European Biotechnology

Autumn 2021

CROs & CDMOs

+ Pharma Packaging

Special

New formats drive growth

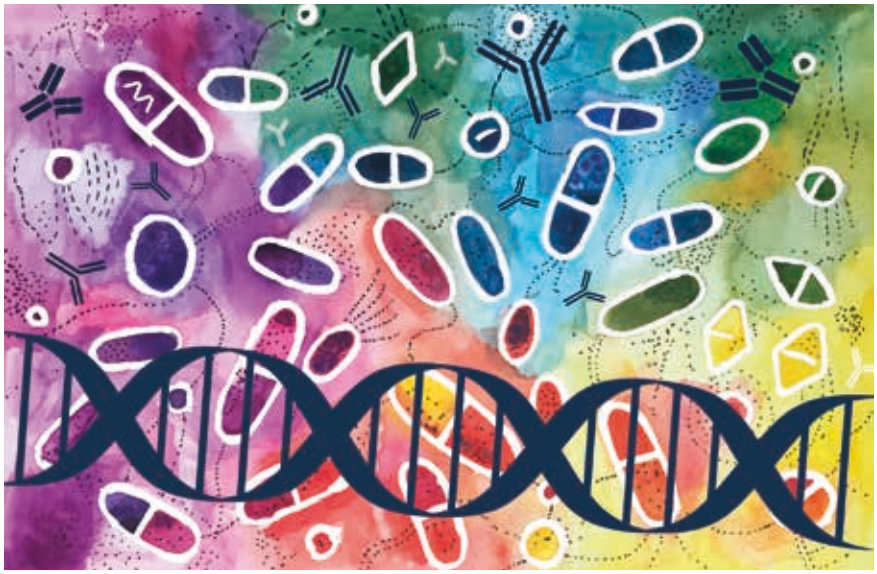
CROs & CDMOs Since the first mRNA vaccine has been approved, there is huge competition in the market to acquire talents and know-how to participate in this market that could grow to 30% of the biopharma market, according to BioNTech's CEO Ugur Sahin. However, other formats are also on.

As more and more policymakers realise the potential of biotech, particularly in medicine, contract research and contract manufacturing organisations (CROS, CMOs) face increasing support from relocation agencies and state funding. Most recently, Germany launched a biomanufacturing initiative called "National Reserve" to prevent shortfalls in raw materials, production capacities vaccine sourcing of essential vaccines and therapeutics including mRNA vaccines or gene therapy. This trend across Europe and Northern America could give an additional boost to the market of outsourced services.

Biomanufacturing hubs

At the live Swiss Biotech Day on 7 September (see page 22), Switzerland formulated its ambition to become a leader in mRNA biomanufacturing. Lonza has "built up the necessary know-how through the partnership with Moderna", explained Lonza Chairman Albert Bähny in Basel. As the US Food and Drug Administration currently reviews its guidelines for the development of AAV-based cell and gene therapies, RNA gene therapies might also play an important role in this emerging market as it doesn't carry the risk of insertional mutagenesis See interview, page 23-25).

According to ex-EFPL head Patrick Aebischer, the advantages such as miscibility of different mRNAs and low production and CAPEX costs are ob-



Picture: iStockphoto/ DrAfter123

vious. "The task now is to establish a production pipeline in Switzerland in which research, public-private partnerships and contract manufacturers producing on a commercial scale work together seamlessly", he said. While he stressed that process development sould be in the hands of academic researchersand professional service companies, he empasized that commercial production should be conducted by Contract Development and Manufacturing companies (CDMOs) Bachem CEO Thomas Meier emphasised that the small-scale approach such as vaccine nationalism observed in the wake of the COVID-19 pandemic must be abandoned in favour of a global orientation and marketing of innovative active ingredient formats, such as peptides. The rapid expansion of Swiss contract manufacturers, such as Lonza, Bachem, Siegfried, Dottikon and Celonic, demonstrate the potential of Switzerland to produce for a global demand. Also, other locations in the Northern hemisphere and Asia are preparing to boost their biomanufacturing capacity, particularly for mRNA vaccines and therapeutics such as si- or miRNAs, gene scissors or antisense medicines.

While antibodies have been a big piece of the current biopharma market, mRNA, gene and cell therapy, transcriptional modulators and engineered peptides and antibody formats with better binding site accessibility and stability have good chances to be included in the policy-driven national sourcing strategies.

Next-gen opportunities

Artificial intelligence-driven virtual drug design might also boost a revival in interest to develop small molecules (see story. p. 36-39). While national sourcing driven by the COVID-19 pandemic might boost the market in the short term, international collaboration and expansion are crucial to growing the activities and sales of CDMOs and CROs.

The consequences of vaccine and drug nationalism in COVID-19 are currently most visible in the care of the global South. Instead of 2 billion vaccine doses, the international vaccination programme Covax will deliver only 1.4 billion doses by the end of the year. The industrialised countries, such as Germany, which have been oversupplied with vaccine for some time, are delivering hundreds of thousands of doses to COVAX. However, the vaccine manufacturers are taking advantage of the high demand to drive up the price of the vaccine in bilateral negotiations - a blinding example for biotech experts of how important international cooperation is. ■

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Different approaches exist to produce biopharmaceutical products, which means different manufacturing strategies can be used, like mammalian cell culture or microbial fermentation of bacteria or yeast.

Microbial manufacturing

Microbial-derived products, made by Richter-Helm, include a variety of product classes including therapeutic proteins and peptides, antibody formats (e.g., VHH), bacterial vaccines, and plasmid DNA (pDNA). pDNA can either be used as drug substance or as specific starting material for mRNA production, virus production or as matrix in cell-free expression systems. Regardless of the type of use all product classes and qualities compete for production in highly complex, multipurpose facilities whose capacities are limited worldwide.

Highly flexible

From the long list of product classes, it is obvious that related production is as versatile as the products themselves. Detailed knowledge of molecules and experience in the production of such is mandatory for each of the classes. Nevertheless, from the technical aspect, manufacturing can be executed in general with the same equipment. A prerequisite for high-class manufacture within short timelines is adequate flexibility of the equipment in line with organizational procedures and the quality system.

Along with the constant growth of Richter-Helm´s business and the expansion of production capacities, both the equipment and the technologies in the areas of development, manufacturing and analytics are constantly being newly established and further developed.

Capacity expansion

Recently, Richter-Helm announced the next important milestone and started the facility expansion of its Bovenau site. By the end of 2023, the expansion will be completed. Richter-Helm´s manufacturing facilities will then provide triplicate capacities within the current range of bioreactor scales, covering fermenter volumes from 10L to 1,500L for cGMP production.

State-of-the-art services

Specific requirements like 100% oxygen aeration technology for high cell density fermentation of Escherichia coli or yeast and methanol feed technology for cultivation of Pichia pastoris as well as highly flexible downstream processing are offered as state-of-the-art CDMO services for all production trains in Bovenau.

Keeping focussed

As a microbial CDMO, Richter-Helm ensures reliable market supply for registered products, including campaign productions with multiple fermentation runs, and sufficient capacities to also further support also new clients with material for clinical studies and development of new products.

Learn more about Richter-Helm´s capabilities and capacities: www.richter-helm.eu and follow us on LinkedIn.

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Let Excelya recruit the right people for the early phase

CRO Early phase clinical trials require expert support, often across many service areas and specialisms. Recruitment for trials can be complicated, with less flexibility and higher costs as you attempt to acquire top talent on a project-only basis. That's why CROs are becoming increasingly indispensable. CROs offer fully formed, multi-skilled teams ready to go, who you can bring on board as and when needed.

› Alan Morgan, CEO Excelya

Clinical trials operational consulting allows you as a drug developer to gain immediate access to a fully-fledged team of individuals who can get stuck into your project. Long gone are the days of spending time and resources recruiting, onboarding, line managing, taking care of project management, and drawing up multiple contracts. Alongside this, there are no long-term commitments since you will have no direct permanent contracts with team members who you only require on a project-by-project basis. By forming one single relationship with Excelya, you can unlock a wealth of scalable resources and exceptional expertise, resulting in faster time-to-market.

Clinical trials consulting is part of the Excelya DNA, having started out in France in 2014 almost exclusively offering this service. Our business offering has evolved greatly over the past seven years, however consulting remains a core pillar of Excelya's business model.

Based on our experience, the best way to guarantee that clinical trials will be delivered on time and on budget is by onboarding the most capable, specialized teams possible, with a work structure that allows us to streamline client needs in a way that is both efficient and cost-effective.

Excelya specialises in early phase consulting for clinical trials. Our services capabilities are extensive, covering data management to safety, project management, medical writing to regulatory affairs, and much more. Our diversity of skills allows us to add real value to clients, with multi-skilled teams and specialists ready to go, with experience running trials of all sizes.

Global capabilies

Our aim is to recruit the right profiles to help developers meet their objectives. Not only do we have an impressive existing network of employees across Europe, but regularly attract high-quality candidates. Our foundations are in Europe, with bases in France, Germany, Belgium, The Netherlands, Greece and beyond, however, our network of partners allows us to offer our clients a fully global reach. After carefully and thoroughly assessing your criteria, we will then propose you a shortlist of candidates who you can choose to interview, assessing their competencies before welcoming them onto your project.

Client-suited talent management is our core product, be it Consulting, Full Service or as a Functional Service Provider. Our people are without doubt our greatest asset, and we have a team dedicated to sourcing, recruiting, and nurturing our talented team members.

We are proud to be the highest quality European CRO, with the most comprehensive service coverage throughout Europe. With a superb, highly qualified, experienced and dedicated team, we are confident that a partnership with Excelya will ensure that your early phase trials go smoothly.

Put your confidence in our 900+ experts and join our list of 500 clients satisfied consulting clients, including 50 Biotech companies based worldwide, by tapping into Excelya's extensive global resources. ■

Pictures: Excelya

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Revolutionary approach for evolutionary research

CROs James Brook, a UK-based senior leader with 25+ years of experience in healthcare and clinical research, joined Tigermed in June 2021 as Head of Europe, Africa and Middle-East to lead and build capabilities in these regions. We recently caught up with James to talk for his attraction to clinical research, and his plan for this new role.

› James Brook – Head of Europe, Africa and Middle-East, Tigermed

The most important lesson learnt from previous experience is consistency of delivery through transparent engaged conversations with our clients, especially in contract research. Research is consistently challenging, the last 18 months and COVID-19 is proof of that, but through open conversations, guiding through expertise, we will grow confidence in our client relationships. Most organisations see one light, provide one solution. Tigermed sees many different rays, many different solutions to discuss and work with our clients to meet their needs.

The long-term pandemic impact

In Europe, countries responded to the pandemic based on their financial capacity and health system capability. This meant variability in clinical research response to COVID-19 and support for non-COVID-19 studies. As Europe slowly emerges as the vaccines are rolled out, the legacy to both our health services and research studies is emerging.

Moving forward, COVID-19 will be seen as transformational in the way we deliver clinical research. We might see a significantly greater willingness of the regulatory authorities to both license earlier and ask for RWE studies to support results, thus accelerating drug development.

James Brook - Head of Europe, Africa and Middle-East, Tigermed

Breaking with traditions

Research, in fact, medicine, was incredibly traditional in its approach. Relationships built over decades often end despite the performance of CROs for Pharma – a 'better the devil you know' approach that still surprises when we get the same results though wish for something different!

To enter this world stage, Tigermed creates differentiated service offerings and progressively builds confidence with our clients on what we can deliver on our promises. So, whenever our clients are evolutionary in their development, we can be revolutionary in our approach. We show them distinctive ways and tailored solutions to meet their requirements – in partnership not 'in hope'.

Tailoring to global Needs

As a contract research organization, the first question we need to understand is, what is the client's top priority? Timing, quality, cost, often all of them. The tailored solution is listening to our clients, ascertaining that need, advising the client, and providing solutions that we jointly agree can be delivered in the time we promise. This approach isn't new, it's not groundbreaking; the difference, at Tigermed, is lived, not just stated.

Expansion to EU, Africa and more

We think about solutions globally rather than regionally because research is global. At all times, Tigermed acts as a global 'trusted partner'. We established a delivery mechanism to support our global vision and seamlessly integrated that into our solutions. As a result, we can deliver clinical research in Europe and beyond and hope to make Chinese companies see Europe and Africa as their next destination of choice, not as Europe but as an extension of what Tigermed can do for them. Truly One global Tigermed, one global standard of delivery. ■

Picture: Tigermed

Assay Development
- Development of molecular biology assays from target (e.g. companion animal diagnostics, IVD, GMO, mRNA vaccines, etc.)
- Validaton of molecular biology assays according to ICH guidelines
- Cross-validation against a reference method

Biologics Testing
- Contamination and impurity testing
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Analytical demand of CRISPR gene therapies

GENE EDITING CRISPR-Cas9 gene editing offers substantial improvements over previous gene editing technologies in terms of ease of use, speed, efficacy, and cost. Not surprisingly, CRISPR-Cas9 editing has taken biomedical science by storm. While the technology is relatively simple in handling at the level of basic research, the use of CRISPR genome editing in therapeutical applications poses a bunch of analytical challenges.

› Dr Christoph Grünig, Head of Contract Research, Microsynth AG

The first CRISPR-Cas9 based therapeutics are now in Phase I/II clinical trials, such as the treatment of sickle cell disease developed by CRISPR Therapeutics and Vertex. Regulations and guidelines valid for cell and gene therapies also apply for CRISPR-mediated therapies (i.e. Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs): Guidance to Industry) published by FDA.

The aim of these regulations is to define the correct characterisation of the drug substance / drug product (DS/DP) to ensure product quality and safety. In the case of CRISPR-Cas9-based therapeutics, the questions to address include but are not limited to:

- (i) on-target editing frequencies,
- (ii) off-target editing frequencies,
- (iii) expression level of transgenes,
- (iv) quantification of putative translocation.

Besides the characterisation of the DS/DP, critical reagents and raw material used in the manufacturing must be quality-controlled. In the CRISPR setting, for example, identity testing of the synthesized single guide RNA sequences is required. Other tools used for the gene editing such as vectors and/or plasmids must also be tested. Each analytical procedure (AP) will follow a life cycle starting with the development phase that might also include some exploratory analysis, such as the identification of putative off-target loci. The development phase is followed by the qualification and finally by the validation of the analytical procedure before entering the routine testing.

Validation of analytical procedure

The aim of the validation is to demonstrate that the AP is suitable for

its intended use. It is critical that the validation complies with the relevant guidelines (i.e. ICH guideline: Validation of analytical procedures: Text and Methodology Q2(R1). The guidelines define different assay classes: for example (1) identity assays that allow unequivocal identification of a component(s), or (2) quantitative assays suited to describe the editing rates (on target edits/off-target edits but also translocations). Thus, depending on the specific task, the validation of an AP may significantly differ and require more or less effort.

Team meeting at Microsynth AG

A close interaction with the sponsor is needed to understand the scope of the analytical procedure and to define its intended use jointly with the sponsor.

Challenges in the validation

Besides general characteristics, it is also important to already know the (product) specification for the analysis, which will help to find the best analysis strategy. A challenge in the validation of CRISPR-Cas therapies is that control material for the validation must be produced and qualified and no certified reference standard (i.e. USP compendial standards) or commercially supplied reference standards are available.

Moreover, the same analytical procedure to be validated is also used to qualify the reference material – orthologous methods to establish the "accepted true value" are usually not available. This may be problematic for addressing the accuracy parameter as the "accepted true value" is already an estimate and can be a source of variation.

Microsynth expertise

Microsynth was involved in several programs for CRISPR-Cas9-related cell therapies and gained key expertise in the development and qualification/validation of different analytical procedures over the last years including routine testing of clinical test items. To request more information, contact us at *info@microsynth.ch*. ■

Picture: Microsynth

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& OCT DACH booth number 33

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