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Establishing a commercial solution for extremely rare genetic diseases

While extremely rare genetic diseases have been present in humans throughout history, only now because of advances in genomic sequencing are the prevalence, characteristics, scale and impact of such diseases becoming apparent. It is estimated that there are 300 million humans affected by rare diseases[1], and it is highly likely that there are tens of millions of patients with extremely rare pathogenic mutations.

No consensus definition for the term 'extremely rare pathogenic mutations' has been published, but nano-rare mutations have been defined as pathogenic mutations with a known worldwide prevalence of less than 30 patients[2], and ultra-rare hwwas been defined as affecting 7,000 or fewer patients in the United States[3]. For this discussion, we define an extremely rare pathogenic mutation as a mutation that has such a low prevalence that most current drug discovery technologies, regulatory paths to commercial approval, commercial models and approaches to pricing may not result in sufficient return on investment to support commercial development.

At present, only regulatory guidance for antisense oligonucleotides (ASOs) of well understood chemical classes designed to treat patients with nano-rare pathogenic mutations has been issued by the US Food and Drug Administration (FDA)[4–6]. No other regulatory body has issued similar guidance, and the FDA indicates that the guidance is not intended for ASOs to be developed commercially. Nonetheless, it appears that there is considerable momentum to create a regulatory path to commercial approval for products to treat patients with extremely rare genetic diseases, and new pricing models have also been proposed[7]. Novel models that support commercialization of medicines to treat patients with extremely rare diseases may be needed to create holistic, sustainable solutions for these patients. Here, focusing on ASOs as a drug modality, we discuss issues to consider and propose potential approaches that could lead to an integrated holistic solution to encourage the commercialization of new therapeutics for these underserved patients.

An efficient drug discovery technology

As the diseases to be addressed are caused by genetic mutations, a drug discovery technology that can rapidly and efficiently convert genetic information into genetically targeted drugs is essential. Because extremely rare mutations occur throughout the genome and result in manifestations in multiple organs, the technology needs to be broadly enabling and, ideally, the drugs derived from the platform need to be amenable to delivery via multiple routes of administration. Drug discovery must be rapid, automated and cost-effective.

Importantly, drugs based on the technology should have sufficiently similar pharmacokinetic, pharmacodynamic and toxicological properties to predict dose, dose schedule, appropriate route of administration and likely adverse events on the basis of the behaviors of previously discovered and tested drugs of the same chemical class. Manufacturing methods, analytical procedures, quality control and formulations should be well understood and applicable to all drugs that are members of the same chemical class. Clinical experience with drugs based on the technology must be sufficient to assure that the risk/benefit profiles of these drugs are generally attractive. The clinical safety profiles and potential adverse events of these medicines must also be well understood, with sufficient long-term clinical treatment experience to identify potential adverse events associated with chronic administration.

Less mature technologies or technologies for which major issues have not been resolved, such as the risk of severe, life-threatening adverse events common to all drugs derived from the technology, should not be considered for broad application. Rather, the development of drugs based on such technologies could be undertaken using existing FDA regulatory processes that limit clinical experimentation to severely affected patients with rapidly progressing disease.

Streamlined non-clinical regulatory requirements

In 2021, the FDA took an important step as it issued special guidance for ASOs of well understood chemical classes for nano-rare diseases[4–6] that created a streamlined non-clinical pathway. The guidance supports the administration of ASOs identified by testing induced pluripotent stem cells derived from patients to severely ill patients with no animal pharmacological data and a single 3-month rodent Good Laboratory Practice (GLP) toxicology study. The guidance results in the savings of substantial time and money by circumventing the need to develop animal models, which would traditionally be used to evaluate new drug candidates; by reducing requirements for GLP toxicology studies; and by providing the opportunity to initiate clinical trials immediately in patients rather than healthy participants. The development of animal models is time consuming, is costly and results in models that often do not predict clinical success. Similarly, the opportunity to limit non-clinical toxicological studies because drugs of the same class behave similarly results in considerable savings in time and cost of development, making putative returns on investment more attractive.

Experience with ASOs developed under the individualized ASO guidance has shown that an organization with deep experience in ASO technology can deliver safe and effective ASOs for a wide range of diseases, despite limited non-clinical data[8]. Furthermore, experience at n-Lorem suggests that if an ASO corrects the entire cellular phenotype in induced pluripotent stem cell-derived cells, it is likely to correct the entire clinical phenotype[9]. Consequently, one possible solution to facilitate commercialization could be to extend the current guidance to support commercial development. If the FDA determined that added toxicologic studies might be needed for specific drugs for certain indications, it could require the studies to be performed before commercial approval.

Streamlined clinical regulatory requirements

Guidance that enables initiating clinical development in patients and advancing from phase 1/2 studies directly to a single phase 3 study would also reduce costs and timeline

considerably, further enhancing net present value assessments to encourage investment in drugs for smaller market opportunities. Modified phase 3 study designs may also be required to contend with several issues. Indications with very few patients present enrollment challenges that might be mitigated by enrolling fewer patients but requiring substantial benefit to be demonstrated in the few patients studied.

As an example, a different phase 3 study design could entail several ASOs designed to alter different molecular causes of a rare disease that are studied in a single composite phase 3 study. This would include prespecified analyses of each ASO to assure that any poorly performing ASO could be eliminated from approval. Similar solutions seem feasible for heterozygous toxic gain-of-function mutations in genes that encode essential gene products and require allele-selective ASOs[10]. Optimized phase 3 designs could reduce development costs and improve the use of the limited number of patients available for enrollment.

Alternatively, the experience at n-Lorem may suggest an approach to assess clinical benefit and infer overall risk/benefit ratio from limited patient populations that relies on intra-patient on-treatment versus pre-treatment evaluations rather than group statistics. If only patients who expressed a specific phenotype at the initiation of treatment show benefit, the approval could be limited to that phenotype. It is likely that, as experience is gained, other approaches to assessing the benefit of genetic medicines in small groups of patients will emerge.

Tailored post-marketing surveillance, clinical study and reporting requirements

In return for access to the streamlined regulatory pathway, companies could be required to engage in more extensive postmarketing surveillance and potentially added studies. While each drug and disease might demand different postmarketing requirements, the agency could provide generic guidance for those requirements. Having a sense of the postmarketing requirements would facilitate investment in molecular targets with smaller patient populations because postmarketing expenses could be better understood at the time an investment decision must be made.

Novel pricing and marketing plans

The commercialization of ASO therapies for extremely rare genetic diseases will require payment and financing models that differ fundamentally from those used for conventional pharmaceuticals. Traditional pricing paradigms — designed for therapies targeting large patient populations and amortizing research and development costs over extended sales horizons — are poorly matched to therapies intended for tens or even single-digit numbers of patients worldwide.

Patient-number-indexed and cost-plus pricing. One foundational approach is to explicitly link pricing to the number of treated patients rather than to therapeutic class benchmarks or international reference pricing. Under such models, the total recoverable revenue for a given ASO would be determined ex ante based on documented discovery and development costs, ongoing manufacturing and pharmacovigilance expenses, and a predefined, risk-adjusted return on capital. This framework lends itself to cost-plus pricing, with per-patient prices declining as patient numbers increase. For extremely small populations, such transparency can reduce payer resistance, mitigate concerns about opportunistic pricing and create a predictable environment for investment decisions. This approach aligns well with ASO platform economics, for which marginal costs of designing and manufacturing additional sequence-specific oligonucleotides are low relative to those of traditional small-molecule or biologic development.

Subscription models for genetic medicines. A complementary approach is the use of subscription-based payment models, particularly for ASO platforms capable of producing a family of therapies addressing multiple ultra- or nano-rare mutations. In this framework, a payer — such as a national health system, consortium of private insurers or reinsurer — makes a fixed annual or multi-year payment in exchange for access to a defined portfolio of ASO therapies. Such subscription-based models have been used in the case of the hepatitis C drugs Sovaldi (sofosbuvir) and Harvoni (ledipasvir sofosbuvir), and have also been proposed as a mechanism to address affordability and access challenges for high-cost medicines such as gene and cell therapies while preserving incentives for innovation[10]. In these formulations, subscription models decouple revenue from per-patient use and instead emphasize population-level access, predictability of spending, and long-term system sustainability. Applied to ASOs, this approach is particularly attractive because it enables risk pooling across multiple rare conditions, smooths budget impact, and reduces administrative friction associated with case-by-case reimbursement decisions.

Drug mortgages and long-term financing. For ASO therapies that provide durable or lifelong benefit — particularly when administered chronically over many years — drug mortgage–style financing[11] presents another option. In these financing structures, high-cost therapies are treated analogously to capital assets, allowing their costs to be amortized over time rather than paid entirely at treatment initiation. Payments are spread over a multiyear horizon, aligning annual expenditures more closely with realized clinical benefit and reducing short-term budget shocks for payers. This approach is especially relevant for extremely rare diseases, where up-front per-patient costs may be large relative to annual healthcare budgets, even if aggregate lifetime spending is modest. Drug mortgages can also be combined with outcomes-based milestones or reinsurance mechanisms to mitigate payer risk.

Outcomes-based payments, risk pooling and precision marketing. Although traditional outcomes-based contracts can be difficult to implement for slowly progressive rare diseases, milestone-linked payment structures — tied, for example, to biomarker engagement or stabilization of disease-specific functional measures — may still be feasible for selected ASOs. Such models allow partial risk-sharing while recognizing the mechanistic specificity of antisense therapies. These approaches should be supported by reinsurance mechanisms and rare-disease risk pools, particularly to protect smaller insurers from the financial impact of individual high-cost cases. At the same time, marketing practices for ASOs should remain highly constrained and precision-focused, emphasizing genetic diagnosis, clinician education and appropriate patient identification rather than traditional promotional activities.

Taken together, cost-plus pricing, subscription models, drug mortgages and risk pooling form a coherent set of options for financing ASO therapies for extremely rare genetic diseases. Rather than relying on any single mechanism, sustainable commercialization is likely to require hybrid approaches that combine transparent pricing, long-term financing and system-level risk sharing. When coupled with streamlined regulatory pathways and platform-based development efficiencies,

these models offer a credible path toward making individualized genetic medicines both economically viable and broadly accessible.

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Author contributions

Both authors contributed conceptually and in writing and editing the manuscript.

Competing interests

A.W.L. is a co-founder of and advisor to Gondola Bio, which is developing commercial ASO products in collaboration with n-Lorem. A.W.L. also has a number of investments in biotech companies and biotech venture capital funds, and holds several advisory positions and directorships in biotech companies — including a directorship at n-Lorem — all of which are disclosed in Supplementary Note 1. S.T.C. declares no competing interests.

Additional information

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