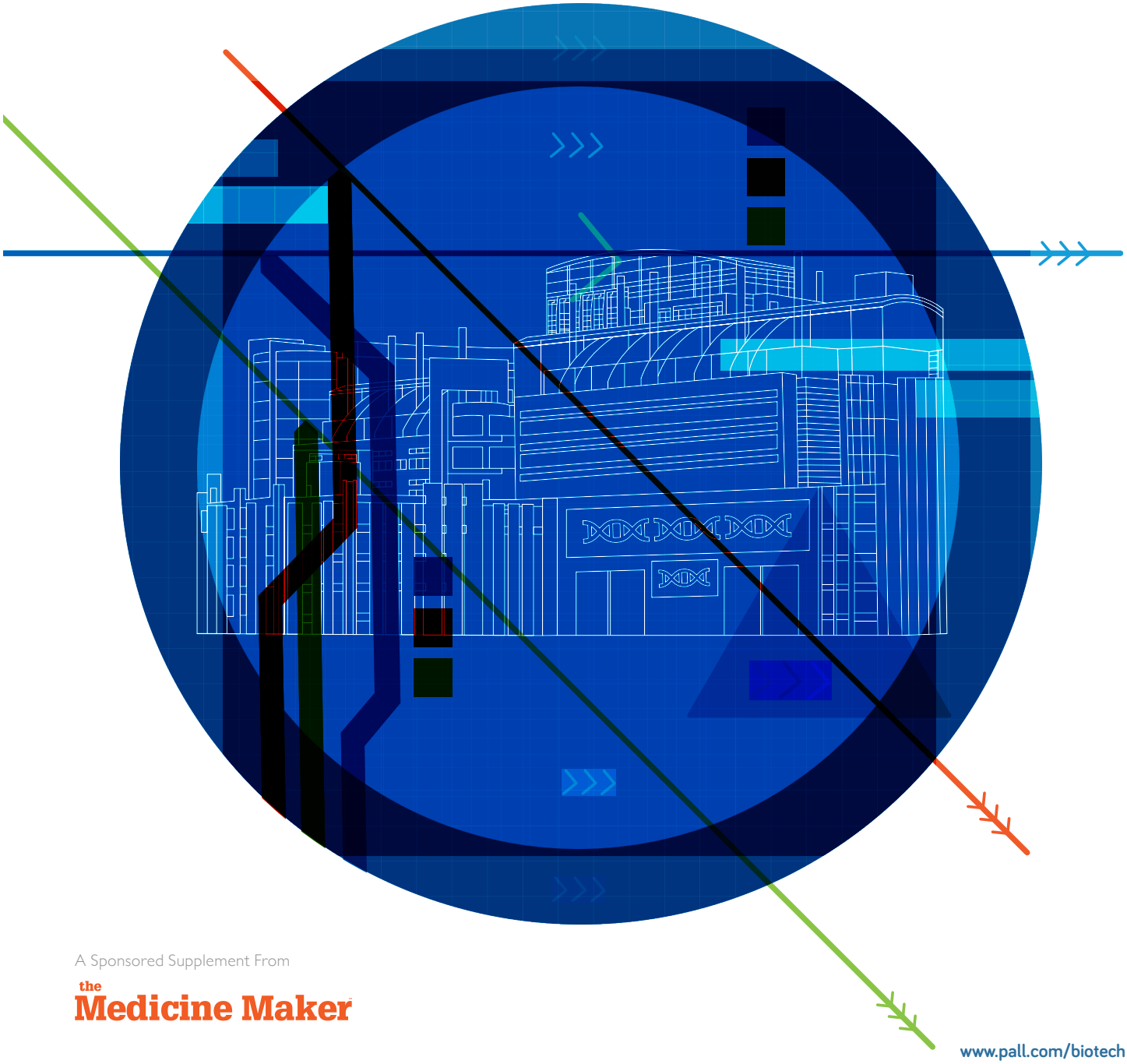
PALL Biotech

The Right Choices in Biomanufacturing

Single use? Stainless steel? Continuous bioprocessing? Experts share their advice to help you choose the best path for your product.



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Meet the Experts

James Thomas

Chief Executive Officer at Just Biotherapeutics, Inc.

Over the course of his career, Jim's passion has been to provide vital medicines to patients, and his vision for Just Biotherapeutics expands this to include patients worldwide. Previously, he served as Vice President of Process and Product Development within the Translational Sciences R&D organization at Amgen.

Jorg Thommes

Head of CMC, Bill & Melinda Gates Medical Research Institute

Jorg has previously held roles at Visterra, Biogen, IDEC Pharmaceuticals, and the Institute of Enzyme Technology at the University of Dusseldorf. Today he is responsible for physical product development, manufacturing and distributions across the entire portfolio of the Bill & Melinda Gates Medical Research Institute.

Martin Smith

Chief Technology Officer, Pall Corporation

Peter Levison

Executive Director Business Development, Pall Biotech

Roel Gordijn

Global Vice President Biotech Integrated Solutions, Pall Biotech

Rick Morris

Senior Vice President, R&D, Pall Biotech

James Hathcock

Senior Director, Regulatory and Validation Consulting, Pall Biotech

Michael Schoeb

Senior Vice President of Process Engineering Biotech, Pall Biotech

Tony Hitchcock

Technical Director of Cobra Biologics

Tony has held a number of senior roles with the company, managing both manufacturing and development functions, and working on over 40 programmes for the development of novel therapeutic products including protein, recombinant virus, bacteriophage and plasmid DNA products.

Veronique Chotteau

Principal Investigator at the KTH Royal Institute of Technology

Veronique has 30 years of experience in mammalian cell culture including more than 10 years in the biopharma industry. Her expertise covers process development, including perfusion and fed-batch from small scale to commercial scale. She has previously worked at Pharmacia Upjohn/Biovitrum.

Making the Right Choices

As technology evolves, the biomanufacturer's toolbox constantly expands. Continuous bioprocessing – made possible by decades of such advances – is ripe for adoption.

Biopharma manufacturers today have many choices. Will you use stainless steel? Single-use systems? Both? Will you opt for batch – or examine the benefits of a continuous approach? In this supplement, we bring together opinion leaders from across the bioprocessing industry to share their thoughts on how the manufacture of biopharmaceuticals is changing.

I'll be the first to admit that stainless steel is not going to disappear – it will likely remain the preferred technology for blockbuster drugs that require high volumes; however, many drugs coming through the pipeline will have different volume requirements, so the ability to select the most appropriate manufacturing method from an expanding toolbox is welcomed. Each approach has pros and cons, depending on the type of molecule you want to produce, but new technology deserves consideration, because it has been developed with a specific aim: to improve upon current manufacturing methods.

Pall is an established supplier to the biopharma industry, with a portfolio of products covering both stainless steel and single-use. But it is the latter technology area that I am particularly excited about. Single-use is now well established in the industry and the benefits have been proven – not least the speed at which it can be deployed. Though single-use is not typically employed for very large volumes, it really lends itself well to continuous bioprocessing; after all, when producing continuously, you don't need such large-scale equipment.

Continuous bioprocessing systems are very new to the biopharma industry and, if you are building something new, then it makes sense to make it as flexible and agile as possible. Single-use technologies allow such flexibility, while also reducing the costs of cleaning and validation. As with all things new, there is, perhaps understandably, some trepidation about how continuous should be used and what the regulators have to say – and we address these concerns in the coming pages. Overall, it appears that most in the industry at least agree that it is a key technology to watch, and I look forward to seeing how it is rolled out in the coming years – and what benefits it brings.

Peter Levison
Executive Director Business Development at Pall Biotech

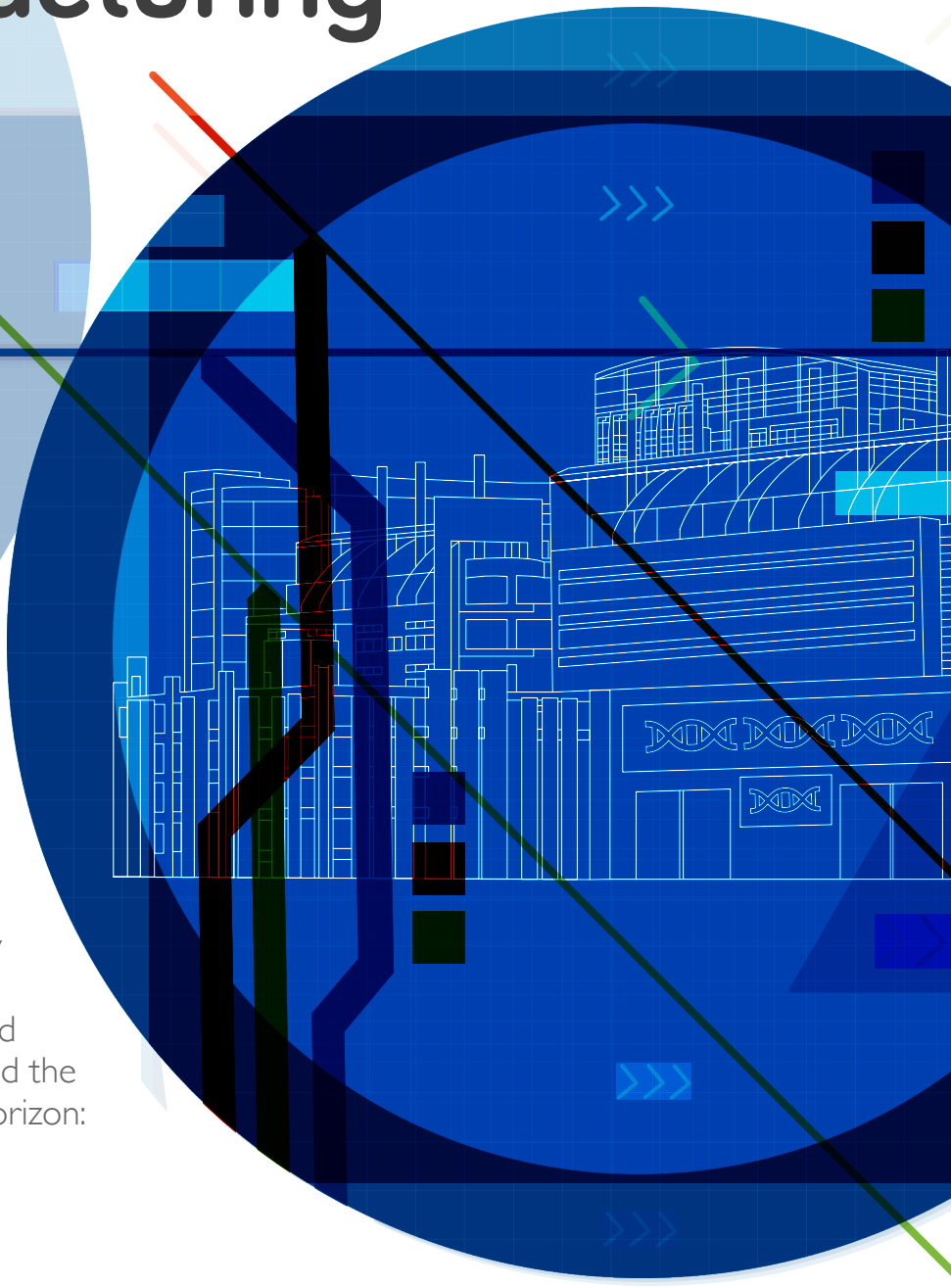
Contents

Foreword

Features

Thought Leader Interview

Mapping the Evolution of Biomanufacturing



It is said that change happens slowly in the biopharma industry – but it does happen. Processing has evolved thanks to single-use technologies and the next big transformation is on the horizon: continuous bioprocessing.

By Rick Morris

There have been many changes in biomanufacturing over the years. Admittedly, none of the changes have been "revolutionary" in nature; rather they have materialized because of a shifting market landscape. In fact, the basic building blocks or unit operations of biomanufacturing processes of today are not substantially different from those developed over 20 years ago. It's true that the basic batch process works effectively – although, I would argue, not efficiently…

First, let's look at what has changed in bioprocessing. Cell-culture media has evolved from serum-containing media, to protein-free media, to now, in many cases, chemically-defined media (at least for production bioreactors). Meanwhile, bioreactor feed optimization, in combination with better analytical methods and sensor technologies, has helped the industry to obtain higher cell-densities – up to around 200 million cells/mL in some cases. Though cell-specific protein productivity has not changed much, the increased cell density can now yield 5-10 g/L in a bioreactor, whereas in the 1980s and 1990s, bioreactors were producing less than 1 g/L in antibody titers. The higher productivity and need for smaller volumes has allowed the industry to transition to single-use bioreactors, which have enormous advantages for the industry.

The improvements upstream have driven end-users to look for new downstream processing solutions that can cope with the higher titers, and that obviate the need for fixed steam-in-place and clean-in-place systems. Typically, primary clarification in mammalian-cell culture processes using fed-batch bioreactors was conducted using centrifugation, but users today need solutions that can cope with higher cell-densities, such as higher capacity depth filters for primary clarification. However, a vast majority of "new" downstream processing technologies, such as the latest chromatography sorbents and filters, usually only demonstrate marginal improvements in productivity.

Another significant change – and challenge – for the industry has been the move to subcutaneous formulations, as opposed to intravenous formulations for certain therapies. It's a change that requires a final protein concentration in the bulk drug substance to around 200 g/L, as opposed to 30-50 g/L. The increased concentrations create processing challenges (increased viscosity) and product quality challenges (higher levels of aggregates), necessitating careful process optimization and effective system design that balances protein yield and quality.

Accepting the newcomers

Of the many changes that have occurred in bioprocessing, the rise of single-use is one of the biggest. And it has been an interesting journey to watch. In the early days of single-use, implementation was in non-product contact applications, such as media/buffer preparation and storage. Though there were a few concerns about leaks and loss of integrity, these were mainly "nuisance" problems. But once single-use systems started to be used in product-contact applications, more serious questions around safety were raised, focusing on leachables, product cleanliness (particulates), sterility assurance, and the adequacy of the supplier qualification process. Loss of control was another concern for some biopharma companies. When a manufacturer has their own stainless-steel infrastructure, they have control – they do their own cleaning in place and validation, and have their own documentation. But when moving to single-use, the manufacturer is dependent on the supplier and receives documentation from them about product specifications, endotoxin specifications, sterility expectations, and so on. Some companies have a tough time with this loss of control. The supplier will obviously need to be vetted and you need to trust their documents and processes – but today there are many established suppliers who have matched their products and procedures to the needs of biopharma companies.

Although single-use is now well accepted, there are still a few issues that have not been fully resolved. Concerns about particulates have not gone away, although suppliers have been very active in terms of understanding what particulates are in their products, where they are coming from, and how to mitigate the risks. However, remember that stainless steel isn't perfect either; valves can leak and gaskets can fail. You can read more about this on page 20. With single-use, there is often heightened awareness of potential issues because the matters are out of the manufacturer's control. That said, confidence in single-use is generally high today and there is increased effort from the industry as a whole to set standards and guidelines.

Some companies still prefer stainless steel, but I'm seeing a real shift toward single-use and hybrid approaches. For new facilities in particular, there is often a drive to implement single-use, which reduces plant design and construction timelines considerably.

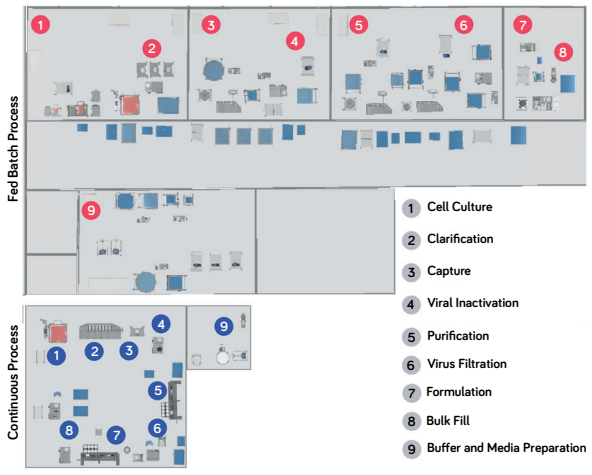
Continuous progress

After single-use, where does the industry go next? It is time for bioprocessing to further evolve. At the start of this article, I admitted that the batch process is at least effective – it gets the job done. But I also shared concerns about a lack of efficiency. It is well accepted in other manufacturing industries that continuous manufacturing is far more efficient. In the small molecule world,

pharma companies are adopting continuous processing – mostly in the conversion of API to drug product (the API is continually blended with excipients, and converted into tablets). Continuous bioprocessing is also starting to emerge – here, we are talking about a continuous chain from the bioreactor to the drug substance. It is a natural evolution for bioprocessing.

One of the main advantages of continuous manufacturing is reduced waste; there is a lot of waste in biologic manufacture! In batch, waiting for all the protein from one operation to collect before you start the next unit of operation, while the second one is waiting, is a waste of resources. Removing this waste should make for a more consistent and robust process.

Although the industry has been talking about continuous bioprocessing for a few years now, many biopharma manufacturers remain concerned about what regulators will think. There is a perception that regulators are a hindrance to evolution or innovation. But I don't think this is true. If you look at what is coming from the US FDA, the EMA to some extent, and other governmental officials, it is clear they are encouraging pharmaceutical innovation – providing it uses a risk-based approach. Over the past 10 years, there has been wider acknowledgement of the principles of Quality by Design and Quality Risk Management, as laid out in ICH Q8 and Q9 respectively. Although there haven't been any notable submissions made under the enhanced regulatory framework as envisaged in these guidelines, there is a clear understanding of the need to manage drug quality seamlessly throughout its lifecycle from early phase clinical manufacturing through post-market changes.



A representation of the facility layout and manufacturing footprint for a fed batch and continuous bioprocess.

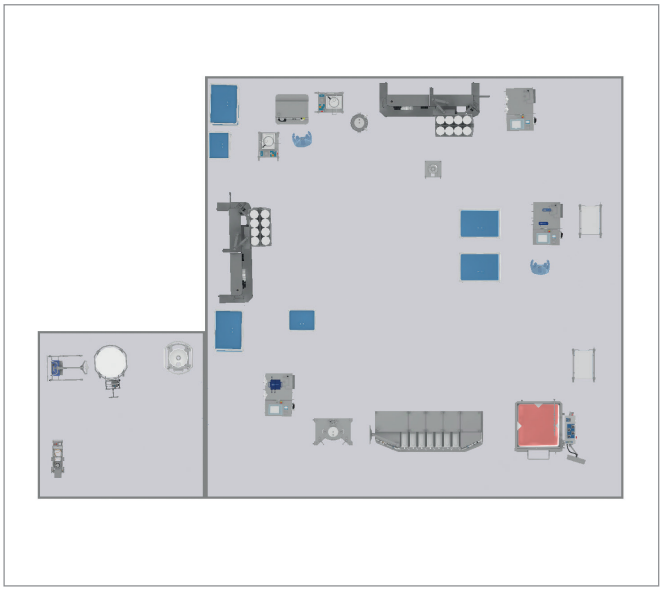
Regulatory authorities are not a monolith and there are differences in enforcement – and sometimes a decision can depend on who inspects your facility or reviews your documents. There are different interpretations and different assessments, and this is where many pharma manufacturers get frustrated. In addition, some regulators are very comfortable with their own way of doing things and have difficulty understanding how any new technologies can produce safe, effective medicines. Many regulators I have spoken with also understand that current processes, whilst adequate, can benefit from newer technologies that make products safer and more consistent from a quality standpoint. From a regulatory standpoint, continuous bioprocessing isn't fundamentally very different to what happens in batch – and regulators have spoken on this at conferences. If you think about all of the steps involved

"The acceptance of continuous bioprocessing is already happening."

"It is well accepted in other manufacturing industries that continuous manufacturing is far more efficient."

in producing a monoclonal antibody, the same steps are still used in the continuous process. Yes, the operations are sequenced differently but they are not in themselves different – you still have a step for removing the cells, a Protein A capture step, a virus inactivation step, column chromatography polishing steps, and filtration… These fundamental unit operations are exactly the same whether they are in a batch process or continuous process.

That said, there is a nuance to how a continuous process works that drug manufacturers need to understand to effectively mitigate risks. First of all, you need to really understand how the continuous process works – for example, a particular pH in one step may affect the performance of the next unit operation. Once you understand your risks you can then look at how to mitigate them. We recommend that companies use small surge vessels in the process.



Ballroom style facility layout for an integrated continuous bioprocess

Another nuance is the elimination of stop/start. In batch, the manufacturer has the luxury of collecting the entire material and can pause to perform testing to ensure it meets requirements, before moving onto the next process steps. With continuous, you don't have the luxury of waiting. Material flows from one step to the next without any pooling and stopping between. In a way, this is a concern – how do you mitigate the risk of contamination passing throughout the process? However, also bear in mind that a continuous line allows manufacturers to use single-use systems and maintain a completely closed system, which should reduce the chance of contamination being introduced. In addition to having a closed process, rapid microbial methods are now available and are well accepted by regulators for bioburden– to confirm there's no ingress in part of the process.

It's not that different

Overall, there's no real concern with continuous that the industry is trying to do something completely novel that regulators have not seen before. From what I have seen, regulators are actively trying to better understand this technology and how they can aid the industry. To facilitate that process, the biopharma industry needs to communicate with regulators. Collectively, the pharma industry spends a lot of time and effort training people about new technologies. And many people don't like change – so a lot of time and effort goes into making change stick and educating workers that this is a natural evolution for the industry. We need to expend this same time and effort in talking with regulators. We've been doing this at Pall – actively speaking with inspectors and regulators about technology offerings, including what the potential risks are and how they can be mitigated. This cannot just be a one-time conversation, or an effort from just one company. Like any training, it must be repeated. The industry is hungry for more efficient biomanufacturing approaches, so we need to work together so that all stakeholders understand and can benefit.

It took time for regulators and the industry to truly accept single-use technologies – the acceptance of continuous bioprocessing is already happening and I believe that it won't be long before continuous takes root. The industry has been discussing continuous bioprocessing for a few years already – and some of Pall's customers are already far along in implementing the technology. In the next two to three years, I expect to see customers filing for investigation of new drug applications making use of different degrees of continuous bioprocessing.

Rick Morris is Senior Vice President of Research and Development at Pall Biotech.

Industry Reflections

Jim Thomas entered the biopharma industry in the 1980s and has seen it all – from roller bottles to single-use. Reflecting on the past makes him confident that the industry will continue to improve.

With Jim Thomas, CEO of Just Biotherapeutics

What was bioprocessing like in the 1980s?

When I first joined Genentech in the early 1980s, we were working on a process for manufacturing rtPA (tissue-type plasminogen activator). It was the first recombinant protein to be made in CHO cells. Genentech had been working on methods for manufacturing recombinant proteins beginning in the late 1970s focusing on recombinant insulin and recombinant human growth hormone, but these were in microbial systems. Expression levels were poor (a few mgs per liter), and because we were initially producing t-PA in roller bottles, serum was needed for attachment and for cell growth. There were all kinds of concerns from a regulatory perspective about viruses, contaminating DNA (would trace levels of DNA from a transformed host cause cancer?) and host cell proteins. It was all new and really cutting edge at the time to be working with mammalian cells, but in retrospect it was also pretty primitive! You can't easily meet market demands using roller bottles because to meet commercial demands would require giant warehouses full of roller bottles. We began considering a move to stainless steel, deep-tank systems – a very challenging decision for the company because it changed the quality attributes of the molecule and some of the initial clinical data was not as relevant and needed to be bridged.

We began experimenting with deep tank systems at small scale and then a 12,000 liter microbial fermenter was purchased and modified in house – there were some great engineering folks in the company and while scale-up was not easy, we were successful developing and scaling up the first processes for making recombinant proteins in mammalian cells. As a scientist, I worked mostly on the process side, developing methods for upstream.

How did you join Amgen?

After Genentech, I moved to a Seattle-based biotech company named Immunex in 1990. I was hired to make fc fusion proteins – one of which eventually became the TNF inhibitor, Enbrel. Amgen acquired Immunex in 2002, mostly because of Enbrel, but we'd also been improving our manufacturing technology as we were struggling to make enough Enbrel to supply the market. Processes were relatively poor back in the 80s and 90s, and it was challenging to produce enough recombinant protein to supply markets. We needed large deep tank bioreactors and massive downstream purification columns housed in very large and complicated plants to make the product mass required – there wasn't as much focus on cost – just making enough to supply the market.

To meet market demand at Immunex, before being acquired by Amgen, we ended up working with several companies to secure the capacity required to supply the market – and there were many challenges along the way! These experiences at Immunex drove me to hire the best people I could find from academia and other places who could work on manufacturing technologies and improve them for making recombinant proteins. When Amgen acquired Immunex, they not only acquired Enbrel and other products, but also the processing technology.

The Immunex process technology became an important foundation for Amgen – and during the years I was with Amgen, we continued to build on the quality and applicability of the technology through a number of technology forums in my organization. This happened during a time when antibodies were growing in therapeutic application due to improvements in affinity and the ability of companies like Amgen to develop human antibodies.

What drew you to single-use?

We used bags for media and buffers very early on, and then the WAVE single-use rocking bioreactor system came along. It was a really innovative yet simple system, but it wasn't that useful as a production reactor due to our drug mass requirements. However, it was intriguing in terms of growing cells to inoculate into bioreactors. In the early 2000s it was interesting to see technologies begin to converge, such as bags for media and buffers, single-use bioreactors, better media for high cell density cultures, improved expression systems, improved purification resins etc. What really pushed me over the edge in my thinking about a different approach for production using mammalian systems was the development of an Alternating Tangential Flow (ATF) unit by a small company called Refine (subsequently acquired by Repligen). It was very useful for gently separating cells from media without fouling the membrane, and eventually could be operated robustly at the 2000 L scale. So we began thinking about how we could use all these developments in single-use technology and process technology to make recombinant proteins more efficiently, and how all this could fit into a new kind of manufacturing facility. Fortunately, I was working with a remarkable team of scientists and engineers at Amgen who brought all of this together to make it a reality.

Within a big company, manufacturing demand is almost never constant and it's a


ZONE A
ELUTION
P03
STRIP
P04
REGEN
P05
STORAGE
P06
P07

"You cannot just focus on what is right in front of you; rather you must look at the variety of products coming through the pipeline."

real challenge to have just the right capacity. You must balance your own internal pipeline but also bear in mind that you may end up licensing in molecules – as well as the fact that many will fail. Big stainless steel plants are fantastic at making a lot of protein. If you run them very efficiently then you can make protein at a fairly low cost, but you have to keep them full because the investment lies in the stainless steel equipment and the number of people required to maintain and run the facilities – these are expensive fixed costs. What we were looking for was the ability to shift from fixed to variable costs. With single-use technology operating in relatively small inexpensive facilities, you incur the majority of your costs only when you are manufacturing through the use of disposables and consumables.

As yields have increased and processes improved, smaller facilities and single-use systems have become more viable. It is now much more practical from both a cost and capacity perspective to manufacture high mass demand products at 2000 L instead of volumes of 12,000 to 25,000 L. Downsizing of processes and facilities has reduced initial capital costs and we've found that we can design, build, and validate facilities much more quickly. Companies like Amgen have the technology to drive cell densities and productivity much higher than traditional fed batch processes (we called it "intensified batch"). They can get a lot of productivity out of small bioreactors, and single-use systems have made manufacturing more flexible.

What were the biggest challenges with stainless steel?

Large, well-run stainless steel plants are amazing engineering feats that may include literally miles of stainless steel piping. I think Amgen was fantastic at building and maintaining this infrastructure, but such plants are expensive and time consuming to build and can be really difficult to get up and running. Back in the 1980s, companies would often encounter problems with leaking seals in the reactor or dead spots in the piping where bacteria could grow. After you built one of these facilities, they would send a little robot with a camera through the piping to examine every weld – because one bad weld could cause significant problems. Using antibiotics in the cell culture was also standard practice in the 80s and for some companies, well into the 90s because it was so difficult to get complete cleaning and sterilization, and to maintain it in these giant plants. We never used antibiotics at Immunex, nor did we at Amgen because we felt it masked the problems that needed to be solved, no matter how painful the solution.

Operating and maintaining a stainless steel plant requires considerable resources if it is to be done well. Amgen was incredibly successful at this, but clearly understood they needed to consider alternatives. They had a significant investment in stainless steel facilities and they were really good at using those systems, but they saw a potentially better way and decided to follow it. It was a huge commitment on Amgen's part, and I still admire the executive management who made those tough decisions.

Pharma companies always have to think about the future. You cannot just focus on what is right in front of you; rather you must look at the variety of products coming through the pipeline. For example, some antibodies require large quantities of API, whereas some of the highly potent APIs may only require a few kilograms to supply the entire global market. How do you do all of this with one type of facility rather than needing to build different facilities for different types of processing? This is one of the strengths of the new manufacturing technology – creating flexibility in a smaller footprint faster and at a lower cost.

How were you involved in Amgen's "next-generation" facility in Singapore?

At Amgen, I was responsible for new process development for the company's large molecule pipeline. Our internal technology forums were examining new technologies and putting them together – some of this work was used in the Singapore facility, which was completed in 2014. I would say it is the first "next generation" biopharma facility. It uses disposable technology, modular manufacturing, intensified processing and some connected processing downstream. It's a highly productive facility – able to produce similar quantities of product as other Amgen sites, despite being significantly smaller. In my view, it's a step up from stainless steel. It was built in just 15 months and uses 80 percent less energy and water, with a 75 percent reduction in carbon dioxide emissions (1).

What are you working on today?

About four years ago, Amgen decided to close the site in Seattle, where I was based. Many of us wanted to stay in Seattle and with such a good workforce it was a great opportunity to start a new company with a lot of wonderful people with fantastic experience. One of our guys led the manufacturing of the future effort on the development side for Amgen, and even trained some of the workers in Singapore.

Our company is called Just Biotherapeutics.

We started with a whiteboard and a lot of smart and experienced people to build what we believe will be an industry leading platform for biologics in this space. From the beginning we set out to deliver better quality, speed, cost and flexibility in the development and manufacture of biologics, and we are well on our way to achieving these objectives. There are many layers to this platform that work in concert; from the way we generate, capture and learn from data to the various vendors that help us reduce the bioprocessing footprint and plant size through disposable technologies and perfusion based process intensification. We're also looking at continuous capture steps and connected downstream processing, and we work with cleanroom pods as our processing space that are highly efficient and very flexible. It's all about putting in place a highly efficient manufacturing operation in a small footprint.

Why is reducing the cost of biologics so important?

I'd conservatively estimate that at least 80 percent of the world's population do not have access to biologics at all because of cost. Biologics are some of the most effective medicines approved on the planet, and there are hundreds of promising biologic therapies in the pipeline, but most of the world population may never have access to them.

"The acceptance of continuous bioprocessing is already happening."

Our mission is to design and apply new technologies that create greater access to biologics worldwide. I'm well aware of the overall costs of biologics and the factors that contribute to these costs. We don't have all the solutions at Just, but we can make a significant contribution to the overall solution set in the CMC space.

We want to enable manufacturing in different geographic settings, and at lower costs. We started the company as a not-for-profit to deliver technology that can benefit both the developed and developing world. For me it's about creating markets through technology that did not exist before - you need a long view for this - but the greater the focus now, the sooner that future state will be a reality. The Gates Foundation has been incredibly helpful for Just, supporting the development of our current platform, and we are working on some molecules in their network for infectious disease. The bar is very high. There is a lot of focus on small molecules and vaccines for places like Africa and there are still a lot of challenges. Biologics cost orders of magnitudes more so we have a long way to go.

There are also many people in developed countries with no access to biologics, so I like to say that we have a dual focus on both the developed and developing worlds. Our work stands to benefit both in a meaningful way.

How do you feel about the future of the biopharma industry?

I actually believe that the problems we faced in the 1980s were more daunting than the challenges we face today. The systems of the past were challenging when it came to maintaining sterility and getting the performance we needed to supply markets. We didn't always have the ability to identify things like bacterial toxins impacting cell performance or media limitations that affect productivity or product quality. We have many of the tools we need to understand those things now.

The industry likes to be a fast follower when it comes to technology, because companies need to focus on product development, not technology development. The industry wants and needs to follow organizations that can help de-risk innovation for them. Regulators are open to innovation but they need to see the data to show that it does not increase risk to patients. In our industry, there will always be the tension of wanting to move products forward in development more quickly, at lower costs, but without impacting product quality and patient safety. I believe Just and others can play an important role delivering on those needs, and do it in a way that serves a global marketplace. In fact, the lives and well-being of millions of patients around the world depend on our ability to do so.

An historical perspective gives me a lot of confidence in the future. As I look back over my career of 35 years in the industry, we have overcome so many challenges. There will be challenges in the future as well, but the sooner and more aggressively we face these challenges, the more quickly an inevitable future state, with substantially greater global access to biologic therapies, will be the present. Literally millions of patients will benefit. The industry has many of the fundamental tools it needs in terms of process and manufacturing technologies – and a growing understanding of how these tools can be used to build a much better way to develop and manufacture biologics. How we collaborate as drug and technology innovators and work with suppliers of technology and regulators will ultimately impact how quickly we can bring life changing biologics to patients around the world.

Reference

1. *Amgen, "2017 Letter to Shareholders" (2017). Available at https://bit.ly/2IlqBgZ. Last accessed October 9, 2018.*

Vendor Views on Innovation

Martin Smith, Chief Technology Officer at Pall, and Rick Morris, Senior Vice President of R&D at Pall Biotech, explain how vendors contribute to improving and enhancing bioprocess operations.

Moving With the Times

By Martin Smith

Pertinent break-through technology is born at the interface of an inventor's passion and market necessity. In the bioprocessing world, regulations have changed, driving the need for higher quality and improved process monitoring. At the same time, there is a trend towards greater process efficiencies and lower manufacturing costs. Vendors have to bear all of these drivers in mind when developing new technologies. It's also important for us to consider the different bioprocessing approaches such as stainless steel, single-use and hybrid formats. Manufacturers all make their therapeutic products in slightly different ways and technology suppliers need to be able to accommodate these different requirements – dictating innovation on all fronts. Even if a manufacturer prefers to use only traditional stainless steel infrastructure, future regulatory developments may force the need to enhance equipment from time to time, which means that vendors should not neglect any area. And being experts in both single-use and stainless steel is essential to serve the growing number of companies implementing hybrid approaches.

Success with continuous

Vendors are always looking for true innovation – the development of breakthrough technologies that can enhance the field and change how a process is viewed. There is a real opportunity right now for continuous bioprocessing – and it is a bioprocess approach that customers are asking for because of the potential for improved process economics, increased process design flexibility, shorter development times, and easier scale up. The equipment for continuous bioprocessing also has a much smaller footprint and pairs very well with the move towards modular and container-style processing.

At Pall we've won a lot of awards for our continuous bioprocessing technologies and we continue to see year-on-year growth. We wouldn't be in business if we weren't on to something! But biopharma is an understandably conservative market. There has already been a lot of education required to help companies embrace single-use, and now we are in the same position with continuous bioprocessing. There is science to back up the benefits of continuous and at the same time regulatory bodies have talked a lot about continuous bioprocessing methodologies. All of this effort is starting to resonate with biomanufacturers.

Continuous chromatography – the most expensive traditional downstream step – has often been the starting point for a manufacturer's entry into continuous bioprocessing. And that's why we chose to innovate in that area first. When a company is looking at how to save money and get the same result, it is logical to look at the chromatography step first – and our Cadence™ BioSMB technology is aimed directly at this space. It uses seven times less chromatography resin compared with traditional batch fill and column chromatography. There is now growing interest from customers in turning other unit operations downstream into continuous.

Today, technology suppliers can't just sell a product and be done with it. To be a good vendor, you need to provide good service. You need to have applications proof, you need to help with the validation service and the FDA package, and you need to fully support your customers. It also helps if you can call on the expertise of different groups. For example, Pall is part of Danaher, which gives us access to a number of sister companies with expertise in process analytics. We've started to expand our customer offerings with process development services and we're doing a lot of work in gene therapy. We are now planning to serve our customers in process design in a continuous mode.

It is also very important for vendors to evolve in terms of their infrastructure and people. You can't just continue to develop new technologies on the back of decades old people (like myself!) – you need to be able to attract and hire new talent. Attracting new talent can be a challenge in the competitive marketplace we live in so you have to continually look at your business and culture and ask what you need to do to attract the best. We've recently been attracting a lot of people from industry, which is great because ex-drug developers provide new insight into emerging technologies and what manufacturers really need.

The Business of Saving Lives

By Rick Morris

A good supplier should always have the goal of speeding up innovation to market. In my eyes, that means we need to incorporate more automation, robotics and on-line sensing into systems, and examine how continuous production and other new technologies and processes can lead to benefits for manufacturers. Everyone who is reading this interview is likely to be in the business of improving or extending quality of life. At the end of the day, all commercial players need to make profits to continue to innovate, but we should also be keeping our eyes on how we can improve the patient experience – whether this is improving the R&D process, the manufacture, or other aspects of the pharma business. From my perspective as a supplier, it means we have to develop efficient technologies that help our customers improve the accessibility and safety of their medicines.

Continuous bioprocessing, supported by a set of novel technologies is emerging as one approach that could make a difference to manufacturers – and ultimately patients. When moving to continuous processing, the biggest challenge in the manufacturing environment is maintaining a closed but flexible system that delivers the necessary controls given the close proximity of the unit operations. For viral clearance, for example, there are typically three main steps that may contribute to the overall virus safety: removal, by filtration, removal by chromatography, and inactivation from a low pH hold step. If you leave any stage open then you risk contamination from a previous stage – and if contamination gets into a continuous process, you can have a real issue. For a well-designed continuous process, once you have your process line fully connected and up and running, there should be significantly fewer chances for the introduction of contamination because it will be a closed and automated process.

Single-use systems are used to help achieve this and there is a lot of pressure on the suppliers of these systems to get it right. Materials and methods must combine with the manufacturing and assembly environments to assure the control of potential process contaminants. Suppliers will also need to carefully consider their own selection of materials and third party components to be able to assure and to meet exacting quality standards. Getting it perfect is an art as much as it is a science.

The future of bioprocessing

My view is that, in general, systems and operations will continue to shrink. But there will always be companies that want to go large; for example, Samsung has been investing in 15,000 L bioreactors. Overall, there is a trend towards personalized medicines and smaller volumes, and this comes with a challenge: you need to balance throughput to actual final dose requirements.

Companies will need to carefully consider their process economics versus the price they can acceptably sell their medicine for. The type of drug being developed may lend itself better to certain processing options. Some blockbusters drugs will require high volumes and high manufacturing throughput, some will require a combination approach of traditional batch matched with automation and some connected systems, and some will be fully continuous. It's going to be an interesting few years as we see how the evolution unfolds. Traditional stainless steel will not go away, but I expect to see more and more new drugs going at least halfway continuous.

I also expect to see more and more work in the drug discovery area. Here are some interesting ongoing developments that I've noticed:

- There is a drive to develop tests to better predict which drugs will be successful in the future; the industry is losing billions of dollars through drugs failing in late-stage trials. We need to figure out how to make better predictions earlier.
- Monoclonal antibodies (mAbs) will continue to improve. mAbs at the moment don't always hit the target. If we can make mAbs with epitopes that are more selective, then it would make them more specific, with fewer side effects. That said, when it comes to selective, targeted therapies, I think mAbs will struggle to beat gene therapies…
- CRISPR continues to generate interesting discussions and will speed up gene therapy development. Gene therapy requires a lot of optimization but, as the area grows, we'll see a greater drive to address the challenges.
- Cell therapy continues to be of interest, but I think we are quite far away from seeing a flurry of new therapies. Technologies, however, continue to emerge that can manipulate individual cells – and some companies have proven that cell therapies can be commercialized.
- Microfluidics is another technology to watch. Micro-capillary devices will facilitate smaller scale down devices and enable further progress in the area of personalized medicines. There is some really interesting research taking place but I think it will be a while before these really translate to commercial production.

Raising Standards Through Collaboration

Agreed standards will drive all industry players towards the same goal: better bioprocessing. And efforts from BPOG, among others, are leading the way.

By James Hathcock

The latest advances in biopharma manufacturing are really exciting – whether you look at innovations from Pall Biotech or across the industry as a whole. Single-use systems have advanced significantly and the flexibility they offer is helping numerous drug manufacturers bring their products to market much faster. Now, continuous bioprocessing is also starting to become a reality. All of the progress that is being made in biomanufacturing will help make therapeutics more globally accessible and lower the cost of drugs in the long run, but to reach that future we must collaborate.

Fortunately, there is a huge amount of collaboration in today's biopharma industry – not just in terms of advancing science, but also in raising standards that will make it easier to implement new technologies. One of the big fears in the industry is that the introduction of new technologies will be hindered by a lack of understanding of what regulators really want in terms of risk assessments and data. Many suppliers, including Pall Biotech, regularly discuss new technologies with the FDA and other regulators, but what we really need are agreed industry standards to bring everyone onto the same page.

It's not unusual for a supplier and a drug manufacturer to work together, but discussions are often one on one. In recent years, there has been significantly more cross-pollination with multiple manufacturers and suppliers – even competitor companies – working together for a larger purpose. The BioPhorum Operations Group (BPOG) is one fantastic example – their "phorums" include insight from manufacturers and supply partners. BPOG has traditionally been an organization for drug manufacturers but today involves many suppliers, and the organization also works closely with the Bio-Process Systems Alliance (BPSA) – traditionally a more supplier focused association. Suppliers and drug manufacturers used to be very different, but there is now a greater understanding of the important role each party plays. When it comes to single-use, there have been a lot of concerns around extractables (1). Although the United States Pharmacopeia (USP) chapter <1663> (2) provides the general driving guidance for extractables assessments associated with pharmaceutical packaging, it refrains from prescribing a fully standardized protocol that can be uniformly applied to single-use process equipment. In recent years, BPOG has been working to establish standardized expectations for extractables (3,4) by publishing a detailed protocol that they felt could be executed by suppliers, and that would provide sufficiently extensive datasets to satisfy internal quality personnel and regulators for the vast majority of biologics applications.

However, the proposed end-user requirement was incredibly expensive – it would have cost tens of millions of dollars to generate that level of data, when not all users required it. Hence, the uptake has been slow. The US Pharmacopeia – which includes representatives of the BPOG end-user community as well as the supplier community - is now engaged in this area, digesting scientific input from end-users, suppliers, regulators, and related industry experts, and I think it has really helped bring the industry together to talk about the issue and what is needed. As USP <665> and <1665> (5,6) prepare for a third and final round of public comment in the pharmacopeial forum, there is good news for early adopters as any BPOG testing performed to date, will be expected to satisfy the extractables profiling requirements of USP <665>. Between the BPOG proposal for extractables testing, as well as the pending USP <665> (3), there is light at the end of the tunnel. One way or another there will be an expectation – we need to make sure it is the best standard possible.

Similarly outside of BPOG, there have been efforts through the American Society for Testing and Materials (ASTM) and Parental Drug Association (PDA) to achieve a consensus on how the industry should approach and examine particulates that come from equipment use and pharmaceutical manufacturing, as the existing USP <788> standard focuses on particulates in the final drug product and does not readily translate in a meaningful way to individual single-use processing equipment. This is especially critical with particulates, as technologies are evolving rapidly, and different methods can lead to very different results, with different types or levels of particulates reported.

There are also many other similar efforts. The American Society of Mechanical Engineers BioProcess Equipment Group (ASME BPE), for example, is focusing on best practices for building biopharma equipment and standards for single-use system fittings to ensure that components fit well together (even if they are from different suppliers) and do not cause leakage. Other ASTM workgroups

are developing consensus standards for leak or integrity testing of single-use systems.

What a waste!

Overall, there is enormous amount of wasted effort in terms of testing and analyzing data because suppliers characterize things in different ways – and end users interpret the data in different ways. Standardization would lead to a more seamless flow of information in which suppliers, end users and regulators all understand very quickly what was done, the rationale behind it, and what the results mean in terms of the manufacturing process and its impact on drug product critical quality attributes.

As an example of how standardization could offer benefits, let us consider material change control. Once a drug product is approved, manufacturers don't like to implement changes as fully assessing the impact on the drug product is non-trivial. However, change invariably happens as biopharma supply chains are complex. As an integrated solution supplier, if something has to change in one of our materials, such as with a filter or biocontainer bag, then we notify the customer, provide timelines and do everything we can to support the drug manufacturer with their risk assessment. Take for example the general industry-wide trend for polymeric resin suppliers to replace phthalate-based polymer resins with non-phthalate-based equivalents. In such cases, not one, but typically multiple single-use component and system suppliers, who often pull from the same pool of available polymer materials, may be impacted by the raw material change. Each impacted component and system supplier will assess the change, make terminal buys, notify their customer base, and then implement a change, which from a holistic industry perspective, may span several years for a single raw material change. As end users often buy from multiple single-use suppliers, they may feel the frustration of a single raw material change working its way into multiple types of single-use components purchased from multiple suppliers over a span of years. Each of the impacted suppliers will be performing costly testing to help support risk assessment, as will many of the drug manufacturers in order to suit their own individual protocols. Manufacturers often claim that supplier data packages lack the details they need, but suppliers don't always know what is expected, as different end-users have different applications, expectations and requirements. If we can agree on what testing needs to be done and exactly what data is needed, it should accelerate the whole process of qualifying new technologies and materials, and give suppliers and end-users more confidence in one another. As a first step, BPOG and BPSA have released a guide on change notification for single-use which focuses on when and how to communicate a change and other groups continue to work on the topic in terms of what data sets are needed and so forth.

As an industry, we are moving away from focusing on the minor competitive advantage in specific areas that benefit us all, to instead collaborating in working groups to discuss overall best practices and come to a consensus on standards that can help grow the entire industry. With the new approach, the rewards are much higher than can ever be achieved by one company seeking a competitive edge. BPOG, BPSA and other organizations have released a number of best practice guides, and now is the time to turn these into standards – and to align them globally. As one good example of global collaboration, consider China's recent joining of the International Conference on Harmonization as well as the joint workshops and extended partnerships being formed between the Chinese Pharmacopeia with USP and the European Pharmacopoeia. With all of these collaborative industry working groups, most have an international flavor because of the recognition that it is in everyone's best interests to achieve a globally common unit of standards and expectations – the rate at which individual regions get to target expectation may be different, but we are all heading in the same quality direction.

Technologies like single-use have proven their worth in the industry. And newer innovations, like continuous processing, will generate enormous impacts as well. It is crucial for suppliers and end users to standardize on what types of data, information, best practices, and risk assessment approaches are needed to support the implementation of these technologies.

Standards won't cover every drug manufacturing scenario, but they will cover a significant proportion. And they will bring much needed clarity to the industry, and allow changes or data sets to be interpreted very quickly – ultimately accelerating the drug development process, as well as the resolution of changes that happen to excipients or equipment during the product life cycle.

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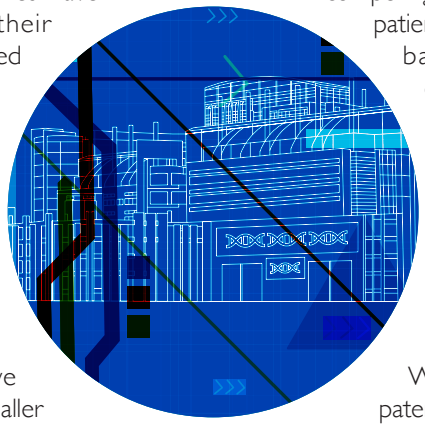
Automated Processing Techniques and Lean Principles are the Future

Why new processing technology and automated processing is key to driving down costs and boosting facility efficiency.

By Roel Gordijn and Michael Schoeb

One of the key drivers for a technology change in the biopharma industry is the need for leaner, more automated manufacturing processes with the target to reduce costs of goods sold. Most other manufacturing industries have already examined their costs and implemented new technologies, manufacturing techniques and process automation to make their work flows more efficient and cost effective. Biopharma has lagged behind in this field. Most new innovative drugs today require smaller batch sizes because they are targeted at smaller patient populations and tailored to specific market demands. This can make manufacturing using traditional technologies and equipment set up expensive. Scientifically, however, it is an exciting time for medicine. We've moved from chemical APIs, to tailored and potent biopharmaceuticals, to ingenious cell and gene therapies that can offer real cures for unmet needs. For the latter therapies, there is a lot of promising activity and clinical trials, but few therapies have been designed with commercial scale in mind. As an industry, we need to find a way to manufacture both traditional biopharmaceuticals and new personalized medicines in a more cost-effective way. The focus on costs will only continue and we need new manufacturing techniques, automated processing and lean principles to be implemented.



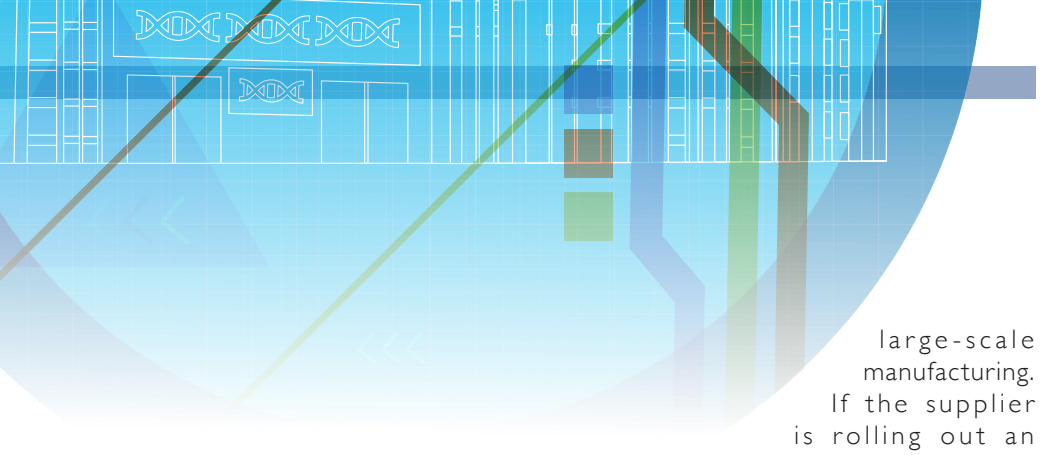
Costs have been a key driver for the wider implementation of single-use technologies. Single-use, amongst other benefits, reduces the costs associated with cleaning and makes it less expensive to build a facility, especially for smaller batch sizes and high variation of different drugs within the same facility. Changeover and cleaning validation is generally faster, which means critical decisions about a product's future and manufacturing capacity can be postponed until more data is available. Single-use is particularly compelling for drugs with smaller patient populations, smaller batch sizes and high changeovers from one to another product - where it's not economically viable to use stainless steel infrastructure. It is a different scenario for large scale batches with low changeovers. With blockbuster patents expiring, more and more biosimilar products are being developed, and in many cases, multiple biosimilars are being developed for the same innovator drugs with the largest profits. Given the heavy competition, biosimilar developers are keen to reduce their costs as much as possible to make their product that little bit more attractive to payers. Therefore, the technologies chosen for each manufacturing set up are key to drive towards the optimal economical model. In most scenarios, hybrid configurations with a combination of new and traditional technology are the result of these evaluations.

The early bird

Initially, the industry was cautious about single-use, but has since found that the approach can be highly successful for certain products and/or markets. Single-use has become more viable thanks to developments in cell culture media and other areas, but higher titers have in turn led to bottlenecks downstream (particularly the chromatography step and cleaning). There is the potential to address these issues using next-generation processing technologies, such as continuous bioprocessing, and automation. As Rick Morris explained on page 13, continuous isn't all that different to batch processing – and is a technology that regulators are encouraging biopharma manufacturers to explore.

If you are going to use new technologies for a product then they need to be introduced early on in the process. Products currently on the market or in late-stage trials that are made in batch will be challenging and costly to switch to continuous. On the other hand, there is a lot of interest in using continuous technologies for products at the pre-clinical phase. Not everyone is willing to switch into a fully continuous train immediately; some companies are continually running just one or two steps and seeing huge benefits. The leaner your manufacturing process becomes, the more costs can be saved. In many cases, the systems for continuous bioprocessing are based on single-use, but some companies are choosing to use a mix of single-use and stainless steel in a hybrid approach.

There are two different approaches that you can take when building a new plant and rolling out new technologies with automation. The first approach involves mixing and matching equipment from different vendors, and then using an automation and engineering firm to help put it all together in a seamless flow. In this



large-scale manufacturing. If the supplier is rolling out an integrated process line for the biopharma customer, there will always be a higher dependency on the supplier, who needs to ensure that the full process line functions and meets the process needs from the customer.

situation, you need to ensure that the different systems fit together and that the consumables you plan to use are compatible. Depending on the systems you are using, making sure everything "plays nicely" and functions smoothly as a complete line can create some challenges, but it is a viable approach for companies that are adamant about using specific systems from different vendors and do not want to rely on a fully integrated automation set up.

The alternative solution is to work with an end-to-end solution provider. It's a very efficient approach because the provider will select the equipment based on the process needs. The provider will then check if the required equipment fits into your clean room design and recommend automation concepts. This approach ensures you start first with the process by selecting the equipment based on process needs rather than fitting the process to the selected equipment with subsequent automation. Consumables will also come from the same provider, so everything will be compatible. The downside of this approach? You're dependent on one supplier, which some companies prefer to avoid. The largest biopharma companies tend to keep their expertise in house and will often ask suppliers not to provide any kind of fully integrated solution because they will implement it themselves.

Smaller companies cannot usually afford to hire such in-depth expertise in house. For them, supplier partnerships are crucial to achieve successful documentation and data collection for drug submissions. In many cases, suppliers can help adapt a customer's process and scale it up to

Focus on processing, resulting in reduced costs

Globally, healthcare costs continue to increase. If you want to dramatically reduce the cost of goods, you need to improve the output of the facility and the team that is making the product. Product titers upstream have already been boosted, but now the industry needs to find a way to efficiently process and purify these high titers downstream. Interestingly the technology does exist! Biopharma may, in some ways, lag behind other manufacturing industries, but there has always been a drive to improve. In the old days, as drugs were developed, production lines were built accordingly, but it didn't take long for the industry to realize that they should develop drug families on certain platform technologies because individual development and manufacture was not sustainable. We now need to push this even further with a move to smaller, flexible facilities that can be rapidly deployed. Such facilities are particularly compelling where drugs are needed for an epidemic, but there is also a global trend for more localized production – many governments in emerging markets are investing to attract pharma companies because they want local production content for their population; effectively made in the region for the region. This especially as the geopolitical situation may change and uncertainties of supply are raised.

Whether you use stainless steel, single-use or hybrid will depend on your batch size, the number of batches, the age of the drug, and what markets you are targeting, but all of us – whether drug producer or supplier – should be focusing on how we can reduce the overall costs of our healthcare systems, and how new processing techniques and technologies combined with automation can help.

Advantages of lean manufacturing and automated processing

- Different processing techniques drive lower production costs
- Higher volume production
- More consistent quality and reproducibility
- Improved floor space utilization
- Less chance for human error
- Improved safety
- Higher process reproducibility and consistency
- Quality by Design (QbD) with automation
- Reduced waste
- Faster processing
- Less employees required
- Competitive edge over other companies

Roel Gordijn is Global Vice President Biotech Integrated Solutions and Michael Schoeb is Senior Vice President of Process Engineering Biotech, both at Pall Biotech.

Making the Medicines of the Future

Cell and gene therapies would be incredibly difficult to commercialize without disposable manufacturing technology.

With Tony Hitchcock, Technical Director of Cobra Biologics

Only a small number of cell and gene therapies have been approved to date by the FDA or EMA, but there is a great deal of excitement in the area. Not only are phenomenal advances being seen in science and discovery, but new developments in manufacturing equipment are making the commercial production of the resulting therapies a reality. According to Tony Hitchcock, single-use has been a key enabler of the cell and gene therapy manufacturing industry.

What's your stance on single-use systems?

I've always been a big fan of single-use systems. When they first began to appear on the market, I was working on drugs and manufacturing processes for plasmid DNA to be used in early phase gene therapy clinical trials. One of the biggest issues for us at the time was product segregation and cleaning validation; we were literally buying stainless steel systems and throwing them away after a single production run because we couldn't validate the cleaning of them.

To that end, single-use systems have been critical to the development of manufacturing process for gene therapy products – I don't think cell and gene therapies would have taken off without single-use. Consequently, I remain strong advocate of disposable systems.

Initially, there were many industry concerns about single-use; with some people even saying that single-use was not "proper engineering". The systems were small and when they first emerged, they weren't suited for commercial production, so it took several years for them to migrate into mainstream manufacture.

What about concerns around extractables and leachables (E&L)?

Patient safety is the number one concern of all regulators, and questions around E&L have been raised within the industry for a number of years. Initially, I don't think people took single-use systems seriously when they first emerged, and the concerns came in alongside the potential for them to be increasingly used for commercial production. Initially, these concerns came from companies' internal regulatory groups, who struggled with these approaches, not least because of the lack of clear guidelines relating to the use of plastic-based systems in manufacturing processes, rather than product storage, and the novelty of these approaches.

However, despite this, nearly all biopharma companies have invested heavily over recent years into single-use technologies and in some cases, whole production facilities. In my mind, these decisions were essentially based on the commercial and operational advantages of single-use systems, backed by risk assessments on multiple issues around quality impacts of which E&L was only one factor. From my perspective, I think the issues with E&L is that it has attracted a disproportionate amount of attention in terms of quality risks associated with the use of single-use systems and also detracted from the advantages that these systems can bring in terms of product segregation and cross-contamination.

Overall, I think a huge amount of progress has been made with regards to quality systems through suppliers and end-users working together to address them, and clearly given the number of products which are now either being produced commercially or in clinical trials, there is widespread acceptance of these systems from the regulatory authorities across the world.

It seems to me attention is now moving to other challenges such as disposal and managing plastic waste. Understandably there are environmental concerns and we need to find a way of managing the lifecycle and disposing of these systems appropriately. Recycling will be difficult, but as an industry we need to show that we are managing that waste stream in a professional and responsible manner.

Can you imagine going back to stainless steel?

The early part of my manufacturing career focused on stainless steel. Trying to get products into the clinical phase involved significant plant capital expenditure and there were issues with time and flexibility. Single-use has given the industry flexibility and allowed us to accelerate process development. Today, I think single-use is pretty much the norm for most companies, even for full-scale production. Big Pharma still tends to use stainless steel plants where very large production capacities are required, but there are companies – like Amgen – that have set up newer, smaller facilities that primarily use single-use. One of the issues with going back to stainless steel would be how do you translate backwards from single-use to stainless steel? The industry knows how to move from stainless steel to single-use – there is a lot of experience there – but going back would be difficult, given the infrastructure required for stainless steel facilities.

What developments will the cell and gene therapy area see in the coming years – both in terms of new therapies and manufacturing technologies?

This is a tough question given the rapid amount of development going on both at a technical and at the business level.

In terms of manufacturing technologies, there is clearly a big drive to reduce the costs of vector production and to

increase production capacities to allow for products to become more accessible to patients. To achieve this, the focus is currently on switching out of cell culture ware such as cell factories into more scalable technologies such as the iCELLis® bioreactor (Pall's automated, single-use, fixed-bed bioreactor) or to suspension culture systems. Additionally, there is a drive towards producer cell lines rather than transient production in suspension cultures, which allow for large-scale production in conventional bioreactors.

In terms of new therapies, I think the key developments will be firstly looking at the broader disease areas with significantly larger patient groups than are currently being treated, but this will require significant cost reductions and investment in treatment centers and staff to be achieved. At the other extreme I think the concept of patient specific medicines is likely to become a reality in the coming years. I find this concept really interesting, but it will require a revolution in manufacturing tools and approaches to achieve. I think it offers huge potential benefits for patient in key disease areas such as cancer treatments.

You're an advocate of single-use. How about other new technologies, such as continuous processing?

Single-use was a game changer because it brought with it such novel benefits. I have less experience with continuous systems, but currently I would say that the benefit is purely commercial, and cost is clearly a critical issue for the industry. I'd like to see the industry exploring what other advantages the technology can bring with regards to different processes and manufacturing strategies.

One of the reasons that single-use ultimately became very successful was that it was very simple and easy to use – workers could put it all together themselves without truly specialized training. If the industry wants continuous biomanufacturing to really take off, then it must be simple and accessible. Right now, many see continuous as a very different type of technology – new and complicated – and adoption is much less likely for therapies with established production platforms, but I think it does have real potential for product areas where there are no established processes.

It is often very hard to change technologies in pharma. The industry does not like change and the implications of change can be severe – in the worst case affecting patient safety so manufacturers and regulators must approach new – even really promising technologies – in a reserved manner. As an industry, I think we need to recognize the gains we've had, but we must carry on innovating to see what else we can change. In a way, I think the industry has become stuck. There is a lot of focus on platforms for antibody manufacture and how it can be improved. Indeed, many single-use systems target antibody processing. I think we need to improve platforms so that they can cope with a wider range of drug products.

When it comes to implementing new technologies, what are the considerations for CMOs/CDMOs and how do these differ to biopharma manufacturers?

CMOs, as service providers, cater to a broad range of customers from small biotech to large pharma, who will very often have variable manufacturing needs and experience. When we look to introduce new technologies, compared to directly guiding existing and potential customers from in-house operational groups, CMOs are often better positioned to advise existing and potential customers that any new technology is the right solution for their manufacturing needs, both for clinical supplies and in-market production.

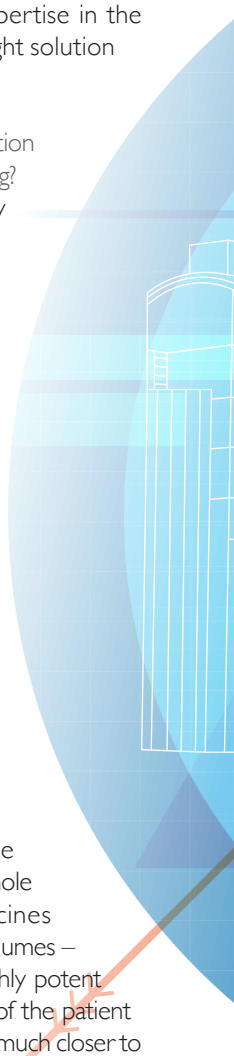
Key issues for our customers are risk and transferability of processes. For these reasons, customers tend to be wary of novel unproven technologies, especially where capital procurement and installation is required that may potentially delay their projects. Additionally, adopting new technologies may also lock them into a specific CMO or process, which may not be acceptable.

On the other hand, customers are also looking for us to provide solutions to their manufacturing needs and see CMOs as "manufacturing experts" especially in areas where they have a proven track record. So when we come to introduce new technologies we need to be able to show that we have expertise in the technology and that it is right solution for the customer's needs.

What's the next likely evolution for biopharma manufacturing?

Cell and gene therapy is a key focus for us; it is an exciting field and it is rapidly expanding. We are also reaching a point where we integrate a lot more with point of care users – particularly in the area of cell engineering. In the future, we'll see a lot more integration with hospitals and how we actually provide these products to the patient. I expect that we'll need to have some interesting discussions about where we draw the line of biomanufacturing.

A key trend in the biopharma industry as a whole is that many new medicines require small production volumes – either because they are highly potent or target only a niche part of the patient population. We are moving much closer to personalized medicine. Of course, there will always be large stainless steel plants making huge volumes of antibodies, but there will be much more innovation in complex therapeutics that are highly targeted and highly effective for certain patients.



Choosing the Right Technology for the Right Problems

Biopharma manufacturers may choose to use stainless steel or single-use equipment. The decision will depend on the product portfolio and the company's own needs and resources.

With Jorg Thommes, Head of CMC, Bill & Melinda Gates Medical Research nstitute. The opinions expressed in the article are Jorg's and not those of his employer, the Bill & Melinda Gates Medical Research Institute.

What are the benefits of stainless steel?

Ultimately, stainless steel has proven to be highly reliable for the manufacture of biopharmaceutical products. Stainless steel systems are operationally robust and straightforward to maintain. The industry is familiar with the equipment and has spent a lot of effort to understand the cleaning and sterilization of stainless steel bioreactors. In addition, scale up is by now quite predictable due to excellent progress in understanding mass transport and mixing phenomena in these reactors. This predictability is a key element of why stainless steel continues to be used by biopharma manufacturers. If a manufacturer purchases a stainless steel bioreactor, they understand what they are getting. In addition, the per batch operational costs, particularly at the high productivities possible today, that are achievable with stainless steel infrastructure are also a strong benefit. Finally, a well automated stainless steel facility run 24/7, 365 days a year can provide enormous productivity for large market products.

And what about the disadvantages?

Stainless steel infrastructures are complex, requiring significant capital investment. Indeed, some companies are reluctant to build stainless steel facilities because of the required investment and the long project timelines to build and commission them. Small companies, in particular, are unlikely to have extensive cash resources at hand to build a brand new stainless steel facility.

Another downside oftentimes cited for stainless steel is that product changeover is more difficult and rigid than in a single-use environment. It takes more time to clean and re-sterilize a stainless steel environment, whereas with single-use you simply remove the used component and install a new one. Since the connections are made aseptically, you can return to normal operations quickly. Experienced organizations that understand their stainless steel infrastructure well can minimize turnover times, but they will still likely be longer than for single-use equipment.

What is your experience with single use?

Like stainless steel, I believe that single-use also has benefits and drawbacks. The single-use reactors are easy to use, but there is the potential of interaction of cells and media components with the single-use plastic surfaces. This is perhaps my main concern. Stainless steel is inert but plastic surfaces can interfere with the media either through absorbing of media components or leaching from the surface, which could be detrimental to growth and productivity of the biological system. To add to the uncertainty, interactions can vary between batches of single-use equipment. Single-use surfaces essentially add a new raw material to the process and raw material variability is certainly of concern in biomanufacturing. When introducing single-use systems, it is crucial for the manufacturer to thoroughly research the potential for variability of single-use surface interactions and the impact of that variability on the consistency of the manufacturing process. Similar to having to study and validate cleaning and sterilization of stainless steel equipment, the onus is on the manufacturer to understand raw material variability issues for single-use equipment.

It's also true that single-use has advantages that may appeal to many manufacturers. As I mentioned earlier, ease of product changeover is a significant benefit. For example, a clinical manufacturing facility that only requires one or two batches of each candidate molecule can perform changeovers rapidly in succession when using single-use. Likewise, for a portfolio of diverse commercial products that all require only a few batches per year (for example, a rare disease product for a small patient population, or a highly potent compound), single-use may be the logical choice as it reduces the turnover time between products. Single-use also has other advantages; as the systems are oftentimes smaller, they are usually easier to transport. Single-use systems have recently been discussed as quite suitable for distributed manufacturing. Stainless steel equipment can, of course, be used for distributed manufacturing too, but single-use systems can be assembled with substantially reduced capital investment and be quickly deployed, ready assembled, for use in different locations.

Stainless steel or single use; ultimately, which option is superior?

It is not about which option is "superior", it is about choosing the right solution for a specific problem. The introduction of single-use systems – and their acceptance by the industry – has given biomanufacturers more choice in how they make their products. Twenty years ago, a manufacturer would have to build a stainless steel facility because that was the only option. Today, companies can thoroughly review which technology will be best for their specific needs, or whether there is benefit in combining both in a hybrid approach.

The decision over which equipment to use can be complex, depending on the company, its strategy, pipeline and resources. For a company with products that need to serve large markets and are manufactured in a large number of batches per year, stainless steel may be considered the optimal solution, but necessitates a large cash investment. The company will also need to have the confidence that investing in a facility is the right use of their limited resources. For a smaller company, the decision can be quite different than for a large entity. Uncertainty around future pipeline and manufacturing requirements may impact the decision making. In this instance, a single-use facility will minimize the capital required and reduce building time. Stainless steel facilities need to be planned far in advance – at a time when uncertainty around the potential of a new product can be high.

How are approaches that use continuous bioprocessing further expanding manufacturing options for companies?

Continuous bioprocessing is attracting increasing interest in the biomanufacturing community. One of the most compelling advantages of continuous manufacturing is the ability to work in a steady state resulting in a continuous, consistent and reliable flow of product. Typically, biopharmaceuticals come with quality attributes where variability within a range of attributes is expected. In a continuous system in steady state, the range of quality attributes can be expected to be narrower. However, in order to run a continuous bioprocessing system, one must have an in-depth understanding of the stability of the manufacturing process and the controls necessary to get to and stay in steady state. Not all products and processes will be suitable for a continuous bioprocess and this must be something that is thoroughly investigated before choosing this approach.

Is single use essential to implement a continuous bioprocess?

Some have described single-use as an important enabler of continuous bioprocessing, but continuous manufacturing can be performed with either stainless steel or single-use. I personally believe that stainless steel complements continuous manufacturing very well because continuous manufacturing is meant to deliver a steady and consistent product output over long periods of time, which plays to the advantage of a stainless-steel infrastructure. A continuous system that produces the same product and the same quality day in, day out lends itself well to fixed infrastructure where few product changeovers are expected.

Ultimately, it is a manufacturer's own responsibility to understand their product and to choose the most appropriate technology. The decision over whether to use stainless steel or single-use, execute batch manufacturing or adopt a continuous operation must be based on science and whether the solution is suitable for the problems at hand. Single-use is not a goal in itself, but is an excellent tool to tackle a number of issues that certain manufacturing scenarios require. The same is true for stainless steel. You should never build a single-use or stainless steel plant just because you fundamentally like or dislike it – whatever you choose should be a good fit with your product and business.

Perfusion Pioneer

Speaking with Veronique Chotteau, Principal Investigator of the Cell Technology group at the KTH Royal Institute of Technology, Sweden.

Why did you choose a career in life sciences?

I was always interested in science and maths, but I was originally planning on a career in electrical engineering. I took a masters in this area because, honestly speaking, it was a safe way to ensure I would have a job! But life sciences was very interesting too and I began studying biology in parallel with my education as an electric engineer. I then took another master's in technology and molecular biology – and began to move further in this direction working with mammalian cell culture. I enjoyed working with cells and I also had the opportunity to see how industry works when I collaborated with SmithKline (which later became GlaxoSmithKline). I worked in industry for a number of years before joining the KTH Royal Institute of Technology.

How did you come to focus on perfusion?

At the start of my career, I worked for Pharmacia & Upjohn (the unit I worked for was later spun out to Biovitrum) and a perfusion process was used to make Factor VIII. This is one of the most challenging molecules for production and, coupled with the perfusion process, it was a challenging but great introduction to the industry. Perfusion was not very popular at the time but it is a really nice way to treat cells because it creates a very favorable and consistent environment. I remember when the company DSM announced that they could work to a really high cell density. They didn't publish on how they did it but simply showed that they could do it – and that really attracted my interest! How did they do it? Could anybody really do it?! At the time, there was no way it could be done. In fact, some companies had previously considered perfusion but ended up walking away because of the technical challenges.

When I started in academia, I chose to focus on high-cell density perfusion systems. There are many factors today pushing high cell density perfusion as a potential system for the future. In the early days, the technology was not quite there but it is becoming increasingly popular in the biopharma industry. It's a very efficient process that is very flexible and works well with disposable equipment. And the small footprint makes for lower costs of goods.

What do you focus on at KTH?

There are a several areas that we focus on, including high cell density perfusion, systematic process development and mathematical modeling. I am Director of the Competence Centre for Advanced BioProduction by Continuous Processing, AdBIOPRO, which includes both continuous upstream and purification, involving several experts of the field from KTH, Lund University and Karolinska Institutet, as well as seven industries. We are working to gain a better understanding on what is happening in continuous processes and want to give the field tools for process development or manufacturing. We are working a lot with mathematical modeling of processes, which is a good way to identify how the process should be, and how to design your medium so that you'll get better performance of the culture, or obtain a target glycosylation, for instance.

We are also part of two other Swedish Competence Centers, the Wallenberg Centre for Protein Research, WCPR, where we develop high cell density perfusion of human cells, and the new Centre for Advanced Medical Products, CAMP, focusing on cell therapy and gene therapy.

In addition, we are involved with a number of European or Swedish projects. One example is the EU project, iConsensus, which I coordinate. It is funded by the Innovative Medicines Initiative and aims to develop real-time tools to monitor a cell culture, models and high-throughput micro-bioreactors. This project will bring very useful tools for perfusion processes.

Could perfusion also benefit cell therapies?

Yes – I believe that perfusion will be really important for cell therapies. Indeed, many of our methods and much of our knowledge can be applied to different types of biologics, including the cultivation of cell therapies. Scientists working on these therapies do so within small systems that are not really scalable. When we say they can use perfusion, their eyes open and they become very excited, saying that this is what they really need for their cells.

Recently, we have started looking at tools for gene therapy as well, because there is a real need for intensification of viral vector production.

What are your thoughts on the future of perfusion?

For perfusion, there is a level of technical challenge that you have to master, and this is where the field is a little bit conservative. Having been in the industry and having worked with large scale, I can understand that view and there will always be some companies who prefer batch, but I think the field will move more towards continuous, especially with new technologies emerging. Some companies are really putting a lot of effort into perfusion, while others are seeking a hybrid approach.

How about the future of biopharma in general?

I've had many engaging discussions at conferences and with partners in the different consortia I'm involved with, and it really feels like the biopharma industry is ready to adopt more tools. Modeling, for example, has for a long time been considered too difficult, but the industry is now seriously putting more effort into it for both batch and perfusion. And once we have real-time monitoring and more models, there will be a real opportunity for perfusion. Perfusion has been around for many years, but we are at the point now where it is becoming more intensified. There is so much effort going into the field that something will certainly come of it.

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