RESEARCH PAPER

Orphan Drug Development and Delivery Systems for Rare Diseases in India: Pharmaceutical Challenges, Regulatory Frameworks, And Innovative Solutions

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ABSTRACT
Rare diseases affect approximately 70 to 96 million individuals in India, representing 6 to 8% of the population. The development and delivery of orphan drugs for these conditions present unique pharmaceutical challenges including limited patient populations, high research and development costs, complex formulation requirements, and inadequate regulatory frameworks. This review examines the current landscape of orphan drug development in India through a pharmaceutical sciences perspective, analyzing formulation challenges, drug delivery innovations, regulatory pathways, and policy frameworks. We evaluate advanced drug delivery systems including nanoparticle-based formulations, liposomal carriers, and targeted delivery mechanisms specifically designed for rare disease therapeutics. The National Policy for Rare Diseases (2021) and its implications for pharmaceutical manufacturing, pricing regulations, and research incentives are critically assessed. Key findings reveal that while India manufactures active pharmaceutical ingredients for approximately 450 orphan drugs, domestic availability remains severely limited due to formulation complexities, regulatory gaps, and economic constraints. Novel drug delivery technologies including lipid nanoparticles, polymeric carriers, and gene therapy vectors show promise in addressing bioavailability and targeting challenges specific to rare disease treatments. The review identifies critical pharmaceutical interventions including establishment of specialized orphan drug formulation facilities, implementation of fast-track regulatory approval processes, and development of cost-effective manufacturing protocols. This comprehensive analysis provides evidence-based recommendations for pharmaceutical scientists, regulatory authorities, and policymakers to enhance orphan drug accessibility while maintaining quality standards.

Keywords: Orphan drugs, rare diseases, Drug delivery systems, pharmaceutical formulation, Nanoparticles, Regulatory framework, National Policy for Rare Diseases, India, Gene therapy, Lipid nanoparticles

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INTRODUCTION

Rare diseases, defined as conditions affecting fewer than 1 in 1000 individuals by the World Health Organization, collectively represent a significant pharmaceutical challenge. With over 7000 rare diseases identified globally and approximately 450 documented in India, these conditions affect an estimated 70 to 96 million Indians.[1] The pharmaceutical industry has historically underinvested in orphan drug development due to limited market size, high research costs, and regulatory uncertainties. However, advances in drug delivery technologies, genomic medicine, and regulatory frameworks are transforming the orphan drug landscape.[2]

Orphan drugs are pharmaceutical agents developed specifically for diagnosis, prevention, or treatment of rare diseases. The development pathway for orphan drugs differs significantly from conventional pharmaceuticals, requiring specialized formulation strategies, innovative delivery systems, and adapted clinical trial designs. Most rare diseases (approximately 80%) are genetic in origin, often requiring complex therapeutic approaches including enzyme replacement therapy, gene therapy, or substrate reduction therapy.[3]

In India, the pharmaceutical sector represents a unique paradox: while the country manufactures active pharmaceutical ingredients (APIs) for nearly all 450 globally approved orphan drugs, domestic availability and affordability remain critically limited. This gap stems from multiple factors including absence of dedicated orphan drug legislation until 2019, limited investment in specialized formulation development, complex regulatory pathways, and prohibitive treatment costs often exceeding Rs 10 lakhs to Rs 1 crore annually per patient.[4,5]

Pharmaceutical Challenges in Orphan Drug Development

The development of orphan drugs presents distinct pharmaceutical challenges. Small patient populations (often fewer than 500,000 patients in India as per CDSCO definition) complicate dose optimization,

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pharmacokinetic profiling, and long-term stability studies.[6] Many orphan drugs are biologics or complex small molecules with poor aqueous solubility, limited oral bioavailability, and short half-lives requiring frequent administration. These characteristics necessitate advanced formulation strategies and novel delivery systems.[7]

Objectives

This review aims to: (1) analyze current pharmaceutical formulation challenges in orphan drug development for rare diseases prevalent in India; (2) evaluate advanced drug delivery systems and technologies applicable to orphan drug formulations; (3) examine the regulatory framework established through the National Policy for Rare Diseases (2021) and its pharmaceutical implications; (4) assess barriers to domestic orphan drug manufacturing and formulation; (5) identify innovative pharmaceutical strategies to enhance orphan drug accessibility while maintaining quality standards.

METHODOLOGY

A comprehensive literature review was conducted covering pharmaceutical sciences databases including PubMed, Scopus, and Google Scholar for publications from 2015 to 2025. Search terms included orphan drugs, rare diseases, drug delivery systems, pharmaceutical formulation, nanoparticles, gene therapy, and regulatory frameworks combined with India-specific terms. Regulatory documents from the Central Drugs Standard Control Organisation (CDSCO), Ministry of Health and Family Welfare, and pharmaceutical industry reports were analysed. Inclusion criteria encompassed peer-reviewed articles on orphan drug formulation, delivery technologies, regulatory pathways, and pharmaceutical manufacturing specific to rare diseases. Exclusion criteria included non-pharmaceutical perspectives, general healthcare policies without pharmaceutical focus, and studies without Indian relevance.

PHARMACEUTICAL FORMULATION CHALLENGES IN ORPHAN DRUG DEVELOPMENT

Physicochemical Properties and Solubility Issues

Approximately 71% of approved orphan drugs are small molecules, many exhibiting poor aqueous solubility (BCS Class II and IV compounds).[8] These physicochemical limitations necessitate advanced solubilization techniques including solid dispersion, co-crystallization, micronization, and complexation with cyclodextrins. For example, drugs like Bosentan (used in pulmonary arterial hypertension) and Deferasirox (for iron overload disorders) require specialized formulation approaches to achieve adequate bioavailability.[9]

Stability and Storage Challenges

Many orphan drugs, particularly biologics and enzyme replacement therapies, exhibit limited stability requiring stringent cold chain logistics. Drugs like Elosulfase alfa for Morquio syndrome and Imiglucerase for Gaucher disease require storage at 2 to 8 degrees Celsius with limited room temperature stability. India's tropical climate and infrastructure gaps in cold chain management complicate distribution, particularly to tier-2 and tier-3 cities.[10]

Dosing and Pediatric Formulations

Rare diseases disproportionately affect paediatric populations, with approximately 31.8% of orphan drug approvals claiming paediatric exclusivity.[11] Pediatrics formulations require considerations beyond dose adjustment including taste masking, age-appropriate dosage forms (liquids, dispersible tablets), and excipient safety. The absence of dedicated paediatric formulation facilities in India for orphan drugs represents a critical gap.

Table 1: Common Formulation Challenges in Orphan Drug Development

Challenge Category	Specific Issues	Impact on Development	Potential Solutions
Solubility	Poor aqueous solubility, Low bioavailability, BCS Class II/IV compounds	Limited absorption, Variable pharmacokinetics, Dose inconsistency	Solid dispersions, Nano formulations, Cyclodextrin complexation, Lipid-based systems
Stability	Temperature sensitivity, Photodegradation, Hydrolytic instability, Limited shelf-life	Cold chain requirements, Distribution challenges, High wastage rates, Limited accessibility	Lyophilization, Protective excipients, Improved packaging, Stabilizing formulations
Manufacturing Scale	Small batch sizes, Limited manufacturing capacity, High per-unit costs, Specialized equipment needs	Economic unviability, Production delays, Quality variability, Limited suppliers	Flexible manufacturing, Contract manufacturing, Technology transfer, Batch optimization

Pediatrics Requirements	Age-appropriate formulations, Taste masking needs	Limited paediatric data, Compliance issues, Delayed market entry, Regulatory hurdles	Dispersible tablets, Oral liquids, Taste-masked granules, Sprinkle formulations

ADVANCED DRUG DELIVERY SYSTEMS FOR ORPHAN DRUGS

Nanoparticle-Based Delivery Systems

Nanoparticle-based delivery systems have revolutionized orphan drug formulation by addressing bioavailability, targeting, and stability challenges. Lipid nanoparticles, particularly those used in Patisiran (Onpattro) for hereditary transthyretin-mediated amyloidosis, demonstrate successful application of RNA interference therapy with lipid nanoparticle delivery achieving FDA approval in 2018.[12] This technology later enabled COVID-19 mRNA vaccine development, showcasing orphan drug innovation's broader impact.

Polymeric nanoparticles utilizing PLGA (poly lactic-co-glycolic acid) offer controlled release capabilities crucial for orphan drugs requiring sustained plasma concentrations. These biodegradable systems enable reduced dosing frequency, improved patient compliance, and minimized side effects through targeted delivery.[13]

Liposomal Formulations

Liposomal drug delivery offers advantages for orphan drugs including enhanced solubility, prolonged circulation time, reduced toxicity, and improved tissue targeting. Liposomal amphotericin B formulations used in visceral leishmaniasis (a rare disease in many regions) demonstrate successful application with reduced nephrotoxicity compared to conventional formulations.[14] PEGylated liposomes (stealth liposomes) further extend circulation half-life, critical for orphan drugs requiring infrequent dosing.

Gene Therapy Vectors and Delivery

Gene therapy represents a paradigm shift for rare genetic disorders, with several approved treatments including Luxturna (voretigene neparvovec) for inherited retinal dystrophy and Zolgensma (onasemnogene abeparvovec) for spinal muscular atrophy. Adeno-associated virus (AAV) vectors dominate gene therapy delivery due to low immunogenicity, broad tissue tropism, and sustained transgene expression.[15] Manufacturing complexities and costs (often exceeding 850,000 USD per treatment) limit accessibility in India, necessitating technology transfer and domestic manufacturing capabilities.

Targeted Delivery to Cross Biological Barriers

Many rare neurological disorders require drug delivery across the blood-brain barrier (BBB), a significant pharmaceutical challenge. Strategies include receptor-mediated transcytosis using transferrin or insulin receptors, cell-penetrating peptides, and focused ultrasound-mediated BBB opening. Nanoparticles surface-modified with targeting ligands show promise for lysosomal storage disorders affecting the central nervous system.[16]

Table 2: Advanced Drug Delivery Technologies for Orphan Drugs

Delivery System	Technology Platform	Representative Orphan Drug	Rare Disease Indication	Key Advantages
Lipid Nanoparticles	mRNA-LNP complex	Patisiran (Onpattro)	Hereditary transthyretin amyloidosis	Hepatocyte targeting, RNA protection, Reduced immunogenicity
AAV Vectors	Gene therapy vector	Luxturna (voretigene neparvovec)	Inherited retinal dystrophy	Long-term expression, Low immunogenicity, Retinal cell tropism
PEGylated Liposomes	Stealth liposomes	PEG-asparaginase	Acute lymphoblastic leukemia	Extended half-life, Reduced immunogenicity, Lower dosing frequency
Polymeric Nanoparticles	PLGA nanoparticles	Experimental formulations	Various lysosomal storage disorders	Controlled release, Biodegradability, Targeting capability

Enzyme Replacement	Recombinant enzymes	Imiglucerase (Cerezyme)	Gaucher disease	Substrate reduction, Direct enzyme supplementation
Antisense Oligonucleotides	Modified RNA	Nusinersen (Spinraza)	Spinal muscular atrophy	Precise gene modulation, Disease modification

REGULATORY FRAMEWORK AND POLICY LANDSCAPE IN INDIA

Evolution of Orphan Drug Regulations

India's orphan drug regulatory framework evolved significantly with the 2019 amendment to New Drugs and Clinical Trials Rules defining orphan drugs as those intended for treatment of conditions affecting fewer than 500,000 patients in India.[17] The Central Drugs Standard Control Organisation (CDSCO) introduced provisions for fast-track processing of orphan drug applications, reduced data requirements for globally approved products, and expedited clinical trial approvals.

National Policy for Rare Diseases (2021): Pharmaceutical Implications

The National Policy for Rare Diseases (NPRD) 2021 introduced several pharmaceutical sector initiatives. The policy categorizes rare diseases into three groups based on treatment characteristics: Group 1 includes disorders amenable to one-time curative treatment (primarily gene and cell therapies); Group 2 encompasses diseases requiring lifelong treatment with documented benefit and relatively lower costs; Group 3 comprises diseases with very high-cost therapies requiring careful patient selection.[18]

Key pharmaceutical provisions include: (1) promotion of research and development for diagnosis and treatment through ICMR, DBT, DST, and CSIR; (2) encouragement of local development and manufacture of orphan drugs at affordable prices through the Department of Pharmaceuticals; (3) customs duty exemptions for imported orphan drugs through designated Centres of Excellence; (4) establishment of National Consortium for Research and Development on Therapeutics for Rare Diseases (NCRDTRD); (5) Production Linked Incentive (PLI) Scheme inclusion for orphan drug manufacturing.[19]

Pricing Regulations and Patent Provisions

The Ministry of Chemicals and Fertilizers amended the Drugs Prices Control Order (DPCO) 2013, exempting newly patented orphan drugs developed outside India from pricing regulations for five years.[20] This exemption aims to incentivize pharmaceutical companies to launch products in India. However, it potentially conflicts with affordability objectives. The Indian Patents Act 1970 provides provisions for compulsory licensing (Section 84) applicable to orphan drugs if unavailable at reasonable prices or not manufactured domestically. In 2012, India granted its first compulsory license for sorafenib, setting precedent for rare disease medications.[21]

Table 3: Regulatory Pathways for Orphan Drug Approval in India

Approval Pathway		Eligibility Criteria	Data Requirements	Timeline	Key Benefits
Fast-Track Designation		Drugs for rare diseases affecting <500,000 patients	Reduced clinical trial data for FDA/EMA approved drugs	6-9 months	Expedited review, Regulatory fee waiver, Protocol assistance
Conditional Approval		Critical unmet need, Preliminary efficacy data	Phase II clinical data with surrogate endpoints	4-6 months	Earlier patient access, Post-marketing commitments
Import License (Personal Use)		Recommendation from CoE, Documented rare disease diagnosis	Prescription and medical necessity documentation	2-4 weeks	Duty exemption, IGST waiver, Individual patient access
Clinical Trial Approval		Investigational orphan drug	IND submission with preclinical data	3-6 months	Patient recruitment support,

					Regulatory guidance
Generic/Biosimilar Route		Innovator product off-patent or CL granted	Bioequivalence/bio similarity studies	12-18 months	Reduced development costs, Affordability

BARRIERS TO DOMESTIC ORPHAN DRUG MANUFACTURING IN INDIA

Economic and Market Constraints

Despite manufacturing APIs for 450 orphan drugs, India faces significant barriers to finished formulation production. The limited patient population (typically 5,000 to 50,000 per disease) creates market uncertainty. High development costs (estimated at 500 million to 2 billion USD per orphan drug) combined with small markets discourage pharmaceutical investment.[22] The cost differential between imported and potentially domestically manufactured orphan drugs remains substantial: for instance, Hydroxocobalamin for cyanide poisoning costs 920 USD imported versus 5 USD if manufactured locally; Nitisinone for tyrosinemia costs 2.6 million USD imported but could cost significantly less with domestic production.[23]

Technical and Infrastructure Gaps

Specialized manufacturing infrastructure for biologics, gene therapies, and complex small molecules remains limited. Few Indian pharmaceutical facilities possess GMP-compliant viral vector production capabilities, aseptic fill-finish lines for lyophilized biologics, or advanced analytical equipment for characterization of complex orphan drug formulations. The technology transfer from innovator companies to Indian generic manufacturers encounters intellectual property barriers, know-how limitations, and regulatory complexities.[24]

Clinical Research and Trial Limitations

Indian patients remain largely excluded from global orphan drug clinical trials, limiting local expertise and regulatory experience. Challenges include small, geographically dispersed patient populations, lack of standardized diagnostic facilities, absence of natural history studies for Indian populations, and limited investigator experience with rare disease trials.[25] The establishment of the National Registry for Rare Diseases by ICMR aims to address epidemiological data gaps, but enrollment remains incomplete.

INNOVATIVE PHARMACEUTICAL STRATEGIES AND SOLUTIONS

Drug Repurposing for Rare Diseases

Drug repurposing represents a cost-effective strategy for orphan drug development. A study identified that 76% of FDA-approved repurposed orphan drugs have marketing approval from Indian regulatory bodies.[26] Examples include thalidomide (originally for morning sickness, repurposed for multiple myeloma and erythema nodosum leprosum), and cannabidiol (repurposed for Lennox-Gastaut syndrome and Dravet syndrome). Artificial intelligence platforms like Healx and Benevolent AI accelerate repurposing candidate identification through computational drug discovery.[27]

Contract Manufacturing and Flexible Production Models

Flexible manufacturing platforms designed for small batch production offer solutions to economic constraints. Modular manufacturing units with scalable capacity (10 to 1000 litres) enable production of multiple orphan drugs with minimal changeover costs. Contract development and manufacturing organizations (CDMOs) specializing in orphan drugs provide expertise without requiring dedicated facilities from pharmaceutical companies.[28]

Pharmaceutical Technology Upgradation

The Pharmaceutical Technology Upgradation Assistance Scheme (PTUAS) aims to upgrade pharmaceutical manufacturing to meet international quality standards. Extending this scheme specifically for orphan drug capabilities including cell and gene therapy manufacturing, viral vector production, and advanced aseptic processing would enhance domestic capacity. Establishment of dedicated Orphan Drug Formulation Centers with specialized equipment and trained personnel represents a strategic pharmaceutical intervention.[29]

Quality by Design (QbD) Approaches

Implementing Quality by Design principles in orphan drug development optimizes formulation and manufacturing efficiency. QbD methodologies including design of experiments, risk assessment, and process analytical technology enable robust formulation development with limited material availability. This approach particularly benefits orphan drugs where extensive traditional optimization studies prove impractical due to API scarcity.[30]

DISCUSSION

This comprehensive analysis reveals that India's orphan drug landscape presents a complex interplay of pharmaceutical capabilities, regulatory evolution, and market constraints. The country possesses substantial API manufacturing capacity yet faces significant barriers to finished formulation development and accessibility. Advanced drug delivery technologies including nanoparticles, liposomes, and gene therapy

vectors offer solutions to fundamental pharmaceutical challenges inherent in rare disease treatments.

The National Policy for Rare Diseases (2021) represents significant regulatory progress, establishing frameworks for research promotion, manufacturing incentives, and patient access. However, implementation gaps persist. The Production Linked Incentive scheme includes orphan drugs but lacks specific implementation guidelines. Fast-track regulatory approvals remain underutilized due to limited awareness and unclear application procedures. The five-year pricing exemption for imported orphan drugs, while incentivizing market entry, potentially conflicts with affordability goals.

Pharmaceutical innovation in drug delivery systems offers promising pathways. Lipid nanoparticle technology, validated through Patisiran and subsequently COVID-19 vaccines, demonstrates feasibility for RNA-based therapies applicable to genetic rare diseases. Gene therapy vectors, while costly, represent curative potential for previously untreatable conditions. Technology transfer and domestic manufacturing of these advanced modalities remain critical priorities. The successful manufacture of hepatitis B vaccine and insulin biosimilars in India provides precedent for complex biologic production.

Drug repurposing emerges as a pragmatic strategy, with 76% of repurposed orphan drugs already approved in India requiring only formulation optimization and clinical validation for new indications. This approach circumvents early-stage drug discovery costs and safety characterization, significantly reducing development timelines and expenses. Artificial intelligence-driven drug discovery platforms accelerate repurposing candidate identification, representing an area for Indian pharmaceutical and IT sector collaboration.

The regulatory framework requires refinement. While CDSCO provisions exist for fast-track orphan drug approvals, standardized guidance documents, clear timelines, and dedicated review divisions would enhance efficiency. The European Medicines Agency and FDA orphan drug offices provide models for structured regulatory pathways. Establishing an Indian Orphan Drug Development Office within CDSCO with pharmaceutical scientists, clinicians, and patient representatives would streamline development and approval processes.

Pharmaceutical education and training require enhancement. Few Indian pharmacy schools offer specialized courses in orphan drug formulation, biologics manufacturing, or advanced drug delivery systems. Establishing Centers of Excellence in Orphan Drug Sciences within leading pharmaceutical institutions would build necessary expertise. Industry-academia collaboration through internships, joint research projects, and technology transfer agreements would accelerate knowledge dissemination.

RECOMMENDATIONS

For Pharmaceutical Industry:

(1) Establish dedicated orphan drug formulation units with specialized equipment for small-scale manufacturing, aseptic processing, and advanced delivery systems. (2) Invest in technology transfer for biologics and gene therapy manufacturing, leveraging existing biosimilar expertise. (3) Collaborate with academic institutions for formulation development research, utilizing Quality by Design methodologies. (4) Implement flexible manufacturing platforms enabling production of multiple orphan drugs with minimal changeover. (5) Develop patient assistance programs providing affordable access while maintaining economic sustainability.

For Regulatory Authorities:

(1) Establish a dedicated Orphan Drug Development Office within CDSCO with specialized reviewers and clear standard operating procedures. (2) Develop comprehensive guidance documents for orphan drug development covering formulation requirements, clinical trial designs, and approval pathways. (3) Implement conditional approval mechanisms for critical unmet needs with post-marketing surveillance requirements. (4) Create incentive structures including regulatory fee waivers, data exclusivity, and accelerated review timelines comparable to global standards. (5) Harmonize orphan drug definitions and approval criteria with international standards while maintaining appropriate Indian context.

For Academic and Research Institutions:

(1) Establish specialized research centers for orphan drug formulation and delivery system development with state-of-the-art analytical and manufacturing equipment. (2) Integrate orphan drug sciences into pharmacy and pharmaceutical sciences curricula including dedicated courses on rare disease therapeutics, advanced delivery systems, and regulatory frameworks. (3) Conduct natural history studies and pharmacokinetic research in Indian populations affected by rare diseases. (4) Facilitate technology transfer from research to commercial manufacturing through incubation centers and startup support. (5) Collaborate with international orphan drug research networks for knowledge exchange and joint clinical trials.

For Government and Policymakers:

(1) Expand Production Linked Incentive scheme with specific provisions for orphan drug manufacturing including higher incentive rates and dedicated allocation. (2) Establish a National Orphan Drug Manufacturing Mission with funding for technology upgradation, facility establishment, and capacity building. (3) Create risk-sharing mechanisms between government, industry, and insurance providers to manage economic uncertainties. (4) Implement strategic use of compulsory licensing provisions for critically needed orphan drugs unavailable at reasonable prices. (5) Enhance National Registry for Rare Diseases integration with pharmaceutical research and clinical trial planning. (6) Provide tax incentives and customs duty exemptions for raw materials and equipment used in orphan drug manufacturing.

CONCLUSION

Orphan drug development and delivery for rare diseases in India represents a critical pharmaceutical challenge requiring integrated solutions spanning formulation science, advanced delivery technologies, regulatory frameworks, and economic models. While significant progress has occurred through the National Policy for Rare Diseases (2021) and evolving regulatory provisions, substantial gaps persist between policy intent and ground reality. India's robust API manufacturing capacity and growing pharmaceutical expertise provide foundation for expanded orphan drug accessibility, but specialized infrastructure, technical knowledge, and sustainable economic models require development.

Advanced drug delivery systems including nanoparticles, liposomes, and gene therapy vectors offer solutions to fundamental pharmaceutical challenges in rare disease therapeutics. Successful implementation of these technologies in approved orphan drugs demonstrates feasibility, while ongoing research promises further innovation. Drug repurposing emerges as a pragmatic pathway to accelerate orphan drug availability with reduced development costs and timelines. The convergence of pharmaceutical sciences, regulatory evolution, and policy support creates unprecedented opportunities for India to emerge as a leader in affordable orphan drug development.

Achieving comprehensive orphan drug accessibility requires sustained commitment from pharmaceutical industry, regulatory authorities, academic institutions, and government. Strategic investments in specialized manufacturing infrastructure, regulatory capacity building, research and development, and innovative economic models will transform the rare disease pharmaceutical landscape. The ultimate goal extends beyond commercial considerations to a moral imperative: ensuring that patients with rare diseases have access to quality, affordable treatments as a fundamental right. Pharmaceutical innovation, coupled with enabling policies and collaborative ecosystems, can transform this aspiration into reality.

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AI DISCLOSURE STATEMENT

During the preparation of this work, the authors used the assistance of generative AI, Claude (Anthropic) on how to improve the language fluency and formatting of the original draft of the manuscript After the result provided by the AI assistant, the authors reviewed and edited the content in the final manuscript manually by themselves and take full responsibility.

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