



Preparing for the future— visions and insights for biomanufacturing

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Preparing for the future— visions and insights for biomanufacturing





Bioprocess insights into next-generation manufacturing

by Sara Corin
General Manager BioProcess
Downstream Hardware
GE Healthcare Life Sciences

The biopharmaceutical industry has a reputation of being averse to change. This is likely because traditional approaches to drug development have withstood the test of time, delivering safe and effective drugs for decades. Yet, new market dynamics, such as growing competition from biosimilars and niche drugs targeting smaller patient populations, are reshaping how drugs are produced and sold. The saying “If it isn’t broke, don’t fix it” no longer suffices in a market focused more on efficiency and flexibility in manufacturing. Instead, these qualities have become the foundation of managing demand uncertainty and appropriately preparing for a wide range of possible launch outcomes.

To achieve more control within a set design space and to mitigate costly risks requires a combination of process intensification, proper facility utilization, and successful technology transfer. Therefore, the time has come to look outside of our

comfort zones and explore alternative processes and technologies to achieve the industry's goals. Exploring a scale-out, rather than scale-up, paradigm allows manufacturers to increase volume to fit the market needs and deliver quality drugs to patients faster than ever before.

At GE, we are committed to understanding our customers' needs in order to address their challenges and offer solutions that prepare them for a new future in healthcare. That is why, in this e-book, you'll find insight and advice from some of the industry's top experts about current trends in biomanufacturing, modern process intensification techniques, and the outlook for digital automation. We explore innovative process approaches that can be applied at various scales and stages of development. Our hope is that it provides you with a visionary guide of how to effectively manufacture your molecule. We look forward to driving valuable change by offering diverse strategies and capable solutions that push the boundaries of innovation and energize industry collaboration.



Sara Corin

General Manager Bioprocess Downstream
Hardware | GE Healthcare Life Sciences



The authors



Dr. Nigel Darby

Advisor | GE Healthcare Life Sciences

Dr. Nigel Darby has held several executive positions at GE. He most recently served as Vice President Bioprocess for GE Healthcare's Life Sciences business from 2008 to 2016. At present, he is Advisor to the CEO of Life Sciences. Nigel has substantial experience from both the medical industry and academia. For example, he has held executive positions at AstraZeneca and spent 16 years in academic research in medicine and molecular biology.



Dr. Stefan R. Schmidt, MBA

Chief Scientific Officer | Rentschler Biopharma, Laupheim, Germany

Dr. Stefan R. Schmidt is an expert in Fusion Proteins, editing the first comprehensive book on that topic. Currently he serves as CSO at Rentschler Biopharma, Laupheim and previously held other senior executive roles including the overall responsibilities for development and production. Before that he was CSO at ERA Biotech in Barcelona, directing the company's R&D efforts around fusion peptides. Prior to that he worked for 7 years at AstraZeneca in Södertälje, Sweden where he led the unit of Protein Sciences as Associate Director. He started his leadership career 1997 at Biotech companies in Munich where he built up protein biochemistry teams first for Connex and later for GPC-Biotech.



Per Lidén

Product Strategy Manager | GE Healthcare Life Sciences

Per Lidén joined GE in 2007 and has since had various positions in product management for products including lab instrumentation, bioprocess solutions and software. At present, he is Product Strategy Manager for Digital and Automation solutions in Bioprocess. Prior to joining GE, Per was founder and CEO of a software company in the field of predictive analytics and data mining for the life sciences industry.



Dr. Mats Lundgren

Customer Applications Director | GE Healthcare Life Sciences

Dr. Mats Lundgren has more than 25 years of experience in vaccinology. After earning his Ph.D. in Immunology, Cell, and Molecular Biology from the Karolinska Institute, Sweden, Dr. Lundgren completed post-doctoral training at the MRC Clinical Sciences Centre, Imperial College School of Medicine, UK. In his industrial career he has held positions at the bench and in management at Pharmacia (now part of GE), AstraZeneca, and several smaller biotechnology companies. In his current role as Customer Applications Director at GE, he helps companies implement modern processes with the goal of achieving more efficient production and higher vaccine quality.



Madhu Raghunathan

Product Strategy Leader | GE Healthcare Life Sciences

As Product Strategy Leader at GE Healthcare Life Sciences, Madhu Raghunathan drives evolution of GE's process hardware equipment to enable next-generation biomanufacturing. He also collaborates with biopharmaceutical companies to identify opportunities for greater downstream process efficiency. In previous roles, Madhu led bioprocess market development for GE in the Asia-Pacific region, developed industrial automation control systems, and commercialized technological innovations.



Dr. Andreas Castan

Staff Scientist | GE Healthcare Life Sciences

During the last 20 years, Dr. Andreas Castan has been working in various positions within biopharmaceutical development including project and line management as well as manufacturing. After studying chemical engineering at the Technische Universität Hamburg-Harburg (TUHH), Germany, he received a Ph.D. in Biochemical Engineering at the Royal Institute of Technology (KTH), Sweden. Before joining GE, Dr. Castan was Director Upstream Development at Swedish Orphan Biovitrum AB, working with expression system development, process development of microbial and mammalian cell based processes and scale-up to cGMP manufacturing scale. At present Dr. Castan is Staff Scientist at GE.

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Trends in the biopharmaceutical market: Are you ready for the future of manufacturing?

by Dr. Nigel Darby
Advisor
GE Healthcare Life Sciences

The launch of many innovative biologic drugs is creating exciting new opportunities for patient care. As these novel medicines become a larger part of the industry's portfolio, it is critical we secure a supply chain and manufacturing processes that produce drugs in a reliable, cost-effective way. Modern technologies can help achieve this by increasing facility flexibility and process intensification, which reduces facility size and costs with resulting decreases in manufacturing costs and financial risk. We now have a toolbox for the future that allows us to bring many different types of molecules to the market quickly and efficiently.

Biopharma market dynamics

Over the last 20 years, a combination of biopharmaceutical proteins, plasma products, and vaccines has driven the value of the world biopharmaceutical market from \$11 billion to \$230 billion.¹ A major factor in this tremendous growth is monoclonal antibodies. Many of the monoclonal antibody therapies first approved in the '90s are now the targets for the first wave of antibody biosimilars. These "follow-on biologics" are expected to be a key factor in the growth of the global market over the next 10 to 15 years.

Biosimilars are nothing new. In fact, biosimilar versions of erythropoietin (EPO) and growth hormone have been around in Europe and emerging markets for more than 10 years. However, what is capturing people's attention are the first biosimilar approvals for the U.S. market and the rate at which biosimilars are emerging for

many of the industry's highest-revenue monoclonal antibody drugs. For example, there are currently 27 different projects in progress aimed at creating a biosimilar for Enbrel™, a first-generation monoclonal antibody and top-selling biopharmaceutical in 2016. When looking at other top-selling molecules from that year, there are currently at least 112 biosimilar projects spread over seven different molecules (as outlined in the chart below).² This emphasizes how competitive the biosimilar market is predicted to become.

Look to Remsima™ as an example of a biosimilar's potential for market success. Korean drugmaker Celltrion introduced Remsima™ as the world's first biosimilar referencing Remicade™ in Europe in 2014. By the end of 2016, Celltrion reported it had taken away nearly 40 percent of the original drug's European sales for that year.³

In the United States, biosimilar adoption has been slower due to regulatory hurdles and a lack of interchangeability harmonization. Nonetheless, there is good evidence from Europe that, under more streamlined conditions, biosimilars can be adopted very quickly. Also, the manufacturing processes used to make biosimilars can be much more efficient than the legacy processes employed to make the originator drugs. This, in addition to other factors such as lower clinical and R&D costs, contribute to overall cost savings that allow biosimilar manufacturers to price their drugs more aggressively.

The pace of therapeutic and molecular innovation is also paving a new path for the future of biopharmaceuticals. A key driving point

in the expansion of breakthrough therapeutic modalities is the development of cancer immunotherapies, such as Keytruda™ and Opdivo™. There are a large number of global clinical trials around the development of these exciting new drugs. However, their high cost is giving healthcare systems pause as to whether these types of therapies could ever be affordable for large populations. There is also a great deal of molecular innovation, such as the rise in antibody-drug conjugates (ADCs), bi-specific antibodies, and gene and CAR T-cell therapies. For gene and cell therapies, an additional challenge is how to efficiently manufacture drugs intended for individual patients, which involves a more complex and “personalized” supply chain.

As our understanding of disease biology becomes more refined, drugs are increasingly targeting smaller patient populations. This means that many of the biologic drugs coming onto the market over the next few years will be manufactured in lower volumes. Yet, there will be more of them. This, combined with the growth of biosimilars, makes for a strong pipeline of biopharmaceuticals for

the future. As a result, by 2022, biopharmaceuticals are expected to make up about half of the top-selling 100 products and about 30 percent of the prescription drug market.⁴ The top 10 is likely to include more small molecule drugs, which are staging a comeback in the industry. As the dynamic biopharma market continues to evolve, there are significant challenges we must overcome in order to deliver these therapies to patients.

How can we manage the key risks of a burgeoning market?

The innovation shaping the industry is creating a lot of excitement and buzz; nonetheless, it also creates a substantial amount of uncertainty in how we configure and develop manufacturing capacity. We must determine a way to construct capacity that ensures we can effectively manage this very dynamic environment moving forward. In terms of capacity uncertainty, three major factors can affect the type of capacity you build and when and where you build it:

API	Reference product	Company	Therapeutic area	2016 revenue [\$ M]	# of biosimilar projects	Biosimilar approvals, companies
Infliximab	Remicade™	Janssen	Autoimmune diseases	8057	9	Celltrion/Hospira (Korea, EU, USA, Brazil, Japan, Russia), Nippon Kayaku (Japan), Ranbaxy/Epirus (India), Samsung Bioepis (EU, USA, Korea)
Bevacizumab	Avastin™	Roche	Bowel, breast & colon cancer	6681	15	Biocad (Russia), Hetero/Lupin (India), Reliance Life Sciences (India)
Etanercept	Enbrel	Amgen/ Pfizer	Arthritis Psoriasis	9265	27	Sandoz (EU), Samsung Bioepis (EU, USA)
Trastuzumab	Herceptin™	Roche	Cancer	6680	16	Celltrion (Korea), Shanghai CP Gujian (China), Shanghai Henlius (China), Biocad (Russia), Biocon/Mylan (India)
Adalimumab	Humira™	AbbVie	Autoimmune diseases	16 524	17	Amgen (EU, USA), Torrent Pharmaceuticals (India), Zydus Cadila (India)
Rituximab	Rituxan™	Roche	Cancer, autoimmune diseases	7190	23	Celltrion/Hospira (Korea, EU), Sandoz (EU), DRL, Hetero, Intas, Zenotech (India), Probiomed (Mexico), Biocad (Russia)
Insulin Glargine	Lantus™	Sanofi	Diabetes	6324	5	Biocon (India, Japan), <i>EMA submitted Nov 2016</i> , Wockhardt (India), Eli Lilly / Boehringer Ingelheim (EU, USA, Japan, Australia), Samsung Bioepis / Merck (EU)
Total				60 721	112	

1. **Market fragmentation**—Niche drugs for smaller patient populations, an intense focus on areas such as immune-oncology, and more biosimilars mean increased competition among companies competing for the same profit pool. This makes capacity planning difficult, as you may not be sure who your competitors will be or how many will exist by the time you go to market. This intense competition also puts supply chains under pressure, and we must make sure we do not compromise process quality in our haste to reach the market.
2. **Globalization**—A significant part of the overall pharmaceutical market growth is predicted to take place in emerging markets. Many countries wish to manufacture in their markets because of the healthcare security it creates and because this type of high-tech manufacturing is seen as a key component of economic development. The cost of building and operating manufacturing capacity in a less-developed environment creates questions about the type and size of capacity we build in and around those different markets.
3. **Demand**—The physical quantity of biopharmaceuticals we need to deliver is changing considerably. There will be more processes where the amount of material required will be less than 500 kilograms and, in many cases, it may even be around the 100 to 200 kilogram level. This is in stark contrast to an industry founded on a small number of relatively large-volume processes. Other demand risks to consider:
 - building too much unused capacity based on expected demand can lead to unfavorable manufacturing economics
 - building too little capacity can result in missed market opportunity
 - manufacturing capacity is often built before regulatory approval
 - a product may not be approved, leaving capacity unused.

With these factors in mind, a manufacturer must ensure it has the appropriate manufacturing capacity and can secure enough of the raw material supply chain to meet the demands of this rapidly growing environment. The challenge is made more complex because of some unique features of biopharmaceutical manufacturing, such as:

- the complexity of the biopharmaceutical drug and manufacturing process, where the process defines the nature and quality of the end drug
- processes that are consequently difficult and expensive to change for regulatory reasons
- supply chains with unique raw materials, which are often natural products and single-sourced
- costly manufacturing infrastructure with long construction lead times

To overcome these challenges, you need robust processes (i.e., processes that tolerate to the greatest extent possible raw ma-

terial and process variation) without impacting batch quality. You must also have transparency and reliability with your supplier, as well as delivery at a high level of consistency. Finally, appropriate choice of manufacturing technology can significantly impact the time and capital risks of building manufacturing infrastructure.

Scale up or scale out?

The breakdown of the cost of goods for manufacturing an antibody shown below provides important insights into managing the costs and risks of manufacturing. The variable costs, such as cell culture media, chromatography resins, disposables, and consumables, are a relatively small part of the equation. Yet, the fixed costs for the necessities that keep a facility up and running, such as electricity, security, and maintaining GMP qualification, account for 60 to 70 percent of an antibody's cost of goods. This percentage also includes the cost of depreciation. Most of these fixed costs have to be maintained irrespective of whether or not the drug is being manufactured (or in what quantity) (Fig 1).

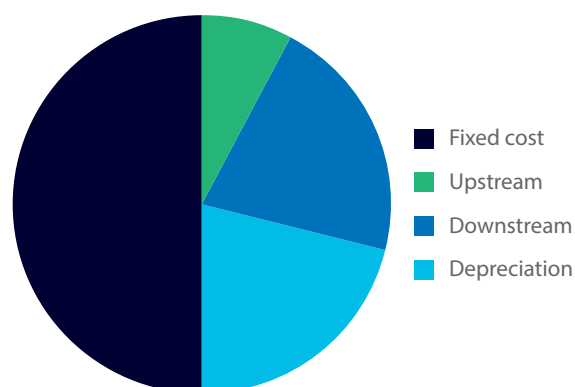


Fig 1: Nearly 70 percent of the cost of goods for manufacturing an antibody can be attributed to the fixed costs for facility maintenance and depreciation.

When you have this type of cost structure, the most resourceful way to manufacture economically is through *process intensification*. This allows you to drive as many batches of material through your facility as possible and to continuously improve throughput. Yet to benefit, you must be able to *sell* these batches. Additional batches of an antibody produced or an extra 1 percent yield over a year could be worth tens of millions of dollars in sales in Western markets. If you can find a way to make your facility more efficient, you can potentially delay investments in new facilities to meet increased demand that range from tens to hundreds of millions of dollars.

Process intensification is driven by many technological trends. In particular, the last 10 years have seen tenfold increases in the efficiency of cell culture, allowing the use of smaller bioreactors.

Purification processes are similarly shrinking as new chromatography resins are adopted to match the increasingly efficient upstream. Many efforts are underway to make manufacturing more continuous, for example, by reducing time-consuming hold steps in processes. Better equipment design is leading to reduced maintenance and cleaning time. The introduction of single-use technology (SUT) is eliminating costly and time-consuming cleaning and changeover costs and delivering more productive manufacturing time.

Some feel they have commercial certainty, based on product demand, and, as a result, continue to build capacity at large scale. However, a desire to mitigate the risks of determining manufacturing capacity before a drug hits the market and less overall appetite for capital risk have increased focus on building smaller facilities. This approach is often based on the benefits of SUT and process intensification technologies to maximize output from the smallest possible facility footprint. Combining those types of technology with new approaches to constructing manufacturing capacity, particularly the design and rapid deployment of modular-type facilities, is changing the way we think about the overall scale paradigm. Rather than scaling up to increase output, for example, by increasing bioreactor volume, a manufacturer instead scales out by rapidly building smaller facilities to increase drug output as demand increases. This reduces capital risks in the early stages and allows a more dynamic matching of capacity to demand.

Two of the biopharmaceutical market's biggest players, Samsung and Amgen, demonstrate the two extremes in the industry when it comes to choosing capacity and technology. In 2015, Samsung BioLogics announced the construction of its third manufacturing plant in Songdo, Incheon, in South Korea. The facility, where commercial production is expected to begin in 2020, will make the company the largest "pure-play" biologics contract manufacturer in the world. The \$750 million, 180 000-liter capacity plant is expected to manufacture 4500 kilograms of biological product each year.⁵ On the other end of the spectrum is the Amgen facility recently built in Singapore, which adopted a flexible, modular design.⁶ It has a footprint of only 120 000 square feet (75 percent smaller than a conventional facility), which can be rapidly reconfigured. In contrast to Samsung's use of 15 000-liter bioreactors, Amgen's facility uses 2000-liter bioreactors that accommodate single-use bags. This setup allows operators to easily switch among equipment to make different products.

So how do you know which type you should build? The answer is dependent on the amount of risk you are willing to take. If you believe you have commercial certainty for your product and expect to need large amounts of material, most likely to supply a global market, building a large, conventional infrastructure can give excellent economics, albeit with a large up-front capital investment. If, on the other hand, you are targeting fragmented markets, niche products, and regional supply, then building a smaller, often SUT-based infrastructure is worth serious consideration. Some questions to consider are: What size of demand are you manufacturing for? What's your

market like? What is your confidence about being able to deliver to market? Make sure you consider the technology progress that has been made with titers, continuous processing, and SUT.

With new technology and facility types, you can build your facility much more quickly than you could in the past. This allows you to make crucial decisions later when you have a better idea about the success of your product in clinical trials and the demand you will potentially face when you go to market. The scale-out, rather than the scale-up, paradigm is becoming a credible way to deliver more volume to the market, as our ability to build manufacturing infrastructure accelerates through modular and single-use technologies and increased focus on process intensification.

References

1. *Jagschies, G. et al., Biopharmaceutical Processing: Development, Design, and Implementation of Manufacturing Processes, Elsevier (2017)*
2. *Generics and Biosimilars Initiative (GaBi online) — <http://www.gabionline.net/Biosimilars>*
3. *The Investor, Celltrion's Remsima will take away half of J&J's original drug share in US market: CEO — <http://www.theinvestor.co.kr/view.php?ud=20170419000819>*
4. *EvaluatePharma, World Preview 2017, Outlook to 2022 — <http://info.evaluategroup.com/rs/607-YGS-364/images/WP17.pdf>*
5. *FiercePharma, Samsung Biologics nears finish line with massive biologics manufacturing project — <https://www.fiercepharma.com/manufacturing/samsung-nears-finish-line-massive-biologics-manufacturing-project>*
6. *Amgen Science, The Next Generation of Biotech Manufacturing — <https://www.amgenscience.com/next-generation-biotech-manufacturing/>*



Modular approaches for diverse molecules: Reinventing smart bioprocessing

by Dr. Stefan R. Schmidt, MBA
Chief Scientific Officer
Rentschler Biopharma

As biopharma companies develop growing numbers of biologic therapeutics and drug budgets are squeezed worldwide, there is an increasing pressure on manufacturers to find more efficient and effective production processes. To reach this goal, Rentschler Biopharma, an independent and family-owned contract manufacturing organization (CMO) based in Laupheim, Germany, is using an approach it calls “smart bioprocessing” to create scalable manufacturing processes rapidly and efficiently.

Manufacturing biologic drugs: Upstream and downstream

Monoclonal antibodies have become one of the most commonly manufactured complex biologic molecules by CMOs. There are also growing demands for hard-to-produce biologics, including fusion proteins, bispecific antibodies, and antibody-drug conjugates to meet specific therapeutic needs. In this burgeoning area of complex molecules, cost-effective manufacturing is critically important. This is particularly true for cost-sensitive applications such as biosimilars and for molecules used to treat rare and orphan indications, where market size is limited. Small companies and startups with financial constraints also look for lower-cost support to be able to move rapidly through proof-of-concept studies to support deals.

To ensure that their manufacturing methods are as efficient and cost-effective as possible, CMOs look to optimize production and

purification using platform processes, continuous processing, and process intensification. Many factors need to be considered when developing a manufacturing process, particularly for a complex biologic (Fig 1).

The first step in development is molecule design. This includes adapting the building blocks of the molecule — for instance, to improve the glycosylation sites or using protein engineering to enforce heterodimerization of bispecific antibodies.

The next step involves the generation of the cell line, which begins with a choice of the mammalian host, such as hamster, mouse, or human cells. The decision depends on the type of protein to be produced, as these hosts differ in their ability to generate glycosylation. The DNA coding for the target protein must then be integrated into the cell genome, and recombinant cells are selected primarily according to expression levels, a process that traditionally takes around 18 weeks. Rentschler Biopharma has developed a process that uses site-directed integration in Chinese hamster ovary (CHO) cells to speed up the transfection process. This, along with fluorescence-activated cell sorting (FACS), halves the cell line development timeline, cutting it to around nine weeks.

One key factor in the economics of protein manufacturing is the level of protein produced (titer). In the early days of protein manufacturing in the 1990s, 0.1 g per liter was an acceptable level. Current commercial manufacturing capacities are more commonly around 5 g per liter, though levels of 10 g per liter or more can be

Codon optimization

Modification of:

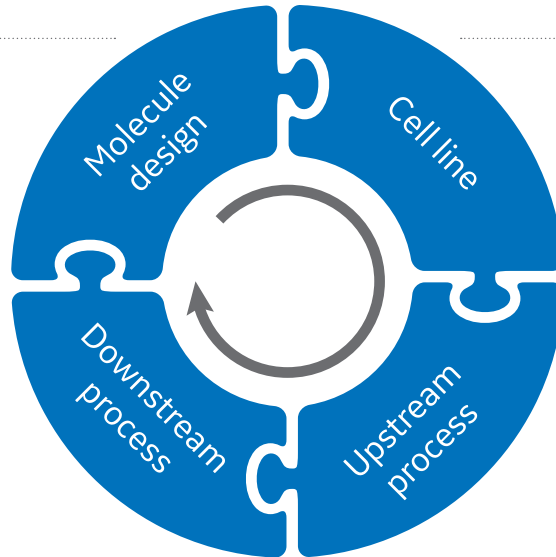
- Protease or PTM sites
- Aggregation prone regions
- Oligomerization

Process-related impurities

Product-related impurities

Virus clearance

Aggregates



Host cell choice

Integration strategy

Clone selection:

- Stability
- Titer

Media & Feed selection

Cell behavior:

- Viability
- Productivity

Product attributes

Fig 1: Considerations at different steps in process development

achieved. Routes to increasing titers include cell line engineering, growing cells in higher densities (which requires higher levels of nutrients and oxygen), and changes in processes, such as moving from batch to continuous perfusion processes.

The final step, downstream processing, is harvesting the proteins and removing any process- and product-related impurities, such as host cell protein, DNA, protein A, fragments, aggregates, and undesired isoforms.

The application of “smart bioprocessing”

The drivers of manufacturing therapeutic proteins are upstream productivity, protein quality, and overall cost. The aim of smart bioprocessing is to use bioinformatics, lab-scale processing, and analytics to create better process designs that can be verified before they are scaled up to clinical trial and commercial-scale production.

The smart bioprocessing approach is modular and iterative (Fig 2). Analysis after each step provides more information that can be fed into the next step, and steps can be repeated to refine the entire production process.

The aim with “smart bioprocessing” is to front-load the critical analytics steps and solve as many issues up front as possible before moving into the small-scale and design steps. Once the initial small-scale production begins, the developers can look for issues in the production or purification process and find ways to solve them before moving up to a larger scale. By gathering theoretical and experimental information as early as possible and then ironing out problems at a small scale, it is possible to verify that the process works before committing to larger-scale production.

The end goal is to create a robust and reproducible good manufacturing practice (GMP)-ready process that meets the criteria for overall yield, achieves the critical quality attributes, and creates a final downstream processing specification ready to scale up for production.

Applying bioinformatics:

Assessing product properties

In silico bioinformatics allow process developers to analyze biologic molecules and predict how they will act in given situations. Screening and modifications at this stage mean the molecule can

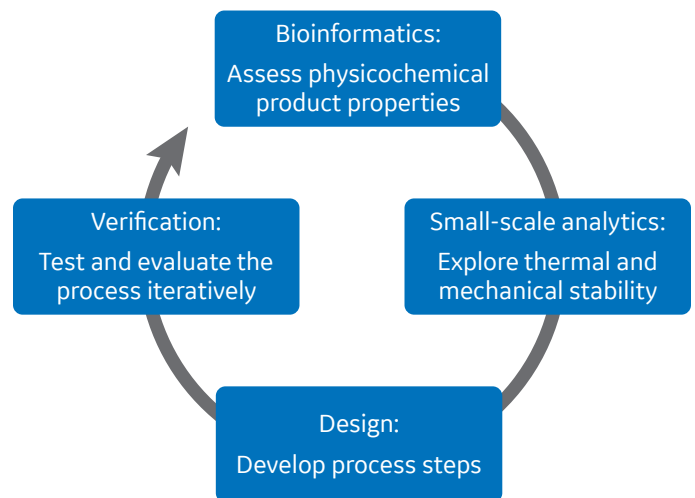


Fig 2: The smart bioprocessing approach

be optimized to refine post-translational modifications (PTMs) or to eliminate protein aggregation and therefore increase yield.

Examples of physicochemical properties that can be predicted using bioinformatics:

- Isoelectric point (pI)
- Charge distribution and hydrophobicity
- Aggregation-prone regions
- PTM sites
- Protease sites
- Immunogenicity

Companies will need training and expertise to make the most of bioinformatics and *in silico* screening, but the hurdles for this are much lower than they have ever been, with resources and applications available online or alternatively as desktop solutions. In that context, it is important to remain aware of security and confidentiality issues.

Small-scale analytics: Exploring stability

Once the physicochemical molecular properties are assessed using bioinformatics and the product is expressed in a cell line, explorative capture studies follow. The preliminarily purified protein is then evaluated for its stability at different temperatures and how it copes with the steps used in virus removal/inactivation, which include low pH, or the use of organic solvents, and detergents.

It is also important to look at the mechanical stability of the protein during stirring, agitation, and shaking, as these will be part of the normal production and purification steps. This practical combination of analytics steps allows confirmation that *in silico* predictions work in the real world.

Design: Process development

The process design stage includes putting together a lab-scale bioreactor and looking at increasing the level of expression of the protein to as high a titer as possible. However, besides expression levels, product quality must also be considered. Several variables can be changed and evaluated in the bioreactor to improve the yield, including:

- Cell culture mode — batch, fed-batch, or continuous perfusion
- Length of culture time
- Cell density
- Oxygen levels
- Media type
- Nutrient levels and feeding strategy
- Temperature

The process development steps are iterative, with the process developers working at a small scale and modifying these variables individually. Analysis of the protein's quantity, purity, and quality attributes shows the impact on the final process, and each change brings an optimized design a step closer.

Verification: Testing and evaluation

The final test is confirming the feasibility of the process, including confirming the purification steps and finalizing the downstream specification. For this, the proteins must reach the appropriate purity and quality targets, and the process must be GMP-ready and economically viable.

Achieving the benefits of smart bioprocessing

A modular approach to molecule optimization and process development will save money, time, and effort. An ideal manufacturing development process would begin at the stage of molecule design to create a molecule that is optimized, for example, with low propensity for aggregation, high stability, and high expression. However, particularly for CMOs developing a manufacturing process on behalf of a client, this is not always possible. Pharmaceutical companies using this approach begin the process much earlier, which saves time and costs in manufacturing. Yet, CMOs often enter an existing process and then have to refine the process as tightly as possible to suit the molecule. In the future, it would be more efficient for CMOs to work with companies at an earlier stage to collaborate over the optimization of the biologic or even help to design the molecule from the beginning.

Overall, the aim of smart bioprocessing is to use bioinformatics, lab-scale processing, and analytics to create better process designs that can be verified before they are scaled up to clinical trial and commercial-scale production. Companies should start by carrying out as much analysis *in silico* as possible up front to identify potential problems and eliminate them by redesigning the biologic, if possible. Then, they would verify the predictions from the *in silico* analysis in small-scale studies. It is crucial to identify the challenges properly either by *in silico* or experimental approaches to be able to react accordingly in the process design.



Industry 4.0: Embracing digital transformation in bioprocessing

by Per Lidén
Product Strategy Manager
GE Healthcare Life Sciences

Since the dawn of manufacturing, we have seen several different industrial revolutions, all enabled by significant leaps in productivity. Each of these revolutions marked a major shift in the economy and changed the way companies do business to meet the demands of their customers. The last big revolution came with the introduction of computers on manufacturing lines. This gave way to the advent of automation, which increases efficiency and speed and minimizes process variability caused by humans. While slower to adopt automation than other industries, the pharmaceutical industry continues to find ways to use it for improving quality and speed to market. Now, another transformation is taking place that will pave the way for even more changes to how the industry approaches drug manufacturing.

In the latest phase, often referred to as Industry 4.0 (Fig 1), cyber-physical systems control and monitor activity through computer-based algorithms. While this may seem like science fiction for an industry that is arguably still working through the former industrial revolution, the *benefits of embracing* it are too substantial to ignore. Experts expect this revolution to trigger a quantum leap in productivity, as these connected machines and software systems can enhance the human workforce in new and exciting ways. In bioprocessing, there is a plethora of possibilities that could be realized over time through this revolution. For example, in the near future, it can be expected that the tools of Industry 4.0 will minimize maintenance downtime and spare part inventory for process equipment and enable the continuous improvement of process robustness and efficiency.

An evolving industry needs connected data

The landscape of today's pharmaceutical industry looks much different than the one manufacturers navigated 20 years ago. An impressive growth in biopharmaceutical innovation has not only brought new possibilities in patient care but also challenges in terms of manufacturing. Many of the new and innovative approaches to medicine involve niche drugs that target smaller patient populations, which means drugs are manufactured in much lower volumes. Because of this, it is critical that manufacturers improve their operational efficiency to reduce the overall cost of drug development and manufacturing, in order to be able to meet the public's demand for access to new drugs and reasonable pricing. The Industry 4.0 paradigm will help achieve this.

According to this paradigm, an isolated, vendor-centric world is inefficient in that it often means end users of manufacturing software systems must develop costly proprietary point solutions. This limits the ability to leverage the best expertise because it inhibits the transfer of already-developed solutions, collaboration, and communication across multiple companies. In a new world of manufacturing, open systems leveraging standards for interoperability and data exchange, such as open platform communications (OPC) and other applicable standards yet to be developed, will liberate data. It can then be connected and contextualized for use in a large variety of applications. The

goal is to facilitate better decision-making, identify improvement opportunities, and, ultimately, optimize operations. Some areas where connected data in bioprocessing could offer productivity gains include:

- **Uptime**—When equipment is connected, it allows better visibility into its condition. Instead of waiting for something to break, a manufacturer can monitor the condition of its equipment and become predictive about maintenance. From a supply chain perspective, it allows visibility into which materials are needed at what time, which can reduce unnecessary inventory as well as operating delays.
- **Process understanding**—The operations systems used today, such as control automation systems, manufacturing execution systems (MESs), and laboratory information management systems (LIMSs), are designed to make sure a batch runs properly and smoothly every time. However, the data these systems generate is typically not aggregated across batches and connected between systems in a way that enables better decision-making. To achieve a more holistic view of the plant and process performance, a manufacturer needs to unlock the data from these silos. This step will shorten the time for carrying out investigations and other process troubleshooting.
- **Robustness and productivity**—As data becomes more readily available, it becomes possible to proactively augment an understanding of the sources of variability in manufacturing processes. This will reduce the number of investigations needed and possibly even eliminate batch failures. Access to data will also result in the identification of process improvement

opportunities and the implementation of changes to increase productivity. It is not uncommon to find that output from a biomanufacturing process can be significantly improved from the optimization of control parameters within the ranges already filed and approved by regulatory authorities.

- **Compliance**—When connectedness between systems and data is leveraged to enable new applications, data integrity becomes even more important. As this happens, new opportunities to maintain compliance will likely present themselves.

Digital transformation of biomanufacturing will be driven by observing the performance of processes and workflows to determine where improvements can be made. This requires a connected infrastructure where the data can flow and be visualized. It also necessitates connecting teams, so people can collaborate around *desired outcomes*. From there, the data to do predictive analytics can be applied, such as building knowledge and focusing on specific, and increasingly bigger, problems. As this scales up successfully, fully integrated prediction models can be achieved, leading to overall process optimization.

How to succeed with digital transformation

To succeed with digital transformation, there are two aspects that must be considered. The first is implementing new technology. Industry 4.0 is about building tools that leverage and interpret data from various systems so they can operate and communicate with each other (Fig 2). Data is the raw material

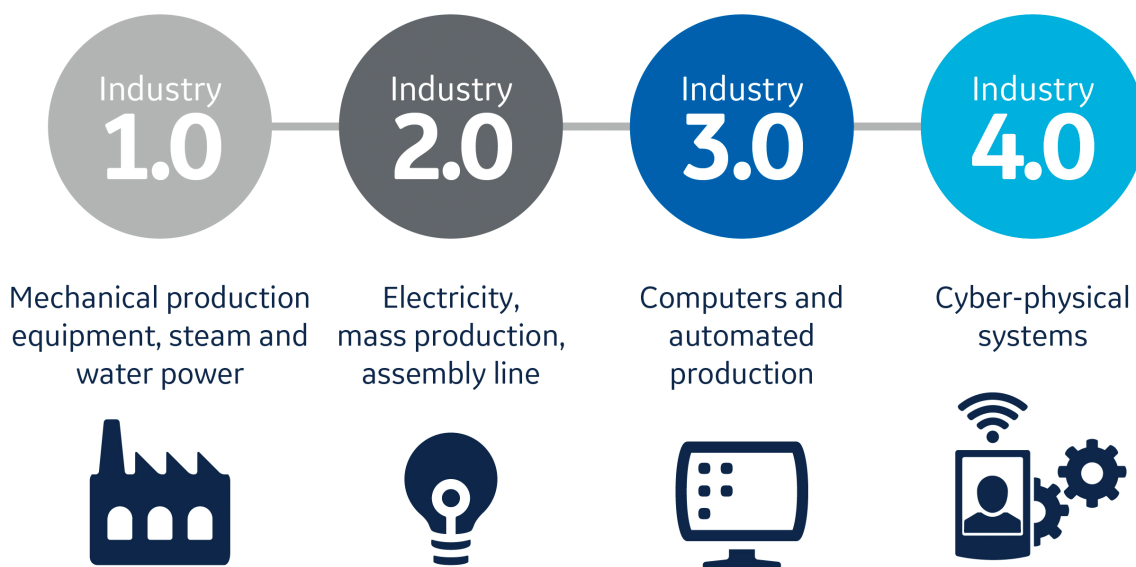


Fig 1: The impact of cloud computing, machines connected to the internet, and more powerful software for industry is expected to lead to a quantum leap in productivity. Other significant industrial productivity leaps in history have had significant impact on the economy, leading them to be called industrial revolutions. The phase we are in now is the fourth such transformation, which is why the term Industry 4.0 has been coined.



Targeted business applications

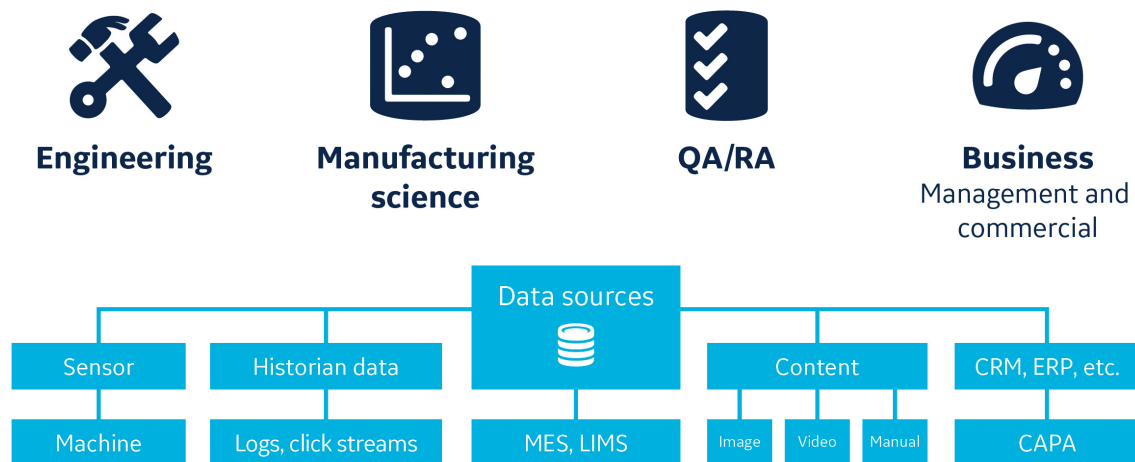


Fig 2: Unlocking data using open standards is one of the first steps in realizing Industry 4.0. Once data is made available through modern software platforms, the quantum leap in overall industrial productivity will come from introducing multiple relatively small gains in a systematic manner across the enterprise. In bioprocessing, this enables addressing improvements across areas that traditionally have been isolated. This includes equipment maintenance and uptime, process performance, compliance, production scheduling in a harmonized manner, leading to the rapid advancement of continuous productivity improvement. Abbreviations: MES – manufacturing execution system; LIMS – laboratory information management system; CRM – customer relationship management system; ERP – enterprise resource planning system; CAPA – corrective and preventive action system

that drives continuous improvement. If it is not possible to access data across your facility, the knowledge needed to make meaningful and effective changes will not be available. If it is accessible, a manufacturer has the ability to discover inefficiencies in its processes. While it is possible to find a few major improvement opportunities, the quantum leap in efficiency will come from many small, incremental gains that, together, result in significant cost savings. Any improvements, whether they are big or small, that are made over time and introduced in a systematic manner will multiply across the manufacturing operations rather than add up.

The other aspect of digital transformation is effectively managing change within an organization. A change in culture usually comes from the top down, so embracing and executing something that could cause fear and resistance (especially due to job security concerns) should begin with a company's senior leadership. There must be an environment where risk is not only encouraged but also embraced. Succeeding with digital transformation also requires a review of how relationships outside of an organization function. For example, in today's industry, the vendor/manu-

facturer relationship is typically very transactional. However, following the principles of open interoperable systems and collaboration outlined above, there are plenty of mutual benefits to be gained for both suppliers and end users through shared data and knowledge.

A case study presented by GE Healthcare and Biogen at the 2016 Recovery of Biological Products Conference showed how collaboration across parties and the sharing of data can lead to greater success.¹ For the study, a problem was identified with how process variability is managed in today's industry. Specifically, there was an inadequate understanding of the impact of raw material variability and how to respond to it. While there is a great deal of rigor in process development, key uncertainties about process robustness still exist in the commercial phase of manufacturing. The related risks are typically being dealt with in a reactive manner. This leads to lengthy investigations, heroic efforts to rectify the process performance, and even batch rejections. Therefore, there is an opportunity to become proactive with this issue, in order to continuously:

- assess variability and retire risks
- build shared process knowledge
- improve efficiency

This case study was performed on a legacy process that had been replaced and was carried out by retrospectively analyzing seven years of data. The objective was to mimic the knowledge and, even more importantly, identify gaps in that knowledge at every point in time. The approach of the study was to combine process data from the manufacturer with detailed raw material data from a supplier, in order to create a holistic view of process performance.

GE and Biogen were able to proactively identify and detect potential variability risks that were missed at the time the process was run and also successfully predict a critical quality attribute. That prediction model can serve as an important detection mechanism for further potential variability risks, which, in turn, helps identify mitigation activities. Using this collaborative approach, manufacturing processes become connected, creating a need for long-term strategic partnerships around process life cycles. This is a major change of mindset from today's typical supplier/end user relationship, as this level of openness requires a lot of trust between the parties.

Suppliers can use data to help users of their material make smart choices from the beginning, understand risks that might be involved in variability, and aid in making the right choices to create control strategies that have a high chance of being successful. Later, when it is time to understand the variability, end users can determine how much effort to put into their characterization in relation to the risk they will be reducing. Suppliers can help by offering knowledge about how materials perform in the targeted applications and assist with making those risk assessments. Depending on what is learned during process development, suppliers can also contribute to the evaluation of possible control strategy options. The relationship then becomes a true

partnership where each side provides guidance and support and works toward the same goal.

What biomanufacturers can do to prepare for industry 4.0

Overall, to realize the long-term benefits of digital transformation, start working on a strategy now. Develop a vision and complement that with pinpointing any problems today that could realistically be solved by greater insights from data. Leverage short-term successes and then make sure to use the returns from these to fund the next project. This way, it is possible to implement programs that have a focus on business outcomes rather than technology, which facilitates the human aspects of digital transformation. Finally, keep in mind that digital transformation requires collaboration with manufacturers, suppliers, and other business partners. Identify those who are willing to share this journey through a foundation of trust, dedicated collaboration, and open communication.

References

1. *Malmquist G, Jiang C; Smart²: a synergistic life cycle approach to understand and control raw material variability through collaborative process analytics; Recovery of Biological Products RXVII, Bermuda, June 2016*

“ Experts expect this revolution to trigger a quantum leap in productivity, as these connected machines and software systems can enhance the human workforce in new and exciting ways. ”



Are today's processes efficient enough for the future of vaccine and viral vector production?

by Dr. Mats Lundgren
Customer Applications Director
GE Healthcare Life Sciences

While vaccines are critical to the survival of many patient populations, especially children, they were previously considered low-revenue products, generating limited interest in the market. Consequently, North America has seen a significant decline in the number of vaccine manufacturers over the years. Nevertheless, new trends are changing the vaccine market, and viral vector-based vaccines and other therapies are becoming essential to the treatment of many diseases, sparking new interest across the industry. Even the groundbreaking area of cell and gene therapy is seeing the application of viral vectors as a platform for vaccines and therapeutic applications. As a shift toward high-value, low-volume vaccines and viral vector-based therapies continues, it is important to recognize the limitations of today's production processes in order to *overcome the challenges, complexity, and high cost of manufacturing* these drugs.

Viral vectors and therapeutic vaccines poised to stimulate game-changing growth

Vaccine manufacturing is a complicated and diverse area of medicine that is expected to see a significant increase in revenue over the next several years. By 2025, the market is expected to reach \$100 billion (up from just \$2.9 billion in 2011).¹ Prophylactic vaccines, such as childhood vaccinations, will always be in

demand. However, *viral vector platforms*, such as Adenovirus, are a promising area of growth emerging at the crossroads of immunotherapy in oncology and vaccines. In 2016, there were over 700 active clinical trials exploring the use of viral vector-based vaccines for viruses, such as retroviruses and vaccinia (Fig 1).²

Another interesting growth area is oncolytic viruses, such as IM-LYGICTM, which is "a genetically modified oncolytic viral therapy indicated for the treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery."³ IMLYGIC became the first approved therapy of its kind in 2015.

While these innovative new drugs are exciting for patient care, they do bring several challenges into focus when it comes to production, due to inefficient and cumbersome manufacturing processes. To understand how to resolve the issues with today's virus production processes, it is important to first understand what challenges they present.

Virus production processes

The processes used today for vaccine production were developed many years ago. Scientists followed an empirical methodology that sometimes resulted in processes that were difficult to scale up or did not have optimal process economy. Considering that viral vector-based vaccines targeting smaller patient populations

come at a higher price but in lower volumes, it is imperative to explore less costly ways to produce vaccines. One way to do this is by taking advantage of the rapid technology advancements in both the upstream and downstream processing of vaccines.

A major issue with legacy processes is that they are not based on platform technologies. For example, they rely on old cell substrates or, in the case of the influenza vaccine, eggs. Many cell lines are excellent for virus propagation. However, they have not been used for the production of approved vaccines and the safety track record of new cell lines is important in order to facilitate regulatory approval. Due to safety aspects and the fact that it is scalable at high volumes, animal origin-free cell culture media is preferred. Also, with anchorage-dependent cells, success is dependent on the surface the cells grow on. Adherent cells were often grown in roller bottles or cell factories, but these technologies are difficult to scale up. In this case, microcarriers can be used instead. With these, there is high volumetric output by maximizing the surface-to-volume ratio. Recently, regulatory authorities discouraged use of roller bottles because of concerns about cross-contamination. This is driving companies to move to microcarrier systems in bioreactors as well. Not only does the use of old processes make it difficult to be compliant with modern-day requirements, but regulatory requirements are also frequently increasing, making it harder to maintain compliance.

Another challenge with early vaccine processes is the use of centrifugation or size-exclusion chromatography for purification and polishing steps. While these are powerful technologies when it comes to purification, they are not easily scalable. This issue can be addressed by using a multimodal chromatography resin,

such as GE's Capto™ Core 700, which allows efficient capture of contaminants while target molecules are collected in the flowthrough. The Capto Core 700 resin can increase speed and improve process economy, which is crucial in vaccine manufacturing in order to keep production costs competitive.

Single-use equipment in vaccine manufacturing

An effective way to improve scalability and process economy is through the use of single-use technology (SUT). Apart from a few exceptions, such as *cell-based influenza*, most vaccines are manufactured in batches in the range of 100 to 500 liters, which makes SUT ideal. The other characteristics of SUT, such as reduced cleaning requirements, improved batch turnaround times, and increased flexibility, also make it an attractive option. Faster turnaround time is especially appealing to those focusing on pandemic preparedness, as it requires even faster development, scale-up, and manufacturing times. While there are concerns related to the amount of consumables needed for SUT, the cost savings of a smaller footprint and fewer cleaning requirements should offset any doubts about the financial benefits. In addition, building a stainless-steel facility can take anywhere from three to five years, while the average time to build a single-use facility is 12 to 18 months. A shorter timeline translates to cost savings, but possibly more importantly, it greatly reduces the risks related to predicting capacity far before a company is sure about demand.

SUT also facilitates multi-product manufacturing, which is common in the vaccine industry, especially in smaller companies.

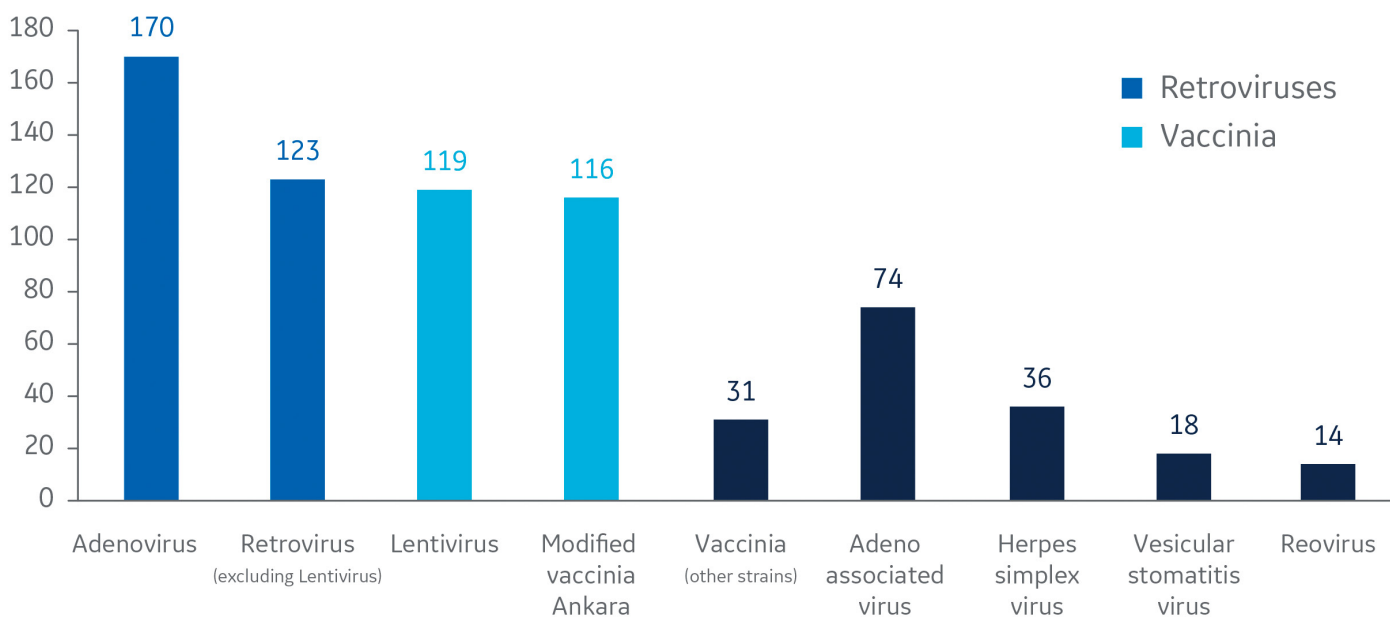


Fig 1



“ There is a paradigm shift taking place where vaccine production is shifting from a lab bench process to rational design that incorporates process economy calculations early. ”

Finally, there are regulatory advantages with SUT as it relates to live virus production, as one can, to some extent, *avoid the risk of cross contamination* that could come from insufficiently cleaned stainless-steel equipment. Nonetheless, SUT would not work for vaccines that have very harsh process chemistry conditions or for any drug with large-scale demand.

In summary, there is a paradigm shift taking place where vaccine production is shifting from a lab bench process to rational design that incorporates process economy calculations early. *Scalability* becomes critical as the industry seeks ways to address disease prevention in multiple populations across the world. Utilizing a combination of SUT and modern resin techniques yields the advantages necessary to be successful in this diverse and growing market.

References

1. World Health Organization, *Global Vaccine Market Features and Trends* — http://who.int/influenza_vaccines_plan/resources/session_10_kaddar.pdf
2. *Based on an internal analysis of worldwide R&D pipelines over a seven-year period (includes active trials in December 2016 but excludes suspended/terminated/withdrawn trials)*
3. Amgen, FDA Approves IMLYGIC™ As first Oncolytic Viral Therapy In The US — <http://www.amgen.com/media/news-releases/2015/10/fda-approves-imlygic-talimogene-laherparepvec-as-first-oncolytic-viral-therapy-in-the-us/>



Striving for bioprocessing excellence: Balancing modern approaches to manufacturing

by Madhu Raghunathan
Product Strategy Leader
GE Healthcare Life Sciences

The key factor driving change in today's pharmaceutical industry is the impressive rise in biologic drugs, which now make up 25 percent of the total pharmaceutical market.¹ Companies targeting biologics face a new frontier in development and manufacturing, as these drugs are complex, diverse, and difficult to produce. This complexity and the emergence of biosimilars are driving cost efficiency, as well as promoting the adoption of more modern bioprocessing technologies. Compounding the challenge of biologic drug development is that manufacturers must gain approval from regulatory agencies on not just the biologic drug itself, but also the process used to manufacture it. This makes changing the production process after a drug and its process are approved both risky and costly, which is why some biopharmaceutical manufacturers are hesitant to try new and potentially more efficient technologies. Nonetheless, manufacturers may have to embrace change to remain competitive in this growing market. Several modern downstream technologies available today can improve efficiency and even quality, such as single-use technology (SUT). It is important to understand the benefits of each these options and how they can be used to forge a path toward bioprocessing excellence.

Weighing the options

Choosing a facility design and unit operation requires a balance among many factors. That is why no two unit operations are identical. Each has different goals from a process standpoint.

For example, the operating costs for a capture step are not the same as the operating costs for a virus inactivation step, due to the difference in tools, buffers, and other equipment used in each process. Some questions to consider during the decision-making process are:

- Is this a startup or a large, established biopharma?
- What type of product is being manufactured?
- What is the scale of operations?
- What is the in-house knowledge and capability?
- What level of demand is expected and, therefore, how much capacity is needed?

The answers to these questions will help determine the most suitable facility design and unit operation for the project. There are specific considerations, though, when reviewing upstream options versus downstream options. With upstream processing, there is a higher processing volume, a growth environment, a greater presence of in-process impurities, and, consequently, a higher risk of bioburden. As a result, the cleaning-in-place (CIP) and sterilization-in-place (SIP) requirements are more complex. In downstream processing, the value of the biologic drug and the burden of demonstrating purity of the drug increase exponentially. Because of this, the complexity of the analytical instrumentation needed also increases, which is reflected in the cost of consumables for a bioreactor versus the cost of consumables for an SUT flow kit.

In many instances, it makes sense to apply SUT upstream. In others, it may not make equal sense to apply it downstream, especially at a commercial scale when manufacturing several batches of the same product. There may be other scenarios, such as preclinical or clinical manufacturing or switching frequently between molecules, where SUT makes sense also downstream. Even though the analytical burden is still there, other drivers, such as getting to market faster, have a greater weight than cost. In this case, operating cost may be sacrificed in lieu of other considerations. At commercial scale, though, the cost profile becomes more important, and other trade-offs may be made that a manufacturer was not willing to make at a smaller scale.

One design option to consider is to start out small and then scale out over time instead of scaling up. The risk being that, if there is not enough capacity when it is time to scale out, the result could be costly production delays as well as a possible loss of market share. Another design option is to make the facility flexible enough to accommodate different types of molecules. This creates its own challenges, as a flexible facility can be difficult to accommodate because it drives up the complexity. An equipment and solutions provider becomes a great resource in this situation, as they can assist in selecting processing tools that fit a project's needs based on the objectives.

The benefits of SUT in the new era of biomanufacturing

When looking at the industry's current pipeline, the vast majority of registered biological drugs have an annual volume between 100 and 500 kilograms. SUT's ability to produce small batch

volumes such as these is one of its major benefits, especially in an era when manufacturers are targeting more niche drugs for smaller patient populations. In addition, future upstream titers are anticipated to be 5 grams per liter and above. At lower volumes and higher titers, the cost benefits shift more toward SUT, although this is not a black-and-white conclusion.

The biggest driver of its popularity is the ability to build out a facility using SUT as opposed to building the entire facility up front and expecting (or hoping) the demand will come at some point in the future. In the case of stainless steel, a facility takes from three to five years to build. It is challenging to know that far ahead what the demand of a drug will be. And when determining which type of facility to build, it is important that capacity matches the demand profile for the drug being produced. The timeline for SUT is much shorter (12 to 18 months). While this does not mean SUT is always the best option, it does offer a distinct advantage in terms of demand forecasting. Other major advantages of SUT include decreased capital investment, smaller footprint, reduced cleaning requirements, and increased process flexibility.

Managing an SUT cost profile

One way to manage an SUT cost profile is to use disposable technology in earlier clinical phases and then shift over to stainless steel once a project moves to commercial scale. Also, SUT does not have to be for only one particular unit operation. It can be combined among unit operations by using a single-use chromatography step combined with a single-use filtration step. This is achieved by using the method queue feature in system control software, which combines different unit operations under *one automation method*. Such a setup eliminates interactions when moving from one unit operation to another, and there are

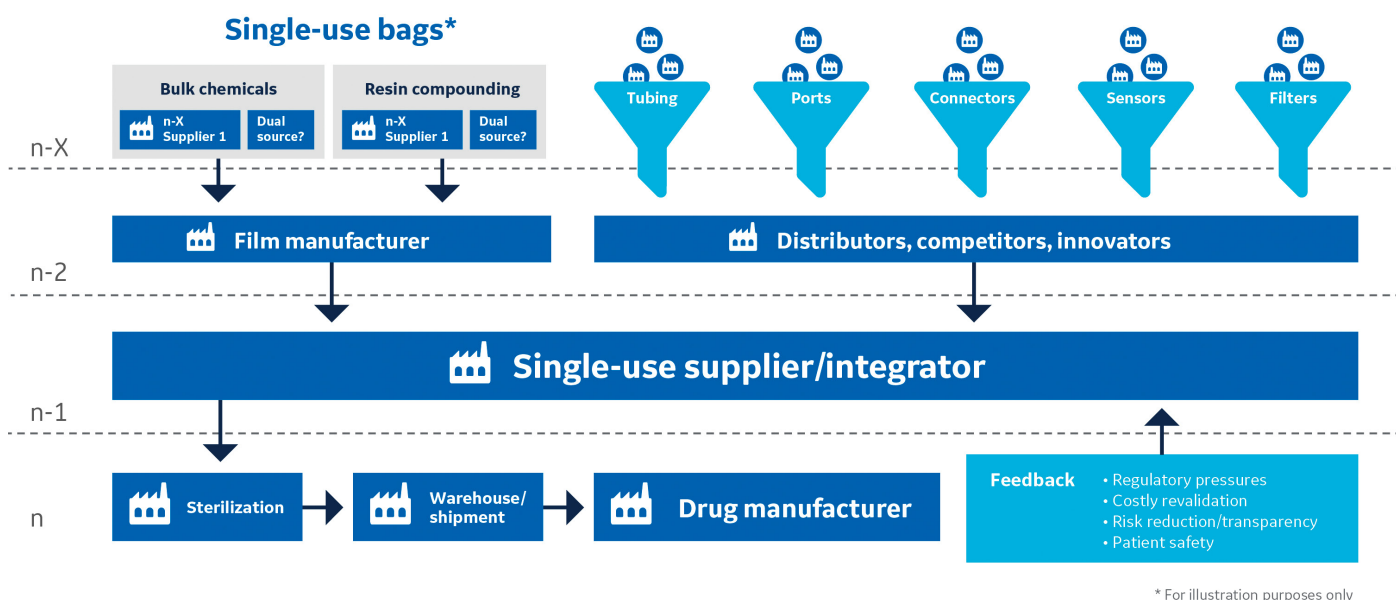


Fig 1: Complexity of single-use supply chain necessitates collaborative relationship across the network.

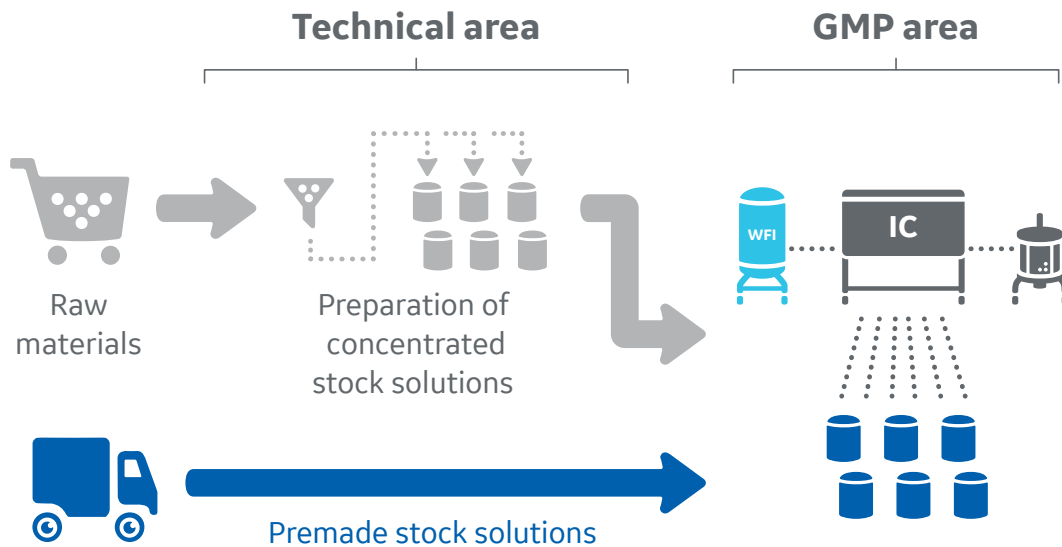


Fig 2: Approaches to realizing full benefits of premade buffers and in-line conditioning technology.

no intermediate pool vessels or holdup vessels. There are also a number of advantages to not focusing on one unit operation but extending the same principle to connecting a few unit operations.

SUT does have its limitations, though. The technology's flow kits have physics-based restrictions on what they can support, such as on maximum pressure rating and flow rate. In terms of sensors, single-use sensors are less sensitive than traditional sensors. In addition, SOPs are often written for the use of traditional sensors and technologies, so it may not be possible to switch to a single-use sensor without changing the SOPs. There is also the consideration of other important factors, such as extractables and leachables, integrity (i.e., bag leakage), and the ordering and management of single-use consumables. Overall, SUT requires more trust with a vendor to make sure there is security of supply in order to have the consumables necessary (Fig 1). If SUT is selected, understanding its benefits and challenges is critical. That knowledge can facilitate implementation and, if applicable, ensure a smoother transition, so the full benefits of SUT can be realized in the unit operation.

Intensification of traditional approaches

While SUT offers appealing benefits, there may be resources or capacity already in use. This does not mean one must abandon those legacy processes and implement single-use processing tools instead. There are a number of ways to intensify traditional technologies.

In-line conditioning

One option is in-line conditioning or in-line buffer formulation. With this technology, the buffer is manufactured by manually combining the necessary components in real time. This can be

done in a buffer kitchen, and the buffers are then transported into the unit operations in a single-use bag. Another method is to manufacture the buffers at the point of usage in a chromatography or filtration step. The benefit of this technology is that manual operation and concerns for out-of-spec buffers are minimized.

It is important to remember that buffer conditioning is essentially diluting the buffer concentration to the concentration needed with the addition of Water for injection (WFI), which is not the same as in-line buffer dilution. Even though buffer conditioning is preferred over manual preparation, it still presents several challenges, such as managing, storing, and cleaning the large tanks where buffers and raw material are stored. With in-line buffer formulation, there is no need for tanks or manual intervention. The system dynamically prepares buffers to the required specifications based on the desired "recipe." If the buffer falls outside of those specifications, the in-line conditioning system automatically detects the deviation and makes necessary adjustments or executes a fallback strategy. By considering *buffer preparation* early, a manufacturer has enough freedom to make those changes and arrive at their desired endpoint (Fig 2). It also allows them to prepare their own stock concentrates or even go further back in the value chain to secure the stock concentrates directly from a vendor.

Buffer preparation is not often thought about up front, but instead only after something has gone wrong. Once that happens, a facility or process has already been designed so inefficiently that the entire process becomes a bottleneck.

Prepacked, disposable columns

The universal benefits of SUT solutions also hold true for prepacked columns. For example, many steps are required today

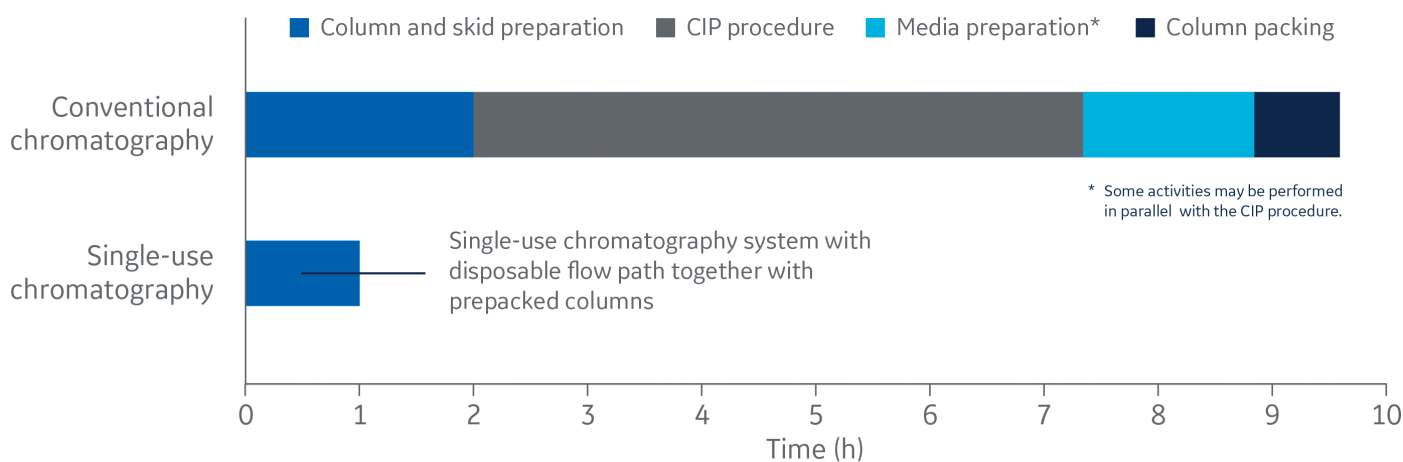


Fig 3: ReadyToProcess chromatography columns enable a nearly tenfold reduction in setup time compared with a conventional setup. Data compiled from GE Healthcare assessment studies.

before a clean-and-reuse column can be applied to a purification step. It can take up to several days to complete these steps. During preclinical or clinical manufacturing, time is precious, and the process for a clean-and-reuse column is very inefficient. A prepacked column comes pre-validated with documentation to demonstrate sanitization and that it is packed within the specified tolerance. This eliminates the time to pack the column and complete the necessary validation activities. It also minimizes the possibility of any cross-contamination risks. A prepacked column can be ready to use as soon as it is plugged in and connected to the system and buffers (Fig 3).

Continuous chromatography

There is a lot of buzz about continuous chromatography. Some see it as a valuable process intensification technology, while others are skeptical about its viability. Just as with SUT, there are situations when applying continuous chromatography makes the most sense, such as when dealing with low annual production. In this case, continuous processing can lower the initial capital investment needed and reduce facility footprint.

From a technical perspective, continuous processes could be considered when working with sensitive molecules or low selectivity operations, wherein a choice needs to be made between yield or productivity. High titers, in combination with periodic counter-current chromatography (PCC) dynamic control functionality, can improve process robustness with fewer safety margins. Preclinical or clinical manufacturing is also a sweet spot for continuous chromatography, as chromatography resins at this scale are not typically utilized to their full life cycle. However, with continuous chromatography, that can be overcome by cycling the purification step more often at smaller resin volumes.

A proper evaluation for a successful forward

In summary, several drivers affect how the appropriate facility design and unit operations for a process are selected. No universally accepted template works across the board, irrespective of business objectives, process outcomes, and resource/knowledge footprint. Regardless of how the process is designed, though, it is clear that many technologies today offer improved functionality and even new benefits. Therefore, while change can be intimidating, this disruptive innovation allows manufacturers to achieve the increased efficiency and quality needed in an industry that is quickly evolving. That is why it is imperative that each option is properly evaluated. This makes it possible to choose the one(s) that can sustainably deliver your desired results and offer the best chance of success in the new and exciting world of biomanufacturing.

References

1. U.S. News, Biologics: The Drugs Transforming Medicine — <https://www.usnews.com/news/healthcare-of-tomorrow/articles/2017-07-25/biologics-the-drugs-that-are-transforming-medicine>



Optimizing process efficiency in upstream manufacturing

by Dr. Andreas Castan
Staff Scientist
GE Healthcare Life Sciences

Process efficiency is a key goal for biopharmaceutical production, focused on increasing the process' speed, keeping costs under control, and building flexibility into the process, all while maintaining the quality of the final product. In this article, several different approaches and technologies will be detailed that can significantly improve the efficiency of upstream processing, including cell line development, process development and process intensification, real-time analytics, and process integration.

The state of manufacturing

Companies have been manufacturing biologics for many years, and until relatively recently the majority of these have been peptides, proteins, monoclonal antibodies, and antibody fragments. Biomanufacturing has largely been based around the use of stainless-steel bioreactors and fed-batch processes, with a conventional quality control (QC) and quality assurance (QA) routine used to release completed batches. The facilities have often been large, requiring high levels of investment, with a focus on fixed costs and a separation between upstream and downstream processing.

As the needs of the industry change, biomanufacturing will also need to evolve along with them (Fig 1). Drug developers are increasingly looking to move toward a greater degree of flexibility and responsiveness. This is due in part to the increasing demand for more complex biomolecules, as bispecific monoclonal anti-

bodies, antibody-drug conjugates, oncolytic viruses, CAR T cells, and RNA interference-based drugs move through the pipelines. This increase in heterogeneity is resulting in the need for more flexibility and responsiveness in biomanufacturing.

Other factors are also driving the need for greater flexibility and responsiveness. When drugs are in clinical trials, companies need differing amounts of product for the different stages of development. As the drug is approved and moves toward the market, supply chains will need to be put in place as quickly as possible.

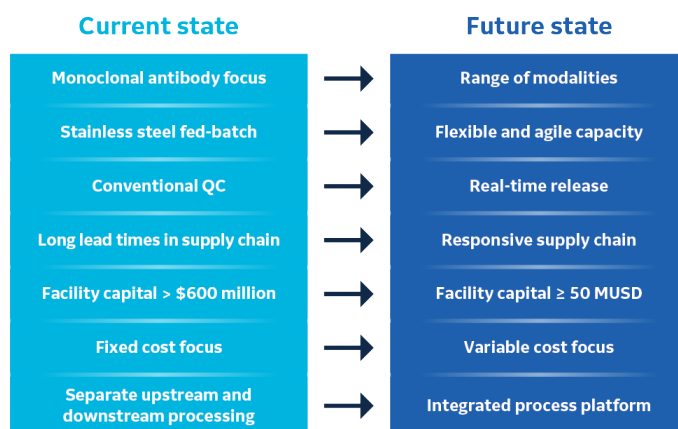


Fig 1: Biomanufacturing now and in the future

Once the drug is on the market, uncertainties in demand will remain. The uncertainties are driven by several different factors, including clinical outcomes; changes in dosage levels based on recommendations and clinical practice; the size of the patient population, which will change as new indications are approved; and levels of market uptake, which will depend on drug price and on competition.

There will also be a need to buffer against cost pressure. This could be because of drug exclusivity, high development costs, or health systems' budgets.

Creating a global presence can support flexibility and agility of response to sudden changes in demand, as well as meet the needs of countries where demands are increasing, such as India or China. Examples include creating smaller facilities using closed single-use systems at lower up-front and fixed costs in a number of different locations.

The goal, therefore, is to create a flexible, efficient, and cost-effective manufacturing program that users can easily scale up or duplicate at the same or a different site, allowing for increased capacity locally or globally. Building this platform relies on streamlining the process step by step, beginning with cell line development, the basis of all biologics manufacturing.

Accelerating cell line development

Traditional cell line development involves random transfection of cells, followed by cell sorting and evaluation of clones based on productivity and growth performance. The development can take around 40 weeks from start to finish. There are a number of potential approaches to enhancing the cell line development process.

The traditional screening process involves placing single cells into wells in 96-well plates, and then screening 50 to 100 plates and picking out the highest producer. Instead, rather than screening individually, the operator can place cells into mini-pools, and then select the highest-performing pool of cells. This smaller population is then screened to get to single cells. The selection system can also make a difference. For example, using fluorescence activated cell sorting (FACS) in combination with the glutamine synthetase (GS) selection system speeds the process up further. Microfluidics can play a role in clone assessment and get results on proliferation rate and cell-specific productivities within five days.

Streamlining the cell line development process begins with transfection. Instead of relying on random events, target integration allows cell line developers to insert genes in predefined "hotspots." This specificity increases the creation of high-producing cell lines and reduces the amount of screening needed in the next step.

When combined, these steps can significantly cut timelines for cell development down to as little as eight or 10 weeks and have a major impact by reducing the time to toxicity studies for the target biologic.

Speeding up process development

The next stage of optimizing the process is moving into process development. This begins with the use of high-throughput systems such as plates, spin tubes, and microbioreactors, and then moves into parallel lab-scale bioreactor systems, from 250 ml up to 5 or 10 L scale bioreactors. These must reflect and predict the conditions and performance seen at pilot and production scale, in order for the scale-up process to be as smooth as possible.

In-process analytics play an important role and should be automated and integrated within the upstream process and instrumentation. These analytics will provide a large amount of very important data, for example, from raw materials such as cell culture media and chromatography resin, from the bioreactor and capture steps, and from the drug product. The challenge, however, is capturing and storing the information and then evaluating it. Data is only valuable if it can be analyzed and made relevant.

The process of data collection and analysis, from feeding all the data into one database or "data lake" through to the data analysis, is shown in Fig 2.

To get more from the data and its analysis, the analytics process needs to look not just at the outputs but at the interactions between the different subsystems. For example, real-time monitoring can be used to predict how a batch will develop and to detect any deviations. Then, by comparing the batch with other batches, the process developers can get a greater understanding of how to improve the process and reduce errors.

The closer analytics can be integrated into the process, the better. In an ideal world, real-time analytics both up- and downstream

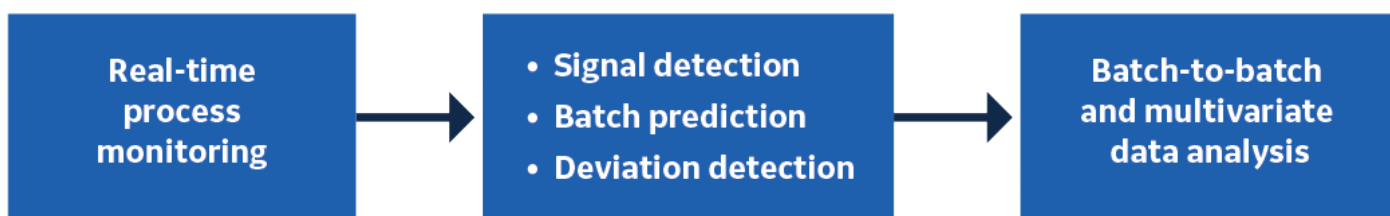
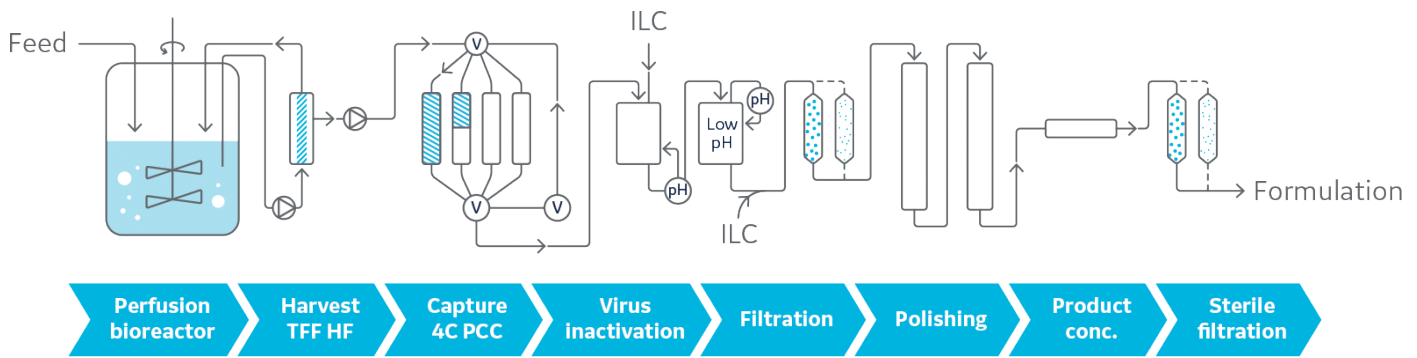


Fig 2: Data collection and analysis



TFF: tangential flow filtration; HF: hollow fiber; 4C PCC: 4-column periodic counter current chromatography
 Fig 3: End-to-end upstream and downstream continuous processing

would mean the process can be modified “on the fly” from beginning to end, in order to improve quality and yield. The data feeds could include information from throughout the process, such as the raw materials going into the bioreactor, any chromatography data, and details from the purification and filtration steps.

Process intensification

Many biopharmaceutical companies seek the benefits of process intensification by focusing on the seed bioreactor (N-1 stage). Two additional approaches are also gaining interest as a strategy to improve volumetric production capacity. The first uses a high-density, high-volume cell bank vial, which is expanded in a single step. The vial is used to inoculate the rocking perfusion bioreactor of 1 to 10 L, expanding the cells to sufficient volume and density to inoculate a bioreactor of up to 2,000 L. The *faster process* takes two weeks or less, halving the process intensification time.

The second works by running the N-1 stage in perfusion to produce enough cells to inoculate the production bioreactor at a substantially higher cell density. As a result, the time in the production bioreactor can be shortened by about five days.

Leveraging system biology into process design

The biology of the cell, as influenced by the genome, the proteome, and the metabolome, has an impact on the outcome of the process. By modeling the pathways and feeding the learnings from this into process development, it is possible to use systems biology not only to improve the host cell lines but also to improve the process design and media development. As an example of this, making changes to the system and then analyzing the mRNA of the cells can show changes in the up- and down-regulation of cell pathways related to cell cycle metabolism. This information can then be used to modify the media, improving cell-specific productivity.

Online release through real-time analytics

As outlined in the desired future state of manufacturing, QC and QA release is cumbersome and can have significant impact on timelines. Therefore, there is a need for methods that capture several quality attributes, and that can be run close online or at-line. Such rapid capture methods would also enable information on quality attributes to be fed back to the process.

Bringing in integration and automation

Integrated analytics and optimized processes open the door to the potential of automated systems. Automated systems can detect and handle deviations in the process and make corrections without human intervention. The next evolution of this automation could be connecting upstream and downstream, creating an integrated continuous biomanufacturing platform (Fig 3). A fully integrated system, however, would require high levels of precision, control, and execution, along with robust protocols to deal with problems.

The end goal

Cell line development, process development and process intensification, real-time analytics, process integration and automation are all important methods manufacturers are using to optimize process efficiency. These steps, along with better approaches to heterogeneity in the pipeline, reductions in costs, and more flexible and agile manufacturing, are all necessary to meet the changing requirements of the biologics industry. The greatest impact, however, is likely to come from taking the next step in the refinement of the processes – increasing the integration of upstream and downstream processing and moving toward greater automation. The eventual goal, which is coming closer to reality, is a fully integrated and fully automated process platform running from cells and media through to a product ready for formulation.



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GE Healthcare Bio-Sciences AB, Björkgatan 30, 751 84 Uppsala, Sweden
GE Healthcare Bio-Sciences Corp., 100 Results Way, Marlborough, MA 01752, USA
GE Healthcare Europe GmbH, Munzinger Strasse 5, D-79111 Freiburg, Germany
GE Healthcare Japan Corp., Sanken Bldg., 3-25-1, Hyakunincho Shinjuku-ku, Tokyo 169-0073, Japan
GE Healthcare UK Ltd., Amersham Place, Little Chalfont, Buckinghamshire, HP7 9NA, UK

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