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Critical Appraisal and Areas for Improvement of the Regulatory Environment for Orphan Drug Approval in India: A Comparative Review of the United States, European Union and Japan

Rituparna Roy

Infoclin LLP, Department of Regulatory Affairs, India

ABSTRACT

Orphan drug regulation must reconcile two competing realities: rare diseases generate severe unmet medical need, yet small and heterogeneous patient populations make conventional development, evidence generation, and commercial return unusually difficult. India has moved beyond a regulatory vacuum. The New Drugs and Clinical Trials Rules, 2019 (NDCT Rules) define an orphan drug as one intended to treat a condition affecting not more than 500,000 persons in India, permit case-specific relaxation of non-clinical and clinical data, provide accelerated approval mechanisms, waive clinical-trial application fees for orphan drugs, and now support local clinical-trial waivers for specified categories of products already approved and marketed in selected reference jurisdictions. However, these provisions remain distributed across the general new-drug framework and are not yet supported by a mature, stand-alone orphan designation and incentive architecture comparable with the United States Food and Drug Administration (FDA), European Medicines Agency (EMA), or Japan's Pharmaceuticals and Medical Devices Agency (PMDA). This paper critically appraises the Indian framework against the United States, European Union, and Japan using a structured comparative regulatory review of legislation, regulator guidance, policy documents, and recent peer-reviewed literature available through August 2026. The comparison focuses on definition and designation, development incentives, evidentiary flexibility, expedited review, regulatory reliance, market exclusivity, post-marketing obligations, and the interface between approval and patient access.

The analysis finds that India's strongest recent advances are regulatory flexibility and reliance, while the principal gaps are the absence of a formal pre-approval orphan designation pathway, limited orphan-specific scientific advice and development incentives, weak integration of registries and real-world evidence into regulatory decision-making, and insufficient linkage between approval, reimbursement, affordability, and supply. A five-domain reform model - Designate, De-risk, Decide, Detect, and Deliver (5D) - is proposed. It recommends a formal CDSCO orphan designation mechanism, early scientific advice, calibrated fiscal and non-fiscal incentives, transparent review standards, reliance and work-sharing, mandatory post-authorization evidence plans, and access-linked incentives. India should not simply replicate Western exclusivity models; rather, it should build a context-sensitive framework that rewards clinically meaningful innovation while preserving affordability, competition, and public-interest safeguards. The proposed reforms could convert India's current collection of orphan-related flexibilities into a coherent lifecycle regulatory ecosystem.

***Corresponding author**

Rituparna Roy, Infoclin LLP, Department of Regulatory Affairs, India.

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Introduction

Rare diseases are individually uncommon but collectively constitute a substantial global health burden. Their scientific and regulatory challenges arise from small patient populations, heterogeneous phenotypes, incomplete natural-history knowledge, diagnostic delay, limited validated endpoints, and difficulties conducting conventionally powered randomized controlled trials. These features increase development uncertainty and can make the commercial return on research and development less predictable than for common diseases. Consequently, many jurisdictions have adopted orphan-drug policies that combine regulatory flexibility with economic incentives to encourage development while maintaining standards for quality, safety, and efficacy [1,2].

The United States pioneered a specific orphan-drug statute through the Orphan Drug Act of 1983. The European Union followed with Regulation (EC) No 141/2000, creating a formal orphan designation process and incentives linked to designation. Japan has also developed a structured orphan designation program combining regulatory priority, development subsidies, fee reductions, and pricing incentives. Although the details differ, these three systems share a common architecture: a product may receive a formal orphan status before marketing authorization, that status unlocks identifiable benefits during development, and additional protections or incentives may apply after approval [3-5].

India's position is more nuanced than the frequently repeated statement that the country has 'no orphan-drug regulation.' The NDCT Rules, 2019 introduced an explicit orphan-drug definition and contain regulatory flexibilities relevant to rare diseases. More recent CDSCO implementation guidance also clarifies circumstances in which local clinical trials may be waived for

orphan drugs already approved and marketed in specified reference jurisdictions. In parallel, the National Policy for Rare Diseases (NPRD), 2021 addresses diagnosis, treatment support, Centres of Excellence, prevention, research, and affordability. These are important advances. Yet the drug-approval rules and the broader health-policy framework remain only partially integrated, and India still lacks a dedicated designation-and-incentive pathway analogous to those used by the FDA, EMA, and PMDA [6,7].

This distinction matters. A regulatory framework can reduce the evidentiary burden or accelerate review without necessarily improving domestic research, timely submission, manufacturing, affordability, or sustained availability. Conversely, generous incentives can stimulate development but may create high prices, strategic use of orphan designation, or prolonged market power unless incentives are carefully targeted. The central policy question for India is therefore not whether it should copy another jurisdiction, but which regulatory mechanisms can be adapted to India's epidemiology, health-system capacity, payer structure, industrial base, and equity priorities.

This paper provides an updated comparative appraisal of orphan-drug approval in India with reference to the United States, European Union, and Japan. Its principal contribution is to frame India as a system in transition: it has acquired meaningful orphan-specific flexibility but has not yet developed a complete orphan-product lifecycle architecture. The paper proposes a practical reform framework intended to improve both regulatory efficiency and patient access while avoiding uncritical transplantation of exclusivity models developed in higher-income markets.

Objectives

The primary objective is to critically compare the regulatory environment for orphan-drug development and approval in India with the United States, European Union, and Japan. The secondary objectives are to identify gaps in the Indian system across designation, incentives, evidence, review, post-marketing oversight, and access; assess which international practices are transferable to India and which require modification; and propose a phased regulatory reform model that aligns innovation incentives with affordability and public-health need.

Methods

A structured narrative comparative review was conducted. The analysis prioritized primary regulatory sources, including the Indian NDCT Rules and CDSCO clarifications, the NPRD 2021, the United States Orphan Drug Act and FDA rare-disease guidance, Regulation (EC) No 141/2000 and EMA orphan-designation materials, and PMDA/MHLW orphan-designation information. Recent peer-reviewed studies published predominantly from 2020 through August 2026 were used to contextualize regulatory performance, evidence requirements, access challenges, and policy evolution. Older landmark publications were included where needed to describe the origins or durable structure of the respective systems.

The Comparison used Eight Domains: (1) statutory or regulatory definition of rarity; (2) existence and timing of a formal orphan designation; (3) financial and administrative development incentives; (4) scientific-advice mechanisms; (5) evidentiary flexibility and expedited authorization; (6) regulatory reliance and international collaboration; (7) post-marketing evidence and lifecycle oversight; and (8) market exclusivity, reimbursement, pricing, and patient access. The review is intentionally regulatory and policy oriented rather than a meta-analysis of clinical outcomes. No human participants, individual-level data, or animal experiments were involved; therefore, ethics committee approval was not required.

Because orphan-drug policy changes rapidly, claims concerning current regulatory pathways were cross-checked against regulator materials available up to 20 August 2026. The analysis distinguishes between formal legal entitlements, regulator discretion, policy commitments, and recommendations in the academic literature. This distinction is particularly important for India, where orphan-relevant provisions are present within general new-drug rules even though a separate orphan designation statute does not exist.

Comparative Regulatory Landscape

• India

The NDCT Rules, 2019 define an orphan drug as a drug intended to treat a condition affecting not more than 500,000 persons in India. This definition is important because it creates a legal anchor for orphan-specific regulatory treatment. The Rules also allow requirements for non-clinical and clinical data to be relaxed, abbreviated, omitted, or deferred in rare diseases and other serious or unmet-need settings on a case-by-case basis. The accelerated approval provisions permit reliance on surrogate endpoints reasonably likely to predict clinical benefit and require post-marketing verification where appropriate. In serious or life-threatening conditions with unmet medical need, marketing authorization may in selected circumstances be considered on the basis of remarkable Phase II efficacy, with additional post-licensure studies required to verify benefit. Clinical-trial application fees are waived for orphan drugs under the Sixth Schedule [8,9].

A particularly significant development is India's increasing use of regulatory reliance. CDSCO's 2025 FAQ on the NDCT Rules clarifies that local clinical-trial waivers may be considered for specified categories, including orphan drugs for rare diseases, when the product is already approved and marketed in the United States, United Kingdom, Japan, Australia, Canada, or the European Union and other stipulated conditions are satisfied. These include the absence of major unexpected serious adverse events, no reasonable expectation of clinically important Indian population differences affecting pharmacokinetics, pharmacodynamics, safety, or efficacy, and an undertaking for Phase IV study where required. The same guidance allows case-specific relaxation of non-clinical and clinical data requirements for rare diseases. This shift reduces unnecessary duplication and is directionally aligned with global reliance principles.

The NPRD 2021 complements the approval framework by addressing prevention, diagnosis, treatment pathways, designated Centres of Excellence, research, data infrastructure, and financial support. Nevertheless, the NPRD is primarily a health-policy instrument rather than a marketing-authorization statute. Recent analyses note progress but continue to identify implementation gaps, fragmented epidemiological data, limited indigenous manufacturing, high treatment costs, and insufficient integration between clinical care, registries, research, and drug-development incentives [6,7].

The central structural limitation is therefore not the absence of all orphan-related provisions, but the absence of a transparent, stand-alone orphan designation process that operates early in development and automatically connects a designated product to an integrated package of scientific advice, development support,

review priority, post-approval evidence planning, and access obligations. India's current approach is largely application-stage and discretion based. Sponsors can benefit from flexibility, but they do not enter a clearly defined orphan-product pathway with predictable lifecycle milestones.

• United States

Under the United States Orphan Drug Act, a rare disease or condition generally affects fewer than 200,000 persons in the United States; an alternative economic criterion can apply when a larger affected population is not expected to permit recovery of development and availability costs. Sponsors may request orphan-drug designation before marketing approval. A designated product can receive incentives that include tax credits for qualified clinical testing, exemption from certain user fees, eligibility for orphan-product grants, and, if approved for the designated use, seven years of orphan-drug exclusivity subject to statutory exceptions [10].

The FDA model also places substantial emphasis on regulator-sponsor interaction and evidence flexibility without lowering the legal standard of approval. The 2023 final guidance on rare-disease drug development discusses the practical difficulties created by small populations, heterogeneous natural history, and endpoint limitations and encourages efficient development planning. In 2025, the FDA introduced the Rare Disease Evidence Principles for certain very small genetically defined diseases with high unmet need. Under this approach, one adequate and well-controlled study may, in appropriate circumstances, be considered together with robust confirmatory evidence such as mechanistic evidence, non-clinical models, pharmacodynamic data, natural-history information, external controls, case reports, or expanded-access data [11,12].

The strengths of the United States system are predictability of designation, strong development incentives, extensive early engagement, and multiple expedited-development tools. Its weaknesses are equally instructive for India. Orphan exclusivity can contribute to prolonged market power, and the incentives may be economically valuable even for products that later obtain broader indications. Differences between US and EU designation practice are substantial; a 2026 comparative study of rare-disease approvals found far more US approvals carrying orphan designation than corresponding EU approvals, demonstrating how apparently similar orphan systems can produce different results depending on designation criteria and interpretation [13]. Therefore, India should borrow the clarity and early engagement of the US model without automatically importing its full exclusivity structure.

• European Union

The European Union uses a prevalence criterion of not more than 5 in 10,000 persons for a life-threatening or chronically debilitating condition, with an alternative insufficient-return route for certain serious conditions. Where a satisfactory method of diagnosis, prevention, or treatment already exists, the sponsor must establish that the proposed product will provide significant benefit to affected patients. Applications are assessed by the EMA's Committee for Orphan Medicinal Products (COMP), and the European Commission grants the designation [14,15].

Designation provides a structured development environment. The EMA offers orphan-specific protocol assistance, fee reductions, and access to the centralized marketing-authorization procedure. An authorized orphan medicine generally benefits from ten years of market exclusivity for similar medicines in the same indication, with defined exceptions; the period can be extended in specified pediatric circumstances. Unlike the US system, the EU's 'significant benefit' criterion acts as a continuing filter when satisfactory treatments already exist, and orphan status is reassessed at marketing authorization [3-16].

The EU model illustrates how designation can be used as a policy gate rather than merely a prevalence label. This may better target incentives toward products that address a genuine unmet need or offer additional benefit. However, centralized regulatory approval does not guarantee homogeneous patient access because pricing and reimbursement remain influenced by national systems. The EU's evolving health-technology-assessment arrangements strengthen joint clinical assessment, but economic and reimbursement decisions remain a separate layer. This separation is relevant to India because orphan-drug policy is incomplete if it addresses approval speed but not the affordability and financing of therapy.

• Japan

Japan operates a formal orphan designation system involving the Ministry of Health, Labour and Welfare and the PMDA. Current PMDA criteria include a patient population of fewer than 50,000 in Japan or a target disease designated as an intractable disease ('Nan-byo'), serious medical need, and a feasible development organization and plan in Japan. The Japanese system connects designation to a broad bundle of incentives: financial subsidies covering up to a proportion of eligible development expenses, tax credits during the subsidy period, reduced application and consultation fees, priority review and priority consultation, additional pricing premiums, and extension of the re-examination period that functions as a form of post-approval market protection [4-17].

Japan's model is particularly relevant to India because it combines regulatory incentives with industrial and access-oriented measures rather than relying principally on exclusivity. It also requires a credible domestic development plan, creating a link between designation and local development capability. For India, an analogous requirement could be adapted to encourage local clinical participation, technology transfer, manufacturing, registry contribution, or defined supply commitments. The Japanese experience also demonstrates that orphan policy can be embedded within a national strategy to address delayed availability of globally developed medicines while still maintaining local regulatory oversight.

Table 1: Comparative Orphan-Drug Regulatory Architecture

Domain	India	United States	European Union	Japan
Rare-disease / orphan threshold	Condition affects <=500,000 persons in India	Generally <200,000 persons in the US; economic alternative also exists	<=5 in 10,000, plus seriousness and unmet need / significant benefit criteria	<50,000 persons or designated intractable disease, plus medical need and development feasibility
Formal pre-approval orphan designation	No stand-alone lifecycle designation comparable with FDA/EMA/PMDA	Yes, FDA orphan-drug designation	Yes, COMP opinion and European Commission designation	Yes, MHLW/PMDA designation
Development incentives	Clinical-trial fee waiver; case-specific evidentiary relaxation; broader policy support	Tax credits, user-fee relief, grants and regulatory support	Protocol assistance, fee reductions, centralized procedure and other incentives	Development subsidies, tax credit, fee reductions, priority consultation and pricing premium
Expedited / flexible evidence	Accelerated approval; surrogate endpoints; Phase II-based approval possible in selected serious unmet-need cases; local-trial waiver/reliance	Accelerated pathways; extensive rare-disease guidance; one trial plus confirmatory evidence possible in suitable cases	Conditional authorization and other centralized tools; orphan protocol assistance; significant-benefit requirement	Priority review/consultation; conditional approaches available in appropriate settings
Post-approval protection	No orphan-specific statutory exclusivity comparable with benchmarks	7-year orphan exclusivity after approval, subject to exceptions	10-year market exclusivity, subject to conditions/ exceptions; possible pediatric extension	Extended re-examination period / market protection
Access interface	NPRD treatment support and CoE framework, but fragmented from	Approval and payer coverage remain separate; high-price	Centralized approval but reimbursement remains	Pricing premium and national insurance system create closer regulatory-
	approval pathway	concerns	largely national	pricing linkage
Key policy strength	Recent flexibility and reliance without rigid duplication	Predictable incentives and early regulatory engagement	Strong designation discipline and significant-benefit filter	Integrated financial, regulatory and pricing incentives
Key policy gap / risk	Fragmented lifecycle architecture and uncertain sponsor incentives	Potential over-incentivization and affordability concerns	Complex designation maintenance and cross-country access differences	Domestic development and access delays can persist despite incentives

Critical Appraisal of the Indian Regulatory Environment

• Definition without a Full Designation Ecosystem

India's statutory definition is a necessary first step, but a definition and a designation are not equivalent. A designation is a regulatory decision made for a particular product and indication at a defined stage of development, normally based on rarity, medical plausibility, unmet need, and other jurisdiction-specific criteria. It can then become the gateway to benefits and obligations. In India, the orphan-drug definition identifies a category, but there is no comparably visible public register of designated candidates, no dedicated designation dossier with published decision criteria, and no systematic link between an early orphan status and later incentives. As a result, sponsors encounter flexibility mainly when seeking trial or marketing permissions rather than entering an orphan pathway early enough to shape development strategy.

The absolute threshold of 500,000 persons also deserves periodic methodological review. Cross-country evidence shows that orphan and rare-disease definitions vary substantially, and prevalence-only definitions can produce inconsistent outcomes when population sizes, disease classification, or molecular subgroups differ [2-13]. India should retain a clear numerical anchor but supplement it with seriousness, unmet need, scientific plausibility, and safeguards against artificial subdivision of common diseases into commercially advantageous rare subsets.

• Incentives are Narrower and Less Predictable

The clinical-trial fee waiver is useful but financially modest relative to the cost and uncertainty of orphan-drug development. In the United States, European Union, and Japan, incentives operate before and during development and can include tax relief, grants, fee reductions across several regulatory interactions, scientific support, priority processes, pricing premiums, or exclusivity. India's framework offers selected regulatory relief but less predictable economic de-risking. This may be especially disadvantageous to academic spinouts, biotechnology firms, and domestic small and medium-sized enterprises attempting to translate rare-disease discoveries into products.

At the same time, India's solution should not be a simple introduction of long exclusivity periods. High orphan-drug prices and fragmented access remain global concerns even in mature systems [18,19]. Any Indian incentive should be proportionate to the unmet need, scientific risk, local investment, and affordability commitment. Grants, milestone-based translational funding, tax credits, reduced scientific-advice fees, priority review, procurement assurances, and manufacturing support may often be preferable to broad post-approval exclusivity.

• Regulatory Flexibility is Advancing, but Predictability Can Improve

India's accelerated approval and data-relaxation provisions are conceptually well suited to rare diseases. The ability to consider surrogate endpoints or substantial Phase II efficacy in serious unmet-need settings acknowledges the impracticality of large conventional trials. The 2025 CDSCO clarification on local-trial

waiver is an important modernization because it recognizes that duplicating development conducted in established reference jurisdictions may delay access without proportionate scientific value.

However, case-by-case discretion without detailed orphan-specific evidentiary guidance can create uncertainty. Sponsors need clearer expectations on when single-arm trials, external controls, natural-history cohorts, Bayesian designs, adaptive methods, biomarkers, patient-reported outcomes, or real-world evidence may be acceptable. The FDA's rare-disease guidance and 2025 evidence principles illustrate the value of explaining not merely that flexibility exists but how multiple evidence streams can be assembled into a persuasive totality of evidence. India can provide similar guidance while retaining the statutory approval standard.

• Early Scientific Advice is Underdeveloped as an Orphan-Specific Tool

Rare-disease programs are highly sensitive to early design errors because patients are scarce and repeated trials may be infeasible or unethical. The EMA's protocol assistance and Japan's priority consultation explicitly reduce this risk. FDA pre-IND and rare-disease engagement also enable sponsors to resolve endpoint, dose, natural-history, manufacturing, and statistical questions before pivotal development. India provides pre- and post-submission meetings under its general framework, but there is a strong case for a dedicated orphan scientific-advice channel with multidisciplinary expertise in genetics, pediatrics, advanced therapies, biostatistics, patient-reported outcomes, and real-world evidence.

• Registry and Real-World Evidence Infrastructure is not yet Fully Regulatory

India has important rare-disease registry and Centre of Excellence initiatives, but the regulatory use of these assets is not yet fully institutionalized. Natural-history data can support endpoint selection, external control construction, prevalence estimation, post-authorization safety monitoring, and reassessment of effectiveness. This is particularly valuable in diseases where randomized trials are very small or infeasible. A national regulator-facing data model should therefore link the ICMR rare-disease registry, CoEs, accredited genetic laboratories, product-specific registries, and pharmacovigilance systems under common data standards and governance.

The goal should not be to replace randomized evidence indiscriminately. Rather, real-world evidence should be graded according to data provenance, completeness, comparability, outcome validity, and risk of bias. Post-authorization obligations should be stronger when pre-approval evidence is more uncertain. This creates a defensible regulatory bargain: greater pre-market flexibility in exchange for more rigorous lifecycle evidence generation.

• Approval Remains Insufficiently Linked to Access

The most important policy weakness is the distance between regulatory authorization and real-world availability. An orphan drug may be approved rapidly and still remain inaccessible because of price, import dependence, limited diagnosis, fragmented reimbursement, or weak supply. The global literature repeatedly shows that regulatory incentives can increase approvals without guaranteeing equitable access [1-18]. India's NPRD partially addresses treatment financing and infrastructure, but the approval process is not systematically connected to health-technology assessment, managed entry, negotiated procurement, outcomes-based reimbursement, domestic manufacturing, or explicit supply commitments.

This gap is particularly consequential for advanced therapies and enzyme-replacement products whose acquisition costs can exceed conventional public financing. Approval policy and access policy should remain institutionally distinct enough to preserve scientific independence, yet operationally coordinated so that evidence requirements, price negotiations, registry collection, and post-market commitments reinforce each other rather than operate in separate silos.

Gap Analysis: India Versus International Benchmarks

Gap in India	Why it matters	Relevant benchmark	Priority response
No formal product-specific orphan designation pathway	Sponsors lack an early, predictable gateway to benefits and obligations	FDA designation; EMA COMP; PMDA/MHLW designation	Create CDSCO orphan designation with public criteria and register
Limited orphan-specific scientific advice	Small populations make development errors costly and sometimes irreversible	EMA protocol assistance; FDA rare-disease meetings; PMDA priority consultation	Establish multidisciplinary orphan scientific-advice meetings and written advice
Narrow development incentives	Fee waiver alone may not offset scientific and commercial risk	US tax credit/grants; Japan subsidies; EU fee reductions	Use milestone grants, tax credits, reduced fees, domestic R&D/ manufacturing support
Flexible evidence but limited operational guidance	Discretion can lead to uncertainty across review teams and sponsors	FDA rare-disease guidance and evidence principles	Publish guidance on external controls, natural history, RWE, adaptive designs and surrogate endpoints
Reliance exists but is not yet a complete work-sharing model	Sequential national submissions can still create avoidable delay	International parallel scientific advice and collaborative review models	Expand reliance, joint scientific advice and work-sharing for rare-disease dossiers
Registry-policy-regulator linkage is incomplete	Post-approval uncertainty is high in small populations	Lifecycle RWE and registries increasingly used by FDA/EMA/ PMDA	Create product-linked national rare-disease registries and common data standards
No orphan-specific market-access compact	Approval may not translate into affordable and sustained supply	Japan pricing linkage; EU HTA evolution; managed entry internationally	Link selected incentives to launch, supply, price/access commitments and outcomes data

No calibrated exclusivity framework	Lack of incentive may deter development, but broad exclusivity could harm affordability	US 7-year; EU 10-year; Japan re-examination protection	Prefer non-exclusivity incentives first; if exclusivity is used, make it conditional and public-interest sensitive

Proposed Reform Framework for India: The 5D Model

A useful Indian reform strategy should be comprehensive enough to influence development behavior but restrained enough to protect affordability and competition. The proposed 5D framework organizes reform into five linked functions: Designate, De-risk, Decide, Detect, and Deliver. It is intended as a policy architecture rather than a new legal definition of an orphan drug.

Designate: Create a Formal CDSCO Orphan-Drug Designation

India should establish a product- and indication-specific orphan designation that can be requested before pivotal development. The application should include prevalence evidence, disease seriousness, medical plausibility, current treatment landscape, unmet need, anticipated benefit, and a development plan. A dedicated multidisciplinary Orphan Products Committee or Rare Disease Regulatory Cell within CDSCO could issue time-bound decisions and maintain a public register of active, withdrawn, and approved designations.

The designation criteria should combine the existing numerical threshold with qualitative safeguards. Where adequate therapy exists, India could adopt a modified significant-benefit concept to ensure that scarce incentives are directed toward products expected to provide clinically meaningful advantage, improved safety, major convenience, or access improvement. To prevent strategic disease subdivision, sponsors should justify why a proposed rare subset is medically distinct rather than commercially constructed.

De-Risk: Strengthen Development Support Before Submission

The principal objective of incentives should be to reduce scientifically necessary risk, not simply increase post-approval revenue. India should expand the current clinical-trial fee waiver into an orphan development package including reduced or waived fees for scientific advice and selected regulatory applications, competitive translational grants, tax credits for qualified domestic rare-disease research, support for natural-history studies, and grants to academic or SME developers. Incentives should be tiered by unmet need, population size, novelty, public-health value, and domestic development contribution.

A formal early scientific-advice program should be central to this package. Written advice should address trial design, endpoint acceptability, external controls, biomarker qualification, pharmacometric modeling, pediatric plans, CMC strategy for small-batch or gene/cell therapies, and post-approval evidence. Joint meetings with HTA or public-payer experts could be offered when a product is likely to require managed entry, thereby reducing the risk that the regulator approves on an endpoint that later proves unusable for reimbursement decisions.

• Decide: Make Review Faster, More Transparent and Internationally Connected

India should retain its emerging reliance approach and convert it into a transparent rare-disease reliance policy. Dossiers approved by trusted reference regulators could be reviewed using abridged or verification pathways when scientific prerequisites are met. The pathway should specify what remains India-specific: benefit-risk relevance to Indian patients, pharmacogenomic differences where plausible, local disease epidemiology, CMC/site considerations, pharmacovigilance, and access planning. Reliance should mean intelligent use of trusted assessments, not automatic recognition. The regulator should publish indicative review clocks for orphan designation, scientific advice, clinical-trial authorization, and marketing applications. Sponsors should be able to request priority review when the disease is serious, lacks adequate therapy, and the product is expected to offer material benefit. Parallel or rolling review may be appropriate for products with compelling early evidence or advanced therapies, provided CMC and safety requirements remain robust.

India should also support multinational rare-disease trials at the earliest feasible stage. Recent cross-regional analysis found that many orphan products rely on similar evidence packages across regulators but still experience multi-year gaps between first and later approvals, suggesting that collaborative development and work-sharing could reduce avoidable delay [20]. Participation in global protocols also improves the relevance of evidence to Indian patients and reduces dependence on post hoc local bridging.

• Detect: Institutionalize Lifecycle Evidence and Pharmacovigilance

Accelerated or evidence-flexible approval should be paired with enforceable post-authorization obligations. Each orphan approval should have a proportionate Rare Disease Evidence Plan defining confirmatory studies, registry participation, pharmacovigilance, long-term follow-up where relevant, and timelines for reporting. For gene therapies and other durable interventions, long-term safety and effectiveness monitoring may extend for years. Failure to complete critical commitments should trigger escalating regulatory responses, including labeling changes, restrictions, financial penalties where legally available, or reconsideration of conditional benefits.

The national registry infrastructure should be redesigned for regulatory usability. Core datasets should include diagnosis/genotype, baseline disease severity, prior treatment, exposure, key clinical outcomes, patient-reported outcomes, safety events, treatment discontinuation, and mortality where relevant. Data standards should enable linkage with CoEs, pharmacovigilance, payer data, and product registries while maintaining privacy and governance. This would also strengthen India's epidemiological estimates, which are essential for designation and resource planning.

Deliver: Connect Incentives to Affordability, Supply and Meaningful Patient Access

India should treat patient access as the final stage of orphan regulation rather than an unrelated post-approval problem. Products receiving enhanced public incentives could be required to submit an India access plan covering expected launch timing, supply continuity, patient-support arrangements, proposed price or financing strategy, technology transfer or local manufacturing where feasible, and registry participation. The access plan should not determine scientific approval, but it should influence eligibility for optional incentives beyond core regulatory flexibility.

If India introduces orphan market exclusivity, it should be narrower and more conditional than the US or EU models. Possible

conditions include timely commercial launch, adequate supply, adherence to agreed access measures, disclosure of public R&D support, and exceptions for clinically superior products, shortages, public-health emergencies, or failure to supply. An alternative is to avoid broad exclusivity and instead offer time-limited procurement preference, outcome-linked price premiums, milestone payments, or manufacturing incentives. Such mechanisms may better fit a price-sensitive health system with substantial out-of-pocket expenditure.

Phased Implementation Roadmap

Phase	Key regulatory actions	Expected output	Safeguards / metrics
0-2 years: Foundation	Issue orphan designation guidance; create CDSCO Rare Disease Regulatory Cell; publish public register; formalize early advice; standardize Rule 101 reliance for orphan drugs; define post-approval evidence templates	Predictable entry point and consistent review practice	Decision timelines; public reasons for designation; number of early advice meetings; waiver and review turnaround times
2-5 years: Integration	Link ICMR/CoE registries to regulatory RWE; introduce grants/tax incentives; build joint regulator-payer scientific advice; expand global trial participation and work-sharing	Stronger domestic R&D and evidence ecosystem	Registry completeness; Indian participation in global trials; percentage of approvals with lifecycle evidence plans; domestic R&D investment
5+ years: Maturity	Evaluate conditional exclusivity or alternative market incentives; institutionalize outcomes-based managed entry; expand international collaborative review; periodic framework evaluation	Lifecycle orphan-drug ecosystem linking innovation, approval, safety and access	Time from global first approval to India; launch delay; affordability indicators; supply continuity; completion of post-marketing commitments

Discussion

The comparative evidence suggests that orphan-drug regulation works best when it is treated as a lifecycle system rather than an expedited marketing-authorization exception. The United States demonstrates the innovation-stimulating effect of explicit designation and strong incentives. The European Union demonstrates the value of a significant-benefit filter, specialized scientific advice, and centralized authorization. Japan demonstrates the potential of combining subsidies, priority review, consultation, and pricing incentives. India has already incorporated a number of technically important flexibilities, particularly through the NDCT Rules and recent reliance guidance. The policy opportunity is therefore to organize and deepen existing tools rather than build an entirely new system from zero.

The first principle of reform should be predictability. Rare-disease developers need to know early whether a product qualifies, what evidence is expected, what data may be deferred, what foreign assessments will be relied upon, and what post-approval obligations will follow. Predictability does not require rigidity. In rare diseases, rigid evidentiary templates can be scientifically inappropriate; the regulator should instead make the basis of flexibility transparent and reproducible across review teams.

The second principle should be proportionality. The evidentiary burden should reflect disease severity, unmet need, treatment effect, feasibility of conventional trials, reversibility of harm, and uncertainty. A fatal childhood disease with a well-understood genetic mechanism and no therapy should not necessarily be regulated through the same clinical-development assumptions as a slowly progressive rare condition with several available treatments. Equally, a prevalence threshold alone should not entitle every product to the same incentives. Tiering incentives according to unmet need and expected public value can preserve both innovation and stewardship.

The third principle should be reciprocity between flexibility and evidence generation. When approval is granted with smaller datasets, surrogate endpoints, external controls, or substantial uncertainty, the sponsor should accept stronger post-marketing responsibilities. Regulators should define in advance what confirmatory evidence is needed and by when. This approach is consistent with the broader evolution of rare-disease regulation toward integrated evidence, including natural-history data, mechanistic evidence, and real-world sources [12-20].

The fourth principle should be accessing conditionality. Mature orphan-drug systems show that stimulating approval alone can increase the number of available products while leaving major affordability problems unresolved. Brown found that regulatory evolution has expanded rare-disease medicine approvals, yet market access remains fragmented [18]. Economic evaluations are also difficult because rare diseases often lack reliable long-term effectiveness, quality-of-life, cost, and natural-history data [19]. India therefore has a strong rationale for coordinating regulatory evidence with HTA and financing evidence from an early stage.

Finally, harmonization should be pragmatic rather than formalistic. Full convergence of orphan definitions across countries is unlikely and may not be desirable because population size, disease epidemiology, and health-system priorities differ. However, harmonizing evidence standards, data formats, core outcome sets, natural-history methods, CMC expectations, and post-marketing datasets can reduce duplicated work. India's 2025 clarification permitting reliance on approvals from specified jurisdictions is already an important step in this direction. The next step is to move from isolated waiver decisions toward structured reliance and collaborative review [21,22].

Policy and Regulatory Implications

For CDSCO, the immediate implication is the need to convert orphan-related provisions dispersed across general new-drug regulation into a clearly identifiable pathway with an accountable organizational home. A dedicated cell would improve consistency, preserve institutional knowledge, and create a focal point for interaction with ICMR, the Department of Biotechnology, Centres of Excellence, patient groups, and international regulators.

For the Government of India, orphan-drug regulation should be coordinated with industrial and health-financing policy. Public

R&D support, production-linked incentives where appropriate, technology transfer, procurement, rare-disease registries, and treatment funding should be designed around a common set of priority conditions and outcomes. Support for indigenous development is especially important because reliance on imported high-cost medicines can create recurrent access vulnerability.

For sponsors, a more structured framework would reduce uncertainty but also increase accountability. Developers benefiting from expedited review or public incentives should expect high standards for transparency, post-marketing evidence, supply continuity, and patient access. For patients and clinicians, a public orphan designation and approval database could improve transparency about development status, pending studies, approved indications, safety commitments, and access pathways.

Limitations

This paper is a structured narrative regulatory review rather than a systematic review or meta-analysis. Regulatory systems evolve continuously, and implementation can differ from written rules or guidance. Direct comparison of prevalence thresholds is also imperfect because the jurisdictions use different population sizes and qualitative criteria. The paper focuses on human medicinal products and does not comprehensively assess medical devices, diagnostics, compassionate-use mechanisms, intellectual-property law, or disease-specific reimbursement programs. Pricing and access systems are summarized only to the extent necessary to explain the regulatory-access interface. Future empirical work should quantify orphan application volumes, review times, waiver use, approval lag, post-marketing completion, launch timing, and patient access in India.

Conclusion

India has established a meaningful foundation for orphan-drug regulation. The NDCT Rules provide an explicit orphan definition, fee relief for orphan clinical trials, accelerated approval, evidence flexibility, and a basis for reduced local data requirements. Recent CDSCO guidance on local clinical-trial waivers for orphan drugs approved in specified reference jurisdictions further strengthens regulatory reliance. These developments make it inaccurate to describe India as having no orphan-drug regulatory pathway.

The remaining problem is architectural. India does not yet have a mature, stand-alone orphan designation ecosystem that systematically connects early scientific advice, development incentives, expedited and reliance-based review, post-marketing evidence, and patient access. The FDA, EMA, and PMDA provide different but complementary lessons: the United States offers predictable designation and strong incentives; the European Union offers a disciplined significant-benefit framework and protocol assistance; and Japan integrates subsidies, consultation, priority review, and pricing incentives.

A context-specific Indian framework should combine these strengths while avoiding excessive exclusivity and affordability risks. The proposed 5D model - Designate, De-risk, Decide, Detect, and Deliver - offers a practical route from the current collection of regulatory flexibilities to a coherent lifecycle system. The objective should not merely be faster approval. It should be timely development of scientifically credible therapies, proportionate management of uncertainty, sustainable domestic participation, and reliable patient access. That balance is the central regulatory challenge for the next phase of orphan-drug policy in India.

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