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FROST & SULLIVAN BEST PRACTICES AWARD

ADC CONTRACT MANUFACTURING SERVICES - GLOBAL

Growth Excellence Leadership 2019

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Background and Company Performance

Industry Challenges

Cancer, the second leading cause of deaths globally, results in an estimated 9.6 million deaths in 2018 worldwide. [1] Traditional cancer therapeutic methods result in the nonspecific killing of cancerous and healthy cells with adverse health impact. There is an urgent need to meet the evolving requirements for personalized cancer therapies with targeted cell killing. As such, Frost & Sullivan observes how biopharmaceutical companies are focusing on innovative drug development strategies targeted to new-generation specialty cancer treatments, with antibody drug conjugates (ADCs) as the fastest growing market segment. Highly specific, ADCs delivers targeted cell killing therapeutics; antibodies attach to specific tumor cells, releasing the cytotoxic drug to act on cancerous cells and preventing damage to healthy cells.

Clinical studies validate the efficacy of third generation site-specific homogenously conjugated ADCs, propelling speedy FDA approval and enhancing clinical trial rates — currently, 600 plus ADC–based clinical trials conducted globally.[2] The ADC market will rise from $2 billion in 2018 to $10.5 billion by 2024, expanding at an estimated 20% compound annual growth rate until 2030; a strong pipeline of over 200 products, 17 new drugs in late-stage development, and currently marketed products, namely brentuximab vedotin (Adcertis®; Seattle Genetics/Takeda), (ado-)trastuzumab emtansine (Kadcyla®; Genentech/Roche), gemtuzuman ozogamicin (Mylotarg®; Pfizer), inotuzumab ozogamicin (Besponsa®; Pfizer) and polatuzumab vedotin-piiq (Polivy™; Genentech/Roche), all fuel the market.[3]

ADC Development Constraints—Supply Chain and Scale-Up Issues

With higher product approval rates and several molecules in late-stage clinical trials, Frost & Sullivan points out that the demand for scaling-up operations to support large-scale ADC manufacturing is rising. However, ADC manufacturing involves significant constraints, as it includes highly potent small and large molecule components with toxic intermediates.

Scaling-up for commercial processes is quite challenging, as ADC manufacturing necessitates an aseptic biological current Good Manufacturing Practice (cGMP) environment, compliant to safety protocols protecting personnel from cytotoxic chemicals exposure. Large-scale clinical and commercial GMP bioconjugation of payloads to antibodies compels accurately configuring process development following critical parameters such as volume-range requirements and in-process monitoring instrumentation for appropriate process equipment design. Factors such as buffer composition, temperature control, pH, and stable cytotoxicity, among others, are all critical, in addition to selecting the appropriate analytical and bioanalytical methods. Likewise, the finished product is photosensitive, demanding excellent packaging and temperature control measures. Furthermore, handling capabilities pose a huge risk

[1] https://www.who.int/news-room/fact-sheets/detail/cancer, accessed June 2019
[2] CPhI Pharma Insights Annual Report. *Pharma's Year of Accelerated Innovation & Convergence. Expert Contribution*. Madrid: CPhI, 2018.
[3] *ibid*

concern for personnel, since highly potent small molecules (payloads) have a high level of toxicity.[4]

The complexity, high-end expertise, and massive costs involved with manufacturing ADC-based specialty drugs force biopharmaceutical companies to rely heavily on outsourcing, presenting immense opportunities for contract development and manufacturing organizations (CDMO). Nearly 70% to 80% of all ADC development is via contract manufacturing.[5]

However, Frost & Sullivan notes that most of the CDMOs are well-equipped to meet clinical trial needs, but either lack the scalability or face the drawbacks of the distributed supply chain. ADCs require a complex supply chain for product manufacturing and final formulation; consequently, a coordinated and consistent antibody, linker, and payload supply are vital. A distributed supply chain developing intermediaries at different independent sites entails product change-over. Sourcing products from multiproduct facilities subsequently increase timelines and manufacturing costs. CDMOs are leveraging an integrated supply chain for antibody, linker, and payload development under a single roof to decrease both cycle timelines and cost.

Frost & Sullivan concludes that safety-adherent CDMOs with cGMP certified clinical and commercial facilities and integrated solutions will continue to grow and expects double-digit ADC approval in the next one to three years. North America will contribute to the majority of market revenue; notably, Asia-Pacific (APAC) and Europe will make an almost equal contribution. The specialist development requirements of small biotech companies and the co-development model favored by large biopharmaceutical companies will further drive the market. Within these current opportunities, Frost & Sullivan believes that CDMOs effectively dealing with the manufacturing challenges to offer large-scale development capacity globally are likely to capture significant market share.

Growth Performance and Customer Impact

Founded in 2013 and headquartered in Yantai, Shandong Province of China, MabPlex International (MabPlex) offers biologics development and manufacturing services, including monoclonal antibodies (mAbs), recombinant proteins, ADC, and bi-specifics, to the pharmaceutical industry. Rapidly expanding its operations to meet the market need in China, the company is foraying into the global market with its expansion in the United States (US), positioning MabPlex as one of the few large-scale ADC production providers worldwide. The company's services cover the entire spectrum - from gene sequencing to cell line development, process characterization, conjugation optimization, and cGMP commercial manufacturing of final drug product (DP) for biopharmaceutical companies.

MabPlex: At the Forefront of Large-scale ADC Manufacturing

MabPlex had a jumpstart over other international CDMOs, driven by the Chinese government's support. Inspired by its founder Jianmin Fang's vision, who was

[4] Challener, Cynthia A. "*Overcoming Challenges in ADC Bioconjugation at Commercial Scale*." October 2018. BioPharmInternational.com. May 2019 <http://www.biopharminternational.com/overcoming-challenges-adc-bioconjugation-commercial-scale>.

[5] Scanlan, Claire. "*Antibody-Drug Conjugates: Manufacturing Challenges and Trends*." ADC Review (2017).

instrumental in influencing the change in the drug development ecosystem, MabPlex became the first company to manufacture an ADC in clinical trials in China.

The company's first manufacturing facility (M1) offers an end-to-end integrated solution. Built in 2015, M1, a 270,000 square foot facility in Shandong, province of China, contains three upstream suites for antibodies, two suites for conjugation and two dedicated downstream suites. Supporting high scale manufacturing, the M1 facility accommodates up to 500 liters (L) of conjugation.

Over the last four years, MabPlex advanced over 60 projects in China. Currently, 30 to 40 ongoing projects have molecules advancing rapidly through the clinical stages. Anticipating the ADCs in late-stage development to move to commercialization sooner, and fueled by rising bio-manufacturing capacity demand globally, the company opened a second facility (M2) in September 2018, also located in Shandong. Complying with international manufacturing regulations, M2 is an over 270,000 square feet facility designed specifically for Phase III and commercial manufacturing of antibodies in global markets. M2 builds upon the current process development facility to add six new cell culture (upstream) suites, each accommodating volumes up to 2 X 2,000 L, with a maximum capacity of 24,000 L, and all single-use stirred tank bioreactors. The M2 facility has four additional purification (downstream) suites and a cGMP warehouse. Providing fill and finish capabilities, M2 also has the expertise for cell-line development and process development in Ambr® 250 modular bench-scale bioreactors.

Establishing an expert track record with Chinese biotechnology companies, the company's business focus initiated with China to fuel its international growth strategy of becoming the preferred global provider of quality GMP manufacturing services to Western markets. To this end, MabPlex developed the San Diego facility in the US, building a team to engage early with clients and communicate with pharmaceutical partners in Europe, the US, and the rest of the Western world. Opportunistically leveraging the post-acquisition closure of US-based Agensys by Astellas, Mabplex recruited the laid-off employees with a high level of experience in antibody and ADC processes. Moreover, the company leased a facility in San Diego, CA, proactively re-forming the Agensys process development team for a seamless transition. Frost & Sullivan recognizes how this strategic move allowed MabPlex to leverage the world-class seasoned expertise of the Agensys team to support its US clients in process development services, synergistically working with the same group and equipment. MabPlex USA's state-of-the-art Process Development Center of Excellence in San Diego, California has a scale-up capacity of up to 200 L and provides an exceptional integrated solution supporting cell-line development, upstream and downstream process development, ADC, analytical testing, and formulation development. The collective capacity of the Yantai, San Diego, and new Shanghai facilities cater to the rising demand of MabPlex's new and current clients for ADCs' early and late-stage development to commercialization.

Integrated Solution under One Roof Improves Efficiencies across the Value Chain

Complying with international GMP requirements, MabPlex manufactures linkers and cytotoxins within its facility. The company's proprietary cysteine conjugation platform is

available to clients flexibly, without complicated licensing agreements, bringing about more cost efficiency. Frost & Sullivan appreciates how MabPlex offers an end-to-end solution under one roof — reducing ADC's time-to-market (TTM) by conducting all ADC manufacturing steps, including conjugation, scale-up, commercial manufacturing, and fill-finish in the same facility.

This integrated offering also minimizes external touch points and facilitates timely inter-facility communication. A unified supply chain enables efficiencies across the board, allowing MabPlex to save scheduling and testing time significantly, eliminate rescheduling (due to supply chain delays), limit inventory and logistical management concerns, and reduce product transfer related risks. The enhanced efficiencies lower the company's overhead costs, translating into one of the most competitive pricing models' in the industry. In addition, the talent pool and real estate cost-benefit factor into the overall production cost, bringing considerable value to clients. MabPlex's supply chain strategy promises seamless delivery of antibody, linker, and payload focusing on local supply; this eliminates the time and cost for cross-continental shipping of vital raw materials (intermediates) to develop final active pharmaceutical ingredients.

Cutting-edge Technologies Lower Time-to-Market and Enhance Quality

MabPlex's superior technical expertise allows timely and cost-effective delivery of innovative products, lowering the overall TTM. Its Chinese Hamster Ovary (CHO) cell line's unique design moves drug candidates from DNA to finished recombinant protein products in the shortest possible time and with high production titers ranging from three to over eight grams per liter. The state-of-the-art quality systems align with US, European, and Chinese GMP requirements. The company's collaboration with Sartorius Stedim Biotech, General Electric and Thermo Fisher Scientific culminated in a high-quality GMP biologics production facility, with flexible scale-up, single-use technologies, shortened production cycles, and 100% cell culture success rates with 0% contamination rates in the new single-use bioreactors.[6]

MabPlex's technology ensures consistent drug-to-antibody-ratio (DAR) for each manufacturing lot - versus competing technologies with diverse DAR from lot to lot, causing quality concerns. An aggressive screening mechanism allows the company to have an impressive research cell bank (RCB) selected within three months. With a two-month real-time stability study on RCB, MabPlex facilitates developing master cell banks in only five to six months — lowering research and development (R&D) cycles, time, costs and risk.

The company's R&D group works on linking technology innovation to enable multiple variations of antibody, linker, and payload for in-vitro efficacy testing against a cancerous cell-line panel in just a few months. Currently developing novel DNA-damaging payloads with an academic institution's collaboration, MabPlex strives to deliver unique ADCs with promising clinical efficacy. The company's world-class facilities and cGMP operations recognized by the US, Australian, and Chinese regulators reinforce customer trust.

[6] https://www.sartorius.com/en/knowledge/resources/case-studies/case-study-mabplex, accessed June 2019

Future Growth Strategy Focus

Exponentially growing its business revenues in China and the US, MabPlex expects the San Diego facility to generate revenues in 2019 with the signing of a significant contract. The recent $59.1 million series A funding will further boost its international growth strategy — technology upgrade and capability and capacity expansion to meet the global need of advancing late-stage ADC's to commercialization more quickly. With a promising ADC pipeline and the filing of four investigational new ADC drugs in China so far, for 2020, MabPlex has slated filing ADCs with the National Medical Products Administration (NMPA), the US FDA and the European Medicines Agency.

An incubator of its Chinese business arm aims to drive the therapeutic programs of around 100 companies from concept to commercialization. In the US, the company's 2019 focus is on ADC pipeline growth, client engagement, and co-development partnerships, all in order to specialize in ADC development. Frost & Sullivan firmly believes that offering quality manufacturing services while lowering TTM makes MabPlex a preferred partner of choice for ADC development.

Conclusion

Driven by an evolving unmet need for novel cancer therapeutics, antibody-drug-conjugates (ADCs) are an emerging medicine class, due to targeted drug delivery to cancer cells. ADC manufacturing constraints relate to cGMP linkers and payloads development, cytotoxic molecule handling risks, supply chain issues, high-end expertise, and massive costs, leading to outsourcing.

MabPlex International (MabPlex), a biologics contract development manufacturing organization, provides state-of-the-art cGMP operations across facilities, specializing as one of the few large-scale ADC producers from late-stage development to commercialization worldwide. By expanding capacity aggressively across China and the United States, the company offers a superior end-to-end solution under one roof. Harnessing supply chain efficiencies, MabPlex reduces a product's time-to-market and overall production costs. The company's proprietary conjugation platform and innovative technologies further deliver novel and clinically efficacious ADCs for cancer therapeutics globally.

With its strong overall performance and aggressive growth strategy, MabPlex earns the 2019 Frost & Sullivan Global Growth Excellence Leadership Award.

Significance of Growth Excellence Leadership

Growth Excellence Leadership is about inspiring customers to purchase from a company and then return time and again. In a sense, then, everything is truly about the customer. Making customers happy is the cornerstone of any successful, long-term growth strategy. Companies that excel in driving growth strive to be best in class in three key areas: meeting customer demand, fostering brand loyalty, and carving out a unique and sustainable market niche.

Understanding Growth Excellence Leadership

Companies that creatively and profitably deliver value to customers ultimately set up their businesses for long-term, rapid growth. This is what Growth Excellence Leadership is all about: growth through customer focus, fostering a virtuous cycle of improvement and success.

Key Benchmarking Criteria

For the Global Growth Excellence Leadership Award, Frost & Sullivan analysts independently evaluated Growth Performance and Customer Impact according to the criteria identified below.

Growth Performance

Criterion 1: Growth Strategy
Criterion 2: Above-market Growth
Criterion 3: Share of Wallet
Criterion 4: Growth Diversification
Criterion 5: Growth Sustainability

Customer Impact

Criterion 1: Price/Performance Value
Criterion 2: Customer Purchase Experience
Criterion 3: Customer Ownership Experience
Criterion 4: Customer Service Experience
Criterion 5: Brand Equity

Best Practices Recognition: 10 Steps to Researching, Identifying, and Recognizing Best Practices

Frost & Sullivan analysts follow a 10-step process to evaluate Award candidates and assess their fit with select best practice criteria. The reputation and integrity of the Awards are based on close adherence to this process.

STEP		OBJECTIVE	KEY ACTIVITIES	OUTPUT
1	**Monitor, target, and screen**	Identify Award recipient candidates from around the globe	• Conduct in-depth industry research • Identify emerging sectors • Scan multiple geographies	Pipeline of candidates who potentially meet all best-practice criteria
2	**Perform 360-degree research**	Perform comprehensive, 360-degree research on all candidates in the pipeline	• Interview thought leaders and industry practitioners • Assess candidates' fit with best-practice criteria • Rank all candidates	Matrix positioning of all candidates' performance relative to one another
3	**Invite thought leadership in best practices**	Perform in-depth examination of all candidates	• Confirm best-practice criteria • Examine eligibility of all candidates • Identify any information gaps	Detailed profiles of all ranked candidates
4	**Initiate research director review**	Conduct an unbiased evaluation of all candidate profiles	• Brainstorm ranking options • Invite multiple perspectives on candidates' performance • Update candidate profiles	Final prioritization of all eligible candidates and companion best-practice positioning paper
5	**Assemble panel of industry experts**	Present findings to an expert panel of industry thought leaders	• Share findings • Strengthen cases for candidate eligibility • Prioritize candidates	Refined list of prioritized Award candidates
6	**Conduct global industry review**	Build consensus on Award candidates' eligibility	• Hold global team meeting to review all candidates • Pressure-test fit with criteria • Confirm inclusion of all eligible candidates	Final list of eligible Award candidates, representing success stories worldwide
7	**Perform quality check**	Develop official Award consideration materials	• Perform final performance benchmarking activities • Write nominations • Perform quality review	High-quality, accurate, and creative presentation of nominees' successes
8	**Reconnect with panel of industry experts**	Finalize the selection of the best-practice Award recipient	• Review analysis with panel • Build consensus • Select recipient	Decision on which company performs best against all best-practice criteria
9	**Communicate recognition**	Inform Award recipient of Award recognition	• Present Award to the CEO • Inspire the organization for continued success • Celebrate the recipient's performance	Announcement of Award and plan for how recipient can use the Award to enhance the brand
10	**Take strategic action**	Upon licensing, company is able to share Award news with stakeholders and customers	• Coordinate media outreach • Design a marketing plan • Assess Award's role in future strategic planning	Widespread awareness of recipient's Award status among investors, media personnel, and employees

The Intersection between 360-Degree Research and Best Practices Awards

Research Methodology

Frost & Sullivan's 360-degree research methodology represents the analytical rigor of our research process. It offers a 360-degree-view of industry challenges, trends, and issues by integrating all 7 of Frost & Sullivan's research methodologies. Too often companies make important growth decisions based on a narrow understanding of their environment, leading to errors of both omission and commission. Successful growth strategies are founded on a thorough understanding of market, technical, economic, financial, customer, best practices, and demographic analyses. The integration of these research disciplines into the 360-degree research methodology provides an evaluation platform for benchmarking industry participants and for identifying those performing at best-in-class levels.

360-DEGREE RESEARCH: SEEING ORDER IN THE CHAOS

About Frost & Sullivan

Frost & Sullivan, the Growth Partnership Company, enables clients to accelerate growth and achieve best-in-class positions in growth, innovation and leadership. The company's Growth Partnership Service provides the CEO and the CEO's Growth Team with disciplined research and best practice models to drive the generation, evaluation and implementation of powerful growth strategies. Frost & Sullivan leverages more than 50 years of experience in partnering with Global 1000 companies, emerging businesses, and the investment community from 45 offices on six continents. To join our Growth Partnership, please visit http://www.frost.com.

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