European Biotechnology

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Bioprocessing cGMP

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GMP and new processes: be prepared for hassle

GMP BIOMANUFACTURING Poor aseptic practices can rapidly ruin market supply of products outsourced for production. This year, Celltrion came under fire from FDA inspectors. At the end of January, the producer received a warning letter affecting the production of Inflectra biosimilar infliximab-dyyb (CT-P13) co-marketed with Pfizer. In mid-February, the FDA added a warning concerning rituximab and trastuzumab biosimilars produced for Teva, as well as for its fast-track migraine mAb fremanezumab.

The warning letter resulted from inspections of the South Korean biosimilar specialist's current 140,000-litre production plant in Incheon conducted last summer. According to the FDA, it followed about 140 complaints concerning contaminations in vials due to insufficient sterile filling procedures affecting products marketed in the US. The contamination problem could affect US and EU market approval for Celltrion's trastuzumab biosimilar CT-P6, which had its BLA accepted by the FDA and received recommendation by the CHMP, both-last year, and FDA approval of the EU-authorised rituximab Truxima. According to Teva, the warning letter could also ruin the planned marketing debut of its anti-CGRP mAb fremanezumab that prevents migraine attacks. In January, the FDA issued a warning letter to Celltrion and its global co-marketing partner Pfizer Inc. concerning infliximab-dyyb, a biosimilar of the autoimmune blockbuster Remicade (infliximab) from Johnson & Johnson, the first biosimilar mAb approved by the agency in 2016. For Celltrion, which is playing down any concerns related to its expanding biomanufacturing plant in Incheon, the warning letters could have a huge impact on its business. Celltrion, which will ramp up its capacity to 310,000 litres by 2019, wanted to outperform European CDMO rivals Boehringer Ingelheim (300,000 litres) and Lonza (280,000 litres). Samsung Biologics Co., another Korean producer of biologic drugs, has a plan to increase its annual production capacity to 360,000 litres by 2018 (see figure, p. 40).

The GMP issues at Celltrion come at a time in which healthcare systems have begun to lobby for adoption of the 15-30% cheaper versions of biologics that have lost patent protection. Australia, following the European practice, no longer labels the INN of biosimilars with a unique numerical identifier to differentiate them from the originals. Though the FDA includes the unique INN identifier for biosimilars, the US government wants to boost biosimilar uptake. At the beginning of February, FDA Commissioner Scott Gottlieb announced the agency will facilitate claims of interchangeability in a forthcoming Biosimilars Innovation Plan, which could promote biosimilar uptake.

Find the right expert

While most GMP problems are currently limited to Indian, Chinese, and other CDMOs from Asia, some have also hit Western companies, such as Pfizer subsidiary Meridian Medical Technologies Inc., whose QC did not meet cGMP requirements, causing the FDA to to reject AstraZeneca's market approval application for ZS-9, an ion trap to treat hyperkalemia.

The cases document what really counts for biopharmaceutical companies: quality and price, but quality first. In Europe, smaller specialised biomanufacturers have found a niche in the inno-

Picture: BSP PHARMACEUTICALS S.P.A. Italy

BSP Pharmaceuticals SpA's validated manufacturing sterilisation department, Sterile 4, was especially designed for anticancer drugs, with the flexibility to manage small molecules and ADC products.

	Projected annual capacity	First plant	Second plant	Third plant
Samsung Biologics	36	3	15	18[1]
Celltrion	31	5[2]	9	12[3]

1) initial operation in 2018 2) +5 by 2019 3) initial operation in 2021

Annual capacity of Celltrion's 140,000-litre biomanufacturing plant in Incheon will be expanded to 310,000 litres by 2019.

vative biotech SME space, providing special expertise suited to the needs of their customers. CDMOs, such as Celonic, no longer want to remain just the lot-makers for clinical trials but have begun to expand into the high-quality commercial production of personalised meds, orphan drugs, etc. Most recently, Celonic took over the manufacturing business from protein glycosylation specialist Glycotope and is also expanding its production capabilities in Basel (see p. 42).

Another tactic to differentiate within the consolidating, but growing, outsourcing market – which had sales of US$5.48bn, according to Visiongain analysts – is to provide novel technologies in selected drug discovery areas for customers.

In February, Teva partnered to get access to ProBioGen's Human Artificial Lymph Node Technology, a 3D-micro-organoid model for predicting the effects of Teva's biopharmaceutical drug candidates on the human immune system in vitro. ProBioGen's CSO, Dr. Volker Sandig, said, "We have demonstrated effects that were impossible to see in conventional models, bridging the existing gap between animal models and first-in-man applications." The technology is based on a patented, miniaturised, and perfused bioreactor for long-term cultivation of immune cells. Human blood-derived dendritic cells, lymphocytes, and mesenchymal stem cell-derived stromal cells are inoculated into the bioreactor's 3D hydrogel matrix, which is perfused with cell culture medium and aerated, just as in a real human lymph node.

Another technological improvement was announced by ADC Biotechnology Ltd in February. The company has patents (WO2012/140433) and patent applications (WO2014/174316, WO2016/005744, WO2016/067013, and WO 2016/067016) on a novel downstream bioconjugation method expected to save 25% of total costs in ADC (antibody drug conjugate) manufacturing. In contrast to the existing approaches – which undertake bioconjugation after both the mAb/targeting moiety and cytotoxic payload have been manufactured – the new approach moves the conjugation step into the later stages of the downstream processing (DSP), with conjugation and antibody purification carried out concurrently by binding them to a resin. The drug conjugate field got a boost in February when ADC heavyweight Seattle Genetics licensed Pieris' antibody-like anticalins for US$1.2bn. In February, Spanish PharmaMar started its own business that identifies structural diversity from sea organisms and resynthesizes novel toxic payloads for ADCs and anticalinDCs. ■

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Picture: Celltrion

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Expanding into the commercial supply space

CELONIC Celonic AG has pursued an ambitious expansion strategy in mammalian cell line contract manufacturing to establish Phase III and commercial supply by mid-2019. A new GMP facility in Heidelberg was acquired, and capacity is also being expanded at the headquarters in Basel. European Biotechnology spoke with Franzpeter Bracht, COO of Celonic, about Celonic's strategy.

EuroBiotech_ Where does Celonic stand today, and where do you want to place your company in the long term?

Bracht_The acquisition of Glycotope's manufacturing business we announced last winter is the starting point for a major expansion of our business focus. We have looked for awhile for a strategic acquisition to expand Celonic's business focus from clinical trial supply to Phase III and commercial GMP manufacturing, which would allow long-term partnerships from early to commercial phases. In Basel, however, we were very confined, and a capacity expansion was a clear strategic focus for us. So, we thought about how to establish an integrated development site in Basel, where we can do everything from cell line development to tox batches and identify another site, where we can produce GMP-compliantly and accelerate GMP capacity growth. Glycotope's Heidelberg site was the optimal fit.

EuroBiotech_ Could you describe why?

Bracht_With the takeover we added five suites to our biomanufacturing capacity, with fermenters ranging from 50 to 1,000 litres, both in single-use and stainless steel. We have already finalised the design for the next growth step in Heidelberg, a 2,500 sqm production hall. By mid-2019, we will start GMP production in three suites there, two with 2-3x2,000 litre fermenters each, and one suite with a 1,000 litre perfusion reactor. This expansion of scale marks the change from a CDMO for clinical supply to a manufacturer of Phase III and commercial supply, according to FDA and EMA standards. At the Heidelberg site, Celonic will have enough space for further GMP capacity expansion.

DR. FRANZPETER BRACHT, (Ph.D.), is Chief Operating Officer at Celonic AG. He has also been COO and Managing Director at Glycotope GmbH, which sold its contract manufacturing business to Celonic in 2017. The pharmacologist co-founded Aplagen GmbH in April 2001 and served as its Chief Executive Officer. Previously he was Principal and Head of Pharma & Life Sciences at Kienbaum Management Consultants and Consultant at EY.

EuroBiotech_To what extent will customers be able to benefit from Glycotope's GEX platform in addition to Celonic's proprietary CHOvolution cell line?

Bracht_Celonic will also benefit from Glycotope's 20-year successful track record producing highly glycosylated proteins in fed-batch and perfusion processes, and its proprietary human GEX cell line. We acquired a non-exclusive licence. So, we are now able not only to produce monoclonal antibodies at up to 7g/l with Celonic's proprietary CHOvolution CHO K1 cell line, but also bispecific antibodies, hormones, or other complex biologics products with human glycosylation pattern in GEX cells. So, the acquisition has fairly broadened Celonic's customer base: we can produce in fed-batch and perfusion, in CHO and in human cell lines, and with the capacity expansion we will serve companies from early development to commercial supply, as well as biosimilar producers looking to be first to the market. That gives Celonic more long-term perspective and allows optimisation of business processes.

Picture: Celonic

Picture: Celonic

Production in perfusion reactors at Celonic

EuroBiotech_Celonic has been part of JRS since 2011. What role does the financial backing of the Rettenmaier family play for your company and its strategy?

Bracht_ Without financial backing from the Rettenmaier family we would not be able to execute an expansion such as currently in Basel and Heidelberg, where we want to start GMP production in mid-2019. It also provides an opportunity to shape business models built around risk sharing for the biotech companies and thus facilitates a real win-win situation.

EuroBiotech_Novel molecule formats such as bispecifics currently flood biopharma pipelines for personalised medicines. How does Celonics manage this technological challenge?

Bracht_ We already have two bispecifics in production. We have experience with achieving improved yields by switching production from CHO to GEX cells in perfusion reactors. So we are flexible enough and have experience with new formats, such as bispecifics and ADCs, while living up to total quality management.

EuroBiotech_The CDMO market is characterised by strong demand but also huge competition. Where do you want to go?

Bracht_ Currently, the market is large enough for all CDMOs. Particularly, the demand for contract manufacturing in the 1,000 to 2,000l range is growing steeply. All projections say that most future products will lie in that production range we are building in the moment. We are focussed on establishing long-term partnerships with biotech SMEs that want to produce orphan drugs, personalised meds, biosimilars etc. Currently, we are producing an in-vivo-antibody diagnostic commercially. We will add a second commercial product in 2019.

EuroBiotech_What are your next goals?

Bracht_ This year, we hope to complete the integration of Glycotope and expansion in Heidelberg and the transformation of our Basel site. In the longer term, we will expand our filling capabilities and look for FDA-accepted methods for continous downstream processing. ■

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Learning from the small molecule supply chain

BIOLIVE Rutger Oudejans, Brand Director at bioLIVE, postulates that the bio supply chain could learn some lessons from the small molecules sector. The bio industry continues to expand at rates above the traditional NCE (New Chemical Entity) sector, yet for the supply chain there are vital synergies that could help further accelerate developments.

› Rutger Oudejans, Brand Director at UBM

It's a key time for bio manufacturing in Europe, as larger supply chains are being built to meet new and rising demand. Thus far, as an industry, we have been pretty successful in adopting to growth in biologicals and biosimilars. But with greater numbers of BLA approvals now coming through (22 in 2017), and many others coming off patent – MAb production is forecasted to grow quickly – there remains a significant challenge for the supply chain to meet. In fact, it is my belief that this year will usher in a new age of increased integration and collaboration across the large and small molecule supply chain. There are many areas in which we can collaborate, from the obvious crossovers like ADCs (antibody drug conjugates) to the softer elements so critical to industry growth, such as supplier directories, talent, and services acquisition. For example, it's already widely acknowledged that there is an impending bio staffing issue, with the industry struggling to bring enough experienced staff into companies. This staffing strain, at least in the short term, will probably increase and integration could help facilitate shared learning.

Growing supply options

With the bio industry now forecast by most respected observers to be growing at a mid-teens pace, put simply, more players entering the market means more

Rutger Oudejans

supply options. But also potentially more complexity as new networks begin to appear to meet demand. It's how we manage this complexity that will be key to maintaining the bio industry's impressive ascent. As well as new and increased capabilities within Europe, we are also seeing an even faster predicted growth in the emerging bio economies in China, South Korea, and India. China is especially significant, as with the successful trial of the MAH (Marketing Authorisation Holder) pilot, license holders can now use a CDMO in the country – which potentially means we will see a more rapid increase in the number of bio CDMOs there. Whilst in India, companies have already been successfully producing cost-effective biosimilars, and several South-Korean companies are striving to have production-ready commercial capacity for biopharma (with some of the world's largest production plants being completed).

So, over the next few years we will see a much larger industry, but also a much more complex one, and how partners meet in the supply chain will be key. The other consideration is that one of the main goals for the bio industry is to simultaneously lower the total cost of production and increase global capacity – which is increasingly becoming a two-tier market of large mammalian capabilities for commercial products, and single-use facilities for newer targets in the pipeline.

Quality and time has an impact

One of the key successes in the solid dose sector has been the ability for a global supply chain to come together at events to establish new partnerships and lower costs. It's also where you are able to find the associated types analytical testing, assays, and partner services so needed to help meet changing commercial requirements. With our new bioprocessing and manufacturing event – bioLIVE – launching alongside CPhI Worldwide this year we will be creating a fully integrated sourcing hub for the industry to facilitate new partnerships.

It often said you are 'only as good as your weakest link,' but I believe the supply chain will be a strength that sustains its next phase of growth – providing manufacturers and product developers much greater flexibility. ■

Pictures: UBM

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Expansion

PACKAGING Vetter has started a major expansion of its Ravensburg secondary packaging facility, with 32,000 square feet of new state-of-the art packaging lines and assembly equipment for pens and autoinjectors. The company said the expansion is a result of increased customer demand and the company's continuous growth in new filling lines and new lyophilisers. It will also increase Vetter's serialisation capacities. A state-of-the-art syringe blister line will include safety device assembly and equipment for packaging in Japan. The company is also building a new administration building at its Ravensburg headquarters. ■

Branding

BUSINESS German biologics CDMO Rentschler Biotechnologie GmbH transitioned into Rentschler Biopharma SE. Rentschler said there will be no operational changes for customers due to the transition. ■

Purification

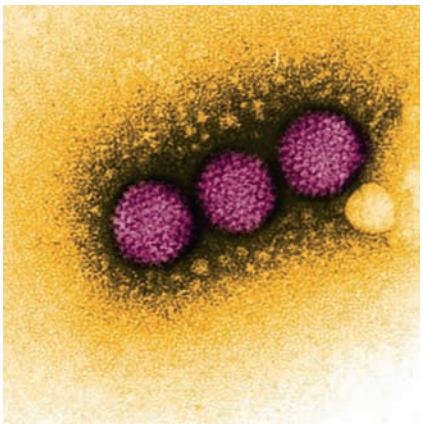
PACKAGING Servier CDMO, the contract manufacturing arm of the French pharma major, is increasing productivity of its preparative chromatography platform at its Bolbec site in Normandy. The expansion will enable chemical purification of 50kg/day, and separation of 10kg/day of chiral high-value APIs with 90% lower environmental impact and 50% higher speed. Meanwhile, the company announced it will invest US$58m in France to expand into the growing market of biologics. ■

Quality

PACKAGING Warning letters from the US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) increased from 63 in 2016 to 85 last year, according to a PwC report. It states that of 98 guidance documents planned to be issued this year by the CDER, thirteen will impact pharmaceutical quality and CMC, and two others cGMP rules. ■

Targeting expanding markets

GENE THERAPY Merck KGaA's US CMO arm SigmaMillipore has underscored its capabilities as a commercial manufacturer of viral and gene therapy products, a market expected to grow at a CGAR of 40% over the next ten years. The company announced its Carlsbad-based manufacturing facility for the production of BioReliance viral and gene therapy products has completed both a US Food and Drug Administration (FDA) Pre-License inspection and a European Medicines Agency (EMA) Marketing Authorisation Application inspection. Merck Life Sciences CEO Udit Batra underscored that Merck was "one of the first CMOs in the industry to complete pre-licensure inspections for this class of therapies," which will enable one of Merck's key customers to launch its novel gene therapy in both the US and in Europe. ■



Picture: Merck KgaA

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