

Review of HTA outcomes and timelines in Australia, Canada and Europe 2014-2015

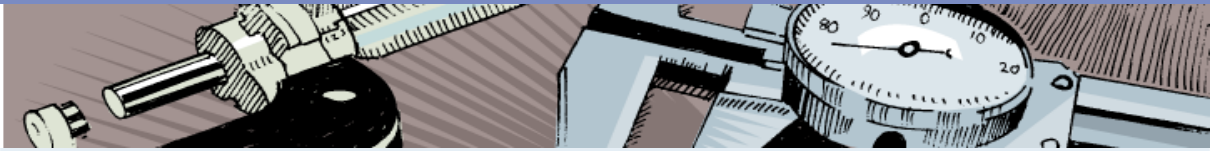
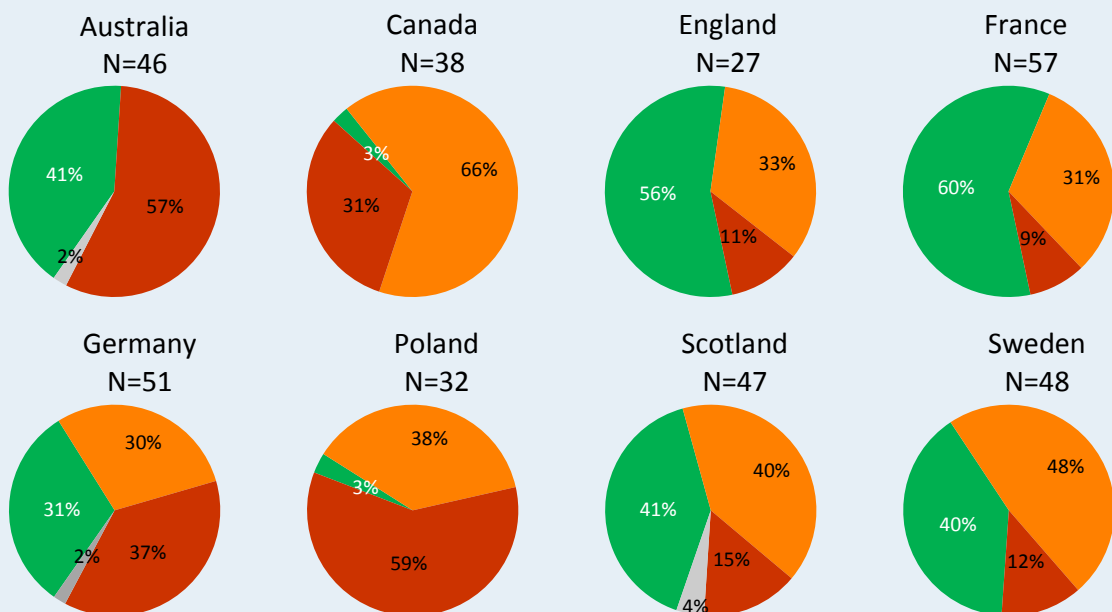


Figure 1: HTA Decisions: comparisons across key jurisdictions 2014 and 2015

Positive Restriction Negative Multiple



Contents

Summary	1
Overview of new drug recommendations	2
Synchronisation of regulatory and HTA decisions	3
Four products appraised by all eight jurisdictions	4
Features of Australia	5
Features of Canada	6
Features of Europe	7
Methodology	8
Definitions	9

SUMMARY

Introduction

Timely recommendation for drug reimbursement by health technology assessment (HTA) agencies is critical to ensure patient access to medicines of therapeutic value. As part of an ongoing study to monitor regulatory and HTA performance, CIRS collected data on new active substances (NASs) appraised in 2014 and 2015 by eight HTA agencies, analysing synchronisation between the regulatory decision and first HTA recommendation in timing and outcome.

Recommendations were collected from the Australian Pharmaceutical Benefits Advisory Committee (PBAC), Canadian Agency for Drugs and Technologies in Health (CADTH), British National Institute for Health and Care Excellence (NICE), French Haute Autorité de Santé (HAS), German Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), Polish Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT), Scottish Medicines Consortium (SMC) and Swedish Tandvårds- & läkemedelsförmånsverket (TLV), for products approved between 2012-2015 by the respective jurisdictional regulatory agencies, the Australian Therapeutic Goods Administration (TGA), Health Canada and European Medicines Association (EMA).

Using a methodology outlined on page 8, the HTA decisions in this report have been classified as *positive*, *positive with restrictions* or *negative*. Figure 17 illustrates how the specific decisions by the eight HTA systems are captured within his trichotomous categorisation. In cases in which more than one HTA dossier was submitted by companies for the same drug based on different sub-indications within an approved regulatory label and the final HTA outcome for these individual sub-indications differed, the outcome was classified as *multiple*.

Observations

- Overall, more than 60% of NASs approved by regulatory agencies received a *positive* or *positive with restrictions* recommendation by HTA agencies in most of the studied jurisdictions except Australia and Poland. In fact, 89% of the products appraised in Poland in 2015 received negative HTA decisions.
- Of all studied HTA agencies, Australia had the highest percentage of products recommended in the same year as regulatory approval (96% in 2014 and 90% in 2015), followed by Scotland in 2014 (95%) and Germany in 2015 (89%).
- Products were rolled out (regulatory submission to receiving a HTA recommendation) in Australia within the shortest median time (1.1 years in 2014 and 1 year in 2015), while Poland was the slowest to roll out new medicines, with a median time of 2.5 years in 2014 and 2.2 years in 2015.
- CIRS analysed products rolled out to eight jurisdictions and identified four products that received a decision by all HTA agencies. Interestingly, these products were the new, but costly hepatitis C virus (HCV) therapies.



In Australia, the TGA/PBAC parallel process proved to be beneficial for reducing time differences between regulatory approval to HTA decision.

Of 46 drug submissions in Australia in 2014-2015, 26 were reviewed through the TGA/PBAC parallel process. The parallel process played an important role in shortening the time until the first HTA decision; PBAC decisions were made a median of less than 1 month after TGA approval in 2014.



In Canada, the Health Canada/CADTH parallel review route was not widely used in 2014 and 2015 by companies.

For products that received a negative HTA decision, the company submission gap from Health Canada approval to CADTH submission was a median of approximately 3 months.

Products that received an expedited Health Canada review made up 21% and 17% of all NASs appraised by CADTH in 2014 and 2015, although their expedited regulatory review status had no impact on the HTA review timelines. However, the parallel review process was used more for products with expedited regulatory review, with 73-day and 7-day time lag between regulatory decision and HTA recommendation in 2014 and 2015.



In Europe, the time lag between EMA approval and HTA decisions varied across the European jurisdictions.

For products approved via the EMA centralised procedure, the time delay to receive the HTA decision was longest in Poland, where in 2014-2015, only 41% of HTA recommendations were made in the same year that EMA granted approval. In all studied European jurisdictions, the time from EMA approval to HTA recommendation was generally longer for those products receiving a negative HTA outcome.

OVERVIEW OF NEW DRUG RECOMMENDATIONS

In 2014 and 2015, France and Sweden had the highest proportion (91% and 88%) of *positive/positive with restrictions* recommendations for NASs appraised by HTA agencies (Figure 1).

More than 60% of NASs approved by relevant regulatory agencies received a *positive* or *positive with restrictions* recommendation by HTA agencies in most of the studied jurisdictions except Australia and Poland. In particular, there was an increase of number of products that received a negative decision in Poland in 2015, to 90% of the total number of NASs appraised (Figure 2).

France appraised the highest number of NASs approved by EMA via the centralised procedure in 2014-2015, (57 products), while England appraised the fewest (27). This is a reflection of the NICE appraisal process, which includes a topic selection step that only allows the appraisal of EMA-approved products that meet specific criteria.

In France and Germany, where added therapeutic benefit are the primary assessment criteria, HTA assessments must be conducted using different comparators for each sub-indication of an approved product, which may result in different reimbursement decisions for each sub-indication.

Products were rolled out in Australia in 2014-2015 in the fastest median time from regulatory submission to HTA recommendation, while Poland took the longest, with a median rollout time of 2.5 years in 2014 and 2.2 years in 2015 (Figure 3). In 2015, Sweden showed the greatest decrease in median rollout time compared with 2014 (115 days).

Figure 2: HTA Decision comparison across key jurisdictions 2014-2015

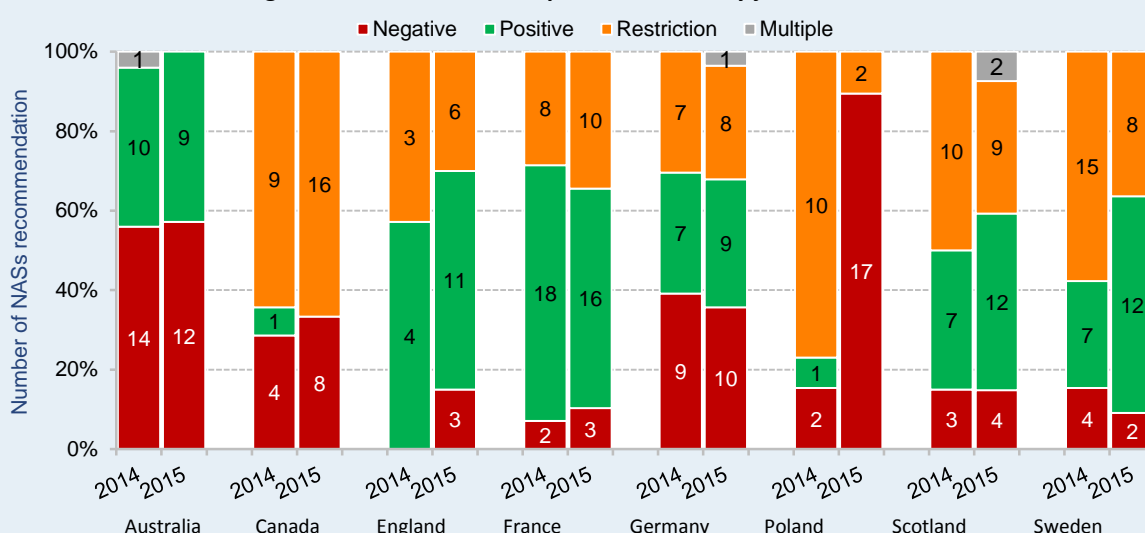
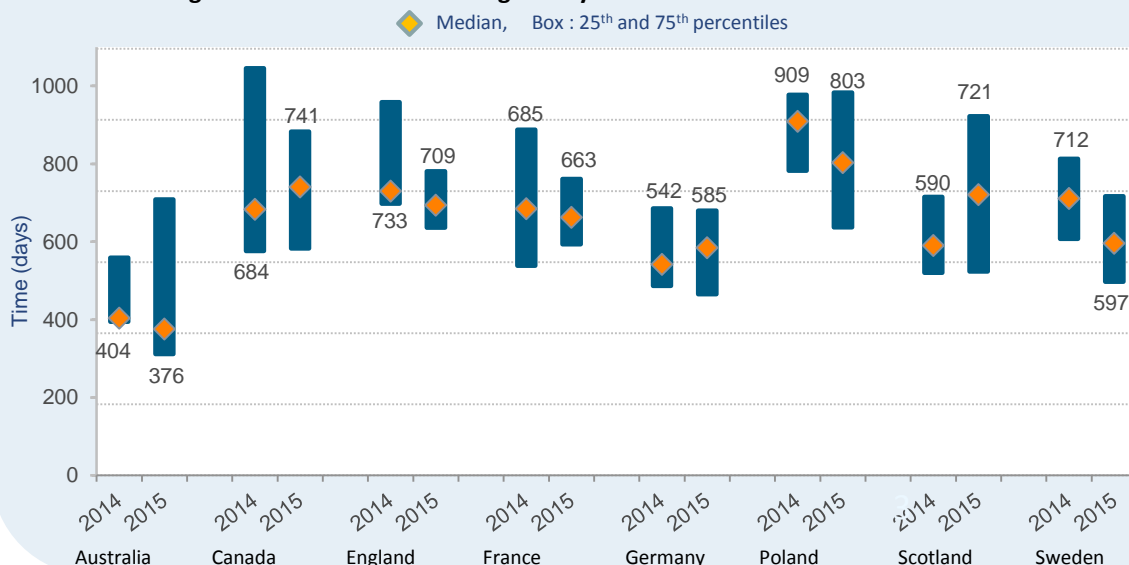


Figure 3: Rollout time from regulatory submission to HTA decision 2014-2015



SYNCHRONISATION OF REGULATORY AND HTA DECISIONS

Figure 4: Time difference between regulatory approval and HTA decision, for products appraised in 2014

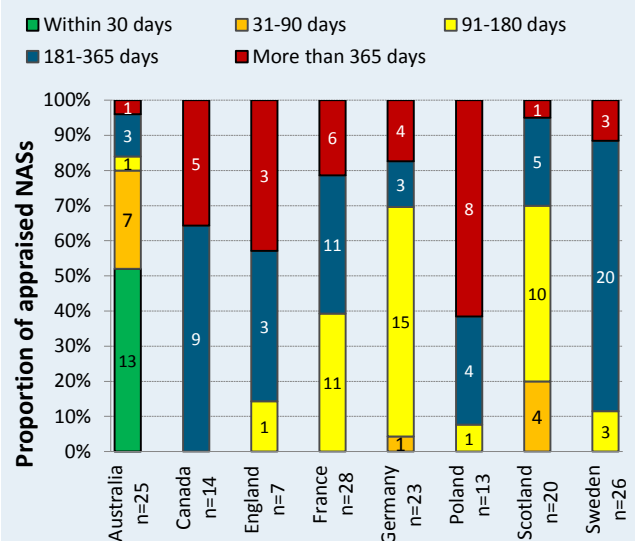
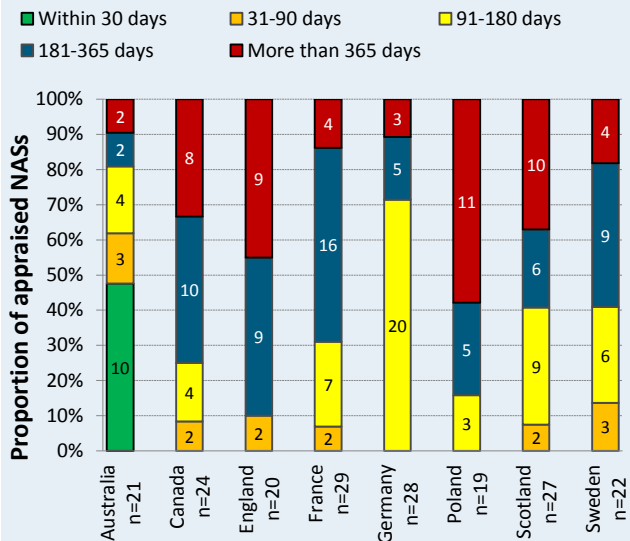


Figure 5: Time difference between regulatory approval and HTA decision, for products appraised in 2015



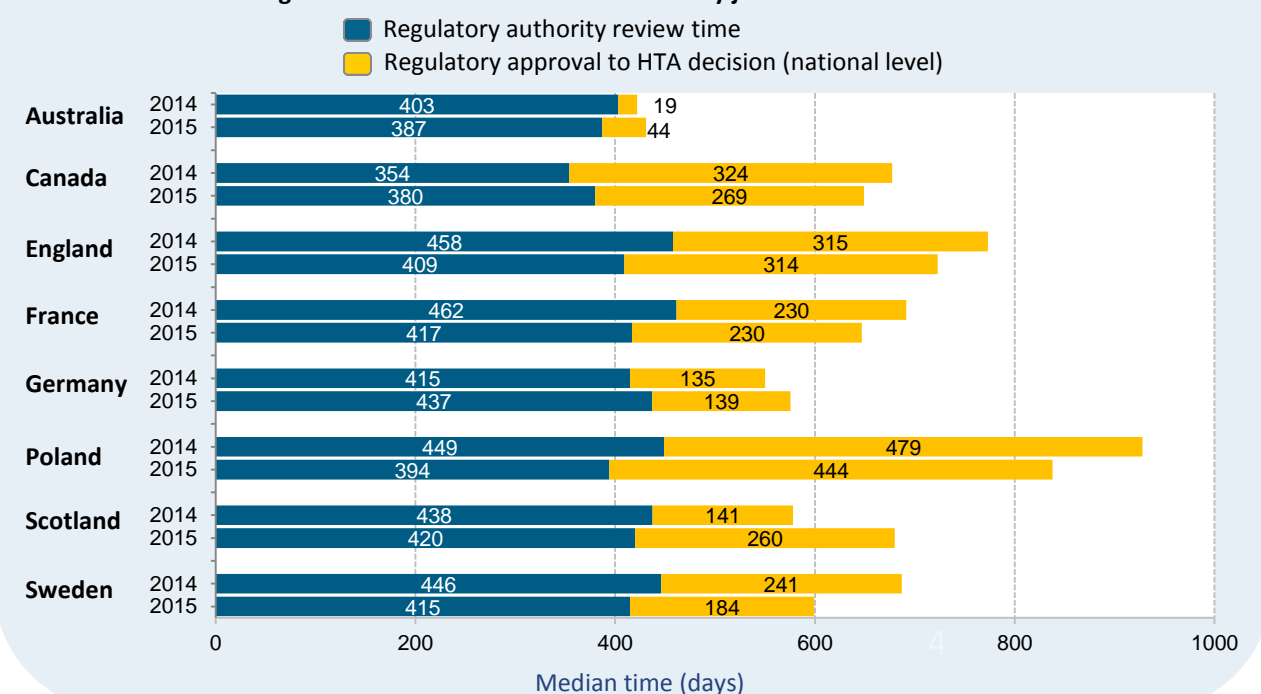
Of all HTA agencies, PBAC had the highest percentage of products recommended within a year from regulatory approval: 96% in 2014 (Figure 4) and 90% in 2015 (Figure 5).

In Australia, since 2011, after the regulatory application is accepted for review, a reimbursement submission may be sent to the PBAC for parallel review. In Canada, from 2012, all drug applications can be submitted to CADTH for HTA review before receiving a Notice of Compliance (NOC) by Health Canada. Comparing all jurisdictions, PBAC appraised the most products in the same year as regulatory approval, suggesting that the proactive approach within Australia to move toward synchronising the timing of HTA and regulatory decision is showing success.

It took more than double the time from regulatory submission to HTA decision in England and Poland compared with Australia (Figure 6).

The results suggest that with the exception of Australia, there was a potentially long waiting time for patients between the regulatory approval and HTA recommendation, which could be attributed to both HTA review time and company submission strategy to HTA agencies.

Figure 6: Breakdown of rollout time in key jurisdictions 2014-2015



FOUR PRODUCTS APPRAISED BY ALL EIGHT JURISDICTIONS

Jurisdiction	Daklinza	Olysio (Galexos)	Sovaldi	Harvoni
Australia	Positive	Positive	Negative	Positive
Canada	Restriction	Restriction	Restriction	Restriction
England	Restriction	Positive	Restriction	Restriction
France	Positive	Positive	Positive	Positive
Germany	Negative	Restriction	Restriction	Restriction
Poland	Negative	Restriction	Negative	Negative
Scotland	Restriction	Positive	Positive	Restriction
Sweden	Restriction	Restriction	Restriction	Restriction

Figure 7: First HTA decision comparison

- The active substance in **Daklinza (daclatasvir)** blocks the action of 'NS5A', an HCV protein.
- The active substance in **Olysio (simeprevir)** blocks the action of 'NS3/4A serine protease', an HCV enzyme.
- The active substance in **Sovaldi (sofosbuvir)** blocks the action of 'NS5B RNA-dependent RNA polymerase', an HCV enzyme.
- The active substances in **Harvoni (ledipasvir and sofosbuvir)** block two proteins essential for the HCV to multiply. Sofosbuvir blocks the action of the enzyme 'NS5B RNA-dependent RNA polymerase', while ledipasvir targets the protein 'NS5A'.

Four NASs were appraised in all eight jurisdictions, all of which were HCV products (Figure 7).

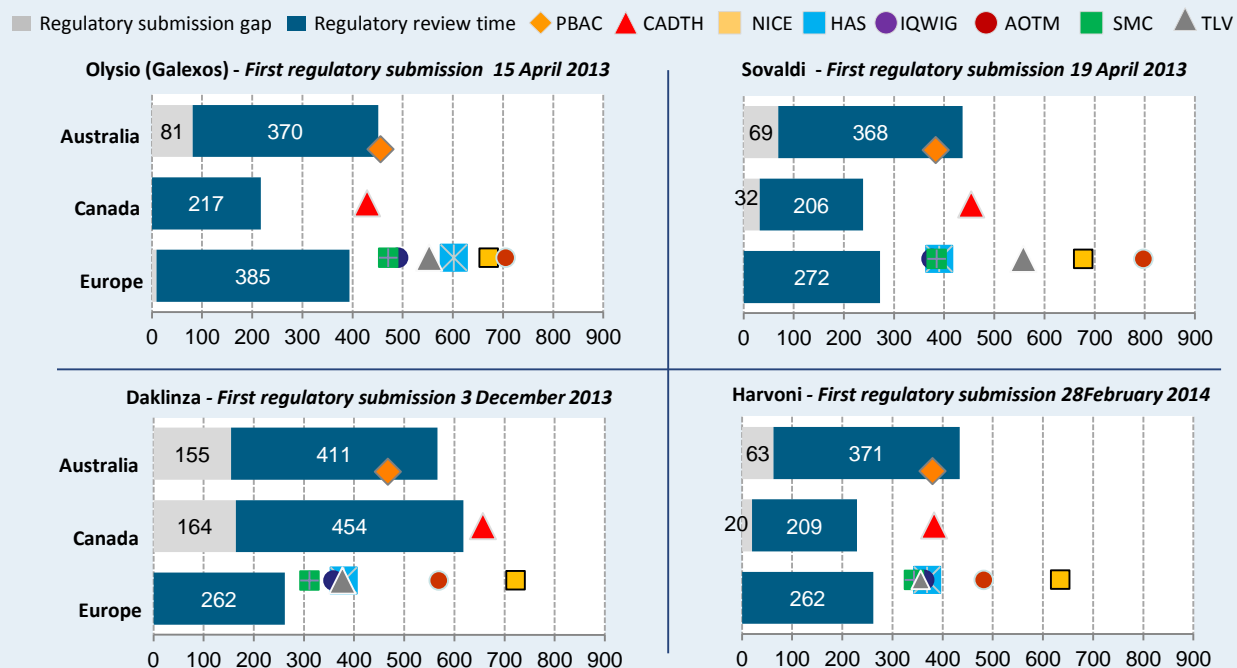
CIRS analysed products rolled out to eight jurisdictions and identified four products that received a decision by all HTA agencies. Interestingly, these were all new but costly HCV therapies. Figure 7 compares how the different HTA agencies perceived the value of these products, which led to various outcome across jurisdictions. France granted positive recommendation for all four products while Poland only recommended reimbursement for Olysio with restriction.

A wide range of rollout times was observed across key jurisdictions in Europe; England and Poland had the longest rollout times for all four HCV products (Figure 8).

Three of the four HCV products were submitted to EMA for review first, followed by submission to TGA and Health Canada. Olysio was submitted to Health Canada first, nine days earlier than submission to EMA. Except for Daklinza, TGA took the longest time to approve these products. The review times by EMA were relatively short for Daklinza, Sovaldi and Harvoni; all three received expedited review and an accelerated approval. Olysio was approved via standard route by EMA, which took approximately four months longer than the review of the other three products.

In Australia, Daklinza, Sovaldi and Harvoni received PBAC recommendation before the regulatory approval, while for Olysio the recommendation was only a few days later than the approval. With the TGA/PBAC parallel process, a TGA delegate provides an overview of regulatory status to PBAC during the HTA decision-making process, allowing the agency to potentially make a reimbursement recommendation even before a formal TGA approval is granted.

Figure 8: Rollout timelines (days) comparison across all jurisdictions



FEATURES OF AUSTRALIA

Anti-cancer & immunomodulating products represented the majority of NASs appraised by PBAC, 36% in 2014 and 52% in 2015 (Figure 9).

Anti-cancer & immunomodulating drugs represented the highest proportion of new medicines appraised by PBAC (20 out of 46 total appraisals). Seven of these products were also given orphan designation and 11 took advantage of the TGA/PBAC parallel review process, with the aim of shortening the overall timeline for access.

However, looking at final HTA decisions, anti-cancer & immunomodulating products received a similar rate of negative recommendations (55%) compared with other products (57%; Figure 10) and 4 of 7 anti-cancer & immunomodulating products with orphan designations were not recommended for listing by PBAC. Three anti-cancer & immunomodulating products were submitted under the Highly Specialised Drug (HSD) programme, which aims to provide access to specialised medicines for the treatment of chronic conditions, which may be restricted in prescription and supply because of their clinical use and other special features. HSD normally applies to expensive medications such as treatments for cancer, HIV and organ transplantation [1]. The three anti-cancer & immunomodulating products under HSD submission were all not recommended for listing due to failure to establish cost-effectiveness.

The TGA/PBAC parallel process proved to be beneficial for reducing time gaps between regulatory approval to HTA decision (Figure 11).

Of the 46 of the drug submissions, 26 were reviewed through the TGA/PBAC parallel process. The parallel process played an important role in shortening the time to the first HTA decision. PBAC decisions were made a median of less than 1 month after TGA approval in 2014 (Figure 10). However, one downside to this approach is the potential waste of HTA resource if a negative regulatory decision was granted based on an unfavourable benefit-risk product profile. In Australia, if regulatory approval is not granted for a product that goes through parallel review, the sponsor company pays a cost-recovery fee to compensate for the resource used for HTA evaluation.

Analysis of regulatory and HTA review revealed that when TGA took a longer than average time to review products, those products typically received a negative recommendation from PBAC, opening the question as to whether similar issues were called into question by both agencies.

1. Australian government Federal Register of Legislation. *National Health (Highly specialised drugs program) Special Arrangement 2010 (PB 116 of 2010)*. Available at <https://www.legislation.gov.au/Series/F2010L03140>

Figure 9: Type of products appraised at Australia

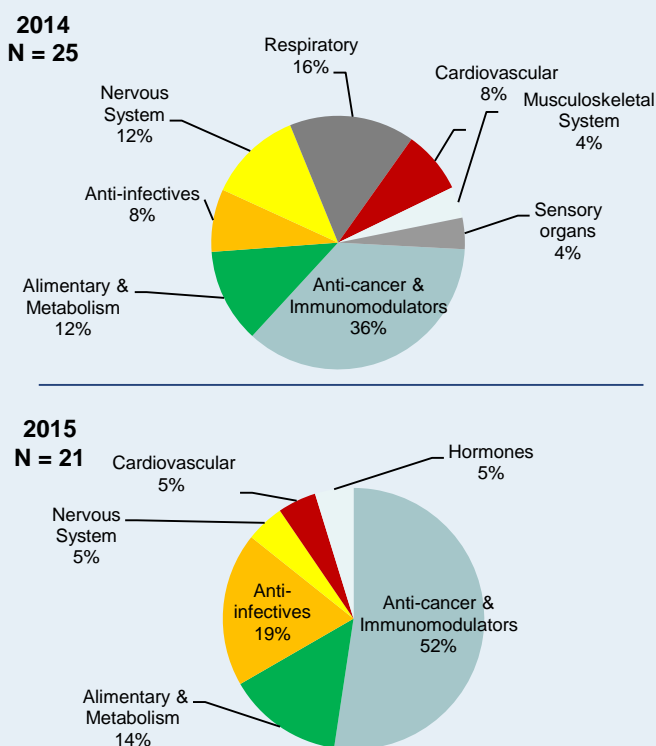


Figure 10: Outcome for anti-cancer & immunomodulators and orphan products

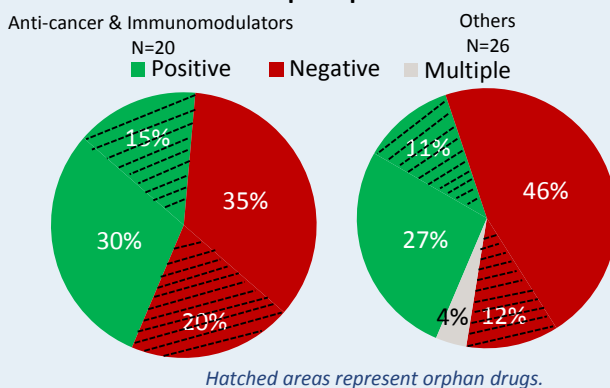


Figure 11: Rollout timelines in Australia by HTA outcome*

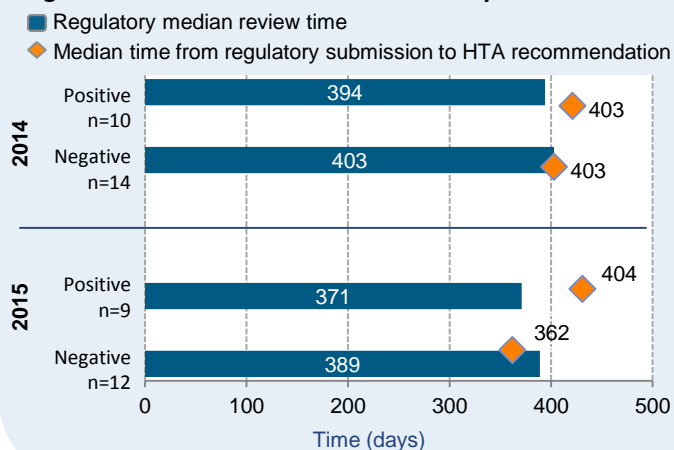


Figure 12: Rollout timelines by HTA outcome

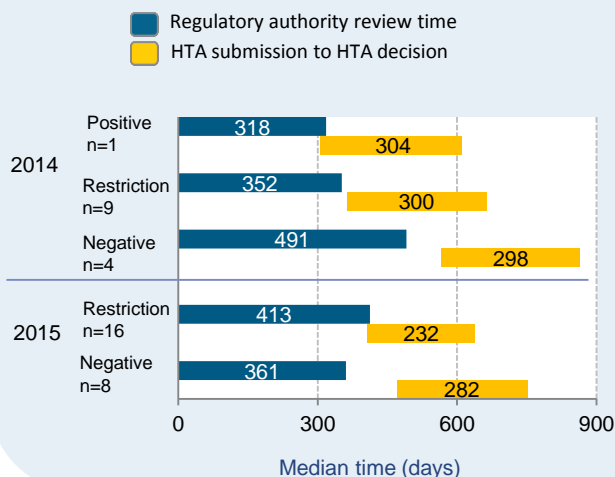
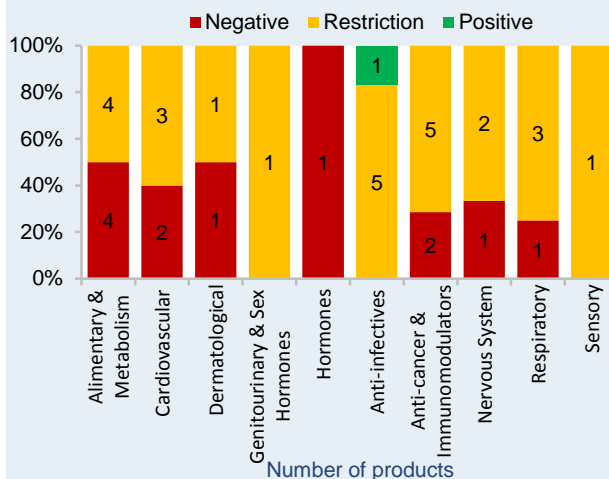


Figure 13: HTA outcome by therapeutic area



For products that eventually received a negative HTA decision, the company submission gap from Health Canada approval to CADTH submission was a median of approximately 3 months. In general, the parallel review route was not widely used by companies in Canada in 2014 and 2015. (Figure 12).

The Health Canada/CADTH parallel review process is available for companies who aim to shorten the time to market, but the Canadian system differs from the Australia system in that submission to CADTH should be within 90 calendar days before the date of anticipated NOC from Health Canada. Figure 12 showed that for most products, the companies tended to submit to CADTH about the same time or just before Health Canada approval; however, for products that eventually received a negative recommendation, the submission gap was 3 months.

Major therapeutic groups for products assessed by CADTH were anti-cancer & immunomodulators, alimentary & metabolism and anti-infective (Figure 13).

Most products received recommendation for listing with criteria/conditions in Canada; only one anti-infective product was granted a positive recommendation during 2014 and 2015.

Products that received expedited regulatory review made up 21% and 17% of all NASs appraised by CADTH in 2014 and 2015, with overall rollout times shorter for these products than for those approved via the standard route at Health Canada (Figure 14).

Whilst expedited regulatory review at Health Canada was a median of 157 and 221 days shorter than standard review in 2014 and 2015 (Figure 14), regulatory review type had no impact on the HTA review timelines. However, the parallel review process was used more for products undergoing expedited review, with 73 days between regulatory approval and HTA review in 2014 and a 7-day gap in 2015. The two factors of faster Health Canada approval and shorter submission gap to CADTH led to an overall shortened rollout times for expedited review products. Despite similar median HTA review times for products receiving standard and expedited regulatory assessment, the variance of the review time for standard review was greater than expedited review (Figure 15).

Figure 14: Rollout timelines by regulatory approval type

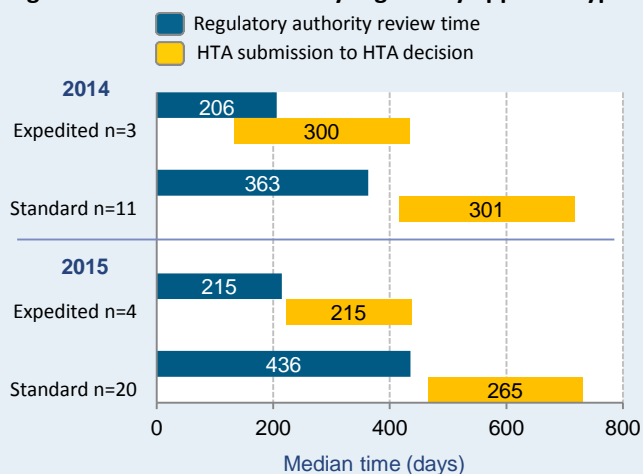
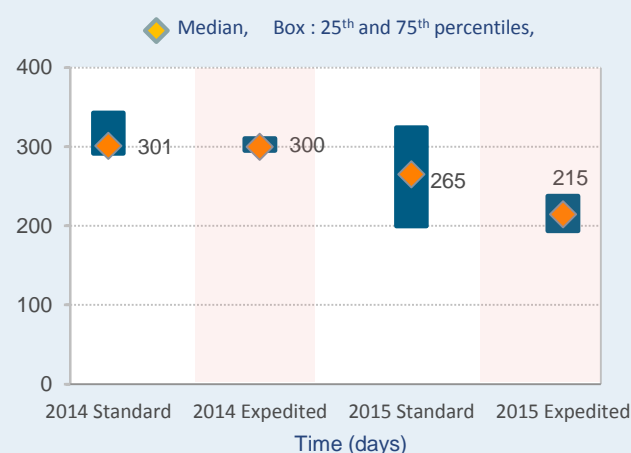


Figure 15: HTA review time by regulatory approval type

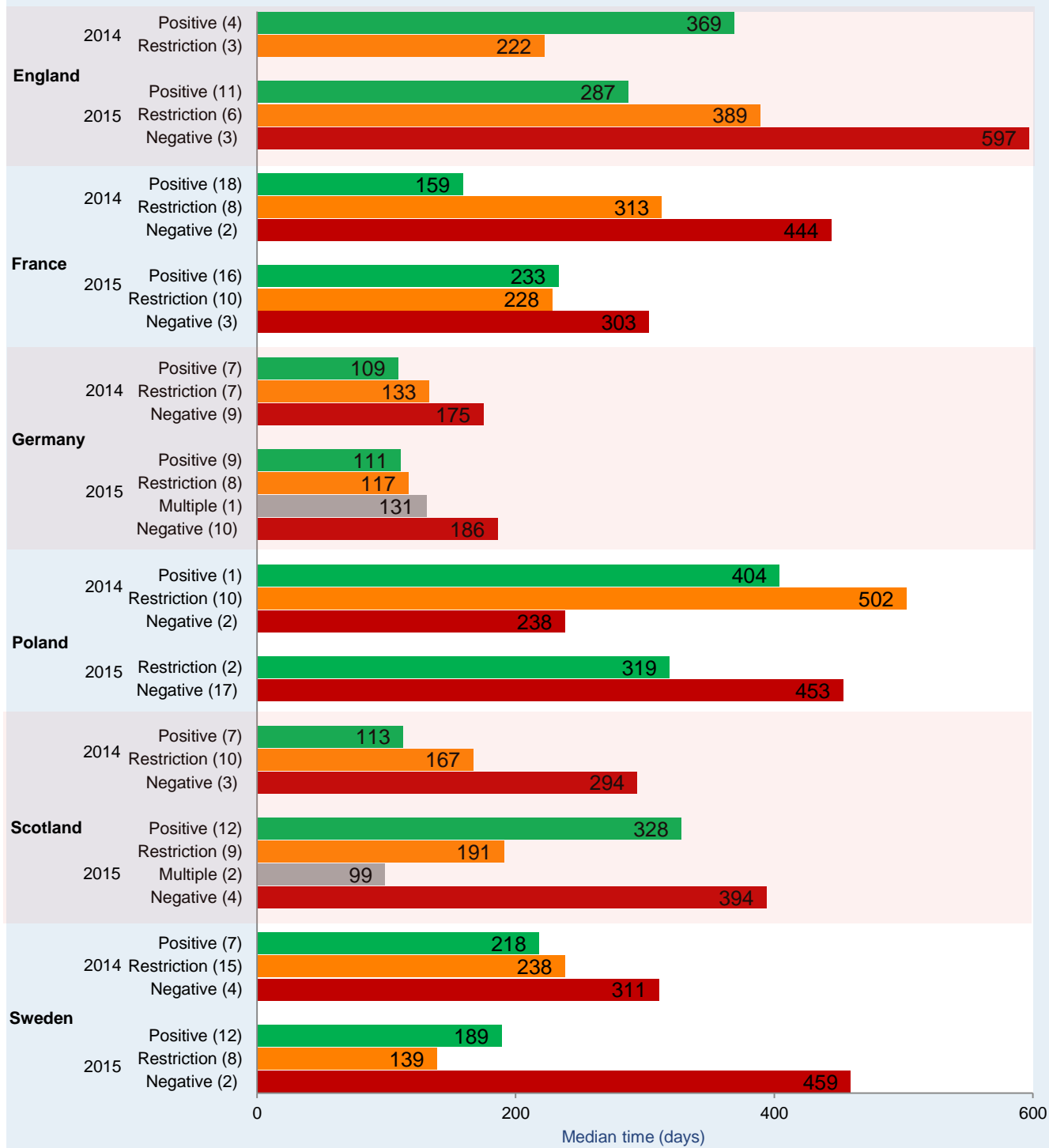


FEATURES OF EUROPE

Generally, products that received a negative recommendation took longer to receive a HTA decision from the time of EMA approval (Figure 16).

Despite the fact that new drugs were approved at the centralised level, Figure 16 showed divergent timing from regulatory approval to HTA recommendation across the jurisdictions. The quickest HTA review time for products that received a positive decision occurred in Germany, at a median of 109 days and 111 days in 2014 and 2015.

Figure 16: Median time comparison by HTA outcome from regulatory approval to HTA recommendation



The data on individual products were collected for NASs appraised by HTA agencies in 2014 and 2015, using information available from agencies' official websites.

Only the first recommendation based on the first assessment reports were considered. HTA agencies provide recommendations/advice on the medicines that can be reimbursed by the healthcare systems. In Australia, England, Scotland and England, HTA recommendations not to list are binding. However, in Canada, France, Germany and Poland, a relevant decision-making body such as the Ministry of Health makes the final reimbursement decision. PBAC can defer a decision pending the provision of specific additional information that would be relevant and important to its decision.









The HTA decisions in this report have been classified into the following categories: *positive*, *positive with restrictions* and *negative*. Figure 17 illustrates how the specific decisions by the eight HTA systems fall into this trichotomous categorisation.

There are a number of cases that reflected the different HTA approaches based on the regulatory approved label; these are illustrated in figure 18.

Scenario 1: For France and Germany, the HTA agencies' assessment of the added therapeutic benefit rating for a product may be for a sub-indication of the approved regulatory label, with possible different assessment outcomes for each sub-indication. The final HTA outcome for these cases was classified in this study as *positive with restrictions*.

Scenario 2: In the case in which more than one HTA dossier was submitted by companies for the same drug based on different sub-indications of an approved regulatory label, the final HTA outcome was classified as *multiple*. In this study, this occurrence was observed in Australia, Germany and Scotland.

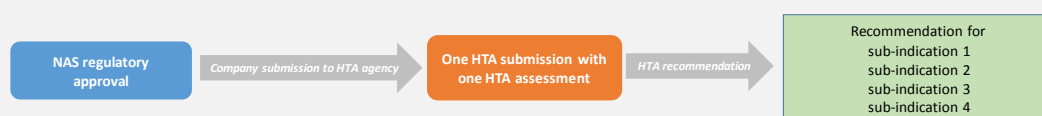
Figure 17: Trichotomous categories of HTA decisions

	Australia 	Canada 	England 	France 	Germany 	Poland 	Scotland 	Sweden 
Positive	List	List	Recommended	Major benefit Important benefit	Major added benefit Considerable added benefit	Recommended	Accepted	General subsidy
Positive with restrictions		List with clinical criteria and/or conditions	Managed Access Scheme Optimised Indications differ from Market Authorisation	Moderate benefit Minor benefit	Minor added benefit Non-quantifiable added benefit	Recommends with restrictions	Accepted with restrictions	Restricted subsidy
Negative	Do not list	Do not list at the submitted price Do not list/reimburse	Not recommended	Lesser benefit	No added benefit proven Less benefit	Not recommended	Not recommended	No subsidy

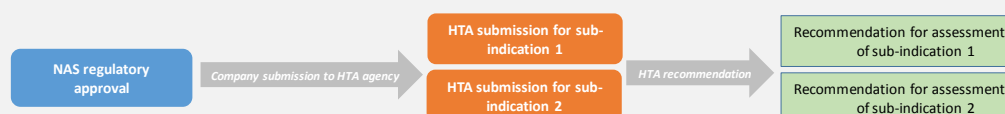
Where a green outline indicates that drug reimbursement is possible while a red outline indicates that drug reimbursement is not possible

Figure 18: Special cases of HTA decisions

Scenario 1 – HTA recommendations were based on assessments of sub-indication of approved regulatory label



Scenario 2 – HTA recommendations were multiple as companies submitted dossier based on sub-indications of approved regulatory label



Health Technology Assessment (HTA)

For the purpose of this project, HTA refers to the assessment and appraisal of pharmaceuticals prior to reimbursement. The HTA process includes clinical assessment, economic assessment and an appraisal that results in either a coverage recommendation or decision.

First assessment report

The first assessment report is the earliest assessment available. Note that for some drugs; for example, those with the same INN, strength and presentation, are listed more than one time. The reasons may be two fold – consideration of the drug in more than one indication or re-assessment of the drug by the agency.

Regulatory review time

Time (calendar days) calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. Note: The EMA approval time includes the EU Commission time.

HTA review time

Time (calendar days) calculated from the date of submission to the date of decision by the HTA agency. Note: The HTA decision refers to the decision at national level.

Rollout time

Date of submission at the regulatory agency to the date of HTA decision at the target jurisdiction (calendar days).

Expedited approval

In this Briefing, expedited review refers to EMA Accelerated Assessment and Canada Priority Review/

Submission gap

Date of regulatory approval to the date of HTA submission to the target jurisdiction (calendar days).

Parallel review

Pharmaceutical companies submit evidence to the regulatory agency that prove efficacy, safety, quality of the product. However, during the regulatory review process, companies submit dossiers to HTA bodies so that the two review steps can occur in parallel. Following the regulatory approval, HTA recommendation will be provided to companies for drug reimbursement.

New active substance (NAS)

A chemical, biological, biotechnology or radiopharmaceutical substance that has not been previously available for therapeutic use in humans and is destined to be made available as a 'prescription only medicine', to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans. The term NAS also includes:

- An isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously available as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously available
- A biological or biotech substance previously available as a medicinal product, but differing in molecular structure, nature of source material or manufacturing process and which will require clinical investigation.
- A radiopharmaceutical substance that is a radionuclide or a ligand not previously available as a medicinal product. Alternatively, the coupling mechanism linking the molecule and the radionuclide has not been previously available.

Exclusion criteria

Applications that are excluded from the study

- Vaccines
- Any other application, where new clinical data were submitted.
- Generic applications.
- Those applications where a completely new dossier was submitted from a new company for the same indications as already approved for another company.
- Applications for a new or additional name, or a change of name, for an existing compound (i.e. a 'cloned' application).



Report prepared by

Tina Wang, MSc, Manager, HTA Programme
Jesmine Cai, PhD, Senior Analyst
Iga Lipska, MD, PhD, former Research Fellow
Neil McAuslane, PhD, Director
Lawrence Liberti, PhD, RPh, RAC, Executive Director

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
United Kingdom

Email: cirs@cirsci.org
Website: www.cirsci.org

©2017, Centre for Innovation in Regulatory Science, Ltd