Integrated mRNA Support Facilitates mRNA Product Development and Commercialization

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The contract manufacturing space for mRNA vaccines and therapeutics is highly fragmented, owing to the specialized technology and skill sets required for each of the processes involved in mRNA production, formulation, and aseptic filling. Arranta Bio is addressing this issue by offering an integrated solution, from mRNA raw material production to aseptic filling for clinical trial material and, ultimately, for commercial products.

Broad Potential Applications Driving Interest in mRNA Therapeutics

The development of mRNA vaccines against the SARS-CoV-2 virus has dramatically increased the awareness of messenger RNA (mRNA) technology and its potential for both vaccine and therapeutic applications. One recent study identified 180 mRNA candidates from 31 companies in the clinical pipeline as of July 2021.1 The candidates were classified as prophylactic vaccines (76, including 22 against COVID-19, 40 targeting other infectious diseases, and 14 with undetermined applications), therapeutic vaccines (32, including 16 single cancer-focused, five personalized, and 11 uncertain) and therapeutic drugs (72, including 13 cancer, 20 rare disease, 17 respiratory, 13 other, and 9 uncertain treatments). The majority of these candidates are in preclinical development, and less than a handful have received regulatory approval.

With respect to the value of the global mRNA product market, COVID-19 vaccines have dominated sales in 2021, which are predicted to surpass $50 billion.[1] As the need for COVID-19 vaccines wanes over the next few years, the value of the market will decline to approximately $20 billion between 2023 and 2025. By 2028, however, other prophylactic and therapeutic vaccine mRNA pipeline candidates will begin to receive regulatory approval, and the market will experience growth once again, anticipated to reach $23 billion in 2035. Prophylactic vaccines will continue to dominate, accounting for ~50% of the market, followed by therapeutic vaccines (~30%) and therapeutics (~20%).

Manufacturing Complexity Limiting CDMO Support

The manufacture of mRNA products is a highly complex set of processes. Each step in the production process requires a high level of specialization and a unique skill set. Production of plasmid DNA raw materials, transcription, capping and tailing of mRNA, mRNA encapsulation for production of lipid nanoparticles (LNPs), final formulation, aseptic filling, and cryopreservation all present challenges for product innovators in this space and contract development and manufacturing organizations (CDMOs) looking to

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support them. For example, mRNA production may require plasmid DNA linearization and clean-up steps prior to start; the mRNA production process then includes an in vitro transcription step using an enzyme that must itself be produced using bioprocessing steps, and then the mRNA will require enzymatic capping and possibly the addition of a poly A tract, and it must be purified and concentrated through a series of chromatographic and different filtration steps. Resultant mRNA can be frozen at this step, but due to inherent mRNA and/or freeze/thaw stability limitations, there can be an advantage to forward processing immediately. LNP production requires larger quantities of organic solvents that need production suites engineered with safety considerations and special permitting. The lipids to be used require a lengthy preparation step before use. The encapsulation step involves blending of mRNA with dissolved lipids to produce encapsulated lipid nanoparticles, which can use different types of lipid and/or specialized mixing technologies. The resultant LNPs then must also be purified, diluted, and/or concentrated to remove process- and product-related impurities, such as unencapsulated mRNA and solvent, and to formulate the product. These sets of LNP production steps must happen quickly owing to instability of the LNP process intermediates. Aseptic filling of the final drug product requires specialized and expensive equipment to ensure sterility of the product. Finally, each of the different products, starting materials, mRNA, and LNPs must be separately evaluated with different analytical methods to ensure quality, safety, purity, and potency of each. One consequence of this complexity is an incredibly fragmented supply chain with few CDMOs offering the manufacturing services needed for mRNA programs, and even fewer capable of providing an integrated suite of complementary services to support all the needs from a single provider.

Major Investments in mRNA

Arranta Bio is committed to providing clients with advanced solutions through its investments in equipment, capabilities, and facilities. In 2020, the company invested $100 million in a state-of-the-art 80,000-ft^2 facility in Watertown, Massachusetts, which is currently producing mRNA starting materials and other advanced therapy products, such as live biotherapeutic products (LBPs). Several Arranta clients have LBPs in phase III clinical trials, and these programs are supported with separate laboratories and cleanrooms at the Watertown facility. The facility has approximately 15,000 ft^2 of segregated labs, with each dedicated to a specific technology platform. A total of 15,000 ft^2 comprises the GMP manufacturing spaces designed for the unidirectional flow of people, materials, products, and waste. Each production suite features dedicated and isolated air flow for the highest possible degree of segregation and contamination-prevention control.

An additional $10 million is being invested in the Watertown facility to add production capacity for mRNA products without impacting current client programs. Several of the process development laboratories and GMP suites will be dedicated to mRNA, LNP, and drug product filling. The cGMP suites are being designed, engineered, and equipped to accommodate Grade C mRNA production, to enable the safe handling of the organic solvents required for larger-scale LNP generation, and to allow immediate transfer of LNPs to the drug product filling area, which will be incredibly valuable to clients. The process development labs should be operational by the end of 2021 or early 2022 and GMP clinical manufacturing capacity for mRNA and LNP production a bit later in 2022. An aseptic filling line for mRNA products should be operational in Q4 2022.

In addition, in March 2021, Arranta Bio leased space for a large 130,000-ft^2 facility in Boxborough, Massachusetts, to ensure that it stays ahead of the manufacturing demand it anticipates coming for its advanced therapy products. The facility will use a modular cleanroom system, with the first modules

expected to be installed in that facility by the end of 2021, to allow production to begin as soon as 2022.

Flexibility and Modularity Allow Tailored Manufacturing Solutions

The mRNA manufacturing capabilities being implemented by Arranta Bio are not only integrated but highly modular and flexible. They incorporate single-use technology where practical and enable Arranta to conduct chemical/enzymatic reactions, purification processes, LNP formulation, and tangential-flow filtration in the same facility. In addition, the platform for LNP processing leverages a flexible, disposable platform for LNP mixing, allowing for the use of different mixing solutions that meet individual customer requirements. Furthermore, the modularity and mobility of Arranta's equipment allows staging unit operations in order to meet different mRNA manufacturing process needs.

Advanced Process Technology

One of the unique advantages that Arranta Bio offers mRNA developers is a robotic flow system for aseptic filling. One of the biggest challenges with the typical filling process is the involvement of operators, because they represent the greatest potential for contamination. The Vanrx system is a completely robotic, entirely isolated Grade A system that eliminates human operator involvement in the aseptic filling process. It is an incredible approach to improving sterility assurance and ensuring that Arranta Bio delivers medicines to patients as safely as possible.

This robotic flow system is part of a process technology platform from Danaher. The suite of technologies, which includes solutions from several of its various portfolio companies (Cytiva and Precision Nanosystems in addition to Vanrx) provides bridges between the individual process steps. Cytiva's process equipment facilitates upstream unit operations, while the Precision Nanosystems system facilitates the LNP formulation process. By assembling and integrating all these assets in the same facility, Arranta can achieve a higher level of automation and generate superior products for our clients.

The integrated approach that Arranta Bio is taking to mRNA client support is unique in this space. Because of the configuration and engineering of its facilities, Arranta has been able to bring the disparate elements of mRNA manufacturing under one roof. Reducing the number of suppliers dramatically reduces the complexity, cost, and time for mRNA product manufacture.

Integrated mRNA Offering from Lab to Commercial Scale

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Furthermore, the flexibility of the Arranta Bio manufacturing network enables support of clients from lab to commercial scale. Process sciences laboratories will accommodate process development and characterization, process transfers, and non-cGMP production of up to approximately one gram of mRNA. GMP manufacturing scales Arranta expects to accommodate will range from 2 grams to potentially up to 100 grams of mRNA and 50 grams of LNP, depending on the processes and required solvent volumes, with the potential for larger capacity if needed. In totality, there is an enormous amount of physical capacity that can be configured for Arranta's clients. "We can help mRNA pioneers take their products into phase I/II, then phase III and on into licensure," explains CEO Mark Bamforth. "We have performed a considerable amount of engineering work and know we can readily scale capacity within our facilities and across that network. Our goal is to make sure clients can supply their products to patients in need."

Experienced Team in Place

At Arranta Bio's Watertown facility, there are approximately 130 employees, with 40 direct manufacturing personnel and 20 involved in process development. Another 20% are involved in quality assurance, quality control, and analytical development. The remainder are involved in facilities engineering, supply chain management, and administrative support. Arranta intends to add an additional 10 process development personnel by the end of 2021 to support the expansion of these labs.

Within its existing manufacturing staff, approximately 30% have previously been involved in the production of COVID-19 mRNA vaccines in Massachusetts. Arranta's head of process engineering is a subject matter expert not only in mRNA process development, but equipment design and operation. Most of Arranta's existing technical leaders have set up many mRNA processes throughout the industry.

A True Partner for mRNA Projects

Arranta Bio works with its clients at the level of interaction they desire. Some clients prefer a single, more traditional contract, such as to make one batch of a product. Others want a deeper relationship and real collaboration for essential services they cannot achieve on their own. Arranta accommodates both approaches, working closely to meet its clients' individual requirements with a dedicated team of experts, combined with clear and transparent communication. The goal is always to deliver what they specifically need when they need it.

"We can provide this level of tailored support because we have the specialized in-house expertise necessary to support complex mRNA development and commercialization projects backed by an experienced executive team that understands the perspectives of both CDMOs and drug/vaccine developers," added Bamforth. "We can anticipate and solve problems quickly for our customers and aim to become a critical part of their success stories."

REFERENCES

1. Xie, Wen, Baiping Chen, and John Wong. "Evolution of the market for mRNA technology." *Nature Reviews Drug Discovery.* 2 Sep. 2021.