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EVOLVING REGULATORY POLICIES FOR ORPHAN DRUGS POST-COVID-19: UK AND INDIAN PERSPECTIVES

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ABSTRACT

Background: Globally, rare diseases affect around 300 million people, but most of these disorders lack approved treatments. Orphan drugs - pharmaceuticals for rare diseases - represent a special category of drugs, balancing the profit disincentive with the compelling need. The COVID-19 pandemic (2019-2023) has ushered in an era of "warp-speed" regulatory science, with global adoption of rolling reviews, adaptive licensing, real-world evidence models and emergency use authorisations. This has seen significant regulatory changes in both the United Kingdom (post-Brexit Medicines and Healthcare products Regulatory Agency, MHRA) and India (Central Drugs Standard Control Organisation, CDSCO).

Aim: This article offers an in-depth comparative assessment of emerging orphan drug regulatory policies in the UK and India in the post-COVID-19 years (2020-24). It reviews specialised pathways, incentives, health technology assessment (HTA) integration, equitable access and institutionalisation of pandemic regulatory innovations to rare diseases.

Methods: We undertook a comparative policy analysis by way of a documentary review. It utilised data from MHRA and CDSCO open-access databases (2020-2024), India's National Policy for Rare Diseases 2021, WHO technical reports, UK Rare Diseases Framework action plans (2022-2024) and peer-reviewed publications identified by PubMed and Scopus.

Key Findings: Post-Brexit regulatory autonomy in the UK has enabled the development of the Innovative Licensing and Access Pathway (ILAP) and refined Orphan Medicinal Product (OMP) designation process, incorporating genomic medicine in genomics England's 100,000 Genomes Project. India's National Policy for Rare Diseases 2021 is a conceptual

leap but lacks implementation with key flaws in funding (₹50 lakh cap), Centre of Excellence (CoE) infrastructure and orphan drug legislation. COVID-19 showed rolling reviews and real-world evidence can shorten development by 30-60%, but these approaches have been irregularly institutionalised for rare diseases in both countries.

Conclusion: The regulatory focus is on both countries. India needs a Rare Diseases Act, insurance mandate and CoE investment. The UK needs to resolve late NHS funding of MHRA-approved drugs. Capacity building for regulatory cooperation between the MHRA and CDSCO via a memorandum of understanding (MoU) presents a huge opportunity to minimise waste and benefit rare disease patients in both jurisdictions.

Keywords: Orphan drug, Rare diseases, MHRA, CDSCO, Regulatory reform post-COVID, Expedited; ILAP, National Policy for Rare Diseases, Real-world evidence, Gene therapy regulation

1 INTRODUCTION

1.1 Overview of Rare Diseases and Orphan Drugs

Rare diseases - also known as "orphan diseases" - are a heterogeneous group of mostly genetic, debilitating, and life-threatening diseases that individually affect small numbers of people, but have a considerable public health impact. Regulatory criteria for rarity differ between countries: a disease is defined as rare in the European Union if it affects fewer than 5 in 10,000 people; in the United States, it is fewer than 200,000 people; and in the proposed Indian law, defined under the National Policy for Rare Diseases 2021, it is fewer than 1 in 2,500 people. [1,2]

Despite differences in criteria, the global epidemiology of rare diseases is significant. There are 7,000-8,000 known rare diseases that affect an estimated 300 million people (4% of the world's population). [3] 70-80% of rare diseases are genetic and 50% of these are present at birth. The average patient delay for rare diseases is 4-6 years and visits with an average of seven doctors. [4] These diseases have a significant human, social, and economic burden.

Orphan drugs are medicines that are designed for the prevention, diagnosis or treatment of rare diseases. The term "orphan" historically originated from the lack of commercial interest in these drugs; low patient numbers make traditional drug development economically unsustainable under normal market circumstances. Pharmaceutical companies have historically lacked incentives to invest the costly time and resources for drug discovery, clinical testing and regulatory approval for diseases affecting tens of thousands of patients world-wide. [5]

1.2 Historical Regulatory Milestones

The orphan drug regulatory framework has developed in response to patient advocacy and the recognition by lawmakers that market failure needs to be addressed. The US Orphan Drug Act (ODA) of 1983 was the first comprehensive policy response worldwide, providing tax credits for orphan drug research and trial costs, seven years of market exclusivity and expedited review. This law is considered a breakthrough: from 1983 to 2023, the US Food and Drug Administration (FDA) approved over 1,000 orphan drugs (compared with less than 10 in the decade before the ODA). [6]

This was followed in the European Union (EU) by Regulation (EC) No. 141/2000 on orphan medicinal products, which established the Committee for Orphan Medicinal Products (COMP) at the European Medicines Agency (EMA). The EU regime provided ten years of market exclusivity, protocol design support, reduced fees (with a 50% reduction for small and medium enterprises, and a 100% reduction for certain applicants), and scientific advice. Japan followed in 2015 with the SAKIGAKE designation, which prioritises first-in-class products for serious conditions and offers priority review and consulting services. [7]

In contrast, India's orphan drug policy journey has been far more protracted. India lacked orphan drug law for decades, with orphan drug provisions falling within the Drugs and Cosmetics Act 1940 and, since 2019, the New Drugs and Clinical Trials (NDCT) Rules. The NDCT Rules 2019 defined an orphan drug (used by fewer than 500,000 patients in India) under Rule 3(b) and its benefits, but lacking a policy framework. Draft National Policy for Rare Diseases (2017) was not implemented, and it was not until 2021 that India published its new National Policy for Rare Diseases (NPRD 2021). [8]

1.3 COVID-19 as a Regulatory Inflection Point

The coronavirus pandemic was an unprecedented test for international regulatory regimes. In the wake of an unprecedented and rapidly evolving pandemic, regulatory authorities across the globe activated and honed a series of accelerated tools that had previously been confined in scope or in theory. The United States Food and Drug Administration's (FDA) emergency use authorisation (EUA), the European Medicines Agency's (EMA) rolling review,

the UK Medicines and Healthcare products Regulatory Agency's (MHRA) conditional marketing authorisation and the Central Drugs Standard Control Organisation's (CDSCO) fast-track emergency approvals facilitated the design, assessment and authorisation of COVID vaccines and medicines at an unparalleled scale - potentially reducing development times from the usual 10-15 years to less than 12 months. [9]

More importantly for the purposes of this article, many of the tools that became available during the pandemic were not completely new but fast-tracked versions of pre-existing models. Rolling reviews, adaptive licensing, reliance on surrogate endpoints, real-world evidence (RWE) studies, and platform trials had all been on the table for some time for the development of drugs against rare diseases. The pandemic offered a world stage "proof of concept" for these approaches, and provided impetus for them to be institutionalised. The question this paper explores is whether - and if so, how - these pandemic-adopted initiatives have been institutionalised in orphan drug frameworks in the UK and India. [10]

1.4 Motivation and Literature Gap

Much of the current research on orphan drug regulation is either US- or EU-focused, with comparative studies typically juxtaposing the FDA and EMA. Published research on the role of the MHRA as an independent regulator is increasing but is in its infancy, and there is little research detailing India's rare disease regulatory framework, particularly since the National Policy for Rare Diseases 2021. Importantly, there is no peer-reviewed literature on a systematic comparison of orphan drug regulation in the UK and India in the post-COVID world. This paper bridges this gap through a systematic policy mapping approach to provide insights useful for regulatory scientists, policy makers, patient and pharmaceutical industry stakeholders in the UK and India. [11]

1.5 Objectives and Scope

The paper aims to critically compare the changing orphan drug regulatory landscape of the United Kingdom (post-Brexit status) MHRA and India (CDSCO/National Policy for Rare Diseases 2021) in the post-COVID-19 era (2020-2024). The secondary objectives are: (i) to map regulatory convergence and divergence; (ii) to assess the degree to which regulatory innovations during the pandemic have been incorporated into rare disease regulatory policies; (iii) to analyse patient access and equity considerations; and (iv) to make evidence-based recommendations for regulatory cooperation and national reform.

The paper's focus includes orphan drug designation criteria, incentives, clinical trial regulatory hurdles, health technology assessment (HTA), real-world evidence (RWE) protocols, gene and cell therapy regulation and pharmacovigilance. Our analysis is based on primary regulatory documents, published guidance and peer-reviewed literature between 2018-2024.

2 MATERIAL AND METHODS

2.1 The Global Market for Orphan Drugs

There has been an explosive growth in the global orphan drug market over the last 20 years. What was once a fledgling market in the early 2000s is now one of the most valuable and innovative areas of the pharmaceutical industry. The global orphan drug market size is now estimated at nearly USD 193 billion in 2023 and is expected to reach USD 350 billion by 2030 due to the success of gene therapies, biologics and precision medicine. [12]

Orphan drug designations and approvals have increased at a rapid pace. In the period 2010-2024, the FDA designated over 6,000 drugs as orphan drugs and the EMA over 2,800. The share of all new drug approvals designated as orphan drugs has grown from around 25% in 2010 to more than 50% in recent years - a trend that is a reflection of true advances in rare disease biology, but also in some cases, commercial strategies. [13]

Biologics and advanced therapy medicinal products (ATMPs), such as gene therapies, gene-edited cell therapies and RNA-based products are increasingly prominent in the pipeline. Blockbuster approvals including Nusinersen (Spinraza) for spinal muscular atrophy in 2016, Onasemnogene abeparvovec (Zolgensma) for SMA Type 1 in 2019 and Etranacogene dezaparvovec (Hemgenix) for haemophilia B in 2022 have highlighted the promise of gene therapy for rare diseases, but also the deep pricing challenges. Hemgenix was priced at around USD 3.5 million per dose (the highest of any medicine at the time of approval). [14]

These issues have contributed to a broader conversation about the future of the orphan drug paradigm and equitable access to improvement of health. The balance between the legitimate commercial need for manufacturers to recoup significant costs in orphan drug research (some estimates are USD 2.6 billion per drug approved) and the need for access, especially in developing countries, are at the forefront of orphan drug policy debates. [15]

2.2 Pre COVID Regulatory Framework: United Kingdom

Before Brexit (officially finalised in January 2020), orphan drug regulation in the UK was entirely controlled by EU regulations. The EMA's COMP evaluated applications for orphan designation and, if granted, orphan drugs received ten years of market exclusivity, protocol design advice, and reduced fees. The EMA's Committee for Medicinal Products for Human Use (CHMP) undertook centralised procedures for marketing authorisation that were automatically valid for all EU countries, including the UK. [16]

In the UK, the National Institute for Health and Care Excellence (NICE) developed health technology assessments for orphan drugs through its Highly Specialised Technologies (HST) scheme, which began in 2013. HST evaluations have higher cost-effectiveness thresholds (up to £100,000 per quality-adjusted life year, QALY) than the standard NICE evaluations (20,000-30,000/QALY), in recognition of the difficulties in obtaining economic evidence in ultra-rare patients. NHS England's Early Access to Medicines Scheme (EAMS) was introduced in 2014 to offer an alternative route for pre-authorisation access for promising medicines, such as for rare diseases. [17]

EU regulations also allowed for conditional marketing authorisations (CMAs), which required less evidence than usually required, but a positive benefit-risk ratio and post-authorisation commitments. This was especially useful for orphan medicines since traditional randomised controlled trials (RCTs) were not feasible owing to the small numbers of patients with rare disease. [18]

2.3 Pre-COVID Regulatory Framework: India

India's orphan drug regulatory framework prior to COVID was fragmented, skewed to regulatory overseas precedent and lacked a clear national policy. India's main legislative framework, the Drugs and Cosmetics Act 1940 - a colonial law - did not address rare diseases. The Central Drugs Standards Control Organisation (CDSCO) was responsible for regulation, which followed a traditional licensing model with limited exemptions for fast-tracked or preferential treatment of medicines for rare diseases. [19]

The New Drugs and Clinical Trials Rules 2019 marked a major update to the regulations. Rule 3(b) defined an orphan drug as one for the treatment of a disease with a prevalence of less than 500,000 persons in India. The advantages granted were waivers of fees for clinical trial applications, protocol advisory and priority review. But these were not backed by the necessary infrastructure, staffing or legislative support as seen in the US and EU. [20]

Crucially, the Indian framework also provided for waiver of local clinical trials for new drugs approved in reference countries (USA, UK, Japan, Australia, EU and Canada - as per Schedule Y) on a case-by-case basis. This measure, pragmatic in facilitating quicker availability of orphan medicines approved in foreign countries, could have implications regarding the safety and efficacy of the drug in the Indian population, given that genetic differences impact drug metabolism between populations. [21]

The draft National Policy for Rare Diseases 2017 was never finalised, resulting in a lack of clarity among patients, advocacy groups and health practitioners in the management of rare diseases, access to drugs and financing. This left a regulatory void in which patients with rare diseases in India, many from economically disadvantaged backgrounds, were left to bear exorbitant out-of-pocket costs for drugs that - when available - can cost tens of millions of rupees per year. [22]

2.4 COVID-19 Pandemic Emergency Mechanisms and Benefits

The COVID-19 crisis led both the MHRA and CDSCO to initiate regulatory measures that could have far-reaching impact on the development of rare disease drugs. The MHRA established a rolling review for COVID-19 vaccines, which allowed ongoing evaluation of the COVID-19 vaccine clinical data as it became available rather than waiting for a full application for marketing authorisation. This process - the first time MHRA had operated rolling review as a product in its own right - allowed the Oxford-AstraZeneca vaccine (Vaxzevria) to be authorised within weeks of receiving complete data. [23]

CDSCO too sped up its regulatory processes during the pandemic, with unprecedentedly frequent meetings of subject expert committees, and an emergency use authorisation system that, though ad-hoc rather than formal, illustrated institutional capability for fast-tracked review. The authorisation of Covaxin (manufactured by Bharat Biotech) under limited emergency use in January 2021 (despite controversy over the completeness of data from Phase 3 trials at the time of authorisation) showcased the benefits and potential pitfalls of emergency authorisation. [24]

Academic literature has since explored whether pandemic regulatory mechanisms have been institutionalised into routine practice. Eichler et al. (2021) considered rolling review to be a "paradigm shift" in regulatory science and should be applied to all serious diseases, including rare diseases. [25] Darrow et al. (2022) reported how FDA EUA regulatory mechanisms, although adapted, could shorten rare disease development time by 30-50% without sacrificing safety. [26]

But opponents such as Lexchin (2022), cautioned against "regulatory normalisation" of emergency measures, arguing that any lowering of the evidential bar could have a negative impact on rare disease patients with little to no recourse for alternative treatments. [27]

2.5 Rare Disease Registries and Patient Advocacy

The past 20 years has seen a growing involvement of patient advocacy organisations (PAOs) in the regulation of orphan drugs. Rare Diseases Europe (EURORDIS), the International Rare Diseases Research Consortium (IRDiRC) and other national entities such as Rare Diseases UK, and the Rare Diseases India Foundation have been successful in lobbying for accelerated approval, larger compassionate use schemes and the formal inclusion of patient-reported outcomes (PROs) into registration dossiers. [28]

A game-changing advance has been the development of rare disease registries as natural history data collection sites, and real-world evidence datasets. In the UK, the National Health Service (NHS) Digital and the National Institute for Health Research (NIHR) Rare Disease Translational Research Collaborative host a range of rare disease registries that have been incorporated in marketing authorisation applications and post-authorisation studies. In the UK, Genomics England's 100,000 Genomes Project, finished in 2018, involved 85,000 participants with rare diseases, leading to a diagnosis for 25% of cases previously without one - highlighting the utility of genetic analysis of rare diseases. [29]

In India, the Indian Council of Medical Research (ICMR) has developed a rare disease registry (the NIRMAL (National Initiative for Rare and Other Non-Communicable Diseases) portal. By 2024, patients with 65 diseases had been registered, and this is an important early development. The Indian Rare Disease Alliance (IRDA) has called for compulsory registry enrolment as a requirement for Government of India funded treatment under the NPRD 2021. [30]

3 REGULATORY FRAMEWORK: UK POST-BREXIT AND POST-COVID

3.1 MHRA Independence Post-Brexit

The UK orphan medicines regulatory landscape changed significantly but ultimately smoothly at Brexit. On January 1 2021, the MHRA achieved full separation from the EMA and was independently able to authorise marketing authorisations, to make orphan designations and to establish its own guidelines and standards. Inter-legislative arrangements ensured continued recognition of all pre-Brexit EMA authorisations, providing commercial certainty for products already in the UK market. [31]

The MHRA's designations for the UK Orphan Medicinal Product (OMP) are no longer dependent on COMP. The UK criteria mirror EU standards: a disease affects fewer than 5 in 10,000 people in the UK; or is life-threatening and severely debilitating, with no satisfactory alternative therapies. A further criterion unique to the UK (and not EU) allows designation if the medicine would not be profitable without incentives. Designated products receive ten years of market exclusivity — the same duration as under EU regulation — along with protocol assistance, fee reductions, and priority access to MHRA scientific advice. [32]

A notable post-Brexit development is the MHRA's capacity for independent regulatory decision-making that may diverge from EMA positions. By 2024, the MHRA had authorised several medicines for which EMA decisions were pending or different, including the approval of certain gene therapy products. This regulatory independence has been both celebrated as an opportunity and criticised as a potential source of market fragmentation that could complicate manufacturers' global regulatory strategies. [33]

3.2 Innovative Licensing and Access Pathway (ILAP)

The Innovative Licensing and Access Pathway (ILAP) is a new initiative launched by the UK's Medicines and Healthcare products Regulatory Authority (MHRA) in January 2021, and is the most exciting post-Brexit development in medicines regulation in the UK and of relevance to orphan drugs. ILAP brings together the entire lifecycle of the product - from development through to post-authorisation - in a coordinated approach between MHRA, NICE, NHS England and the devolved health administrations. [34]

ILAP is based on three mechanisms. The Innovation Passport is granted very early in the development process, signalling that the medicine may be suitable for ILAP and a dialogue between the developer and the regulatory, HTA or access bodies may commence. The Target Development Profile (TDP) is a living document created in collaboration between the medicine's developer and MHRA, NICE and NHS England, which defines the evidence needed to gain regulatory approval and reimbursement - a major failure of the current linear regulatory process. The Rapid Review allows MHRA to set time frames to review a product, with the current goal for non-priority products to be reviewed in 150 days and priority products in 100 days. [35]

Furthermore, for orphan drugs, ILAP has provided opportunities for early discussions of evidence strategies with both MHRA and NICE - potentially preventing the "cliff-edge" that has historically existed between regulatory and HTA approvals. From January 2021 to December 2024, the MHRA issued Innovation Passports for 47 products, including 19 (40%) products for rare diseases. Examples of early ILAP experience include therapies for spinal muscular atrophy, Fabry disease and transthyretin amyloidosis. [36]

3.3 Incentive Framework for Orphan Medicines

The UK orphan medicines incentive structure is largely equivalent to the previous EU system, although there have been some Brexit amendments. The 10-year period of market exclusivity provides commercial protection far in excess of the normal 8+2+1-year data and market exclusivity protection for non-orphan medicines. This prohibits the MHRA from accepting or approving a product with an identical or similar active ingredient for the orphan indication throughout the exclusivity period, unless such product has been shown to be superior. [37]

Protocol assistance — equivalent to scientific advice — is available at reduced fees specifically for orphan drug developers. Fee reductions range from 80% for small and medium enterprises to 100% for academic and non-profit developers. The MHRA has also introduced a 'rolling review clock-stop' mechanism allowing developers to submit data packages progressively and request temporary pauses in the review clock for data generation without losing review priority. [38]

Post-Brexit, the UK government introduced additional incentives through the Life Sciences Vision (2021) and the Medicines and Medical Devices Act 2021, which expanded the Secretary of State's powers to provide for new licensing routes and to confer additional regulatory flexibilities. The Health and Care Act 2022 further strengthened these provisions, including enabling regulations for international regulatory cooperation that have implications for orphan drug access through harmonised reviews. [39]

3.4 NICE Highly Specialised Technologies and Rare Disease Access

NICE's Highly Specialised Technologies (HST) programme applies to medicines for ultra-rare conditions (broadly, those affecting fewer than 1 in 50,000 persons in England). HST appraisals use a modified cost-effectiveness framework, with QALY weights of 0.85 (rather than the standard 1.0) applied beyond an annual cost of £100,000 per patient, and a maximum QALY weight of 0.85 applied at a willingness-to-pay threshold of £100,000–300,000 per QALY. These accommodations acknowledge the evidential and economic realities of ultra-rare disease evaluation. [40]

Despite these modifications, several high-profile HST appraisals have resulted in negative recommendations or prolonged managed access agreements (MAAs), delaying patient access to medicines already approved by MHRA. Treatments for spinal muscular atrophy, Duchenne muscular dystrophy, and some lysosomal storage disorders have experienced delays of 12–24 months between MHRA approval and positive NICE guidance. The NHS England Blueteq system — a prior authorisation mechanism for high-cost, low-volume medicines — controls prescribing of HST-recommended drugs, adding an additional administrative layer between guidance and patient access. [41]

The 2023 NICE methods review introduced further modifications to the HST framework, including greater acceptance of real-world evidence, Bayesian statistical approaches for small trial analysis, and explicitly patient-centred value frameworks. These reforms were welcomed by rare disease advocacy groups but have not yet been tested in a sufficient number of completed HST appraisals to permit systematic evaluation of their impact on patient access. [42]

3.5 UK Rare Diseases Framework (2021–2024)

The UK Rare Diseases Framework, published in January 2021 by the four UK health departments, established a shared vision for improving lives of people with rare diseases over a five-year period. The Framework identified four priority areas: helping people get a diagnosis faster; increasing awareness of rare diseases among healthcare professionals; better coordination of care; and improving access to specialist care and treatments. [43]

The Framework is supported by annual action plans from England, Scotland, Wales, and Northern Ireland, each specifying jurisdiction-specific initiatives. England's 2024 Action Plan highlights progress in genomic medicine (rapid whole-genome sequencing available within 24 hours in NHS), development of the National Genomic Medicine Service's Rare Disease Discovery network, expansion of the Genomics England National Genomic Research Library, and piloting of multi-disciplinary rare disease advisory services. Scotland's Action Plan has focused on the Scottish Genomes Partnership and specialist rare disease clinical networks. [44]

Independent evaluation of Framework progress suggests significant achievements in genomic diagnosis and professional awareness, with the proportion of rare disease patients receiving a molecular diagnosis within 12 months improving from approximately 25% (2019) to 40% (2023). However, access to approved treatments remains the area

of weakest progress, with persistent delays between MHRA authorisation and NHS reimbursement representing a gap between regulatory and access system performance. [45]

3.6 International Collaboration Post-Brexit

Post-Brexit, the MHRA has pursued an active agenda of international regulatory collaboration, partly to compensate for loss of EMA membership and partly to position the UK as a global hub for regulatory science innovation. The most exciting update is the UK's joining of Project Orbis - an initiative led by the US FDA that allows drugs to be submitted and reviewed simultaneously for approval in a group of countries including Canada (Health Canada), Australia (TGA), Brazil (ANVISA), Singapore (HSA), and Switzerland (Swissmedic), and now the UK (MHRA). [46]

Several orphan oncology medicines have been submitted under Project Orbis, allowing the MHRA to approve products simultaneously with the FDA (and other participating agencies) - thereby eliminating historic delays to market that impacted UK rare disease patients compared to their counterparts in the USA. In 2022, the MHRA and FDA also signed an information exchange agreement to share inspection reports, clinical trial information and post-market safety information to facilitate regulation without formal mutual recognition. [47]

An arrangement signed by the MHRA and Health Canada in 2023 pioneered reliance procedures, allowing MHRA to rely on assessment reports from Health Canada for some products. This "informed reliance" (not formal mutual recognition) approach means MHRA can expedite the decision-making process while maintaining final decision-making autonomy. This approach could be applied to EMA assessments (political agreement pending) and would be invaluable to orphan drug developers who submit to the UK and EU. [48]

4 REGULATORY LANDSCAPE: INDIA POST COVID

4.1 Orphan Drug Designation by CDSCO

India's orphan drug program, introduced under Rule 3(b) of the New Drugs and Clinical Trials Rules 2019 (NDCT Rules 2019), classifies an orphan drug as a new drug for the treatment of a disease that worldwide affects fewer than 500,000 people in India. This definition of prevalence (0.04%) is significantly lower than the EU/UK standard of 5 in 10,000 (0.05%) and, on a relative basis, slightly more restrictive, but is appropriate to India's vast population where even rare conditions may affect hundreds of thousands of people (in absolute terms). [49]

The NDCT Rules 2019 provide orphan drug designations with certain benefits, including: exemption from the clinical trial application fee; protocol assistance from CDSCO's Subject Expert Committees (SECs); preferential review in the review backlog; and a waiver of local clinical trials under Rule 101 in the case of product approval in at least one ICH reference country. But these measures have not been applied consistently. CDSCO's lack of a dedicated orphan drug evaluation unit (similar to the FDA's Office of Orphan Products Development), its limited number of staff dedicated to orphan drug evaluation, and its failure to provide reasons for orphan drug designations have been cited by industry as areas of improvement. [50]

CDSCO received about 45 applications for orphan drug designation and designated 31 products between 2019 and 2024. Yet, less than 10 of these have been granted marketing approval in India in the same timeframe. The high attrition rate is due to both business decisions by manufacturers to not market the product in India, as well as regulatory delays. [51]

4.2 National Policy for Rare Diseases 2021

The National Policy for Rare Diseases 2021 (NPRD 2021) is the most detailed attempt by the Indian government to tackle rare diseases in a policy document. The policy classifies rare diseases into three types: Group 1 (one-time curable treatment) diseases (e.g., bone marrow transplantation for haemoglobinopathies); Group 2 (chronic diseases with moderate cost of treatment) diseases (e.g., hormone therapy for growth hormone deficiency); and Group 3 (chronic diseases with high cost of treatment and uncertain benefit) diseases (e.g., lysosomal storage diseases requiring enzyme replacement therapy). [52]

Government financial support under NPRD 2021 is concentrated on Group 1 diseases, for which eligible patients may receive up to ₹50 lakh (approximately USD 60,000) from the Rashtriya Arogya Nidhi (RAN) fund. This ceiling is far below the actual cost of treatment for many rare conditions: enzyme replacement therapies for lysosomal storage disorders may cost ₹30–50 lakh per year, while gene therapies such as Zolgensma (onasemnogene abeparvovec) were priced at approximately ₹16 crore (approximately USD 2 million) per dose as of 2022. [53]

The NPRD 2021 designated eight Centres of Excellence (CoEs) — multidisciplinary hospitals responsible for diagnosis, management, and research in rare diseases. As of 2024, these include AIIMS New Delhi, SGPGI Lucknow, NIMHANS Bengaluru, PGIMER Chandigarh, CMC Vellore, SSKM Kolkata, and JIPMER Puducherry. However, the CoE network suffers from severe geographic maldistribution — none are in Maharashtra, Gujarat, or Rajasthan, which together have populations exceeding 250 million — and inadequate funding for the operational costs of providing specialist rare disease care. [54]

Implementation of NPRD 2021 at the state level has been highly heterogeneous. Tamil Nadu, Karnataka, and Gujarat have supplemented the central policy with state-level rare disease funds and specialist services. In contrast, many north-eastern states and union territories have made minimal progress in establishing state action plans. The policy's success in reaching patients depends critically on state-level implementation, as healthcare is a concurrent subject under the Indian Constitution. [55]

4.3 Waiver of Local Clinical Trials

One of the most practically significant provisions for orphan drug access in India is the Rule 101 mechanism under the NDCT Rules 2019, which permits CDSCO to grant a marketing authorisation without requiring local (India-based) clinical trials for new drugs approved in at least one of the designated reference countries. This rule (available for all new drug applications but highly relevant for orphan drugs) was explicitly extended in 2019 to include simultaneous new drug applications - in other words, Indian marketing authorisation could be applied for in parallel to (rather than after) approval in the reference countries. [56]

The Rule 101 waiver has been extensively used for orphan medicines, and has allowed for a major speed-up of the availability of foreign-approved orphan medicines for patients. Over the period 2019-2024, about 60% of Indian marketing authorisations for orphan medicines relied - in part - on foreign clinical data. But the tool has come under scholarly scrutiny for pharmacogenomic equity concerns: Indians carry genetic variants that can influence drug metabolism, efficacy and safety differently from what has been observed in Western populations. [57]

CDSCO has sought to balance speedy access to new drugs with scientific rigour by requiring, in some cases, post-approval pharmacovigilance studies or bridging studies involving Indian populations as approval conditions. However, there are inconsistent compliance with these post-approval requirements, as well as limited capacity of CDSCO to follow up on post-approval commitments given the number of approvals it issues. [58]

4.4 Post-COVID Regulatory Reforms

COVID-19 triggered a number of India's regulatory reform efforts that are relevant to orphan drug development. The handling of emergency approvals, including for COVID-19 vaccines and drugs, highlighted the institutional readiness of CDSCO for expedited review procedures, as well as the challenges of relying on ad hoc emergency responses. [59]

The New Drugs, Medical Devices and Cosmetics Bill 2023 - which was introduced in the Lok Sabha but as of 2024 remains in the review stage - contains a number of orphan drug initiatives. These include: provision of an explicit definition of orphan drugs and incentives (uplifting the current rules to the status of law); establishment of a new special licensing authority for gene and cell therapies; introduction of conditional approval with post-marketing studies; and the creation of an accelerated approval pathway similar to that of the US Food and Drug Administration (FDA), specifically citing rare diseases as an area of priority indications. If passed, the Bill would represent the biggest leap forward in drug regulation in India since NDCT Rules 2019. [60]

CDSCO has also invested in digital infrastructure post-COVID, with e-CTD (electronic Common Technical Document) submissions now mandatory for new drug applications submitted from January 2023. The SUGAM portal — CDSCO's online application management system — has been expanded to support orphan drug designation applications and track their progress. These digital reforms improve transparency and should reduce administrative delays, though they do not address the underlying capacity constraints in scientific assessment. [61]

4.5 Pharmacoeconomics and the Affordability Crisis

India faces a profound and growing rare disease affordability crisis. Several high-profile cases have illustrated the magnitude of the problem. In 2022, a public interest litigation (PIL) was filed in the Supreme Court of India on behalf of children with spinal muscular atrophy, seeking government-funded access to onasemnogene abeparvovec (Zolgensma), then priced at approximately ₹16 crore per dose. The Supreme Court issued directions to the Union government to establish a mechanism for funding Zolgensma treatment, leading to a government announcement of a single-window clearance for SMA treatment funding — though actual implementation remained incomplete. [62]

The National Pharmaceutical Pricing Authority (NPPA), which regulates prices of scheduled drugs under the Drugs (Prices Control) Order 2013, lacks authority to price-cap orphan drugs. Orphan drugs are not included in the National List of Essential Medicines (NLEM), and manufacturers successfully argue that price controls would eliminate already-weak incentives for product registration in India. This creates a regulatory paradox: India's framework incentivises orphan drug development with fee waivers and priority review, but provides no mechanism to ensure the resulting approved products are financially accessible to the patients who need them. [63]

Insurance adds to difficulties in access. Rare diseases are excluded from government health insurance, such as PM-JAY (Pradhan Mantri Jan Arogya Yojana), and private health insurance policies also exclude treatment for rare diseases. An individual's annual cost of treatment for rare diseases in India is estimated to be greater than ₹10-30 lakh, which is beyond the financial means of most families with rare diseases, 80% of which live below or near the poverty line. [64]

4.6 Role of ICMR and DBT in Domestic R&D

While orphan drugs in India are mainly imported, the national orphan drug ecosystem is now emerging with a limited research and development (R&D) capability. The Indian Council of Medical Research (ICMR) and the Department of Biotechnology (DBT) have jointly funded research initiatives in rare diseases that are epidemiologically significant in India, such as haemoglobinopathies (thalassaemia, sickle cell disease), lysosomal storage disorders and primary immunodeficiencies. [65]

The Department of Biotechnology's National Biopharma Mission has funded development of biosimilars of enzyme replacement products for Gaucher disease and Fabry disease, where the cost of the original biologic therapies has made them inaccessible to most Indian patients. Cerezyme (imiglucerase) for Gaucher disease, from Sanofi Genzyme, costs roughly ₹20-40 lakh annually; development of local biosimilars is anticipated to bring down the cost 60-70%, hopefully to levels covered by the government's reimbursement schemes. [66]

The 'Make in India' program has been slow to impact rare diseases. Although major pharmaceutical companies, such as Sun Pharma and Cipla, have shown interest in rare diseases, commercial viability - due to low market potential, complex manufacturing processes required for biologics, and uncertain reimbursement - has limited their interest. India has limited capacity for gene therapy manufacturing, with no gene therapy products approved in India in 2024. DBT has supported the development of pilot-scale gene therapy manufacturing in India, but these are not yet commercially feasible. [67]

5 COMPARATIVE ANALYSIS: UNITED KINGDOM AND INDIA

5.1 Comparative Policy Matrix

Table 1 presents a comprehensive side-by-side comparison of orphan drug regulatory frameworks in the United Kingdom and India across 15 key parameters.

Table 1: Comparative Orphan Drug Regulatory Policy Matrix – UK vs India (2024)

Parameter	United Kingdom (MHRA)	India (CDSCO / NPRD 2021)
Regulatory Authority	Medicines and Healthcare products Regulatory Agency (MHRA)	Central Drugs Standard Control Organisation (CDSCO)
Orphan Definition	<5 per 10,000 population OR life-threatening with no satisfactory alternative	<500,000 patients in India (~1 in 2,500)
Designation Body	MHRA Orphan Unit (post-Brexit, independent of EMA)	CDSCO Subject Expert Committee
Market Exclusivity	10 years (from date of marketing authorisation)	Not formally legislated; proposed in New Drugs Bill 2023
Fee Reductions	80–100% reduction on regulatory fees	Fee waiver for clinical trial applications only
Clinical Trial Waiver	Not applicable (standard full review)	Rule 101 waiver if approved in ICH reference country
Priority Review	ILAP Rapid Review (100–150 days)	Priority review provision (operationally inconsistent)

HTA Integration	NICE HST (threshold: £100k–300k/QALY); ILAP TDP integrates HTA early	No formal HTA body; no cost-effectiveness threshold established
RWE Acceptance	MHRA RWE Framework 2023; accepted in HST appraisals	Evolving; limited formal guidance; some ad hoc acceptance
Gene Therapy Regulation	MHRA ATMP framework; outcome-based NHS payment models	Gene Therapy Advisory Committee (GTAC); no approved gene therapies as of 2024
Patient Registries	NHS Digital, Genomics England NGRL; multiple disease-specific registries	NIRMAN portal; limited coverage; 65 diseases registered
Genomics Integration	National Genomic Medicine Service; rapid WGS in NHS; 100,000 Genomes Project data	GenomeIndia project (ongoing); limited clinical integration
Pricing Mechanism	Voluntary Scheme for Branded Medicines; outcome-based MAAs for some products	No price regulation for orphan drugs; NPPA lacks authority
Government Funding	NHS full reimbursement (subject to NICE approval); Highly Specialised Technologies programme	NPRD 2021: ₹50 lakh cap (Group 1 only); limited scope
International Cooperation	Project Orbis, MHRA-FDA information sharing, informed reliance with Health Canada	No formal bilateral regulatory cooperation mechanisms

Source: Compiled from MHRA guidance documents, CDSCO public domain data, NPRD 2021, NICE HST framework, and peer-reviewed literature (2021–2024). WGS = whole genome sequencing; MAA = managed access agreement; NGRL = National Genomic Research Library.

5.2 Regulatory Timeline Analysis

Comparing the median time-to-approval for orphan drugs in the United Kingdom (UK) and India from 2018 to 2024, there are important differences in the speed of regulatory processing, as well as in the time-to-access post-approval. For the UK, the median review time for orphan medicines approved through the standard pathway (from marketing authorisation application [MAA] to approval) was 150 days in 2023, down from 210 days in 2019. This 30% improvement is a testimony to the adoption of ILAP, digitisation of MHRA's dossier management and learnings from review acceleration during the COVID-19 pandemic. [68]

In India, the median time for orphan drug reviews by CDSCO was about 18–24 months in 2022–2023, significantly longer than the MHRA's target. Stakeholder analyses highlight the key bottlenecks as: low frequency of holding relevant Subject Expert Committee (SEC) meetings (4–6 meetings a year, per therapeutic area); lack of in-house expertise in gene therapy and advanced biologics review; and linear rather than concurrent review mechanisms. The 2023 e-CTD mandate will help streamline administrative processing, but will not directly increase the expertise for scientific assessment. [69]

Crucially, UK approval times are only the first step to patient access. MHRA authorisation is followed by NICE HST appraisal and NHS England reimbursement, which historically takes 12–36 months. Managed access agreements — used as an interim measure while HTA evidence is gathered — have improved access during this period but involve complex administrative mechanisms that can delay patient enrolment. In India, there is no equivalent systematic mechanism bridging regulatory approval and funded access; approved orphan drugs may remain commercially unavailable to the majority of patients indefinitely pending individual case-by-case funding applications. [70]

5.3 Trial Design Innovations for Small Populations

Both the UK and India have engaged with methodological innovations in clinical trial design for rare diseases, though at different stages of regulatory acceptance and practical implementation. The fundamental challenge in rare disease clinical development is well-recognised: conventional parallel-group randomised controlled trials (RCTs) are frequently infeasible when global patient populations number in the hundreds or thousands. This has driven substantial innovation in adaptive, Bayesian, and platform trial designs. [71]

The MHRA has progressively expanded its acceptance of novel trial designs for rare diseases. Bayesian statistical approaches — in which prior information (from natural history studies, expert opinion, or comparable diseases) is formally incorporated into statistical analysis — are now explicitly accepted in MHRA scientific advice for rare diseases. Basket trials (testing a single intervention across multiple rare diseases defined by a shared molecular marker) and adaptive platform trials (with pre-specified rules for modifying patient allocation, dosing, or endpoints mid-trial) have been reviewed and, in some cases, supported by MHRA scientific advice teams. The UK's experience with the RECOVERY platform trial during COVID-19 — which identified effective treatments for COVID-19 far more efficiently than conventional trials — has strengthened regulatory and scientific confidence in adaptive platform methodologies. [72]

CDSCO's position on novel trial designs is more conservative. While the NDCT Rules 2019 and subsequent CDSCO guidance acknowledge adaptive designs in principle, the agency has limited experience with Bayesian statistical submissions and has been cautious in accepting single-arm trials without robust natural history comparators. The absence of a dedicated biostatistics team focused on novel designs within CDSCO, and the limited track record of domestic sponsors submitting rare disease trials with innovative designs, creates a regulatory environment in which conservative, conventional trial designs dominate. [73]

5.4 Real-World Evidence Acceptance

Real-world evidence (RWE) — derived from electronic health records, disease registries, claims data, and patient-generated data — has become increasingly central to orphan drug regulation globally, particularly for post-approval monitoring in small populations where randomised controlled trials cannot generate adequate long-term safety and efficacy data. The MHRA's Framework for Real World Evidence, published in 2023, represents a comprehensive and detailed set of standards for RWE generation, quality assessment, and integration into regulatory decision-making. [74]

The MHRA RWE Framework explicitly addresses the challenges of rare diseases, including small sample sizes, heterogeneous disease phenotypes, limited comparator data, and potential biases in registry-based cohorts. MHRA acknowledges RWE as suitable for supporting: pharmacovigilance activities; conditional marketing authorisation confirmatory data; extensions of indication; and — in limited circumstances — initial marketing authorisation for conditions where RCTs are infeasible. The Genomics England National Genomic Research Library, linked to NHS patient records, is cited in the framework as an exemplar of high-quality, longitudinal rare disease RWE infrastructure. [75]

India's regulatory acceptance of RWE is at an earlier stage of development. CDSCO has not published a dedicated RWE framework, though the topic is addressed in passing in various guidance documents and has been discussed at CDSCO advisory committee meetings. The NIRMAL rare disease registry, while valuable, currently lacks the linkage to health records and clinical outcome data necessary to generate RWE of the quality required to support regulatory submissions. Developing a fit-for-purpose RWE infrastructure — encompassing digital health records, standardised data collection tools, and regulatory guidance — is one of the most important medium-term priorities for India's rare disease regulatory system. [76]

5.5 Patient Access and Equity Gaps

'Approved' and 'accessible' are far from synonymous in either the UK or Indian context, though the nature of the access gap differs fundamentally between the two systems. In the UK, the MHRA's regulatory approval is the gateway to an NHS reimbursement system that, when it functions optimally, provides universal access to approved medicines regardless of personal financial circumstances. The challenge is the structural delay between MHRA authorisation and NHS England reimbursement: an ABPI analysis of rare disease medicines approved between 2018 and 2022 found a median gap of 18 months between MHRA authorisation and positive NICE HST guidance, and a further 3–6 months before prescribing restrictions were lifted. During these periods, some patients secured access via managed access agreements, exceptional individual case funding, or NHS England named patient schemes, but these mechanisms are inconsistently available. [77]

In India, the access gap is more severe and systemic. Even for the small proportion of rare disease patients who receive a diagnosis, the majority have no realistic prospect of accessing approved treatments. With insurance exclusion near-universal, government funding capped at ₹50 lakh for eligible patients only, and no price regulation for orphan drugs, treatment costs are borne entirely out of pocket by families who in most cases cannot remotely afford them. Crowdfunding campaigns on platforms such as Milaap and Ketto have become a primary mechanism through which rare disease families raise funds for treatment — an indictment of systemic policy failure. Supreme Court interventions in specific cases (SMA, Gaucher disease, Fabry disease) have created ad hoc relief for individual patients but do not constitute a sustainable policy solution. [78]

5.6 Digital and Genomic Policy Integration

Genomics and digital health represent areas of genuinely profound divergence between the UK and India in terms of rare disease policy integration. The UK's National Genomic Medicine Service (NGMS), fully operational from 2021, offers whole genome sequencing (WGS) as a NHS diagnostic service for patients with rare diseases and cancers. Rapid WGS — with a turnaround time of 24 hours for critically ill neonates and children — is now available at 11 NHS Genomic Laboratory Hubs across England, with equivalent services in Scotland, Wales, and Northern Ireland. Genomic diagnoses are increasingly being linked to MHRA-approved targeted therapies, creating a precision medicine ecosystem directly relevant to rare disease orphan drug access. [79]

India's GenomeIndia project, a DBT-funded initiative to sequence 10,000 Indian whole genomes to characterise population genetic diversity, was largely completed by 2023. While this project provides important scientific

infrastructure for understanding pharmacogenomics in Indian populations, it has not yet been linked to clinical diagnostic pathways or rare disease therapy access. The development of a clinically integrated genomic medicine service — analogous to the UK's NGMS — would require substantial investment in sequencing infrastructure, bioinformatics capacity, clinical genetics workforce, and regulatory guidance on the use of genomic data in drug labelling and prescribing. [80]

6 EMERGING CHALLENGES AND NOVEL ISSUES

6.1 Gene and Cell Therapy Regulation

Gene therapies and advanced therapy medicinal products (ATMPs) represent both the greatest therapeutic promise and the most complex regulatory challenge in the rare disease space. In the UK, ATMPs are regulated under the MHRA's ATMP framework, which is modelled closely on the EU Regulation 1394/2007 and applies specific requirements for quality, safety, and efficacy assessment that account for the novel characteristics of these products — including viral vector manufacturing, insertional mutagenesis risk, long-term durability of effect, and immune responses. [81]

An important factor for gene therapies is that they provide a one-time cure, which poses unique challenges for existing health-care financing models. Chronic disease treatments providing ongoing revenue streams for manufacturers, potentially alignable with healthcare financial cycles, contrast with a single dose of gene therapy potentially benefiting patients for life, at a cost of millions of pounds. The National Health Service (NHS) in England has negotiated outcome-based pricing models for a number of approved gene therapies - such as atidarsagene autotemcel (Libmeldy) for metachromatic leukodystrophy and betibeglogene autotemcel (Zynteglo) for transfusion-dependent beta-thalassaemia - in which payment is tied to outcome at a set time point, sharing the risk between payer and manufacturer. [82]

The Department of Biotechnology's (DBT) Gene Therapy Advisory Committee (GTAC) provides scientific advice on conducting gene therapy research and trials. But the regulatory process for marketing approval of gene therapy products is not yet established in India. The New Drugs, Medical Devices and Cosmetics Bill 2023 includes formation of a separate advanced therapy division at CDSCO, but is yet to become law. Meanwhile, gene therapy products approved in reference countries can be assessed for authorisation in India under existing provisions for new drugs, but with lack of guidance on ATMPs, assessment processes are ad-hoc and not established. [83]

6.2 Role of Artificial Intelligence and Machine Learning

Artificial intelligence (AI) and machine learning (ML) are increasingly being used in rare disease drug discovery and development, and provide an opportunity where processing of data-driven approaches are constrained by small sample sizes and complex phenotypes. AI applications in rare disease encompass: variant interpretation in genomic diagnosis (enabling identification of pathogenic mutations in genes not previously associated with disease); protein structure prediction (AlphaFold's capabilities have particularly benefited rare diseases characterised by protein misfolding, including transthyretin amyloidosis and several lysosomal storage disorders); patient matching for clinical trials (reducing the geographic and logistical barriers to rare disease trial enrolment); and synthetic control arm generation (using AI to model what untreated patients would have experienced, potentially enabling single-arm trials to achieve regulatory-grade evidence). [84]

The MHRA published draft guidance on AI and ML in drug development in 2024, acknowledging both the transformative potential of these technologies and the need for robust validation frameworks. The guidance emphasises transparency in algorithm development, the need for training data diversity (acknowledging that many AI tools have been developed on predominantly European-ancestry datasets, with uncertain performance in South Asian populations), and the importance of regulatory-grade validation studies before AI-generated evidence is incorporated into marketing authorisation applications. [85]

CDSCO has not yet published dedicated guidance on AI/ML in drug development, placing India behind the regulatory frontier in this area. The risk is that Indian regulators will be inadequately prepared to assess AI-based evidence packages submitted by developers of novel rare disease medicines — potentially leading to either inappropriate rejection of valid evidence or uncritical acceptance of algorithmically generated data of uncertain reliability. [86]

6.3 Drug Repurposing: The COVID Legacy

One of the most practically significant regulatory legacies of the COVID-19 pandemic for rare diseases is the demonstrated viability of large-scale drug repurposing — the systematic evaluation of approved drugs for new indications. The RECOVERY trial (Randomised Evaluation of COVID-19 Therapy), coordinated by the University of Oxford, enrolled more than 45,000 patients across 185 UK hospitals and identified dexamethasone, baricitinib, and

tocilizumab as life-saving treatments for severe COVID-19 using an adaptive platform trial design that could evaluate multiple candidate drugs concurrently at relatively modest per-drug cost. [87]

The RECOVERY model has inspired rare disease researchers and advocates to propose analogous platform approaches for conditions where multiple drugs require evaluation in small, geographically dispersed patient populations. The UK's NIHR has funded the International Rare Diseases Research Consortium (IRDiRC) to explore RECOVERY-style trial networks for rare diseases, and the MHRA has expressed support for this concept in its 2023 clinical trial framework review. For regulators, the key challenge is establishing the evidential standards for repurposed drugs in rare indications: given that safety data exist from the primary indication, expedited safety assessment may be appropriate, but efficacy evidence must still be adequate to justify the rare disease indication. [88]

India's CDSCO has less formal engagement with drug repurposing policy for rare diseases, though the NPRD 2021 acknowledges repurposing as a potential mechanism for expanding therapeutic options in resource-limited settings. The ICMR conducted several COVID-19 repurposing studies and the experience gained — including in adaptive trial design and emergency regulatory review — represents an underutilised institutional learning opportunity for rare disease applications. [89]

6.4 Evergreening and Orphan Drug System Abuse

A significant and growing concern in global orphan drug policy is the practice of 'indication salami-slicing' or 'orphan creep' — the strategic use of orphan designations by pharmaceutical companies to extend market exclusivity for commercially successful medicines by obtaining separate designations for narrowly defined subpopulations or indications within larger disease categories. Analysis by the US Senate Finance Committee (2021) identified numerous instances where companies obtained orphan designations for subsets of common conditions, securing market exclusivity and FDA fee waivers for products with annual revenues exceeding USD 1 billion. [90]

The EMA and MHRA have both introduced measures to combat orphan drug system abuse. EMA's revised orphan regulation guidance (2023) tightened the definition of 'significant benefit' required for designation, and the MHRA has adopted equivalent standards post-Brexit. A renewed emphasis has been placed on the criterion that the drug must treat a condition for which there is no satisfactory alternative treatment - with "satisfactory alternative" interpreted more narrowly to avoid marginal improvements to existing medicines being dubbed "new" orphan medicines. [91]

India has little safeguards against orphan drug abuse. Neither the NPRD 2021 nor the NDCT Rules 2019 mention a criterion requiring significant benefit, or feature anti-orphan-creep provisions similar to those of the EMA. Relative to developed markets, the commercial appeal of the Indian market for orphan drugs (diminishing the abuse incentive) may be limited, so the risk of deliberate abuse may be correspondingly low - but the lack of safeguards exposes the system to the possibility of abuse as India's economic status evolves and the orphan drug market expands. [92]

6.5 Post-Market Surveillance Challenges

Pharmacovigilance for orphan drugs presents unique methodological and operational challenges in both jurisdictions. The fundamental challenge is statistical: with patient populations numbering in the hundreds or thousands, adverse event signals that would be readily detected in large-population pharmacovigilance databases may take years to emerge — or may never achieve statistical significance — in orphan drug post-marketing surveillance. This means that pre-approval safety assessment carries greater decisional weight for orphan medicines than for common-indication drugs, and post-marketing safety monitoring must be both more sophisticated and more proactive. [93]

The MHRA Yellow Card scheme — the UK's spontaneous adverse event reporting system — is supplemented for orphan drugs by additional post-marketing requirements, including periodic safety update reports (PSURs) and, for conditionally authorised medicines, specific safety assessment milestones linked to confirmatory study conduct. The MHRA's pharmacovigilance risk assessment committee (PRAC) — mirroring the EMA body of the same name — evaluates aggregate safety signals and may require label changes, risk minimisation measures, or, in extreme cases, withdrawal of authorisation. [94]

India's Pharmacovigilance Programme of India (PvPI), overseen by the Indian Pharmacopoeia Commission (IPC), has expanded considerably since its inception in 2010, but is still under-resourced for its scope. India's adverse drug reaction reporting rates are much lower than global standards, due to a lack of awareness among health care professionals and failure to integrate electronic reporting mechanisms into most clinical practice. Pharmacovigilance reporting through PvPI is especially important for orphan drugs - medicines for small patient groups with serious disease conditions. If well-funded, the CoE network proposed in the NPRD 2021 could provide a specialised pharmacovigilance network for rare disease drugs, and could provide better quality data compared to the broader PvPI system. [95]

7 METHODOLOGY

7.1 Study Design

This paper adopts a comparative policy analysis approach, using a documentary review method by Howlett and Cashore (2009) for the comparison of policy instruments. [96] This process includes: (i) identification and collection of policy documents; (ii) systematic analysis of policy instrument features across a set of parameters; (iii) comparison using a pre-formatted policy matrix; (iv) thematic analysis of similarities, differences and policy gaps; and (v) normative assessment using reference frameworks (WHO model of regulatory maturity). This methodology allows robust interjurisdictional policy comparison while recognising policy context.

7.2 Data Sources

Primary data sources included: MHRA orphan drug designation and approval databases (2020–2024); CDSCO public domain data on new drug applications and orphan designations (2019–2024); the National Policy for Rare Diseases 2021 and associated implementation reports; UK Rare Diseases Framework 2021 and action plans (England, Scotland, Wales, Northern Ireland) 2022–2024; WHO Technical Report Series on regulatory systems strengthening; and NICE HST appraisal documents (2020–2024).

Peer-reviewed literature was identified through systematic searches of PubMed and Scopus using the following search strings: (orphan drug OR rare disease) AND (regulation OR regulatory) AND (United Kingdom OR MHRA OR India OR CDSCO), with a publication date filter of 2018–2024. Additional searches included: 'COVID-19 regulatory reform'; 'ILAP rare disease'; 'National Policy for Rare Diseases India'; 'gene therapy NHS payment model'; 'real-world evidence orphan drug'. Searches were conducted in January 2025 and returned 847 total results, of which 142 were assessed as relevant following title and abstract screening, and 78 were included in the final analysis.

7.3 Analytical Framework

Three analytical frameworks were applied. First, a comparative policy matrix (Table 1) was constructed comprising 15 parameters covering designation criteria, incentive structures, clinical trial requirements, HTA integration, market exclusivity, patient registry requirements, and pricing controls. Second, a SWOT (Strengths, Weaknesses, Opportunities, Threats) analysis was conducted for each country's orphan drug regulatory framework (Table 2). Third, each country's regulatory system was assessed against the WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory authorities, focusing on the sub-indicators most relevant to orphan drug regulation (indicators 04, 05, 07, 08 covering registration, post-marketing surveillance, regulatory inspections, and laboratory testing capacity).

Table 2: SWOT Analysis of UK and Indian Orphan Drug Regulatory Frameworks

	United Kingdom	India
Strengths	ILAP pathway; MHRA autonomy post-Brexit; NICE HST framework; genomic medicine integration; Project Orbis participation; robust pharmacovigilance (Yellow Card)	Large patient population (absolute numbers); biosimilar manufacturing capacity; NPRD 2021 framework; Rule 101 waiver enabling faster access; GenomeIndia project; ICMR research infrastructure
Weaknesses	18+ month MHRA-to-NHS access gap; high drug pricing in small populations; geographic NHS variation in access; limited manufacturing for advanced therapies domestically	No standalone Rare Diseases Act; inadequate NPRD 2021 funding; no HTA framework; limited CDSCO orphan drug expertise; weak pharmacovigilance for rare diseases; insurance exclusion
Opportunities	MHRA-FDA-HC regulatory alignment; ILAP expansion; outcome-based payment models; AI/ML regulatory guidance leadership; UK-India FTA pharmaceutical provisions	New Drugs Bill 2023 enactment; MHRA-CDSCO MoU; DBT domestic gene therapy manufacturing; PM-JAY expansion to rare diseases; NIRMAN registry scaling
Threats	Orphan drug market exclusivity abuse (salami-slicing); NHS cost-containment pressure; gene therapy post-market safety unknowns; post-Brexit market fragmentation	Affordability crisis deepening with gene therapy approvals; brain drain of regulatory scientists; political instability affecting NPRD implementation; counterfeit drug risk in orphan medicine supply chain

8 DISCUSSION AND POLICY RECOMMENDATIONS

8.1 Convergences and Divergences

Despite operating in fundamentally different healthcare, economic, and legislative contexts, the UK and India exhibit several areas of regulatory convergence in the post-COVID period. Both jurisdictions have embraced rolling review as a mechanism for accelerating assessment of data generated progressively rather than submitted in a single complete dossier. Both have articulated commitments to real-world evidence as a complement to randomised controlled trial data, particularly for post-marketing surveillance in small populations. Both have recognised the transformative potential of genomic medicine for rare disease diagnosis and have invested in national genomic infrastructure, albeit at markedly different scales. And both have acknowledged the limitations of sequential regulatory and HTA processes and have moved — in the UK case operationally, in the Indian case aspirationally — towards more integrated, lifecycle-spanning regulatory pathways. [97]

The divergences are, however, more numerous and more consequential than the convergences. The most fundamental is the maturity gap between the two regulatory systems. MHRA is a mature, well-resourced, internationally respected regulatory authority with a long track record in novel medicines assessment, established HTA integration through NICE, and a functioning universal healthcare system ensuring that regulatory approval translates, at least eventually, into patient access. CDSCO, while significantly strengthened since the implementation of NDCT Rules 2019, lacks dedicated orphan drug assessment capacity, operates without a formal HTA framework, and functions within a healthcare system that lacks universal coverage and provides minimal protection against catastrophic rare disease treatment costs. [98]

The HTA gap is particularly significant. NICE's HST programme, despite its limitations in access delays, provides a systematic, transparent, and evidence-based mechanism for determining which orphan drugs represent sufficient value to justify NHS expenditure. India has no equivalent body. The absence of any cost-effectiveness threshold or formal HTA process means that CDSCO marketing authorisation for an orphan drug in India carries limited practical meaning for most patients — approved products may be commercially available but financially inaccessible to the overwhelming majority of patients who need them.

8.2 A Blueprint for India

Based on the comparative analysis conducted in this paper, the following specific legislative and policy recommendations are advanced for the Indian orphan drug framework:

First, enactment of a standalone Rare Diseases Act — analogous in structure to the US Orphan Drug Act 1983 but contextualised for India's epidemiological and economic realities — is the single most important systemic reform available. Such legislation should: establish a statutory definition of rare diseases (adapting the current rule-based definition to primary legislation); create formal market exclusivity of 7–10 years for designated orphan medicines; provide tax credits for clinical trial expenditure by domestic developers; mandate insurance coverage of rare diseases under PM-JAY and Central Government Health Scheme (CGHS); establish a Rare Disease Fund (analogous to Brazil's rare disease component within its Universal Health System); and create a dedicated orphan drug division within CDSCO with appropriately qualified specialist staff. [99]

Second, the ₹50 lakh funding cap under NPRD 2021 is dangerously inadequate in the context of modern rare disease treatment costs. A tiered funding mechanism — with caps calibrated to disease group and treatment modality — combined with outcome-based payment provisions for high-cost one-time therapies (such as gene therapies) would significantly improve the policy's practical impact. Government negotiations with manufacturers for significant price reductions as a condition of NPRD-funded access — following the model of NHS England's managed access agreements — should be formally instituted.

Third, the Jan Aushadhi scheme — which provides generic medicines at subsidised prices through a network of government-run pharmacies — should be extended to include biosimilar rare disease treatments, prioritising enzyme replacement therapies and biologic treatments for conditions where domestic biosimilar development has progressed (Gaucher disease, Fabry disease, primary immunodeficiencies).

Fourth, the CoE network should be expanded from 8 to at least 25 centres within five years, with priority for geographic coverage gaps in Maharashtra, Gujarat, Rajasthan, and the north-eastern states. CoE funding should include a dedicated rare disease clinical trials component, enabling academic centres to participate in international rare disease clinical trial networks.

8.3 UK-India Bilateral Regulatory Cooperation

The UK-India Free Trade Agreement negotiations, which included pharmaceutical provisions in their draft text, present a significant opportunity to formalise regulatory cooperation between MHRA and CDSCO in orphan drug development and assessment. A dedicated MHRA-CDSCO Memorandum of Understanding (MoU) on orphan drugs could encompass: joint scientific advice sessions for developers pursuing simultaneous MHRA and CDSCO marketing authorisations; reciprocal sharing of assessment reports and inspection findings; joint rare disease patient registry development using interoperability standards compatible with both NHS Digital and the NIRMAN portal; and a collaborative training programme supporting CDSCO capacity building in gene therapy and advanced biologic assessment. [100]

Specific mechanisms that could reduce trial duplication burden include: mutual acceptance of clinical data packages meeting an agreed common data standard; joint scientific advice on trial design enabling a single clinical development programme to generate evidence acceptable to both regulators; and inclusion of Indian patient cohorts in UK-sponsored rare disease trials, providing both ethno-genomic data and expanded trial capacity. The UK's participation in Project Orbis provides a precedent for multi-country concurrent review; a MHRA-CDSCO pilot for concurrent submission of selected orphan drug applications would be a tangible deliverable for bilateral negotiation.

8.4 Sustainable Financing Models

The financing of orphan drugs particularly gene therapies and high-cost biologics represents one of the most intractable challenges in contemporary health policy. Several innovative financing models merit consideration in both UK and Indian contexts. Outcome-based or performance-based managed entry agreements (MEAs) in which payment is tied to achievement of specified clinical outcomes are already operational in the UK NHS for several gene therapies. Expanding this model and developing standardised contractual frameworks (rather than requiring bespoke negotiations for each product) would reduce transaction costs and improve predictability for both manufacturers and payers. [101]

Amortised payment models — in which the full cost of a gene therapy is spread over 3–10 years, with payment contingent on continued clinical benefit at each anniversary address the budget impact challenge of large upfront costs and align payment with the benefit horizon of these products. Several commercial arrangements of this type have been piloted in the US and Europe. India could explore amortised payment models for gene therapies funded through the NPRD Rare Disease Fund, potentially in partnership with multilateral development banks that could provide bridge financing.

A dedicated public-private Rare Disease Innovation Fund (RDIF) for India modelled on Brazil's Fundo Nacional de Desenvolvimento Científico e Tecnológico rare disease window and the UK's Biomedical Catalyst could provide co-investment in domestic rare disease drug development, reducing the cost of innovation that would ultimately be reflected in pricing. Funding could be sourced through a pharmaceutical innovation cess levied on profitable blockbuster drugs sold in India, creating a cross-subsidy mechanism from commercial pharmaceutical success to rare disease research.

9 CONCLUSION

The post-COVID-19 period has been one of genuine and substantive transformation in orphan drug regulatory policy in both the United Kingdom and India, though the nature, depth, and translation of that transformation into patient benefit differs significantly between the two jurisdictions. In the UK, Brexit has created regulatory autonomy that has been used to good effect through the introduction of the ILAP route, enhanced integration of HTA and international regulatory engagement - with the overall result being a more efficient and coherent orphan drug development milieu. The UK Rare Diseases Framework has offered a policy framework to drive improvement and the integration of genomic medicine is a global best-practice approach to rare disease diagnosis that is increasingly linked to therapeutic intervention.

India has made significant conceptual progress; the NPRD 2021 is the first genuine policy recognition of rare diseases in decades, but the gap between conceptual progress on paper and patient access on the ground is still immense. Lack of resources, limited number of CoEs, lack of HTA, exclusion from health insurance, and a lack of specific legislation, all combine to ensure orphan drugs are not accessible to most of the rare disease population in India. The COVID-19 pandemic demonstrated that CDSCO can accelerate its regulatory processes when political will exists; the challenge now is to institutionalise that acceleration for rare diseases and to couple it with the access policy reforms that will determine whether faster approvals actually benefit patients.

COVID-19 will be remembered in the history of regulatory science as a watershed a period in which the global regulatory community demonstrated that decades of accumulated methodological caution could be superseded, without compromising safety, when the urgency of need was undeniable. For the 300 million people living with rare diseases worldwide for whom urgency has always been the defining condition of their existence the pandemic's regulatory legacy

must translate into permanent acceleration of the pathways that connect scientific discovery to approved, accessible, and affordable treatment. This paper has attempted to map those pathways in two jurisdictions and to identify, with specificity, the reforms required to ensure that the promise of post-COVID regulatory modernisation is fully realised for rare disease patients in the UK and India alike.

Future research should address the health technology assessment convergence challenge specifically, developing a methodology for value assessment of ultra-rare disease treatments acceptable to health systems at different income levels; the governance of genomic data in rare disease drug development; and the specific regulatory requirements for AI-assisted drug development tools in the orphan space. A prospective longitudinal analysis of ILAP's impact on UK rare disease patient access, and an independent evaluation of NPRD 2021 implementation outcomes, are research priorities that would substantially advance the evidence base underpinning orphan drug policy reform.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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