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The Rise of Lipid Nanoparticles

Navigating Technology Transfer for LNP Formulations

Keeping the Show on the Road

The Rise of Lipid Nanoparticles

Lipid nanoparticles (LNPs) are typically seen as a niche approach to formulation, but with more complex molecules filling company pipelines, is it time for LNPs to finally shine? Rahul Keswani and Benjamin King are formulators at Exelead specializing in early stage LNP development. We asked for their take on the current market for LNPs.

Why are LNPs so compelling for certain drug molecules?

Many of today's drug molecules are small molecules and biologics, but increasingly there is a move beyond traditional biopharmaceuticals to more specialized and complex therapies. These include oligonucleotides — including RNA, mRNA, siRNA, and even DNA-based molecules — that can trigger an effect at the genetic level to combat disease. As one example, a drug molecule could include siRNA to inhibit expression from messenger RNA (mRNA) in cells to enable therapeutic activity. Drug products are also being developed that deliver mRNA to a cell to provide expression of therapeutic proteins.

LNPs are receiving increasing attention in the industry because of their ability to act as drug carriers for these complex but highly promising therapeutics. Oligonucleotides are susceptible to degradation in the body, but LNPs provide a stable matrix for the drug molecule to reside in. They can also facilitate entry into target cells.

One common misconception is that liposomes and LNPs are interchangeable terms. They are similar — and both can be effective for drug delivery — but liposomes are simpler vesicular formulations made up of a mostly aqueous interior core. Liposomes for drug delivery were developed in the 1970s. LNPs can be seen as a new generation of liposomes that have a more complex internal lipid architecture with low or minimal internal aqueous presence that is well suited to stable and efficient encapsulation of various genetic payloads.

Are companies reluctant to use LNPs?

LNPs are not the go-to formulation approach for routine pharmaceutical development; they are better suited to highly complex APIs, such as those based on oligonucleotides or products requiring unique biodistribution profiles or delivering multiple payloads. These types of therapies are appearing more frequently in drug development pipelines as companies focus more on identifying druggable targets at the genetic level. Because of this growing activity, the LNP market is set to expand significantly in the coming years. The main advantages of LNPs are improved stability and delivery efficiency for oligonucleotide APIs. Simply put, the API is much less likely to degrade before it can deliver its therapeutic effect because it is protected by the by the LNP. Moreover, the LNP can be specifically targeted using customized ligands attached to its surface.

Drug developers can be wary of LNPs because of the perceived complexity — and they are certainly more involved formulations than the industry is typically used to! But this is where companies like Exelead come in. We do the heavy lifting to help clients reap the benefits of LNP formulations to create effective oligonucleotide-based medicines. We find that clients are often pleasantly surprised at the flexibility these platforms can offer. For example, the library of lipid excipients that can be used in these formulations is sizeable, and it is growing rapidly with the current interest in oligonucleotide-based therapies.

What are the main challenges of working with LNP formulations?

Synthesizing nanoparticles is a complex process, and requires a different sort of formulation expertise compared to traditional fill-finish activities for parenteral products where the API is essentially combined with a mixture of buffer and excipient ingredients. With LNPs, you need a good understanding of exactly how to mix the molecules; flow rates, temperatures, composition, and component ratios are all crucial to influence formation of the nanoparticles and efficiently encapsulate the API.

Other challenges relate to filterability and stability. LNP formulations need careful optimization of the filtration to achieve high flux and throughput while also maintaining the nanoparticulate morphology. While there is always an option to synthesize the formulation in an aseptic environment, the process becomes very challenging and expensive. Again, developing a good understanding of the design space, and how design variables impact

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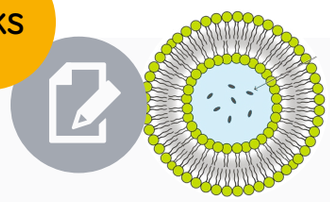

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product attributes such as encapsulation, nanoparticle diameter, and formulation stability can help set you up for success at sterile filtration as well.

It is also worth noting that LNPs demand extra attention in the supply chain in terms of getting all of the different raw materials ready at the same time – and made to cGMP standards. However, the growing interest and investment in oligonucleotides has led to significantly more research in the area – including how to make and modify LNPs. Often, just changing a few ingredients can lead to enormous benefits. The additional know-how and development to optimize these variables are well worth the effort. Oligonucleotides are becoming a go-to approach to tackling disease, and LNPs go hand in hand with them, ensuring that the best therapeutic benefit currently possible reaches the precise location where it is most effective. When these processes can be made scalable and easily transferable to many different kinds of products, it becomes clear that the technology is becoming truly relevant, and more important to the overall pharmaceutical market. And that's where we are with LNPs right now.

After years of R&D, the first siRNA-based therapy, patisiran, was approved in the US in 2018 for the treatment of a rare form of hereditary peripheral nerve disease – and it uses an LNP formulation. The drug inhibits the expression of an abnormal protein by interfering with the segment of RNA that creates it. Patisiran is just the first approved drug; many more oligonucleotides using LNPs are in pipelines and clinical trials.

What is your advice for companies interested in pursuing LNP formulations?

Our guiding principle, and advice to any company, is to always consider scalability from the very start. Clients often come to us with a product in the early stages of development that they wish to scale up, but it's clear they have not fully considered its feasibility. It is never too early in your development process to start thinking about paths to scale-up. We would even go so far as to recommend looking at developing with unit operations that are scaled down from manufacturing scales to bench scales rather than developing a bench scale process and trying to fit into manufacturing scale after-the-fact.

At Exelead, we've been working with LNPs for years, so we have the technology and expertise to improve the LNP formulation process, and develop a more scalable format. We've been able to form the same particles seen in the client's early stage process using a much more scalable method, such as in-line mixing (a simple ratio matrix mixing involving the right ingredients, pH and temperature) or, in some cases, extrusion (although the latter is not typically suitable for oligonucleotides, which tend to be shear sensitive). We can help clients with formulation development wherein we can suggest lipid choices and potential vendors based on desired pharmacological performance, develop these formulations at bench-scale volumes (<20 ml) rapidly within a short time-frame and provide a bank of potential candidate formulations for use in their screening assays. When we execute these pseudo-high-throughput approaches to development, we are able to present a panel of options to a client who can then select a candidate based on fulfillment of their desired quality attributes. We also use tangential flow filtration to remove organic solvents, which is a low-cost unit operation.

What other expertise does Exelead bring to LNP development?

Nanomedicinal formulations require careful attention to detail, comprehensive expertise and complementary teams to design and manufacture successful products. Exelead's primary expertise is in parenteral drug products focused on LNP/liposomal formulations and PEGylated (polyethylene glycol) formulations.

We have more than 150 employees from diverse backgrounds and areas of expertise, and we offer end-to-end solutions to our customers — from pre-clinical development through commercial supply, from project management to stability testing. We offer considerable support for nanoparticle formulation development and optimization, using lipids, polymers and other traditional ingredients.

Currently, the pharmaceutical industry is seeing an explosive growth in the oligonucleotide market, particularly with hard-to-treat diseases. Our development teams can help scale up manufacturing processes to support commercial production, and our in-house analytical capabilities involve the whole spectrum of specialized assays for the lipids, particle size and surface charge, residual solvents, and APIs required to release a product.

By offering end-to-end solutions, a dedicated team with deep expertise and a robust cold chain, Exelead clients can expect to reduce supply chain risks and proceed with confidence. With our multi-decade history and proficiency with complex formulations, Exelead is uniquely poised to support clients who wish to bring exciting new treatments to the clinic and market.

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Navigating Technology Transfer for LNP Formulations

Technology transfer can be a challenge with any drug product, but even greater vigilance is needed with more complex formulations, like lipid nanoparticle-based drugs

By Larry Beiter

A clear advantage of lipid nanoparticles (LNPs) and traditional liposomal formulations is their structural similarity to naturally occurring biological vehicles; as a result, they are generally well tolerated by the body. Increasingly, LNPs are being used to deliver highly specialized therapeutic molecules, such as oligonucleotides, which are seeing increased attention in drug development because of their ability to tackle disease on the genetic level (1).

The focus on oligonucleotides has translated into more research on LNPs, including the best ways to approach manufacturing and analytical challenges. Despite the growing body of research and scientific knowledge, LNPs remain a complex area that necessitates expertise beyond the formulation work required for more traditional therapies. The stability profile of the finished formulation is very dependent on lipid selection and the manufacturing process. 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. Because of this, it is common for drug developers to seek out an external partner with the right expertise to assist with the challenges.

Technology transfers are common in the pharmaceutical industry – a result of the prevalence of outsourcing and collaboration. But the process can be difficult for LNPs or liposomal products, which are inherently complex and require a more comprehensive manufacturing and testing approach. Naturally, more precautions must be taken; for example, in-process stability is a concern, and an expanded test panel is required to evaluate all critical quality attributes. Compared with a typical parenteral formulation, there will be more unit operations and analytical methods being transferred for an LNP formulation, and the manufacturing environment may need a higher classification.

Perhaps the biggest challenge is the journey into the unknown. Many LNP formulations involve novel payloads or APIs, and interactions between the various raw materials are not always 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.

Common questions, unique answers

When looking for the partner who will ultimately be working on your drug product, you need to ask questions. At Exelead, the most common question asked by potential clients is about our experience. Clients, understandably, want to know their project is in experienced hands – and that's at least one easy question for us to answer, as we've worked with many LNP products. Exelead currently supports 15 ongoing liposomal and LNP projects across preclinical, clinical and commercial landscapes and has been supporting the GMP manufacturing and testing of liposomal and lipid-based drug products for over 20 years.

Clients also like to ask how long a project will take. 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, we can be manufacturing clinical batches within a year. If a client only has knowledge of the API and a research paper or two, then additional time needs to be invested in laboratory development to establish a robust formulation. We have the expertise to help companies at any stage, but generally the speed of a project will relate to current development progress and pre-planning. 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 raw materials.

Another question that often comes up relates to engineering batches, sometimes referred to as test batches or pilot batches. Are they needed – and, if so, how many? 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 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 studies. We understand that the need to verify design of the process prior to GMP production must be balanced with the finite supply of raw materials and resource.

At Exelead, as soon as we begin evaluating a request for proposal, we start initial process design activities, including identification of unit operations and equipment requirements. We devote process engineering resources, validation and laboratory resources to your project before we've even signed a contract. We start by creating standardized block flow diagrams that identify key equipment, unit operations, testing requirements, and key parameters that need to be maintained. We want to have as much understanding of your manufacturing process as possible, and ensure the scope of work and the proposal address all the necessary decisions and assumptions required to clear the way for the tech transfer team to be successful.

We follow our block flow diagrams with a project definition document

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that identifies all of the project assumptions. This document includes assumptions related to process design, validation, method transfers, raw material supplies, packaging requirements, outside studies, and more. We put these detailed assumptions down on paper and incorporate them into the proposal to clearly define project scope and provide full clarity for the project team. In some cases, aspects such as method transfers may already be finalized at the proposal stage. That allows us to get started quickly once a contract is signed. Depending on how far the process has been developed by the client, initial steps usually include some evaluation of process operations and methods in a laboratory setting. While those evaluations are happening, we finalize the block flow diagrams and process descriptions, and establish a validation plan.

A team effort

Getting the final drug product to the clinic – and eventually over the finishing line of final approval – is very much a team effort. You need to be confident in your chosen partner. My golden rule for choosing the right company to work with: take time to adequately gauge their level of interest and engagement. Your partner should be as dedicated as you are when it comes to getting your product to market. You should expect them to ask difficult questions about process and product robustness, manufacturing scale, method reliability, and your experience. If they provide limited technical details in their proposal, tell you everything will be fine once the project starts, or show little interest in discussing potential problems? Definitely a red flag.

Communication is key. You need to be prepared for active discussions throughout the project. Any risks or issues should be raised as quickly as possible – ideally during the initial proposal stage. This allows for a comprehensive project plan that avoids problems before they can negatively impact schedule or cost. However, if issues do arise during the tech transfer, the important thing is to quickly address and rectify them. The focus should be on getting back on track as quickly as possible.

My advice to drug manufacturers is to ask questions as early as you can. Don't wait until the contract is signed. Working together to develop a solid base design early will lay the foundation for success – and from there you can focus on continued evaluation and optimization.

Larry Beiter is Director of Process Engineering & Development at Exelead

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1. *R Keswani and B King, "The Rise of Lipid Nanoparticles," The Medicine Maker (2020). Available at https://themedicinemaker.com/manufacture/the-rise-of-lipid-nanoparticles*

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Keeping the Show on the Road

The COVID-19 pandemic has put additional supply pressures on cold-chain products, such as those encapsulated by LNPs – but delays can be avoided with sufficient safety stocks, additional suppliers, and good communication

By Kim Rice

Lipid nanoparticles (LNPs) are a great way to encapsulate and protect fragile molecules, such as nucleic acids, from degradation and deliver them to specific tissues and cells (1). A large number of RNA- and DNA-based therapies have made use of LNPs – perhaps most notably, gene therapies. As a contract manufacturer, it's incredibly rewarding to work with a number of clients to help deliver their potentially life-changing advanced medicines. But there are also challenges when working with LNPs, especially when it comes to supply chain management.

Many of the raw materials that go into these therapies and the final drug products themselves are transported via cold chain – at temperatures as low as -80 °C. Even during the manufacturing process, there are restrictions on how long a product can be outside the confines of the cold storage unit. Temperature monitors are needed in each cold storage unit and each is fitted with alarms to indicate if a unit is opened or if there is an excursion. Back-up cold storage capacity is also available in the unlikely event that something goes wrong with the main units. And, as a CDMO, we must rely on our logistics providers to use validated shipping lanes, trucks, and temperature monitors to transport the drug product to its final destination. Clearly, finding a reliable logistics provider is important.

One thing that often catches developers and sponsors

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off guard is underestimating the lead times associated with LNP-encapsulated products. Many of these therapies have specialized raw materials that are only manufactured by a limited number of companies, with set slots in their production schedules. When we begin working with a client, they may request a supplier we haven't worked with before – and that means we need to dispatch our quality team to audit and approve the supplier. These factors can extend lead times considerably compared with a product that uses more commonly used or off-the-shelf components and approved suppliers. In our experience, the sooner a company starts working with us, the better we can avoid potential delays from the beginning.

Dealing with COVID-19

The COVID-19 pandemic has caused numerous issues in supply chains. Some of our clients, for example, have struggled to secure flights for their products, forcing them to validate new shipping lanes. With cold chain products, such changes are more challenging, because companies must ensure there are no temperature or safety issues. Specialized temperature-controlled containers for cold chain transport have also been in short supply. And there have been delays in customs – a problem that also applies to raw materials. For us, flexibility has been key, as well as continuous communication with clients and their shipping partners. This has enabled us to avoid delays in most cases and minimize delays where they have occurred.

However, the pandemic has certainly revealed the importance of building redundancy into the supply chain where possible, and fully understanding the supply chain of all items you require for manufacturing. And that doesn't just apply to critical, expensive items, but also everyday consumables. For example, the industry is seeing shortages of basic items, such as face masks, beard covers, and other attire required for aseptic processing – items that companies have historically paid little attention to as they were always so easily sourced. At Exelead, we are fortunate to have set our safety stocks at a level that has enabled us to continue "business as normal" during the pandemic with no delays to our customers. We're also looking at adding backup sources for certain items, but we are confident that we have enough of everything we need to get us through the year.

Another crucial aspect for us right now is keeping clients up to date. Communication was important before COVID-19, but now – given the high uncertainty in the world – customers need to know that they can count on their partners more than ever before. As well as general updates on a customer's product and project, we also send updates regarding the status of where we are in the plant, what we're working on, and the safety of employees. If anyone tests positive for the virus, we will also notify customers (though, thankfully, we have not had to do this yet). But a conversation shouldn't be one-way, so we've also ensured that the communication path is open for clients to ask questions or raise concerns.

The safety of our own employees is paramount – and we've put a lot of thought into how we can keep as many employees away from the manufacturing site as possible through homeworking, but without disrupting the manufacture of products. Right now, only those employees essential to the manufacture and testing of the products are on site. We are careful to monitor and follow all CDC guidelines to protect employees and the manufacturing environment.

The long-term impact

Supply chain robustness has been an important topic since well before COVID-19, with some companies and contract manufacturers taking the topic more seriously than others. Broadly speaking, the industry has coped well with the epidemic; companies have moved quickly to mitigate risks and gaps in the supply chains. But some businesses will have found serious chinks in their armor after taking ease of sourcing for granted. I don't think this will be the case going forward. The fragile nature of the supply chain has been exposed – and the industry can learn from this. Setting appropriate safety stocks for certain items – without going overboard or hoarding – will soon become the norm…

If you are a developer with needs in the LNP space, we encourage you to come to us as early as possible. LNPs are complex products with complex supply chains, so even before you have a manufacturing date it is good practice to engage with partners so that the project can run smoothly. As soon as you know the key materials you are going to need, we can give you an estimate on when we will be ready. Coming to us early also gives us the time to really look at our supply chain, contact suppliers, and qualify them, if required. An LNP product will likely require cold chain and may rely on difficult-to-source raw materials. The sooner we start the conversation, the easier it will be to meet your projected timelines and keep things on track – despite COVID-19.

It is imperative that the pharma industry keep the supply chain moving for the medicines it produces. We regularly encapsulate late-stage cancer drugs, treatments for neurological diseases, and other groundbreaking therapies. One mishap during transit could not only be extremely expensive, but also potentially devastating for a patient in a clinical trial. In short, all of our employees appreciate the importance of the products they are working with; we treat every medicine we work with as if it is extremely precious – because it is. After all, it may be a patient's last option.

Kim Rice is Director of Supply Chain and Project Management at Exelead

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1. *R Keswani and B King, "The Rise of Lipid Nanoparticles," The Medicine Maker (2020). Available at https://themedicinemaker.com/ manufacture/the-rise-of-lipid-nanoparticles*