Simplifying Progress

Flexibility in Next-Generation Facilities Through Rocking Motion Bioreactors

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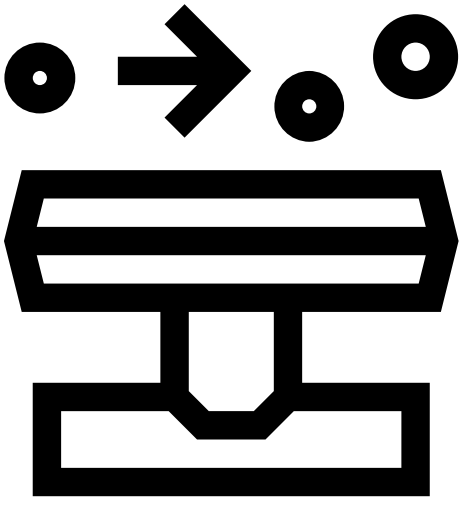
Meeting Demands With Seed Train Intensification

The trends of the biopharmaceutical industry in 2022 and beyond continue to push manufacturers toward solutions for more productive and adaptable bioprocessing. Rising demand, stiff competition, the emergence of new modalities, and digital transformation accelerate growth, creating new operational challenges. These pressures include the need for shortened timelines and greater yields of increasingly diverse products.

Increasing productivity in the upstream process is an excellent starting point for satisfying some of these business drivers. One of the fastest and least disruptive ways to achieve this is to intensify your seed train, which helps overcome time and cost constraints and makes upstream manufacturing more agile.

There are many approaches to seed train intensification. Rocking motion bioreactors offer a reliable strategy for performing seed train intensification as part of a perfusion process or, more commonly, a hybrid fed-batch/perfusion process. Here, we discuss how using rocking motion bioreactors to maximize the productivity of your seed train is a reliable way to make your bioprocess more efficient and flexible.



Current Challenges in The Biopharmaceutical Industry

Biopharmaceutical industry players face significant barriers to setting up and maintaining a successful bioprocess.

1. Constant time pressure: the need to be first to market shapes many of the decisions made by drug developers today. Solutions that promote speed and agility are essential.

2. Tightening regulations: the biopharmaceutical industry exists in an increasingly stringent regulatory landscape. Drug developers require robust, reproducible, and traceable solutions to ensure compliance.

3. Supply chain problems: global issues continue to affect the supply of many critical materials. Therefore, finding robust solutions with security of supply is a key driver.

4. Increased demand: the requirement for existing and upcoming modalities continues to rise. Manufacturers need to ensure their process produces sufficient yields.

5. Handling multiple molecules: outsourcing production steps to smaller, specialized players like contract manufacturing organizations (CMOs) and contract development manufacturing organizations (CDMOs) is becoming more commonplace in the industry. Eventually, these CMOs will have multiple molecules in their pipeline, increasing the need for flexibility in their facility.

In order to overcome many of these challenges, manufacturers need to design a lean, highly productive facility. Taking advantage of process intensification principles in the upstream bioprocess is a relatively simple way to maximize a facility's output and agility.

N-Stage Perfusion With Rocking Motion Bioreactors

Implementing a rocking motion bioreactor with an integrated perfusion membrane in the N-stage of the seed train is the simplest and most cost-effective opportunity for process intensification. In N-1 perfusion, the production bioreactor is seeded at a higher cell density, increasing common seed ratios between 1:5 – 1:20 to 1:100 or even above. These simple adjustments mean higher yields can be achieved in less time and with fewer process steps (Figure 1).

Rocking motion or wave-induced motion bioreactors typically consist of a single-use bag containing cells and media attached to a rocking platform. A gentle rocking movement provides the mixing and aeration required for the cells to grow efficiently and reach high densities. Key process parameters such as pH, dissolved oxygen (DO), and viable cell biomass can also be monitored and controlled.

Since their working volume ranges from 100 mL to 25 L processed on the same device, rocking motion systems have been a popular option for seeding into larger stirred-tank bioreactors.

However, there are now rocking motion bags on the market that support intensified cultivation up to 100 L cell suspension, thus broadening the systems' use. N-X perfusion using rocking motion bioreactors enables the population of high-density cell cultures to inoculate all intermediate steps up to the production bioreactor. The gentle wave movement offers a low-shear mixing and gassing technology, allowing cultures to reach higher densities without the risk of cell damage by submersed bubbles or foam build-up. Consequently, rocking motion technology is suitable for sensitive cell types without addition of complex media components or further adaption efforts.

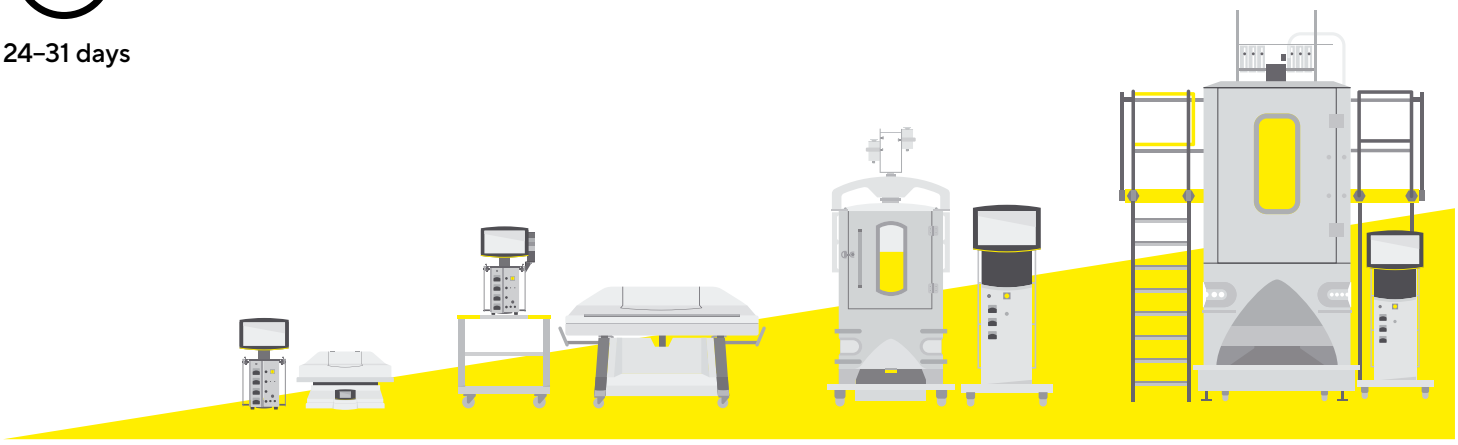
The generated surface aeration provides sufficient oxygen to meet the requirements of mammalian cell populations with high-oxygen demand, supporting the exponential growth of cells. In fact, at high rocking frequencies, the utilization capacity of the pure oxygen gas phase in 2 L rocking motion vessels is often superior to single-use stirred-tank systems of the same size reaching 170 million cells/mL. There is also the possibility of thawing frozen vials of high-density cell cultures in 100 mL RM batch culture, bypassing all flask steps.

Process analytical technologies (PATs) can be combined with rocking motion systems to support tight control of the cell culture environment. Sensors and analyzers collect critical process data that help unlock new insights to better define parameters. This information can be used to automate and promote consistency across the process.

Classical Fed-Batch Seed Train

24–31 days

	N-4 and N-3	N-2	N-1	Production
	5 L → 25 L	100 L	500 L	2,000 L
Starting → End VCD (million cells/mL)	**Biostat® RM 20 & 50** 0.5 → 5	**Biostat® RM 200** 1 → 5	**Biostat STR® 500** 1 → 5	**Biostat STR® 2000** 1



Intensified RM 200 N-1 Seed Train

21–23 days

	N-2	N-1	Production
	5 L → 25 L	100 L	2,000 L
Starting → End VCD (million cells/mL)	**Biostat® RM 50** 1 → 5	**Biostat® RM 200** 1 → 50	**Biostat STR® 2000** 2.5

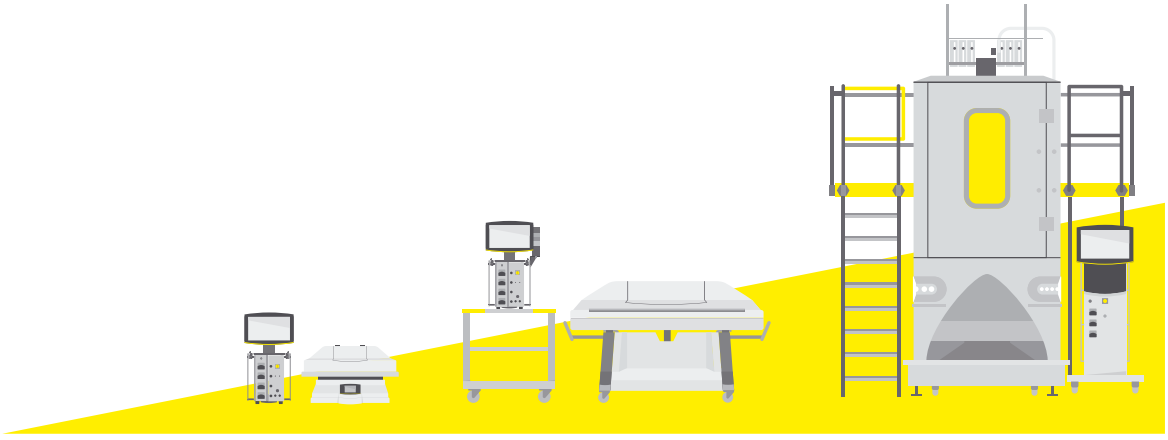


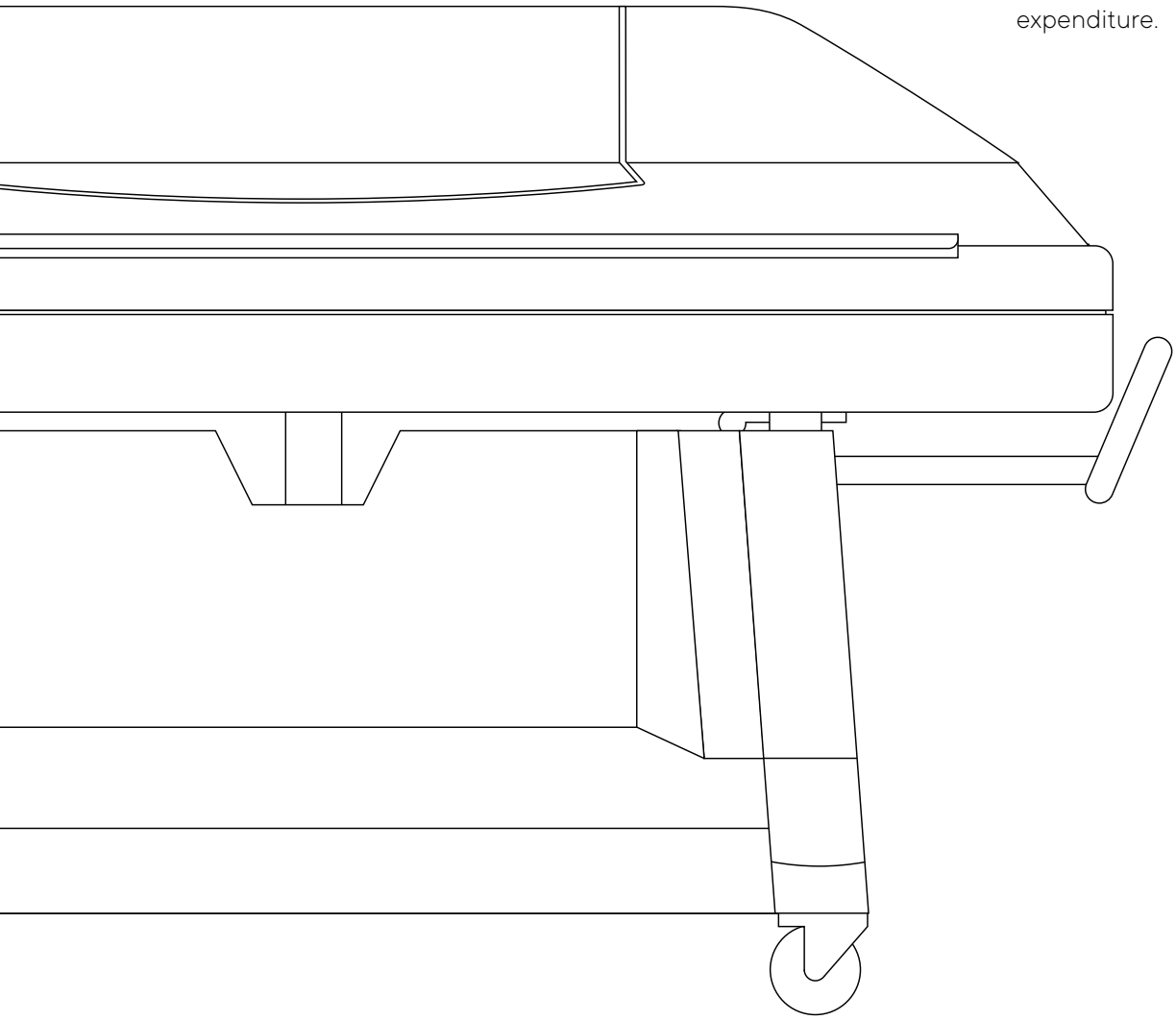
Figure 1: *An example of an N-1 intensified seed train with rocking motion bioreactors (Biostat® RM) compared to a standard fed-batch process.*

Accomplishing Key Business Goals With Rocking Motion Bioreactors

In the following sections, we discuss how - from an operational perspective — rocking motion bioreactors allow you to reap the benefits of process intensification. Together with their automation and SU compatibility, we discuss how rocking motion technologies help you satisfy key business objectives and design a robust and flexible next-generation facility.

Economical
Reduce Costs and Footprint

Seed train intensification reduces the number of culture steps required before the production bioreactor can be inoculated. Limiting these intermediate scaling steps reduces the number of bioreactors, saves space, limits the facility footprint, and reduces capital expenditure.



Flexibility
Managing Multible Modalities

Innovation in the biopharma field has led to the development of increasingly diverse biologics. Coupled with this trend is the growing demand for multi-product facilities, a key focus in the wake of the COVID-19 pandemic.

Once the seed train has been intensified, the reduced amount of equipment required in the process saves space, allowing greater flexibility with the same facility layout. To enhance this benefit, customers should look for modular concept bioreactors when setting up processes and switching between production scenarios for different molecules.

This flexibility is vital for CMOs and CDMOs, which will likely work not only with multiple products but may have to employ vastly different manufacturing approaches and process conditions to meet the requirements of their clients.

Not all cells are the same: some cell types may have special features such as shear-stress-sensitivity or high oxygen consumption, and some products are also particularly sensitive to agitation, such as bioconjugates. Seamless integration of wave-based bioreactors into a seed train with stirred-tank production bioreactor in either perfusion or fed-batch mode provides the flexibility to manage multiple molecules in your pipeline, as a single approach can be used for all N-stage steps across different products and processes.

Adaptability
Modular Equipment

Linked to its present flexibility, rocking motion technology can also be adapted as your seed train strategies evolve to meet your changing needs over time. For example, you might decide to use traditional fed-batch production strategies initially. Later, your business objectives may change, such as developing new biologics or greater yields in response to changing commercial and clinical needs. Since rocking motion technology is perfusion enabled, you can quickly adapt your equipment to suit your new process.

Speed
Reaching Your Goals More Quickly

Persistent time pressure represents one of the most significant challenges for biopharmaceutical companies today. N-1 perfusion using rocking motion bioreactors represents a simple tool to produce more cells and skip intermediate scaling steps. Using this method, biomanufacturers can reduce their production bioreactor culture days by around 20% and maintain the same product titers[1] (Figure 1).
The same principles can be applied to produce greater yields; almost double the amount of product can be manufactured in the same time frame by intensifying the seed train. This increased output could amount to an additional 3-5 batches per year.

Additionally, the multiple steps required in a standard fed-batch process introduce opportunities for variability and human error. Overall process robustness can be improved when process transfer steps are streamlined.

What Features Should You Look For To Help Facilitate These Changes?

Manufacturers need to leverage compatible tools and software solutions to streamline process development and production processes.

Digital Tools

Embracing the ongoing digital transformation can help manufacturers remain agile in the dynamic biopharmaceutical market while maintaining process robustness. Integrated solutions that deliver automation and analysis tools simplify process configuration and help you maintain consistent conditions and achieve reproducible results. This means you can stay flexible and quickly adapt your equipment to suit changes, including fluctuating demand, the development of new modalities, and changing process scenarios.

Single-Use Technology

Single-use technologies are becoming more and more established in modern biopharmaceutical manufacturing. Single-use cell culture solutions drive consistency in bioprocesses while promoting flexibility and faster processing. As a result, single-use bags can help drug developers streamline validation, fulfill regulatory requirements, and reduce their time-to-clinic or time-to-market.

When implemented in tandem with seed train intensification, single-use solutions can improve consistency, speed, and flexibility in a bioprocess.

Biostat® RM – Making Waves in the Industry

The Biostat® RM portfolio is a range of rocking motion bioreactors from Sartorius (1 L to 200 L). Powered by Biobrain® and compatible with single-use Flexsafe® bags, the Biostat® RM ticks all the boxes to help you start your journey towards efficient and reliable upstream processing in an intensified, next-generation facility.

Biostat® RM bioreactors are fully GMP-compliant and compatible with both standard fed-batch and perfusion culture, meaning they are an excellent addition to an evolving seed train strategy. Perfusion culture is enabled through the integrated perfusion membrane, meaning there is no need for an external cell retention device, no further risk of contaminations, and no additional interfaces. Moreover, the gentle, rocking motion is particularly attractive to those working with shear-sensitive cell lines or products.

The Biostat® RM portfolio's modular design gives you the flexibility to address your unique process requirements and modify your setups to maximize yields and reduce culture times. The modular concept also helps you save space and reduce capital expenditure, as pre-qualified configurations can be run on a single device and adapted according to process needs. As such, the Biostat® RM successfully addresses the key pillars of seed train intensification.

The integrated Biobrain® automation platform is compatible with a broad range of single-use BioPAT® sensors, allowing you to monitor and control your process parameters and even automize seed transfer. This feature is significant for multi-product facilities and scaling up from process development to manufacturing.

Conclusion

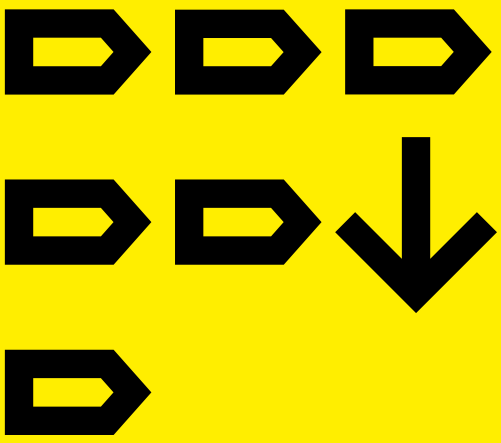
Seed train intensification using rocking motion technology is an excellent starting point for getting more out of your production process.

The Biostat® RM portfolio is suitable for various applications, including the culture of sensitive cell lines used in regenerative medicine applications and end-to-end single-use processing, which can streamline the production of vaccines and recombinant proteins.

Biostat® RM bioreactors are suitable for cell cultivations for a wide range of working volumes, and its modular concept provides the flexibility to manage multiple molecules in a single pipeline.

The integrated single-use bags and automation platform supports robustness and control, streamlining reconfiguration and transfer from scale to scale.

In summary, seed train intensification using rocking motion technology enhances flexibility and boosts yields while reducing footprint, costs, and timelines. Together, these features contribute to overall improvements in efficiency and agility, allowing a facility to respond to the changing biopharmaceutical landscape.



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Karl is a global expert for Sartorius, covering the field of single-use bioreactors. As an interface between product development, marketing, and field organizations, Karl's responsibilities include supporting the creation of marketing assets, technical knowledge transfer to application specialists, and developing the scientific intercompany dialogue.

He started his career at Sartorius in 2001 as a sales engineer before later switching to application services. Before this, Karl spent several years in research as a scientific assistant developing photobioreactors and aquatic life support systems.

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Yuliya works within the Cell Culture Technologies team at Sartorius, where she is responsible for developing the product strategy for the rocking motion bioreactor portfolio, conducting business analysis, and devising future product developments.

Before joining Sartorius in October 2020, she worked as an Application Specialist and a Post-Doctorial Researcher. She earned her PhD in Molecular Biology from Johannes Guttenberg University, Mainz, Germany, in 2015.

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Katy is part of the Marketing Communications team at Sartorius, where she supports the creation of a variety of written pieces, from published articles to web content.

Before joining Sartorius in 2021, Katy was employed as a Post-Doctoral Research Associate at the University of Edinburgh, where she also completed her doctoral studies. Here, she carried out research in genetics and cellular biology and began taking on writing projects, eventually entering into a career as a freelance writer for various biotech companies and agencies.

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