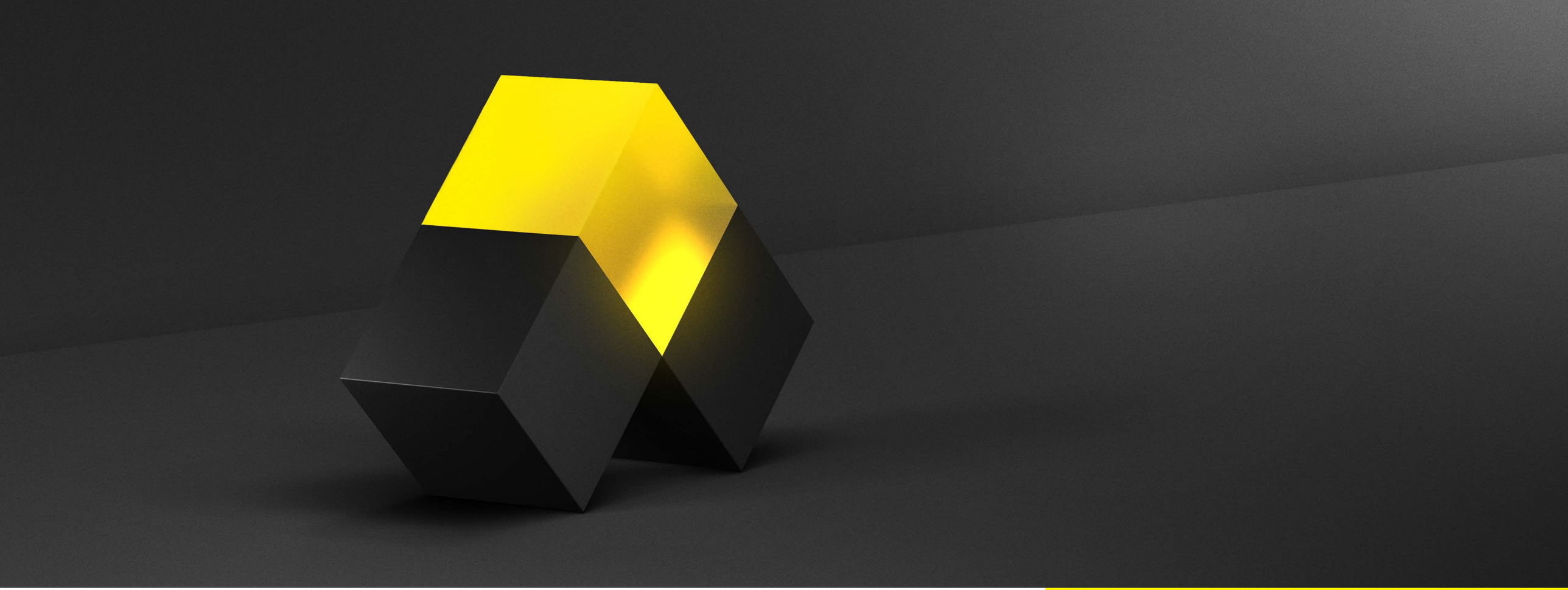


Process Intensification

Key Considerations and Expert Insights

SARTORIUS

For 150 years, Sartorius has stood for innovative solutions that meet the challenges faced by scientists and engineers in bioprocess development and manufacturing worldwide. Process intensification represents a major trend that we are focused on that enables our industry to address a variety of challenges.

As current biological product pipelines become more diverse, product demand and cost pressures are increasing. To meet these demands, manufacturers often move towards process intensification. By making changes to unit operations, to the process or even to the type of facility, our industry can identify areas of potential improvement that can increase productivity, reduce timelines, downsize process footprint, lower cost of goods, and | or unlock additional manufacturing flexibility.

Multiple intensified process schemes for upstream and downstream processes are being developed by the bioprocess industry to fulfill these and other market demands.
To discuss these real-world scenarios, Sartorius reached out to a wide range of industry experts and academics from across the globe.

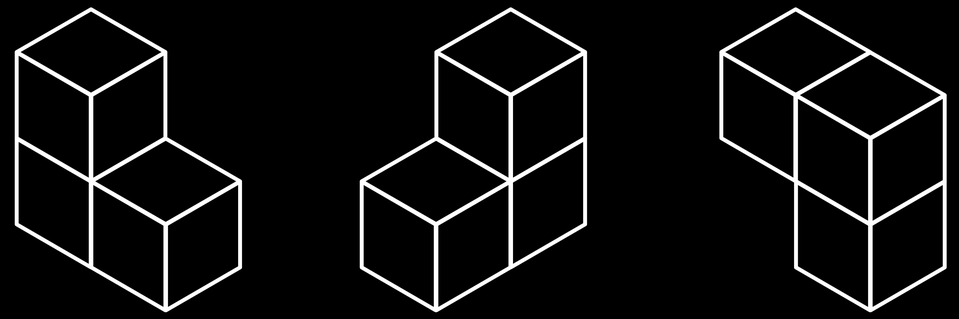
Miriam Monge
Head of Protein-Based Therapeutics Marketing Segment, Sartorius Bioprocess Solutions

I want to thank the industry leaders that partnered with us in this important discussion regarding their experience of implementing process intensification strategies as they relate to unique organizational goals. Each expert provided their own experience of implementing process intensification, what the motivating drivers were, as well as specific insights into the outcomes. Their insights provide readers with a holistic perspective, but also outline the top considerations to factor into your internal calculations, deliberations, and decision making.

We hope you will enjoy reading this supplement — and we would like to continue this dialogue and collaboration with our customers and partners.

There is a massive amount of information to consider when performing process intensification. This adds to the already complicated nature of biomanufacturing and its unique regulatory challenges.

As a result, the first step is learning about the advantages and disadvantages of available strategies, collecting a wide range of perspectives, and applying that information to your specific requirements and goals.



There is no one-size-fits-all approach to process intensification, especially given the variety of modalities and novel biologic drugs.

Table of Contents

Each chapter centers on a key benefit of process intensification to help readers match tactical insights to their most important business need. These chapters focus on five pillars of process intensification:

Contributors

Andrew Sinclair
President and Founder
at Biopharm Services

Ankur Bhatnagar
General Manager
at Biocon

David Johnson
Head of
Chromatography
at Sartorius

David Pollard
Head of Advanced
Materials and
Processing, Corporate
Research at Sartorius

Dieter Eibl, Ph.D.
Professor at Zurich
University of Applied
Sciences

Himanshu Gadgil, Ph.D.
Chief Scientific Officer
and Whole-Time
Director at Enzene

Jon Coffman, Ph.D.
Senior Director of
Bioprocess Technology
and Engineering
at AstraZeneca

Jonathan Haigh, Ph.D.
Vice President of
Process Development
at FUJIFILM Diosynth
Biotechnologies

Kenneth Kang
Vice President of
Manufacturing at
Innovent Biologics

Kurt Brorson, Ph.D.
Vice President,
Technical at Paraxel

Mandar Dixit
Principal Process Expert
at Sartorius

Markus Wieland
Head of Product
Development
at Sartorius

Contributors

Patrick O'Sullivan
Advanced Analytics Program Manager at Janssen Pharmaceutical Companies of Johnson & Johnson

Rajib Malla
Senior Manager at Intas Bio Pharmaceuticals

Regine Eibl-Schindler, Ph.D.
Professor at Zurich University of Applied Sciences

René Labatut
Vice President of Biologics Technology Innovation Strategy at Sanofi

Stefan Safta
GMP Fermentation Group Manager at Octapharma

Susan Dexter
Chief Technical Officer at Sonnet BioTherapeutics

Suzanne Farid, Ph.D.
Professor at University College London

Weichang Zhou, Ph.D.
Chief Technology Officer and Executive Vice President at WuXi Biologics

The Biologics Industry and Process Intensification

The Growing Promise and Potential of Biologic Therapies

The molecular biology revolution of the 20th century offered promise for better and wider treatment of human diseases. These efforts ultimately spawned the modern biotech and biopharmaceutical industries, which have since produced some important therapeutics, like Humira®, Rituxan®, and Enbrel® (Stone, 2020). While it has been decades since the first biologic therapeutics hit the market in the 1980s, we are only now beginning to grasp the enormous breadth of opportunities that remain for diagnosing and treating human diseases with biologics (Oxtoby, 2019).
As new targets and mechanisms emerge, biologics are expected to represent an increasing percentage of new drugs, especially innovator drugs and those with orphan indications (Kinch, 2015) (Darrow et al., 2020).

Additionally, many industry experts anticipate the number of biologic drug approvals to further increase as new modalities—such as gene therapy, cell therapy, RNAi, mRNA, and bi-specific antibodies—mature and more candidates enter the clinical pipeline.

The Next Stage of Production: Process Intensification

As every industry matures, there exists a constant pressure to optimize and improve manufacturing processes to respond to increasing demand, complexity, and competition. Biopharma is no exception, as more and more biologics are approved to treat various conditions and older patent exclusivities expire.

To meet growing needs, manufacturers often gravitate towards process intensification. With this approach, an organization reviews its production processes and sites to identify areas of potential improvement that can increase productivity, reduce timelines, downsize process footprint, lower cost of goods, and | or unlock additional manufacturing flexibility.

As the biologics industry continues to mature, more organizations will need to intensify their biomanufacturing and bioprocesses. In doing so, a greater number of individuals will realize the benefits of moving to intensified processes and facilities in order to remain competitive. Even now, many leaders in the biologics space have already intensified processes or are actively doing so.

Why Intensify a Bioprocess?

In the end, the goal for biologic drug manufacturers is always to bring more high-quality therapeutic products to more patients, faster, and at lower cost. As organizations discover new drugs that treat common, debilitating, and | or chronic diseases, there will be greater need to provide those medicines to more people. Yet, demand alone does not make a blockbuster drug — meeting that demand does. Thus, many choose to intensify their bioprocess in order to prepare their organization to deliver on the promise their drug offers.

With unpredictable and changing environments, manufacturers need to be prepared to increase product scale massively and | or accelerate time to market. This is particularly true for infectious diseases when emerging pathogens arise. There is no clearer example of this than the COVID-19 pandemic. While devastating, it has showcased both the incredible power of biologics (namely vaccines and antibody therapeutics) and the need to mobilize in a matter of weeks to save countless lives.

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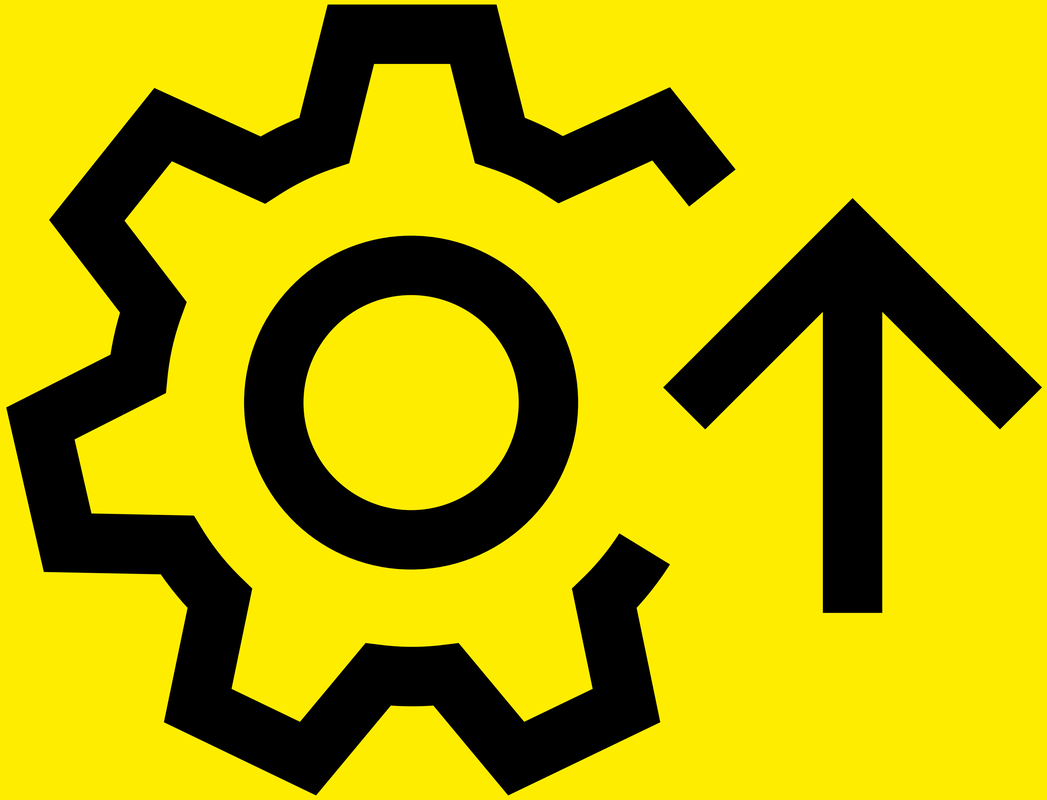
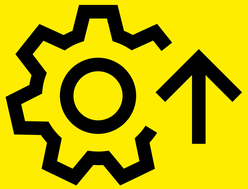
Increasing Productivity

This chapter will discuss process intensification as it relates to increasing total process productivity. Therefore, this productivity discussion includes insights for increasing bioreactor titers, maximizing capture efficiency, and avoiding material loss, culminating in greater final collected product amounts.





Key Considerations and Questions for Intensifying Process Productivity

- What scale of material do you need in the short and long term, factoring in clinical trials and product launches?
- What is your total potential market? Could you pursue additional approvals for other indications down the road?
- How stable is your product?
- Can your downstream process manage upstream productivity without bottlenecks?
- Do you have the time and resources for process R&D?
- Have you considered or conducted trials of bioprocess data analytics software to further develop your process?

When manufacturers consider process intensification, they usually think first about increasing productivity. In the context of biomanufacturing and bioprocesses, what does productivity really mean? In general terms, increasing productivity means making more of a biological product relative to a standardized metric—often volumetric titer (grams/liter) or product mass per cell utilized (grams/cell). However, increased productivity can also describe generating the same amount of material in a shorter time period, with a smaller manufacturing footprint, or at lower cost (Whitford, 2020). For the purpose of this chapter, we will focus our productivity considerations on volumetric and cellular optimizations for biopharmaceuticals, while exploring the remaining definitions in subsequent chapters focused on manufacturing timeline (Chapter 2), footprint (Chapter 3), and cost of goods (Chapter 4), respectively.

Advantages of N-Stage Perfusion Bioreactors

While a growing number of bioprocesses include perfusion approaches (Bielser et al., 2018), the biologics industry standard remains traditional fed-batch culture. However, when designing your bioprocess, selecting between fed-batch and perfusion N-stage bioreactors represents a key decision point.

"Intensifying a bioprocess by implementing perfusion-based bioreactors can offer as much as a three- to ten-fold improvement in volumetric productivity, depending on scale and the molecule. Perfusion approaches facilitate these productivity increases largely by enabling much higher viable cell densities (VCD) in the final bioreactor through constant cycling of cell culture media" (Bausch et al., 2018). Jonathan Haigh, Ph.D., VP of Process Development at FUJIFILM Diosynth Biotechnologies, also notes that the nature of perfusion bioreactors—where product is harvested throughout the process as opposed to at its end—facilitates "scaling with time within the same perfusion-enabled facility, as opposed to transferring to a facility with larger physical vessels." While this feature can offer advantages for footprint reduction (discussed further in Chapter 3) or improved product quality (as the residence time of the product residing within the bioreactor is reduced), manufacturing in perfusion mode for larger batches (>15 KL) may require longer timescales, which may be prohibitive.

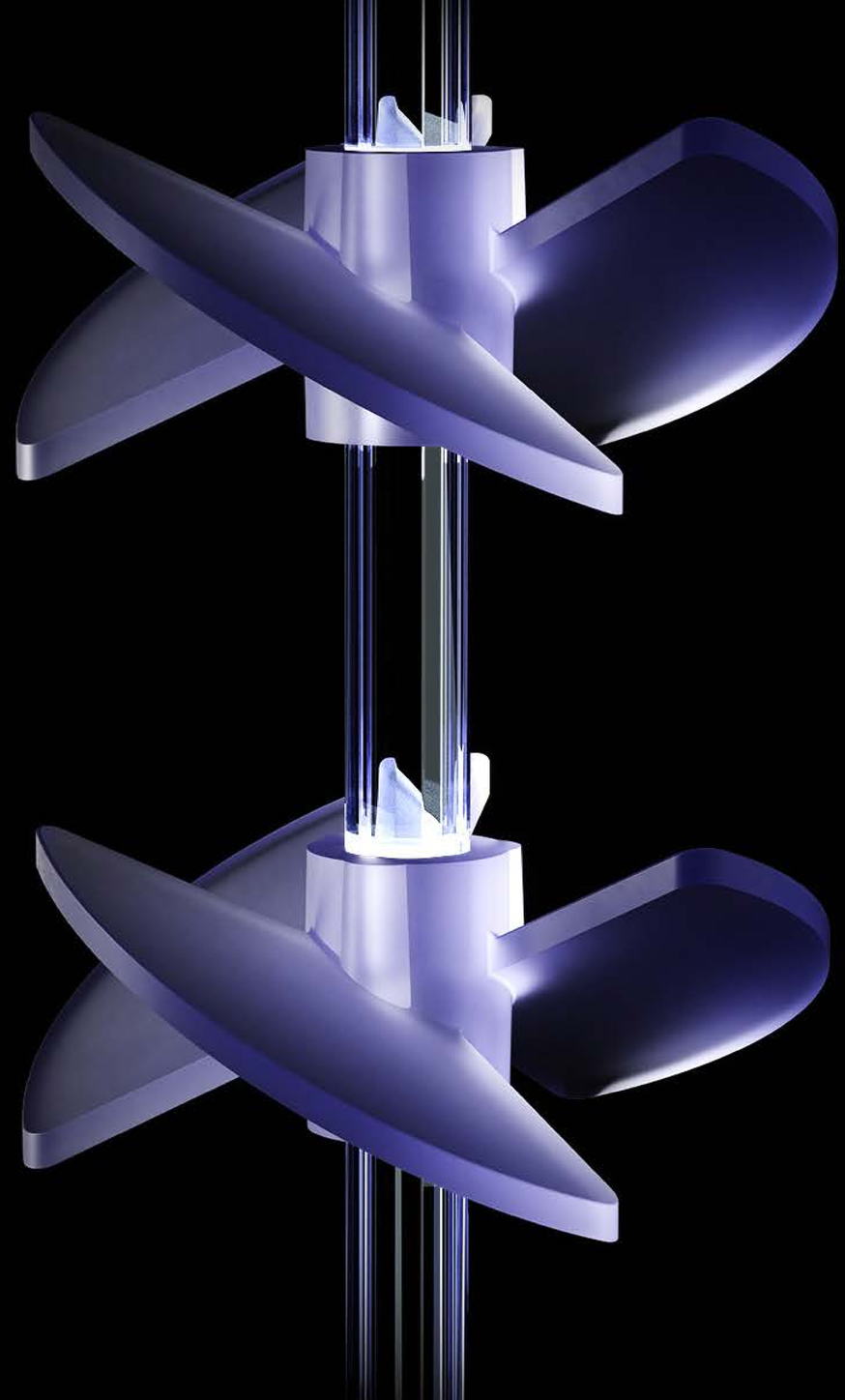
Overarching Considerations:

What scale of material do you need in the short and long term, factoring in clinical trials and product launches?

What is your total potential market? Could you pursue additional approvals for other indications down the road?

Consideration for
Increasing Productivity:

How stable is your product?



Where product demand is massive and on a shorter time scale, large stainless steel fed-batch bioreactors can still offer an advantage. This is largely true for organizations with existing traditional stainless steel facilities, where the infrastructure investment already occurred and production processes are well established.

By cycling fresh media, perfusion bioreactors maintain a more consistent cellular environment, which can lead to improved critical quality attributes. These can include reduced post-translational modifications (e.g., glycosylation) and charge isoforms, as well as decreased heterogeneity in harvested biomolecules (Bausch et al., 2018 | Walther et al., 2018). Perfusion also reduces the incidence of cell lysis, which spills host cell contaminants into the media. Reducing cell lysis simplifies purification and minimizes enzymatic digestion of product. Additionally, generated biomolecules spend less time sitting in the bioreactor, since perfusion processes harvest product throughout a manufacturing run. In turn, this reduces interactions with cellular byproducts and media components that can lead to material degradation.

An Inside Look at the Benefit of Perfusion Bioreactors for Sensitive Biologic Therapies

Sonnet BioTherapeutics, a developer of immunomodulatory therapies, adopted perfusion in their biomanufacturing to improve product quality and stability. Sonnet's first-wave drug pipeline includes five cytokine-derived candidate therapies; these types of molecules are notorious for being proteolytically active. "We have implemented a perfusion process upstream to keep the product integrity intact over the course of the manufacturing process," said Susan Dexter, Sonnet's Chief Technology Officer.

Sonnet selected perfusion for its ability to generate more robust process yields. "We had initially implemented a 14-day fed-batch protocol, that doubled the material from day 10 to day 14, however, product quality was diminished, due to protein degradation that occurred in the fed-batch process," said Dexter. Despite cutting overall bioreactor yields by harvesting four days earlier, the 10-day harvest maintained better product quality, resulting in better starting material downstream with lower host cell contaminants, while improving overall process yield. These data ultimately showed that perfusion could offer tremendous benefits over fed-batch.

Susan Dexter
Chief Technical Officer at
Sonnet BioTherapeutics, Inc.

With greater consistency, simplified purification needs, and reduced degradation, perfusion bioreactors often mitigate material loss and increase output quality. These advantages are particularly stark when manufacturing more sensitive biologics, like enzymes, proteolytically-active proteins, and mRNA therapeutics, that have a tendency to degrade more rapidly. For an example of this principle in action, check out the call-out box on sensitive biologics.

While these features explain why many have adopted perfusion bioreactors, it is important to remember that perfusion comes with additional complexities that can offset greater volumetric productivity. In particular, the media cycling essential to perfusion leads to dramatic increases in media use, escalating costs. Similarly, if users continuously harvest product from their N-stage perfusion reactor with a continuous or semi-continuous downstream capture step, users will likely end up using greater buffer volumes as well (discussed further in Chapter 3). The increased amount of liquid handling also requires greater investment and infrastructure for media and buffer management, which can quickly complicate manufacturing. For these reasons, many still rely on traditional fed-batch systems for well-established and stabler modalities needed in massive quantities, like blockbuster monoclonal antibodies.

Comparison of Perfusion and Concentrated Fed-Batch (CFB) Bioreactors

While the discussion above indicated relative strengths of perfusion compared with traditional fed-batch approaches, it is also important to discuss concentrated fed batch (CFB), an intensified fed-batch process that also increases productivity.

Like perfusion processes, concentrated fed-batch techniques perform media cycling and viable cell retention through the use of alternating tangential flow (ATF) filtration devices. As a result, CFB reactors can increase VCD and batch productivity significantly over traditional fed-batch reactors (Yang et al., 2016). According to Mandar Dixit, Principal Process Expert at Sartorius, concentrated fed-batch processes can have titers two to three times higher than traditional fed-batch.

Many users make the decision to intensify an existing process using CFB because the process change between fed-batch and CFB is smaller compared with switching to perfusion from fed-batch. This means that users can often more readily modify their existing site infrastructure, including cell culture suites and existing bioreactors, to work with CFB. As such, intensifying by establishing CFB may require less investment.

The key difference between CFB and perfusion is that the ATF returns concentrated product to the reactor in CFB rather than removing the product from the reaction. This means CFB users harvest product from the bioreactor at the end of a production cycle, just as they do with traditional fed-batch. This means that CFB does not offer the same advantage to sensitive modalities that perfusion does.

In short, CFB ends up somewhere in between traditional fed-batch and perfusion. Like perfusion, it generates increased titers with higher media expense and process complexity (Xu et al., 2017), but its similarity to fed-batch means it requires less overall change to an existing fed-batch process.

Consideration for Increasing Productivity:

Can your downstream process manage upstream productivity without bottlenecks?

Intensifying Downstream Processes

The Importance and Challenge of Matching Upstream and Downstream Productivity

It is critical that your downstream process can handle upstream scale and subsequent productivity increases that occur during intensification. Carefully matching the two process stages eliminates cumbersome bottlenecks.

This concept is taken to an extreme for manufacturers interested in moving towards continuous bioprocesses. While continuous processes can offer productivity increases (~30 percent and beyond) by maximizing downstream flow rates, they often require advanced automation and logistics to reach this benefit. Many manufacturers also opt for "connected" processes instead, which include surge tanks and bioreactor batch pooling. This approach unlocks some of the benefits of fully continuous processes without the greater challenge of having bioreactors directly flow into downstream steps. Jon Coffman, Ph.D., Senior Director of Bioprocess Technology and Engineering at AstraZeneca, expects an off-the-shelf, truly continuous downstream system to be the "next big thing" in process intensification.

Downstream Technology Advancements: Multi-Column Chromatography and Rapid Cycling Chromatography

In addition to experimenting with downstream parameters, vendors have worked to produce purification systems that increase downstream productivity, building on traditional column and membrane chromatography. The clearest examples of these advancements are multi-column chromatography and rapid-cycling chromatography.

Multi-Column Chromatography Expands Capacity and Productivity

Multi-column chromatography (MCC) increases capacity and productivity (roughly three- to five-fold) by purifying harvests on multiple columns (either parallel or sequential), rather than a single one. The most advanced MCCs provide potential for truly continuous column chromatography, while also better maximizing resin utilization. Many users find the adoption of MCC ideal, due to its close similarity with traditional chromatography and its built-in capacity to scale up. With MCC systems, like the BioSMB platform, "it's the same chromatography process. It's just done more efficiently. So, it's a relatively acceptable way and an easy step to take on the path to process intensification," said David Johnson, Head of Chromatography at Sartorius.

Advancing Membrane Chromatography With Rapid-Cycling Chromatography

Separate from column and resin use, membrane chromatography has a long history in bioprocesses, particularly during polishing steps, where it is complementary to column purification. However, its technological advancement has led to increased application of membrane chromatography as a direct replacement for columns (Orr et al., 2013). Many users now enjoy the use of membrane chromatography due to higher flow rates, excellent selectivity, the elimination of column management, and applicability for certain large and more complex modalities (like viral vectors) where purification yields are lower (Boi, 2019). Historically, the major limitation of membrane chromatography has been lower capacity compared to columns, which has prevented its wider adoption. However, **rapid-cycling chromatography (RCC), where membranes are rapidly cycled throughout purification, provide the benefits of membrane filtration but at greater capacity.** With RCC, an individual membrane can be recycled over 100 times in the same day, compared to ~1-3 cycles with resin. In addition, membranes are relatively cheap to use up and discard. This is especially valuable for purification efforts in pre-clinical and early clinical stages, where expensive resin columns must be purchased, used lightly, and stored for purification cycles needed in later clinical studies. However, if the molecule does not advance further to the clinic, the resin is not used for its full life cycle, becoming a sizable sunk cost. Johnson indicated that viral vector purification might end up being a key RCC utilization, due to notoriously low virus yields when purified by column chromatography. That said, the industry needs to see more proof points before adopting RCC for viral vectors and other complex modalities more widely.

Consideration for Increasing Productivity:

Do you have the time and resources for process R&D?

Process Development: Improving Productivity by Optimizing Process Materials

Biomanufacturers should also consider undertaking intensifications that improve cellular productivity or final product yield that deal directly with key material components within your process. Process intensifications like those achieved with cell line development, media | buffer optimization, and resin | membrane selection, can offer profound improvements.

An Inside Look at Optimizing Perfusion Productivity With Cell Line Development

Jon Coffman, Ph.D., Senior Director of Bioprocess Technology and Engineering at AstraZeneca, indicated that by implementing perfusion without changing any other components, his team was able to see approximately a three-fold improvement in process productivity. However, they are not finished yet, setting their sights on even greater improvements. To achieve this, his team is actively researching cell line clone selection. Dr. Coffman indicated that this exercise represents a sizable part of getting between five- to 10-fold improvements. To reach this level of productivity, "I think you're going to have to fiddle with the cell line and then choose clones differently than you did for perfusion fitness," he said.

Jon Coffman, Ph.D.
Senior Director of Bioprocess Technology and Engineering at AstraZeneca

Consideration for
Increasing Productivity:

Have you considered or conducted trials of bioprocess data analytics software to further develop your process?

Manufacturers need specific processes in place to obtain a license for a therapeutic used in clinical research and beyond. Changing the cell line, media, or other key material components represents a major change in a process. This means regulatory agencies will often require sizable comparability studies and a new submission to re-license your intensified process (discussed further in Chapter 2). **Manufacturers need to make the decision to begin process development efforts as soon as possible, by considering whether they can afford the R&D labor, cost, and time spent upfront and whether the potential increases in productivity are worth it relative to expected product demand.**

Using Predictive Modeling and Data Analytics to Find Ideal Optimizations in Process Development

The use of predictive modeling and data analytics are another major factor when deciding whether to invest in process R&D and where to focus your attention. Naturally, accurate modeling can help provide more quantitative expectations for process development, which ultimately helps users weigh productivity increases against their upfront investment. Admittedly, accurate predictive modeling requires experience and expertise, which your team may lack. In this circumstance, seek out organizations and individuals who can partner with you to fill this gap. As Himanshu Gadgil, Ph.D., Chief Scientific Officer and Whole-Time Director at Enzene, put it, **"Collaborate, collaborate, collaborate! If you think that you can do everything just by yourself, you're just unnecessarily putting a lot of burden on yourself."**

Undergoing intensification of your process through component optimization means you need high-throughput data collection, management, and analysis capabilities, which can then help feed future data modeling activities as well. Finding an ideal process for your biologic therapy likely will require analyzing data for a large number of manufacturing conditions. In particular, users need to be able to accurately measure VCD and final yield productivities in relation to changing process parameters. Additionally, users will want to perform Process Assessment Technology (PAT) (Reid et al, 2012) (US FDA, 2004) (Glassey et al., 2011) and Design of Experiments (DoE) (Sartorius, 2020) analyses to understand how quality attributes and productivity relate to process parameters. Naturally, advanced tools like analytic software and real-time data collection (such as viability measurements using in-line Raman spectroscopy) make vital data collection and analysis easier. While both of these examples incur greater upfront costs, they simplify process analysis and later streamline monitoring efforts during commercial manufacturing.

An Inside Look at Data Analysis Software

It can be difficult to understand how high-throughput data analytics software, like SIMCA®, offer ROI. Because users can't envision how the software generates tangible benefits without actually using it, many choose to go without, according to Patrick O'Sullivan, Advanced Analytics Program Manager at the Janssen Pharmaceutical Companies of Johnson & Johnson. That said, data modeling and analytic software has repeatedly paid productivity dividends for O'Sullivan's work and team.
For example, data analytic software helped reveal an opportunity to increase productivity by 2-4 percent by changing downstream parameters. While some required encouragement to implement the changes at first, Patrick's team was able to simulate the suggested change with data and modeling, eventually convincing the group to run trials. O'Sullivan excitedly mentioned the thrill of finding clear optimizations with large ROI for Janssen's bioprocesses, "Once you find one thing that works, you're hooked."

Patrick O'Sullivan
Advanced Analytics Program Manager at Janssen Pharmaceutical Companies of Johnson & Johnson

“Collaborate, collaborate, collaborate!
If you think that you can do everything
just by yourself, you’re just unnecessarily
putting a lot of burden on yourself.”

Himanshu Gadgil, Ph.D.
Chief Scientific Officer
and Whole-Time Director
at Enzene

Upstream Parameters to Optimize: Cell Line Development, Clone Selection, and Media Optimization

The first goal of process R&D is to find a high-performance cell line clone that grows to high titers quickly, while producing large amounts of target material per cell. Several experts indicated that many cell lines can readily handle the switch from fed-batch to perfusion but optimizing for perfusion can offer some tangible improvements in some cases. In addition, it is especially important in perfusion processes that the cell line clone pair with a media that further maximizes production (Mayrhofer & Kunert, 2020). Perfusion users should also monitor their cell-specific perfusion rate (CSPR) and bleed rates to optimize productivity (Castan et al., 2018). Perfusion users must also balance the costs of media at this stage to make sure the productivity gains are not drastically outweighed by massive increases in media cost. That said, frequent media replacement can mean that the cells do not fully consume their media, so manufacturers can sometimes utilize less nutritious media or less frequent media replacement in perfusion to cut costs without a drop off in productivity.

Downstream Parameters to Optimize: Buffer, Resin, Membrane, and Flow Rate Optimization

Similar to optimizing media components and cell clones, manufacturers can gain sizable productivity benefits by experimenting with downstream process parameters such as buffer composition, product loading, flow rate, elution rate, capture resins, and membrane materials. As discussed earlier, analytical tools can play a central role in identifying these opportunities. As a clear example, small changes in anions or cations in buffer salts can massively impact column capture efficiency and capacity. As with media, there remains a balance between improving the buffer and keeping buffer costs and management low.

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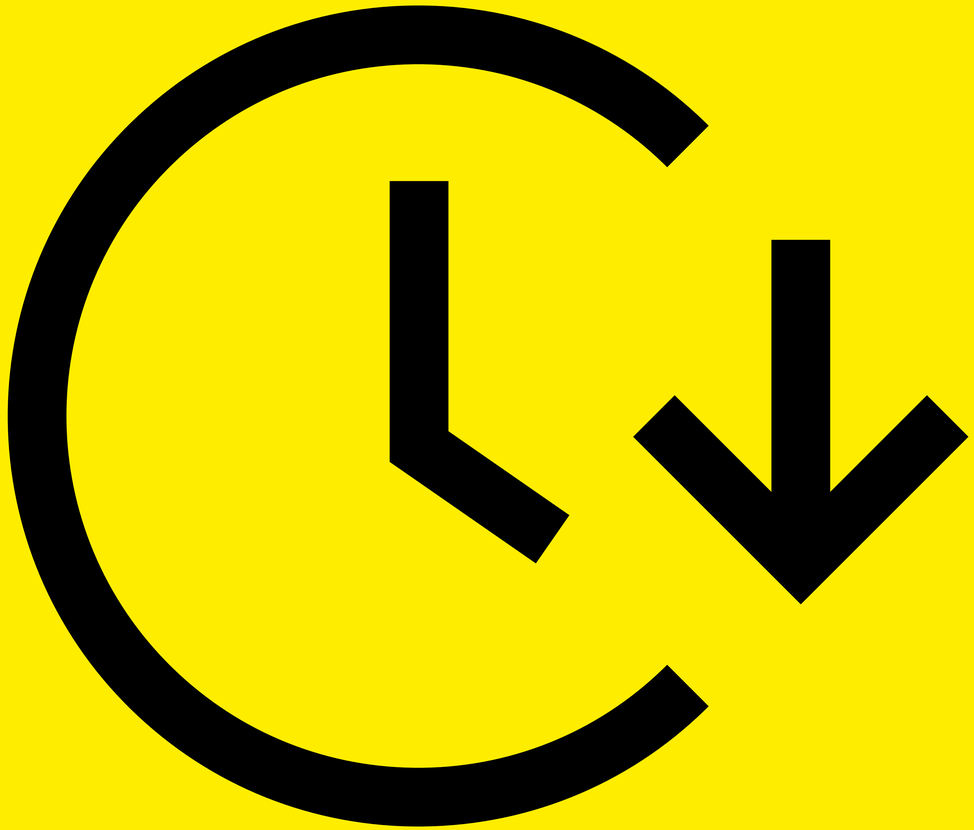
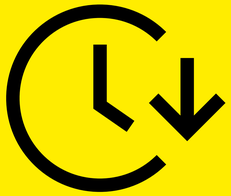
Shortening Timelines

This chapter will discuss the ways that process intensification can reduce timelines on multiple levels—shortening start-to-finish batch processes and accelerating time to market.





Key Questions to Consider When Intensifying Process Timeline

- Is there a target batch production speed that you would like to achieve?
- How can you balance shortening batch production with managing risk and complexity to streamline regulatory approval?
- Do you have the resources (time, labor, and capital) to make the up-front investment in intensified process development and reap rewards later?

In any highly competitive market, time is of the essence. This is undoubtedly the case for biotechnology and pharmaceutical companies, which have seen continued demand for novel, highly specific treatments. This demand often comes with great urgency, even when patient cohorts require smaller quantities of each individual product. Timelines are particularly important in pre-commercial phases because being first to market can have massive benefits in terms of capturing market share.

There are multiple angles to consider when addressing the timeline of your biomanufacturing process. Most obviously, intensified bioprocessing can result in a shorter overall process run, thereby allowing manufacturers to produce more batches in the same amount of time without sacrificing yield or quality. In addition, it is always important to factor in time to market when considering the costs and benefits of process intensification. In many cases, intensification can make it easier to scale up, minimize risks, and pave the way to a faster regulatory approval. However, some intensification technologies introduce additional failure modes, necessitating especially robust risk management strategies.

Intensifications for Shortening Process Timeline

Upstream intensifications that expedite timelines generally do so by eliminating growth steps or reducing the number of production days required in the N-stage production bioreactor. Factors to weigh when choosing intensification technologies include ease of implementation, downstream processing capacity for additional product, and ability to manage added process complexity.

High-Density Cell Banking Increases Viable Cell Density and Eliminates Growth Steps

High-density cell banks can reduce the number of growth steps required in the seed train, since traditional processes often start with a single cryopreserved vial that requires lengthy thawing and expansion times. **Depending on other parameters such as final production bioreactor volume, high-density cell banking can reduce seed expansion time by as much as one third, saving 10 days or more** (Horry et al., 2019). Susan Dexter of Sonnet BioTherapeutics, an immunomodulatory therapy drug developer, found that high-cell-density (20 million cells/mL) inoculation of the N-1 seed bioreactor shortened their production schedule by up to six days. High-cell-density culture techniques are relatively easy to combine with other intensifications such as perfusion and concentrated fed-batch.

Consideration for Shortening Timelines:

Is there a target batch production speed that you would like to achieve?

N-1 Perfusion Reduces Time in Production Bioreactor

For many manufacturers, implementing perfusion at the N-1 bioreactor stage while otherwise maintaining a fed-batch process is an attractive hybrid option. Adding bioreactor capacity can be costly and time intensive, so shifting to N-1 perfusion can reduce the potential for upstream bottlenecks when scaling up a process. Overall, N-1 perfusion can reduce time in the production bioreactor by approximately five days (Castan, 2019).

Compared to many other intensification options, including dynamic perfusion, N-1 perfusion is relatively easy to implement. It requires minimal equipment changes, and it is usually possible to adopt the same cell line clones used in fed-batch bioreactors. It also presents fewer separation challenges. However, Andrew Sinclair, President and Founder at Biopharm Services, a developer of process analysis and economic modelling tools, cautions that manufacturers must be prepared to manage higher amounts of product on the downstream side following the intensification of the N-1 step, especially when retrofitting a process that is already underway.

“Compared to many other intensification options, N-1 perfusion is relatively easy to implement. It requires minimal equipment changes, and it is usually possible to adopt the same cell line clones used in fed-batch bioreactors.”

Andrew Sinclair
President and Founder
at Biopharm Services

Dynamic and Steady-state Perfusion Processes Are Much Faster, But More Complex

According to Mandar Dixit, Principal Process Expert at Sartorius, dynamic and steady-state perfusion processes can be up to 10 times faster than producing the same amount of product using traditional fed-batch processes. Like concentrated fed-batch, dynamic and steady-state perfusion have more failure modes and introduce greater operational complexity compared to traditional fed-batch culture (Castan, Ohrvik, & Nelson, 2018). In particular, longer or continuous process runs have greater risk of microbial contamination. This is made more problematic since continuous processes don't have "batches" in the traditional sense. Meaning, if contamination occurs, it can be more challenging to determine what product must be pulled. Additionally, long, continuous processes using single-use systems must fully evaluate bag stability to ensure extractables and leachables do not enter the reaction. It's important to weigh these complications against the potential gains. If you proceed, look for ways to offset these risks in other aspects of your process design.

"Dynamic and steady-state perfusion processes can be up to 10 times faster than producing the same amount of product using traditional fed-batch processes."

Mandar Dixit
Principal Process Expert
at Sartorius

An Inside Look at Shortening Process Development With Multi-Parallel Bioreactor Systems

As mentioned, process development is time-intensive, especially as users seek to experiment with multiple process changes. Some users are overcoming this burden with sophisticated multi-bioreactor or multi-parallel bioreactor systems that include in-line data collection. These systems enable users to pilot bioprocess in a much higher throughput setting to arrive at higher productivity sooner.

Stefan Safta, GMP Fermentation Group Manager at Octapharma, a human protein manufacturer, is a firm believer in the benefits of these technologies. "Multi-bioreactor systems are increasingly important as every process needs to be developed using DoE. What Sartorius's Ambr® and other similar systems do is to fast-track the development and mapping of the process," he said. In fact, he indicated that it is increasingly a "requirement of process intensification to have parallel bioreactor systems." Furthermore, they facilitate "process characterization and development of a control strategy, while maintaining the pressure to be faster to the clinic and market."

Stefan Safta
GMP Fermentation Group Manager at Octapharma

For example, **since perfusion processes can be more difficult to implement, it may be worth investing in additional technologies and services that can accelerate your process development and minimize risk.** These can include specialized bioreactors, such as automated Ambr® systems. These allow manufacturers to proceed with multiple parallel process characterization runs at small scale, saving up to two months of development time and facilitating faster IND application. Consulting services can save you time by assisting with overall process development or with specific steps such as cell line development.

Streamlining Process Changeover and Equipment Installation with Single-Use Technologies

Switching from stainless steel to single-use technologies can allow facilities to produce more batches in a shorter amount of time. Stainless steel bioreactors require intensive cleaning between batches, which can take two to four weeks. Single-use technologies eliminate these steps and make equipment changeover more streamlined when switching between biologic products or scaling up production of the same molecule. In some cases, manufacturers can start a new

batch within just two days. Additionally, many users report that single-use technologies are faster to install and easier to use than their stainless steel counterparts (Shukla & Gottschalk, 2013).

Accelerating Time to Market

Early Implementation and Communication Expedite Regulatory Approval

In cases of biosimilar development, optimizing the speed of batch production over volumetric productivity can lead to faster regulatory approval and greater overall benefit. "Biosimilar companies need to produce enough batches to get around the regulatory hurdles associated with demonstrating biosimilarity to the innovator product. This essentially requires them to make at an absolute minimum six batches of their own product per guidance, but 10 or more is preferable for better statistics during the comparison to perform a similar analysis with the reference products. So, they're incentivized to be able to turn around batches in a short period of time. The regulatory clock comes with deadlines," said Kurt Brorson, VP, Technical at Parexel, who formerly worked for the United States Food and Drug Administration (FDA) and is now an expert process consultant for many companies in the biotech and pharma industries.

Experts agree that manufacturers considering process intensification for new products should implement it as early as possible in the molecule life cycle—ideally during or before phase I clinical trials. For approved products, companies that are intensifying to meet increased demand must account for the extent to which each new technology introduced can slow re-licensing procedures.

Customers and industry experts report that process intensification requires early communication with regulators, well before filing an application. The landscape is promising for these dialogues. For example, the FDA has indicated a willingness to engage with intensified processes through the release of guidelines on related topics, such as continuous manufacturing (CDER, 2019).

Consideration for Shortening Timelines

How can you balance shortening batch production with managing risk and complexity to streamline regulatory approval?

When the time comes to submit applications to regulatory agencies, it is not safe to assume that all regulators are familiar with any of the intensified technologies implemented. As a result, it is important to explain these as clearly and succinctly as possible, emphasizing robustness, reliability, quality control, process monitoring strategies, and improvements over previous technologies.

"Process intensification will give you a very high level of knowledge of your process, which by itself has value. You will go faster, have fewer surprises, and be able to address liability better," said René Labutat, VP of Biologics Technology Innovation Strategy at Sanofi. "Regulatory bodies like the FDA expect better cost and risk management from companies that have intensified processes. They like to see that people have a very high-level knowledge base."

Risk Management Through Analytics and Minimizing Tech Transfer

Chapter 1 discussed the value of analytical and monitoring tools for optimizing process development for productivity. These technologies can also save time by minimizing risk. Real-time monitoring can prevent cascading mistakes that could otherwise require facilities to restart entire batches, losing weeks or months. Furthermore, demonstrating robust risk management is part of crafting an attractive regulatory package.

According to Andrew Sinclair of Biopharm Services, some of the other benefits of process intensification—especially increased productivity and reduced footprint—can allow manufacturers to reach late-stage clinical trials while still producing their molecule at the same scale of equipment that was used in initial research and development experiments. Minimizing technology transfer in this way dramatically reduces risk and can help avoid delays and hurdles in the licensing application process, since technology transfer often introduces failure points and attracts increased scrutiny from regulators.

"Process intensification will give you a very high level of knowledge of your process, which by itself has value. You will go faster, have fewer surprises, and be able to address liability better."

René Labatut
VP of Biologics Technology Innovation Strategy at Sanofi

In Focus: Small Biotech and Pharma Companies

"For development-stage, publicly listed companies like Sonnet, it is critical to remain nimble and execute within a timeframe that investors find compelling." – Susan Dexter, Chief Technical Officer at Sonnet Biotherapeutics.

Smaller companies are more likely to have everything riding on a discrete number of molecules. This further incentivizes teams to produce these molecules as quickly as possible, in order to generate a sustainable stream of commercial revenue. As a result, saving time at every individual step from R&D to commercial manufacturing can mean the difference between success and failure.

However, implementing process intensification requires what Dexter calls "runway" on the front end—time and financial resources available to invest in intensified technologies and process development. It is crucial for small biotech and pharma companies to accurately assess whether they have the short-term capacity to reap the long-term benefits of process intensification.

Overarching Consideration:

Do you have the resources (time, labor, and capital) to make the up-front investment in intensified process development and reap rewards later?

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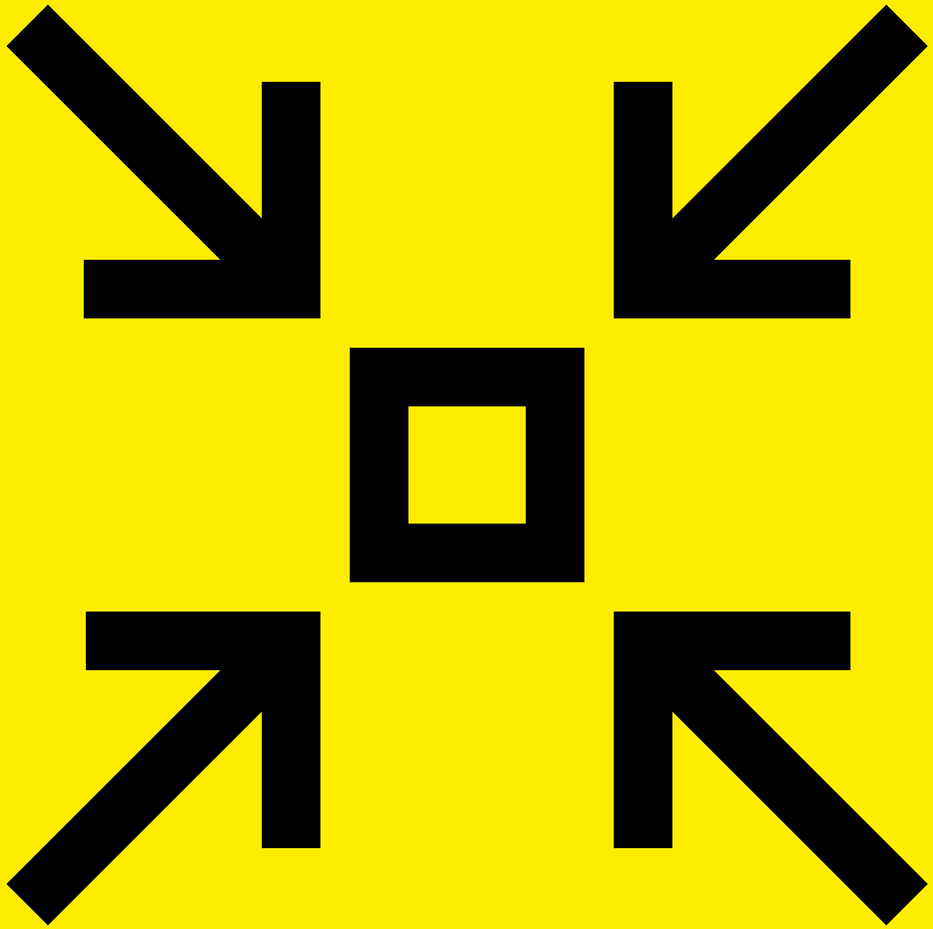
Reducing Footprint

In this chapter, we discuss another rich target for process intensification: manufacturing footprints.

Used wisely, various intensification strategies can be used to conserve space and resources without limiting the long-term productivity, flexibility, and profitability of the site.



Key Questions to Consider When Intensifying Process Timeline

- Do you intend to perform cell banking on site? What does your seed train look like?
- What is your ratio of seed trains to N-stage bioreactors?
- How much media and buffer do you need for your bioprocess to reach the target scale and future maximum scale?
- Do you intend to prepare solutions in-house or purchase premade buffers?
- Do you have the capital for installing in-line conditioning systems?
- Have you considered optimizing productivity to permit downscaling of bioreactor size?

It's no surprise that a manufacturing facility and its infrastructure make up one of the largest components of upfront | overhead cost for biologic production. Upgrades require a major investment, whether you're developing in an existing space, expanding a site, or creating an entirely new facility. Conversely, inaction comes with a price: The size and layout of your space can be a limiting factor for long-term productivity, revenue, and profit.

Given its integral role in site success, the footprint of a bioprocess is a rich target for process intensification. Done well, it allows biomanufacturers to minimize their overhead facility costs, increase space utilization, and minimize the costliest spaces found in GMP facilities, such as cleanrooms. Having a smaller bioprocess footprint also allows organizations to rapidly deploy new production lines and | or whole facilities.

Three Common Strategies for Reducing Process Footprint

1. Seed Train Footprint Reduction: Cell Banking & N-1 Perfusion

Reducing seed train size and complexity is a relatively straightforward mechanism for process intensification (Wright et al., 2015) (Tao et al., 2011). Perhaps the clearest example is through the use of off-site cell banking. A number of bioprocess service providers now offer cell banking services, where master cell banks (MCB) and | or working cell banks (WCB) are generated and stored in GMP facilities. These services can free up significant capital and space that would otherwise be invested in on-site incubators, shakers, freezers, liquid nitrogen, and other equipment for generating cell banks or growing a seed chain. Some providers have advanced their cell banking offerings further to include high-cell-density banking (~50-100×106 viable cells/mL) (Zijlstra, 2019). **While safe storage of high-cell-density vials and bags offers massive timeline acceleration, it can also reduce footprint by eliminating even more steps within an individual seed train, particularly when bags can be used to directly seed bioreactors at later seed train stages.**

Separately from cell banking, using an N-1 perfusion bioreactor represents another opportunity to reduce seed train footprint. By growing high cell densities in continuous culture with an N-1 bioreactor, manufacturers can generate more cells for N-stage production bioreactors (Xu, J. et al., 2020) than N-1 fed-batch reactors of equal or larger volume. The high cell densities can also drive a reduction in the total number of seed trains in operation, further reducing the bioprocess footprint (Biopharm Services, 2018) if multiple N-stage reactors are in use.

Considerations for Reducing Footprint:

Do you intend to perform cell banking on site?

What does your seed train look like?

Consideration for
Reducing Footprint:

What does your ratio of seed trains to N-stage bioreactors look like?

Consideration for Reducing Footprint:

Have you considered optimizing productivity to permit downscaling of bioreactor size?

2. Use of Higher Viable Cell Density Bioreactor Systems

High-cell-density bioreactor systems, namely perfusion and concentrated fed-batch reactors, can achieve impressive productivity in smaller bioreactor volumes that occupy less space (Fenge, C. et al., 2018). Perfusion bioreactors can also increase product scale over time. This isn't possible with traditional stainless-steel fed-batch reactors, which are inherently limited by decreases in viable cell density as N-stage reactor time increases (as discussed in Chapter 1 and 2). As a result, manufacturers can use a perfusion bioreactor with a smaller volume compared to other fed-batch reactors—while still reaching the same product mass by running the process longer.

This footprint reduction can be negated if intermediate holding tanks are used ahead of purification and downstream processing. According to Himanshu Gadgil, Ph.D., Chief Scientific Officer and Whole-Time Director at Enzene, hold tanks commonly occupy as much as 60-70 percent of a process footprint. Biomanufacturers considering perfusion for footprint reduction should therefore be prepared to reduce or eliminate holding tanks by implementing more continuous processes.

3. Building Increasingly Continuous Bioprocesses

While more continuous processes come with greater management and logistical challenges, they pay dividends when it comes to footprint reduction. A recent review from Coffman et al. reported that switching from stainless steel batch processes to integrated continuous bioprocesses using single-use bioreactors can provide a 50 percent reduction in process footprint and a 15-20 percent reduction in energy use (2021). However, Andrew Sinclair, President and Founder at Biopharm Services , a developer of process analysis and economic modelling tools, cautioned that you have to look at the whole facility, not just the process line in isolation. **"Automation and instrumentation control are key aspects of making either intensified processing or formal continuous processing work effectively,"** he said.

Manufacturing teams need to capitalize on these footprint benefits by efficiently managing the total process and carefully uniting upstream and downstream elements. For example, Dr. Gadgil's team at Enzene implemented a more continuous process using a perfusion-based upstream that significantly cut hold tanks. **In effect, it reduced their footprint by 60 percent, while increasing productivity and decreasing cost of goods.**

It is important to note that continuous process have historically required embedding processes and piping into a facility, which comes with some loss of site flexibility and longer process implementation timelines despite impressive footprint reductions. Users should factor this tradeoff into their considerations. Continuous modular facility concepts that circumvent these limitations are beginning to gain momentum. Essentially, users purchase a "box" unit for running an aspect of their process that includes the piping and hook-up components that would typically be built into the facility. Individual boxes can be then united to build up to a more continuous process. Importantly, these boxes are not permanently embedded, so they can be moved within one site to minimize | alter footprint or moved to another side as needed. In effect, these modular facilities provide smaller footprints through continuous process implementation, while also increasing site flexibility and reducing continuous process build-up timeline. Though not yet fully realized, it is expected that these kinds of approaches will grow in importance in the coming decade or so. This concept is discussed further in Chapter 5.

“Automation and instrumentation control are key aspects of making either intensified processing or formal continuous processing work effectively.”

Andrew Sinclair
President and Founder at
Biopharm Services

In Focus: Footprint Reduction Benefits for Organizations Large and Small

All organizations are to some extent limited by their size and capital availability. This directly impacts their ability to invest in and acquire manufacturing sites. Despite this, process intensification and subsequent footprint reduction can benefit organizations depending on their goals and scale.

Smaller biopharma companies operating out of compact manufacturing sites can make room for future growth. Larger organizations also maximize their existing space or plan for more efficient site development.

Generally speaking, the set-up involved for a smaller process footprint is faster. In other words, compact sites can get up-and-running sooner with their first production cycle. (Bielser et al., 2018) This increased speed makes smaller sites an attractive option even for some larger organizations that have the capacity to purchase or build more expansive facilities. The COVID-19 pandemic emphasized this value like never before as companies raced to create new sites to meet public health needs.

Lastly, both large pharma companies and CDMOs can use footprint downsizing to increase capacity or make room for additional production lines within an existing site. This allows organizations to produce more batches or a wider product portfolio from one site. This advantage is particularly valuable to CDMOs, since it enables them to fulfill more contracts.

The Elephant in the Room: Overcoming the Burden of Solution Management & Storage

Naturally, the seed train and bioreactors in a production line make up a large component of a given site's footprint. However, it is also extremely important to factor in liquid management and storage when evaluating site footprint utilization. This is particularly true for perfusion bioreactor strategies, which consume greater volumes of media and buffer during the process. More continuous processes take this even further as manufacturers need these solutions around the clock.

Andrew Sinclair, President and Founder at Biopharm Services, a developer of process analysis and economic modelling tools, estimated that for every liter harvested from the bioreactor, **"you need to make, in downstream, probably eight to ten times that volume in solutions. So, that's why there's a lot of capital and operations devoted to it."** Users undergoing process intensification should consider how their decisions affect solution management, while working to devise approaches that minimize the solution footprint.

Increasingly, manufacturers are storing more concentrated media and buffer, which proportionally shrinks footprint. It is important to achieve this benefit without sacrificing stability. In short, a media that can be stored stably at much higher concentrations and thereby massively reduce footprint may outweigh productivity or cost-benefits associated with a different media that can't be stored at higher concentrations.

Sefan Safta, GMP Fermentation Group Manager at Octapharma, noted that Octapharma has seen sizable footprint reduction through the storage of dehydrated media and buffers, which are then hydrated in a GMP process ahead of use. Like concentrated media, users will want to confirm that dehydrated solution storage does not impact stability.

Another popular tactic is to purchase more pre-made solutions (concentrated or otherwise) from trusted suppliers. These can be regularly delivered in sufficient volumes to reduce the amount of solution stored on-site. While convenient, it's important to remember that supply chain disruptions—while rare—can occur.

Manufacturers can also consider building systems into their sites that enable in-line buffer creation and dilution. While they require greater automation and upfront investment, piping and wall connections can massively reduce footprint, especially if they eliminate cleanrooms needed for buffer generation. This option may not be possible for smaller organizations or for biologics in pre-commercial stages.

Downscaling Bioreactor Size With Increasing Cellular Productivity

In discussing bioprocess footprints, it is important to mention the footprint impact of titer productivity improvements from intensification. With greater cellular productivity, manufacturers can opt to shrink their bioreactor sizes without compromising productivity. This downscaling creates opportunities to increase both facility capacity and the number of batches made in the same time period.

Consideration for Reducing Footprint:

Have you considered optimizing productivity to permit downscaling of bioreactor size?

An Inside Look at Solution Management With FUJIFILM Diosynth Biotechnologies

Investment into more efficient solution management has offered tremendous footprint reduction benefits to FUJIFILM Diosynth Biotechnologies (FDB), a biopharmaceutical CDMO that provides process development and cGMP services to a worldwide client base. Jonathan Haigh, Ph.D., VP of Process Development at FDB indicated that his team has explored and successfully implemented new strategies to reduce solution footprint. In particular, they focused on advancing their approaches to buffer management, as buffer generation, storage and disposable occupied 60 percent of their existing facility footprint. Haigh said their sites were moving towards the utilisation of pre-made concatenated buffers, made in-house or sourced through GMP-approved supply chains. Furthermore, FDB have developed in house a multi-functional bioprocess skid called SymphonX™, capable of in-line dilution and conditioning on-demand and directly at the point-of-use combined with a range of unit operations. "A large part of our overall process intensification is through advancing our buffer management and we have demonstrated significant footprint reduction with this approach".

Regulatory bodies want to see demonstrated batch consistency, so many drug companies can downsize to produce a higher number of batches faster (also discussed in Chapter 2). **Markus Wieland, Head of Product Development at Sartorius, explained that to grow site capacity "you need to try and limit your GMP footprint as much as possible."**

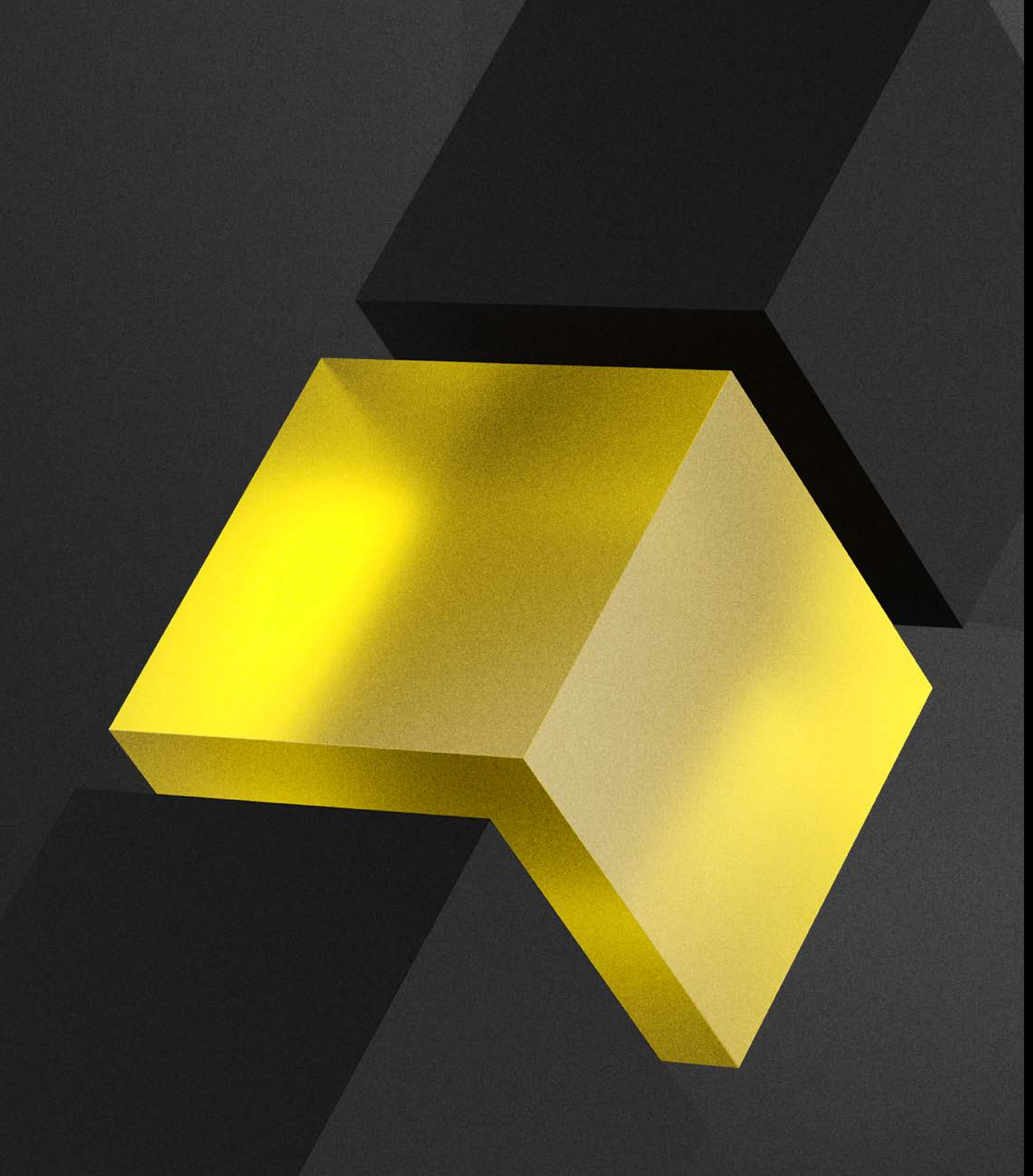
Downscaling and reducing a site's overall footprint offer another advantage: They allow manufacturers to reduce energy and water consumption, particularly around the processes performed in cleanrooms. According to Biopharm's Sinclair, "if you look at the benchmarking studies in our industry and related industries, a lot of the energy requirements for our facilities are based on the fact that we are running our operations in cleanrooms."

Sinclair estimated that maintaining the careful environments of cleanrooms consumed approximately 70 percent of the site's total energy used. **"By shrinking the footprint, you're actually reducing very significantly the volume of these facilities. And we are envisaging quite dramatic reductions in terms of carbon footprint... a very valuable outcome."**

Dieter Eibl, Ph.D., and Regine Eibl-Schindler, Ph.D., two professors at the Zurich University of Applied Sciences (ZHAW) within the School of Life Sciences and Facility Management, echoed this point. Using monoclonal antibodies as an example, their theoretical assessments put energy and water savings from footprint downsizing between 20 percent and 30 percent.

“By shrinking the footprint, you’re actually reducing very significantly the volume of these facilities. And we are envisaging quite dramatic reductions in terms of carbon footprint … a very valuable outcome.”

Andrew Sinclair
President and Founder at
Biopharm Services



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Reducing Cost of Goods

This chapter will help biologics manufacturers consider ways to address cost pressures—current and future—that are specific to their individual company. We will focus on intensifications that can lower overall material and consumable costs, as well as technologies that are cost-effective to implement while offering other benefits that ultimately lower the volumetric product cost.

Closely overseeing manufacturing costs and profit margins is critical for biopharma companies, both for commercial success and to ensure their vital therapies are viable and accessible to those who need them. Intensification can lower costs by making processes more efficient or reducing the overall cost of materials. As competition becomes fiercer in the biopharmaceutical industry, cost savings are increasingly a driving factor in the decision to pursue process intensification.

It is worth noting that many of the other intensification benefits discussed in this report come with cost benefits. For example, reducing footprint can lower overhead costs and make it cheaper to build new facilities. Similarly, increasing volumetric productivity can lower the overall cost per gram of a given product. However, since those benefits are highlighted in Chapters 1, 2, and 3, this chapter will primarily focus on choices that help manufacturers minimize costs directly.

"Most people in the world are not rich, so it is our mission to provide affordable drugs to the patients. That means we have to be mindful of the cost of goods when producing drugs. We must take every opportunity to intensify our process in order to provide affordable, high-quality drugs to our patients, to fulfill the mission of Innovent expressed by our CEO Dr. Michael Yu, 'To develop and commercialize high-quality biopharmaceuticals that are affordable to ordinary people'. "

Kenneth Kang, Ph.D.
Vice President of Manufacturing at Innovent Biologics

Key Questions to Consider When Intensifying Process Cost

- Where are your greatest cost pressures?
- How do you expect your cost distribution to change as you scale up production?
- Do you have the up-front capital to invest in process development and intensification to reap cost benefits later?

Getting Company-Specific With Key Cost Considerations

Specific cost pressures are often unique to each company, based on their manufacturing modality, existing infrastructure, geography, and target market. For example, René Labatut, VP of Biologics Technology Innovation Strategy at Sanofi, noted that companies operating in areas where water is scarce have greater incentive to opt for single-use technologies that eliminate liquid-intensive cleaning steps.

Multiple experts emphasized that cost distributions also vary dramatically with scale. Suzanne Farid, Ph.D., a professor in University College London's Department of Biochemical Engineering, explained that at low production volumes, facility overhead and labor costs tend to dominate the cost of goods. However, as production scales up, raw materials such as reagents (e.g., media, buffer) and consumables (e.g., resins, filters) become the major expense. As a result, when considering process intensification, it is important to think about the production scale you will ultimately need to reach and use that knowledge to inform your priorities throughout your development phase (Pollock et al., 2013) (Pollock et al., 2017).

Farid offered specific projections for how these factors can play out. **"At lower production scales, the cost of goods for mAbs is several hundreds of dollars per gram, but at large scales (tons of material being manufactured) it's more like 50 to 100 dollars per gram. Continued innovation may bring costs closer to tens of dollars per gram,"** she said.

Considerations for Reducing Costs of Goods:

Where are your greatest cost pressures?

How do you expect your cost distribution to change as you scale up production?

“At lower production scales, the cost of goods for mAbs is several hundreds of dollars per gram, but at large scales (tons of material being manufactured) it’s more like fifty to a hundred dollars per gram. Continued innovation may bring costs closer to tens of dollars per gram.”

Suzanne Farid, Ph.D.
Professor at University College London

In Focus: Cost Considerations for Biosimilars and Highly Competitive Markets

By their very nature, companies making biosimilars aim to generate comparable product quality at lower cost. Kurt Brorson, VP, Technical at Parexel, consults with many companies looking into process intensification solutions. He said biosimilar producers are particularly well positioned to benefit from process intensification, due in large part to their need for rapid development cycles.

Ankur Bhatnagar, General Manager at Biocon—a biopharmaceutical company that produces many biosimilars along with other molecules—echoed Brorson's sentiments. "The aim is to get the best quality with an acceptable cost of goods," he said. He also explained that biosimilar producers have more opportunities to adopt new technologies when compared to innovator drug companies. Even for molecules that have already secured regulatory approval, Bhatnagar considers intensification worthwhile when it increases productivity by at least 80 percent or lowers costs by at least 40 percent—thresholds that have been achieved in Biocon facilities.

Ankur Bhatnagar
General Manager at Biocon

"The aim is to get the best quality with an acceptable cost of goods."

Intensifications for Reducing Process Cost

According to theoretical modeling by Dieter Eibl, Ph.D. and Regine Eibl-Schindler, Ph.D., professors at the Zurich University of Applied Sciences (ZHAW) within the School of Life Sciences and Facility Management, **process intensification can offer cost savings of up to 50 percent.** There are multiple routes by which it is possible to achieve these savings. Here we will highlight key differences between several technologies and approaches.

N-1 Perfusion and Concentrated Fed-Batch are Cost-Efficient Intensifications

Manufacturers who already have processes and facilities in place often want to avoid intensifications that require extensive retrofitting.

N-1 perfusion and concentrated fed-batch technologies allow these companies to increase productivity and reduce footprint without making expensive, difficult changes in media, N-stage bioreactors, or downstream processes (Perfusion overview, 2020).

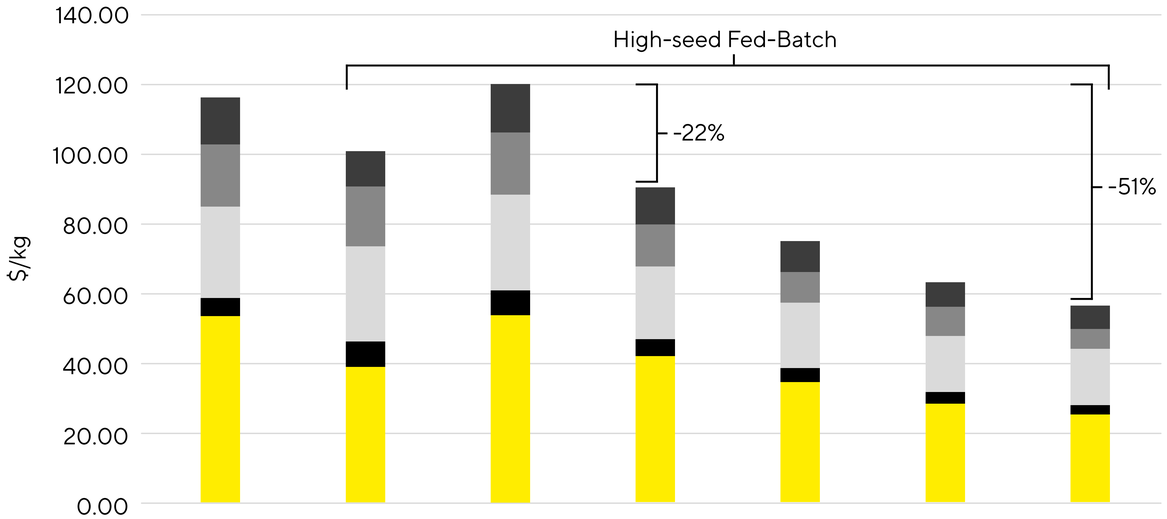
According to modeling by one group of researchers, N-1 perfusion can contribute to cost savings of up to 51 percent (Barna et al., 2020).

Dynamic and Steady-state Perfusion Offer Cost Benefits at Scale

When approaching your process purely from a cost perspective, dynamic and steady-state perfusion primarily offer advantages to manufacturers who expect to reach large production scales. This is mostly because these technologies require facilities to install new bioreactor systems that come with higher media and buffer costs, even though their volumetric productivity benefits can eventually lower product cost per gram.

According to Mandar Dixit, Principal Process Expert at Sartorius, cost advantages of dynamic and steady-state perfusion are generally actualized at the commercial stage, when high productivity in terms of volume or expedited timelines can allow companies to capture majority market share, especially if they can be first to market. In turn, this confers greater ability to control cost and market pressure, making it easier and cheaper to maintain market share in the long term.

Total Cost of Goods



	Traditional 4 g/L	**(pN-1) 4 g/L - 10 day**	(pN-1) 4 g/L	(pN-1) 6 g/L	(pN-1) 8 g/L	(pN-1) 10 g/L	(pN-1) 12 g/L
CoG's ($/g)	116.40	101.20	120.10	90.60	75.60	64.00	57.00
Throughout (kg/yr)	90.18	125.25	90.18	135.27	180.36	225.45	270.54
Batches/yr	18	25	18	18	18	18	18

Capital Materials Consumables Labor Other

Constant production duration 14 days
Control: (pN-1 4 g/L) operated at 10 days
(Barna et al., 2020)

“Process intensification can offer cost savings of up to 50 percent.”

Dieter Eibl, Ph.D.
Professor at Zurich University of Applied Sciences

Regine Eibl-Schindler, Ph.D.
Professor at Zurich University of Applied Sciences

100–300 kg's Process Scenario's — Same Facility Layout for USP

Description	Titer (g/L)	Actual Throughput (kg's)	Production BR Size (L)	Totel No. of Batches	Total No. of Harvest	Total No. of Production BR's	€/g Cost
Fed batch single-use	5	137	2,000	19	19	1	106.44
High Inoculum FB (N-1 Perfusion)	10	254	2,000	22	22	1	71.39
Concentrated Fed Batch	15	346	2,000	16	16	1	78.53
Dynamic Perfusion	1.75	272	1,000	13	195	1	94.62

Process USP	Buffer Volume/ Batch	Media Volume/ Batch	Batches for 100 kg	Total Buffer Volume	Total Media Volume
Fed batch	10,000	2,000	19	190,000	38,000
N-1 High Ino. FB	14,000	3,000	7	98,000	21,000
CFB	28,000	30,400	5	142,500	152,000
DP	15,500	15,200	5	77,500	76,000

Volumes in liters
Source: BioSolve Modeling, Sartorius.

Multi-Column Chromatography Decreases Use of Expensive Resin

Resins, such as Protein A resins commonly used for mAb capture, are often one of the greatest cost pressures for downstream processes. Ankur Bhatnagar of Biocon said these costs can be especially intimidating in the clinical stage. Resins must be purchased up front and may not be completely used up before the company seeks regulatory approval for their product. They become a sunk investment if the product is not approved.

David Johnson, Head of Chromatography Systems at Sartorius, explained that implementing multi-column chromatography (MCC) is a "low-hanging fruit" when it comes to intensifying downstream processes. **"What MCC enables you to do is to process on a much smaller amount of resin and get greater utilization from it. It's a direct, visible saving on the cost of goods.** That's a nice entry point because it replaces one unit operation with another unit operation, but it's not so divorced from the original unit operation to be completely unacceptable," he said. MCC can also reduce buffer quantities required for downstream operations, thereby saving additional material costs.

Automation Reduces Labor Costs and Streamlines Quality Control

René Labatut of Sanofi pointed out that companies often overestimate the extent to which they can cut labor costs without automation. "Cutting the number of bioreactors in half might still leave you using 80 percent or more of your labor," he said.

But as the industry moves towards Bioprocessing 4.0, "cyber-physical systems" that implement cloud computing, connected systems, and digital process control will continue to become more of a reality (Lidén, 2018) (Branke et al., 2016). Automation options such as Ambr® bioreactor systems and real-time monitoring systems are already available (Branke et al., 2016). It may be worth implementing them now to stay ahead of trends and make the transition towards Bioprocessing 4.0 easier. Automation can reduce the amount of labor needed in a facility, while making manual work more efficient as employees can work on multiple processes simultaneously and respond to issues more quickly.

"What MCC enables you to do is to process on a much smaller amount of resin and get greater utilization from it. It's a direct, visible saving on the cost of goods."

David Johnson
Head of Chromatography
at Sartorius

An Inside Look at Cost Modeling to Select Intensification Technologies

Andrew Sinclair, President and Founder at Biopharm Services, understands the difficulties that manufacturers face when attempting to make informed decisions about process design and intensification technologies. “The key challenge is that there is no single massive step change that brings cost reduction if you’re just looking at the prices … You need to consider where you can get the best benefit in terms of investment,” he said.

Sinclair developed his company’s BioSolve Process software to help companies perform specific modeling with their own variables. This allows them to make cost comparisons between different combinations of intensifications prior to purchasing any new equipment.

“We’re really working with people to better understand what’s driving the cost and economics of these processes. I think one of the key issues is that you have to look at the whole facility in operation. We can’t just look at a single process line in isolation,” he said.

Process Development: Reducing Cost of Goods by Optimizing Your Materials

ROI of Using Predictive Modeling and Data Analytics for Process Optimization

Not every intensification step requires a major investment. Seemingly small changes to material inputs can generate massive cost savings over time. Process modeling and analytics are some of the best options for identifying those changes before putting your processes in place, avoiding retrofitting challenges and regulatory delays.

Patrick O’Sullivan, Advanced Analytics Program Manager at the Janssen Pharmaceutical Companies of Johnson & Johnson, acknowledged that robust data analytics software, like SIMCA®, can feel like an expensive investment. However, he said the ROI is significant and worthwhile. As mentioned in Chapter 1, predictive modeling allowed Janssen to identify process optimizations that ultimately yielded in significant value through increased productivity.

Consideration for Reducing Cost of Goods

Do you have the up-front capital to invest in process development and intensification to reap cost benefits later?

Data analytics can also prevent unnecessary expenditures due to facility crisis management. O'Sullivan cited an example in which real-time process monitoring prevented a tank from overfilling in a Janssen production facility. Without the software-enabled intervention, the cascading effects of this overflow could have led to significant unnecessary costs.

Optimizing Media and Cell Lines Minimizes Consumption of Expensive Materials

According to Andrew Sinclair of Biopharm Services, media is often used inefficiently—despite being a significant driver of process costs—especially as manufacturers scale up. Therefore, optimizing media early (ideally before phase II) can significantly improve process cost efficiency. It is also important to note that cell line development and media optimization are linked, because the efficiency of media usage depends in large part on cell metabolism.

For companies adopting perfusion processes as part of their intensification strategy, it is worth making the switch to perfusion-specific media. This can reduce media costs and media usage by up to 40 percent, while also offering potential footprint reduction and water savings (Horry et al., 2019).

Cell line development and clonal selection can also have an impact on downstream costs. One of the cost pressures that experts most commonly mentioned was viral clearance filters, which are expensive but critical. David Pollard, Head of Advanced Materials and Processing at Sartorius, said it is possible to select cell lines that have a lower viral load and less host cell protein (HCP). Doing so can reduce the filtration capacity required per batch, allowing facilities to use each viral clearance filter for a longer period of time.

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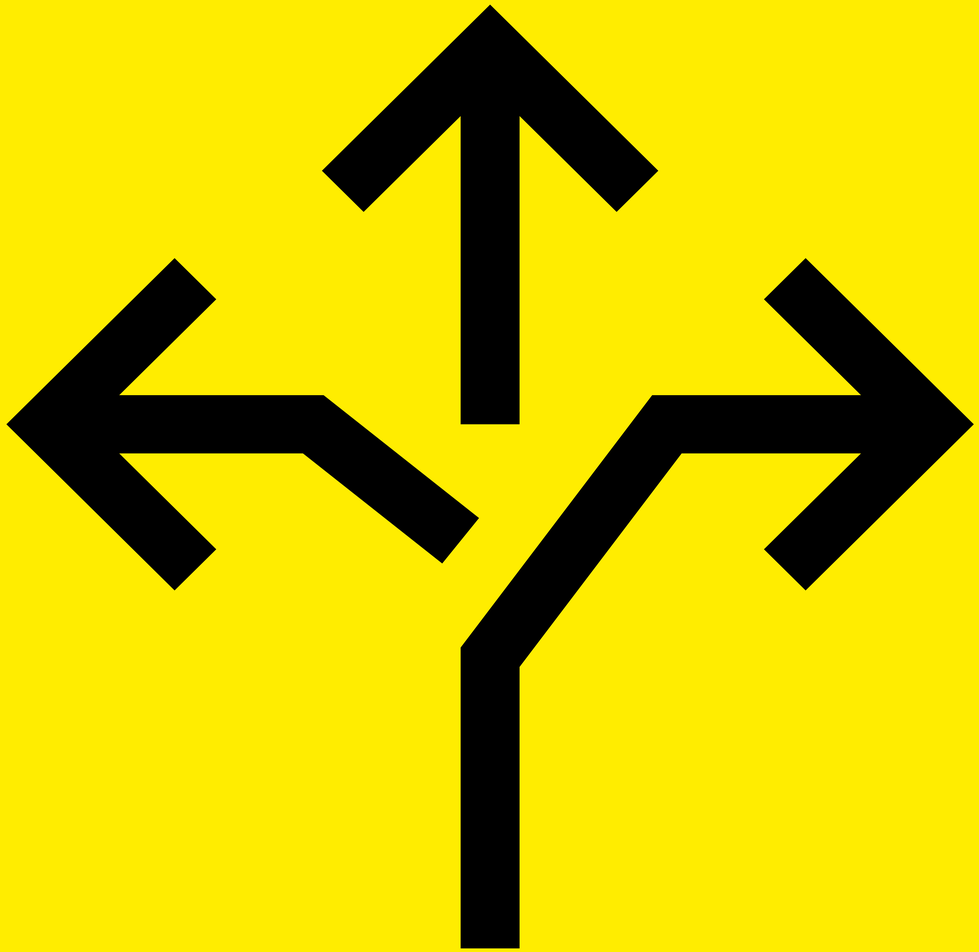
Increasing Flexibility

This chapter will highlight process intensifications that retain flexibility while providing other benefits, along with specific technologies and approaches that increase facility flexibility.



Many successful biopharmaceutical manufacturers prioritize flexibility in the design of their processes and facilities. This approach allows them to refine and optimize their processes at multiple stages and to add or remove products rapidly from their production lineup as markets shift.

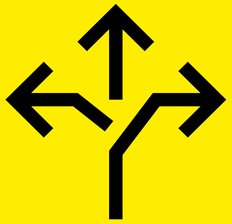
Facility flexibility can be especially crucial at the development stage. Over 90 percent of drugs in phase I do not advance to the final stages of regulatory approval (Thomas et al., 2016). With this in mind, companies need to fail fast and move on to the next promising candidate. Many manufacturers are also producing multiple modalities within a single facility, which requires them to have wide-ranging capabilities.

In Focus: CROs, CMOs, and CDMOs

CROs, CMOs, and CDMOs have extra incentives to prioritize flexibility when setting up facilities and processes. The nature of their business requires them to cater to each client's needs and goals and to pivot quickly from project to project in order to remain profitable. Experts like Kurt Brorson of Parexel, a large global CRO, recommend companies in this space have both fed-batch and perfusion bioreactors available and ready to go, as different clients may prefer or require one over the other.

While process intensification is valuable, it can be difficult for CROs, CMOs, and CDMOs to find the necessary time and funds in the absence of an immediate business need. Most have established processes and equipment in place, and it feels arduous to intensify when their facilities are already busy with client work. But for how long? Potential customers are increasingly asking CROs and CDMOs to develop intensified processes on their behalf, especially perfusion processes. Seeking out these types of clients can give companies the opportunity to develop leading intensified facilities with funding and direction.

Kurt Brorson, Ph.D.
Vice President, Technical
at Paraxel



Key Questions to Consider When Intensifying Process Flexibility

- Where in your process do you experience the greatest difficulty with product changeover?
- Are you aiming to produce multiple modalities simultaneously within the same facility? Consider current and future needs as well.
- When scaling up to commercial production, will you likely require large stainless steel equipment—or will it be possible to continue with single-use technologies?

Flexible Seed Train Intensifications

High-cell-density inoculation is an attractive intensification option for companies pursuing flexibility. This is because the cell lines used in high-density cell banking are generally suitable for both perfusion and fed-batch processes (Wright et al., 2015). Markus Wieland, Head of Product Development at Sartorius, explained that **high-density cell banking can decrease process development work and allow manufacturers to switch back and forth between various process types with relative ease.**

Advantages of Perfusion for Multiple Modality Production

Perfusion processes allow manufacturers to produce a larger number of disparate products within a single facility by maximizing bioreactor capacity along with facility efficiency (Horry et al., 2019). Since perfusion bioreactors are well-suited for less stable and more complex modalities (see Chapter 1), they can also be successfully used for a wider range of products. You could use the same perfusion bioreactor to produce more common stable modalities, like mAbs, as you do more instable biologics, like bi-specific antibodies (Brinkman & Kontermann, 2017) (Wang et al., 2019).

Because steady-state perfusion processes run for an especially long time (30-60 days compared to ~20 days with dynamic perfusion), they may not be the best choice when optimizing specifically for flexibility. With continuous processes, your downstream will be occupied for as long as you are operating your perfusion bioreactor, so longer runs equate to longer occupancy of your downstream equipment, which can limit flexible utilization for other production runs. Ankur Bhatnagar, General Manager at the large pharma company Biocon, explained: "If you do continuous perfusion, then the downstream has to be completely aligned to that. We have multi-product facilities, and if you have some processes that are fed-batch and you do continuous in between, then you block the whole downstream during that time," he said.

Consideration for Increasing Flexibility:

Are you aiming to produce multiple modalities simultaneously within the same facility?

An Inside Look at Using an Intensified Seed Train to Seed Multiple Bioreactors

Rajib Malla, Senior Manager at Intas Bio Pharmaceuticals Ltd., said his company frequently manufactures as many as 10 to 12 products in a single facility. To increase flexibility, one key focus for the company was intensifying their seed trains by implementing single-use bioreactors and high-cell-density inoculation.

Malla explained that even when seed train intensification does not save time in a singular process, it makes multiple modality production more efficient. "Depending on market demand, I can seed multiple production bioreactors from one seed train instead of having a one-to-one correspondence," he said. This strategy reduces changeover time while maximizing facility and equipment utilization.

Rajib Malla
Senior Manager at Intas Bio Pharmaceuticals

“High-density cell banking can decrease process development work and allow manufacturers to switch back and forth between various process types with relative ease.”

Markus Wieland
Head of Product Development at Sartorius

Jonathan Haigh, Ph.D., VP of Process Development at FUJIFILM Diosynth Biotechnologies, a global CDMO, said the flexibility benefits that can come with perfusion processes have many ripple effects:

"Historically, biopharmaceutical development companies would reach late-phase development (phase III and beyond) and either continue outsourcing to CDMOs, or were required to make significant capital decisions on their multi-billion dollar stainless steel facility investments and scale. Assumptions were made on market penetration, dosage, and beyond to predict product demand forecasts. However, with intensified processes such as a perfusion bioreactor feeding into a connected and integrated downstream train, the biomanufacturer may choose to process for a longer period of time to generate more product instead of transferring to a larger stainless steel commercial facility. The approach may offer greater flexibility, not only in your process, but also in terms of capital deployment and decision-making regarding large-scale investments."

Jonathan Haigh, Ph.D.
Vice President of Process Development at FUJIFILM Diosynth Biotechnologies

Single-Use Technologies Build Flexibility Into Your Process

Single-Use Upstream Systems Allow Downscaling and Eliminate Cleaning Steps

Stainless steel equipment requires extensive cleaning and sterilization with harsh chemicals between each production batch, and when switching between products. These cleaning procedures can be costly and time-consuming, causing each changeover to last a week or more. According to Mandar Dixit, Principal Process Expert at Sartorius, **switching your process to single-use bioreactors can eliminate chemical cleaning steps almost entirely. Product changeout can then occur in just one or two days. Single-use technologies can also minimize engineering and validation requirements during facility or process setup** (Shukla & Gottschalk, 2013).

An Inside Look at Facility Flexibility Through Process Intensification

WuXi Biologics, a global company with leading open-access biologics technology platforms, has successfully applied process intensification principles to achieve the flexibility necessary to support its clients' various needs across different scenarios.

For instance, production of recombinant proteins and bispecific antibodies may be quite complicated due to potential product stability issues and may require continuous processing such as cell culture perfusion. On the other hand, production of stable proteins like mAbs, may need higher capacity and productivity while reducing costs. Process intensification is necessary to achieve this goal.

"These two cases would eventually converge. To increase the flexibility, we need to build facilities capable of supporting intensified processes," explains Dr. Weichang Zhou, Chief Technology Officer and Executive Vice President at WuXi Biologics. Through a concerted effort, WuXi Biologics established the flexible manufacturing facility necessary to enable their global clients' diversified biologics projects.

Weichang Zhou, Ph.D.
Chief Technology Officer and Executive Vice President at WuXi Biologics

Single-use technologies can also help enable downscaling, which was discussed further in Chapter 3. Kenneth Kang, VP of Manufacturing at biopharmaceutical company Innovent Biologics, said using disposable bioreactors for orphan products and personalized medicines is particularly beneficial, as those therapies are manufactured in smaller quantities.

Downstream Single-Use Technologies Enable Easy Changeout

While the bulk of current single-use options are for upstream processes only, David Johnson, Head of Chromatography Systems at Sartorius, noted that the field is evolving quickly. One example is rapid cycling chromatography (RCC) involving single-use membranes, an emerging approach that can add flexibility to downstream processes. "If you have a membrane with the right characteristics, you can have a single-use system where the membrane is exhausted in one batch, so once you throw it away the system is ready for the next product," he said.

Consideration for
Increasing Flexibility:

Where in your process do you experience the greatest difficulty with product changeover?

Johnson also says membranes can serve a "plug-and-play" functionality within a highly flexible setup. "You can reorder your equipment and use things in a different order, and then all you have to do is plug in a membrane of the right selectivity. The membranes are convenient—they require less validation, and you don't have to manage them and store them," he said.

David Pollard, Head of Advanced Materials and Processing, Corporate Research, at Sartorius, highlighted single-use, multi-column chromatography (MCC) as an additional downstream technology that can enable flexible processes. "I would say that you could have your plug-and-play approach where you would keep the hardware systems similar. For example, you could have an MCC system and run that in different modes that would fit different platforms … You would just change the methods and the column sizes," he said. Similarly, MCC systems can be operated with columns in parallel or in sequence, and the option to use either in your process adds further downstream process flexibility.

Addressing Potential Challenges of Single-Use Systems

Single-use technologies offer many advantages in terms of convenience and flexibility; however, there are risks and downsides that must be taken into consideration. For example, there are still some concerns regarding extractables and leachables from single-use products, particularly in longer running perfusion processes (Shukla & Gottschalk, 2013). Companies using single-use technologies throughout their process should also have robust monitoring in place to ensure consistent product quality.

Rajib Malla, Senior Manager at Intas Bio Pharmaceuticals, says that while switching a process from stainless steel to single-use technologies tends to be relatively simple, changing over in the opposite direction is more difficult. This can cause problems for companies that must achieve a massive change in scale to go between clinical and commercial production stages. The solution: Take a holistic view when considering single-use technologies, weighing the benefits against potential difficulties in later stages or if massive scale-up could be in your products' future.

Overarching Consideration:

When scaling up to commercial production, will you likely require large stainless steel equipment—or will it be possible to continue with single-use technologies?

An Inside Look at Building a Modular Facility

Large pharmaceutical company Amgen put these principles into practice when planning and building its manufacturing plant in Singapore. The facility design is "modular and reconfigurable," with a footprint of just 120,000 square feet. This enabled the company to construct it in just 15 months, an accomplishment that they anticipate replicating in future building projects (Amgen, 2016).

Within the facility, Amgen implemented multiple intensification technologies that maximize productivity while maintaining flexibility, including single-use bioreactors. Due to the modular design, they can transition between multiple types of equipment in order to alter scale or manufacture different products (Amgen, 2018).

Modular Facilities Maximize Agility and Simplify Scale-Up

Especially when designing new processes and facilities, a modular approach can be one of the most comprehensive ways to maximize flexibility. It can reduce construction time, eliminate the need to retrofit equipment to respond to changing demands, and increase efficiency on multiple levels.

René Labatut, VP of Biologics Technology Innovation Strategy at Sanofi, points out that most modalities require the same basic processing elements: bioreactors, media, gas, downstream filtration, and so on. In a modular facility, sizes and quantities of these processing elements can easily be adapted to meet the needs of different modalities. With this agility, companies can avoid getting "stuck" when attempting to scale out from development to commercial-stage manufacturing.

"Think of process intensification as an assembly of steps where you have elements that are common to different processes," said René Labatut. "You can change elements to continuously fine-tune your process to get what you want at the end."

One of the greatest benefits of modularity is that users can often change out or add certain elements without interrupting production. For example, when scaling up to meet sudden increased demand, a manufacturer can put new modular equipment units into place while keeping existing processes running.

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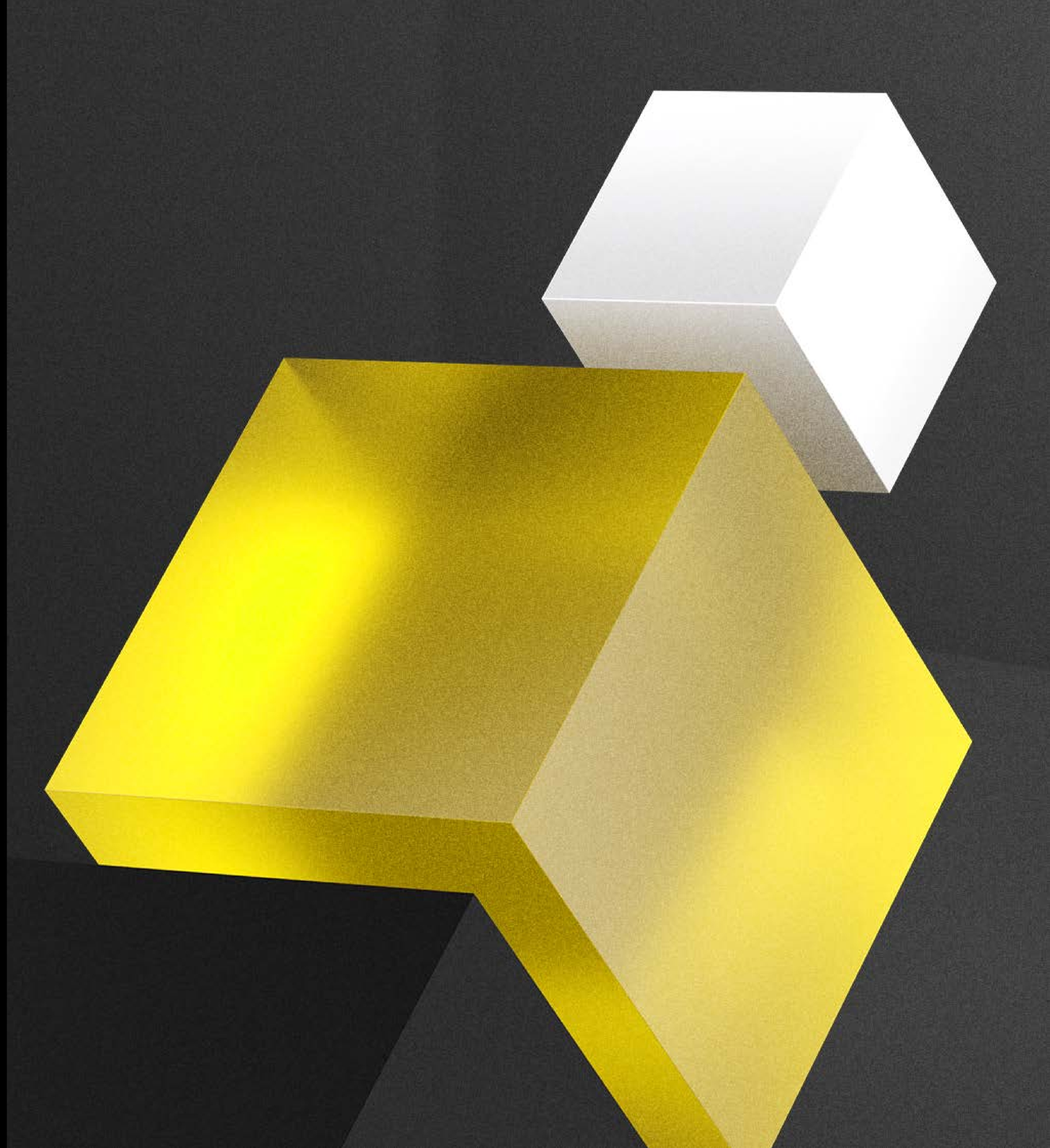
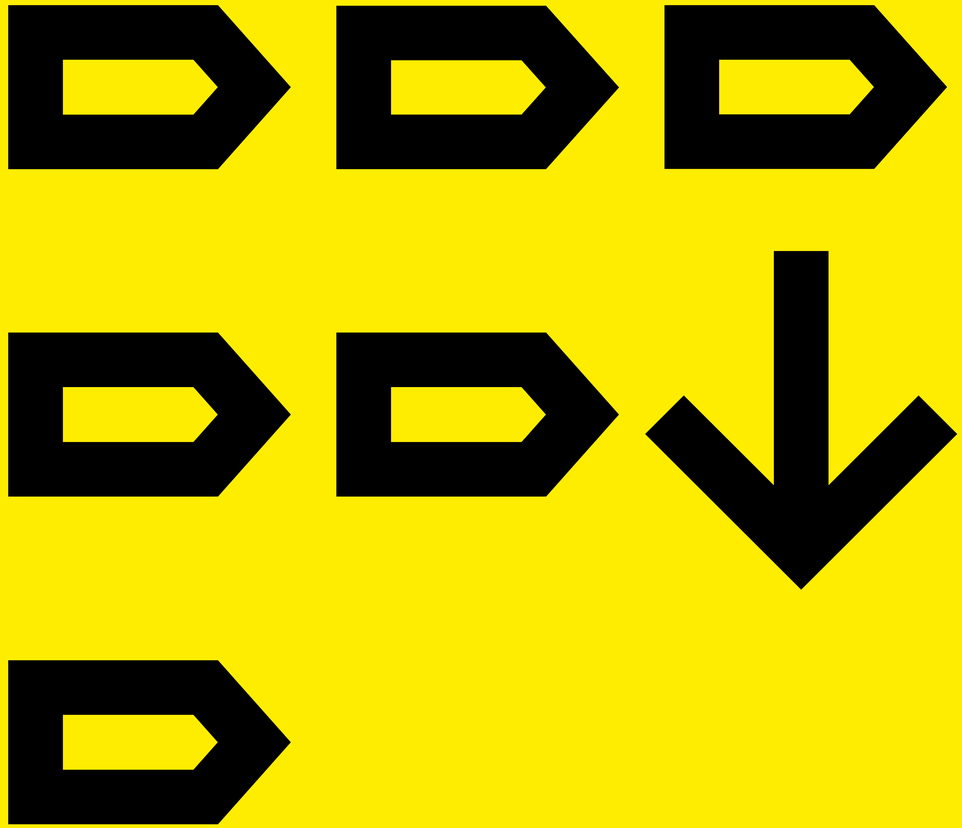


Process Intensification: Your Next Steps

One unifying sentiment from the many experts that we interviewed is that there is no one-size-fits-all solution to intensifying a bioprocess. There is a vast amount of information to weigh and consider alongside your company's short-, mid-, and long-term needs. While sometimes overwhelming, having a broad and realistic vision of process intensification will help your team find an overarching strategy for successful implementation.



Getting Started:

1. Know Your Process and Set Your Baseline
2. Prioritize Your Goals
3. Match Goals to Process Intensification Pillars & Approaches
4. Select Strategies You Can Manage
5. Find Help to Fulfill More Complex Strategies
6. Make it Happen!

A summary of Next Steps ...

First, delve deeply into your existing process well in advance of making any major intensification changes. As with any scientific endeavor, be prepared to establish a reliable quantitative baseline—complete with measurement strategies—to access process improvements.

Next, determine which process intensification pillars make the most sense to focus on, what drivers affect those pillars, and what outcomes you can expect. Prioritizing and ranking the pillars of increased productivity, shortened timelines, downsized process footprint, lower cost of goods, and greater manufacturing flexibility allows you to bite off manageable improvements.

Finally, a number of experts indicated that to make complex and profound improvements, you often need to grow your organization's manufacturing brain trust. Don't be afraid to seek help from vendors and consultants or to hire additional in-house expertise. While this does increase costs, pushing through alone often involves tremendous risks and lost opportunities. Bringing in fresh experts can help an organization zoom out to find holistic approaches.

We see this firsthand: Sartorius has helped countless organizations identify the right intensification strategies and product solutions to meet their goals. Part of our role is to supply the most advanced tools and services that fully unite bioprocesses and generate complete solutions that work in harmony.

The Future of Process Intensification

Process intensification is not a static concept. It will continue to evolve as the biologics industry matures and actualizes more of its potential. Process intensification should therefore be approached as an iterative journey, with ongoing improvements to remain competitive and viable. While looking inward helps determine immediate steps, part of the process intensification exercise entails looking ahead and planning for future developments.

From the perspective of this report's expert panel, there are two key developments to look out for that are very likely to impact your work.

“I do find that automation is very critical for smooth implementation of continuous processing for process intensification.”

Weichang Zhou, Ph.D.
Chief Technology Officer and Executive Vice President at WuXi Biologics

1. Industry 4.0 or Bioprocess 4.0:

Our expert panel referenced Industry 4.0 several times, which will become reality in approximately one decade. In short, Industry 4.0 describes a manufacturing industry initiative that incorporates greater automation and AI involvement in bioprocesses to streamline efficiency through the reduction of manual activity (Grieb, 2019) (Morrow Jr., 2019) (Demesmaeker et al., 2020). According to Weichang Zhou, Ph.D., Chief Technology Officer and Executive Vice President at WuXi Biologics, a global company with leading open-access biologics technology platforms, “I do find that automation is very critical for smooth implementation of continuous processing for process intensification.” To accomplish this, Industry 4.0 requires improved in-line process monitoring for timely control of critical process parameters, and potentially remote management, which help make processes truly and fully continuous. Naturally, better and higher throughput data analytics and process modeling will play an essential role in Industry 4.0 as well, as sophisticated computation tools continue to take off.

2. Process and Site Sustainability:

Without a doubt, manufacturers should always consider the sustainability of their process. It can be tempting to deprioritize sustainability when there are so many other demands on your time, capital, and resources, but many experts pointed out that this is short-sighted and can doom long-term prospects. According to David Pollard, Head of Advanced Materials and Processing, Corporate Research, at Sartorius, there is already "pressure on companies, particularly within Big Pharmaceutical, to support sustainability." Leadership teams from large pharmaceutical companies are now realizing that "through intensification, you can reach some of your corporate sustainability goals, including reduced water use, footprints, and electrical capacity." Some organizations take this to the next level. For example, Amgen announced an impressive 2027 Environmental Sustainability plan (Amgen, 2021), which charts ambitious targets for carbon emission and water conservation on the "road to net zero."

"Through intensification, you can reach some of your corporate sustainability goals, including reduced water use, footprints, and electrical capacity."

David Pollard
Head of Advanced Materials and Processing, Corporate Research at Sartorius

Pollard stressed the need to think big picture when it comes to sustainability. While there is a lot of attention on plastics use in single-use bioreactor systems, users need to think critically about what truly impacts the sustainability of their process. Once identified, tackle aspects of the biggest drivers first. As Pollard noted, water consumption makes up approximately 90 percent of life cycle assessment, while HVAC electrical loading has the greatest impact on energy consumption. By the time the industry minimizes water and HVAC use, plastics will become a bigger focus. For plastic reduction, solutions like biodegradable single-use materials or plastic recycling into packaging materials may offer tangible benefits. All manufacturing organizations need to be cognizant that sustainability will become more and more important. In short, companies that want to stick around long term must act like it, and there are strong financial incentives for doing so.

A Word on the Most Important Stakeholders: Patients

At the end of the day, our industry is working toward something more vital than footprints, costs, and productivity. We're producing therapies that can change—and save—lives. We hope this report helps organizations like yours improve the standard of care in a highly accessible and affordable way, helping unlock the life-saving potential of biologics.

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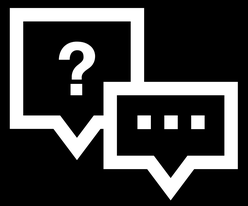

Key Definitions Used Throughout the Text

Upstream Process
The stage of a bioprocess dealing directly with generating necessary cell densities and expressing product in bioreactors.

Downstream Process
The stage of a bioprocess involved with product purification, viral clearance, and generation of final product.

Continuous Process
A bioprocess where users fully connect upstream and downstream processes, such that the system perpetually harvests product at the same rate to its purification. As a result, truly continuous processes don't have traditional product "batches."

Connected Process
A bioprocess where users link unit operations throughout an entire process, but intermediate and surge tanks manage flow differences between units. Connected processes that specifically unite upstream and downstream processes are of particular importance.

Bioreactors

Fed-Batch
A bioreactor where users input production cells and media into the reactor, close the system, incubate for a set period of time, and harvest all material at once. Historically, the most commonly used bioreactor system for bioprocesses to date.

Perfusion
A bioreactor that generates high viable cell densities (VCD) and titers using either a tangential flow filtration (TFF) or alternating tangential flow filtration (ATF) system to actively replace cell media and retain viable cells. Perfusion bioreactors create a consistent, high-nutrient cellular environment while constantly harvesting product from collected spent media.

- N-1 Perfusion is when manufacturers use a perfusion bioreactor in their seed train just ahead of the production bioreactor (N-stage) to generate high cell densities and speed up production.
- Dynamic perfusion uses high perfusion rates to generate high VCDs by maintain-ing high specific growth rates. Typically, dynamic perfusion can be run for longer periods than fed-batch, but not for periods equivalent to steady-state perfusion.
- Steady-state perfusion uses low perfusion rates but can maintain constantly high VCDs over very long periods of time (~30-90 days). This is sometimes referred to as continuous perfusion or continuous cell culture.

Concentrated Fed-Batch (CFB)
A fed-batch bioreactor that utilizes an ATF system to cycle fresh media into the system, while returning both viable cells and product back into the reactor.
As with traditional fed-batch, CFB product is harvested as a batch at the end of the reactor run.

Single-Use
A bioreactor system that makes products using a disposable bioreactor chamber and additional components. Single-use bioreactors eliminate the need for bioreactor cleaning | validation and can be either fed-batch or perfusion-based.

Intensified Chromatography

Continuous Capture
A downstream system that constantly catches product as it is harvested from a bioreactor.

Multi-Column Chromatography (MCC)
A column chromatography system that uses more than one column (either in sequence or in parallel) to increase throughput, productivity, and capacity. Users commonly adopt MCC to enable continuous capture.

Rapid Cycling Chromatography (RCC)
A membrane chromatography system that can be operated at higher flow rates than traditional column or membrane chromatography. As a result, RCC recycles membranes much faster, achieving 100+ cycles on the same membrane in one day compared with 1-3 cycles using resins. Spent membrane can then be discarded. Overall, RCC increases membrane chromatography productivity, and capacity.

Germany
Sartorius Stedim Biotech GmbH
August-Spindler-Strasse 11
37079 Goettingen
Phone +49 551 308 0

USA
Sartorius Stedim North America Inc.
565 Johnson Avenue
Bohemia, NY 11716
Toll-Free +1 800 368 7178

Learn More About Process Intensification

www.sartorius.com/process-intensification

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