European Biotechnology

Autumn 2017

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CUSTOMBIOTECH

Preparing for the next generation of biologics

BIOMANUFACTURING While the FDA and EMA have for the first time okayed the switch from batch to continuous manufacture of a pill – Janssen Cilag's HIV protease inhibitor darunavir (Prezista) – the industry is still waiting for such a signal in the biologics field. The FDA wants to boost adoption, and biopharma majors, such as Novartis, Amgen and Biogen, launched a pilot project to lay the groundwork for the next generation of production: continous USP and DSP, and alternatives to CHO cells.

While Biogen claims its 4 x 18,500L fed-batch biologics manufacturing plant – set to take up operations by 2019 in Luterbach, Switzerland – is "next generation," Basel-based pharma major Novartis will be completing a 10-year collaboration with MIT to establish a Novartis-MIT Center for Continuous Manufacturing only a bit later. US and EU regulators have sent out strong signals supporting the shift from fed-batch to continous processes. Apparently, regulators are convinced it would allow more consistent process control and simpler application of process analytical technology, resulting in more reproducible product quality.

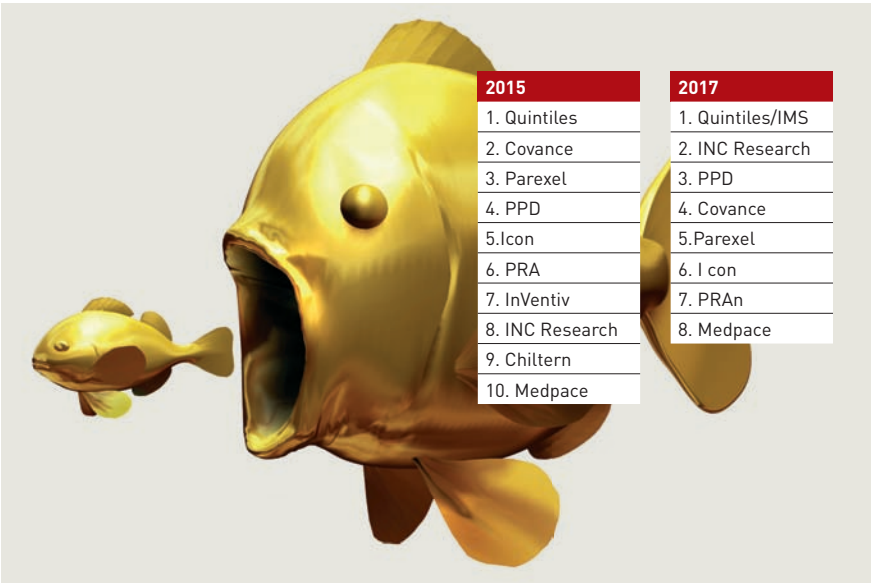
Switch to new processes and production systems

Suppliers, such as Pall and Lewa Process Technology, have taken up the idea and most recently launched systems for continous chromatography (see European Biotechnology, Summer edition 2017) expected to overcome the bottleneck in downstream processing capacity the industry has suffered in the past decades of growing yields from mammalian cell-based biomanufacturing. The move could energise the market for bioprocessing equipment, which suffered from a drop to mid-one-digit-per cent growth in H1/2017 compared to double digit expansion in previous years. Projections from Bioplan Associates' 14th Annual Industry Survey, however, point to the "optimism" of suppliers that could "translate into investment," says Eric Langer, the company's president.

Feeling the cost pressure from drug developers, cell line developers and CDMOs are seeking to further improve productivity of CHO cells, the industry's working horse for biologics manufacturing, a market that has grown to more than US$70bn in annual sales. In August, Horizon Discovery published the complete annotated DNA sequence of its CHO-K1 cell line in hopes of driving cell line innovation. While 81% of biologics manufactured today stem from mammalian cell culture, companies such as Bio-

Picture: Boehringer Ingelheim

Biomanufacturing of biosimilar adalimumab at Boehringer Ingelheim. The Humira copycat drug received FDA approval at the end of August. Currently, only a fraction of the roughly 650 marketed biologics are biosimilars. To date, six biosimilars have been approved by the FDA and 29 got the green light from the EMA.



Consolidation of the world's largest clinical research organisations (CROs) already shows impact on the market of mid-size CROs.

gen and Dyadic International are already testing alternatives. This April, Biogen's VP of International Manufacturing Operations, Eliana Clark, said CHO cells wouldn't be Biogen's first choice for cheap production of biologics in the future. Dyadic International, which produces yeast strains, wants to make its C1 expression platform as effective for biologics production as it is for biofuels manufacture, where it yields up to 80g/l.

Clark said that Biogen co-funds a project with the Bill & Melinda Gates Foundation and the MIT Center for Biomedical Innovation (led by Biogen's Head of QbD, Rohin Mhatre) that would allow a departure from the safe but costly production in CHO cells. In an 18-month effort, researchers at MIT and Biogen have engineered eight alternative hosts for the production of human antibodies, including fungal (such as yeast and chytrids), algae (diatom) and trypanosome (leishmanial) systems to produce full-length mAbs. Results of the systematic comparison will be presented in Q3/2017. Mark Emalfarb, CEO of Dyadic International predicts that limitations of CHO cells in the production of modern, engineered antibody formats will convince producers to select more effective production systems.

Serialisation: 50% of CMOs not prepared

Full CDMO service providers such as Polpharma (see p. 64) told European Biotechnology that they have just begun to test alternative cell lines besides its proprietary mammalian cell lines and bacterial expression systems for biologics and biosimilar production. According to Markets & Markets, the Global Healthcare Track and Trace Solutions Market is projected to reach US-$2.81bn by 2021, at a CAGR of 17.3% from 2016 to 2021. However, deadlines for including unique product identifiers on prescription drugs are putting a strain on biopharma companies and CMOs, many of which are ill-prepared to meet the targets. Accordingly, the US Food and Drug Administration (FDA) extended the deadline this summer for the US Drug Supply Chain Security Act (DSCSA) to November 2018. European companies, however, won't be able to sell any prescription drugs after 9 February, 2019, unless they meet the serialization requirements set out by EU regulators. In September, serialization solutions company Adents passed the certification test at the European Medicines Verification Organization (EMVO) for connection to the European Hub. Five hundred days before the EU's falsified medicines rules will get into application, many companies are far away from uploading their serialisation data through the gateway provider. According to supply chain services provider Tracelink, as many as 400 contract manufacturing organisations (CMOs) will not be ready for upcoming US and EU track-and-trace regulations.

CROs: Brexit to impact 1,000 companies

Globally, companies in the contract research market face strong headwinds. Following criticism from Big Pharma about the pricing of CRO services, analysts expected a downturn in bookings. However, as bookings from small and mid-sized biotechs increased in Q2/2017, big shots in the CRO segment, such as INC, seemed to sidestep critics from larger firms by increasingly focussing on small biopharma clients. In fact, SMEs contributed to 47% of INC's sales in H1/2017 vs 41% as of H1/2016. The big CROs' interest in SME customers puts pressure on mid-sized CROs, which have traditionally made a good deal (70–80%) of their revenues) in the SME segment.

In Europe, Brexit puts pressure on UK-based companies. While the UK government announced in September it wants to increase the number of clinical trials by 50%, the expected move of the EMA from London to (most probably) Amsterdam shows that it is totally unclear what will happen after the nation's EU exit in 2019 to CROs located in the UK. According to the CEO of IAOCR, Jacqueline Johnson North, Brexit will have a big impact on about 990 entities related to the contract research sector, which mostly believe that Brexit will have a negative impact on the UK's CROs. According to EU rules, non-EU drug manufacturers

Picture: fotolia-cion/ diezartwork

will need to import their drugs and cannot participate in the EU's centralised procedure for market authorisation which applies to all biological medicines. After UK's pharma major GlaxoSmithKline announced it will turn away its investments from its home base (see p. 64), the UK government published a position paper calling on it to maintain close ties with the EU's Horizon2020 programme and the EMA.

Real world data integration

Another long-term challenge for CROs may come from their clients' interest in collecting real-world evidence for assessing the safety and efficacy of drug candidates (see p. 16). "This would bring speed into the system," Roche Pharma AG's Head, Hagen Pfundner, told European Biotechnology.

Real-world evidence could become relevant in drug development very rapidly. In-mid September, FDA Commissioner Scott Gottlieb stressed the development costs of pharmaceuticals had become "unsustainable" and announced that the FDA will modernize the collection of clinical data through adaptive or seamless trials, which would go from first-in-man testing through approval in a single continuous trial. Previously, CDER director Janet Woodcock and colleagues had reinforced the FDA's stance on the incorporation of real-world evidence into clinical trials. According to Woodcock, clinical trials and real-world evidence are complementary and studying electronic medical records (EMRs) can be cheaper than RCTs and help answer questions regarding individual dosing and long-term outcomes and side effects. In June, EMR specialist Flatiron Health announced upcoming collaborations with the FDA and the National Cancer Institute (NCI) to explore how real-world evidence derived from de-identified patient data captured at the point of care can be used for clinical trial design and prospective research studies. The collaboration will explore how real-world evidence derived from Flatiron's melanoma and non-small cell lung cancer datasets can be used to improve study planning, inform sample size calculations, ease study implementation, better understand current trends in standard of care, and address specific study planning questions.

Cheaper than expected

Overall, biopharma companies are apparently searching for partners to help them adapt to increasing costs in order to meet shareholder expectations. A new estimate on the average development cost of cancer meds, published 9/11 in JAMA (doi: 10.1001(jamainternmed.2017.3601), however, could become a earthquake to the sector. Sham Mailankody from Sloan Kettering Cancer Center estimated the median development cost of 10 single cancer meds at US$648m each, while median revenues of every drug almost hit US$6.7.bn ■

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Celonic is a strong believer in risk/reward sharing business models to create win-win value propositions. Celonic is ambitious, driven by the courage to think big and the commitment to **get it done**.

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EXCELLENCE

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Expanding scale and reach

POLPHARMA BIOLOGICS Flexible and reliable contract manufacturing and development have become the key success factor in the development of biopharmaceuticals. Due to the long process time and high investment needed to build up production capacities, outsourcing of biologics manufacturing provides both access to advanced technologies and necessary capacity along with flexibility in timing and output.

› Federico Polano, Global Business Development & Contract Manufacturing Director, Polpharma Biologics

One-stop shop CDMOs that offer a comprehensive portfolio of services supporting the entire biopharmaceutical development cycle have a clear competitive advantage. Ideally, such CDMOs are located where they can readily support the European and North American markets, which account for most of the consumption of biologic drugs.

In 2013, Polpharma Group started to establish state-of-the-art capabilities to support in-house and contract development of biopharmaceuticals. With more than 80 years of experience producing generics and small molecule medicines, and as one of the largest pharmaceutical companies in Central and Eastern Europe, Polpharma has extensive expertise in GMP/regulatory compliance and quality assurance to support such an endeavor in the EMA regulatory environment.

Polpharma Biologics, established as a division of Polpharma Group in 2013, today has a biopharmaceutical pipeline in advanced stages. Cell-line development capabilities were added in 2016 with the acquisition of Bioceros in the Netherlands. Polpharma Biologics is currently expanding its capability to produce final drug product (5 million vials/syringes per year) at its Gdansk facility. Construction of a commercial manufacturing facility at Duchnice, near Warsaw, is underway, which will eventually have 12 x 2,000-liter production trains and an annual fill-finish capacity of 30 million vials and syringes. Both expansions will be operational for drug substance and drug product manufacturing in 2019.

Committed to quality, pace and cost-efficiency

Polpharma Biologics has been specifically structured as a European CDMO that serves global market needs and offers fully integrated solutions along the development and production value chain for biologics and biosimilars. It provides fast, flexible, responsive service with a focus on mammalian cell culture and capabilities, spanning the full-range from cell line, process and analytical development to GMP manufacture of drug substance and drug product meeting international quality standards.

Low production costs have become compulsory to keep a project successful. High-yielding cell lines allow the use of smaller scale upstream and downstream processing equipment, resulting in reduced capital expenditure and the potential for fewer batches per year for lower operating costs. For more than 25 years, Bioceros has generated high-yield production cell lines for both biosimilar and innovative proteins through its proprietary CHO-BC® platform. It is complemented by a comprehensive toolbox for targeted modulation of posttranslational modifications to accomplish fingerprint biosimilarity, which can be readily analysed using robust in-house bioassays.

With its one-stop shop approach, Polpharma Biologics is positioned to provide a comprehensive range of services tailored to each individual project, including de novo process development, process optimisation, and manufacturing of fully developed processes.

Clinical manufacturing takes place at the Gdansk site, which houses bioreactors that contain volumes up to 1,000 or 2x1000 liters for cell culture and 500 liters for *E. coli* fermentation processes. Commercial GMP manufacturing using scale-down models, as well as high-throughput mini- and regular bioreactor systems for parallel screening will be operational at the new Duchnice facility by 2019. With up to 12x2000 liters disposable high-end production set-up, we represent the new benchmark within Europe in terms of cost of production and flexibility. ■

2019 in operation: large scale cell culture plant (up to 12x2000l) incl. fill&finish (30 million vials/PFS p.a. incl. lyophilsation) at Duchnice close to Warsaw

Picture: Polpharma Biologics

Rentschler Biopharma

Passion for Performance

Rentschler Biopharma – A world-class biopharmaceutical CDMO

Full service from gene to vial and from concept to market

Best-in-class formulations provide significant competitive advantages

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LEUKOCARE BIOTECHNOLOGY

Complete solutions with state-of-the-art fill and finish facilites

Strategic Partnership with

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Insight into biomarkers

AYOXXA'S LUNARIS™ PLATFORM In a case study "Translational proteomics: a new perspective for ophthalmology research," Ayoxxa gives insights into the capabilities of its Lunaris multiplex protein analysis platform.

› Dr. Matthias Jansen, Senior Product Manager, AYOXXA Biosystems, Germany

Up to 80% of people who have suffered from diabetes for 20 years or more are afflicted with diabetic retinopathy (DR), which is the leading cause of blindness through damage to the retina. The longer a patient suffers from diabetes, the higher the risk to develop DR. It has been estimated that up to 90% of new cases could be eliminated or reduced in severity, if reliable screening tests were available. By being integrated into routine screenings, such tests could help to identify initial signs of retinopathy as early as possible and help physicians to initiate the right treatment in time.

Inflammation and vascularisation play a significant role in ophthalmic diseases and reliable monitoring techniques are required for the analysis of related biomarkers from vitreous and aqueous humor of diabetes patients. However, samples from such sources are limited and current proteomic biomarker detection methods require relatively large sample volumes, which in some patients may be difficult to obtain without having to undergo a vitrectomy. This is where AYOXXA's innovative automated beads-on-a-chip multiplex protein analysis system kicks in. LUNARIS™ assays can be performed with sample volumes as low as 3µl – which represents about 1/10 of the volume required by comparable multiplex technologies.

Assays for translational research

But this is not the whole story. Scientists in clinical laboratories who correlate proteomic interactions to pathogenesis in various fields, including ophthalmology and immunology, need to build on a robust and reliable platform. To transfer lab findings through to validation in clinical trials, the platform needs to deliver scalability, flexibility and robust data quality.

AYOXXA's LUNARIS™ system combines the advantages of a bead-based multiplexing approach plus the reliability and scalability of a plate-based format with the simplicity of image-based analysis. The system is comprised of a dedicated reader, automated analysis software, and a growing portfolio of LUNARIS™ multiplex protein assay kits for the detection and quantification of soluble inflammation and immune-response markers.

Highest quality of data through superior accuracy and precision

AYOXXA offers a variety of disease related panels, including the newly introduced LUNARIS™ Human 11-Plex Ophthalmology Kit for the detection of the most important biomarkers for age-related macular degeneration and diabetic retinopathy. Additionally, AYOXXA offers the LUNARIS™ Mouse 12-Plex Th17 Kit to help elucidate Th17 cell biology in murine models of autoimmune disorders and immune mediated conditions.

Picture: Ayoxxa

Image-based readout combined with the planar beads-on-a-chip format make the LUNARIS™ system very robust and capable of delivering best-in-class data quality. The spatial separation of the individual coated beads in a pre-defined array help to avoid quenching effects and to reduce artifacts due to potential bead clumping, ensuring the best possible accuracy and precision. The readout captures an image of all of the thousands of beads within the reaction well, leaving no bead unread. This exhaustive sampling, combined with robust plate-based workflow, helps achieve coefficients of variation (CVs) in the range of 10% or better.

Flexibility in scalability and formats

LUNARIS™ BioChips have been designed as a modular system with formats from 32- to 384-well density and are compatible with liquid handling system integration, allowing full scalability for low- to high-throughput applications. LUNARIS™ has proven to be highly efficient for multiplex immunoassays – which are the primary format commercially available today. However, the system can potentially also be used for other binding or capture assays in the same modular plate-based format.

Researchers in academia and in leading pharmaceutical companies have already tested thousands of samples using LUNARIS™ and have found the assays enable their research. The superior features make LUNARIS™ an ideal choice for state-of-the-art biomarker screening and validation. ■

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Advanced formulations for biopharmaceuticals

BIOLOGICS In the past, the role of customised and tailored formulations have been largely underestimated in the field of biopharmaceutical product development. An advanced formulation strategy can strongly improve the product, leading to significant customer benefits. The growing and increasingly competitive biopharmaceutical market requires individual solutions, particularly for better product stability and prolonged shelf life.

› Martin Scholz, CSO, Leukocare AG, and Stefan Schmidt, CSO, Rentschler Biotechnologie GmbH

Advanced and customised formulations not only enable the biopharmaceutical manufacturer to be more economical with even a higher product quality compared to competitor products but also help to generate intellectual property and to extend patent life span.

Customer benefits in focus

Advanced biopharmaceutical formulations enhance product stability, allowing the manufacturer to avoid a variety of additional indirect costs, which may include costs related to regulatory issues, brand risk, loss of product efficacy, back office invoicing, packaging, management time, patent safety, monitoring, and product recovery.

Achieving maximum product potential, which requires highest stability, is essential for the biopharmaceutical manufacturer. Improved stability through advanced formulations provides many advantages to manufacturers: i.e. allowing for higher temperature storage with self-applied biopharmaceuticals in pre-filled devices, for high concentrated subcutaneous application, or for the avoidance of lyophilisation steps. For all these approaches the cold chain aspect has to be considered. For example, it is a clear advantage for a manufacturer to provide products with longer shelf life, either when stored at 2–8 °C or even at ambient temperature. For instance, competitive advantages have been achieved by modified formulations that increased stability of therapeutic antibodies against psoriasis. Specifically, the antibody secukinumab (Cosentyx®) has a shelf life of only 18 months in the EU when stored at 2–8 °C. Advanced formulation by competitors resulted in a 24 month shelf life at 2–8 °C and was approved in the EU for storage up to five days at ≤ 30 °C (Taltz®) and in the US for up to 14 days at room temperature ≤ 25 °C (Siliq®).

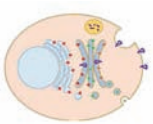
Molecule design	Host cell selection	Upstream process	Downstream process	Fill finish
				
› Sequence › Hydrophobicity	› Proteases › Oxidative stress › Media components › Posttranslational modifications	› Stirring › Temperature › pH › Trace metals › Osmolality › Air/liquid interface	› Pressure › Shear forces › Mixing › pH › Air/liquid interface › Light	› Agitation › Shear forces › Excipients › Oxidation › Freeze-thaw › Light

Figure 1: Stress factors during processing

Formulation matters

Currently, standards do not leverage the strategic opportunities of advanced formulation development and consider formulation too late in product development. This can delay development programmes, if product opportunities are not maximised prior to Phase II trials. Changes of formulations after Phase II may require additional studies, costs, and delays. Early product stabilisation and selection of a commercially viable formulation during manufacturing ensures shorter time lines and greater probability of success later in clinical studies and commercialisation. Multiple processing steps associated with mechanical, chemical, and temperature

Picture: Rentschler

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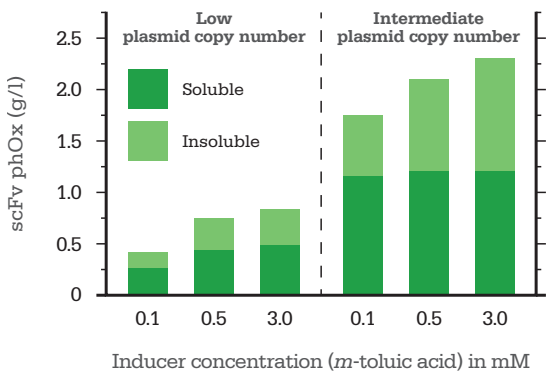

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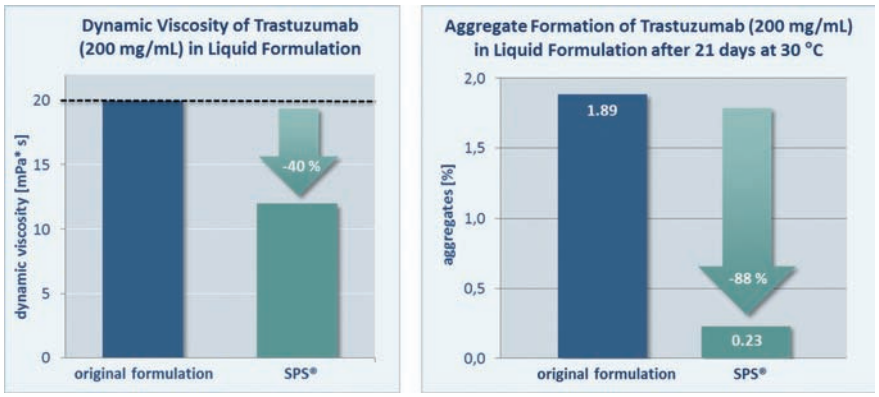

Figure 2: Example for quality increase by SPS®

stress during drug substance and drug product development result in cumulating molecular changes. Therefore, tailoring the stabilising formulation by considering process-specific stresses should be integrated early in the manufacturing process, i.e. immediately after harvesting the biomolecule.

From gene-to-vial processing

Current strategies of biologics manufacturers are aimed at increasing product quality. This already starts with molecule design and the selection of producer cell lines optimising the output while limiting side products such as protein fragments. But it also includes efforts in upstream processes through chemically defined media or tighter online monitoring. Similar efforts have been undertaken for downstream steps focusing on chromatography resins with higher specificity and resolution.

Particularly during the downstream manufacturing process, protein molecules are exposed to physical stress factors, such as stirring and mixing in conditioning steps, or shear stress in filtration operations or under high pressure. Chemical stress impacting protein stability is often connected to non-physiological pH values – for instance in low pH elutions from affinity columns at high protein concentrations. Both stress sources (Figure 1) can result in degradation or aggregation of the proteins, ultimately leading to loss of function or causing immunogenicity problems. High molecular weight aggregates can be eliminated during downstream processing. However, this will reduce the overall yield and the process efficiency by potentially requiring additional unit operations.

It has been shown in long-term stability studies that trace amounts of aggregates can act as nuclei for further aggregation thus limiting the shelf life of parenteral drugs in liquid formulation. As low-level product-related impurities are very hard to eliminate completely, other strategies, such as formulation optimisation to prevent the increase of aggregation during the shelf life, are strongly recommended.

Currently, most standard formulations are sufficient to support the typical short shelf life in clinical programmes. However, they are often not sufficient to support storage expectations for commercialisation. This means efforts should be undertaken relatively early to establish an advanced formulation and its implementation strategy to facilitate the delivery of competitive formulations. This holds particularly true in crowded indications or for second generation biosimilars where optimised formulations might give the competitive advantage to gain a larger market share.

SPS® in gene-to-vial processing

The SPS® formulation technology development platform is a best-in-class formulation platform for the stabilisation of proteins, like biopharmaceuticals, to intensify the development of better products. This includes improved product stability during refrigerated or even unrefrigerated distribution and storage, prolonged shelf life, as well as subcutaneous administration of high concentration liquid products etc. The sophisticated backbone of the SPS® technology platform is a library and database-based rational design approach. By means of this approach more than 100 different, regulatory well-known excipients are combined in order to select the most suitable excipient combinations, concentrations, and ratios for the individual biopharmaceutical product. The strength of the SPS® technology platform lies in the IP-protected amino acid-based formulation strategy in conjunction with the SPS® database, excipient library, and DoE support. All excipients used in SPS® are listed in relevant pharmacopoeias (USP, EP, JP, etc.) and/or as inactive ingredients by the FDA. According to the principles of preferential exclusion and preferential binding, SPS® formulations were already shown to be easily adaptable to a broad range of target molecules and requirements for dry and liquid products. The molecular integrity and functionality are the key analytic aspects to monitor the efficacy of the iteratively optimized and finally tailored SPS® formulations. As an example, SPS® significantly improved stability of the therapeutic IgG antibody trastuzumab during different processing stress conditions – i.e. accelerated aging – even in high concentration liquid formulation. SPS®-formulations avoided aggregation and fragmentation of trastuzumab even at concentrations ≥ 200 mg/ml and exhibited significantly reduced viscosity versus the original formulation (Figure 2).

Benefits of SPS®

The better product quality achieved by SPS® included in gene-to-vial processing and manufacturing helps the customer to realise significant competitive advantages in the market. ■

Picture: Leukocare

AYOXXA
Biosystems

LUNARIS™

AYOXXA's innovative multiplex protein technology for translational proteomics

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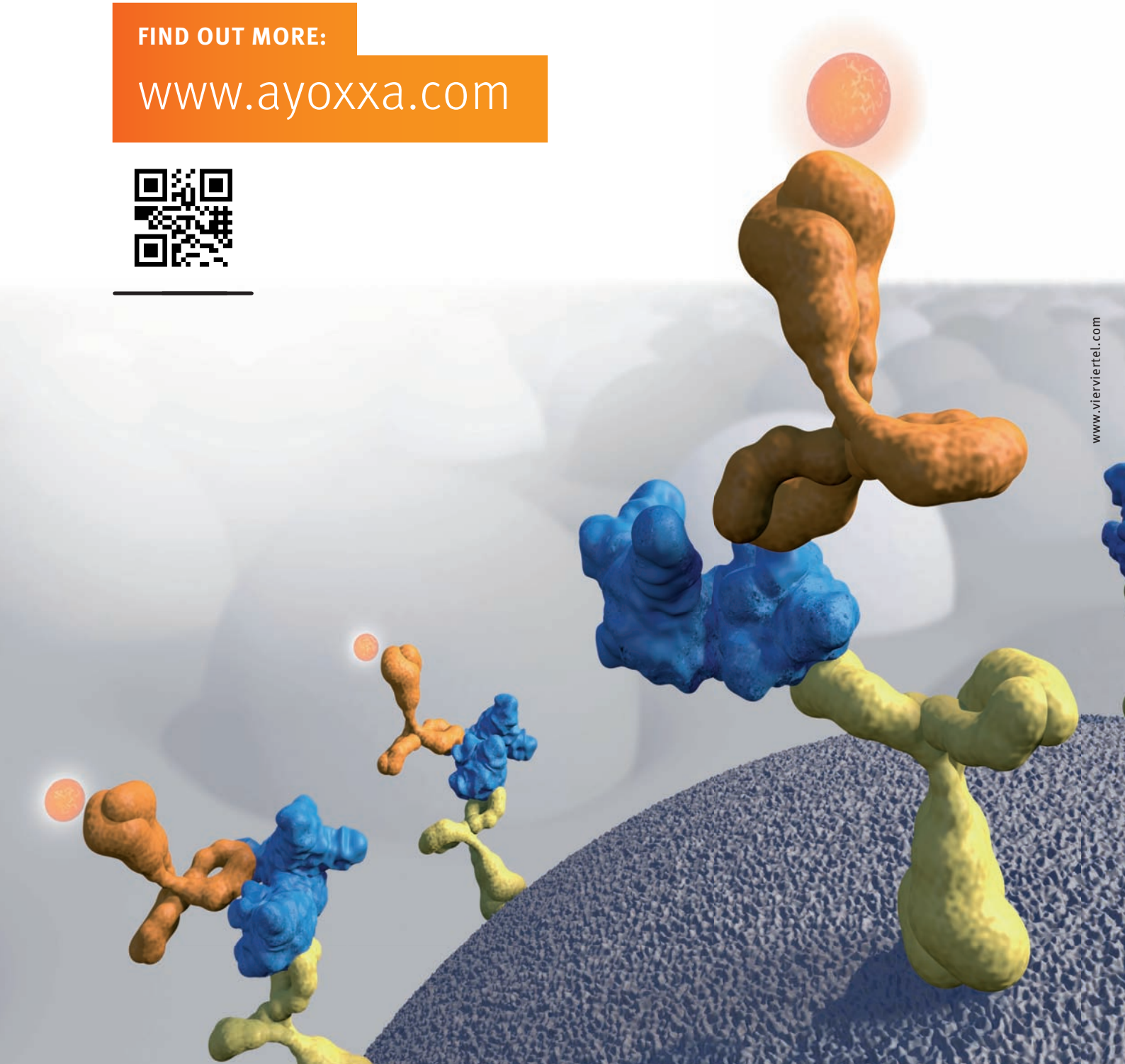

3P Biopharmaceuticals celebrates 10th anniversary

3P BIOPHARMACEUTICALS 3P Biopharmaceuticals celebrated its tenth anniversary this past September 12 in the Pamplona Cathedral. More than 150 guests had the opportunity to listen to a global leader in biomedicine: Dr. Barry Marshall, Nobel Laureate, who received the award in 2005 for his co-discovery of the bacterium Helicobacter pylori and the role it plays in gastritis and peptic ulcer disease.

The company brought together everyone who has participated in its success: clients, suppliers, members of the Board of Directors of ASEBIO (Spanish Bioindustry Association), partners, financial institutions, media outlets, and governmental representatives.

The event opened with a speech by Dámaso Molero, General Manager of 3P Biopharmaceuticals. Molero looked back at the past 10 years and thanked everyone for their commitment towards creating the company and making it a success.

The main feature of the event was the conference by Professor Barry Marshall, titled "H. pylori: History and Future." Marshall explained the process that led him and his research partner, Dr. Robin Warren, to confirm what the scientific community had denied: that most stomach ulcers are caused by the Helicobacter pylori organism. Marshall injected the bacteria into his own body, resulting in severe gastritis and confirming his hypothesis. This revolutionary discovery meant ulcers and gastritis could be cured with antibiotics, thereby avoiding surgery and its complications.

Professor Marshall also presented future research possibilities on Helicobacter pylori bacteria, a project that he is carrying out alongside the Australian company Ondek, which he founded, and with whom 3P has signed a partnership agreement. As part of this project, a new molecule is being developed and manufactured that will be used in preclinical and clinical research for the treatment of autoimmune diseases.

3P Biopharmaceuticals

3P Biopharmaceuticals, founded in 2007, is a leading European CDMO specializing in process development and GMP manufacturing of biologics and cell therapy products. Over the past decade, it has built a top-level facility with a complete GMP Quality System perfectly in line with international regulations.

3P's commitment is based on a clear objective: to offer each of its clients high-quality, cost-effective, flexible, and adaptable solutions to make their projects succeed.

A highly qualified team joins their clients as a robust manufacturing partner to offer support at all stages of bio drug development: from initial research to cell-line development to preclinical, clinical and commercial phases.

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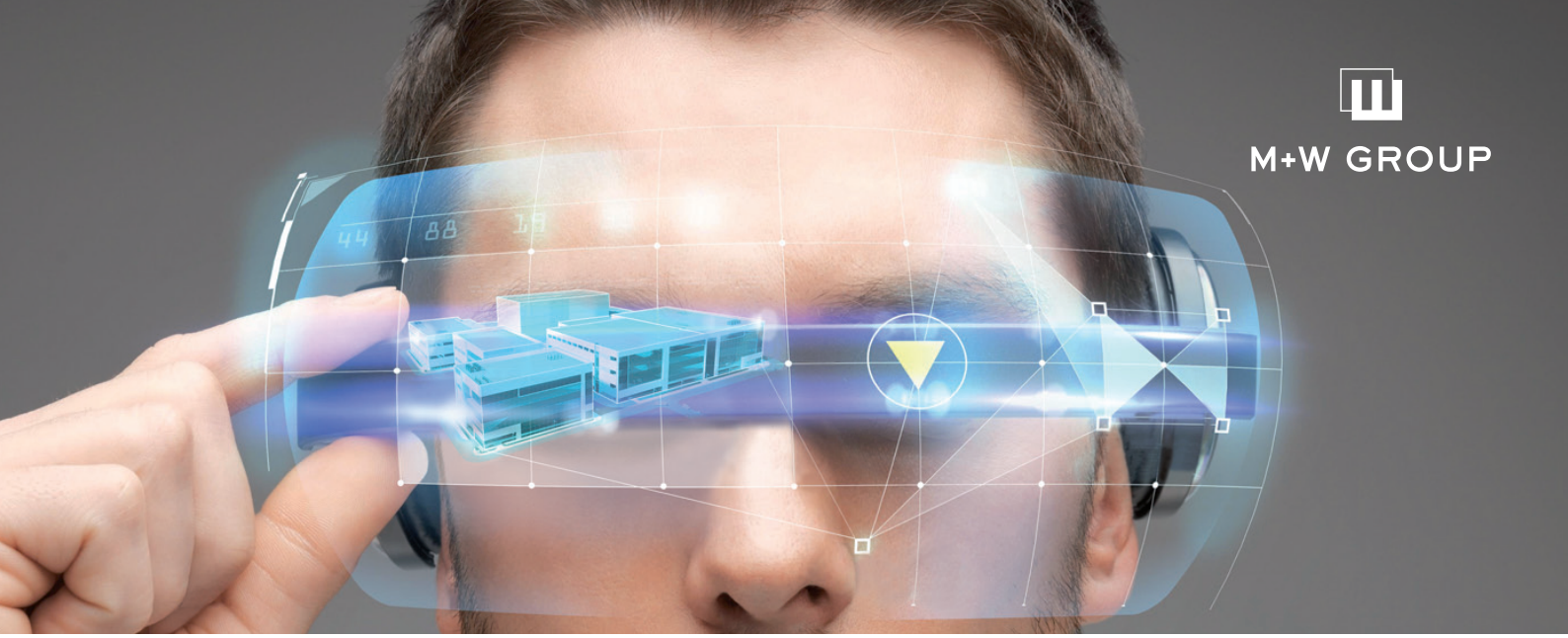

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- Variable single-use systems
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pic: GlaxoSmithKline


pic: Leon Nanodrugs


pic: GEHC

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A suited approach to rare disease trials

OPIS Accelerated approval for orphan drugs and the possibility to have market authorisation after a successful Phase II trial have made research in rare diseases more attractive to sponsors. However, challenges and uncertainties remain numerous and designing scientifically robust, patient-centered trials requires proper conceptualisation.

EuroBiotech_You are currently involved in a project for a Phase II study on an ultra-rare disease. That means dealing with extremely low patient populations. How did this fact influence the conceptualisation of the trial?

Poli_Rare disease trials imply small and heterogeneous groups of subjects with often very little possibility to select trial subjects through inclusion and exclusion criteria with the aim of getting a more homogenous population. A standard Phase III randomised, controlled trial is not always possible, so it is important to make sure that one optimises and maximises data from smaller trials. The current project in Becker's disease is based on a classic Phase II design, but there are a few interesting aspects that need mentioning. Being a controlled study, unequal randomisation with a 2:1, 3:1, or 4:1 ratio makes the use of placebo possible and stratified randomisation controls known factors of clinical relevance that might influence the treatment. Building cautions into the protocol to continuously monitor patients and check the primary variable closely eventually safeguards against unethical use of placebo. The concept of endpoints needs mentioning. Apart from the obvious recommendation to define the primary endpoint with signs or symptoms that express the course of the disease best, secondary endpoints can help collect as much information about the disease as possible and setting surrogate endpoints, such as biomarkers or composite endpoints, may really help support your proof of concept. Quantification of risk is another concept that can be adjusted for rare disease trials. To be less rigid and allow a greater type 1 error (risk of false positive or α error) makes sense when one definitely does not want to lose the slightest or smallest signs of efficacy of treatment.

DR. ALDO POLI,
Founder and CEO of OPIS, is a specialist in clinical research methodology, trial design and biostatistics. With a degree in medicine and surgery from the University of Milan, he has over 30 years of experience in the pharma industry and in clinical research. He regularly collaborates with major academic institutions and serves as an industry consultant in trail design/methodology.

EuroBiotech_Many rare disease trials use adaptive trial designs. What are the advantages and disadvantages of adaptive designs?

Poli_There are numerous types of adaptive designs. These designs are often based on Bayesian statistical models that focus on estimation, rather than hypothesis testing, and allow a range of possible observed trial results and prior distributions. Adaptive randomisation, sample-size re-estimation, "drop the loser" –i.e. stop the least effective treatment on the basis of predefined criteria – all give one the possibility to identify non-beneficial treatments early and redistribute your valuable resources to more promising treatments. It is also possible to use Bayesian elements in a standard trial design because it would allow an opportunity to include external information in the form of subjective clinician estimation of treatment effect, for example. However, adaptive designs are not always well accepted by ethical and regulatory bodies, and whereas conventional trial designs are well endorsed, adaptive designs are still seen as speculative.

Picture: OPIS

EuroBiotech_A low number of trial subjects available does not only influence trial design but it also brings challenges related to recruitment and patient retention. How does one target such small patient populations?

Poli_There are quite a number of solutions to help recruitment. Patient networks and close collaboration with patients' families can help design patient-friendly elements directly into a trial. It is more important than ever to approach rare disease trials with a truly patient centered approach. Moreover, the advantages for patients participating in such trials should be underlined clearly. The fact that these patients will be treated with advanced therapies that might cure something yet untreatable, is an opportunity.

EuroBiotech_To conclude, your current project is an example of collaboration among academic research institutions, the study sponsor, a CRO and regional funding. How has this combination helped in overcoming some of the obstacles related to rare disease research?

Poli_National Health Systems may benefit from clinical trials and their sponsors that absorb costs for treating patients that would otherwise be covered by National Health budgets. However, getting all stakeholders to work together to come up with solutions that consider research aspects/opinions, patient and patient network aspects/opinions as well as country and cultural aspects can optimise possibilities to have adequate patient numbers to conduct a trial. Looking at all available resources and finding ways to attract attention from a much wider audience, certainly contribute to advancement of rare disease research. ■

Orphan diseases

In Europe, an estimated 30 million people suffer from rare or orphan diseases. A disease is classified as rare when the European Medicines Agency (EMA) estimates that fewer than 5 in 10,000 people suffer from the disease. Around 70% of patients are children. Currently there are between 7,000 and 8,000 diagnosed rare diseases, mostly in oncology, metabolism and CNS indications. Globally, there are an estimated 460 approved orphan drugs on the market. Between 2002 and 2015, the EMA authorised 87 orphan drugs, 15 of them in the last year. In 2015, 23.6% of clinical trials carried out in Europe affected treatments for rare diseases. ■

Need a contemporary manufacturing strategy?

GMP MANUFACTURING Considering the high development costs of medications and the time invested before a drug goes from discovery to market, it is critical to develop not only a solid drug development strategy, but a contemporary manufacturing strategy as well. A parallel development strategy could be one possible approach.

› Dr. David Brett, Product and Service Manager, Vetter

Beginning with in-human Phase I trials, significant thought is applied to study design, logistics, CRO selection, patient populations, study centers, software and clinical distribution. These are all important considerations, but what is often missing is an equally important, well-thought through manufacturing strategy for the clinical material. Choosing a manufacturing partner with the contemporary manufacturing capabilities and expertise to offer advice on future drug product development is critical. The wrong choice can mean biotech companies must switch partners midstream, resulting in high costs and risks, such as failure to produce, the loss of API, or trial delay.

Plan prior to entering first-in-human studies

The best time to involve a manufacturing partner is from the very start. At that time, it is important to have answers to three fundamental questions:

- What are the market requirements for your new molecule, i.e. what is the clear unmet need for your target market, the drugs indication, and the market potential?
- What are the desired product attributes for your drug? For example, what is the clear benefit in the dose scheme/application form?
- What is your commercialisation strategy? Will you license the drug to other companies? If you intend to market it yourself, what markets will you target?

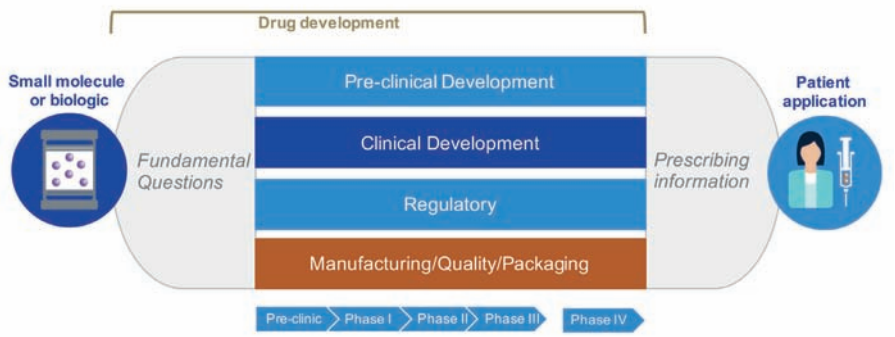
This is why the choice of an experienced manufacturing partner and the development of a clinical manufacturing strategy should be considered prior to entering first-in-human studies.

Proven manufacturing strategies for a biologic or small molecule

From a CDMO perspective, there are three proven development strategies: full-vial development, parallel-development, and full-syringe or full-cartridge development. Your choice will depend upon your product's attributes, market requirements, and commercialisation strategy.

The majority of new products are initially filled in vial form since it is easier to carry out dosing studies and the regulatory path is clear. Many biotech companies choose this development path due to their restricted resources, budget, and market-entry strategy. Some exceptions to this rule include accelerated drug development trials or biosimilars. In such cases, the dosing is pre-defined, based on a previous gold standard for a similar compound, and it is known from the start that the final presentation will be a syringe or cartridge.

For a new product or biosimilar where an approved treatment for a patented biologic already exists in syringe or cartridge form, there can be a competitive advantage in using a parallel manufacturing development strategy employing a pre-filled syringe or pen and cartridge combination. This is true in less price sensitive markets where there is a need



Manufacturing is a critical element in the integrated drug development process

Picture: Vetter

It's impossible to anticipate the challenges you'll face on the journey to market. Choose a nimble nonclinical study partner who has the versatility and know-how to help you scale scientific hurdles, overcome regulatory snags, and clear a path to approval – come what may.
Begin the adventure at www.criver.com/safetyassessment

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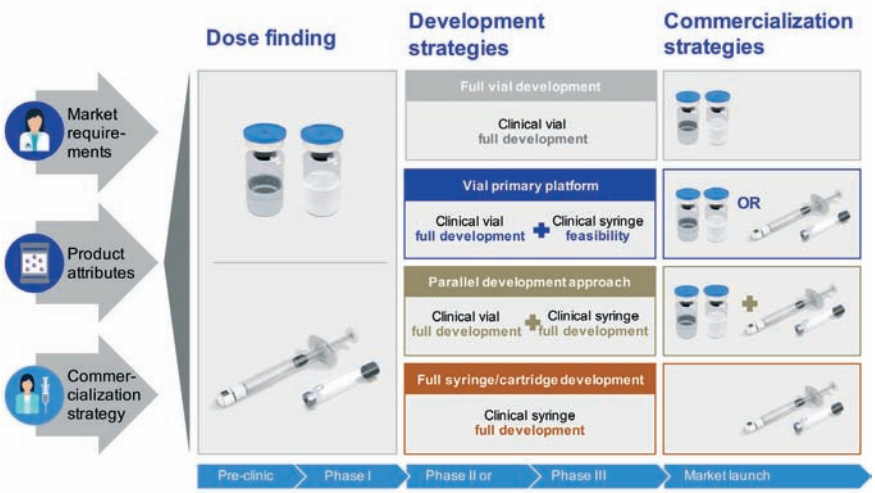


Proven packaging strategies

to attract patients, and vials offer a price advantage. This is also the case when health care workers are paid per administration step, and receive higher reimbursement from insurance companies when using a vial.

The best phase to consider parallel development is following dose-finding studies (Phase IIb). When choosing the parallel development approach, the regulatory pathway can be pursued in parallel. Working with a partner that has strong regulatory experience and is consistently audited to the highest manufacturing quality standards for all clinical phases will help in getting the right answers for submission. Each primary packaging material has its specific regulatory requirements.

In summary, having different packaging presentations is often a choice made when your commercialisation strategy demands a differing price point.

Choosing the right manufacturing partner

There are many local and regional CDMOs and formulation companies with extended small-scale filling services in the market. Many of these companies offer a discount strategy for early phase clinical filling. Their focus is on small-scale preclinical, and early phase filling. This is often sufficient to begin. As soon as your drug product surpasses early clinical phases, however, these partners may have reached their capacities. Thus, you may face issues such as the lack of a plan to limit loss of API in scale up, time delays, and non-cGMP practices, all of which may require additional feasibility, pump and filter studies, and added costs for knowledge and technology transfer to prepare for scale-up.

About Vetter

Headquartered in Ravensburg, Germany, Vetter is a global leading contract development and manufacturing organization (CDMO) with production facilities in Germany and the United States. The company has long-term experience offering services ranging from early development support, including clinical manufacturing, to commercial supply and various packaging solutions for vials, syringes, and cartridges. Vetter's customers range from small and midsize to the world's top 20 pharmaceutical and biotech companies. As a leading solution provider, the CDMO recognizes its responsibility to support the needs of its customers in developing devices that contribute to increased patient safety, convenience, and enhanced compliance. Learn more about Vetter at *www.vetter-pharma.com*. ■

Picture: Vetter

Rapid implemenation of off-line serialisation

PACKAGING Serialisation of drugs is confronting pharmaceutical companies all over the world with challenges, especially in relation to data handling and the integration of additional equipment and functions into existing packaging lines. Offline solutions, where secondary packaging is serialized directly by the folding-box manufacturer, combined with sophisticated data flow architectures, are a reliable, flexible, and immediately available alternative to inline serialisation.

› Hans-Peter Süsslack, Business Process Manager, Rondo AG, Switzerland

By means of Delegated Regulation (EU) 2016/161, the European Union has drawn up a mandatory standard to prevent the penetration of falsified medicines into the legal supply chain and to increase patient protection. According to this Regulation, all prescription medicines – with the exception of those on the "white list," and those medicines for self-medication cited on the "black list" – must be provided with an individual distinguishing feature (serialisation) and with protection from manipulation (tamper evidence).

In addition to improved patient safety, pharmaceutical manufacturers hope, through serialisation of their drugs, to contain the substantial world-wide increase in economic damage due to product piracy and theft. Apart from economic damage, manufacturers are also afraid that their brand image will be seriously damaged.

From an economic viewpoint, pharmaceutical companies can benefit from other aspects of serialisation. For example, recognisability in the event of returns and clear identifiability in the event of recalls – which can be carried out in a more targeted fashion, therefore affecting a smaller quantity of products – reduce costs substantially in some cases. Also, the grey marketing of drugs, particularly the selling of original products outside designated commercial channels, can be better controlled in this way.

More and more governments throughout the world require the application of an individual distinguishing feature (in this case: China Code) and protection from manipulation (tamper evidence) on all prescription drugs.

Picture: Rondo AG

Pharmaceutical companies therefore have an interest in promoting serialisation of their products. However, above all they must comply with national standards in order to be allowed to continue to supply after the respective introductory periods. Its introduction confronts pharmaceutical companies with major challenges, in particular with regard to the assignment of data to packaging lines and to the integration of serialisation equipment into existing packaging lines. In the case of retroactive integration, the pharmaceutical contractor is the general contractor, who, however, frequently does not have available the necessary technical personnel with the qualification required for this.

Challenges for manufacturers

Apart from the EU, a large number of governments throughout the world are tackling serialisation of medicines and are in the process establishing standards which differ greatly from each other. Manufacturers who wish to sell their drugs world-wide must, permanently and at short notice, get to grips with and react to new requirements, some of which may change suddenly.

Application of the codes on the individual medicine pack requires secure man-

agement within the company of the serial numbers of each individual product and, if necessary, of each individual destination country. During printing using digital print technology there is a requirement for a system at the production machine which prevents duplications, particularly in fault situations and exceptional situations, and which can reliably record the successfully printed codes despite interference factors. Because of the use of Asian fonts, the need to apply specific information to medicine packaging which people can read leads to a large quantity of characters to be processed and to exponentially demanding requirements in terms of data processing.

Outsourcing serialisation

The alternative to inline serialisation on the packaging line – offline serialisation by the folding-box manufacturer – spares the pharmaceutical company the cost of integrating printing technology, cameras, and ejection equipment into each individual packaging line, as well as training employees in the use of print technology. The lost production time for the integration and validation period can likewise be saved.

In the case of inline solutions, print heads for applying the codes with the required print quality and permanence, as well as cameras to check them and software for central control of the new modules, must be integrated into existing installations. In addition, for some countries, aggregation with balancing must be installed. The latter is also necessary for the offline variant, where serialisation is handled by the folding-box manufacturer. However, any further investment or delicate interventions in systems is not necessary, so their efficiency remains to a large extent unaffected. The basis for offline serialisation is reliable data exchange with the folding-box manufacturer.

For the EU, and for most other countries (except China), coding of the expiry date and batch information is required. Depending on the medicine, this data can subject the coding process to time pressure. If serialisation takes place at the folding-box manufacturer, then the latter must have a database system and a quality assurance system that have been proven in practice to guarantee fast, error-free deliveries.

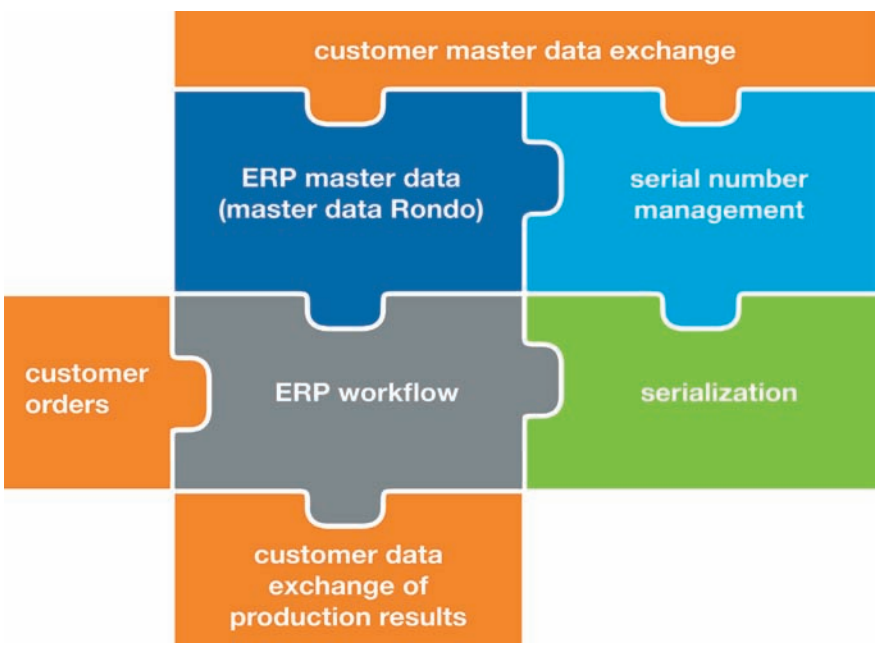
Whether inline or offline, serialisation demands the perfect interaction of hardware, software, and reliable, qualifiable processes. Different IT systems must be combined at the equipment level (line server), production level (plant server), and as part of enterprise resource planning (ERP).

Serialisation by the folding-box manufacturer provides ultramodern printing techniques combined with reliable data flow architectures and processes which comply with pharma requirements.

The offline variant is an attractive option for medium-sized pharma companies in particular, allowing them to avoid additional investment for each individual packaging line and maintain the efficiency of existing equipment – especially if the time for converting all lines is tight. In addition to solutions for tamper evidence and the application of special security features, Rondo also offers its customers this service. The Swiss company has invested in an Atlantic Zeiser DIGILINE Single Pharma 450, which covers all the requirements for reliable offline serialisation. All current codes are applied using OMEGA Drop-on-Demand inkjet technology in high-quality, high-contrast print and codes, using UV-hardening ink, and are therefore resistant to abrasion, water, alcohol and other solvents. The legibility of bundles, which are packed in shrink foil, is significantly improved as a result, and this reduces finishing costs to a minimum. Almost all typical materials can be printed on with a print quality of at least 1.5, according to ISO/IEC 15415:2011 (Grading C).

With its extensive format range of 80 x 100 mm to 450 x 500 mm, the system handles all common sheet and cardboard sizes in the pharmaceutical industry. Up to 240 folding boxes per minute can be printed with consistent high-quality, and provided with serial numbers. In this way, Rondo is providing its customers with solutions that can also handle fairly large orders at short notice.

All modules of the coding machine, such as the mix-up and inspection cameras, are controlled via central production software. The seamlessly integrated Unique Code Software enables as many sets of numbers as required to be man-



At Rondo, all processes and systems required for generation, provision, and exchange of data are fully integrated.

Picture: Rondo AG

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aged, and ensures consistent serialisation results. For example, in the event of interruptions in production, whether intended or not, no duplicate serial numbers are assigned. If desired, the list of successfully printed serial numbers can also be made available to the customer. Integration into Rondo's existing ERP system makes duplicate inputs impossible and guarantees error-free, secure data exchange. The software has been specially adapted for Rondo, in order to enable secure management of print orders and their assignment and distribution across one or more machines for parallel production.

In addition to the software, the data flow architecture has also been adapted to the specific requirements of the pharmaceutical industry. Importing of data from the customer is also automated, as is data export of the resulting files. Assignment of serial numbers to the production order is performed using unique naming with automatically generated file names. For production, the data is provided automatically via an enhanced master data management system.

For quality assurance, a second camera that checks the correctness and quality of the codes is installed in the equipment. The production results report and the balance file can be generated in different data formats according to the customer's wishes and sent to the customer via electronic data exchange.

Picture: Rondo AG

Outsourcing the serialisation of their medicines to a folding-box manufacturer, such as Rondo, offers pharmaceutical manufacturers a number of benefits.

Secure offline solutions

Customers can access the very latest print technologies with high-contrast print images for optimum verifiability and secure software solutions without having to invest several times in production equipment or impair their efficiency. In addition, outsourcing serialisation does not increase the cost of line clearance during the packaging process.

With Rondo, pharma companies can rely on secure data handling and reliable balancing. Data management runs in the background and cannot be influenced by users in any of the individual process steps. Input errors are therefore prevented.

Furthermore, pharmaceutical manufacturers can access the expertise of folding-box manufacturers in terms of print, materials, and solutions. For instance, in addition to serialisation of flat cardboard blanks, Rondo also offers its customers reliable, high-quality printing of glued folding boxes, significantly reducing the quantity of serial numbers required by the process. Integration of additional security features and tamper evidence are also possible. This means that Rondo can provide its customers with both standardized and customized solutions for secure packaging which meet all international standards. ■

Serialisation using labels

SERIALISATION Every company has its own specific approach to comply with the FMD 2011/62. Those who are aware of their unique needs should consider the option of pre-serialised labels. Here are a few good examples of how companies can benefit from this technology.

› Philip Falkenstein, Product Manager Serialization & Tamper-Verification, Bähren Druck

Serialisation can be implemented at several stages throughout the manufacturing process: (A) at the folding box manufacturer; (B) at the pharmaceutical company; or (C) in coordination with the label supplier (see graphic).

The time-sensitive release of batch and expiry information requires a just-in-time packaging coordination. Labels allow a fast and easy supply, and bridge the gap between offline and online/inline serialisation.

Drugs using single-dose units or a pouch as sales package provide the most obvious use for pre-serialised labels. The label supplier can combine all required information, including serialisation, in just one label. Such all-in-one labelling is also conceivable for pharmaceutical importers who usually relabel the folding boxes. But there are also drugs on the first market that are packed in blank folding boxes assembled with labels.

The majority of drugs are packed in pre-printed folding boxes and serialised inline during the packaging process. However, the inline process reaches its limits with unusual packaging dimensions. For example, so-called shoe box formats are, in many cases, not suited for inline serialisation processing and need another solution. Using a labeling machine — a low-cost investment compared to stand-alone serialisation systems — the packaged units can be labeled automatically with pre-serialised labels. The level of automation required and speed of the system depend on the batch size and must be decided on a case-by-case basis.

Especially in the case of medium and small batch sizes, the set-up times of inline systems and the risk of rejection of faulty products due to misprints should be considered so that pre-serialised labels can be an alternative. This batch range is also characterised by manual packaging processes – the possibility of manual label application is another strength. This is particularly true with regard to a 2-in-1 label solution, which allows two processes to be completed in one step.

Furthermore, there may be some scenarios in which pharma companies want to avoid high investment in serialisation equipment. Examples may include smaller companies, and companies with very few prescription drugs (Rx) affected by the legislation.

2-in-1 Label Solution by Bähren Druck. Manual and machine application are possible.

Pre-serialised labels can even allow companies to outsource the entire complex serialisation processes to a packaging specialist, who will guarantee that print quality, data structure, and specific barcode requirements will comply with Regulation 2016/161. Pharma companies can save resources and rely on the manufacturer.

Given the fact that the clock is ticking away, plus the fact that some companies have not started their serialisation project at all, pre-serialised labels are also a possible interim solution to fulfil the requirements by February 9th 2019.

Of course, the use of pre-serialised labels requires a clear agreement between the pharma company and the packaging manufacturer. Main questions relating to the serial number, data interfaces, and reporting are important tasks, which must be defined in the onboarding process. ■

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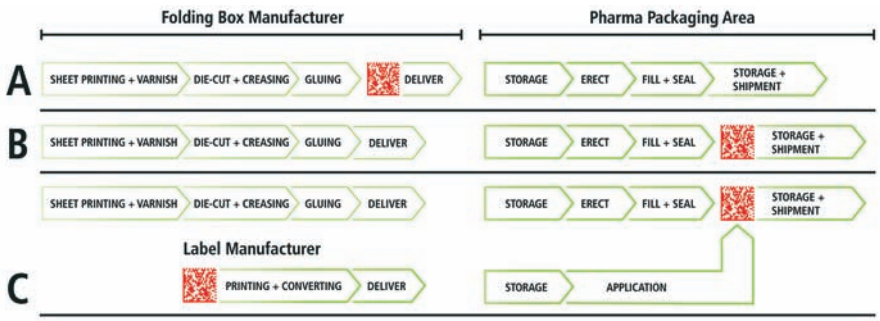

An example of serialisation implementation: (A) offline at the folding box manufacturer; (B) online/inline at the pharmaceutical company; (C) in coordination with the label supplier

Pictures: Bähren Druck

Injection pens in clinical trials

PACKAGING Due to the high cost pressure in health services, for a product launch to be successful in the long run, it is necessary for a drug to be not only safe and effective but also more economical than the existing forms of therapy. Haselmeier's injection pens provide the flexibility and efficiency required to run an effective clinical trial.

› Dr. Fred Metzmann, CBO; Konrad Betzler, Chief Pharma Officer, Haselmeier Group, Stuttgart, Germany

Whoever is the first to bring a new therapy to the market determines the price. Therefore, every company will make the best effort to ensure a quick start to, and smooth conduct of, clinical trials.

If the drug has to be injected subcutaneously, injection pens offer a great opportunity to control the time factor. Generally, during the clinical phase, medication is stored in vials and administered to the patient through a disposable syringe. However, vials can be inconvenient to use and harbour safety risks, especially with regard to shelf life after opening, contamination, and injury to the staff due to the cannula. An alternative is the prefilled syringe, but this does not permit any dose adjustment and, thus, would mean a substantial additional demand for the trial drug.

Moreover, both forms of dosage are unsuitable for use by medical laypeople. Administering the drug once or several times a day would require substantial nursing care and hospital treatment.

Self-administration by the patient – for example, with injection pens – is a solution that offers several advantages. The patient has more flexibility to choose the place and time of treatment, thereby greatly reducing therapy costs.

A clinical supply manager should demand the following of an injection pen for clinical studies:

- The form is permitted in the countries in which the studies are being conducted.
- It is simple and safe to use, and permits a predefined flexibility in the adjustment of the dose.
- It permits therapy-appropriate labelling, including relabelling for dose adjustment as well as the option of multilingual labels.
- It can be used continuously or with minimum adjustments for all phases of the clinical study up to the approval of the drug.
- It can be delivered ready-to-use to the trial participants without having to establish a manufacturing competence in-house.

Haselmeier has developed a new product platform, the D-Flex, that is highly suitable for clinical trials. It is a disposable pen for use with 3ml cartridges.

The D-Flex platform can be flexibly configured to suit the desired dose values from the first clinical study to series production, significantly reducing capex and time to market.

Picture: Haselmeier

The D-Flex can be configured for several fixed doses, bridging the gap between fixed and variable-dose pens.

D-Flex solution to meet clinical requirements

These dose values can be freely selected when designing the pen. This is particularly of interest for dose-escalation studies. The system does not allow any intermediate settings between the set doses. This significantly reduces the risk of an incorrect dose and enhances safety for the patient. The D-Flex pen means that only one device needs to be used throughout the clinical trial, making trials much easier for the pharmaceutical company. Regulatory bodies may also impose a device design that only enables dial-labelled doses. This would disqualify the use of current prefilled pens, which have intermediate dose increments.

Using D-Flex for clinical trials and later as serial device enables the customer to decide which set-up he prefers for market introduction. This makes the D-Flex the ideal, flexible platform for adapting to set doses in accordance with the therapy. It has been so well developed and validated that only minimal molecule-specific and customer-specific adjustments are necessary; they can be integrated into the clinical supply chain process seamlessly up to serial production following market authorisation. The D-Flex can also be assembled at Haselmeier's site up to the drug-device combination product. ■

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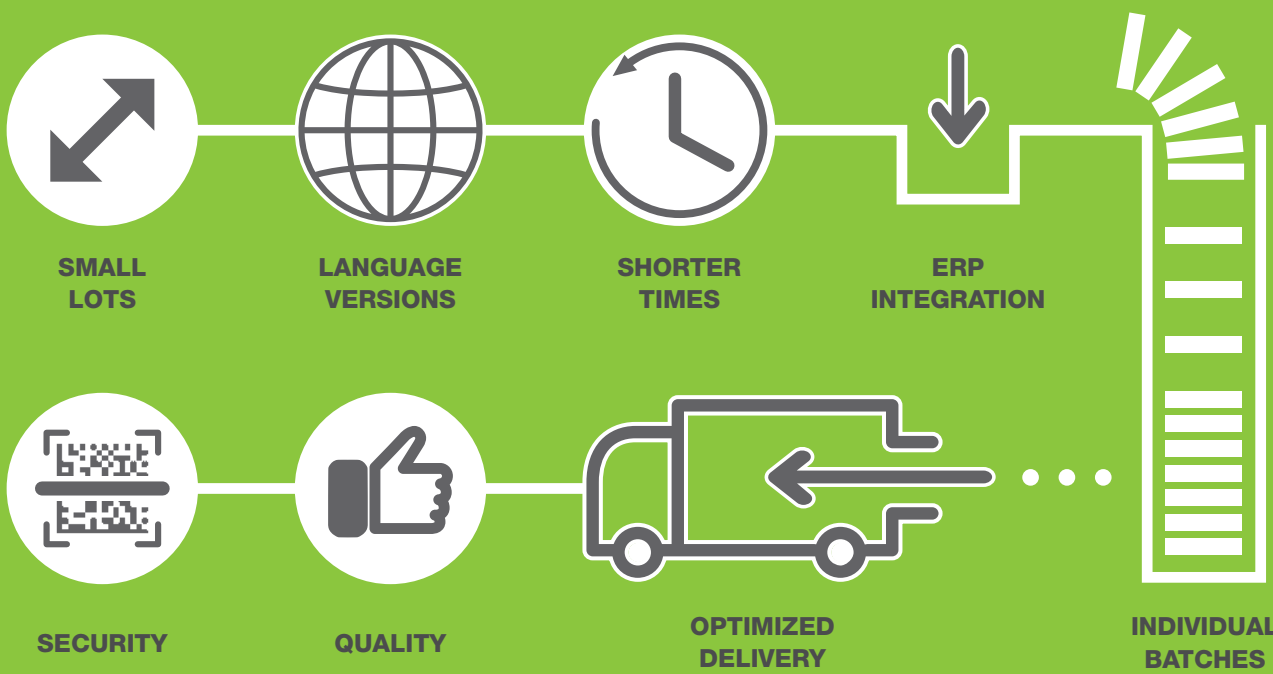

Your requirements: no storage of pharmaceutical packages on your premises and flexible delivery of small quantities in combination with highest product quality and greatest possible process security. Our solution: needs-based delivery of high-quality folding boxes within one week.

Supply on Demand is another innovative, GMP compliant solution developed by Rondo, technology pioneers in folding boxes for the pharmaceutical industry. Find out more about Rondo's Supply on Demand solution on

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UGA BIOPHARMA GMBH The company provides customised cell line development services for biosimilars and New Biological Entities (NBEs), including clone generation, bio-process optimisation, downstream development, and analytics. Their success is based on the choice of an appropriate host cell line, optimized expression vectors, First CHOice® cell culture medium, and longstanding expertise. UGA Biopharma seeks partners to (a) out-license ready-to-use research cell lines (RCB) or (b) start a new development project for a biosimilar/NBE-expressing cell line together with clients.

The portfolio consists of cell lines expressing Adalimumab (Humira®), Aflibercept (Zaltrap®), Anakinra (Kineret®), Bevacizumab (Avastin®), Certolizumab (Cimzia®), Dupilumab (Dupixent®), Eculizumab (Soliris®), Imiglucerase (Ce-

rezyme®), Ipilimumab (Yervoy®), Laronidase (Aldurazyme®), Natalizumab (Tysabri®), Nivolumab (Opdivo®), Omalizumab (Xolair®), Pembrolizumab (Keytruda®), Pertuzumab (Perjeta®), Vedolizumab (Entyvio®).

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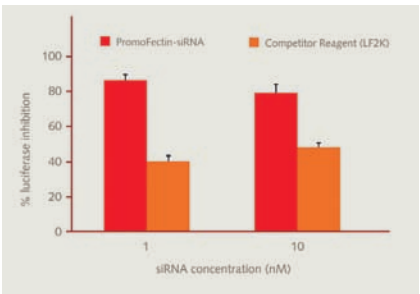
PROMOCELL GMBH PromoFectin-siRNA is a non-liposomal, cationic transfection reagent designed for an optimized delivery of siRNA as well as miRNA, oligonucleotides and other ribonucleic acids into a wide variety of cell types, including problematic cell lines and primary cells. PromoFectin-siRNA enables a functional and highly efficient gene silencing (›90%) with very low amounts of siRNA (‹1 nM), avoiding cytoxic and off-target effects. The formulation is compatible with both serum and antibiotics and the fast, easy-to-use protocol is adapted to adherent as well as suspension cell culture. PromoFectin-siRNA shows a very low cytotoxicity for more robust data and excellent cell viability. See our current promotion at http://www.promokine.info/promotion.



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Reduce matrix effects & interferences

CANDOR BIOSCIENCE GMBH LowCross-Buffer® improves ELISA and immunoassays and replaces HAMA blockers.

LowCross-Buffer® is a substitute for HAMA blockers and prevents matrix effects and interferences. The antibody and sample diluent is applicable for ELISA, EIA, RIA, protein arrays, Western blotting, immuno-PCR, and immunohistochemistry. False positive or false negative signals and high background can be prevented by using LowCross-Buffer®.

The unique formulation of LowCross-Buffer® helps to shield the specific signal from low or medium affinity cross-reactivities or interferences in immunoassays like an "affinity gate keeper." Thus quality of detection can be significantly improved. In addition matrix effects – coming from blood sera or plasma specimen, for example – are reduced, and thus no longer exacerbate detection of analytes. Minimising all these negative effects upgrades the quality of the assay and improves the reliability of the results.

LowCross-Buffer® is ready-to-use and available in bottle sizes of 50 ml, 125 ml and 500 ml.

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Pictures: UGA Biopharma (left), Promocell (above), Candor Bioscienc (bottom)

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The leading Life Sciences Conference in Switzerland and Annual General Assembly of the Swiss Biotech Association

Picture: © Basel Tourismus

Mark your calendar for next year's Swiss Biotech Day, the leading biotechnology conference in Switzerland.

Now in its 20th year, the event is not just the place to be for members of the Swiss Biotech Association, who traditionally meet there for the association's Annual General Assembly. As always, the event targets entrepreneurs, investors, researchers, analysts, political decision makers and industry stakeholders. So, don't miss the chance to meet around 600 experts from across Europe.

Pre-register online at www.swissbiotechday.ch to be one of the first to receive all information on programme, exhibitors, sponsoring and the partnering system as soon as it is available.

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