European Biotechnology

Autumn 2020

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Pandemic logistics

CONTRACT RESEARCH/CONTRACT MANUFACTURING The ongoing COVID-19 pandemic and lockdown has had significant impact on drug and vaccine development, including the business of contract research organisation (CROs) and contract manufacturers (CDMOs) as it led to bottlenecks in supply of APIs and delays in clinical trails. It may also hit biologics, the next wave of therapeutics. As first lots of COVID-19 drugs and jabs may be available in 2021, fair allocation is the next big topic.

After allocation of more than US$10bn to the makers of potential COVID-19 vaccines through the US agency BARDA, the US administration requested preferred access for US citizens to vaccine candidates nearing market approval. Copying this sort of vaccine nationalism, the European Commission in August started to negotiate similar Advance Purchase Agreements (APAs) for the EU member states with vaccine producers. As of September 2020, the Commission had reserved enough doses to vaccinate more than 60% of EU citizens twice by 2021 – provided the candidates proved safe and efficient and will get EU market approval. Low-income countries, in contrast, will be able just to vaccinate 20% of their population guaranteed through APAs signed through COVAX, the COVID-19 Vaccine Global Access Facility. COVAX is a global purchasing pool that is using APAs to guarantee markets for COVID-19 vaccines established by the vaccine alliance GAVI, the WHO, and CEPI in June based on donations from rich countries. The Manufacturers Alliance for Global Equitable Access to Coronavirus Vaccines (Manage-Cov) is set to complement the activities of COVAX.

Hopes rely on vaccination

The financial risk-sharing of vaccine developers and governments allowed the nine vaccine developers in the clinical testing state to reserve extra vaccine production capacities at CMOs, such as Catalent, Lonza or German IDT Biologika. Based on Pfizer's public price tag of US$38 for a two-shot vaccination of BioNTech SE's mRNA vaccine candidate BNT162b2, a world-wide vaccination campaign would cost about US$266bn. Vaccine makers use a range of technologies to speed up the development of vaccine candidates, besides vector-based vaccines, the potentially novel class of lipoformulated mRNA vaccines offer antigen expression in the body. Novel baculovirus-based expression systems (see p. 66) rely on vector vaccines expressed in butterfly pupae enclosed in single-use plastic devices. However, according to experts, it is still unclear if any of the vaccine candidates in clinical testing will be safe and highly protective, particularly in the risk group of older people, in which about 70% of COVID-19-related deaths occurred.

mABs as next wave vs COVID-19

Producers of monoclonal antibodies such as US start-up Adagio Biother-

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Manufacturing of Curevac's COVID-19 vaccine

apeutics or Germany's Yumab GmbH stressed that both are needed – vaccines and therapeutics, which are able to reduce the mortality rates of almost infected people. According to Tillmann Gerngross, the Austrian CEO of Adagio Biotherapeutics, which received a US$50m Series A financing in August, mAbs could be the better alternative to vaccines against the new coronavirus SARS-CoV-2.

"Because the immune system of older people does not respond as well to vaccinations as young individuals, and because previously published data suggest that multiple vaccinations per year will be necessary to protect them effectively, we see passive immunisation with our antibodies as a real alternative to vaccines against the new coronavirus." Current estimates on how long COVID-19 vaccines may be protective range from 4 to 12 months.

In contrast to polyclonal convalescent patient sera, which have come under critics in the US, because an FDA-EUA (Emergency Use Authorisation) was claimed to be politically motivated instead of being science-based, virus-neutralising mAbs are quality-controlled products of defined composition and do not carry any infection risks.

"SARS-CoV-2 vaccines cannot cure COVID-19. If a COVID-19 vaccination similar to an influenza vaccination would immunise only 60% of people over 60, there would still be more than 20 million deaths worldwide. And that is a conservative estimate," says Yumab founder Stefan Dübel. He criticised that funding almost completely is dedicated to vaccines though mABs show proven safety, can be produced quickly and might even being used for passive immunisation of high-risk groups. German COVID-19 therapeutics developers, cluster managers and industry associations are currently in discussion how to bring the topic on the political agenda as long as Germany holds the EU presidency and wants to demonstrate its actionability to master the corona crises.

Waiting for EU funding

After the German EU Commission president Ursula von der Leyen has started talks on establishing EU production of essential APIs, masks etc, the next logical step must be to avoid dependency from therapeutic antibody supply of US companies under the current restrictive US export regulations. In contrast to Adagio Therapeutics, Yumab spin-out CORAT Therapeutics has closed its seed financing with an amount ten times lower than the US competitor was able to hire.

Impact on service providers

In the US, systematic testing of monoclonal antibodies had been started under the supervision of the BARDA. Under the adaptive trial design ACTIVE, in which other mAbs can be added to the Phase II/III study, Eli Lilly has begun enrolment for safety and efficacy assessment of its COVID-19 antibody LyCoV555.

As similar funding schemes will become available in the European Union, antibody manufacture specialists such as Rentschler Biopharma will be able to expand its portfolio. CROs, which currently recover from delays or stops of clinical studies due to the COVID-related shutdown, have rapidly established remote monitoring or patient stratification that allowed them to hold up their important activities within the crisis. ■

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Advanced Purchase Agreements

APAs are legally binding contracts whereby one party, such as a government, commits to purchasing from a vaccine manufacturer a specific number or percentage of doses of a potential vaccine at a negotiated price if it is developed, licensed, and proceeds to manufacture. These bilateral agreements often secure priority access to vaccine and manufacturing capacity. APAs were used so extensively in 2009 that more than 56% of pandemic influenza vaccine manufacturers surveyed by the World Health Organization were not able to commit to guaranteeing 10% of real-time vaccine production for purchase by UN agencies due to pre-existing commitments under APAs. ■

Picture: CureVac

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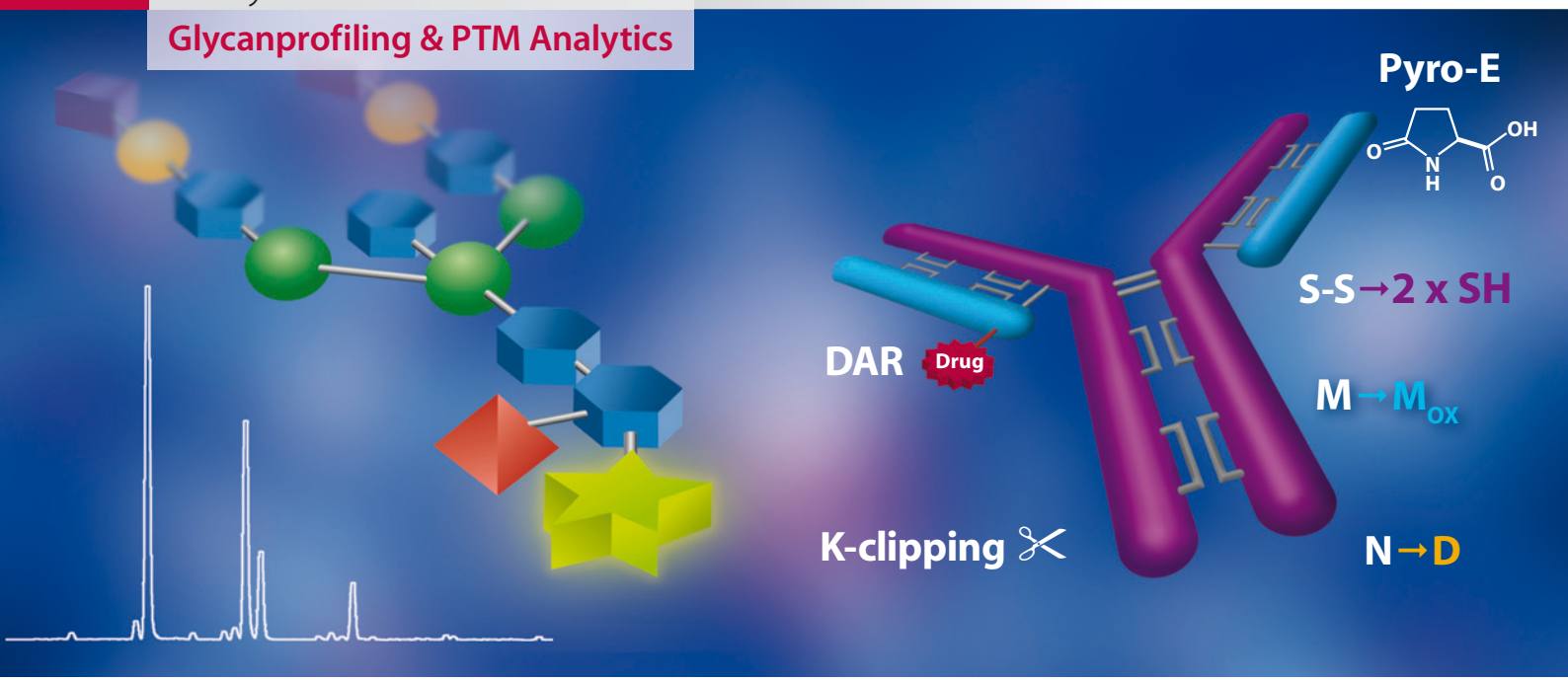

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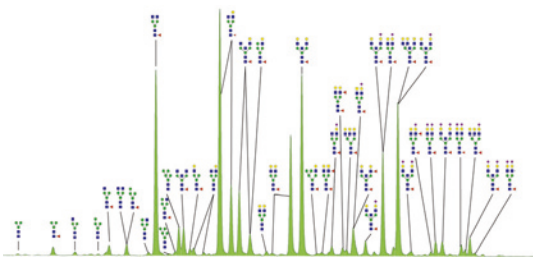

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High need for antiviral mAbs

COVID-19 In September, AstraZeneca announced a stop of its pivotal Phase III study with its COVID-19 vaccine AZD1222 because a volunteer unexpectedly developed spinal cord inflammation. European Biotechnology spoke with Thomas Schirrmann, CEO of YUMAB GmbH, about the prospects of pandemic vaccine development and the prospective alternative approach using passive antibody immunisation against viral antigens – in case that vaccines won't work against SARS-CoV-2.

EuroBiotech_What are the major differences between active and passive COVID-19 vaccination?

Schirrmann_ Vaccines activate the immune system against viral antigens by induction of T-cell responses and virus-neutralising antibodies. This process always needs a minimum of two weeks. That is why, for people, who are already infected, vaccination comes too late. Vaccines need to be given in advance to protect healthy, still not infected people. Unfortunately, the success of vaccination is not very efficient in older people, the largest COVID-19 high-risk group. We know from influenza vaccines that the efficacy ranges between 20% and 60% in this age group leaving many people not sufficiently protected. Recent data demonstrate, that convalescent patients have SARS-CoV-2-neutralising antibodies only for a few months in their blood. Should that be different in case of SARS-CoV-2 vaccines? More recently, reinfections of former COVID-19 patients have been reported, which fueled speculations if vaccines will ever stop this pandemic. Based on this, I would rather expect, that vaccination needs to be refreshed once or several times per year. The situation of antiviral antibody therapy is different, because the active compound immediately blocks the virus, prevents further virus spread and the immune system of the patient gets time to develop immunity – antibodies used either as a therapy or as passive immunisation can save lives. GMP-compliantly manufactured recombinant antibody drugs have the same antiviral effect in every patient, independent of age making clinical outcome and treatment much more predictable from age or other individual factors than – in the current development stage – immune protection by vaccines.

Dr Thomas Schirrmann is the CEO of YUMAB GmbH and CORAT Therapeutics GmbH in Braunschweig, Germany. He is a biochemist by training and completed his PhD in immunology. He worked as a scientist and research group leader for 20 years and published more than 70 scientific articles in the fields of immunology, immunotherapy, and antibody technologies. In 2012/13, he founded YUMAB, which is dedicated to antibody drug development. In May 2020, YUMAB spun out Corat Therapeutics to bring a fast-track COVID-19 antibody program to clinical trials.

EuroBiotech_In the US, there is criticism regarding the approval of plasma use from convalescent patients for the treatment of COVID-19. Rightly so, and if so, why?

Schirrmann_ Blood plasma is derived from different convalescent donors and contains mixtures of undefined antibodies and serum proteins with not well known antiviral activity. Accordingly, neither the clinical efficacy nor adverse effects are predictable, particularly, not all virus-specific antibodies in these mixtures support neutralization, some may even push the infection and inflammation through antibody-directed enhancement. Another important issue is the availability of anti-COVID-19 plasma, which is limited and cannot fulfil the needs of the COVID-19 market.

EuroBiotech_Why do you believe that monoclonal antibodies are the better alternative and should be developed as a priority?

Schirrmann_ Recombinantly produced monoclonal antibodies are produced in a well-defined bioreactor process and have always the same quality and antiviral activity. Therefore, monoclonal antibody therapy is much more reliable in respect of clinical efficacy and safety. The production is endlessly scalable and world-wide antibody production capacities are sufficient to supply the whole COVID-19 market.

Picture: CORAT GmbH

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EuroBiotech_What experience has been gained in regards to safety, the potential to accelerate the speed of development and effectiveness in the target group, e.g. with antigen-induced antibodies produced by vaccines?

Schirrmann_ I do not expect general safety concerns for vaccination nor antibody drugs if the developers do a proper clinical development. Some temporary side effects of vaccines are normal and even a positive sign for a successful immune stimulation. Antibody drugs should not have any significant adverse effects. However, vaccines and drugs against SARS-CoV-2 are needed to be developed much faster than ever before. Vaccines are ahead in the early development, but antibody drugs speed up, when it comes to clinical development, mostly due to the small number of subjects required to observe clinical efficacy. Moreover, vaccines are used to protect healthy people and we need to vaccinate billions world-wide, which is fundamentally different than to treat a few millions of severe COVID-19 patients with an antibody drug. Therefore, rare adverse effects become a significant safety concern for vaccines and need to be carefully tracked in huge clinical studies even after approval. Antibody drug manufacturing is extremely reliable due 30 years of experience, whereas the new COVID-19 vaccines are much more complex in manufacturing (e.g. viral vector-based vaccines) or they are relatively new designs without long-term experience (e.g. RNA-based vaccines). Nevertheless, even under fast track authorisation, vaccines and antibody drugs need to fullfil the highest standards.

EuroBiotech_What can be said about cost-effectiveness and technical reliability?

Schirrmann_ Vaccines are known to be cheap, but this is only true for a single dose. To have a big impact on the pandemic, we need to vaccinate the majority of all people worldwide. Depending on the duration of the immunity, we may have to vaccinate every half a year or year to achieve sufficient protection. This huge number of required vaccine doses explodes the total costs into the range of billions of euros in the EU, probably tens of billions worldwide. The EU already started to reserve hundreds of millions doses of potential future SARS-CoV-2 vaccines without knowing when and if they will be approved. The situation for anti-COVID-19 antibody therapies is the opposite. The single-dose antibody treatment will cost much more. However, we only need to treat some ten thousand severe COVID-19 cases per year in Germany.■

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Target COVID-19 – Antibody Therapy, when it is too late for vaccines.

Picture: shutterstock/alphaspirit

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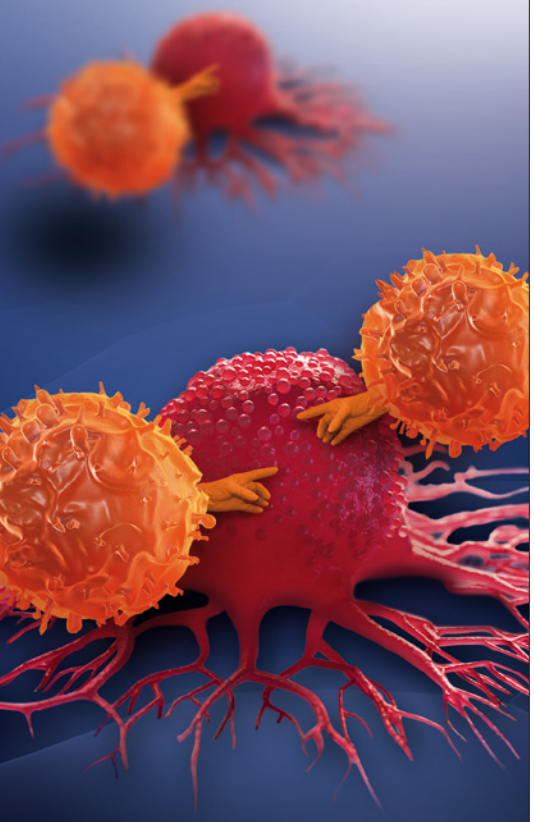

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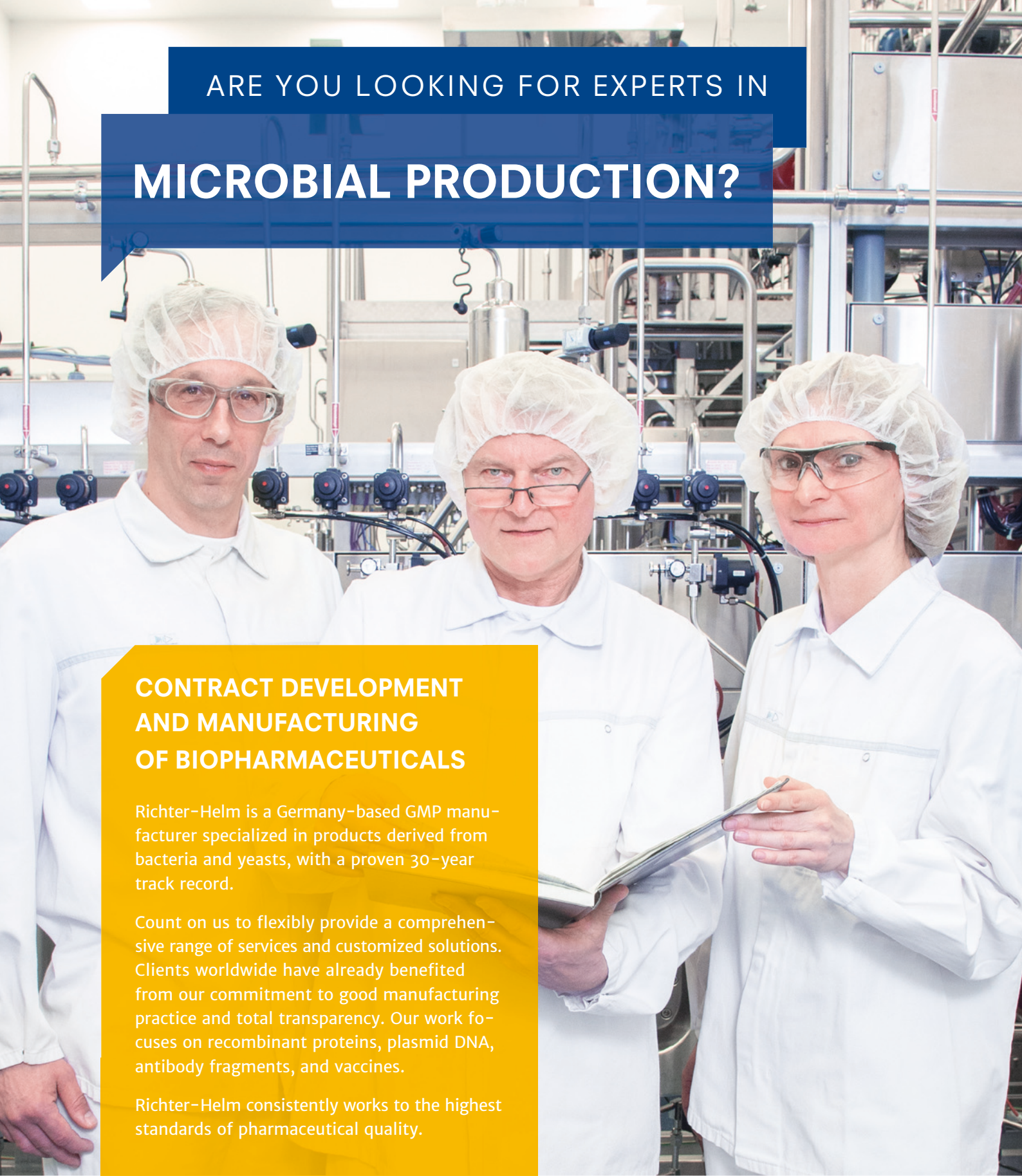

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CDMO Continuous growth and diversification of the biotechnology market for pharmaceutical production have been recorded in the past years. It is expected that both trends, growth and diversification from blockbusters towards niche products, will continue. What requirements are derived from customers' point of view and what are the advantages of Richter-Helm as a successful CDMO to fulfil such needs?

Biotechnology production includes a broad range of various approaches to produce pharmaceuticals. Different sources for products can be used, like mammalian cell culture or microbial fermentation processes in bacteria and yeast. While mammalian products are in large part monoclonal antibodies, microbial-derived products, especially, including a broader variety of product classes: therapeutic proteins, some of them modified, e.g. pegylated, peptides, antibody formats e.g single domain antibodies, bacterial vaccines and plasmid DNA as critical raw material or drug substance compete for production capacities. All of these classes need to be produced to the highest international standards of cGMP. From this long list of product classes, it is obvious that related production is as versatile as the products themselves. In conclusion, flexible manufacturing capacities at different manufacturing scales and highly variable production trains are needed. To cope with such needs a CDMO with a broad technical and scientific expertise, flexibility and highest cGMP standards is required. Richter-Helm offers such flexible services to the highest standards. Richter-Helm process and analytical development is located in Hamburg, Germany. Richter-Helm operates two state-of-the-industry manufacturing facilities in Hannover and Bovenau. At Richter-Helm, new projects can be initiated at various stages, e.g. starting with the gene, strain and process development or via technology transfer in all phases of development or commercial phase. Process development is based on a broad range of experience in microbial fermentation and related purification approaches. Additionally, supportive characterisation studies and models for large scale process validation are executed.

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In conclusion, Richter-Helm is able to help customers to meet their individual demands. Richter-Helm is well known for its unique combination of quality, flexibility and experience (Figure). This triangle in combination together with the excellent manufacturing facilities capacity manifests the current market position.

CONTACT
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BusinessDevelopment@richter-helm-biologics.eu

Picture: Richter-Helm

Brexit: the how of EU clinical trials post 2020

CLINICAL TRAILS With the end of the Brexit transition period on 31 December 2020, the known conditions will change and pharmaceutical companies not prepared will face serious issues and uncertainties. No extension of the transition period has been requested, and according to a joint technical notice by the European Commission, EMA and HMA, no further prolongation beyond 2020 is possible. EU pharmaceutical law will no longer apply for the UK.

› Amina Covic, Head Proposal & Competence Management / Qualified Person, ABF Pharmaceutical Services / Member of GBA Group Pharma

Early this summer the EU Commission and regulatory authorities warned in a technical notice that healthcare companies could meet significant business difficulties when running EU clinical trials through UK-based Qualified Persons (QPs).

As of 1 January 2021, UK-based QPs will no longer be able to certify clinical trial batches for the EU. Pharmaceutical companies are at this time in the last months to establish the required changes to comply with the EU pharmaceutical law. Consequences, such as high economic costs or even trial failure will be unavoidable for unprepared pharmaceutical companies.

The EU notice

The technical notice issued by the European Commission, the European Medicines Agency (EMA) and the Heads of Medicines Agencies (HMA) stated, "Investigational medicinal products used in clinical trials can be imported only after their batch-release has been certified by a qualified person in the EU". Highlighting, "Failure to do so could in the worst-case result in discontinuation of trial and jeopardise trial participants' safety."[1]

The note also stated that as of July, within the last 3 years there were 250 trials registered in the European Clinical Trials database (EudraCT), with UK-established QPs. These trials are authorised in at least one Member State other than the UK.[2]

Clear message is "sponsors of all ongoing trials need to establish a QP in the EU". Further according to Article 19 of Directive 2001/20/EC, "the sponsor of a clinical trial or a legal representative must be established in the EU".

The Solution

GBA Group Pharma is established in EU with GMP manufacturing and testing sites including a central laboratory and offers a one-stop-shop solution for pharmaceutical companies to deal with BREXIT issues. So, how to deal now with the clinical trials in EU from 1 January 2021? The GBA Group Pharma brings solutions for the sponsors and represents the key partner for clinical trial services in compliance with EU pharmaceutical law. The GBA EU QP Team is responsible for the QP certifications. Further IMP services as import, testing, storage & distribution or labelling and packaging services are part of the one-stop-shop solution. Furthermore, in services for authorised medicinal products GBA Group Pharma will be a key partner. ■

[1] Technical notice to sponsors regarding continuous compliance with the EU legislation for clinical trials1 following the withdrawal of the United Kingdom from the EU, Joint technical notice by the European Commission, EMA and HMA from July 2020

[2] As of 1 July, 2020, based on data registered in the European Clinical Trials database (EudraCT)

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