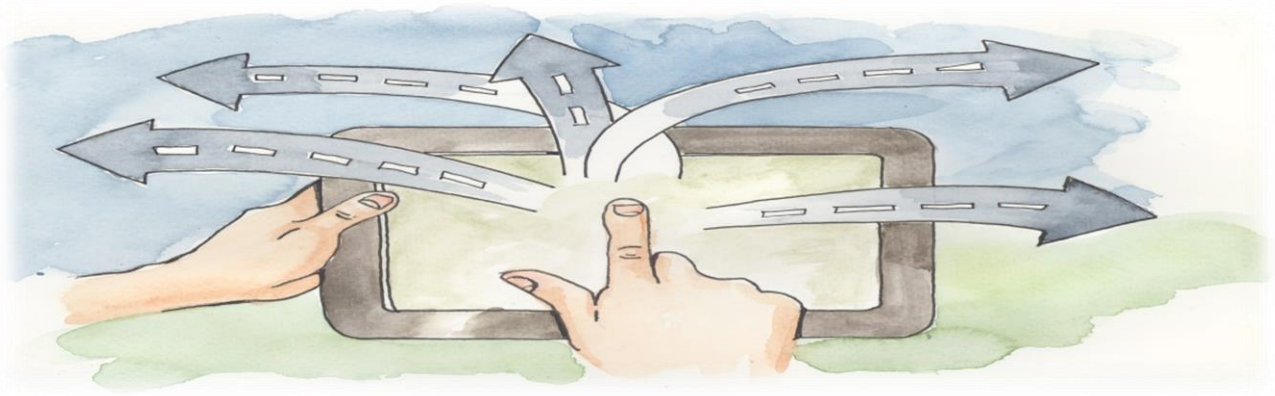
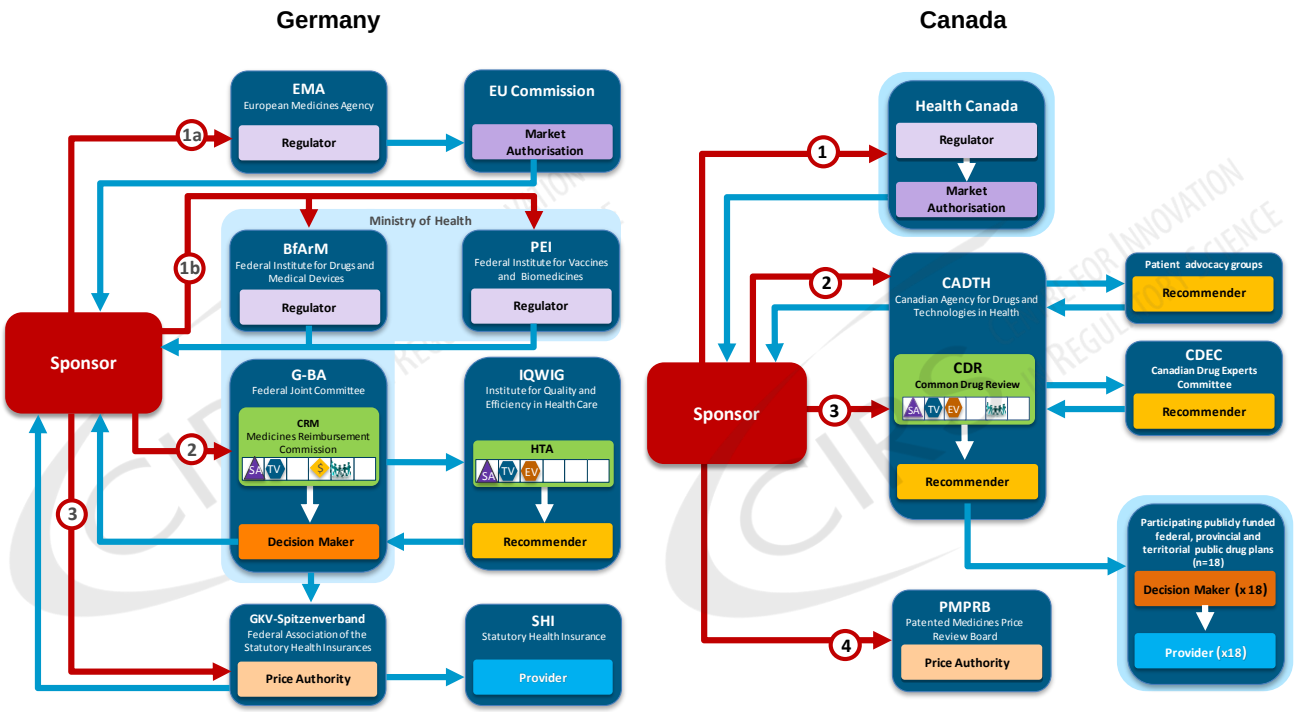


HTA Process Maps:
Identifying similarities and differences for alignment



Update August 2017

Figure 1. Process maps for medicines' regulation and health technology assessment in Germany and Canada

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R&D Briefing 63

This report on the HTA Process mapping project was developed by Patricia Connelly and Tina Wang based on research conducted as part of the CIRS ongoing HTA programme. The work underpinning this report was conducted by Dr Nicola Allen at CIRS as part of her Mpharm and PhD research in conjunction with Cardiff University.

About CIRS

CIRS - The Centre for Innovation in Regulatory Science - is a neutral, independent UK-based subsidiary company, forming part of Clarivate Analytics. The mission of CIRS is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science. It is governed and operated for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities and grants.

Centre for Innovation in Regulatory Science (CIRS)
Friars House, 160 Blackfriars Road, London, SE1 8EZ
Email: cirs@cirsci.org
Website: www.cirsci.org

HTA process maps: Background and methodology

Background to HTA process mapping project

The considerable diversity within healthcare systems in the appraisal and reimbursement of new medicines produces multiple challenges for patient access to new medicines at different stages of the system process. For industry, the lack of harmonised health technology assessment (HTA) methodologies leads to inefficiencies in drug development and uncertainty in outcome, even for those drugs approved by regulatory authorities. The varying requirements of different systems may result in delays in submission and when assessment requirements or methods are unclear, the quality of submission may also be compromised.

Likewise, the different systems present a challenge to attempts at harmonisation or alignment of methods of assessment or appraisal, including the sharing of resources across jurisdictions. The diversity also acts as a barrier to the understanding and meaningful comparison of the different systems and the identification of the best and most efficient practises. Ultimately, such variety in systems can lead to a variety in outcomes in which a drug may be reimbursed in one country but not another. Such outcomes can undermine public confidence in healthcare systems.

As part of its HTA programme, CIRS initiated a HTA process mapping project. HTA process maps were created using systematic methodology to facilitate the comparison for a range of different HTA systems, following the movement of new pharmaceuticals from regulatory approval through HTA appraisal, reimbursement and pricing to adoption at the national level. By 2017, process maps were created for more than 75 jurisdictions, these maps were built into an online platform CIRS Regulatory and Reimbursement Atlas. The Atlas serves as a simple visual communication tool to facilitate the explanation and comparison of different jurisdictions to multiple stakeholders.

This R&D Briefing summarises the background and methodology of process mapping with examples to demonstrate the steps involved in regulatory, HTA and coverage processes for new medicines. In addition to their comparison and educational function, the process maps were utilised to address a number of research questions. The briefing highlights the outcome of these research studies and also outlines the practical utility of the process maps.

Systematic mapping methodology

Step 1: The primary agencies directly involved in the processes from market authorisation, HTA assessment and appraisal, pricing control and reimbursement decision making for each country were identified. Because of mandated reviews, the European Medicines Agency (EMA) and European Union (EU) Commission were included in European maps in addition to local regulatory agencies. Once the agencies were identified, connections between the agencies were added to the maps in order to show the movement of evidence through the process. Connections were also added to indicate where the sponsor interacted with the agencies, either at the times of submission of a dossier, through scientific advice or other discussion, or where there were opportunities for sponsors to comment on the findings, appraisals or review of the agencies. It was also indicated whether an agency was part of the national government or was independent.

Step 2: Seven functions that represented significant and measureable key components of the system were defined and then mapped onto the agencies that conducted those functions (Figure 2). This allowed the identification of where in the system such functions occurred and how they related to one another.

Step 3: For the HTA function, a "task bar" of key activities was developed to characterise a selection of defining elements of the HTA process (Figure 3). Each activity was given an identifying icon that is shown in the HTA task bar if it was a normal part of that agency's actions.

Figure 2. Seven key functions were identified and mapped to the system.

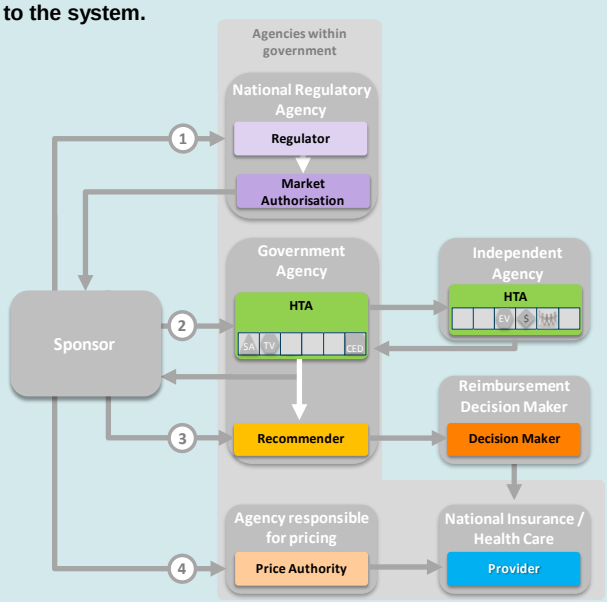


Figure 3. A task bar of defining elements of the HTA process.

Scientific Advice: Provision of scientific advice to the sponsor in relation to the drug development program or the submission of evidence to that agency.

Therapeutic Value: Evaluation of the clinical evidence in order to determine if there is added-therapeutic value in the new medicine.

Economic Value: Determination of the cost-effectiveness, cost-utility, cost-benefit and/or budget impact of the new therapy.

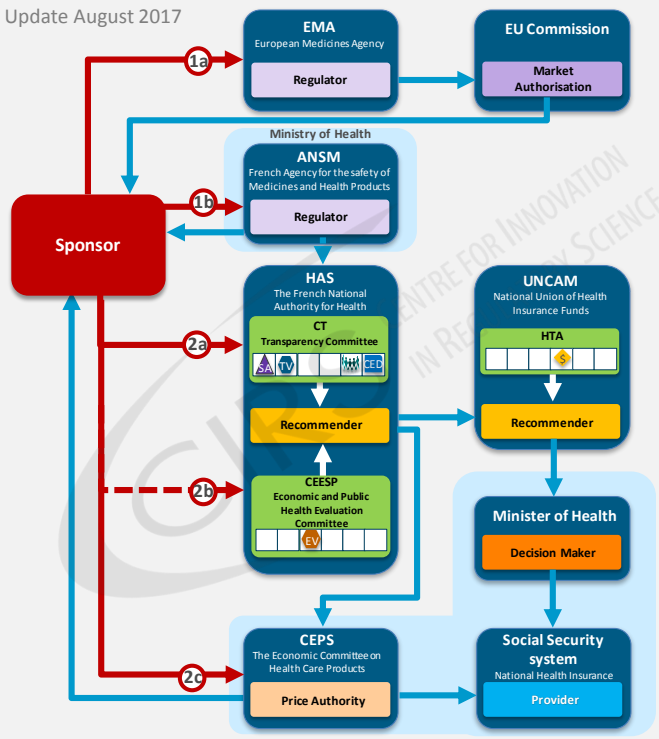
Reimbursement rate: Determination of the rate of reimbursement for the new medicine, usually into pre-defined categories.

Public consultation: Involvement of patients, patient advocates and/or public representatives, this includes both formal and informal forms of consultation.

Coverage with Evidence Development: Provision of release of the new medicine where data is limited with the condition of further evidence development.

Regulatory and Reimbursement Atlas: Process map examples

Figure 4. Processes and stakeholders for France



Following the regulatory approval, manufacturer dossier is submitted simultaneously to the Commission de la Transparence (CT, Transparency Committee), the Commssion d'Evaluation Economique et de Santé Publique (CEESP, Economic and Public Health Evaluation Committee), the Comité Economique des Produits de Santé (CEPS, Economic Committee for Healthcare Products), and the Union Nationale des Caisses d'Assurance Maladie (UNCAM, National Union of Health Insurance Funds).

CT (Transparency Committee) determines the drug's service médical rendu (**SMR; medical benefit**) and amélioration du service médical rendu (**ASMR, improvement in medical benefit**). CEESP (Economic and Public Health Evaluation Committee) issues opinion on **cost-effectiveness**. These two assessments are submitted to the CEPS.

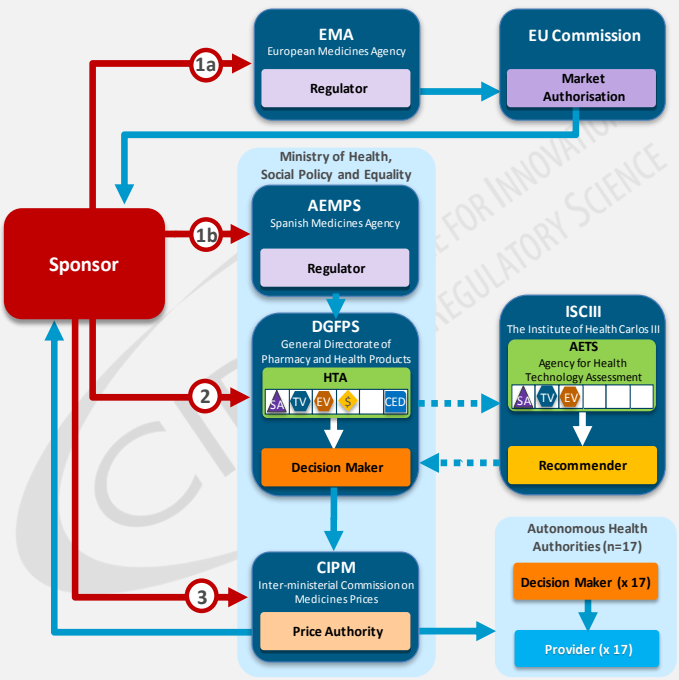
UNCAM (National Union of Health Insurance Funds) determines whether a drug will be reimbursed and at what rate (15%,30%, 65% or 100%).

The CEPS (Economic Committee for Healthcare Products) and the manufacturer negotiate the price based on the drug's ASMR ratings, the prices of drugs with similar indications, actual/forecas sales, and actual/forecast consumption.

The Ministry of Health takes final decision. Details of reimbursed drugs are published in the Journal Officiel.

SA Scientific advice | TV Therapeutic value | EV Economic value | Reimburse rate | Public consultation | CED Coverage with evidence generation

Figure 5. Processes and stakeholders for Spain



Following the regulatory approval, manufacturer submits application to the Dirección General de Farmacia y Productos Sanitarios (DGFPS General Directorate of Pharmacy and Health Products) who produces a summary dossier.

AETS (Agencia de Evaluacion de Tecnologias Sanitarias) is the national HTA Agency within ISCIII (the Institute of Health Carlos III). It is an autonomous public institution attached to the Spanish Ministry of Health, which proposes and develops guidelines related to health care. The ISCIII provides HTA reports to DGFPS, the ultimate decision maker for benefit policy. Currently, seven regional HTA agencies in the autonomous regions (Comunidades Autonomas) collaborate with the ISCIII. Recently a new Cost-Effectiveness Committee for Medicines and Healthcare Products was created , whose reports would be taken into account by the CIPM.

The CIPM (Interdepartmental Committee on Pharmaceutical Prices) uses the summary dossier as the basis for pricing negotiations with the manufacturer.

The CNURM (National Commission for the Rational Use of Medicines) sets reimbursement terms based on price, cost and efficacy relative to similar products, therapeutic role, and health economic data.

If a reimbursement status is approved, the pricing is decided simultaneously. If the reimbursement decision is **positive** (inclusion in the national reimbursement list), this decision is valid (mandatory) throughout the country. If the outcome is **negative**, the product will be put on the negative list and price is determined by the manufacturer ("free pricing").

SA Scientific advice | TV Therapeutic value | EV Economic value | Reimburse rate | Public consultation | CED Coverage with evidence generation

Data source: © 2017 CIRS Regulatory and Reimbursement Atlas http://www.cirs-atlas.org/

Development of HTA archetypes based on comparative mapping

Using systematic mapping method, process maps were developed for more than 75 jurisdictions to illustrate the steps involved in regulatory, HTA and coverage processes for new active substances. These maps identified notable differences in the extent to which agencies conducted a defined set of core functions, the number of decision-making bodies, their sequence within the overall process and key HTA tasks undertaken.

Comparing the process maps created for 31 European nations, Allen and colleagues constructed a European taxonomy of healthcare systems, determined relationships between the taxonomy sets, developing archetypes that could potentially be used to facilitate alignment of and collaboration among HTA agencies.[1,2]

Taxonomy One: System taxonomy
Each European HTA agency was assigned to one of five external system process groups indicating its position relative to regulatory, HTA and coverage bodies.

Taxonomy Two: HTA process taxonomy
Each European HTA agency was also assigned to one of four internal HTA assessment type groups according to the key functions performed within the agency. By distinguishing the ways in which agencies employ therapeutic evaluations, this taxonomy may suggest the most suitable points of collaboration among agencies.

HTA Archetypes
The confluence of these two taxonomies was used to create eight archetypes, allowing the grouping of HTA agencies performing similar tasks and occupying similar positions in their reimbursement systems (Figure 6).

Taxonomy One: System taxonomy

S1–The regulatory, HTA and coverage body functions are performed by separate agencies

S2–The regulatory and HTA functions are performed by a single agency and the coverage body functions are independent

S3–The HTA and coverage body functions are performed by a single agency with the regulatory function performed independently

S4–The regulatory, HTA and coverage body functions are all performed within a single agency

S5–No HTA is performed within the national regulatory to reimbursement system

Taxonomy Two: HTA process taxonomy

H1–The therapeutic value assessment, economic evaluation and appraisal are performed within the same agency

H2–The therapeutic value assessment is conducted within the same agency as Economic evaluation but the appraisal is performed independently, usually by health professionals rather than civil servants

H3–The therapeutic value is assessed prior to independent appraisal

H4–The appraisal is conducted using information from an external HTA report or by considering the coverage decisions of reference countries.

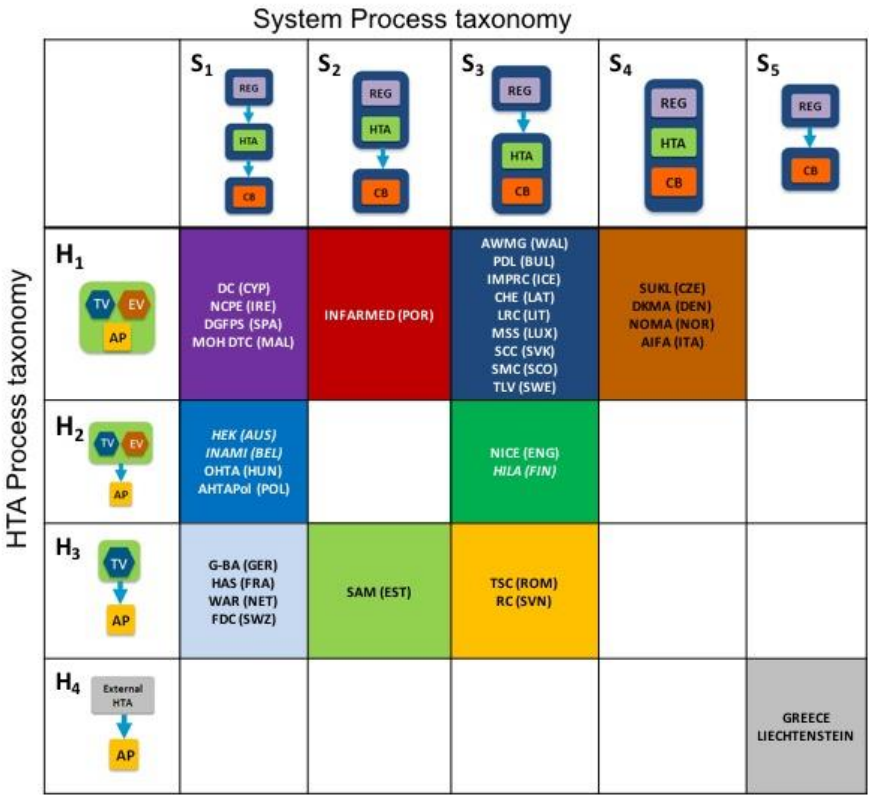


Figure 6. Countries grouped according to HTA archetypes[1, 2]

No association was found between a jurisdiction's reimbursement system or HTA processes and its ability to pay or its geographical location. Potential collaboration among countries could be based on similarities in HTA factors, resulting in a more effective and timely HTA environment.

1.Allen N, Pichler F, Wang T, Patel S, Salek S. Development of archetypes for non-ranking classification and comparison of European National Health Technology Assessment systems. *Health Policy*. 2013;113:305-312.
2. Allen N, Liberti L, Walker S, Salek MS. Comparison of European reimbursement recommendations: Opportunity for further alignment? *Frontiers*. 2017;8:34.

Correlation of HTA types with reimbursement recommendations

Allen and colleagues collected HTA recommendations or listing outcomes for EMA-approved new active substances from 2008-2012 from agency websites for Belgium England, France, Germany, Ireland, Italy, Netherlands, Scotland and Sweden.[2] These recommendations or listings were categorised as *recommended; recommended with restrictions* or *not recommended*.

The nine jurisdictions were grouped according to their system taxonomy, that is, the relationship of the HTA agency within the regulatory and reimbursement system (Figure 7) and HTA process taxonomy, that is the HTA agency model for economic and therapeutic assessment (Figure 8) to identify congruent outcomes by taxonomy and congruence of outcomes among taxonomic groups.

Figure 7. Congruence of HTA recommendations with system taxonomy.[2]

HTA Process taxonomy subsets	Alignment of HTA recommendations (number of products reviewed)	Belgium	Scotland	Ireland	Sweden	France	Netherlands	Germany
H_2 (TV, EV → AP)	England	68% (31)	45% (38)	55% (29)	53% (30)	58% (38)	63% (35)	60% (15)
	Belgium		23% (60)	67% (42)	54% (46)	88% (68)	81% (57)	96% (24)
H_1 (TV, EV → AP)	Scotland			51% (49)	50% (56)	26% (74)	43% (63)	33% (21)
	Ireland				33% (42)	54% (50)	51% (47)	54% (24)
	Sweden					46% (57)	54% (54)	31% (16)
H_3 (TV → AP)	France						79% (72)	93% (30)
	Netherlands							76% (25)
	Germany							

For the HTA process taxonomy sets outlined, the H_1 set includes Scotland, Ireland and Sweden; the H_2 set includes England and Belgium and the H_3 set includes Germany, France and the Netherlands. None of the jurisdictions reviewed were classified as H_4 taxonomy.

Figure 8. Congruence of HTA recommendations with process taxonomy.[2]

System taxonomy subsets	Alignment of HTA recommendations (number of products reviewed)	Ireland	France	Netherlands	Belgium	England	Scotland	Sweden
S_1 (REG → HTA → CB)	Germany	54% (24)	93% (30)	76% (25)	96% (24)	60% (15)	33% (21)	31% (16)
	Ireland		54% (50)	51% (47)	67% (42)	55% (29)	51% (49)	33% (42)
	France			79% (72)	88% (68)	58% (38)	26% (74)	46% (57)
	Netherlands				81% (57)	63% (35)	43% (63)	54% (54)
	Belgium					68% (31)	23% (60)	54% (46)
S_3 (REG → HTA, CB)	England						45% (38)	53% (30)
	Scotland							50% (56)
	Sweden							

For the System Taxonomy sets outlined, the S_1 set includes Germany, Ireland, France, Netherlands, and Belgium and the S_3 set includes England, Scotland, and Sweden. None of the jurisdictions reviewed were classified as S_2, S_4, or S_5.

Congruence Key		
High congruence ≥ 75%	Medium congruence < 75% to ≥ 50%	Low congruence <50%

The authors identified some alignment between the organisational structure of reimbursement systems and HTA recommendations but there was less congruence between recommendations and HTA processes. These results may indicate a relationship between recommendations and the regulatory, and HTA roles and thus an opportunity for HTA alignment, but more research is required.

Although extreme differences among countries in healthcare budgets, standards of care and social and political environments present challenges to European HTA alignment, the investigators point to the successful implementation of the EMA despite similar challenges.

2. Allen N, Liberti L, Walker S, Salek MS. Comparison of European reimbursement recommendations: Opportunity for further alignment? *Frontiers*. 2017;8:34.

Case studies: Differing HTA recommendations from four agencies

Allen and colleagues compared initial Canadian (CDR) national HTA recommendations with the initial recommendation decisions of HTA agencies in Scotland (SMC), Australia (PBAC) and England (NICE) from January 2009 to May 2013, to identify factors for divergent national HTA recommendations among the four HTA agencies.

Seven case studies were developed for products that were assessed by all four agencies and that received negative recommendation from one of the agencies.(Figure 9)[3]

Each of the four countries have a national HTA agency. Other similarities include the fact that all of the agencies' reimbursement recommendations are based on assessment of clinical efficacy and cost effectiveness with the use of a threshold for quality-adjusted life years. In addition, all four agencies operate under a mandate to incorporate patient input into their recommendations.

Despite these similarities, wide-ranging differences in political and social factors exist. These cases illustrate instances of variability in HTA recommendations because of differing requirements or interpretations regarding issues such as cost-effectiveness, comparator choice, clinical benefit, safety, trial design, submission timing and the ability to negotiate price.

3. Allen N, Walker SR, Liberti L, Salek S. Health Technology Assessment (HTA) case studies: Factors influencing divergent HTA reimbursement recommendations in Australia, Canada, England, and Scotland. *Value Health*. 2017; 20: 320-328.

Case study 1

Fingolimod (Gilenya) for multiple sclerosis

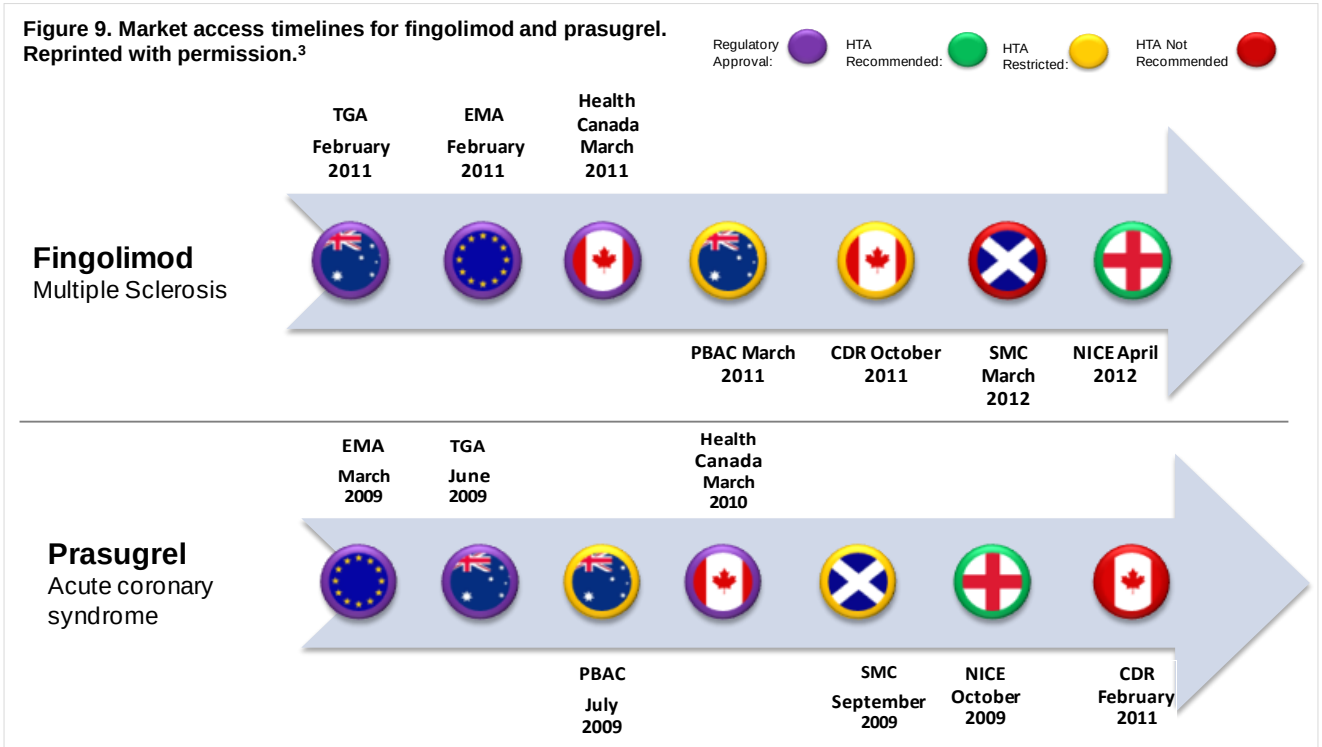
All four HTA agencies agreed that fingolimod, The first oral medicine for active, relapsing multiple sclerosis, produced a significant reduction in annualised relapses with general acceptance that its efficacy was comparable to the main included comparator Interferon beta-1a. Only the SMC issued a negative recommendation, owing to uncertainties regarding comparator choice, potentially because of a different treatment population specified in the treatment label in Scotland. After a resubmission that included additional comparators, Fingolimod was later recommended by the SMC for restricted use.

Case study 2

Prasugrel (Effient) for acute coronary syndrome

Prasugrel first received restricted positive recommendations from PBAC and SMC and a "recommended" assessment from NICE. However, the CDR delivered a negative "do not list" recommendation, citing uncertainty regarding the applicability of the trial design to Canadian clinical practice and safety concerns regarding a statistically significant increase in major bleeding events for prasugrel versus the comparator, clopidogrel. After the sponsor's resubmission, which included additional data and a lower price, the CDR published another "do not list" recommendation because clopidogrel had become available as a generic and the new trials did not meet Canadian requirements and results were not considered generalisable to the Canadian context.. However, the CDR did recommend resubmission at a lower price and this case may ultimately illustrate difference in HTA recommendations owing to an agency's ability to negotiate price.

Figure 9. Market access timelines for fingolimod and prasugrel. Reprinted with permission.[3]



Practical utility of process maps

Applying archetypes outside of Europe

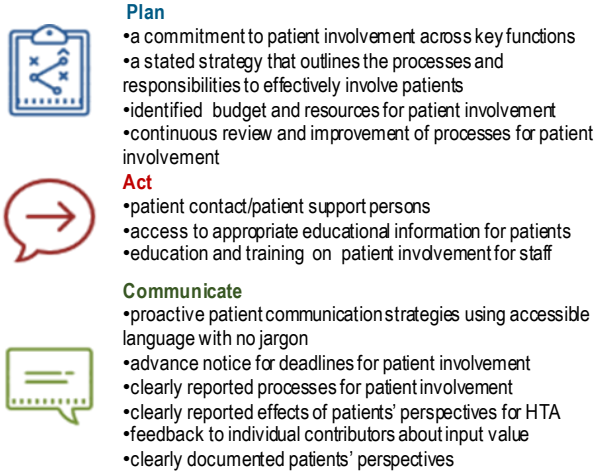
Using information from websites and scientific literature that was verified through direct agency contact, Skaltska and colleagues developed system and process taxonomies for 12 countries in Latin America: Mexico, Cuba, Costa Rica, Colombia, Venezuela, Ecuador, Peru, Bolivia, Brazil, Uruguay, Argentina and Chile. The authors combined system and process taxonomies to group the countries into five HTA archetypes. The percentage of countries assigned to each archetype showed strong correlation to similar research in the EU. Archetype classification may change in the future as a result of Latin American network alignments, which may also expedite HTA alignment in the area.[4]

Creating country profile using key factors to assess patient interactions with HTA agencies

As healthcare decision-making processes evolve, the voice of the patient is playing a growing role in educating and informing HTAs, and sometimes providing crucial influential input that can have a major impact on an therapeutic area recommendation. However, the extent to which HTAs have policies and procedures in place to effectively interact and gain advice from patients is not well characterised.

Current process maps illustrates regulatory and HTA processes and whether HTA incorporates patient input, providing understanding of what is in place with regard to patient interactions in each country. Moving forward, a detailed country profile of HTA-patient interaction could be created based on guidance published by Health Technology Assessment International (HTAi) and recommendations promulgated by attendees at the recent CIRS-sponsored Workshop *What is the patient's role in informing the decision process for approval and reimbursement of new medicines?* These profiles could be built on the current process maps and determine the feature of each HTA organisation using key factors (Figure 10), which will provide a roadmap to understand the current systems and gaps across jurisdictions.

Figure 10. Profile of HTA agencies can be developed based on potential aspects of patient involvement.



Educational and training tool for patient groups

The Regulatory and Reimbursement Atlas provides value as an educational and training tool to patient groups. The maps show a clear picture of the regulatory and HTA processes in each country and provide insights into how HTA agencies reach their recommendations across jurisdictions as a comparative tool.

Supporting cooperation in HTA

Responding to the need to move toward a more collaborative reimbursement environment in Europe, the European Network for Health Technology Assessment (EUnetHTA) was established in 2006 to create an effective and sustainable network for HTA agencies. In 2013, the EU Commission set up a permanent, voluntary HTA network to enhance cooperation between countries in Europe. More recently, the European Commission started an initiative to strengthen the EU cooperation on HTA and commenced development of an Impact Assessment [5] in 2017.

To this end, the CIRS Regulatory and Reimbursement Atlas has been presented at the 6th meeting of the HTA Network (Brussels, 20 May 2016) to demonstrate the comparative mapping method and identification of differences and similarities of HTA systems in Europe. The Regulatory and Reimbursement Atlas has also been shared with the EU commission to support a mapping project that will inform the 2017 Impact Assessment.

Comparative mapping provides the baseline for true agency and industry benchmarking

As the global development environment becomes more complex, the need to understand the confluence of these pathways has become a driver of the medicines' development process. Process mapping allows the planning of development strategy by identifying potentially rate-limiting process steps. Benchmarking industry, regulatory and HTA performance against peers with similar mandates and processes can encourage good practices and promote timeliness, predictability, consistency, transparency, clarity, efficiency and quality.

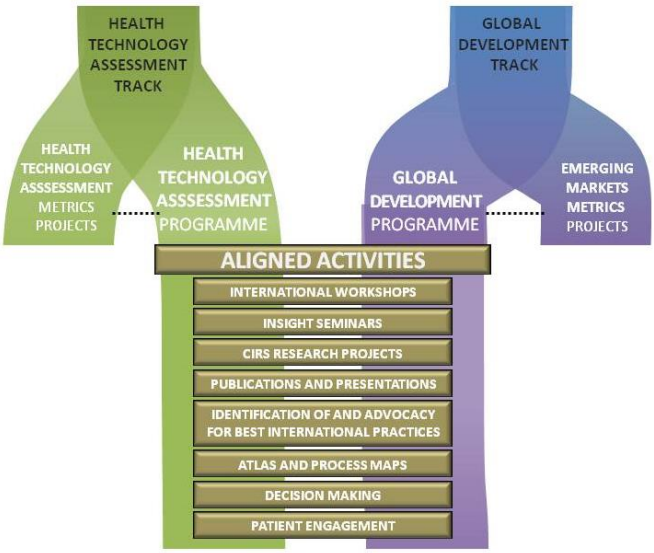
Tracking and measuring performance can convey achievements and needs to policy makers, promote continuous improvements and opportunities for work optimisation and build trust in each other's systems and approaches.

4. Skaltsa K, Allen N, Blogg K. *An archetype for classification and comparison of HTA activities in Latin America.* Poster, ISPOR, Amsterdam, the Netherlands; November 2014
5. Strengthening EU cooperation beyond 2020 https://ec.europa.eu/health/technology_assessment/eu_cooperation_en

The Centre for Innovation in Regulatory Science

The Centre for Innovation in Regulatory Science
CIRS provides a neutral, independent, international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science. CIRS achieves its mission of advancing regulatory and HTA policies and processes by means of the aligned activities of its Health Technology Assessment and Global Development programmes – activities that include international Workshops, Insight Seminars, research projects, publications and presentations and the identification of and advocacy for best international practices.

Through these activities, CIRS regularly interacts with international pharmaceutical companies, regulatory agencies and HTA and coverage bodies to address the overlapping themes of *metrics*, to manage uncertainty and improve predictability; *quality of process*, to improve the development of development, regulatory and health technology assessment processes and ultimately the quality of decision making and *alignment,* promoting convergence within and across organisations and stakeholders.



CIRS has organised its activities into the Global Development and Health Technology Assessment programmes.

Through its research, Workshops and other activities, CIRS focuses on the themes of metrics, quality of process and alignment.

Metrics

Managing uncertainty and improving predictability

- Collection, curation and analysis of data, information and processes to provide insights into the performance of companies and agencies in the development review and access of new medicines
- Supported by company- and agency-led benchmarking programmes and topic-specific surveys

Quality of process

Improving development and regulatory processes and ultimately, the quality of decision making

- Building on CIRS experience in benefit-risk, activities focus on developing a framework for a structured, transparent and logical approach to quality decision making applicable throughout all stages of medicine development and review and the regulatory HTA review processes

Alignment

Promoting convergence within and across organisations and stakeholders

- Activities that assess approaches and identify building blocks to help regulatory and HTA agencies determine best practices and share resources
- With industry develop best practices that result in more efficient and timely development and access to medicines

CIRS HTA programme activities

•**International Workshops** facilitate networking, constructive discussion, recommendations and actions.

•**Industry and agency-supplied and publicly available data** are collated by CIRS into informative HTA performance measures, which enable contextualisation of review procedures across various jurisdictions.

•**The CIRS Regulatory & Reimbursement Atlas** systematically maps regulatory review to reimbursement in more than 70 countries/jurisdictions.

•**Surveys and other research** focus on specific areas of interest within pharmaceutical regulation, HTA and government affairs.

•**Insight seminars** for member companies and meetings with HTA agencies centre on HTA programme research outcomes.

•**Technical fora** concentrate on timely topics of special interest to industry