Rare Disease Day 2021 Conference

RARE DISEASE DAY®

Canadian Organization for Rare Disorders

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Canada's Rare Drug Ecosystem
Aiming for Mars: With Perseverance You Can Get Anywhere!

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CORD Canadian Organization for Rare Disorders

Preventive & Risk-reduction Therapies for Rare Blood Disorders

Hemophilia

- Inherited blood disorder with missing clotting factor resulting in bleeding into joints, muscles, soft tissues
- Treatment: Clotting factor infused regularly; bleeds still occur; risk infection and thrombosis
- NEW: Emicizumab: MAB mimics clotting factor leading to steady state with fewer bleeds
- CADTH: if emicizumab price ≤ cost of factor product

Preventive & Risk-reduction Therapies for Rare Blood Disorders

Acquired Thrombotic Thrombocytopenia Purpura (aTTP)

- Blood clots slow blood to vital organs, leading to potentially fatal kidney failure, strokes or heart attacks
- Treatment is plasmapheresis plus steroids and rituximab
- Complications: relapse, neurological deficits, cognitive abnormalities
- NEW: Caplacizumab: reduces time to platelet normalization, mortality, recurrence
- CADTH & INESSS: negative recommendation due to limitations in RCT design

Preventive & Risk-reduction Therapies for Rare Blood Disorders

Thalassemia Major

- Genetic blood disorder whereby body does not make enough hemoglobin for red blood cells to deliver sufficient oxygen leading to low energy, organ damage, and risk of death
- Treatment with regular blood transfusions leads to iron overload requiring chelation with daily drug therapy
- NEW: Luspatercept leads to 33% reduction in transfusion
- CADTH recommendation still pending

Emerging Therapies (FOP)

- Fibrodysplasia Ossificans Progressiva (FO):
  - muscle and connective tissue gradually replaced by bone (creating second skeleton) limiting movement
  - harder to breathe, eat, maintain balance, speak, walk, sit
  - No current treatment
  - Palovarotene: Canadian “repurposed” drug in Phase 3 CTs may reduce bone formation
  - Other trials: Rapamycin, REGN2477 (garetosmab), others

Emerging Therapies (EB)

- Epidermolysis bullosa (EB)
  - skin diseases with (severe) blister formation, complicated by infection, sepsis, and death
  - Current treatment: antihistamines, anti-itch agents, pain medications, corticosteroids, other supportive care; bone marrow (stem cell) transplant (limited effectiveness and survival)
  - EB Pipeline: 20+ emerging therapies including Topical agents, gene therapies

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Canada TODAY: Capacity vs Performance; Canada Access vs ROW

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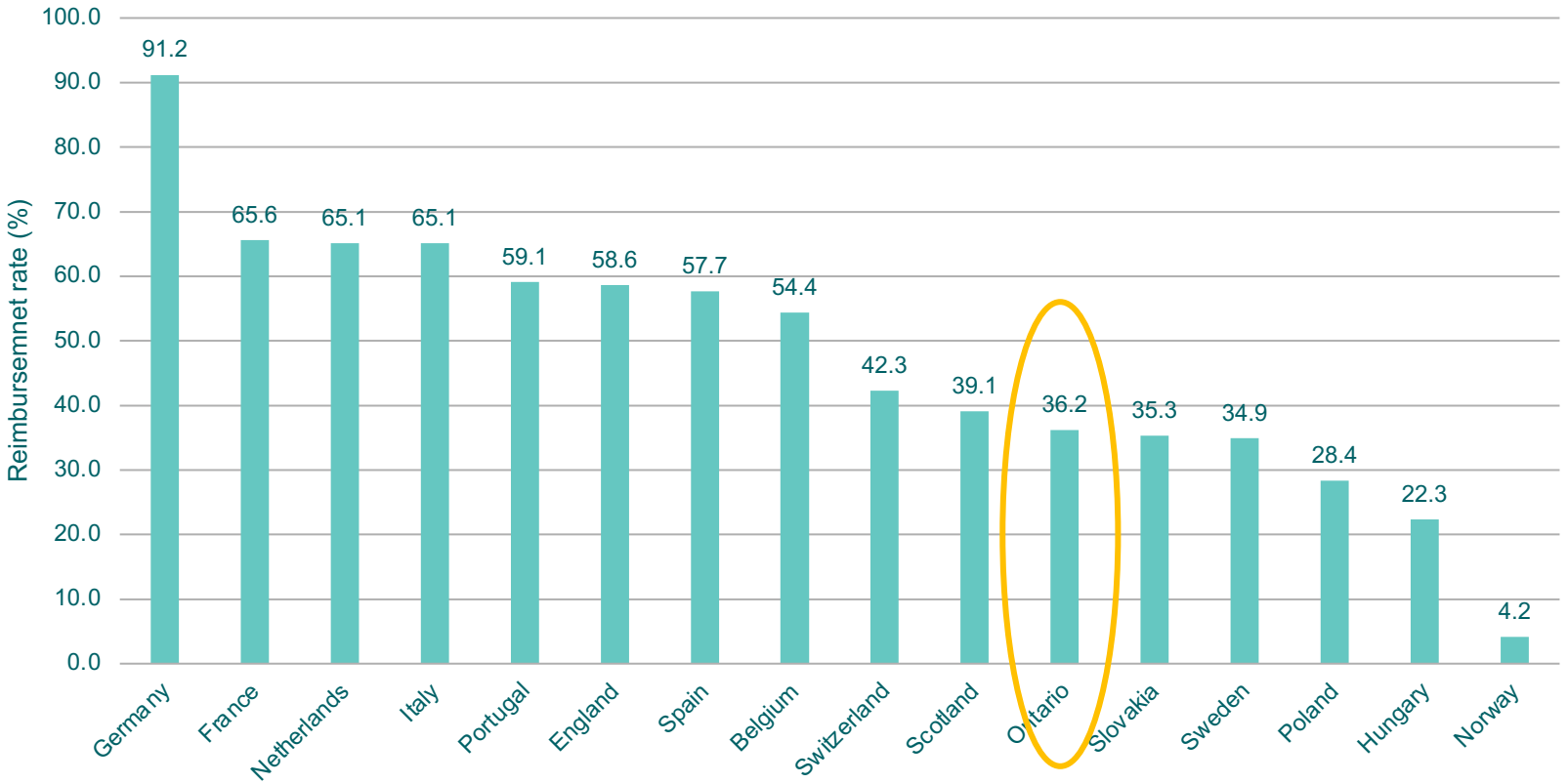
Rate of reimbursement of OMPs (2001 – 2019) %

- The country with the highest level of coverage is Germany (with over 90%), followed by France, the Netherlands and Italy (with around 65%)
- The three countries with the lowest level of coverage are Poland, Hungary and Norway (below 30%)
- **Canada (represented by Ontario) had a 36% reimbursement rate**



Average time to reimbursement (2001 – 2019)

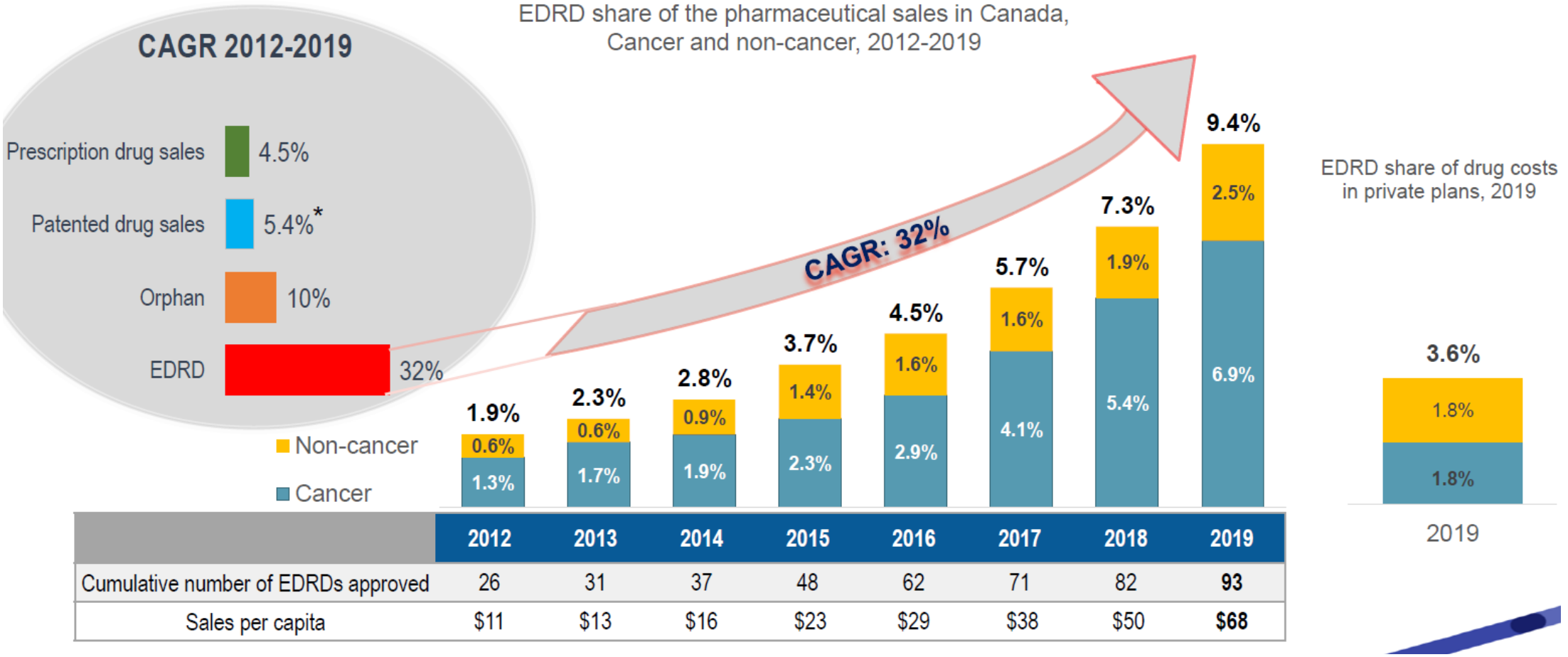
'Time to reimbursement' is defined as the average time in days from marketing authorisation to available reimbursement decisions date.

Germany has shortest timelines to reimbursement, followed by Switzerland and Scotland (less than 500 days), Italy, Spain and Sweden (less than 600 days)

- **Canada (represented by Ontario) had an average time to reimburse of just under 800 days**
- Poland, Slovakia and Hungary have low rates of reimbursement and are also associated with the longest delays (1200 days and higher)

N.B. Time to reimbursement for Ontario is calculated using the Health Canada marketing authorisation date, not EMA date.
Time to reimbursement for Switzerland is calculated using Swissmedic marketing authorisation date.

“EDRDs are the fastest growing market segment”



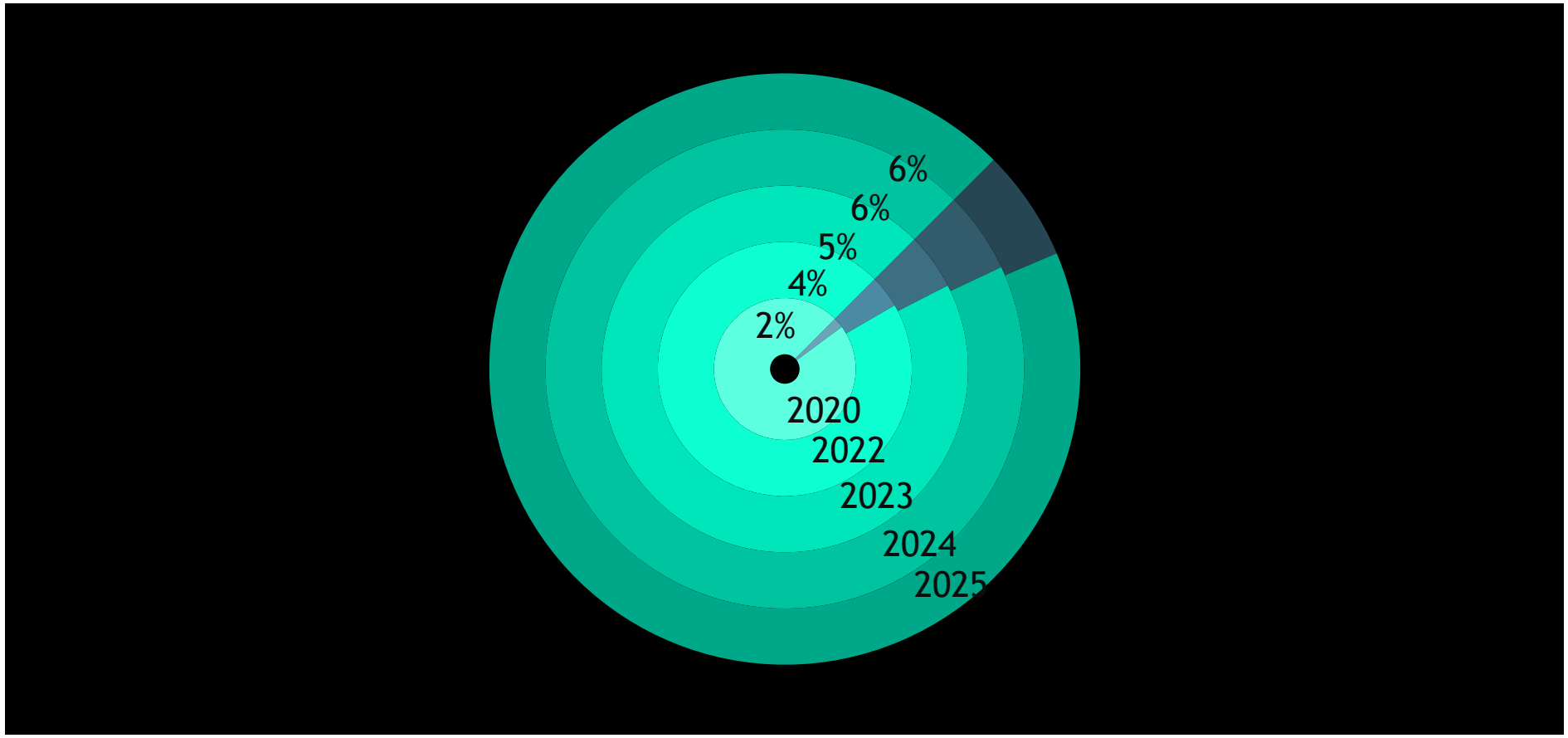
	2012	2013	2014	2015	2016	2017	2018	2019
Cumulative number of EDRDs approved	26	31	37	48	62	71	82	**93**
Sales per capita	$11	$13	$16	$23	$29	$38	$50	**$68**

From: PMPRB Research Webinar. Insight into the spending on expensive drugs for rare diseases. June 23, 2020. Page 10.

Alternate analysis of DRD costs in Canada

- Patient Access Solutions undertook an analysis of the current and future budget impact of DRDs in Canada; presented at the 2019 International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Meeting in Copenhagen
- Methods:
  - The cost of DRDs was included while cancer drugs were excluded
  - DRDs are used lifelong; oncology drugs are used for a more limited duration of treatment
  - CADTH has recognized the differences between oncology and non-oncology drugs and reviews the drugs through different pathways
  - Cancer drugs usually are approved for more than one indication and/or more than one line of therapy superseding the initial “orphan” designation
  - The prevalence of cancers typically increases over time while rare diseases are genetic aberrations and rates of inheritance are more stable

The total expenditure on DRDs was ~2% of the total drug budget in 2019



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From Draft to Action Plan

March 9 - 10, 2021

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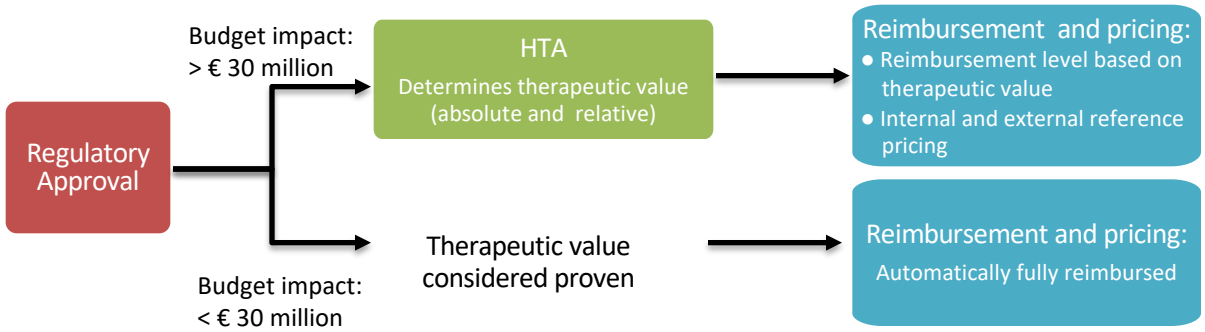
International Rare Disease Drug Models

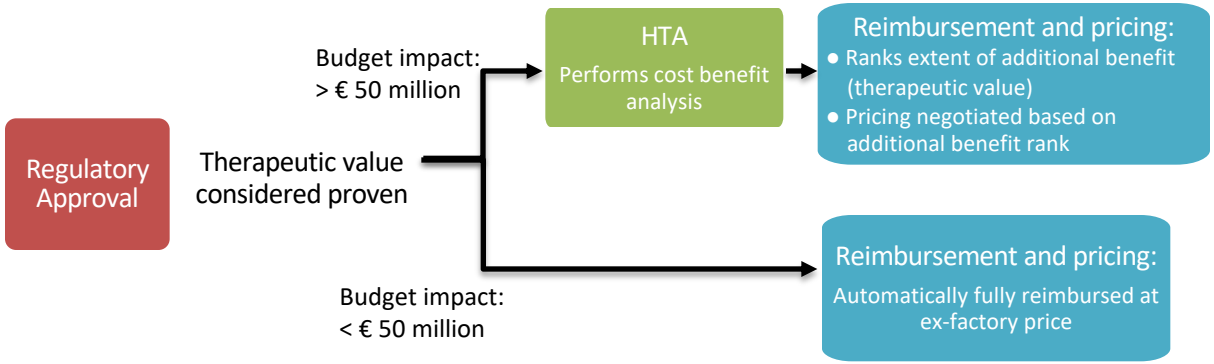
WHAT DO P&R PROCESSES FOR DRUGS FOR ULTRA-RARE CONDITIONS LOOK LIKE IN THESE COUNTRIES?

'Ultra rare': no formal definition; ranges from 1/50,000 to 1/1,000,000 individuals

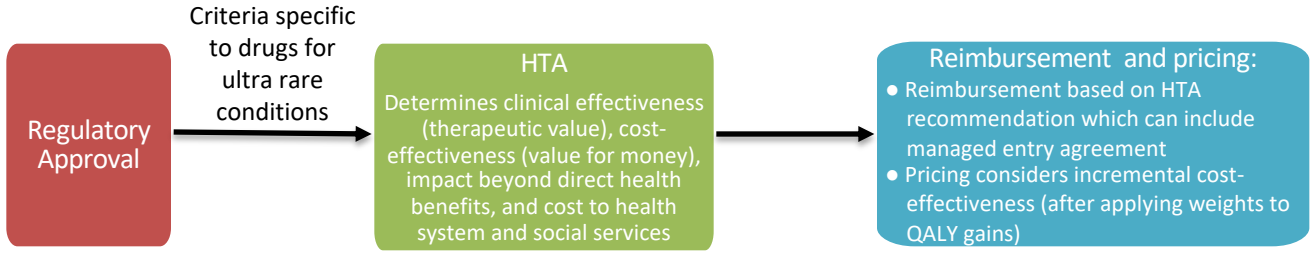
France:



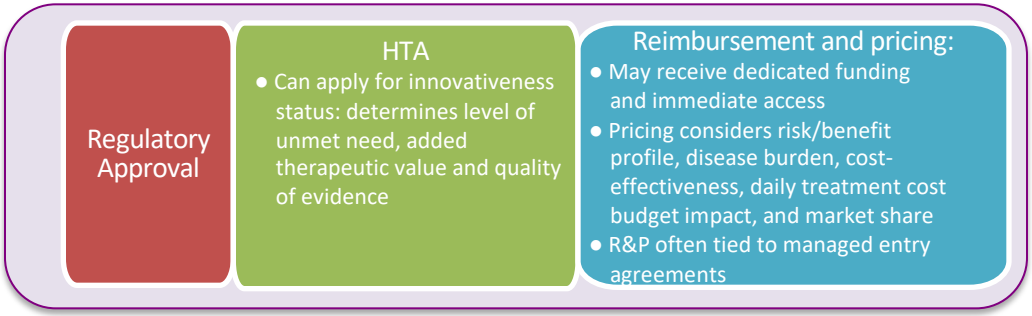
Germany:



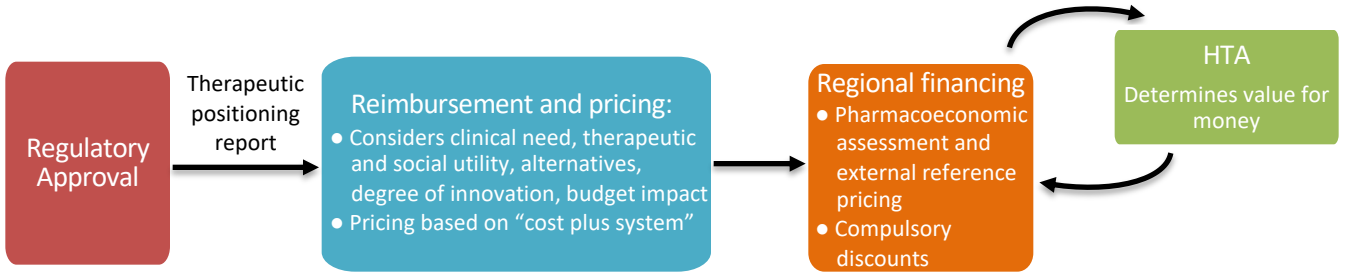
United Kingdom:



Italy:



Spain:



WHAT FACTORS MATTER?

Country	Unmet need	Therapeutic value	Cost	Cost-effectiveness analysis	ICER threshold	Innovativeness
France	Yes	Impact on patients Direct health related PROs	Budget impact on health system (whether exceeds €30 million)	Yes, if budget impact exceeds €30 million	No	Accelerated process
Germany	Yes	Impact on patients Direct health related PROs	Budget impact on health system (whether exceeds €50 million)	Yes, if budget impact exceeds €50 million	No	Accelerated process
Italy	Yes	Impact on patients Direct health related PROs	Budget impact on health system Cost/patient	No, if "innovative"	No	Accelerated process Decision factor
Spain	Yes	Impact on patients Direct health related PROs	Budget impact on health system	Yes	No	Accelerated process Decision factor
United Kingdom	Yes	Impact on patients and caregivers/ Families Direct and indirect health PROs	Budget impact on health and social systems	Yes	Yes, £100,000/QALY to £300,000/QALY	Decision factor

WHAT DOES THE PROPOSED SUPPLEMENTAL PROCESS LOOK LIKE?

Additional Components

Individual Patient Access:

- Centralized panel of experts to assess individual patient cases for public funding eligibility (e.g., starting criteria)

Communications:

- Important throughout the supplemental process
- Multiple consultations with stakeholders is recommended

Early Screening and Identification of Potentially Eligible Drugs

Screen potentially eligible drugs for the process based on Health Canada acceptance for review through an expedited pathway, and other potential criteria such as severity, unmet need, disease prevalence, evidence, cost per patient, budget impact

Concurrent Submission Process

Drugs that meet the criteria would be targeted for parallel regulatory/HTA review by Health Canada and CADTH.

Submissions to PMPRB and pCPA would also be at this time.

HTA Review Process

For drugs that treat conditions with a low prevalence and with limited evidence, additional RWE requirements, start/stop criteria and cost-effectiveness targets would be identified.

pCPA Negotiations & Implementation

For drugs with insufficient evidence, high costs and budget impact, managed access agreements may be sought taking into consideration RWE requirements and pre-determined cost-effectiveness thresholds. These would be encoded in a PLA for the product.

Collection & Re-Assessment of RWE

At pre-determined time points, RWE would be evaluated and assessed against pre-negotiated targets.

After the reassessment, changes to the listing criteria, price, or de-listing would occur, as encoded into the PLA at the outset.

Adapted from EDRD working group stakeholder consultation presentation, November 2018

WHAT IS THE PROPOSED SUPPLEMENTAL PROCESS?

Key elements:

1. Builds upon existing national and jurisdictional review processes

2. Early identification of eligible drugs
   - Health Canada's expedited pathway (priority review or NoC with conditions)
   - Potential additional criteria (e.g., disease severity, unmet need, cost/patient, budget impact, disease prevalence, potential for evidence generation)

3. Enhanced provider (clinician) and patient/caregiver input

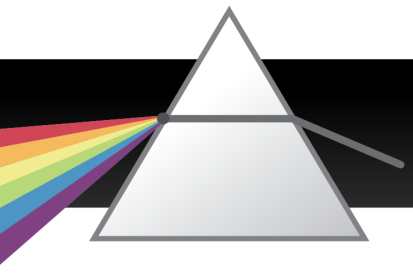
4. Enhanced consideration of real world evidence to address uncertainties

ARE THERE SEPARATE PROCESSES AND WHICH DRUGS ARE ELIGIBLE?

Country	Separate process?	Eligible drugs	RWE-based agreements?
France	Innovative drugs	• Associated with a new type of care • Brings a clinically significant advance compared to what is currently available • Meets a need not sufficiently covered	Yes, where budget impact exceeds €30 million/year
Germany	Yes	Received orphan drug status at regulatory approval	Yes, where budget impact exceeds €50 million/year and relative therapeutic benefit is considered "non-quantifiable"
Italy	Innovative drugs	High unmet therapeutic need High therapeutic value Low quality of evidence (applying rare disease exception)	Yes, where quality of evidence is "low"
Spain	No (national) Yes (regional)	Regional level: not specified but typically ultra rare	Yes
United Kingdom	Yes	• Target population is so small that treatment is concentrated within a few centres • Condition is chronic and severely debilitating • Therapy is expected to be used in a highly specialized service • Therapy has high acquisition cost and potential for life long use • There is a need for national commissioning	Yes, where long term effectiveness and/or cost-effectiveness is uncertain (often for specific subpopulations)

WHAT OTHER FACTORS ARE CONSIDERED FOR DRUGS FOR RARE DISORDERS ONLY?

Country	Special considerations
France	Small patient population is an inefficient argument for determining that a drug has no public health impact during assessment process
Germany	Specifically states that lower evidence thresholds are accepted for orphan drugs (higher p-values and use of surrogate endpoints)
Italy	Cost-effectiveness is considered positive if there is no other effective therapy
Spain	Mandatory price deduction for orphan drugs that is less than that for non-orphan drugs
United Kingdom	Methods and process take into account the “challenge for companies needing to make a reasonable return on investment with small populations



WHAT RWE-BASED DECISION OPTIONS/MANAGED ACCESS PATHWAYS ARE AVAILABLE?

Country	Types of RWE based assessments
France	• Financial-based reimbursement schemes • Conditional approval with request for data collection and re-assessment
Germany	• Performance and financial-based reimbursement schemes • Assessment of real-world benefits of all orphan drugs 12 months post-market authorization using disease-based registries
Italy	• Performance and financial-based reimbursement schemes • AIFA Monitoring Registries
Spain	• Financial-based reimbursement schemes • Catalan Managed Access Programme
United Kingdom	• Performance-based reimbursement schemes (managed access agreements) • Financial outcomes based reimbursement schemes