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Global Justice and Access to Orphan Drugs: A Bioethical Analysis

Giulia Benitez^{1*}, Agnieszka Ferraro² and Sylvie Eberhardt³

¹Division of Clinical Ethics, Nordfjord University Center for Health Ethics, Norway

²Institute for Health Policy and Ethics, Danube University Center for Medical Law and Ethics, Hungary

³Institute for Health Policy and Ethics, Nordfjord University Center for Health Ethics, Norway

ABSTRACT

Orphan drug policy was designed to correct a market failure -- pharmaceutical firms had little commercial incentive to develop treatments for very small patient populations -- by offering regulatory exclusivity, tax incentives, and expedited review.

Four decades on, the policy has produced hundreds of approved treatments but has not closed, and arguably has widened, the gap between drug approval and actual patient access, particularly outside a small number of wealthy jurisdictions.

This analysis examines the ethical architecture of orphan drug incentives, the health-technology-assessment and pricing mechanisms that mediate access once a drug reaches the market, the documented scale of disparity between high-income and low- and middle-income countries, and the particular affordability challenge posed by curative but extraordinarily expensive gene therapies.

We argue that the accident of being born with a rare disease and the accident of being born in a country without a functioning reimbursement pathway compound in ways that a global-justice framework should treat as morally arbitrary rather than acceptable.

We conclude by reviewing proposals -- pooled procurement, dedicated multilateral financing, price transparency, and equity-by-design manufacturing -- that treat global access, not domestic approval alone, as the relevant measure of policy success.

Keywords: orphan drugs; global justice; health technology assessment; rare diseases; drug pricing

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Corresponding Author: Giulia Benitez

E-mail Address: g.benitez@nuche.no

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INTRODUCTION

A drug that costs two million dollars for a single dose

is, on the numbers alone, an odd thing to call a triumph of medicine. Yet that is roughly the sticker price of some of the gene therapies now approved for

rare genetic disorders, and defenders of the price point insist it reflects a genuine achievement: a disease that had no treatment at all now has one [1]. The tension in that sentence is the subject of this article. Orphan drug policy was built, beginning with the US Orphan Drug Act of 1983 and later mirrored in the EU, Japan, and elsewhere, to solve a real market failure -- pharmaceutical firms had little commercial reason to develop treatments for diseases affecting only a few thousand patients worldwide -- by offering market exclusivity, tax credits, and expedited review in exchange for taking on that development risk [2]. Four decades on, the policy has unambiguously worked as an innovation lever: hundreds of orphan drugs have reached approval that almost certainly would not exist otherwise. What it has not done, and arguably was never designed to do, is guarantee that the patients the policy was meant to serve can actually obtain the resulting treatment.

That gap between approval and access is where the bioethical questions concentrate, and they are not confined to any one country's pricing dispute. A treatment approved by a stringent regulator in the United States, the European Union, or Japan may sit entirely outside the reach of health systems in the majority of the world's countries, not because the biology of the disease differs but because the reimbursement and health-technology-assessment machinery in most jurisdictions was never built to accommodate a therapy priced for a market of a few hundred patients [3]. This article surveys the ethical architecture of orphan drug policy, the pricing and health-technology-assessment mechanisms that mediate access once a drug is approved, the empirical scale of global disparity, the particular problem posed by curative but extraordinarily expensive gene therapies, and the proposals now circulating for making the whole system more defensible in distributive-justice terms. Table 1 and Figure 1 summarize, respectively, how access mechanisms differ by income setting and how far apart the resulting access levels tend to be.

THE ECONOMICS OF ORPHAN DRUG DEVELOPMENT AND THE INCENTIVE BARGAIN

The ethical case for orphan drug incentives rests on a fairly narrow argument: without some artificial correction, a purely market-driven pharmaceutical industry would systematically underinvest in treatments for small patient populations, because the fixed costs of drug development do not scale down with the number of patients who will eventually use the product [4]. Regulatory exclusivity and tax incentives are, in this framing, not gifts to industry but a deliberate distortion of the market that corrects for a distributive failure the market would otherwise produce on its own. Analyses of the original Orphan Drug Act generally credit it with a substantial increase in rare-disease drug

development relative to the pre-1983 baseline, and more recent reassessments still treat the basic incentive logic as sound even as they flag problems with how it now operates in practice [5].

The trouble is that the incentive bargain has drifted from its original terms. Critics note that orphan designation has increasingly been used to carve out narrow, commercially convenient sub-populations of otherwise common diseases, capturing the tax and exclusivity benefits meant for genuinely rare conditions, and that market exclusivity, once granted, gives manufacturers pricing power with essentially no competitive check for the life of the exclusivity period [6]. A 2015 discussion in the *AMA Journal of Ethics* framed the resulting policy dilemma plainly: the same regulatory tools that make orphan drug development commercially viable in the first place are also the tools that make the resulting prices very difficult to challenge [4]. Ethical evaluation of the Orphan Drug Act model, in other words, cannot stop at whether it produces new drugs; it has to ask whether the exclusivity and pricing power granted to secure that production remain proportionate to the risk actually taken on, a question a systematic review of the ethical literature identified as one of the field's least settled [7].

PRICING, HEALTH TECHNOLOGY ASSESSMENT, AND THE LIMITS OF COST-EFFECTIVENESS

Once an orphan drug reaches the market, the next gatekeeper is the health-technology-assessment apparatus that most high- and middle-income health systems use to decide what to reimburse. Standard cost-effectiveness thresholds, built around a fixed cost per quality-adjusted life year, were designed for interventions serving large populations where the health system's overall budget impact and comparative value are reasonably legible. Orphan drugs routinely fail these thresholds by wide margins, sometimes by an order of magnitude, which has forced HTA bodies across many countries to construct separate, more permissive evaluation tracks specifically for rare-disease treatments [8]. A scoping review of these adapted HTA criteria found substantial variation across public healthcare systems in how far countries are willing to bend standard cost-effectiveness rules for orphan drugs, and no clear consensus on how much special treatment is ethically warranted before it starts crowding out other health priorities.

The result is a genuinely difficult opportunity-cost problem rather than a simple villain narrative. A national formulary that reimburses one ultra-rare gene therapy at several million dollars per patient is, by definition, choosing not to fund some other set of interventions with that same money, and the health gains foregone from that displaced spending are real even though they are diffuse and hard to attribute to any single decision [9]. Proposed reforms include

outcomes-based and installment payment arrangements that spread cost over years and tie payment to demonstrated durability of clinical benefit, pooled or cross-border procurement to increase negotiating leverage for very small national markets, and dedicated financing vehicles -- one recent proposal is a European fund specifically for genomic orphan therapies, financed collectively rather than negotiated market-by-market -- intended to separate the price a system pays from the price a single small country can be made to accept in isolation [10]. Reviews of international pricing and reimbursement strategy generally converge on the same conclusion: transparency about actual net prices, which are often obscured by confidential rebates, is a prerequisite for any of these reforms working as intended, not an optional add-on [11].

GLOBAL DISPARITIES IN ACCESS:
HIGH-INCOME VERSUS LOW- AND
MIDDLE-INCOME COUNTRIES

The HTA debate above describes a genuine dilemma even within wealthy health systems. It becomes a starker justice problem once the comparison shifts to low- and middle-income countries, most of which have neither a dedicated orphan-drug reimbursement track nor the fiscal capacity to seriously consider one. A global policy review covering 194 countries and six territories found that formal orphan drug policies, legal definitions of rare disease, and dedicated reimbursement pathways are heavily concentrated in high-income regions, leaving the large majority of the world's population with rare diseases facing not merely high prices but the near-total absence of any policy mechanism through which access could even be considered [3]. A companion analysis comparing orphan drug list prices across income tiers found that, contrary to a simple ability-to-pay adjustment, prices in lower-income markets are often not meaningfully discounted relative to high-income benchmarks, undermining the assumption that manufacturers voluntarily tier prices to local purchasing power [12].

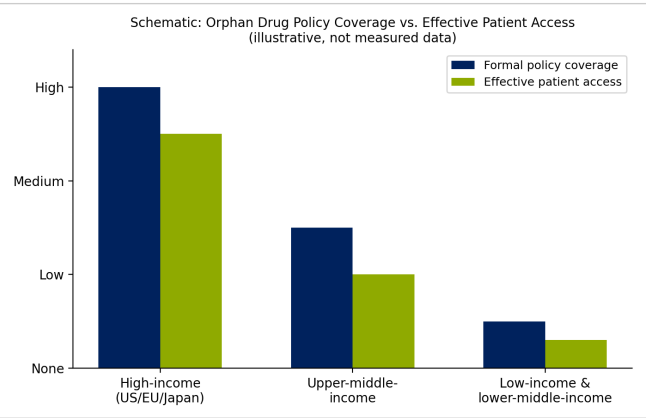
Recent policy commentary has described this as a widening rather than narrowing gap: as more countries adopt formal orphan-drug frameworks, the distance between the small set of jurisdictions with functioning access pathways and the much larger set without one becomes more visible rather than less, simply because there is now something concrete to be excluded from [13]. The World Health Organization's own essential medicines apparatus illustrates the structural mismatch: a recent analysis of the WHO Model List of Essential Medicines found that only a small fraction of approved orphan drugs have ever been proposed for inclusion, in part because the list's evaluation criteria -- built around affordability and public-health impact at population scale -- do not map cleanly onto ultra-rare, ultra-expensive therapies, even when those therapies are clinically transformative for the individual patient

[14]. An older but still-cited analysis argued for a broader conception of "essential" that would not automatically exclude rare-disease treatments from national medicines lists on cost grounds alone, though that argument has had limited practical uptake two decades on [15]. Patient advocacy organizations working across jurisdictions have made global access, rather than approval in any single wealthy market, their explicit organizing goal, precisely because approval in the United States or the European Union does close to nothing for a patient in a country without a corresponding reimbursement mechanism [16].

Table 1. Orphan drug access mechanisms and typical patient-facing barriers, compared across income settings.

Setting	Regulatory/incentive framework	Typical reimbursement pathway	Main access barrier
High-income (e.g. US, EU, Japan)	Formal orphan designation with exclusivity, tax credits, expedited review	Dedicated HTA track with relaxed cost-effectiveness thresholds; managed-entry agreements	High list price even where reimbursed; opportunity cost to other health spending
Upper-middle-income	Partial or emerging orphan drug legislation in some jurisdictions	Case-by-case reimbursement decisions; limited dedicated rare-disease budget lines	Absence of a standing evaluation pathway; long delays between approval and any funding decision
Low-income and many lower-middle-income	Largely no formal orphan drug definition or incentive framework	No dedicated pathway; orphan drugs rarely appear on national essential medicines lists	Drug effectively unavailable through the public health system regardless of price

Figure 1. Schematic comparison of relative orphan drug access across income settings on illustrative Low/Medium/High scales for policy coverage, reimbursement likelihood, and effective patient access. Illustrative only, intended to convey the general pattern described in the policy literature rather than measured data from a single study.



GENE THERAPIES AND THE NEW FRONTIER OF UNAFFORDABILITY

Gene and cell therapies for rare monogenic diseases sharpen every issue discussed so far, because they are frequently curative or near-curative in a single administration rather than chronic treatments paid for over years, which changes the ethical shape of the pricing argument without necessarily making it easier to resolve. Manufacturers argue that a one-time price in the low millions of dollars can still be cost-effective relative to a lifetime of chronic disease management, hospitalization, and lost productivity, and that comparing the sticker price to conventional drug pricing benchmarks understates the value delivered [17]. Critics respond that "value-based" framing does not resolve the affordability problem for any health system that has to pay the price up front, in a single budget cycle, regardless of how the value is theoretically amortized over a patient's remaining lifetime, and that this liquidity mismatch is precisely what has driven interest in installment and outcomes-based payment models [1].

A recent overview of therapeutic and translational challenges in orphan drug development argued that global health equity considerations need to be built into gene therapy development pipelines from an early stage -- manufacturing scalability, technology transfer, and pricing strategy for lower-resource settings -- rather than treated as an afterthought once a therapy has already been optimized for approval in a small number of wealthy reference markets [18]. Whether that kind of equity-by-design approach is commercially realistic, given how orphan drug economics currently work, remains genuinely contested, and it is arguably the sharpest open question in the entire field: gene therapy has demonstrated that some rare diseases can be effectively cured, but the same technology has also produced the most extreme test yet of whether a market-incentive model built in the 1980s can deliver that cure to more than a small fraction of the patients who have it.

TOWARD FAIRER GLOBAL GOVERNANCE OF ORPHAN DRUG ACCESS

No single reform proposed in the literature resolves the distributive problem on its own, but several converge on a common structural insight: national-level negotiation, drug by drug and country by country, systematically disadvantages any health system too small or too poor to extract meaningful concessions from a manufacturer holding an effective monopoly. Pooled procurement across smaller or lower-income countries, dedicated multilateral financing mechanisms for the highest-cost therapies, and mandatory price transparency requirements all aim at the same target -- shifting negotiating leverage away from the single-country, single-drug bargaining table where it currently sits overwhelmingly in the manufacturer's favor [9] [10]. A comparative review of orphan drug

reimbursement systems across twelve Eurasian countries with widely varying income levels found that the countries with the most functional access pathways were not necessarily the wealthiest, but those that had built explicit, rules-based rare-disease policies rather than handling each orphan drug as an ad hoc exception to standard HTA processes [19].

From a bioethical standpoint, the case for treating orphan drug access as a matter of global rather than purely national justice rests on a fairly simple observation: the accident of being born with a rare genetic disease is not distributed any differently across countries than the accident of being born in a country too poor to fund the resulting treatment, and neither accident is one a person can be held responsible for. A policy architecture that lets both accidents compound -- rare disease and poor-country birth -- produces an access gradient that tracks national wealth far more than it tracks medical need, which is precisely the pattern a global-justice framework asks us to treat as morally arbitrary and therefore in need of correction rather than acceptance [7]. Health technology assessment reform, pooled financing, and manufacturing equity-by-design are not, on their own, sufficient to close that gradient, but the recent literature surveyed here suggests they are the plausible starting points available, given that abandoning the underlying incentive structure that produces these drugs in the first place is not a serious option either [4].

CONCLUSION

The orphan drug incentive model has done what it was built to do: it has turned diseases that pharmaceutical markets would otherwise have ignored into diseases with approved, sometimes curative, treatments. What it was never built to do, and what four decades of policy patching has not fixed, is ensure that approval translates into access anywhere near evenly across the roughly three hundred million people worldwide estimated to live with a rare disease. The gap is starkest at the extremes -- ultra-expensive gene therapies approved in a handful of wealthy jurisdictions and functionally unavailable everywhere else -- but it runs through the entire system, from health-technology-assessment thresholds that were never designed for ultra-rare conditions to essential-medicines frameworks that still struggle to accommodate them. Closing that gap will require treating global access, not just domestic approval, as the measure of whether orphan drug policy is actually succeeding, and it will require pricing and financing mechanisms built for that purpose rather than retrofitted onto a system designed around a different, narrower problem.

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Conflict of Interest

The authors declare no conflicts of interest relevant to this work.

Author Contributions

Giulia Benitez conceived the analysis and drafted the initial manuscript. Agnieszka Ferraro performed the literature synthesis on pricing, health technology assessment, and global access disparities and critically revised the manuscript. Sylvie Eberhardt contributed the sections on gene therapy affordability and global governance reform and provided final approval of the submitted version. All authors read and approved the final manuscript.

Ethics Statement

As a literature review and policy analysis synthesizing previously published, publicly available research, this article did not involve new data collection from human participants and did not require institutional ethics committee approval.

Data Availability

No new data were generated or analyzed for this review. All sources discussed are cited in the reference list and are publicly available through their respective publishers.

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