A National Approach to Reimbursement Decision-Making on Drugs for Rare Diseases in Canada? Insights from Across the Ponds

Démarche nationale quant aux décisions de remboursement des médicaments pour maladies rares au Canada? Pistes provenant d'outremer

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Table B2. Information requirements of reimbursement review processes

Country	Advisors and/or decision-makers	Information inputs	Information sources	Evidence requirements		Role of stakeholders
				Clinical	Economic	
Australia *General Reimbursement- The Pharmaceutical Benefits Scheme* (PBAC 2008a, 2008b, 2008c, 2008d, 2013b; AGDH 2013c)	Department of Health (decisions) Pharmaceutical Benefit Advisory Committee (PBAC) (recommendations)	• Requested listing & pharmacological class and action • Indications for drug • Burden and severity of illness • Disease incidence and prevalence • Current standard treatment • Clinical management algorithms • Safety • Clinical efficacy and effectiveness • Budget impact • Most likely utilization and	Submission prepared by applicant in standard format PBAC secretariat overview and sub-committee secretariat commentaries Submissions consider: • Published studies • Unpublished studies • Ultimately, a sponsor may include any information that is relevant to the PBAC submission • Expert opinion	• Strong preference for clinical evaluations based on direct randomized trials that compare drug with main comparator (meta-analysis of all relevant patient outcomes recommended • Recognition that direct randomized trials are not always available • Alternatives might be (in order of	• Economic evaluation required: cost-utility analysis (preferred), cost-effectiveness analysis, cost-benefit analysis (supplementary option), cost-consequences analysis (if disaggregation of outcomes would be helpful) **objective usually being to justify a price advantage for the proposed drug over its main comparator**	Submits information: • Applicant • PBAC Secretariat • Experts • Patients, carers, public, health professionals and consumer interest groups

		financial estimates (including epidemiology and market share) • Issues relating to quality use of drugs • Issues relating to equity • Patient, carer, public, health professional and consumer groups input to the following questions: 1. What treatment are you using now? 2. What do you see as the benefits of this new medicine for you? 3. How will your life and that of your family and carers be improved by the new medicine? 4. What other benefits can you see from having this medicine on the PBS? 5. Do you have any comments on the consumer input process?	considered where there are no observed data available • PBAC may seek expert opinion from relevant professional bodies and/or specialists, and may meet with reps of relevant medical professional organizations and colleges • PBAC may also seek input from appropriate consumer bodies (where advice is obtained, due process is followed in which the relevant sponsor is informed and given an opportunity to reply) Patient, carer, public, health professional and consumer interest group comments using standard form. Comments must be received by dates posted on website (typically about 2 weeks after publication of the list of applications for consideration).	priority): 1.Indirect comparison across 2 or more sets of RCTs involving one or more common reference 2.Non-randomized studies (including comparisons involving sing arms extracted from randomized trials *Does not imply that a minimum standard must be met. Will consider all levels of evidence	• Methods must comply with the PBAC economic guidelines • Comparator: most commonly used alternative. If no PBS-covered drug currently available, main comparator could be non-covered drug, a surgical procedure or conservative treatment • Perspective of economic analysis should be the payer • Budget impact analysis	
Australia	Department of	• Disease natural	Submission prepared by	• Epidemiological	• Cost of the drug,	Submits

Life Saving Drugs Program (LSDP)(AGDH 2011; PBAC 2008a; Australian Government Solicitor 2013; AGDH 2010a)	Health (decision-maker) PBAC (recommendations) Disease Advisory Committee (advisory)	history • Efficacy and clinical effectiveness • Alternative therapies • Financial burden • Pricing information	applicant in standard format PBAC secretariat overview and sub-committee secretariat commentaries Submissions consider: Published studies Unpublished studies Expert opinion where no observable data available Any relevant information may be submitted Ultimately, a sponsor may include any information that is relevant to the PBAC submission (Elements-guidelines-b part 2-Section F) Expert opinion considered where there are no observed data available	and other studies providing evidence that disease causes significant reduction in age-specific life expectancy • Evidence that drug will substantially extend lifespan and is clinically effective	defined as cost per dose multiplied by expected number of doses in one year, constitute unreasonable financial burden • Proposed price of drug	information: • Applicant • Secretariat • Experts • Patients, carers, public, health professionals • Consumer interest groups
Australia *Highly Specialised Drugs Program (HSDP)*(AGDH 2010b; State Government of Victoria 2013, Mabbot et al. 2010)	Highly Specialised Drugs Program: Highly Specialised Drugs Working Party Pharmaceutical Benefits Advisory Committee	Same as PBAC general reimbursement process	Same as PBAC general reimbursement process	Same as PBAC general reimbursement process	Same as PBAC general reimbursement process	Same as PBAC general reimbursement process

	(recommendation) Minister of Health (final decision)					
Austria *General Reimbursement: Extramural drugs* (Ayme and Rodwell 2013b; Bucholz 2009; PHARMIG 2013)	Association of Austrian Social Security Institutions (HVB) (decisions) Pharmaceutical Evaluation Board (HEK) (recommendations) Independent Drug Commission (UHK) of the Federal Ministry of Health, Family and Youth (BMFGJ) (oversees HVB and HEK; can veto decisions)	• Indication/target population • Therapeutic claim • Treatment characteristics (duration, frequency) • Clinical effectiveness • Budget impact • Economic evaluation (for innovative pharmaceuticals with substantial benefit) • Market status in other EU member states • Price comparisons with the same or similar products in Austria and EU prices of their own drug • Sales volume forecast (3 years) • Current sales	• Submission prepared by manufacturer • Evaluation of manufacturer submission prepared by HEK	• Evidence from systematic review with or without meta-analyses of RCTs preferred • Systematic review and/or meta-analysis should comply with internationally recognized guidelines	• Comparator should be the most commonly used alternative or treatment most likely to be replaced by new treatment • Perspective for economic model should be specified	Submits information: • Manufacturers
Austria *Generalized reimbursement: Intramural drugs* (Ayme and Rodwell 2013b; Bucholz 2009; PHARMIG 2013)	Drug Commissions of Individual Regional Hospital Cooperations (decisions) The Horizon Scanning Program (on oncology drugs) of LBI-HTA (advisory)	No information found	No information found	No information found	No information found	No information found

Austria *Individual (case-by-case) reimbursement* (Ayme and Rodwell 2013b; Bucholz 2009)	Regional Sickness Fund (decision-maker) • head physician of sickness fund/chief medical officer	• Proof of medical necessity • Proof of pharmacological necessity • Appropriateness and other options (no economic evaluation)	Submission prepared by prescribing physician	• No formal evidence requirements • However, at least one phase III trial should be in progress or completed	No formal evidence requirements	Submits information: • Physicians
Belgium *General Reimbursement* (Denis et al. 2009; Bogaert and Klasa 2009; Denis et al. 2011)	Minister of Social Affairs (decision-maker) Drug Reimbursement Committee (DRC) (advisor)	The manufacturer introduces two dossiers: an application form sent to the secretariat of the DRC and a price demand to the Federal Public Service (FPS) Economy The DRC dossier must contain three types of data: • the indication of the orphan drug as set by the Community register of orphan medicinal products and the important motivations on which the approval was based • a copy of the demand sent to the FPS Economy • a proposal regarding the reimbursement level and a justification thereof (including therapeutic value, budgetary	Submission prepared by manufacturers Evaluation report reviewing submission prepared by internal staff with support from external clinical and methodological experts Submissions consider: • Published studies • Unpublished studies	• At least efficacy, but preferably effectiveness, on a clinically relevant outcome should be demonstrated • Clinical data may include randomized controlled trials (RCTs) with or without active control, dose-finding studies, clinical endpoints and/or surrogate endpoints, adequate trial sample size (considering the rarity of disease), presence of long-term safety and efficacy data • Systematic review should comply with internationally recognized guidelines	• Economic evaluation only required for "Class 1 pharmaceuticals (demonstrated added value relative to alternatives) • Perspective for economic analysis should be the payer • Budget impact analysis should be based on epidemiological data from registries • Standardized cost information submitted to the Federal Public Service Economy in the context of pricing	Submits information: • Manufacturers

		impact and therapeutic and social needs)				
Belgium *Special Solidarity Fund (SSF)* (Guillaume et al. 2010; Denis et al. 2009)	College of Medical Doctors for Orphan Drugs (CMDOD) (decision-maker) National Institute for Health and Disability Insurance (NIHDI)	Information indicating that: • Rare indication/ rare disorder, life threatening • Expensive treatment • Treatment beyond the experimental stage • No reimbursed alternative available	Submissions prepared by the prescribing physician	Reimbursed treatment should demonstrate a proven scientific value	Reimbursed treatment should be demonstrated as expensive	Submits information: • Physicians
Denmark *General Reimbursement* (Moller 2003; Danish Health and Medicines Authority 2012)	The Danish Medicines Agency (DMA)-pharmacoeconomic division (decision-maker) The Reimbursement Committee (recommendations)	• The marketing authorization • The summary of product characteristics • Indications for drug and therapeutic claim • Clinical efficacy and effectiveness • Cost-effectiveness • Expected consumption (e.g. number of patients for the first five years) • Expected utilization • Budget impact • Clinical assessment and comparable clinical efficacy and safety studies • Reimbursement status and prices in other EU countries	Manufacturer submissions using standard template Evaluation report reviewing submission prepared by internal staff with support from external clinical and methodological experts	Evidence available from RCTs and non-RCTs comparing drug to standard treatment	• Formal economic analysis voluntary (often included to justify higher price) Methods should comply with Danish Guidelines for the Socio-economic analysis of Medicines Perspective for economic analysis should be societal • Budget impact analysis	Submits information: • Manufacturers

Denmark *Individual Reimbursement* (Moller 2003; Danish Health and Medicines Authority 2012)	Danish Medicines Agency (DMA)-pharmacoeconomic division (decision-maker) The Reimbursement Committee (recommendations)	• Medical history • Description and explanation for specific treatment • Explanation for more expensive treatment if alternative exists and/or indication of very high medical expenses • Expected duration • Product information • Copy of the medical records • Planned monitoring of the course of the disease	Submissions prepared by prescribing physician	No information found	No information found	Submits information: • Physicians
Finland *General Reimbursement* (Ministry of Social Affairs and Health 2013; Ayme and Rodwell 2013c; Mossialos and Srivastava 2008; Pharmaceutical Pricing Board 2013; International Society for Pharmacoeconomics Outcomes and Research 2014)	Pharmaceutical Pricing Board decides on wholesale prices and reimbursement (Decisions)	• Severity and burden of illness • Clinical efficacy and effectiveness • Indications for drug and therapeutic claim • Experience of use, including extent of use in Finland and elsewhere, patient exposure and sales information, in which countries the product has market authorization • Prices in other EEA states • Potential harms and changes related to safety made after	Copy of the marketing authorization decision Submission prepared by applicant using standard format Evaluation report reviewing submission prepared by internal staff with support from external clinical and methodological experts Submissions consider: • Published studies • Unpublished studies • Expert opinion (should be reported clearly)	• Evidence from head to head RCTs preferred • Evidence from available RCTs and non-RCTs, as well as meta-analyses and review articles should be included • Treatment recommendations and systematic reviews by a reliable, independent source	• Economic evaluation required • Methods must comply with guidelines of the Ministry of Social Affairs and Health. Could include cost utility analysis, cost-minimization analysis, cost-effectiveness analysis or cost-benefit analysis (reason must always be given for the choice of the method) • Comparator: the most appropriate therapeutic	Submission of evidence for consideration: • Manufacturers • Patients • Providers • Kela • Experts

		authorization • Dosage • Treatment recommendations • Specifications of the costs and cost-effectiveness of the treatment • Market forecast	Kela provides written statement		alternative. Choice must be based on Finnish clinical practice and reasons must be given for choice of the comparator • Perspective for economic analysis should be societal • Estimate of sales of the product with special reimbursement status during the current year and the following three years after the approval of the product	
France *General Reimbursement* (Aymes and Rodwell 2013e; Chicoye et al. 2009; Pelen 2000)	Ministry of Health and Social Services *(decisions)* Transparency Commission (under French National Authority for Health (HAS)) *(recommendations)*	• Disease burden/severity • Target population • Existing treatments • Safety • Clinical efficacy/effectiveness • Cost of treatment • Budget impact • Legal implications • Ethical implications • Public health implications	Submission prepared by manufacturer Evaluation report reviewing submission prepared by internal staff Submissions consider: • Published studies • Expert opinion • Surveys of practice • Analyses of original and commercial data	• Data from all RCTs, uncontrolled trials, observational studies, and post-marketing studies • Head-to-head RCTs preferred • Systematic review should comply with published systematic review guidelines	• Economic evaluation may or may not be required • Methods must comply with economic guidelines • Perspective of economic analysis should be the payer • Budget impact analysis	Submits information: • Manufacturers
France *Individual (case-by-case) or cohort reimbursement* (Natz and Campion	1) Temporary use authorization (ATU) (individual or cohort) Transparency	Individual ATU: • Patient name • Indication • Treatment dose • Treatment duration	• Submission prepared by prescribing physician or Centre of Excellence (individual) and dossier provided by	No formal evidence requirements	Not required	Submits information for consideration for individual reimbursement:

2012; Garau and Mestre-Ferrandiz 2009; Belorgy 2012; Ministre des Affaires Sociales et de la Santé 2014)	Commission (under French National Authority for Health (HAS)) *(decisions)*	• Justification of use • Pharmaceutical quality • Safety • Efficacy • Authorization abroad • List of ongoing or scheduled clinical trials in France Cohort ATU: • Indication • Target population • Estimated number of patients to be treated • Treatment dose • Treatment duration • Justification of use • Pharmaceutical quality • Safety • Efficacy • Authorization abroad • Details of ongoing or scheduled clinical trials in France • Statement of intent to submit MA application • Protocol for therapeutic use and data collection • Orphan medicinal product designation, if applicable	manufacturer • Submission prepared by manufacturer (cohort)			• Physician • Centre of Excellence Submits information for consideration for cohort reimbursement: • Manufacturer
France *Individual (case-by-case) or cohort reimbursement* (Natz and Campion 2012; Garau and Mestre-	2) Recommendation for therapeutic use (RTU) (cohort) Ministry of Health and Social Services	• Justification of off-label use • Informed consent	No information found	No formal evidence requirements	Not required	No information found

Ferrandiz 2009; Belorgy 2012; Ministre des Affaires Sociales et de la Sante 2014)	*(decisions)* Transparency Commission (under French National Authority for Health (HAS)) *(recommendations)*					
France *Individual (case-by-case) or cohort reimbursement* (Natz and Campion 2012; Garau and Mestre-Ferrandiz 2009; Belorgy 2012; Ministre des Affaires Sociales et de la Sante 2014)	3) Temporary protocol of treatment (PTT) Transparency Commission (under French National Authority for Health (HAS)) *(decisions)* *Note: all three mechanisms involve assessment and regulatory approval by the French Agency for the Safety of Health Products (AFSSAPS) and simultaneously, reimbursement approval by HAS	• Justification of off-label use • Informed consent	No information found	No formal evidence requirements	Not required	No information found
Germany *General Reimbursement*(Holtorf et al. 2013; Ayme and Rodwell 2013e; Heron et al. 2012)	Joint Federal Committee (G-BA) (decision-maker)	• Severity and burden of illness • Cost-benefit assessment (except for orphan drugs)	Submissions prepared by manufacturers Assessments on specific drugs may be prepared by internal staff or commissioned to independent academic	• Clinical trials submitted by the manufacturer for licensing • Evidence from RCTs preferred, but must include quality of life data	• Cost-benefit assessment (except for orphan drugs (medical benefit is considered to be proven as a result of the market authorization)	Other potential sources of information: • Manufacturer • Patients • Healthcare providers • Insurance

			groups Submissions consider: • Published studies • Unpublished studies • Expert opinion (clinician, patient, and carer)	• Systematic review should comply with published systematic review guidelines	• Efficiency frontier analysis • Methods must comply with internationally recognized economic guidelines • Budget impact analysis	representatives • G-BA
Germany *Compassionate Use* (Federal Ministry of Health; 2010)	Federal Institute for Drugs and Medical Devices (BfArM) (decision-maker)	• Description of disease for which medical product is intended • Person who is to be responsible for the compassionate-use program must be appointed and notified • Criteria for the patient group and an estimate of its size must be submitted • Reasons why treatment alternatives are lacking • Data on the quality and efficacy of the product • A draft summary of product characteristics or, in the alternative, the investigators'	Submissions prepared by manufacturers	• Quality and efficacy data • Product characteristics • Clinical trial data, if available	Not required	No information found

		brochure used for the clinical trials • A copy of the product information intended for the patient (equivalent to the package information leaflet) must be provided, along with a description of how the treating physician shall obtain informed patient consent • Criteria for suspension of the program • Application for market authorization				
Iceland *General Reimbursement* (Icelandic Medicine Pricing and Reimbursement Committee, 2011; Martikainen and Rajaniemi 2002; Ayme and Rodwell 2013a; Icelandic Medicine and Reimbursement Committee 2013: Ministry of Welfare 2011)	Icelandic Medicine Pricing and Reimbursement Committee (decision-maker)	• The drugs SPC (supplementary protection certificate) • Comparators on the Icelandic market • Information on reimbursement status in the other Nordic countries (Denmark, Finland, Norway, Sweden) • Information on budget impact in Icelandic settings e.g. number of patient estimated and comparator(s) • Sales forecast for the next three years based on the above	Submissions prepared by pharmaceutical companies or license holders	• Demonstration of significant clinical effect on well-defined indications • Clinical comparison to other medicines, DDD, effectiveness, side effects, indications, etc.	• Economic evaluation required • Budget impact analysis • Price relative to efficacy and in comparisons to already reimbursed drugs	Submit information: • Pharmaceutical companies • Distribution license holders

		The committee can request further information from the applicant				
Ireland *General Reimbursement-Community Drug Schemes* (Coughlan et al. 2009; National Centre for Pharmacoeconomics 2013b; National Centre for Pharmacoeconomics 2010; Arthur Cox 2012; National Centre for Pharmacoeconomics 2013a; Health Service Executive 2006)	<u>Relevant Community Drug Schemes for Orphan Drugs:</u> • **Long term illness** (Entitles patient suffering from any one of the 15 specified chronic conditions to full drug reimbursement irrespective of income) • **High-tech drugs** (Facilitates the supply by community pharmacies of certain high cost medicines) Health Information and Quality Authority (HIQA)/National Centre for Pharmacoeconomics (NCPE) Health Services Executive—Corporate	• Product description • Regulatory information (including if the medicine is available on compassionate basis pre-market authorization and FDA orphan drug status) • Clinical effectiveness • Economic evaluation • Budget impact analysis	Submissions prepared by manufacturers in standard format Evaluation report reviewing submission prepared by staff of independent agency who may seek support for external clinical experts	• Overview of all clinical studies reviewed for drug (i.e., Phase III studies [RCTs], Phase I/II studies, open-label extension studies, etc.)—with explicit overview of study design, patient selection criteria, outcomes • Direct evidence from head to head RCTs preferred, although indirect comparisons and other study designs are accepted (case reports, observational and controlled trials) • Systematic reviews with an appendix outlining the method of conducting the systematic review	• Type of evaluation required not specified, but submission must the detail the type of evaluation and criteria mainly pertain to cost-utility analysis. Cost-utility, cost-effectiveness, cost-benefit, and cost-minimization analyses are accepted) Cost-utility analysis is preferred • Pharmacoeconomic assessment conducted in accordance with the agreed Irish Healthcare Technology Assessment Guidelines. Needs to state the reimbursement scheme under which the base case is undertaken (e.g., GMS or HTDS)	Submit information: • Manufacturers • HIQA/NCPE • Local experts

	Pharmaceutical Unit (HSE-CPU)				• Comparator: Not specified, but comparator should be clearly identified and justified. Preferred is routine care • Perspective for economic evaluation should be societal • Budget impact assessment (using target population prevalence and annual incidence and costing over 5 year period)	
Ireland *Named Patient Regime (*Arthur Cox 2013)	Irish Medicines Board	• Explanation of the circumstances requiring the supply of the unauthorized product • Cost of product • Product information	Application submitted by: • Provider	No information found	No information found	Submits information: • Provider
Italy *General Reimbursement* (Ayme and Rodwell 2013f; Bakowska et al. 2011; Folino-Gallo et al. 2008; Taruscio et al. 2011)	Italian Medicines Agency (AIFA) – Scientific Technical Committee (CTS) and Board of Directors *(decisions)* AIFA Pricing and Reimbursement Committee (CPR) *(advice)*	• Indication/target population • Therapeutic claim • Existing treatments • Safety • Clinical efficacy/effectiveness • Cost of treatment compared to alternatives • Budget impact • Economic evaluation • Utilization in other EU countries • Reimbursement status	• Submissions prepared by manufacturers in standard format • • Evaluation of manufacturer submission prepared internally (CTS) Information on expenditures and consumption of comparator drugs provided by National Observatory on the Use	• Comparative data from RCTs (preferred), uncontrolled trials, or observational studies • Comparison to standard of care preferred • Methods of systematic reviews or meta-analyses should adhere to Italian guidelines	• Cost-effectiveness analysis or cost-utility analysis preferred • Methods must comply with Italian guidelines • P • Budget impact analysis required • Perspective for economic evaluation should be societal • •	Submits information: • Manufacturer

		in other EU countries • Price in other EU countries	of Medicines			
Italy *Individual or cohort reimbursement* (Garau and Mestre-Ferrandiz 2009; Taruscio et al. 2011)	**<u>Cohort reimbursement (Law 648/96)</u>** AIFA – CTS *(decisions)*	• Safety • Clinical efficacy/effectiveness	Submission prepared by physician, university, Centre of Reference, or patients/patient organization	Data from phase II/III clinical trials	Not required	Submits information: • Physician • University • Centre of Reference • Patient organization
Italy *Individual or cohort reimbursement* (Garau and Mestre-Ferrandiz 2009; Taruscio et al. 2008)	**<u>Individual reimbursement (Law Decree 23/98)</u>** Ministry of Health – Ethics Committee *(decisions)*	• Safety • Clinical efficacy/effectiveness	Physician-provided documentation of safety/benefit (no formal application)	• No formal evidence requirements • Physician must provide documented evidence, preferably from published internationally renowned journals	Not required	Submits information: • Physician
Italy *Individual or cohort reimbursement* (Garau and Mestre-Ferrandiz 2009; Taruscio 2008)	**<u>(AIFA 5% Fund)</u>** AIFA – CTS *(decisions)*	No information found	Submission prepared by physician	No information found	No information found	Submits information for consideration: • Physician
Japan *General Reimbursement* (Liu et al. 2009; Nagae 2012; Orphanet 2014)	Drug Pricing Organization (DPO) (recommendations) Central social insurance medical council (Chuikyo) (decision-maker)	<u>Specific requirements for orphan drug application:</u> • Number of patients, with objective statistical data for whom the drug will be indicated • Clinical need • Disease etiology and symptoms • Current standard	Submissions prepared by manufacturers Evaluation report prepared internally by Medical Economics Division	Higher efficacy and safety than an existing alternative	• Cost effectiveness and or cost utility analysis • Economic evaluation not required, but expected to demonstrate value-for-money	Submits information: • Manufacturer

		treatment (availability of similar drugs and treatment) • Theoretical rationale for the use of the drug • Summary of the orphan drug characteristics • Safety • Clinical efficacy • Cost				
Korea *General Reimbursement* (Ngorsuraches et al. 2012)	Health Insurance Review & Assessment service (HIRA) (recommendations) Ministry of Health & Welfare. Drug Pricing & Reimbursement Committee (DPRC) / also called the Drug Reimbursement Evaluation Committee (DREC) (decision-maker)	• Clinical benefits • Cost-effectiveness results • Impact on health-care budget • Reimbursement status and prices in other countries • Potential impact on other aspects of public health	Submissions prepared by manufacturers	Evidence demonstrating "clinical value"	• Cost-effectiveness analysis is required if an alternative treatment is on the market • Budget impact assessment	Submits information: • Manufacturer
Luxembourg *General Reimbursement* (Ayme and Rodwell 2013g; Caisse National de Sante 2003; Caisse National de Sante 2011)	Ministry of Health (decision-maker) Commission of Experts (advisor)	• Drug information and composition • Indications for drug and therapeutic claim • Whether the product is an "ethical drug" • Pricing in other	Submissions prepared by manufacturers using standard format. Expert recommendations	No information found	No information found	Submit information: • Manufacturer • Other experts

		European jurisdictions				
The Netherlands *General Reimbursement-Medicines Reimbursement System (GVS)* (Stolk et al. 2009; Ayme and Rodwell 2012; Niezen et al. 2007; International Society for Pharmacoeconomics and Outcomes Research 2007)	Minister of Health, Welfare, and Sport (decision-maker) Dutch Health Care Insurance Board (CVZ) (advisor) Centraal Indicatieorgaan Zorg, (CIZ) (advisor)	• Severity and burden of illness • Disease incidence and prevalence • Target population • Clinical efficacy and effectiveness • Alternative treatments • Expected utilization (length of treatment and mode of delivery) • Price • Info for off-label use • Cost effectiveness • Budget impact	Submissions prepared by manufacturers in standard format Evaluation report reviewing submission prepared by internal staff who may seek support from external clinical and methodological experts Submissions consider: • Published studies • Unpublished studies • Expert opinion (clinician, patient, and carer)	• RCT evidence preferred • Systematic review should comply with Internationally recognized guidelines for systematic reviews and meta-analyses	• No pharmo-economic data required if no alternative exists; if alternative does exist, no pharmo-economic data is required if the drug is for a disease with a prevalence of no more than 5 persons per 10,000 (orphan drugs) • Methods must comply with CVZ guidelines • Perspective for model should be societal • Budget impact analysis • Cost analysis	Submits information: • Manufacturers • CVZ • Ministry of Health, Welfare, and Sport • Health Council • Insurance funds • Patients & carers • Healthcare providers
New Zealand *General Reimbursement Pharmaceutical Schedule* (PHARMAC 2010)	Pharmaceutical Management Agency of New Zealand (PHARMAC) (decision-maker) Pharmacology and Therapeutics Advisory Committee (PTAC) (advisor)	• Indications for drug and therapeutic claim • Proposed changes to the Pharmaceutical Schedule • Severity and burden of illness • Price • Market information • Patent information	Submissions prepared by manufacturers in standard format Evaluation report reviewing submission prepared by internal staff Submissions consider: • Published studies	• All identified RCTs published as full articles in peer-reviewed journals that report outcomes by intention-to-treat • Clinical study report summaries form the pivotal RCTs • A register of all ongoing trials on the	• Cost-utility analysis (CUA), with benefits measured in terms of quality-adjusted life years (QALYs) • Other forms of economic evaluations may be accepted but rationale must be presented	Submits information: • Manufacturers • Clinicians • Interest groups • PHARMAC committees • Consumers

	Consumer Advisory Committee (CAC) (advisor)	• Impact on health sector • (methods and outcomes) • Quality of the evidence • Safety (Incidence and descriptions of adverse drug reactions) • Clinical effectiveness • Applicability of the evidence to the New Zealand health sector • Economic evaluation • Cost • Budget impact • Reimbursement status and prices in other countries	• Unpublished studies • Expert opinion (clinician, patient, and carer)	pharmaceutical for the relevant indications known to the applicant, including trials not directly funded by the pharmaceutical supplier • Copies of all published errata (or corrections), retractions, editorials, and journal correspondence directly relating to the published trials included in the application • A declaration that all unpublished clinical trials known to the applicant have been disclosed • Information on the incidence and descriptions of adverse drug reactions should include data collected from observational longitudinal clinical studies, RCTs, case reports on adverse drug reactions and expected/unexpected side effects, and	• Methods must comply with PHARMAC economic guidelines • Perspective for analysis should be the payer • Budget impact analysis	

				post-marketing surveillance data		
New Zealand *Named Patient Pharmaceutical Assessment (Exceptional Circumstances) Policy (NPPA)* (PHARMAC 2011; Haga and Sverre 2002)	PHARMAC (decision-maker) NPPA Advisory Panel (recommendations)	• Patient details • Details of applying physician • Details of any other practitioners who need to be informed • Details of the drug sought, including cost • Disease/condition being treated with the requested drug and any other co-morbidities experienced by the patient • Treatment details (dosage regimen, duration, administration) • Details of the pharmacy that will be dispensing the pharmaceutical • All other therapies that have been tried by the patient for the disease/condition • All alternative treatment options that were considered not appropriate for the patient • How patient will be treated if requested treatment is unavailable	Submissions prepared by the prescribing physician	• Clinical effect on the patient if they do not receive the requested treatment • Expected benefit of treatment • Description of any complicating or unusual clinical factors	• If the treatment is expected to provide cost savings to the DHB, provide details	Submit information for consideration: • Physicians

		• Prevalence and incidence of the patient's condition and any complicating or unusual factors • Details of the expected benefit of treatment, including whether or not it is likely to become a new standard of care and if it is expected to be cost saving to the DHB				
Norway *General Reimbursement* (International Society for Pharmacoeconomics and Outcomes Research 2013b; Festoy et al. 2011; OrphaNews Europe 2009)	NoMA (decision-maker)	• Indications for drug and therapeutic claim • Proposed changes to the Pharmaceutical Schedule • Severity and burden of illness • Target population • Current standard treatment/management • Position of drug in care pathway • Safety • Clinical effectiveness • Economic evaluation • Expected utilization • Cost • Budget impact • Reimbursement status and prices in	Submissions prepared by manufacturers in standard format Evaluation report reviewing submission prepared by internal staff Submissions consider: • Published studies • Unpublished studies	• Evidence from head to head RCTs preferred • Evidence from all other RCTs and non-RCTs • Systematic review should comply with Internationally recognized guidelines for systematic reviews and meta-analyses	• Economic evaluation required – may be any type but rationale for selection should be present • Perspective for analysis should be societal • Budget impact analysis	Submits information: • Manufacturer • Norwegian Knowledge Centre for the Health Services

		other countries • Market forecasts • Social considerations				
Norway *Individual Reimbursement* (Festoy et al. 2011)	The Norwegian Health Economic Administration (HELFO) (decision-maker)	"The application process is complex and resource intensive"	Submissions prepared by the prescribing physician	No information found	No information found	Submits information for consideration: • Physician
Spain *General Reimbursement* (Bakowska et al. 2011; Ayme and Rodwell 2013b; Seoane-Vazquez 2009)	Ministry of Health, Social Services, and Equality (Directorate General of National Health Service and Pharmacy) (decisions)	• Indication/target population • Disease burden/severity • Safety • Clinical efficacy/effectiveness • Cost of treatment • Budget impact • Economic evaluation • Utility	Submissions prepared by manufacturers in standard format Evaluation report prepared by Ministry	• Evidence from head to head RCTs preferred • Evidence from all other types of studies should be submitted • Systematic review should comply with Internationally recognized guidelines for systematic reviews and meta-analyses	• Not required, but cost-effectiveness or cost-utility analysis preferred • Budget impact analysis	Submits information: • Manufacturer Evaluation of information submissions: • Ministry of Health
Spain *Individual (case-by-case) or cohort reimbursement* (Garau and Mestre-Ferrandiz 2009; Whitfield et al. 2010)	1) Temporary Use Authorization Spanish Medicines Agency (AEMPS) (decisions)	• Justification of clinical need • Treatment duration • The number of packages required • Scientific documentation for use	Submission prepared by physician and treating hospital	No formal evidence requirements	Not required	Submits information for consideration (individual reimbursement): • Physician • Treating hospital

		• Patient written informed consent • Compliance of manufacturer				Submits information for consideration (cohort reimbursement): • Manufacturer
Spain *Individual (case-by-case) or cohort reimbursement* (Garau and Mestre-Ferrandiz 2009; Whitfield et al. 2010)	2) Royal Decree 1015/2009 Spanish Medicines Agency (AEMPS) (decisions)	• Justification of clinical need • Treatment duration • The number of packages required • Scientific documentation for use • Patient written informed consent • Compliance of manufacturer	Submission prepared by physician and treating hospital	No formal evidence requirements	Not required	Submits information for consideration: • Physician • Treating hospital
Spain *Individual (case-by-case) or cohort reimbursement* (Garau and Mestre-Ferrandiz 2009; Whitfield et al. 2010)	3) Act 29/2006 Spanish Medicines Agency (AEMPS) (decisions)	• Justification of clinical need • Patient written informed consent	Submission prepared by physician	No formal evidence requirements	Not required	Submits information for consideration: • Physician
Sweden *General Reimbursement* (Davidova et al. 2008; Moise and Docteur 2007; TLV 2012b; Ayme and Rodwell 2013h)	Dental and Pharmaceutical Benefits Agency (TLV) (decision-maker)	• Indications for drug and therapeutic claim • Severity and burden of illness • Current standard management/treatment • Clinical effectiveness • Economic evaluation • Estimated number of patients receiving the drug	Submissions prepared by manufacturers in standard format Evaluation report prepared by allocated executive officer, health economist, legal expert, and Pharmaceutical Benefits Group for County Councils	• Preference for direct comparative studies • Pivotal phase 2 and all phase 3 studies that were conducted as well as a description of ongoing and/or planned studies and references to those studies	• Economic evaluation required (cost-effectiveness analysis preferred; if different type performed, rationale for selection must be presented) • Exceptions may be made for orphan drugs	Submits information for consideration: • Manufacturers

		• Cost	Submissions consider: • Published studies • Unpublished studies		• Methods must comply with TLV guidelines • Perspective for economic analysis should be societal	
Switzerland *General Reimbursement- List of Specialties* (Blankart et al. 2011; International Society for Pharmacoeconomics and Outcomes Research 2011b; United States Food and Drug Administration2014; Goodman 2014; Ayme and Rodwell 2013i; Office Federal de la Sante Publique 2013)	Federal Office of Public Health (FOPH) (decision-maker) Federal Drug Commission (FDC) (recommendations)	• Safety • Clinical effectiveness • Appropriateness • Cost-effectiveness (value-for-money)	Submissions prepared by manufacturers in standard format (including preliminary or final market authorization from the SATP) External experts may be consulted	• Three most significant clinical papers from recognized journal—effectiveness must be based on controlled clinical trials for allopathic drugs • Comparative effectiveness (with existing therapies) • International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (IHC) Common Technical Document module 2 nonclinical and clinical overviews(safety, quality and efficacy information)	• Value-for-money considers: 1) External price referencing (international benchmarking): certified ex-factory prices and approved indications from Germany, UK, Denmark, Netherlands, France and Austria 2) Therapeutic benchmarking (e.g., daily treatment costs or cost per cure) • Request for and justification of an innovation bonus • Declaration of refund for excessive pricing • Economic evaluation, if available	Submit information: • Manufacturers • External experts

				• If available: epidemiological data, number needed to treat		
United Kingdom *General Reimbursement- Highly Specialised Technologies* (AWMSG 2012b; NICE 2013b, 2013e)	National Institute for Health and Care Excellence (NICE) (recommendations) Department of Health (decision-maker)	• UK approved name, brand name, marketing status • Formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment • Severity and burden of illness • Indications for drug and therapeutic claim • Current standard management/treatment • Clinical effectiveness • Position of drug in care pathway • Cost-effectiveness • NHS resource implications • Acquisition cost Note: Information requirements are the same as general technology appraisals	Submissions prepared by manufacturers in standard format Evaluation report reviewing submission prepared by commissioned independent academic group Submissions consider: • Published studies • Unpublished studies • Patient surveys • Expert opinion (through invited written statements from "consultees" and oral statements from patient experts and clinical specialists during committee meeting	• Evidence from all available RCTs and non-RCTs (experimental and observational) • Systematic review must comply with NICE methods guidelines • Preference for studies of effectiveness over efficacy	• Cost-effectiveness analysis or cost-utility analysis required • Methods must comply with NICE economic guidelines • Perspective for economic analysis should be the payer	Submits information: • Manufacturer • Sponsor • Patient organizations • Health professional associations • Department of Health • NHS England • Clinical Commissioning Groups
Scotland	Scottish Medicines	• Severity and burden	Submissions prepared by	• Evidence from all	• Economic evaluation	Submits

General Reimbursement (Scottish Medicines Consortium 2007, 2013b)	Consortium (SMC) (recommendations) NHS Boards (decision-maker)	of illness • Indications for drug and therapeutic claim • Current standard management/treatment • Comparative safety • Clinical effectiveness • Position of drug in care pathway • Cost-effectiveness • NHS resource implications	manufacturers in standard format Evaluation report reviewing submission prepared by internal staff Invited written statements from patient organizations and clinical experts Submissions consider: • Published studies • Unpublished studies • Expert opinion (clinician, patient, and carer)	available RCTs and non-RCTs (experimental and observational) • Systematic review must comply with NICE methods guidelines	required (preference for cost-effectiveness or cost-utility analyses, but any type accepted as long as rationale for selection is presented • Methods must comply with SMC economic guidelines • Perspective for economic analysis should be the payer • Budget impact analysis	information: • Manufacturer • Patients • Clinicians
Wales *General Reimbursement* (AWMSG 2013, 2014)	The All Wales Medicine Strategy Group (AWMSG)	• Approved drug name and formulation(s) • Severity and burden of illness • Licensed indications for drug and therapeutic claim • Current standard management/treatment • Comparative safety • Clinical effectiveness • Position of drug in care pathway	Submissions prepared by manufacturers in standard format Evaluation report reviewing submission prepared by internal staff Invited written statements from patient organizations and clinical experts Submissions consider:	• Evidence from all available RCTs and non-RCTs (experimental and observational) • Systematic review and meta-analysis (where appropriate) should comply with submission guidelines • Indirect comparisons or	• Cost-effectiveness analysis, cost-utility analysis or cost-minimization analysis required (rationale for selection must be presented • Methods must comply with economic guidelines • Perspective for economic analysis should be societal	Submits information for consideration: • Manufacturer

		• Cost-effectiveness • NHS resource implications • Budget impact	• Published studies • Unpublished studies • Expert opinion (clinician, patient, and carer)	mixed treatment comparisons • Ongoing studies from which additional evidence will be available • Information on safety from clinical studies and regulatory summaries, particularly those comparing the drug with alternative treatments	• Budget impact analysis	
United Kingdom *Innovation Pass* (UK Department of Health 2015)	Department of Health (decision-maker) Innovation pass advisory committee (advisor) National Institute for Health and Clinical Excellence (NICE) (screens applications)	• Severity and burden of illness • Indications for drug and therapeutic claim • Current standard management/treatment • Comparative safety • Clinical effectiveness • Position of drug in care pathway • Additional planned studies planned • Budget impact • Costs of additional monitoring to the NHS	Submissions prepared by manufacturers/sponsors in a standard format	• All available clinical data • Plans for additional studies	No information found	Submits information: • Manufacturers
England & Wales *Patient Access Scheme*	Department of Health (decision-maker)	• Scheme type, product and documentation • Operation of the	Submissions prepared by manufacturers/sponsors in a standard format	No information found	No information found	Submits information for consideration:

(NICE 2013d, 2013e)	National Institute for Health and Care Excellence (NICE) (recommendations) The Patient Access Scheme Liaison Unit (PASLU) (subcommittee of NICE)	scheme • Any data monitoring • Benefits of the scheme • Financial flows (Schemes should be consistent with existing financial flows in the NHS and with local commissioning) • Governance (The Patient Access Scheme should meet the criteria of NHS governance mechanisms and the laws governing England and Wales)				• Sponsors • Manufacturers
Scotland *Patient Access Scheme* (Scottish Medicines Consortium 2013a)	Patient Access Scheme Assessment Group (PASAG) Scottish Medicines Consortium (SMC)	• The drug and indication to which the PAS relates • The relevant dosages and formulations • Operation of PAS in NHS Scotland • The rebate due to NHS Boards • Data that the NHS Board will be required to maintain in order to confirm the validity of any claims	Submissions prepared by manufacturers in a standard format	No information found	No information found	Submits information for consideration: • Manufacturer
Wales *Patient Access Scheme* (AWMSG, 2012a,	All Wales Therapeutics and Toxicology Centre (AWTTC) (advisory)	• The purpose and type of proposed scheme • The patient population, and any	Submissions prepared by manufacturers	No information found	No information found	Submits information for consideration: • Manufacturer

2012b)	Patient Access Scheme Wales Group (PASWG) (recommendations) Welsh government (decision-maker)	subgroups, to which the scheme applies • Additional tests and monitoring associated with the proposed scheme • Any equity or equality issues related to the scheme • Patient confidentiality and data protection • If commercial implications have been considered • The duration of the scheme and circumstances for termination • The impact of the scheme on the choice of other available treatments • The entire administrative process and expected net cost of the scheme to NHS Wales • The grounds for their proposed scheme format should other simpler schemes for a similar drug be available • If the drug being evaluated has other indications not				

		covered by the scheme • The proportion of patients expected to meet the scheme inclusion criteria • The clinical benefits of the scheme • A financial and organizational flow diagram showing how the scheme will operate • Operational details of the scheme in different settings • If relevant to the scheme, the process of claiming rebates • Whether the scheme has been previously assessed by PASWG or PASLU				