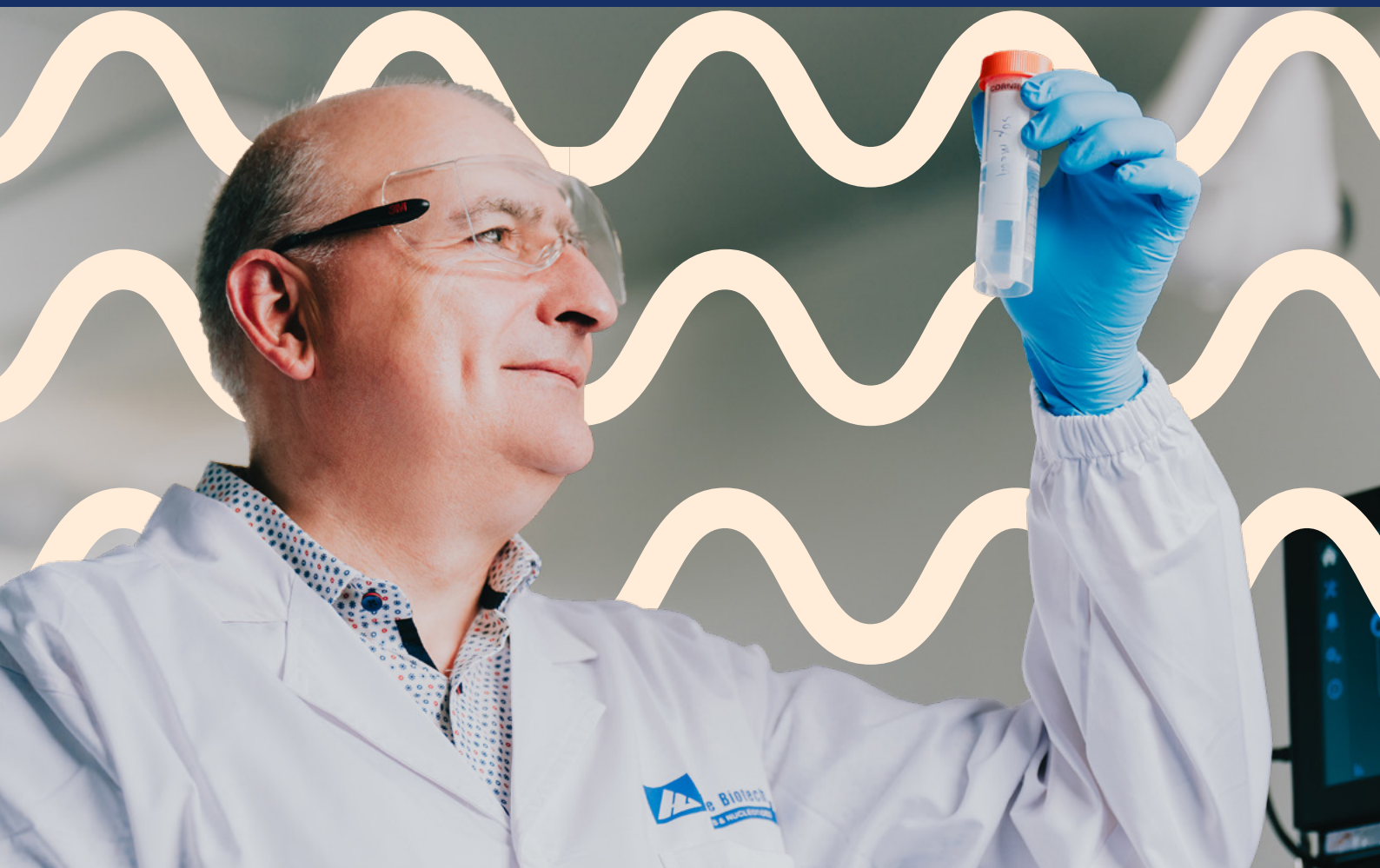
Hongene Biotech

Scaling nucleic acid therapeutics

Addressing supply chain complexity through vertical integration



Executive summary

Nucleic acid therapeutics (NATs) are transforming the biopharmaceutical landscape, and the field's rapid expansion has revealed manufacturing vulnerabilities that challenge scalability, quality consistency, and speed to clinic.

The fragmented nature of traditional supply chains contributes to inefficiencies and variability that are increasingly unpalatable at scale. By contrast, a vertically integrated approach — where raw materials production and cGMP services for drug substance and drug product are unified within a single organization — offers a robust and streamlined path to clinical and commercial success.

This whitepaper describes practical strategies for overcoming NAT manufacturing challenges. It outlines how vertical integration can reduce development risk and streamline progression to clinic. Drawing on expert insight and real-world case examples, it also provides strategic guidance for selecting a vertically integrated contract development and manufacturing organization (CDMO) with the technical depth, regulatory readiness, and operational flexibility to support complex NAT programs from concept to clinic.

Surging demand and rising complexity in NAT manufacturing

NATs, including mRNA-based products, siRNAs, ASOs, and CRISPR single guide RNAs (sgRNA), are rapidly altering the therapeutic landscape across numerous disease areas. Their programmable nature and high specificity offer compelling advantages for targeted intervention. However, their molecular complexity necessitates highly specialized production capabilities [1,2], and global manufacturing infrastructure will need to adapt to meet the large volumes of NATs that are expected to be needed in the future to support cardiometabolic disease targets such as ApoC3, LPa, PCSK9, AGT, HSD and INHBE. As demand accelerates, developers are under pressure to manage increasingly complex workflows. These often span multiple vendors and geographies, a challenge further examined in the next section.

The global CDMO market for nucleic acid therapeutics was valued at USD 20.3 billion in 2023 and is projected to reach USD 33.86 billion by 2030, reflecting both rising demand and growing pressure on infrastructure [3].

Pandemic vaccine supply chain vulnerabilities

The COVID-19 pandemic exposed critical weaknesses in mRNA vaccine manufacturing infrastructure, including shortages of key raw materials, limited fill–finish capacity, and inadequate cold-chain logistics. These limitations were acutely felt in mRNA vaccine programs where unusually accelerated timelines amplified the impact of even minor disruptions. Many regions were underserved or experienced significant product loss or surplus, underscoring the fragility of existing supply chains [4].

Challenges of a fragmented supply chain model

In conventional NAT manufacturing, production is typically divided among multiple vendors, each responsible for discrete steps such as raw materials production, cGMP drug substance, drug product manufacture, and analytical testing. Each transition of materials or documentation between vendors introduces risk with potential for misalignment and delays.

With no single point of control, progress is constrained by the slowest transition, and coordination becomes more difficult as programs advance.

In a fragmented supply chain model, conducting root cause analysis and implementing corrective actions becomes more complex and time-consuming due to the involvement of multiple stakeholders and disparate systems. Furthermore, smaller developers may be deprioritized in vendor scheduling queues, particularly when their programs compete against higher-volume or strategically significant accounts.

Strategic benefits of vertical integration

When all manufacturing activities — from raw material synthesis to final fill–finish of drug product — are consolidated within one organization, developers can benefit from efficiencies gained with improvements in quality, cost and timelines.

Comparison: Operational gains from supply chain integration

Fragmented supply chain	Vertically integrated model
• Multiple vendors across steps	• One partner across the full process
• Shipping delays and QC mismatches	• Single quality system with continuous custody
• Disjointed timelines and documentation	• Aligned production and unified oversight
• Limited traceability	• Full batch-level traceability
• Frequent tech transfers	• Streamlined operations, no revalidation needed

Vertically integrated CDMOs offer streamlined project management, centralized tracking, harmonized documentation, and precisely coordinated timelines, removing the burden for developers to reconcile disparate schedules or navigate misaligned quality systems. Regulatory visibility is also enhanced, with full traceability that facilitates document preparation and compliance. Health agencies emphasize the importance of supply chain visibility, and this operational model offers a clear path to demonstrating end-to-end compliance.

What to look for in a high-performing CDMO partner

A vertically integrated supply chain and a true end-to-end partner should offer deep technical expertise, regulatory competence, and operational scalability. What follows are key selection considerations.

1. Full-spectrum capabilities: From raw materials to finished product

An ideal CDMO partner can effectively manage the entire supply chain, from raw material synthesis through to drug product fill-finish. For example, for oligonucleotide therapeutics, there will be proven capabilities in nucleosides, phosphoramidite and other raw materials production, solid-phase synthesis, drug product manufacturing, and next-generation technologies like chemoenzymatic ligation and liquid phase synthesis. For mRNA-based products, there will be capabilities for cationic lipid, enzymes, nucleotides and cap analogs manufacturing, mRNA synthesis, and LNP formulation. End-to-end operations will be overseen by expert technical leaders and carried out in modern facilities using state-of-the-art equipment by an appropriately trained workforce.

2. Built for compliance: Regulatory readiness and traceability

The selected CDMO must support regulatory success. Facilities should be cGMP-certified and backed by a robust quality system that has successfully supported regulatory submissions to global health agencies. Equally important is the quality infrastructure for traceability; the partner should be able to track every raw material lot through its life cycle to the final product, supported by appropriate documentation and batch records for cGMP compliance. This streamlines quality oversight and supports smoother audits and regulatory submissions.

3. Capacity with cohesion: Scalability and technical strength

Scalable infrastructure enables long-term continuity with a single partner from early development through to commercial production. There should be capacity available to support scale-up and parallel projects without delays. Dedicated facilities with flexible layouts and adaptable workflows are strong indicators of long-term fit.

Interdisciplinary teams spanning project management, manufacturing, process development and engineering, chemistry, biology, formulation, QA and analytics enable sound technical decisions and problem resolution with timely communication to customers.

A coordinated model compresses development timelines by aligning production activities and minimizing the delays introduced by fragmented supply chains.

Key differentiators of industry-leading NAT CDMOs

Full-spectrum supply chain capability: From raw materials to oligonucleotide and mRNA production, lyophilization, drug product and fill–finish.

Next-generation oligonucleotide manufacturing technologies: Chemoenzymatic ligation and liquid phase synthesis.

Capacity aligned with future therapeutic needs: Scalable infrastructure to meet rising demand in high-volume areas such as cardiovascular disease.

Cross-functional scientific teams: Coordinated subject matter experts for efficient communication with customers, decision-making and problem solving.

Regulatory-ready quality systems: End-to-end traceability, cGMP facilities and experience supporting global regulatory submissions.

Operational flexibility: Responsive processes and adaptable business models that support businesses and projects of all sizes.

These attributes support long-term program continuity, from preclinical development through to commercial launch.

Modality-specific benefits of vertical integration

Each NAT modality presents unique manufacturing demands, shaped by its structure, therapeutic mechanism, and regulatory needs. While these modalities share core quality and compliance requirements, each demands a tailored manufacturing strategy reflecting its distinct complexity and material inputs. This section outlines how CDMOs can be aligned with the specific requirements of oligonucleotide, mRNA, and CRISPR-based programs (Figure 1).

Oligonucleotide therapeutics

Oligonucleotide synthesis relies on highly specialized Starting Materials, including phosphoramidites, nucleoside-loaded solid supports and ligands like GalNAc, all of which require multiple synthetic steps to produce. Starting Materials mark the start of the cGMP process and are subject to stringent regulatory requirements for sourcing, justification, and quality control.

The synthesis of oligonucleotide drug substance (DS) and drug product (DP) from Starting Materials and other raw material inputs involves a sequence of tightly controlled chemical reactions for nucleotide chain elongation, including sequential coupling of phosphoramidites, protection and deprotection of reactive functional groups, and oxidation steps. Chemoenzymatic ligation technology might optionally be employed, necessitating sourcing of ligase. A comprehensive understanding of these processes is essential to meet both technical and regulatory needs.

Hongene is ideally positioned to mitigate supply chain risk and streamline oligonucleotide program development by producing its own Starting Materials and ligase at commercial scale in-house, then seamlessly transitioning into cGMP drug substance and drug product manufacturing.

mRNA-based products

mRNA workflows are characterized by a series of interdependent, technically demanding steps, each sensitive to variation in raw material inputs and process conditions [1,2].

By consolidating control over key inputs like modified NTPs, enzymes, cap analogs, and plasmid-derived DNA templates, Hongene ensures alignment of the entire workflow. Integrated management across mRNA synthesis, purification, LNP formulation, and fill-finish allows developers to manage complexity with agility.

CRISPR-based gene editing drugs

At the forefront of advanced therapeutics manufacturing, CRISPR-based gene editing drugs require a chemically synthesized sgRNA payload which is co-formulated with an mRNA-encoded Cas enzyme and lipid nanoparticle components.

Through its partnership with ReciBioPharm, highly complex programs are executed within a vertically integrated manufacturing framework. The sgRNA is synthesized at ReciBioPharm using Hongene's proprietary chemoenzymatic ligation technology, yielding high-purity sgRNA optimized for gene editing applications. End-to-end oversight eliminates handoff risks and accelerates delivery of innovative CRISPR therapeutics.

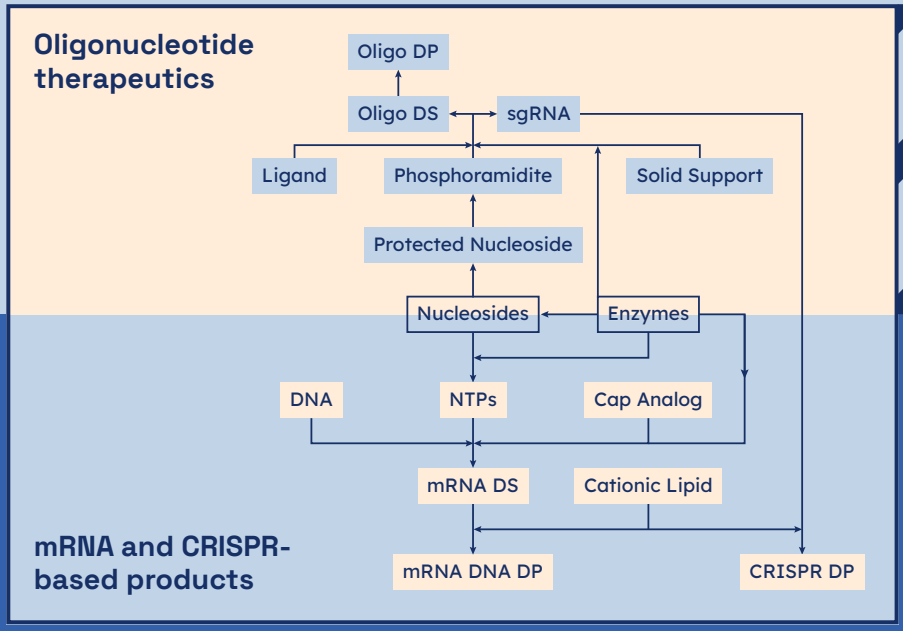


Figure 1. Schematic of the major material components of workflows for oligonucleotide, mRNA, and CRISPR-based products, each of which may be independently sourced or manufactured at commercial scale with end-to-end oversight within Hongene's vertically integrated global facilities.

Meeting different needs, from emerging biotech to pharma companies

While the operational benefits of vertical integration are consistent across the nucleic acid therapeutics (NAT) sector, the strategic priorities of early-stage biotechnology firms and global pharmaceutical companies differ significantly. An effective CDMO must possess the agility and breadth of capability to support both profiles.

Emerging biotechs typically operate under constrained budgets and accelerated timelines, with critical milestones tied to funding events and clinical advancement. These organizations often prioritize flexibility, rapid iteration, and deep technical collaboration. Their CDMO partner will therefore serve as an extension of the internal team, providing essential CMC guidance, regulatory strategy support, and responsive program management.

An effective CDMO is not just a supplier, but a partner that provides continuity, visibility and responsiveness across the development lifecycle.

Global pharmaceutical companies demand infrastructure capable of delivering commercial-scale volumes with unwavering quality, regulatory compliance, and environmental sustainability. They seek partners with commercial-ready quality systems, proven capacity, and the ability to align with their global supply chains. For these clients, the CDMO must offer the documentation rigor, scalability, and operational maturity required to support late-stage development and commercial launch.

Hongene is a vertically integrated partner that bridges these needs, offering tactical agility for early-stage programs while maintaining the commercial scale infrastructure and systems to support long-term commercial success.

The greater the knowledge, the lower the risk. Choose a partner who understands the science and the stakes. Let's bring your RNA to life.

Contact us

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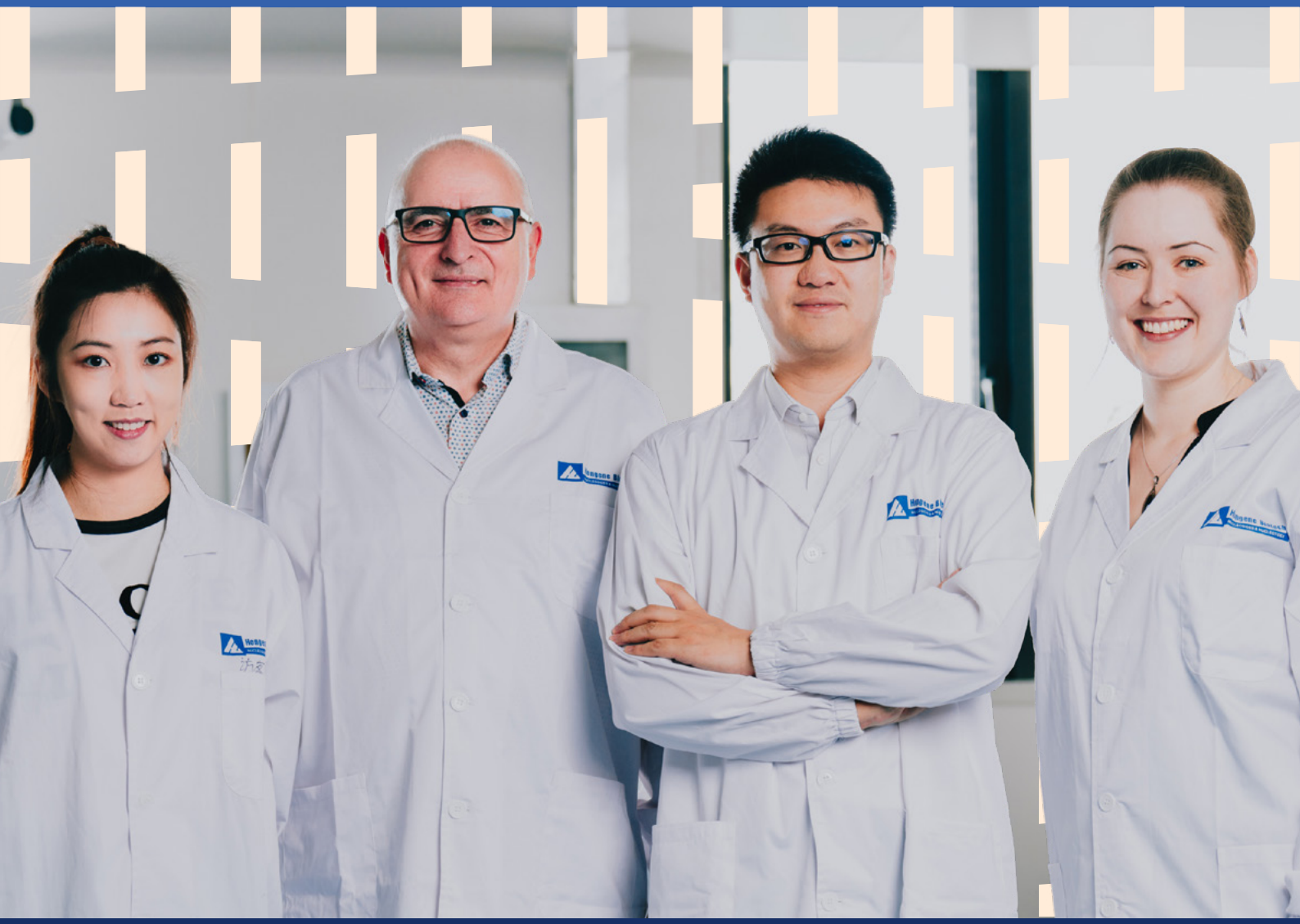

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