European Biotechnology

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Bioprocessing

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Sustainability: the new must

CDMOS Despite full books due to the booming market for biologics, CDMOs are facing major challenges in the face of the climate and Ukraine crises. In addition to the diversification of drug formats, the industry, which is built on plastic, has to convert to sustainability.

The green challenge comes in addition to the global competition for qualified specialists, who have become scarce due to capacity expansions through progress with new drug formats such as CAR-Ts, gene therapies, mRNAs, synthetic vaccines, peptides, conjugates during the last decade. Experts are rightly asking how this is to be achieved.

ESG criteria

"Those who don't convert by 2030 will be out of the market. Then, major pharma companies will no longer place orders with CDMOs or customers who do not produce in a demonstrably sustainable way," one of the medium-sized contract manufacturers for biologics and cell therapies told European Biotechnology.

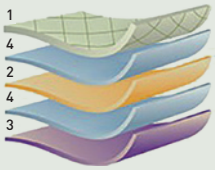
Therefore, the numerous specialists in the production of antibodies, recombinant proteins, virus-based cell and gene therapies, mRNAs as well as conjugates are feverishly looking for solutions to solve the three main problems of the deeply unsustainable industry: to reduce the high consumption of energy, water and single-use plastic consumables.

It is precisely the replacement of the multi-layer bags, fittings, tubing, filter cartridges, which emit a minimum of leachables, that have approval for the demanding cGMP production, that causes problems. This is because their essential components, polyethylene, polyamide and polyvinyl chloride are still based on fossil raw materials and are neither biodegradable nor readily recyclable. Also, for reasons of patent protection of the drug candidates adhering to them even after use, they are incinerated to this day – not exactly favourable for the decarbonisation or eco-balance of the processes.

Under the dictates of ESG criteria and newly pending EU regulations on sustainable production, CDMO customers are now looking for solutions to make these hitherto anything but climate-neutral or waste-avoiding processes more sustainable.

The new normal

Sustainability will affect biopharma developers and contractors in many ways in the near future as sustainability parameters are going to be mandatory audited within the EU. According to the recent CPHI annual survey among (bio-)pharma professionals, 83% believe that specific sustainability metrics will be implemented within the next five years in all CDMO contracts. Nearly 60% believe CDMOs will be required to provide their partners with both sustainability metrics for projects and specific corporate ESG goals. Greenhouse



Layer	Thickness	Typical materials	Function
1 Outer	20–150 µm	Polyethylene nylon, polyesters, polyamides	Abrasion & puncture resistance, strength, feel
2 Barrier	5–50 µm	Ethylene vinyl alcohol	Prevent transmission of O_2 and CO_2
3 Product contact	50–300 µm	Various densities of polyethylene	Biocompatibility, strength, sealing
4 Tie	Various	Modified polyethylene	Bonding between layers

Standard single-use bags ranging from 100-2,500 litres are used for batch fermentation of most biologics and are typically composed of three sterilisable plastic layers that are not biodegradable.

gas (GHG) emission reduction, energy efficiency, abatement of water or resource adoption, waste management as well as driving health equity and improving diversity in clinical trials are some concrete examples of what matters for producers and its contractors when it comes to sustainability.

Sustainability standards

According to Heiko Schmidt, Strategy & Consulting Life Sciences lead, Accenture AG, establishing sustainability metrics is an investment for the future as investment decisions will be affected by the sustainability footprint of Big Pharma companies in the medium-term. These pass this on to their service providers and are expected to demand documentation of a CDMO's sustainability performance that is aligned with the corporate strategy.

Since there is no common reporting standard for sustainability, currently companies are applying various principles. Rating agencies build their own metrics and indices. For the moment, GHG emission-related sustainability ambitions and corresponding plans can already be certified by the Science Based Targets initiative, a coalition of UN agencies, business and industry leaders. "Since 2020, our German sites are climate-neutral and no longer have a CO_2 footprint. Our production sites and sales offices in Austria, the US and Asia have followed this CO_2 neutrality in 2021," says Henryk Badack, Senior VP Technical Service and Internal Project Management at Vetter.

Improvement of pharma packaging, reuse loops, manufacturing efficiencies including yield optimisation and improvements in monitoring waste of materials and takeback programs are among the low-hanging fruits to achieve an apparently greener footprint. Using regenerative energy to fuel the energy-costly automated air circulation systems in cleanroom facilities and advanced water management strategies are also a topic for CDMOs such as Vetter. However, the sustainable recycling or incineration of bags and other cGMP-compatible single-use plastics, which form the basis of flexible, fast and cost-effective biomanufacturing, will remain an unsolved problem for at least the next decade

The biopharma dilemma

The single-use plastics topic is a dilemma for many CDMOs who want to prepare for a greener future: On the one hand, contract manufacturers, must, continue to achieve the high regulatory requirements. On the other hand, they must strive to enable environmentally-friendly usage of resources to contribute to meeting the Green Deal climate goals.

Plastics substitutes

However, replacing high-performance plastics such as polyethylene, polyamides and polyvinyl chloride in approved processes would require costly new process certifications by the regulatory authorities. This is something that will take some time as the sector is conservative and patient safety is a priority over sustanainability, yet.

Currently, there are neither biodegradable alternatives to PE, PA or polyethers nor enzymes that are able to degrade these persistant oil-based polymers. Thus, a sustainable solution is not in sight in the mid-term. Some companies, however, are developing nano-cellulose-based polyethylene, polypropylene and polystyrol alternative "bioplastics" that are fully biodegradable. In the long-term metagenome mining, structural motif mining or even synthetic biology might identify plastic-degrading enzymes or alternatives. However, it's a long way to market adoption so that the sector will remain only semi-sustainable. ■

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The plastics problem

Currently, only 9% of the 391 million tonnes of plastic produced annually worldwide and 14 % of the almost 142 million tonnes of plastic packaging are recycled. Incidentally, the large amounts of plastic waste that the EU and North America export to Asia are also considered recycled. In fact, 40% of non-degradable plastics containing toxic additives end up in landfills, 14% are incinerated and about 32% end up in the environment. Since packaging is supposed to be lightweight, functional and durable, the chemical industry mainly produces plastics that take at least 500 years to be ground into microplastics; plastics that are biodegradable at 37° C in industrial recycling plants currently account for only 2% of global production. ■

Picture: GE Global Research

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Transition to industrial-scale AAV manufacturing

PRODUCTION The switch from lab-scale to industrial-scale AAV production requires deep hands-on expertise in various technological solutions, their limitations, and their suitability for GMP large-scale manufacturing. Direct application of lab-scale process leads to expensive AAV-based products and unnecessarily laborious industrial processes. The complexity and growing demands for controllable critical quality attributes (CQAs), create a challenging blend.

› Artur Padzik, Ph.D., AAV Technology Manager, Biovian

Broadly, AAV manufacturing consists of the upstream process, where producer cells, upon transfection, start generating proteinous and genomic components that self-assemble to form active AAV particles. Breaking cells to release AAVs marks the end of the upstream production and transition to downstream purification.

Numerous hurdles

Large-scale clinical AAV production poses numerous hurdles not visible in a preclinical scale. The early discovery phase typically utilises adherent cells, which at a scale translate to fixed-bed reactors. The expansion phase in the adherent cells process introduces variability due to difficulty in delivering consistent parameters such as pH, oxygen concentration, or cell distribution across multiple vessels. While fixed-bed reactors allow effective viral particle collection from the supernatant recovering AAV from biomass is more challenging. Depending on the serotype and harvesting time, about 20-40% of AAV particles remain in cells.

Optimizing the upstream

Biovian believes in its AAV platform process approach, where true scalability is possible with serum-free suspension culture in stirred tank bioreactors and a well-characterised in-house cell line. In suspension culture, volume dimension increases faster than surface area. Based on our experience, huge differences exist between HEK293 cell clones available on the market in their aggregation susceptibility, growth speed, and toxicity response to commercial transfection reagents leading to up to 10-fold titer differences. Above mentioned differences still do not consider the substantial effect on titer imposed by transfection conditions, plasmid ratios, the genetic background of plasmids, and plasmid quality. Our in-house plasmid production allows a comprehensive understanding and control of each quality attribute that converts into consistency in AAV manufacturing. Simultaneously, we generated a well-defined upstream process design space using the Design-of-Experiments methodology to control production with titers >10^{14} vg/l or >10^{5} vg/cell. The suspension process has lower cell densities per volume than adherent cultures and can be further intensified by perfusion, with transfections possible even at 9x10^{6} cells/ml and titers improved by 5-10-fold.

Picture: © Biovian

Purification in downstream

The small-scale downstream process utilises problematic procedures such as cell collection by centrifugation, freeze-thawing to release AAV from cells, or centrifugation to separate empty AAVs. Through our AAV platform process philosophy, we focused on scalable chromatography. We achieved a uniform affinity chromatography process that produces stable >80% recovery with multiple serotypes. When looking at empty-full AAV separation, a typical preclinical scale cesium chloride and ultracentrifugation-based separation generates challenges in upscaling. We tackled scalable anion exchange chromatography and developed a robust protocol allowing stable baseline separation of empty and full AAV particles regardless of therapeutic gene size and serotype. The compatibility with large-scale should happen early to deliver low-cost, high-quality products. ■

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Tackling pharma's footprint

PHARMAPACK Pressures to handle sustainability risks are increasing globally, and the pharmaceutical industry is no exception. There is a growing feeling of urgency to replace traditional cutting-edge processes to meet the requirements for environmentally-friendly packaging alternatives. These were extensively discussed at this year's Pharmapack Europe.

Whether it be glass vials, cardboard applications, auto-injectors, or biodegradable containers, at the first post-pandemic in-person Pharmapack Europe 2023 (1-2 February, Paris) the shift in priorities of the industry was clearly visible. Nearly 5,000 on site visitors, more than 4,000 online attendees, and over 350 exhibitors discussed the transformation the pharmaceutical packaging industry is experiencing, and showcased innovations emphasising the priority of environmentally friendly packaging. Despite some still existing travel restrictions and the strike rendering the commute within France a challenge, 78 countries were represented, and 42 content sessions held.

The displayed products, the eager exhibitors and alluring goodies were not the only attraction of this year's Pharmapack. The "learning labs", a space for research and product presentations, were well attended, as well as the innovation gallery, which allowed the close-up inspection of high-end products. All of this was sprinkled with the luxurious feeling of Paris by the provided crêpes, coffee, and croissants for everyone, as well as live music. The latest innovations from packaging companies within the sector were celebrated at the annual awards, which recognised improved efficacy, user safety and environmental impact reduction of the products. The entire event reflected the new confidence, positivity, and relief coming out of a pandemic instilled in the public.

The pandemic's aftereffects

Challenges posed by the COVID-19 pandemic lay in the numbers of novel vaccines, medical equipment, and medications needing to be rapidly manufactured, parcelled, stored, and distributed all over the world while preserving the day-to-day business as usual. The supply chain was heavily affected by the pandemic, especially early on. This crisis demanded creativity, action, and collaboration which generated a wide spectrum of opportunities in new possible methods across the industry. The rapid development of digital applications and connected gadgets is one such beneficiary. For instance, many countries have introduced track and trace schemes, vaccine cards, virtual appointments, digital doctor's notices, digital prescriptions, and have quickly increased the use of self-administration of therapies, with apps possibly becoming the new model for mental health treatments.

The innovation gallery showcased all exhibitor innovations that were submitted to the Pharmapack awards.

Another post-pandemic trend is the shift toward self-administration. One only needs to consider the impact of overburdened institutions during the epidemic to see the long- and short-term advantages. With a growing number of patients now using injectable devices that can also be monitored at home, it is perhaps predictable that wearable injectors capable of providing high-volume biologics, another field of recent innovation, is growing financially in the industry. Unsurprisingly, gadget usability is a critical component of future design of new medications, and there has been a change in how companies perform R&D, with patient experience teams and usability studies now being a necessity rather than an option. Patient centricity as well as painless delivery are essential elements in device choice, especially in terms of the need to optimise safety and efficacy while minimising possible user errors.

The road towards sustainability

While the COVID-19 pandemic has obviously captured the attention of the world, including the pharmaceutical industry, there is also another looming issue on the horizon: the climate change. Pharma has seen a drive towards sustainability in the last years, with an increasing number of companies looking to minimise the impact they have on the environment by measuring their carbon footprint, reducing waste, lessening emissions, and removing plastics wherever possible. Since most medical packaging is derived from polymers, with the majority of waste being disposed of in landfills, the packaging sector has come into focus in this discussion. Waste and energy management, as well as the supply chain are the three biggest contributors to the industry's carbon footprint, thus those are the things that need to be tackled. "What we are seeing, particularly at this year's

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Pharmapack, is how pharma is now taking a very holistic view to sustainability and looking more deeply at how we can reduce 'Lifecycle impact' of products and therapies", affirms the event's brand manager, Laura Murina-Indriksone.

The technological surge towards digitalisation and the apparent advantages that would bring in the medical care sector are pushing towards building digital into single-use devices. This of course raises the issue of electronic waste and how it should be dealt with. Governments are creating wider sustainability strategies, with a recent drive towards green chemistry like solvent use reduction initiatives in API manufacturing. Investment in eco-packaging is expected to radically increase within the next years, and this will be largely driven by companies looking to lower their carbon footprint in line with the global goals in the 2030 agenda, as set out by the United Nations.

The biggest hindrances

At the same time, one must remember the delicacy of handling medical equipment and medication in a way that complies with a whole array of regulatory requirements. For example, aseptic manufacturing and cold chain are both energy intensive but crucial to supplying injectables safely. It would be potentially detrimental to cut corners around regulatory requirements. Additionally, the search for reusable and plastic-free alternatives is in stark contrast to the expectations the industry had a few decades ago and the trajectory it has had to date. If one asked what the trend is going to be in the pharma and the packaging industry 15 years ago, they would have explained that we were heading into a future where everything was going to be single use and thus easy and safe to use.

Indeed today, the use of fast hybrid processes that allow to quickly get medications to patients are widespread. So, it requires a break-free of the traditional ways of manufacturing and regulatory regime, which raises many concerns about the feasibility, necessity and most importantly the quality of the final product. That in turn takes a lot of time, data, and confidence, since it is linked to the switch from one process to another for an already established and successful product. This is one of the biggest hindrances. To respond to this element of risk, new technologies, and support for the developers from a financial and political point of view are needed.

Innovations for the future

It is understandable, thus, that even though sustainability has been at the forefront of global discussions for years now, the pharmaceutical industry has been slow to react. This cannot be used as an excuse any more sustainability should be heavily embedded in each company's strategy and balancing economic performance with social and ecological responsibility.

This year's Pharmapack Awards mirrored the sentiment and showed how a focus on improving sustainability and reducing waste by replacing single-use plastic devices with reusable ones through modular systems one can still create novel drug delivery solutions, reusable connected devices, and recyclable packaging. In the category "sustainability initiative" for example, the winner, Körber Pharma Packaging Materials AG – who won the sustainability initiative award for their pharmaceutical grass paper packaging in 2022 as well – got awarded for their sustainable COVID Rapid Tester out of recyclable cardboard mono material. The award of "Eco-Design" went to the 100% PET, PVC- and aluminium-free, and thus recyclable blister by Rotor Print SL and even the "Drug delivery Innovation" award, which didn't need to be a sustainable product was awarded to Owen Mumford GmbH for UniSafe®, the reusable connected auto-injector. "Different parts of the industry are responding to this challenge differently. We have seen companies looking to make plastic only devices so that they can be recycled [anything with multiple components parts is often unsuitable for recycling], and others that are reducing or replacing plastic", explains Murina-Indriksone. "Then there are many device manufacturers exploring how to make single use devices reusable or to have parts of these devices made reusable. We also see companies looking at how automation and even AI can make the manufacturing of devices more efficient."

For such solutions to be feasible and widely used to make a difference, collaboration between the industry, investors, and politicians is crucial. There is no way for a single company to tackle sustainability in the entire production circle, while preserving standards and regulations that are not designed for such a huge undertaking. Real change can be enacted with a collaborative strategy that acknowledges the obstacles and establishes standards. This change is what we are striving towards. ■

Rotor Print S.L. won the award of "Eco-Design" for their 100% PET blister.

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From lab to industrial scale bioreactors

BIOPROCESS EQUIPMENT Sweden's Belach Bioteknik has been partnering mostly with researchers and pharma customers to design suited bioreactor systems for biomanufacturing. Most recently, the company has entered the growing cultured meat sector, in which many companies are currently scaling up their production and thus need expertise to get optimal results.

EuroBiotech_Can you tell us about Belach Bioteknik's background and how it became the biotechnology company that it is today?

György Rajkai_Belach was established in 1985 by Swedish engineers –our name is the acronym of the founders – and aimed to design and build lab-scale bioreactors for universities, research institutes and R&D departments of production companies.

The first customers contacted Belach from the Swedish universities (KTH, Lund, Uppsala University), but we also had industrial partners, mostly pharmaceutical companies. The first products were developed jointly with the academic researchers, in line with their needs. I can mention two of our unique products, a high-throughput multibioreactor system that was developed in a cooperation with academic researchers of Karolinska Institute and the biogas research reactor system that was developed together with SLU, Uppsala. In the 90`s, the company started to offer digital control systems for reactors and bioprocess systems, which was a cutting-edge and pioneer solution at that time. Besides, the Swedish market, Belach entered the Scandinavian market as well. The business philosophy remained the same, we started to serve Norwegian and Finnish universities and research institutes.

The business policy has been unchanged since the beginning: we are at our potential customers/users' disposal from the very beginning of their projects, supporting them to create and describe the exact requirements that bioreactors and bioprocess systems shall fulfil. We are their partners from the design of the simplest equipment to manufacturing of the most complex automated system.

György Rajkai started his career as an Automation Engineer at Belach Bioteknik in the 90s. Using its expertise, the company developed fully automated bioprocess systems. In 2013, he was appointed CEO. Since 2019, he has been working as CTO, managing the technical design and execution of projects, product developments and unique solutions.

EuroBiotech_What have been some of your major milestones?

Rajkai_In the 2000s, the company was entrusted by a Swedish vaccine producer to design and build an automated production plant. That was a big challenge for Belach, but this plant had been in operation for 20 years. It meant a real milestone in progression for Belach, by gaining robust experience from the design and execution of stainless steel to in-situ sterilisable bioreactors and production-scale automated bioprocess systems.

We also enlarged our portfolio, developing a parallel multibioreactor system, that is suitable for research purposes, but for small-scale production as well. The last was originally designed for a customer in Germany, a couple of years ago, who produces animal vaccines especially cultivated for farms individually. So low volume for production purposes is needed. These multibioreactos can be run by only one or two persons. At the same time, they can produce a diversity of products, for which different parameters define the process. These reactors can also run several functions such as cultivation, CIP or sterilisation, in parallel in its different vessels.

Belach enlarged the portfolio with other equipment relating to bioprocesses, like decontamination equipment. These can be good solutions in terms of environmental requirements for laboratories, hospitals, as well as industrial user.

Picture: © Bekach Bioteknik

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EuroBiotech_Can you discuss your current biotechnology projects and their potential impact on the market?
Rajkai_ In recent years, we have been contacted by several companies that are dedicated to make research with cultured meat. We were also contacted by a start-up company from the USA, who intended to start their production in this field. The process has been developed by the researchers, but the bioprocess system has been designed by Belach. Since the bioprocess and the equipment is strictly confidential, I just can mention that as a very interesting and challenging task for our engineers. Should the experiments deem successful in the current lab scale and pilot scale systems, we could step ahead to design the production scale reactors and systems.

The significance of this sort of research and experiments to the market can be revolutionary, of course, if they prove realistic and the scale up becomes applicable. We are glad to be among the first "bioneers".

EuroBiotech_How do you see your company's expertise in biotechnology translating to success in the cultured protein industry?
Rajkai_ The cultured protein industry is expected to continue growing in the coming years, driven by concerns over environmental sustainability, animal welfare, and food security. Biotechnology companies need to stay up to date with emerging technologies and market trends to remain competitive in this rapidly changing field. Additionally, biotechnology companies may need to focus on developing unique technologies or products that differentiate them from competitors. Our philosophy follows the same approach that we have been believing for decades: the bioprocess technology shall be developed by the researchers and users, but we can provide design and build the hardware and the software solutions for the bioprocess so that the researchers can achieve their goals. Belach Bioteknik has senior engineers, like chemical engineers, automation engineers, and mechanical and electric engineers, who have designed and built many systems, with unique solutions. Besides the internal team, Belach also works with constant external engineers, consultants and subcontractors who have robust industrial experience in their professional area and our cooperation has lasted for years or decades.

EuroBiotech_What are the key challenges your company is facing now and how are you overcoming them?
Rajkai_ One of the key challenges is the uncertainty of the customers, who have become more cautious in the last three years, due to the turbulent circumstances. Based on our experience, the investments are limited, suspended, postponed, or eventually cancelled. Therefore, the pricing strategy is a crucial factor. Our goal is that the customers can continue their research work, and their investments in production plants and find us for mutual professional cooperation, for an affordable price. An additional challenge for the company is to find additional specialists for various key roles. This is crucial to ensure the company's continuity and expansion.

EuroBiotech_Can you discuss which geographic markets your company is currently targeting for expansion?
Rajkai_ Belach Bioteknik – being a small enterprise – entered the European biotech market five to six years ago. We are now present in eleven European countries with benchtop and stainless steel bioreactors that are applicable for both microbial and cell cultivation. In addition to sales, we can reliably provide parts supply and service from our office in Stockholm. We already have – mostly completely unique – equipment in the USA, too, and this expansion – in addition to further expansion in Europe – is also part of our long-term vision.■

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Production-scale fermenter from Belach Bioteknik

Picture: © Bekach Bioteknik

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Biopharma partnership – intensifying purification

DSP Tosoh Bioscience recently launched Octave© BIO, the first in a series of MCC instruments targeting all stages of biomolecule manufacturing. Here, Tosoh discusses the potential of MCC to help alleviate downstream bottlenecks and a process intensification collaboration they recently performed with Catalent Biologics. Emily Schirmer, Interim General Manager at Catalent Biologics, provides selected insights on Catalent's findings from the collaboration.

With broad expertise in development sciences, delivery technologies, and manufacturing, Catalent is a reliable drug development and delivery partner for the industry. In an ongoing approach to increase the efficiency of manufacturing processes, scientists at Catalent evaluated a newly developed multi-column chromatography system, the Octave BIO, that was released in September 2022 by Tosoh Bioscience.

Emily Schirmer explained the background of this project and how bioprocessing needs are changing the industry: "From large pharma companies to contract manufacturers, several trends are changing the industry landscape. We are seeing higher productivity cell lines and increased use of process intensification and continuous processing methods to further drive higher productivity. These technologies and product development approaches have enabled a significant increase in the amount of material that can be generated upstream. The increase in upstream material means there is a need for efficient downstream purification methods – to avoid bottlenecks and reduce manufacturing footprints."

The Catalent Biologics facility in Madison, WI, USA offers expanded mammalian cell line engineering and biomanufacturing capabilities.

Purification of antibody modalities

Purification platforms for monoclonal antibodies (mAbs) typically contain an affinity capture step based on protein A followed by polishing steps for further impurities reduction. Today these steps are typically performed in batch chromatography with process columns. Innovations in downstream mAb processing, including continuous chromatography approaches such as multi-column chromatography (MCC), have been shown to increase purification productivity and reduce operating costs significantly. Although batch processes are inherently less complex, MCC takes significant advantage of spreading the sample load across multiple columns in a more efficient cyclical process. As a result, a several-fold increase in productivity typically is achieved.

Multi-column chromatography

Multi-column chromatography relies on a series of small columns instead of one large column, reducing the total resin volume required by as much as 90 percent. The various operations of the process protocol (loading, washing,

Picture: © Catalent Biologics

elution, and cleaning) are carried out simultaneously in different columns under the control of individual pumps. Periodic switching of the inlet and outlet streams to downstream column positions via a valve system enables the progression of process steps in a continuous cycle. MCC also allows maximum productivity, as mass transfer to the Protein A chromatography resin allows the total capacity of columns to be reached as fast as possible while maintaining high purity and recovery.

Some biopharma manufacturers no longer want or need to deal with the large stainless steel equipment, as well as buffer and resin volumes associated with batch processes. MCC addresses the bottlenecks that companies may experience and can provide significant economic advantages compared to traditional batch methods for mAb purification, including 3–10-fold increased productivity, 85–95 percent resin capacity utilisation, 30–50 percent reduced buffer consumption, decreased column volume, and smaller versatile process skids.

From batch to continuous

Emily stated: "Catalent has been and is continuing to consider alternatives to traditional batch chromatography to address process intensification upstream. Protein A media can be costly – often requiring a large upfront investment to establish the downstream process. The investment required for high-cost chromatography matrices can be limiting for biotechnology firms and can be mitigated by using MCC since smaller columns are used, which reduces resin usage. And that is how our partnership with Tosoh came about. We worked with Tosoh's MCC systems and completed several pilot and manufacturing scale demonstration runs."

The holistic MCC solution

Octave BIO is a comprehensive and versatile multi-column chromatography system with a modular design and added functionalities that support a range of process scales, implementations,

Tosoh Bioscience Octave MCC Instrument.

and applications, including continuous purification. Octave BIO is the first in a series of MCC instruments targeting all stages of biologic manufacturing, from pre-clinical to clinical and commercial GMP manufacturing. SkillPak™ BIO pre-packed columns are designed with standard shorter bed heights optimised for the fast flow rates and short residence times of MCC. The Octave solution consisting of the MCC instrument combined with bespoke columns enables customers to quickly and efficiently develop pre-clinical processes.

MCC affinity capturing of mAbs

TOYOPEARL® Protein A and Protein L resins provide the ideal combination of capacity, flow properties, and resulting product purity to achieve the highest productivity when used in MCC methods for the capture of antibody-based therapeutics. Octave systems paired with TOYOPEARL AF-rProtein A HC-650F resin, for example, allow flow rates of >600 cm/h and loading residence time as short as 0.25 min for Protein A adsorption of the mAb versus 4 min or more in a single column batch process. As all non-loading steps are carried out simultaneously in the other columns, there is no delay in completing each step. Protein A capture is achieved with greater speed and efficiency than a single-column process. Flexibility is afforded by adjusting the column number, size, and configuration to suit feed and adsorbent properties, accommodate all process steps, and satisfy run time requirements.

MCC expertise and training

Tosoh has been investing in the support infrastructure to help educate current and future MCC users with virtual and in-person offerings. At MCC Centers of Excellence in the U.S. headquarters in King of Prussia, PA, and in the European headquarters in Griesheim, Germany, Tosoh's renowned chromatography experts are ready to train and support the industry from the lab to the field.

Proof of concept

Emily Schirmer's conclusion after the demonstration runs: "The results of the in-depth MCC evaluation clearly illustrated the potential for significant time and cost savings for Catalent's partners. The automated system also provides benefits to operating costs and time. As the industry looks to overcome the bottlenecks that can occur during intensified processes, MCC can offer a pertinent solution." Based on the positive feedback from the industry, we at Tosoh Bioscience are convinced that MCC fits the growing industry trend of switching from batch to continuous processes and meets the four design principles for biologic facilities of the future: fast, flexible, small, and sustainable.

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Pictures: © Tosoh Bioscience

High value biopharma process development

BIOMANUFACTURING Implementing high-quality process development that considers GMP manufacturing from the start is critical to reducing costs and timeline disruptions associated with raw material supply chain insecurity, adhering to regulatory compliance, and avoiding process re-design at a later stage.

› Vladas Algirdas Bumelis, Prof., CEO, and André Markmann, PhD, VP Business Development, at Northway Biotech

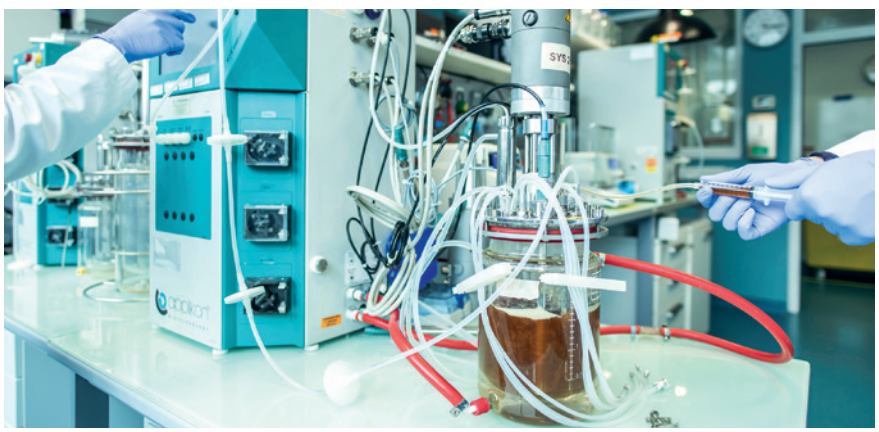
In overly ambitious biopharmaceutical development timelines, overlooking a GMP-suited process is common. The key milestone is producing during a pre-booked GMP slot to achieve first-to-clinical Phase I status, but manufacturing capacity is typically booked far in advance, making rescheduling difficult and costly.

Amidst the rush to meet timelines, biopharma companies and their partners often overlook crucial factors such as raw material availability and equipment compatibility. For instance, limited availability of resins may impede timely scaling up of a process, while a process designed for Phase I may lack scalability for commercial production. As an example, only a portion of USP material is utilised in Phase I's downstream process since minimal material is needed, but a scalability issue arises when moving to commercial scale.

In some instances, biopharma companies collaborate with CROs who have different objectives, solely focused on developing the drug substance process for early-phase development, which permits sponsors to evaluate the protein's/antibody's mode of action in a research environment. Sponsors may be at fault for overlooking this, prioritising meeting pre-set milestones in Phases I, II, and III, while compromising on complete process development, often leading to issues like yield or purity shortcomings, or a non-scalable/non-robust process. Only after that they consider scale-up, commercialisation, and ways to increase efficiencies and reduce process costs.

Inadequate process development has severe consequences. If significant process redesign is necessary, it may require repeating toxicology and Phase I/Phase II studies, resulting in a loss of both time and money. This further shortens the commercialisation period until patent expiration, exacerbating the situation. Consequently, finding a licensing partner for commercialisation becomes challenging, even with a persuasive scientific mode of action. The cost of goods sold (COGS) for that partner, potentially during a shorter commercialisation phase due to the impending patent expiration, does not warrant the investment needed to redesign a suboptimal GMP production process.

Ultimately, high-quality process development aims to maintain consistency from toxicology through GMP production runs. Process adaptations are usually necessary for tech transfer or scale-up to achieve higher yield, greater purity, or a more stable supply chain (e.g., changing to a resin with a shorter lead time). However, significant changes invite additional regulatory scrutiny.



Picture: © Northway Biotech

Engage a CDMO partner ASAP

To ensure thorough, well-considered process development, it is crucial to secure a CDMO partner as early as possible in a project. Biopharma companies often understand that their proposed process needs optimisation and seek external expertise to achieve this. The CDMO-client

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conversation covers various areas, such as yield and purity improvement, investment in the process, and desired outcomes. An experienced CDMO will prioritise optimising process steps that need attention. However, some companies demand running their heavily invested process exactly as designed or resist changes due to regulatory compliance concerns. Supply chain issues may arise, leading to missed GMP runs. Even if the GMP run occurs on time, issues may expose the process as unsuitable for the scale, equipment, or facility, affecting the entire process. Therefore, regardless of when the CDMO joins a project, discussing process optimisation is crucial to ensure yield and purity improvement.

Picking the right CDMO partner

A biopharma company typically knows what kind of CDMO it wants to work with and seeks out expertise and experience with a certain process or protein. However, it is unlikely that any CDMO will have experience with a client's exact process or protein, so adaptability and capability in handling diverse molecules are essential. Northway Biotech stands out in this regard, with experience not only in monoclonal antibodies but also bispecific and trispecific antibodies, as well as microbially produced recombinant proteins, which have different purification requirements. This expertise allows for the development of optimised processes, overcoming specific problems, and is facilitated by in-house knowledge of equipment limitations, supply chain, and facility, ensuring a suitable process for GMP-scale production.

Do not underestimate the importance of process development. A process that works in the early stages may not respond well to GMP manufacturing and scale-up, leading to additional costs and time loss. Process development is crucial not only for on-time GMP production but also for presenting a complete package to potential partners or acquirers. For more information, contact the authors and visit *www.northwaybiotech.com.*. ■

Successor for CEO found

BAYER The Supervisory Board of Bayer AG has appointed Roche Pharmaceuticals CEO Bill Anderson (56) as new Chairman of the Management Board of Bayer AG, with effect from June 2023. Anderson will join the life sciences company based in Leverkusen, Germany, as a member of the Management board on April. Bayer's current CEO, Werner Baumann (60), will work closely with him to ensure a smooth transition before he retires at the end of May after 35 years of service at Bayer. The chemical engineer Bill Anderson has held various leadership positions in the life sciences industry over the past 25 years. In 2019, he became CEO of Roche Pharmaceuticals, based in Switzerland. Prior to that, Anderson was CEO of biotech pioneer Genentech, and he held several senior positions in general management, product development and finance at Biogen and at technology and electronics company Raychem. ■

Bill Anderson

Scientific team strengthened

BIOSENIC Dr Carole Nicco took up her position as CSO of Belgium-based BioSenic SA in mid-January. Nicco will oversee the development of BioSenic's cell therapy and autoimmune disease platform pipeline and be responsible for R&D programmes. She has more than two decades of experience in cancer biology and immunology, inflammation, immunity, novel target identification and drug discovery. From 2005 to 2023, Nicco was one of the principal investigators and laboratory manager of the research team "Pathogenesis and innovative treatments for chronic fibro-inflammatory diseases" at the Institute Cochin, a biomedical research centre affiliated to INSERM (Unit 1016), CNRS (UMR 8104) and Paris Cité University. In 2023, Dr Nicco will become President of the international non-profit organisation Redox Medicine Society (formerly the International Society of Antioxidants in Nutrition and Health). She holds a PhD in Human Physiology and Physiopathology from Denis Diderot University in Paris, France. ■

Carole Nicco

Changes in management

OXFORD BIOMEDICA Former Rentschler-CEO Dr Frank Mathias officially takes up his new position as CEO and board member of Oxford Biomedica plc at the end of March. He has led Rentschler Biopharma SE since 2016. In addition, Oxford Biomedica announced two changes to its Board, both of which will also take effect on the 27th March 2023. Stuart Henderson will become Vice Chair, a newly created position which replaces the previously combined role of Deputy Chair and Senior Independent Director, the position Stuart has filled since June 2020. Professor Dame Kay Davies will assume the role of Senior Independent Director, following her appointment as a Non-Executive Director in March 2021. ■

Frank Mathias

Pictures: © Bayer AG/BioSenic/Rentschler