Boehringer Ingelheim BioXcellence™

Winner of the honorable mention Facility of the Year Award 2020 by the International Society of Pharmaceutical Engineering (ISPE)

Boehringer Ingelheim Biopharmaceuticals China Ltd.

Executive summary

Boehringer Ingelheim is one of the world's largest manufacturers of biopharmaceuticals. With over 35 years of experience in this field, the company is an industry pioneer and has produced more than 35 biopharmaceuticals for the global market. Represented by the brand Boehringer Ingelheim BioXcellence™, it offers tailor-made contract development and manufacturing services to the industry, providing the entire production technology chain from DNA to finished product through its global network in Biberach (Germany), Vienna (Austria), Fremont (USA) and Shanghai (China). Boehringer Ingelheim BioXcellence™ secures supply throughout the entire product lifecycle – transferring customer projects at any stage, delivering to almost any scale and thereby making outsourcing easy.

With regard to China, Boehringer Ingelheim is the first international provider of biopharmaceutical contract manufacturing solutions offering all-round services to its clients in China and all over the world. Boehringer Ingelheim Biopharmaceuticals (China) Ltd.'s facility was officially put into operation in May 2017. As the first and only biopharmaceuticals facility in line with global standards set by a multinational pharma company in China, the facility has become a major milestone in Boehringer Ingelheims' strategic blueprint for its biopharmaceuticals business globally.

The commercial facility OASIS is located directly at the heart of the Zhangjiang Hi-Tech Park in Shanghai, China, which has become a landmark region with the most concentrated R&D facilities, strongest innovation abilities and the biggest number of new medicines in China. As a metropole, Shanghai offers excellent infrastructure with regard to workforce, patient population and traffic connection.

The commercial facility OASIS is designed to fulfill a maximum degree of flexibility: this includes a modular approach to fit out distinct manufacturing modules sequentially, implementing a single-use bioreactor design to react to various customer needs until the mode of operation. The interior installations as well as the enabling utilities are set-up in such a way to allow for further expansions. The spatial layout of the equipment in each floor of the sites' heart, the production building, is arranged to synergistically merge procedures and building. This is also reflected in the way in which the installations are distributed through the floors: while ground and roof floor locate enabling systems, the center floors are fully dedicated to drug substance manufacturing and drug product

manufacturing, respectively. The closed proximity ensures operational efficiency and in the end secured product supply.

This highly flexible setup is combined with Boehringer Ingelheim's vision 'value through innovation' and the biopharmaceutical ambition to bring biopharmaceutical progress to patients. In light of that, Boehringer Ingelheim BioChina actively participated in a trial project with the local authorities to establish a Marketing Authorization Holder (MAH)/CMO model in China.

The commercial facility was of essential significance for this regulatory refinement as it had provided evidence of a real product derived from these bioreactors. The first commercial product Tislelizumab was approved by China National Medical Products Administration (NMPA) under the new regulatory setup in December 2019.

Boehringer Ingelheim's biopharmaceutical contract manufacturing focusses on the development and production of therapeutic proteins for severe diseases and unmet medical needs.

Tislelizumab is used to treat relapsed/refractory classical Hodgkin's Lymphoma. Specific sub-types of lymphoma vary geographically in their relative frequency and differ in clinical features, responses to treatment and prognoses. Thus, local immune-oncologic R&D activities will support bringing innovative drugs to this patient population.

As a contract manufacturer, Boehringer Ingelheim not only ensures the supply of medicines for patients in China and worldwide, but also for the rapidly emerging Chinese biopharmaceutical Research & Development landscape. From Boehringer Ingelheim's perspective, the provision of biopharmaceutical contract manufacturing is an opportunity to boost China's advances in life sciences.

As present in all other sectors of public life, also the health care sector is changing rapidly in China.

Thus, short project timelines were of essential importance in construction and start of operation. However, at no point in time this should jeopardize the quality of biopharmaceutical drugs. Boehringer Ingelheim addressed this challenge by combining Chinese speed with German quality standards. Globally harmonized systems and standards as well as the same technology throughout the entire global manufacturing network allow for smooth transfers between Boehringer Ingelheim's biopharmaceutical manufacturing sites resulting in securing supply at highest quality for customers and in the end patients.

The symbiosis of a sophisticated infrastructure and high quality standards thus contributes to giving patients in China access to biopharmaceutical progress.

Boehringer Ingelheim BioChina - Breakthrough investment in the Chinese market

In 2013, Boehringer Ingelheim decided to build a manufacturing facility in the Shanghai area. With this decision, the company's main goal was to support the growing patient demands for biopharmaceutical medicines in China.

Back then, biopharmaceutical contract manufacturing was not permitted by the Chinese regulations. At this point Boehringer Ingelheim took up: The Company put all its efforts into anchoring a trial project exploring the ways of establishing the Market Authorization Holder (MAH) / CMO model in China – with success. The implementation of the trial project into the Chinese legal and economic system represented an important milestone to widen access to healthcare for Chinese patients.

Boehringer Ingelheim entered the Chinese market with the vision in mind to become the number 1 international biopharmaceutical contract manufacturer and leading CMO in China supplying full range of development, clinical and commercial services. Only six years later, the view of the present shows: this vision has become true.

During the business establishment and 6 years operation period, Boehringer Ingelheim BioChina greatly benefits from the highly reputable international Boehringer Ingelheim contract manufacturing business image, e.g. a strong reputation for reliability, quality and cutting-edge technical expertise. Many local and global customers are aware of Boehringer Ingelheim's substantial global track-record boosting Boehringer Ingelheim Bio China's reputation as a fully functional, productive and reliable international standard CMO based in Shanghai, China.

Based on our leadership position in technology areas, Boehringer Ingelheim capitalizes on performance (including global quality standards) as a competitive advantage. In this context, Boehringer Ingelheim's large global biopharmaceutical network excels to be an advantage for its operations – e.g. regarding technology transfers, expertise for technology innovations, global sourcing, global QA systems, procurement and outsourcing.

The Boehringer Ingelheim BioChina biopharmaceutical site consists of two different locations operating at two different modes: The Bio Lab facility is at the Boehringer Ingelheim Shanghai Pharma Logistics site (BISPL). There are biologics CMC services for early stage projects of national and international customers offered, like seeking Clinical Trial Application (CTA) and supply for clinical Phase I studies at 100 L and 500 L scale under cGMP conditions.

OASIS, the other location, features cGMP compliant manufacturing at 2 kL scale and sterile F&F for phase III commercial products.

In this setup, Boehringer Ingelheim BioChina provides the entire value chain from cell line development (transferred from the competence center in Biberach, Germany) until vial filling in Shanghai, China in a one-stop shop approach.

Finally, it needs to be highlighted that the Shanghai site is the one and only biopharmaceutical site of a multinational company (MNC) on the Chinese market offering contract manufacturing that meets global standards – what demonstrates the great importance to quality the company attaches comprehensively.

Features of the Facility

General description of the facility OASIS

The OASIS GMP facility is located directly in the heart of the Zhangjiang Hi-Tech Park in Shanghai, China, which has become a landmark region with the most concentrated R&D facilities, strongest innovation abilities and the biggest number of new medicines in China. The facility has been built under a collaboration between Boehringer Ingelheim and the Zhangjiang Biotech & Pharmaceutical Base from 2013.

In August 2015, the jointly developed Boehringer Ingelheim BioChina Manufacturing Building shell OASIS was completed and the successful handover took place after which Boehringer Ingelheim started the fit-out, and introduced its equipment, know-how, and technology following international standards.

The inauguration of the new OASIS facility took place in May 2017 and even one year later Boehringer Ingelheim BioChina received the manufacturing license by the Chinese government. The facility itself is set up in a modular approach with module 1 covering first bioreactors including an auto isolator fill & finish line and an expansion option for module 2. The second module could house further bioreactors to be linked to the already existing utilities of this facility.

The planning, construction and GMP operations readiness of the OASIS facility is a great example for the successful combination of “Chinese Speed and German Quality”.

Figure 1: OASIS facility overview

The OASIS site covers approx. 23,615 m^2, and consists of six building structures:

1. Production Building 1
2. Central Utility Building
3. Dangerous Goods warehouse
4. Fire Fighting Pump House
5. Waste Water Treatment Plant
6. Security Guard House

Facility setup – Maximizing flexibility

In contrast to western markets, the Chinese society, economy and regulatory environment are changing more rapidly. To keep up with this speed from a construction and technology perspective, OASIS is setup with a maximum of flexibility. Boehringer Ingelheim went for this strategic investment and therefore applied a modular approach of using an existing outer shell of a building and a step-by-step option for getting certain modules up and running. Boehringer Ingelheim started the operations in 2013 with a 2 kL bioreactor in the first module. In the meantime, expansions in the second module are ongoing.

Also with regard to technologies, the focus is clearly on maximizing flexibility: The entire production is based on single-use equipment to be put together following a toolbox concept, which allows for various combinations and which can cope with the requirements of different processes. The bioreactors and vessels are connected through a flexible tube system instead of pipes offering options for putting together equipment barely independent of hardware installations.

Further benefit of the integration into an existing building is the small ecological footprint. The modular fit out follows environmental friendly principles of Boehringer Ingelheim: utilities and manufacturing areas will only be expanded and in operation based on confirmed product supply demands. This approach supports the most efficient use of resources (water, power, capacity) at the site.

The project embraced energy efficiency and environmental impact throughout the detailed design, to fulfil Boehringer Ingelheims standards and practices for the carbon reduction strategy. Examples of energy efficient design within the HVAC systems include VAV (Variable Air Volume), exhaust air heat recovery, optimized / limited air duct velocity and reduced ductwork resistance. For the electrical drives and pumps, VFD's (Variable Frequency Drives) and high efficiency motors have been utilized throughout. Metering is also installed throughout the facility, to provide accurate monitoring of energy and clean media consumption, and to enable continuous improvements in waste reduction initiatives.

In addition, the design, construction and technology used within the OASIS production facility allows for a modular development of the site itself.

Starting with the production building (PB1), currently the shell is fully constructed, together with its core infrastructure. However, only approx. 30% of the shell was fitted out for GMP manufacturing and its associated operations during phase 1 of the project. Two additional project phases are already conceptually scoped in order to enable seamless modular expansion and corresponding fit-out to increase the production capacities as required. At time of the application, Phase 2 project is already under construction.

Concerning manufacturing, the single use technology employed throughout OASIS significantly strengthens the flexible modular expansion approach compared to traditional stainless steel processing facilities. As the product contact materials e.g. bags, flow paths, hose etc. are supplied pre-sterilized, and disposed after each batch, the process is absent of fixed CIP/SIP systems. Furthermore, the modular equipment offers process flexibility in terms of design footprint – as the equipment can be arranged or rearranged with more freedom. In addition, the single-use technology also reduces the levels of complexity for the automation system requirements compared to stainless steel, leading to faster and cheaper implementation, and reduced start-up times.

The Central Utility Building (CUB) is currently 55% utilized in terms of area. This provides sufficient utility capacities for the current production process and facility requirements, and allows for further fit-out as required. Moreover, Boehringer Ingelheim reserved an additional footprint for the CUB buildings expansion, enabling further black utility expansion to accommodate an additional production building at a later stage.

Distribution of the utilities across site is also well considered by means of a flexible utilities pipe rack. The pipe rack and its additional tie in points, future-proof the increasing demands of OASIS' growing manufacturing footprint.

Social impact of contract manufacturing business model: boosting China's advances in life sciences

Biopharmaceutical manufacturing is one of the major industries encouraged by the 13th Five-Year Plan both in Shanghai and at the national level. Biopharmaceutical MAH and contract manufacturing system, which is a new form and model for the industry, has been included in the

2015 Shanghai Municipal Government Work Report and the latest "22 Measures to Promote Shanghai's Development of a Technology and Innovation Center." The MAH/CMO model is expected to facilitate implementing the innovative strategy of the biopharmaceutical industry in Shanghai. It is also expected to lead significant impact on the development of Shanghai's

biopharmaceutical industry and facilitate the initiative to build Shanghai into a technology and innovation center with global influence.

As mentioned above, until very recently Chinese regulations did not permit contract manufacturing of biopharmaceuticals at all. "The rule was: if you own the drug, you have to manufacture it yourself and are not allowed to outsource the manufacturing to a third party," remembers Dr. Jiali Luo, General Manager and Site Head of Boehringer Ingelheim Biopharmaceuticals China. Therefore, in 2013 Boehringer Ingelheim began working to support the revision of the regulations with the China National Medical Products Administration (NMPA) – hardly an easy task. With years of hard work, courageous entrepreneurship and diplomacy lie behind the Boehringer Ingelheim team of BioChina. Finally, in late August 2019, China's Standing Committee of the National People's Congress approved a significant revision of the Drug Administration Law. The first biologic was approved under the new Chinese Drug Administration Law in December 2019: Through its collaboration with BeiGene Ltd. and the provision of production services for their anti-PD-1 antibody Tislelizumab, Boehringer Ingelheim Biopharmaceuticals China managed to be the first company to successfully complete the process for biopharmaceutical contract manufacturing in China.

This is a major milestone for the Chinese biopharmaceuticals market and has the potential to greatly enhance China's standing in the life sciences and in ensuring the supply of medicines. For the future, Boehringer Ingelheim BioChina established a strong and sustainable project pipeline, which serves as a solid basis to support Boehringer Ingelheim providing better innovative drug accesses to patients.

For Boehringer Ingelheim, ensuring product quality and control are of crucial importance. We address these concerns by our one-stop-shop concept: From cell-line development, until fill and finish our entire process is ensuring the full understanding and knowledge of the complex processes in biopharmaceutical manufacturing based on living systems. Based on our tremendous experience in biopharmaceutical manufacturing according to authority requirements we secure strict work under cGMP conditions. A global quality system is in place to safeguard compliance to all regulatory rules.

Our business model services our customers in two directions: On the one hand, we offer high-quality local manufacturing for MNC pharma customers for the Chinese market and also for their home countries. On the other hand, we focus on collaborations with Chinese companies to support them in bringing their innovative products to the global markets.

To summarize, the business model and the infrastructure provide a flexible and sustainable basis for adaptations regarding working modes, expansions and a growing portfolio of market products.

The latter facilitates to minimize risks and carry out a sound personnel planning for highly qualified workplaces.

Ensuring high quality output - Operational excellence

Single-use equipment enables shorter changeover times between different processes because the time-consuming cleaning and water treatment steps are avoided (CIP and SIP). Furthermore, this concept reflects the current market situation: up to now, the focus of the facility is on late stage clinical supply and commercial supply, where the demands are usually smaller resulting in smaller volume of bioreactors and shorter manufacturing campaigns. Once the demands increase, Boehringer Ingelheim is able to accommodate manufacturing of larger volume products in their global network.

Furthermore, manufacturing of biopharmaceuticals is a very complex process. It requires in-depth understanding of biotechnological process, regulatory requirements, a thorough GMP-mindset and global thinking-skills. Regarding our staffing, we follow the strategy to employ both local and global talents and train & integrate them into BI's operating and quality systems. Our vision is to build up a highly knowledgeable subject matter experts team which combines the above-mentioned requirements with thorough understanding of the local circumstances leveraging best-practice sharing within the global network. Operation based on single-use equipment is easier to handle as it limits the risk for cross-contamination and thus prevents failed batches.

Finally, corporate culture and values are critical success factors for operational excellence as they guide employees at Boehringer Ingelheim in how to work together in a highly competitive environment. In the family owned company Boehringer Ingelheim employees work along the principles of accountability, agility and intrapreneurship. These three principles are regarded as a maxim for the daily business: The Boehringer Ingelheim leitbild fosters a culture where every employee is asked to challenge his or her own behavior.

As quality of pharmaceutical products is made by people, the company has established global Quality Culture principles. The so-called business process excellence standards in the development and manufacturing network have been established to challenge the mode of operation and in order to stay at the cutting edge of manufacturing. The use of performance dialogues in each department is a key metric to monitor operational excellence on all hierarchical levels.

The combination of hard facts, like product quality, facility design and efficiency as well as the soft facts like highly trained staff are key factors for Boehringer Ingelheim with regard to the fulfilment of its vision: delivering progress to the customers from which patients worldwide can benefit in the end.

Further information:

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