European Biotechnology

Autumn 2024

CDMOs & CROs

SPECIAL

Biosecure Act impacting CRO and CDMO business

CONTRACT RESEARCH & BIOMANUFACTURING A draft US Biosecure Act being passed by the US House of Representatives and discussed by the US Senate could prohibit US biotech developers from collaborating with Chinese CROs, CDMOs and drug developers from 2032 by excluding the partners from federal contracts. US companies are unsettled, according to a survey. But how will the impending ban affect innovation, licences and the European sector in short term?

European biotechs often envy their US competitors for their wholehearted support of biotechnology, which is peppered with government statements. However, after China has been increasingly attacking the USA's leading role in future biopharmaceutical markets such as antibody drug conjugates (ADC) since 2010, the US House of Representatives and the US Senate are set to pass a bill – the US Biosecure Act – to push back China's influence, also for political reasons. Following the same model that was used to target Chinese telecommunications companies in the late 2010s, the Act would prohibit federal "executive agencies" from contracting with or extending loans or grants to any company that has certain commercial arrangements with a "biotechnology company of concern," which includes a death list of specific Chinese biotechnology companies and a procedure for identifying additional companies in the future.

Outlicencing deals of Chinese ADC developers in 2023

Programme	Licencer	Licencee	Total Value US$m	Date
unnamed	Evopoint Bio	AmMax Bio Inc	871	09/01/2023
YL-202	MediLink Therapeutics	BioNTech SE	1,000	12/10/2023
Sys-6002	CSPC Pharma	Corbus Pharma Holdings Inc	692.5	23/02/2023
LM-305	La Nova Medicines	AstraZeneca plc	600	12/05/2023
DITAC	Duality Bio	Adcendo ApS	undisclosed	05/01/2023
DB-1305	Duality Bio	BioNTech SE	undisclosed	07/08/2023
BL-B01D1	Sichuan Biokin Pharma Co.,Ltd	BMS	8,400	12/12/2023
BB-1701	BlissBiopharma Co.,Ltd	Esai	2,000	08/05/2023
HS-20093	Hansoh Pharma	GSK	1,710	20/12/2023
DB-1303, -1313	Duality Bio	Duality Bio	1,670	03/04/2023
HS-20089	Hansoh Pharma	GSK	1,570	20/10/2023
HRS-1167, SHRA-1904	Jiabgtsu Hengrui Pharma	Merck	1,530	30/10/2023
CMG-901	KYM Biosciences	AstraZeneca plc	1,188	23/02/2023
HBM-9033	Harbor Biomed	Pfizer	1,103	15/12/2023

Discussions in Senate were not expected to progress until after the US presidential elections in November 2024 at the earliest. However, companies such as the BGI Group, MGI, Complete Genomics, WuXi Apptec, WuXi Bio and their subsidiaries are already on the presumably growing death list, whereby, according to the news agency Reuters, the CDMO Wuxi alone has contributed to the development of a quarter of the drugs on the US market. As the leading ADC CDMO Wuxi generates 65% of its turnover in the USA. After the US biotech association BIO signalled support for the law this March, Wuxi withdrew from the US biotech industry interest group.

"Our adversaries abroad have stated that they intend to become the biotechnology centre of excellence in the world," BIO CEO John Crowley previously stated. "America and our allies cannot let this happen. Securing and expanding our pre-eminence in bioproduction will be a key component of a multi-pronged approach to securing and advancing this strategic imperative in biotechnology."

Race over leadership

A strategy paper published in 2023 by the think tank SCSP, founded by former Google CEO Eric Schmidt in 2021, fits in with this: its "National Action Plan for U.S. Leadership in Biotechnology" pro-

Picture: L.E.K. Consulting Ltd

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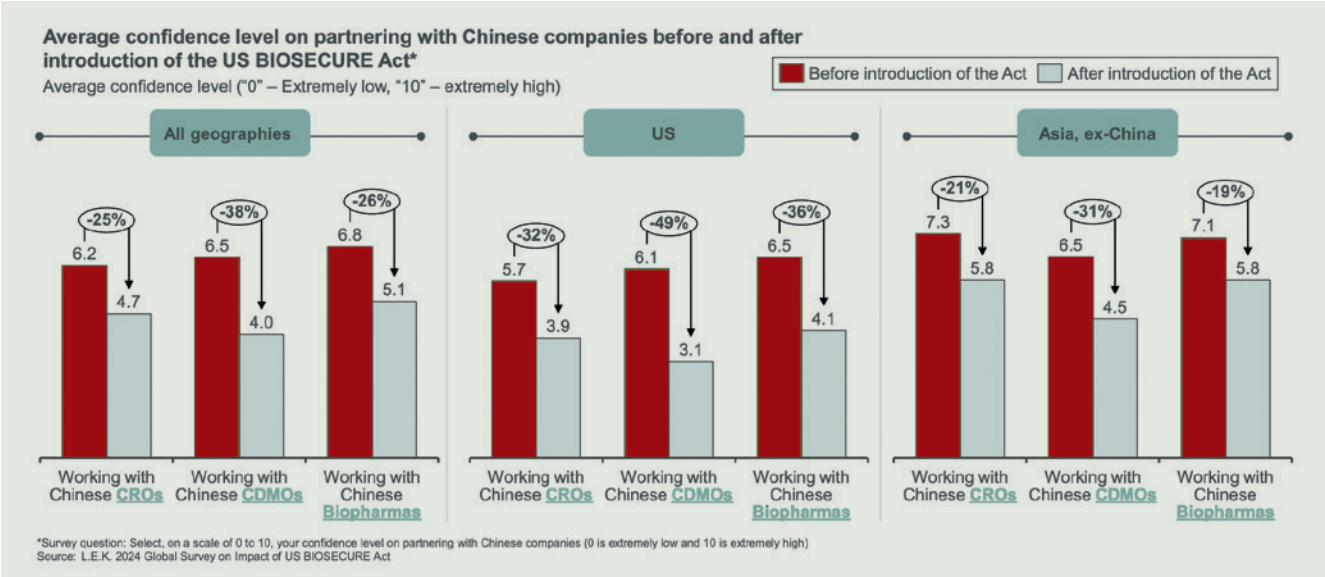


Fig. 1: Perceived impact of the US Biosecure Act on partnering with Chinese companies

poses a biomanufacturing alliance of democratic states to counter China's state-subsidised biotech offensive.

As a reminder: in 2023, China accounted for 50% of the top 10 ADC drug developers, i.e. the one with the largest development pipeline. According to UBS Investment Bank, 42% of the ADC development pipeline, which Chinese authors in a first global ADC database (ADCdb) put at 6,572 projects, 346 of which were clinical, at the end of 2023 (doi: 10.1093/nar/gkad831), were Chinese. In addition, Chinese ADC developers are attracting more and more licensing income – US$19.79bn last year alone, excluding two companies that did not disclose financial details (see Table 1) – out of more than US$41bn raised by Chinese biotechs in 2023, according to China's largest CRO Tigermed (Hangzhou).

The study situation in the field of cell and gene therapy and the rapidly growing market for CGT CDMOs (according to data from RWD; 2022: US$2.048bn, 2028: US$4.13bn) and CROs (according to data from Markets&Markets, 2024: US$82bn; 2029: US$129.8bn) seem currently to go down, according to the reported deal activity.

Cell and gene therapies

DealForma identified a peak of US8.2bn invested in CGT developers in 2021, Nature reported, while in H1/2024 only

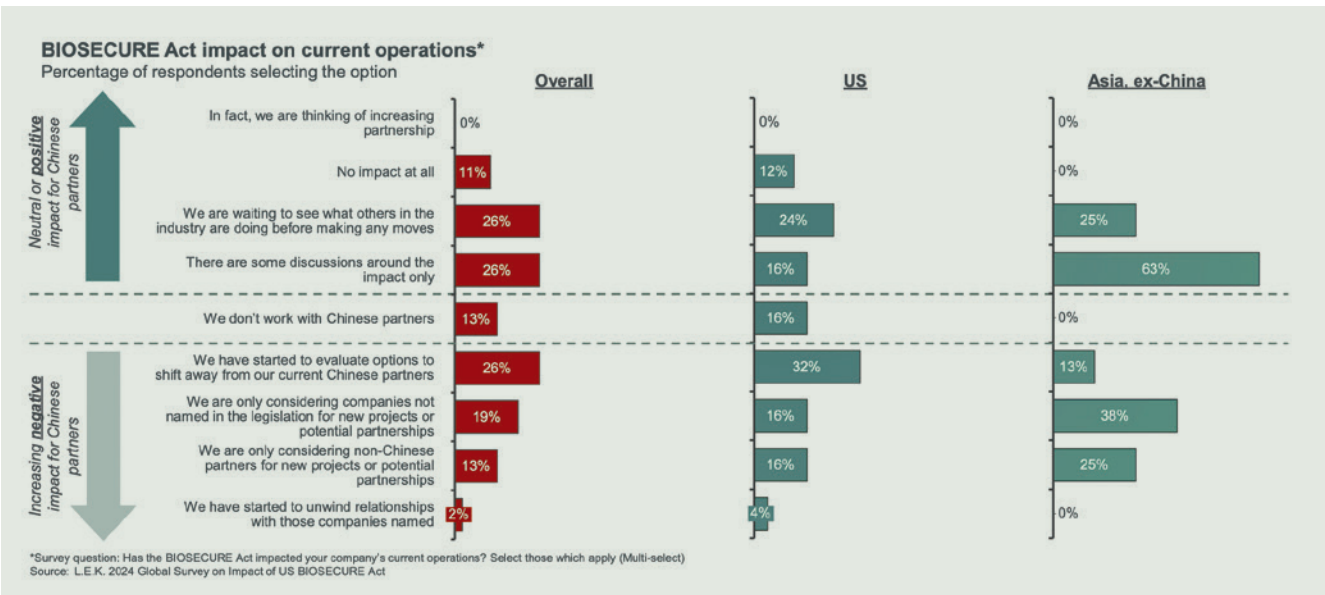
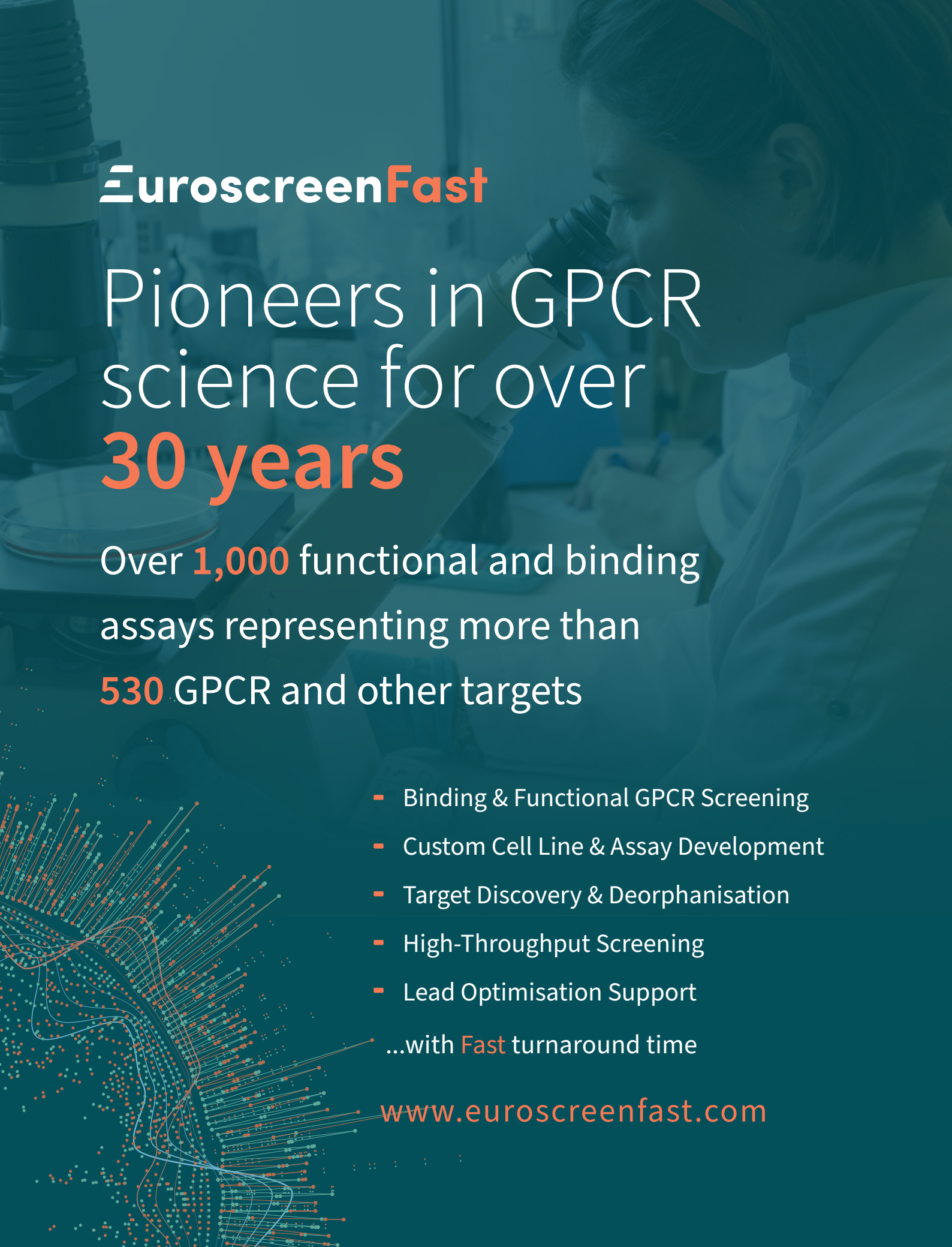


Fig. 2: Potential impact of the US Biosecure Act on current operations



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Top7 (*biologic) blockbuster drugs by 2030, according to Evaluate's World Pharma Report

Product	Company	Therapy Area	2030 Sales US$bn	NPV US$bn
Cagrisema*	Novo Nordisk	Obesity/Diabetes	20.2	80
Orfoglipron*	Eli Lilly	Obesity/Diabetes	8.3	34
Retatrudite*	Eli Lilly	Obesity/Diabetes	6.0	32.3
VX-121	Vertex	Respiratory	7.7	30.4
Pembro-lizumab*	MSD	Adcendo ApS	8.0	19.7
Datopomab deructecan*	Daiichi Sankyo	ADC	4.4	17.5
Maritide*	Amgeno	Obesity/Diabetes	2.1	12.4
Sum			56.7	235.7

US$0.5bn were invested. In contrast Evaluate's "World Preview Report 2024" predicts a pharma growth boost in areas such as ADCs, multi-specific antibodies, RNA-based therapies, gene & cell therapies, and radiopharmaceuticals by 2030.

For 2023, figures of the Alliance for Regenerative Medicine (ARM) demonstrate that the USA (1101) is still ahead of China (765) and Europe (430) in terms of the number of CGT clinical trials and global licence deals of US$ 11.7 bn. In gene therapy trials for rare diseases, which fuels the business of most CROs and CDMOs, however, China (492) is already ahead of the US (478) and Europe (199). "If the US Biosecure Act goes into effect, it will impact any company that wants to win US government contracts, like most global pharmaceutical companies, and prevent them from partnering with companies of concern, including certain Chinese CROs/CDMOs," L.E.K. Consulting said in June 2024 upon publishing a survey with a tremendous 66% response rate that examined the global impact of the Act on the biopharma industry. Respondents included investors (13%), biopharma executives, primarily business developers (54%, including 52%) from the US, but also from China (17%), CROs (4%) and CDMOs (6%).

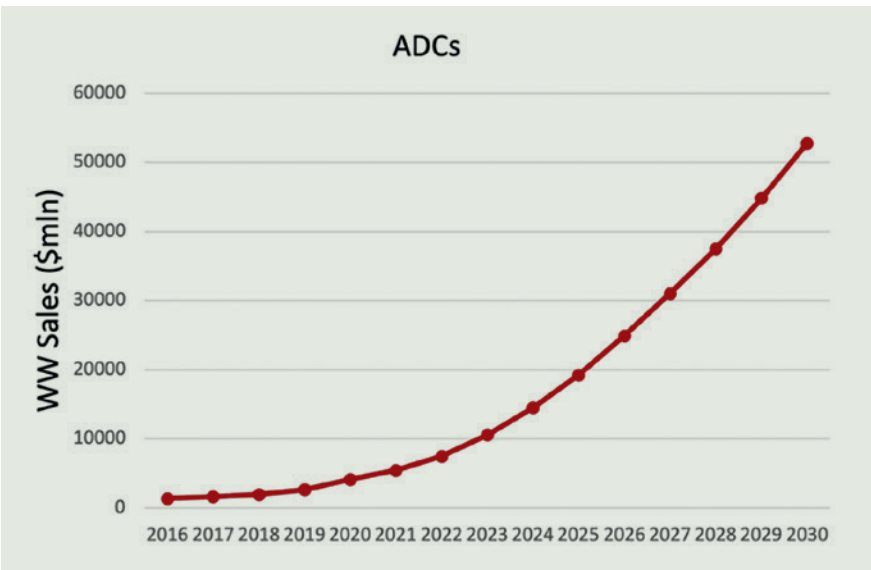

Fig. 3: Sales of ADCs, which promise to replace chemotherapy, are expected to grow significantly by 2030.

Pictures: Evaluate

According to the survey results and Jeremy Levin (see p. 3) – one of the 25 most influential CEOs in the US biotech sector –, the Act has the potential "to transform the entire industry". While about 50% of US-based biopharma developers said they have lost confidence in long-term relationships with Chinese CDMOs and 30% with Chinese CROs, about a third of respondents said they will maintain their partnerships for at least the next three years. While 26% of life sciences companies surveyed said they plan to move away from their current Chinese partners, 68% said they will adapt their approach. Despite the looming decoupling of biotechnology between the US and China, the majority of biopharma companies continue to show strong interest in partnering with Chinese companies for product commercialisation (see figures 1 and 2).

"The Biosecure Act is a threat," says Thomas Heimann, analyst at the investment firm HBM Partners. "However, it is difficult to say to what extent it is a threat. The main problem at the moment is the uncertainty." Non-Chinese CROs/CDMOs could potentially benefit from the bill as pharmaceutical companies seek to diversify their production from these companies or even from China. Contract companies such as Evotec and Fujifilm Diosynth have reportedly already received an increasing number of enquiries and exploratory applications, according to the L.E.K. survey.

Federico Polano, VP Business Development at expanding CDMO Rentschler Biopharma SE (see p.72), said to European Biotechnology: "As a global biopharma CDMO navigating the complexities of our industry, we recognise that legislation such as the Biosecure Act reflects genuine concerns about national security and the integrity of our supply chains. Having said that, we are also mindful of the potential impact on global collaborations and the broader biotech community. Realigning supply chains, for example, does not happen overnight, and this could lead to major adjustments for US biotechs, potentially increasing costs and timelines

for bringing drugs to patients. "Over the last 20 years, many Western-headquartered companies have become reliant on manufacturing and CDMOs in China, making agreements with Chinese companies central to the sector's productivity. An A U.S. survey of 124 biopharma companies found that 79% have at least one contract or product with a China-based or Chinese-owned CDMO/CMO. China is one of the largest suppliers of complex peptide, immunotherapy, and antibody drugs to US and European pharmaceutical companies. It is estimated that 13% of the world's manufacturing facilities supplying APIs to the US are in China and China is a major global supplier of APIs for generic drugs. Additionally, China is responsible for approximately 42% of global export value of antibiotics. "Biotechs may need up to eight years to switch manufacturing partners, potentially affecting millions of patients. For preclinical and clinical work, changing vendors may require anywhere from six months to six years, depending on the service and availability of other providers," told Dr Jeremy Levin, Emeritus Chairman of US BIO and Chairman and CEO of Ovid Therapeutics and Chairman of Opthea, European Biotechnology after the US House of Representatives passed the Act on 9th September. "The situation with clinical trials is similarly complicated," he said. "Many promising medicines currently in clinical trials in China could be impacted by the Biosecure Act, particularly if governments make it more difficult to share participant data across borders. While China's share remains smaller than that of Western Europe or the US, it has been on the rise. If international relations continue to deteriorate, patients in all regions may suffer as trials take longer to recruit, and patients may be restricted from accessing investigational medicines," Levin outlines the short-term impact. He proposes "Biosecure can serve as a call to action. The US and EU should implement a forward-looking BIOBUILD plan to maintain global leadership and pair divestment from China with strategic domestic investment.

Progress with novel drugs

According to Evaluate's World Report, in 2030, total pharma sales will top US$1.7tr, about 14% thereof will be made by the top-7 drugs, six out them biologics mostly in the areas of immuno-inflammation, oncology and obesity. Furthermore, new modalities and technologies continue to open up novel targets and targeting mechanisms: antibody drug conjugates (ADCs), multi-specific antibodies, RNA-based therapies, gene/cell therapies and radiopharmaceuticals are all expected to grow steeply until 2030. ■

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Capacity tripled

MANUFACTURE After three and a half years of construction, the Richter BioLogics CDMO has inaugurated a new multipurpose production facility that triples its capacity for the bacterial production of pDNA, vaccines, nanobodies and recombinant proteins. European Biotechnology spoke to CEO Kai Pohlmeyer about the background.

EuroBiotech_Dr Pohlmeyer, at the opening of the new P2 production facility at the Bovenau site, the first thing you noticed was that the company logo no longer says Richter-Helm BioLogics, but Richter BioLogics. Why?
Pohlmeyer_ Apart from the name and e-mail addresses, nothing will change for our customers. The new company name reflects the change in ownership of our company, which was founded by the current Gedeon Richter Chairman Eric Bogsch and Dieter Schnabel, the CEO of Helm AG, through the acquisition of Strathmann Biotec GmbH. Back in March, our Hungarian parent company Gedeon Richter announced that it was taking over the shares of Helm AG and increasing its stake in Richter-Helm BioLogics to 30% and its stake in Richter-Helm BioTec to 50%. The name change concludes the process agreed in autumn 2023, in which Gedeon-Richter exercised its contractually agreed first right of refusal, and the company value was subsequently determined. As announced, Helm will focus on its chemicals business in future.

EuroBiotech_Richter BioLogics, together with its parent company Gedeon-Richter, has invested €100m to expand the capacity of its microbial biologics production at the Bovenau site, Germany. How did this decision come about in the midst of the coronavirus pandemic?
Pohlmeyer_ With the opening, we tripled our production capacity for recombinant proteins, antibody fragments, pDNA and vaccines and doubled our workforce. The reason for this was a very strong demand from our existing customers at full capacity utilisation of our former single-line production in Bovenau. In 2019, we had three customers with products in clinical phase III who approached us and asked whether we could produce on a commercial scale in the event of approval. One big pharma company put the gun to our chest and said that the risk of working commercially with just one production line is too high for us. We needed more backup capacity. So if we wanted to grow, we had to do something. One of the products has received market authorisation and its production will fully utilise the capacity of our new, large 1,500 litre line from next year. Thus, the capacity expansion in Bovenau was not a poker game, but was based on a solid business case. We also benefitted from our balanced project mix, where we are excited to fill our production pipeline with innovative products from the biotechnology sector. At the same time our long-standing customers from the pharmaceutical industry provide a reliable foundation. We are noticing the dip in the biotech sector in the number of new project enquiries, but we can more than compensate for this with existing customers. We will increase turnover again this year, for the 12th time in a row.

Dr Kai Pohlmeyer is Managing Director at Richter BioLogics since 2018. He holds a PhD in cell biology and started his career at Richter BioLogics in 1999 as Head of Process Development. From 2001 onward he focussed on business development. Here he established the Business Development Department for the CDMO and until 2018 also took responsibility for Marketing&Sales and Project Management. He initiated and developed strategic partnerships and alliances.

EuroBiotech_Scaling up from one production facility to another is always difficult. What specific challenges does Richter BioLogics face in the new production unit?
Pohlmeyer_ With the 1,500 line, we are lucky that the product from the Phase III trial was already at final scale, so we only have to manage the tech transfer to the new plant.

EuroBiotech_Due to the good capacity utilisation of the new production facility, a third production line is already under discussion, you said at the official opening of P2. What is planned?
Pohlmeyer_ With the new large 1,500 litre and the smaller 300 litre production line, we expect the output of the

Picture: © RichterBiologics

Bovenau site to increase from 40 to 120 batches per year. Additional capacity is available at our Hannover facility. Our goal for the next two years is to fully utilise the new production lines. We are currently planning another 3,000 litre line, as we have several customers with antibody-products in Phase II and III who are considering commercial production at our site, which usually requires higher doses.

EuroBiotech_More than 60 skilled workers were hired as part of the production expansion in Bovenau. How is this possible in the midst of a global skills crisis in the CDMO sector?
Pohlmeyer_ We started the search well in advance – as early as last year – although this wasn't great for the profit and loss account. We were also aware that rural Bovenau is not the centre of the world and would not automatically attract skilled workers. Today, we are in a better position than I would have expected. The fact that the German biotech sector is currently weakening and experienced engineers and scientists have been made redundant has helped us in recruiting staff – even in southern Germany, where we previously had no chance.

EuroBiotech_The expansion that has already taken place and is still planned is considerable. What are the long-term plans of Richter BioLogics mentioned by Gedeon Richter's Chairman Erik Bogsch at the opening ceremony?
Pohlmeyer_ In the long term, we want to gain a better foothold in the US market, where we already generate the majority of our sales. I can't imagine any growth through M&A today, except in terms of breadth, i.e. in terms of strain development and processes upstream of production. Instead, we will continue to focus on organic growth. The 2024plus strategy envisaged a branch for Marketing & Sales in the USA. In view of the fact that the capacity of our production expansion in Bovenau is already more than 50% utilised, we have postponed these plans by two to three years. With regard to the product mix, we will continue to focus on pDNA and antibody fragments. Although we find the currently rapidly growing market for antibody conjugates interesting, we will not address it because parallel production of such toxic products would neither be accepted by our customers nor can it be realised in-house. However, we do see great opportunities for growth in the area of nanobodies and antibody fragments. ■

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Aerial view of Richter BioLogics' production facility with the new extension, which has space for a third line.

Picture: © Richter BioLogics

Celonic: A "Pure Play" Biologics Swiss-based CDMO

CDMO The biologics contract development and manufacturing (CDMO) market is experiencing rapid growth and is dominated by global players with investments in large scale stainless steel capacity. But is larger always better? Not necessarily says Celonic, a mid-sized, privately owned CDMO, who has been embracing next generation technologies to help small to large biotech customers bring their drugs reliably, effectively and efficiently to the market.

Celonic, Basel: New "Next Generation" Biologics Development Center (BDC) Laboratory. From left to right: Alex Villiger (CFO), Samanta Cimitan (CEO), Ricky Abbas (Strategy Advisor).

The Celonic Group is a fast rising, mid-sized biologics CDMO focusing uniquely on mammalian expressed drugs. It provides end to end drug substance development and manufacturing solutions for monoclonal antibodies, bispecifics and other complex molecules from development all the way to commercial supply. Celonic combines the expertise like larger CDMOs with the agility and a collaboration mindset of a family owned business. The Celonic Group is privately-owned and part of the independent German family business J. Rettenmaier & Söhne Group (JRS). Celonic's history is a success story. Over 30 years, the company has continuously expanded from research projects to GMP manufacturing.

Celonic's roots trace back to the world renowned Max Planck Institute and the Jülich Research Institute in Cologne, Germany more than three decades ago. In 2011, the JRS Group acquired Celonic AG headquartered in Basel, Switzerland, followed by the acquisition of Glycotope in 2017 which provided the company its current GMP manufacturing site in Heidelberg, Germany. Today, Celonic has a state-of-the-art Biologics Development and Innovation Center (BDC) in Basel, Switzerland, and clinical and commercial GMP manufacturing facilities in Heidelberg, Germany. At present, more than 500 highly qualified employees work at Celonic across the two locations.

Market trends

In the past decades, Biologics manufacturing has seen an advent of disposable single-use technology (SUT). The industry practice has been to utilize disposables for development and small scale clinical or launch supply, and then scale up to large scale stainless steel for market supply. One of the key benefits of integrated single-use solutions is its flexibility and minimizing lengthy changeover times between products or batches coupled with the reduced risk of cross-contamination which helps to avoid costly downtime and the risk for failed batches. Its main drawback is higher costs per gram of the pharmaceutical active ingredient driven by the smaller scales and the cost of consumables. However, a number of market factors are shifting, making it easier for bio-manufacturers and CDMOs to adopt single-use technologies and further broaden its appeal.

First, is the trend towards increased protein titers. Historically companies developed blockbuster drugs with very low titers, often in the 0.5 to 1 g/L range. Today, with improvements in expression platforms, new processes routinely achieve titers in the 2 to 5 g/L range and sometimes even ti-

ters exceeding 8 to 10 g/L with process optimization. Higher titers means that commercial demand for these new molecules can be addressed with smaller size bioreactors.

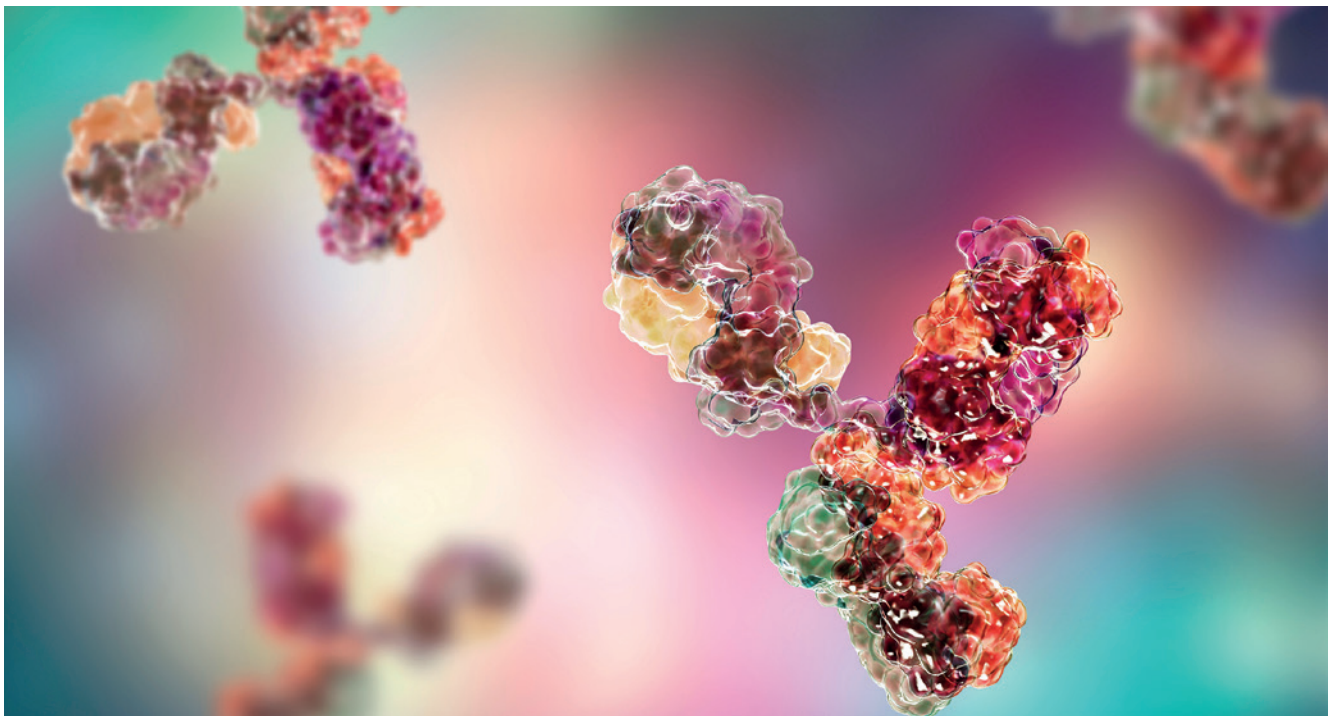
Second, is the portfolio mix of new generation drugs. While historically the market was driven by large blockbuster standard monoclonal antibody (mAb) drugs, which required up to a ton of drug substance, newer molecules are more diverse, more complex, and in general require less volume with the possible exception of new large indications (e.g. Obesity, Alzheimer's). With scaling out (e.g. multiplexing 2,000L reactors), it is estimated that single-use facilities can address nearly two thirds of all new mammalian molecules including some biosimilars, ranging from niche orphan indications all the way to hundreds of kilograms, providing flexibility and speed to market without the need for technology transfers between sites or assets.

Third, is increased scrutiny by pharma and biotech company shareholders and industry watchdogs on sustainability, demanding that bio-manufacturers and CDMOs adopt stricter sustainability practices, and explore how to adapt manufacturing processes to minimize environmental impact. Stainless steel-bioprocessing has significantly higher process mass intensity (PMI) versus single-use technology standard fed-batch processes. PMI is defined as the total mass of materials used (raw materials, consumables, water and ancillary products) to produce 1 kg of active drug substance. This is because the high amount of water and steam required by stainless steel-bioprocessing during cleaning- and steam-in-place (CIP and SIP) and its larger facility footprint relative to a disposable facility. With global warming, long term water scarcity is becoming increasingly a concern worldwide. The consequence is that some companies are starting to evaluate their decisions based on the combination of speed, flexibility, sustainability, and cost of goods per gram rather than cost of goods per gram alone, which provides additional momentum for single-use technology.

Next generation technologies

Georg Blaser, VP of the Celonic Biologics Development Center, is passionate about next generation technologies. After a successful 13 year long career at a larger well-known CDMO, Georg joined Celonic to bring his vision of accelerating the adoption of next generation technologies in the biologics CDMO market. He states "Next generation technologies enable im-

Georg Blaser, VP of the Celonic Biologics Development Center



Pictures: © Celonic Group

State of the art: alternating tangential flow (ATF) cell retention devices from Repligen

proved bioprocessing productivity leveraging the flexibility of disposable technology with lower cost of goods per gram versus standard fed-batch processes. Simply put, it is about getting more for less". Next generation technologies include process intensification which uses a perfusion-based cell culture process in the N-1 reactor as well as full perfusion which refers to perfusion in the N stage reactor. Separately, the downstream processes can also be intensified using latest generation resins as well as other optimisations.

Expression systems

Getting more for less starts with a robust expression platform to deliver solid base titers. Blaser explains "Celonic's GS-CHOvolution® offers a gene-edited Chinese Hamster Ovary (CHO) K1 cGMP-compliant cell line with Glutamine Synthetase genes ("GS") knocked-out, combined with TnT transposon technology, which facilitates the selection of high expressing clones during cell line development, resulting in higher titers". The GS selection system is recognized by regulators as the industry standard for the manufacture of biologics, it offers accelerated cell line development timelines with high efficiency cell line screening, and is a robust and scalable platform with no glutamine supplementation required. Blaser is quick to point out that, Celonic's GS-CHOvolution® has a simplified milestone based licensing model without any royalties, which is attractive to many small to large biotech companies.

Process intensification

Intensified fed-batch, also known as N-1 perfusion, has been discussed in whitepapers and conferences for many years now. However, very few companies have actually adopted it in reality. Celonic is different. It recently inaugurated a new Biologics Development Center with the aim of developing and optimizing processes using process intensification via perfusion technology. Perfusion bioprocessing involves exchanging fresh medium for spent medium within a bioreactor while retaining the cells, allowing for higher-cell densities and lower concentrations of waste product inside the bioreactor.

Extending the duration of the N-1 step and applying a perfusion cell culture process allows operating the N bioreactor such that it results in higher titers, a reduction in cycle time or both. Specifically, Celonic has developed a proprietary toolbox based on multiple molecules types, cell lines, media and feed systems which has demonstrated the doubling of titers, improvement in downstream capture step productivity by 50%, and a reduction of cost of goods per gram of up to 30 to 40% versus a traditional fed-batch process. At the same time these improvements significantly re-

Picture: © Repligen Corporation

duce process mass intensity (PMI) and thereby, improve sustainability.

Full perfusion

Celonic has been a pioneer in perfusion-based technologies for decades. The company has run GMP manufacturing for full perfusion up to 1,000L SUT scale and has produced over 50 batches above 50L using CHO and GEX cell lines. Celonic has run perfusion processes up to 40 days, handling up to 60,000L of bulk harvest. Celonic uses state of the art alternating tangential flow (ATF) cell retention devices from Repligen. A full perfusion process can increase total output by a factor of eight to tenfold and significantly reduce cost of goods per gram. This means a 1,000L SUT bioreactor perfusion process can compare itself to a 10,000L Stainless Steel Bioreactor in terms of output. Historically, full perfusion was reserved for hard to manufacture, so called labile molecules such as blood factors. Today, perfusion can be applied to even standard monoclonal antibodies and biosimilars that seek to get large scale volumes with the flexibility provided by disposable systems.

GMP manufacturing

Celonic has more than 20 years experience in GMP manufacturing. Whether a scale-up from a small scale or a straight technology transfer at scale from a third party, Celonic's multifunctional expert team can help to bring customer's products speedily and reliably into Celonic's Heidelberg Site. Celonic's small scale asset provides 200L SUT up 1,000L SUT scale bioreactors ideal for IND filings. Celonic's new mid-scale 6 x 2,000L SUT asset offers opportunities to scale up and scale-out which minimizes inter-site technology transfer times and provides a faster pathway to PPQ and Marketing Authorization Approval. Both assets are equipped to handle process intensified processes as well as traditional fed-batch. The Celonic manufacturing assets use Cytiva's Xcellerex XDR single-use bioreactor system.

Cytiva: the technology enabler

As an industry innovator, Cytiva understands the immense responsibility you have when it comes to advancing human health. That's why Cytiva is Celonic's ideal solutions provider and scientific thought collaborator. Their technologically advanced solutions offer flexibility, capacity, quality, and efficiency, helping you accelerate your clinical and commercial milestones.

The Cytiva Xcellerex™ XDR Bioreactor single-use system is designed to scale from process development to full-scale manufacturing. Its robust and flexible system integrates with the Xcellerex™ Automated Perfusion System (APS) to ensure consistent production during continuous manufacturing processes. The system's automation capabilities include filter switching, liquid management and cell bleed which reduces risk for human error and increases process robustness.

ÄKTA ready™ XL single-use chromatography system is designed to meet the capacity demands from single-use upstream processes (2,000L high-titer feeds). ÄKTA ready XL operates large scale columns (up to 1200 mm), using the two flow kit sizes that cover a broad range of flow rates from 45 to 3,500 L/h. The single-use flow path minimizes the need for cleaning and cleaning validation, allowing for quick changeover between productions, while eliminating the risk of carryover. ÄKTA ready XL offers the accuracy and documentation required for use in a GMP-regulated environment.

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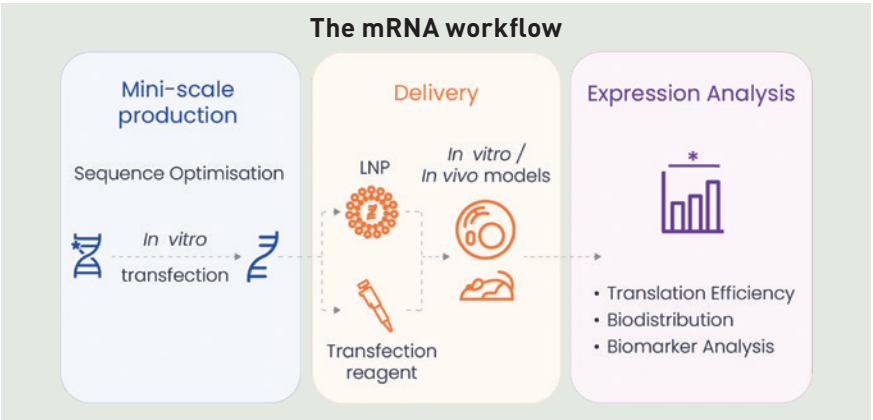
Your mRNA Partner in Europe

MRNA PRODUCTION Messenger RNA (mRNA) has gained significant attention since being used in the Pfizer-BioNTech and Moderna COVID-19 vaccines. mRNA holds potential for preventing and treating many difficult-to-treat or genetic diseases, including cancers. However, its production is complex and raises challenges for researchers developing new therapies: Discover Tebubio.

› Flavien Carpentier, Contract Research Services Director, Tebubio SAS, Le Perray-en-Yvelines, France

Demand for mRNA has skyrocketed and researchers developing mRNA-based vaccines and therapies face the optimisation of stability, immunogenicity, translation efficiency, and delivery. EU-based Tebubio Contract Research Services provides mini-scale mRNA production to support proof of concept work. It produces µg to mg amounts of custom mRNA in Europe, to be used for screening purposes in preclinical research. This unique, personalised, mini-scale mRNA optimisation and production service guarantees support for researchers from start to finish, with successful transfer to scale-up with the end product in mind, from the outset.



Accelerate your mRNA project from proof of concept to GMP

Mini-scale production

Researchers no longer struggle to get a functional mRNA sequence. Having completed more than 300 projects in the last three years, Tebubio experts are skilled in optimising the template pDNA sequence to increase its stability, transcription efficiency, final mRNA and protein expression, and decrease immunogenicity. Once the sequence is optimised, research grade mRNA can be produced as of 100 µg at Tebubio's dedicated, state-of-the-art mRNA laboratory in France.

Delivery

Intracellular delivery of mRNA represents a challenge, due, in part, to its large molecular weight and high negative charge density. Customised delivery tools are required to suit the specific requirements of the final model (target, tissue, cells, disease). Tebubio employs either chemical delivery with a transfection reagent, or customised lipid nanoparticle formulations. With the knowledge and expertise to develop the best formulation, Tebubio streamlines production and provides mini-scale quantities of formulations, that are scale-up-ready.

Expression & analysis

Tebubio validates the expression of the mRNA in the chosen *in vitro* model, whether in cells, 2D and 3D culture, or on *in vivo* models. Further analysis can include protein expression, quantification and localisation, and the response of the *in vitro* models, such as: toxicity, inflammatory cytokine release, cytokine storm, phosphorylation, and secretome profiling. Once the encapsulated mRNA has been optimised, Tebubio provides seamless handover to trusted partners to develop the *in vivo* models, with close support provided by a PhD-level Tebubio project manager throughout. All of the pre-clinical variants are validated *in vitro*, which reduces the number of candidates needed for *in vivo* testing, prior to clinical trials. Furthermore, Tebubio's in-house biostatistics platform delivers complete biomarker analysis, with reports including robust proof of concept data that can be used in publications and grant/patent applications.

Upscale + GMP

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RICHTER BIOLOGICS

Well Prepared to Tackle New Pandemics

BIOMANUFACTURING If you want to successfully guard against future pandemics, you're going to need a good plan – and the right kind of vaccine producers. WACKER and CordenPharma have been commissioned by the German government to prepare their mRNA vaccine production lines for a new pandemic.

It pays to play safe. The Covid pandemic made that pretty clear. Better to be safe than sorry. A great many people took this advice to heart. Everyone was able to do something to stop the spread of the virus – such as wear a mask, keep their distance, or get tested. But the pandemic only became manageable once Covid vaccines - which were developed in record time - were made available, preventing further death and suffering. Innovative vaccines based on mRNA (messenger RiboNucleic Acid), in particular, were in high demand at the start. "The experience with scarce vaccines led to the German government's decision secure production at home, so to speak," explains Dr. Andreas Anton, head of Wacker Biotech's pandemic-preparedness project in Halle (Saale). Pharmaceutical producers with appropriate vaccine expertise and capacity were then invited to apply for pandemic-preparedness contracts. Having joined forces with CordenPharma, we did precisely that, because in combination, we cover the entire process chain for producing mRNA vaccines. Alongside four other companies, we were awarded a contract in April 2022."

That was the go-ahead for these companies to start taking all the necessary steps to achieve pandemic preparedness. In particular, the managers that WACKER and CordenPharma put in charge of the project now faced a herculean task involving an ambitious schedule: both companies needed to create the relevant setup and capacities in just two years. "In the event of a new pandemic, with Germany needing huge amounts of a particular vaccine for its population, the government would put our two companies in contact with the company that had developed the mRNA vaccine in question," explains Dr. Alexander Radspieler, CordenPharma's Global Project Manager, whose coordinating role is similar to that of his WACKER counterpart. CordenPharma has in-depth expertise in lipids and lipid nanoparticles and has many years of experience in terminal and aseptic filling. Wacker Biotech has become a specialist in therapeutic proteins, living biotherapeutic products, plasmid DNA and conventional vaccines based on microbial systems. It was one of the first companies to address the production of mRNA vaccines. Both companies jointly take on the vaccine's complete production: from the bioengineering of the mRNA, starting out from plasmid DNA, through to formulation with lipid nanoparticles and the sterile filling of the final vaccine (see chart). "All the critical manufacturing steps must take place in Germany. That was specified by the German government to ensure the country's vaccine supply. Equally, all the production steps must take place in the European Union," explains Radspieler. "The idea is to stop being dependent on global supply chains. The importance of being independent in this respect was made patently clear by the Covid pandemic."

This was the reason for Wacker Biotech's choosing the site in Halle, Germany. A major expansion project was taking

Picture: © WACKER

Dr Alexander Radspieler (left), Global Project Manager at CordenPharma, and Dr Andreas Anton, head of Pandemic Preparedness at Wacker Biotech

Four new production lines for biopharmaceuticals were installed in Halle (Saale), Germany.

place at Halle's Weinberg Campus Technology Park. CordenPharma decided to obtain pandemic-preparedness status for its production sites in Frankfurt am Main (Germany), Chenôve (France) and Caponago (Italy). All these sites were required to provide suitable production capacity by Q2 2024 to enable the annual production of 80 million vaccine units. "To meet this target, we mainly invested in Halle," says Anton, who coordinates this large-scale project. "We have drawn up extensive schedules and project plans to achieve everything by the two-year deadline. After all, it was necessary to plan and erect a new building, obtain the requisite equipment, and take on and train considerably more staff."

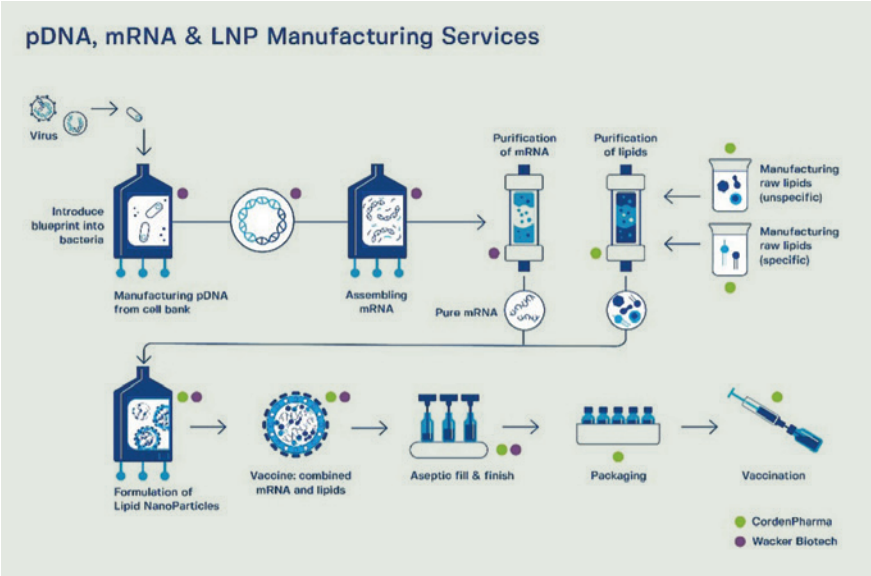
Bodyguards for the mRNA Active Ingredient

As the central process steps take place in Halle, the site plays a key part in the pandemic project. "Put simply, the first thing we do there is to use the pharmaceutical company's specifications to make the plasmid DNA. That is the starting material for producing the mRNA active ingredient," explains Anton. CordenPharma's expert Radspieler adds: "The next stage involves our various lipids, as the vaccine is formulated in Halle, too. This is almost the last process stage, in which the mRNA is combined with lipids to form lipid nanoparticles, or LNPs, and packed into a lipid envelope that protects the sensitive vaccine on its way into the muscle cells at the injection point. But first, the frozen vaccine is sent to our sterile filling center in Caponago, northern Italy, where the vaccine is put in prefilled syringes or vials." As part of measures to combat pandemics, CordenPharma launched two major expansion projects. In one project, the size of the lipid production area was increased to make it possible to produce the necessary quantities. This project also involved investing in supercritical liquid chromatography, which is an environmentally compatible purification strategy for lipids. In the other project, CordenPharma extended its existing sterile filling capacity so that it would be able to supply clinics, vaccination centers and doctor's surgeries with the necessary vaccine doses.

After being successfully qualified and confirmed by the German government, WACKER and CordenPharma have been in a state of pandemic-readiness since June 1, 2024. To make it possible for mRNA vaccines to be produced in huge quantities, if need be, the new building in Halle includes four production lines for biopharmaceuticals – thus quadrupling Wacker Biotech's capacity. Anton, as project manager, and his team have everything under control there: time management, adjustment of schedules, coordination of, and communication with, partners, service providers and Germany's Center for Pandemic Vaccines and Therapeutics (ZEPAI). On 1 October 2021, the German Federal Ministry of Health (BMG) established ZEPAI at the Paul-Ehrlich-Institut (PEI) in an effort to better manage pandemic response in the field of medicinal products by establishing a framework for making pandemic vaccines available as fast as possible. Anton and Radspieler ensure that everything is good to go – first and foremost the necessary state-of-the-art equipment for

Capacity for 80 million vaccine doses a year

Pictures: © WACKER



Tried-and-tested LNP formulation & commercialization route

bioprocess engineering. "As we don't know the name of the customer who will be approaching us with his vaccine on day X, we basically need to be prepared for everything," explains Anton. "When we built the new facility, we adopted a modern model process and planned for as much flexibility as possible."

Flexibility for Production Lines

Luckily, WACKER and CordenPharma are used to rapidly switching from one customer project to another: both are CDMOs, or contract development manufacturing organizations, so it's standard procedure for them to switch to different production processes quickly and adeptly. "As CDMOs, we make our production lines available to a wide variety of customers from the chemical and pharmaceutical sectors so that their complex modalities can be manufactured, with WACKER taking on this role for biotech firms," explains Radspieler. "Alongside our production sites, we provide additional customer support in the form of our many years of in-depth experience. We also make our expertise relating to process management and process engineering available."

To ensure maximum flexibility, WACKER relies on what is known as the ballroom concept in Halle. "This means that there are no permanent piping systems in our production facilities. Everything is designed to be as variable and modular as possible. It's particularly easy to move equipment in or out of rooms. We are trying to represent a cross-section of technologies that are highly likely to be needed." Wacker Biotech and CordenPharma have likewise adopted the notion of 'warm base': production facilities and staff can be deployed instantly. The necessary starting and auxiliary materials are on hand as well. The intersite logistics strategies, too, can be implemented immediately. "If the German government gives the order to produce mRNA vaccines, we switch over to pandemic mode and can start the production process shortly after," explains the WACKER expert. "The strategy put into effect here is one of permanent pandemic preparedness, which also benefits our customers. This makes us very flexible, enabling us, during normal customer business, to implement projects rapidly and with a high degree of supply security."

So as not to run the risk of delays, both companies need sophisticated HR strategies, production planning and stockkeeping. Radspieler explains the reasons why: "During non-pandemic periods, our facilities are busy dealing with customer projects. As a result, we always keep production areas available for standby capacity, just like Wacker Biotech does. Or we can switch to other sites in the case of established customers - as would be the case with us when it comes to lipid production. This means that we must plan in great detail to avoid bottlenecks elsewhere," explains Radspieler. Anton adds: "We use at least 50 percent of our capacity for customer projects, while the other half is reserved as standby capacity for vaccine production. The German government pays us compensation for doing so. Our production sites need a good mix of projects that make it easier for us to move

"Ballroom": production suites featuring equipment that can be used with great flexibility.

Pictures: © WACKER

something from A to B. For this reason, we are setting up redundant production lines." Stockkeeping is of equal importance for the pandemic project: all the raw materials required, such as chemicals, enzymes and single-use systems, i.e. filters or plastic bags, must be present. "That's why we designed a special storage and monitoring system so that stocks can always be kept fresh, so to speak", explains Anton.

Both WACKER and CordenPharma profit from the fact that they were directly involved with their own projects at the start of mRNA vaccine development, which allowed them to gain experience. "For instance, our expertise meant that we were the ones that produced the lipids for the Moderna vaccine. These lipids relate, on the one hand, to cholesterol and phospholipid – two standard products – and on the other hand, to two specialty lipids that Moderna developed," says Radspieler. "The LNPs are important for mRNA vaccines in two respects: first, as a protective envelope, second, to enable bioavailability," explains the CordenPharma expert. During the Covid pandemic, Wacker Biotech successfully produced a clinical mRNA candidate vaccine, thereby gathering invaluable experience. The process technology needed for industrial-scale mRNA vaccine production was scaled up at WACKER's Amsterdam site and laid the groundwork – not only in terms of the pandemic-preparedness plan, but also as regards setting up the mRNA competence center in Halle. WACKER invested more than 100 million euros in this expansion project. Over the coming years, the Group intends to spend an annual average of some 80 million euros on its biotech operations. This is yet more proof of WACKER's confidence in this future technology.

Successful Recruitment

"To join the top league, we had to take on a lot of staff in a very short period of time and we put a great deal of effort into recruiting highly talented personnel. As we cover the entire value-creation chain, we need to recruit employees from different disciplines such as chemical and pharmaceutical technicians, IT specialists and quality managers," says Anton. "We've been very successful here so far, thanks to an advertising campaign featuring influencer videos to target young people as well. It took us just one year to recruit more than 100 people," he recounts proudly. An equally state-of-the-art approach was adopted when it came to familiarizing new staff. "On the one hand, we involved new employees in ongoing production at other corporate units. On the other, we set up dedicated training rooms so that new staff members could learn how to operate the various pieces of equipment needed for their work. If a particular piece of equipment wasn't yet physically available, we used virtual reality modules to make the most of the familiarization phase," explains Anton.

Aseptic filling equipment at CordenPharma in Caponago (Italy)

It's All About Well-Laid Plans

The experts from Wacker Biotech and CordenPharma repeatedly stress that a huge number of aspects need to be taken into consideration. Pandemic preparedness depends on well-laid plans – and it's essential to be in close contact with all the various parties involved in the project. After all, you want to play safe in the event of a new pandemic.

Partner for Innovative Biopharmaceuticals

The pandemic-preparedness project is not the only result of the very close cooperation between Wacker Biotech and CordenPharma. The two companies collaborate in other areas too: for instance, they started a development partnership in December 2021. Its focus is on creating an extensive pool of experience in terms of lipids and lipid nanoparticles (LNPs) so as to provide a broad portfolio for mRNA vaccines. The two companies are also working on the production processes and scale-up for industrial manufacturing of lipids to meet increasing market demand. Lipids are an essential part of advanced drugs because they safely convey the active pharmaceutical substances to their destination in the patient's body. LNPs form a protective envelope around mRNA actives, antibody or protein replacement therapeutics. What's more, the work performed by Wacker Biotech and CordenPharma on innovative lipids includes collaboration with two German universities: Humboldt-Universität in Berlin and Ludwig-Maximilians-Universität in Munich. The idea is to integrate the knowledge gained into an artificial intelligence model with the aim of issuing statements about suitable lipids more quickly in the future.

www.wacker.com/biologics www.cordenpharma.com ■

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The key versus larger CMOs is agility and flexibility

BIOMANUFACTURING The Celonic Group, a Swiss Based quality biologics Contract Development and Manufacturing Organization (CDMO) just opened its "Next Generation" Biologics Development Center and Pilot Plant in Basel, Switzerland. Another site is located in Heidelberg, Germany. European Biotechnology spoke to CEO Samanta Cimitan about their strategy.

EuroBiotech_Huge growth rates are predicted for the contract manufacturing market. How can a smaller company like Celonic position itself for success?
Cimitan_ Celonic is a mid-sized "Pure Play" Biologics CDMO with over 500 employees. We focus uniquely on the Mammalian (CHO based) modality from development all the way to commercial manufacturing. Our target is primarily small to large Biotech customers and Biosimilar companies. We provide the technical expertise like larger CDMOs, but with the agility and collaboration mindset of a family owned business. We are also a trailblazer in adopting next generation technologies with the aim of reducing cost of goods per gram which is essential to make biologics more accessible to patients globally.

EuroBiotech_How important is the "D" in CDMO, i.e. involvement in project development, for the corporate strategy?
Cimitan_ Development is crucial to deliver high titers and yields, with robust processes that can smoothly run during GMP manufacturing. We just inaugurated a new, state of the art Biologics Development Center in Basel, Switzerland where all development, process optimization and non-GMP manufacturing occurs. Celonic offers cell line development using GS-CHOvolution®, an expression platform based on a gene-edited Chinese Hamster Ovary (CHO-K1) cGMP-compliant cell line with Glutamine Synthetase ("GS") genes knocked-out and the TnT transposon technology to accelerate cell line development timelines and to streamline the selection of high expressing clones.

Biopharma customers can also tech transfer to us at any clinical phase for process optimisation and GMP manufacturing, including conversions to next generation technologies.

Samanta Cimitan CEO Celonic Group Dr. Samanta Cimitan is an expert in the CDMO industry, holding a deep and unique combination of scientific, commercial, and operational expertise. Prior to Celonic, she held several leadership positions at Lonza for almost 13 years including Vice President of Lonza Group Operations Strategy, developing and leading transformational programs across R&D, Operations, and Commercial functions.

EuroBiotech_What exactly is meant by "Next generation" bioprocessing?
Cimitan_"Next generation" bioprocessing includes process intensification (intensified fed-batch) and Full Perfusion (N reactor) with the aim of increasing productivity, reducing the cost of goods per gram, and improving sustainability. The Celonic Biologics Development Center is fully equipped with automation and equipment capable to support conversions from classical fed-batch to next generation technologies and is led by some of the brightest minds in the field with a wealth of expertise.

Celonic has more than two decades experience with GMP manufacturing using full perfusion processes up to 1,000L in its GMP facility in Heidelberg, Germany.

EuroBiotech_In order to keep costs under control for the smaller indications, there is a lot of innovation in the processes. Automation, continuous production, digitalisation ... Where do you see the biggest levers for successfully responding to specific demand even better than the competition?
Cimitan_ Celonic works very closely with its supplier partners to leverage the latest technologies and is an early adopter of innovative solutions that address pain points in the development or manufacturing process.

The key for Celonic versus other larger CDMOs is agility and flexibility. Celonic has two manufacturing assets in its GMP facility in Heidelberg, Germany.

Picture: © Celonic Group

One for small scale (200L up to 1,000L) and one for mid-scale (6 x 2,000L). Both assets use disposable single-use technology (SUT) and are equipped with intensification and perfusion in mind, including the ability to handle high titer processes up to 8g per liter. Like this, whether by scaling up or out via multiplexing, Celonic can handle flexibly a range of molecules from small indications, all the way to commercial supply for mid-scale drugs requiring hundreds of kilograms.

EuroBiotech_Any other trend in the CDMO landscape that is keeping you very busy at the moment?
Cimitan_The political pressures to lower the cost of biological drugs will continue to accelerate, fueling growth in biosimilars over the next several years. In addition, geopolitics, in particular the US Biosecure Act, will impact the CDMO landscape and offer new opportunities for mid-scale players such as Celonic.

EuroBiotech_Does a smaller company inevitably only have the smaller indications and batch sizes, or should this not be seen so narrowly?
Cimitan_Small biotech customers are a key engine for innovation in the biologics world. They work on a range of disease areas from narrow orphan indications to broader high volume indications. At Celonic, we value all customers whatever their size.

EuroBiotech_Flexibility, agility and finding the right answer to customer requirements 24/7. That always sounds nice in theory, but how can you realize this in reality with the team?
Cimitan_It traces, first and foremost, to mindset and culture. Many of our experts and leaders have left larger organizations, because of the bureaucracy, inertia, and politics. Celonic is a family owned business, and Celonic employees have a high affinity to entrepreneurship and genuinely thrive on collaborating to help our customers achieve their goals. We have a flat internal structure which enables responsiveness.

Inauguration of Celonic Biologics Development Center (BDC) in Basel, Switzerland Christof Klöpper, CEO Basel Area Business & Innovation, Samanta Cimitan, CEO Celonic Group, Samuel Hess, Head of Economic Affairs Canton Basel Stadt

The other aspect is that, unlike some other CDMOs, Celonic does not work with rigid platforms. Instead we have toolboxes that can be flexed to meet specific customer needs, balancing customisation and cost efficiency.

EuroBiotech_What is the division of labour between the Heidelberg and Basel sites?
Cimitan_In Basel, we have Celonic's headquarters and the Biologics Development Center, including a Pilot plant of up to 200L non-GMP for the manufacturing of Tox material.

Heidelberg is the GMP manufacturing site in the heart of Europe, with small and mid-scale assets for clinical and commercial supply.

EuroBiotech_At the Basel site in particular, people think that the competition must be huge and that any new player would have a very difficult time. How do you experience the reception in the local community?
Cimitan_The reception of the newly inaugurated Biologics Development Center has been very strong including from the Basel City/Canton and the Basel Area Business & Innovation organization. We also had several visits from customers and suppliers, who welcome Celonic's expansion to the Basel biologics ecosystem.

EuroBiotech_The biotech companies have realised that there will probably hardly be any blockbusters. But then GLP-1 or something else comes along and everyone tries to conquer a market worth billions again. Is there a need for size in order to be able to play along, or can you survive well in a special niche?
Cimitan_Celonic has a diversified portfolio of clients which includes some of these growing segments with larger volumes. We bring value through our development, process optimisation, scale up and manufacturing capabilities which are agnostic to size. On the contrary, some of these new indications have development risks and volume uncertainty. A flexible manufacturing asset such as Celonic's mid-scale is ideal.

EuroBiotech_ What is it that attracted yourself to Celonic?
Cimitan_Celonic is a smaller, entrepreneurial and agile organization. The bioprocessing industry is at a crossroads with several game changing innovations being available to transform the market. I believe Celonic is a thought leader and a rising star in the industry in adopting next generation technologies to make drugs more accessible and affordable worldwide. Additionally, Celonic has a young and dynamic culture with some of the brightest minds in the field. ■

g.kaeaeb@biocom.eu

Ensuring sustainability and continuity in biomanufacturing

CDMO Biomanufacturers must balance the development of new therapeutic modalities and reduce manufacturing costs while maintaining environmental responsibility. Efforts are centered on improving process robustness and efficiency and creating more flexible manufacturing facilities that can accommodate diverse biopharmaceutical products.

› Balu Guduri, Global Product Manager - Process Consumables, Tosoh Bioscience

The biopharmaceutical industry is entering an exciting and transformative phase. Increasing demand for treatments that address unmet medical needs while remaining affordable is driving significant changes. This is reflected in the rising number of FDA approvals for biologics each year. Biopharma manufacturers are expanding beyond monoclonal antibodies (mAbs) into new modalities, such as cell and gene therapies, without losing focus on the substantial market potential of mAbs.

Key strategies to improve development and manufacturing while aiming for sustainable operations include adopting single-use technologies, implementing process intensification and continuous manufacturing, enhancing process analytics, and developing digital capabilities to leverage AI.

Sustainable product development

At Tosoh Bioscience, we are committed to supporting biopharmaceutical manufacturers in achieving their goals of producing affordable, high-quality medicines. In addition, sustainability is a core value at Tosoh, integrated into every facet of our business. We are dedicated to implementing robust sustainability measures at the corporate level and incorporating eco-friendly practices into our product development to enable more sustainable production processes in the biopharma industry. One of the ways the industry pursues sustainability is through process intensification and continuous manufacturing. Continuous manufacturing not only enables more sustainable manufacturing but also streamlines production and enhances the flexibility and scalability of biopharmaceutical operations, allowing for faster responses to market demands and regulatory changes.

SkillPak prepacked columns for biopurification

Continuous manufacturing

To simplify continuous biomanufacturing, we have developed flexible and scalable Multi Column Chromatography (MCC) skids: Octave BIO for process development and Octave™ PRO for GMP scale production, along with SkillPak™ Prepacked Chromatography Columns. Through collaboration with Catalent Pharma/Novo, one of the largest global contract development and manufacturing organisations (CDMOs), we have optimised both the hardware and software for the Octave PRO skid to facilitate GMP operations. This partnership accelerated the implementation of multi-column chromatography (MCC) in the highly regulated clinical-materials production stage.

Partnering for future innovation

To further develop MCC instruments to anticipate future developments in the industry, we joined the ECOnti project to develop innovative technologies that enable smaller production facilities, reduce water and energy consumption, and help companies limit their CO_2 emissions. This project, led by enGenes Biotech GmbH

Pictures:Tosoh Bioscience

and supported by the Austrian Research Funding Agency (FFG), aims to develop a fully integrated and automated continuous upstream and downstream process at up to 10L batch size, featuring the Octave BIO MCC Skid. The technology developed within the ECOnti project offers several key advantages, including smaller production facilities, reduced water consumption, lower energy consumption and CO_2 emissions, end-to-end process control, full digitisation and automation, higher product yields, and enhanced process stability.

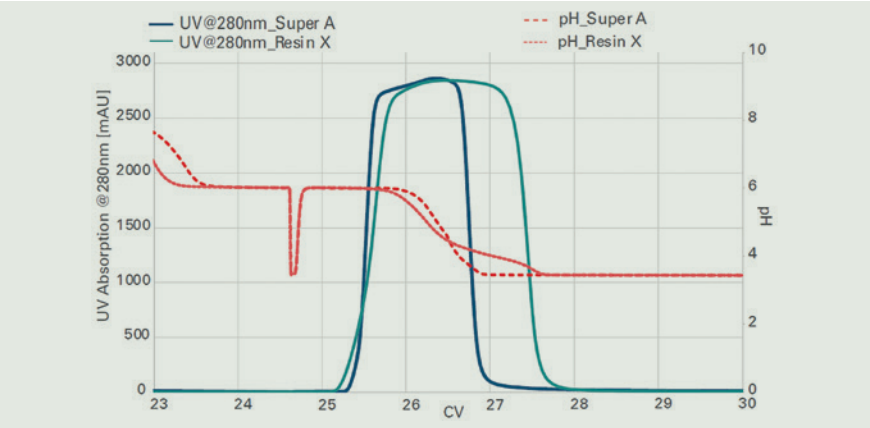
Additionally, Tosoh Bioscience has announced a pioneering partnership with Prof D. Michael Wolff from the University of Applied Sciences Mittelhessen (THM) Gießen, Germany. This collaboration focuses on developing continuous purification processes for viruses and viral vectors. By financing a researcher position and supplying essential equipment, including an Octave BIO Multi-Column Chromatography system, Tosoh Bioscience is dedicated to advancing solutions that meet the critical needs of the cell and gene therapy (CGT) industry. This partnership exemplifies our commitment to innovation and industry-academic collaborations, aiming to make CGT manufacturing processes more cost-effective and accessible.

Single-use products

The commitment to provide advanced solutions extends to the design of single-use consumables. A first example is our SkillPak Prepacked Chromatography Columns. By 2025, we will introduce columns for GMP production, with dedicated product lines for both batch and MCC applications. They will use significantly less plastic than traditional options and incorporate recycled glass fibers, further supporting sustainable practices.

More efficient mAb manufacturing

To enhance process robustness and flexibility, our brand new TOYOPEARL® Super A resin offers significant advantages for mAb manufacturers looking to implement a capturing platform to reduce their time-to-market. This high-performance protein A resin offers industry-leading critical performance parameters along with flexible operational parameters: high binding capacity at shorter retention times, robust alkaline stability, reduced pressure loss, and minimised aggregation with elution at pH 4.0. These attributes bring more process flexibility and robustness to antibody manufacturing, improving overall efficiency and product quality. TOYOPEARL® Super A resin is the ideal choice for small and large-scale bioprocessing. Its advanced features improve process economics and ensure high-quality, safe, and effective monoclonal antibody purification.



Reduced elution volume (-30%) and shorter process time for the capturing of an IgG1 through the novel TOYOPEARL Super A resin (vs. competitor).

Business continuity

Post-COVID, the emphasis on business continuity has intensified, with manufacturers forging closer collaborations with suppliers of critical consumables to ensure supply chain resilience. To bolster business continuity, we are expanding our manufacturing capacities. This includes constructing Tosoh's fifth manufacturing facility at the Yokkaichi Complex in Yokkaichi City, Mie Prefecture. This facility complements the fourth plant currently under construction in Nanyo, Yamaguchi Prefecture, which will be operational in 2025. Our fifth site for chromatography media is tentatively expected to be operational by mid-2027. These expansions ensure that our customers can confidently plan for business continuity and have assured supply for their future expansion needs.

Future developments

The biopharmaceutical industry is navigating a period of rapid change and growth. The drive to address unmet medical needs with new and affordable treatments pushes manufacturers to innovate and adapt. Tosoh Bioscience is committed to supporting these efforts through our capacity expansions, process intensification initiatives, and unwavering commitment to sustainability. We are also engaged in numerous promising R&D projects at various stages of development aimed at supporting customers in their process development efforts for novel modalities like Oligonucleotides, AAVs and others. We view innovation and sustainability as an ongoing journey. Our approach includes continuous improvement, investing in research and development for more efficient and sustainable products, and partnering with stakeholders. By working closely with our partners and continually investing in research and development, we strive to help the biopharmaceutical industry meet its ambitious goals and improve patient outcomes worldwide. ■

Pictures: Tosoh Bioscience

Aequorin: superior choice for GPCR calcium signalling

AEQUORIN TECHNOLOGY The study of G protein-coupled receptor (GPCR) signalling is crucial for understanding a wide range of physiological processes. Among the methods used to monitor calcium signalling, Aequorin stands out for its high sensitivity, specificity, and sub-cellular compartment targeting. While many CROs are still using fluorescent calcium dyes, EuroscreenFast is making use of Aequorin's unique properties as an invaluable tool to delve into the complexities of cellular communication.

› Dr Laurent Meeus, Chief Scientist & General Manager, EuroscreenFast

In the realm of cellular signalling, GPCRs are pivotal in transmitting extracellular stimuli to intracellular responses, often involving calcium ions (Ca^{2+}) as secondary messengers. To effectively study these intricate pathways, a precise reporter system is essential. Aequorin, a photoprotein originally derived from the jellyfish Aequorea victoria, has emerged as a superior reporter for GPCR Ca^{2+} signalling.

A primary advantage of Aequorin is its high sensitivity to Ca^{2+}. Upon binding with Ca^{2+}, Aequorin undergoes a conformational change, leading to the oxidation of its coelenterazine substrate and the emission of blue light. This bioluminescent reaction is highly specific to Ca^{2+}, ensuring minimal interference from other ions or cellular components. Because background noise is greatly reduced compared to other approaches that use fluorescent dyes, the use of Aequorin offers a larger assay window and allows for more accurate real-time monitoring of Ca^{2+} fluxes within living cells, providing invaluable insights into GPCR-mediated signalling events.

Another critical benefit of Aequorin is its ability to be expressed in various subcellular compartments, such as mitochondria, using a dedicated signal peptide sequence. Ca^{2+} fluxes are more intense in the mitochondria, upon cytosolic Ca^{2+} increase. This improves the sensitivity of mitochondria-targeted Aequorin reporters. Moreover, progressive mutagenesis has allowed the generation of variants beyond wild-type Aequorin with improved stability, light emission, Ca^{2+} affinity.

Illuminating Cell Communication

Aequorin's versatility in various experimental setups is noteworthy, including single-cell analyses, high-throughput screening, and even whole-organism studies. This adaptability makes Aequorin an ideal choice for a wide range of applications, from basic research to drug discovery. Furthermore, the bioluminescent signal generated by Aequorin is compatible with most standard laboratory equipment which allows EuroscreenFast to facilitate seamless integration into existing workflows.

The resolution offered by Aequorin is another advantage. GPCR signalling events occur on rapid timescales, necessitating reporters that can keep pace with these dynamic changes. Aequorin's fast response to Ca^{2+} binding allows for the real-time tracking of transient Ca^{2+} signals, capturing the nuances of GPCR-mediated processes that might be missed by slower-responding indicators.

Aequorin's bioluminescence is also advantageous in reducing background noise, a common issue with fluorescence-based indicators. Since bioluminescence does not require external excitation light, it minimizes autofluorescence and photobleaching, thereby enhancing signal-to-noise ratio and improving the accuracy of measurements. This feature is especially beneficial in complex biological environments where autofluorescence can obscure subtle changes in Ca^{2+} levels.

The application of Aequorin in GPCR Ca^{2+} signalling has already yielded significant insights. For instance, it has been instrumental in elucidating the role of Ca^{2+} in neurotransmitter release, hormone secretion, and sensory perception. In EuroscreenFast's hands, Aequorin has helped advance understanding of cellular communication and even led to the deorphanisation of a number of GPCRs.

The advantages of Aequorin as a reporter for GPCR Ca^{2+} signalling are manifold. High sensitivity, specificity, sub-cellular compartment targeting, versatility, and superior temporal resolution make it an invaluable tool. By illuminating the intricate dance of Ca^{2+} ions within cells, Aequorin paves the way for groundbreaking discoveries in cellular signalling and beyond. As EuroscreenFast continues to explore the depths of cellular communication, Aequorin will undoubtedly remain a beacon of clarity and precision in the study of GPCR Ca^{2+} signalling. ■

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Empowering tomorrow's therapies today

CDMO A specialist for complex biopharmaceuticals, the CDMO Rentschler Biopharma SE has once again reinvented itself: in 2021, the company set up a centre of excellence in the UK for manufacturing of cGMP-compliant viral vectors for gene therapies and more recently, it doubled its global production capacity with a new manufacturing line in the US. European Biotechnology spoke with CEO Benedikt von Braunmühl to explore the developments and future directions of the company.

EuroBiotech_Mr von Braunmühl, what is the strategy behind Rentschler's expansion of its business and management?

von Braunmühl_As a CDMO, being successful means being ready to evolve with the fast-moving market. In 1983, we were industry pioneers, with the world's first market approval of a native interferon-b (fiblaferon). In 2023, we contributed to nearly 25% of all FDA-approved biologics alone. Our ability to respond to client needs has always been a driving force behind our decisions. The move to the UK was part of our effort to offer advanced therapies, the Stevenage Bioscience Catalyst, being an ideal location to grow in ATMPs and further evolve our business. With our Milford site in the US, we tapped into the country's dynamic innovation landscape whilst moving closer to our clients. We transformed the site near the Boston biotech hub into a cutting-edge multi-product facility for biopharmaceuticals. Along with our expansion, we also evolved our leadership to reflect our new positioning as a global company.

EuroBiotech_How is Rentschler Biopharma positioned as a CDMO and where does it want to go in terms of clients, especially in the US market, and in molecule formats, sites and sales?

von Braunmühl_We are the experts for complex modalities from concept to market. We currently offer cGMP drug substance production for over 140 therapeutic modalities, more than 50% of which are advanced antibody formats and complex proteins. Our pledge is to find best-fit solutions for our clients' endeavors. With our new state-of-the-art production line in Milford, we have not only doubled our global cGMP capacities but are also strengthening our local presence for years to come, also welcoming new clients.

Benedikt von Braunmühl
Chief Executive Officer of
Rentschler Biopharma SE

EuroBiotech_The CDMO sector is rapidly growing – CAGR 11% by 2030 – and consolidating. Is it sensible for a CDMO of Rentschler's size to continue to develop organically?

von Braunmühl_Consolidation for large-scale CDMOs will continue. But specialised CDMOs, like Rentschler Biopharma, will likely gain more importance. We add value by manufacturing therapeutics for rare and serious diseases that require substantial experience and expertise. Being free from capital market influences enables us to prioritise sustainable growth and long-term objectives over short-term profits. Moreover, we offer our clients full-service solutions across the biopharmaceutical value chain by building meaningful strategic alliances, like our collaborations with Vetter for fill & finish and Leukocare for formulation.

EuroBiotech_How do you envisage Rentschler's business in five years' time at the existing and possibly new locations? What role will the current growth areas like CGT play – especially in the early phase of clinical development?

von Braunmühl_Innovation is at the heart of what we do. We don't limit our clients when it comes to exploring new possibilities. We give them space to test their ideas, especially in early phases of development projects. I firmly believe that this is how great results happen. We proved this during the global pandemic, when we rapidly adapted, becoming a manufacturer of about 2.5 million doses of the COVID-19 vaccine. By combining the client perspective

Picture: Rentschler Biopharma SE

with technological know-how, we drive innovation. Take CGTs: according to Global Data, about 5,000 CGTs are currently in preclinical phases. Many of which are working with viral vectors as gene ferries. We recently launched our new lentiviral vector manufacturing toolbox which complements our existing adeno-associated viral (AAV) vector services at our UK site.

EuroBiotech_What role do talent recruitment and site coordination play for Rentschler Biopharma?
von Braunmühl_Today's employers face many challenges. No company has the luxury of attracting talent and retaining them until their retirement. Rentschler is well-positioned, nevertheless, staying attractive for existing and future talent is vital. We actively invest in collaborations with universities and education initiatives, and partner with our peers in research clusters, strengthening the local biopharma regions our sites operate in. We also live by this spirit in our daily work and foster cross-site collaboration.

EuroBiotech_Which strengths of its team, logistics and client relations can Rentschler rely on and where do you see room for improvement?
von Braunmühl_When I look at the work our employees do across sites, I am deeply impressed. Here are people working across three different countries, with many different nationalities and professional backgrounds. All share one vision: advancing medicine to save lives. Our two bio-pharmaceutical sites, for instance, are closely connected, not only when it comes to seamless technology transfer from Germany to the US, but also on a collaborative level. Our employees work in cross-site teams, regularly visit their counterparts, from production to business development or IT. The same is true for our site in the UK. This directly translates into our client relations: we believe that we achieve the best results when we work together as their partners. They place their trust in us when they commission us. So, their projects are our projects. No client is ever the same and we learn with every project. The smaller ones may require more batches and consulting, while the larger ones are in need of specific processes. A client from the US may face different market challenges than one in Europe.

With a new state-of-the-art manufacturing line in Milford, US, Rentschler Biopharma has recently doubled its global cGMP capacities

EuroBiotech_Cooperation with a CDMO is a matter of trust. In light of the shortage of qualified personnel, how do you address the fields of automation and AI in your services?
von Braunmühl_Trust is the key. Digitisation and automation play a central role in our short- and long-term strategy to ensure that we remain a reliable partner. Our roadmap is geared towards four areas of management, operations, clients and client business in a holistic strategy. We are in the process of digitising and networking our systems and processes end-to-end, also looking into AI solutions. Deloitte estimates that the adoption of AI in biopharma could reduce manufacturing costs by up to 20% and improve process efficiency by 30%. In the long run, this can translate into more efficient services, freed-up capacity, and increased transparency for clients along the entire value chain. These changes also pave the way for new professions in biopharma, like bio-data engineers or oversight officers, who combine scientific expertise with data know-how.

EuroBiotech_How do you assess the increasing orphanisation of drug indications for your company's business?
von Braunmühl_Orphan drugs are part of our core business. At the same time, we are on the doorstep of the era of personalised medicine, with increased demand for new modalities, mainly driven by the growing need for new treatments for the rising incidence of cancers and other diseases globally. As modalities become increasingly complex, our expertise positions us well in both production and regulatory consultation. This allows us to effectively pave the path to clinic and market for therapeutic solutions.

EuroBiotech_Your next goals and priorities?
von Braunmühl_We have worked with clients from across the globe for five decades now. We know what it takes to adapt to local conditions and tailor our approaches. We will continue to build on this experience and are committed to empowering tomorrow's therapies today, addressing unmet medical needs of patients worldwide. ■

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Picture: Rentschler Biopharma SE

Pichia protein production

BIOPROCESS DEVELOPMENT Recombinant protein production in Pichia typically relies on AOX1 promoter-driven expression using methanol for induction. However, some companies avoid methanol due to safety concerns or operational demands. VALIDOGEN's unique AOX1 promoter variants enable methanol-free protein production at high space-time yields, offering advantages beyond safety. Latest case studies underscore the strength of this technology.

› Rosie Maddock, Evelyn Trummer-Gödl and Thomas Purkarthofer, VALIDOGEN GmbH

Methanol-induced protein expression in *Pichia pastoris*, leveraging the strong AOX1 promoter, is a highly efficient system for producing recombinant proteins. This approach is well-established and scalable, making it suitable for both laboratory and industrial-scale bioreactors. However, due to safety concerns and the operational challenges associated with methanol handling, recent advancements have focused on developing methanol-free alternatives.

Methanol-free expression

Validogen develops high-performance MeOH-induced and MeOH-free Pichia protein production strains for various industries. Their MeOH-free system utilizes a specialized subset of their library of AOX1 promoter variants, eliminating the need for methanol while maintaining the beneficial characteristics of the original AOX1 promoter.

Unlike constitutive promoters, this system enables strong, time-controlled initiation of protein expression while reducing the metabolic burden from carbon source switching, as well as minimizing oxygen consumption and heat evolution. This technology is already in commercial use in bioreactors up to 100,000L.

Process Intensification

In collaboration with Boehringer Ingelheim, Validogen has developed optimised MeOH-free bioreactor cultivation processes. A recent collaborative case study highlighted two of these approaches: one process in bacterial-like fermentation time (64 hours), and one in Validogen standard process time of 111 hours, both applied for secreting a bivalent VHH.

The optimised MeOH-free short cultivation process achieved high product yields of 12 g/L and significantly increased space-time yield. The optimised 111-hour process, applying a specialised feeding strategy to maximise product titer, achieved a yield of 19 g/L, while maintaining high space-time yield.

Validogen's methanol-free processes provide a safe, efficient, and flexible alternative to conventional methanol-based or constitutive Pichia expression systems, offering enhanced safety and streamlined efficiency without compromising performance. ■

UNLOCK PICHIA® protein production strain generation and process development at VALIDOGEN: high-yield expression strains and intensified processes considering safety, economic efficiency, and regulatory requirements. Serving industries including biopharma, food and feed, industrial biotechnology, and diagnostics

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