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The Innovation Drug Discovery

The oligonucleotide therapeutics boom: FDA approvals from 2021 to 2025 and emerging innovation in drug discovery

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Dear Editor,

From 2021 through May 1, 2026, oligonucleotide therapeutics have evolved from a specialized rare-disease niche into a prominent driver of drug discovery. The FDA approved 11 new oligonucleotide or oligonucleotide-like therapeutics during this period, spanning antisense oligonucleotides, phosphorodiamidate morpholino oligomers, GalNAc-conjugated siRNAs, and an oligonucleotide-based telomerase inhibitor. This expansion reflects not merely a quantitative increase in approved products, but also a fundamental shift in the logic of therapeutic innovation. Increasingly, drugs are being designed as programmable information molecules that silence, redirect, or modify disease-relevant gene-expression states, rather than simply binding to protein targets. This review summarizes recent trend in FDA approvals, highlights key technological drivers such as GalNAc-mediated delivery and chemical modification, and identifies persistent bottlenecks, including extrahepatic delivery, off-target effects, immune activation, manufacturing complexity, pricing, and evidence generation. We conclude that the next phase of oligonucleotide therapeutics will be defined by platform-based, sequence-programmable, and data-driven therapeutic development. However, successful clinical translation will depend critically on overcoming delivery barriers beyond the liver and developing regulatory models capable of accommodating ultra-small patient populations without compromising standards for safety and efficacy.

INTRODUCTION

The past five years have made it increasingly clear that nucleic-acid therapeutics are no longer peripheral to pharmaceutical innovation. While traditional small molecules and antibodies remain highly effective, many disease mechanisms are encoded upstream of proteins, including RNA abundance, splicing, translation, or genetically defined toxic gain-of-function pathways. Oligonucleotide therapeutics therefore introduce a distinct conceptual framework: short sequences whose complementarity to RNA or interaction with nucleic-acid structures, enables programmable target selection. In computational terms, their design space more closely resembles constrained sequence optimization than classical ligand docking. This feature allows similar chemistry, analytical methods, and manufacturing strategies to be reused across targets, particularly when delivery chemistry is modular.

Clinical translation has increasingly validated this principle. According to a 2026 review, approximately 29 oligonucleotide-based therapeutics have been approved over the past two decades, with approvals remaining concentrated in liver-targeted indications, whereas efficient extrahepatic delivery continues to be a major limiting factor.[1-3] The 2021-2025 period is therefore particularly important, as it captures the transition from proof-of-concept approvals to broader platform expansion.

FDA APPROVAL TREND FROM 2021 TO 2025

Using the FDA CDER Novel Drug Approval reports and prescribing labels as primary sources, eleven new oligonucleotide or oligonucleotide-like therapeutics were approved between 2021 and 2025. As of May 1, 2026, the FDA approval list had not yet included an additional therapy within this tracked category.[4-8] Although the annual approval pattern was uneven, several important trends emerged.

In 2021, casimersen extended exon-skipping therapy for *Duchenne muscular dystrophy* (*DMD*), while inclisiran established twice-yearly PCSK9 silencing as a practical cardiometabolic intervention. In 2022, vutrisiran further validated the GalNAc-siRNA platform for hereditary transthyretin amyloidosis. Approvals in 2023 broadened into nervous and renal-metabolic diseases: tofersen targeted SOD1--associated amyotrophic lateral sclerosis (ALS), nedosiran reduced oxalate production in primary hyperoxaluria type 1, and eplontersen introduced an antisense strategy for hereditary transthyretin-mediated polyneuropathy (hATTR).[3-4]

The 2024-2025 period further expanded the clinical scope of oligonucleotide therapeutics. Imetelstat, an oligonucleotide telomerase inhibitor, was approved for lower-risk myelodysplastic syndromes, and olezarsen targeted APOC3 for familial chylomicronemia syndrome.[5-6] The FDA's 2025 report identified donidalorsen, plozasiran, and fitusiran as novel first-in-class oligonucleotide therapeutics approved during the year.[6] Fitusiran introduced antithrombin-lowering prophylaxis for hemophilia A and B, donidalorsen established an RNA-targeted prophylactic strategy for hereditary angioedema, and plozasiran added another APOC3-directed RNA therapeutic for familial chylomicronemia syndrome.[6]

TECHNICAL INSIGHTSFROM RECENT FDA APPROVALS

Three major technical lessons emerge from these approvals.

First, liver-directed delivery remains the dominant center of gravity in the field. GalNAc conjugation has enabled highly efficient hepatocyte uptake, supporting infrequent subcutaneous dosing schedules and making targets such as PCSK9, TTR, LDHA, SERPINC1, and APOC3 clinically tractable. Second, chemical modification is not merely an auxiliary optimization step; it represents the core stability and safety layer that transforms a nucleotide sequence into a viable therapeutic agent. Phosphorothioate backbones, 2'-O-methyl, 2 ' -fluoro, 2 ' -MOE, PMO chemistry, and conjugation strategies collectively regulate target affinity, nuclease resistance, tissue distribution, and dosing intervals.[7-8] Third, recent approvals show that oligonucleotide therapeutics should not be regarded as a single modality. The field now encompasses RNase H-dependent gapmers, steric-blocking antisense oligonucleotides (ASOs), splice-switching PMOs, siRNAs, and structure-targeting oligonucleotides. Conceptually, each therapy can be understood as a three-component system consisting of sequence, chemistry, and delivery. Clinical success generally depends on the coordinated optimization of all three components (Figure 1).

These observations also help explain why some earlier programs succeeded only partially or failed to translate. For example, exon-skipping and RNA-silencing candidates have repeatedly demonstrated that strong target rationale alone is insufficient if tissue exposure, durability, or tolerability are suboptimal. The approved drugs in this review therefore offer not just efficacy examples, but also a benchmark for how modern oligonucleotide engineering should be benchmarked against prior limitations.

More specifically, earlier programs such as systemic RNA interference candidates and several extrahepatic antisense approaches highlighted the difficulty of achieving durable tissue exposure and acceptable tolerability outside the liver, whereas approved drugs such as inclisiran, vutrisiran, and eplontersen demonstrate how chemical optimization and delivery design can convert a concept into a clinically viable product.

BOTTLENECKS AND RISKS

The dominant bottleneck remains delivery beyond hepatocytes. Efficient delivery to the central nervous system, skeletal muscle, lung, tumor, and

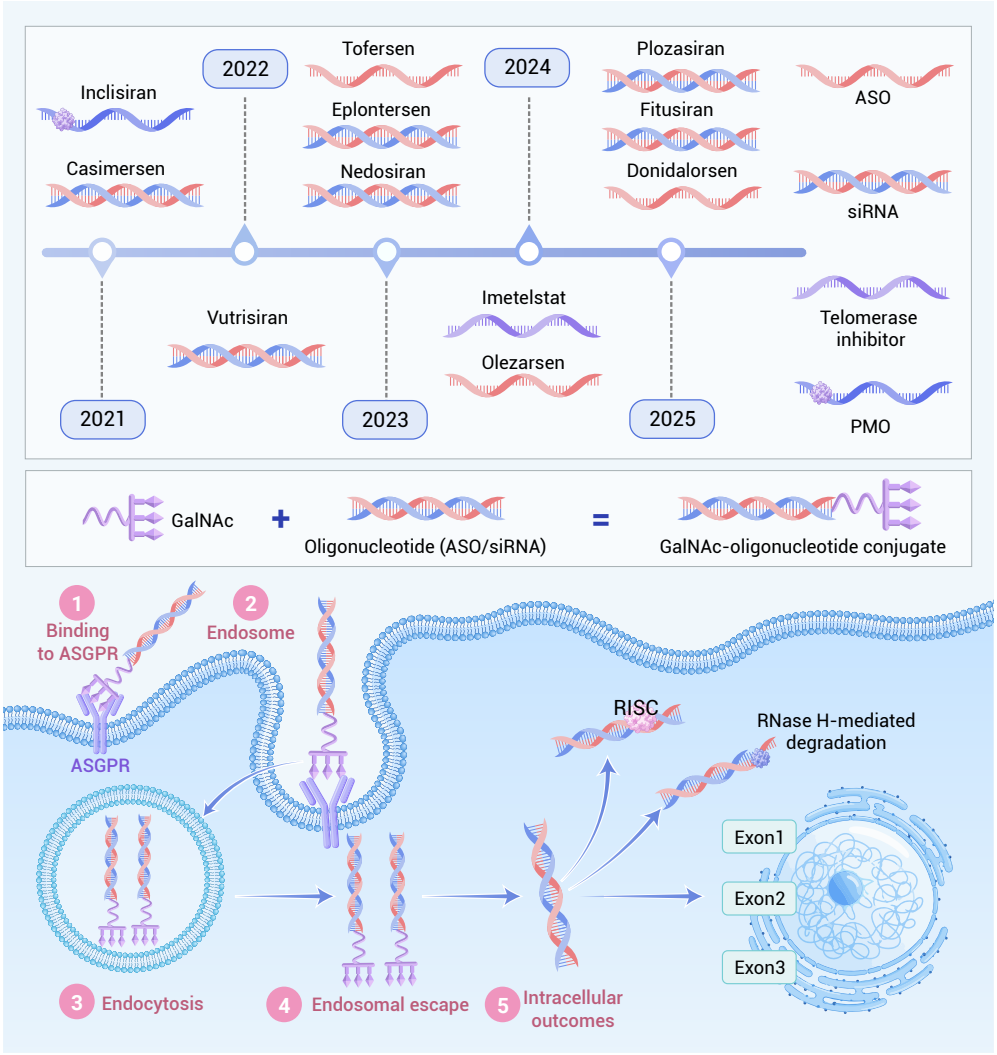

Figure 1. Temporal and technological overview of oligonucleotide therapeutics from 2021 to 2025 The figure delineates the annual approval trajectory, therapeutic modalities, disease indications, and key developmental trends. It further illustrates the core technological framework, integrating sequence programmability, chemical optimization, delivery engineering, and intracellular pharmacology.

immune cells requires distinct receptor biology and endosomal escape mechanisms. Tofersen showed that intrathecal administration can effectively target CNS disease biology, and casimersen demonstrated splice-switching strategies in muscle tissue. However, neither approach fully addresses the broader challenge of systemic extrahepatic delivery.

Safety considerations are also multidimensional. Sequence complementarity may result in off-target hybridization, backbone chemistry can alter protein-binding profiles, innate immune sensors may recognize nucleic-acid motifs, and prolonged tissue half-life may convert a pharmacokinetic advantage into a safety liability if toxicity occurs. Evidence generation represents an additional challenge because many approvals involve rare diseases characterized by small populations, reliance on surrogate biomarkers, or accelerated regulatory pathways. Pricing and accessibility are likewise critical issues rather than secondary social concerns. Ultimately, they will determine whether programmable medicines evolve into a broadly accessible public health platform or remain highly specialized premium therapies.

NEXT PARADIGM IN OLIGONUCLEOTIDE THERAPEUTICS

The next paradigm in drug discovery is likely to be programmable and platform based. Rather than developing each drug as an entirely independent entity, future research will increasingly focus on discovering reusable design principles, including sequence motifs that minimize off -target effects, chemical architectures that enhance tissue exposure, receptor systems that facilitate delivery, and biomarkers capable of linking small clinical studies to meaningful therapeutic outcomes.

Artificial intelligence (AI) may contribute substantially to this transition by prioritizing sequence candidates, predicting RNA secondary structure, modeling tissue exposure, identifying toxicity-associated motifs, and integrating chemistry and manufacturing constraints during the design stage. However, AI is valuable only when integrated with experimental validation and mechanistic pharmacology; otherwise, it simply accelerates uncertainty rather than reduce it.

Regulatory frameworks are evolving in parallel. In 2026, the FDA issued draft guidance on Plausible Mechanism for individualized therapies targeting genetically defined diseases with established biological mechanisms.[9-10] This development is particularly relevant to oligonucleotide therapeutics because ASOs and RNA-based products are among the most feasible modalities for N-of-1 or ultra-small-population interventions. The opportunity is substantial: rapid therapeutic design for molecularly defined patient. However, the associated risks are equally significant, including limited evidence generation, manufacturing variability, and post-approval uncertainty. A sustainable future regulatory pathway will require platform-based toxicology strategies, standardized chemistry, manufacturing, and controls (CMC) frameworks, integration of real-world evidence, and clearly defined stopping criteria.

CONCLUSION

The FDA approval pattern from 2021 to 2025 suggests that oligonucleotide therapeutics have crossed an important conceptual threshold. They are no longer merely alternatives to small molecules drugs, but are increasingly functioning as programmable tools for modulating disease biology at the RNA level. Although current approvals remain concentrated in rare diseases and liver-targeted indications, the broader strategic direction of the field is becoming increasingly clear.

If advances in extrahepatic delivery, safety prediction, and evidence-generation frameworks continue to mature in parallel, oligonucleotide therapeutics could become one of the most productive engines of next-generation drug discovery. The key challenge is no longer whether a therapeutic sequence can be designed. Rather, it is whether the sequence design, chemistry, delivery systems, clinical endpoints, and regulatory evidence can be rationally co-designed as a single integrated translational platform.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND MATERIALS AVAILABILITY

Data will be available upon reasonable request to the corresponding author, following the signature of a data use agreement.