Optimizing Regulatory Review & Approval for Rare Disease Therapies

Global Rare Disease Policy Network

October 2025

Executive Summary

Rare diseases (RDs), though individually uncommon, collectively affect an estimated 6-8% of the global population, yet most remain without effective treatment. Even when therapies exist, regulatory bottlenecks often delay or prevent access, especially in low- and middle-income economies. Conventional regulatory systems were designed for large, randomized trials in well-characterized conditions. They are poorly matched to the realities of RDs: very small and geographically dispersed patient populations, heterogeneous phenotypes, limited natural history data, and constrained clinical evidence. The result is a structurally inefficient and inequitable landscape in which patients in many APEC economies wait years for therapies that may already be available elsewhere.

This paper examines how regulatory agencies across APEC economies and globally can optimize the review and approval of RD therapies to accelerate equitable access while maintaining scientific rigor. It identifies four interlocking problems that systematically hinder RD therapy development and availability:

- **Fragmented concepts and incentives**: Definitions of "rare disease" and "orphan medical product" (OMP) vary widely across jurisdictions, as do criteria for incentives and designation. This undermines predictability for sponsors, complicates cross-border collaboration, and constrains coherent policy planning.
- **Limited data and trial feasibility**: Small, heterogeneous populations and poorly understood natural histories make traditional Phase I–III trial structures difficult or impossible to execute, limit statistical power, and increase uncertainty at the time of initial review.
- **Inefficient, duplicative regulatory processes**: Many agencies lack dedicated pathways for RD therapies, apply standard evidentiary expectations without adaptation, or run sequential assessments with little work-sharing or reliance. This is particularly burdensome in smaller markets with limited regulatory capacity.
- **Underdeveloped life-cycle oversight**: Post-market surveillance, registries, and real-world evidence (RWE) systems for RD therapies are often fragmented or weak, reducing the ability of regulators to refine benefit–risk assessments over time.

At the same time, there is a growing body of practice demonstrating that these constraints are not immutable. Leading regulators have begun to deploy a toolkit of regulatory, scientific, and collaborative innovations that better fit the RD context:

- **Adaptive and flexible pathways**, including conditional approvals, accelerated and rolling reviews, and staged authorization with targeted initial indications, have enabled earlier access while evidence matures, particularly where surrogate endpoints are used.
- **RWE and networked registries** are being used to complement small trials, serve as external controls, and underpin approvals under exceptional circumstances.
- **Collaborative review and reliance mechanisms** such as Project Orbis, the ACCESS Consortium, ASEAN Joint Assessment, and EMA OPEN have shown that parallel work-sharing and structured use of reference-agency assessments can significantly shorten timelines and build capacity.
- **Stakeholder engagement and patient-centric approaches** have improved trial feasibility, endpoint relevance, and alignment between regulatory decisions and what patients value.
- **Regulatory science innovations** in biomarkers, pharmacogenomics, modeling and simulation, and natural history modeling have enabled more nuanced and context-appropriate evidentiary standards.

Drawing on these examples, the paper sets out six priority reforms to optimize regulatory review and approval of RD therapies, with a particular focus on feasibility in resource-limited settings and alignment with APEC's regulatory harmonization agenda:

1. **Converge definitions and designations**: Move toward a harmonized framework for defining RDs and OMPs, including convergence around core definitional elements such as prevalence thresholds, while

explicitly not imposing a single universal definition. International forums (WHO, ICH, ICMRA, APEC) should lead workstreams to align methodologies for defining and periodically revising RD criteria and to promote mutual recognition or reliance for orphan designation among trusted regulators. Within APEC, establishing a Priority Work Area on RDs under the RHSC, coordinated with the Health Working Group, would provide a platform to operationalize this convergence.

2. **Streamline and adapt regulatory requirements**: Establish dedicated, proportionate pathways for RD therapies that incorporate accelerated review timelines, rolling submissions, and conditional approvals as standard options where appropriate. Update guidance to explicitly recognize adaptive and innovative trial designs, surrogate endpoints, and the use of historical or external controls, including Bayesian methods for small populations. Apply targeted flexibilities for requirements that disproportionately burden RD products (for example, certain local testing or stability studies) where strong global quality data exist, while maintaining clear, risk-based justifications.
3. **Enhance global and regional regulatory collaboration**: Expand multi-agency review and work-sharing initiatives for RD therapies and pilot an "Asia-Pacific OMP Work-Sharing" model in which a single dossier is jointly assessed by interested APEC regulators. Systematically use reliance on WHO-listed authorities to avoid duplicative full assessments and focus local review on context-specific issues. Develop common assessment templates and standardized review-report formats to facilitate information exchange. Promote structured training, secondments, and exchange programs so regulators in emerging agencies can learn directly from more experienced authorities.
4. **Increase transparency and communication**: Publish clear, accessible guidance on orphan designation, evidentiary expectations, and RD-specific pathways, including in local languages. Routinely issue public assessment reports that explain the rationale for decisions on RD therapies. Communicate anticipated timelines and milestones and provide non-confidential reasons for delays. Institutionalize early scientific advice procedures, with involvement of patient and clinical experts where appropriate, to clarify expectations and reduce avoidable deficiencies. Use public dashboards and reporting on the use of incentives to strengthen accountability and trust.
5. **Strengthen post-market surveillance and evidence gathering**: Make robust post-market evidence generation a core feature of RD regulation. Require and enforce post-marketing studies and registries as conditions of approval where appropriate and prioritize participation in regional or global RD registries to overcome small sample sizes. Modernize pharmacovigilance through digital reporting channels and use of electronic health record data, supported by clear standards for data quality and privacy. Establish collaborative post-market surveillance networks that share responsibilities for signal detection and analysis. Use RWE in structured life-cycle reassessment frameworks to adjust, restrict, or expand indications as evidence evolves.
6. **Engage and empower patients and advocacy groups**: Institutionalize patient participation in advisory committees, scientific advice, and decision forums for RD products, including through RD patient advisory councils in APEC economies. Support advocacy organizations to build data capabilities, including registries and patient-preference studies that inform benefit-risk assessments. Convene multi-stakeholder workshops early in development to align trial design and endpoints with patient priorities and feasibility constraints. After approval, partner with patient groups to disseminate accurate information on indications, benefits, and risks to improve appropriate uptake.

Taken together, these reforms outline a pragmatic pathway for transitioning RD regulation from a fragmented, reactive system to a more coherent, learning-oriented, and collaborative ecosystem. For APEC economies, the agenda leverages existing regional structures while addressing specific capacity and equity gaps. For regulators globally, it provides an integrated framework for using flexibility, collaboration, and patient engagement to manage uncertainty without lowering standards. Implementing this agenda would help ensure that the promise of scientific innovation in RDs translates more quickly and reliably into meaningful access for patients and families.

Introduction

Rare diseases (RDs), though individually uncommon, collectively affect a significant share of the global population, an estimated 6-8% of people worldwide (roughly 300-500 million individuals).[1,2] About 80% of RDs have a genetic origin and many manifest in early childhood, leading to chronic health issues, severe disability, and high mortality if left untreated.[3] Some RDs such as certain autoimmune disorders disproportionately affect women, often during the prime years of their lives. As such, RDs often impose a high socioeconomic burden on patients, families, health systems, and economies.[4] For example, in the United States (U.S.) the cumulative economic burden of RDs was recently estimated at nearly $1 trillion per year when factoring in direct medical costs and lost productivity.[5] Safe and effective RD therapies can improve quality of life and productivity for patients who would otherwise suffer severe disability or early death and can help reduce long-term costs to individuals and societies. Historically, however, because patient populations are small and development costs high, there was little financial incentive to develop therapies for RDs; so, such potential therapies were termed "orphan" drugs, as they were "orphaned" or neglected by the market. In response, policymakers around the world have introduced special incentives and regulatory pathways to encourage development. Since the U.S. Orphan Drug Act of 1983, hundreds of new therapies for RDs have been approved, bringing hope to millions of patients.[6] Nevertheless, still no therapy exists for most RDs; and for many RDs, just one therapy is available. Access to RD therapies also remains uneven globally, particularly in low- and middle-income economies (LMIEs).

This paper explores how regulatory review and approval processes for RD therapies can be optimized in APEC economies and around the world to accelerate patient access while ensuring the safety and efficacy of therapies and the efficiency and effectiveness of regulatory authorities. The situation, challenges, best practices, and recommendations described in this paper were sourced from publicly available research as well as private discussions with stakeholders in regulatory authorities, health ministries, academic and clinical institutions, biopharmaceutical companies, and patient advocacy groups. Most of these stakeholders are from APEC economies and participate in the Global RD Policy Network (www.rarediseasepolicy.org).

Defining RDs & OMPs Across Jurisdictions

What qualifies as a "rare disease" or an "orphan medical product" (OMP) varies by jurisdiction. Generally, a *rare disease* is defined by a prevalence threshold in the population, and an *orphan medical product* (or *orphan drug* or *orphan medicinal product*) is a therapy intended for such a disease that is granted special status by regulators. It is important to note that therapies can still be authorized to treat RDs without being designated as OMPs. Orphan designation primarily confers specific incentives, such as regulatory support, market exclusivity, and reimbursement or pricing pathways, rather than being a prerequisite for approval. (This paper uses the terms "RD therapy" more generally and "OMP" more specifically where appropriate.) Table 1 summarizes prevalence criteria for qualifying as an OMP or RD in select APEC economies.

As seen in Table 1, definitions can differ dramatically. The U.S. defines RDs by an absolute number (200,000 people), while the European Union (EU), Japan, and others use population prevalence rates.[7] Some economies also include additional criteria in their definitions. For instance, the EU's OMP regulation (EC 141/2000) not only uses a prevalence threshold of 5 in 10,000 people but also requires that no satisfactory treatment exists for the condition, or if one does, the new therapy must provide a significant benefit to patients.[8] (This highlights that therapies can exist for treating a RD but still not qualify for orphan designation if they do not meet the "significant benefit" criteria.) Japan's definition of OMP similarly requires the disease to be serious and lacking adequate treatment options, in addition to affecting fewer than 50,000 people.[9] P.R. China has published an official RD list rather than a numerical prevalence definition, reflecting the government's prioritization of certain conditions for regulatory support. Notably, some jurisdictions extend the orphan designation to medical devices or novel therapies for RDs. For example, Japan can designate orphan medical devices and regenerative medicines under its orphan framework.[10]

Table 1. Prevalence Criteria for Qualifying as an OMP or RD in Select APEC Economies

Jurisdiction	Prevalence Criteria
United States (FDA)	< 200,000 people (approximately 6.4 per 10,000)[11]
European Union (EMA)	< 5 per 10,000 people[12]
Japan (PMDA)	< 50,000 people (approximately 4 per 10,000)[13]
Republic of Korea (MFDS)	< 20,000 people[14]
Chinese Taipei (TFDA)	< 1 per 10,000 people[15]
P.R. China (NMPA)	No fixed prevalence cutoff; a designated list guides orphan status
Australia (TGA)	~1.2 per 10,000 people or not financially viable without incentives[16]
Brazil (ANVISA)	< 65 per 100,000 people[17]
Mexico (COFEPRIS)	< 5 per 10,000 people[18]
Chile (ISP)	< 5 per 10,000 people[19]
Peru (DIGEMID)	< 1 per 100,000 people[20]

Definitional inconsistencies have real implications for global regulatory harmonization. A therapy considered an OMP in one economy might not qualify in another due to these threshold differences. For example, a disease affecting 1 in 5,000 people may be considered rare in the EU and the U.S. but might fall outside Chinese Taipei's much stricter criterion of 1 in 10,000 people.[21] Likewise, Brazil's relatively broad definition (65 in 100,000 people) could classify more diseases as rare than Peru's definition (1 in100,000 people).[22] This lack of alignment means a sponsor could obtain orphan designation and incentives in one region but not in another, complicating multinational development strategies. It also makes regulatory cooperation more difficult. If each agency is working with a different set of eligible diseases, pooling resources or recognizing each other's approvals becomes challenging. Recently, there have been moves toward convergence: in 2022 a WHO-affiliated panel proposed a global RD definition of "≤1 in 2,000 people" to standardize the concept.[23] While not legally binding, such efforts indicate a recognition that common definitions could facilitate international collaboration. While there is probably no need for a *universal* definition, establishing clearer and more consistent definitions of "RD" and "OMP" across jurisdictions would lay the groundwork for harmonized regulatory approaches and easier mutual recognition of orphan status, benefiting patients worldwide.

Challenges in the Development & Regulation of RD Therapies

Limited Patient Population Size for Clinical Trials

By definition, individual RDs each affect very few patients, which makes it difficult to enroll large clinical trials. Traditional trial designs that require hundreds or thousands of participants are usually not feasible. Small sample sizes reduce statistical power and complicate the demonstration of an RD therapy's efficacy.[24] Recruiting sufficient patients often requires multicenter or international studies, which increases operational complexity and cost. In some economies, local patient data is still required despite progress in adopting and implementing ICH E17 guidance on multiregional clinical trials, which can further delay development.[25]

Limited Data Quality & Natural History Knowledge

Many RDs lack extensive medical literature or long-term observational studies, and there may be only a small number of clinical or scientific experts for any given condition. As a result, regulators reviewing a RD therapy often have limited reference data on disease progression in the absence of treatment. Understanding the natural history of the disease is essential for assessing a therapy's effect, yet assembling robust natural

history data can take many years. Patient registries and disease-specific databases can support this process, but they are unevenly available across economies, and many RDs still lack high-quality registry data.[26]

Complexity of Clinical Trial Designs

Because of small population sizes and heterogeneity in disease phenotype, developers of RD therapies frequently rely on non-traditional or innovative trial designs. Adaptive designs, single-arm studies using historical or external controls, and basket trials that group multiple small populations are increasingly used. These approaches can improve feasibility and efficiency but may be more difficult for regulators to evaluate, particularly where statistical and methodological capacity is limited. Selecting appropriate clinical endpoints is an additional challenge. For many RDs where the natural history is poorly characterized, it is difficult to determine which outcomes to measure and over what time horizon. Surrogate endpoints, such as biomarkers, may be used when long-term clinical outcomes are not yet well understood, but the degree of acceptance and comfort with surrogate endpoints varies widely across APEC economies and globally.[27]

Inconsistent or Inefficient Regulatory Processes & Pathways

In many economies, there has historically been no dedicated review pathway for RD therapies, so these products proceed through standard, often lengthy, approval processes.[28] Inconsistent criteria and differing evidence requirements across agencies mean that sponsors may need to prepare multiple, tailored dossiers, increasing cost and time. Lengthy and unpredictable review timelines are also a recurrent concern, especially in LMIEs. For example, while some WHO Listed Authorities typically review OMP applications within 8 to 12 months, less mature regulators have taken several years years due to less streamlined procedures.[29,30] Additional layers of review introduced to enhance safety can inadvertently slow decisions if not clearly scoped and well managed. In one APEC economy, every OMP application is also assessed by a RD review committee of experts, which can add time to the review if its role and timelines are not well integrated into the overall process.[31]

Post-market surveillance presents further challenges. Small patient populations make it more difficult to detect rare adverse events or long-term safety and effectiveness issues. Many regulators, particularly in LMIEs, lack robust pharmacovigilance systems and real-world evidence (RWE) infrastructure to systematically collect, analyze, and act on safety and utilization data for RD therapies.[32]

Innovative Models & Best Practices for Regulating RD Therapies

To address these challenges and accelerate the development, review, and approval of RD therapies, regulators and other stakeholders have begun to implement innovative regulatory models and best practices. Several of these approaches have shown promise in shortening development and review timelines while maintaining evidentiary standards.

Use of Real-World Evidence and Global, Regional & Networked Patient Registries

RWE, defined as data on a therapy's use and outcomes in routine clinical practice, is increasingly recognized as a valuable complement to clinical trial data, particularly for RDs. Given the difficulty of conducting large, randomized trials for RDs, some regulators have accepted RWE to support initial approvals, indication expansions, or post-authorization changes for RD therapies. For example, historical patient registry data have been used as external control arms in trials for RDs, allowing single-arm studies to demonstrate a therapy's benefit by comparison with the natural course of the disease.[33] The U.S. FDA, under the 21st Century Cures Act, has established pilot programs to assess how RWE can inform regulatory decisions, and one early application involved using registry data to confirm the benefit of an RD therapy.[34] In Europe, several OMPs have been authorized under "exceptional circumstances" with the requirement that registries be established to collect efficacy and safety data over time, effectively making RWE generation a condition of approval.[35] Japan and P.R. China are also developing RD registries to generate locally relevant data for regulatory and policy decision-making.[36]

There is ongoing debate about the optimal scale and structure of registries. Some regulators and stakeholders advocate for global registries to maximize statistical power and enable more robust analyses. Others emphasize the advantages of regionally coordinated registries that align with local clinical practice, health system characteristics, and data standards. A promising example is the European Reference Networks (ERNs), which link centers of excellence, key opinion leaders, and disease-specific registries across economies. ERNs illustrate how networked, federated registries, supported by clinical, research, and policy infrastructure, can generate high-quality RWE and inform regulatory decision-making. Similar models could be adapted in other regions to support cross-border pooling of RD data, especially for ultra-rare conditions.

Despite these advances, important challenges remain, including variability in data quality, completeness, and comparability across registries and health systems. International standards and guidance, including those developed by organizations such as ICH, aim to improve the reliability and interpretability of RWE. Overall, leveraging RWE through both global and regionally coordinated collaborations is increasingly regarded as a best practice for augmenting limited trial data in the regulation of RD therapies.

Adaptive & Flexible Regulatory Pathways

Traditional linear development (Phase I → II → III → approval) can be inefficient for addressing urgent needs in RDs. A key emerging best practice is regulatory agility: adapting evidentiary expectations and review processes to the specific context of an RD, rather than rigidly applying uniform requirements. Adaptive pathways, conditional approvals, and rolling reviews are notable examples.

Adaptive pathways (also known as adaptive licensing) grant approval in stages, with progressive expansion to broader patient populations as additional evidence is generated. In the European Medicine Agency (EMA)'s Adaptive Pathways pilot, a promising therapy could first be authorized for a narrowly defined subgroup, with indications later expanded as more data from pragmatic trials or RWE studies became available. In one case, a therapy was initially approved for a rare subset of a disease and then extended to a wider population following confirmatory data, illustrating how staged authorization can balance early access with ongoing evidence generation.[37]

Conditional approvals represent another tool. Both the EMA and U.S. FDA have mechanisms that allow therapies to be approved on the condition that post-marketing studies are conducted. This approach is particularly relevant when surrogate endpoints suggest substantial benefit (e.g., improvement in a laboratory measure in a metabolic disease), but definitive clinical outcomes require longer follow-up. Many oncology products, including those targeting rare tumor subtypes, have been approved through such pathways, enabling earlier patient access while obligating further trials.[38] Regulators in other regions have adapted similar concepts. For instance, Japan and P.R. China have established conditional approval pathways for both OMPs and regenerative therapies.[39]

Rolling review is an additional procedural innovation. Instead of waiting for a sponsor to submit a complete dossier, a regulator may accept data in modules as they become available (e.g., under Fast Track designation in the U.S.). By the time final data, such as Phase III study reports, are submitted, reviewers have already examined earlier components such as preclinical and initial clinical data, thereby reducing overall review time. During the COVID-19 pandemic, rolling reviews were widely used to accelerate vaccine approvals. Applying similar approaches to RD therapies, particularly those addressing high unmet need, can deliver comparable gains in timeliness. Some agencies have institutionalized these practices through dedicated review teams or specialized RD or OMP offices. For example, Australia's Therapeutic Goods Administration created an Orphan Drug Program to help coordinate and expedite the review of OMP applications and administer incentives such as fee waivers.[40]

Collaborative Review Initiatives & Reliance Mechanisms

Collaborative regulatory programs provide platforms for simultaneous, parallel, or shared review of therapies by multiple authorities, which is particularly valuable for RD therapies whose markets are small in each individual economy. Project Orbis, led by the U.S. FDA, brings together regulators from economies such as Australia, Brazil, Canada, Singapore, and others to conduct parallel reviews of oncology therapies. Some of

these products have orphan designation for rare cancers, and Project Orbis has enabled approvals in participating economies within days of the U.S. FDA decision, substantially narrowing access gaps.[41] Similarly, the ACCESS Consortium (Australia, Canada, Singapore, Switzerland, United Kingdom) is implementing work-sharing for the evaluation of innovative medicines. In Southeast Asia, the ASEAN Joint Assessment procedure enables several ASEAN economies to collectively evaluate medicines. To date, it has been used predominantly for vaccines and some widely used medicines, but it establishes a procedural and institutional precedent that could be extended to RD therapies. Another noteworthy initiative is EMA OPEN, launched by the EMA to provide collaborative scientific and regulatory support to non-EU regulators. Although initially focused on oncology and high unmet-need conditions and aligned with EU PRIME candidates, EMA OPEN has clear relevance for RD therapies. Brazil and the Republic of Korea have participated in the program, and there are indications of interest in expanding such collaboration, including for RD therapies.[42]

Reliance mechanisms, where one regulator formally relies on all or part of the assessment conducted by a trusted reference authority, are also gaining traction as a pragmatic form of collaboration. For example, Mexico and several other Latin American regulators have procedures to fast-track approval of a therapy already authorized by the U.S. FDA or EMA, reducing the local review primarily to economy-specific considerations such as labeling and pharmacovigilance arrangements.[43] These collaborative and reliance-based models are emerging best practices because they reduce unnecessary duplication of effort, promote more consistent evaluation standards, and can significantly shorten approval timelines in smaller or resource-constrained economies. The sharing and structured use of external expertise are particularly valuable for complex RD reviews, where an economy that lacks in-depth experience with a specific condition or product can leverage the assessment conducted by another agency with greater familiarity.

Stakeholder Engagement & Patient-Centric Approaches

Successful approvals of RD therapies frequently involve structure engagement among patients, caregivers, clinicians, regulators, and industry. A central best practice is systematic incorporation of patient perspectives and data into development and review. Regulators are increasingly considering patient-reported outcomes (PROs) and quality-of-life (QoL) measures when evaluating RD therapies, recognizing that conventional clinical endpoints may not fully capture what matters to patients. Patients and advocacy organizations have contributed to protocol design, making trials more feasible and aligned with real-world needs, and have provided critical input on acceptable levels of uncertainty and risk given the severity and prognosis of many RDs.

Multistakeholder collaborations are well established in the RD field. The International RD Research Consortium (IRDiRC), for example, brings together public and private partners to share research data and align on objectives for new therapies. Although primarily research oriented, IRDiRC maintains a policy function that engages with regulators to address development and regulatory bottlenecks. Public-private partnerships have also been used to support and de-risk development. The EU's Innovative Medicines Initiative has funded collaborative projects for specific RDs, generating data and methodological tools that subsequently inform regulatory assessment.

Regulators have created mechanisms to embed such engagement earlier in the development pathway. The EMA's Scientific Advice Working Party (SAWP), for instance, offers scientific advice procedures that can include patient representatives and external experts, enabling sponsors and regulators to jointly anticipate key evidentiary questions and reduce avoidable delays later in review. A frequently cited example is Spinraza (nusinersen) for spinal muscular atrophy, where patient advocacy organizations supported early research, the sponsor engaged in frequent consultations with regulators in the U.S. and Europe, and regulators applied expedited review tools.[44] This coordinated, patient-centric approach contributed to rapid authorization and availability, with ongoing patient registries continuing to inform its long-term safety and effectiveness profile.

Regulatory Science Innovation

Regulators are also adopting novel scientific tools to support the evaluation of RD therapies. Biomarkers and surrogate endpoints are increasingly being qualified through formal programs, such as U.S.

FDA's Biomarker Qualification initiatives and EMA's adaptive pathway discussions, so that they can be used more reliably in clinical development and regulatory decision-making. Advances in pharmacogenomics and characterization of genetic subsets enable more precise targeting of therapies, which regulators generally encourage because it can improve trial efficiency and success rates in RDs.

Another emerging best practice is the use of modeling and simulation, including disease progression models and AI-based analytical methods, to help predict outcomes when empirical data are limited. For example, in one rare pediatric disease, U.S. FDA accepted model-derived natural history data as a critical complement to evidence from a small clinical trial. These scientific tools, while technically complex, are becoming part of the standard toolkit that mature regulatory agencies use to exercise flexibility in RD regulation, while remaining grounded in transparent, evidence-based assessment.

Recommendations for Optimizing Review & Approval of RD Therapies

Improving the regulatory ecosystem for RD therapies requires coordinated action on multiple fronts. The following evidence-informed recommendations are meant for policymakers, regulatory agencies, the biopharmaceutical industry, and patient advocacy groups. They prioritize feasibility in resource-limited settings and aim to strengthen global regulatory convergence, transparency, biomedical innovation, and access.

1. Converge Definitions & Designations

Regulatory agencies should move toward a common global understanding of RDs and RD therapies. Agencies should collaborate through platforms such as WHO, ICH, and APEC to standardize criteria for RD designation, for example by adopting a prevalence threshold in the range of 1 in 2,000 people (as recently proposed by RDs International and supported by the UN).[45] The objective is not to impose a single, universal definition of RDs across all jurisdictions, but to promote a harmonized framework and methodology for defining RDs and revising those definitions over time as evidence, epidemiology, and policy priorities evolve. Convergence on core definitional elements does not require identical legislation across jurisdictions, but it would substantially ease regulatory cooperation, industry planning, and comparative policy analysis.

A harmonized definitional framework would help align R&D incentives globally, allowing companies to design development programs around clearly defined RD population and consistent eligibility criteria for incentives. International regulatory forums such as ICMRA, ICH, and APEC should establish dedicated workstreams on RD and OMP definitions and designations to drive this convergence. Within APEC, a Priority Work Area under the Regulatory Harmonization Steering Committee (RHSC), coordinated with the APEC Health Working Group (HWG), could ensure that efforts address both technical regulatory alignment and upstream policy reforms.

Regulators should also explore mutual recognition or reliance models for orphan designation. Where a product has been granted orphan status by a trusted reference authority, other agencies could accept that designation and focus their own review on benefit-risk assessment and local safety, efficacy, and pharmacovigilance considerations. This would reduce duplicative work, shorten timelines, and enable more efficient use of limited regulatory resources.

2. Streamline and Adapt Regulatory Requirements

Regulatory processes should be made more flexible and efficient for RD therapies while maintaining rigor. Regulatory agencies, particularly in LMIEs, should establish or refine dedicated pathways for RD therapies that provide clear, predictable, and proportionate requirements. This can include setting accelerated review timelines for RD applications (e.g., 6- to 9-month targets), and systematically enabling tools such as rolling reviews and conditional approvals where appropriate. Guidance should be updated to explicitly recognize adaptive trial designs and the use of surrogate endpoints for RDs, providing sponsors with clarity on acceptable evidentiary approaches. For instance, regulators can issue guidance on the use of historical or external controls and Bayesian statistical methods in small populations.

Regulators should also encourage innovative trial designs that are particularly well suited to RDs, such as platform trials (i.e., testing multiple therapies in a single disease) and basket trials (i.e., testing a single therapy across multiple RDs sharing a common biomarker), and signal that robust results from such designs can be considered for approval. In parallel, agencies can consider targeted flexibilities for requirements that may disproportionately burden RD therapies, such as local sample testing prior to approval, routine post-import testing, or extensive climate-specific stability studies, especially where global manufacturing controls and stability packages are strong. For example, the Republic of Korea has waived certain sample-testing requirements for orphan-designated therapies, instead relying on post-approval monitoring and commercial batch trend data.

Internally, regulators may wish to create centers of excellence or specialized review teams or offices focused on RD evaluations to organize and build technical expertise, ensure consistent application of flexible approaches, and improve review efficiency. By streamlining requirements and tailoring expectations to the realities of RD development without lowering evidentiary standards, agencies can reduce development costs and timelines and make investment in RD therapies more attractive and feasible.

3. Enhance Global Regulatory Collaboration

Regulatory agencies should leverage cooperation to maximize efficiency, reduce duplication, and build regulatory capacity. Programs such as Project Orbis, the ACCESS Consortium, and ASEAN Joint Assessment should be expanded to include additional therapeutic areas or more participating economies. APEC economies could pilot an “Asia-Pacific OMP Work-Sharing” initiative in which a single dossier is reviewed jointly by interested regulators, analogous in concept to the EU’s centralized procedure. This approach is particularly valuable for small economies: instead of each authority evaluating an RD therapy sequentially over several years, a joint review can enable near-simultaneous approvals.

Where robust local trial data are not available, agencies should make systematic use of work-sharing and reliance on assessments conducted by WHO-listed authorities rather than duplicating full reviews. This approach is endorsed by WHO and has precedents in collaborative initiatives such as Project Orbis. Reliance allows regulators to focus on context-specific issues, including labeling, pharmacovigilance, and risk management, while leveraging the scientific assessments of reference authorities. For agencies in LMIEs, formal reliance agreements that commit them to largely accept the decisions or assessments of designated reference authorities for RD therapies can help ensure that patients are not left waiting for access due to limited local capacity.

International organizations should facilitate structured training, secondments, and exchange programs in which regulators from LMIEs work within more experienced agencies to learn best practices in RD evaluation and bring that expertise back to their home institutions. In parallel, regulators should develop common assessment templates for RD therapies, or standardized review-report formats, that can be shared across agencies to ease information exchange and support convergence in evaluation criteria. Collaboration should extend into the post-approval phase as well. Regulators can agree to share the burden of monitoring global post-market studies, registries, and other RWE efforts. For example, one agency might lead analysis of safety data while another focuses on effectiveness or utilization, with findings shared across participating authorities.

4. Increase Transparency and Communication

Regulatory agencies should build trust and predictability through openness. Regulatory bodies should make their processes, criteria, and expectations for RD therapies as transparent as possible. This includes publishing clear, accessible guidance on orphan designation and approval requirements, ideally in local languages, and issuing public assessment reports for approved RD therapies that explain the basis for regulatory decisions, as the EMA already does. Regulators should also communicate anticipated review timelines and key milestones so that sponsors, clinicians, and patient groups can plan accordingly. When delays occur, providing non-confidential reasons (for example, requests for additional data or need for expert consultation) enables stakeholders to respond constructively and reduces uncertainty.

Early and structured scientific advice should become standard practice, including, where appropriate, participation by patient representatives and clinical experts. Proactive dialogue at the protocol- and development-plan stage can clarify evidentiary expectations, prevent avoidable deficiencies, and reduce the risk of complete response letters or rejections due to misaligned trial designs or endpoints. Transparency should extend to oversight of processes and incentives, too. Public-facing dashboards can track applications for RD therapies (without disclosing proprietary information), indicating how many are in process, their stage of review, and high-level statuses. The U.S. FDA's Orphan Drug office provides a model that others could adapt. Likewise, governments and regulators should report on the use and impact of incentives such as grants, tax credits, and fee waivers, to demonstrate policy commitment, identify bottlenecks in uptake, and inform potential adjustments to better support RD development.

5. Strengthen Post-Market Surveillance and Evidence Gathering

Invest in robust follow-up to ensure long-term safety and effectiveness. Because many RD therapies are approved on the basis of limited or non-traditional data, strong pharmacovigilance and phase IV evidence generation are essential. Regulators should routinely require and actively facilitate post-marketing studies and registries as conditions of approval and should monitor and enforce their completion. Where feasible, regulators should encourage sponsors and clinical networks to participate in regional or global RD registries, or to join existing platforms, rather than relying solely on fragmented domestic registries. For example, an Asia-Pacific registry for a particular RD could aggregate patients from multiple economies, providing each regulator with more robust data than would be possible at the jurisdictional level. Governments and companies can share costs and governance responsibilities for such initiatives.

Pharmacovigilance systems should be modernized to improve signal detection in small populations. This can include enabling adverse-event reporting via mobile applications, portals managed by patient organizations, and other user-friendly channels that capture information which might be missed in traditional, provider-based systems. Where electronic health records and other digital health infrastructures are available, regulators should promote the use of these real-world data sources to monitor outcomes, utilization patterns, and off-label use. Clear guidance on data standards, privacy protections, and analytic methods will be important to ensure that these data are fit for regulatory purpose.

Regulators should periodically re-assess RD therapies in light of emerging evidence. If post-market data fail to confirm expected benefits or reveal safety concerns, agencies may need to adjust approval conditions, update prescribing information, or in some cases restrict indications. Conversely, if real-world experience demonstrates consistent benefit in additional rare subsets or in broader populations, regulators should be prepared to expand indications without imposing unnecessary new trials where the totality of evidence justifies such decisions. To address capacity constraints, economies can establish collaborative "post-market surveillance networks" that share responsibilities for monitoring global safety signals, analyzing registry and real-world data, and disseminating findings. Structured collaboration of this kind, combined with systematic use of RWE in ongoing regulatory decision-making, allows initial approvals made under uncertainty to be refined over time based on actual patient experience. This strengthens confidence in RD therapies and supports more informed, effective use in clinical practice.

6. Engage and Empower Patients and Advocacy Groups

Regulatory agencies should make patients structured partners in regulatory decision-making. Policymakers and regulators should institutionalize the role of patient advocacy organizations in the development and evaluation of RD therapies. This includes formal inclusion of patient representatives in advisory committees, scientific advice procedures, and decision forums for RD products, as is already standard in the EU and increasingly at U.S. FDA. In the APEC region, regulators could establish RD patient advisory councils that provide regular input on upcoming policies, review paradigms, and priority-setting.

When evaluating an RD therapy, regulators should systematically seek patient input on which outcomes matter most and explicitly consider qualitative and experiential evidence, including patient testimonies and preference studies, alongside clinical data. Multi-stakeholder workshops early in

development, bringing together sponsors, regulators, clinicians, and patients, can align trial design, endpoint selection, and evidence requirements, reducing the risk of avoidable delays due to misaligned expectations. Industry should embed patient engagement in protocol design and feasibility assessments to ensure that studies are realistic and responsive to lived experience. Patient organizations can also play a central role after approval. By partnering with health authorities and professional societies, they can support dissemination of accessible, accurate information about new therapies, including eligibility, expected benefits and risks, and access pathways.[46] This can improve uptake, support appropriate use, and help ensure that the benefits of RD innovation reach affected communities.

Conclusion

RDs present a persistent mismatch between urgent patient needs and the structure of most regulatory systems. Small, heterogeneous patient populations, incomplete natural history data, and limited trial feasibility create inherent evidentiary constraints. Standard, linear development and approval models were not designed for this context. If regulators apply them without adaptation, promising therapies arrive late or not at all, particularly in smaller and resource-constrained markets.

The evidence and examples reviewed in this paper demonstrate that regulators already have a growing toolkit to respond more effectively. Adaptive and conditional pathways, rolling reviews, and the structured use of surrogate endpoints and innovative trial designs can shorten time to decision while maintaining a clear focus on benefit-risk. RWE, supported by well-governed global and regional registries, is increasingly central to initial approvals and to the lifecycle re-evaluation of RD therapies. Collaborative review initiatives, work-sharing arrangements, and formal reliance on trusted reference authorities reduce duplication, support convergence in standards, and build capacity in agencies, particularly in LMIEs. Regulatory science innovations in biomarkers, pharmacogenomics, and modeling and simulation provide additional flexibility that is still grounded in explicit, transparent methods.

Building on this foundation, the recommendations in this paper set out a practical agenda for optimizing regulatory review and approval of RD therapies. Converging definitions and designations through harmonized frameworks and methodologies can make orphan status more predictable and portable across jurisdictions, without requiring a single universal definition. Streamlining and adapting regulatory requirements for RD therapies, including through dedicated pathways and calibrated flexibilities, can reduce unnecessary barriers while preserving rigor. Deepening global collaboration, particularly through APEC and other regional platforms, can institutionalize work-sharing, reliance, and joint oversight of post-market evidence. Greater transparency about processes, timelines, and decisions will increase trust and enable more efficient planning by sponsors and patient groups. Strengthening post-market surveillance and systematic RWE use will allow agencies to refine initial decisions in light of real-world experience. Finally, embedding patients and advocacy groups as structured partners will ensure that regulatory choices align with the outcomes and trade-offs that matter most to affected communities.

For APEC economies, these steps are both an opportunity and a necessity. Many face constrained regulatory resources, fragmented RD data, and varying levels of policy maturity, yet they also have active regional forums and a growing base of technical expertise. By prioritizing RD therapies within existing regulatory harmonization agendas, piloting RD-focused work-sharing mechanisms, and investing in shared registry and pharmacovigilance infrastructure, APEC regulators can move quickly toward more consistent and efficient approaches. The same principles are applicable in other regions and at the global level.

Optimizing regulatory review and approval for RD therapies is not a single reform but an ongoing process of alignment, learning, and adjustment. Agencies that adopt a lifecycle approach to evidence, collaborate across borders, and engage patients as core partners will be better positioned to manage uncertainty while delivering earlier, more equitable access to effective therapies. If regulators, policymakers, industry, and patients act on the agenda outlined here, RD regulation can shift from being an obstacle to becoming an enabling platform for innovation and access.

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