Vertical Integration:
Building Resilience and Scalability in Nucleic Acid Therapeutics Manufacturing

The Shift Towards an Integrated Supply Model
The biopharmaceutical sector is entering a new phase shaped by the clinical and commercial momentum of nucleic acid therapeutics (NATs), which include mRNA-based products and oligonucleotide therapeutics such as siRNA and ASOs, as well as sgRNA used in gene editing programmes. Together, these technologies are expanding treatment options by enabling precise genetic targeting and adaptable therapeutic design.

Since the first nucleic acid-based therapeutic approval in 1998, the field has expanded to more than 20 approved products, with hundreds of ongoing clinical trials.[1] As more programmes move toward larger studies and commercial supply, manufacturing expectations are tightening around consistency and scalable execution. The field's expansion is exposing vulnerabilities that challenge scalability, quality consistency and speed to clinic.

In response, some contract development and manufacturing organisations (CDMOs) are adopting a vertically integrated supply model that unites raw material synthesis with GMP production of drug substance and drug product within the same company. By aligning key production stages, this approach can support reliability and scalability while strengthening operational control.

This article examines how vertically integrated models are being applied to mRNA and oligonucleotide manufacturing and how this approach is influencing the standards of efficiency and quality in NAT development and manufacturing.

Managing NAT Manufacturing Complexity as Demand Increases

The therapeutic potential of NATs has advanced rapidly in recent years, driven by their programmable nature and high specificity, which support targeted intervention for diseases previously considered undruggable.[1,2] Reflecting this shift, the global market for NATs is projected to reach USD 16.4 billion by 2030, growing at a compound annual growth rate (CAGR) of 16.3% as the technology matures towards wider clinical and commercial use.[3]

Meeting this growing demand will be challenging. The molecular complexity of NATs necessitates highly specialised production capabilities, and existing manufacturing infrastructure must 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.[2,4] To support this expanding pipeline, supply chains must also scale to accommodate unprecedented volumes while maintaining the rigorous quality standards required for commercial approval.

As demand for NATs accelerates, developers are also under pressure to manage increasingly complex workflows that often span multiple vendors and geographies. In this fragmented environment, supply chain resilience is a practical determinant of speed to clinic and manufacturing consistency, particularly when programmes are scaling and have a low tolerance for disruption. A fragmented supply chain makes coordination more difficult, increasing the risk of unwanted variability and delays, as seen during the COVID-19 pandemic, when accelerated timelines, raw materials supply and constraints in fill–finish capacity amplified disruption risk.[5]

Fragmented Supply Chains Compound NAT Programme Risks

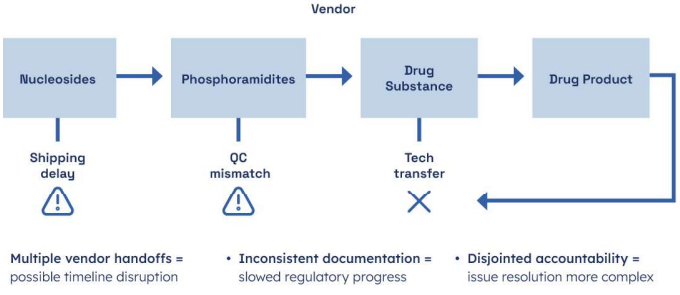
In conventional NAT manufacturing, production is typically fragmented across multiple vendors spanning raw materials (including building blocks and regulatory starting materials [RSMs]), cGMP drug substance production, drug product formulation and fill–finish and analytical testing. Each handoff of materials or documentation between organisations introduces operational risk, increasing the likelihood of misalignment or delays that can compound as programmes advance.

Fragmentation also makes investigation and issue resolution more complicated. When problems occur, root cause analyses and corrective actions can become more difficult and time-consuming when decisions, data and batch records are dispersed across multiple stakeholders and quality systems.

For some developers, supplier scheduling dynamics add another layer of uncertainty. Smaller programmes may be deprioritised in vendor queues, particularly when competing against higher volume accounts, which could impact timelines that are already sensitive to upstream or downstream handoffs.

Managing Complexity With a Vertically Integrated CDMO Partner

As demand for NATs continues to grow, the limitations of a fragmented supply chain model will become more pronounced. A vertically integrated CDMO model mitigates these constraints by consolidating all manufacturing activities within one organisation, from building block and RSM production through to cGMP CDMO services. With the elimination of vendor handoffs, project management and documentation are better



A fragmented supply chain can introduce inefficiencies that compromise timelines, cost efficiency, quality and supply security.

coordinated, traceability is strengthened and development timelines can be accelerated.

This structure also enhances regulatory readiness. When batch records, raw material traceability and quality documentation are maintained within a single organisation, it streamlines audit preparation and simplifies the compilation of data packages for regulatory submissions.

Key Features of a Robust Vertically Integrated CDMO Partner:

1. Full Spectrum Capabilities from Raw Materials to cGMP Services
The CDMO will be competent to manage the entire supply chain from building block and RSM production through to cGMP drug substance manufacturing, drug product formulation, fill–finish, packaging and QC as a "one-stop-shop", "under one roof".

2. Technical Leadership, Facilities and Workforce Readiness
A vertically integrated CDMO will have end-to-end operations overseen by expert technical leaders and executed in modern facilities using state-of-the-art equipment by an appropriately trained workforce.

3. Built for Regulatory Compliance
Facilities will be cGMP-compliant and supported by a robust quality system that has successfully supported regulatory submissions to global health agencies. Traceability infrastructure will enable lot-level tracking from building blocks through to the released batch, with comprehensive documentation and batch records.

4. Capacity to Support Scale-up and Continuity
Scalable infrastructure supports continuity with a single partner from early development through to commercial production. A vertically integrated CDMO's capacity will support scale-up and parallel projects without delays, with dedicated facilities, flexible layouts and adaptable workflows as indicators of long-term fit.

5. A Cross-functional Project Team That is an Extension of Your Team
Bringing programme leadership and manufacturing teams together helps to ensure that technical decisions are made quickly and issues are resolved efficiently. When the CDMO works closely with the sponsor as a partner, it's easier to stay aligned and respond quickly when problems arise.

6. Next-generation Technologies
As part of a full spectrum of end-to-end capabilities, a vertically integrated CDMO will be capable of leveraging next-generation technologies like chemoenzymatic ligation and liquid phase synthesis, where it makes sense to do so to enhance scalability, sustainability and control costs.

7. Organisational Flexibility Aligned to Different Developer Profiles
A vertically integrated CDMO provides the flexibility to support different types of developers and clinical stages. Staying with one partner from early development through to late-stage manufacturing helps maintain quality, consistency and smooth execution as the programme grows.

Modality-specific Considerations for Vertically Integrated Manufacturing
The potential benefits of a vertically integrated approach become even clearer when viewed through the lens of specific NAT modalities, which differ in chemistry, raw materials and process sensitivities, creating distinct pressure points across their manufacturing workflows:

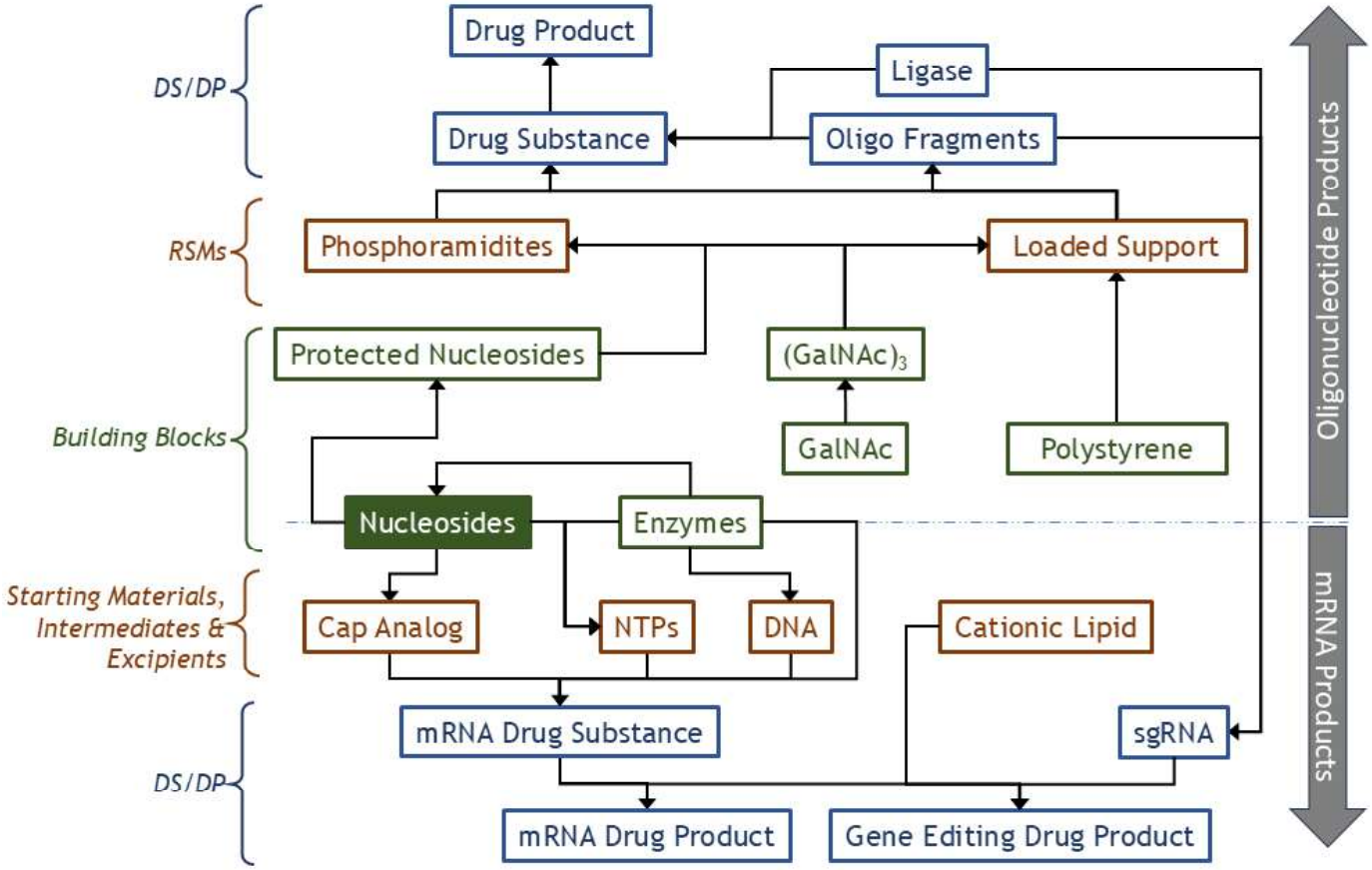
Oligonucleotide-based Therapeutics
Oligonucleotide synthesis relies on specialised RSMs, including phosphoramidites, loaded solid supports and ligands such as GalNAc. These inputs, which are manufactured from building blocks such as nucleosides, are typically treated as the point where cGMP controls begin for oligonucleotide manufacture, with stringent expectations for sourcing justification and quality control.

- From these RSMs, oligonucleotide drug substance manufacture involves tightly controlled chemical steps for chain elongation, including protection and deprotection steps plus sequential coupling and oxidation steps.
- Chemoenzymatic ligation may optionally be used for siRNAs and other oligonucleotides. Where it is used, enzymes and buffer components are introduced as raw materials, which also require sourcing and control as part of the manufacturing strategy.
- In a vertically integrated model, aligning RSM manufacture with downstream drug substance production can simplify traceability and change control when specifications or processes evolve.

mRNA-based Therapeutics
The workflow to manufacture mRNA therapeutics involves complex, interdependent steps with sensitivity to raw material inputs and process conditions. Consolidating control over key raw materials such as modified nucleotides, enzymes, cap analogs and DNA templates can help maintain alignment across the workflow and reduce variability as scale increases.

- Downstream of the raw materials, integrated management across cGMP mRNA production by IVT, purification, LNP formulation, fill–finish and packaging support faster technical iteration because changes can be evaluated within the context of a single quality environment and the need for transfer between vendors is eliminated.
- **Gene Editing Programmes That Use Long Guide RNA**
  In addition to all the components described in the workflow for mRNA therapeutics, gene editing programmes also require coordinated manufacture of guide RNA, such as sgRNA and pegRNA. These long, chemically modified RNA molecules can be produced with exceptionally high purity using chemoenzymatic ligation with a CDMO partner that is competent with that technology.

Implications for the Future of NAT Manufacturing
As the NAT industry continues its march toward large-scale volumes to address chronic global health burdens, the need for more efficient and scalable manufacturing will grow. By consolidating materials, processes and documentation "under one roof", from



A vertically integrated oligonucleotide and mRNA manufacturing platform in which a single CDMO partner controls the entire supply chain, from raw material building blocks through to drug substance and drug product.

production of building blocks and RSMs like phosphoramidites to final drug product fill–finish, vertically integrated CDMOs eliminate the vendor handoffs that have historically hindered speed and increased operational risk. This integrated model ensures that quality is embedded throughout the manufacturing lifecycle, with a transparent and traceable trail of documentation that simplifies regulatory submissions and strengthens long-term supply security.

For developers, shifting to an integrated partner means moving beyond fragmented vendor relationships toward a collaborative model that prioritises de-risked scaling, execution efficiency and programme continuity. As the global NAT pipeline continues to diversify and expand, those who leverage this model will be best positioned to bridge the gap between clinical promise and commercial reality, bringing transformative genetic medicines to patients with greater speed and confidence.

REFERENCES

1. Belgrad, J., Fakih, H. H., & Khvorova, A. (2024). Nucleic Acid Therapeutics: Successes, milestones, and upcoming innovation. Nucleic Acid Therapeutics, 34(2), 52–72. https://doi.org/10.1089/nat.2023.0068; https://pmc.ncbi.nlm.nih.gov/articles/PMC11302270/
2. Dzau, V. J., & Hodgkinson, C. P. (2024). RNA therapeutics for the cardiovascular system. Circulation, 149(9), 707–716. https://doi.org/10.1161/circulationaha.123.067373 https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.123.067373
3. Nucleic Acid Therapeutics Market Report, Industry and market Size & Revenue, Share, Forecast 2024–2030. (n.d.). https://www.strategicmarketresearch.com/market-report/nucleic-acid-therapeutics-market
4. Obexer, R., Nassir, M., Moody, E. R., Baran, P. S., & Lovelock, S. L. (2024). Modern approaches to therapeutic oligonucleotide manufacturing. Science, 384(6692), eadl4015. https://doi.org/10.1126/science.adl4015
5. Kis, Z., Kontoravdi, C., Shattock, R., & Shah, N. (2020). Resources, production scales and time required for producing RNA vaccines for the global pandemic demand. Vaccines, 9(1), 3. https://doi.org/10.3390/vaccines9010003; https://pubmed.ncbi.nlm.nih.gov/33374802/

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