SELECTING A MICROBIOME CDMO PARTNER FOR THE LONG TERM

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As more microbiome-based therapies progress through the clinic toward approval for market launch, concerns over the lack of outsourcing capacity for process development and commercial manufacturing of live biotherapeutic products are increasing. Arranta Bio is investing heavily in both its process development and cGMP manufacturing capabilities for the supply of clinical trial material and in a new commercial-ready facility to ensure that companies in the microbiome space have access to the specialized expertise and facilities needed to bring novel medicines to patients.

In addition, Arranta Bio can provide an accelerated path to first-in-human trials through actALIVE™, Arranta's Fast-to-Clinic Program, which delivers high-yielding, high-viability live biotherapeutic products (LBPs) in an accelerated timeline based on Arranta's deep development history and proprietary AMB™ media blends and ACP™ cryopreservatives.

MARKET GROWTH CREATES MANUFACTURING CHALLENGES

While no microbiome-based drugs have yet been commercialized, growth of the global human microbiome market, including diagnostic tests and drugs, is expected to reach $1.7 billion by 2027.[1] By 2022, the therapeutics segment is expected to account for the largest share, driven by increased R&D funding for microbiome-based therapies worldwide. Other annual growth estimates for the microbiome segment range from near 20% to more than 60%.[2-4]

ALIVE Biotherapeutic Products™ (aLBP)

ALIVE Biotherapeutic Products™ (aLBP) is Arranta Bio's proprietary platform for world-class development and manufacturing of aLBPs using over a decade of process development expertise in manufacturing aerobic, anaerobic, and spore-forming organisms. Notably, aLBPs produced by Arranta Bio have the advantages, embodied by the ALIVE acronym, as shown below.

- **A:** Accelerated development
- **L:** Long-lasting stability
- **I:** Immediate release & recovery
- **V:** Viable, high activity
- **E:** Efficient, scalable process

Most of the activity has been initiated by emerging biotechs, but big pharma firms are developing microbiome-based therapies as well – on their own and through licensing deals and development partnerships.[5] Between January 2016 and July 2019, more than $5.4 billion was spent on partnerships and acquisitions in the therapeutic microbiome space.[6] At least 200 firms are actively working on different aspects of the microbiome, and the number of clinical trials reached 2,400 in 2018, up 1.5 times compared with 2017.[7]

The vast majority of these candidates are in the preclinical or early phase clinical development stage, but some have progressed to phase II, and several are in phase III clinical studies. There is real concern among developers of microbiome-based therapies about commercial manufacturing if their products receive approval because there is a lack of purpose-built commercial manufacturing capacity for LBPs.

Since most LBPs comprise commensal organisms or microbes that are already present in and well tolerated by the human ecosystem, microbiome-based drugs – once their efficacy has been demonstrated – have a higher probability of reaching the market than traditional small molecule or biologic drugs. Consequently, many of the drugs that have reached phase II/III have a good likelihood of receiving marketing authorizations. For many of these products, the indications cover large patient populations, so securing large-scale manufacturing capacity is critical.

Some companies with products in clinical development have invested in their own manufacturing facilities at a limited scale, because there were very limited options for outsourcing early clinical GMP production. A small number of established biopharmaceutical contract development and manufacturing organizations (CDMOs) offer limited services in the microbiome space; however, there are several appreciable challenges across the outsourcing options available. Specifically, many of the CDMOs touting their LBP capability do not have the expertise or equipment to successfully deal with anaerobic bacteria. Moreover, they lack the procedural and/or physical controls to maintain the regulatory compliance standards required to work with live organisms with the potential to form spores.

Therefore, there is a paucity of CDMOs dedicated to the microbiome space, and none are yet positioned to support the commercial launch of multiple products. Adding to the challenge is the fact that most of the very early stage microbiome companies lack some of the necessary process development capabilities in-house and really need to partner with a CDMO that has significant specialized expertise to support process development and scale-up of LBPs.

EARLY PARTNERING IS ESSENTIAL

Selecting a microbiome CDMO partner with an eye on the long term from early process development through clinical phases – who can also undertake and complete effective process characterization to support process qualification enabling commercial approval and ongoing manufacturing and supply – is the optimal solution for overcoming all of these challenges. It is essential that the CDMO has foundational expertise in process development and manufacturing of microbiome products. We frequently see products developed using the traditional approaches to drug development and manufacturing typically applied to small molecules or biologics. However, most LBPs do not respond well to these approaches given their unique characteristics and processing requirements, and as such it is vital that companies start with the end goal in mind.

It is essential to consider the entire process from the start rather than limiting the focus to just the most proximal stages at a given time. As products are scaled up, many of the critical product attributes become exponentially more important – it is critical that this is understood at the earliest possible stages of development to avoid expensive and time-consuming development rework during the later stages of clinical development. Arranta Bio offers customers a comprehensive development program that considers all stages on the path to commercialization from the very beginning via actALIVE™, "Arranta's Fast-to-Clinic Program," which ensures production of high-yielding, high-viability LBPs with increased stability, providing an accelerated path through LBP development to first-in-human trials and beyond. Special considerations are required for promoting maximum cell growth and supporting and maintaining optimum cell viability during downstream processing and freeze-drying. The complexity of anaerobic organisms with respect to cell banking, freeze-drying, and even encapsulation under low-humidity conditions can pose serious roadblocks in microbiome LBP manufacturing.

Retaining this vital product and process knowledge within a single organization and program team is essential when looking ahead toward the late-stage activities on the critical path to commercial launch. By selecting a CDMO with comprehensive capabilities and expertise across early process development, clinical GMP, and commercial supply capabilities, it is possible to simultaneously accelerate timelines, minimize cost and risk, and deliver a high-quality outcome.

ARRANTA BIO RESPONDING TO MARKET NEEDS

Arranta Bio is that CDMO. Since our establishment in 2019, Arranta Bio has focused on serving companies seeking to develop and commercialize therapies targeting the human microbiome. Partnering to secure the deep microbiome expertise that has become the foundation of Arranta was critical, so, in November 2019, Arranta Bio acquired Captozyme (Gainesville, Florida), which focused solely on process development and early clinical scale-up of LBPs. Captozyme's founder Dr. Aaron Cowley (now Arranta's Chief Scientific Officer) and his team bring to bear more than a decade of institutionalized knowledge and experience gained developing microbiome products that achieve critical product attributes (such as high final form cell viability, long-lasting stability, and the appropriate administration release profile), enabling microbiome products to have the best opportunity for clinical success.

Our vision and strategy is to create a value proposition that is capable of serving the pioneers at the frontier of these exciting developments in the relatively new modality of the microbiome, providing outsourced development and scalable manufacturing through to commercialization, using a range of proven platform technologies that accelerate development timelines, and give microbiome innovators' pipelines the best chance of success.

To achieve this goal, recognizing Gainesville, Florida, as Arranta Bio's center of excellence for early microbiome LBP development, we immediately embarked on a significant capital expansion program for our process development capacity. Arranta has capacity for up to 50 process development scientists and capacity to manufacture early clinical supply of live biopharmaceutical products. Arranta's world-class, commercial-ready facility in Watertown, Massachusetts, that will comply with current and anticipated regulatory requirements to support manufacture of phase III and commercial microbiome LBPs will come online in Q3 2020. As such, Arranta is offering microbiome innovators outsourced partnership opportunities that are simply not available anywhere else in the worldwide market.

The agile, flexible, and experienced team at the Gainesville facility can efficiently and effectively support early development efforts. Our program management capabilities will ensure that tech transfer from Gainesville to Watertown occurs seamlessly. At Watertown, the successful validation and production of late-stage clinical and commercial products are assured by our supply reliability enabled by our specialized LBP facility design/controls, significant installed capacity, and quality systems.

SUPPORTING CLIENTS FROM START TO FINISH

In addition to our differentiated focus on microbiome-derived products, Arranta Bio brings to customers our actALIVE™ Fast-to-Clinic Program, which provides an accelerated development timeline from the start of process development to the supply of clinical material for proof of concept, using Arranta's proprietary AMB media blends and ACP cryopreservatives for superior performance.

Arranta understands the significant rolled throughput yield (RTY) jeopardy at every step of the production process associated with LBP microbiome products. Accordingly, a carefully planned and executed quality by design (QbD) approach at the earliest stages of development for every unit of operations in the manufacturing process – from cell bank to encapsulation – is absolutely critical to give the product the best opportunity for success in clinical trials and beyond.

When it comes to process characterization and the process validation, the amount and quality of information available is typically predictive of the time and cost required to complete it. The more information that is available, the better positioned the intended commercial launch facility will be to optimize the process. Information sharing requires a high level of trust between sites. Arranta is in the unique position within the microbiome space that it is able to facilitate this entire life cycle from the bench to market for a client. Moreover, the technical team that performed the basic scientific work early

Arranta Bio's LBP Facilities

Gainesville: A Center of Excellence for Early Process Development

At the Gainesville purpose-built GMP facility, our scientists, engineers, and operators have worked with more than 135 different isolates, producing LPBs of all types (obligate, facultative, and microaerophilic organisms) up to the 400-L scale. The facility has capabilities for the production of drug substance and drug product from fermentation through encapsulation. The management team and technical experts at the site have a proven track record in both process development and contract manufacturing.

In 2019, expansion of early-phase capacity, including additional PD and QC labs and additional GMP manufacturing capacity, was initiated, which will be online this year.

Our experienced leadership team has brought best-practice approaches to many of the supportive elements required to be considered a best-in-class CDMO, such as considerable investment in IT systems, performance management, and quality systems, and we recently kicked off the deployment of Lean Six Sigma to further enhance our reliability and foster a culture of continuous improvement by putting the customer and patient at the heart of everything we do.

Something of which we are very proud is that every employee has a bonusable element of their compensation linked to both the financial performance of the company and our ability to deliver for our customers. As an organization, we want to keep everyone connected to those goals and ensure meaningful recognition of the importance of meeting customer commitments on time and in full across the organization.

The team in Gainesville has also developed a set of 22 proprietary Arranta Media Blends (AMB™) and 16 proprietary Arranta Cryo-Preservatives (ACP™), which we use to rapidly screen against client microorganisms to identify optimum process conditions. Using this approach with our actALIVE™ program, we will develop a process and provide a GMP batch in a shorter timeframe than a typical development program.

Watertown: Commercial-Ready Facility on the Way

A new large-scale facility in Watertown, Massachusetts, will support clients through late-stage clinical supply to approved, commercial manufacturing of their products. Arranta Bio is building an 80,000-ft^2 site with manufacturing clean rooms and laboratories for late-stage process characterization, QC laboratories, and offices. Conversion of the building to a state-of-the-art commercial manufacturing facility that can handle spore formers and anaerobic organisms is underway, and the facility will be operational by the end of Q3 2020.

Once completed, the site will include multiple suites with single-use fermenters ranging in scale from 500 L up to 4,000 L of capacity, as well as lyophilization and encapsulation capabilities.

on can be involved and actually on hand to support and troubleshoot the launch from our Watertown commercial-ready facility. The result will be compressed timelines and reduced cost and risk to the client.

SERVICE, ARRANTA BIO STYLE

Serving clients, whether large or small, involves transparent and proactive communication and effective execution of program requirements. Providing this level of service on a continual basis requires the right people, processes, and systems embedded in the client program management organization. CDMOs have the opportunity to differentiate themselves by embracing program management as critical to achieving the agility, flexibility, and responsiveness required to meet evolving customer needs and ongoing expectations for quality, communication, and delivery. When it comes to customer team programs, the entire senior leadership routinely meets to ensure proactive resolution of risks before they impact client timelines or their expectations around cost or quality.

Arranta's leadership team shares a strong conviction that, for strategic partnerships to be successful, investment must be a two-way street for effective and timely communication and decision-making. We strive to move hand in hand with our long-term partners, working on the fundamental premise that if they are successful, Arranta will be successful by proactively considering future needs to provide optimal service and assurance of ongoing support.

INVESTED IN THE SUCCESS OF MICROBIOME-BASED THERAPEUTICS

While other CDMOs are waiting for the first product to be approved and actual demand for commercial manufacturing capacity to materialize, Arranta Bio is already investing significantly in a commercial-ready production facility, even though the full capacity is not yet needed. A limited number of other CDMOs are expanding existing facilities to support early clinical projects, but overall other CDMOs are not committing to commercial capacity until there is an established demand for it.

Arranta Bio has committed $100 million to build end-to-end capacity as the first dedicated microbiome CDMO. Doing so represents a real belief and commitment by Arranta Bio's management to support the commercialization of novel LBPs once they are approved in a facility that is custom designed to support microbiome products.

By taking this approach, we believe that Arranta Bio is as much a pioneer in the field of microbiome-based therapies as the companies developing novel LBPs. Customers recognize and appreciate this fact, particularly that Arranta has as much at stake as they do in the success of these novel medicines. Our intent is to enable companies focused on unlocking the microbiome to get their products to market and support the further growth of the industry.

The future is certainly exciting. The bounty of evidence linking the microbiome to many aspects of human health can no longer be ignored. Once the first products receive approval for commercial launch, funding will almost certainly accelerate into the microbiome space and validate the activity that is already occurring. The first therapies that will reach the market will target gut-related diseases. But it is the microbiome-based therapies already in the clinical development pipeline for other indications – from oncology to diabetes to autism – that are likely to have the greatest impact on human health and to further propel sector growth. P

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In the role of Chief Operations Officer, **Mr. Stevens** is responsible for Arranta's operations functions, including laboratories, manufacturing, client program management, and engineering. Mr. Stevens brings over 20 years of broad international operations and commercial experience in the CRO and CDMO sectors. He was formerly the Senior Vice President & Head of AMRI's Drug Product business unit, and previously held senior leadership roles at AMRI and Aptuit. Mr. Stevens holds an MBA in strategy, finance, and marketing and an undergraduate degree in business from the University of Edinburgh.

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Jason Rahal has over 25 years of experience in biotechnology. Before joining Arranta, Jason was a member of the senior management team at Cobra Biologics, a CDMO providing ATMP services including Live Biotherapeutic Products (LBPs). Prior to Cobra, Mr. Rahal worked at Excell Biotech and Stratagene Cloning Systems in various business development and sales positions. Mr. Rahal began his career at Northwestern University managing a molecular endocrinology laboratory with several peer-reviewed publications. Mr. Rahal holds a BA in biology and studio art from Knox College.

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