

## ENVIRONMENTAL SCAN

# Drugs for Rare Diseases: A Review of National and International Health Technology Assessment Agencies and Public Payers' Decision-Making Processes

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## Abbreviations

CDR	Common Drug Review
DRD	Drugs for Rare Diseases
DURD	Drugs for Ultra- Rare Diseases
EDRD	Expensive Drugs for Rare Diseases
G-BA	Gemeinsamer Bundesausschuss or Federal Joint Committee
HST	highly specialised technologies (NICE)
HTA	health technology assessment
ICER	Institute for Clinical and Economic Review
INESSS	Institut national d'excellence en santé et en services sociaux
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen or Institute for Quality and Efficiency in Health Care
LSDP	Life Saving Drugs Program (Australia)
NHS	National Health Services (UK)
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
pCODR	pan-Canadian Oncology Drug Review
PHARMAC	Pharmaceutical Management Agency
SMC	Scottish Medicines Consortium

## Context

Drugs for Rare Diseases (DRD) are medicinal products intended for the diagnosis, prevention, or treatment of rare diseases or disease subtypes.<sup>1,2</sup> These medical products include small-molecule drugs or biopharmaceuticals (hereafter, “drugs”). There is a lack of consensus on how rare diseases are defined, as well as a variation in the terminology used to identify the DRD.<sup>3,4</sup> In addition to the prevalence of the diseases, other criteria such as disease severity, lack of alternative treatment, and the hereditary nature of the disease are also used to define these diseases. Based on the rate of disease prevalence, DRD are sometimes classified further as DRD, drugs for ultra-rare diseases (DURDs), or drug for other rare diseases<sup>5</sup> Additionally, terminologies such as “orphan drugs” and “ultra-orphan drugs” are also commonly used to identify these drugs.<sup>4,5</sup> Some researchers may also use the term “expensive drugs for rare diseases (EDRD)” to represent the costly treatments developed for rare diseases.<sup>6,7</sup> For the purposes of this Environmental Scan, the term “drugs for rare diseases (DRD)” is used to identify these drugs, in general terms.

In Canada, the term “rare disease” is generally used to refer to a condition affecting fewer than 1 in 2,000 people.<sup>8,9</sup> Rare diseases are severe and chronic conditions, with many being seriously debilitating, degenerative, and life-threatening.<sup>8,9</sup> It is estimated that rare diseases affect about 2.8 million (1 in 12) Canadians, about two-thirds of them being children.<sup>2,10</sup> There are more than 7,000 identified rare diseases and this number has been increasing.<sup>2,11</sup> However, each rare disease affects a relatively small number of patients, resulting in a limited understanding of potential diagnosis and possible treatment options for these diseases.<sup>2,9</sup> Further, DRDs are often very expensive, with costs often exceeding \$500,000 per year for one patient.<sup>2</sup> These high costs are attributed to factors such as the high cost of research, the limited number of patients, and hence a small market size and lack of generic competitors.<sup>2</sup> The high cost of drugs, the increasing prevalence of the rare diseases, and the severity of rare disease pose a significant societal, clinical, and economic burden to patients and caregivers, as well as to the health care system.<sup>2,9</sup>

Over the past two decades, several DRDs have been developed that have offered potentially effective therapies. The biopharmaceutical industry’s shift in focus toward niche markets such as DRDs is evident from the increase in the number of DRDs in the pipeline and those being marketed.<sup>3,9,12,13</sup> The expected yearly growth of DRDs is approximately 11%, which is more than twice that of conventional drugs on the market.<sup>13</sup> The number of DRD submissions to the CADTH Common Drug Review (CDR) almost doubled between 2004 and 2015. There were four to five submissions for a DRD per year between 2004 and 2012, which increased to 10, nine, and eight in 2013, 2014, and 2015, respectively.<sup>12</sup>

Various factors make it challenging to apply standard health technology assessment (HTA) methodologies to assess these drugs, such as uncertainty of evidence, low prevalence of rare diseases, and poorly explored epidemiology, absence of comparable treatment alternative on the market, and failure of DRD to meet the set economic benchmarks because of their high cost.<sup>13</sup> To address these challenges posed by standard HTA methodologies, some HTA agencies and public payers have established separate or modified processes and programs to review and make funding recommendations or decisions on DRDs. Such new or modified decision-making processes are expected to make these expensive drugs available to patients, while ensuring that effective and cost-effective treatments are reimbursed.

## Objective

The objective of this Environmental Scan is to identify, describe, and compare how HTA agencies in Canada and internationally make reimbursement recommendations on DRDs. The Environmental Scan will also present information on how funding agencies – that is public payers – evaluate and make funding decisions on DRDs. This Environmental Scan will aim to answer the following key questions:

- How do HTA agencies review and make reimbursement recommendations for DRDs?
- How do public payers make funding decisions for DRDs?
- Do any of Canada’s publicly funded drug plans use a DRD-specific evaluation framework to evaluate DRD funding?

Comparison of the review and decision-making process, for both HTA organizations and public payers, will include (but is not limited to) definitions, program eligibility criteria, the submission process, and evaluation frameworks including clinical and economic assessments. Publicly available reports, guidelines, and evaluation frameworks from the HTA organizations in the countries listed in Table 1 will be reviewed to gather the information. These countries were selected because of commonalities with the Canadian context, including geography and regulatory HTA or reimbursement processes. If available, this Environmental Scan will also present information on a separate funding program for DRDs in these countries. Information on the Canada’s public drug plans, specific to their evaluation and decision-making process for DRDs, will also be presented. Some of these HTA agencies and public payers make a distinction between DRDs and DURDs, and have established separate or modified processes for each of these categories, whereas some categorize DRDs under life-saving drugs or highly specialized technologies. This Scan will include information on the HTA process and funding program for all of these categories, as long as they were explicitly designed to address the unique needs of DRDs.

**Table 1: National and International Health Technology Associations Organizations**

Country	HTA Organizations and Relevant Bodies
Canada	<ul style="list-style-type: none"> <li>• CADTH:               <ul style="list-style-type: none"> <li>◦ Common Drug Review (CDR)</li> <li>◦ Pan-Canadian Oncology Drug Review (pCODR)</li> </ul> </li> <li>• Institut national d’excellence en santé et en services sociaux (INESSS)</li> </ul>
UK	<ul style="list-style-type: none"> <li>• National Institute for Health and Care Excellence (NICE)</li> <li>• Scottish Medicines Consortium (SMC)</li> </ul>
France	<ul style="list-style-type: none"> <li>• Haute Autorité de santé or French National Authority for Health (HAS)</li> </ul>
Germany	<ul style="list-style-type: none"> <li>• Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen or Institute for Quality and Efficiency in Health Care (IQWiG)</li> <li>• Gemeinsamer Bundesausschuss or Federal Joint Committee (G-BA)</li> </ul>
Australia	<ul style="list-style-type: none"> <li>• Pharmaceutical Benefits Advisory Committee (PBAC)</li> </ul>
New Zealand	<ul style="list-style-type: none"> <li>• Pharmaceutical Management Agency (PHARMAC)</li> </ul>
US	<ul style="list-style-type: none"> <li>• Institute for Clinical and Economic Review (ICER)</li> </ul>

## Limitations

This Environmental Scan does not present information on the regulatory framework around orphan drugs or DRD designation or definition, the market approval process, manufacturer incentives, or information on specific DRDs that are in the pipeline or those currently being marketed in these jurisdictions and their reimbursement status. Readers are referred to the 2016 CADTH Environmental Scan *Drugs for Rare Diseases: Evolving Trends in Regulatory and Health Technology Assessment Perspectives* for this information.<sup>3</sup> This Scan only highlights information on separate or modified HTA processes or funding programs specific to the reimbursement recommendation or decisions on DRDs. The details of the standard HTA processes that could also apply to rare diseases — such as patient input, reconsideration, or appeals — are not discussed in the Scan. Readers are referred to the 2016 Environmental Scan *Single Drug Technology Assessment Processes Across Health Technology Assessment Organizations* for information on standard HTA processes at national and international HTA agencies.<sup>14</sup>

Furthermore, this Scan is not a comprehensive review of HTA agencies or public payers funding recommendations or decision processes on DRDs. Readers are requested to refer to individual organizations websites and guidance documents for up-to-date and detailed information on the processes and evaluation frameworks.

## Methods

The findings of this Environmental Scan are based on a limited literature search. Key informants from the countries of interest were contacted via email to request documents or website links related to DRD processes for their organization. No formal survey was conducted, nor was the information validated. Additionally, CADTH's federal, provincial, and territorial jurisdictional clients were consulted to identify information on DRD-specific evaluation processes or programs in public drug plans in Canada. The literature search was conducted using key resources, including MEDLINE and PubMed (for In-Process records), selected grey literature sites from the *Grey Matters* checklist (<http://www.cadth.ca/resources/grey-matters>), and through a focused Internet search. The literature search was completed on January 25, 2018 and updated with regular search alerts until May 28, 2018.

## Summary of Assessment and Decision-Making Processes for DRDs

The following tables (Tables 2a and 2b) provide an overview of the organizations and a summary of features of assessment and decision-making processes in Canada and internationally for DRDs. This Scan did not identify DRD-specific assessment, evaluation, or recommendations frameworks, or any special consideration for DRDs in standard processes, in France and for INESSS in Canada. They are therefore not included in Table 2b. Of note, public drug plans in some Canadian provinces have established a separate evaluation framework and decision-making process for DRDs. They are discussed in the sections that follow but are not included in Table 2a or Table 2b.

**Table 2a: Summary of HTA Organizations in Canada and Internationally, and Their Drugs for Rare Diseases-Specific Decision-Making Process**

Country	Which HTA Agency or Government Body is Involved in Assessments or Decision-Making Processes for Drugs?	Does the Evaluation Framework Recognize the Unique Needs of DRDs (i.e., a Distinct Review Process for DRDs versus other drugs), or Address the Unique Needs of DRD Within the Standard Process (i.e., Modified Process)? (See Section entitled Overview of HTA Processes or Funding Programs for Drugs for Rare Diseases for details.)	How are DRDs Defined by These Agencies?  (See Section entitled Definition and Program Eligibility, and Table 3a, for details)
Canada	CADTH (HTA agency) makes recommendations to public drug plans in Canada, except Quebec; reviews are conducted through its CDR (for all drugs except oncology) and pCODR (for oncology drugs) programs. <sup>14</sup>	No separate review process for DRDs, but, in March 2016, the standard HTA Recommendation Framework was revised, which makes special consideration for DRDs	DRDs not defined by CADTH <sup>a</sup>
	INESSS (HTA agency) makes recommendations to the public drug plan in Quebec. <sup>14</sup>	No separate review process for DRD identified by this Environmental Scan	DRDs not defined by INESSS
UK (England)	NICE (HTA agency) conducts HTA and advises the NHS in England on the clinical effectiveness, cost-effectiveness, and service impact of new and emerging, as well as established, health care technologies. <sup>1</sup>	A separate review process for “very rare condition” through an HST program; the process largely follows the NICE standard technology appraisal process for the review but has issued guidance on the appraisal of HST, which makes additional consideration for assessing DRDs	Drugs for Very Rare Condition ( <i>Note: The guidance document does not specify a definition for this term</i> )

UK (Scotland)	SMC (HTA agency) advises NHS Scotland regarding which medicines provide good value for money. <sup>14</sup>	No separate review process for DRD but established additional processes within their evaluation framework to assess DRDs	<p><i>Orphan medicine:</i> Orphan status designed by EMA; i.e., conditions affecting &lt; 2,500 per 5 million or a “medicine to treat an equivalent size of population irrespective of designated orphan status”</p> <p><i>Ultra-orphan medicine:</i> “used to treat a condition with a prevalence of 1 in 50,000 or less (around 100 people in Scotland)”<sup>15</sup></p>
France	HAS (HTA agency) and the Transparency Committee within HAS assesses medicines and makes recommendations on their inclusion on the list of reimbursable drugs. <sup>1,14</sup>	No separate review process for DRD identified by this Environmental Scan	A DRD definition for HAS was not identified by this Environmental Scan
Germany	G-BA (government body) issues directives for the benefit catalogue of the GKV in Germany. The G-BA commissions IQWiG (HTA agency) to conduct early assessments to examine the added benefits of a medicine and to make recommendations. <sup>14</sup>	No separate review process for DRD but legislation in Germany grants orphan drugs a special status in the early benefit assessments of pharmaceuticals; that is, the added benefit of DRD is considered to be proven with market authorization	<p><i>Orphan drugs:</i> (as per EC regulation) intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition affecting &lt; 5 in 10,000 persons, and there is a lack of satisfactory alternative method of diagnosis, prevention or, if alternatives exist, the product offers significant benefit to those affected<sup>16,17</sup></p>

Australia	PBAC (HTA agency) is an independent expert body appointed by the Australian Government to primarily recommend new medicines for listing on the Pharmaceutical Benefits Scheme. <sup>18</sup>	No separate evaluation framework for DRDs in PBAC, but their standard process has the provision to invoke “rule of rescue” that could apply to DRD  The Australian Government has established a separate funding program, the LSDP, for expensive and life-saving medicines for very rare and life-threatening medical conditions	(Proposed definition <sup>b</sup> ) <i>Rare disease</i> : “a disease with prevalence of 1:50,000 people or less” in the Australian population; i.e., about 500 people <sup>19</sup>
New Zealand	PHARMAC (a government agency) decides which pharmaceuticals to publicly fund in New Zealand. <sup>20</sup>	No separate review process for DRD exists, but, in 2014, PHARMAC piloted a new approach to assess and fund DRD through a “contestable funding pilot,” which is now closed	<i>Rare diseases</i> as “an identifiable and measurable patient population with a prevalence of 1:50,000 or less” <sup>21</sup>
US	ICER, an independent and non-partisan research organization, objectively evaluates the clinical and economic value of health care and health care delivery innovations, including prescription drugs. <sup>22</sup>	In November 2017, ICER made modifications to its Value Assessment Framework for reviews of ultra-rare diseases <sup>23,24</sup>	The modified framework assesses ultra-rare diseases; that is, when the condition is estimated to affect <10,000 individuals, with no ongoing or planned clinical trial on a patient population >10,000 individuals <sup>23</sup>

CDR = Common Drug Review; DRD = drugs for rare diseases; EC = European Commission; EMA = European Medicines Agency; G-BA = Gemeinsamer Bundesausschuss or Federal Joint Committee; GKV = Germany’s Statutory Health Insurance Funds; HAS = Haute Autorité de santé or French National Authority for Health; HST = highly specialised technologies (NICE); HTA= health technology assessment; ICER = Institute for Clinical and Economic Review; INESSS = Institut national d’excellence en santé et en services sociaux; IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen or Institute for Quality and Efficiency in Health Care; LSDP = Life Saving Drugs Program (Australia); NHS = National Health Services (UK); NICE = National Institute for Health and Care Excellence; PBAC=Pharmaceutical Benefits Advisory Committee; pCODR = pan-Canadian Oncology Drug Review; PHARMAC = Pharmaceutical Management Agency; SMC =Scottish Medicines Consortium.

<sup>a</sup> The Recommendation Framework (Appendix 1) gives examples of “Considerations” such as rarity of condition, (small) population, and the absence of an alternative that could apply when making recommendations for exceptional cases such as DRDs.<sup>25</sup>

<sup>b</sup> In January 2018, based on the review of the LSDP, the Australian Government announced several measures to improve the program, including the adoption of the above-noted definition of “rare diseases.”<sup>19</sup>

**Table 2b: Summary of Features of Assessment and Decision-Making Processes for DRDs in Canada and Internationally**

	CADTH (Canada)	NICE (England)	SMC (Scotland)	G-BA /IQWiG (Germany)	PBAC (Australia)	PHARMAC <sup>c</sup> (New Zealand)	ICER (US)
Are there criteria to be met for a drug to be considered under the DRD review process or modified review process?	No specific criteria to be met <sup>a</sup>	Eligibility criteria are defined; all criteria have to be met to be eligible for HST	Eligibility is confirmed based on evidence provided (criteria not defined in guidance document)	As per the definition of “orphan drugs”	<i>Rule of rescue:</i> <sup>b</sup> There are four defined eligibility criteria that must be met to invoke the rule  <i>LSDP:</i> Criteria and conditions are pre-defined; and the drug has to be considered by PBAC but rejected for PBS listing on the basis of cost-effectiveness	Prerequisites outlined in the RFP had to be met	As per the definition of ultra-rare diseases
Is there a separate submission template, or does the standard submission template require additional information for DRDs?	No separate process or template	A separate submission form is used for HST evaluation	Uses standard HTA submission form, which accounts for additional information required for orphan and ultra-orphan drugs; additionally, companies have to fill “ultra-orphan decision-making framework” for ultra-orphan drugs	Only requires information on the “extent of additional benefit”	<i>Rule of rescue:</i> no separate submission required to invoke the rule  <i>LSDP:</i> intent to be considered for LSDP must be expressed when submitting to PBAC for PBS listing (i.e., standard HTA process)	A separate submission process and template were used to submit proposals for the “contestable funding pilot”	No

	CADTH (Canada)	NICE (England)	SMC (Scotland)	G-BA /IQWiG (Germany)	PBAC (Australia)	PHARMAC <sup>e</sup> (New Zealand)	ICER (US)
Does a special evaluation committee review and make recommendations on DRDs?	No	Yes; Highly Specialised Technologies Evaluation Committee	Yes; applicants can request SMC to convene a PACE meeting	No	No	Yes; Medicine for Rare Disease Subcommittee	No
Does the membership of the special evaluation committee vary according to the DRD (i.e., according to the therapeutic area) being reviewed?	No (no special evaluation committee)	No (Note: The consultee and commentator organizations identified are specific to each review) <sup>d</sup>	Yes; each PACE meeting is tailored to the medicine in review	No (no special evaluation committee)	No (no special evaluation committee)	No (no special evaluation committee)	No (no special evaluation committee)
Are patients or patient groups part of the special evaluation committee? <sup>d</sup>	No (no special evaluation committee) <sup>e</sup>	Yes <sup>d</sup>	Yes; patient groups and clinicians from the relevant specialty are also a part of each tailored PACE meeting	No (no special evaluation committee) <sup>e</sup>	No (no special evaluation committee) <sup>e</sup>	Not specified	No (no special evaluation committee) <sup>e</sup>
Are any considerations made for economic evaluation?	Yes; recognizes that there are exceptional cases where there is uncertain clinical and pharmacoeconomic evidence	Yes; consideration made in the benchmark for QALY and discounting	Yes; economic analysis, although a factor, will not be the predominant factor in the decision for ultra-orphan drugs	Yes; only cost of treatment is considered	Yes; <i>Rule of Rescue</i> , when invoked, may result in PBS listing even when the additional aspects of societal value and distributional preferences are not currently captured in the incremental cost-effectiveness ratio metric	Yes; the relativity of the costs and benefits of the medicines selected in the context of the severe health need of people with rare disorders was considered, rather than	Yes; consideration made in the willing-to-pay-threshold; inclusion of broader societal costs in its economic model; including “mapping” studies to help translate surrogate outcomes into quality of life measures, and allowing vote on “long term value for money” even if the base-case cost-effectiveness falls outside the standard range (\$50,000 to \$175,000 per QALY)

	CADTH (Canada)	NICE (England)	SMC (Scotland)	G-BA /IQWiG (Germany)	PBAC (Australia)	PHARMAC <sup>e</sup> (New Zealand)	ICER (US)
Are any considerations made for economic evaluation?					<i>LSDP</i> : by definition, LSDP considers only those drugs that are reviewed by PBAC but rejected for PBS listing on the basis of cost-effectiveness	attempt to estimate the net present value of the allocation decision and the next best alternative	
Is financial risk-sharing arrangement a part of the proposal or recommendation for DRDs?	Not specified	Yes (managed access arrangement could be a part of the recommendation)	Not specified	Not specified	Not specified <sup>f</sup>	Yes (risk-sharing mechanisms were accepted as a part of the proposal)	No

DRD = drugs for rare diseases; G-BA = Gemeinsamer Bundesausschuss or Federal Joint Committee; HST = highly specialised technologies (NICE); HTA = health technology assessment; ICER = Institute for Clinical and Economic Review; IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen or Institute for Quality and Efficiency in Health Care; LSDP = Life Saving Drugs Program Australia); NICE = National Institute for Health and Care Excellence; PACE = Patient and Clinician Engagement; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Schedule; PHARMAC = Pharmaceutical Management Agency; QALY = quality-adjusted life-years; SMC=Scottish Medicines Consortium.

<sup>a</sup> CADTH does not have a separate process for DRD and therefore there are no specific criteria to be met. However, the Recommendation Framework (Appendix 1) gives examples of “Considerations” such as rarity of condition, (small) population, and absence of alternatives that could apply when making recommendation for exceptional cases such as DRD.<sup>25</sup>

<sup>b</sup> “Rule of rescue” refers to the value for rescuing life regardless of the cost of the treatment.<sup>1</sup>

<sup>c</sup> Pilot is now closed.

<sup>d</sup> Highly Specialised Technologies Evaluation Committee members are drawn from National Health Services, patient and carer organizations, academia, and pharmaceuticals and medical devices industries. The Highly Specialised Technologies Evaluation Committee may also seek consultation and comments from organizations representing health care professions, patients, carers, manufacturers, and governments, who are identified and specific to each evaluation. However, the recommendations are independent of any external interests.<sup>27,28</sup>

<sup>e</sup> Regardless of whether a special committee reviews DRD or the standard committee reviews DRD (i.e., similar to the standard HTA process), it should be noted that patient input is considered by these HTA agencies in their standard HTA processes, which would also apply to a DRD-specific process and program.<sup>1,4,26</sup>

<sup>f</sup> Sponsors and the Australian Government may negotiate an Risk-Sharing Agreement or a Managed Access Program after PBAC has made its recommendation, including DRDs.<sup>29</sup> Additionally, PBAC can convene stakeholder meetings where there is a submission for a medicine that has not been recommended or deferred. Meetings are allocated by PBAC for medicines that treat serious, disabling, or life-threatening conditions, where there are no other realistic treatment options for that condition but where insufficient cost-effectiveness prevents PBAC from recommending listing. Outcomes of the Stakeholder Meeting may include the formulation of research questions to address information needs identified by the PBAC consideration, such as those that may be used to develop and implement performance-based risk-sharing arrangements or Managed Access Programs.<sup>30</sup>

## Findings

The sections that follow present information on how HTA agencies and public payers, in Canada and internationally, make reimbursement recommendations or decision on DRD. An overview of the evaluation process or programs in each of the countries is provided, followed by a description of the process or processes under the following three sections: Definition and Program Eligibility, Submission Process, and Evaluation Process. In addition, some public drug plans in Canada also have a separate evaluation framework or decision-making process for DRDs, which are also provided in the sections that follow.

### Overview of HTA Processes or Funding Programs for Drugs for Rare Diseases

Some HTA organizations have a separate evaluation framework or additional processes that assess and make reimbursement recommendation or decisions on DRDs; e.g., the Scottish Medicines Consortium (SMC) and the National Institute for Health and Care Excellence (NICE). However, there are other HTA agencies that do not have a separate evaluation framework or additional processes for DRD, but some of its standard drug assessment processes or decision-making frameworks do address the unique needs for assessing DRDs; e.g., CADTH and the Pharmaceutical Benefits Advisory Committee (PBAC). Additionally, some countries or HTA organizations have separate funding programs and related evaluation frameworks for DRDs; e.g., Australia's Life Saving Drugs Program (LSDP); and the Pharmaceutical Management Agency (PHARMAC), although its contestable funding piloted in 2014 is now closed. The following presents an overview of these HTA agencies or drug plans within the countries of interest.

**Canada:** There are two major HTA agencies in Canada, the Institut national d'excellence en santé et en services sociaux (INESSS) in the province of Quebec and CADTH (for all of Canada, except Quebec). These agencies make drug reimbursement recommendations to the respective public drug plans in Canada.<sup>14</sup>

- A separate evaluation framework for DRDs was not identified for CADTH. However, the guidance document for CADTH's Drug Expert Committees for CDR and pCODR processes discusses exceptional cases where there is "uncertain clinical and pharmacoeconomic evidence." In these cases, CADTH drug expert committees may "issue a recommendation to reimburse with clinical criteria and/or conditions, due to practical challenges in conducting robust clinical trials and pharmacoeconomic evaluations and in the presence of significant unmet medical need." The guidance outlines considerations for "significant unmet need" and identifies factors that contribute to uncertainty of clinical benefit. The framework states that these considerations and factors could also apply to DRDs.<sup>25</sup> Except for these considerations made when developing "recommendation" for DRDs, CDR and pCODR follow the same HTA process for both DRDs and non-DRDs; that is, eligibility criteria, timelines, fees, submission requirements, clinical and economic evidence requirement and assessment processes, stages of stakeholder involvement, and the type of stakeholders involved. Although the same review committee makes recommendations for all the drugs, clinical experts engaged during the review process and patient input from patient groups or individual patients (in the absence of patient groups) are specific to the drug under review, as is with all the other drugs; i.e., a similar process is followed for both DRDs and non-DRDs.<sup>14</sup>
- Research conducted for this Scan did not identify a separate evaluation framework for DRDs at INESSS. A 2016 CADTH Environmental Scan specifies that INESSS follows the same HTA process for both DRD and non-DRD; that is, eligibility criteria, timelines, patient input, submission requirements, clinical and economic evidence requirement and assessment processes, stages of stakeholder involvement, and the type of stakeholders involved.<sup>14</sup>
- In addition to the HTA agencies, public drug plans in the following provinces in Canada have processes for DRD reimbursement: Alberta, British Columbia, and New Brunswick.<sup>1,14</sup> These processes are discussed further under the DRD-Specific Evaluation Framework or Decision-Making Processes at Canadian Public Drug Plans section of this Scan.

## UK:

- NICE conducts HTA and advises the National Health Service (NHS) in England on the clinical effectiveness, cost-effectiveness, and service impact of new and emerging as well as established health care technologies.<sup>1</sup> NICE has issued a guidance on the appraisal of Highly Specialized Technologies (HST), which only considers drugs for very rare conditions (Note: the term 'very rare conditions' is not defined in guidance document)<sup>27,31</sup> The HST guidance was revised in May 2017, and currently there are four drugs proposed to be reviewed through HST program.<sup>27,32</sup>
- SMC advises NHS Scotland regarding which medicines provide good value for money.<sup>14</sup> SMC has established additional processes within its evaluation framework for DRDs. These guidance documents include *Guidance to Manufacturers for Completion of New Product Assessment Form* (NPAF) – Supplement on medicines for end of life and very rare conditions; and PACE (Patient & Clinician Engagement) Overview Document – Process for End of Life and Very Rare Conditions (orphan and ultra-orphan medicines).<sup>15,33</sup>

**France:** Haute Autorité de santé or French National Authority for Health (HAS) is the French HTA body, and the Transparency Committee within HAS assesses medicines and makes recommendation on their inclusion on the list of reimbursable drugs.<sup>1,14</sup> Research conducted for this Scan did not identify a separate evaluation framework for DRD at HAS. Some criteria outlined within the standard HAS process may be applicable to rare diseases. For example, "high unmet need" is one of criteria that could make a drug eligible for accelerated procedure for assessment.<sup>1,34-36</sup> However, none of these specifically mention that these criteria are intended to address the needs of rare diseases and are therefore not discussed further in this Scan.

**Germany:** The Gemeinsamer Bundesausschuss or Federal Joint Committee (G-BA) issues directives for the benefits catalogue of the statutory health insurance funds in Germany. The G-BA commissions the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen or Institute for Quality and Efficiency in Health Care (IQWiG) to conduct early assessments to examine the added benefits<sup>a</sup> of a medicine and to make recommendations.<sup>14</sup> Legislation in Germany grants orphan drugs a special status in the early benefits assessments of pharmaceuticals, whereby its added benefit is already considered proven through market authorization, with IQWiG only assessing information provided by the manufacturers on the number of patients affected by the rare disease and the cost of treatment.<sup>14,16</sup> It should be noted that this provision only applies to "orphan drugs with revenues not exceeding 50 million euros in the past twelve months based on market authorization and its substantiating studies." Should the orphan drug's revenue exceed 50 million euros<sup>b</sup> over the past 12 months, the drug undergoes the standard HTA processes; i.e., an early benefits assessment conducted by IQWiG, as commissioned by the GB-A, using the same method as for other drugs.<sup>14,16</sup>

**Australia:** PBAC is an independent expert body appointed by the Australian Government to primarily recommend new medicines for listing on the Pharmaceutical Benefits Scheme.<sup>18</sup> Research conducted for this Scan did not identify a separate evaluation framework for DRDs at PBAC. There is, however, a provision within the standard PBAC process, called the "rule of rescue;" that is, the value for rescuing life regardless of the cost of the treatment.<sup>1</sup> Criteria outlined in the "rule of rescue," if met, allows flexibility in exceptional

<sup>a</sup> In general, there are six classifications concerning the extent of the additional benefit: (1) major additional benefit, (2) considerable additional benefit, (3) minor additional benefit, (4) non-quantifiable additional benefit, (5) no additional benefit, and (6) less benefit. Based on this classification, one of two courses of action concerning the price-setting of a pharmaceutical will follow. The number and characteristics of studies provided, the certainty of results, and the observed effects determine the level or quality of evidence ("proof," "indication," or "hint").<sup>37</sup>

<sup>b</sup> The limit of 50 million euros is based on revenues from the pharmaceuticals paid by statutory health insurances at pharmacy retail prices, including VAT, over the past 12 calendar months. Revenues are calculated in accordance with SGB V, section 84, paragraph 5, sentence 4. Regular monitoring is conducted.<sup>16</sup>

circumstances and may be particularly influential in favour of listing. For details on the criteria, see the section Definition and Program Eligibility in this Scan. These could be applied as a supplement to orphan drugs submissions.<sup>1</sup>

Additionally, the Australian Government has established the LSDP to provide “fully subsidised access for eligible patients to expensive and life saving medicines for very rare and life-threatening medical conditions.” Through the LSDP program, there are currently 13 medicines available to eligible patients for the treatment of nine conditions.<sup>38</sup> Drugs have to meet certain criteria to qualify for the LSDP, and the funding program is separate from the Pharmaceutical Benefits Scheme.<sup>38</sup> For details on the criteria, see the section on Definition and Program Eligibility in this Scan. In January 2018, based on the review of the LSDP, the government announced several measures including “introducing a more structured system for consideration of the clinical benefits of very high cost medicines referred to the Life Saving Drugs Program by the Pharmaceutical Benefits Advisory Committee, including establishing an expert panel which will provide advice and assistance to the Chief Medical Officer.”<sup>39,40</sup> These changes are proposed to be implemented by July 1, 2018.<sup>19</sup> Currently 13 medicines are available through LSDP to eligible patients for the treatment of nine conditions.<sup>41</sup>

**New Zealand:** PHARMAC, a government agency, makes decisions on which pharmaceuticals to publicly fund in New Zealand.<sup>20</sup> Research conducted for this Scan did not identify a separate evaluation framework for DRD at PHARMAC. PHARMAC assesses all drugs including DRD – to be funded on the Pharmaceutical Schedule – through its standard HTA process.<sup>14,42</sup> However, PHARMAC piloted a new approach to assess and fund DRD in 2014.<sup>43</sup> A request for proposal (RFP) for this “contestable funding pilot” for DRD was released in August 2014, which resulted in 28 proposals for drugs for rare disorders. Out of the 28 proposals, 10 DRD were approved for funding between September 2015 and December 2016. PHARMAC identified up to \$25 million over five years for funding drugs for rare diseases on an open-ended basis. This “contestable funding pilot” is now closed.<sup>43,44</sup> Based on the evaluation of this “contestable funding pilot,” a set of dedicated features for considering DRDs will be introduced to the standard HTA processes later in 2018. Specific to the decision-making process, these new measures will include (but are not limited to) establishing a standing Pharmacology and Therapeutics Advisory Committee expert subcommittee for rare disorders and regular calls for rare disorder funding applications.<sup>43</sup>

**US:** The Institute for Clinical and Economic Review (ICER) is an independent and non-partisan research organization that objectively evaluates the clinical and economic value of health care and health care delivery innovations, including prescription drugs.<sup>22</sup> ICER follows its standard process for topic selection and assessment of the evidence, which also includes several opportunities for stakeholder input. The assessment of the quality of evidence is based on ICER’s Evidence Rating Matrix and the assessment of value of the technology is based on ICER’s Value Assessment Framework.<sup>45</sup> In November 2017, ICER made modifications to its Value Assessment Framework for reviews of ultra-rare diseases.<sup>23,24</sup>

## Definition and Program Eligibility

Some HTA agencies use specific definitions for rare diseases, orphan drugs, or ultra-orphan drugs to categorize drugs that can be eligible to be assessed through their evaluation frameworks or additional processes specific to DRDs. Additionally, drugs have to meet certain criteria to be eligible to be reviewed through these programs or processes.

A prevalence rate of 1 in 50,000 is considered an “ultra-orphan” condition by NICE’s “highly specialized technologies,” SMC’s (for ultra-orphan medicine), and “rare disease” by LSDP (Australia) and PHARMAC (funding pilot). A prevalence rate of 1 in 2,000 is considered an “orphan” condition by SMC (for orphan medicine) and G-BA. ICER considers a condition “ultra-rare” when it is estimated to affect less than 10,000 individuals. Some HTA agencies or funding programs also specify that the definition of these terms have to apply to a population level regardless of how the applicant wishes to position the drug; that is, to a specific subpopulation. Table 3a presents the definitions used by HTA agencies or funding programs.

**Table 3a: Definitions**

HTA Agency	Definition of Rare Diseases or Drugs for Rare Diseases
CADTH	CADTH does not have a specific definition for “rare diseases” or “DRDs.” However, the Recommendation Framework (Appendix 1) gives examples of “Considerations” such as rarity of condition, (small) population, and the absence of alternatives that could apply when making recommendations for exceptional cases such as DRDs. <sup>25</sup> See details in the section Evaluation and Decision-Making Process in this Scan.
SMC	<p><i>“Orphan medicine: A medicine with the European Medicines Agency designated orphan status (i.e., conditions affecting fewer than 2,500 people in a population of 5 million) or a medicine to treat an equivalent size of population irrespective of whether it has designated orphan status.</i></p> <p><i>Ultra-orphan medicine: A medicine used to treat a condition with a prevalence of 1 in 50,000 or less (or around 100 people in Scotland).”<sup>15</sup></i></p> <p>These definitions of orphan and ultra-orphan status are based on a population level, irrespective of whether or not the company wishes SMC to consider the product when positioned for use in a subpopulation of the licensed indication.<sup>15,46</sup></p>
G-BA	<p><i>Orphan drugs: “A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish: (a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment; and (b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.”<sup>16,17</sup></i></p>
Australia’s LSDP	The LSDP program has proposed to adopt the following definition of “rare disease,” which is in line with the current LSDP prevalence rates: “a disease prevalence of 1:50,000 people or less in the Australian population (around 500 people).” <sup>19</sup>
PHARMAC <sup>a</sup>	<i>Rare diseases: “An identifiable and measurable patient population with a prevalence of 1:50,000 or less.”<sup>21</sup></i>
ICER	ICER’s modified Value Assessment Framework assesses ultra-rare diseases; that is, when the condition is estimated to affect < 10,000 individuals, with no ongoing or planned clinical trial on a patient population >10,000 individuals. <sup>23</sup>

DRDs = drugs for rare diseases; G-BA = the Gemeinsamer Bundesausschuss or Federal Joint Committee; HTA = health technology assessment; ICER = Institute for Clinical and Economic Review; LSDP = Life Savings Drug Program; PHARMAC = Pharmaceutical Management Agency; SMC = Scottish Medicines Consortium.

<sup>a</sup> For the “contestable funding pilot.”

Regarding the program eligibility, rarity, and severity of disease (that is, clinically definable and identifiable, with a reasonable diagnostic precision), the lack of alternative treatment and causing significant financial burden to patient and caregivers generally make a drug eligible for these processes and programs. Table 3b provides further details on the eligibility criteria.

**Table 3b: Program Eligibility Criteria**

HTA Agency	Program Eligibility Criteria
NICE – HST	NICE has outlined the criteria, all of which have to apply, for the technology to be selected for a HST evaluation. These criteria are relevant to the rarity and severity of the diseases, distinct patient population, and the high acquisition cost, life-long use, significant need, and specialized nature of the technology. <sup>27</sup>
SMC	<p><i>Orphan medicine:</i> In their submission, companies are asked to state whether the medicine is an orphan medicine and provide the relevant evidence. SMC considers the evidence to confirm eligibility for consideration as a medicine used to treat an orphan condition prior to the New Drugs Committee meeting. Companies may be asked to provide further justification of status within this time period.<sup>46</sup></p> <p><i>Ultra-Orphan Medicine:</i> The intent to submit as an ultra-orphan medicine must be stated, and supporting evidence (i.e., data on disease prevalence for the full indication in NHS Scotland) must be provided to SMC by the companies during SMC’s routine contact with companies about submission requirements after receipt of a positive opinion from the Committee for Medicinal Products for Human Use. Based on the evidence, SMC confirms the eligibility of the medicine to be assessed through the ultra-orphan assessment process before the submission is made.<sup>46</sup></p>
G-BA	<p>Eligibility Criteria: As per the definition of “orphan drug” (see Table 3a)</p>
PBAC – “rules of rescue” and Australia’s LSDP	<p><i>Rule of Rescue:</i> There are four factors that must be applied concurrently to invoke the “rule of rescue” criteria in listing recommendations. These factors relate to the following: lack of alternative; medical condition that is severe, progressive, and expected to lead to premature death; a very small number of patients; and evidence of clinical improvement in the medical condition. It should be noted that the rule of rescue is not intended to replace but rather to supplement the need for the evidence-based consideration of comparative cost-effectiveness.<sup>47</sup> Please see Appendix 2 for details on the factors.</p> <p><i>LSDP:</i> Only drugs that were first considered by PBAC and rejected on the basis of cost-effectiveness are considered for inclusion in LSDP. The Chief Medical Officer also advises the Minister for Health on drugs proposed to be included in LSDP.<sup>38</sup> Strict criteria and conditions must be met to be eligible for LSDP funding. These include criteria for funding of a drug, pricing issues, and patient conditions for the initial and ongoing subsidy through the LSDP. These criteria and conditions are related to rarity and severity of the medical condition that are clinically definable, identifiable with reasonable diagnostic precision, and with evidence from epidemiological or other studies; evidence of clinical effectiveness, but rejected for PBS listing for failing to meet cost-effectiveness criteria; lack of alternative drug<sup>a</sup> listed on the PBS or available for public hospital in-patients, or recognized<sup>b</sup> non-drug therapeutic options; and cost of the drug causing unreasonable financial burden. Additionally, consideration and advice will be sought, as applicable, on the proposed price of the drug compared to the overseas market, as well as the cost of comparable drugs funded through LSDP.</p>

HTA Agency	Program Eligibility Criteria
<p>PBAC – “rules of rescue” and  Australia’s LSDP</p>	<p>LSDP will only fund the cost of the drug. Patients’ conditions include (but are not limited to) satisfying the relevant criteria for treatment with the drug, and patients participate in the evaluation of the effectiveness of the drug by periodic assessment (unless there is acceptable reason to not participate), as detailed or directed in the relevant drug/condition LSDP guidelines. Patients must not be suffering from any other medical condition that might compromise the effectiveness of the drug treatment. Clinical improvement or stabilization, generally evaluated every 12 months, is the required criteria that would continue to make a patient eligible for LSDP funding.<sup>48</sup> Please see Appendix 3 for details of the criteria and conditions.</p>
<p>PHARMAC<sup>c</sup></p>	<p>The RFP outlined the prerequisite criteria to be eligible for consideration for the “contestable funding pilot.” These prerequisites were related to the disorder, its treatment, and treatment alternatives. The disorder must be “rare” but “must be a clinically defined long-term disorder, identifiable with reasonable diagnostic precision” (see definition of “rare” in Table 3a), and “with evidence that it causes significant reduction in either absolute or relative age-specific life expectancy or quality of life.” The medicine must have been approved by Medsafe or a “recognized” international regulatory authority for the identified indication, confirming that it is a “proven therapeutic modality for an identifiable patient population.” There must be “acceptable” evidence of clinical effectiveness of the medicine, and that the treatment can directly and substantially improve the patient’s absolute or relative age-specific life expectancy and/or quality of life, as measured by absolute or proportional QALY gain. Additionally, a treatment is considered for the RFP only if it is “not registered for another, non-rare disorder, or if it is, the cumulative prevalence across all the indications still falls within the definition of ‘rare.’” Lack of a suitable comparable alternative treatment on the Pharmaceutical Schedule or a funded alternative non-drug therapeutic modality will be required to make the medicine eligible for the RFP.<sup>21</sup> PHARMAC accepted proposals that included a sole subsidized supply, provided the sole supply did not extend beyond June 30, 2018. PHARMAC also accepted proposals with expenditure risk-sharing mechanisms such as caps, rebates, etc., as long as they were applicable to all patients with similar clinical circumstances; that is, the risk-sharing mechanism was not based on a restricted number of patients. Proposals with cross-deal or bundling arrangements for more than one chemical entity, therapeutic group, or sub-group was accepted, as long as at least one of the pharmaceuticals involved was for the treatment of a rare disorder. Proposals with clinically acceptable and measurable entry and exit criteria were also accepted. Proposals where the net expenditure exceeds \$5 million in any 12-month period were not eligible.<sup>21</sup></p>

HTA Agency	Program Eligibility Criteria
ICER	<p>ICER uses the modified Value Assessment Framework for the treatment of URD when the condition is estimated to affect &lt; 10,000 individuals, with no ongoing or planned clinical trial on a patient population of &gt; 10,0000 individuals.<sup>23</sup></p> <p>In the initial draft scoping document for all topics, ICER includes whether a treatment will be assessed as a treatment for an URD. Formal public comments are sought on the recommendation, which is factored in ICER’s final decision whether the treatment will be assessed under the modified Value Assessment Framework for treatments for URD.<sup>23</sup></p>

G-BA = the Gemeinsamer Bundesausschuss or Federal Joint Committee; HTA = health technology assessment; HST = highly specialized technologies; ICER = Institute for Clinical and Economic Review; LSDP = Life Savings Drug Program; NHS = National Health Services; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical benefits Advisor Agency; PBS = Pharmaceutical Benefits Scheme; PHARMAC = Pharmaceutical Management Agency; QALY = quality-adjusted life-year; RFP = request for proposal; SMC = Scottish Medicines Consortium; URD = ultra-rare diseases.

<sup>23</sup>The availability of an alternative drug under the LSDP does not necessarily disqualify the proposed drug from consideration for the LSDP.<sup>48</sup>

<sup>48</sup>Non-drug therapeutic modality (e.g., surgery, radiotherapy), which is recognized by medical authorities as a suitable and cost-effective treatment for the condition.<sup>48</sup>

<sup>e</sup> For the “contestable funding pilot.”

## Submission Process

There were some variations in the submission process for these processes and programs for DRDs.

- NICE: NICE’s HST submission process is similar to its standard HTA process, but uses a separate submission form.
- SMC: SMC uses the same submission form as it does for standard HTA process; however, the form does account for additional information required to make a decision on orphan and ultra-orphan drugs. Applicants also have the option to request a Patient and Clinician Engagement meeting. (See further details in the Evaluation Process section.) Additionally, to be considered as “ultra-orphan medicine,” applicants must also complete the ultra-orphan decision-making framework in the SMC’s standard submission form.
- PBAC: No separate submission is required to invoke PBAC’s “rule of rescue.” An applicant must express their intent to be considered under the LSDP when they are making a submission for a standard PBS listing. However, if a treating physician is applying for LSDP for their patient, they have to fill out a separate form and provide related evidence.
- PHARMAC: A separate submission form had to be completed to submit a proposal to the PHARMAC’s “contestable funding pilot” for DRDs.
- ICER: A submission process is not applicable for ICER. ICER follows its standard process for topic selection and prioritization for all drugs including DRDs.

Additional information required by these processes or programs are generally related to the condition and its impact, often supplemented by epidemiological studies. Although economic evaluations are required by almost all processes and programs, the lack of robust economic evaluation for these DRDs were generally recognized, and some considerations were made as to the type of economic evaluation required. Table 4 provides additional details of the submission process.

**Table 4: Submission Process**

HTA Agency	Submission Process
NICE – HST	<p>The submission process for HST evaluation is similar to the NICE’s standard technology appraisal. The submission template for HST evaluation seeks information about the disease and technology under the following four sections:</p> <ul style="list-style-type: none"> <li>• <i>Nature of condition</i> including impact of the disease and current treatment options</li> <li>• <i>Impact of new technology</i> including clinical effectiveness and overall health benefits</li> <li>• <i>Value for money</i> including incremental cost-effectiveness, budget impact, and any commercial agreements</li> <li>• <i>Impact of the technology beyond direct health benefits</i> including any societal cost savings or long-term benefits, and impact on health care resources such as staffing and infrastructure needs.<sup>49</sup></li> </ul>
SMC	<p>Applicants must use the standard New Product Assessment Form – applicable to all new products – for submission of an orphan or ultra-orphan drug.<sup>46</sup> However, this form accounts for the additional information required by SMC for orphan or ultra-orphan conditions.<sup>46</sup></p> <p><i>Orphan medicine:</i> Companies also have the option to indicate whether they wish their submission to be considered under the end of life/orphan process in the event of a “not recommended” advice from the NDC; that is, with the option for a PACE meeting and/or opportunity for new or revised Patient Access Scheme. However, if a company that requests their submission be considered under the standard process, it cannot request a PACE meeting at a later stage. Companies opting for an assessment via the PACE process must provide additional information on the categorization of the medicine, and supporting evidence and rationale for this categorization. This should include data on the prevalence of the condition in the full licensed indication in NHS Scotland. All other sections of the NPAF, including economic analysis, are the same for all full submissions or re-submissions of any new product.<sup>15,46</sup></p> <p><i>Medicines with ultra-orphan status:</i> Companies must complete the ultra-orphan decision-making framework in addition to the pharmacoeconomic case and budget impact template. The ultra-orphan decision-making framework includes information on the nature of the condition, the impact of the new technology, costs to the NHS and Personal Social Services, value for money, and impact beyond direct health benefits and on specialist services. (See Appendix 4.)<sup>15,46</sup> Recognizing the challenges in providing robust economic evaluations for ultra-orphan drugs, SMC allows cost-utility analysis, cost-effectiveness analysis using appropriate natural outcome measures, or cost-consequence analysis, as appropriate. Although in some conditions the economic evaluation will have significant uncertainty, SMC still requires an estimate. Additionally, companies are allowed to provide a sensitivity analysis supporting the base-case economic evaluation that adopts a wider perspective than the conventional NHS perspective.<sup>15</sup></p>

HTA Agency	Submission Process
G-BA	<p><i>For orphan drugs with revenues not exceeding 50 million euros in the past twelve months based on market authorization and its substantiating studies:</i></p> <p>Pharmaceutical companies do not need to submit proof of medical benefit and additional medical benefit over an appropriate comparator. A relevant scientific assessment of the pharmaceutical as a foundation is not required. Essentially, an additional benefit of the orphan drug is assumed to be proven, once it has received market authorization. Only the extent of an additional benefit must be proved for the number of patients and patient groups for whom a therapeutically significant additional benefit exists.<sup>16</sup></p>
PBAC – “rules of rescue”  Australia’s LSDP	<p>There is no separate submission required to invoke the ‘rule of rescue’ criteria.<sup>1,14</sup> It is a part of the standard review process (see section below on <i>Decision-Making Process</i>)</p> <p><i>LSDP:</i></p> <p>Submission for a drug to be considered for inclusion in the LSDP must be filed in conjunction with submissions to the PBAC for a PBS listing.<sup>1,14</sup> Given that a drug is considered for LSDP following rejection from PBAC for failure to meet cost-effectiveness criteria, the original submission stands.<sup>1</sup></p>
PHARMAC <sup>a</sup>	<p>Applicants were allowed to submit more than one proposal, to be considered separately. Once submitted, withdrawal of the proposal was not allowed while the RFP process was continuing. Among others, the RFP requested information related to the following from suppliers of the DRD: “pricing including any related conditions or proposed terms affecting the cost for PHARMAC (e.g., price in return for sole supply, reference price protection, risk-sharing mechanisms, etc.)”; “proposals or suggestions (e.g., pricing, risk-sharing arrangements, etc.) regarding the pharmaceutical not expressly identified in the RFP” for PHARMAC’s consideration; “cost-effectiveness analysis, preferably based on the proposed commercial terms;<sup>b</sup> evidence that the proposal meets the “prerequisites for medicines for rare disorders” (see Table 3b); and “any additional information that PHARMAC should consider when evaluating the proposal, including information on the clinical benefits and risks of the pharmaceutical, the health needs of people diagnosed with the rare disorder, information on the particular health needs of Maori and Pacific peoples with the rare disorder.”<sup>21</sup></p>
ICER	<p>A submission process is not applicable for ICER. ICER follows its standard process for topic selection and prioritization for all drugs including DRDs. Individuals can also suggest topics for consideration by filling out a form on the ICER website. In general, the topic selection process includes an internal horizon scanning and input from the public, as well as other stakeholders (a broad range) that comprise the Advisory Boards of its independent appraisal committees. ICER has outlined the various considerations that determine the prioritization of a topic. These considerations include (but are not limited to) new treatments that can potentially offer improved patient outcomes, treatments that have the potential for significant financial impact, treatments that are likely to receive regulatory approval within a year, or treatments that are relevant due to the prevalence, severity, and cost.<sup>51</sup></p>

HTA Agency	Submission Process
ICER	ICER's reviews largely rely on publicly available, peer-reviewed literature. However, ICER may also consider evidence shared by manufacturers and other stakeholders, as well as evidence gathered through other sources such as grey literatures. <sup>45</sup> Specific to the treatments for URDs, ICER invites manufacturers to submit information on the development or manufacturing cost of the treatment. <sup>23</sup>

G-BA = the Gemeinsamer Bundesausschuss or Federal Joint Committee; HTA = health technology assessment; HST = highly specialized technologies; ICER = Institute for Clinical and Economic Review; LSDP = Life Savings Drug Program; NDC = New Drugs Committee; NHS = National Health Services; NICE = National Institute for Health and Care Excellence; NPAF = New Products Assessment Form; PACE = Patient and Clinician Engagement; PBAC = Pharmaceutical benefits Advisor Agency; PBS = Pharmaceutical Benefits Scheme; PHARMAC = Pharmaceutical Management Agency; RFP = request for proposal; SMC = Scottish Medicines Consortium; URD = ultra-rare diseases.

<sup>a</sup>For the “contestable funding pilot.”

<sup>b</sup>The RFP states “[W]hile PHARMAC may give greater weight to analyses that follow the standard New Zealand guidelines, we will consider English-language analyses prepared for other jurisdictions and/or from international literature.”<sup>21,50</sup>

## Evaluation Process

NICE HST and PHARMAC's funding pilot established a separate Evaluation Committee to evaluate DRDs, under their processes. Both the organizations, as well as SMC, also considered patient input in their decision-making frameworks. However, it should be noted that patient input is generally considered by these HTA agencies in their standard HTA processes, which would also apply to DRD-specific processes and programs.<sup>14,45</sup> Evaluations on DRDs are generally based on clinical and economic evidence, but most organization do recognize the paucity of robust clinical and economic evidence, and that a simple utilitarian approach to these evaluation do not sufficiently recognize the unique needs of the rare diseases. Although economic evidence is considered by these HTA organizations and funding programs, they do make some consideration (e.g., NICE 's HST, CADTH, PBAC, PHARMAC, ICER) or do not consider it a predominant factor (although a factor nonetheless) in their decisions (e.g., SMC). Table 5 provides further details on the evaluation process and special evaluation committees (if any).

**Table 5: Evaluation and Decision-Making Process**

HTA Agency	Evaluation and Decision-Making Process
CADTH	<b>Recommendations Framework:</b> The drug expert committees for CDR and pCODR programs could issue a “recommendation to reimburse with clinical criteria and/or conditions” in exceptional cases. These are cases where there is uncertain clinical and pharmacoeconomic evidence “due to practical challenges in conducting robust clinical trials and pharmacoeconomic evaluations and in the presence of significant unmet medical need.” However, the available evidence in these cases must “reasonably suggest that the drug under review could substantially reduce morbidity and/or mortality associated with the disease” even if there is “uncertainty with the clinical evidence.” Significant unmet clinical need is identified on a population or subpopulation basis (i.e., not on an individual basis) through the CDR and pCODR processes. These considerations could be related to rarity of condition, identified on a population basis and absence of alternative. However, “rarity of the condition will not be the sole consideration for defining significant unmet need,” and “the condition

HTA Agency	Evaluation and Decision-Making Process
CADTH	<p>must be identifiable with reasonable diagnostic precision.” The factors that contribute to “uncertainty of clinical benefit” could include (but is not limited to) “small sample sizes (e.g., due to rare disease that affects a relatively small number of patients (incidence of fewer than 5 in 10,000 but typically closer to 1 in 100,000), absence of comparator groups, alternative or adaptive trial designs for rare diseases, inability to distinguish disease severity in heterogeneous manifested rare diseases, limited to surrogate end points.” These consideration and factors are discussed in details in the Recommendation Framework. (See Appendix 1.)<sup>25</sup></p>
NICE – HST	<p><b>Evaluation Committee:</b> An independent advisory committee called HSTEC makes recommendations to NICE for or against the technology. HSTEC members are appointed on a three-year term, and members are drawn from the NHS, patient and carer organizations, academia, and pharmaceuticals and medical devices industries. Recommendations are based on evidence reviewed by the Evidence Review Group. HSTEC may also seek consultation and comments from organizations representing health care professions, patients, carers, manufacturers, and the governments, who are identified and specific to each evaluation. However, the recommendations are independent of any external interests. HSTEC meetings are held on a monthly basis.<sup>27,28</sup></p> <p>The evaluation and decision-making process for HST is largely similar to NICE’s standard technology appraisal. HSTEC therefore considers advice from NICE on the appropriate approach to making scientific and social value judgments. HSTEC considers the following factors in its deliberation (as noted in the previous section on Submission Process): the nature of the condition, the clinical effectiveness, value for money, and the impact of Technology beyond direct health benefits.<sup>27</sup></p> <p><b>Clinical Evaluation:</b> The HST evaluation guidance document outlines factors to be considered in making judgments on the clinical effectiveness of the technology, which are taken into account at the Committee’s discretion and in light of the particular features of the condition and the technology. Among other factors, the committee’s judgment is also informed by the views expressed by the clinical experts and patients who have experience with the condition or the technology. Additionally, the Committee also considers the uncertainty in evidence, differences between evidence submitted for licensing and evidence related to real-world effectiveness, and the potential differential benefit or safety outcomes in different patient groups.<sup>27</sup></p> <p>The guidance document also outlines the factors to be considered when considering a “treatment continuation rule.” These factors are related to the robustness, appropriateness, fairness, or plausibility of the end point on which the rule is based, achieving the “response” criteria, the time at which response is measured, incorporating the rule into routine clinical practice, predicting patients for whom the technology is cost-effective, and withdrawing treatment from people who do not respond to treatment.<sup>27</sup></p>

HTA Agency	Evaluation and Decision-Making Process
NICE – HST	<p><b>Economic Evaluation:</b> NICE recognizes that a simple “utilitarian” approach that puts a higher value on “greatest gain for the greatest number” will not produce guidance that recognizes the unique needs of very rare conditions, such as a very small patient group with limited treatment options; the nature and extent of evidence on these technologies, which is generally limited; challenges for companies to make a reasonable return on investment because of the small population being treated. Nevertheless, the Committee must still consider a balance between the cost and benefit of the technology, using an incremental cost-effectiveness ratio expressed as cost per QALY.<sup>27</sup></p> <p><b>QALY:</b> Regarding value for money, the preferred method for calculating the incremental cost-effectiveness ratio and the QALYs gained for HST, and the general principles for applying the reference case and for considering non reference-case analysis is consistent with the standard technology appraisal process.<sup>27</sup> However, some considerations are made for HST. All QALYs are regarded as being of equal weight in the reference case, but, the Committee can accept an analysis that explores the QALY weighing differently from the reference case – when considering the overall health benefits – in certain circumstances where there is strong evidence of significant QALY gains. A weight between 1 and 3 can be applied, using equal increments, for a range between 10 and 30 QALYs gained over the lifetime of patients, when comparing the new technology with its relevant comparator(s).<sup>27</sup></p> <p><b>Discounting:</b> The Evaluation Committee can consider applying a discount rate of 1.5% for costs and benefits if the presented evidence shows that it is highly likely that the long-term health benefits can be achieved, while not committing NHS to significant “irrecoverable costs” with the introduction of the technology.<sup>27</sup> The term ‘irrecoverable costs’ is not defined in the guidance document.</p> <p>Additionally, it is also noted that the recommendation for HST may include a managed access arrangement, a financial risk-sharing agreement with the pharmaceutical company, when there is a significant uncertainty in the evidence base identified by the Evaluation Committee.<sup>27</sup></p>
SMC	<p><b>NDC Meeting:</b> Submission for both orphan and ultra-orphan drugs are assessed by the NDC according to standard processes – that is, based on the clinical and economic cases – before consideration by the SMC Committee. As previously discussed in the Submission Process section, SMC allows flexibility in the economic evaluation for ultra-orphan drugs. Additionally, for ultra-orphan drugs, the NDC will review the information provided by the company on the ultra-orphan decision-making framework (see Appendix 4 and the Submission Process section), but this will not be part of the decision-making process for NDC.</p> <p>In the event that the NDC’s draft advice is a negative recommendation for orphan and ultra-orphan drugs, the company can chose to request SMC to convene a PACE meeting<sup>a</sup> (see subsequent details). At this point, the company will also have the option to submit a new or revised PAS aimed at improving the cost-effectiveness of the medicine and show that their product is a better value for NHS Scotland.<sup>15,33</sup></p>

HTA Agency	Evaluation and Decision-Making Process
SMC	<p><b>PACE:</b> The purpose of PACE is to gather detailed information on the drug – not always fully captured within the conventional clinical and economic assessment process – allowing a discussion on the benefits of a medicine, including its impact on the quality of a patient’s life.<sup>52</sup> The company is given the opportunity to provide this information (PACE statement) at the same time it provides comments on the NDC Detailed Advice Document. The PACE statement can include information on unmet need, severity of the condition, added value of the medicine for the patient, and family and carers (e.g., impact on quality of life for the patient, family or caregivers, improved functionality, convenience of treatment, maintaining patient’s independence and dignity, out-of-pocket expenses), place in therapy, and details of any subgroups the medicine may specifically benefit.<sup>15,33</sup> Each PACE meeting is tailored to the medicine under consideration. In addition to the NDC Vice-Chair or someone with specific experience with the SMC process (Chair of the meeting) who is supported by SMC staff and a public partner, representatives from patient groups and clinicians from the relevant specialty (identified by Managed Clinical Networks and regional Cancer Networks) are also a part of each tailored PACE meeting. Output from the PACE meeting will be a major factor in the SMC decision.<sup>33</sup></p> <p><b>Evaluation and Decision-Making Process Specific to Ultra-Orphan Medicine:</b> SMC adopts a broader decision-making framework; i.e., the “Ultra-orphan decision-making framework” (see Appendix 4 and the previous Submission Process section). SMC considers information provided by the company within this framework, as well as other sources of evidence to populate the framework; e.g., from SMC clinical experts, patient group submissions and, where relevant, the output from PACE meetings. It is noted that the economic analysis, although a factor in the decision-making process, will not be the predominant factor in the SMC decision.<sup>15</sup></p>
G-BA/ IQWiG	<p><i>For orphan drugs with revenues not exceeding 50 million euros in the past twelve months based on market authorization and its substantiating studies:</i></p> <p>The G-BA decides the extent of the additional benefit, rated as rate as “major,” “considerable,” “minor,” or “non-quantifiable.”<sup>b,37</sup> IQWiG is only commissioned to assess information provided by the manufacturers on the number of eligible patients (plausibility check of the epidemiological model) and the costs of the treatment.<sup>14,37</sup></p>
<p>PBAC – “rules of rescue”</p> <p>Australia’s LSDP</p>	<p><b>Rule of Rescue:</b> The rule of rescue is invoked if the drug meets specific criteria (see <i>Definition and Program Eligibility</i>). The rule of rescue is not a substitute for evidence-based consideration of comparative cost-effectiveness but, rather, a supplement. A decision to invoke the rule of rescue is relevant only when “PBAC would be inclined to reject a submission because of its consideration of comparative cost-effectiveness (and any other relevant factors).” In these exceptional circumstances, PBAC will decide if the rule of rescue is relevant, and would consider the applicability of all the “four factors” and if they are “sufficiently influential in favour of a recommendation to list that the PBAC would reverse a decision not to recommend listing if the rule of rescue were not relevant.”<sup>47</sup> A positive recommendation for a PBS listing may be favoured under the rule of rescue, irrespective of a relatively high incremental cost-effectiveness ratio or quantitative assessment of “value,” acknowledging “the additional aspects of societal value and distributional preferences that are not currently captured in the incremental cost-effectiveness ratio metric.”<sup>53</sup></p>

HTA Agency	Evaluation and Decision-Making Process
<p>PBAC – “rules of rescue”</p> <p>Australia’s LSDP</p>	<p>Note: PBAC can convene a Stakeholder Meeting where there is a submission for a drug that has not been recommended or deferred. Meetings are allocated by the PBAC for drugs that treat serious, disabling, or life-threatening conditions, where there are no other realistic treatment options for that condition but where insufficient cost-effectiveness prevents PBAC from recommending listing. Stakeholder meetings do not replace pre-submission or post-PBAC consideration meetings between the department and the sponsor. The aim of each meeting is to inform stakeholders of the situation and seek their views, and all relevant stakeholders may provide PBAC and stakeholders with a greater understanding of the issues and suggest ways to resolve some of the outstanding matters. These meetings provide information and are not a <i>de facto</i> appeals mechanism.</p> <p>The following stakeholders could be invited to the meeting: representatives of relevant organizations, both clinical and consumer-based; sponsors making submissions to list and those with current PBS-listed drugs treating the condition; individual clinical experts with expertise in prescribing, managing, and administering the treatment; or consumers with the disease or condition.</p> <p>The outcomes of the meeting are published on the Pharmaceutical Benefits Scheme website. Among others, the outcomes of the Stakeholder Meeting may also include the formulation of research questions to address information needs identified by the PBAC consideration, such as those that may be used to develop and implement performance-based RSAs or MAPs.<sup>30</sup></p> <p><b>LSDP.</b> As per the Program Eligibility Criteria previously discussed. In addition, the Chief Medical Officer advises the Minister for Health on drugs proposed to be included in the LSDP.<sup>41</sup></p>
<p>PHARMAC<sup>c</sup></p>	<p><b>Clinical Evaluation:</b> An internal PHARMAC Evaluation Committee comprised of PHARMAC staff evaluated the proposals to assess its eligibility; i.e., if the proposal met the prerequisite set in the RFP; and selected preferred proposal(s).<sup>21,44</sup></p> <p>Proposals were evaluated at the sole discretion of the Evaluation Committee; i.e., weight given to the criteria and other matters it considered relevant. However, the Evaluation Committee did take into account the nine “Decision Criteria”<sup>d</sup> as per PHARMAC’s policies, and as applicable; and any clinical advice from the PTAC sub-committee for rare disorders; i.e., the MRD sub-committee. The MRD sub-committee was a time-limited sub-committee set up specifically to advise on the proposed RFP and prerequisites, as well as on bids submitted to the RFP.<sup>21,44</sup> The MRD sub-committee provided advice to the Evaluation Committee on:</p> <ul style="list-style-type: none"> <li>• “Whether bids meet the RFP’s prerequisites.</li> <li>• Quality of the clinical evidence (particularly regarding health need and treatment efficacy) submitted or otherwise available for any bids for medicines that had not already been assessed by PTAC.</li> <li>• Advice on any bids for medicines that had already been assessed by PTAC, to account for new evidence and/or pricing changes.</li> <li>• Clinical acceptability and measurability of possible or bidder proposed eligibility criteria and on-going eligibility for funding.”<sup>44</sup></li> </ul>

HTA Agency	Evaluation and Decision-Making Process
PHARMAC <sup>c</sup>	<p>The MRD sub-committee ranked eligible proposals in order of priority. Sub-Committee members ranked the proposals individually (blinded) and then prepared a consensus ranking for PHARMAC as a group. The basis for the ranking were the nine decision criteria including clinical efficacy data and their knowledge of the disorder, with an understanding that the “medicines being reviewed had lower levels of evidence compared with that typical for Pharmaceutical listings.”<sup>44</sup></p> <p>The Evaluation Committee, with the support of other PHARMAC staff (financial analyst, health economist, and Medical Directors) prepared its final ranking of the proposals. The nine decision criteria formed the basis of this ranking, and the most relevant criteria determined the proposal’s position on the priority list.</p> <p><b>Economic Evaluation</b></p> <p>The same nine decision criteria were used to evaluate the proposals, similar to any standard applications for listing on the Pharmaceutical Schedule. However, because of the wide variation in estimates of the cost and benefit, the discussion focused on “the relativity of the costs and benefits of the medicines selected in the context of the severe health need of people with rare disorders, rather than attempt to estimate the net present value of the allocation decision and the next best alternative.”<sup>44</sup></p> <p>The <b>benefit assessment</b> for each medicine was based on “information on incidence and treatment outcomes from suppliers and other countries modified by the advice of patient advocate groups and New Zealand clinicians’ and RCT’s evidence where available, as an input into a simple ranking of each medicine by both the MRD Subcommittee and PHARMAC’s internal evaluation committee.”<sup>44</sup> Further, the assessment also included “quality-adjusted life years (QALY) per \$1 million cost usually expressed as a range for medicines that were funded and the medicines that were considered but not funded.”<sup>44</sup></p>
ICER	<p><b>Clinical Evaluation</b></p> <p>ICER uses its standard Evidence Based Medicine matrix – the Evidence Rating Matrix – to assess the comparative clinical effectiveness of treatment for URD.<sup>23,56</sup> Overall, the Matrix evaluates the magnitude of difference in “net health benefit” and its level of certainty.<sup>45,56</sup> However, recognizing the potential challenges in generating evidence for treatments for URD, ICER provides specific context around these challenges and any considerations in its reports and related documents. Examples of these challenges and considerations include challenges in conducting RCTs, validating surrogate outcome measures, obtaining data on long-term safety, and durability of clinical benefit, as well as a common approach used to evaluate these treatments against historical controls.<sup>23</sup></p>

HTA Agency	Evaluation and Decision-Making Process
ICER	<p><b>Economic Evaluation</b></p> <p>Several modifications have been made in ICER’s economic evaluation to address the unique need of DRD, such as producing a cost-effectiveness model for every new treatment; broadening the analysis for willingness-to-pay threshold results from \$50,000 per QALY to \$500,000 per QALY; highlighting in the report that decision-makers, nationally and internationally, may accept higher cost-effectiveness ratios (compared to other non-DRD) by giving additional weight to other benefits and considerations; inclusion of broader societal costs in its economic model when such costs are substantial; and, when necessary, conducting a search for “mapping” studies to help translate surrogate outcomes into quality of life measures. It should be noted that ICER uses the standard range from \$100,000 to \$150,000 per QALY to calculate the value based price benchmark for the treatment of URD.</p> <p>Additionally, ICER’s independent appraisal committee’s public meetings vote on “long term value for money,”<sup>6</sup> even if the base-case cost-effectiveness falls outside the standard range; that is, \$50,000 to \$175,000 per QALY.<sup>23</sup></p> <p><b>Stakeholder Input</b></p> <p>From topic selection to report development, and as a part of its standard process, ICER seeks input from various stakeholders such as clinical experts, patients and patient groups, manufacturers, payers, and other stakeholders.<sup>45</sup></p> <p>Specific to the review of treatments for URD, ICER seeks evidence and perspectives on the potential positive effects of the treatments on family, school, and community. Specific templates are developed to gather these inputs; and the information provided is used to inform the voting in the public meeting, and the “other benefits and disadvantages” and “contextual considerations” sections of the ICER report.<sup>23</sup></p>

CDR = Common Drug Review; DRD = drugs for rare diseases; ERG = Evidence Review Group; G-BA = the Gemeinsamer Bundesausschuss or Federal Joint Committee; HST = highly specialized technologies; HSTEC = Highly Specialised Technologies Evaluation Committee; HTA = health technology assessment; HST = highly specialized technologies; ICER = Institute for Clinical and Economic Review; IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen or Institute for Quality and Efficiency in Health Care; LSDP = Life Savings Drug Program; MAP = Managed Access Program; MRD = Medicine for Rare Disorder; NDC = New Drugs Committee; NHS = National Health Services; NICE = National Institute for Health and Care Excellence; PACE = Patient and Clinician Engagement; PBAC = Pharmaceutical benefits Advisor Agency; pCODR = pan-Canadian Oncology Drug Review; PBS = Pharmaceutical Benefits Scheme; PHARMAC = Pharmaceutical Management Agency; PTAC = Pharmacology and Therapeutics Advisory Committee; QALY = quality-adjusted life-year; RCT = randomized controlled trial; RFP = request for proposal; RSA = risk-sharing arrangement; SMC = Scottish Medicines Consortium; URD = ultra-rare diseases.

<sup>a</sup> A request to SMC to convene a PACE meeting can add an additional one to three months onto the assessment timelines.

<sup>b</sup> In the case of orphan drugs, the categories “no additional benefit” or “less benefit” are not applicable, as well as a categorization of the probability of the additional benefit in the form of “proof,” “indication,” or “hint,” which only applies to non-orphan drugs.<sup>37</sup>

<sup>c</sup> For the “contestable funding pilot.”

<sup>d</sup> The nine “decision criteria” include “the health needs of all eligible people within New Zealand; the particular needs of Maori and Pacific peoples; the availability and suitability of existing medicines, therapeutic medical devices, and related products and related items; the clinical benefits and risks of pharmaceuticals; the cost-effectiveness of meeting health needs by funding pharmaceuticals, rather than by using other publicly funded health and disability support services; the budgetary impact (in terms of the pharmaceutical budget and the government’s overall health budget) of any changes to the Pharmaceutical Schedule; the direct cost to health service users; the government’s priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, in PHARMAC’s Funding Agreement or elsewhere; and any other criteria that PHARMAC thinks are relevant.”<sup>55</sup> As of July 2016, the nine decision criteria were replaced by Factors for Consideration.<sup>56</sup>

<sup>e</sup> The concept of ‘long term value for money’ comprises of multiple domains; comparative clinical effectiveness; incremental cost-effectiveness; other benefits or disadvantages; and contextual considerations. For further details, please consult ICER’s framework; Overview of the ICER value assessment framework and update for 2017-2019.<sup>24</sup>

## DRD-Specific Evaluation Framework or Decision-Making Processes at Canadian Public Drug Plans

Public drug plans in Alberta, British Columbia, and New Brunswick have established processes for DRD reimbursement or a DRD-specific formulary.<sup>1,14,57</sup> Alberta and New Brunswick have a DRD-specific formulary (Alberta's Rare Diseases Drug Coverage Program and New Brunswick Drugs for Rare Diseases Plan), with a defined set of eligible DRDs.<sup>57-59</sup> The public drug plan in British Columbia makes funding decisions for DRDs on a case-by case basis.<sup>57</sup> These processes and programs are subsequently discussed. Of note, Ontario used to make funding decisions on DRDs under its publicly funded drug program through a separate evaluation framework, the DRD Evaluation Framework. However, this evaluation framework is no longer used.<sup>3,60,61</sup>

### Alberta

Within the Alberta Health Drug Benefit List, a Rare Diseases Drug Coverage Program provides access to DRDs for eligible Albertans.<sup>57,58</sup> This program was developed for ethical and compassionate reasons, recognizing that the exceptionally high cost of DRDs is beyond the reach of most Albertans.<sup>62</sup>

*Eligible Drugs:* For the purposes of the Program, a rare disease is defined as a genetic disorder that occurs in fewer than one in 50,000 Canadians or fewer than 50 Albertans.<sup>62</sup> Drug products approved by Health Canada for the treatment of rare diseases may be considered for coverage under the Program. The Alberta Minister of Health makes the final decisions regarding coverage under the Program and drugs may be listed when the Minister considers it is in the public interest to do so. Examples of diseases currently eligible for coverage consideration under the Program include Gaucher disease, Fabry disease, Mucopolysaccharidosis type I (MPS-I or Hurler/Hurler Scheie), Hunter syndrome, and Pompe disease.<sup>58,62</sup>

*Review Committee:* Applications submitted to the Program are reviewed by a ministry-appointed review panel, Alberta's Rare Diseases Clinical Review Panel, composed of specialists treating rare diseases and other health professionals with clinical expertise.<sup>58,62</sup> The function of the Review Panel includes:

- "Providing advice to Alberta Health regarding the Rare Diseases Drug Coverage Program;
- Reviewing and applying clinical knowledge and skills to individual applications for Rare Diseases Drug Coverage; and
- Providing advice to the Expert Committee on Drug Evaluation and Therapeutics regarding drug products under consideration for coverage under this section, clinical criteria for rare diseases drug products and identifying appropriate 'Rare Disease Specialists'."<sup>58</sup>

*Patient Eligibility:* Individuals must have Alberta-government sponsored drugs coverage, and must be continuously registered in the Alberta Health Care Insurance Plan for a minimum of five years unless they are less than five-years-old at the date of application; or if they moved to Alberta from another Canadian province or territory and immediately prior to moving to Alberta were covered by the public drug plan in the province of origin, and that the individual has been registered in the Alberta Health Care Insurance Plan. Individuals must meet the clinical criteria published on the drug benefits list, and must consent to regular monitoring for continued coverage (see the subsection Process for Rare Diseases Drug Coverage that follows). Additionally, the individual must not have a significant illness, not including one of the rare diseases, that is likely to substantially alter or reduce life expectancy.<sup>58</sup>

#### *Process for Rare Diseases Drug Coverage*

A participating "Rare Disease Specialist" must complete a Rare Diseases Drug Coverage Application form specific to the rare diseases drug product being requested, for each individual, and forward it to Alberta Blue Cross by mail or by facsimile. The Rare Disease Specialist must confirm that the individual (or individual's parent, guardian, or legal representative) has been provided with information regarding the Rare Diseases Drug Coverage Program and has completed the required forms.<sup>58</sup> Individuals must also complete required forms and consent to and acknowledge that:

- “approval for initial and continued coverage is conditional upon clinical outcomes;
- regular monitoring of the individual’s clinical outcomes will be required, and
- that coverage will be discontinued if there is inadequate response or the individual’s condition deteriorates as outlined in the withdrawal criteria established in relation to a specific rare diseases drug product and/or as assessed by the Review Panel.”<sup>58</sup>

Each application is received and screened for completeness by Alberta Blue Cross and then forwarded to Alberta Health to confirm that the individual has met the Alberta Health Care Insurance Plan registration requirement. Once confirmed, Alberta Blue Cross forwards the application to the Review Panel for assessment. Alberta Blue Cross notifies the individual’s Rare Disease Specialist and the individual (or the individual’s parent, guardian, or legal representative) about the Review Panel’s decision. Eligibility will be effective on the date the coverage is approved by the Review Panel. Any renewal will require a new drug product-specific Rare Diseases Drug Coverage Application form completed by a Rare Disease Specialist.<sup>58</sup>

Prescriptions must be written by a Rare Disease Specialist, as identified by the eligibility criteria for the drug product, to be eligible for Rare Diseases Drug Coverage, and prescription quantities are limited to a one-month supply to avoid any wastage. Prior approval must be granted to ensure coverage, and approvals are granted for a specific period, to a maximum of 12 months. If continued treatment is necessary, one has to re-apply for drug product coverage prior to the expiry date of the authorization period.<sup>58</sup>

## British Columbia

For the British Columbia Ministry of Health, the drug review process for all drugs begins at a national level with the CADTH CDR recommendation. Drugs are then reviewed by the British Columbia Drug Benefit Council, an expert advisory group who makes a recommendation to the British Columbia Ministry of Health on the population level informed by the CDR recommendation and British Columbia context. British Columbia will then potentially participate in pan-Canadian Pharmaceutical Alliance negotiations to achieve better reimbursement value. Once a drug is deemed a PharmaCare non-benefit, the British Columbia Ministry of Health then makes a decision whether to consider case-by-case requests on an exceptional, last-resort basis. If so, then British Columbia utilizes an EDRD process for making reimbursement decisions on DRDs. (British Columbia Ministry of Health, BC PharmaCare, Victoria, BC: personal communication, 2018 May 23).

Depending on the outcome of the CDR, Drug Benefit Council, pan-Canadian Pharmaceutical Alliance, and Ministry decision, the EDRD process makes funding decisions for DRDs on a case-by case basis. Reimbursement requests are made by physicians for specific patients. The EDRD process uses the following as guidance but eligibility is determined on a case-by-case basis: Drugs that have an annual cost of > \$100,000 per patient and indicated for a non cancer-related condition with a prevalence of < 1.7 per 100,000 Canadians (British Columbia Ministry of Health, BC PharmaCare: personal communication, 2018 May).

An expert advisory committee reviews the patient-specific request and makes a recommendation on a case-by-case, exceptional, last-resort basis. The committee is comprised of pediatric and adult rare diseases specialists, a medical geneticist, pharmacists, health administrators, a health economist, and an ethicist. The committee’s recommendations are also supported by an initial review and recommendation from clinical expert subcommittees. (British Columbia Ministry of Health, BC PharmaCare: personal communication, 2018 May).

The committee considers the severity of the disease, the clinical effectiveness of the drug, and the availability of alternatives in its recommendations, including pre-determined end points and a monitoring plan. The final funding and approval decisions are made by the Ministry of Health. (British Columbia Ministry of Health, BC PharmaCare: personal communication, 2018 May).

## New Brunswick

New Brunswick has the New Brunswick Drugs for Rare Diseases Plan that provides assistance with the cost of certain drugs for specific rare diseases.<sup>59</sup>

*Eligible Drugs:* Request for the following DRDs are considered by the plan: Aldurazyme (laronidase) for the treatment of Hurler and Hurler Scheie forms of mucopolysaccharidosis I (MPS-I); Elaprase (idursulfase) for the treatment of Hunter syndrome; Ilaris (canakinumab) for the treatment of cryopyrin-associated periodic syndrome (CAPS); Myozyme (alglucosidase alfa) for infantile/early- and adult/late-onset Pompe disease; Naglazyme (galsulfase) for the treatment of mucopolysaccharidosis VI (MPS VI); and Zavesca (miglustat) for the treatment of Niemann-Pick type C (NPC).<sup>59</sup>

*Patient Eligibility:* Permanent residents of New Brunswick with a valid Medicare card are eligible to be considered for coverage. The individuals must meet the clinical criteria for the drug requested.<sup>59</sup>

*Decision-Making Process:* A request form for a listed drug must be completed by the physician. New Brunswick partners with the Province of Ontario to deliver the plan; that is, it includes drugs that have been evaluated through the Ontario DRD Evaluation Framework. Of note, Ontario's DRD Evaluation Framework is no longer used in Ontario. Requests for coverage for individual New Brunswick patients are assessed by the Ontario Public Drug Programs' external medical experts.<sup>59</sup>

## Conclusion

Rare diseases are severe and chronic conditions, with many being seriously debilitating, degenerative, and life-threatening. Although the term "rare diseases" are referred to conditions affecting fewer than 1 in 2,000 people, there are more than 7,000 identified rare diseases, and it is estimated that about 2.8 million (1 in 12) Canadians have rare diseases. DRD are medicines intended for the diagnosis, prevention, or treatment of rare diseases or disease subtypes. Several drugs for rare diseases have been developed that have offered potentially effective therapies; however, these drugs are exceptionally expensive. Assessing the value of DRD is often challenging because of the uncertainty of the evidence, the low prevalence of rare diseases and poorly explored epidemiology, the absence of comparable alternatives on the market, and the failure of DRD to meet the set economic benchmarks because of their high cost. These factors make it challenging to apply standard HTA methodologies to assess DRD.

Canadian and international HTA agencies and public payers have established separate or modified processes and programs to review and make funding recommendations or decisions on DRD. Some of these HTA agencies and public payers make a distinction between DRD and DURD, and have established separate or modified processes for each of these categories, whereas some categorize DRD under life-saving drugs or highly specialized technologies. NICE and SMC have respectively established separate evaluation frameworks (NICE's highly specialised technologies guidance) or additional processes within their standard HTA processes (for orphan and ultra-orphan drugs) to assess and make reimbursement recommendation or decisions on DRD. CADTH and PBAC do not have a separate evaluation framework or additional processes for DRD, but their decision-making frameworks do address the unique needs for assessing DRD. Additionally, Australia's Life Saving Drugs Program and PHARMAC's "contestable funding program" piloted in 2014 are separate funding programs with related evaluation process for DRD. In Germany, orphan drugs are granted a special status in the early benefit assessments of pharmaceuticals, whereby the drug's added benefit is already considered proven through market authorization with IQWiG only assessing information provided by the manufacturers on the number of patients affected by the rare disease and the cost of treatment. ICER, in the US, modified its Value Assessment Framework for reviews of ultra-rare diseases in November 2017. DRD-specific assessment, evaluation, or recommendations framework, or any special considerations for DRD in standard HTA processes, were not identified in France and for INESSS in Canada.

Some HTA agencies or DRD-specific funding programs use specific definitions for DRD, orphan drugs, ultra-orphan drugs, or DURD, based on prevalence rate, to categorize drugs that can be eligible to be assessed through their evaluation frameworks or additional processes specific to DRD. Most of the HTA agencies also specify that the definition of these terms have to apply on a population level regardless of how the applicant wishes to position the drug; that is, for a specific subpopulation. Additionally, drugs have to meet certain criteria to be eligible to be reviewed through these programs or processes, which are largely related to the rarity and severity of disease, lack of alternative treatment, and causing significant financial burden to patients and caregivers.

There were some variations in the submission process for these programs for DRD in whether they use the same submission forms and processes or separate ones. Regardless of the use of a separate or the same submission form, additional information specific to the disease condition and its impact is required. Although economic evaluations are required by almost all processes and programs, the lack of robust economic evaluations for these drug were generally recognized, and some consideration was made as to the type of economic evaluation required.

Some HTA agencies have established separate evaluation committees to evaluate DRD, under their processes, and all of them consider patient input in their decision-making framework. Evaluations on DRD are generally based on clinical and economic evidence, but most organization do recognize the paucity of robust clinical and economic evidence, and that a simple “utilitarian” approach to these evaluations do not sufficiently recognize the unique needs of the rare diseases. Although economic evidence is considered by these HTA organizations and funding programs in their decision-making processes, most either make some consideration or do not consider economic evaluation a predominant factor (although a factor nonetheless) in their decisions.

In Canada, public drug plans in British Columbia, Alberta, and New Brunswick have established processes for DRD reimbursement or DRD-specific formulary. Alberta has established the Rare Diseases Drug Coverage Program, and New Brunswick has established the New Brunswick Drugs for Rare Diseases Plan. New Brunswick makes decision on listing DRD in the New Brunswick Drugs for Rare Diseases Plan using the DRD Evaluation Framework that was originally developed and used in Ontario. Currently, coverage decisions for individual New Brunswick patients are assessed by Ontario Public Drug Programs’ external medical experts. For non-PharmaCare drug benefits, British Columbia has an expert advisory committee that reviews patient-specific requests and makes recommendations on a case-by-case, exceptional, last-resort basis. Alberta’s public drug program has a separate review committee for reviewing and making funding recommendations to the Minister on specific DRD.

The evaluation of DRDs is challenging because of the lack of robust clinical and economic evidence and the exceptionally high cost of the drugs. However, rare diseases cause a significant societal, clinical, and economic burden to patients and caregivers, as well as to the health care system. HTA agencies and public payers have made an effort to address the unique needs of DRD – to make these expensive drugs available to patients, while ensuring that effective and cost-effective treatments are reimbursed – by establishing separate evaluation processes or funding programs or by modifying their standard HTA processes, or by making special considerations in their decision-making processes when evaluating DRD.

## Appendix 1: Examples of Scenarios Where There Could be Significant Unmet Need and Contributing Factors for Uncertainty of Clinical Benefit<sup>25</sup>

Source: *Recommendation Framework for CADTH Common Drug Review and pan-Canadian Oncology Drug Review Programs: Guidance for CADTH's Drug Expert Committees.*<sup>25</sup>

**Table 6: Considerations for “Significant Unmet Need”**

Consideration	Description
Rarity of Condition	<p>The drug under review is approved by Health Canada for the treatment of a rare disease. Specifically, the condition for which the drug is indicated has the following characteristics:</p> <ul style="list-style-type: none"> <li>• is life-threatening, seriously debilitating or both serious and chronic in nature</li> <li>• affects a relatively small number of patients (incidence of fewer than 5 in 10,000, but typically closer to 1 in 100,000)</li> <li>• is often genetically based, onset at birth or early childhood, and leads to a shortened life-span</li> <li>• places a heavy burden on caregivers and the health care system</li> <li>• is difficult to study because of the small patient population.</li> </ul>
Population	<ul style="list-style-type: none"> <li>• Need is identified on a population or subpopulation basis (i.e., not on an individual basis)</li> </ul>
Absence of alternatives	<ul style="list-style-type: none"> <li>• There is an absence of clinically effective drug or non-drug alternative treatments.</li> <li>• Substantial morbidity and mortality exist despite the available drug or non-drug alternative treatments.</li> </ul>

**Table 7: Factors That Contribute to Uncertainty of Clinical Benefit**

Consideration	Description
Clinical data	<ul style="list-style-type: none"> <li>• Limited number of clinical studies</li> <li>• Small sample sizes (e.g., due to rare disease that affects a relatively small number of patients (incidence of fewer than 5 in 10,000 but typically closer to 1 in 100,000)</li> <li>• Absence of comparator groups</li> <li>• Alternative or adaptive trial designs for rare diseases</li> <li>• Short study durations or follow-up</li> <li>• Inability to distinguish disease severity in heterogeneous manifested rare diseases</li> <li>• Limited to surrogate end points</li> <li>• Insufficient evidence on meaningful clinical end points</li> <li>• Greater uncertainty in statistical analyses</li> </ul>

The above-noted scenario examples are intended to serve as illustrations, only, to help guide the reader to better understand some of the factors that CADTH's drug committees will assess as part of their deliberations in formulating a reimbursement recommendation. They are by no means exhaustive or impose any procedural obligations that would constitute grounds for a procedural review.

In these situations, although there is uncertainty with the clinical evidence, the available evidence must reasonably suggest that the drug under review could substantially reduce morbidity and/or mortality associated with the disease.

Significant, unmet clinical need is identified on a population or subpopulation basis (i.e., not on an individual basis) through the CADTH CDR and pCODR processes.

The rarity of the condition will not be the sole consideration for defining significant unmet need. In addition, the condition must be identifiable with reasonable diagnostic precision.

## Appendix 2: PBAC – Basis for Any Claim for the “Rule of Rescue”<sup>47</sup>

Source: *Pharmaceutical Benefits Scheme. 5.4 basis for any claim for the 'rule of rescue'. In: The Pharmaceutical Benefits Advisory Committee guidelines [Internet]. Canberra (AU): Australian Government, Department of Health; 2016 [cited 2018 Mar 7]. Available from: <https://pbac.pbs.gov.au/section-5/5-4-basis-for-any-claim-for-the-rule-of-rescue.html>*

### 5.4 Basis for any claim for the ‘rule of rescue’

The four factors described below apply in exceptional circumstances and are particularly influential in favour of listing. When all four factors apply concurrently, this is called the ‘rule of rescue’:

- No alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction. This means that there are no non-pharmacological or pharmacological interventions for these patients.
- The medical condition defined by the requested restriction is severe, progressive and expected to lead to premature death. The more severe the condition, or the younger the age at which a person with the condition might die, or the closer a person with the condition is to death, the more influential the rule of rescue might be in the PBAC’s consideration.
- The medical condition defined by the requested restriction applies to only a very small number of patients. Again, the fewer the patients, the more influential the rule of rescue might be in the PBAC’s consideration. However, the PBAC is also mindful that the PBS is a community-based scheme and cannot cater for individual circumstances.
- The proposed medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition. The greater the rescue, the more influential the rule of rescue might be in the PBAC’s consideration.

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## Appendix 3: Australia – Life Saving Drugs Program (LSDP) Criteria and Conditions<sup>48</sup>

Source: *Life saving drugs program criteria and conditions [Internet]. Canberra (ACT): Australian Government, Department of Health; 2016 Aug 17. [cited 2018 Feb 20]. Available from: <http://www.health.gov.au/internet/main/publishing.nsf/Content/lscp-criteria><sup>48</sup>*

### Criteria for the Funding of a Drug

The following issues must be addressed in considering a submission to fund a drug through the Life Saving Drugs Program, and in formulating a recommendation to the Minister for Health.

- A) The drug must be found to meet each of the following criteria:
1. There is a rare but clinically definable disease for which the drug is regarded as a proven therapeutic modality, i.e. approved for that indication by the Therapeutic Goods Administration.
  2. The disease is identifiable with reasonable diagnostic precision.
  3. Epidemiological and other studies provide evidence that the disease causes a significant reduction in age-specific life expectancy for those suffering from the disease.
  4. There is evidence to predict that a patient's lifespan will be substantially extended as a direct consequence of the use of the drug.
  5. The drug must be accepted as clinically effective, but rejected for Pharmaceutical Benefits Scheme (PBS) listing because it fails to meet the required cost effectiveness criteria.
  6. There is no alternative drug listed on the PBS or available for public hospital in-patients, which can be used as lifesaving treatment for the disease. However, the availability of an alternative drug under the LSDP does not disqualify the proposed drug from consideration for the LSDP.
  7. There is no alternative non-drug therapeutic modality (e.g. surgery, radiotherapy) which is recognised by medical authorities as a suitable and cost-effective treatment for this condition.
  8. The cost of the drug, defined as the cost per dose multiplied by the expected number of doses in a one year period for the patient, would constitute an unreasonable financial burden on the patient or his/her guardian.
- B) Consideration and advice will also be sought, if applicable, on:
1. The proposed price of the drug compared with the effective price of the drug in comparable overseas markets.
  2. The proposed cost of the drug compared with the cost of comparable drugs, if any, that are already funded through the LSDP.

### Pricing Issues

1. Only the cost of the drug will be funded through the LSDP. This may include a factor for importation and transportation of the drug by the manufacturer direct to the place of administration to the patient. No other transport, storage, administration, or any other hospital or medical expenses associated with the use of the drug, or management of the disease or condition, will be funded through the LSDP.

## **Patient Conditions for Initial and Ongoing Subsidy Through the LSDP**

- A) Following an Australian Government decision to fund a drug, a patient must meet the following conditions to receive subsidised drugs through the LSDP:
1. Satisfy the relevant criteria for treatment with the drug, as detailed in the relevant drug/condition LSDP Guidelines.
  2. Participate in the evaluation of effectiveness of the drug by periodic assessment, as directed by the relevant LSDP drug/condition Guidelines, or have an acceptable reason not to participate.
  3. Not be suffering from any other medical condition, including complications or sequelae of the primary condition, that might compromise the effectiveness of the drug treatment.
  4. Be a permanent Australian resident who qualifies for Medicare.
- B) Patient eligibility will be reviewed in accordance with the frequency set out in the relevant drug/condition LSDP Guidelines, but generally 12 months after commencing therapy and every 12 months thereafter.

Continued eligibility will be subject to the assessment of evidence, as outlined in the relevant drug/condition LSDP Guidelines, which demonstrates:

1. clinical improvement in the patient, or
2. stabilisation of the patient's condition.

The assessment of eligibility will be made with regard to the natural course and stage of the disease, as described in the relevant drug/condition LSDP Guidelines, and any exceptional circumstances that may apply.

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## Appendix 4: SMC – Ultra Orphan Drug Decision-Making Framework

Source: *Guidance to manufacturers for completion of New Product Assessment Form (NPAF): supplement on medicines for end of life and very rare conditions*. November 2015. Glasgow (GB): Scottish Medicines Consortium; 2016. [cited 2018 Feb 15]. <https://www.scottishmedicines.org.uk/making-a-submission/>

**Table 8: Factors to Consider When Completing the New Product Assessment Form**

Decision Making Criteria	Guidance on Evidence
Nature of the condition	<ul style="list-style-type: none"> <li>• Description of symptoms and functioning with current treatment</li> <li>• Limitations of current treatment options</li> <li>• Effect on carers' quality of life</li> </ul>
Impact of the new technology	<ul style="list-style-type: none"> <li>• Summary of key efficacy findings from section 3 of NPAF</li> <li>• Summary of any important adverse events associated with treatment from section 4 of NPAF</li> <li>• Summary of key clinical effectiveness points from section 5 of NPAF including clinical significance of health gain associated with treatment</li> <li>• Discussion of spectrum of benefits within the patient group and potential for treatment continuation rules</li> </ul>
Costs to the NHS and Personal Social Services	<ul style="list-style-type: none"> <li>• Summary of year 1 and year 5 gross and net budget impact from section 7 of the NPAF, with and without PAS where relevant</li> <li>• Assessment of any significant budget impacts falling on any non-NHS organisations</li> <li>• Summary of key uncertainties in relation to budget impact</li> </ul>
Value for money	<ul style="list-style-type: none"> <li>• Summary of the base-case cost-effectiveness ratio or cost-consequence analyses, from the economic analysis in section 6.</li> <li>• Summary of key sources of uncertainty in the economic analysis and impact on base-case cost-effectiveness ratio</li> </ul>
Impact beyond direct health benefits and on specialist services	<ul style="list-style-type: none"> <li>• Impact of the technology in allowing patients to contribute to society / improve family functioning/continue in education</li> <li>• Impact on carers quality of life of the new treatment (note development of formal tools such as Carer Experience Scale)</li> <li>• Cost-effectiveness ratios showing the adoption of a wider perspective on costs and benefits</li> <li>• Assessment of impact on NHS staffing, infrastructure and training requirements</li> </ul>

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