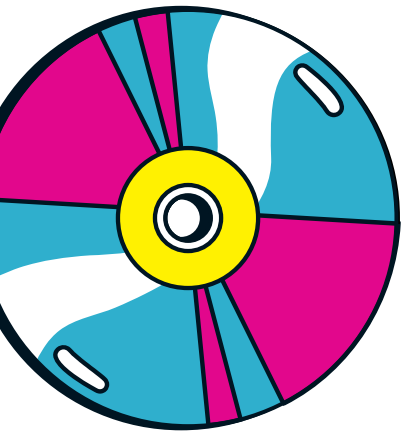
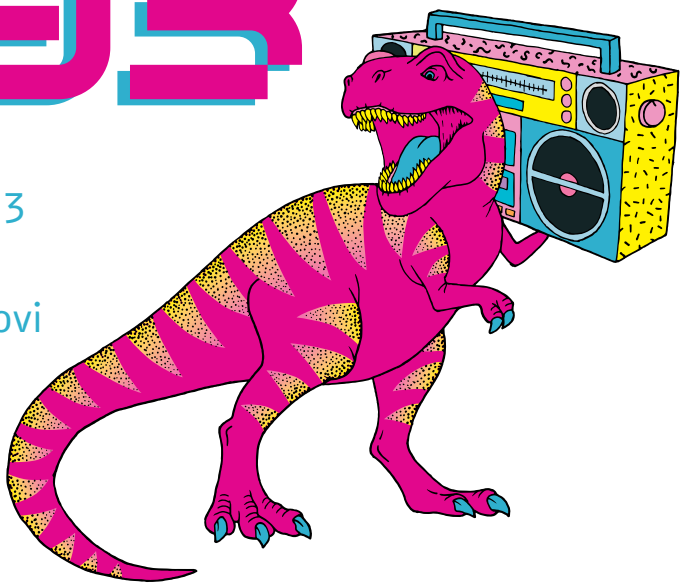
European Biotechnology

Autumn 2023

mlm medical labs®

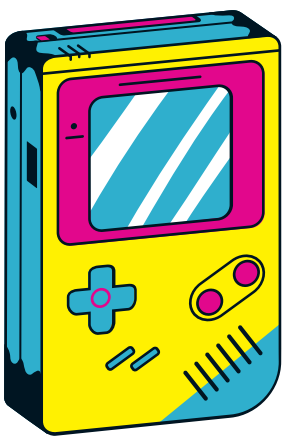


1993



- Jurassic Park stormed theaters in '93
- 4 Non Blondes, Culture Beat, Bon Jovi and Meat Loaf ruled the world of music

- Adobe publishes the first version of the PDF format
- Francisco Mojica first characterizes what becomes later known as the CRISPR locus



- MLM Medical Labs started its operations to grow into a global full-service central and specialty lab in Mönchengladbach
  MLM has been delivering high-quality lab services to support pharma and biotech for 30 years

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Hiring staff = growth

CUSTOM SERVICES Since 2006, the share of biomanufacturers producing everything in-house have declined from 57.6% to 34.9% in 2022. According to biopharmaceutical companies, the percentage is to decrease to 20% by 2026, according to the 19th biomanufacturer's survey from Bioplan Associates International.

As production capacity demand for gene and cell therapies has been growing since 2021 by about 20% per year, qualified personnel is increasingly becoming a growth-limiting factor, according to current figures of Bioplan Associates International.

No capacity constraints

This is especially true for the USA, which accounts for 27.8% of global production capacities, and for Europe with a share of 30.8%. In contrast, China's 13% production capacity is facing an order boom. According to data from BioPlan 's annual industry survey, more than 45% of CDMOs want to order services there. When biomanufacturing professionals were asked to identify which major constraining factors limited their organisation's growth, 34.2% answered, "the inability to hire new, experienced technical and production staff". "Another finding we saw this year was an inability to retain experienced scientific staff, which increased by 13.3% (32.5% in 2022 vs. 19.2% in 2021). In addition, the concern for retention of experienced technical and production staff increased by 10% from 2021 to 2022," says Bioplan research associate Shriya Bhatkhande.

On top of that, new advances like cellular therapy are pulling experienced employees from mainstream biologicals such as antibody production. Large US companies, thus have begun to hire experts in Europe and other parts of the world.

Bioprocessing efficiency and productivity improvements concerning titer levels increased to an average of 2.92 g/l, up from 2.65 g/lL in 2021. The average cost-per-gram monoclonal antibody was at its lowest point on record. The market has been expanding at a rate of 12% to 13% per year over the past decade, virtually doubling in size every five years. With this growth, efficiencies and economies of scale have resulted in lower unit costs. Cost savings from process automation and other factors continue to expand.

International biomanufacturing and offshoring are growing, especially in major markets and Asia. An upcoming wave of facilities making biologics, as well as pandemic and biodefense preparedness products, is increasing regional capacity, and growth among regional CDMOs, especially in Asia. The demand for biologics in these regions is also creating ready-made markets for innovative therapies.

The number of cell and gene therapy pipeline products and facilities, including commercial manufacturing, is increasing. However, more than 50% of the industry is having trouble finding qualified employees. As this continues to get worse each year, market success more and more depends on a company's ability to hire experts. ■

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Challenges in the central lab

TRANSATLANTIC Clinical trials have to be coordinated as a safe process where monitoring, analytics and handling of patient samples is streamlined – even cross oceans. German MLM Medical Labs is quickly establishing itself as an emerging central and specialty lab in the U.S.

EuroBiotech_Mr. Houlton, let´s start with the ecosystem of central and specialtiy labs, where MLM is entering the crowd.
Scott Houlton_MLM has a track record of three decades, that´s quite a number and much has happend. In today's landscape, the industry is made up of a broad base of very diverse, specialised suppliers, the same is true for the customer base. Typically the largest pharmaceutical companies like to work with the really large vendors. The size fits them well.

EuroBiotech_Where did MLM find its position?
Houlton_Although the large vendors do a lot of things very well, still no one is perfect. The larger companies are not good in providing nimble customised service that many of the customers want and complex studies require. These customers, the smaller to mid sized biopharmaceutical and biotech companies, don´t feel like they get the attention they need, and frankly want, from the large vendors. And that´s the niche, we are trying to go after: to provide highly customised and flexible services.

EuroBiotech_Now you are 'copying' the German, European success story of MLM as a blueprint for the US markets, is it really that simple?
Houlton_So what we wanted to do was to take what MLM is already doing very well and help broaden the scope and the geographic reach to help MLM grow. That was really the focus and the thesis for the investment to help MLM expand into the US in 2020, which we have done. We acquired two labs in the U.S. and have mirrored our offerings from Mönchengladbach, Germany, to Memphis, Tennessee, and are now expanding both - our revenue and customer base.

Scott Houlton, CEO MLM, has over 25 years of leadership experience in the pharmaceutical services industry across the drug development, clinical trial and commercial segments. He was most recently CEO of Clinical Supplies Management and has held past leadership roles at Catalent, Aptuit, Quintiles and Cardinal Health. He is a member of the CEO Advisory Board at Great Point Partners.

EuroBiotech_Are you changing your offering regarding other market needs?
Houlton_In late 2020 we acquired a business offering preclinical testing and histology services as a means to provide begining-to-end support along the drug development timeline. However, our primary focus remains on the clinical trials market. We want to continue with what we are good at in the safety and biomarker testing world and focus on drug development.

EuroBiotech_Since the company is in different positions on both sides of the ocean, the CEO must fill also different roles transatlantically, I guess?
Houlton_Yes. In the US, it is really about getting people on board, training them and getting operations ramped up efficiently. When I am working with the German team, it´s how do I help them expand and scale their business even further.

EuroBiotech_What can you take to the other side of the ocean, practically?
Houlton_We were lucky that we were able to take the operating systems that Germany had developed over the last few decades and transfer it to the US. A huge benefit for us. In our world, our customers want the labs to be harmonised so that they get comparable results. We really mirror the German set-up with processes, equipment and shared IT-systems.

EuroBiotech_What is it you are adding to the US ecosystem?
Houlton_We now add the central lab which is a good complimentary offering in the US. Together, this will help us to grow the customer basis very fast. Most of our activity is on phase one through phase four trials. We do have a small part of our business focused on preclinical research.

EuroBiotech_But the sample is still the core of your service, the 'tissue is the issue'?
Houlton_The sample is the starting point. Collecting samples on a global scale is not an easy job. We have developed a process for collecting samples from over 80 countries via validated collection kits and tracking those samples at every step of their journey from collection to real-time, digital reporting of test results through our mlm online® platform. ■

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Pictures: © MLM Medical Labs

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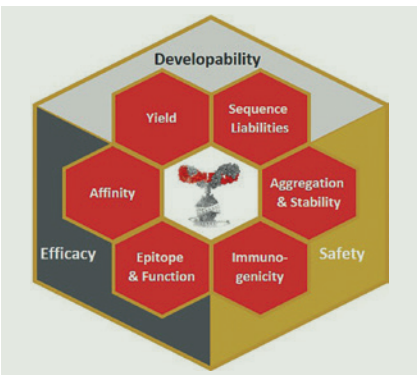
Derisking drug programs by early lead optimisation

ANTIBODY ENGINEERING The development of therapeutic antibodies is a time and cost intensive process. Biological and physicochemical properties of the lead molecules influence almost every step in the development. Investing into antibody engineering and lead optimisation during early development pays off in later steps and does not only accelerate the programme, but also increases the chance of success.

› Dr. Thomas Schirrmann, CEO, YUMAB GmbH

Therapeutic antibodies have become the most important class of biopharmaceutic drugs and are indispensable for the treatment of many diseases. Fully human and humanised antibodies can be generated by different technologies, such as in vitro display technologies from naïve or immune libraries or from transgenic animals. Selection and screening of early antibody candidates can be tailored to define many if not most properties of the final drug, such as target specificity and selectivity, or important features for preclinical development such as cross-reactivity with the animal model. However, it is unlikely, that the first antibody lead possesses all favourable features that are required for a therapeutic drug. Often problems occur in later development stages such as manufacturing, process development, formulation, or clinical development.



YUMAB's early lead optimisation approach ensures developability, safety and efficacy of an antibody drug candidate.

Early introduction of antibody engineering and lead optimisation that take these stages in consideration can help to improve functional properties and to address manufacturing or formulation issues in the early development process. Therefore, performing optimisation steps at early stages of drug development can save valuable time, costs and de-risk decisions on critical paths in upcoming process steps.

Exchanging only a single amino acid in an antibody sequence can influence functional properties, stability, expression levels, aggregation, and immunogenicity, all critical properties which can decide the fate of an entire drug programme. Many properties are interdependent, for example higher stability often improves expression levels and facilitates process and formulation development, or lower aggregation propensity may allow high dose formulations, a prerequisite for the subcutaneous administration route, and reduces the likelihood of immunogenicity.

Engineering and optimisation of early lead candidates need to be done in the context of each individual molecule. Optimising lead panels instead of single lead candidates increases the chance of success instead of relying on one molecule. The combination of computer-aided predictions, for example to generate focused libraries, with experimental studies accelerates antibody engineering and lead optimisation compared to pure bioinformatic approaches or random *in vitro* evolution. The employment of next generation sequencing offers a much deeper analysis of screening outputs and accesses larger pools of sequence variants. The access to more data also opens the door for machine learning and artificial intelligence, which will become an essential part of drug development in the future.

Accelerating and derisking antibody drug development by early lead panel optimization

In conclusion, the introduction of antibody engineering and lead optimisation very early in drug development by using a combination of experimental and bioinformatic approaches does not only accelerate the entire process, it also reduces costs, avoids failures, and increases the chance of success. ■

Manufacturing biopharmaceuticals

CDMO Within the competitive CDMO market, Richter-Helm has developed into a highly valued partner when it comes to the manufacturing of biopharmaceuticals. Richter-Helm is well recognised by pharmaceutical companies, including Big Pharma, as a professional partner offering flexible CDMO solutions from gene to product, all from one source, including consultancy services. This makes Richter-Helm one of the key players in CDMO business.

› Dr. Thilo Kamphausen, Director of Business Development, Dr. Kai Pohlmeyer, Managing Director

Richter-Helm´s expanded manufacturing site at Bovenau, Germany on 29.08.2023

According to various reports and surveys, the biologics market is constantly growing. Pharmaceutical companies focus on bringing their pipeline products to the market quickly and with minimum risk, and therefore increase their outsourcing activities to reliable partners, such as Richter-Helm. On the other side, CDMOs compete to win the project(s). In the end, decision-making is dependent on the most suitable fit between two partners. The trend seems to go in the direction of one-stop-shop offerings, where projects are outsourced to a single partner able to provide services from process development to analytical development, manufacturing, QC testing and filling of finished product. The goal is to build strong and long-term partnerships on equal footing to strengthen and extend business.

With a 35-year-long track record in GMP manufacturing, Richter-Helm provides its clients with a unique knowledge base in process and analytical validation, process performance qualification (PPQ) procedures, commercial production of therapeutic proteins and peptides, antibody-like scaffolds (e.g., VHH/ Nanobodies, Fab-fragments), bacterial vaccines, and plasmid DNA (pDNA) products.

Service along the value chain

On the company's sites, new projects can either begin from scratch for full development or involve the direct transfer of existing process technologies into large-scale production sites for market supply or to support with materials for clinical studies and the development of new products.

The increasing demand for further services offers very promising new opportunities for CDMO companies like Richter-Helm with respect to the business growth, the implementation of new technologies, and the establishment of expertise in certain areas. Richter-Helm is using this positive development to expand both its production and development capacities along with its technology pipeline.

To serve the demand for drug production and offer attractive manufacturing solutions for especially large and commercial scales, Richter-Helm is installing a new multipurpose facility, which is designed for maximum flexibility and opens opportunities for new projects. A total area of about 10,000 m^2 enables Richter-Helm to take on projects at 300L and 1,500L fermentation volumes for microbial production, as well as related mid- and downstream operations, ensuring high product yields. The new site includes additional space for huge analytical laboratories, warehousing, and technical areas designed for further growth. That makes the delivery of technically advanced services at different scales, especially large clinical scales up to commercial scale, possible.

Via the application and implementation of digital technologies (e.g., digitalisation of process design and targeted process characterisation to facilitate process development) into the whole manufacturing process, the biomanufacturing efficiency at Richter-Helm´s production sites increase further. ■

Picture: © Richter-Helm

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Gearing up on NANO: Pharmatech for nanodrugs

FR-JET TECHNOLOGY Manufacturing of COVID vaccines showed that large-scale production of lipid nanoparticles (LNPs) as a delivery vehicle for mRNA vaccines is already possible. As nanocarrier-based formulations became mainstream, however, insufficiencies in existing technologies for routine GMP manufacturing became apparent. LEON is committed to bridging these technology gaps through its unique FR-JET technology and innovative manufacturing equipment.

EuroBiotech_How accessible are LNPs for developing and manufacturing new therapeutic modalities?

Dr Setu Kasera_The two most popular techniques used for lipid-based nanocarrier formulations are jet impingement and microfluidics, using mixing processes that operate in very different flow regimes. Jet impingement, which was the primary method used for making COVID vaccines, has clearly distinguished itself due to superior output of product volume. Yet, problems with the technique also persist, which need to be solved to enable its full utilisation. For example, finding the right process parameters to make nanoparticles with desired properties and quality currently is a tedious process, mostly based on trial-and-error. There can also be batch-to-batch variability and other issues with consistent particle quality. These issues can largely be attributed to poor mixer design.

The aim of LEON is to fully enable access to these nanocarrier-based formulations. Our FR-JET technology features a near-ideal mixer geometry constructed in a modular fashion, where different segments of the mixing system can be adjusted depending on client's needs. This design offers precise control over the process parameters and makes it possible to approach process development in a systematic manner. Importantly, the same mixer is used on the bench scale and commercial scale. This approach de-risks batch scale up and eliminates the need to invest time and resources for intermediate scale up and pilot equipment. Our devices are built especially for aseptic GMP-compliant manufacturing, featuring closed designs and using sterile single use components among others. Our NANOme® manufacturing device is a gamechanger, designed such that batch changeover (including product changeover) takes less than a few minutes. Its operation is similar to inserting a cartridge into a printer and pressing a few buttons, bringing us much closer to making beside manufacturing a reality.

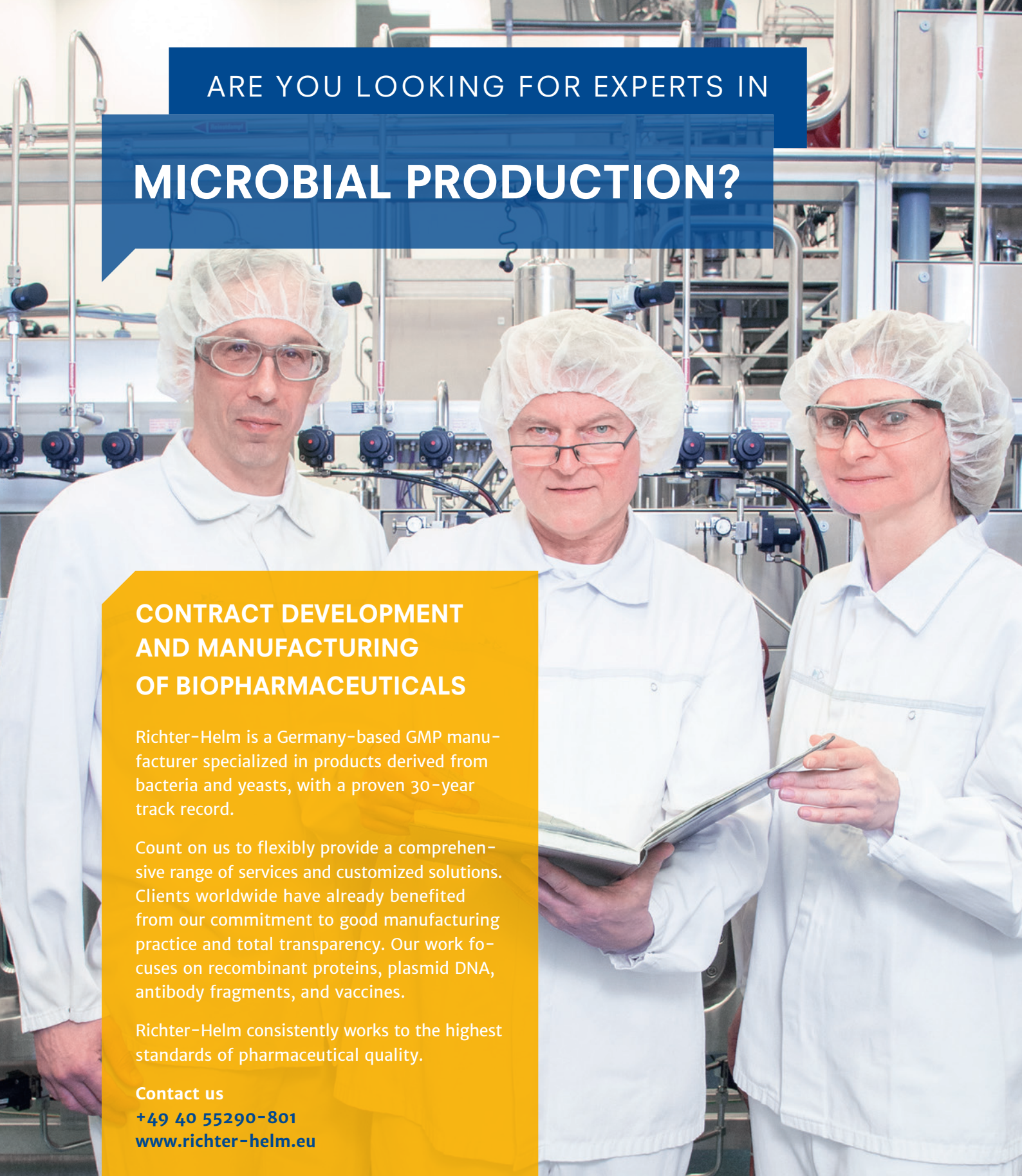
Dr Setu Kasera serves as chief scientific officer at leon-nanodrugs GmbH. With nearly a decade of hands-on experience in nanotechnology, she is directing research at LEON and is responsible for managing product development and data generation as well as strategic collaborations. She received her PhD in chemistry from the University of Cambridge, UK, followed by positions in research and business strategy in the biotech industry, with a focus on nanotechnology, drug development, CMC and science management.

EuroBiotech_How close is your product portfolio to maturity?

Dr Setu Kasera_The development of our lab scale and GMP manufacturing equipment and their performance testing have been concluded successfully. We are now in the final stages of functional testing with industry partners. The benchtop NANOlab® device for process development and our small-scale GMP NANOme® device for on-site manufacturing are planned for market rollout in 2024. We are already prospecting customers for our larger, high-volume GMP manufacturing device NANOus®, which has been designed in partnership with leading pharma production equipment manufacturer, Harro Höfliger.

EuroBiotech_How do you enable access to your technology for potential clients?

Dr Setu Kasera_Our pre-market benchtop units are already accessible for conducting feasibility projects in our laboratory in Munich. We can also ship the equipment to the client's site. Given the plug-and-play nature of our systems, installation and operations are not complicated and support from our expert team is available. ■



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Navigating the CDMO proposal process

BIOMANUFACTURING When businesses receive a proposal from a contract development and manufacturing organisation (CDMO), it's much like a first date: first impressions matter. The proposal process not only reveals a CDMO's services but also hints at the potential relationship's quality. This is gauged mainly through metrics like timing, quality, and price.

› Prof. Vladas Algirdas Bumelis, CEO, Northway Biotech

CDMO Response Time Matters: The speed of a CDMO's response is critical in an industry where timely responses to requests for proposals (RFP) and timely revisions indicate a CDMO's dedication to timelines.

Qualities of a Good Proposal: A standout proposal is customised, focusing on the client's unique needs, rather than a one-size-fits-all approach. It begins ambitiously, then hones details, rather than the other way around.

Evaluating CDMO Responsiveness: Initial interactions, even before the RFP, can indicate a CDMO's responsiveness. How quickly they handle preliminary processes and customise their proposals speaks volumes about future collaborations.

Understanding a CDMO's Qualification: An efficient proposal process reflects a CDMO's project management skills. Speedy communication between a CDMO's business and technical teams is a positive sign. CDMOs should also convey enthusiasm, connecting their technical staff with the project's larger mission.

Checking CDMO References: Potential clients should verify a CDMO's track record. Current, relevant references offer insights into the CDMO's recent performance, aiding decision-making.

Technical Call Significance: Technical calls help prospective clients understand the CDMO's capabilities. The presence of the right personnel and detailed note-taking during these calls is vital for project success.

Transparency is Key: A CDMO's proposal should be clear about risks and solutions. Access to the CDMO's sites and management team further emphasises transparency.

Flexibility of a CDMO: Adaptability is essential. A good CDMO will work collaboratively, even when unexpected challenges arise, showcasing their problem-solving skills.

The Final Proposal Revisions: The end revisions transform proposals from generic to specific, ensuring clients know exactly what to expect. This step prevents unforeseen costs and ensures clarity.

Conclusions

Prospective CDMO clients can gauge a lot from the proposal process, from responsiveness and creativity to the depth of technical understanding. Proactive CDMOs, like Northway Biotech, stay ahead by anticipating client needs, offering innovative solutions, and prioritising clear, swift communication. ■

Picture: © Northway Biotech