

Q&A WITH AJINOMOTO BIO-PHARMA SERVICES: — OLIGONUCLEOTIDE THERAPEUTICS: — PARTNERING WITH THE RIGHT CDMO

The oligonucleotide market is poised for high growth over the next few years driven by a few factors, including high application potential of oligonucleotides for a variety of medical conditions, a growing number of FDA approved oligonucleotide drugs, an increased focus on personalized medicine, and a continued emphasis on the development of therapeutics for rare diseases. As a result, contract development and manufacturing organizations (CDMOs) are seeing increasing requests for oligonucleotide production from small to commercial scale. The challenge to a CDMO partner is to cost-effectively, quickly and easily scale up your oligonucleotide from research to commercial quantities, as well as having the facilities in place to manage commercial scale quantities.

Noriyasu Kataoka, M.Sc., is the Quality Manager & President and Akihiro Oota is the General Manager of Oligonucleotide & GMP Manufacturing at the Osaka site of Ajinomoto Bio-Pharma Services (Aji Bio-Pharma), which recently constructed and opened a new Oligonucleotide API Manufacturing Center. The Osaka site has been successfully synthesizing oligonucleotides for research use for over 20 years prior to developing GMP manufacturing for oligonucleotides. In this Q&A, they discuss the resources and capabilities needed for a CDMO to seamlessly scale oligonucleotides from research to commercial manufacturing.

What are oligonucleotide therapeutics?

Noriyasu Kataoka: Oligonucleotide synthesis involves making changes to nucleobases, the sugar backbone, or the phosphodiester bonds to create a specific DNA or RNA molecule, for example BNA (bridged nucleic acids) and LNA (locked nucleic acids). These chemical modifications have led to the development of new drugs for various diseases and therapies that previously were difficult to treat using conventional drug treatments. Additional nucleic acid technologies include the custom synthesis of antisense oligonucleotides (ASO), RNA interference (RNAi), small interfering RNA (siRNA) and microRNA (miRNAs), which are used to modulate gene and protein expression, as well as aptamer RNAs, which modulates protein functions.

What is the benefit of using oligonucleotides for therapeutics?

Noriyasu Kataoka: With the broad variety of platforms and modalities, oligonucleotides hold a strong promise and a growing portfolio for researchers and biopharma drug companies in developing effective, targeted, next-generation therapeutic drugs and vaccines. Since oligonucleotides can target errors in the genetic code, many diseases and conditions that were previously untreatable using traditional medicines, can now be managed and with better safety and efficacy. Vaccines are of particular interest in the oligonucleotide field, especially for the rapid development of vaccines for emerging diseases, such as malaria or COVID-19. Oligonucleotides can be used as vaccines

adjuvants, which can enhance the effect of the innate immune response by targeting cells' toll-like receptors (TLR).

Are oligonucleotides considered large or small molecules?

Noriyasu Kataoka: Oligonucleotides are sized between small and large molecules, but with a large range in the mode of action at the cellular level. Therefore, while oligonucleotides are manufactured in a manner similar to small molecule active pharmaceutical ingredients (API), once administered they act more like a large molecule drug product. This has made for unique regulatory challenges, especially in regards to Chemistry, Manufacturing and Control (CMC) standards and characterization of the final drug product, to ensure safety and quality. Regulatory agencies are working with CDMOs and biopharmaceutical companies to help define these aspects during investigational New Drug (IND) applications, which can then be updated as the drug substance manufacturing is scaled-up.

What are some of the challenges between manufacturing for research vs. commercial use?

Akihiro Oota: Custom oligonucleotide manufacturing is accomplished through traditional solid phase synthesis (chain elongation) using fully automated oligonucleotide synthesizers, which can manufacture to a specific quantity size batches. The customizable configurations of the synthesizers allow for flexibility and yield improvements of the oligonucleotide. Large scale production of oligonucleotides has been a challenge due to increasing manufacturing costs, due to cost-inefficiencies from reagents and materials using small quantity synthesizers. To address this, in 2019, Ajinomoto Bio-Pharma Services opened a large scale oligonucleotide API manufacturing facility, which houses a synthesizer with the capability to produce up to 20 kg quantities. This helps alleviate the cost-inefficiencies, while maintaining the flexibility both of the individual oligonucleotide and between different lots.

What was your area of focus when designing the new API Manufacturing Center?

Akihiro Oota: Our main focus was to build a development and manufacturing facility that can manufacture large scale, high quality

oligonucleotide therapeutics to meet the needs of our clients. The 2,000 m² manufacturing facility provides a Class 100,000 clean area for cGMP manufacturing of oligonucleotide APIs, with two fully-separated production lines including, a multipurpose room to custom synthesize heavily modified oligonucleotides, two tray lyophilizers and an OligoProcess synthesizer area for large scale solid phase oligonucleotide manufacturing. The facility also houses R&D labs for the development of novel oligonucleotide manufacturing technologies, a dedicated warehouse, sampling room, and QC lab. With this facility, we have built a robust oligonucleotide development and manufacturing center able to meet the needs of later clinical and commercial quantities.

What are the most important factors when considering a CDMO for oligonucleotide manufacturing?

Noriyasu Kataoka: There are a few factors to that a sponsor should consider when selecting a CDMO to work with. Quality systems are of upmost importance. A CDMO should have a QA group, preferably onsite that is able to detail their quality strategy and demonstrate that they are able to effectively handle any investigations and/or resolve any deviations that might occur. Additionally, an onsite process development or tech transfer team that can work with customers during the scale-up process and actively troubleshoot activities in a timely manner. Another advantage would be for the CDMO to be able to perform the majority of the analytical testing (for example: purity, sequence confirmation, molecular weight confirmation, impurity analysis, oligonucleotide content, endotoxin, counter ion testing) onsite. It is also important to know if analytical development is available onsite, in case these methods need to be developed or optimized. Lastly, it is important to consider the internal value chain of the CDMO. If the CDMO has an onsite or related site that can perform the next steps, such as fill finish and/or packaging and labeling, this allows for a smoother transition than transferring to another company directly.

The oligo market is rapidly adapting to produce these new therapeutics. Can you share any new technologies or innovations that customers might see on the horizon?

Noriyasu Kataoka: The future of oligonucleotide synthesis and the ability to successfully manufacture large scale quantities of oligonucleotides that can be used in drug therapies are dependent on a CDMO's ability to effectively scale up at a lower cost, while maintaining a high yield and purity. A specific example of this is long chain RNA, in which the yield goes down as chain length increases. The Research Institute of Bioscience Products and Fine Chemicals, a R&D arm of Ajinomoto Co., Inc., is working on a novel RNA producing system based on microbial fermentation of *Corynebacterium glutamicum*. In this innovative approach, *C. glutamicum* provides a novel RNA producing system for the production of various types of long chain RNA (60 - >300 mer) with high scalability and yield at a low cost with high purity profiles. Another example is AJIPHASE®, which is a hybrid of solid and solution phase synthesis providing equivalent quality and yield to traditional solid phase synthesis. This advanced technology allows Ajinomoto Bio-Pharma Services to manufacture high quality, commercial quantities of various oligonucleotides, PMOs and peptides under GMP.

Overall, there is a considerable amount of work and expertise necessary to make sure oligonucleotides are manufactured to the highest quality and the right cost. As the biopharmaceutical industry ventures further into the rapidly growing oligonucleotide market, it is important to consider the right CDMO partner for your project and to ensure they have the correct resources, equipment, process know-how and quality expertise in place. The lack thereof can have detrimental effects to the timeline, costs and overall success, and therefore the ability to seamlessly supply oligonucleotides as they transition from a research project to a commercial drug product on the market.



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