



Better Health, Brighter Future

Strategies for Rare Diseases: International Landscape Report

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Introduction

Our Unique Perspective on Developing Drugs for Rare Diseases (DRDs)

Takeda is one of the world's oldest and fastest-growing pharmaceutical companies. Founded in Japan in 1781, we now operate in more than 80 countries worldwide, including Canada. More than a decade ago, Takeda made the strategic decision to become a specialty medicines company and today, we have evolved into the global leader in drugs for rare diseases (DRDs). 40% of our marketed products are DRDs, and more than 50% of our pipeline products have an orphan drug designation (as per the U.S. FDA and EU EMA definitions). Taken together, our longstanding commitment to DRDs and our extensive global footprint provides Takeda with a unique opportunity to synthesize how different countries have developed their own tailored approaches to expediting and expanding access to new treatments for rare diseases.

In anticipation of Health Canada's consultation on DRDs, Takeda Canada engaged a wide range of experts from across Takeda's network of international affiliates to provide us with a foundational understanding of multiple policy approaches. The research and interviews we conducted generated numerous insights and a set of key themes that added context to our formal submission to Health Canada's consultation on high-cost rare drugs.

As our work progressed, we quickly realized that the insights gathered from around the world could have independent value beyond our formal consultation submission. This document is Takeda Canada's effort to capture the rare disease policy experiences of more than 20+ colleagues from around the world. As a result, it is intended as a **descriptive** document, and one we hope complements Health Canada's own independent analysis. We are pleased to share this report as a companion piece to our submission, and we look forward to any questions, comments or feedback it generates.

Methodology

Takeda Canada adopted a three-part plan to assemble this report. First, we reviewed the membership of the Paris-based Organization for Economic Cooperation and Development (OECD) and identified 16 countries we felt were valid comparator jurisdictions to Canada (and, where applicable, the European Union (E.U.) as a 17th analogue):

EUROPE	ASIA	NORTH AMERICA
Austria Belgium Denmark U.K. – England* European Union France Germany Ireland Italy U.K. – Scotland* Spain/Iberia Switzerland The Netherlands	Australia Japan South Korea	United States

**England and Scotland are countries within the United Kingdom of Great Britain and Northern Ireland, and each is responsible for the assessment, access, and reimbursement of drugs for its constituent population.*

Second, we conducted secondary research on each country’s rare disease regulatory and reimbursement frameworks. From this foundational research, we developed a detailed interview guide shaping our follow-on discussions. Third, we identified and interviewed senior colleagues with knowledge of – or direct experience working in – those comparator jurisdictions. Two key questions informed our discussions:

1. *From your local or regional expertise, are there policies or pathways supporting access to drugs for rare diseases that Canada should consider?*
2. *Conversely, are there policies or pathways for rare diseases that are inadvertently or unintentionally impeding better access to drugs for rare diseases? If so, what was the imperative behind them?*

As we engaged our colleagues around the world, we also kept in mind the three objectives upon which Health Canada is basing its consultations:

1. *How to improve patient access to high-cost drugs for rare diseases and ensure that access is consistent across the country?*
2. *How to ensure decisions on funding high-cost drugs for rare diseases are informed by the best available evidence?*
3. *How to ensure spending on high-cost drugs for rare diseases does not put pressure on the sustainability of the Canadian health care system?*

Combining information from both primary and secondary research, Takeda Canada identified the key insights outlined over the coming pages (and comprehensively documented in Appendix A). Although this report is inherently written from the company's perspective, considerable effort was taken to ensure that the findings focus on objective policy analysis rather than subjective policy recommendations.

Key Conclusions

Our research identified the following elements that have informed the successful implementation of rare disease approaches throughout 17 comparator jurisdictions:

1. Identifying an Objective and Harmonized Definition of “Rare Disease”
2. Incorporating DRDs into a Holistic Rare Disease Strategy
3. Reflecting Disease Rarity in Market Exclusivity & Investment Support
4. Creating Accelerated Regulatory and Early Access Pathways
5. Maximizing Shared Value Through HTA, Pricing and Reimbursement
6. Leveraging the Benefits of Accessible Data Collection, Diagnostic Screening, and Patient Registries
7. Improving and Extending Networks of Researchers, Clinicians and Patients

1. Identifying an Objective and Harmonized Definition of “Rare Disease”

Aligning on a definition of rare disease is essential to building a strategy

From our interviews, a clear consensus emerged around the importance of establishing a single objective definition of what constitutes a “rare disease.” In many countries, access to DRDs was seen to have been slowed because of the different definitions used by different stakeholders or the inconsistent application of a definition across different DRD reviews.

Identifying a standardized and transparent definition to designate rare disease status aligned with stakeholders and international jurisdictions is essential. The definition must avoid setting the bar in a way that excludes relevant rare disease patient populations. Absent this alignment, the likelihood of individual rare diseases and their related DRDs “falling through the cracks” rose significantly.

While England’s National Institute for Health and Care Excellence (NICE) has a health technology assessment (HTA) pathway that has been adapted for very rare diseases, the criteria for entry into this pathway are open to interpretation, which can lead to variation between how different DRDs are chosen for review. For example, a condition to enter NICE’s rare disease HTA pathway is “the

condition is chronic and severely disabling,” a highly subjective criterion and can therefore easily vary from review to review depending on many factors.ⁱ

In contrast, Germany was highlighted as a jurisdiction that took a more consistent and objective approach to evaluate DRDs.ⁱⁱ If a DRD has received an orphan designation from the European Medicines Agency (EMA), a special legal framework automatically comes into force, and the medicine is evaluated along a separate pathway from non-DRDs. Further, Germany applies an objective revenue test to these products: following market authorization, if the annual sales of a DRD exceed a predefined threshold (50M Euro), the drug is re-evaluated within the non-DRD HTA pathway.

2. Incorporating DRDs into a Holistic Rare Disease Strategy

DRDs should be part of a comprehensive rare disease strategy that addresses all parts of the rare disease journey

In many cases, rare diseases are life-threatening, debilitating and genetically acquired. As rare diseases are more commonly seen in children, their impact is felt well beyond the patient and they frequently require considerable attention and care from families and caregivers. By definition, each rare disease innately represents a small population that is often under-studied. This contributes considerable clinical uncertainty to the medical care and outcomes of patients with rare diseases. Moreover, few rare diseases have medicines for treatment. This reality accounts for the jurisdictions whose policies, regulatory review, and HTA pathways distinguish between DRDs and other medicines to increase treatment options for patients living with rare diseases.

Many jurisdictions we reviewed have adopted a holistic approach to treating rare diseases – one that embeds a set of specific DRD-focused protocols and processes within an overarching policy framework that incorporates multiple measures to support patients with rare diseases.ⁱⁱⁱ In our interviews, it became clear that a number of common factors were instrumental to the success of comprehensive national strategies targeting rare disease policy.

- **Sufficient Scope:** The most successful overarching strategies include measures and programs to identify, treat and support patients with rare diseases and their caregivers. It was noted that an implementation plan to accompany a strategy was vital to action and accountability.
- **Senior Political Advocacy:** Strong political support and sponsorship from a Government Minister was highlighted as instrumental to the rare disease strategy of the United Kingdom.

- **Sustained Stakeholder Engagement:** Once the scope of the rare disease strategy was defined, the U.K. and Denmark were identified as leading examples of countries that established a dedicated, formalized Working Group to oversee the development of the Rare Disease strategy. Giving all relevant stakeholders – especially patients – significant and sustained representation on any Working Group is the mechanism most likely to ensure that the strategy ultimately developed is regarded as credible and legitimate.
- **Dedicated Funding:** The availability of dedicated funding won't automatically guarantee the success of a specific national rare disease strategy – but the absence of dedicated funding makes success almost impossible.
- **Ongoing Evaluation and Updating:** Effective rare disease strategies have to be consistently and transparently evaluated on a regular basis, with findings incorporated into future iterations of the strategy. To name one prominent example, France regularly updates its national rare disease strategy every few years.

3. Reflecting Disease Rarity in Market Exclusivity & Investment Support

Incentives can be an effective tool to promote R&D for DRDs

Several jurisdictions use extended market exclusivity to incentivize and reward the development of DRDs. A 10-year period of market exclusivity is legislated in the E.U.,^{iv} and that general period is not uncommon across the countries we reviewed. South Korea has adopted an 11-year time frame, while France adds two years to the E.U. standard for a 12-year period of exclusivity for orphan drugs for pediatric use.^v Interestingly, the U.S. provides seven years of exclusivity for orphan drugs.^{vi}

Beyond measures to protect the intellectual property of DRDs, multiple countries – including the U.S.,^{vii} Belgium,^{viii} Japan,^{ix} Switzerland^x and Australia^{xi} – also offer incentives to pharmaceutical manufacturers, either through tax credits, research grants or waiving regulatory fees (e.g., to encourage local research and development activities into orphan drugs). France's approach to funding some of the research & development costs associated with the development of DRDs contributed to a critical mass of rare disease clinical trials taking place across the country, which in turn provided early DRD experience to physicians and early access to patients.^{xii}

4. Creating Accelerated Regulatory and Early Access Pathways

Accelerated regulatory and early access pathways can deliver needed treatments to patients faster and address risk for payers

As part of their process for market authorization, many developed economies have accelerated regulatory processes for medicines based on disease severity or unmet need. These expedited processes typically take two non-mutually exclusive forms – either a compressed review period (e.g., the E.U.) or exemptions from typical technical dossier requirements (e.g., Japan, Germany).

A common approach to expediting access to DRDs is through Early Access Programs (EAPs) – also known as Expanded Access Programs in the U.S.^{xiii} EAPs provide a mechanism for patients to access medicines during the pre-regulatory approval phase via their treating physician when specific criteria are met. As an added benefit, EAPs not only provide physicians with early experience in using new medicines, they also offer payers an opportunity to evaluate those medicines in a real-world setting. In some countries, post-regulatory early access reimbursement schemes are used to reduce the time between regulatory approval and access.

In one interview, it was highlighted that French authorities view clinical trials for rare diseases as a “proof-of-concept,” and local real-world evidence is required to decrease clinical uncertainty and inform the country’s HTA process following regulatory approval from the European Medicines Agency (EMA).^{xiv} Known as “Temporary Authorization for Use” (ATU), the French program provides DRD access on a case-by-case basis – known as Nominative ATU – or for a group of patients that are treated and monitored according to a defined management algorithm – known as Cohort ATU. In both models, the authorized DRD is reimbursed by the payer for a specific duration.

Although the ATU initially reimburses the cost of a DRD at its list price, once the drug-specific program is over and the drug is listed, a new price is negotiated, and the manufacturer must retroactively refund the public payer the difference between the list and negotiated price.

Most jurisdictions with EAPs have designed the programs to be explicitly time-bound with clear and detailed steps leading to either product delisting and/or patient grandfathering. This approach mitigates the risk of patients with a rare disease losing access to a treatment prescribed through an EAP if pricing and access negotiations are ultimately unsuccessful.

5. Maximizing Shared Value Through HTA, Pricing & Reimbursement

DRDs require alternative HTA approaches that include reimbursement with evidence generation and decisions based on budget impact rather than traditional HTA measures

While most countries interviewed have a process to evaluate the benefit of a DRD within their HTA bodies, there is no universally accepted HTA framework used to assess DRDs. On one end of the HTA spectrum, some countries, such as Germany and France, assume an inherent clinical benefit to DRDs that received regulatory approval. Other countries, including Germany, France, and Italy, do not require a formal cost-effectiveness analysis in the assessment of DRDs.

On the other end of the HTA spectrum, some countries have adapted existing frameworks to account for the characteristics of DRDs. For example, England and Scotland use cost-effectiveness analyses (CEA) as part of their deliberation framework, but they adapt the assessment and/or interpretation of the CEA to allow for greater uncertainty. Additionally, several of the jurisdictions we studied, such as Scotland and England, incorporate a mix of clinical expertise and patient perspectives – with England’s NICE explicitly including patients with rare diseases as part of its expert committee deliberations^{xv}.

Scotland and The Netherlands use the initial assessment to identify the areas of uncertainty and work with industry to generate the information required to decrease the uncertainty in anticipation of an HTA re-evaluation once the data have been collected. In The Netherlands, the conditional coverage mechanism required to generate the information has pre-arranged parameters including duration, price, and execution plan to provide clarity through the process.

Austria and Italy have created case-by-case pathways that reimburse patient access to drugs that have not gone through an HTA but meet specific regulatory and clinical requirements.

The majority of pricing frameworks incorporate the incremental benefit of the DRD in the final negotiated price, but the countries we reviewed were divided between those that took a formulaic approach to price-negotiations (e.g. France and England) and those that relied on price-setting through less formulaic negotiations with manufacturers (Spain and Germany). The U.K. is creating a separate fund for drugs with considerable uncertainty – called the Innovative Medicines Fund – intended to fund DRDs for a defined period during which sufficient real-world evidence is gathered to support a second appraisal of effectiveness.^{xvi,xvii} Italy’s orphan drug funding structure is unique in that AIFA’s National Fund is partially funded by industry using a formula based on a company’s annual costs for promotional activities.

Jurisdictions have also introduced a number of mechanisms to limit payer financial risk, including capping prescribing volumes (France and at the sick fund level in Germany). As a tool that promotes risk-sharing between manufacturers and payers, flexible confidential agreements and outcomes-based reimbursement models were highlighted as especially useful for DRDs.

6. Leveraging the Benefits of Accessible Data Collection, Diagnostic Screening, and Patient Registries

National accessible data collection drives early diagnosis and research in drugs for rare diseases

Since so many rare diseases manifest themselves in childhood, newborn screening often plays a pivotal role in identifying certain conditions at an early enough stage to initiate therapy and change the natural course of the disease.^{xviii} Many countries, including the U.K. and Austria, fund national newborn screening programs (on a mandatory or opt-out basis) that are universally available to ensure high population coverage.^{xix,xx} These newborn screening programs usually cover a wide range of rare diseases that are amenable to early intervention and treatment. Austria's nationwide newborn screening program appears to screen the highest number of conditions – 28 diseases and conditions.^{xxi}

Many European countries have developed and implemented national patient registries to further support the treatment of rare diseases. Registries allow data to be used to expedite diagnosis, improve patient treatment pathways, reduce uncertainty, and support outcomes-based agreements, all while ensuring appropriate patient confidentiality. Given their importance, registries have been highlighted in The Netherlands and other European countries as a key data collection tool for multiple stakeholders – including regulators and HTA bodies, clinicians, academic organizations, patient groups and manufacturers.^{xxii,xxiii}

7. Improving and Extending Networks of Patients, Researchers and Clinicians

Centres of excellence that include patients, researchers and clinicians are a key model of success in Europe

Focusing on patients and patient groups, several countries – including Italy, France, England and Scotland – have taken important, tangible steps to integrate patients and patient groups into

developing, implementing, and evaluating their rare disease strategy. Substantial trust has been established between patient groups and government, allowing patient groups to act as a “trusted partner” in the design and ongoing implementation of a rare disease strategy. Transparency of funding and a code of conduct governing the relationship between industry and patient groups was instrumental in developing this trust.

It was noted that rare disease strategies incorporated different types of rare disease patient organizations, such as a national rare disease umbrella patient organization versus a disease-specific patient organization, in different facets of the strategy.

Focused on promoting better coordination and improved information exchange between researchers and physicians, European Reference Networks (ERNs) are virtual networks formed to aggregate and leverage the knowledge and resources required to address complex or rare diseases. The first ERNs were launched in March 2017 and involved more than 900 highly specialized healthcare units from over 300 hospitals in 26 countries²⁵. The ERN initiative continues to receive support from several E.U. funding programs, including the Health Program, the Connecting Europe Facility and Horizon 2020.^{xxiv,xxv} At the national level, countries across Europe have created rare disease reference centres that bring together specialized medical teams, supporting the transition to more patient-centred care. Rare disease reference centres for a particular indication are easily found in a central database.^{xxvi}

Final Thoughts

Reflecting on the information gathered from across 17 comparator jurisdictions, three key insights emerged that cut across multiple countries outlined in the pages above.

First, a widespread belief that rare diseases require a distinct set of policies and strategies.

The countries we reviewed shared a belief that diagnosing, treating and managing rare diseases cannot be done successfully using the same set of tools and tactics that are applied to more common diseases. This fundamental belief underpins the existence of many dedicated and holistic rare disease strategies. Although these strategies invariably include multiple measures aimed at increasing affordable access to medicines, their scope and mandate extend well beyond pharmaceuticals to encompass the entire arc of the patient experience.

Second, there is no one perfect model for Canada from among the jurisdictions we reviewed.

Instead, examples of innovative policies and programs can be found throughout comparator countries, which means Canadian policymakers have a wide array of examples to learn from – and then adapt and modify to reflect this country’s unique objectives and dynamics. What was also notable was the extent to which countries were willing to evaluate their strategies and then revise and improve them based on objective analysis and stakeholder feedback. By identifying and integrating peer-identified “best practices,” multiple jurisdictions delivered progressively better patient care by avoiding policy stasis.

Third, more responsive strategies emerged through sustained and committed stakeholder engagement.

Based on their small numbers and often debilitating conditions, rare disease patients have struggled to have their voices heard by policymakers. Creating robust and dedicated mechanisms to engage a multiplicity of voices would go a long way to addressing this issue.

Through the research captured in this report, Takeda Canada has identified a number of elements used by 17 countries and regions worldwide to reduce the burden of rare diseases. As Health Canada works through its dedicated consultation process, we hope that the information distilled above – and elaborated upon in the Appendix that follows – offers a helpful complement to the department’s efforts. We would be pleased to elaborate on any of the findings contained herein.

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Appendix

Country-Specific Examples Informing Trends

AREA	BEST PRACTICES TRENDS	EXAMPLES
1. Rare disease policy process	<ul style="list-style-type: none"> Acknowledge that a rare disease strategy extends beyond drugs for rare diseases and should include all facets of identifying, treating and supporting patients with rare diseases. Strong ongoing political support is key to successful implementation. A working group that includes all relevant stakeholders, including patients and their caregivers, to have a meaningful discussion on the development of the rare disease strategy with ongoing evaluation and oversight. Ensure there is appropriate ongoing funding for the rare disease strategy. 	<p>Germany Rare disease strategy, the National Action League for People with Rare Diseases (NAMSE), was developed via a meaningful discussion with all relevant stakeholders (28 partners) including: regulators, patient organizations, insurance, hospitals, HCPs, industry, academia.</p> <p>Denmark National Rare Disease strategy was developed via a transparent discussion with a multi-stakeholder working group to provide input to ensure the strategy has a broad foundation representing the right actions. Once the strategy was finalized, funding was secured to begin implementation of the plan, and there has afterwards been follow up and evaluation activities.</p> <p>Ireland Ensured that their rare disease strategy extended beyond a drug negotiation framework, but also encapsulated a wholistic strategy around identifying, treating (e.g. care pathways), and supporting patients with rare diseases understanding that drugs were a single component of the overall patient needs. Further, not only were patients involved in the design of the rare disease strategy, but so too were patient caregivers.</p> <p>Spain Ensured that the strategy was evidence based and consistent (e.g. a common definition of a rare disease) accounting for the innate heterogeneity of rare diseases.</p> <p>U.K. A single strong political advocate – with a deep understanding of rare diseases – responsible for the overall strategy implementation was important for success.</p>
2. Policy and regulatory Framework: Orphan Medicinal Product Definition and Designation	<p>A standardized, clear, and transparent framework to define and designate rare disease status at the earliest stage of DRD development is essential as it provides all stakeholders a consistent framework to develop an implementation plan with a lower likelihood of individual R.D. and DRDs “falling through the cracks”.</p> <p>A consistent definition of a R.D. translates to a consistent review by the regulator, HTA, and pricing pathways.</p>	<p>E.U. As defined under legal framework at E.U. level - CE 141/2000. “A product intended for the treatment of a life-threatening or chronically debilitating disease and that has a prevalence of not more than 5 in 10,000” (9).</p> <ul style="list-style-type: none"> France and Germany rely on the EU OMP designation in their review of drugs for rare diseases <p>U.S. Designation for DRDs allows for orphan status for products defined as those intended for use for rare diseases that affect fewer than 200,000 people in the U.S. FDA approves orphan designations (35, 36). A similar framework has been adopted by South Korea.</p>

AREA	BEST PRACTICES TRENDS	EXAMPLES
	<p>Formal definition for R.D.s should:</p> <ul style="list-style-type: none"> • Have a clear objective criteria and a quantifiable prevalence for what constitutes a Rare Disease. • Not be too restrictive focusing only on very small populations. • Be in line with international standards as there is evidence that these have proven to be effective. 	<p>Scotland Has an official ultra-orphan category defined as (37):</p> <ul style="list-style-type: none"> • Condition has a prevalence of 1 in 50,000 or less in Scotland, • The medicine has an EMA orphan designation for the condition and this is maintained at time of marketing authorization, • The condition is chronic and severely disabling; and • The condition requires highly specialized management. <p>Japan In Japan, orphan diseases are defined as diseases with fewer than 50,000 patients</p> <p>Intractable diseases are rare diseases that fulfill the criteria below:</p> <ul style="list-style-type: none"> • Pathogenic mechanism is unknown • Treatment method is not yet established • Long-term treatment is required <p>Designated intractable diseases are intractable diseases that also fulfill the following criteria:</p> <ul style="list-style-type: none"> • Patients account for about 0.1% of the national population • Can be clearly diagnosed
<p>3. Policy and regulatory Framework: Market Exclusivity</p>	<p>Governments should implement a specific market exclusivity period for DRDs that:</p> <ul style="list-style-type: none"> • Takes into consideration the research and development hurdles for DRDs relative to other innovative drugs and the smaller patient population. • Is in line with international standards. 	<p>Nearly 75% of developed markets have extended market exclusivity provisions that are specific to orphan drugs.</p> <p>E.U.: 10 years (9)</p> <p>South Korea: 10 years maximum (11)</p> <p>Japan: 10 years maximum for orphan drugs</p> <p>United States: 7 years (12)</p>
<p>4. Policy and regulatory Framework: Financial Incentives such as tax credit and grants</p>	<p>Governments should encourage more R&D activities into orphan drugs by providing incentives with no requirements for local activity, but do encourage collaboration between industry and local organizations through research grants or tax incentives, with the objective of offsetting production costs.</p>	<p>Incentivising research is more commonly done through national grants. Tax credits are available in several countries.</p> <p>Belgium In 2016, the Belgian government formally announced the innovation deduction, as the successor of the patent income deduction. The deduction rate is increased to 85% of the net qualifying I.P. income. This results in an effective tax rate of 5.10% (13).</p> <p>U.S. The Office of Orphan Product Development has funded over 500 studies through the Orphan Products Grants Program with approximately \$15.5 million per year. Manufacturers can request tax credit equal to 50% of the qualified clinical testing expenses for the taxable year (2).</p> <p>Japan Orphan drugs are entitled to multiple subsidies (38):</p> <ul style="list-style-type: none"> • through the National Institute of Biomedical Innovation (NIBIO) to reduce financial burden of product development (470million yen in 2019)

AREA	BEST PRACTICES TRENDS	EXAMPLES
		<ul style="list-style-type: none"> • NIBIO is supporting up to 50% of expenses for clinical and non-clinical research • For rare diseases only, a 20% tax credit is available <p>Australia Orphan drug policy in Australia has facilitated the waiver of application and evaluation fees on the Australian Register of Therapeutic Goods for drugs with orphan designation; and a waiver in the application and evaluation fees for a first submission to the Pharmaceutical Benefits Scheme(39)</p> <p>Switzerland Switzerland offers a fee waiver for the marketing authorization application process.</p>
<p>5. Policy and regulatory Framework: Accelerated Regulatory Approval</p>	<p>Governments should ensure an accelerated regulatory process that:</p> <ul style="list-style-type: none"> • Is applicable to all DRDs that address the unmet need for rare diseases including the severity of disease and the lack of effective treatment options). • Allows for faster process, ensures technical advice and dialogue and provides exemptions on evidence requirements 	<p>Majority of developed markets have accelerated regulatory processes that can be categorized into those that have shortened review duration and/or those have exemptions from typical technical dossier requirements.</p> <p>E.U. countries An accelerated regulatory process reduces the procedure from 210 to 150 days (40)</p> <p>U.S. The “fast-track” approval status from the FDA shortens the process to 6 months from 10 months. The FDA reviews drugs with priority review vouchers (introduced in 2007 for companies developing drugs for treatment of topical diseases) within 6 months. Further, the rare disease pediatric voucher was created in 2012 (12). The U.S. also has a “Breakthrough Designation” process, which is not limited to DRDs, but many would qualify given that rare diseases often have unmet needs.</p> <p>Japan Has a 9-month priority review system (42). In 2014, Japan introduced Sakigake (forerunner), a priority review requirement that is applied to products that address an unmet clinical need. Applicants must make sure the Japanese submission is before or at the same time as other marketing authorisation submissions in the rest of the world (43).</p> <ul style="list-style-type: none"> • Sakigake Framework: <ul style="list-style-type: none"> - For orphan drugs, the interval for regulatory approval is 9 months at the 80th percentile, and 10 months for orphan medical devices. - (For normal drugs, and medical devices, the interval is 12 months and 14 months, respectively) • Japan also has a conditional early approval system: This is a system for approving drugs, medical devices, and regenerative products for treating rare & severe diseases, because it is difficult to conduct valid clinical trials such as P3 clinical trials due to a small number of patients. Thus, the government will approve the drugs/devices/products on the condition that the efficacy and safety of the products are evaluated after launch.

AREA	BEST PRACTICES TRENDS	EXAMPLES
<p>6. Access: Early Market Access Programs</p>	<ul style="list-style-type: none"> • Use early access programs to generate RWE to decrease clinical uncertainty • Clearly stipulate that early access programs are time-bound with clear delisting/grandfathering next steps • Allocate and communicate patient caps to authorized prescribers to ensure physicians prescribe to likely responder candidates <p>Create a structure that separates access and reimbursement so that access is granted earlier, and funds are refunded to the payer once price is negotiated</p>	<p>All developed countries offer pre-regulatory access, but variations exist in the types of programs and degree of coverage. Countries offer access on nominative basis, cohort, and both.</p> <p>France The Authorization for Temporary Use (ATU) program in France (44) provides access to medicines that have not yet received market authorization. Products in the ATU program must be designed to treat, prevent, or diagnose serious or rare diseases where no appropriate treatment exists. The ATU program has both a nominative and a cohort process, both of which are reimbursed (15, 16).</p> <p>Italy Italian laws provide three routes for pre-regulatory access (17). These offer an option for distinct situation with regards to current level of drug development (e.g. Phase II vs Phase III) and responsibility for initiation between physician and AIFA. DRDs can be covered under all three laws, while one i.e. 326/2003 (AIFA Fondo 5%) is dedicated to DRDs only (18).</p> <p>Law 648 allows physicians, physician associations, and patient associations to request reimbursement of DRDs, before EMA approval, in cases where there is no available alternative. The decision considers the degree of additional clinical benefit, the quality of the evidence, and the unmet need.</p> <p>U.K. The Early Access to Medicines Scheme (EAMS) under Medicines and Healthcare products Regulatory Agency (MHRA) was established in 2014 to help patients to access promising new medications that are not yet licensed in the U.K. In just a year from 2014 to 2015, over 500 patients received early access and 11 promising innovative medicine designations were granted (19, 30).</p>
<p>7. Access: Health Assessment Technology</p>	<p>Value assessments should be holistic patient-centric processes, incorporating clinical expertise, best available evidence, are transparent, objective, and aim to accelerate patient access to DRDs. This should be reflected in:</p> <ul style="list-style-type: none"> • the importance of QoL in rare diseases • Patients with rare diseases should be included in reimbursement deliberations at the committee level • Do not calculate CUA, instead decouple it and report the clinical benefit as part of the clinical review and the budget impact as part of the economic review 	<p>To have a tailored process to overcome the challenges of rare diseases, the most common provisions include no cost-effective analysis, flexible ICER threshold and fast track process. However, the majority of developed countries continue to apply the standard value assessment procedure to orphan drugs which generate uncertainties, and this policy area continues to be one of the key challenges</p> <p>France HAS assesses improvement of actual benefit on an ASMR scale (1-5). Innovative drugs (ASMR 1-3) benefit from an accelerated procedure. Also, a formal cost-effectiveness analysis is not required for DRDs—which are assumed to have an improvement in medical benefit (ASMR score of 1-3)—that have a turnover below €20 M in year 2 (15, 21-23)</p> <ul style="list-style-type: none"> • Patients are involved in the assessment and decision, and get a vote as to reimbursement. • QoL data can play an important role in assessment of DRDs (if the data are of sufficient quality; collected as part of clinical trial)

AREA	BEST PRACTICES TRENDS	EXAMPLES
	<ul style="list-style-type: none"> HTA assessments that identify areas of uncertainty within the clinical and cost-effectiveness evaluation, and allow for conditional reimbursement while evidence is collected to reduce that uncertainty, followed by a reassessment to determine the value. Work collaboratively with patient groups, physicians, and the manufacturer and HTA to develop the data collection protocol, funded by the manufacturer. Clear guidelines that ensure consistent application of methodology across reviews 	<p>Germany Special regulations exist in Germany for HTA of orphan drugs. The AMNOG early benefit assessment treats products with orphan drug designation differently in that their additional benefit is already considered proven, provided their budget impact is less than 50M EUR per annum.</p> <ul style="list-style-type: none"> DRDs with annual revenue less than €50 million (22) go through abbreviated early benefit dossier which includes <ul style="list-style-type: none"> Authorized application areas Additional benefit for the number of patients and patient groups for which a therapeutically significant additional benefit exists Cost of OMP Requirements for a quality-assured application DRDs with annual revenue more than €50 million (22) go through full early benefit dossier which also includes: <ul style="list-style-type: none"> Medical benefit Medical additional benefit versus comparator G-BA can re-evaluate benefit assessment outcome for DRDs on an annual basis, utilizing RWE (45), for those with conditional approval or approval under exceptional circumstances and if it is impossible to provide comparative data. In practice, this has applied to only a very small number of products per year. <p>U.K. In England, most DRDs go through the standard NICE single-technology appraisal, with a WTP threshold of £20k-£30k/QALY (46). Some DRDs go through the highly specialized technologies (HST) process, and while the criteria are opaque, ultra-rare diseases are more likely to go through this route. The HST process has a higher WTP threshold of £100,000/QALY to £300,000/QALY, depending on the amount of QALY gain.</p> <p>Australia PBAC first assesses DRDs through the same criteria as other medicines including comparative costs and effectiveness. If an OMP is not acceptably cost-effective for PBS listing, AND the medicine meets the criteria for the Life Savings Drugs Program, then reimbursement is considered by a Rare Disease Expert Panel for funding by an administrative program (LDSP)(3, 47).</p> <p>Japan For Designated Intractable Diseases, a cost-effectiveness assessment does not apply. However, cost-effectiveness could be applied for drugs for treating Rare Diseases, or have exceptionally high prices. The final decision for applying CEA depends on the government. When CEA is applied, the value premium/sales profit of the drug might be subjected to adjustment (not the whole price).</p>

AREA	BEST PRACTICES TRENDS	EXAMPLES
		<p>Scotland Scottish HTA assessments include special considerations for DRDs where evidence required for positive assessments are distinct from other pharmaceuticals. Lower levels of evidence are accepted for clinical trials (e.g. on efficacy and safety), but with possible requirement for additional data in other areas (e.g. surrogate markers and quality of life data). A higher cost per QALY is also accepted in HTA (> £30,000) (21).</p> <p>The Scottish Medicines Consortium (SMC) also has an ultra-orphan medicines pathway (1 in 50,000 prevalence) that allows for reimbursement of up to three years while evidence is collected to reduce uncertainty, followed by a reassessment of the clinical value and cost-effectiveness (37, 48).</p> <p>For end of life and DRDs, if the decision of the committee is to “not recommend,” the manufacturer can request that SMC convene a Patient and Clinician Engagement (PACE) meeting, which gives patients and clinicians a stronger voice in the SMC decision making process.</p> <p>South Korea Normally, a cost-effectiveness analysis is conducted within the HTA process. However, if fewer than 200 patients with a rare disease are expected use a product and life expectancy is less than 2 years, then the manufacturer can apply for a pharmacoeconomic waiver.</p> <p>Italy New guidelines from the Italian Pharmaceutical agency (AIFA) are published and in place from March 2021, which include cost-effectiveness in the assessment process, including for DRDs, in addition to the budget impact. AIFA uses ISPOR Guideline ICER as a reference. However, cost-effectiveness is not mandatory.</p>
<p>8. Access: Reimbursement Funding</p>	<ul style="list-style-type: none"> • Separate budget for DRDs that covers all Canadians, where access is defined by the overarching rare disease definition • Support for risk-sharing agreements, leveraging volume caps and value-based agreements, with patient volumes allocated to approved prescribers. • Provide transparent reimbursement mechanism for DRDs that did not go through HTA, at the lowest price of a basket of comparable countries 	<p>Germany Germany provides the fastest access across the EU5 markets and reimburses approximately 93% of authorised medicines, the most from the EU5 countries [14]. Orphan drugs, like all innovative pharmaceutical products (i.e. those offering an additional clinical benefit following a G-BA assessment) are fully reimbursed and are not included in the reference system for products with no additional benefit (25). Volumes also go into contracts, but are not visible. If volumes are exceeded there is the possibility of a new negotiation.</p> <p>France DRDs are reimbursed in France. The preferred type of agreement uses capping (i.e., an annual budget for an OMP) (15, 23). Often, financial agreements with a price volume are utilized and very few risk sharing agreements are used.</p> <p>Austria Immediate access to drugs after Regulatory approval may be available through individual funding requests via “no-box”; however, approvals are on a case-by-case basis and are inconsistent.</p>

AREA	BEST PRACTICES TRENDS	EXAMPLES
<p>9. Access: Pricing</p>	<p>Government should allow for confidential net prices negotiated with payers</p>	<p>Switzerland Switzerland recently started to introduce confidential pricing models including confidential net prices, limitation to predefined populations, yearly cost cap per patient, yearly sales or volume caps, etc.</p> <p>Ireland Ireland considers both cost-effectiveness and budget impact. DRDs go through the same HTA assessment process as other drugs. In some instances, DRDs may be referred to the Rare Disease Technology Review Committee for further review post-HTA assessment. There are discussions and research ongoing around outcomes based agreements and alternative payment models.</p> <p>South Korea If a DRD received a pharmacoeconomic waiver in the HTA process, pricing is set based on published prices in seven countries (U.S., U.K., Germany, France, Italy, Japan, and Switzerland)</p> <p>Germany Once a pharmaceutical product has been authorized, it is immediately eligible for reimbursement from the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband). The initial price for a product can be freely set by the manufacturer for a period of 12 months after market launch; this initial price must be officially declared and subsequently applies to all sales of the product (25). After a 6-month HTA assessment period, the price is then negotiated with the Federal Joint Committee (G-BA, in charge of deciding on the coverage of health goods and services). As orphan drugs are often characterised by having no therapeutic alternatives and as additional benefit is already considered proven, G-BA will decide only on the extent of the additional benefit and use this in price negotiations, if needed, along with the prices of the product in other E.U. countries and prices of comparable products in Germany (25).</p> <p>France The pricing committee (CEPS) compares the price requested by the manufacturer with the price of orphan drugs in other countries (21, 22)</p> <ul style="list-style-type: none"> • During ATU access, evidence can be collected which can be used during price negotiations <p>U.K. In England, most DRDs go through the standard NICE appraisal; however, a higher willingness-to-pay threshold of £100,000/QALY to £300,000/QALY is used (46). NICE has also instituted a risk-sharing scheme for select drugs that if treatment effects were not achieved, the scheme included the option to reduce the drug price to guarantee its cost-effectiveness at a certain cost/QALY threshold [21].</p>

AREA	BEST PRACTICES TRENDS	EXAMPLES
10. Care: Newborn Screening	<p>Governments should implement well-funded national newborn screening programs that are:</p> <ul style="list-style-type: none"> • Mandatory or on opt-out basis and available to all newborns across hospitals to ensure high coverage • Cover a wide range of Rare Diseases that are amenable to early intervention and treatment 	<p>Newborn screening is implemented widely, however, large disparities exist in the reimbursement level and access to an extensive number of tests.</p> <p>Austria Austria has had a well-established, nationwide newborn screening program since the late 1960s that is performed on all newborns in one centre, operated by the University Children's Hospital in Vienna. This program screens for 28 diseases and conditions (28, 29).</p>
11. Care: Patient Registries	<p>Governments should develop national registries across centres of excellence in partnership with clinicians, academic organizations, patient groups, manufacturers, HTA and regulators and should allow data to be used to improve diagnosis, improve patient treatment pathways, reduce uncertainty, and support outcomes-based agreement, while ensuring patient confidentiality.</p>	<p>Majority of developed countries have national registries for rare diseases but there is variability in their centralization, disease scope and amount of data gathered. 5 countries – Belgium, England, France, Italy, and South Korea – have a single national registry for all rare diseases.</p> <p>France The second national plan for rare diseases established a system through which centres of excellence could electronically register rare disease patients. In January 2021, this registry contained information on 700,000 patients with over 4,800 rare diseases (33). France also has Orphanet, a registry for rare diseases and orphan drugs to improve diagnosis, care and treatment of patients. This initiative began in Europe in 2000 with 41 countries across Europe and around the world.</p> <p>England PHE has established the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS). The registry provides information to support clinical practice, epidemiology data and monitoring, patient information, research, planning and commissioning, screening, etc. (39). Data are allowed for cross-EU monitoring and comparisons.</p> <p>South Korea In July 2009, a nationwide registry for rare and intractable diseases (Rare Diseases Registry, RDR), was established. The RDR database gathers information on each patient with a physician-certified diagnosis, making it possible to know the cumulative number of patients regardless of the usage of the NHI (51)</p>
12. Care: Centres of Excellence	<p>Governments should work on better coordination between centres of excellence through the development of research networks that facilitate information exchange between researchers and physicians, leading to better diagnosis and treatment of Rare Diseases.</p>	<p>E.U. At the European level, 23 European Reference Networks cover 370 hospitals and 960 highly specialized units in 25 E.U. countries and Norway. By pooling expertise, these networks facilitate patients' wider access to diagnosis, treatment, and top-quality care (34).</p> <p>France France has several rare diseases reference centres that bring together specialized medical teams in the fields of treatment, research, and training. In 2017, there were approximately 130 centres, and 23 healthcare pathways coordinate action between centres (34). Currently there are 387 reference centres, but 131 accredited centres.</p> <ul style="list-style-type: none"> • Care is well organized and coordinated in France. No competition between hospitals

AREA	BEST PRACTICES TRENDS	EXAMPLES
<p>13. Patient Voices</p>	<p>Several countries, including Italy, France, England and Scotland have taken steps to integrate patients and patient groups into the rare disease strategy, including the assessment and decision-making process.</p>	<p>France Patients groups were involved in the overall development of the rare disease strategy and are involved in the assessment process.</p> <p>Italy Patient groups are involved in the assessment process for DRDs.</p> <p>England Patient groups are involved in the assessment process for DRDs.</p> <p>Scotland For end of life and DRDs, if the decision of the committee is to “not recommend,” the manufacturer can request that SMC convene a Patient and Clinician Engagement (PACE) meeting, which gives patients and clinicians a stronger voice in the SMC decision making process.</p>

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Addendum: Takeda Canada's Submission for the Consultations on a National Rare Disease Strategy

About Takeda Canada

Founded in Japan in 1781, Takeda now operates in more than 80 countries worldwide, including Canada. More than a decade ago, Takeda made the strategic decision to become a specialty medicines company and today, we have evolved into the global leader in drugs for rare diseases (DRDs).

In anticipation of Health Canada's consultation on DRDs, Takeda Canada engaged a wide range of experts from across Takeda's network of international affiliates to gain knowledge of their DRD strategies. Details can be found in 'Supporting Material' and serves as the basis for Takeda's recommendations contained in this report.

Takeda Canada is a member of Innovative Medicines Canada and BIOTECanada and submits our recommendations in addition to those made by our industry associations.

Takeda Canada believes an effective Canadian rare disease strategy must encompass the following recommendations:

Summary of Recommendations

Recommendation One: Expand the scope of the consultation to include developing a holistic rare disease strategy and implementation plan.

Recommendation Two: Establish an objective and replicable rare disease definition to be used by all stakeholders throughout a DRD's lifecycle.

Recommendation Three: Enhance the use of early access pathways to generate pre-NOC real-world data to reduce clinical uncertainty for regulatory and HTA reviews.

Recommendation Four: Encourage clinical research and early patient experience by extending data protection to DRDs that operated clinical trial sites in Canada.

Recommendation Five: Realign Federal policies to promote access to DRDs.

Recommendation Six: Facilitate a multi-stakeholder working group dedicated to recommending a made-in-Canada framework for DRD health technology assessment.

Recommendation Seven: Improve the infrastructure needed to implement a holistic rare disease strategy including medical training, early diagnosis, and data collection.

The Development and Incorporation of Drugs for Rare Diseases (DRDs) in a Holistic Rare Disease Strategy

Recommendation One: Expand the scope of the consultation to include developing a holistic rare disease strategy and implementation plan.

In countries with successful strategies to address drugs for rare diseases, governments have incorporated access and reimbursement strategies within a holistic rare disease strategy. These countries recognize that DRDs are only one essential part of a robust rare disease strategy. The strategy must also address improved screening, timely diagnosis, data collection and patient and caregiver support.

Incorporating key learnings from international jurisdictions, Canada's DRD strategy requires:

- **Government Champions:** Enduring advocacy and support by senior government officials
- **Sustained Stakeholder Engagement:** Establish a dedicated, formalized Steering Committee to oversee the Rare Disease strategy development and implementation plan. Giving all relevant stakeholders – especially patients – significant and sustained representation will ensure that the strategy is comprehensive and credible. An implementation plan to accompany a strategy will be vital to action and accountability.
- **Sufficient Scope:** Include measures and programs to identify, treat, and support patients with rare diseases and their caregivers.
- **Dedicated Funding:** Dedicated funding won't assure the success of a national rare disease strategy – but the *absence* of dedicated funding makes success almost impossible.
- **Ongoing Evaluation and Updating:** Regular and transparent evaluation of the implementation progress, with findings incorporated into the strategy's future iterations.

An Objective and Harmonized Definition of a “Rare Disease”

Recommendation Two: Establish an objective and replicable rare disease definition to be used by all stakeholders throughout a DRD's lifecycle.

To determine the scope of a rare disease strategy, an objective “rare disease” definition is required. Further, designating a drug as a DRD at the outset of its lifecycle would align stakeholder actions and expectations to help prevent the DRD from “falling through the cracks.” Qualitative definitions can be subjectively interpreted and may result in inconsistent application. Takeda Canada suggests a definition akin to the European Union (E.U.) rare disease definition of 1 in 2,000.

Creating Early Access Pathways

Recommendation Three: Enhance the use of early access pathways to generate pre-NOC real-world data to reduce clinical uncertainty for regulatory and HTA reviews.

Uncertain clinical effectiveness highlighted within the regulatory and Health Technology Assessment (HTA) pathways is a well-documented challenge with DRDs. Broadly, clinical uncertainty stems from gaps in our knowledge of the rare disease's natural history, a patient pool insufficient to conduct adequately powered randomized clinical trials, and a lack of accepted disease-specific tools required to measure clinical effectiveness. Done concurrently with clinical trials, early access pathways provide a unique opportunity to generate local real-world evidence (RWE) to address this challenge. Adopting a mechanism similar to France's Temporary Authorization for Use (ATU) program would facilitate generating Canadian RWE for regulatory and HTA reviews.

Most international early access programs are explicitly time-bound, with clear steps leading to either drug reimbursement or discontinuation. This approach mitigates the risk of patients with a rare disease losing access to treatment if pricing and access negotiations are ultimately unsuccessful. Further, a funded early access pathway encourages timely negotiations while minimizing financial risk to payers and manufacturers.

Reflecting Disease Rarity in Market Exclusivity & Investment Support

Recommendation Four: Encourage clinical research and early patient experience by extending data protection to DRDs that operated clinical trial sites in Canada.

Given smaller patient populations, some DRDs may face challenges in recovering research and development (R&D) investments. By extending data protection for rare diseases, the Federal government can create an environment that promotes bringing more DRD innovations to Canadian patients.

Extending data protection to DRDs that have operated clinical trial sites in Canada promotes local research and provides early DRD access to Canadian patients. Also, more Canadian clinical trials will result in the benefit of improved physician experience in treating rare diseases and increased research infrastructure.

As noted in our report, incentives for DRDs have proven effective in other jurisdictions. For example, in the E.U., orphan drug legislation has dramatically increased clinical research activity, and the number of DRDs approved by the European Medicines Agency (EMA), with more than a third of these products treating pediatric populations.

Maximizing Shared Value Through HTA, Pricing & Reimbursement

Recommendation Five: Realign Federal policies to promote access to DRDs.

The Government of Canada has articulated the desire to address the affordability of DRDs. Takeda Canada believes that any pricing regime needs to be sustainable for payers, manufacturers and Canadians. The challenge facing government is creating and implementing a framework that balances affordability with access to new drugs.

There are currently several activities shaping DRD policy in Canada – in particular, this consultation and the Patented Medicine Prices Review Board's (PMPRB) new pricing framework. Takeda Canada continues to have concerns with the new pricing framework. We recommend that the Federal government delay implementing the pricing framework, particularly as it applies to DRDs, and revisit its implementation after a national rare disease strategy has been developed to ensure the two policies are aligned.

Takeda Canada also suggests the Federal Government consider, at a minimum, amending the new pricing framework to assume that DRDs deliver a clinical benefit and remove the pharmacoeconomic factors. These changes would be aligned with international comparators (e.g. Germany and France), which seem to heavily inform the structure of PMPRB's new pricing framework.

Recommendation Six: Facilitate a multi-stakeholder working group dedicated to recommending a made-in-Canada framework for DRD health technology assessment.

There are several examples of the challenges faced by DRDs progressing through the current HTA framework. As DRDs do not have the same level of evidence as non-DRDs, applying the current one-size-fits-all HTA framework to a DRD may result in recommendations that do not consider the unique challenges inherent in rare diseases. Adapting existing HTA pathways for DRDs or creating a fit-for-purpose solution should be considered to ensure that correct reimbursement recommendations are made.

Given the complex nature of amending an HTA framework, Takeda Canada recommends the government facilitate a multi-stakeholder working group to determine a path forward for Canadian HTA on DRDs. This working group would operate under the direction of the Rare Disease Strategy Steering Committee.

Leveraging the Benefits of Accessible Data Collection, Diagnostic Screening, and Patient Registries

Recommendation Seven: Improve the infrastructure needed to implement a holistic rare disease strategy including medical training, early diagnosis, and data collection.

Throughout the Health Canada discussion paper, the need for pan-Canadian collaboration was made clear. The Federal government should work with provinces and territories to develop capacity for medical training, early genetic testing, and centralized data collection and sharing to improve patient treatment and care. The strategy should establish and promote a national network of centres of excellence for rare diseases (e.g., Europe's Orphanet).