

# From promise to patients: de-risking the next wave of nucleic acid medicines

**How can the next generation of nucleic acid innovators turn promising science into transformative medicines?**

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**Nucleic acid therapeutics are reshaping the future of medicine. mRNA vaccines have already proven themselves at global scale, RNA-based therapies are moving into rare disease and oncology pipelines, and increasingly sophisticated delivery systems are opening the door to gene therapy. Yet for the biotechnology innovators driving this wave, the path from a compelling piece of biology to a clinically viable, regulatorily credible product remains one of the most demanding journeys in the industry.**

Ask founders of nucleic acid-focused biotechs where and why their programme stalled and the answer rarely involves the core science. The lead candidate performs in a preclinical in vivo model. Investors are engaged by the story. What derails timelines is what happens next: converting a promising construct into a process that can be manufactured robustly, reproducibly; characterised with fit-for-purpose analytics; formulated into a stable and deliverable product, and documented in a way that satisfies regulators who are still building their own experience with these modalities.

### The translational gap

This is the translational gap and it is not a niche problem. It is the defining challenge of the nucleic acid therapeutics field right now. The numbers bear this out: across the gene and RNA therapy pipeline, roughly 60% of programmes are still preclinical.<sup>1</sup> Unlike small molecules or monoclonal antibodies, where decades of manufacturing experience have created well-worn playbooks, RNA and lipid nanoparticle (LNP) formulations are still maturing as manufacturing disciplines.

Every new modality variant, circular RNA, self-amplifying RNA, or targeted and conjugated LNPs, reopens problems the field has not yet fully solved or foreseen. Despite this, capital is already following that shift: Eli Lilly's acquisition

of Orna Therapeutics for up to \$2.4bn in Q1 2026, built around its engineered circular RNA technology, shows how much confidence major pharmaceutical places in newer modality variants even while their manufacturing playbooks are still being written.<sup>1</sup> LNP formulation is a case in point: the shift from laminar microfluidic mixing at bench scale to turbulent jet mixing at commercial scale routinely disrupts, eg particle size, which is why process scientists call it the 'valley of death' of nanomedicine scale-up.<sup>2</sup> RNA purity is a related, more understated challenge: mRNA synthesis reliably yields immunostimulatory double-stranded RNA as a byproduct and removing it can add real complexity to an already delicate downstream processing train. And how can a stability-indicating analytical package for a molecule class that did not exist in a regulatory guidance document five years ago be built?

Regulatory classification is less a fixed rule than a negotiation: Moderna's dossier framed Spikevax's ionisable lipid as part of the active drug substance and the Food and Drug Association accepted it. Near-identical lipids in Onpatro and Comirnaty were filed, and accepted, as mere excipients, showing how much the outcome hinges on a company's own assertiveness in a field whose playbooks are still largely unwritten.<sup>3</sup>

### Why CMC thinking has to start early

The instinct in early biotech is understandable: focus scarce capital on proving biology, and worry about chemistry, manufacturing and controls (CMC) once a lead candidate is locked. In nucleic acid therapeutics, that sequencing is increasingly a liability rather than a discipline. Decisions made at the bench have direct, and sometimes irreversible, consequences for manufacturability, scalability and long-term stability: the choice of untranslated regions and poly(A) tail design in an mRNA construct; the backbone architecture of a plasmid, or the lipid composition in an LNP. A construct

optimised purely for potency in a transfection assay can turn out to be extremely difficult to produce at gram-per-litre yields, or to formulate into a product that survives a freeze-thaw cycle.

This is why early integration of CMC thinking, fit-for-purpose analytics and formulation understanding is no longer a late-stage concern. It is a strategic prerequisite. Quality-by-design principles applied from the earliest research-grade material, rather than retrofitted once a candidate reaches investigational new drug-enabling studies, allow developers to make informed trade-offs while options are still open and capital is still flexible. Building the right analytical toolbox early, even at milligram scale, means that developability red flags surface while a programme can still be redesigned, rather than after months and millions that have been spent producing good manufacturing practice (GMP) material for a molecule that will not survive scale-up.

### Why this increasingly means collaboration

A 2021 analysis in *Nature Biotechnology* found that biotech start-ups engaging a large pharma partner as early as the preclinical stage were 32% more likely to succeed than those that waited until later in

development.<sup>4</sup> The same logic extends naturally to contract development and manufacturing organisations (CDMO), which fulfil a similar role on the development and manufacturing side of the equation: an experienced partner brought in early, does not just supply capacity, it absorbs process and financial risks that a small team would otherwise have to shoulder alone.

Few biotech innovators, and realistically few pharma R&D organisations either, carry deep, current expertise across pDNA and RNA design, RNA in vitro transcription chemistry, LNP formulation development, analytical development and GMP scale-up simultaneously. That breadth of capability is precisely what advanced-therapy-focused CDMOs are built to provide and it is why the relationship between developer and manufacturing partner is changing shape. The CDMO of the nucleic acid era is not a vendor engaged once a process is frozen; it is a collaborator embedded from the earliest stages of lead development and optimisation, working alongside R&D teams to stress-test manufacturability assumptions before they become expensive commitments.

Some of the worst bottlenecks are within inputs that rarely make it into a pitch deck. Enzymes for linearising plasmid



**Expanding capacities for research in manufacturing processes for biopharmaceuticals including a strong focus on the technology development for nucleic acid-based therapies**

templates ahead of in vitro transcription can be themselves a constrained GMP-grade supply category, prone to the same lead-time pressure as any other specialty reagent. Untranslated regions and poly(A) tail design, meanwhile, carry a growing freedom-to-operate footprint, since much of the well-characterised sequence space has already been staked out by early movers' patents, turning what looks like a routine construct decision into an intellectual property (IP) question. Access to clinically relevant ionisable lipids is frequently gated by licensing terms that few start-ups have the scale or leverage to negotiate well, leaving them scrambling for usable lipid chemistry at exactly the moment they need to lock down a formulation. CDMOs that hold their own lipid IP, or that have already built supply relationships with a small number of qualified lipid vendors, can absorb a meaningful share of that friction on a developer's behalf.

This kind of partnership looks different in practice. It means process optimisation conversations are happening in parallel with construct design, not after it. It also means analytical characterisation and stability testing are built around the specific liabilities of a given modality, such as extra-low double-stranded RNA content for an RNA programme, supercoiled plasmid purity for a pDNA programme, or particle stability for an LNP, rather than using a generic impurity panel. It means material supply strategies that can support in vitro and preclinical studies cost-effectively at small scale, with a credible, pre-planned route to scale-up and transfer into GMP manufacturing when the programme is ready, rather than a scramble to find capacity at the point of clinical need. Lastly, it means regulatory and IP know-how being available as a resource throughout development, since much of the nucleic acid regulatory landscape is still being written in real time alongside the science itself.

### De-risking as capital efficiency

This collaborative model matters more than ever in the current funding environment. Investors are rewarding focus and capital efficiency, not broad platforms chasing every possible indication. The financing data shows: seed and Series A activity for gene, cell and RNA therapy companies held steady at thirteen rounds in Q1 2026, yet total capital raised fell 30% quarter over quarter to \$388.4m, indicating investors are writing more selective, better-substantiated cheques rather than simply funding more rounds.<sup>1</sup>

A biotech that can demonstrate early that its lead candidate has a credible and de-risked path to scalable, well-characterised clinical supply is telling a more fundable story than one relying on biology alone. Realistic clinical supply planning, meaning not just that a molecule can be made but more importantly how, at what scale, at what cost and on what timeline, have become

diligence questions that sophisticated investors and pharma partners now ask as a matter of course.

### From promise to patients

The promise of nucleic acid medicines is not in question. mRNA vaccines demonstrated what the modality class can achieve under pressure; the next wave of RNA-based therapies, plasmid DNA products and advanced delivery systems is now working through the harder, slower task of proving it can be done repeatedly, safely and at commercial scale for a much wider range of diseases. Closing the translational gap between promising biology and robust, regulatorily credible development will not happen through scientific creativity alone. It will happen through development models that connect creativity with deep process insight, quality-by-design thinking and honest, early conversations about manufacturability. That is the kind of collaboration that turns a compelling early-stage result into a medicine that actually saves patients.

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