European Biotechnology

Autumn 2016

# CMOs & CROs

SPECIAL

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# Damned to outsource

**CRO & CMO** As industry pressures increase, companies are actively reviewing what's core activity and what can be outsourced to specialised CROs and CDMOs. While manufacturers have an eye to awake end-to-end continuous bioprocessing from theory, drug developers increasingly switch to the acquisition of real-world data. The overall goal is an old one: improving productivity, flexibility, and product quality, while reducing cycle and development times, inventory, waste and costs.

While continuous processing has proved a very successful model in many other industries, biomanufacturing is still lagging behind. "In USP, continuous bioprocessing is well established and will continue to be utilised," says Stefan Schmidt, VP Process Science & Production at German CMO, Rentschler Biotechnologie GmbH. The company is currently using continuous USP processes for very different purposes:

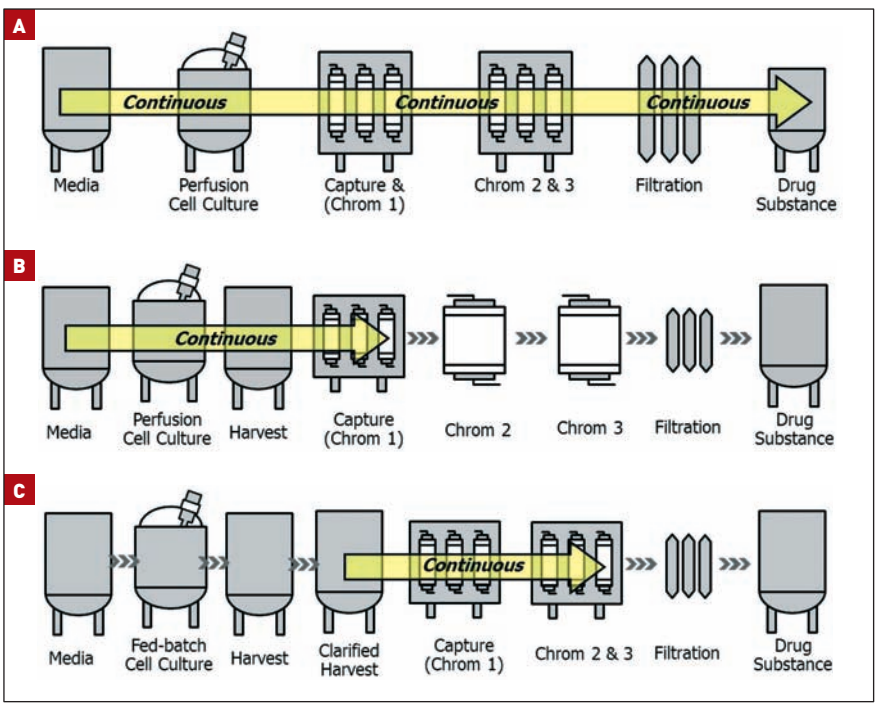
- Proteins which are difficult to express and result in low product concentrations.
- Therapeutic molecules such as interferon that have either a negative impact on the production cell line, or which are degraded if exposed to host cell proteins such as blood coagulation factors.
- Finally, there are biosimilars where it is important to match certain critical quality attributes which are easier to maintain during a plateau phase instead of the exponential growth phase or late post-peak growth.

However, though high costs for protein A capture of antibody drugs has driven the switch to continuous downstream processing (DSP), certain bottlenecks remain that currently block the adoption of so-called end-to-end-solutions. According to Schmidt "a major limitation is the limited availability of chromatography skids that allow continuous downstream processing and the lack of established process analytical technology (PAT) for the majority of processes."

## Dreams of cost reduction

According to Veena Warikoo, Director Purification Development at Genzyme/Sanofi, her company has been working toward developing an integrated continuous bioprocessing manufacturing facility with a manufacturing scale of 10–4,000 kilograms per year modelled on a single use perfusion bioreactor and four-column periodic countercurrent chromatography (PCC) system. Usage of such unit-based systems would allow multiple production processes to be carried out in parallel, without the danger of cross-contamination.

The business impact of such systems is thought to be tremendous. According to Monte Carlo simulations of a group headed by Andrew Sinclair (Biopharm Services, Chesham, UK), integrated biomanufacturing platforms can reduce average cost by 55% compared to conventional batch processing. Potentially, the savings in cost and space can be further increased by 25% in situations where demand is higher as expected.




**A. End-to-end biomanufacturing model. B.+C. represent current hybrid models with continuous USP or DSP.**

Picture: MIT

The vision of having end-to-end continuous processing, however, has not yet become reality. There are only few data on the cost efficiency of so-called hybrid solutions, which rely only in part on continuous bioprocessing.

## Back to reality: hybrid models

"We expect to see hybrid solutions for the foreseeable future," says Schmidt. "Though single-use bioreactors are ideally scaled to enable continuous bioprocesses, and the dimensions of commercially available, pre-packed chromatography columns fit nicely into the scale required for continuous processes, it must be noted that chromatography skids with exchangeable (single-use) flow paths are not yet fit for their application in fully disposable conti-processes," he explains

## CROs' next challenge: integration of real-world data

Takeda is doing it. Boehringer is doing it. And since the EMA launched its Priority Medicines (PRIME) highway (see interview p. 26) of accelerated market access for urgently needed medicines, virtually every big Pharma company is thinking about how to replace or complement the timely and costly randomised clinical trails (RCTs) by so-called real-world data.

Accordingly, contract research organisations (CROs) have taken the opportunity to diversify from competitors. Some of them are now offering algorithms that link a patient's very personal medical records to track patterns in disease presentation, patient characteristics, treatment and outcomes of therapies he or she is undergoing. The overall goal, both of CROs and drug developers, is to collect information on medicines in daily use in a population that is not as accurately preselected than in the more or less artificial and biased RCTs, pharma industry interest groups say.

Although, companies such as Takeda (on multiple myeloma patients) or Boehringer (in patients that take blood-thinners) started first real-world data acquisitions, critics such as the Cologne-based health technology assessor, IQWiG, remain sceptical. As the selection criteria of real-world data provided by pharma companies to regulators remain nontransparent, it's still unclear whether real-world data are really more representative than those obtained by RCTs. Another point of criticism is that real-world data deliver just statistical associations or – in best case – correlations instead of clear outcomes. Regulators in the EU and the US, however, appear to be convinced of the advantages of real-world data. At the end of August, the FDA's Center for Devices and Radiological Health recommended best practices in the use of real-world evidence for medical devices. According to experts, it's just a matter of time beforemedicines will follow.

**Fitness trackers are thought to support acceptance for tracking of real-world data by third parties such as private companies, which have huge interest to use the private data in R&D and clinical research.**

Picture: maridav/123rf.com

## Lesson for drug developers

The current PRIME and MAPP schemes forsee accelerated market approval of novel medicines for selected patient groups based on preliminary safety and efficacy and post-market verification with RCTs or real-world data in further indications. What could save companies a lot of time and money prior to approval, however, could also end in disappointment. In mid-August, results from real-world data acquisition from patients with wet age-related macular degeneration that were treated over 24 months with three different VEGF blockers went public. The results obtained from US ophthalmology practices fell far short of the promise of clinical trial results, according to Principal Investigator, Thomas Ciulla. The analysis of 750,000 patients is the first large study in the United States of anti-VEGF results outside of randomised, controlled clinical trials, and it echoes the findings from similar European studies. "In the real world, patients do poorly", he said, mentioning that within the trials patients obtained double as many injections into the eye than in a real-world setting. The patients' mean age was 82 years at initial presentation. About 70% received bevacizumab. Of the remaining 30%, half received aflibercept and half were given ranibizumab. ■

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# Upgrade for Pichia pastoris production system

**BIOMANUFACTURING** Pichia expression system enables methanol-free high-level protein production.

› Dr. Thomas Purkarthofer, VTU Technology GmbH

Not only because of its simplicity, but also because of its diversity and outstanding performance *Pichia pastoris* is a highly valued host for recombinant protein production. Although many improvements have been accomplished in the past, VTU Technology has added more benefits to the *Pichia pastoris* system. Using *Pichia´s* inherent potential, VTU Technology established an exclusive and yield-enhancing technology platform. The core of this platform is a synthetic AOX1 promoter library constructed by modifying regulatory elements for fine-tuned expression in *P. pastoris*. Subtle differences in each promoter's expression properties allow for optimisation of protein expression by fine-tuning the transcript level.

## Without Methanol

A subset of VTU Technology´s promoter library has been found to elicit high productivities already during the glycerol-based derepression phase, obviating the use of methanol and facilitating strong expression even with just glycerol or glucose as the sole carbon source. "Besides abolishing toxic and explosive methanol as a substrate, major advantages of our new technology are a reduced oxygen consumption and therefore a significantly reduced heat production and cooling effort in bioreactor cultivations. Additionally, there is a high potential to reduce process time and cost of goods," explains Thomas Purkarthofer, VTU Technology's Head of Business Development.

The performance of VTU Technology's methanol-free approach was demonstrated by the production of phytases. Harnessing VTU Technology's promoter library and screening platform, the expression of an engineered variant of Buttiauxella sp. phytase in the methanol-induced and methanol-free approach yielded 22 g/L and 20 g/L of the enzyme in the supernatant, constituting the highest amounts of recombinantly produced phytases in yeasts reported so far. "Additionally, the recombinant production of cellobiohydrolase (CBH2) in a methanol-free environment was optimised in cooperation with Graz University of Technology and reached outstanding 15 g/L of target enzyme," says Roland Weis, Head of Operations at VTU Technology.

## Economic biomanufacturing

To conclude, VTU Technology´s promoter variants enable the economic production of recombinant target proteins in commercial quantities using a robust, reproducible and scalable processing method even without the need for methanol induction. Double-digit g/L levels of recombinant proteins are achievable in cultivations with glycerol as the sole carbon source. ■

Pictures: VTU Technology GmbH

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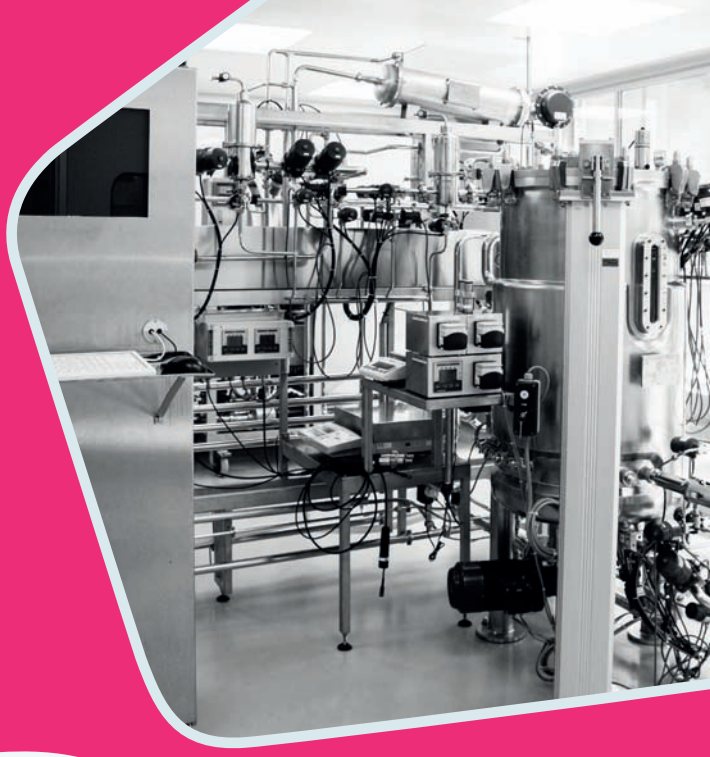

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# Ethics approval in an average of six weeks in Adelaide

**CLINICAL TRIALS** No IND application is required for First in Human clinical trials, and Human Research Ethics Committee (HREC) approval requires an average of only six weeks and is valid in all participating jurisdictions. This means trials in Adelaide are shorter by six to nine months compared to trials in the US or Europex

› Marco Baccanti, Chief Executive, Health Industries South Australia

Ethics submissions consist only of a protocol, investigator brochure and – when required – an independent toxicology report. Trials in Adelaide are compliant with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP). This means your trials will be compliant with the US Food and Drug Administration, European Medicines Agency, and Japanese and Canadian regulatory bodies.

Adelaide is a one-stop-shop offering smooth transition from preclinical research to clinical trials.

## Local infrastructure and expertise

It features a world-class large animal research facility and one of Australia's largest and most experienced Phase I clinical trials units, with a database of more than 13,000 active volunteers. Established facilities for Phase II and Phase III trials are available, and there are frequent ethics committee assessments via Australia's first and largest group of private HRECs (multiple monthly meetings).

Adelaide has a full range of local providers for study drug manufacturing; clinical, data and bioanalytical services for small and large molecule clinical

Pictures: Health Industries South Australia

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trials; and applied clinical pharmacogenomics (PGx) services.

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## Adelaide BioMed City

The South Australian Government is committed to the health industries, overseeing the construction of the $3.6bn Adelaide BioMed City (see photo). Bringing together research, education, clinical care, business development and incubation, it will be one of the largest life sciences clusters in the southern hemisphere.

The centrepiece is the new Royal Adelaide Hospital. Construction of this 800-bed hospital is nearing completion, with all beds in private single rooms, providing patients with comfort and privacy.

The South Australian Health and Medical Research Institute (SAHMRI) at Adelaide BioMed City opened in 2014 and is designed to accommodate 675 researchers, providing nine fully flexible wet and dry laboratories to PC2 standards.

Currently under construction at Adelaide BioMed City are two university buildings. The University of Adelaide's Health & Medical Sciences Building will support medical, nursing and dentistry students, and around 400 health sciences researchers. The University of South Australia's building will open in 2018 and will house the Centre for Cancer Biology, focusing on fundamental research relevant to many types of cancer.

The government is planning the next stage of Adelaide BioMed City, including a new Women's and Children's hospital to give women, children and babies access to the most advanced acute hospital care, as well as Australia's first proton therapy unit, set to be located at Adelaide BioMed City.

## Contact us

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Health Industries South Australia is an agency of the South Australian Government helping health and life sciences companies investing and conducting research in Adelaide. ■

**Animation of the US$3bn campus being developed in Adelaide**

Picture: Health Industries South Australia

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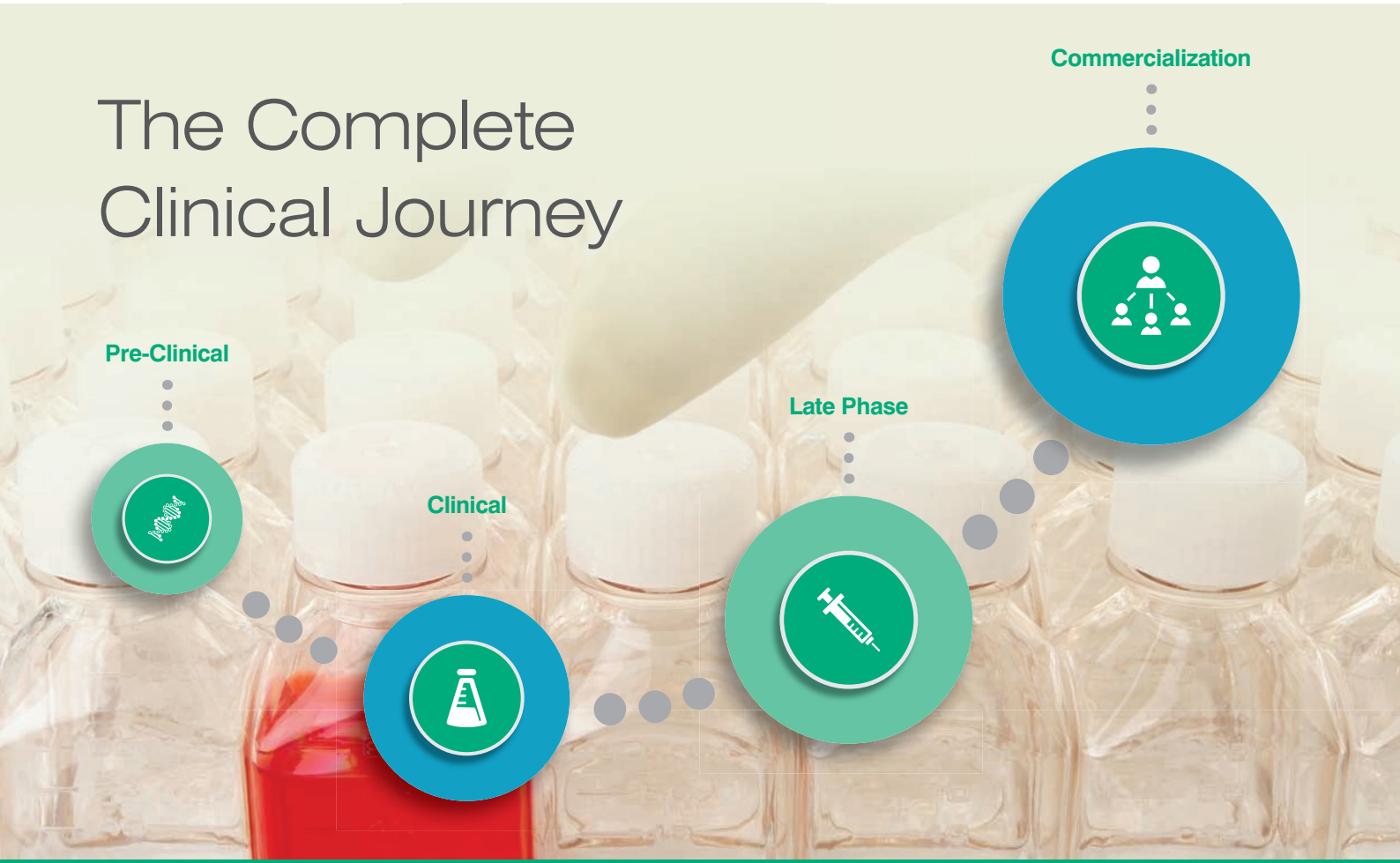
# The Complete Clinical Journey

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# CHOvolution – an innovative development platform

**CELL LINE DEVELOPMENT** Celonic's CHOvolution™ kit comes with a wide range of exceptional services and solutions, on top of high performance cells, delivering commercial success. In addition to robust and highly efficient technology, Celonic offers excellent technical support, including comprehensive protocols, audits, tailored workshops, and a 24/7 information access in Internet-based platform with a hotline.

› Stavros Theocharidis, Celonic AG, Switzerland

For any drug developer or service provider, cell line development is one of the most challenging phases in drug development, especially when subsequent GMP compliance is required. To boost and support the successful commercial introduction of biological drugs to the market, Celonic has developed CHOvolution™, a cell line kit that can be used for a broad range of applications ranging from non-GMP R&D testing to GMP development and commercial market supply, with a support system to help throughout every step of development.

Celonic AG is privately owned CDMO based in Basel, Switzerland providing comprehensive GMP development and manufacturing services for new biological eEntities (NBEs) and biosimilars worldwide.

## Celonic: beyond manufacturing

Applying empathy, efficiency and excellence, Celonic goes one step beyond expectations in all business aspects in order to help its clients attain their goals better, more efficiently and reliably.

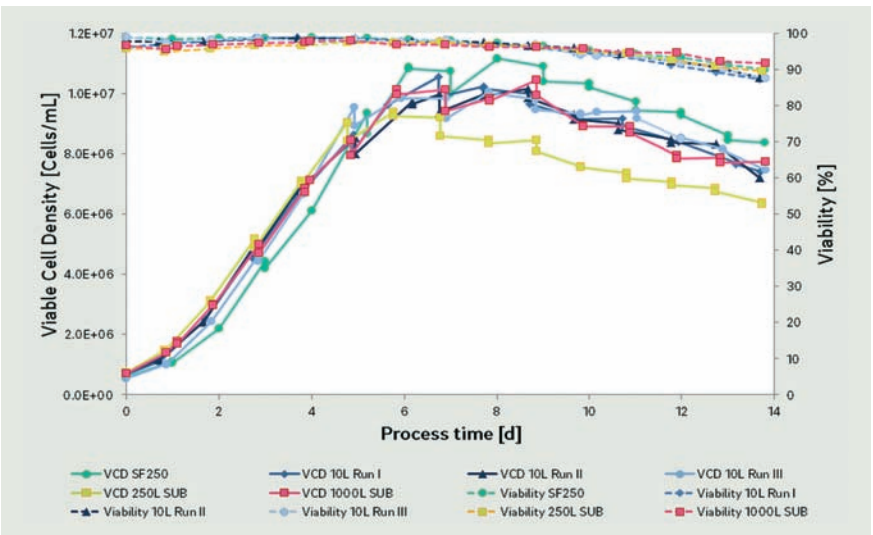


**Figure 1: Scalability of a SEFEX antibody production cell line. VCD = Viable Cell Density; SF250 = Shake Flask 250 ml; 10 L = 10 L stainless steel bioreactor; 250 L SUB = 250 L single-use bioreactor; 1000 L SUB = 10000 L single-use bioreactor**

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Unparallelled expertise and deep insights – honed over almost two decades of extensive experience in the development of expression vectors, cell lines, and media – have enabled Celonic to establish advanced techno-commercial tools and from these, its own proprietary SEFEX (SErum Free EXpression) technology. Celonic now offers its own CHO-K1 host cell line, vectors, and development protocols in the path-breaking CHOvolution™ kit, developed using this innovative technology.

Unlike other GMP CHO cell line kits, CHOvolution™ enables convenient, reliable, easy, and safe regulatory compliant development with high titers (up to 7 g/L). The stable and robust cell line is adapted for suspension culture and growth in chemically defined and commercially available media.

Moreover, CHOvolution™ is royalty-free for partners and customers wishing to use their production cell lines for clinical purposes or market supply. Pragmatic and simplified commercial mod-

Picture: Celonic

els enable business partners to use, sublicense, sell, or transfer their developed production cell line later down the development road.

## CHOvolution™ takes you further

CHOvolution™'s advantages lie in its unique business model and its superior support in helping to integrate a new cell line.

The support Celonic offers includes:

- Quality management system audits available; based on that a guaranteed upgrade of a generated production cell line to a GMP-compliant master cell bank
- Risk-mitigation methodologies, shaped on pillars of greater transparency and communication
- Comprehensive protocols describing Celonic's optimised screening and selection processes to establish production cell lines for monoclonal antibody products
- Tailored workshops and hands-on training to develop the product
- Extended support alongside GMP development and GMP manufacturing
- Help with filling for investigational new drug (IND) applications
- Technical and scientific support from the CHOvolution™ internet platform; customers can connect with the worldwide CHOvolution™ user community in a dedicated forum moderated by Celonics' cell line specialists
- A telephone hotline for expedited additional support.

Celonic's business model features

- Partnership allows "co-marketing" via Celonic's homepage
- Attractive new business offers to extend service portfolio and attract new customers and increase revenue, especially for non-GMP-service providers
- Competitor advantage by expedited time to market
- Substantial cost saving due to detailed user guide/protocols for the handling, selection, and screening process of drugs and training/workshop offering
- A compliance guarantee based on a quality management system audit to turn the established RCB into an MCB at Celonic
- Derisking technology implementation and usage due to training/workshops offering excellent support (partnerships).

Celonic AG is an internationally active biotechnology service company and part of the JRS Pharma Group. The CDMO operates state-of-the-art facilities in Basel for Research & Development, GMP manufacturing, and Quality Control. ■

# The future of the biotech outsourcing market

**REGULATORY** CDMO's must be able to provide in-depth regulatory assistanceover the entire preclinical and early clinical development range to win Big Pharma as contractors, says Menzo Havenga

› from Menzo Havenga, President & CEO, Batavia Biosciences, Leiden, The Netherlands

The current outsourcing market for biopharmaceuticals encompasses about US$5.5bn annually with by far the biggest spending in early development. It is estimated that about two-thirds of that annual spending is currently outsourced with about 90% being spent by small and mid-size biotech companies. In contrast, only 10% is outsourced by globally operating, large pharma companies, responsible for at least one quarter of the new drug pipeline.

Menzo Havenga, President & CEO at Batavia Biosciences, has been working in both innovative biopharmaceutical drug development companies as well as service providers for more than 20 years. During his career, he has experienced both the benefits and hurdles associated with outsourcing. He has used this knowledge, together with his business partner Chris Yallop, to build their own uniquely positioned contract development organisation, Batavia Biosciences.

## Compliance is key

The biopharmaceutical product development market is highly dynamic, fuelled on one side by scientific discoveries that lead to novel classes of drugs and on the other side by innovative technologies that shorten development times, reduce costs and improve product efficacy. Both these market drivers, scientific discoveries and innovative technologies, constantly raise new challenges to ensure compliance with relevant biopharmaceutical regulatory guidelines. Therefore, quality assurance, rigorous in-process testing and in-depth knowledge on the development of for instance release assays is indispensable for a service provider to ensure manufacturing control and the ability to gather all information required for successful regulatory filing. In addition, a service provider must fully understand novel technologies to guide optimal translation of such technologies into regulatory documentation.

**Menzo Havenga, CEO Batavia Biosciences, "Entrepeneur of the year" 2015/16**

Menzo Havenga firmly believes that the lack of contract organisations capable of providing such in-depth product development know-how over the entire preclinical and early clinical trajectory has resulted in globally operating large pharma companies deciding not to outsource. Without a doubt, consistency in the regulatory dossier is essential for a smooth registration process, which is poorly supported when forced to work with multiple contract organisations, each responsible for parts of the investigational new drug dossier (IND).

It is therefore believed that contract organisations will evolve into full product development partners, capable of overseeing an entire IND project trajectory. Therefore, contract organisations will transform into biopharmaceutical development powerhouses, capable of offering end-to-end services for a full development process. As such, it can be predicted that they will become leading experts. This will transition the relationship between a sponsor company and its contractor from typical one-off deliverable driven contracts to a more long-term partnership whereby both partners share equally in a symbiotic and quality driven drug development programme.

Needless to say Menzo Havenga and Chris Yallop build on their vision the high quality biopharmaceutical product development organisation; Batavia Biosciences (*www.bataviabiosciences.com*). This R&D organisation, which consists of staff with more than 45% PhD's and 30% MSc's with an average of 17.2 years of industry experience, knows the challenges its sponsors faces, and has demonstrated in numerous cases its ability to provide practical, innovative solutions fully in line with current and future regulatory requirements. ■

Pictures: Batavia

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# Preventing resistance sequences in AAV vectors

**DRUG SAFETY** PlasmidFactory's Minicircle technology has reached another milestone in the manufacture of adeno-associated viruses

› Dr. Marco Schmeer, PlasmidFactory GmbH & Co. KG, Bielefeld, Germany

While adeno-associated viruses (AVV) can be used as "gene ferries", they also have the potential to transfer bacterial resistance genes. In the manufacture of AAV vectors, such resistance genes can be transferred to AAV particles by transient plasmid transfection, and as such can reach the target organism.

For this set of problems, the company PlasmidFactory in Bielefeld, the Medical University Hanover (MHH), the Centre for Molecular Medicine (ZMMK) at the University of Cologne, as well as the Kornea Laboratory at the University of Erlangen have developed a strategic solution as part of a collaboration. Thereby they have reached an important milestone for the future manufacture of therapeutically applicable viral vectors without such contaminations.

The researchers used recombinant AAV vectors as a model system. These vectors are derived from AAV and have to date been successful in tests within the framework of gene therapy studies. The partners were able to show concrete evidence that AAV vectors can be produced based on Minicircle DNA, instead of conventional plasmids, what prevented incorrectly-packaged bacterial sequences such as antibiotic resistance genes to be packed into the AAV capsids.

These DNA Minicircles are recombined from so-called parental plasmids to circular derivatives. Subsequently, the prokaryotic plasmid components, which are only required for the replication of constructs in a bacterial culture, are removed from the construct and purified. This results in a monomeric, circular, supercoiled DNA molecule, which almost exclusively contains the gene sequences needed for the actual application in AAV vector production, but not the ones required solely for the replication in *E. coli* bacteria.

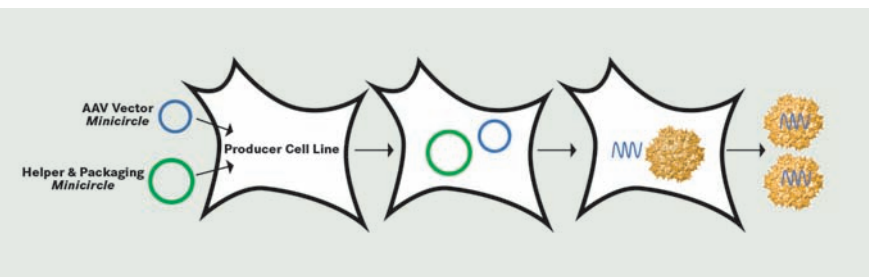
The research work was supported on the part of BMWi with government funds (ZIM Project). The initial results have now been published by the interdisciplinary research team in Molecular Therapeutics: Nucleic Acids (2016) 5, e355).

## Experienced producer

The frequently-used viral vectors are generally produced based on plasmids as the most important original substance. In this way, the plasmids are coded for the therapeutic gene and contain information on the intracellular production and packaging of this gene in the AAV particle. Bielefeld-based Plasmid Factory has been successfully manufacturing the basic plasmid in a special laboratory for customers all over the world for several years. Currently, more and more AAV vectors are being successfully implemented in clinical studies for the introduction of genetic information into certain target tissues.

Aside from the application as an agent for complementing genetic defects in terms of cell and gene therapy, there are further future clinical applications of plasmid DNA as non-viral or viral vectors, such as AAV vectors. These applications could include DNA-based immunisation, i.e. against viruses, pathogenic spores or tumour tissue (genetic immunisation), or the activation of tissue regeneration, for example for cardiovascular diseases (angiogenesis).

PlasmidFactory holds an exclusive global licence for the manufacture and application for the Helper & Packaging plasmids of the pDG/pDP family by DKFZ Heidelberg, which are used in the production of AAV vectors. These plasmids enable simple and safe production of AAV vectors of different serotypes with high titres. Additionally, PlasmidFactory owns the essential rights to Minicircle technologies worldwide. ■




**Transduction process of a AAV production cell line**

Pictures: Plasmid Factory

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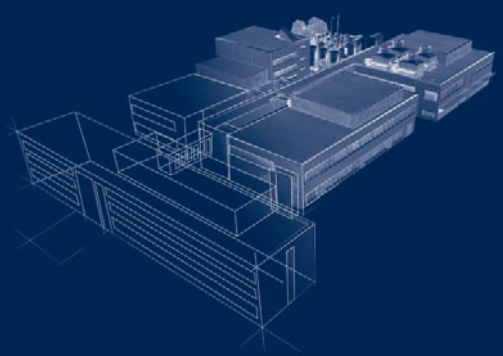

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# End-users and patients have the first and last say

**CONTRACT RESEARCH** OPIS promotes patient-centred thinking with a portfolio of user-centred solutions to optimize clinical trial management.

› Raphaela Schnurbus, OPIS, Italy

Designing products or developing services in a framework of processes where needs, wants and even limitations of end-users take the centre stage is not a new concept. It is called User-centred design (UCD) or User-driven development (UDD) and can be characterised as a multi-stage problem solving process that not only requires designers to analyse and foresee how users are likely to use a product, but also to test the validity of their assumptions with regard to user behaviour in real world tests.

The chief difference from other product or service design philosophies is that user-centred design tries to optimise the product or service around how users can, want, or need to use the product, rather than forcing the users to change their behaviour to accommodate the product. Smartphone producers are doing it, airlines are doing it, and even delivery services are doing it. Healthcare and pharma companies are no exception and it is evident that voices of their end-users, i.e. patients, are no longer ignored. A whirlwind is sweeping through the industry and more than ever, patients are at the forefront of future thinking.

## Patient-centred thinking

The pharmaceutical industry is ready to embrace the possibility of connecting all clinical stakeholders to benefit patients. The process is facilitated by

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A personal touch.

renewed Principal Investigator awareness and by initiatives of patient associations and nursing agencies – this is fundamental for homecare services especially in orphan drug and paediatric indications where every patient counts. Connecting all these players can be accomplished through a user-friendly digital platform.

Furthermore, clinical study protocols are ideally built and based on pa-

# BUILDING SMARTER ANTIBODY-DRUG CONJUGATES

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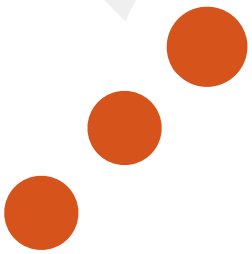

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**The OPIS suite of clinical trial solutions supports patient-centred thinking with user-centred design.**

tient input. The biometry and medical writing departments draft study material that is as patient and user-friendly as possible and for the first time, OPIS has recently collected informed consent form signatures electronically in a clinical trial.

So, to no surprise, it is technology driving this transformation. Electronic Medical Records or digital versions of patient charts are facilitating data tracking and record-keeping. It is a known fact that user-driven development is steering patient education. The creation of on-line patient communities and social media platforms to spread information about disease and therapeutic possibilities also helps to promote clinical trial awareness.



For medical research, gathering patient insights has the potential to assist outcome-driven innovation and create breakthrough products and services. It is only a matter of time until patient involvement in drug development processes becomes standard practice.

## EDC and trial design with an end-user approach

At OPIS, user-centred design is a philosophy and the company is continuously striving to optimise its services around what their end-users want and need. As an e-Clinical service provider, OPIS is committed to providing Sponsors with EDC solutions that have the potential to enhance patient-centred drug development. Applied to clinical trials, the OPIS platform is designed with web-based patient data collection tools for ePRO (electronic patient reported outcomes) that measure symptoms, mental state or the effects of a disease and eCOA (electronic clinical outcome assessments) that are used to determine whether a drug provides a treatment benefit.

As a next step, OPIS is implementing wearables with digital applications to enhance patient experience in clinical trials.

## COMPASS – compassionate use programmes

Medical professionals use the term "compassionate use" or "extended access" to refer to the treatment of a seriously ill patient using a new, unapproved drug when no other marketed treatments are available. Upon a medical practitioner's request, a Pharma company will enroll a patient in a compassionate use programme and provide the medication free of charge for the entire pre-market authorisation period. Ensuring patient safety is a priority, OPIS has just released an in-house developed e-product to manage workflow and processes related to compassionate use programmes very effectively.

Fully compliant with global, EU and local requirements, the independent, web-based, modular platform is accessible to password protected and profile specific users. Highly customisable and extremely user-friendly, the system allows for guided compilation of all documents and a validated audit trail tracks all processes. Other features include centralised document management with easy document upload, online reporting and a customisable report builder.

## e-Clinical environment today

The e-Clinical environment today is all about EDC that provides patient-centred, data-driven, technological solutions that ensure on time and on budget execution of projects.

Providing sponsors with high-tech, user-centred solutions for clinical trials is what OPIS does best. ■

**Raphaela Schnurbus, Clinical Solutions Director**
**raphaela.schnurbus@opis.it**

Figure: OPIS

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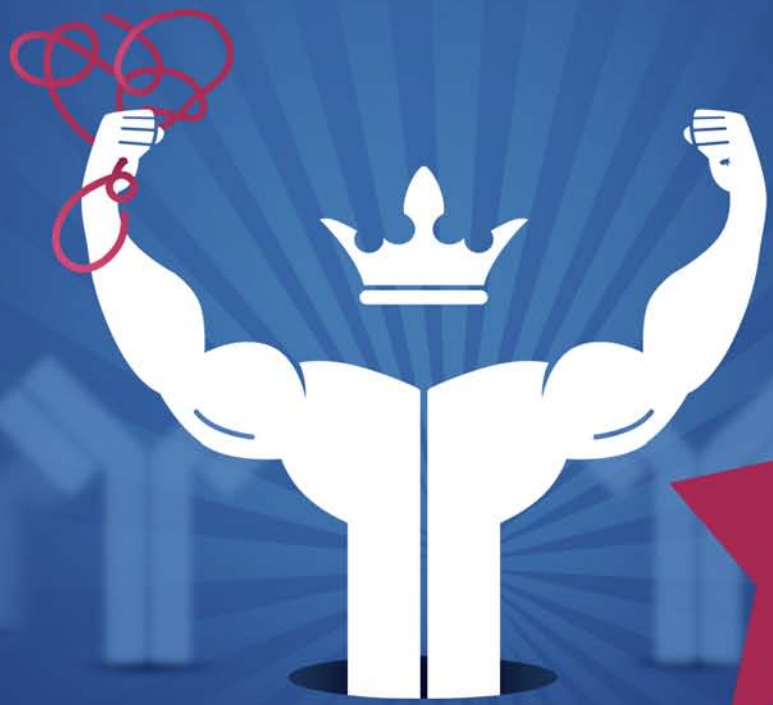

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# The many faces of fucose

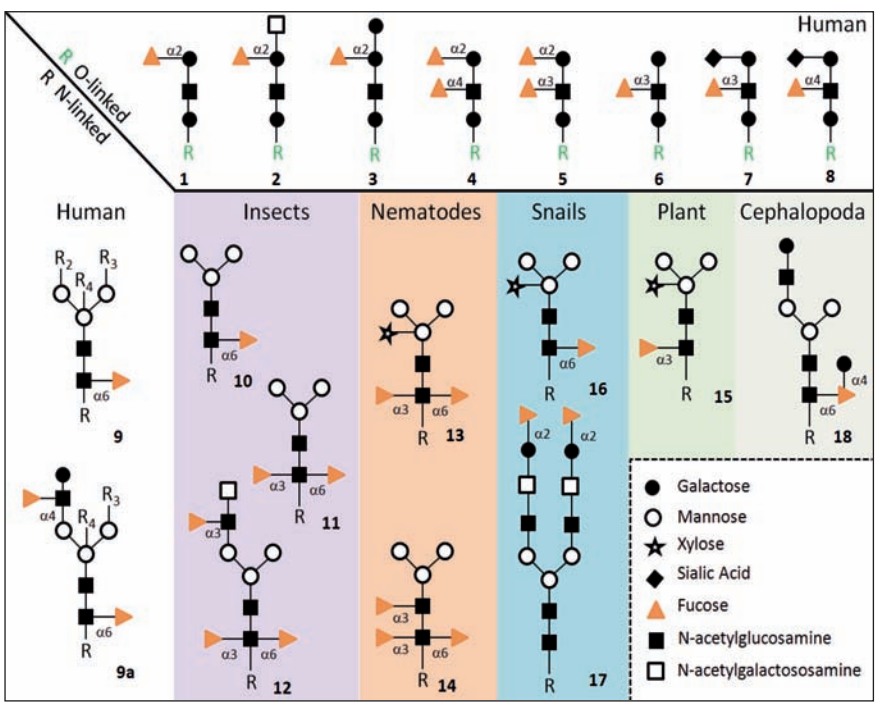
**PROTEIN GLYCOSYLATION** Fucose is a critical determinant of signal transduction, functionality and immunogenicity.

› Sven Krügener & Volker Sandig, ProBioGen AG, Berlin, Germany

Fucose, a simple six-carbon sugar like glucose, mannose and galactose is not just another energy source or building block – it occurs throughout nature, often playing a delicate regulatory role. Its structure is unique: it lacks the hydroxyl group on the carbon at position C-6 and is the only monosaccharide naturally found in the L configuration.

Fucose was first isolated from *Fucus*, a genus of brown algae, in 1890. It is the main constituent of fucoidan, which makes 5–20% of the dry weight and is secreted during ebb to protect the algae from drying out. More importantly, it is a critical component of glycans of glycoproteins where it is either attached to threonine or serine directly as a single sugar or as part of more complex O or N glycans (see fig.1). When present on cell surface receptors, fucose modulates interactions between bacteria and host: it serves as an attachment site for *Pseudomonas*, and fucose released from mucin in the gut represents an important signal for expression of virulence genes in enterohemorrhagic *E.coli* (EHEC).

In embryonic development of mammals and insects, O-fucosylation of Notch receptors is essential for signalling. The human ABO blood group antigens are well-known fucosylated glycans. Both the ABO and Lewis systems are dependent on the H antigens to serve as precursor substrates that give rise to the A, B or Lewis epitopes (1–8).




**L-fucose in O- and N-glycans. Popular examples: H Antigen (1), A Antigen (2), B Antigen (3), Lewisb Antigen (4), Lewisy Antigen (5), Lewisx Antigen (6), silalyl Lewisx Antigen (7), silalyl Lewisa Antigen (8), fucosylated IgG (9), MMF6 (10), MMF3F6 (11), MMXF3 (15) and other nameless glycol structures (12–14, 16–18)**

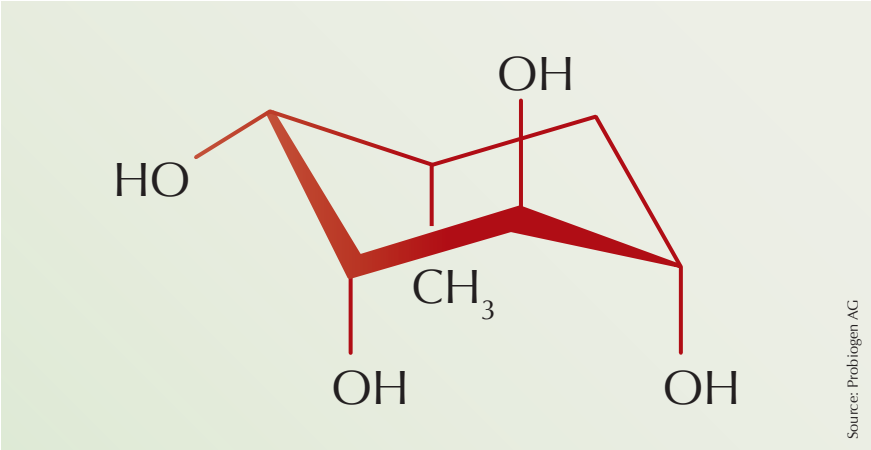
## Application in biotechnology

In biotechnology, fucosylation of the proximal N-acetylglucosamine (GlcNAc) of the complex-type N-glycan attached to Asparagine 297 in the Fc-part of therapeutic antibodies has received major attention (9). Antibodies lacking fucose in this core position have increased affinity to CD16 receptors of NK cells and exhibit more potent antibody-dependent cell-mediated cytotoxicity (ADCC). The mechanism is utilised to increase potency of anti-cancer antibodies relying on this mechanism of action, such as mogamulizumab, obinutuzumab and many others in clinical development.

## Fine-tuning of glycosylation in CHO cells

To produce such antibodies in CHO cells where fucosylation is efficient, the glycan can be modified to contain an additional (bisecting) GlcNAc, thereby inhibiting fucose incorporation. Commonly, a gene knock out for the fucosyltransferase Fut8 is employed. These approaches result in a defined low fucosylation level (no fucose in case of the knockout). Alternatively, synthesis of activated fu-

Pictures: ProGloGen




**Structure of beta-L-fucose**

cose by the host cell can be prevented when a pathway intermediate is converted into a potent inhibitor of fucose synthesis using the *Pseudomonas* enzyme RMD (GlymaxX® technology). Because the fucosyltransferase remains unaffected in this case and fucose can be supplied via the culture medium at desired concentrations, this approach allows the fine-tuning of fucosylation levels and potency.

## Challenges for insect cell lines and plant systems

Fucosylation in glycans from insects (10, 11, 12) and plants (15) is not desired for other reasons. It's the type of linkage that matters! While in mammalian N-Glycans fucose is attached to the proximal GlcNAc only in the α 1.6 configuration, an α 1.3 linkage of fucose to the inner GlycNac in plant cells and α 1.3, α 1.6 bifucosylation is recognised as foreign by the mammalian immune system. Fucosylated glycoproteins are involved in bee venom-, pollen- and food allergy. This needs to be considered when glycoproteins are produced in some insect cell lines or plant systems. Again, knock-out strategies for the respective glycosyltransferases are employed. Interestingly, in contrast to the fucose-bearing glycans the fucose synthetic pathway is well conserved among higher eukaryotes. Therefore, fucosylation in either system can be inhibited using RMD and the GlymaxX® Technology.

## Fucosylation in basic research

Even if the focus of glycan structure enlightenment and functional studies have been mostly on vertebrates, insects, plants and pathogenic prokaryotes some of the functional aspects remain elusive, even more for exotic fucosylated glycan antigens that are expressed by nematodes (13, 14), snails (16, 17) and cephalopods (18). Fucose depletion and knockout of fucosyltransferases may shed some light on these mechanisms. ■

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