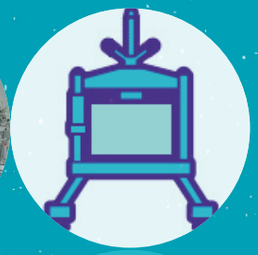
WHAT'S NEXT

Exploring the Future of Bioprocessing Together.

Visualizing the Future of Bioprocessing

Facing the Future

The Connected Process



Making Next Generation Manufacturing Work

New Horizons

Spotlight Interview

Foreword

Please click the circles to navigate

Visualizing the Future of Bioprocessing

Rickey Lu, Director, Manufacturing Technology Innovation, AstraZeneca:
"We want to deliver the right amount of medicines of the right quality as quickly and as inexpensively as possible. I can envision, in the not too distant future, continuous processes that drive down cost, PAT technologies that provide real-time process control, and contemporaneous batch disposition, plug and play equipment that allows us to manufacture new products efficiently. All of this will work in concert to make biopharma supply chains tremendously more efficient and to alleviate the impact of demand uncertainty."

Michael (Mike) Phillips, Director, Next Generation Bioprocessing R&D, Merck:
"From my perspective, the ideal bioprocess would be a fully automated, continuous process optimized to achieve high product yield and purity while simultaneously minimizing process cost and environmental impacts. I realize that there are key enabling technologies that need to be developed before this vision can be fully realized. Consequently, the ideal bioprocess of today would be an inherently batch process that leverages high productivity technologies that ultimately support the evolution to a fully continuous process."

Jonathan Souquet, Head of Technology Innovations for Bioprocessing Sciences, at the healthcare business of Merck:
"The industry needs high performance manufacturing processes through establishment of next generation solutions in order to improve efficiency and effectiveness of our manufacturing networks. Technologies are evolving quickly and are creating huge leaps in productivity and intensity of production operations. In the future, I envision a more commoditized manufacturing model as the industry matures. Supply chains as a whole will also experience significant evolution with considerable gains in the reduction of lead times and progression towards an on-demand supply infrastructure to best meet market needs.

Merrilee Whitney, Head of Next Generation Bioprocessing, Merck:
"My vision for the future of bioprocessing is having flexible, easily-connected intensification blocks that enable a process to easily meet a particular customer's needs. Every customer is going to have different templates and different objectives, so it is incumbent on us as suppliers to have these building blocks that can seamlessly be integrated, as well as independently of one another, in case a customer is having a problem with one particular part of a process."

Janmeet Anant, Regulatory Advocate, Merck:
"Right now, there are different drug development teams for the upstream and downstream process, but in the future I believe there will be a more holistic approach. I also see collaboration as an important driver for improved bioprocessing because it is crucial to share best practices and ideas. In time, there will be a move to connected processes – and regulatory acceptance of these – leading to huge cost savings in the industry, lower drug prices, and improved access to treatments worldwide."

Herb Lutz, Global Principal Consultant, Manufacturing Sciences & Technology, Merck:
"At the beginning of biotech, each mg of protein was very precious and manufacturing processes had frequent batch failures and contaminations. In the 30 years hence, risk reduction enables linking steps together. The recent advent of sterile single-use technology provides rapid, low-cost implementation. Other technology developments combine to enable new, intensified processes and linked operation that can be run continuously. This is an exciting time for biomanufacturing!"

Delia Lyons, Head of Perfusion Media Development, Merck:
"Intensified continuous processes are key to enabling biopharma companies to manufacture drugs that otherwise would not be available to certain populations, such as patients in developing countries or who suffer from extremely rare illnesses. This is possible because of the shorter development times, in smaller and potentially portable plants, and with reduced cost supported by these processes. Suppliers can contribute to a better future in which drugs are available to an extended population by developing the tools biopharmaceutical companies need to manufacture these drugs with reduced cost and time."

Gorazd Hribar, Project Manager and DSP Development Scientist, at Lek Pharmaceuticals, a Sandoz company:
"When you compare biopharma to the oil or automotive industry, where everything runs automatically and continuously, biopharma just isn't well optimized. Continuous approaches can lower costs and speed up processes, but greater adoption is held back by the requirement for tricky real-time monitoring and control. We're not quite there yet but innovative solutions are being developed as we speak."

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The Next Generation of Bioprocessing

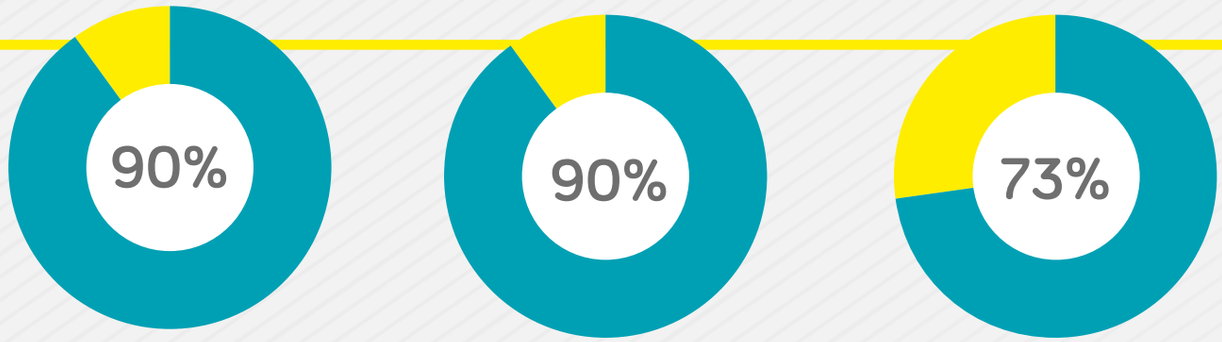
Merck commissioned an extensive market analysis with respect to next generation processing. Displayed here is a selection of the findings.

Respondents viewed intensified technologies as mostly single use at the clinical-stage and as mostly hybrid at the commercial scale.

What are the main barriers to adoption?

- On-line analytics
- Batch definition
- Company culture

Respondents said that these intensification methods are already being used...

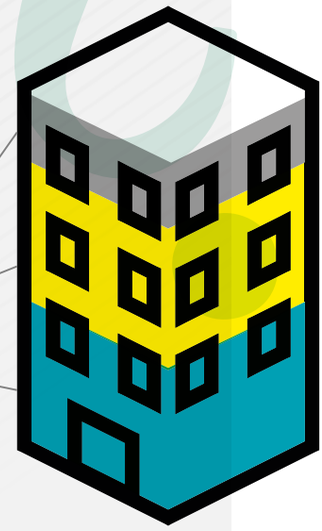


Flow-through chromatography

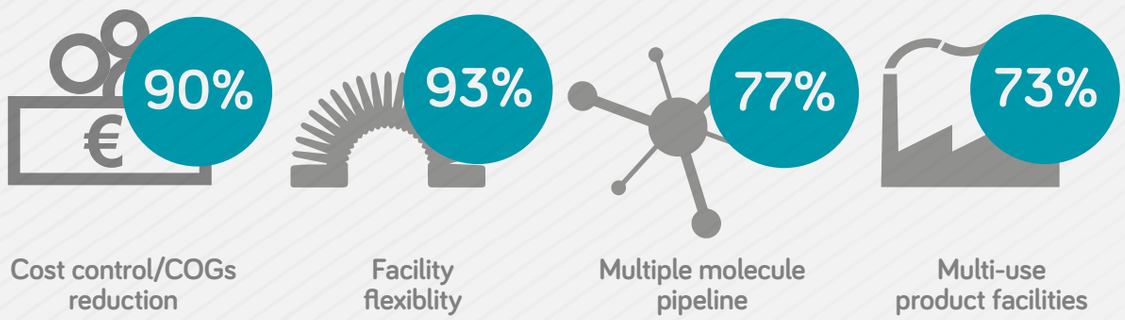
Cell line & media optimization

Flow-through polishing/ purification ion exchange

Respondents believe that intensified processes will be incorporated into:



Respondents viewed the following as the most important drivers for adoption of intensified processing



Cost control/COGs reduction

Facility flexiblity

Multiple molecule pipeline

Multi-use product facilities

Respondents said that the largest adoption of process intensification will happen for:

1. New molecules in development
2. Second generation processes for commercial molecules
3. Biosimilars

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FACING THE FUTURE

Why could next generation bioprocessing be so valuable for the biopharma industry? A supplier and a manufacturer share their views.

What are the key challenges shaping the future of bioprocessing?

Jonathan Souquet (JS): From a development perspective, pipelines are diversifying and molecules are becoming increasingly complex. Some of today's processing technology platforms are not adapted to new molecular formats, which can bring about unprecedented challenges that we, developers and manufacturers, have to resolve quickly and efficiently. In addition, clinicians are becoming very creative in terms of reducing clinical development timelines and, therefore, time to establish a viable manufacturing process is becoming limiting. For some oncology products and indications, there are no longer phase II trials, while regulatory authorities are also establishing accelerated pathways for breakthrough therapies and products addressing unmet needs. R&D strategies are also focusing on increasing the number of candidates in the pipeline to mitigate against high attrition rates in clinical development. In order to maximize candidate numbers we must minimize the effort and resources deployed on any one asset, which leads us to find technology solutions to improve efficiency and effectiveness of bioprocess development.

There are also considerable commercial challenges facing the industry. There is significant competition in the marketplace – with similar therapeutic modalities aiming at identical targets with similar modes of action. In addition, pricing pressures are increasing through globalization towards emerging markets, and drug costs being increasingly challenged by payers and health authorities. Added to all of this is a high level of volatility – it is very difficult to predict what manufacturing capacity is required and when it will be needed to supply a future portfolio. Excess capacity should be minimized as it results in significant costs, but under-estimating capacity needs would limit supply to the market and impact patient access, as well as potential market share.

Merrilee Whitney (MW): Bioprocessing today, especially for monoclonal antibodies, is a well-established process – not only from a technology perspective, but also in terms of regulations. Biopharma companies understand what they're doing, what they need to measure and how to validate a process. Suppliers, like ourselves, also understand the field and know that we need to develop efficient products, and demonstrate the performance and claims of products from a scientific standpoint. But although bioprocessing is fairly mature, is it really meeting the true needs of today's industry? And will it be suitable for the future, given

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that more and more biopharma products are being developed? As Jonathan said, there are many challenges facing the industry and I feel that current processing models and approaches have been pushed as far as they can go in terms of flexibility, utilization, risk mitigation, and speed to market. If we want to see real step changes in manufacturing costs, efficiencies and plant utilization now, then we need to look at bioprocessing in a new way – which will involve new technologies and methodologies. A number of stakeholders in the industry are now focusing on the possibility of developing a connected, fully continuous bioprocess. Of course, revolutionizing biomanufacturing is never easy and there are many questions to answer. How do we validate new products and technologies to show performance? What will regulators want to see? How do we define a batch in the future if we move to fully connected, continuous bioprocessing? Manufacturers, suppliers and regulators need to be working in lockstep to answer those questions.

What is "next generation" bioprocessing?

JS: The industry needs to be much more efficient in how it manufactures and supplies products. Manufacturing platforms need to be agile, able to adapt to specific requirements, extend capacity rapidly, and be responsive – able to react to market demand quickly. A key enabler is to establish high performance processes, which will reduce the manufacturing footprint and, hence, lead time to adapt and establish manufacturing assets, significantly mitigating risk of uncertainty in capacity needs. Today's facilities take an average of 5 years to build and commission, but future facilities will target 18 months. Process intensification will also decrease cycle time to produce and release product, facilitating an on-demand supply chain. Both of these characteristics, reduced footprint and cycle time, will also have a significant impact on capital and operational costs. This is where "next generation" technologies and methodologies come into play as a means to increase the performance of manufacturing processes. There is no established industry standard for what next generation manufacturing looks like; every organization has their own flavor as the industry is exploring potential technology solutions, but perhaps in a few years the industry will start to converge towards one or two overarching platforms. Right now, everyone is addressing their own unique challenges and prioritizing based on their most pressing needs, resulting in significant diversity. Continuous bioprocessing is seeing a lot of attention, but implementation seems to be slow. In my view, next generation bioprocessing is about targeting high productivity, high intensity processes – and continuous mode manufacturing operations are a significant contributor either as a full end-to-end integrated process or as a hybrid setup.

What is Next Generation Bioprocessing?

Any technology, expendable, or system which significantly changes the existing monoclonal antibody manufacturing template to deliver:

- ↑ Higher productivity
- ↑ Increased manufacturing flexibility
- ↑ Increased speed
- ↓ Reduced risk

Merck definition of next generation bioprocessing.

Contributors

The Supplier Perspective
Merrilee Whitney, Head of Next Generation Bioprocessing, Merck, is a chemical engineer by training. "Our business unit is not directly involved in drug discovery or the manufacture of commercial drugs, but our products do contribute and that is really motivating for me," she says. "Next generation bioprocessing is a newly emerging, complex area, and there are a lot of questions that need answering, and a lot of problems to be solved. The chemical engineer in me is really excited to be involved in this field."

The Manufacturer Perspective
Jonathan Souquet is Head of Technology and Innovation for Bioprocess Sciences within the healthcare business of Merck. Part of his role is to design, develop and deliver a strategy for a next generation manufacturing platform to support the emerging pipeline. He says, "I've always been interested in technology, but the appeal of Bioprocess Sciences is that it sits between discovery and commercial operations, and is an applied science aimed at translating research output into a manufacturing environment. Solving the challenges in today's bioprocess operations is very rewarding as it is a relatively immature industry with significant scope for advancement."

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> "There are clear benefits in terms of reduced footprint and capital, and improved product quality."

MW: There are many different definitions in the industry. For some people, next generation bioprocessing means a completely single-use manufacturing facility; others think it is a fully connected and fully continuous process. From my perspective, the goal is the latter, but the true definition of next generation bioprocessing is the technologies that will get us there. I consider next generation to be any technology, expendable, or system which significantly changes the existing monoclonal antibody manufacturing template to deliver higher productivity, increased manufacturing flexibility, increased speed, and reduced risk. The fact is that we need more flexible approaches to biopharma production and the evolution is already underway with the intensification of specific unit operations. Companies are now looking at how they can connect those operations together, with the ultimate vision being a fully connected, fully continuous process involving intensification, single use, process analytics, and monitoring. The big challenge will be jumping from process intensification to connection, but I'm seeing a lot of resolution in the industry to get there.

What technologies do you think are the ones to watch?

JS: The approach to next generation manufacturing technologies at the healthcare business of Merck is focused on two main areas. We have a significant amount of installed capacity that we seek to maximize and we are also working on our future manufacturing model in anticipation of new facility needs as a result of a rapidly growing pipeline.

Advanced process and quality control analytical applications will play an important role in next generation manufacturing, as well as automation and digitalization, including data management and modeling. Technologies that enable a highly integrated and parallelized manufacturing operation with reduced volume requirements will come to the fore. One particular example encompassing a challenge that is often underrated is the buffer bottleneck. The amount of buffer required for a process is not a function of the process scale, but a function of the quantity of product that is being produced. Therefore, even if the core manufacturing process is shrunk through intensification, similar amounts of buffers will be required. Technologies and methodologies with the ability to reduce the amount of buffer, and the numbers of individual formulations will have a significant impact on manufacturing cost and footprint requirements.

MW: There are new technologies across the board. Perfusion has really made a big difference in upstream processing because it allows you to increase the productivity of the capital intensive upstream stage. Many companies are leveraging perfusion in a hybrid way; for example, they may run their inoculum and seed train in perfusion mode and then move to fed batch. The industry is also looking to optimize not just the operation of the bioreactor, but also its feeding strategies, the cell culture media, and other ancillary operations. Importantly, the industry needs to look at how to most efficiently handle the media that is going into the bioreactor for perfusion – because when you operate in perfusion you increase your media consumption by around three times in terms of volume. Technologies focused on media management will perhaps be compelling for manufacturers in the future.

Looking downstream, systems for continuous multi-column chromatography are improving, but it is also necessary to optimize chromatography technologies. There is some interesting work going on there, as well as in the flow-through polishing piece, such as cation exchange and anion exchange. For instance, our recent acquisition of Natrix Separations, Inc. and its unique single-use membrane

A New Manufacturing Approach

For Broader Patient Accessibility to Highly Efficient Biopharmaceuticals

Industry Trends

Target medicines
Driving production volumes to less-than-blockbuster levels.

Market forces (e.g. aging population)
Creating pressure on the therapeutic development & manufacturing industry to contain drug costs.

FDA strong supporter of continuous processing
Advocating that continuous manufacturing reduces manual handling of products and allows for better process control.

Paradigm shift
faster, cheaper, better

The Solution:
Next Generation Bioprocessing

* Flexible production schemes
* Continuous vs. batch mode
* Multi-product facilities
* Single-use consumables

= more efficient production

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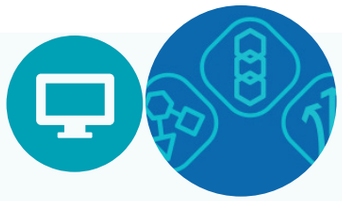

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chromatography technology platform that is capable of delivering high productivity and impurity removal in a single-use format. These products are compact and single use, eliminating validation, cleaning, sanitization, and storage, while also enabling flexible downstream processing; an ideal fit with intensified processing. I also find in-line viral inactivation fascinating because it's very beneficial in terms of establishing a truly continuous process. If you can perform an inactivation step in a continuous mode of operation, rather than in multiple large hold tanks, then it could have a positive impact on capital investments. There are clear benefits in terms of reduced footprint and capital, and improved product quality. Not only will the large tankage be eliminated, but it can be done in a way that meets regulatory requirements and overcomes the hurdles and validation strategies associated with in-line viral inactivation.

What advice would you give to a company that is curious about next generation bioprocessing, but unsure of where to start?

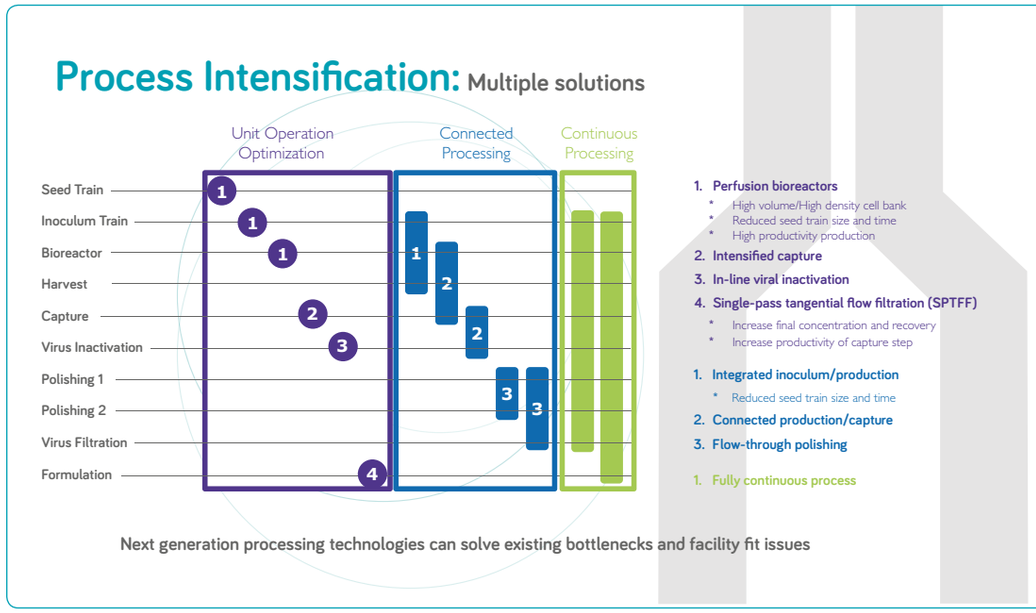
JS: There are many opportunities in leveraging next generation technologies to alleviate manufacturing bottlenecks. I would recommend not to fully commit before identifying the value and applicability of the solution. There is a wide palette of "next gen" bioprocessing technologies being developed, and there is probably something to meet everyone's needs, but specific challenges should be approached in a methodical way to ensure the application is fit for purpose and results in a robust solution. In the healthcare business of Merck, we have established a technology development workflow with well-defined stage gates to ensure a successful implementation and to maximize the value of our innovation process. We start by analyzing our needs and gaps, and look for solutions to resolve them through ideation exercises. Then, we embark on an exploration phase where a number of technologies and/or methodologies are tested or developed, before moving into a proof of concept exercise for the most promising candidates. Once proof of concept criteria are met, the selected solution is taken through a feasibility testing cycle, normally incorporating a scale-up prior to implementation into our routine operations. Overall, I strongly believe it is important to be curious and to take the time to explore new technologies. The industry is ever changing and you can't keep still if you want to be competitive.

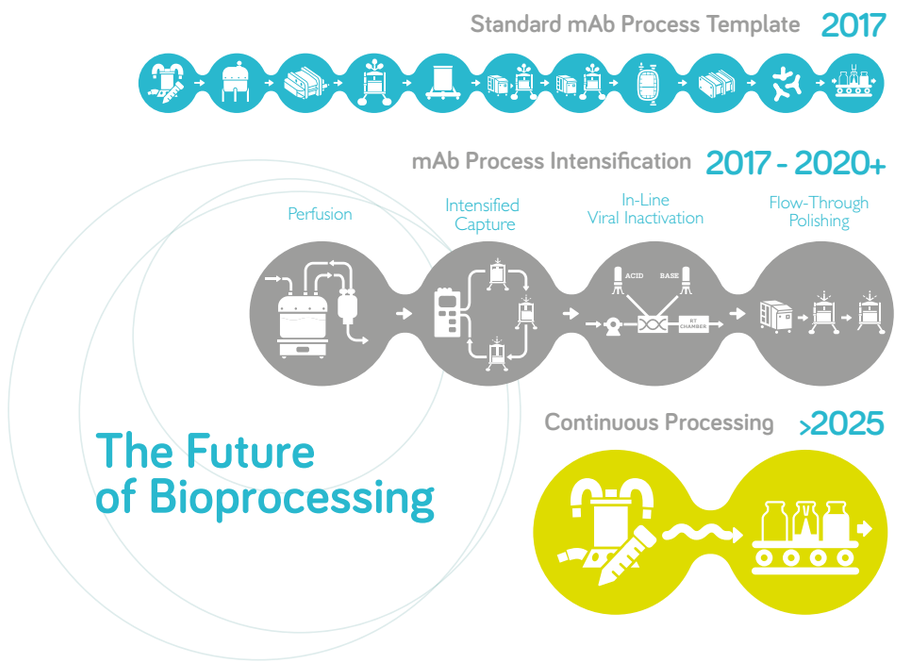
MW: At the outset, it is important to have an idea of what you're trying to achieve and the bottlenecks you are facing. My advice is to obtain a good understanding of what connecting processes means at the bench scale first, because addressing the challenges early on will make it easier when you are moving to the larger scale. Partnerships are also going to be incredibly important if we want to move into this new generation of advanced bioprocessing. Suppliers, like ourselves, have a role to play since we are developing solutions to help manufacturers overcome the challenges of next generation bioprocessing. Each molecule and manufacturer is unique with different processing priorities. Working with a vendor offering a wide portfolio of manufacturing options, coupled with deep technical expertise enables manufacturers to best tailor processes to meet their needs. Partnerships with regulators will also be crucial.

How are the life science and healthcare businesses of Merck collaborating to usher in the next generation of bioprocessing?

JS: We are part of the same parent company and we have established a strong collaboration model between the two businesses. The healthcare business provides the life science business a clear viewpoint on the development and manufacturing challenges being faced in the industry, an early customer voice in the technology development process and real world case studies to apply prototypes, helping Merrilee and her colleagues to ensure that their products and solutions are relevant. In return, the healthcare business gets early access to new technologies influencing the process to meet our exact needs. We view the collaboration as highly synergistic with complimentary skills sets and know-how, with an overall impact of accelerating the technology development process.

MW: Our collaboration with the healthcare business has given our engineers and scientist the opportunity to observe real-life challenges in bioprocessing – and help overcome these. The fact that we are both part of the same organization has made for a really open collaboration. We want the right products and solutions to help our customers drive down cost and increase the flexibility of their facilities. The healthcare business is looking to make significant advancements in terms of flexibility, infrastructure and being ready for the future, so they are looking for new technologies and approaches to make their lives easier, and to help them get the most out of their current facilities. Our goals are aligned, with both businesses demonstrating a strong dedication to next generation bioprocessing.





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The Connected Process

Connecting processes can be considered the next stage in evolution for biopharma manufacture, but how should companies approach the challenges?

In the early days of biomanufacturing, companies focused primarily on approvals, with process optimization being a much lower priority. This remained the case while the prices of biologics far outstripped the costs of manufacture, but in the age of biosimilars and cost-conservative payers, companies are now re-examining cost drivers in biologics manufacture. "Today, manufacturing is a strategic imperative and an area for differentiation – an opportunity to look at new technologies that can really drive down costs," explains Michael Phillips, Director, Next Generation Bioprocessing R&D, at Merck. "Companies are now focusing on how to get more out of their processes, how technologies, such as single use, can help, and looking to implement in-line sensors and analytics. Increasingly, companies are also looking at the potential to connect bioprocesses."

On page 4, Merrilee Whitney and Jonathan Souquet described next generation bioprocessing as continuous, connected processes, but what is a connected process? In traditional biopharma manufacturing, each operation is performed in isolation from other operations in the manufacturing process. One group manages the production bioreactor, another the clarification step, another the chromatography, another the polishing, another the virus removal, and so on.

"Connected processing is about running adjacent unit operations as a single unit, which results in improved efficiencies," says Phillips. "For example, upstream processes have been made more productive by replacing fed-batch with perfusion operation, and downstream bottlenecks can be addressed by employing multi-column Protein A chromatography. But how can you improve productivity when you have reached the limits of engineering? At this point, "adjacency" makes sense. The logical outcome is a fully continuous manufacturing system, in which all unit operations are connected to their neighbors, or run simultaneously."

A connected process would reduce operational footprint – by making holding tanks redundant for example – but there is still a big question about how processes should be connected. Continuous and connected processes demand communication between unit operations, so that any process can adjust for variations in preceding processes. "The industry is going to need very reliable sensors and process analytics, which will be a challenge," says Phillips. "Ultimately, however, I believe that a shift to connected processing is inevitable and part of the evolution of biopharma."

Regulatory disconnects

Change is rarely straightforward, and a move to connected processes in the heavily regulated biopharma industry will certainly create challenges. Janmeet Anant, Regulatory Advocate at Merck, explains, "Right now, connected systems for large molecules are new to regulators, but I am optimistic. Regulators understand that there is a lot of variability in biomanufacturing processes and are encouraging the industry to develop innovations that can produce more consistently high quality products."

Phillips adds, "From the presentations and discussions I've heard, I'd say that regulators are trying to be very accommodating. We have also seen some encouraging progress, such as regulatory approval for Janssen to switch from batch to continuous processing for an already approved small-molecule drug. Amgen has also implemented

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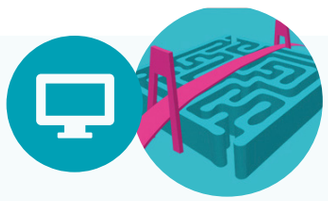

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connected processing for a biologic. A continuous bioreactor expression (i.e. perfusion) has been approved by regulators to commercially manufacture 23 different molecules."

But according to Anant, one of the biggest regulatory hurdles is that regulators are not always well-versed on innovative connected or continuous manufacturing approaches, unlike their extensive experience with batch processing. It is difficult for manufacturers to know what data will be required by regulators to prove that a connected process delivers products clinically equivalent to those manufactured by traditional approaches. To ease the process, Anant has highlighted that experts within Merck will guide manufacturers in terms of validating and comparing processes, which is one core element of regulatory acceptance. "Typical questions that manufacturers need to answer include, how long can continuous operations be sustained before equipment wear and tear becomes an issue? How should validation testing be changed to accommodate the new process? In non-connected systems, you can validate the bacterial filter by challenging it with a pulse of micro-organisms; how should this approach be modulated in continuous processing?" says Anant. "Similarly, where validation technology has improved – for example, virus inactivation processes once required several hours but can now maybe accomplished in a few minutes – how can we persuade regulators to accept these advances?"

The industry, including its regulators, are going through a learning curve regarding continuous, connected processes, but the end result should be more consistently high quality products. For these innovative manufacturing approaches, regulatory compliance needs to move beyond checklists towards an emphasis on product and process understanding and control based on sound science and quality risk management. A compliance-based checkbox exercise will not work – evidenced by the fact that many companies still experience quality problems, despite meticulously checking off their checkboxes. "Between now and the next five years, the industry will look to make connected processes more continuous, which will involve a true understanding of processes and variability – in other words, quality by design," says Anant. "This will also benefit the development of advanced online monitoring techniques, since you will know what to measure and how it affects the final drug product. Anticipating the future era of connected bioprocessing, regulators are now looking to expert organizations, vendors or suppliers that can develop suitable analytical process technologies."

For Phillips, there are still some regulatory questions that need answering, such as the definition of 'batch' – in the context of perfusion systems. "Is the batch the entire perfusion bioreactor run of, say, 60 days? Or do you cut it into smaller units based on time?" asks Phillips. "We still need consensus about this. Another ongoing issue is the lack of harmonization between different regulators. Clearly, there is less incentive to change when process alterations will require the manufacturer to satisfy several sets of guidelines."

Breaking barriers and building links

As well as regulations, companies also face internal challenges when they want to connect processes. "People are impeded by the traditional paradigm of process development," says Phillips. "In current practice, process development typically involves the independent optimization of each unit operation. The implementation of connected processing will necessitate a more holistic approach to process development. Optimizing the conditions for one unit operation may make subsequent operations less efficient, so process development experts will need to think about more global optimization at the whole process level that will require an understanding of all unit operations. Good communication and collaboration between the groups responsible for different unit operations will be essential; upstream experts will need to understand the language of downstream experts, and vice versa.

"Also, don't forget training," adds Phillips. "For example, optimizing a multi-column chromatography operation requires a different thought process compared to the optimization of a traditional single-column approach. Process development scientists and manufacturing operators will need direct exposure to these new technologies before they would be willing to adopt them."

The potential for significantly improved process robustness and process economics definitely justifies efforts in uncovering opportunities for connected processing and more holistic process optimization. Improvements can be significant and are often unanticipated. For example, a typical downstream process optimized at the unit operation level may require upward of 10 to 15 different buffers. For a process optimized more holistically, Phillips has seen instances where the total number of buffers has been decreased to only 4 or 5. "You may sacrifice some efficiency in one operation, but gain a more efficient overall process. As always, there is usually resistance to change, but change is usually required to perform at a different level."

Continuously Hooked

Mike Phillips relates how a colleague was converted to connected processing.

At Merck, we developed a novel flow-through polishing platform for mAb purification where residual impurities post-protein A capture were effectively removed through a series of 2 to 3 connected flow-through unit operations. One of our operators who was highly proficient in traditional bind-elute chromatography operations was reluctant to adopt this new approach, saying "Bind-elute cation exchange chromatography works so well for aggregate removal, so why change?"

I persuaded him to try the new approach. Within a week, he had declared that he'd never go back. He realized that not only does the connected flow-through process give comparable impurity clearance, but the new template was much more efficient, enabling 10 times more experiments to be run within a given time.

The moral of the story is that people have to experience the benefits for themselves; otherwise, they will never be convinced. Many of the barriers to the adoption of connected processing are psychological, rather than practical.

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Making Next Generation Manufacturing Work

When it comes to downstream bioprocessing, we already have many of the technologies we require – we only need to focus on adapting them.

Putting Single-Pass Tangential Flow Filtration (SPTFF) into Place

By Herb Lutz, Global Principal Consultant, Manufacturing Sciences & Technology, Merck.

Next generation manufacturing covers a collection of technologies aimed at improving productivity, i.e., getting higher throughput and/or better quality out of a process. Single-pass tangential flow filtration is widely used in other industries but has only recently been considered for bioprocessing. By inserting an in-line tangential flow filter before a given bioprocess step, we can significantly concentrate the input for that step and, in many cases, also improve its productivity. We routinely see concentrations increased by factors of two to three-fold using this method. In fact, I have achieved 30-fold concentration factors like this, but admittedly it's not easy.

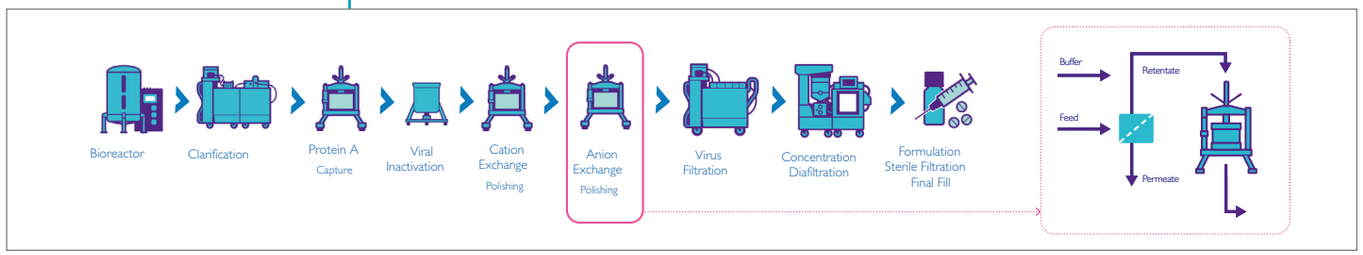
There are a number of advantages associated with a more concentrated bioprocess input. One is the ability to shrink the footprint of a process. For example, Genentech published on a case where they wanted to introduce a new molecule for manufacture at one of their plants and found that the necessary process would not fit in the tanks they had on site (1). By employing a single-pass filter, they shrank the volume sufficiently to fit their existing infrastructure – far more cost-effective than spending hundreds of millions of dollars on another manufacturing plant! Similarly, another case used a single-pass filtration system to debottleneck a large stainless steel, European facility.

Inserting a SPTFF step to increase product concentration can also improve a subsequent step, such as polishing. In a typical manufacturing process, polishing is the third chromatography step, and tends to be a flow-through ion exchange step intended to remove viruses and host cell proteins from the antibody product. The mechanism relies on running the system at pH 7-8 (i.e., at a pH below the isoelectric point of the antibody and above the isoelectric points of contaminants). It turns out that pre-concentrating the input fluid increases the polishing efficiency due to a characteristic of the equilibrium isotherm in adsorption chromatography; basically, at higher host cell protein concentrations, proportionally more of these impurities will bind to the resin. By using SPTFF to pre-concentrate not only the antibody but also the host cell protein, we improve the efficiency of the process by a factor of four or more. People often get excited about a new resin giving a 15 or 20 percent increase in capacity, but adding a SPTFF step gives a 400 percent improvement! And there's more – given that we shrink the volume of liquid as we concentrate it, we can run the process more quickly. In this way, manufacturers can run more process cycles in the same time and actually get a five-fold productivity improvement from running a filter in SPTFF mode of operation before the polishing step.

A further advantage of single-pass filtration relates to problems associated with the high salt concentrations remaining after eluting from the cation exchange purification step upstream of the polishing step. Normally, these salts interfere with protein binding in the quaternary amine polishing column, and thus reduce clearances of viruses and host cell proteins. Manufacturers often try to get around this by diluting the feed to reduce the salt concentration, but this volume expansion has the unwelcome effect of dramatically increasing column sizing and process time. With SPTFF, you both concentrate the proteins and eliminate the salts, meaning you can enhance protein binding without the inefficiencies of a diluted input. Similarly, for those processes associated with species of host cell proteins that are very difficult to eliminate by normal processes, the concentration and desalting associated with a single-pass filtration application can be very helpful and provide better product purity. And improved product quality always goes down well with regulators.

At Merck, we are combining these advances into new systems for new applications. For example, we are running our strong anion exchanger in-line with our TFF cassettes, and have devised procedures for assessing the feasibility of these systems with various molecules (2-4). We have also demonstrated excellent virus clearance with concentrated feed and high loadings, and worked on scaling up these systems, and on implementing them as part of a continuous manufacturing process. It's also worth noting that intensified polishing is flexible so that it can be used either continuously or as part of a batch process. The addition of in-line SPTFF does not significantly increase complexity but rather is easy to use like an in-line prefilter. Our new gamma irradiated UF capsule is ideal as it does not require holder compression or extensive pre-flushing.

Because our intensification processes provide significant economies, we've had much interest from pharma companies seeking a competitive edge. Biosimilars companies are particularly intrigued, as their cost-competitive model puts them under immense pressure to shrink the manufacturing process. That said, manufacturing space is tight for any company, so when we say that we can shrink the process by a factor of five, we tend to get people's attention. We are now in the process of setting up collaborations with clients to demonstrate the levels of savings they can achieve through implementing our approach.



Intensified polishing compared to conventional AEX polishing in a mAb process, intensified polishing utilizes a SPTFF pre-concentration step to reduce process volumes and improve resin mass loading.

The Benefits of Intensified mAb Polishing

- Capacity increase 4x
- Productivity increase 5x
- Product quality increase 3x
- Footprint reduction 5x
- Buffer use reduction 2.3x
- Tankage reduction 20x

References

1. *CA Teske et al., "Inline Ultrafiltration", Biotechnol. Prog., 26, 1068-1072 (2010).*
2. *Merck, Application Note, AN5364EN00 Ver 1.0, "Intensified Polishing Using Single-Pass Tangential Flow Filtration (SPTFF) with Anion Exchange Chromatography" (2017).*
3. *Merck, Poster, PS1282EN00 Ver 1.0, "Intensified mAb Polishing: Linking Single-Pass Tangential Flow Filtration with Anion Exchange Chromatography" (2017).*
4. *Merck, Webinar, "Intensified mAb Polishing: Linking Single-Pass Tangential Flow Filtration with Anion Exchange Chromatography" (2017). Available at: http://bit.ly/2ykVbeQ*

LINKS

On-Demand Webinar
Intensified mAb polishing: Linking single pass tangential flow filtration with anion exchange chromatography

Application Note
Intensified polishing using single-pass tangential flow filtration (SPTFF) with anion exchange chromatography

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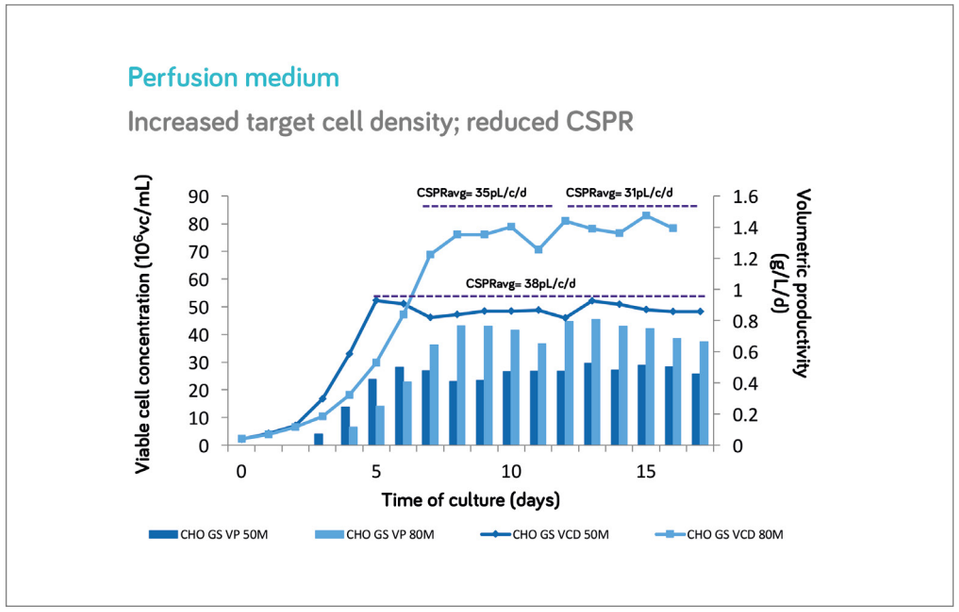
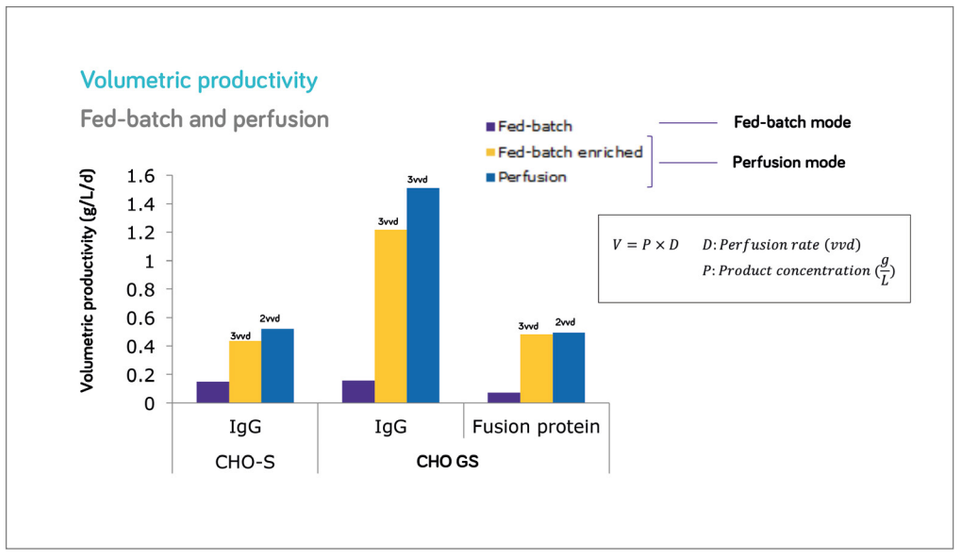


Steady-state maintained at 80x106vc/mL at 2vvd.



Up to ~10-fold increase volumetric productivity in perfusion when compared to fed-batch; higher volumetric productivity and/or lower perfusion rates using perfusion catalog than using enriched fed-batch medium.

Perfecting Perfusion

By Delia Lyons, Head of Perfusion Media Development, Merck.

As the need for smaller plants, flexible manufacturing and competition intensifies in the biopharma industry, so does the need for intensified processes. Increased speed to market, reduced cost of goods and increased volumetric productivity are some of the benefits offered by perfusion cell cultures. For a perfusion process to be economically feasible, high cell densities need to be attained with low volume of cell culture medium. Achieving and maintaining steady-state conditions with low perfusion rates require specific media – ideally fine-tuned to the needs of the particular perfusion application. For example, in an N-1 bioreactor, maximized high growth rates and viability are required. In contrast, in a production bioreactor, such high growth rates may be detrimental, due to increased bleed rates and associated product loss. A high performing perfusion cell culture medium needs to not only provide the required nutrients, but also to minimize the generation of toxic by-products. A critical step, therefore, is to appropriately balance and optimize perfusion media according to the metabolic needs of each specific process – and steady-state perfusion is the most challenging of these applications.

At Merck, we have developed a catalog CHO cell perfusion medium specifically designed for intensified perfusion processes, including steady-state. We developed this novel cell culture medium with seven different industrially-relevant CHO cell lines producing various types of proteins. The results at bench-top bioreactor scale have been excellent. In particular, we have found significant differences between our perfusion medium and enriched fed-batch medium (EFBM): the new product allows us to simultaneously increase volumetric productivity, as compared to EFBM, while at the same time increasing specific productivity and reducing cell-specific perfusion rate (CSPR) from 80 to 40 picoliters per cell per day in steady-state. In non-steady-state applications, CSPRs lower than 20 picoliters per cell per day have been generally achieved.

The flexibility of perfusion technology is apparent at two levels. On the one hand, variable drug production amounts can be achieved with the same equipment just by modifying the duration of a steady-state perfusion run. On the other hand, perfusion can be processed for different applications such as a tool for high density cryopreservation, for N-1 bioreactor intensification, or as production bioreactor. The breadth of applications as a production bioreactor is quite extensive as well, varying from steady-state and dynamic perfusion to different types of perfusion/fed-batch hybrid systems. Studies show the potential economic advantage of perfusion and continuous manufacturing overall, compared to batch-based processes. Ultimately, the choice between any of the types of perfusion, fed-batch or hybrid processes will depend on many factors that relate to the specific manufacturing plant and drug being manufactured.

LINKS

Weblink
EX-CELL® Advanced HD perfusion media

On-Demand Webinar
Intensified perfusion - How a High Density Cell Culture Medium Can Positively Impact Your Upstream Productivity and Economics

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New Horizons

Increasing the productivity of biopharma production processes would reduce costs and improve efficiency, flexibility and competitiveness – leading to greater patient accessibility and job creation. That is why we have set up a consortium to help bring biopharma into the 21st century.

By Gorazd Hribar, Project Manager of the "next BioPharm DSP" project, and DSP Development Scientist, Lek Pharmaceuticals, a Sandoz company.

The biopharmaceutical industry has made extraordinary strides in recent years, but when compared with other industries – oil or automobile, for instance – you will notice a distinct lack of automation and continuous processes. Although there will still be need for the large stainless steel facilities, the current standard in the biopharma industry, competition in the marketplace is also demanding more efficient and flexible manufacturing models. Continuous approaches can lower costs and speed up processes, as well as allow companies to manufacture several products at the same time and adapt more quickly to market needs, but greater adoption is held back by the requirement for tricky real-time monitoring and control.

In considering how the industry might overcome these limitations, the European Union made some funds available (through "Horizon 2020") for a consortium to find solutions. At Lek Pharmaceuticals, a Sandoz company, we have been puzzling over these problems for some time, so we set out to build a team spanning various countries – involving large and small companies, as well as academics. The European Commission recognized the expertise of our seven-strong consortium members and awarded us the competitive grant. The project is called "Next-generation biopharmaceutical downstream process" (next BioPharm DSP).

The main goal of this project is the implementation of a fully integrated manufacturing platform based on continuous chromatography, in combination with single-use disposable technology for all unit operations of downstream process development (DSP). The end goal is to build the platform on a small scale, together with the incorporation of advanced analytical tools, but there are also detailed objectives for the downstream process. For instance, for the primary separation, we are aiming for a substitution of the standard process suites with flocculation and flow filtration – wherein we have already found some beneficial results.

Another important part of the project is the integration of continuous chromatography into the capture step, and the development of new single-use disposable equipment. For other parts of the DSP, we are evaluating different disposable and single-use technologies to replace the classical hard pipes, which includes the testing of different flow approaches and different membrane adsorbers. Finally, the process requires line control, and we are developing advanced analytical tools for in-line monitoring of different quality attributes. We have already filed some patent applications for inventions in this area. We have been able to detect product content in real time while differentiating from impurities – aggregates and HCPs for instance – and additional publications and patent applications are being prepared in other areas of the project.

We are confident that our work will culminate in more efficient drug production processes, with reduced costs, and greater productivity, flexibility and competitiveness – ultimately leading to greater patient accessibility and lower burdens on healthcare systems. A second aim is to create a more sustainable process, with a reduction in the amount of chromatography resin, buffers and water used. This will substantially reduce the environmental footprint of the biopharma industry and reduce investment and operating costs for companies.

The consortium recently submitted and received approval for its 18-months periodical report and the project was highlighted as a success story by the European Commission Directorate-General for Research and Innovation.

This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 635557.

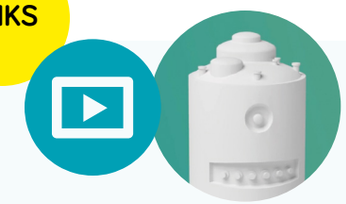
Read more about the project at: http://nextbiopharmdsp.eu

"The Magnificent Seven"

Members of the consortium include:

- *Lek Pharmaceuticals*, a Sandoz company, Slovenia. Expertise in: biosimilars development, continuous chromatography, perfusion bioprocess, disposable solutions for DSP, final process execution.
- *Karlsruhe Institute of Technology*, Germany. Expertise in: advanced analytical tools, process modelling, precipitation and continuous chromatography approaches.
- *Merck*. Expertise in: continuous chromatography, single-use equipment development, flow-through chromatography approaches, flocculation for primary separation, continuous virus inactivation.
- *National Institute of Chemistry*, Slovenia. Expertise in: alternatives for capture step, optimized batch processes, process modelling and advanced analytical tools approaches.
- *National Systems*, Italy. Expertise in: lab on a chip for particle detection in real time.
- *Sandoz GmbH*, Austria. Expertise in: biosimilars production, final process support and later implementation of solutions in manufacturing.
- *University of Natural Resources and Life Sciences Vienna*, Austria. Expertise in: continuous flocculation approaches, continuous precipitation approach to substitute chromatography.

LINKS



Video
nextBioPharmDSP project introduction

Press Release
Merck Provides Update on EU's Horizon 2020 Program to Improve Biopharmaceutical Downstream Processing

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Mastering Continuous Biomanufacturing

With Rickey Lu, Director of Manufacturing Technology Innovation at AstraZeneca.

What drew you to work in pharma?

We scientists look at the world a little differently and have an innate curiosity to know how things work. Because of that, I've always been interested in all areas of science. However, this wide interest made it quite challenging to select just one field of study. I ultimately landed on what was a newly created field at the time: biochemistry. This intersection between molecular biology and chemistry combined at least 2 areas of study.

But during my college career, I quickly found that I didn't really enjoy basic research. Basic research is, of course, the foundation that allows us to make scientific and technological advances but for me, I needed something more immediately impactful. Eventually, I came across a guest lecturer from the pharmaceutical industry speaking about the challenges of drug development at the biochemical level. The speaker and the subject matter was so engaging that it was at that moment that I realized where my career path would lead. The pharmaceutical industry provided a stimulating environment for scientific curiosity and a connectedness to society by positively impacting people's lives.

I now work at AstraZeneca, in an organization called Global Technical Operations. We drive strategy and provide support to our internal and external biologics manufacturing sites. And my goal within that space is to develop, manage, and carry out our manufacturing science and technology strategy.

What are the biggest challenges you've faced over your career?

Most of my career has been in manufacturing, and I think the biggest challenge we face in the manufacturing space is the uncertainty in market demand; understanding what to build and when, and ensuring we have the capacity to meet patient needs. This uncertainty means that companies are always either building manufacturing facilities early, or building them late. From a personal perspective as project lead or validation head, this has meant tremendous pressure to quickly bring new facilities online, ready to manufacture products as well as the less desirable position of idling a plant due to negative product news.

In more recent times, I think the biggest challenge I've had in the manufacturing technology space is convincing people that there may be a better way of doing things. The basic process by which we manufacture products is not that different from the way the earliest biopharmaceuticals were produced. The manufacturing equipment is largely the same as the benchtop equipment, just bigger. It's a big challenge to get folks to look at things differently. Changes to manufacturing equipment and processes can be expensive, time consuming and carry the potential for significant risk. Overcoming these hurdles requires the confluence of good science and technology, anticipation of industry needs, collaboration with industry partners and above all else, timing.

How did your relationship with Merck develop?

They are one of the key suppliers in the industry and have long standing relationships with many companies in the industry. My earliest work with them was troubleshooting an ultrafiltration skid over 20 years ago, so they've been an industry partner for quite some time. Judging by their history and the innovations they are providing in the single-use space, I expect they'll continue to be a key industry partner in the future.

What are the most fascinating advances in biopharma?

The way we manufacture products and the equipment that we use have not drastically changed, but one major shift is the integration of information technologies. Information that used to be mined through hours of painstaking data gathering via large amounts of paper documentation is now readily available at peoples' fingertips. This technology allows us to monitor processes with historical context in real-time. We can use multivariate analysis to predict the outcomes of ongoing batches before they've even completed manufacturing. I also think multi-attribute soft sensors give us a new way of getting information in a real-time, continuous manner. Our concept of process control in batch processes have been largely defined by the available technology. However, these approaches will not be suitable for optimizing the benefits of continuous processing.

What "next gen" bioprocessing technologies interest you the most?

There are some huge, exciting advance in the continuous biomanufacturing space. It's not all available at commercial scale at this time and fully continuous processes may not be cost effective in all cases but downstream continuous manufacturing is certainly something to keep an eye on. Because downstream has traditionally been extremely inefficient in terms of capital expense and the materials used. Continuous manufacturing really provides us with a better return on investment, whether it's from a working capital standpoint, or from the perspective of capital equipment and facility size. The efficiency of a continuous downstream allows for large volumes of product intermediates to be processed through smaller equipment within a reasonable process duration, making single-use equipment an option whereas single use was too small in the past. Continuous is where I see a lot of advantages for the biopharmaceutical industry.

What's your vision of the perfect future for biopharma?

My vision for the distant future is a "Jetsons" kind of world where you can walk up to a panel and select the medicines you need, which are made right there in the exact dosage required. There are some great strides being made that are setting the course for that future, such as an MIT program aiming to put a biotech plant in a backpack. It's in the early stages, but it's those kinds of novel concepts that are going to sculpt the far future of the field.