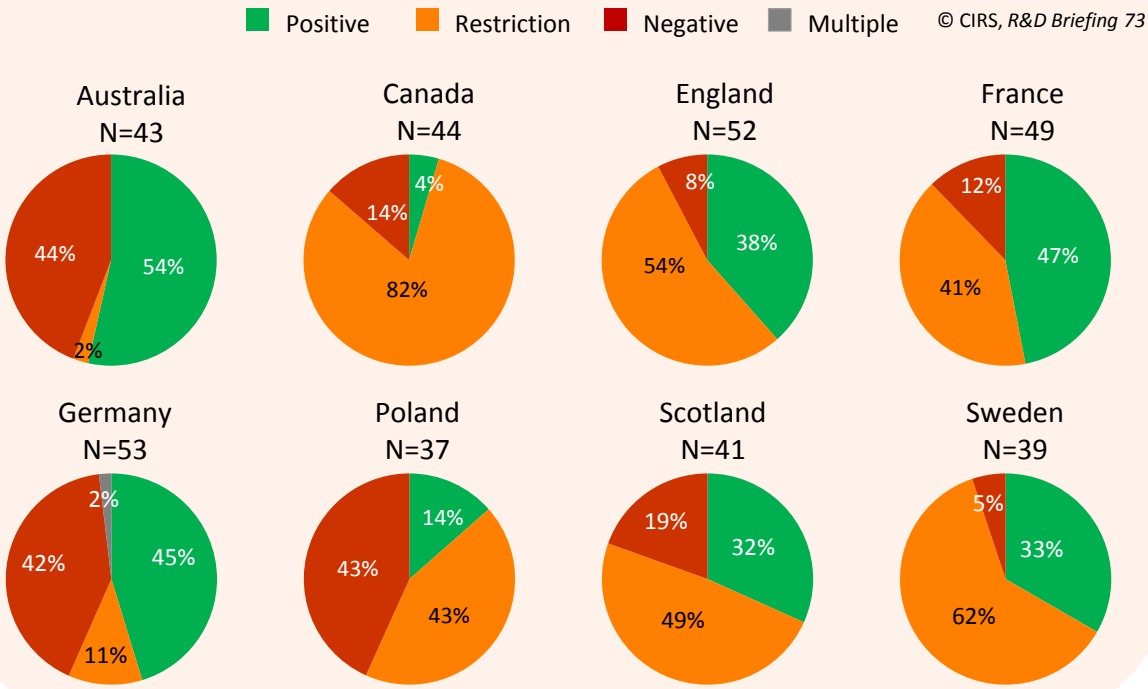
Review of HTA outcomes and timelines in Australia, Canada and Europe 2014-2018

Figure 1: First HTA recommendations: comparisons across key jurisdictions 2017 and 2018



Contents

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 2018 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 2012-2018 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 10, the HTA recommendations in this report have been classified as *positive, positive with restrictions* or *negative*. Figure 27 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 across all of the studied jurisdictions between 2017-2018. Sweden and England had the highest proportion of positive/positive with restrictions recommendations for NASs appraised by HTA agencies.
- Of all studied HTA agencies, Australia had the highest percentage of and greatest increase in products recommended within one year of regulatory approval (94% in 2018).
- Australia had the shortest median time between regulatory approval and HTA recommendation (19 days) in 2014-2018, followed by Germany (129 days).
- CIRS analysed NASs rolled out to seven jurisdictions, excluding Poland, and identified 38 NASs that received a recommendation by all HTA agencies during the period of 2014-2018. Interestingly, NAS approval by US FDA via Breakthrough Designation did not translate to quicker time from regulatory approval to HTA recommendation nor an increase in proportion of positive or positive with restrictions HTA recommendations.

In Australia, more than 70% of NASs were reimbursed after receiving a positive or positive with restrictions first recommendation.

Of 85 drug submissions in Australia from 2015-2018, 64 were reimbursed. In the last two years, the proportion of products with a one-cycle review with a positive/ positive with restriction recommendation increased from 52% in 2015-2016 to 77% in 2017-2018. Multiple review cycles can increase the time to the final reimbursement decision. The difference between the one-cycle and multiple-cycle review for median time taken from HTA submission to reimbursement decision was 380 days between 2015-2016 and 212 days between 2017-2018.

In Canada, the HC/CADTH parallel process reduced the time from regulatory approval to HTA recommendation.

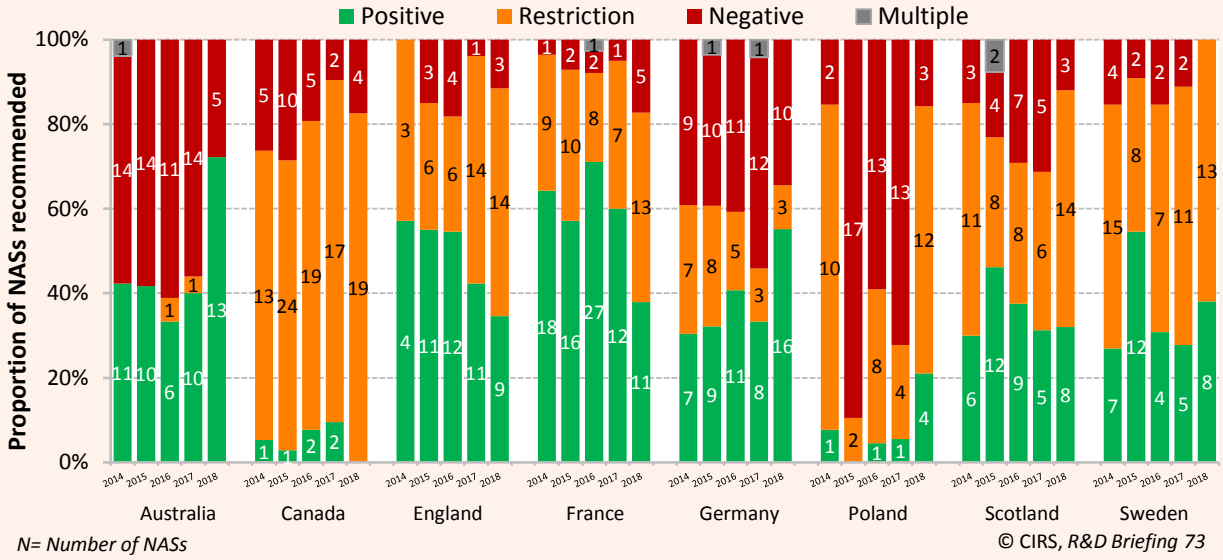
In 2014-2018, approximately half of the NASs submitted for HTA recommendation underwent the Health Canada/ CADTH parallel review process. The parallel review process was a success in reducing the time taken to reach the first HTA recommendation. The reduction in median time taken from regulatory approval to HTA recommendation using the parallel process (152 days) was shorter than the sequential process (361 days).

In Europe, the lag between EMA approval and HTA recommendations varied across the European jurisdictions, from 129 median days in Germany to 521 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. Among 40 commonly appraised NASs approved by EMA, accelerated products generally had the fastest median time from regulatory approval to HTA recommendation.

OVERVIEW OF NEW DRUG RECOMMENDATIONS

Figure 2: First HTA recommendation comparison across key jurisdictions by year of HTA recommendation Between 2014-2018



N= Number of NASs

In 2017 and 2018, Sweden and England had the highest proportion (95% and 92%) of positive/positive with restrictions recommendations for NASs appraised by HTA agencies (Figure 1).

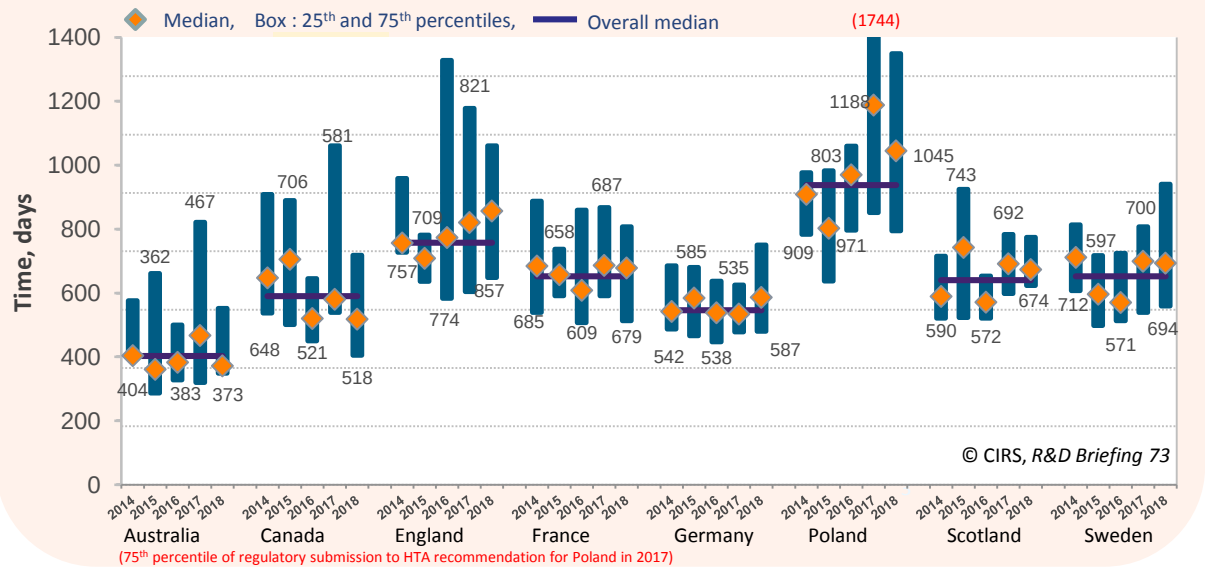
Germany appraised the highest number of NASs in 2017-2018 (53 NASs), while Poland appraised the fewest (37 NASs) (Figure 1). The biggest difference in the number of HTA recommendations between 2017 and 2018 was seen in Scotland, with an increase of 56%. The year-on-year variation in the number of recommendations is due to a number of reasons, including the number of regulatory approvals, the company submission strategy and the review time by the HTA agencies.

More than 60% of NASs approved by relevant regulatory agencies received a positive or positive with restrictions recommendation by HTA agencies in all of the studied jurisdictions in 2018. In particular, Poland showed the greatest increase in proportion of NASs appraised receiving a positive or positive with restrictions recommendation, from 28% in 2017 to 84% in 2018. There were no negative recommendations for products appraised by TLV in 2018 (Figure 2).

Australia had the fastest median rollout time from regulatory submission to HTA recommendation in 2018 (373 days), followed by Canada (518 days). Lower timing variation was also seen in these two countries in 2018 compared with 2017, which indicated an improved consistency (Figure 3).

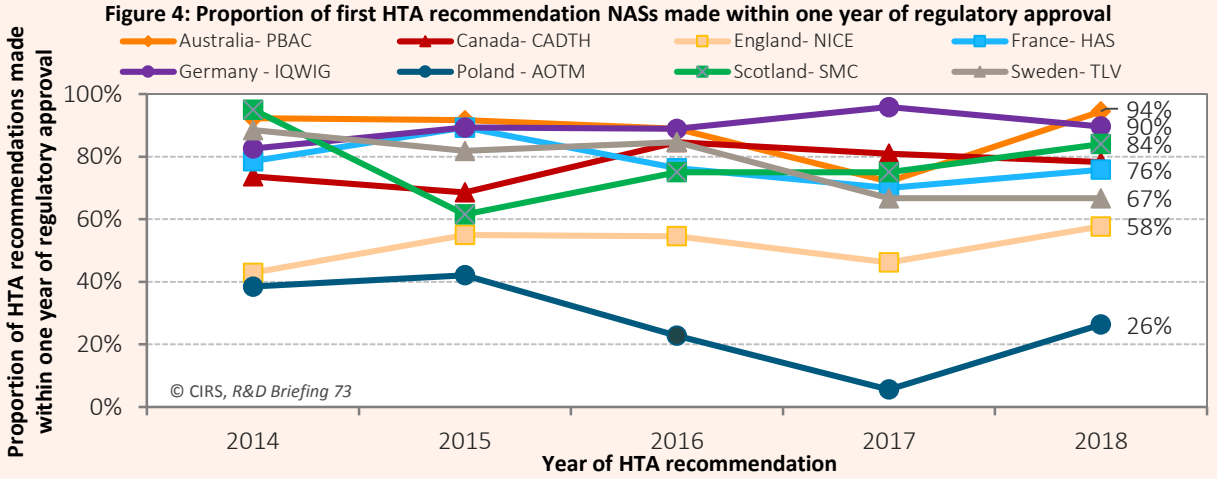
The median rollout time was shortened in 2018 in most jurisdictions compared with 2017, while England showed an increased review time over the past four years. The biggest improvement in the rollout time was seen in Poland, with a decrease of 143 median days from 2017 to 2018. However, it still took the longest time for products to roll out in Poland compared with other jurisdictions.

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 one year of regulatory approval



Of all HTA agencies, PBAC had the highest percentage of and greatest increase in NASs recommendations made within one year of regulatory approval: from 72% in 2017 to 94% in 2018 (Figure 4).

On average, IQWiG appraised the most NASs within one year of regulatory approval (89% across 2014-2018), while PBAC appraised the most NASs within one year of regulatory approval in 2018. The breakdown of rollout time is shown in Figure 5. A longer median time from regulatory approval to HTA recommendation in 2018 compared with 2017 was seen in France, Germany and Sweden; this can be attributed to both company submission strategy and HTA review time. The parallel review mechanism in Australia and Canada has shortened the time from regulatory approval to HTA submission (Figure 6).

Figure 5: Breakdown of rollout time in key jurisdictions 2014-2018

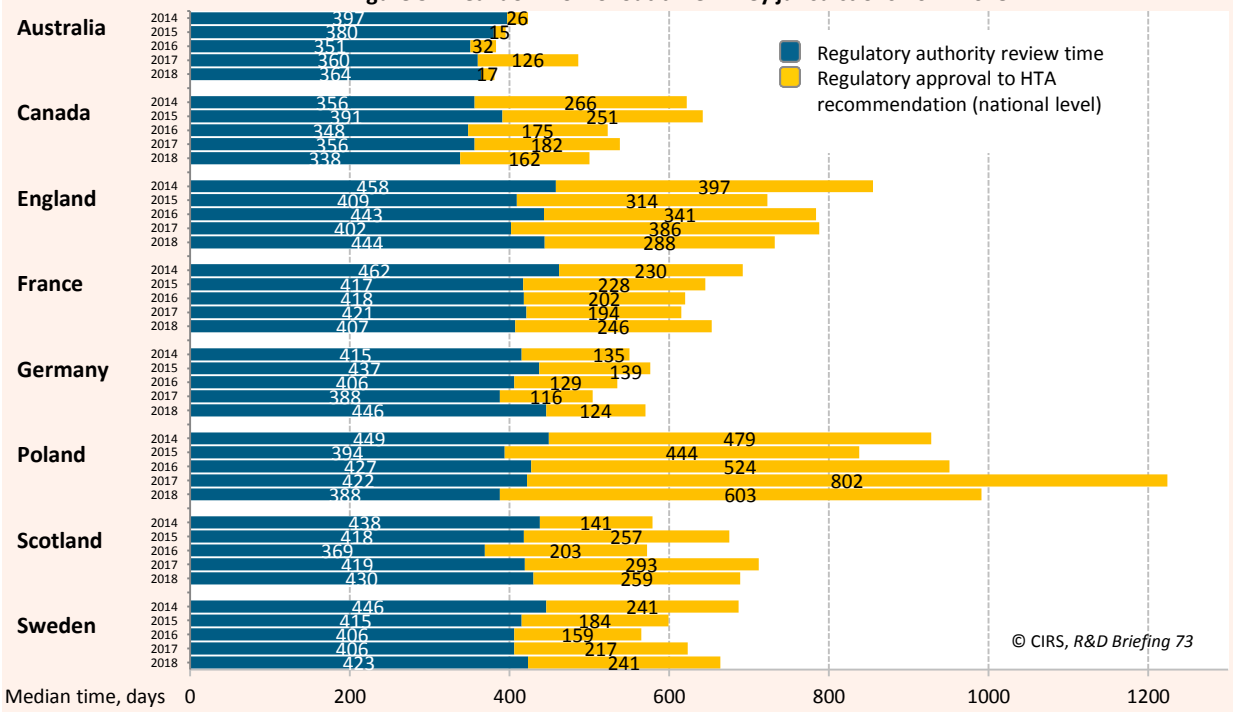
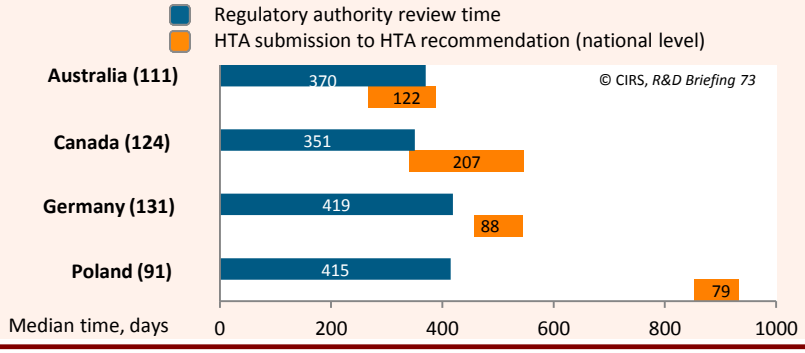


Figure 6: Breakdown of rollout time in jurisdictions where HTA submission date is provided 2014-2018*



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

38 NASs APPRAISED BY ALL SEVEN JURISDICTIONS IN 2014-2018

Figure 7: First HTA recommendation comparison across all jurisdictions for 38 common NASs

Positive | Restriction | Negative | Multiple | n = Date order of the HTA recommendations | FDA Breakthrough Designation

Country	AUS	CAN	ENG	FRA	GER	SCO	SWE
ombitasvir; paritaprevir; ritonavir	6	5	7	2	3	4	1
simeprevir	2	1	7	6	4	3	5
glecaprevir / pibrentasvir	4	6	7	5	3	2	1
ixekizumab	1	4	6	3	7	5	2
secukinumab	1	6	4	7	5	2	3
ledipasvir; sofosbuvir	5	6	7	4	3	1	2
sarilumab	7	1	2	5	3	6	4
daclatasvir	5	6	7	4	2	1	3
tofacitinib citrate	1	2	6	5	4	7	3
venetoclax	4	6	5	2	1	3	7
sofosbuvir / velpatasvir	6	5	7	4	3	2	1
empagliflozin	1	7	6	5	3	2	4
ceritinib	7	4	6	2	1	3	5
alectinib hydrochloride	2	1	7	5	3	6	4
midostaurin	1	2	6	6	3	5	4
eliglustat tartrate	2	6	5	3	1	7	4
sacubitril / valsartan	2	3	6	7	4	1	5
ibrutinib	5	2	7	4	1	6	3
migalastat hydrochloride	6	7	5	4	1	2	3
idelalisib	4	6	7	5	1	2	3
elbasvir + grazoprevir	2	1	5	4	7	6	3
ribociclib succinate	1	7	3	5	2	6	4
vedolizumab	1	7	6	4	2	5	3
palbociclib	3	1	7	4	2	6	5
evolocumab	1	5	7	3	2	6	4
nintedanib	2	7	6	5	3	1	4
lenvatinib	4	5	7	2	1	6	2
sofosbuvir	4	5	7	3	1	2	6
mepolizumab	1	5	7	6	2	3	4
osimertinib mesylate	7	5	3	2	1	4	6
guselkumab	4	2	6	7	3	5	1
alirocumab	7	5	3	2	1	4	6
trifluridine/tipiracil hydrochloride	5	7	1	3	4	6	2
lumacaftor	2	6	5	4	1	3	7
apremilast	1	5	6	7	3	2	4
daratumumab	4	2	7	5	1	3	6
olaparib	6	7	5	2	4	3	1
dupilumab	5	3	6	4	1	7	2

France had the highest proportion of positive recommendations for 38 NASs appraised by all seven HTA agencies (58%), with Canada showed the lowest proportion (3%).

CIRS analysed NASs rolled out to seven jurisdictions, excluding Poland, and identified 38 NASs that had been approved between 2012 and 2018 and that had also received an HTA recommendation between 2014 and 2018 by all seven HTA agencies. Figure 7 shows a traffic light system to compare the different HTA outcome across jurisdictions in 2014-2018, reflecting the diverse perception on the value of these NASs across the agencies. The recommendation dates for each product were compared across all seven agencies and the order of first HTA decisions was ranked accordingly.

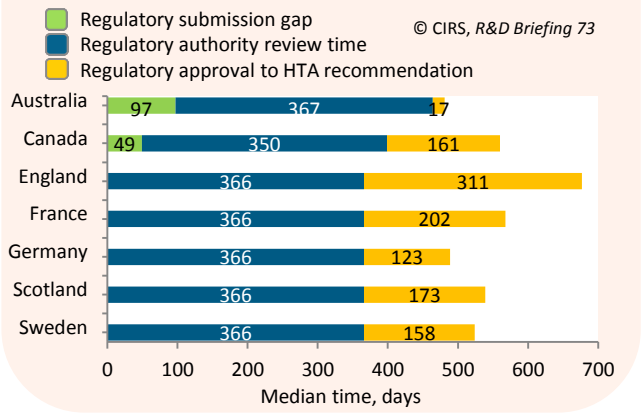
In England and France, the majority of NAS received a positive/ positive with restrictions recommendation (95% and 92% respectively). In comparison, in Australia and Germany the first HTA recommendation were mostly negative (61% and 45% of the NASs review respectively). NASs were mostly likely to receive a restrictive recommendation in Canada (76% of the 38 products). In this cohort, none of the NASs had the same first HTA recommendation but 7 NASs received positive/ positive with restrictions outcome from all seven jurisdictions.

Germany provided the highest number of recommendations as the first country of appraisal (34%), followed by Australia (26%).

In England, the majority of NASs (66%) received a NICE decision as the 6th or 7th country among all jurisdictions; none of the 38 products received a first HTA decision in France.

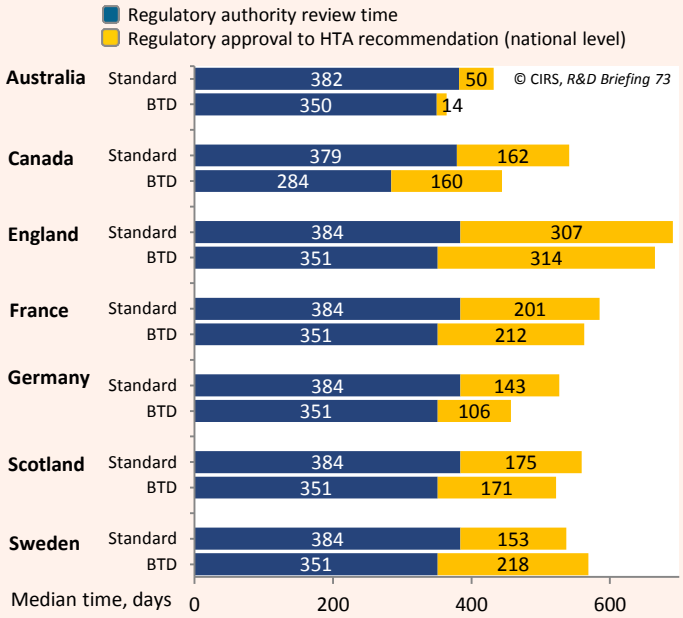
Australia had the shortest median time from first world-wide regulatory submission to jurisdictional HTA recommendation although it had the largest median regulatory submission gap of 97 days (Figure 8).

Figure 8: Breakdown of rollout time (days) across all jurisdictions for 38 common NASs



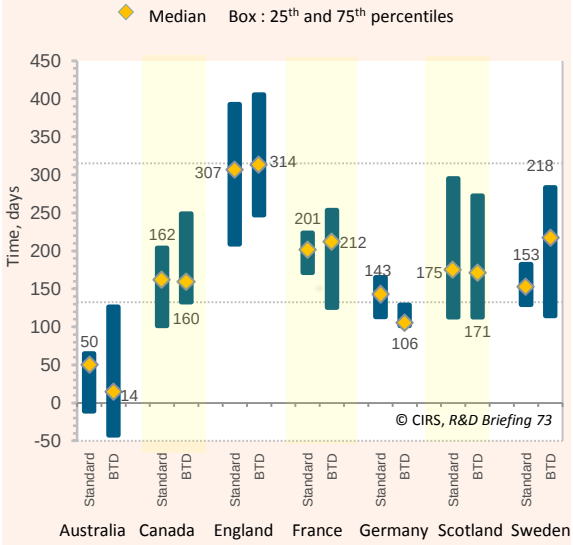
FOCUS ON BREAKTHROUGH DESIGNATION OF 38 COMMON NASs

Figure 9: Breakdown of rollout time by US Breakthrough Designation (BTD) for 38 common NASs



Number of standard = 19; Number of BTD = 19

Figure 10: Time taken from regulatory approval to HTA recommendation by US Breakthrough Designation (BTD)



Number of standard = 19; Number of BTD = 19

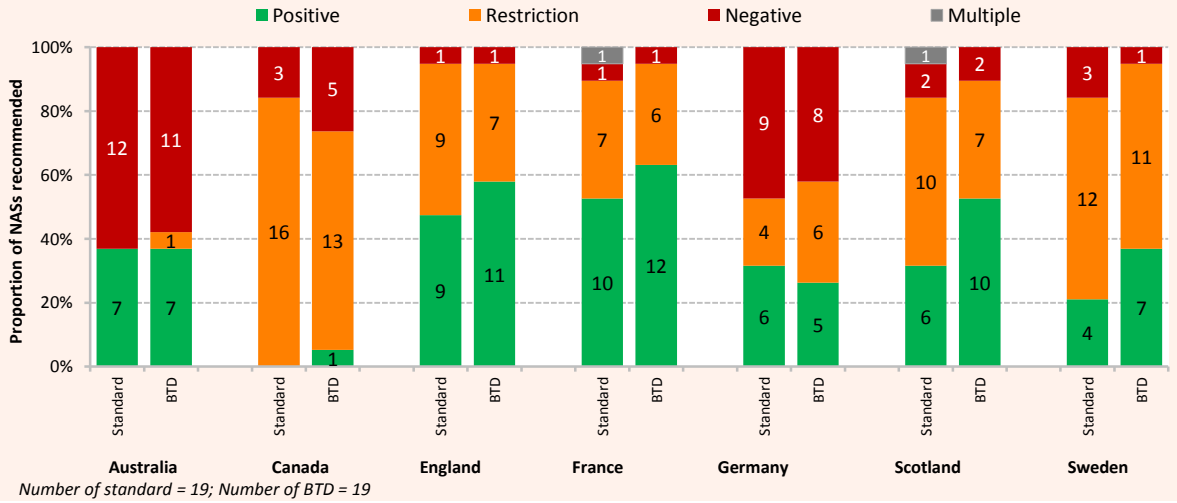
50% of the common NASs had been approved by US FDA via Breakthrough Designation (BTD).

In an effort to expedite the approval of drugs treating serious illnesses or addressing unmet medical need, breakthrough therapy designation (BTD) has been used by the FDA. The BTD designation has resulted in a shorter timeline in both development (IND to submission) and FDA approval (*CIRS R&D Briefing 70*). The FDA approval status was explored for 38 common NASs in terms of the BTD; 19 products among the common NASs were approved via BTD, reflecting the innovativeness of these products.

The NASs approved by FDA BTD process had shortened regulatory review time across all jurisdictions (Figure 9).

NASs with BTD had a faster regulatory review time in each jurisdiction as compared with non-BTD; this was in line with the expedited approach by FDA. However, it did not translate to quicker post-regulatory processes in all jurisdictions. The time taken from regulatory approval to HTA recommendation was shorter in Australia, Canada, Germany and Scotland. In general, there were more variations in time from regulatory approval to HTA recommendation for the 19 BTD NASs, except in Germany and Scotland. (Figure 10).

Figure 11: First HTA recommendation comparison by US Breakthrough Designation (n=38)

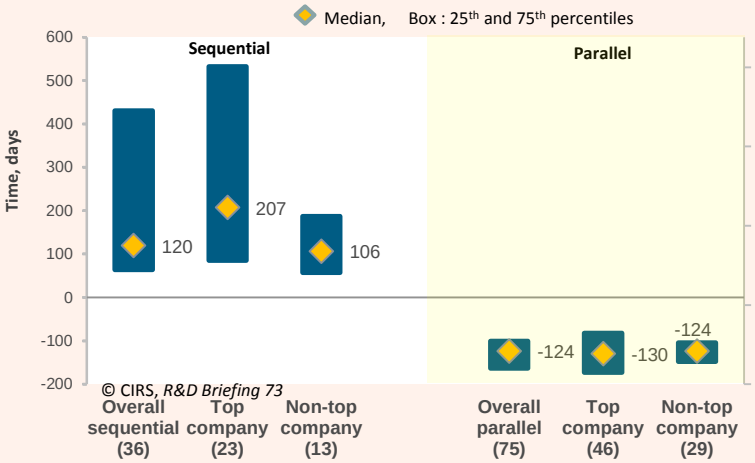


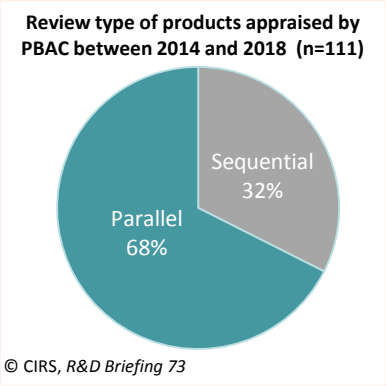
Number of standard = 19; Number of BTD = 19

BTDs do not lead to an increase in proportion of positive/positive with restrictions compared with non-BTDs (Figure 11).

The proportion of NASs receiving a positive/positive with restriction recommendation between BTD products and non-BTD products were similar across all jurisdictions. BTD products had faster timeline from regulatory submission to HTA recommendation; however, this was mainly driven by the shorter regulatory review time.

Figure 12: Time taken from regulatory approval to HTA submission according to company size in 2014-2018





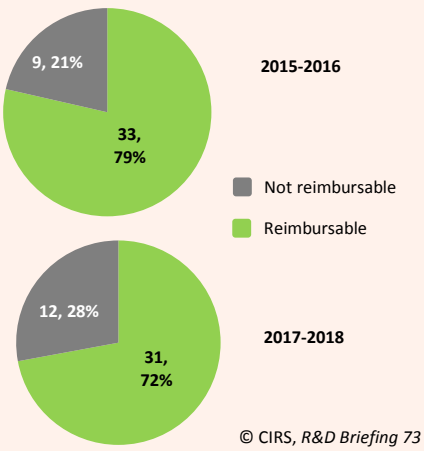
N= Number of NASs

Top company is defined as having R&D budget >3 billion USD in 2017.

Companies have taken advantage of the parallel review mechanism in Australia, with 68% products undergoing this process and saving approximately 4 months from PBAC submission to TGA approval (Figure 12).

Median submission to PBAC was 124 days prior to TGA approval for products that went through parallel review, compared with a 120-day delay in HTA submission with sequential review. Size of the company was assessed and used to stratify the trend of review process, showing no difference in preference for review process between top companies and non-top companies: 67% of top companies submitted products through parallel review, compared with 69% non-top companies.

Figure 13: Proportion of products that received reimbursement in Australia



More than 70% of products were reimbursed in Australia in 2015-2018 (Figure 13). However, 36% appraised by PBAC took more than one cycle to receive the reimbursement decision (Figure 14) in this cohort.

In Australia, a negative PBAC recommendation will lead to non-reimbursable decisions. When the first HTA recommendation does not support a reimbursement decision, companies can re-submit an application with an improved dossier. Consequently, a number of review cycles may take place until a positive/positive with restriction recommendation is achieved to support reimbursement. The proportion of products with one-cycle review increased in 2017-2018 (77%), compared with 2015-2016 (52%). Multiple review cycles may increase the time to receive the final reimbursement decision (732 median days in 2015-2016 and 535 median days in 2017-2018, Figure 15). In the last two years, the difference in time taken from HTA submission to reimbursement decision between one-cycle and multiple cycle review decreased by a median of 168 days compared with 2015-2016. The decrease in re-submissions and improvement in time to reimbursement is in line with the commitment by the Department of Health and Medicines Australia since late 2017 under *clause 10 of the Strategic Agreement* to streamline medicines listing processes, including a target of 50% reduction in the number of resubmissions to the PBAC and reduction in time from PBAC recommendation to listing by an average of two months.

Figure 14: Number of cycles to first positive/ positive with restrictions HTA recommendation in 2015-2018

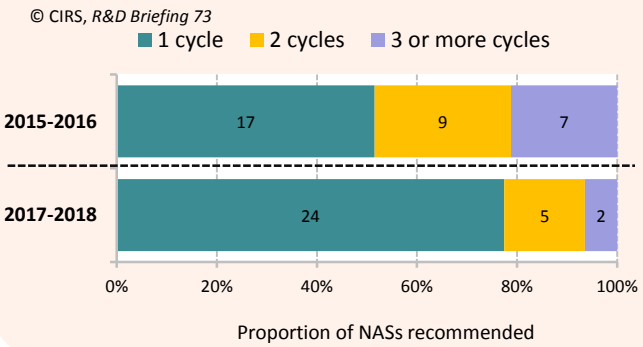
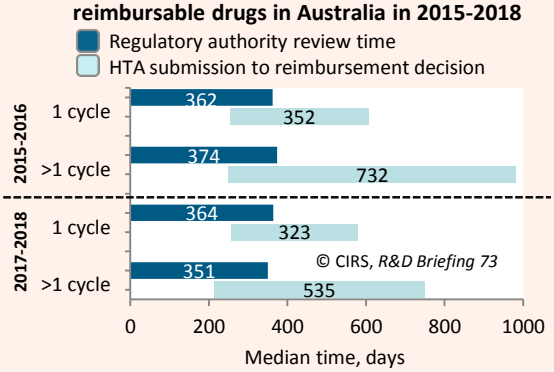


Figure 15: Breakdown of rollout time for reimbursable drugs in Australia in 2015-2018



Compared with 2015-2016, alimentary & metabolism products appraised in 2017-2018 took a shorter time from regulatory approval to HTA recommendation (Figure 16).

The top four therapeutic groups from the 105 NASs assessed by CADTH in 2015-2018 were anti-cancer & immunomodulators (42%), alimentary & metabolism (22%), anti-infectives (10%) and cardiovascular (6%). Looking at the overall median time taken from regulatory approval to HTA recommendation, anti-infectives were fastest, followed by anti-cancer & immunomodulators and cardiovascular NASs (Figure 16). In addition, all four anti-infectives products appraised in 2017-2018 received a positive CADTH recommendation (Figure 17).

In 2015-2018, 32 anti-cancer & immunomodulators were submitted under the pan-Canadian Oncology Drug Review (pCODR), which evaluates oncology drugs and makes recommendations and guides 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; pCODR moved to CADTH in 2014. In 2015-2016, anti-cancer & immunomodulators that underwent the pCODR evaluation were faster from regulatory approval to HTA recommendation than those that underwent the CDR review process; however, in 2017-2018, pCODR timelines were slightly longer than those for CDR (Figure 16).

The Health Canada/CADTH parallel process shortened the overall time taken from regulatory approval to HTA recommendation (Figure 18).

The Health Canada/CADTH parallel review process, which allows for a submission to CADTH within 90 days before the date of anticipated Notice of Compliance (NOC) from Health Canada, has been available for companies since 2012. However, on 2 April 2018, CADTH submission criteria were changed to within 180 days before the anticipated NOC from Health Canada. In 2015-2018, 51% of the NASs submitted for HTA recommendation underwent the Health Canada/CADTH parallel review process. In the last two-year cohort, an increased proportion of NASs were submitted through the parallel process: 46% in 2015-2016 to 59% in 2017-2018. Assessed in two-year cohorts, products that underwent the parallel review process in 2015-2016 and in 2017-2018 had faster regulatory and HTA review times. In 2017-2018, the median time taken from regulatory approval to HTA recommendation for the parallel process was a median 220 days faster that the sequential process.

A higher proportion of NASs submitted to the Health Canada/CADTH parallel process underwent pCODR review compared with CDR review (Figure 19). Thus, the rollout time from regulatory submission to HTA recommendation for NASs submitted for pCODR review was shorter than those submitted for CDR review. In 2017-2018, NASs submitted to pCODR had a faster time to HTA recommendation than CDR, which was mainly driven by shorter review time by Health Canada.

Figure 16: Time from regulatory approval to HTA recommendation by therapeutic area

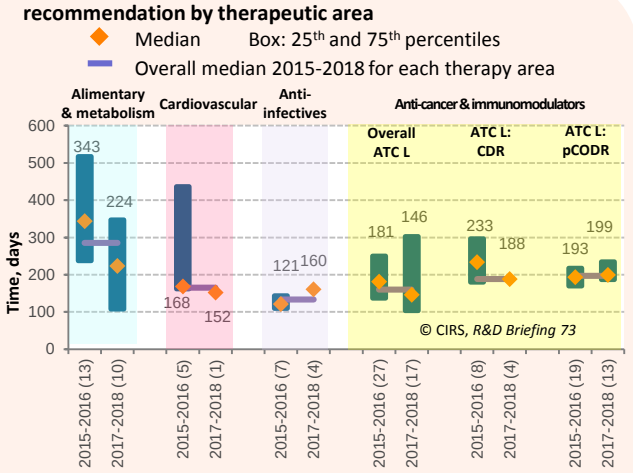


Figure 17: HTA outcome by therapeutic area © CIRS, *R&D Briefing 73*

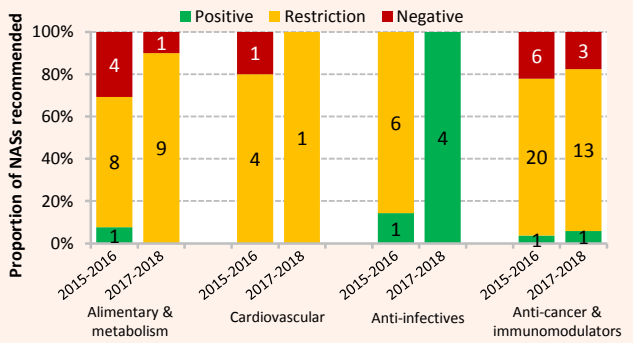


Figure 18: Breakdown of rollout time by type of sequence

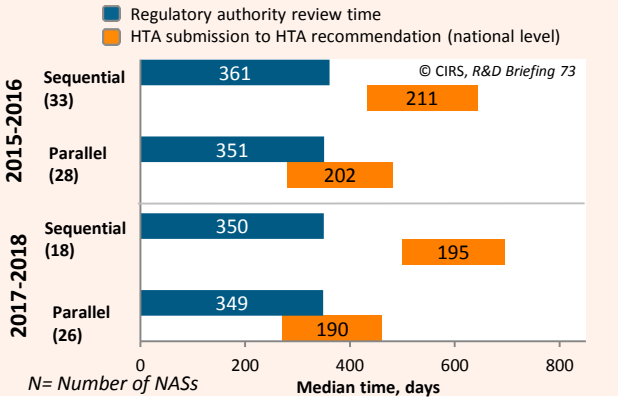


Figure 19: Time taken from regulatory approval to HTA recommendation by review type

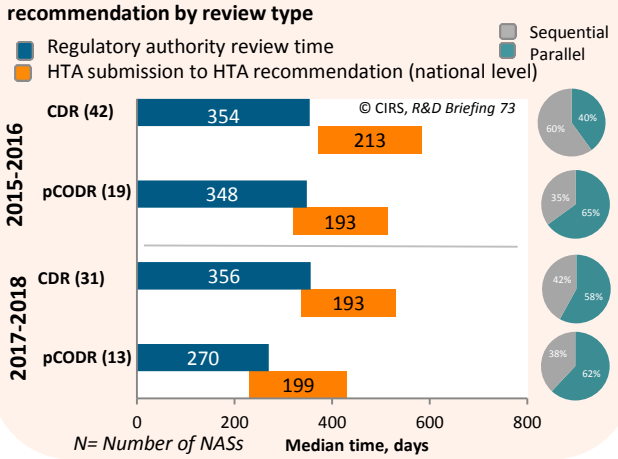
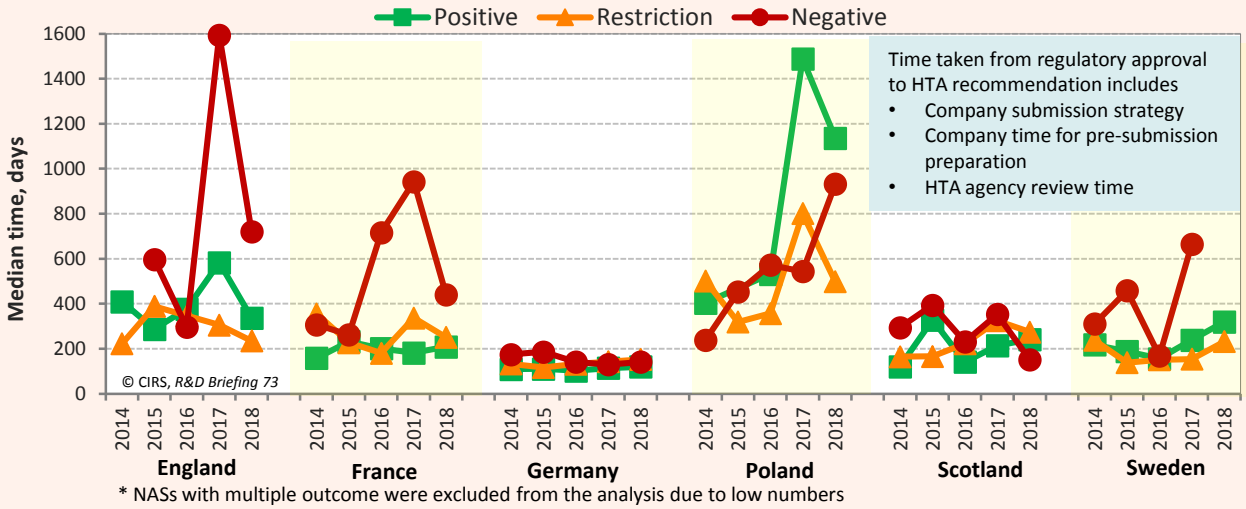


Figure 20: Time taken from regulatory approval to HTA recommendation by HTA outcome

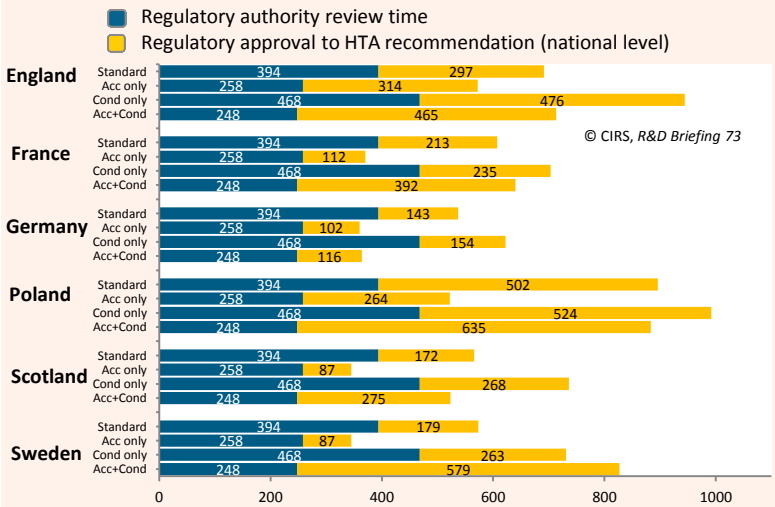


* NASs with multiple outcome were excluded from the analysis due to low numbers

Generally, NASs that received a negative recommendation took longer to receive that HTA recommendation from the time of EMA approval. However, the median time from regulatory approval to HTA recommendation in 2018 shortened in England, France and Scotland for all HTA outcomes (Figure 20).

Despite the fact that new drugs were approved at the centralised level, Figure 20 shows divergent timing from regulatory approval to HTA recommendation across the jurisdictions. The shortest time from regulatory approval to HTA recommendation for NASs that received a positive recommendation occurred in Germany, at a median of 113 days in 2014-2018.

Figure 21: Breakdown of rollout time (days) by EMA approval type for 40 common NASs



Number of Standard = 26; Number of Accelerated = 8; Number of Cond only = 4; Number of Acc+Cond = 2

40 NASs approved by EMA have been appraised by all six EMA jurisdictions, of which 21 were anti-cancer products and 9 were anti-infectives.

Among the 40 commonly appraised NASs, eight were approved as accelerated approval by EMA, four were conditional approvals and two were accelerated and conditional approvals. Accelerated products had the fastest median time from regulatory approval to HTA decision in all jurisdictions except England. In particular, in Poland, the median time was nearly half of the standard approvals. (Figure 21). In general, anti-infective NASs showed the fastest median time from regulatory approval to HTA recommendation and the highest proportion of positive or positive with restrictions HTA recommendation (Figure 22 and 23).

Figure 22: Time taken from regulatory approval to HTA recommendation by therapeutic area in for 40 common NASs

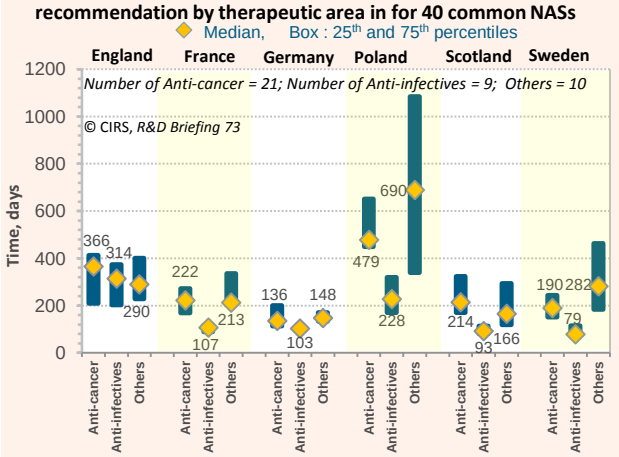
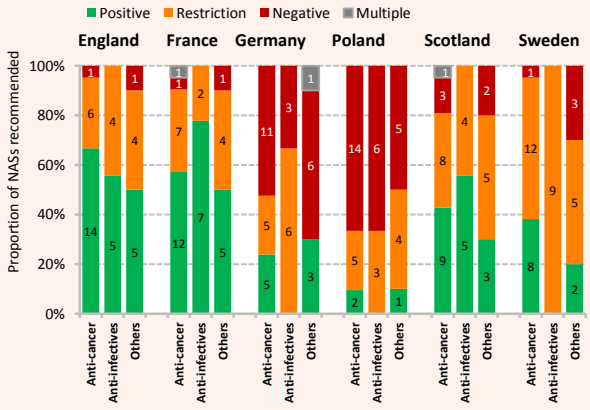
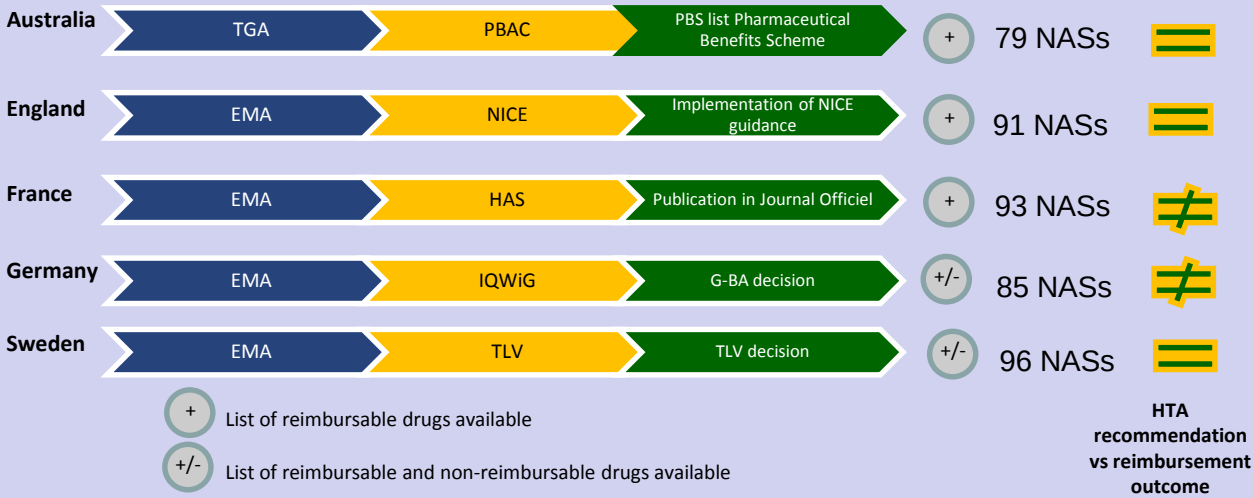


Figure 23: First HTA recommendation comparison for 40 common NASs by therapeutic area © CIRS, *R&D Briefing 73*



OVERVIEW OF REIMBURSEMENT OUTCOMES

Figure 24: Comparison of the regulatory and reimbursement system across targeted jurisdictions



HTA recommendations are used by payers to support reimbursement decisions. In this report, the database was extended beyond HTA information to collect reimbursement outcome decisions and dates. Figure 24 illustrates the key agencies involved in the regulatory and reimbursement systems and the connection between the HTA recommendation and reimbursement outcome. Data were collected only on reimbursable drugs in this cohort up to May 2019 to explore the availability of new medicines in these jurisdictions.

Figure 25: Breakdown of rollout time for reimbursable drugs with HTA recommendation in 2014-2018

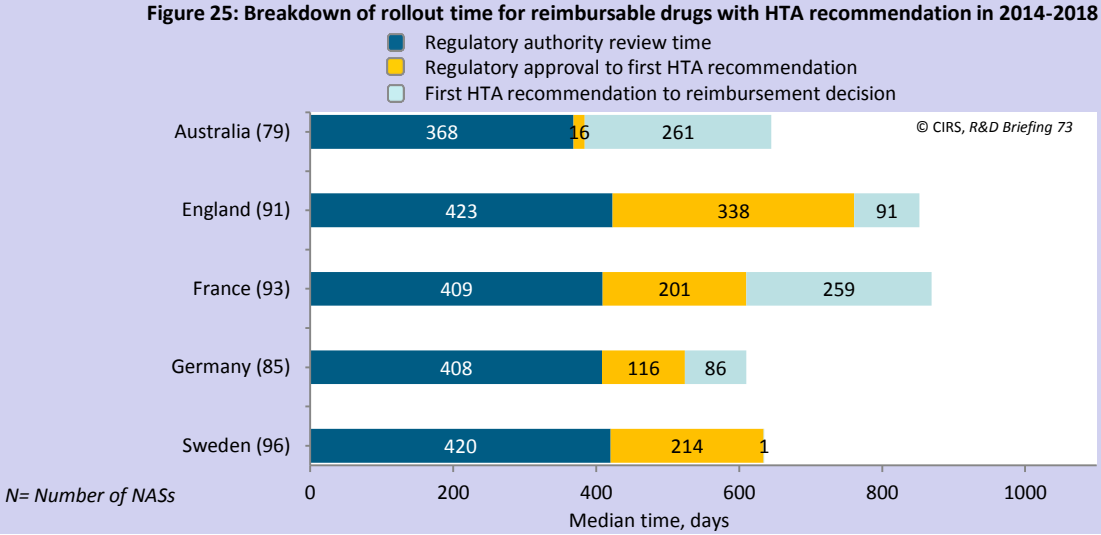
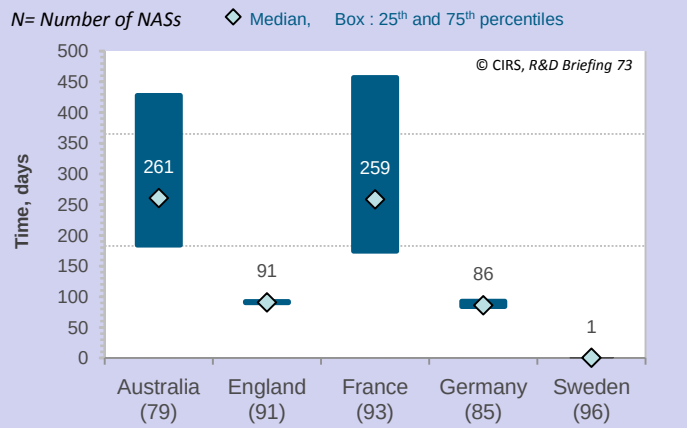


Figure 26: Rollout time from first HTA recommendation to reimbursement



France took the longest time to receive a reimbursement decision for new medicines, approximately 1.5 years after EMA approval (Figure 25).

Reimbursement decision dates reflect the availability of new medicines. Germany showed the quickest time from regulatory approval to reimbursement decision (median, 206 days). The variation between time from first HTA recommendation to reimbursement decision shows the diversity of reimbursement systems (Figure 26). In Sweden, reimbursement was granted immediately after TLV recommendation. In England, drugs must be reimbursed within 3 months of a NICE recommendation by law and 30 days for NASs on the Early Access to Medicines Scheme (EAMS) and fast track appraisal. In Germany, according to The Act on the Reform of the Market for Medical Products (AMNOG), G-BA needs to make a decision 3 months after an IQWiG recommendation.

METHODOLOGY

The data on individual NASs appraised by HTA agencies in 2014-2018 were collected 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 Sweden, 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 recommendation pending the provision of specific additional information that would be relevant and important to its recommendation.

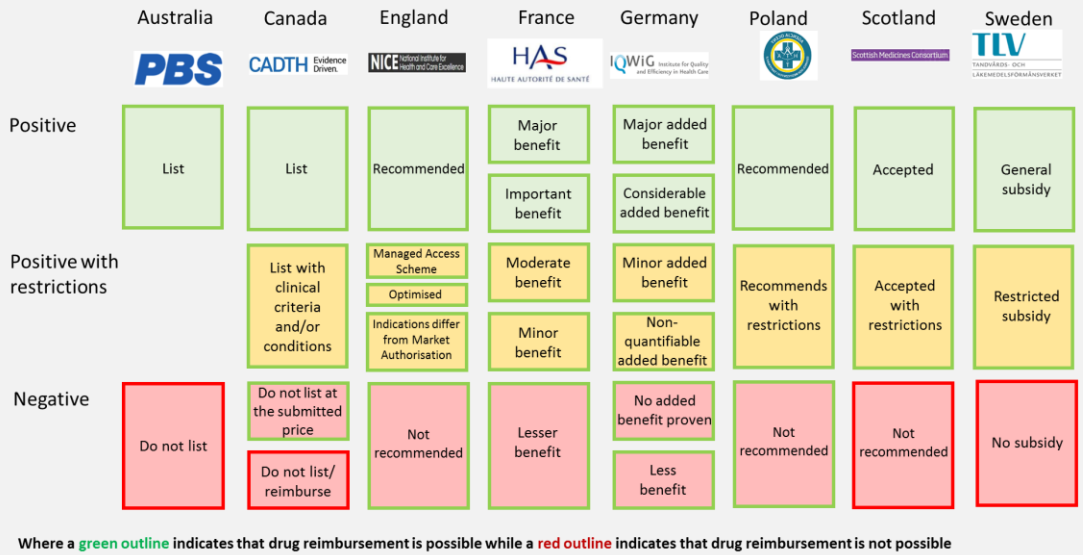
The HTA recommendations in this report have been classified into the following categories: *positive, positive with restrictions* and *negative*. Figure 27 illustrates how the specific recommendations by the eight HTA systems fall into this trichotomous categorisation.

There are a number of cases that reflected the different HTA approaches based on the regulatory approved label; these are illustrated in Figure 28.

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.

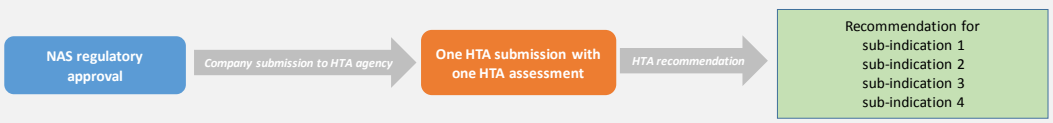
Figure 27: Trichotomous categories of HTA recommendations



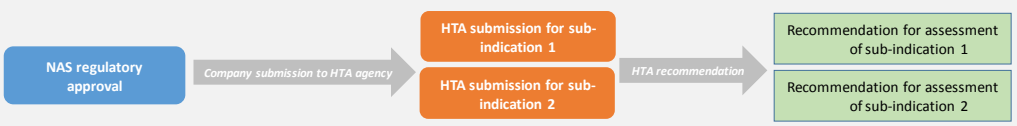
Where a green outline indicates that drug reimbursement is possible while a red outline indicates that drug reimbursement is not possible

Figure 28: 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

Anti-cancer drugs

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

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)

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 twofold – 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 as a medicinal product, but differing in molecular structure, nature of source material or manufacturing process and which will require clinical investigation.
- 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.

Parallel review

Pharmaceutical companies submit evidence to the regulatory agency that prove the 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.

US Breakthrough Designation

An FDA process designed to expedite the development and review of drugs that may demonstrate substantial improvement over available therapy.

Reimbursement date

Publication date of reimbursement decision.

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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CIRS - The Centre for Innovation in Regulatory Science Limited - is a neutral, independently managed UK-based subsidiary company, forming part of Clarivate Analytics (UK) Limited. CIRS' mission 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 and to facilitate access to medical products through these activities. This is CIRS' purpose. CIRS is operated solely for the promotion of its purpose. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities, special projects and grants.

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