European Biotechnology

Autumn 2018

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Vertical integration: time is money

BIO-PHARMA OURSOURCING Financial pressure on Big Pharma and biotechs increases the need for drug developers to outsource their development and manufacturing capabilities. The CDMO and CRO sector, which is further consolidating through M&A, looks well set for continued growth. As developers have to balance the need to reduce their development risk with time to market or – for biotechs – time to next financing, contract manufacturing and contract research companies clearly favour offering fully integrated services.

The best example to illustrate Big Pharma's risk aversion, even in possibly highly lucrative future markets, is Sanofi's recent outsourcing of its anti-infectives R&D to drug discovery service firm Evotec: Under the licence option deal, the French pharma major transfered more than 10 early-stage antimicrobial development programmes, plus its anti-infectives research unit in Lyon to Evotec while retaining option rights for development and commercialisation. The highly profitable CRO received €60m upfront plus long-term R&D funding and sales royalties for development of the assets. Evotec's CDO Enno Spillner told EUROPEAN BIOTECHNOLOGY that Evotec sees big expansion potential in the €130bn drug development R&D market, in which drug developers currently outsource just 10%–30% of their early and preclinical work, but about 40% of clinical development (see Figure 2).

Find the right expert

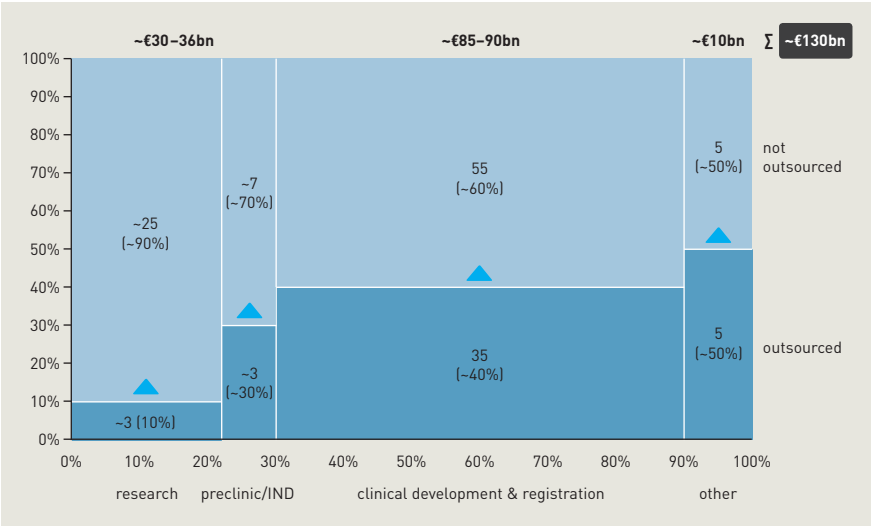
In the fragmented US$62bn+ CDMO market, the ten largest players currently control less than 30% of the revenues, according to a EY report published last September. As the CDMO industry's annual growth rate of 6% to 7% is slightly outpacing the growth of the pharmaceutical sector (5% to 6% CAGR), the consultancy sees a lot of space for outsourcing and consolidation. EY point to 2017 mergers, such as the US$7.2bn deal of Patheon/ThermoFisher or the US$5.5bn acquisition of Capsugel by Lonza, both aimed at creating full-service providers.

As manufacturing of new drug formats such as fusion proteins, gene or cell therapies such as CAR-Ts, modified or multispecific antibodies is becoming highly complex, specialised CDMOs are predestined to become preferred future targets for the handful of integrat-

	Drug discovery	Development	API production	Formulation	Packaging
Service offering focus	Target identification	Drug development	Extraction	Solids	Primary packaging
	Lead discovery	Sourcing	Synthesis	Semi-solid	Secondary packaging
	Medical chemistry	Cell line development	Fermentation: small molecules	Non-sterile liquids	Tertiary packaging
	Preclinical studies: in vitro	Scale up	Fermentation: large molecules	Sterile liquids	
	Preclinical studies: in vivo	Tech transfer	Other methods	Other finished dosage forms (FDF)	
	Formulation development	Process analytics development			
Scale	Small-scale	Small-scale production (preclinical Phase II)			
		Large-scale production (Phase III, commercial)			

Picture: EY (9/2017)

Overview of the value chain for bio-pharma outsourcing



Visiongain's analysis of the accessible R&D outsourcing market.

ed providers. Medium-sized biologics CDMOs have also made significant investments to become one-stop-shops.

With the establishment of FDA Breakthrough and EMA PRIME status, speed from clinic to market has become even more significant in the commercialisation of biopharmaceuticals. For biotechs, the speed at which a CDMO can achieve milestones is crucial because short development times allow them to achieve next-stage funding.

In a way this market pressure is compensated by growing demands for more capacity: scale of production is expected to expand due to longer life expectancy, even in emerging parts of the world, and expansion of drug development markets beyond the US and the EU.

Niche for CAR-T cell- and gene therapy specialists

Currently, one of the most targeted fields of expertise is the lucrative field of cancer immunotherapies and gene therapies, with annual cost of treatments of up to US$400,000 per patient. In the highly lucrative field of cancer immune therapies with genetically engineered T-cell receptors (i.e. CAR–T cells), the complex and costly process of production of autologous CAR-T cells is a major roadblock, according to MediGene's CFO Thomas Taapken. Everyone in the market thus tries to find ways to reduce cost by trying to establish allogeneic CAR-Ts. According to Taapken, however, "this may take some time." Furthermore, the currently used lentiviral gene vectors often integrate into highly expressed coding regions of the T cell genome boosting the risk for cancer. However, tech providers are already working for a solution.

The second field of particular interest for M&A, but also for niche player expertise, is gene therapy as shown by the recent Shire-Servier deal (see European Biotechnology, Summer Edition 2018). The dynamic is also demonstrated by the fact that 50% of the eight currently approved gene therapies – Imlygiuc (Amgen), Strimvelis (GlaxoSmithKlaine) Invossa (TissueGene/Kolon Life Sciences/Mitsubishi Tanabe), and Luxturma (Spark Therapeutics) – have been authorised in the past two-and-a-half years. And more than 350 gene therapies are under preclinical and clinical development – the majority of them gene replacement approaches (59%); 10% onkolytic therapies; and 20% cell-based immune therapies. With the first generation of products on the market to guide the way, and supportive regulatory partners, the time is right for new chapters on cell and gene therapy. ■

t.gabrielczyk@biocom.eu

Source: Visiongain

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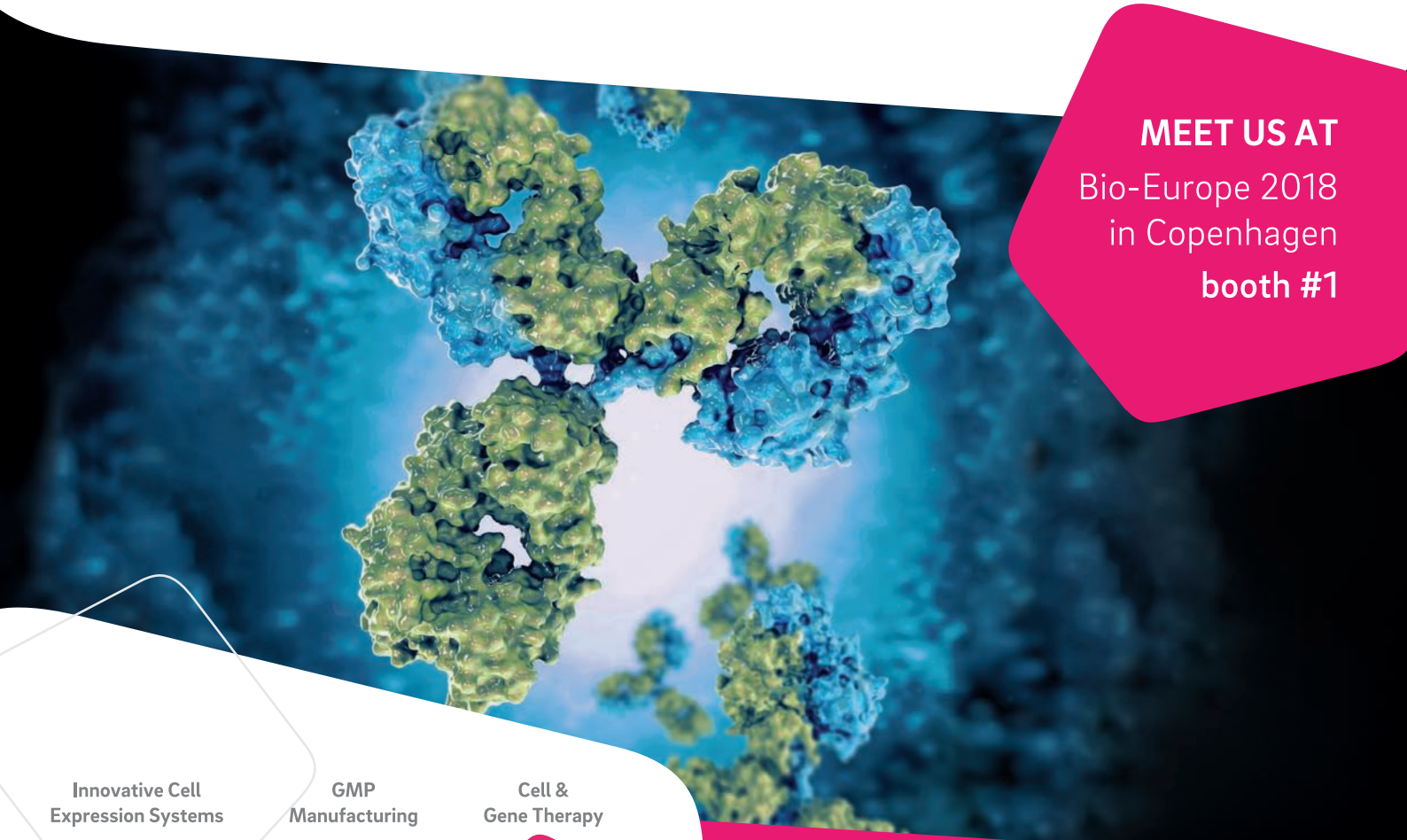

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"Formulation matters"

RENTSCHLER BIOPHARMA/LEUKOCARE Back in February 2017, CDMO Rentschler Biopharma SE and formulation specialist Leukocare AG joined forces to give biologics and biosimilar makers a competitive edge through significantly stabilised end products. European Biotechnology spoke with Leukocare's CEO Michael Scholl about the impact of formulation on drug product performance.

EuroBiotech_ When Rentschler Biopharma joined Leukocare as exclusive partner back in February 2017, you and Rentschler Biopharma's CEO Frank Mathias said you hope to elevate the role of formulation strategy on the biopharmaceutical industry's agenda. Why?

Scholl_ We both figured out that formulation or, spoken more generally, drug product development, is underestimated in the schedule of biopharma development. Frank and I concluded that by elevating the awareness about the impact formulation has on the features of therapeutic proteins, we could provide a competitive advantage to Rentschler Biopharma's clients. Therefore, Rentschler Biopharma and Leukocare commissioned a just recently finished industry survey with the goal to gain strategic insights on the importance, expectations, common challenges and future directions of drug product formulation. Results will be published shortly.

EuroBiotech_ The industry has had a lot of discussion on, for example, protein aggregation or impurities associated with single-use equipment – so why is the topic still under the radar?

Scholl_ We can already see a change of attitude in the industry. But it's still in its beginning. Rentschler Biopharma and Leukocare thus see themselves at the forefront of drug optimisation through advanced formulation technologies.

EuroBiotech_ Could you please outline how Leukocare's SPS® (Stabilizing and Protecting Solutions) formulation technology works and how it differentiates from the platforms of competitors?

Scholl_ Basically, the SPS® technology platform consists of two major elements: an excipient library and the way we combine five to eight of these excipients to improve the quality of a biological product. We have approximately 100 well-characterised excipients in our library, which we specifically combine towards the degradation pathways, hot spots, and the product needs of our customers. We only use well-established and -approved excipients in order to prevent regulatory complexity. For identification of the optimal combination of excipients for a certain drug, we have a rational algorithm-supported development approach, which starts with a basic characterisation of the molecule and then reduces the design space by using deep learning algorithms before going into the lab. We are currently in the process of strengthening the use of artificial intelligence for automatic preselection of the optimal formulation components. As this approach currently is unique in the industry, it is a differentiator per se.

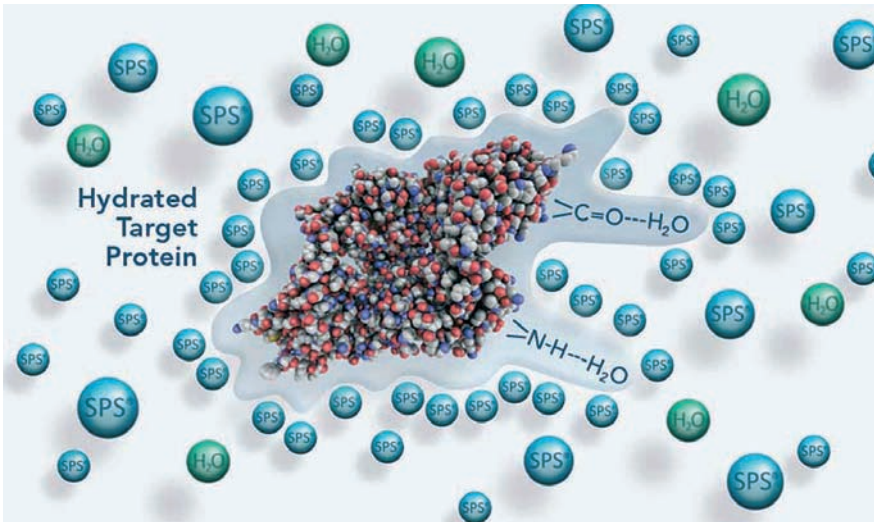
MICHAEL SCHOLL
is the Chief Executive Officer of Leukocare AG (Martinsried), where he heads the division's strategy, finance, corporate law, marketing and sales, and human resources. Before co-founding Leukocare in 2003 with Prof. Dr. Martin Scholz, the business engineer worked as a business consultant at Boston Consulting Group and led the foundation and business development of a range of technology and IT companies.

EuroBiotech_How can your technology help biologics and biosimilar developers to get an edge over their competitors?

Scholl_ There are multiple aspects. First, by increasing thermal stability of protein therapeutics, our technology prevents degradation and allows for room temperature storage in many cases, which is also very relevant for vaccines. Second, many biopharmaceuticals today have to be lyophylised for stability reasons. We can transfer lyophilised to liquid formulations, which reduces manufacturing costs, adds convenience in administration, and comes without any loss of drug

Picture: Leukocare AG

activity. We recently announced a collaboration with the Danish peptide anti-infectives developer Xellia, who will switch its lyophilised anti-infectives to liquid products using the SPS® platform. Third, our technology allows for subcutaneous, instead of intravenous formulations, which are mainly restricted by protein aggregation that occurs at high protein concentrations. Fourth, formulation can increase time-to market for biosimilar manufacturers such as Leukocare's partner Laboratorios Liomont. By providing freedom to operate towards originator formulation patents, their biosimilar candidate can reach the market two to three years earlier. Both examples – the case of Xellia and of Laboratorios Liomont – illustrate how advanced formulation technology can create competetive advantages.



Leukocare's SPS® technology helps stabilise proteins in liquid formulations. Water-protein interactions are stronger than SPS®excipient-protein interactions, resulting in a stabilised hydration of the protein. The hydration shell prevents interaction with co-solvents, resulting in lower free energy and thus increased protein stability.

Picture: Leukocare AG

EuroBiotech_Where do you see the strategic fit of the partnership with Rentschler Biopharma?

Scholl_ The partnership with Rentschler Biopharma allows us to integrate formulation into the broad range of CMC and CDMO offerings Rentschler Biopharma has to make, providing clients a three to six months acceleration in time-to-clinic and time-to-market and appropriate cost savings. As Leukocare, we benefit from the strong market position of Rentschler Biopharma. The alliance allows us to reposition formulation as a key success factor in biopharmaceutical development.

EuroBiotech_How was the feedback from the sector in the 18 months since the deal has been announced?

Scholl_ Of course, I cannot disclose exact figures but Leukocare and Rentschler Biopharma have started several new fully integrated projects, particularly with new clients from the US.

EuroBiotech_What are your next goals?

Scholl_ As the collaboration now is up and running, next we would like to learn more about the formulation needs of potential clients. Formulation is currently still an undeveloped market with some small players around. Our alliance, for the first time, has created some momentum to raise the awareness of formulation development in the drug product development. ■

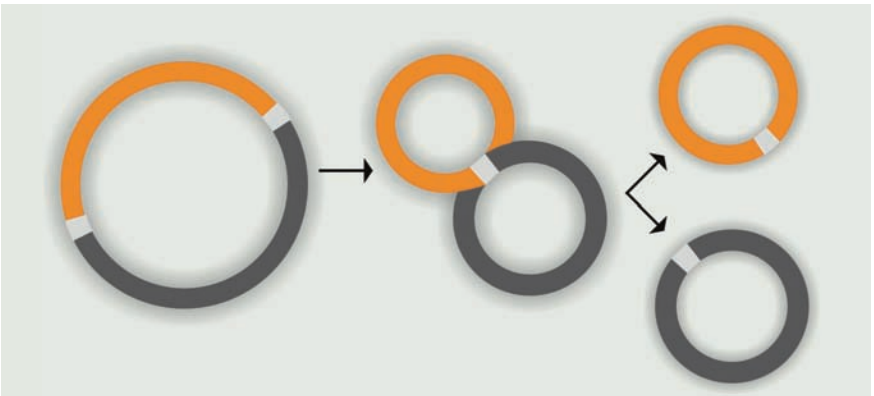
t.gabrielczyk@biocom.eu

Providing future markets with robust technologies

CAR-T- & GENE THERAPY Recent approvals in gene therapies and CAR-T-cell therapies have triggered a flood of clinical and translational R&D projects both in industry and in academia. Over the past five years, US$9.5bn have been invested globally into gene therapy R&D. For the developers of future therapies, one important question is how to overcome limitations and intrinsic safety risks of viral vectors used to express chimeric antigen receptors in T cells or to transfer therapeutic genes into target cells.

› Dr. Martin Schleef, PlasmidFactory GmbH & Co., Bielefeld, Germany

With 354 CAR-T cell therapies currently under development – 76% thereof in preclinical stage – and about 300 gene therapy projects, both fields are just emerging. Last year, the boom culminated in the FDA market approval of the CAR-T therapies Kymriah (Novartis) and Yescarta (Gilead Science) and Spark's first gene therapy for retinal dystrophy. Many companies and research groups are now jumping on the bandwagon. Since 2016, the quantity of ordered plasmids needed to engineer lentiviral and AAV vectors – the current gold-standards for CAR-T and gene therapies, respectively – has increased 5 to 10-fold. PlasmidFactory had to expand its production capacities in April to keep pace with the demand.



PlasmidFactory's minicircle technology offers efficient transfer of target genes.

Economies of scale in gene therapy

Most industry offers currently involve use of PlasmidFactory's plasmids for the GMP production of AAV vectors for gene therapy. The reason is that PlasmidFactory has exclusively licenced the global rights on a technology from German Cancer Centre that makes it possible to transfect AAV vectors with only two plasmids instead of three – which results in a 30% reduction in costs-of-goods. The technology allows for placing all genes required for virus particle packaging and propagation into one plasmid instead of using a separate helper plasmid and plasmid vector for the viral packaging genes besides the transfer plasmid for the therapeutic gene. Futhermore, using only two plasmids is more productive. Only a mixture of two vectors must be optimised to achieve the highest possible yield.

Eliminating safety risks from CAR-T vectors

In the CAR-T-cell therapy field, PlasmidFactory is currently expanding its research to eliminate safety risks attached to the frequently used lentiviral vectors. Industry is actively testing PlasmidFactory's minicircle-based non-viral vectors for CAR gene delivery after researchers at Würzburg University and at the German regulatory authority PEI together with PlasmidFactory demonstrated that sleeping-beauty transposition of PlasmidFactory's proprietary minicircle DNA in mice offers advantages over lentiviral gene transfer. The problem with lentiviral vectors is that they preferentially integrate CAR genes into highly expressed genes of T cells, a known risk factor for insertional mutagenesis. In contrast, the combination of the sleeping-beauty transposition and minicircle DNA integrates almost randomly into the T cell genome, it's less immungenic, cheaper, and easier to handle than lentiviral vectors. PlasmidFactory is working to offer the materials in a quality that can be used in clinical studies by Q4/2018. The technology is not only suitable for CAR-Ts but also for vaccines. ■

Pictures: PlasmidFactory

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› Sebastian Lambert, Senior Scientist, Celonic AG, Switzerland

The CHOvolution™ platform is based on a CHO-K1 host cell line and its proprietary SEFEX (SErum Free EXpression) technology platform to provide the best screening and selection processes. CHOvolution™ is adapted for creating robust and stable cell lines that express biologics in serum and protein-free suspension culture and commercially available media. This feature ensures regulatory compliance in numerous customer projects entering clinical development phases.

Reducing time to clinic with CHOvolution™

Bringing a drug from discovery to the marketplace remains a costly, complex, and time-consuming process, especially in high-stakes races such as to be first-to-market. Celonic recognises this and appreciates that improvements to major bottlenecks and reductions in timelines add up. For any drug developer or service provider, cell line development is one of the most challenging phases, especially when subsequent GMP compliance is required.

To enable the same excellent results within shortened timelines, Celonic invested in state-of-the-art technologies and optimised project workflows to create high-producing cell lines (Fig. 1). Successful implementation of technologies such as FACSAria® Fusion cytometer and cell printing have facilitated fast track workflow options for high priority projects, bringing the entire timeline from biological sequence to GMP-compliant material from 18 months down to approximately 14 months.

Figure 1: Celonic project cell line development timelines.

Scalable high-titer production of therapeutic proteins

At Celonic, CHOvolution™ forms the workhorse for mAb production and demonstrates high titers (up to 8 g/L) with the median productivity of a CHOvolution™ cell line in the 2–4 g/L range (Fig. 2).

One of the most important characteristic of any cell line is its scalability. Effects such as increased generation cycles and the subtle differences in the upscaling of processes can often accumulate and sometimes result in dramatic losses in productivity. CHOvolution™ cell lines, tested up to 100 generation cycles, retain their ge-

Pictures: Celonic

netic stability, which allows the cells used for development to be used in commercial manufacturing. Combining this stability and in-house expertise results in processes with CHOvolution™ being predictably scalable and displaying almost identical behaviors from the shake flask to 1,000 L bioreactor scales (Fig. 3).

This combination of a fully scalable cell line with high titers that can be developed in a competitive time-frame makes CHOvolution™ a powerful tool in the drug developer's arsenal.

CHOvolution™ licensing

Since July 2015, Celonic has been licensing its CHOvolution platform to drug developers and to other service providers. The license package includes the host cells, vector set, and detailed protocols for the handling, screening, and selection processes necessary to generate high-performing production cell lines. The license is royalty-free and with a guarantee to licensees: we will take over the developed cell line from our licensees and upgrade it to a GMP compliant Master Cell Bank.

The CHOvolution™ is a proven production cell line technology for:

- antibodies of different isotypes (e.g. IgG1, IgG2, IgG4);
- bispecific and single-chain antibodies;
- enzymes, growth factors, and hormones.

Key features include:

- cell line adapted to serum-free EMA and FDA-compliant media;
- high productivity (up to 8 g/L for mABs);
- high scale-up stability (over the 120 generation cycles and easily scalable from shake flask to 1000L volume);
- GMP-compliant, from R&D to market manufacturing;
- tailored workshops and hands-on training to develop the product;
- technical and scientific support on the CHOvolution™ platform.

Pictures: Celonic

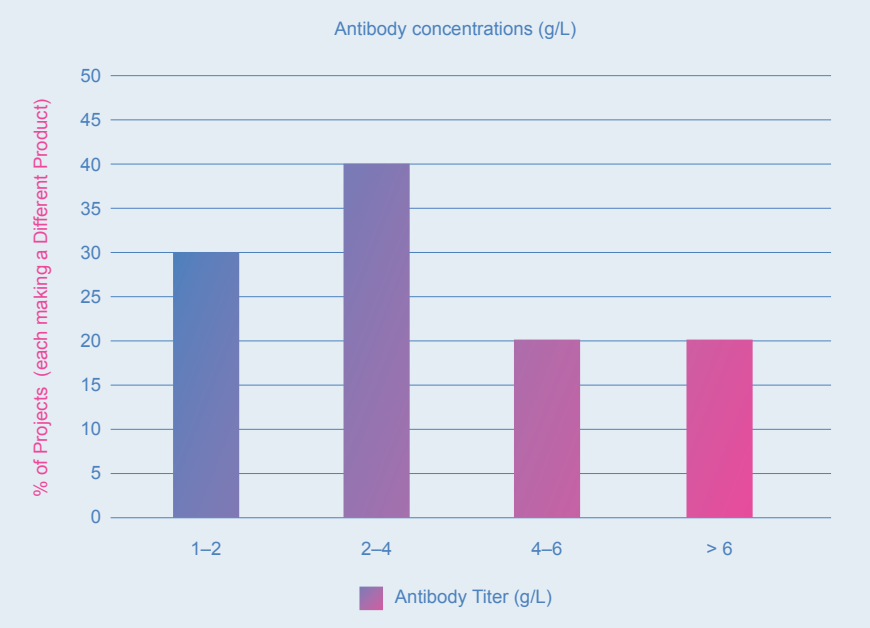

Figure 2: High productivity of Celonic antibody projects.

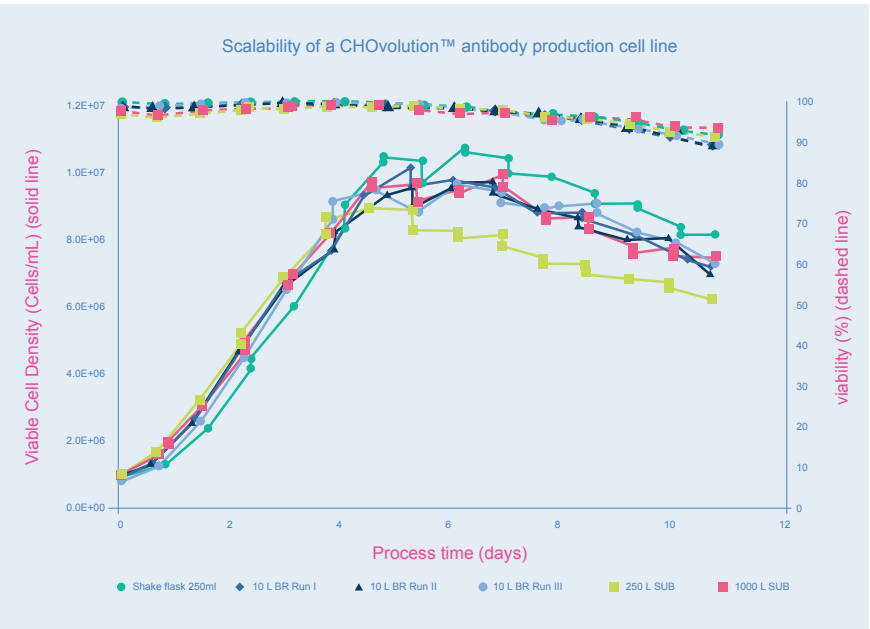

Figure 3: Scalability of Celonic's antibody production cell line. Solid lines show Viable Cell Density. Dashed lines show viability. 10 L BR = 10 L stainless steel bioreactor; 250 L SUB = 250 L single-use bioreactor; 1000 L SUB = 1000 L single-use bioreactor.

Celonic is a privately owned CDMO based in Basel, Switzerland. The company provides a range of services from cell line engineering and process development to cGMP manufacturing for new biological entities (NBEs) and biosimiliars worldwide. Celonic's ethos focuses on applying empathy, efficiency, and excellence in all business aspects to ensure its clients attain their goals more efficiently and reliably. ■

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Innovative delivery: dual-chamber systems

LYOPHILISATION As the global demand for injectables grows, so does the demand for innovative delivery systems. For lyophilised forms, dual-chamber systems offer advantages. They have been on the market since the mid-1980s, mainly for emergency or chronic medication. The systems have been developed for the convenience of the patients/caregivers, but they also offer benefits for the pharma/biotech companies in regards to low residual volume and increased API yield.

› Joerg Zimmermann, Vice President Development Service, Vetter Pharma-Fertigung GmbH & Co. KG

When considering lyophilisation in a dual-chamber system, it is important to understand the development process. A five-step approach can help determine whether it is a viable option for an injectable drug.

Step-by-step approach

The first step is to determine compatibility utilising a series of lyophilisation cycle feasibility studies. Trials based on existing vial lyophilisation development are performed, as are concentration/ fill volume studies and cycle options to test the product viability. The drying process is governed primarily by convection and radiation rather than direct heat conduction and needs to be adjusted accordingly.

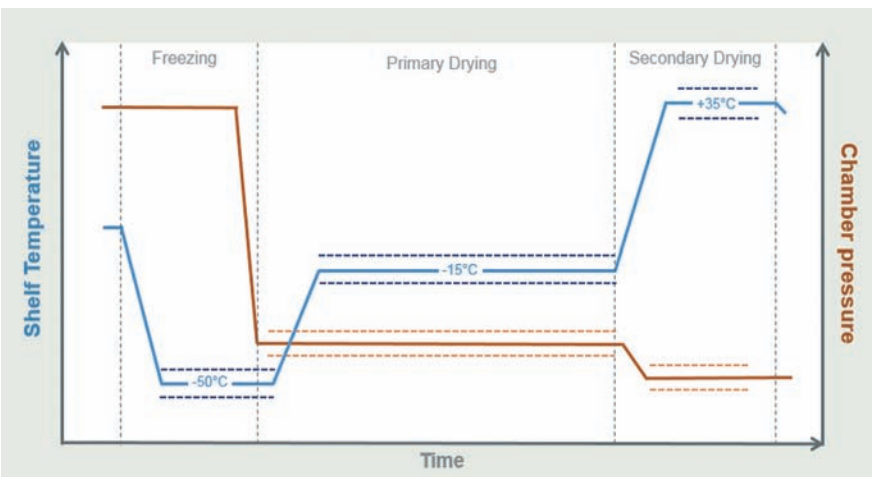
The second step focusses on process characterisation studies. An assessment of the current process and a variety of compounding, filtration, and pumping tests provide guidance for further studies required for the development in a dual-chamber system to identify suitable settings for accurate dosing.

The third step includes design of experiment (DoE) cycle development and robustness. This is carried out with varying temperature and pressure combinations to test the design space limits (edge of failure) for both primary and secondary drying. Visual appearance of the lyo-cake, reconstitution times and residual moisture, and further critical quality attributes such as potency, stability, and sterility are analysed.

The fourth step involves siliconisation and functionality testing. While necessary as a lubricant, silicone oil must be kept to a minimum and evenly distributed to maintain acceptable break-loose and glide forces. Closure integrity and stability tests are also performed with methods like dye-ingress or vacuum decay testing.

The fifth step entails engineering runs to ensure scalability. The first stage is a non-GMP commercial scale-up testing general feasibility. It also includes temperature mapping and sample analyses. The second stage concentrates on lyophilisation-cycle adaptation and testing. Trials with a variety of concentrations are performed under "seeded run conditions." This allows for a minimisation of used drug substance while still obtaining a good indication of the performance. Finally, process qualification based on the results from development is performed.

In summation, dual-chamber systems offer an innovative delivery option for lyophilised drugs and can also extend the shelf-life of complex compounds. Taking the right approach is essential to determine if such a system is suitable for your compound. ■



Simplified presentation of freeze-drying cycle development including the boundaries of DoE.

Pictures: Vetter Pharma-Fertigung GmbH & Co. K

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Data Managers are worth their weight in gold

CONTRACT RESEARCH Across industries, end-to-end digitalisation is creating one of the biggest value chain transformations in history. However, adopting corporate strategies to sustain the implementation of often disruptive technology remains a challenge. For most of us, it involves significant investment of time and resources and re-thinking payment and pricing models.

› Dr. Raphaela Schnurbus, Clinical Solutions and BD Director in OPIS S.R.L

In the life science industry, digital health solutions aim to offer opportunities for seamless data sharing and highly personalised care. Drug development increasingly relies on highly sophisticated data platforms and clinical trials are asking for complex study databases, risk based monitoring, and adequate processes to ensure data integrity, data encryption, and real-time data availability as standard practices.

Data: the common denominator

It is clear that data and data analytics have become core capabilities that drive business decisions, quality and risk management processes and product/service development. Genomic data and technologies such as voice data entry, eCOA (Electronic Clinical Outcome Assessment), and Real World Evidence (RWE) generate huge and often very different types of data to integrate and analyse. Overall, the industry relies on data: existing data, new data, personal data, unstructured-data-turned into-structured-data, data in real-time, and data available anywhere. As a result, the days of thinking about data management as "boring data entry and cleaning" are gone forever.

Data scientists are needed in the place of data managers. Theys are expected to have programming skills and a good deal of statistical skills as well. To manage information effectively in an increasingly inter-connected digital environment, data handling teams of statisticians, data managers, and system developers collaborate closer than ever with scientists and the healthcare industry alike.

Data standardisation and sharing

An emerging trend to create models that allow diverse stakeholders to benefit from shared initiatives is making companies think about forming valuable partnerships with platform owners or investing in developing data sharing platforms. However, it is quite evident that for such models to work and contribute toward establishing opportunities where patients benefit the most, agreement on standardization of data is urgently needed. Hopefully, all stakeholders involved in research, treatment, and management of diseases will opt for solutions where an interface with other solutions and/or models become possible.

Strategic re-think

To conclude, digitalisation is here to stay, but how much future value we are going to capture will depend on how skilfully we implement solutions that unlock the power of data. We rely on infrastructures that can help predict things and we insist on data models that feed systems with structured and extractable data. We are talking about machine learning and artificial intelligence but without clever people able to create the right concepts in the right and appropriate contexts, we are not going to benefit to the full. Investing in a team of highly skilled data scientists is the best move your company will ever make. ■

Pictures: Opis

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Managing complexity to bring drugs to clinic faster

CDMO Integrating the disparate stages of drug development is the most time and cost-efficient way of turning a promising candidate compound into a pharmaceutical product. A CDMO that offers coordinated end-to-end services simplifies oversight.

› Torkel Gren, Senior Director Scientific & Technology Officer, Recipharm AB

The pharmaceutical contracting sector is thriving, fuelled by ever-growing drug industry demand for outsourced development and manufacturing solutions. The first CDMOs focused on the provision of basic manufacturing services, primarily finished product formulation, fill/finish, and packaging.

Broad expertise

In recent decades, specialist contractors have emerged to cater to the increasing range of work being outsourced. However, while such firms provide the drug industry with access to expertise, managing the efforts of multiple specialist contractors is a challenge that potentially outweighs the benefits of outsourcing in the first place.

Taking outsourcing one step further, Recipharm has added capabilities by acquiring specialists and investing in in-house capabilities to provide our customers with a full range of services. Our approach simplifies and accelerates drug development.

Managing complexity

The development of each drug is different, although there are common stages. All drugs start as compounds that show therapeutic potential in the laboratory which, if they continue to show promise in preclinical studies, are selected for clinical development. The path from laboratory to first-in-human (FIH) studies involves many different steps, each requiring expertise.

For example, producing a drug product for an FIH study requires both formulation expertise and a detailed understanding of the trial protocol. In addition, while drug stability and bioavailability are less critical in FIH studies, knowledge of such characteristics gained during early formulation development can accelerate development of dosage forms used in later phase studies.

It is possible for multiple contractors to support each stage of a drug candidate's journey from laboratory to clinic separately while ensuring materials and data are transferred. However, it is far more cost and time efficient if a contractor with expertise in all stages carries out such projects in a fully integrated manner. Likewise, a full service contractor that can help with each step significantly reduces a customer's oversight burden.

With this in mind, Recipharm's Pathway to Clinic® service provides pharmaceutical industry customers with a comprehensive range of fully integrated development, manufacturing, and clinical trial planning and execution services.

Picture: Recipharm

CDMO success

Integration is core to Recipharm's offering. From our early development through clinical and commercial manufacturing, including serialisation, we focus on providing co-ordinated expertise that reduces complexity for our customers and gets high quality products to market faster and more efficiently. ■

Cancer: The long-term downsides of checkpoint inhibition

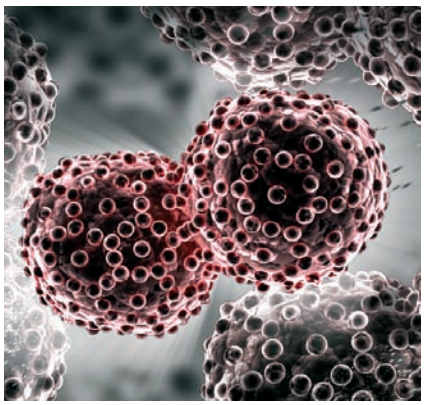
CANCER Contract Research Organisations (CROs) that conduct clinical trials with PD1-PDL1 checkpoint inhibitors must consider new safety problems associated with the overhyped drug class. A retrospective study on 377 patients with advanced non small cell lung cancer (NSCLC) who received PD-1 blockers as second-line therapy indicates that therapy outcomes are worse than those observed with classical chemotherapeutics (JAMA Oncology, doi: 10.1001/jamaoncol.2018.3676).

After median follow-up of 12 months, 13.8% of patients had hyperproliferative disease (HPD), which is characterised by accelerated tumour proliferation, tumour outgrowth, and worse prognosis.

Picture: Fotolia.com/rajcreationzs

Patients experiencing HPD within the first six weeks of PD-1/PD-L1 inhibitor treatment had significantly lower OS (3.4 months) vs patients with progressive disease (OS 6.2 months). In contrast, only 3 in 59 patients receiving chemotherapy (5.1%) developed HPD.

"Our study suggests that HPD is more common with PD-1/PD-L1 inhibitors compared with chemotherapy in pretreated patients with NSCLC and is also associated with high metastatic burden and poor prognosis in patients treated with PD-1/PD-L1 inhibitors," conclude the authors, headed by Caroline Caramella from French Gustave Roussy cancer centre in Villejuif. As HPD previously was reported in 9% of advanced cancers and in 29% of patients with head and neck cancer, they say that "additional studies are needed to determine the molecular mechanisms involved."



Lung cancer cells

Patients investigated had received either the anti-PD-1 mAbs nivolumab (Bristol-Myers Squibb) or pembrolizumab (Merck & Co.) or the anti-PD-L1 mAbs atezolizumab (Roche) or durvalumab from AstraZeneca plc.

Fully human antibodies for advanced immunotherapies

ANTIBODY GENERATION Answering the increasing demand for novel fully human antibodies in immunotherapy, German biotech pioneer YUMAB GmbH accelerates drug discovery and development with a comprehensive and versatile technology platform.

› Dr. Thomas Schirrmann, CEO, YUMAB GmbH

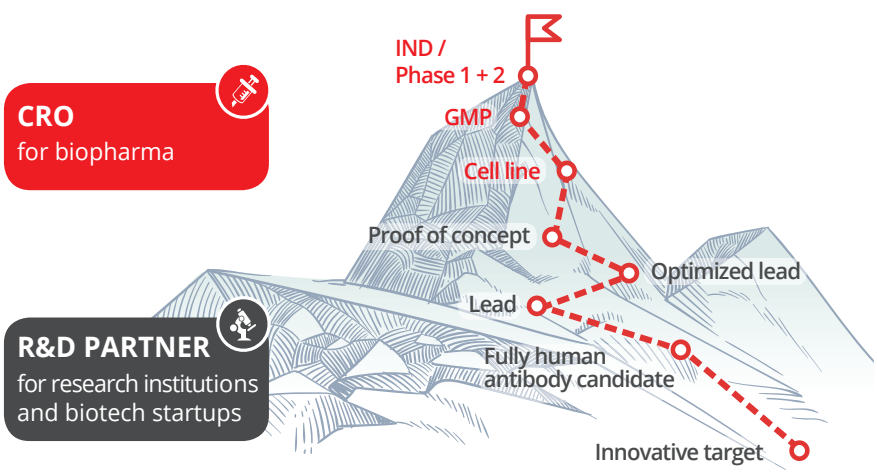
Immunotherapies based on fully human monoclonal antibodies have been extremely successful since their first approval in 2002 (AbbVie's Humira®, adalimumab), and today, the majority of newly approved antibody drugs are of human origin. This trend calls for a paradigm shift in antibody discovery and development to an advanced process that enables flexible drug design and accelerates translation into clinics. YUMAB is a pioneer in fully human antibody development that offers an optimised discovery process tailored to the need of the pharmaceutical industry for a rapid, robust, and reliable generation of novel drug candidates.

Diverse and safe antibody leads

The YUMAB® platform generates fully human antibodies that are the closest to natural germline among those available on the market. Unlike animal-derived, chimeric, humanised, or synthetic antibodies, each YUMAB® antibody combines the maximum epitope diversity of very large universal antibody libraries with minimal immunogenicity. This approach is also efficient for difficult targets, such as G-protein coupled receptors (GPCRs), ion channels, and even whole cells or virus particles. Additionally, YUMAB optimises antibody properties, such as affinity, stability, or interspecies X-reactivity in early discovery. First antibody candidates are identified within weeks and the versatility of the technology allows flexible manipulation and variable drug formats. YUMAB's advanced human antibodies cover a broad therapeutic spectrum. Tailored to customer needs, YUMAB also generates custom libraries, and offers antibody engineering in fee-for-service or attractive licensing options.

Enleofen – a success story

In early 2016, YUMAB started a cooperation with Stuart Cook and Sebastian Schäfer at the National Heart Centre Singapore and Duke–National University Singapore Medical School to generate novel antibody candidates that target interleukin-11 (IL-11) in fibrotic disease. Their research revealed the critical role of IL-11 in fibrosis and set the stage for potential anti-IL-11 therapies that could transform the treatment of fibrosis of the lung, heart, liver, kidneys, and other organs[1]. In April 2017, Cook and Schäfer founded Enleofen Bio Pte. Ltd. with a focus on the development of first-in-class antibody therapeutics for the treatment of fibrotic diseases. Using YUMAB's expertise in antibody engineering, the startup rapidly generated high-quality antibodies as a basis for the development of antifibrotic therapies. "Owing to YUMAB's rapid and reliable antibody platform, we could shorten preclinical development and are now confident to accelerate the translation of a novel antifibrotic antibody candidate from bench to bed," said Stuart Cook, Enleofen Bio's director. "Successful drug development requires interdisciplinary expertise and technologies that are most easily accessed through collaborations," added André Frenzel, CSO of YUMAB. "Being able to support our colleagues in Singapore in their quest to rapidly translate their new insights into fibrosis into a startup company was very rewarding for us, and we are excited to have played a small but crucial part in that process." ■



Reference [1] Schafer, S. et al. Nature 552, 110–115 (2017)

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