European Biotechnology

Autumn 2015

# CROs & CMOs

SPECIAL

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- vaccines

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# Outsourcing set to increase

**CRO/CMO** Cost-effective development and manufacture of biopharmaceutical products is rapidly gaining in importance, while healthcare systems across the globe are looking to contain costs and improve efficiency. To adapt to these changes, industries need to review and streamline their in-house processes. Outsourcing to Contract Research Organisations (CROs) and Contract Manufacturing Organisations (CMOs) have become a major trend and the markets are still going to expand.

According to market intelligence published in April 2015, the current trend in the biotechnology and pharma industries to outsource research and manufacturing services – such as target discovery, assessment of biosimilarity, clinical development, regulatory affairs, pharmacovigilance and manufacture, formulation and fill and finish of small-molecule and biologic therapeutics – is set to grow at a stable rate.

The authors of the recent Research & Markets "Outlook of Global Pharmaceutical Outsourcing Market" expect the global pharmaceutical outsourcing market to expand by 8.7% annually, from about US$131bn in 2014 to US$215bn in 2020. For the past six years (2009–2014) they have reported a Compound Annual Growth Rate (CGAR) of 9.4%. Outsourcing to Contract Research Organisations (CROs) or to Contract Manufacturing Organisations (CMOs) has become a foundation for pharmaceutical and biotechnology drug developers.

## Outsourcing services for new technology trends

In order to streamline its lengthy, inflexible and inefficient drug development and approval procedures, major players from the pharmaceutical industry have cut their R&D teams to focus on top priorities and outsourced the rest.

One of the challenges for them is selecting the right partner that is capable of coping with the rapid technological progress in the field. Currently, the US$16.5bn contract manufacturing market as well as the US$25.6bn contract research market is dominated by a handful of large, public players.

However, even in a consolidating market, special expertise in the analysis and production of glycooptimised antibodies, antibody conjugates, gene and cell therapies, regulatory submission or electronic data capture has become a competitive advantage. The same is true for companies that offer advanced contract research services such as stochastical data analytics to flesh out a medicine's safety and efficacy just before a clinical trial has started enrolment. ■

# HAbE: complete registration of novel antibody formats

**HELM ANTIBODY EDITOR** Bioinformaticians at Roche have created a software that allows an automatic description and registration of the full molecular structure of antibodies, conjugates and antibody-derived drug formats just from its raw sequence.

› by Stefan Klostermann, Roche Innovation Center Penzberg, pREDi, Penzberg, Germany

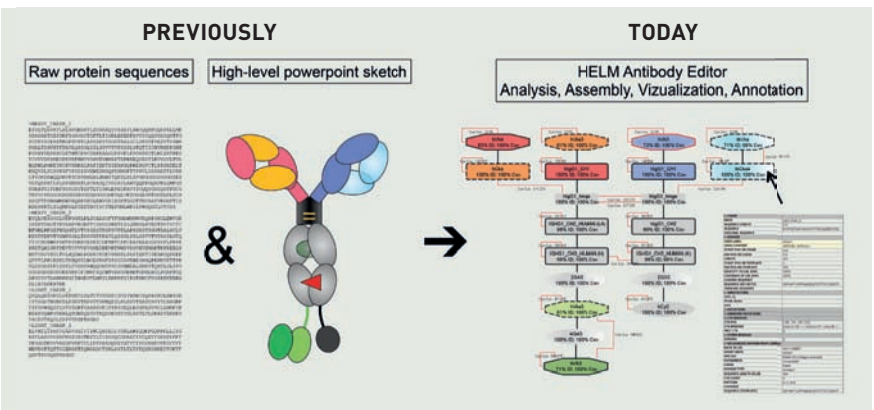
In the past, therapeutic antibodies followed nature's standard format: a set of two identical light and heavy chains interconnected by Cys-Cys bonds at defined positions. Increasingly complex formats such as antibody conjugates, glycoengineered antibodies or bispecific antibodies, however, challenge the industry to fully describe their chemical structure and record every change in its molecular structure over the whole life cycle of the biological product. Until recently, there was no longer a system available that could describe all molecular characteristics of complex antibodies in a systematic and automatic fashion. Based on the HELM Editor, a notation for smaller macromolecules provided by the Pistoia Alliance in 2013, we have developed the HELM Antibody Editor (HAbE). The software package and documentation was published in April on the website of the global alliance of pharma companies, which jointly aim to lower the barriers of innovation (*www.pistoiaalliance.org/helmantibodyeditorreleased/*). In the spirit of open innovation, member companies are currently working on further enhancements.

## The HELM Antibody Editor

The HELM Antibody Editor employs a domain library to describe functional building blocks of advanced antibody formats. The systems delivers a graphical notation of all functional domains of an antibody and its arrangement just a few moments after its amino acid raw sequence has been entered. Additionally, all extra connections (such as Cystein-Cystein bridges) between the antibody chains are automatically recognised. The molecule displayed represents the final drug in full detail. However, the system not only depicts all protein domains, mutations, and functional modules. It also provides an exact description of the localisation of every atom, bond and their position within the antibody.

When combined with an additional in-house designed system module called TaPIR (Therapeutic Protein Identifier and Registration) the software package, which has been developed since February 2014, can do much more than just register and visualise. You can insert novel parts into an antibody, retrieve every single functional module that has been stored in a database previously, and use it for the design of a novel antibody with optimised properties. Before a novel antibody module can be stored in a database, the system checks if its structure is already registered. Otherwise, it gets a unique identifier.

This kind of antibody registration is not only beneficial for collaboration at different Roche sites. As other pharma companies plan to adopt this system as well, in the future it could also support the documentation of appropriate products to the regulatory authorities. Currently, the Pistoia Alliance is striving to convince them to accept the HELM notation for submissions. The system is now free for optimisation in the interest of all players. ■




**The HELM Antibody Editor easily handles complex biologics and fully automatically generates a full-blown visualisation.**

Picture: Roche Innovation Center Penzberg

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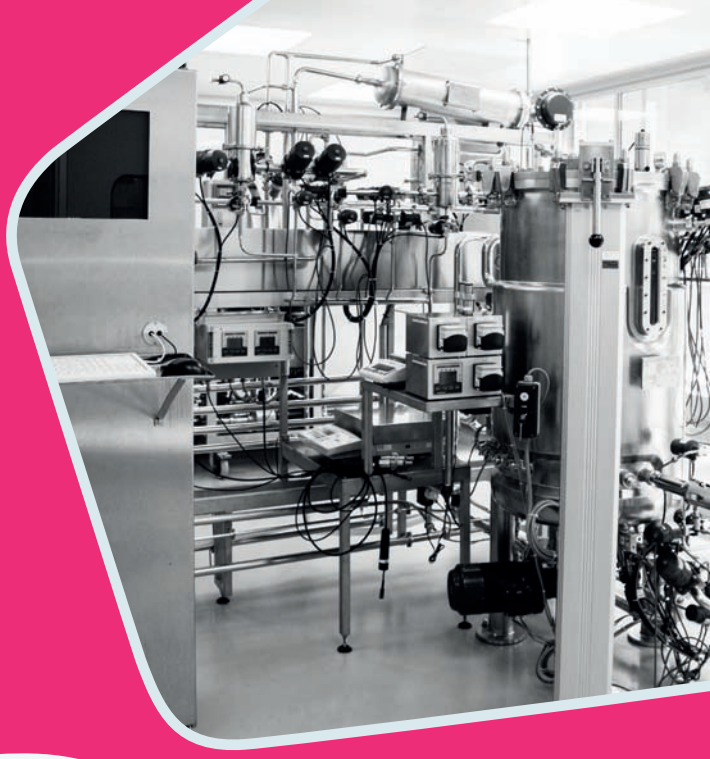

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# Cell line development for biopharma production

**CELL LINES** CHO production cell lines need high productivity but also robustness and scalability too. Celonic's licencable SEFEX serum-free expression platform can provide both.

› by Daniel Lüscher, PhD, Director USP, Celonic AG, Basel

Since the approval of tPA derived from Chinese hamster ovary (CHO) cells in 1986, stable expression of recombinant proteins has become a very important system for the manufacturing of therapeutic proteins. During the last 30 years, the productivity of stable recombinant cell lines could be increased from less than 100 mg/L to several grams per liter. The huge increase in productivity has been achieved by optimisation

- of the culture media, resulting in higher viable cell densities, higher productivities and longer cultivations in fed-batch mode and
- of expression vectors resulting in higher productivities, more efficient selection systems and higher stability of production cell lines.

But a good production cell line requires more than a high titer alone. During large-scale production in bioreactors, shear force as well as limited availability of nutrients and oxygen put stress on the cells, which are expected to grow fast and maintain high expression yields in a consistent manner over time and also from batch to batch. This requires a high degree of physical and genetic robustness, which is reported to be lacking even in cell lines meant for industrial production.

One of the most important characteristics of a cell line is its scalability. As the scale becomes larger during the development of a product – from 1–10 l during R&D over 100-250l in phase I to 1000 l for phase II/III and commercial manufacturing, the upscaling is performed in three or more steps. Every step means more generation cycles, often resulting in small, and sometimes dramatic loss of productivity.

## SEFEX technology

For 17 years, Celonic has extensively worked on the development of expression vectors, cell lines and media, resulting in its proprietary serum-free SEFEX expression platform. It is based on a CHO-K1 host cell line, a set of high level-expression vectors and repeatedly refined protocols for the best screening and selection processes. The result is a highly robust and scalable platform where growth behaviour in the shaking flask is almost identical to the one from a 10 l, 250 l and 1000 l batch (Figure 1). Extremely high titers beyond 7 g/l make SEFEX an ideal system for the manufacture of biologics.

Celonic out-licenses SEFEX. The license includes not only the host cells and vector set but also 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.

Celonic (www.celonic.com) is a CDMO located in the heart of pharmaceutical industry in Basel, Switzerland. It is providing services from cell line to cGMP manufacturing. ■

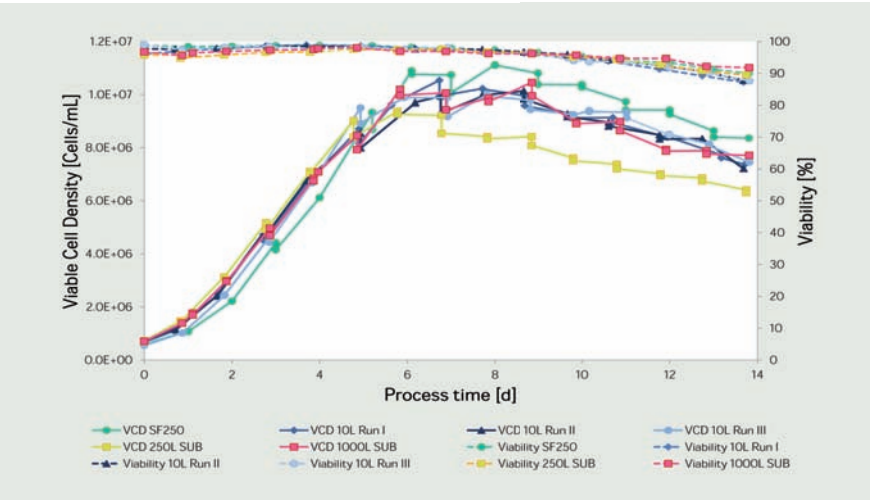


**Figure 1: Scalability of a SEFEX antibody production cell line. VCD = Viable Cell Density; SF250 = Shake Flask 250 ml; 10 L = 10 L stainless steel bioreactor; 250 L SUB = 250 L single-use bioreactor; 1000 L SUB = 10000 L single-use bioreactor**

Picture: Celonic

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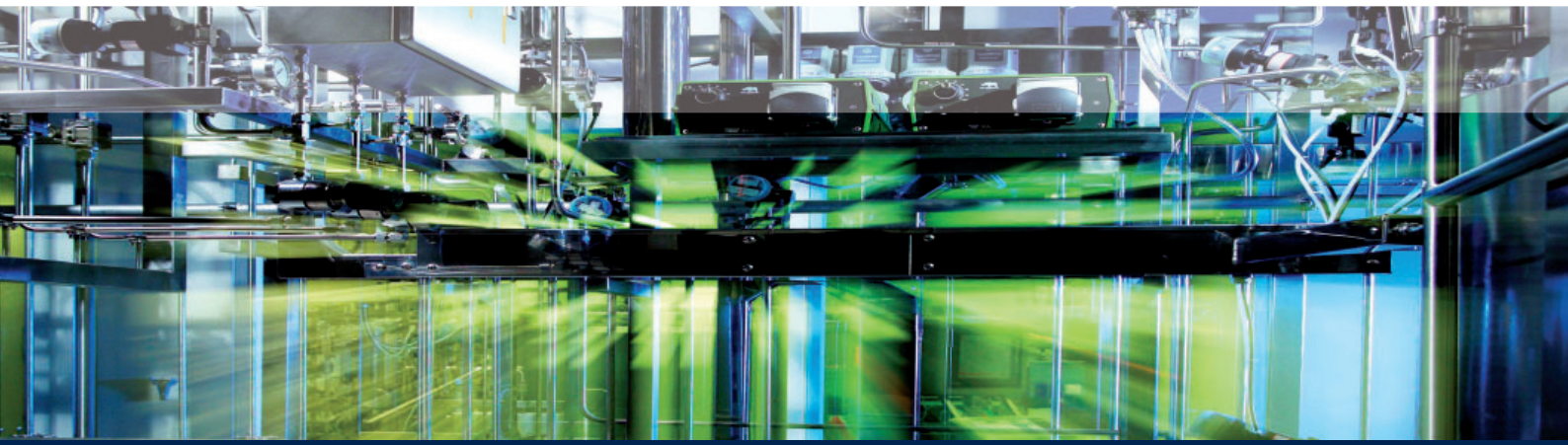

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# Pichia – competitive through diversity

**BIOMANUFACTURING** Austrian protein production expert VTU Technology is set to achieve yet another boost in productivity benefitting from its unparalleled spectrum of diverse Pichia pastoris expression tools

› Dr. Evelyn Trummer-Gödl, Dr. Thomas Purkarthofer, VTU Technology GmbH, Grambach, Austria

The global pharmaceutical market is set to double in the coming years, reaching $400bn (€365m) by 2020.

The soaring cost of biologics development is forcing drug developers to increase productivity and efficiency in biomanufacturing through achieving excellence in process development. Reductions in upstream- and downstream development costs are indispensable.

To cope with these challenges, VTU Technology acquired and further developed a *Pichia* pastoris technology platform facilitating the competitive production of biopharmaceuticals and other recombinant proteins. The yeast *P. pastoris* combines the advantages of prokaryotes, such as easy genetic manipulation and fast growth to high cell densities on inexpensive and chemically defined media with eukaryotic features such as a subcellular protein processing machinery needed for post-translation modification and secretion. These *Pichia* specific properties enable the efficient production of a wide range of proteins at high yields and high initial purities allowing for a fundamental reduction in processing costs.

Using *Pichia´s* inherent potential, VTU established an exclusive and yield-enhancing technology platform, standing out due to its diversity of expression tools and expression strategies. A proprietary AOX1 promoter library and a diverse set of platform strains provide the genetic diversity necessary for the fine-tuning of protein expression. Timely adjusted co-expression of helper proteins from a proprietary set of auxiliary proteins allows for maximisation of protein production. Based on this broad genetic diversity, thousands of *Pichia* strains producing the target protein are generated that differ in their genetic configuration. A high-throughput microscale screening and cultivation regime is applied for the rapid identification of the best performing genetic constellation.


## New dimension in protein production

*Pichia* processes at VTU show extraordinary high space-time yields due to short process times and typical product concentrations of 10 – 20 g/l at initial purities of 80 – 90% before downstream processing.

*Pichia's* biological limit has not yet been reached so far, as VTU recently developed an exceptionally high performance expression strain yielding 35 g/l of secreted product. These high-yielding processes are based on protein synthesis under the control of the strong and methanol-inducible AOX1 promoter. Additionally, AOX1 promoter variants showing high protein yields (up to 20 g/l) using only glucose or glycerol as the sole carbon source have been developed by the company. Major advantages of this new technology – besides abolishing toxic and explosive methanol as a substrate – are reduced oxygen consumption in fermentation and therefore clearly reduced heat production as well as a significant potential to reduce process times. Optimised fermentation- and feeding strategies further reduce process times without sacrificing product titer or quality going along with a substantial increase in volumetric productivity.

## Tailor-made glycoprotein production with VTU P. pastoris

VTU has expanded its technology platform by adding *Pichia* Glycoswitch® to the company´s technology portfolio. *Pichia* Glycoswitch® is a platform allowing for the specific production of glycoproteins with Man5-or higher human like glycoforms. Beside the elimination of immunogenic effects from *Pichia* specific glycans, tailor-made glycoproteins with a homogenous glycosylation pattern can be efficiently produced. ■

Picture: VTU Technology

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- Specialists in the use of QbD, design and implementation of laboratory process characterization and validation programs
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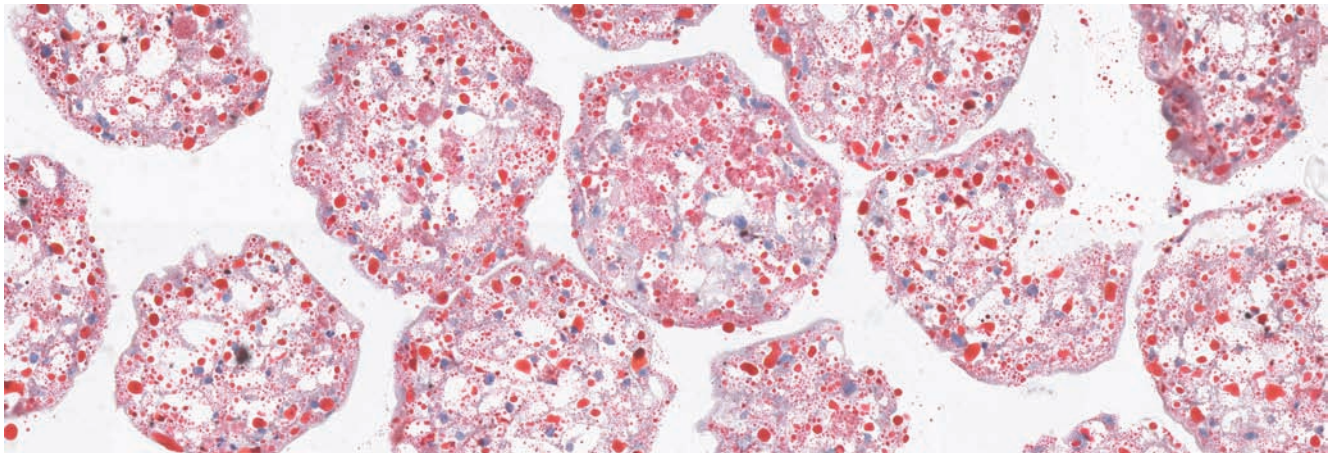

# AnaPath GmbH founds Safety Alliance

**CONTRACT RESEARCH** AnaPath has founded a strategic alliance of a selected number of well-established, complementary CROs located in Europe. This "Safety Alliance" is a one point of access to full preclinical development and regulatory packages.

Safety Alliance
www.safety-alliance.net

› The Safety Alliance (http://www.safety-alliance.net) was founded in April 2015 by AnaPath as a coordination and monitoring function for multi-site studies in order to facilitate the collaboration and communication between CROs and clients. The involved CROs are located in Europe and well established in their specific field of expertise (see below). The strategic alliance of these CROs offers the possibility to join their expertise and to provide the complete services for preclinical development and registration from a single point of contact.

› **Accelera** is a reliable partner in pharmacokinetics, metabolism and toxicology potential issues. They support all stages of drug discovery and development by offering integrated services, including Attrition Reducing Technologies (ART) and Toxicology Screening to help "pick the best" drug candidates, as well as Regulatory Drug Safety, Safety Pharmacology, ADME, Bioanalysis and Pharmacokinetic studies.

› **AnaPath** is a CRO for histology and pathology evaluation in the fields of toxicology and experimental pathology and anatomy. Next to high quality performance of standard histological techniques, the scientists and technicians are specialised in neuropathology, inhalation pathology, bone marrow evaluations, immunological processes, pathology in unusual laboratory species (fish, amphibian, birds, and invertebrates), hard material techniques, immunohistochemistry, fetal pathology and image analysis.

› **BSL BIOSERVICE Scientific Laboratories Munich GmbH** is a specialist in non-clinical testing. BSL offers a broad range of biological safety and activity testing for pharmaceuticals, chemicals, medical devices, agrochemicals, cosmetics and food ingredients.

› **Jesus Usón Minimally Invasive Surgery Centre Services(JUMISC)** belongs to the pharma-biotech and medical devices industry. It is a multidisciplinary institution that has large experience in translational research and covers several fields of expertise: laparoscopy, endoscopy, microsurgery, endoluminal therapy and diagnosis, anesthesiology, pharmacology, bioengineering and medical devices, stem cell therapy and assisted reproduction.

› **IBACON** is a competent partner for contract research and efficient per-

Picture: Anapath

formance of GLP-compliant studies in the fields of ecotoxicology, environmental fate, physico-chemical properties and analytical chemistry.

› **IES** is a Swiss GLP-certified CRO. In its state of the art laboratories they perform tailor-made environmental fate, metabolism, ecotoxicological, OPEX and analytical chemistry testing to support global development, registration and stewardship of agrochemical, pharmaceutical, biocidal and chemical products.

› **PDS Life Sciences** provides the all-encompassing services to get your preclinical data SEND-ready. PDS aggregates and translates data to produce SEND export files, including the Study Data Reviewer's Guide as recommended by the FDA. From assessment, to implementation, to comprehensive submission guidance, PDS is your all-in-one FDA-compliant partner for SEND.

› **Dr. Knoell Consult GmbH** is one of the leading regulatory service providers worldwide. With its nine subsidiaries, Knoell is offering notification and registration services (actives and products) in the business areas of agrochemicals, biocides, industrial chemicals, product safety & compliance, cosmetic ingredients, food packaging and pharmaceuticals (e.g., veterinary pharmaceuticals and medical devices).

## Know-how from 10 partners

› **Selcia** is one of the leading independent providers of $^{14}C$ GMP radiolabelling services and produces $^{14}C$ radiolabelled compounds for a global customer base encompassing both the life sciences and chemical industries. Selcia also offers GLP NMR and mass spectrometry services to support regulatory submissions, as well as analytical/preparative HPLC, chiral separations and specialised purification capabilities from analytical (µg) to multi-100g scale.

› **Vivotecnia** offers services to support the preclinical development of biotechnology and pharmaceutical products (general toxicology, safety pharmacology, genotox, carcinogenicity, etc.) as well as safety studies for chemical and agrochemical companies. It is specialised in large animal studies (non-human primates, dogs, mini pigs, etc.) and inhalation toxicology.

**Contact**
**Safety Alliance**
**Hammerstr. 49**
**4410 Liestal, Switzerland**
**www.safety-alliance.net**
**info@safety-alliance.net**
**Tel.: +41-61-906-4018**
**Fax: +41-61-906-4001**

# Plasmid DNA as raw material adjuvant

**PLASMID DNA** The small circular DNA molecule is often resorted to for the production of RNA and viral vectors for clinical gene therapy studies.

› by Marco Schmeer, PlasmidFactory GmbH & Co. KG, Bielefeld

Supervisory authorities have set particularly strict requirements on the production of RNA and viral vectors to be used during clinical studies involving humans. These requirements concern, for example, the purity, safety and tolerability of each individual ingredient.

Procedures analogous to the EMEA Directive CHMP/BWP/2458/03 provide one possibility for so-called High Quality Grade Plasmid DNA to meet these specifications during the manufacturing process. PlasmidFactory GmbH & Co. KG in Bielefeld has developed such a procedure. This procedure involves plasmid DNA that is produced entirely without the use of substances of animal origin due to product safety. During the production process of the product, impurities are removed as much as possible, e.g. by bacterial chromosomal DNA or damaged plasmid forms.

At the beginning of 2011, PlasmidFactory put its own separate, dedicated production area into operation with new laboratories to produce ultrapure plasmid DNA. To avoid cross-contamination, only one plasmid is produced there. Parallel plasmid production does not occur on the same premises. "The High Quality Grade Plasmid DNA is produced here using a cell bank (RCB) created by PlasmidFactory and particularly effective patented ccc Grade technology," explains Martin Schleef, the company's Managing Director. PlasmidFactory provides a variety of quality controls for the cell bank as well as for the plasmid DNA product, so that a product can finally be tailored to a specific use or to the relevant regulatory requirements. Research institutes and companies in Europe and the US use the High Quality Grade Plasmid DNA produced in Bielefeld as a raw material or adjuvant to produce RNA and viral vectors used in clinical studies.

Picture: PlasmidFactory

Since its inception in 2000, PlasmidFactory has provided industrial and academic researchers with high quality plasmid and Minicircle DNA (circular DNA structures without a bacterial backbone) for uses ranging from laboratory research to clinical applications.

## Successful for 15 years

As a partner in the European Network of Excellence "Clinigene", combined valuable expertise from academic and industrial research for the clinical applications of plasmid DNA could be gained. In this way, for example, the immune-stimulating effects of genes inserted into cells by special microarrays were studied in collaboration with Fatima Bosch from the Universitat Autónoma de Barcelona. The effects of the so-called S/MAR elements on gene expression were studied together with Lausanne University and the Centre National de la Recherche Scientifique in Paris. In collaboration with the Technical University of Munich, experiments were conducted to develop a potential minicircle-based vaccine for fibrosarcomas in cats. The company Genosafe in Évry (France) determined the biodistribution of plasmid and minicircle DNA. "Sleeping Beauty Minicircles" were produced and tested in various applications in close cooperation with MDC Berlin. PlasmidFactory also conducts research and works closely with many other institutions. ■

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PROCESS DEVELOPMENT

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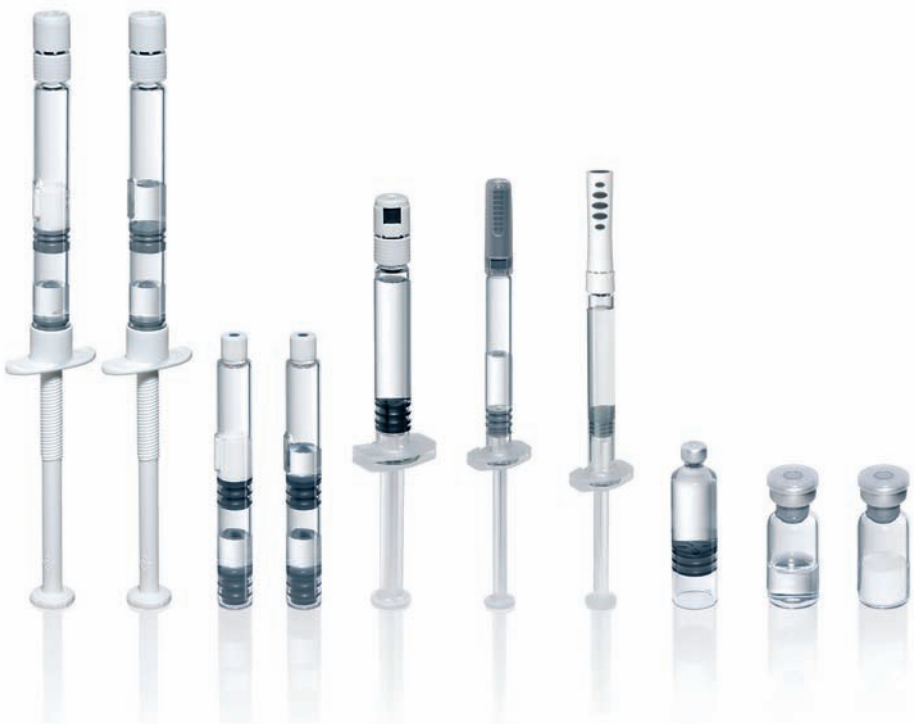
# Outsourcing in process development – a case study

**PROCESS DEVELOPMENT** Innovative R&D-focused biotech companies often face challenges when it comes to rapid transfer of a project to clinical or commercial manufacturing, finding the best formulation or validation of raw materials, bulk solutions, in-process materials, and finished product for cGMP-compliant manufacture. Outsourcing is an option of growing interest in the biotech industry.

› Dr. Claus Feussner, Senior Vice President Vetter Development Service, Vetter



**Multiple delivery systems to optimise your development approach**

In the perilous world of biotechnology, companies face a difficult journey. With limited budgets, failure to reach milestone payments is a constant threat. Everything that can be done to increase the chance of success must take precedence. Because the focus and expertise of small biotech firms is the research and development of promising drug candidates, they have very limited expertise and resources in process development, including the choice of the right drug delivery system, packaging, and product lifecycle management (PLM). Therefore, early and careful planning for the future is important.

Executing a well-defined product development process from the start is the key, and affords the biotech firm the best opportunity for creating the most advanced and complete drug candidate package possible. Having the right partner, like an experienced Clinical Development and Manufacturing Organization (CDMO), from the start can elevate the entire drug package's value from development on through to market.

## Multistep process to prevent protein aggregation

To illustrate how a well-defined drug development process works, consider a case history involving a multivalent vaccine; a complex compound that can present especially challenging issues in the early clinical development phase.

All highly sensitive biologics, including vaccines, are affected by filtration in the scale-up and filling processes. Many require multiple complex filtration processes with key variables to control, including fill concentration, viscosity, and pumping pressure. In this case, a complex, multistep filtration process had to be developed to prevent protein aggregation during pooling, eliminate leaching of any filter particles or extractable compounds in final drug solution, and to maintain targeted viscosity and concentration during scale-up.

To achieve this goal, specialised teams worked together to develop a novel, customised process design that delivered a high-yield, biologically potent vaccine, which was then planned

PPictures: Vetter

for smooth scale-up from clinical to full commercial production.

## Drug delivery systems

The choice of the right drug delivery system is also a critical decision, given the increased complexity of today's compounds. A variety of factors must be considered, including the compound itself and its specific environmental conditions e.g. possible adverse reaction of the drug compound to packaging material, contact packaging specifications relating to contaminant levels, and possible defects, etc. In addition, factors such as time-to-market and long-term market success following the products' launch, also need to be considered.

These include:

- Is the drug compatible with materials such as rubber stoppers, closure systems, and other related components? What materials are compatible for add-on systems, such as safety devices?
- How much silicone can the substance endure?
- Which rubber components should be used?
- How does the substance behave with break-loose and glide force?
- What washing procedures are necessary? Should sterilisation be performed?

The choice of the right drug delivery system from the very start is critical and will impact the products' lifecycle, even following expiration of the patent. This process, or PLM, is critical for addressing issues, such as market share and return on investment. For example, a company might launch a drug in a vial/diluent system and then change to an innovative end-user-friendly application system, such as a prefilled syringe, cartridge/pen, or dual chamber system to add a valuable benefit over a competitor's product. The key to successful PLM is to create and evolve a proactive strategy for the product throughout its entire useful life, from its launch through to its long-term growth and acceptance in the market.

There will never be an end to 'perfect storms' in the world of biotechnology and drug development. However, executing a well-defined drug development process that takes into account the proper drug delivery systems and manufacturing process, including longer term PLM strategy could be the answer to navigating the storm successfully. ■

Pictures: Vetter

**DR. CLAUS FEUSSNER** is Senior Vice President of Vetter Development Service, responsible for the company's development centres in both Ravensburg and Chicago. Dr. Feussner's responsibilities encompass the divisions of Chemical Analysis, Process Development and Implementation, Packaging Material Development, as well as the newly created department of Innovation Management. He joined Vetter in 2010 as Vice President, Quality Control and was named Senior Vice President in September 2014.

# Manufacturing at its best

**CDMO** Contract Development Manufacturing (CDMO) is not only about being a key part of the biopharmaceutical development, but also about feeling and understanding clients´ needs. This is how 3P Biopharmaceutical works: with a highly personalized service for each client and providing solutions that go further.

3P has defined a solid differential project management model based on high flexibility and adaptation capability at any moment to the circumstances, needs and requirements of the clients. This is possible thanks to a broad reaction capacity of the team that embark in every project as a unique one.

## About the company

3P Biopharmaceuticals is a European based Contract Development Manufacturing Organisation (CDMO) specialised in the Process Development and GMP Manufacture of biopharmaceutical and cell therapy products from early stages up to clinical and commercial. The company is headquartered in Navarra, Spain, a region well known for its large pharmaceutical tradition and for having one of the top national universities, the University of Navarra.

3P has experience working with different expression systems: microbial (*Escheria Coli, Saccharomyces Cerevisiae, Hansenula Polymorpha, Pichia Pastoris)* and mammalian (CHO, BHK, HEK, Hybridomas) for the development and manufacture of Biosimilars and New Biological Entities (NBEs) like fusion proteins, vaccines, and monoclonal antibodies among others.

The company is GMP certified by AEMPS* for:

- API for clinical trials and commercial manufacture.
- QC and release of medicinal products for clinical trials and commercial manufacture.

As part of its strategy of providing an integral and complete bioproduction service; the company also offers project specific customization of many manufacturing related services, such as process validation, stability studies, formulation, advanced therapy services (cell therapy) and Master and Working cell bank generation, characterization and storage.

3P is doing an important investment not only in state-of-the-fart equipments and technology but also in qualified team with the incorporation of a downstream area that will double the current capacity for GMP DSP activity. This gives the company the control over the processes on their own premises by minimizing outsourcing that result in increased costs and production time, and in a loss of control over processes and knowledge of molecules.

## Team

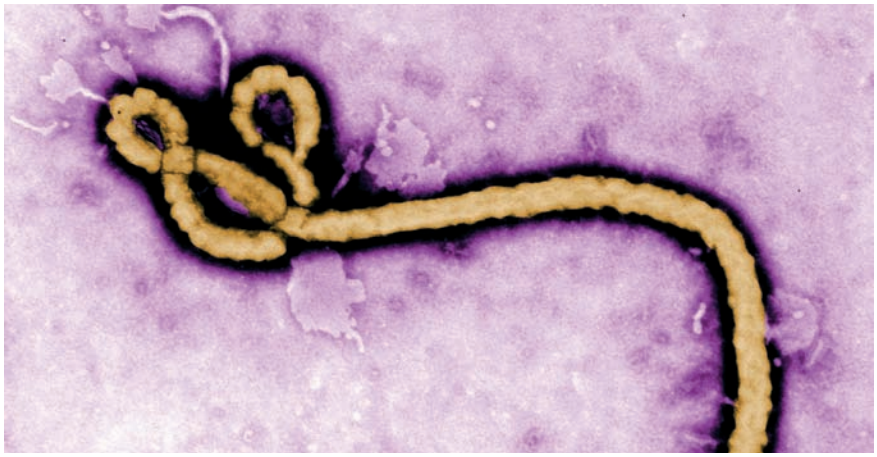
Its human resources are the most important asset of the company. In addition to high caliber and professional qualifications, it is the human qualities of the people that make 3PBiopharmaceuticals the best possible environment that works for its customers, suppliers and technology partners. In just eight years, 3P has grown its staff considerably and now has 109 people at its facilities. The 3P team is composed of highly skilled technical professionals (over 40% hold PhDs or Master Degrees) and advanced vocational education employees that offers the company a real capability of growth and development. 3P boasts a multicultural team made up of different nationalities, such as Cuban, Moldavian, American or Lithuanian that represent 20% of the complete team. The growth of the team is part of a strategic plan of consolidation to meet customers' needs in a sector where finding experienced new employees is sometimes difficult.

## Clients

3P is a global CDMO and about 70% of its clients are international. The company focuses on international strategy to expand its services to new potential markets around the world, especially across Europe and the US. The company is in particular centered on reaching FDA approval. This certification will give 3P the solidness to enter the US market and also access to clients that are interested in expanding their brand in this market. The company is working on this approval, which it expects to reach by summer 2016.

* Spanish Medicines and Sanitary Products Agency (equivalent to EMA)

**Contact**
**Edurne Gil**
**Marketing & Communications Manager**
**Tel. + 34 984346480**
**Email: egil@3pbio.com**



Picture: CDC

# Accelerating clinical studies

**Clinical Trials** The organisation and coordination of multicenter Phase II and III trials is nothing unusual for CTC North. At least half of the clinical trials, for which the full service contract research organisation (CRO) provides clinical trial management services, are initiated by non-commercial sponsors.

However, the clinical conduct of phase I trials with a non-commercial sponsor is even unusual for CTC North. Only two of the 29 Phase I trials conducted at the 35-bed study ward of the CRO within the last few years, have been Investigator-Initiated Trials (IIT).

## Case study: Ebola vaccine

One of them was the Ebola vaccine trial (NCT02283009), which is one of four harmonised clinical trials conducted within the VSV Ebola consortium (VEBCON) established by the World Health Organization (WHO) with the VSV ZEBOV vaccine. Sponsor of the trial is the University Medical Center Hamburg-Eppendorf (UKE), Principal Investigator Prof. Marylyn Addo (UKE).

What made the project special apart from the "IIT-status" were the challenging timelines. "If somebody would have told me before that we only have six weeks for protocol development and regulatory approval, I would have said that this is crazy and not feasible; but I was proven wrong," says Saskia Borregaard, Director Clinical Trial Management at CTC North. "Imagining the current Ebola situation in West Africa with the increasing amount of infected patients, a lot of night shifts and most importantly a fabulous team, we managed what seemed impossible at the beginning. It took us three weeks to develop the protocol and compile the submission package, and within three more weeks, we received regulatory approval". The following week, milestones were reached on a daily basis:

- Monday: Site initiation visit,
- Tuesday: Recruitment start,
- Wednesday: Screening start,
- Thursday: Arrival of the vaccine in Hamburg,
- Friday: Release of study drug by the QP.
- At the beginning of the following week the first patient was vaccinated in Hamburg.

The study began in November 2014, and will be completed by the end of this year. The first results, which were published in April of this year (NEJM, doi: 10.1056/NEJMoa1414216), showed antibody responses as well as mainly mild-to-moderate adverse events. A Phase II/III study is currently underway with the VSV ZEBOV vaccine in West Africa. Interim results published at the end of July in Lancet (doi: 10.1016/ S0140-6736(15)61117-5) showed that the vaccine is highly effective and safe. ■

# Value-adding perfusion-based biomanufacturing

**CONTINUOUS BIOPROCESSING** The current driver in cell culture-based manufacturing of biopharmaceuticals – increasing product yield and reducing cost – challenges the fed-batch paradigm. Because continuous processes can be conducted today in flexible single-use facilities, and because new robust and scalable cell retention devices have been developed, rational decision criteria have to be applied to choose the optimal process with respect to product quality attributes, economics and efficiency.

› by Prof. Dr. Roland Wagner, Rentschler Biotechnologie GmbH, Laupheim, Germany

Advanced fed-batch cell culture processes enable manufacturers to produce monoclonal antibodies (mAbs) in 10 gram per liter quantities within 14 days of cultivation. Using a sophisticated feeding strategy, cell concentrations above $2\times10^7$ $mL^{-1}$ are routinely reached even in 10 $m^3$ culture volumes. Until the millennium, these high cell concentrations were the exclusive field of continuously perfused cultivation concepts. Here cells were concentrated within the bioreactor by a cell retention device, and continuously supplied with as many nutrients as necessary for an optimal cell growth. However, the substantial higher risk for failure during the long-term cultivation over weeks displaced a continuous operation mode from being evaluated by biopharmaceutical manufacturing companies. This process was also supported by the dominant focus on mAbs that can be robustly produced under fed-batch conditions with an acceptable quality. Today more than 70% of all biopharmaceutical proteins produced with cell culture processes are mAbs. When the patent protection for the first generation of biopharmaceuticals expired, increased interest was aroused for participating in the market with a respective product copy. However, modern Chinese hamster ovary cell-based processes are characterised by a substantially higher efficiency, compared to the original process 20 years ago, and can therefore result in an altered product composition and quality. The high regulatory demands for these biosimilars being produced at a quality closest as possible to the original product, has forced manufacturers to re-dig into their knowledge about continuous bioprocessing. At this stage continuously perfused processes were limited to a small niche of highly complex glycoproteins, which could only be produced under quasi steady-state conditions at a constant quality.

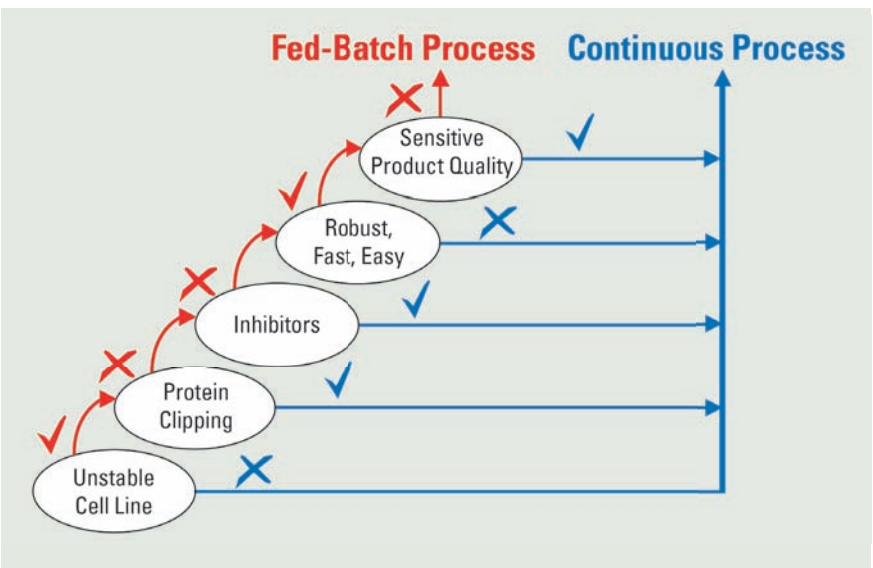



**Fig. 1: The 5-boxes guidance provides a decision diagram for easy evaluation of a fed-batch versus a continuous production process.**

Picture: Rentschler Biotechnologie

## New cell retention solutions

Although a handful of different cell retention devices are available, only the gravity settler was considered as robust enough for being scaled-up for market production. The advantage of a near-faultless operation is loaded by a high retention time and an incomplete cell filtration resulting in a cell-containing harvest. The development of new robust cell retention devices combining separation and filtration

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**Fig. 2: The 1,000 L continuously perfused single-use production bioreactor system can be connected to an alternating tangential flow filtration cell separation device.**

revealed a microfiltration module that prevents membrane clogging by an alternating tangential flow (ATF). It has been shown as robust and scalable in several processes up to 1,000 L process volume even in single use bioreactor concepts, which is one pillar of Rentschler's manufacturing capability (Fig. 2).

## Evaluating fed-batch versus continuous perfusion processes

Today, the availability of approved cell retention systems offers manufacturers the possibility to evaluate alternative process technologies with respect to economy and efficiency. Figure 1 shows a clear 5-boxes guidance which simplifies the decision process. An inevitable prerequisite for a continuous process is a long-term stability of the cell line (first box). Degradation of the protein product – e.g. by proteolytic activities (second box) during extended exposure in a fed-batch process – can be prevented by a continuously perfused operation. Cells can secrete inhibitors, which accumulate in batch processes, or feed medium components can reach inhibitory concentrations which affect cell growth and productivity such that a fed-bath process is unsuitable (third box). When a process is characterised by robustness with a high cellular growth rate and high productivity, a fed-batch process can be performed in a comparably short time period (fourth box). The last box refers to the product quality. When a suitable quality can only be obtained under constant environmental production conditions, a continuous process is without any alternative.

In conclusion, there is no fundamental philosophy but an imperative necessity that put pressure on manufacturers to decide on a continuously perfused production process. The far-reaching evaluation should be based on a rational decision strategy covering aspects of product quality and process economy as well as sustainability. Although various cell retention systems using centrifugation, filtration, settling, acoustic, hydrodynamics as well as entrapment and immurement techniques are available, tangential flow filtration is increasingly accepted when processes touch the production scale.

The product costs per gram are in the same range when comparing a 14-day 10,000 L fed-batch process with 23 batches over the year with a 40-day 1,000 L continuously perfused cultivation comprising 30 harvests and eight yearly batches. ■

# Next-gen capsules

**Sartorius** The Göttingen-based provider of cutting-edge bioprocess products and services has redesigned its Sartobind membrane adsorber capsules to offer higher binding capacities, reduced void volumes, less buffer consumption and lower operational costs.

"Traditionally, membrane adsorbers have been using available filter housings, often ignoring chromatographic process parameters, such as backmixing effects and elution volumes. The next generation membrane adsorber capsules takes these specific requirements into account and reflects substantial progress for bind and elute

**Sartobind® membrane adsorbers: the new design of capsules enables higher binding capacities and reduced void volumes**

applications," commented Dr. Fischer-Frühholz, membrane chromatography expert at Sartorius.

Furthermore, Sartorius Stedim Biotech has added new 400 ml and 800 ml Sartobind Q, S and Phenyl capsules with an 8 mm bed height to its portfolio. The optimised capsules increase dynamic binding capacity up to 48% when compared to adsorbers installed in filter housings.

**CONTACT**
**Sartorius Stedim Biotech**
**Göttingen, Germany**
**Tel.: +49-551-308-2967**
**Fax: +49-551-308-3289**
**info@sartorius-stedim.com**
**www.sartorius.com**

Pictures: Rentschler Biotechnologie (left), Sartorius Stedim Biotech (right)

# The key to EDC efficiency and effective eCRF design

**CLINICAL TRIALS** OPIS responds to the latest industry requirements in electronic data capture (EDC) with CLINICAL.NET version 3.0.

› by Fabio Renna, Opis s.r.l, Desio, Italy

Information Technology is transforming the clinical research industry and clinical trial execution has long moved away from paper-based processes. Today, electronic data capture (EDC), mobile, social, cloud and big data are revolutionising the business. These technologies have led to the development of increasingly sophisticated medical devices, they have reshaped the collection of clinical research data processes and they have allowed for more responsive trial design, alternative monitoring possibilities and real time data processing.

## Clinical.net study portal

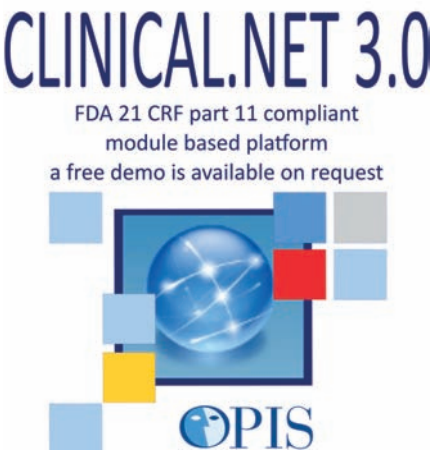
The OPIS clinical IT team have just released version 3.0 of the CLINICAL.NET Study portal. It is an upgrade from the previous version 2.0 and Clinical IT Manager, Fabio Renna and Head of Systems Development, Salvatore Scarciglia explain that the new version is the fruit of intelligent design stemming from the latest developments and trends in the industry. Encouraging innovation undeniably helps to unlock potential in the ad-

vancement of medical research but it remains a daunting task for IT developers and system analysts. Not only do they need to satisfy increasing demand from Sponsors and Regulatory bodies to ensure data authenticity and compliance with stricter data protection regulations, they also need to facilitate the importation, integration and elaboration of more data, more frequently, anywhere, anytime and on any device.

OPIS has found the key to successful electronic Case Report Form (eCRF) design: doing it in-house makes all the difference; it is faster, it is cheaper and above all, the fact that there is no dependency on external software suppliers or commercial clinical software, means that OPIS provide its clients with extremely customisable solutions.

## Seamless single-source service

A highly specialised, in-house Clinical IT team collaborates closely with the OPIS Medical, Biometrics and Quality departments to streamline all processes of clinical software development. Protocol design, user requirements, functionality specifications and validation requirements are tailored to suit Sponsor and Regulatory specifications to a T. The OPIS




team guarantees an average time of ten days to create a ready-to-launch platform that needs only collection of study specific data. The system is module-based and any additional modules can be added at a later stage. Removing modules and upgrading the system are painless and can be done when need arises.

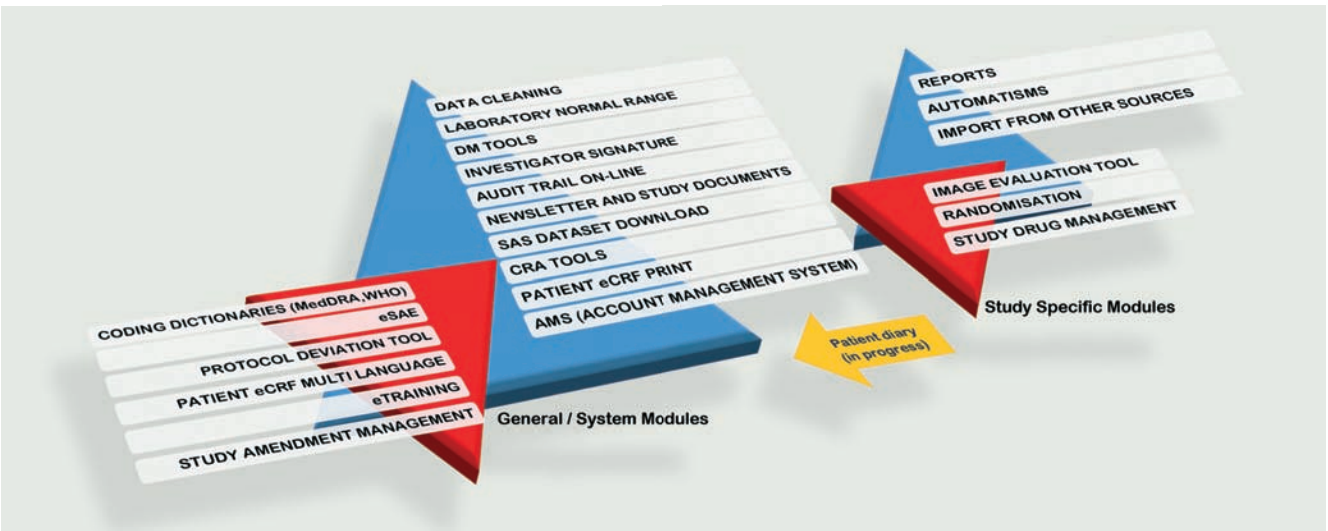
Version 3.0 is fully FDA 21 CFR part11 compliant, web-based and able to interface with validated systems of Sponsors, central laboratories, Imaging providers and even mobile and wearable devices. Version 3.0 was designed to integrate and facilitate e-Data Capture and e-Imaging frequently required by treatments based on NGS (Next Generation Sequencing) technologies for example. Added modules for eSAE and protocol deviation allow for immediate data processing and an embedded IWRS ensures proper online randomization and drug supply management.

Another attractive aspect of the upgraded version is improved user experience. CLINICAL.NET 3.0 is extremely user-friendly and the need for extensive training in how to use the platform is greatly reduced. Status of elaborated data is easily extractable as reports or graphs and feedback and alerts e.g. about new randomisation, SAE or clinical worsening, are communicated via email. All communication goes through the server and no other forms of communication is necessary.

## Conclusion

In short, EDC efficiency for OPIS means putting into place processes that streamline data collection and data cleaning, facilitate monitoring, query reporting, guarantee data access in real time, and ensure compliance with FDA guidelines and Sponsor SOPs. A highly skilled team, proper management of resources and respecting timelines guarantee value, a cut above the rest.

For more information about OPIS and its services, please visit our website www.opis.it or contact *fabio.renna@opis.it*. ■




**OPIS CLINICAL.NET 3.0 : a Customisable platform with user-friendly modules for unimpeded EDC**

Pictures: Centers of Disease Control

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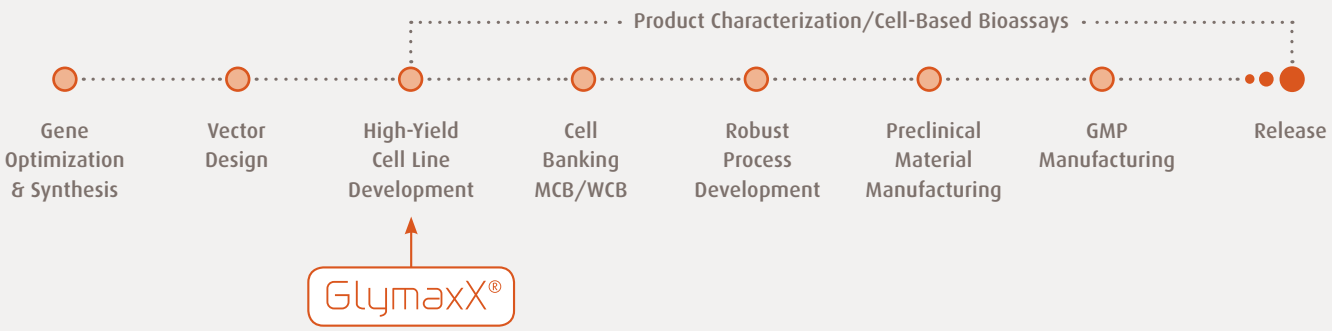


# A CMO perspective on in-vitro testing of biosimilars

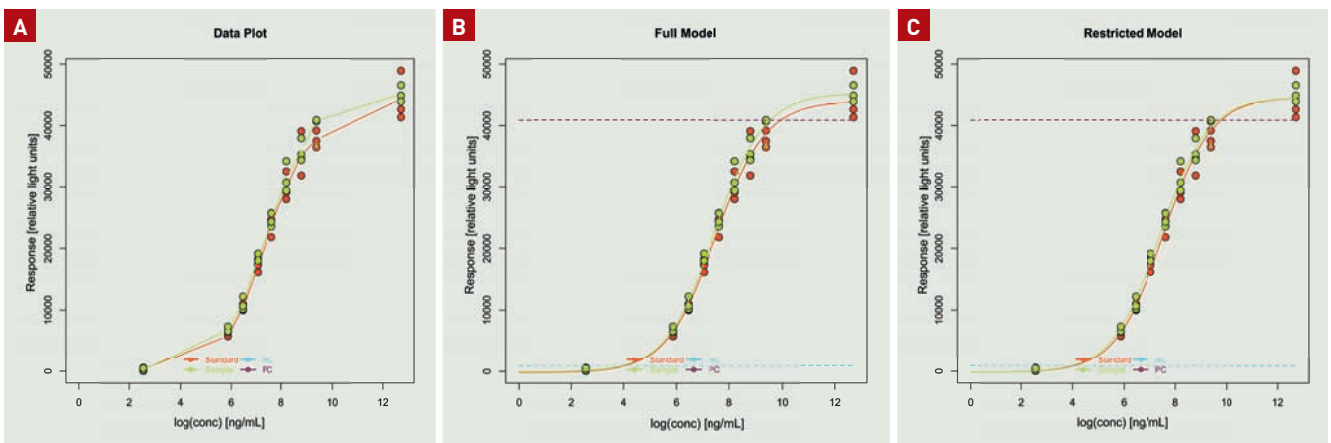
**CONTRACT DEVELOPMENT & MANUFACTURING** In-vitro studies gain high recognition in the authorisation package for biosimilars. They define the extent of in-vivo studies required both in the antibody biosimilar guideline released by the EMA three years ago, and in this year's FDA guideline for biosimilars.

› by Christian Demmler and Christoph Giese, Bioassay Group, ProBioGen AG, Berlin, Germany

As early as in 1998, the European Medicines Agency (EMA) started to discuss guidelines for "comparability of biotechnology-derived products", later designated as "biosimilars". Besides those referring to general quality aspects, a portfolio of guidelines for specific products was issued in the following years. Because of this and viewed from a global perspective, the EMA became a regulatory pioneer in the field of biosimilars. In the US, for example, this process took significantly longer. It wasn't until April 2015 that the US Food and Drug Administration (FDA) issued their guidelines for demonstrating the biosimilarity of therapeutic proteins[1, 2].

Although EMA was the first to start regulating the biosimilar field, it took until June 2012 before the authority published the requirements for therapeutic antibodies, one of the most important classes of biologicals. The draft was adopted by the Committee for Medical Products for Human Use (CHMP) and came into effect in December 2012[3]. Meanwhile, many other regulated markets have followed this model with comparable guidelines. As a result of this, the non-clinical part has gained higher recognition, with a focus on in-vitro studies since these are regarded as more specific and sensitive than in-vivo studies in animals. The results of the in-vitro studies also define if, or to what extent in-vivo studies will be required.

The first in-vitro studies should be conducted in an early phase of development because they will already give details about the properties of the molecule, e.g. in respect of its biologic activity and its immunological properties. Based on these data, the future quality limits may be set and the decision for the optimal host cell line and the most suitable process parameters will be facilitated. Although they are often time-consuming and laborious, in-vitro studies can prevent project delays and, thus financial loss if the final product does not match the originator product, or if later clinical studies fail due to non-matching biosimilarity. Therefore, it is vital to select a development partner (CMO) who is experienced to carry out, optimise and validate the required assays along the cell line and process development, up to GMP manufacturing for clinical trials supplies. The assays have to be com-




**Dose-response curves derived from a TNF-α neutralising assay in the course of an adalimumab biosimilar development at ProBioGen. The three diagrams show the raw dataset (A), an unrestricted (B) and a restricted (C) curve fit derived from PLA 3.0 software.**

Pictures: VTU Technology

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parative in nature and an appropriate number of originator batches must be sourced to confirm the future specification limits of the biosimilar, at best on a statistical base. The guideline on "Similar Biological Medicinal Products Containing Biotechnology-derived Proteins ..."[4] is more specific regarding the number of originator batches needed. It states that this is dependent on batch-to-batch variances with numbers between 10 and 30 seen in the industry, and is also dependent on the availability of batches and their intended geographical markets.

## Classification of MoAs

The mechanisms of action (MoA) of antibodies can be classified into Fab- and Fc-associated ones and they can be typically divided into three groups comprising (evoking) cell killing, blocking/activation or neutralisation of soluble factors. A list of respective assays is mentioned in the guideline in order to assess the differences between the biosimilar and the reference product. These assays can be divided into binding and functional assays and include:

- Binding to the target antigen
- Binding to all Fc receptors, FcRn and complement
- Fab-associated functions (e.g. neutralisation, receptor activation/blockade)
- Fc-associated functions (ADCC and CDC assays, complement activation).

The assays should be conducted in a full set, even though some may not be considered necessary for the proposed MoA. This is especially relevant for antibodies which neutralise soluble factors or block or activate cell-bound antigens such as receptors. In the latter case, it should be demonstrated that cell killing is not mediated by the antibody or by receptor-bound antigen-antibody complexes.

Early establishment and qualification of such assays for the establishment of equivalence margins is crucial in biosimilar development and these assays must be optimised in order to generate meaningful datasets. Functional and binding assays have gained more focus due to the detailed guidance by the EMA and can be regarded as a cornerstone during biosimilar development. ■

## References

[1] Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product; April 2015. www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291134.pdf
[2] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; April 2015. www.fda.gov/downloads/DrugsGuidance-ComplianceRegulatoryInformation/Guidances/UCM291128.pdf
[3] Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-clinical and Clinical Issues; May 30, 2012. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf
[4] Guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues; Dec. 18, 2014. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf

# Sartorius' tech for GE brands

German-French bioprocessing supplier Sartorius Stedim Biotech from Göttingen, and GE Healthcare's US-based Life Sciences business entered into a worldwide OEM supply agreement at the beginning of September. Sartorius will manufacture membrane adsorbers based on its Sartobind technology. GE will market the products as part of its "ReadyToProcess" product offerings. Membrane adsorber ion-exchange technology is widely used in the industry for the removal of contaminants such as endotoxins and viruses during the production of protein-based drugs. Financial terms were not disclosed. ■


**Sartorius Stedim Biotech's production site in Aubagne, France**

Picture: Sartorius

# Going Nuclear

Danish Novo Nordisk decided at the end of August to build up API manufacturing capabilities in the US. The drugmaker plans to invest up to $2bn to build both a new plant in Clayton, North Carolina – in the neighbourhood of an existing plant – and to expand a finished product site in Måløv, Denmark. "The US is by far our largest market," said Katrine Rud von Sperling, Spokeswoman of Novo. When the new facility becomes operational in 2020, it will focus solely on producing finished API from raw material shipped to the site. A large proportion of staff employed in Clayton have military backgrounds. The reason: according to a Novo spokesperson the veterans' familiarity with strict military rules is an ideal preparation for working in the regulated pharmaceutical industry, citing veterans with aviation experience and those who have served on nuclear submarines, as particularly well suited. ■

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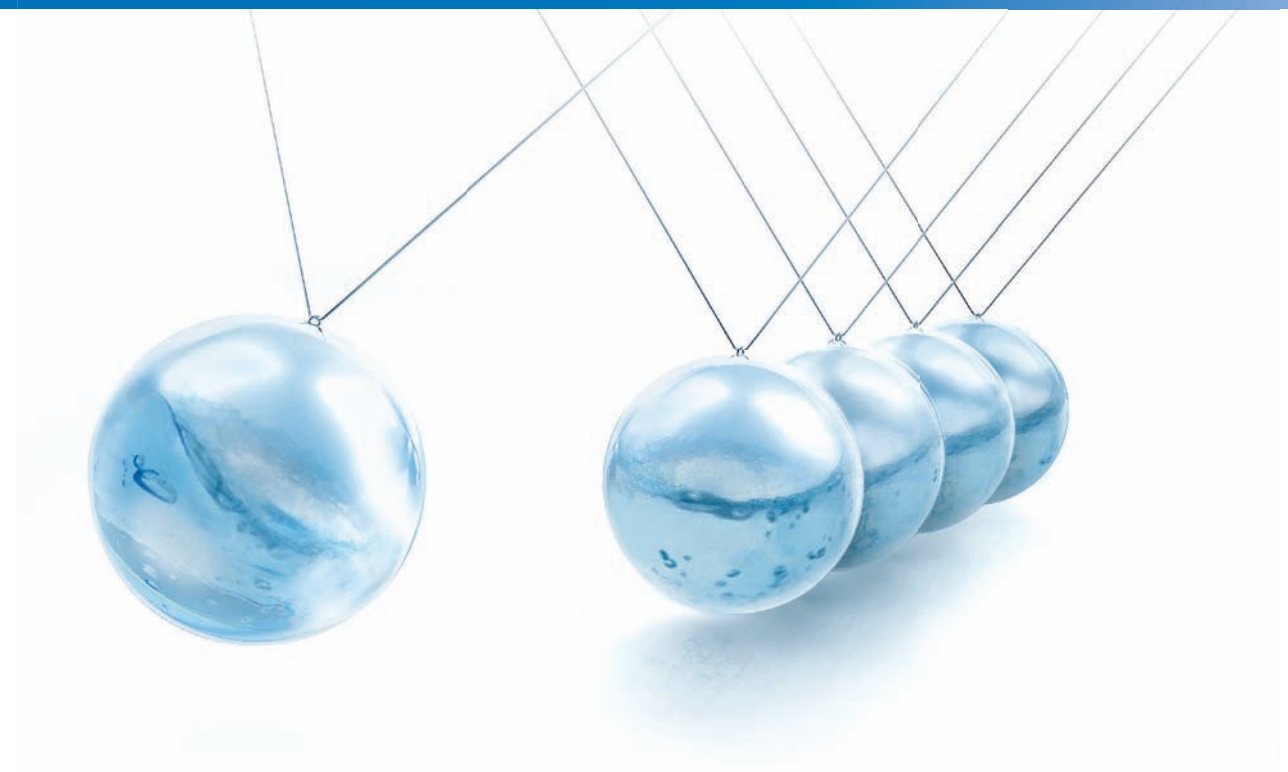

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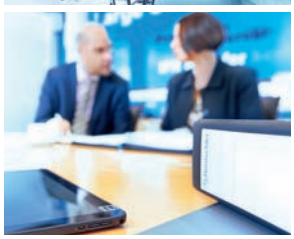

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