoughtout processes, unforeseen challenges occur, with the root cause generally being a lack of communication between groups. Below is an example where communication between groups and a systems thinking approach would have prevented timeline delays and process rework.

Scenario

The upstream bioreactor group increased monoclonal antibody (mAb) titer by 300 percent. However, the downstream purification group reported the following challenges in purification:

- Extended processing time
- Elevated host cell protein levels
- Issues in filtering material due to the higher-than-expected cell density
- Ultrafiltration issues due to antifoam

Result

The purification team spent significant resources to solve the challenges with the new high-concentration process, and the required changes needed were extensive and costly.

Ultimately, the upstream group modified the process and accepted a lower concentration of mAb in upstream in order to increase the overall yield later in downstream.

How could this have been prevented?

The upstream and downstream teams should have discussed the development process together to better understand how the increased titer might impact purification. With advance notice of the process and also a thorough joint data review, including online digital profiles, both teams could have mitigated the impact.

Knowledge and data acquisition begins in the discovery phase and ends once the product life cycle is completed. Data gathering, and how that data is translated across the workflow, plays a critical role, as a tremendous amount of information (quantitative and qualitative) is collected during drug development, and there are many factors to explore and consider as scale changes. It is important to minimize and control issues during those changes while facilitating communication as much as possible.

Using the CMC pathway as a guide is a useful tool in seeing how multifaceted the process is for bringing a drug to market and how connected the teams are that deliver each portion of the journey. Process characterization is a great example of when scales, timing, and data from multiple teams are coordinated to further de-risk a process for Phase 3 and commercial manufacturing. While risk assessments should be conducted throughout development, they are critical—as well as a regulatory requirement—and a prerequisite to process characterization.

Technology transfer is another challenging step in the development and commercialization process. Having fluid communication and detailed documentation between R&D, manufacturing science, and operations during tech transfers can decrease miscommunication, thereby increasing the likelihood of success.

Below is an example of where a technology transfer took place, but issues occurred when the bioreactor profiles were different.

Scenario

R&D transferred a mAb process to a contract manufacturing organization (CMO) using a CO_2 overlay. However, the CMO does not typically use a CO_2 overlay, nor do they have the capability to do so.

Result

Manufacturing executed the batch using the information sent by the tech transfer team.

There were no issues with equipment during batch execution, but the growth profiles were slightly different, leading to questions about whether this was due to typical variability and/or differences in scale.

Upon further investigation, it was identified that the gassing profiles were slightly skewed.

How could this have been prevented?

Several factors could have helped prevent this issue:

- Data and profiles should have been shared between R&D and manufacturing (having a common reporting platform would have expedited this)
- Walk-through of the process with R&D and manufacturing
- Risk assessment
- Implementation of platform standard operating procedures

Data management for improved communication in the product life cycle

Software programs, such as data historians, capture vital data, but they are then stored in disparate locations. Without transparency across processes, decisions are made based on only a portion of a process rather than a holistic analysis of it. This has led to increased interest and a tightened embrace by the pharmaceutical industry around improving communication between R&D, manufacturing science, and operations.

In addition, innovation in today's biologics combined with a complex supply chain has intensified regulatory oversight to ensure continuous drug delivery that is safe and effective, even as the pharmaceutical landscape grows and changes—all while doing so at the fastest speed possible. Having a unified data management strategy and platform that can collect and connect data as a biopharmaceutical manufacturing process transfers from small-scale to large-scale production would streamline communication across the entire process development workflow, enabling responsive decision-making and preventative action that would save valuable time (as demonstrated by the above examples). This focus on communication requires a fundamental shift toward real-time data feedback that supports data integrity and allows for the use of analytics and risk analysis.

These key elements provide an opportunity to demonstrate the effectiveness of utilizing the same automation control and data historian analysis from the beginning of the product life cycle to the end. Providing a digital fingerprint as the development of a drug's production process is thought out helps align goals between process development and manufacturing.

So, how can you implement data-driven decisions in your lab that help you be effective at any scale without creating new challenges during the life cycle of the product? Begin by partnering with companies that base their solution on a robust, proven, and widely trusted platform that can be used from the beginning of the product life cycle in R&D through to manufacturing. It helps the scientists in R&D and process development to be mindful of 21 CFR Part 11 and ISA-88 compliance as required in manufacturing and to employ this standard in their software and automation choices to streamline the scale-up and tech transfer process. You can also utilize automation platforms that exchange data between scales and campaigns using a digital fingerprint that eliminates the risks associated with manual data transfer.

The data system and how the information is communicated should be easy to use and flexible enough to work across the product's life cycle from process characterization and development to manufacturing. It should also allow for open architecture that helps enable the integration of third-party products, so you can add other equipment or monitoring solutions as your company grows and changes.

The solution you choose—and the partner that offers it—must provide innovative and state-of-the-art technology, in order to support your growing needs throughout development and manufacturing. Your partner must also demonstrate proven expertise to provide you with the tools necessary to prevent the challenges that will inevitably surface along the way. And with the global footprint of the industry growing bigger every day, it is important that, no matter where you are, they have the resources to support you during discovery, process development, manufacturing, and beyond.

An automation platform that can be used for R&D and process development to manufacturing allows for real-time data (current and past) during scale-up and scale-down, decreases the chance of miscommunication, and as a result, helps guide a more informed decision-making process. The benefits help mitigate errors in manual data transfer, minimize deviations and losses, and uphold communication, which ultimately provides a consistent, high-quality product and increases the likelihood of success and a faster time to market.

Learn more at **thermofisher.com/bioprocessing**

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