Takeda

Better Health, Brighter Future

Defining Rare Disease in Canada: Lessons from G20 Nations

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Abstract

As Canada takes meaningful steps toward developing and deploying a national strategy for rare diseases, it finds itself as one of a few G20 nations lacking a publicly and consistently articulated definition of “rare disease.”

To better understand the global rare disease definitional landscape, Takeda analyzed the different approaches taken by other G20 countries – and came to four important conclusions:

1. Due in part to their uncommon nature, rare diseases are often harder to diagnose and more challenging to treat than their more common counterparts. For that reason, a rare disease can have a significant impact on the lifespan and quality of life for an individual patient. Defining what is a rare disease, is a critical early step in formulating policies and funding frameworks for patients with a rare disease.
2. The majority of Canada’s G20 peers have adopted a reasonably simple, quantitative definition: fewer than **1 patient per 2,000 people**. Other approaches involve qualitative definitions built around criteria like “medical need” and prescriptive definitions that call out designated diseases or disease groups.
3. With quantitative-only definitions susceptible to becoming blunt, rigid, or static, some countries have adopted blended definitions that combine quantitative and qualitative elements. With this model, the key risk to mitigate is the inherent challenge of objectively measuring and comparing “medical need” across disease populations and stakeholders.
4. Canada has lessons to learn from every jurisdiction reviewed in this report – and can benefit, in particular, from studying the approach taken by the European Union (E.U.). By marrying a prevalence threshold with a set of adaptable guidelines, the E.U. relies on a global quantitative norm, but offers policymakers a set of measures designed to instill flexibility and nuance into complex and dynamic deliberations.

Landing on a single, pan-Canadian definition of a rare disease is long overdue. Through this report, Takeda hopes to make a meaningful contribution to achieving not only this essential goal, but also to accelerating the launch of the country’s essential Rare Disease Strategy itself.

Background

The Debilitating Burden of Rare Disease

A "rare" disease is any disease that affects a very small number of individuals. It is often genetic, chronic throughout a patient's life and life-threatening.[1] With rare diseases affecting a relatively small set of patients, innovative treatments are often unavailable. In fact, only 5% of rare diseases have an approved treatment.[2,3] This reality has a distressing effect on patients and their families: studies suggest that at least 50% of rare diseases affect children, 30% of whom die before their fifth birthday.[2,4,5,6]

The journey toward appropriately managing a rare disease is long and challenging. On average, it takes 6-8 years before a patient receives a correct diagnosis; in this time, a patient will see an average of eight physicians and receive two to three misdiagnoses.[7] The treatment delays caused by these diagnostic challenges often result in avoidable disease progression, which only amplifies the effect of the diseases on the patient and their caregivers.[8]

The Need for Targeted Strategies

Around the world, many countries have recognized that patients with rare diseases experience a unique set of barriers to appropriate care.[1] As a result, governments have created holistic rare disease strategies to remove these barriers and ensure that stakeholders are working collaboratively and in concert towards a common goal of improved health outcomes for vulnerable patients.

To its great credit, the Government of Canada committed to developing and funding a national rare disease strategy in 2019. However, its efforts are complicated by the fact that there is no internationally agreed-upon definition for rare diseases, and Canada has not officially adopted one of its own.

To support the development of a Made-in-Canada definition of "rare disease," Takeda has produced this report summarizing and assessing the respective approaches that Canada's peers across the G20 have taken in defining what constitutes a "rare disease."‡

‡ The definition of 'drugs for rare diseases' or 'rare diseases' may be different from 'orphan drugs' or 'orphan disease'. In the United States, the Orphan Drug act of 1983 defines orphan drugs as those for whom the market is too small to reasonably expect recuperation of investment costs. As such, orphan drugs and their corresponding diseases can include both rare diseases and more common conditions. As a result, this report will use the term rare disease instead of orphan disease to avoid confusion.

This report explores a wide range of qualitative and quantitative definitions, focusing on definitions used by national government/regulatory agencies and Health Technology Assessment (HTA) organizations. A comprehensive overview of country-by-country rare disease definitions can be found in Appendix 1, following the body of this paper.

From Takeda's previous research into the global rare disease landscape – further outlined below – it's clear that the first step in driving towards an effective and impactful rare disease strategy is to establish a rare disease definition. It's our hope that this paper can meaningfully contribute to accelerating the development of a single, inclusive pan-Canadian definition of what constitutes a "rare disease" – a definition that not only aligns with other countries but also reduces the risk that a disease or patient population "falls through the cracks."

About Takeda's Commitment to Rare Diseases

Takeda is a global, values-based, R&D-driven biopharmaceutical leader headquartered in Japan, committed to discover and deliver life-transforming treatments, guided by our commitment to patients, our people and the planet. Takeda focuses its R&D efforts on four therapeutic areas: Oncology, Rare Genetics and Hematology, Neuroscience, and Gastroenterology (GI). We also make targeted R&D investments in Plasma-Derived Therapies and Vaccines. www.takeda.com.

In 2021, Takeda conducted a landscape analysis of 16 comparator countries to understand better how other nations addressed the unique health system challenges posed by rare diseases.[9] Our research identified seven key elements instrumental to the success of a comprehensive national rare disease strategy:

1. **Identifying an Objective and Harmonized Definition of "Rare Disease"**
   Aligning on a definition of rare disease is essential to building a strategy
2. **Incorporating DRDs into a Holistic Rare Disease Strategy**
   Drugs for rare diseases should be part of a comprehensive rare disease strategy that addresses all parts of the rare disease journey
3. **Reflecting Disease Rarity in Market Exclusivity and Investment Support**
   Incentives can be an effective tool to promote research and development for drugs for rare diseases
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

5. **Maximizing Shared Value Through HTA, Pricing and Reimbursement**
   Drugs for rare diseases require alternative health technology assessment (HTA) approaches that include reimbursement with evidence generation and decisions based on budget impact rather than traditional HTA measures

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

7. **Improving and Extending Networks of Researchers, Clinicians and Patients**
   Centres of excellence that include patients, researchers and clinicians are a key model of success in Europe

Multiple Approaches to Defining a Rare Disease

Across the G20 group of countries, health system leaders use a combination of three approaches to defining a rare disease: (1) quantitative definitions; (2) qualitative definitions; and (3) prescriptive definitions.

1. Quantitative Definitions

Most of the rare disease definitions used with G20 countries include a quantitative component. Whether referencing an absolute number of patients diagnosed within a given geography or using a prevalence estimate, these definitions rely on a numerical threshold to delineate rarity. For example:

- The United States' Rare Disease Act (2002): a disease affecting fewer than 200,000 Americans.[10,11]
- European Union's Orphan Regulation No 141/2000 (1999): a life-threatening, seriously debilitating or serious and chronic condition affecting not more than 5 in 10,000 people in the E.U. [12,13]
- Japan's Pharmaceutical Orphan Drug Law (1993): serious diseases where fewer than 50,000 patients in Japan are treated and for which there is a high medical need.[14]

While there is no universally accepted quantitative threshold, multiple countries and numerous stakeholders have defined a rare disease as one afflicting **1 patient in 2,000 people in the general population**.

For example, as the United States (U.S.) has a population of 332 million, the legislative rare disease threshold of fewer than 200,000 affected Americans translates to less than **1.2 in 2,000** people. Similarly, Japan's threshold of fewer than 50,000 treated patients in a population of 125 million translates to less than **0.8 in 2,000** people. The E.U. uses exactly **1 in 2,000** people as its threshold.

Most G20 countries with a formal rare disease definition have adopted the same quantitative approach:

- Nine governments/regulatory agencies – Australia,[15] Argentina,[15] the European Union,[17] France,[18] Germany,[19] Italy,[20,21] Mexico,[22] Saudi Arabia[23] and the U.K.[24] – use the not more than **1 in 2,000** definition (or a multiple thereof).
- Brazil is the only country defining rare diseases as up to 65 in 100,000, which amounts to not more than **1.3 in 2,000**.[25]

- South Korea, like the U.S. and Japan, defines rare diseases using a fixed number of people: fewer than 20,000 people. With South Korea having a population of around 52 million people, this definition approximately amounts to less than **0.8 in 2,000** people.[26,27]
- Turkey[28] and Russia[29] apply much stricter definitions for rare diseases compared to the rest of the G20 countries: **1 in 100,000** and **10 in 100,000**, respectively.
- Although Canada is one of five G20 countries that lacks an official quantitative rare disease definition – along with China, India, Indonesia and South Africa – a 2014 press release from Health Canada defined a rare disease as a "life threatening, seriously debilitating, or serious chronic condition that only affects a very small number of patients (typically less than 5 in 10,000 persons" – which simplifies to 1 in 2,000).[30,31] Recently, a province in Canada has announced they have adopted the 1 in 2,000 definition.[32]

Some of these quantitative definitions have been adopted in legal or regulatory frameworks, while others are alluded to in policies, documents or other official statements.

Beyond the common 1 in 2,000 threshold, the use of a prevalence metric appears to be almost ubiquitous within quantitative definitions. There are, however, exceptions, such as France's National Cancer Institute and the U.S.'s National Cancer Institute, both of which use an incidence metric. The former defines rare cancer as having an incidence threshold of 6 in 100,000 per year or requiring specialized treatment due to atypical tumor location or complex disease characteristics.[28,33] The latter uses an incidence threshold of fewer than 15 in 100,000 per year.[34] Neither incidence metric can be directly compared to their prevalence-based counterparts.

2. Qualitative Definitions

Most stakeholders (national government/regulatory and HTA organizations) define rare diseases using a quantitative threshold element. However, some stakeholders also incorporate a qualitative component to their rare disease definition.

Generally, the used qualitative definitions delineate rare diseases from other diseases by focusing on lower prevalence diseases that are **progressive, degenerative, severe, and chronically debilitating or life-threatening**.[31] The addition of the qualitative component seems to address the concern that rarity by itself does not always translate to high medical need.[35]

Although the Canadian Agency for Drugs and Technologies in Health (CADTH) has not published a formal rare disease definition, the Agency uses both quantitative and qualitative factors to designate a rare disease within its Procedure for Reimbursement Reviews document for oncology drugs, non-oncology drugs and plasma protein products. The Agency describes a rare disease as one that:

- is life-threatening, seriously debilitating, or both serious and chronic in nature
- affects a relatively small number of patients (incidence of fewer than 5 in 10,000, but typically closer to 1 in 100,000)

- is often genetically based, onset at birth or early childhood, and leads to a shortened lifespan
- places a heavy burden on caregivers and the health care system
- is difficult to study because of the small patient population.[36,37]

Health Canada's 2014 press release on a proposed rare disease definition also includes both qualitative and quantitative components: life-threatening, seriously debilitating, or serious chronic condition that only affects a very small number of patients (typically less than 5 in 10,000 persons).

Furthermore, the E.U.,[12] European Medicines Agency,[13] and Japan's Ministry of Health, Labour and Welfare's rare disease definitions are similar to Health Canada's proposed definition.[14]

Of the 20 sources Takeda reviewed, only the U.K.'s National Institute for Health and Care Excellence (NICE)'s Highly Specialized Technology (HST) program defined rare disease using an entirely qualitative definition. The HST program only considers drugs for very rare conditions.[38] The definition used to describe the disease characteristics to be eligible for this program include three criteria:

- The target patient group [...] is so small that treatment will usually be concentrated in very few centres in the NHS;
- The target patient group is distinct for clinical reasons; and
- The condition is chronic and severely disabling.

3. Prescriptive Definitions

Finally, some stakeholders use a prescriptive definition for rare disease. This involves explicitly designating diseases or groups of diseases as rare diseases.

For example, Italy adds a list of diseases regarded as rare to its quantitative definition. It lists nearly 546 rare diseases or groups of diseases but excludes rare cancers, which are captured in the country's cancer framework. The list of rare diseases determines which patients are entitled to benefits and access to care.[21,39,40]

On the other hand, China has taken a purely prescriptive approach to defining a rare disease – in part due to a lack of local epidemiological data on rare disease prevalence. As a result, China has refrained from any quantitative definition and has instead published a list of 121 diseases it defines as rare.[41,42]

Like China, India has limited local epidemiological data with which to develop quantitative thresholds. It has, therefore, opted to lay out a list of rare diseases defined by qualitative criteria. However, the Indian National Policy for Rare Diseases has made it clear that its list is not exhaustive and will be reviewed periodically by a technical committee. Concurrently, India has operationalized a national rare disease registry to eventually allow for the implementation of a prevalence-based rare disease definition.[43,44]

Advantages and Disadvantages of Different Approaches

Adopting a Quantitative-only Definition

As we reviewed the comparative approaches taken by G20 countries, the appeal of quantitative definitions was clear. Our analysis also revealed three distinct challenges that weaken the robustness of a quantitative-only model. Thankfully, the E.U.'s approach offers lessons from other jurisdictions looking to mitigate those risks.

A quantitative definition benefits from being precise and relies on limited discretion in its interpretation. Once a disease is designated as rare within a particular geography, stakeholders can work together to reduce the risk that a disease or patient population "falls through the cracks." This clarity can also provide a level of repeatability when determining if other diseases are rare diseases and consistency when implementing a process to treat rare diseases.

Defining rare diseases based on prevalence only is neither straightforward nor without risk. For example, this approach could inadvertently:

1. **Exclude or include some rare diseases due to grouping.** For example, a disease can be categorized too broadly, like a rare cancer classified within an umbrella cancer group. Similarly, sub-setting or salami slicing an indication is a possibility.
2. **Exclude a disease that is slightly above the prevalence threshold.** Significant medical need may exist in a rare disease slightly over a particular quantitative threshold.
3. **Fail to address changes in disease prevalence over time.** Improved awareness and survival may increase prevalence, while a cure may decrease prevalence.

These examples shine a light on some of the challenges that come with solely relying on a quantitative definition. However, a number of potential solutions are helpfully outlined in the policies and guidelines describing the implementation of E.U.'s Orphan Regulation No 141/2000 (1999), aligned to the three challenges identified above:

1. Exclude or include some rare diseases due to grouping.

To alleviate this challenge, when a particular disease is being evaluated against the rare disease threshold, the E.U. has policies and guidelines to define the disease grouping. For example, the E.U.

requires a clear and precise description of the disease using published references[45]; sub-setting where artificial subsets of a non-orphan condition are created, is rarely accepted.[46] This approach reduces the likelihood that a disease population contained within a broader patient cohort will be excluded from receiving the rare disease designation, and conversely a subset of a common disease will be included.

2. Exclude a disease that is slightly above the prevalence threshold.

The ultimate goal of using a rare disease quantitative definition is to identify populations with a high medical need using a simple, replicable and repeatable method. However, there can be populations that sit slightly above a particular threshold where significant medical need still exists due to the infrequent nature of a given disease. To inject flexibility, the E.U. guidelines include the statement: *"a prevalence of not more than five affected persons per 10 thousand is generally regarded as the appropriate threshold; medicinal products intended for a life-threatening, seriously debilitating or serious and chronic condition should be eligible even when the prevalence is higher than five per 10 thousand."*[47]

In other words, a disease can still be reasonably considered rare even if the prevalence rate modestly exceeds the established E.U. threshold – a nuanced approach that offers policymakers helpful flexibility.

3. Fail to address changes in disease prevalence over time

Some diseases that initially were classified as rare can eventually outgrow this definition. This occurs if the disease spreads (e.g., infectious diseases), if diagnostics capabilities and surveillance systems improve, and if the emergence of life-prolonging treatments allows more patients to live longer with their condition. The epidemiological history of AIDS offers an excellent example of this dynamic. When AIDS first emerged in the U.S., it initially fit the legislative threshold and definition of a rare disease by affecting fewer than 200,000 individuals. Over time, however, the spread of the disease – coupled with better diagnostics, surveillance and treatment options – led to a significant increase in the total number of individuals with AIDS. As a result, by 2007 the number of HIV infected exceeded 1.1 million.[48]

Conversely, effective prevention strategies can turn a common disease into a rare one. Examples include mumps and measles – conditions that were once common childhood infections. Primary prevention strategies such as immunization have prevented the disease from ever occurring in the vast majority of children, thereby decreasing the prevalence and incidence of both diseases. For example, in 1968, the U.S. reported 152,209 cases of mumps. Between the years 2000 and 2022, there were approximately 37,000 cases total.[49]

These examples highlight how disease prevalence changes over time – along with their prevention, diagnosis and treatment. To account for this, the E.U. guidelines require a critical review of how

disease epidemiology may evolve and call out the scenario where increased patient survival due to improved treatment could be used as a reason to remove a rare disease designation.[17]

The mitigating measures embedded within the E.U. Guidelines highlight the importance of providing policymakers with flexibility to ensure that quantitative definitions are robust but not rigid, and adaptive rather than archaic.

Pairing Quantitative and Qualitative Definitions

Jurisdictions whose rare disease definitions contain quantitative and qualitative components blend the consistency of prevalence thresholds with the targeted lens of medical need. Policymakers must take care to create a process to assess that medical need that is both rigorous and respected.

Combining qualitative and quantitative definitions adds helpful depth to a rare disease definition. For example, adding a significant medical need criterium to a prevalence threshold increases specificity towards an underserved population.

The rare disease definitions adopted by the E.U. and Japan differ from the U.S. definition in this regard. The E.U. requires the disease to be a "life-threatening, seriously debilitating or serious and chronic condition" in addition to "affecting not more than 5 in 10,000 people in the community".[12]

Note that adding a medical need component does not come without risks. Objectively determining relative medical need is a challenging endeavour, and overlaying that lens with a prevalence threshold may create discrepancies in perspectives and even inequities in policymaking. It is possible that a particular stakeholder along the patient journey considers a disease as having a higher medical need than a second stakeholder present along the same patient journey. To address this concern, significant effort must be made to ensure that stakeholders are collectively aligned with the deliberative process of how medical need is determined.

Considerations for Canada

As Canadian policymakers and health system stakeholders lay the cornerstones of a national rare disease strategy, it's clear that a critical milestone will be settling on a single, consensus pan-Canadian definition of what constitutes a rare disease.

For many of Canada's G20 peers, a simple quantitative definition was sufficient. As Takeda reviewed the policy approaches taken by a broad range of comparators, one quantitative definition emerged time and time again: **a rare disease is one whose prevalence is not more than 1 patient per 2,000 people in the general population**. This prevalence threshold would translate to a rare disease affecting not more than 19,300 Canadians, considering the Canadian population as of 2022.[50]

These findings are corroborated by a 2015 ISPOR systematic review on rare disease definitions.[51] ISPOR found that 88% of all countries it reviewed relied on a prevalence-based threshold to define a rare disease, with the majority using a threshold between 0.8 and 1 per 2,000.

Reflecting on the ubiquity of this approach, it's clear that Canada's rare disease community and its government partners will need to consider a number of key questions carefully:

- *Should Canada simply adopt the 1 in 2000 prevalence threshold that currently exists in many comparator nations?*
- *If Canada adopts a blended definition that combines quantitative and qualitative approaches, by what trusted and legitimate mechanism will the country determine relative and absolute "medical need"?*
- *How can advocates, researchers, clinicians and decision-makers from provincial and territorial health systems unite around a single definition that reflects their realities and meets their needs?*

Answering these questions will be neither speedy nor straightforward. Still, it is imperative to establish a singular rare disease definition for Canadians – and not simply a definition that works for one rare disease but a definition that works for all of them. From this foundation, Canada can develop and deliver a long-overdue rare disease strategy that will provide some of the most medically vulnerable Canadians with the support, the tools and the treatments they need.

Through this report, Takeda aspires to have created a resource that will support crucial definitional policy discussions to come and also bring the completion and launch of a Canadian Rare Disease Strategy that much closer.

Appendix 1: Rare Disease Definitions in G20 Nations

	BODY USING DEFINITION	QUANTITATIVE COMPONENT WITHIN DEFINITION	QUALITATIVE COMPONENT WITHIN DEFINITION	OTHER CONSIDERATIONS
Argentina[16,52]	National Government/ Regulatory	≤ 1 in 2,000 Prevalence		
Australia[53,54]	National Government/ Regulatory	< 1 in 2,000 Prevalence (< 5 in 10,000)	And condition is life-threatening or seriously debilitating	
Brazil[25,55]	National Government/ Regulatory	≤ 1.3 in 2,000 Prevalence (≤ 65 in 100,000)		
Canada[32]	Local Government (Quebec)	≤ 1 in 2,000 Prevalence		
China[41,56,57]	National Government/ Regulatory		A published a list of 121 rare diseases	
European Union[12,13]	National Government/ Regulatory	≤ 1 in 2,000 Prevalence (≤ 5 in 10,000)	And a disease that is life-threatening or chronically debilitating	
France[18]	National Government/ Regulatory	≤ 1 in 2,000 Prevalence	And a disease that is life-threatening or chronically debilitating	
France[28,33]	National Government	≤ 6 in 100,000 Per Year Incidence	Or requiring specialized treatment due to atypical location of complex disease characterises	Cancer-specific
Germany[19]	National Government/ Regulatory	≤ 1 in 2,000 Prevalence	And a disease that is life-threatening or chronically debilitating	
India	National Government/ Regulatory		A published a list of 3 umbrella rare disease groupings	Due to limited local epidemiological data, cannot use a quantitative based definition. Working towards a prevalence-based rare disease definition
Indonesia		No definition		
Italy[21,39,40]	National Government/ Regulatory	≤ 1 in 2,000 Prevalence (≤ 5 in 10,000)	And a disease that is life-threatening or chronically debilitating; Or a published list of 546 rare diseases or groups of diseases	Published list excludes cancer

	BODY USING DEFINITION	QUANTITATIVE COMPONENT WITHIN DEFINITION	QUALITATIVE COMPONENT WITHIN DEFINITION	OTHER CONSIDERATIONS
Japan[14,58]	National Government/ Regulatory	≤ 0.8 in 2,000 Prevalence (Fewer than 50,000 treated patients in Japan)	And a serious disease; And high medical need	
Mexico[59,60]	National Government/ Regulatory	≤ 1 in 2,000 Prevalence (≤ 5 in 10,000)		
Russia[28,29,61]	National Government/ Regulatory	< 1 in 10,000 Prevalence (< 10 in 100,000)		
Saudi Arabia[62]	National Government/ Regulatory	< 1 in 2,000 Prevalence		
South Africa		No definition		
South Korea[26,27]	National Government/ Regulatory	< 0.8 in 2,000 Prevalence (Fewer than 20,000 patients in South Korea)	Or whose number of patients is unknown because diagnosis of the disease is difficult	
Turkey[28]	National Government/ Regulatory	≤ 1 in 100,000 Prevalence		
United Kingdom[63,64]	National Government/ Regulatory	≤ 1 in 2,000 Prevalence	And a disease that is life-threatening or chronically debilitating	
United Kingdom[38]	HTA		The target patient group [...] is so small that treatment will usually be concentrated in very few centres in the NHS; And the target patient group is distinct for clinical reasons; And the condition is chronic and severely disabling.	
The United States[10,11]	National Government/ Regulatory	≤ 1.2 in 2,000 Prevalence (Fewer than 200,000 patients in The United States)		
The United States[34]	National Government	<15 in 100,000 Per Year Incidence		

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