

ABL Europe's GMP manufacturing facility for viral vector production

New Production Capacity for Viral Vectors



Success Story

ABL Europe

GMP manufacturing of viral vectors from non-adherent cell cultures

January 2018 – A new production facility for the GMP manufacture of viral vectors from non-adherent cell cultures is opening in Strasbourg, France. This will alleviate growing concerns that a lack of suitable manufacturing capacity is restricting the speed with which this nascent industry is able to bring viral vector products from the laboratory to the patient.

Fully Integrated Service Offering

Patrick Mahieux, General Manager of ABL (Advanced Bioscience Laboratories) Europe, the contract manufacturing organization responsible for the site expansion said, "The introduction of non-adherent cell culture capacity complements our existing adherent cell culture viral vector production technologies. It is the only pure-play, dedicated viral vector production site capable of manufacturing drug substance and drug product materials for toxicological studies, all clinical phases and even commercial launch. Everything from process development, manufacturing and QC release testing is performed under one roof."

This "all under the one roof" concept is key to Mahieux's vision. The company's clients face considerable costs and avoidable risks when having to transfer processes between CMOs and production facilities, during clinical development. "Many of our customers are at a very early stage with little more than a concept for a product. We can support them throughout their product's lifecycle with process development, clinical batch production and then through process validation for commercial launch; all from within the Strasbourg facility. I also firmly believe that the development of processes and analytical testing must go hand-in-hand. Other manufacturers outsource QC testing or perform it at different locations within their group but this gets more complicated and risky. Lead times increase as a consequence," Mahieux said.

He believes CEOs of companies developing viral vectors are coming under increasing pressure to bring their products to market since Amgen's successful registration of the T-VEC oncolytic viral vector product showed that these products could receive regulatory approval. This is increasing demand for a long-term production strategy.

Crucially, the French regulatory authorities (ANSM) have inspected ABL's facility and it is GMP licenced in accordance with European Medicines Agency regulations. Many US contract manufacturers producing early stage clinical trial materials are not GMP certified, as it is not an FDA requirement until product approval. However, producing clinical lots from ABL's Strasbourg site will assure cGMP compliance throughout all phases of development allowing customers to perform worldwide clinical trials.

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Patrick Mahieux, General Manager of ABL



The new capacity will help the company manufacture viral vectors for a wide range of applications such as oncolytic, vaccines and gene therapy products. Even established multinational pharmaceutical companies often do not have the capabilities and / or expertise to manufacture viral vectors that are large ($> 0.2 \mu\text{m}$) or replicating or both, especially at industrial-scale batch sizes. ABL Europe has the virology know-how and quality systems management that allows it to perform aseptic production of drug substance and drug product, developing the necessary analytical tests and preparation of the required documentation for the health authorities that justify the adopted approach. While the company believes that most clients' products will only require Biological Safety Levels 1 and 2, they have designed the facility to be able to handle products requiring Biological Safety Level 3 containment.

Mahieux considers that the biggest demand will come from those companies developing oncolytic and immunotherapy virus products for the treatment of cancer. "Customers expect us to be flexible and agile. Their top priority is reaching the clinic as quickly as possible. We have created a facility that will allow them to meet this objective. Our new state-of-the-art viral vector production suite contains a single-use, fully disposable production line and can produce 15 to 20 batches per year", he said.

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Patrick Mahieux, General Manager of ABL



Single-Use Platforms Bring Flexibility

ABL Europe considered single-use technologies to be the obvious choice when designing the facility. "Customers don't want to pay for cleaning validation. It adds no value. We could never have gotten the new facility up and running in 11 months with stainless steel equipment. We never even prepared a business case for a stainless steel plant," said Mahieux.

The new facility has separate suites for cell production and virus propagation then downstream processing. The company has installed single-use bioreactors and cell cultivation technologies from Sartorius Stedim Biotech (SSB) including a BIOSTAT STR® 200. It has equipped this 200 L bioreactor with an alternating tangential flow filtration system from Repligen to allow upstream process intensification and even greater productivity. The suite has space and utilities in place for the rapid installation of a 500 L single-use bioreactor. The downstream processing of the viral vectors will be performed using a combination of SSB's FlexAct 2.0 platform with associated mixing systems and GE's AKTA chromatography systems.

Anthony Da Silva, Process Development Specialist explained, "We took the decision to work with a very limited number of suppliers, with Sartorius providing a large proportion of the consumables. This simplified our supply chain and allowed us to accelerate the construction of the suites. Using a supplier's entire platform for viral vector production allowed us to integrate the single-use automation into our MES platform easily. The Sartorius downstream processing systems were selected because of their flexibility and their ability to handle a wide variety of process volumes with a small footprint."

Mahieux said, "Sartorius delivered the project exactly on-time and according to our expectations. It all ran very smoothly and we received good support during qualification. There were a small number of minor non-conformances but these were rectified very quickly".

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Amélie Boulais Raveneau,
Vaccine Platform Marketing Manager, SSB



Installing the new capacity within the existing building has allowed ABL Europe to bring it online very quickly. The company commissioned the €3 million investment in the fourth quarter of 2016 and the facility was qualified and GMP-ready in Q4 2017. Amélie Boulais Raveneau, Vaccine Platform Marketing Manager at SSB, said of the project, "We're very proud to have been selected by ABL Europe to supply upstream and downstream processing technologies. It is a significant endorsement of SSB's platform for viral vector processing and the single-use design capabilities of the Sartorius Integrated Solutions team. Our process development experts can teach clients how to make the best use of our technologies to overcome challenges in viral vector applications."

"Producing viral vectors in non-adherent cell culture allows for greater scalability and the ability to produce economically at the largest scales, globally", said Da Silva. "Certain viruses, such as Poxviruses, are easier to produce in adherent cell culture; however, there are benefits to propagating viruses in suspension cell cultures. The production capacity of 60 m² of adherent cell culture capacity is approximately equivalent to that of a 100 L bioreactor. There are companies out there producing viral vectors in 2,000 L single-use bioreactors," he continued.



Empowered Employees with Unique Expertise

Mahieux has been keen to instil lean principles into the organization, which has become highly focussed on continually improving its operations to deliver greater value to its customers with less waste. "Empowered employees underpin ABL Europe's lean enterprise and lean green belt training is being rolled out across the organization. We try to maintain a very flat structure at ABL Europe. The business has a hierarchy with only three layers. In future, as the company expands, we may need more but even then five layers should be enough for a large but lean organization."

"We are fortunate to have access to a great pool of talented people", said Valenteen Sterling, Human Resources Manager. "We are located in the Alsace BioValley, a hotbed for European pharma and biotech, yet our location is very accessible and only two hours away from Paris. We are located right next door to both the Faculty of Pharmacy of Strasbourg University and the École Supérieure de Biotechnologie de Strasbourg, one of the leading schools for biotechnology teaching and research in France. Getting and motivating the people with the right skills is critical to our operations. It is our people's know-how that is the real value of the company", she continued.

The company has also recognised the importance of breaking down many of the 'silos' that often exist across organizations. Project owners take hands-on responsibility for the successful development, transfer and then operation within the GMP environment of customer processes. "It cuts out a lot of the waste that can occur during process transfer activities", explained Mahieux. "Engineers that are developing processes have first-hand experience of what works at the production scale and can feed this back into development activities. It is an excellent opportunity for our staff to develop and hone new skills. They get to experience all aspects of viral vector bioprocessing", he said.

Mahieux is already seeing strong demand from customers for the company's services. He is focussed on executing projects for its existing clients while finding new clients for the site's available capacity. "We believe the service offering we have put together here is very compelling. We have a state-of-the-art single-use facility and a dedicated team of fantastic people. I'm sure the model is going to be very successful. In the future I expect we will need to expand by buying new sites to operate according to the same principles."