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Building Better RNA Medicines Through Smarter LNP Formulation Strategy

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Key Takeaways:

- LNP formulation has evolved from a delivery-enabling technology for mRNA vaccines into a product-defining discipline that shapes delivery, potency, stability, tolerability, manufacturability, and clinical viability.
- As RNA therapeutics expand into gene editing, rare diseases, oncology, *in vivo* CAR-T approaches, and chronic disease applications, LNP strategy must be tailored to the intended payload, dose, route of administration, tissue target, and dosing frequency.
- Promising bench-scale LNP performance does not guarantee scalable manufacturing. Developers must look beyond particle size, PDI, encapsulation efficiency, and RiboGreen data to understand critical formulation and process parameters.
- Robust analytics, stability planning, supply chain redundancy, and comparability strategies are essential for reducing development risk and supporting toxicology studies, regulatory filings, GMP manufacturing, and clinical supply.
- Integrated CDMO support across plasmid DNA, xRNA production, LNP formulation, and fill–finish can help sponsors reduce handoffs, improve visibility, and move RNA–LNP programs from concept to scalable drug product.

From Enabling Technology to Product-Defining Strategy

The first wave of mRNA vaccines made lipid nanoparticles (LNPs) synonymous with RNA delivery. Their success demonstrated that messenger RNA (mRNA) could be protected, delivered, and translated into a clinically meaningful response at global scale. But it also narrowed the way many developers initially understood the role of the LNP, particularly in vaccine applications where the primary goal was to deliver enough RNA to generate the intended immune response. As RNA therapeutics move into broader and more complex applications, including therapies for chronic and genetic diseases, delivery remains essential, but it is only one part of what the LNP must contribute.

For drug developers working with mRNA and other xRNA modalities, the LNP has become a defining feature of the drug product. Its composition, structure, and manufacturing process can influence not only delivery but also biodistribution, potency, tolerability, stability, storage requirements, scalability, and the ability to support a credible chemistry, manufacturing, and controls (CMC) strategy. Clinical translation of LNP–mRNA systems requires attention to good manufacturing practice (GMP), stability, storage, and safety, while the expanding use of RNA therapeutics is increasing the need for customizable delivery strategies that can be matched to specific organs, tissues, routes of administration, and therapeutic goals.

That shift changes how developers should approach LNP formulation. A formulation that works well for a low-dose vaccine administered intramuscularly may not be appropriate for a higher-dose, systemically delivered therapy, a gene editing application, an *in vivo* cell therapy approach, or a product intended for repeat administration. Lipid composition can affect biodistribution, and increasingly complex formulations may include additional lipids, adjuvant-like components, or targeting moieties designed to improve performance in a particular therapeutic context.

As such, the LNP should not be treated as a generic delivery vehicle selected late in development. It should be understood as part of the product-definition process itself. The right formulation strategy begins with the intended clinical and development outcome: the payload, dose, route, target tissue, desired duration of expression, safety profile, stability requirements, manufacturing scale, analytical package, and regulatory pathway. When those factors are considered together from the beginning, LNP formulation becomes a discipline that connects biological intent with manufacturable, scalable, and clinically viable RNA drug products.

Speed-to-Clinic Requires More Than Speed

For most drug developers, the LNP conversation begins with a development goal rather than a formulation question. They prioritize the next milestone, whether that is a toxicology study, an investigational new drug (IND) submission, first-in-human dosing, or a later clinical manufacturing campaign. The central concern is often speed, but speed only matters if the program arrives at that milestone with a formulation, process, analytical package, and manufacturing strategy that can withstand scrutiny.

Developers tend to fall into two broad categories as they engage with a contract development and manufacturing organization (CDMO) partner. Some already have a drug substance process, an RNA construct, and access to a clinically familiar LNP platform. These developers are usually trying to move as quickly as possible into toxicology or the clinic. Their focus is less about whether an LNP can be developed from scratch and more about whether the available process can be transferred, scaled, characterized, and documented in a way that supports the intended regulatory path.

Other developers begin working with a CDMO earlier in the process. They may have encouraging bench-scale data, a generic or research-level LNP formulation, and some evidence of biological activity, but they do not yet have a platform that can support larger-scale production. For these companies, the problem is not only execution but translation: how to move from small-scale feasibility into a process that can generate enough consistent material for toxicology, clinical studies, and eventual GMP manufacturing.

Those decisions also affect when and how toxicology material is generated. A biopharma customer may need to determine whether process development–scale material is sufficient for the next study or whether an engineering run is needed to produce material that more closely reflects the intended manufacturing process. Making that decision too late can create avoidable delays, especially if the formulation, process, and analytical package have not been designed to support the transition from feasibility to toxicology supply.

That distinction helps explain why many developers gravitate toward proven or clinically familiar LNP technologies when timeline, financing, and regulatory risk are pressing concerns. However, using an established LNP system does not eliminate the need for product-specific development discipline. The formulation still has to match the payload, route, dose, target product profile, and manufacturing pathway. The process must generate material of the right quality and quantity. The analytical strategy must demonstrate that the product is consistent, stable, and suitable for its next development stage. Speed-to-clinic is therefore not a shortcut around formulation and process understanding but an outcome that depends on building enough understanding early to avoid losing time later.

Why Formulation Strategy Begins with the Product

The starting point for LNP development should be the therapy itself. Before formulation decisions are locked in, developers need to understand the disease they are targeting, the RNA modality they are using, the intended dose, the route of administration, the desired tissue distribution, the likely dosing frequency, and the durability of expression needed to achieve a meaningful therapeutic effect. Those considerations should guide the formulation and process strategy, rather than being layered on after an LNP system has already been selected.

This is especially important as RNA programs move beyond vaccine-like applications. Intramuscular vaccine delivery is comparatively forgiving: doses are generally lower, administration is infrequent, and the desired biological effect can be achieved without sustained systemic exposure. Therapeutic applications often create a more demanding set of requirements. Gene editing, *in vivo* chimeric antigen receptor T (CAR-T) cell approaches, rare disease programs, oncology applications, and chronic disease strategies may require higher doses, repeat administration, intravenous delivery, more precise tissue targeting, improved tolerability, and greater durability of RNA or protein expression.

Those differences can change the meaning of an effective LNP formulation. For a systemic therapy, the formulation must be considered in the context of circulation, clearance, tissue exposure, and potential toxicity. For a targeted application, the presence or absence of a targeting moiety may influence the probability that the RNA payload reaches the intended tissue. For a repeat-dose therapy, lipid safety, immunogenicity, tolerability, and clearance may become more important than they would be for an infrequently administered vaccine. Questions around polyethylene glycol (PEG)–lipid behavior, lipid adducts, and potential immunogenicity have therefore become part of the formulation discussion rather than late-stage analytical details. The relevant question is not whether an LNP works in a general sense but whether it is suited to the therapeutic job it is being asked to perform.

Formulation complexity is also increasing. Many clinically familiar LNP systems are built around four lipid classes: an ionizable lipid, cholesterol, a helper phospholipid, and a PEGylated lipid. That basic architecture can be modified with additional lipids, adjuvant-like components, targeting moieties, or other features intended to tune delivery, biodistribution, stability, or tolerability. Each added element can create new opportunities, but it can also introduce new process-development and scale-up risks if critical parameters are not well understood. For example, lipid designs that support faster clearance may be attractive from a tolerability perspective, but those same chemistries can introduce stability or process-development challenges that must be understood before scale-up.

The same principle applies to payload diversity. Different RNA payloads can behave differently during both RNA production and LNP formulation. mRNA, guide RNA (gRNA), circular RNA (circRNA), self-amplifying RNA (saRNA), and other payloads may each create distinct process considerations. circRNA, for example, can avoid some features of linear mRNA production, such as capping and polyadenylation, but that does not make it automatically simpler. In practice, temperature and agitation during *in vitro* transcription (IVT) can be critical, and shear sensitivity during LNP mixing may create unexpected challenges during scale-up.

The most effective LNP strategy therefore begins by working backward from the intended product. The disease, modality, route, dose, tissue target, safety profile, durability requirements, and development timeline should define the formulation approach. The goal is not to identify a universal best formulation but to define the formulation best suited to the intended therapy and the pathway required to bring it forward.

Building Scale-Up Readiness into LNP Development

One of the most common risks in LNP development is mistaking promising small-scale performance for a process that is ready to scale. At the bench, formulation work is often performed with very small volumes and limited amounts of expensive lipid and RNA material, particularly for emerging companies trying to preserve scarce drug substance while generating enough early data to support the next funding, partnership, or development decision. Under those conditions, a formulation may show encouraging biological activity even when the process parameters have not yet been fully defined.

Early development often focuses on a core set of measurements: particle size, polydispersity index (PDI), encapsulation efficiency, and RNA concentration by RiboGreen. Those attributes can provide important early evidence that a formulation is behaving as expected, but they do not provide a complete picture of whether the product can be scaled, manufactured reproducibly, or supported through regulatory review. A formulation can have attractive particle size, acceptable PDI, and high apparent encapsulation efficiency while still containing hidden risks that only become visible when the process advances toward larger-scale production.

Those risks can arise from parameters that are easy to overlook when the immediate goal is proof of concept. The nitrogen-to-phosphate (N:P) ratio, lipid composition, RNA content, lipid content, lipid adducts, capping efficiency, poly(A) tail integrity, degradation profile, and yield can all influence whether an LNP-based drug product is truly development-ready. The same is true for process choices, such as tangential flow filtration (TFF) membrane format, molecular weight cutoff, buffer conditions, and recovery. If the wrong TFF membrane or cutoff allows RNA to permeate unexpectedly, for example, the formulation may retain acceptable particle size and PDI while losing yield, skewing the N:P ratio, or creating material-balance questions that become significant at larger scale.

In a low-dose setting, a modest yield issue may be manageable. In a program requiring larger manufacturing quantities or multiple administrations, poor recovery can become a major process and cost concern. Similarly, a formulation that appears acceptable based on a narrow set of physical measurements may not provide enough information to support toxicology material generation, comparability, stability studies, or GMP manufacturing.

Scale-up also places greater pressure on the formulation and process design. Mixing conditions, flow rates, buffer selection, lipid ratios, and purification strategy may behave differently when a process moves from microliter or milliliter volumes to larger development or manufacturing scales.

The lesson is not that every possible attribute must be perfected before a program can move forward, but that the small-scale process must be interrogated deeply enough to understand which parameters are critical, which tradeoffs are acceptable, and which gaps could create problems later. The goal is to avoid discovering during scale-up that a formulation that looked strong at the bench was not yet prepared to become a reproducible, manufacturable drug product.

Characterization, Stability, and Supply as Development Infrastructure

If formulation connects the RNA payload with the intended biological outcome, analytics provide the visibility needed to determine whether that formulation can become a development-ready drug product. For LNP-based therapies, analytical strategy is not simply a release-testing requirement at the end of manufacturing. It supports process development, scale-up, toxicology material generation, comparability, stability, regulatory filings, and product release. The more clearly developers can characterize the product early, the less likely they are to encounter avoidable surprises later.

RiboGreen-based measurements play an important role in early development, particularly for assessing RNA concentration and encapsulation. As programs advance, however, developers need a broader and more discriminating analytical package. High-performance liquid chromatography (HPLC) methods for RNA and lipid content, assays for lipid adducts, component ratios for gene-editing applications, RNA integrity and purity, degradation patterns, endotoxin, sterility, particle size, and PDI all contribute to a clearer understanding of product quality.

This analytical depth becomes particularly important when developers need to generate material for toxicology studies or support early regulatory interactions. A product that appears promising based on a small set of measurements may still lack the data needed to explain its composition, consistency, stability, and degradation behavior. That gap can become more consequential as programs move toward GMP manufacturing, where process changes, scale changes, raw material variability, or changes in equipment can create comparability questions. In that context, analytics serve as the bridge between a promising formulation and a product that can be advanced with confidence. That means testing broadly enough early in development to understand the full cycle of the drug product, rather than relying on a narrow set of favorable early indicators.

Process analytical technology (PAT) may eventually shorten feedback loops for some aspects of LNP production, but many critical methods still rely on established offline analytics, making method selection and qualification central to development planning.

Stability should be treated with the same early discipline. Translating LNP–mRNA systems into the clinic requires attention to stability and storage, along with GMP and safety considerations. Long-term, intermediate, room-temperature, and accelerated stability studies can all provide insight into how the drug product behaves under conditions relevant to storage, handling, transport, and potential temperature excursions. Those studies also help define whether the final presentation is realistic for the intended clinical and commercial pathway.

Supply chain planning adds another layer of risk management. The COVID-19 pandemic highlighted how vulnerable advanced therapy manufacturing can be when critical inputs are constrained, but redundancy remains important even in a more stable environment. Hollow fibers, flat sheets, IVT enzymes, capping reagents, buffers, and other materials may all have lead times that cannot be compressed simply because a program is urgent. Even with strong vendor relationships, lead time remains lead time; urgent development timelines cannot eliminate the need for early planning, backup sourcing, and comparability work. That responsibility should be shared: a CDMO can help identify risks and alternatives, but developers also need to support comparability planning before a supply issue forces a change.

Across analytics, stability, and supply chain, the underlying goal is visibility. Developers cannot eliminate every risk in an LNP-based RNA program, but they can reduce the number of unknowns carried forward. Investing early in characterization, stability planning, and supply chain resilience creates a stronger foundation for scale-up, regulatory engagement, and clinical execution.

An Integrated Path from Sequence to Drug Product

The interdependence of RNA production, LNP formulation, analytics, scale-up, and final drug product manufacturing makes partner selection especially important for RNA–LNP programs. A formulation issue may be rooted in the RNA payload. A scale-up challenge may reflect the mixing strategy, purification approach, or material inputs. A stability concern may connect back to RNA integrity, lipid composition, process conditions, or final presentation. When those activities are divided among multiple providers, sponsors can face added communication burden, longer feedback loops, more complex technology transfers, and greater difficulty identifying where a problem began.

Recipharm Advanced Bio's model is built around reducing those handoffs. We integrate plasmid DNA production, RNA synthesis, and LNP formulation technologies to support the path from sequence to final drug product. Our broader offering spans plasmid DNA, xRNA production, LNP formulation, and fill–finish, allowing formulation and process decisions to be considered in the context of the full development pathway rather than as isolated technical steps.

That integration is particularly valuable because LNP development rarely proceeds in a straight line. A client may arrive with a defined RNA process and a licensed LNP platform, needing rapid execution and GMP readiness. Another may have promising bench-scale data but require process development before the formulation can be scaled. In either case, the ability to connect process development, analytical characterization, technology transfer, manufacturing, and fill–finish can help sponsors move faster and with greater visibility into the risks that matter most.

Our LNP capabilities include support from early clinical stages through commercialization, formulation capacity from one to over 100 grams, modular single-use platforms, multiple mixing technologies, and TFF capabilities. Those capabilities matter not simply because they expand technical options but because they allow the process to be matched to the product's requirements. A program that is sensitive to shear, requires a particular mixing approach, or needs careful purification and recovery can be evaluated with scale-up, quality, and manufacturability in mind from the beginning.

That integrated structure is supported by teams that have developed platforms across plasmid, RNA, and LNP process development. Process development results can be transferred within the organization to technology transfer and manufacturing teams, creating a more connected path from early work to GMP execution. That internal continuity can reduce the friction associated with moving plasmid, RNA, LNP drug product, and fill–finish activities across disconnected providers.

Technical integration also has a human dimension. Complex development programs inevitably encounter unexpected results, especially during scale-up. The real test of a partner is not whether every project proceeds without complications but whether issues are recognized quickly, escalated appropriately, and communicated clearly. In that setting, clients need more than equipment and capacity. They need subject matter experts who understand the process, escalation pathways that bring the right people into the discussion, and transparent communication when problems arise. Visibility becomes part of the value proposition: when sponsors can see what is happening, why it matters, and how the team is responding, they can make better decisions and maintain confidence in the development path.

For RNA–LNP programs, integration is therefore not just an operational convenience. It is a way to manage the interdependencies that define the product. The strongest CDMO partner is one that can connect the RNA payload, LNP formulation, analytical package, scale-up strategy, supply chain, and fill–finish requirements into a coherent development plan rather than handing each piece off as a separate transaction.

From RNA Promise to Patient Access

The next phase of RNA therapeutics is likely to look different from the first. Vaccine programs remain important, but much of the current momentum is moving into rare diseases, genetic diseases, gene editing, *in vivo* CAR-T approaches, oncology, and other therapeutic areas where the demands on RNA delivery, expression, safety, and manufacturing are more complex. These programs carry enormous promise, particularly for diseases that are poorly served by conventional therapeutic models, including single-mutation genetic diseases.

For those of us who have seen the burden of monogenic diseases in communities where treatment options remain limited, the possibility of more accessible RNA-based interventions is not an abstract scientific ambition. In these diseases, a durable molecular intervention could meaningfully change the course of disease. Real-life cases like these are a reminder that formulation, delivery, manufacturing, and cost are not only technical questions. They help determine whether promising science can become a therapy that reaches the patients who need it.

That promise depends on solving several connected challenges. RNA technologies have matured significantly, but durability of RNA and protein expression remains a major question for many therapeutic applications. Lipid and RNA safety, tolerability, clearance, tissue targeting, and immunogenicity must be understood in the context of the intended route, dose, and dosing frequency. Scale-up and cost also matter, especially if RNA-based approaches are to reach broader patient populations rather than remain limited to narrow or high-cost use cases. At the same time, analytical methods and process understanding must continue to advance so that developers can characterize increasingly complex products with the depth needed to support clinical and regulatory confidence.

For LNP-based RNA therapies, those challenges reinforce the importance of beginning with the intended patient and product outcome. A developer pursuing a systemic gene-editing therapy, an *in vivo* CAR-T approach, or a repeat-dose treatment for chronic disease cannot rely on the same assumptions that may have been appropriate for a low-dose vaccine. The formulation strategy, analytical package, process design, stability program, and manufacturing model all need to reflect what the product is intended to achieve and what it will need to withstand on the path to patients.

That is where the role of an integrated CDMO partner becomes especially important. Recipharm Advanced Bio's plasmid DNA, xRNA, LNP, and fill–finish offering is designed to help sponsors connect the scientific and operational decisions that shape RNA drug product development. By bringing those capabilities together, the company can support programs moving from early concept or technology transfer toward scalable, development-ready drug product.

The future of LNP-enabled RNA therapeutics will depend on more than payload delivery. It will depend on whether formulation and manufacturing strategies can support the full development pathway, from biological intent to clinical execution and, ultimately, patient access.

Recipharm Advanced Bio, Advancing Together.

Recipharm Advanced Bio, a division of Recipharm, is a contract development and manufacturing organization (CDMO) specifically established to focus on serving companies seeking to develop and commercialize advanced therapy medicinal products (ATMPs). Recipharm Advanced Bio's specialized CDMO capabilities include pre-clinical to clinical and commercial development and manufacture for new biological modalities encompassing technologies based on live viruses and viral vectors, live-microbial biopharmaceutical products, nucleic acid-based mRNA and plasmid DNA production. Led by a management team and technical experts with a proven track record in both process development and contract manufacturing, Recipharm Advanced Bio offers the knowledge and resources necessary to help customers develop and manufacture promising new therapies to meet the needs of patients across the world.

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