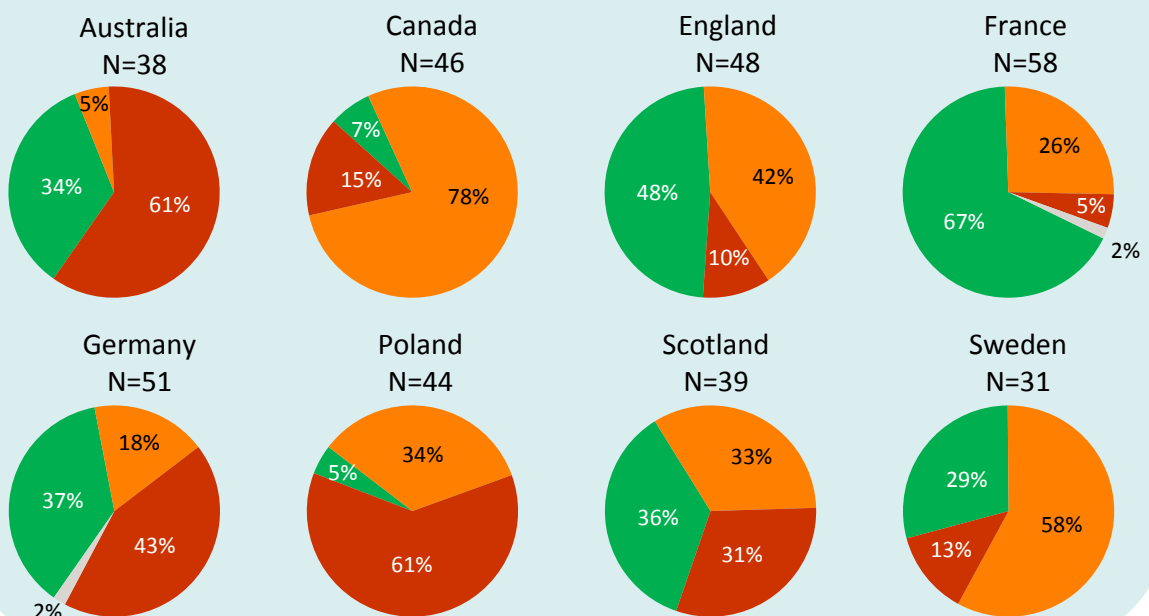


Review of HTA outcomes and timelines in Australia, Canada and Europe 2014-2017



Figure 1: First HTA recommendations: comparisons across key jurisdictions 2016 and 2017

■ Positive
 ■ Restriction
 ■ Negative
 ■ Multiple
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SUMMARY

Introduction

Timely recommendation for drug reimbursement by health technology assessment (HTA) agencies is critical to ensure that patient access to medicines of therapeutic value is not delayed. As part of an ongoing study to monitor regulatory and HTA performance, CIRS has been collecting data on new active substances (NASs) appraised between 2014 and 2017 by eight health technology assessment (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; both Common Drug Review [CDR] and pan-Canadian Oncology Drug Review [pCODR]), English 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 NASs approved 2012-2017 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 9, the HTA recommendations in this report have been classified as *positive*, *positive with restrictions* or *negative*. Figure 24 illustrates how the specific recommendations by the eight HTA systems are captured within this trichotomous categorisation. In cases in which more than one HTA dossier was submitted by a company 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 50% of NASs approved by regulatory agencies received a *positive* or *positive with restrictions* first recommendation by HTA agencies in most of the studied jurisdictions except Australia and Poland. During the period of 2016-2017, France and England had the highest proportion of positive/positive with restrictions recommendations for NASs appraised by HTA agencies.
- Of all studied HTA agencies, Germany had the highest percentage of and greatest increase in products recommended within a year from regulatory approval (96% in 2017).
- Australia had the shortest overall median time between regulatory and HTA recommendation (43 days) in 2014-2017, followed by Germany (130 days).
- CIRS analysed NASs rolled out to seven jurisdictions, excluding Poland, and identified 24 NASs that received a recommendation by all HTA agencies during the period of 2014-2017. Interestingly, when evaluated as an aggregate, anti-infectives were given a first HTA recommendation faster (based on time from regulatory approval to HTA recommendation) than anti-cancer & immunomodulators.



In Australia, the TGA/PBAC parallel process reduced the time from regulatory approval to HTA recommendation.

Of 88 drug submissions in Australia from 2014 to 2017, 58 were reviewed through the TGA/PBAC parallel process. However, in the last two years, the proportion of NASs going through the parallel process decreased from 76% in 2014-2015 to 52% in 2016-2017. The parallel process played an important role in shortening the time until the first HTA recommendation. In 2016-2017, the difference between the sequential and parallel process for median time taken from regulatory approval to HTA submission was 32 days faster than in 2014-2015.



In Canada, in 2016-2017 NASs had a shorter rollout time and a higher proportion of positive/ positive with restrictions first HTA recommendations than in 2014-2015.

In 2014-2017, approximately half of the NASs submitted for HTA recommendation underwent the Health Canada/ CADTH parallel review process. The parallel review process was a success in reducing the time taken to reach the first HTA recommendation. The reduction in median time taken from regulatory approval to HTA recommendation due to the parallel process was 49 days shorter in 2016-2017 than in 2014-2015 (Figure 20).

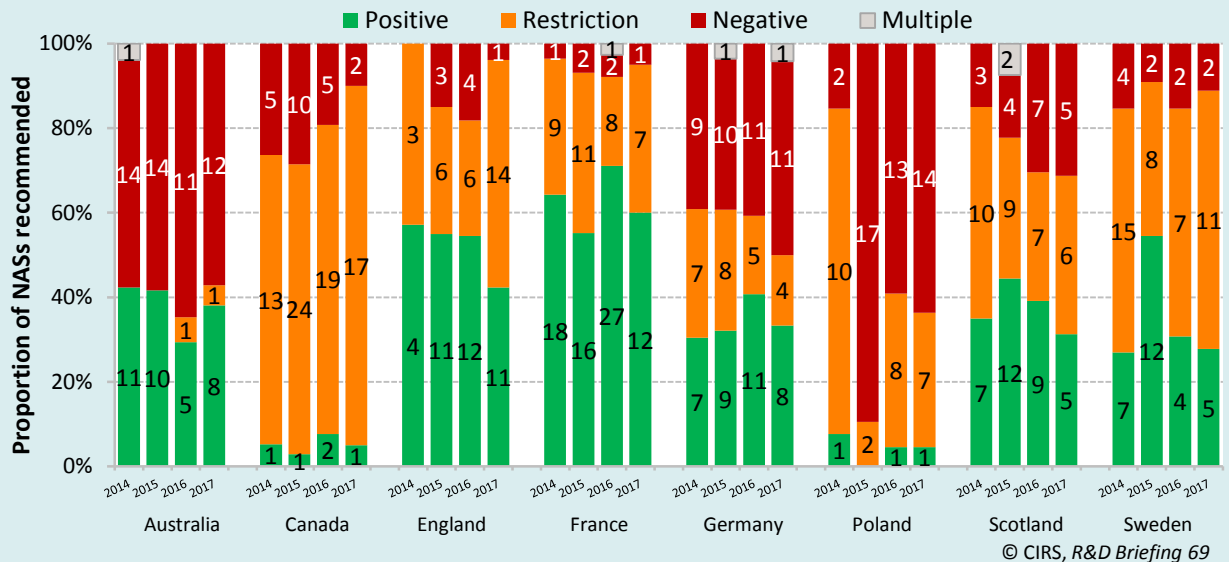


In Europe, the lag between EMA approval and HTA recommendations varied across the European jurisdictions, from 130 median days in Germany to 510 median days in Poland.

In the studied European jurisdictions, the time from EMA approval to HTA recommendation was generally longer for those NASs receiving a negative HTA outcome. In Germany, Poland and Sweden, anti-cancer & immunomodulators had a shorter time from regulatory approval to HTA recommendation compared with other therapeutic areas.

OVERVIEW OF NEW DRUG RECOMMENDATIONS

Figure 2: First HTA recommendation comparison across key jurisdictions by year of HTA recommendation



In 2016 and 2017, France and England had the highest proportion (93% and 90%) of positive/positive with restrictions recommendations for NAs appraised by HTA agencies (Figure 1).

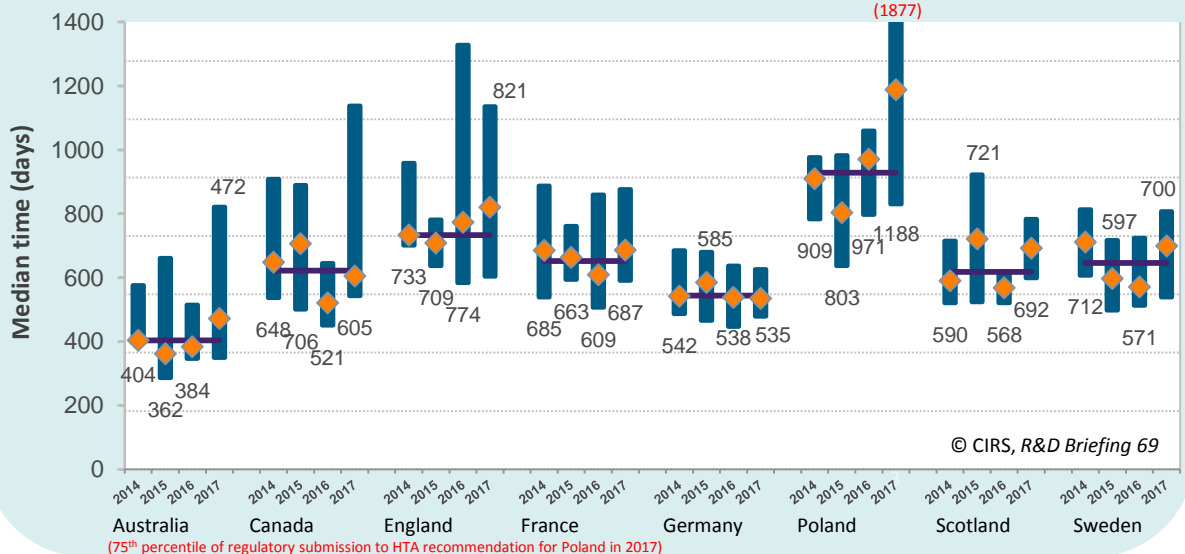
France appraised the highest number of NAs approved by EMA via the centralised procedure in 2016-2017, (58 NAs), while Sweden appraised the fewest (31) (Figure 1). In England, the number of NAs assessed increased over the years from 27 in 2014-2015 to 48 in 2016-2017. This is a reflection of the changes in the NICE appraisal process for cancer drugs. Previously, cancer drugs were selected for technology appraisal using published elimination and prioritisation criteria. Since July 2016, all new cancer drugs are referred to NICE for appraisal.

More than 50% of NAs 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, Canada showed the greatest increase in proportion of NAs appraised receiving a positive or positive with restrictions recommendation from 74% in 2014 to 90% in 2017 (Figure 2).

Australia had the fastest median rollout time from regulatory submission to HTA recommendation (404 days), followed by Germany (544 days) in 2014-2017 (Figure 3).

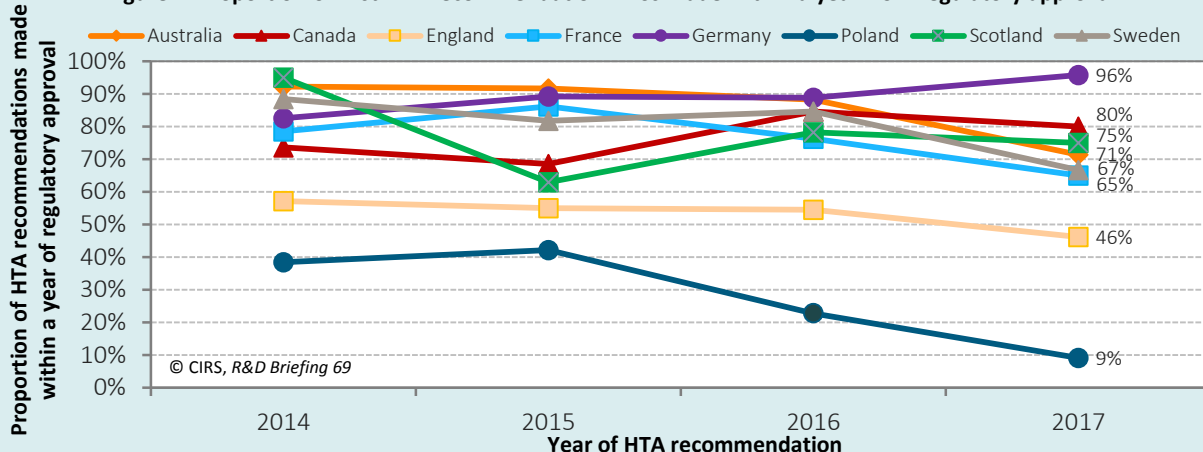
Over these four years, the median rollout time has been relatively constant with the exception of Australia, England and Poland, which showed an increase in 68, 88 and 279 days respectively from 2014 to 2017. It took more than double the time from regulatory submission to HTA recommendation in Poland compared with Australia.

Figure 3: Rollout time from regulatory submission to HTA recommendation by year of HTA recommendation



SYNCHRONISATION OF REGULATORY AND HTA RECOMMENDATIONS

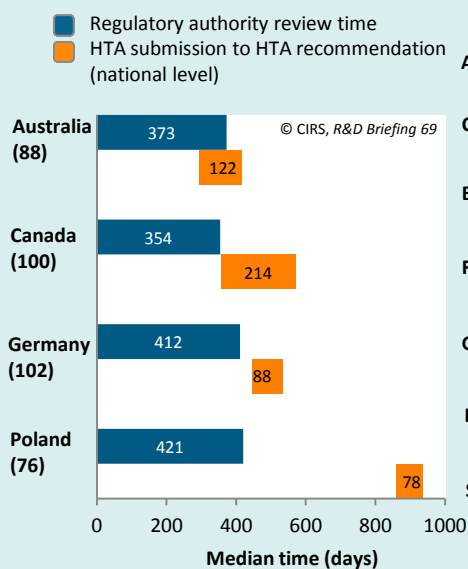
Figure 4: Proportion of first HTA recommendation NASs made within a year from regulatory approval



Of all HTA agencies, IQWiG had the highest percentage of and greatest increase in NASs recommendations made within a year from regulatory approval: 83% in 2014 to 96% in 2017 (Figure 4).

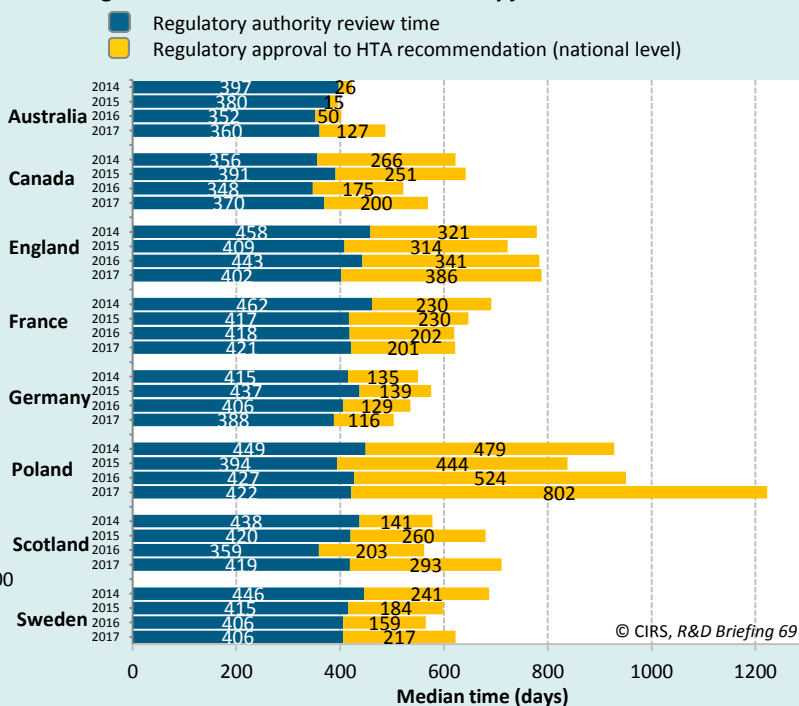
Comparing all jurisdictions, IQWiG appraised the most NASs within a year from regulatory approval. This can be attributed to a combination of short median HTA review time (88 days) and company submission strategy to HTA agencies (35 days from regulatory approval to HTA submission) (Figure 5). Although Poland had a shorter HTA appraisal time (78 days), it took a longer time for the product to reach patients due to the gap between regulatory approval and HTA submission.

Figure 5: Breakdown of rollout time in jurisdictions where HTA submission date is provided 2014-2017*



* Only jurisdictions with HTA submission dates available in the public domain were included in this figure.

Figure 6: Breakdown of rollout time in key jurisdictions 2014-2017

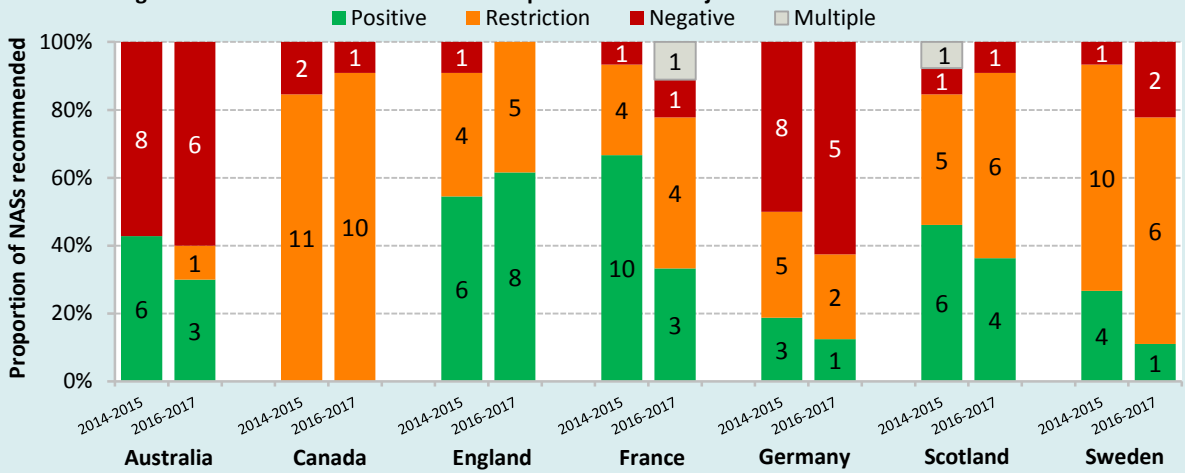


Patients in Australia had the shortest median time between regulatory approval and HTA recommendation of 43 days in 2014-2017 (Figure 6).

PBAC had the shortest overall median time between regulatory approval and HTA recommendation, suggesting that the proactive approach within Australia to move toward synchronising the timing of HTA and regulatory recommendation is achieving its purpose. Over 2014-2017 in Australia, the median regulatory approval to HTA recommendation time increased. This may have been influenced by the increase in HTA submissions through the sequential process over the study period. A regulatory/HTA parallel process is available in Australia and Canada. In Australia, since 2011, after the regulatory application is accepted for review, a reimbursement submission may be sent to the PBAC for parallel review. The Health Canada/CADTH parallel review process is available for companies who aim to shorten the time to market since 2012, but the Canadian system differs from the Australia system in that submission to CADTH should be within 90 days before the date of anticipated NOC from Health Canada. However, effective from 2 April 2018, CADTH submission criteria will be changed to within 180 days before the anticipated NOC from Health Canada.

TWENTY-FOUR NASs APPRAISED BY ALL SEVEN JURISDICTIONS IN 2014-2017

Figure 7: First HTA recommendation comparison across all jurisdictions for 24 common NASs

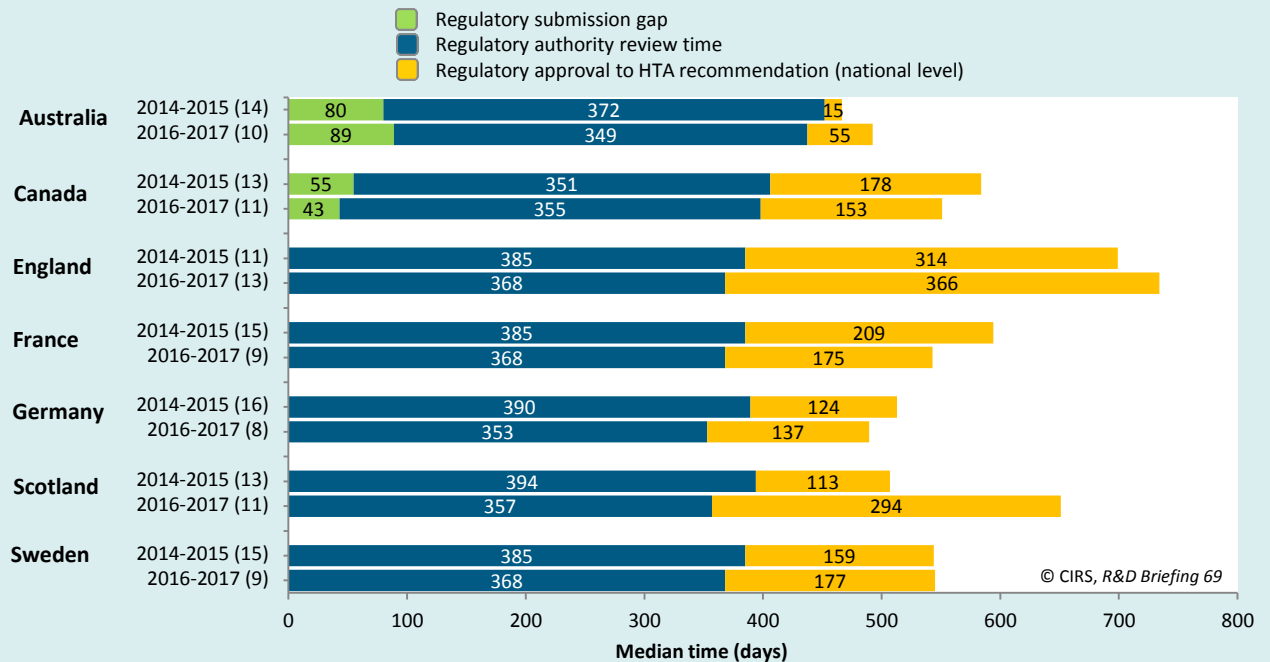


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England had the highest proportion of *positive/ positive with restrictions* recommendations for NASs appraised by all seven HTA agencies.

CIRS analysed NASs rolled out to seven jurisdictions, excluding Poland, and identified 24 NASs that had been approved between 2012 and 2017 by all seven regulatory agencies and have also received a HTA recommendation between 2014 and 2017 in all HTA agencies. Figure 7 compares how the different HTA agencies perceived the value of these NASs, which led to divergent first recommendations across jurisdictions in 2014-2017. In England, all but one NAS received a positive/ positive with restrictions recommendation (96%) while in Australia and Germany, approximately half of the NASs received a negative recommendation. In this cohort, none of the NASs had the same HTA recommendation but five NASs received positive/ positive with restrictions first HTA recommendations from all seven jurisdictions.

Figure 8: Breakdown of rollout time (days) across all jurisdictions for 24 common NASs



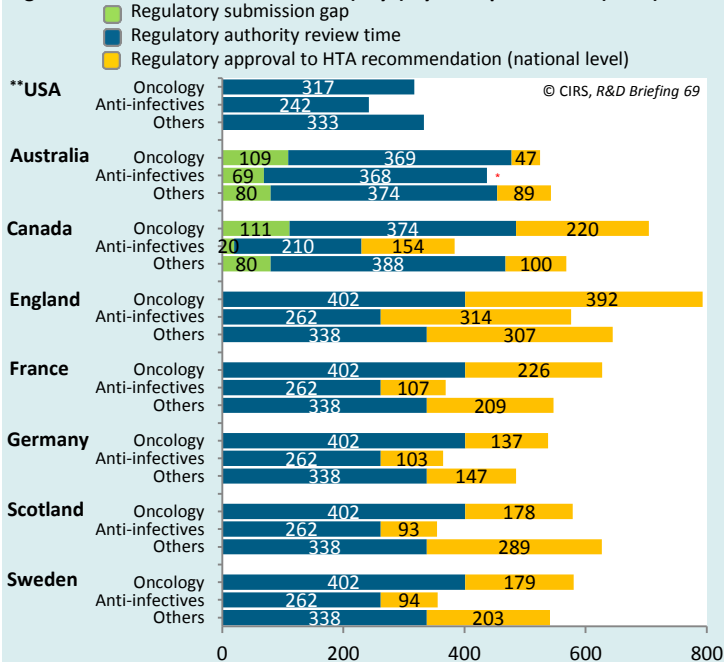
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Australia had the shortest median time from first world-wide regulatory submission to jurisdictional HTA recommendation (497 days) although it had the largest median regulatory submission gap (80 days).

Twenty of the 24 NASs that were appraised by all seven HTA agencies were submitted to EMA for review first, followed by submission to TGA and Health Canada. As 4 NASs were submitted to Health Canada first, NASs were submitted to Health Canada 31 median days earlier than to TGA. Although NASs took the longest time to reach TGA compared with the other regulatory agencies, Australia had the shortest overall time taken from first world-wide regulatory submission to HTA recommendation. This can be attributed to the TGA/PBAC parallel process. In the parallel process, a TGA delegate provides an overview of regulatory status to PBAC during the HTA recommendation-making process, allowing the agency to potentially make a reimbursement recommendation even before a formal TGA approval is granted. In 2016-2017, France showed the greatest decrease in median rollout time taken (85 days).

FOCUS ON THERAPEUTIC AREA FOR 24 COMMON NASs

Figure 9: Breakdown of rollout time (days) by therapeutic area (n=24)*



** Submission gap not calculated for USA as the submission gap is calculated as the time from date of submission at the first regulatory agency in Australia, Canada and Europe to the date or regulatory submission to the target agency.

* Regulatory approval to HTA recommendation (national level) for anti-infectives in Australia took -28 days.

Out of the 24 NASs appraised by all seven jurisdictions in 2014-2017, anti-cancer & immunomodulators (ATC code L, 12 NASs) represented the majority of NASs, followed by anti-infectives (ATC code J, 7 NASs).

Anti-cancer & immunomodulating drugs represented the highest proportion of new medicines appraised by all seven jurisdictions, compared to anti-infectives (7 NASs) and other therapeutic areas (5 NASs). Interestingly, all seven anti-infectives are Hepatitis C drugs.

In this cohort, when evaluated as an aggregate, anti-infectives received HTA recommendation faster than anti-cancer & immunomodulators.

Although anti-cancer & immunomodulators represented the majority of NASs appraised by all seven jurisdictions, anti-infectives showed the shortest median time from first world-wide regulatory submission to HTA recommendation (Figure 9) as compared with anti-cancer & immunomodulators. In Australia, first HTA recommendation for anti-infectives were received a median of 28 days earlier than regulatory approval.

The short median rollout time for anti-infectives may be a reflection of the more frequent use of expedited review pathways. Expedited regulatory pathways were used for a higher proportion of anti-infectives than anti-cancer & immunomodulators in USA, Canada and Europe (Figure 10). In this cohort of NASs, there are no expedited NASs in Australia, as an expedited review programme was introduced by TGA in 2017.

* Oncology in Figures 9-12 refers to anti-cancer and immunomodulators (ATC code L).

Figure 10: First HTA recommendation comparison by regulatory approval type (n=24)*

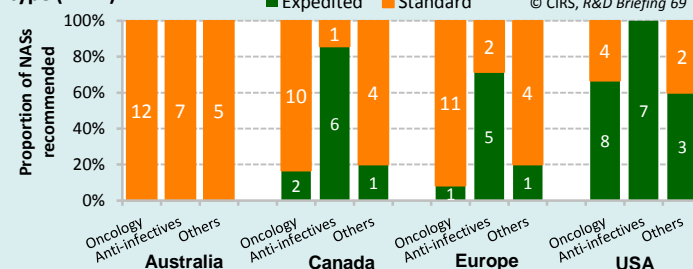


Figure 11: Time taken from regulatory approval to HTA recommendation by therapeutic area for 24 common NASs*

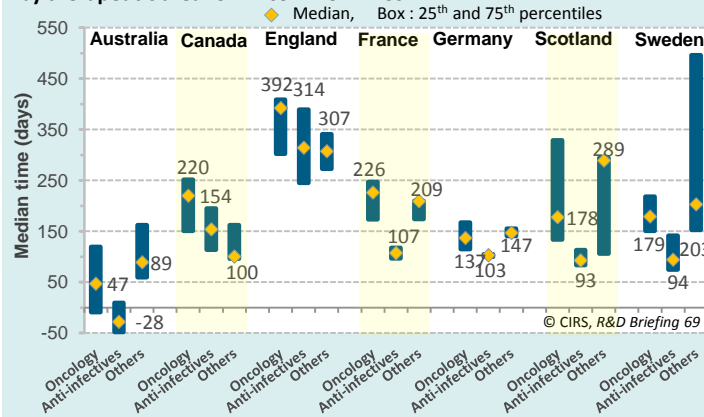
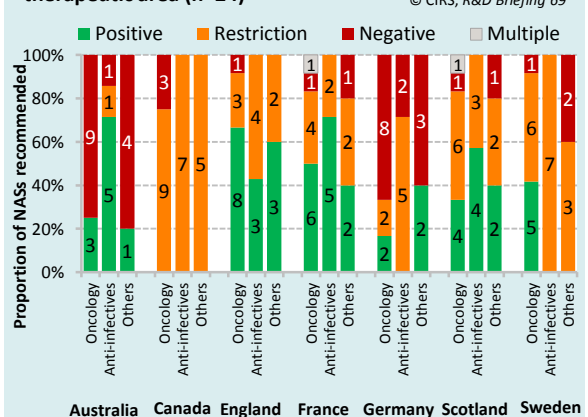


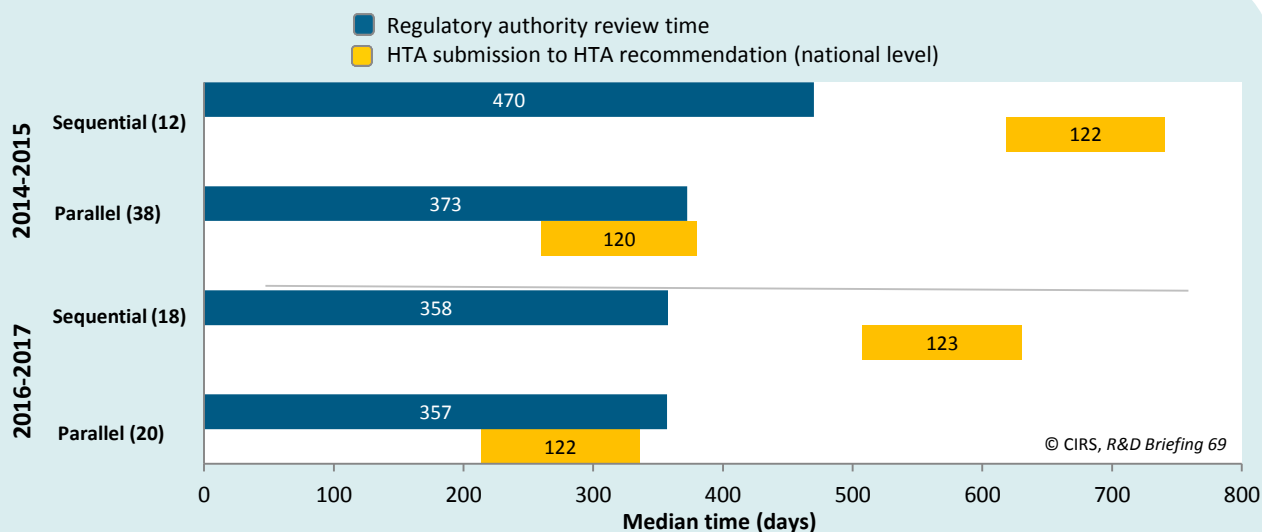
Figure 12: First HTA recommendation comparison by therapeutic area (n=24)*



Anti-infectives had a shorter time between regulatory approval and HTA recommendation (Figure 11) than anti-cancer & immunomodulators. The largest median difference was seen in France, where anti-infectives were 119 days faster than anti-cancer & immunomodulators. There was also a higher proportion of positive and positive with restriction recommendations for anti-infectives than for anti-cancer & immunomodulators (Figure 12). This may relate to the increased focus on Hepatitis C drugs. In 2014-2015, there were four Hepatitis C drugs appraised by all seven jurisdictions – Daklinza (daclatasvir), Olysio (simeprevir), Sovaldi (sofosbuvir) and Harvoni (ledipasvir and sofosbuvir). In the last two years, three more Hepatitis C drugs were appraised by all seven jurisdictions – Eplusa (elbasvir and grazoprevir), Viekirax (ombitasvir, paritaprevir and ritonavir) and Zepatier (elbasvir and grazoprevir).

FEATURES OF AUSTRALIA

Figure 13: Breakdown of rollout time (days) by type of sequence



Fewer drugs were submitted through the TGA/PBAC parallel process in 2016-2017 than in 2014-2015.

Under the TGA/PBAC parallel process, the TGA delegate’s overview is informative to PBAC consideration to appraise a drug and companies can submit the regulatory delegate overview up to a week prior to the PBAC meeting.

The proportion of drugs submitted through the TGA/PBAC parallel process dropped from 76% in 2014-2015 to 52% in 2016-2017 (Figure 13). Nevertheless, the parallel process played an important role in shortening the time to first HTA recommendation. In 2016-2017, the difference between the sequential and parallel process for median time taken from regulatory approval to HTA submission was 32 days faster than in 2014-2015 (Figure 14). The large variation seen in time taken from regulatory approval to HTA recommendation in sequentially reviewed products, especially in recent years, may be a reflection of company submission strategy since PBAC review time was constant (4 months).

In 2014-2017, 57% of both sequential and parallel NASs receive a negative first HTA recommendation (Figure 15).

Analysis of the first HTA recommendations 2014-2017 revealed that more than half of the drugs submitted in both sequential and parallel processes typically received a negative recommendation from PBAC (Figure 15). In 2016-2017, the parallel process had a higher proportion of negative reimbursement (65%) compared with the parallel process in 2014-2015 (55%).

Although the first HTA recommendation may be negative, given the faster time to first HTA recommendation due to the TGA/PBAC parallel process, NASs may still take a short time to obtain an overall positive recommendation after re-submissions.

Figure 14: Time taken from regulatory approval to HTA recommendation by type of sequence

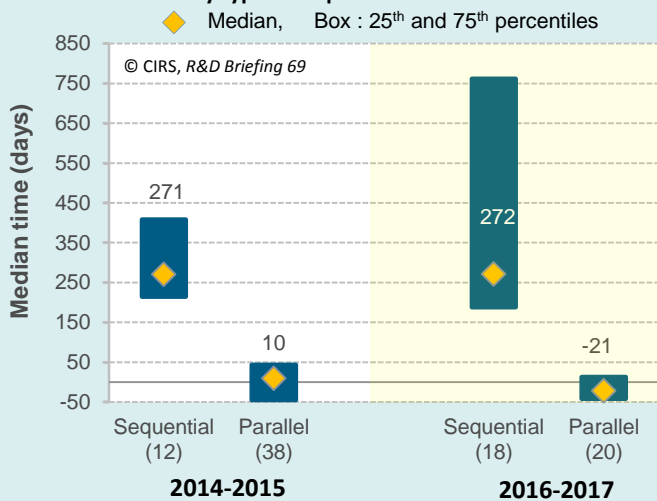
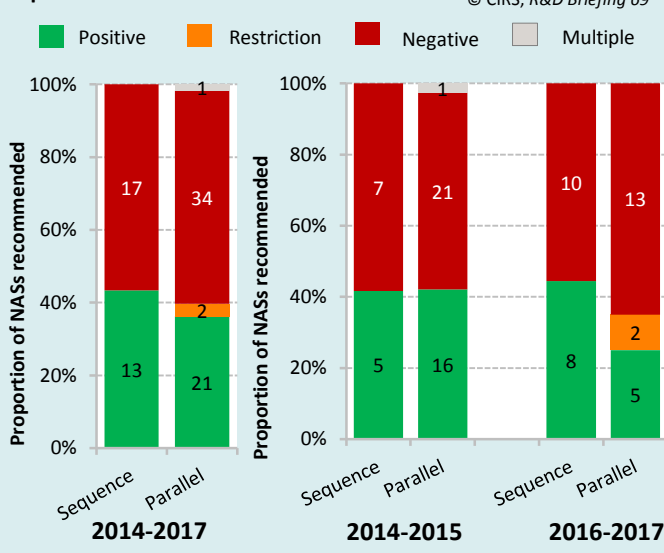


Figure 15: First HTA recommendation comparison by type of sequence



FEATURES OF CANADA

Compared with 2014-2015, NASs in 2016-2017 took a shorter time from regulatory approval to HTA recommendation (Figure 17) and had a higher proportion of positive/positive with restrictions recommendations (Figure 18).

This positive scenario may be due to a combination of company submission strategy and shorter HTA review time. In 2016-2017, the median time taken from regulatory approval to HTA submission time was 25 days faster and the HTA review time was 76 days shorter than in 2014-2015.

The top four therapeutic groups from the 100 NASs assessed by CADTH in 2014-2017 were anti-cancer & immunomodulators (40%), alimentary & metabolism (18%), anti-infectives (10%) and cardiovascular (9%). Looking at their overall time taken from regulatory approval to HTA recommendation, anti-infectives took the fastest time, followed by anti-cancer & immunomodulators and cardiovascular NASs (Figure 17).

In 2014-2017, 28 anti-cancer & immunomodulators were submitted under the pan-Canadian Oncology Drug Review (pCODR), which evaluates oncology drugs and make recommendations and guide the drug funding recommendations of provinces. Established in 2010, pCODR enables all provinces and cancer agencies to take a single approach to cancer drug evaluation. Anti-cancer & immunomodulators that underwent the pCODR evaluation were 14 median days faster from regulatory approval to HTA recommendation than those that underwent the CDR review process (Figure 17). In 2016-2017, the time taken from regulatory approval to HTA recommendation for anti-cancer & immunomodulators undergoing the pCODR process remained constant while those undergoing CDR was 117 median days faster compared to 2014-2015.

The Health Canada/CADTH parallel process shortened the overall time taken from regulatory approval to HTA recommendation (Figure 19).

In 2014-2017, approximately half of the NASs submitted for HTA recommendation underwent the Health Canada/CADTH parallel review process. In the last two years, there was an increased proportion of NASs submitted to the parallel process: 44% in 2014-2015 to 54% in 2016-2017. In 2014-2015, NASs that underwent the parallel process was 105 days faster than those that underwent the sequential process in terms of median time taken from regulatory approval to HTA recommendation. In 2016-2017, the difference between the parallel process in terms of median time taken from regulatory approval to HTA recommendation was even faster by 189 days compared with the sequential process.

There is a higher proportion of NASs submitted to the Health Canada/CADTH parallel process that undergo pCODR review than CDR review (Figure 20). Thus, the rollout time from regulatory submission to HTA recommendation for NASs submitted for pCODR review is shorter than those submitted for CDR review. In 2016-2017, NASs submitted to CDR had a faster time to HTA recommendation due to a combination of company submission strategy and shorter HTA review time than in 2014-2015.

Figure 17: Time from regulatory approval to HTA recommendation by therapeutic area

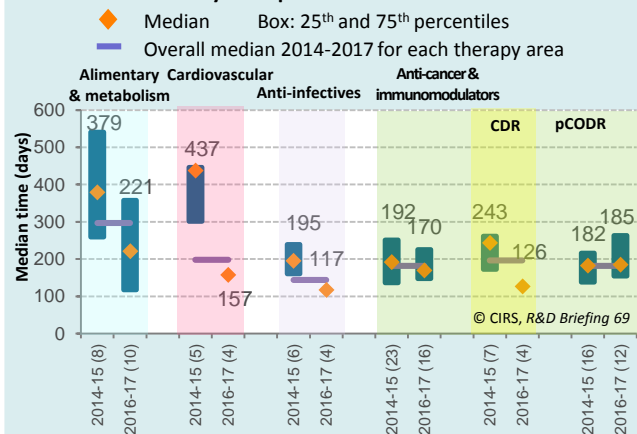


Figure 18: HTA outcome by therapeutic area

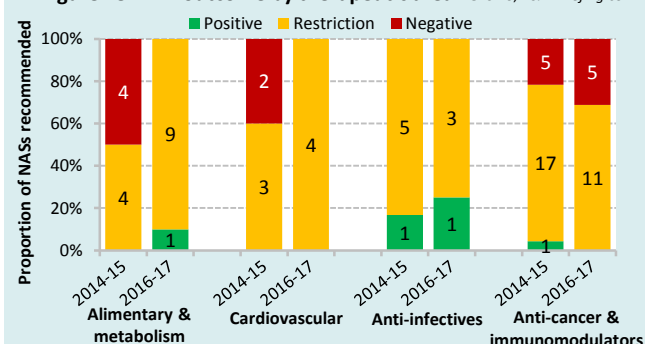


Figure 19: Breakdown of rollout time by type of sequence

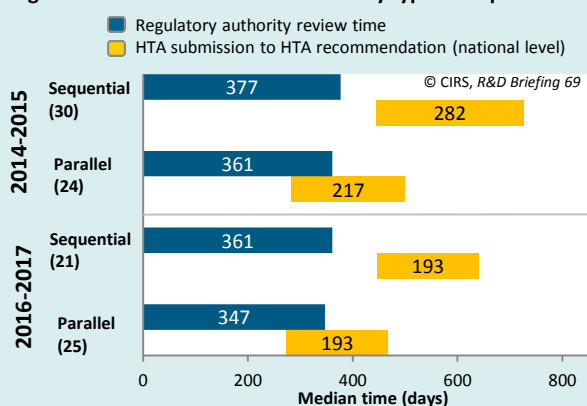
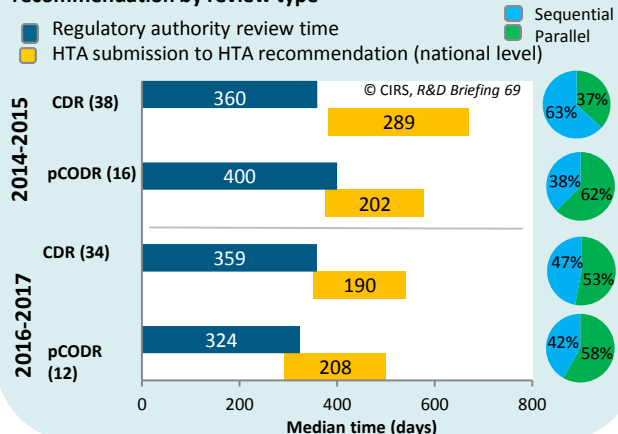
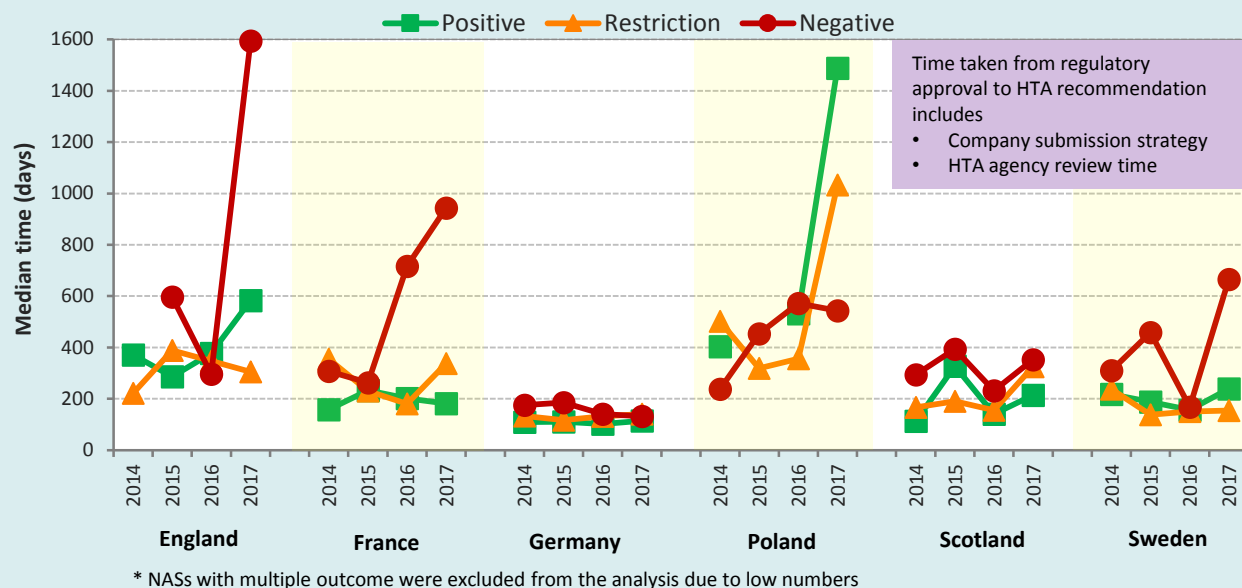


Figure 20: Time taken from regulatory approval to HTA recommendation by review type



FEATURES OF EUROPE

Figure 21: Time taken from regulatory approval to HTA recommendation by HTA outcome



Generally, NAs that received a negative recommendation took longer to receive a HTA recommendation from the time of EMA approval in 2014-2017 (Figure 21).

Despite the fact that new drugs were approved at the centralised level, Figure 21 shows divergent timing from regulatory approval to HTA recommendation across the jurisdictions. The shortest time from regulatory approval to HTA recommendation for NAs that received a positive recommendation occurred in Germany, at a median of 109 days in 2014-2017.

A wide range of rollout times was observed across key jurisdiction in Europe; In Germany, Poland and Sweden, anti-cancer & immunomodulators took a shorter time from regulatory submission to HTA recommendation compared with other NAs (Figure 22).

In 2014-2017, the majority of NAs approved in Europe were anti-cancer & immunomodulators. In Germany, Poland and Sweden, anti-cancer & immunomodulators had a shorter median time from regulatory approval to HTA recommendation than other NAs (Figure 23). Germany had the least variation in median rollout time and anti-cancer & immunomodulators were 15 days shorter than other therapeutic areas. In Poland and Sweden, anti-cancer & immunomodulators were more than a month faster than other therapeutic areas.

In 2014-2017, anti-cancer & immunomodulators took a longer time to reach a first HTA recommendation in England, France and Scotland. A similar trend was seen in NAs approved by all jurisdictions except Poland (*Focus on therapeutic area, Pg 6*). The largest difference was seen in Scotland, where anti-cancer & immunomodulators took three months longer from regulatory approval to HTA recommendation than other NAs. The introduction of Patient and Clinician Engagement (PACE) in May 2014, which involves patient and clinicians in the SMC decision-making process, may be influencing the time from regulatory approval to HTA recommendation. A higher proportion of anti-cancer & immunomodulators (62%) underwent the PACE process compared with the rest of the NAs (22%). NAs that undergo the PACE process take more than double the median time from regulatory approval to HTA recommendation compared with those NAs that do not (186 days longer).

Figure 22: Breakdown of rollout time (days) by therapeutic area

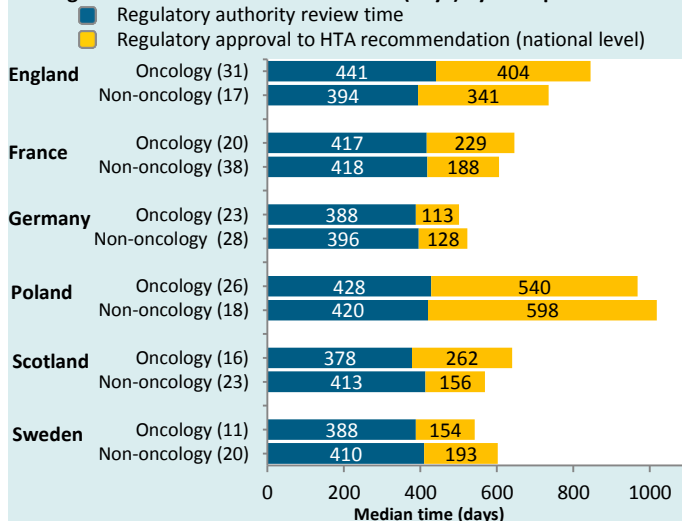
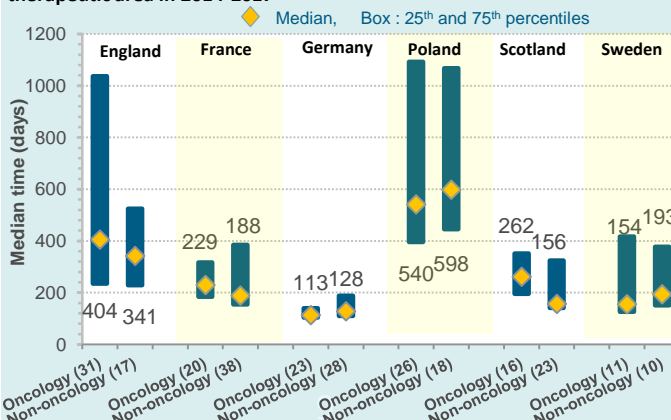


Figure 23: Time taken from regulatory approval to HTA recommendation by therapeutic area in 2014-2017*



* Oncology refers to anti-cancer and immunomodulators (ATC code L).

METHODOLOGY

The data on individual NASs were collected for NASs appraised by HTA agencies in 2014-2017, using public domain data derived from the 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 recommendation-making body such as the Ministry of Health makes the final reimbursement recommendation. PBAC can defer a recommendation pending the provision of specific additional information that would be relevant and important to its recommendation.









The HTA recommendations in this report have been classified into the following categories: *positive*, *positive with restrictions* and *negative*. Figure 17 illustrates how the specific recommendations 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 and obtained different first HTA recommendations, the final HTA outcome was classified as *multiple*. In this study, this occurrence was observed in Australia, Germany and Scotland.

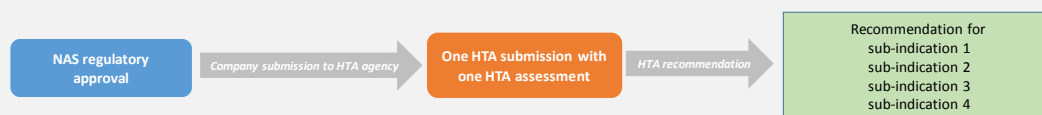
Figure 24: Trichotomous categories of HTA recommendations

	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

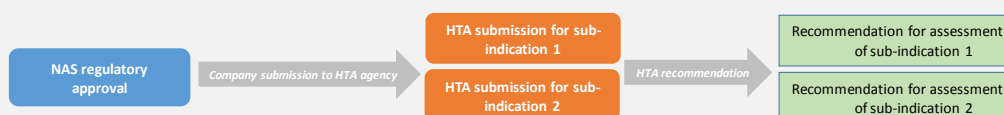
Where a green outline indicates that drug reimbursement is possible while a red outline indicates that drug reimbursement is not possible

Figure 25: Special cases of HTA recommendations

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



DEFINITIONS

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).

Expedited approval

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

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.

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 recommendation.

HTA review time

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

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.

Oncology drugs

In this Briefing, oncology drugs refers to anti-cancer and immunomodulators (ATC code L).

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. This sequence is available in Australia and Canada. In this report, a drug is identified as parallel if HTA recommendation is earlier than regulatory approval.

Regulatory submission gap

Date of submission at the first regulatory agency to the date of regulatory submission to the target 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.

Rollout time

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

Sequential review

Regulatory review is conducted first to determine the benefit-risk profile of a new medicine, followed by the HTA review to assess the value of the medicine for a reimbursement decision. The regulatory-HTA sequence is seen at a national level in many countries, and also at a super-national level in Europe where a centralised regulatory decision made by the European Medicines Agency is followed by jurisdictional HTA recommendations by member states.



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