

— MANAGING OUTSOURCING FOR COMPLEX FORMULATIONS: A Q&A WITH AJINOMOTO BIO-PHARMA SERVICES EXPERTS —

Source: Ajinomoto Bio-Pharma Services

A well-established technology transfer, process development, scale-up, and formulation are key to positioning a successful clinical trial preparation. While technology transfers can be a challenge with any drug product, even greater vigilance is needed with more complex formulations such as lipid nanoparticle-based (LNP) drugs.

These complex formulations have structural similarities to naturally occurring biological vehicles; consequently, they are generally well tolerated by the body. As a result, LNPs are increasingly being used to deliver highly specialized therapeutic molecules, such as oligonucleotides, which are likewise seeing increased attention in drug development due to their ability to tackle disease on the genetic level. These formulations are inherently complex and require a more comprehensive manufacturing and testing approach.

Despite the growing body of research and scientific knowledge, perhaps the biggest challenge with LNP formulation is the journey into the unknown. The stability profile of the finished formulation is very dependent on lipid selection and the manufacturing process. Many involve novel payloads or APIs, and interactions between the various compendial raw materials are not fully understood. The supply chain requires careful and collaborative scheduling, and as such, a successful tech transfer will often

rely on parallel transfer and development efforts at raw material suppliers. The development of an LNP-formulated drug product can be a daunting task unless one has preliminary data to work with or previous experience with lipids.

Getting the final drug product to the clinic — and eventually over the finish line of final approval — is very much a team effort. In a recent webinar, “Considerations for Complex Formulations: How to Simplify Your Outsourcing,” experts from Ajinomoto Bio-Pharma Services explored the necessary components of a smooth tech transfer for LNP-based drugs, including the variables that impact LNP formulation and the outsourcing strategies needed to avoid common pitfalls. Following the webinar, Brannon Ly, Associate Director of Technology Innovation, Ajinomoto Bio-Pharma Services, and Ron Chantung, Director, Drug Product Manufacturing, Ajinomoto Bio-Pharma Services, answered audience questions relating to Aji Bio-Pharma’s work and expertise.

Q: Can you provide a general timeline from contract signature to GMP manufacturing?

Chantung: After signing a contract, the activities we perform include project kickoff between Aji Bio-Pharma and the client, as well as material procurement. Our word of advice is to start that discussion well before a signature, so that we can vet our commonly used stock that we have in-house and start procurement of any specialty materials a project might need. There's information transfer, test method development, test method verification, and studies including filtration, mixing, or formulation as well that are planned and executed. In general, a client can anticipate anywhere from four to six months between signing a contract to the start of production in our suites.

Q: What has been the biggest challenge for the formulations team?

Chantung: I think the biggest challenge recently – it's impacted business segments worldwide – has been material lead times. Starting with the pandemic in March of 2020, the supply chain has geared a lot of our manufacturing needs toward COVID-19 campaigns, and that put a lot of projects on hold. We're starting to see that decrease as we relax restrictions and ease out of the pandemic. That's been a tough position for us the last couple of years. We did leverage our existing vendor list over that time. And I'll give Brannon a lot of credit, because behind the scenes when the pandemic started, he would source secondary providers to help reduce material lead time as well. As far as formulation expertise is concerned, we're very lucky to have Brannon and his team for well over a decade progressing projects to completion.

Q: If someone is looking for additional information, who do they contact?

Chantung: Please feel free to reach out through our company's website, www.ajibio-pharma.com, to be put in direct contact with our marketing, client services, and business development teams, which can reach out internally and connect you with us.

Q: Are you able to formulate mRNA into LNPs, and if yes, on which scales under GMP?

Ly: Currently, we have completed 1.5 grams of mRNA. Obviously, there is a limitation to mRNA drug substance availability for this client, but we have done 1.5 grams.

Q: For an LNP process, what is your standard turnaround time from project inception to GMP manufacturing?

Ly: The answer to this question depends on many variables. We can move through a project very quickly, but it depends on how far the client has progressed with formulation and process development. If a client has a functional formulation with an idea of the key methods for GMP, Aji Bio-Pharma can be manufacturing clinical batches within a year. We have the expertise to help companies at preclinical through commercial manufacturing, but generally the speed of a project will relate to current development progress and preplanning. As early as possible, the team must agree on the scope of work and the project boundaries in terms of raw material supply, final product presentation, batch size, product specifications, and client or supplier responsibilities. In our experience, selection of standardized materials and components always helps to facilitate and accelerate the transfer. For instance, if the client can accept a vial and stopper combination that we have already validated, it will save both time and money associated with component procurement and validation. The transfer and scale up to GMP manufacturing will also be smoother if we can use our existing qualified suppliers and existing qualified materials.

Q: Are the engineering batches needed and, if so, how many?

Ly: The API and raw materials are often very expensive for LNP formulations; manufacturing operations may extend across multiple days, and more than one batch may be required to confirm critical parameters and replicate the quality attributes defined at the feasibility or laboratory scale.

Companies can be reluctant to spend money manufacturing batches that won't be used in the clinic, but successful clinical batches are dependent on the ability to work out the bugs in the process, verify batch records and supporting documentation, and confirm process parameters. The engineering batches ensure we can transition to repeatable GMP manufacturing and provide a reliable clinical supply. Engineering batches can provide additional

value by generating the requisite process material for validation activities, such as sterility-related method validation and filter validation. These materials may also be suitable to supply GLP animal and stability studies. We understand that the needs to verify design of the process prior to GMP production must be balanced with the finite supply of raw materials and resource.

About Ajinomoto Bio-Pharma Services

Ajinomoto Bio-Pharma Services is a fully integrated contract development and manufacturing organization, with sites in Belgium, United States, Japan, and India, providing comprehensive process development services, cGMP manufacturing and drug product fill finish services of small molecule and large molecule APIs and intermediates. Ajinomoto Bio-Pharma Services offers a broad range of innovative platforms and capabilities to rapidly scale from clinical and pilot programs to commercial quantities, including: Corynex technologies, oligonucleotide synthesis, antibody drug conjugations (ADC), high potency APIs (HPAPI), biocatalysis, continuous flow manufacturing, and more. Ajinomoto Bio-Pharma Services is dedicated to providing a high level of quality and service to meet our clients' needs.