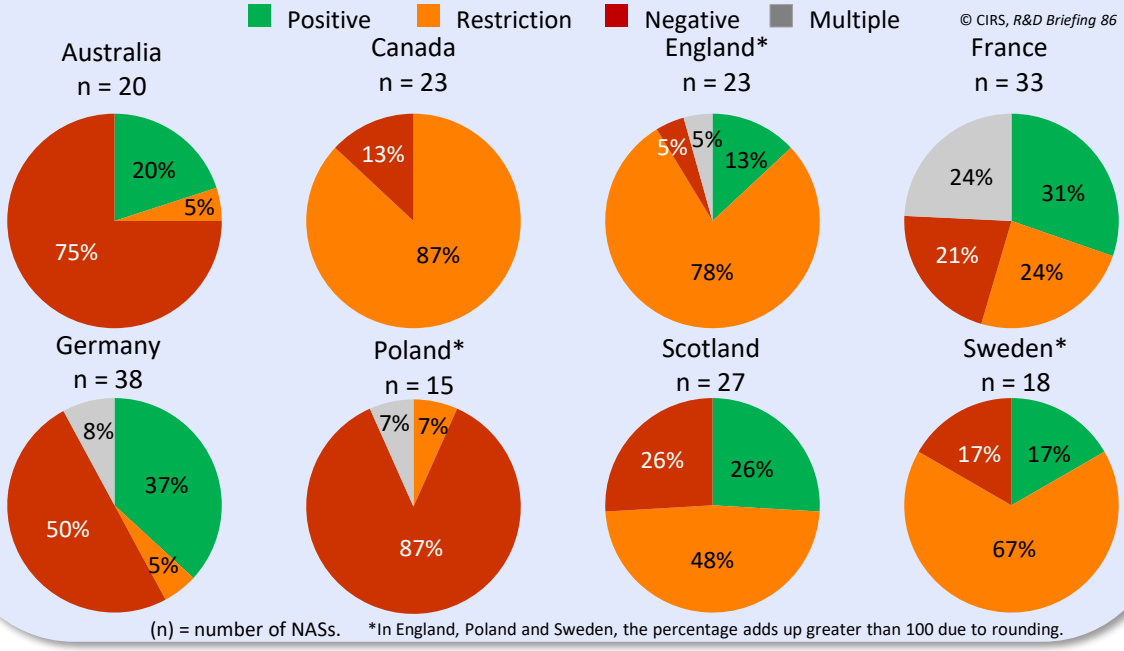
Review of HTA outcomes and timelines in Australia, Canada and Europe 2017-2021

Figure 1: First HTA recommendations: comparisons across key jurisdictions in 2021



(n) = number of NASs. *In England, Poland and Sweden, the percentage adds up greater than 100 due to rounding.

Contents

WHAT DO WE MEASURE IN THE HTADOCK?

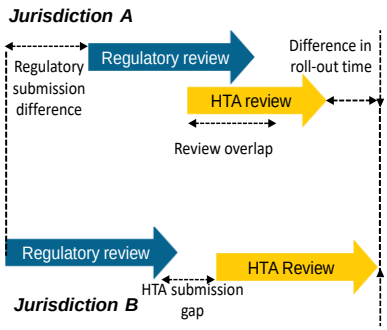
Timely recommendation for drug reimbursement by health technology assessment (HTA) agencies is critical to ensure that patient access to medicines of therapeutic value is not delayed. As part of an ongoing study to monitor regulatory and HTA performance, CIRS has been collecting data on new active substances (NASs) appraised by eight HTA agencies, analysing synchronisation between the regulatory decision and first HTA recommendation in timing and outcome.

The data on individual NASs appraised by HTA agencies in 2017-2021 were collected from the agencies' official websites. Using our described methodology, the HTA recommendations in this report have been classified as positive, positive with restrictions or negative. Only the first recommendation based on the first assessment reports were considered.

Regulatory and HTA process timelines

	Regulatory submission	Regulatory approval	HTA submission	HTA Recommendation
Australia	Submission to TGA	Approval by TGA	17 weeks before PBAC meeting	Month of PBAC meeting in Public Summary Document
Canada	Submission to Health Canada	Approval by Health Canada	Submission received by CADTH	Final recommendation issued to sponsor and drug plans
England	Submission to EMA	Approval issued by EU Commission*	Company evidence submission date	Technology appraisal guidance publication
France	Submission to EMA	Approval issued by EU Commission	Not available from Public domain	Publication of Commission de la transparence review
Germany	Submission to EMA	Approval issued by EU Commission	Datum des Auftrags at IQWIG	Publication of Dossierbewertung
Poland	Submission to EMA	Approval issued by EU Commission	Order of the Minister of Health publication	Publication of Rekomendacja Prezesa
Scotland	Submission to EMA	Approval issued by EU Commission*	Not available from Public domain	The first statement of advice by SMC
Sweden	Submission to EMA	Approval issued by EU Commission	Not available from Public domain	Publication of the first released report by TLV

Roll-out timeline comparison model based on milestone metrics



*from the 1st of January of 2021, it is collected as the date of **MHRA** decisions*

The first HTA recommendations*: Trichotomous categories

	Positive	Positive with restrictions	*Implication for "positive" or "positive with restrictions"*	Negative
Australia PBS	List	List with conditions	Listing in the Pharmaceutical Benefits Scheme	Do not list
Canada CADTH Evidence Driven.	Reimburse	Reimburse with conditions	Recommendation for reimbursement	Do not reimburse
England NICE National Institute for Health and Care Excellence	Recommended	Recommended + restrictions	NHS Implementation of NICE guidance	Not recommended
France HAS	Majeur/Important	Modéré ou faible	The NHI defines the reimbursement rate accordingly	Insufficient
Germany IQWiG	Considerable/Major added benefit	Minor/non-quatifiable added benefit	G-BA makes the binding resolution based on benefit assessment	Added benefit not proven/less benefit
Poland	Prezes Agencji rekomenduje	Prezes Agencji rekomenduje+restrictions	Agency's president's recommendation	Prezes Agencji nie rekomenduje
Scotland Scottish Medicines Consortium	Accepted for use within NHS Scotland	Accepted for restricted use within NHS Scotland	Accepted for use within NHSScotland	Not recommended for use within NHS Scotland
Sweden TLV	Ngå i läkemedelsförmånerna	Begränsningar	Include in pharmaceutical benefits scheme	Avslår

The terminology used here was collected based on the individual agency's guidance on the official website.

KEY MESSAGES

- In 2021, England and Canada presented the highest proportion of positive/positive with restrictions recommendations for NASs appraised by HTA agencies (91 and 87%, respectively) (Figure 1).
- In 2021, an increased number of first HTA recommendations was observed for all jurisdictions, except Poland, compared to 2020 (Figure 2).
- Australia had the fastest median rollout time from regulatory submission to the first HTA recommendation in 2021 (403 days), followed by Canada and Germany (562 and 563 days, respectively). Germany showed the least variation in rollout time, which enabled better predictability for companies' marketing strategies (Figure 3).
- In 2021, the number of parallel submissions in Australia remained consistent with the average per year from 2017-2020 (10 vs 12), however, in Canada, it decreased (8 vs 13) (Figure 6).
- The parallel process shortened the overall time taken from regulatory submission to HTA recommendation in both Australia and Canada (Figure 7).
- The regulatory orphan designation generally presented a longer time to HTA recommendation (Figure 9) and did not have a considerable effect on the type of HTA recommendation in all jurisdictions except Germany (Figure 10).
- The top four therapeutic areas made up 68% (182/263) of all the products assessed by at least one country between 2017-2021, with anti-cancer and immunomodulators making up 57% (104/182) of the top therapeutic areas (Figure 11).
- In total, 7 products approved via the Access route were included in the HTADock dataset this year (Table 2).
- The time taken from regulatory approval to HTA recommendation was marginally faster for anti-cancer and immunomodulators, compared to other therapeutics in all jurisdictions, except Australia (Figure 12).

In Australia, 64% (61/96) of drugs with PBAC recommendations in 2017-2021 were listed in the PBS list in Australia, of which 57% (35/61) appraised by PBAC were listed at the first submission.

The proportion of PBS-listed drugs that were recommended by PBAC at the first submission was similar from 2017-2020, with an average of 42%. However, this dropped to 15% in 2021 (Figure 24).

In Canada, submissions to CADTH under the parallel process are being made earlier.

The overlap between the median regulatory and HTA reviews increased from 2017 to 2020 and 2020 remained similar in 2021, with the overlap time between the median regulatory and HTA review time being 53, 84, 94, 166 and 154 days in 2017, 2018, 2019, 2020 and 2021, respectively, indicating that the parallel process is being optimised (Figure 27).

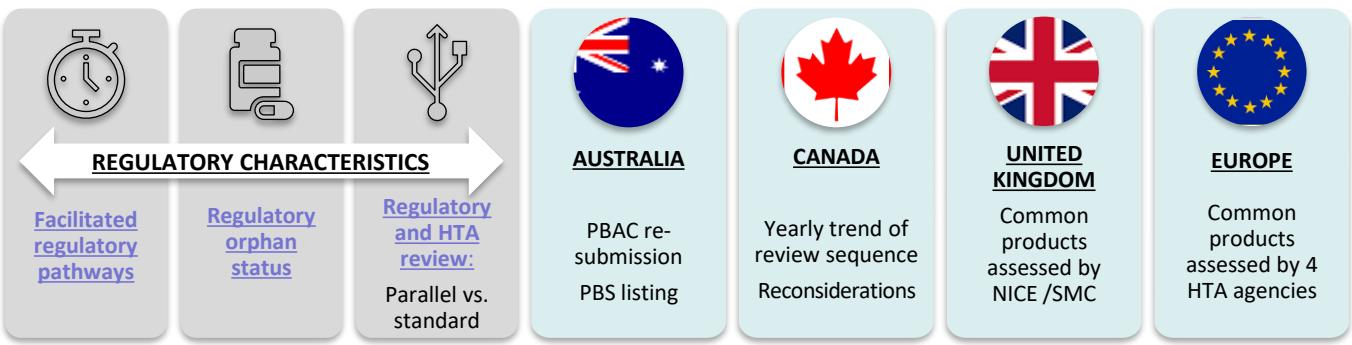
In the UK, NICE and SMC displayed a similar time from regulatory approval to HTA recommendation of common NASs between 2017 and 2021.

74 common products were evaluated in both England and Scotland. Of these common products, the median time from EMA approval to the NICE and SMC recommendation was 297 and 261 days, respectively, in 2017-2021 (Figure 32).

In Europe, 37 NASs approved by EMA have been appraised by all 4 jurisdictions in 2017-2021.

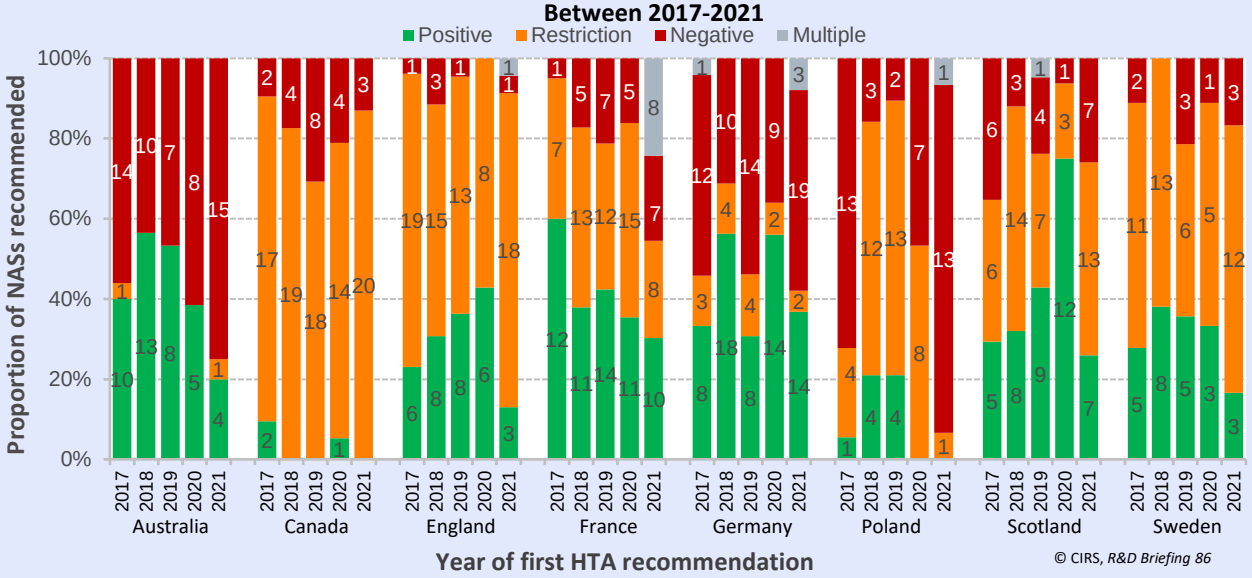
The common compounds consisted of 25 anti-cancer and immunomodulators NASs, 2 anti-infectives and 10 belonged to other therapeutic areas (Figure 36).

Different regulatory review characteristics and jurisdictional processes and policies have been assessed to understand the impact on the first HTA outcome and timing, as detailed in the infographic below:



OVERVIEW OF NEW DRUG RECOMMENDATIONS

Figure 2: First HTA recommendation comparison across key jurisdictions by year of HTA recommendation Between 2017-2021



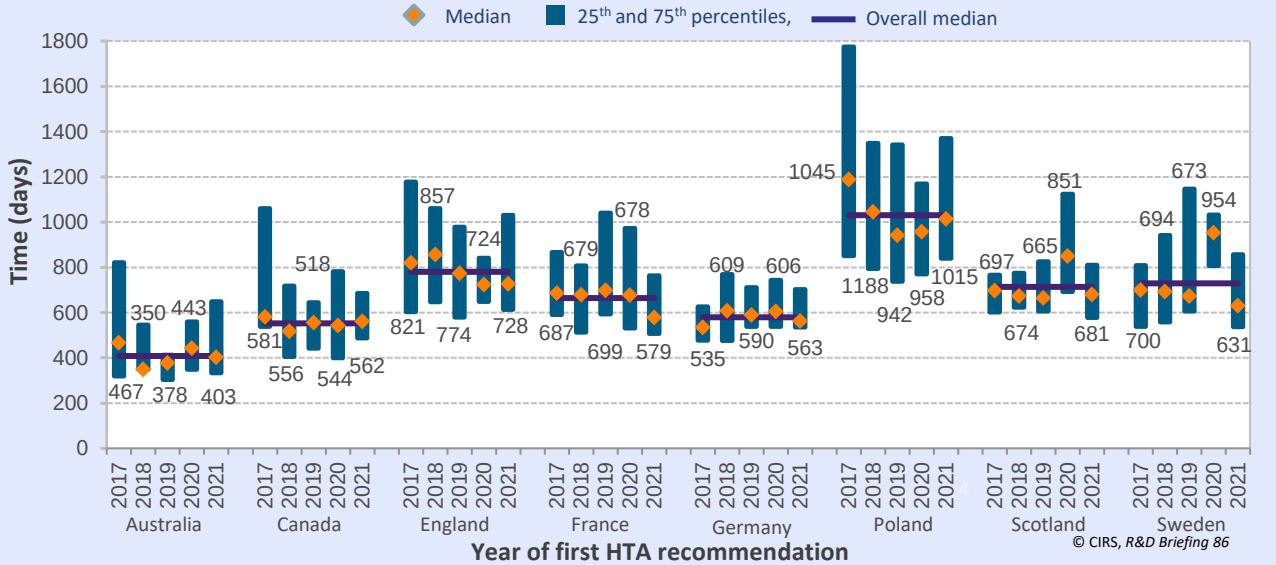
In 2021, England and Canada presented the highest proportion of positive/positive with restrictions recommendations for NASs appraised by HTA agencies (91 and 87%, respectively) (Figure 2).

In 2021, Germany appraised the highest number of NASs (n=38), followed by France (n=33), Scotland (n=27), Canada (n=23), England (n=23), Australia (n=20), Sweden (n=18) and Poland (n=15) (**Figure 2**). We observed an increasing number of 1st HTA recommendations in 2021 in all countries, except Poland, compared to 2020, In particular, Sweden doubled its appraisals (18 in 2021 vs 9 in 2020) and an increased number of appraisals was observed in Scotland and England by 68 and 64%, respectively. Interestingly, the proportion of positive/positive with restriction recommendations decreased for all countries, except for Canada, in 2021 when compared with 2020 (Australia: 25 vs 38%, Canada: 87 vs 79%, England: 91 vs 100%, France: 55 vs 84%, Germany: 42 vs 64%, Poland: 7 vs 53%, Scotland: 74 vs 94% and Sweden: 83 vs 89%).

Australia had the fastest median rollout time from regulatory submission to the first HTA recommendation in 2021 (403 days), followed by Canada and Germany (562 and 563 days, respectively) (Figure 3).

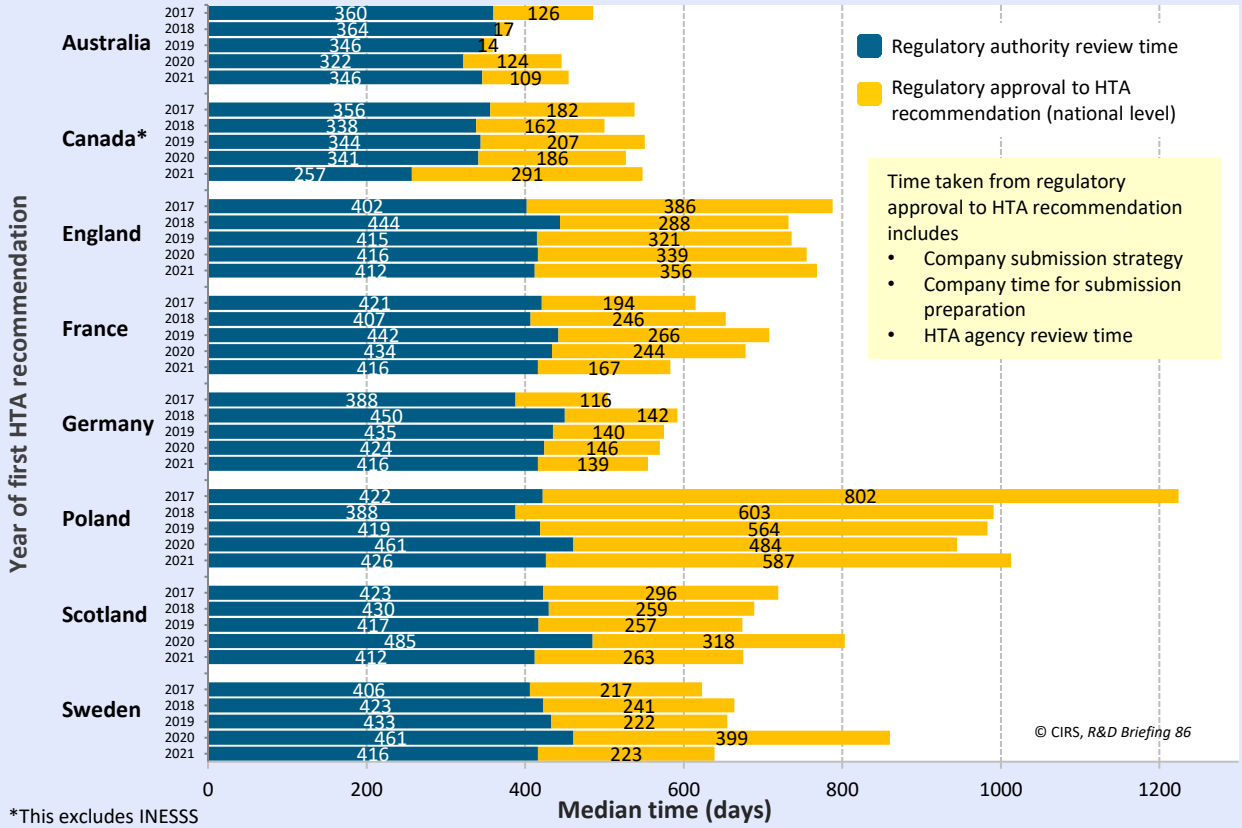
Canada showed the highest consistency in the median rollout time from regulatory submission to HTA recommendation over the years 2017-2021, with an overall standard deviation (SD) for the median rollout times of ±23 days. Sweden has the biggest variance due to the decrease in rollout time in 2021. As noted by the 25th – 75th percentile bars, there were variations in the rollout time. Germany showed the least variation in rollout time, which enabled better predictability for companies' marketing strategies. In addition, a decrease in the median rollout time was observed when comparing 2021 vs 2020 for Australia (403 vs 443), France (579 vs 678), Germany (563 vs 606), Scotland (681 vs 851) and Sweden (631 vs 954).

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



SYNCHRONISATION OF REGULATORY AND HTA RECOMMENDATIONS

Figure 4: Breakdown of rollout time across all jurisdictions in 2017-2021

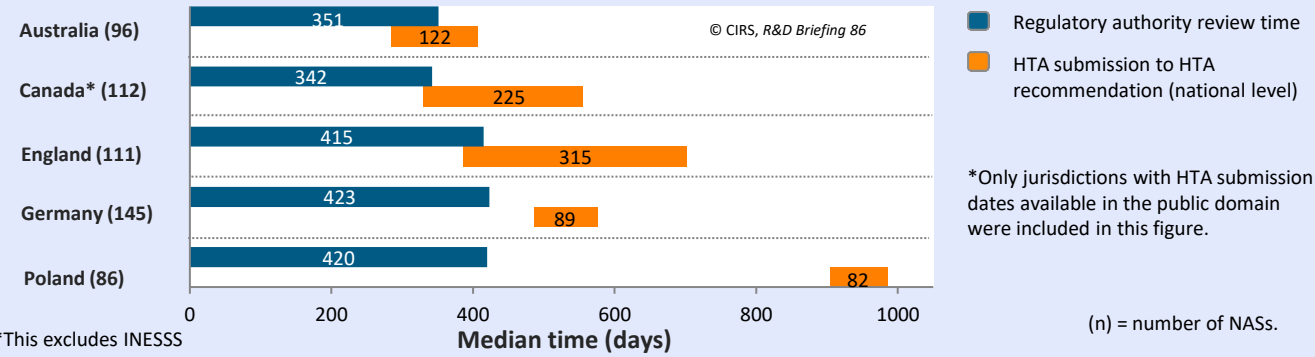


Australia presented the fastest time from regulatory approval to HTA recommendation in 2021 (109 days), followed by Germany and France (139 and 167 days, respectively) (Figure 4).

This suggests that the proactive approach within Australia to move toward synchronising the timing of HTA and regulatory review is achieving its purpose. The time taken from regulatory approval to HTA outcome can be attributed to company submission strategy, company time for pre-submission preparation and HTA agency review time. In addition, the median time from regulatory approval to HTA recommendation decreased in 2021 compared to 2020 for all the studied countries, except for Canada, England and Poland (**Figure 4**). We could also observe a shorter regulatory review time for the products that received an HTA recommendation by CADTH in 2021 compared to the overall review time in 2017-2020 (257 vs 345 days, respectively).

The HTA submission dates are only available in the public domain in Australia, Canada, England, Germany and Poland (**Figure 5**). Among these, Australia and Canada allow the HTA process to start before the regulatory approval is granted. In England, not all NASs undergo the NICE appraisal process; scoping is first developed before marketing authorisation is achieved, and then companies will be invited to submit HTA dossiers to NICE. In Germany, companies can set their drug prices freely at market entry, but they must submit an HTA dossier to G-BA (Federal Joint Committee, Gemeinsamer Bundesausschuss) who then request IQWiG to assess the added therapeutic benefit of the drug over the appropriated comparator within three months. Poland had the shortest median HTA appraisal time (82 days) however it took a longer time for the product to reach patients compared to the other jurisdictions due to the gap between regulatory approval and HTA submission.

Figure 5 : Breakdown of rollout time in jurisdictions where HTA submission date is provided 2017-2021*



CHARACTERISTICS: REGULATORY AND HTA REVIEW SEQUENCE

Figure 6: Number of NASs assessed by Australia (PBAC) and Canada (CADTH) between 2017 and 2021, by HTA submission sequence

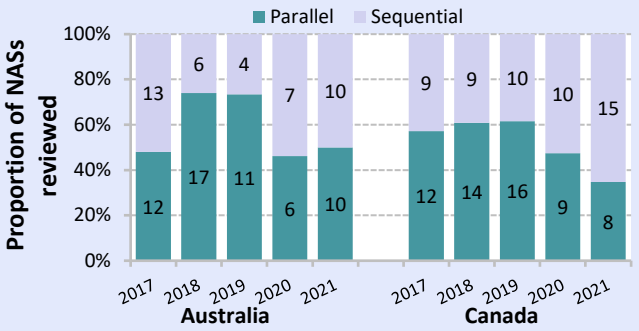


Table 1: HTA submission sequence by top 5 therapeutic areas in Australia (PBAC) and Canada (CADTH) between 2017-2021

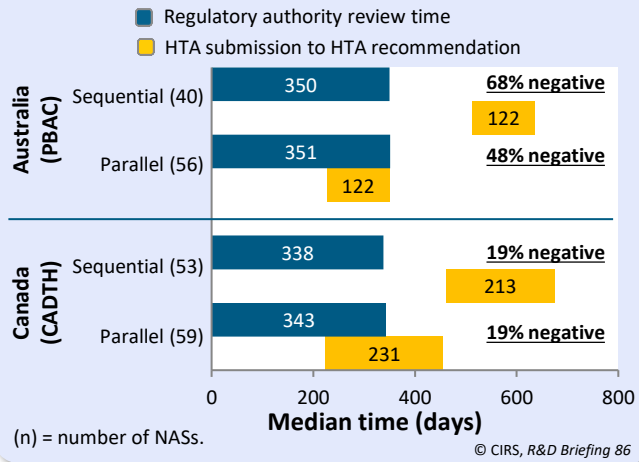
	Alimentary and metabolism	Blood and blood forming organs	Anti-infective	Anti-cancer and immuno-modulators	Nervous system
Australia Sequential	4 (40%)	3 (100%)	0 (0%)	21 (44%)	4 (31%)
Australia Parallel	6 (60%)	0 (0%)	5 (100%)	27 (56%)	9 (69%)
Canada Sequential	8 (50%)	3 (60%)	3 (43%)	23 (45%)	7 (64%)
Canada Parallel	8 (50%)	2 (40%)	4 (57%)	28 (55%)	4 (36%)

Number of products (percentage within the therapeutic area)

In 2021, the number of parallel submissions in Australia remained consistent with the average per year from 2017-2020 (10 vs 12), however, in Canada, it decreased (8 vs 13) (Figure 6).

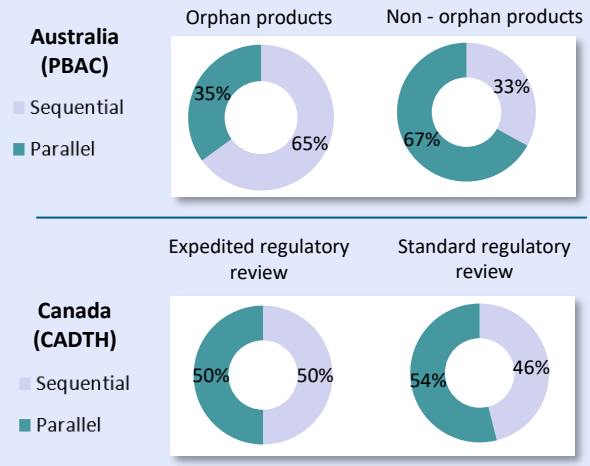
To receive an HTA recommendation for drug reimbursement, companies submit evidence to the regulatory agency for market authorisation, then sequentially to the HTA agency for assessment and appraisal. In Australia and Canada, during the regulatory review process, companies can submit dossiers to the HTA agency so that the two steps can occur in parallel. This sequence is established with the aim of shortening the overall time for the two-step decision-making process and promoting timely access to new medicines. Companies have taken advantage of the parallel review mechanism: in 2017-2021, 58% of products in Australia and 53% of products in Canada were submitted under the parallel process (**Figure 6**). In total, 115 products were submitted in parallel in both jurisdictions in the last 5 years, of which 55 (48%) were anti-cancer and immunomodulators (**Table 1**). Looking at the type of products, all anti-infective products were submitted under a parallel process in Australia.

Figure 7: Breakdown of rollout time of NASs assessed by Australia (PBAC) and Canada (CADTH) in 2017-2021 by submission sequence



(n) = number of NASs.

Figure 8: Impact of regulatory characteristics on the HTA submission sequence (2017-2021)

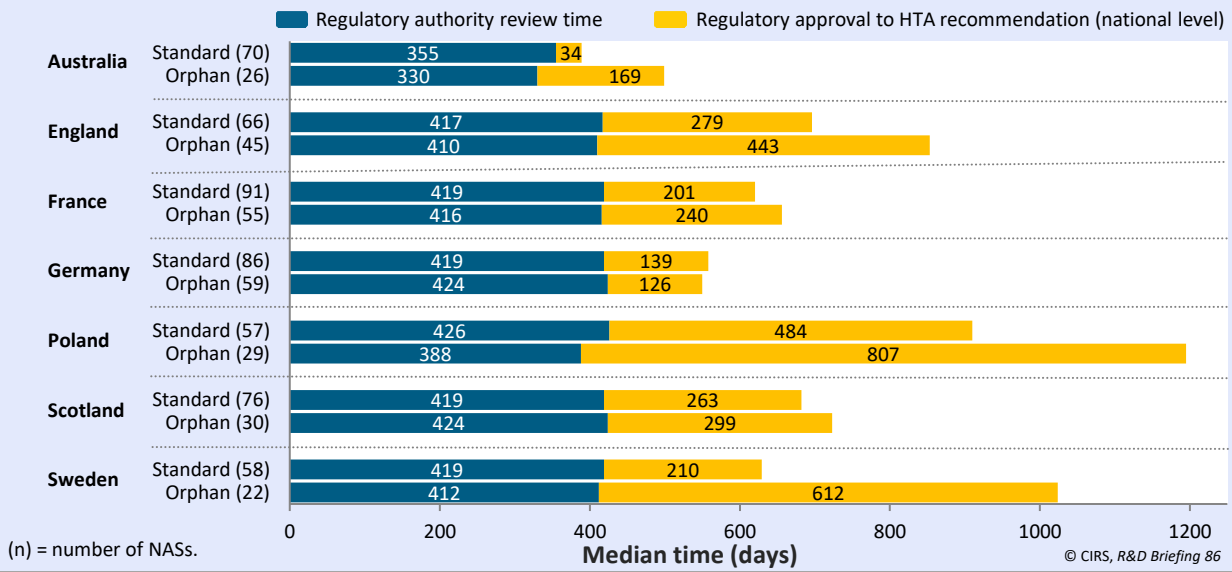


The parallel process shortened the overall time taken from regulatory submission to HTA recommendation in both Australia and Canada (Figure 7).

Under the TGA/PBAC parallel process, the TGA delegate's overview is informative to PBAC's consideration to appraise a drug; companies can submit the regulatory delegate overview up to a week prior to the PBAC meeting. In 2017-2021**,** the median time for submission to PBAC was 124 days prior to TGA approval for parallel review, compared with a 163-day delay in HTA submission with the sequential review (**Figure 7**). The Health Canada/CADTH parallel review process has specific submission criteria: within 180 days before the date of anticipated Notice of Compliance (NOC) from Health Canada. The gap between NOC and submission to CADTH was 123 days for sequential review, which was shorter than the sequential process in Australia.

A higher proportion of submissions in Australia received negative recommendation (68%) under the sequential process, compared to the parallel process (48%) (**Figure 7**). However, Canada showed the same percentage of negative recommendations in both parallel and sequential submissions. In Australia, regulatory orphan products preferentially followed a sequential submission, while non-orphan products presented a higher percentage of parallel submissions (**Figure 8**). The expedited regulatory review in Canada showed no preference for any type of submission sequence and similar results were observed for products that followed a standard regulatory review (**Figure 8**).

Figure 9: Breakdown of rollout time of NASs reviewed by HTA in 2017-2021, by regulatory orphan designation

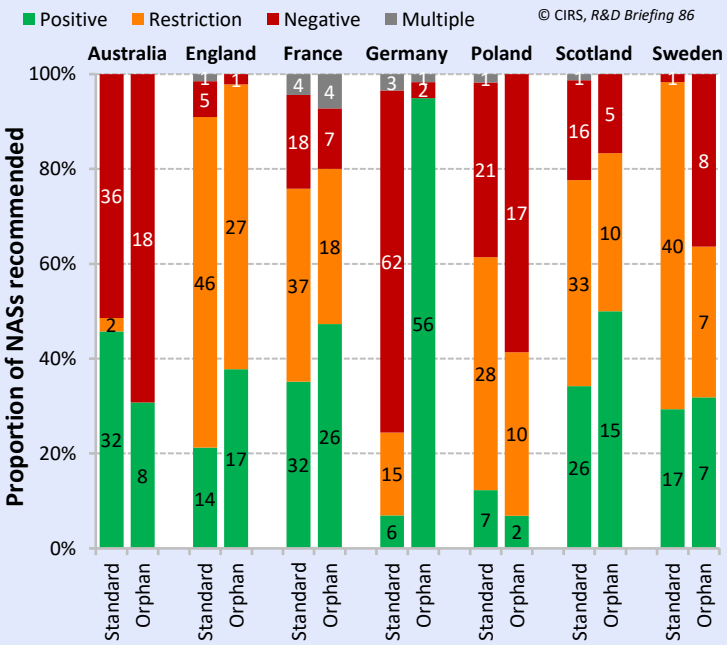


The regulatory orphan designation generally presented a longer time to HTA recommendation (Figure 9) and did not have a considerable effect on the type of HTA recommendation in all jurisdictions except Germany (Figure 10).

The orphan designation has been used by regulatory agencies (TGA in Australia and EMA in Europe) in an effort to expedite the approval of drugs treating serious illnesses or addressing unmet medical needs. Health Canada does not currently have an orphan policy. The results showed that NASs with regulatory orphan designation had a longer time to rollout compared to standard in all jurisdictions, except for Germany (**Figure 9**), which could be due to their relatively weak evidence and the relatively high cost per patient. This finding suggested that further efforts are needed to accelerate the access to orphan drugs. The time taken from regulatory approval to HTA recommendation includes company strategy and HTA review time.

In addition, the regulatory orphan designation does not have a considerable effect on the type of HTA recommendation with the exception of Germany (**Figure 10**). In this briefing, IQWiG recommendations for orphan drugs are considered as positive because additional therapeutic benefit is considered to be proved at marketing authorisation. The assessments of orphan drugs are conducted by G-BA and the assessment report outcomes were out of scope for this briefing.

Figure 10: First HTA recommendation comparison across key jurisdictions in 2017-2021, by regulatory orphan designation



Not all NAS that received a regulatory orphan designation undergo an HTA orphan/rare disease-related pathway.

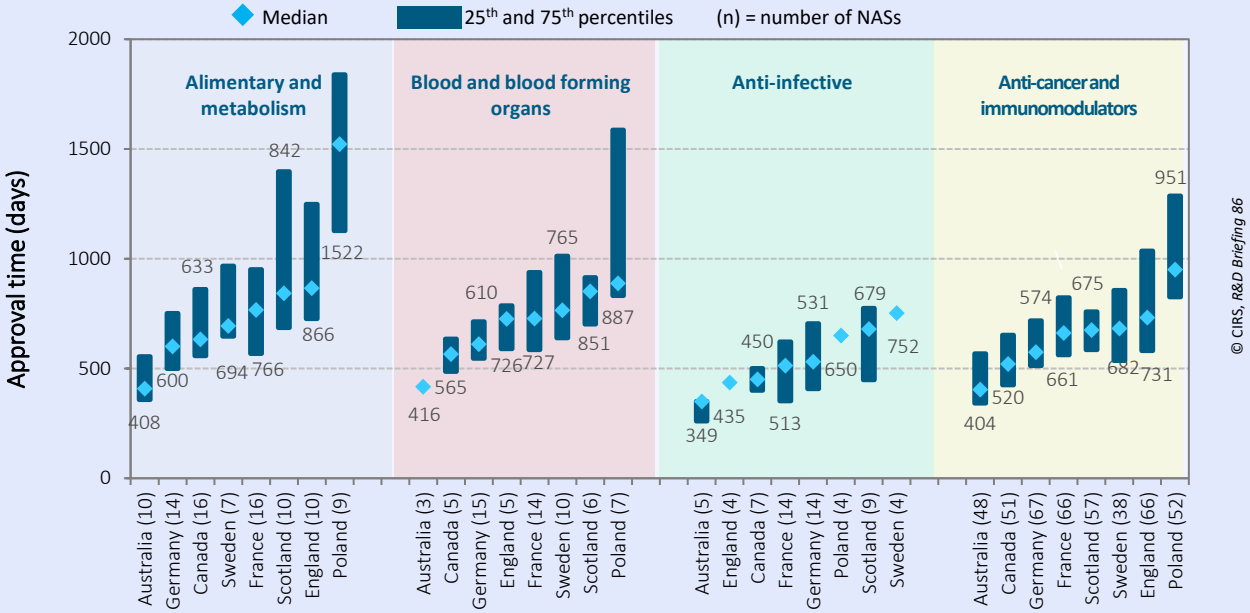
The list of HTA orphan/rare disease-related pathways across all jurisdictions is elaborated in **Table 6** in the appendix (HTA orphan/rare disease-related pathways).

In Germany and Scotland, the majority of the NASs that received a regulatory orphan designation underwent an HTA orphan/ rare disease-related pathway (95% and 93%, respectively), while in Australia and England less than half of the NASs that received a regulatory orphan designation went on to an HTA orphan/ rare disease-related pathway (42% and 27%).

In England and Germany, all the NASs that underwent an HTA orphan/ rare disease-related pathway received a regulatory orphan designation. In these countries, the EMA orphan designation criteria are used in the HTA orphan/ rare disease-related pathways (**Table 6**). In Australia, the HTA orphan/ rare disease-related pathways identified do not apply to only orphan drugs and thus, there is less congruence in the orphan-related criteria between regulatory and HTA.

CHARACTERISTICS: THERAPEUTIC AREA

Figure 11: Time taken from regulatory submission to 1st HTA recommendation in 2017-2021, by top therapeutic area



The top four therapeutic areas made up 68% (182/263) of all the products assessed by at least one country between 2017-2021, with anti-cancer and immunomodulators making up 57% (104/182) of the top therapeutic areas (Figure 11).

Australia was the fastest for all four therapy areas in terms of rollout time from regulatory submission to HTA outcome, while Poland was the slowest country for the top therapeutic areas, except for "anti-infectives", where Sweden showed the highest median rollout time(**Figure 11**). As noted by the 25th-75th percentile bars, there were also wide variations for certain jurisdictions across therapy areas. The variation of rollout time may be attributed to expedited review pathways by regulatory agencies across the four therapy areas, companies' submission strategy (parallel vs. sequential), and time taken during the HTA process.

Time taken from regulatory approval to HTA recommendation was marginally faster for anti-cancer and immunomodulators in all jurisdictions except Australia (Figure 12).

As the HTA review time in Australia is consistently around four months based on the frequency of committee meeting, the time difference could be attributed to the submission strategy by companies. Sweden and England recommended (including both positive and restriction recommendations) the highest percentage of anti-cancer and immunomodulators for reimbursement, 95% and 91% of submissions, respectively (**Figure 13**). Although 80% of submissions to Canada were recommended, the HTA recommendations were mostly restricted (76%).

Figure 12: Breakdown of rollout time by therapeutic areas (2017-2021)

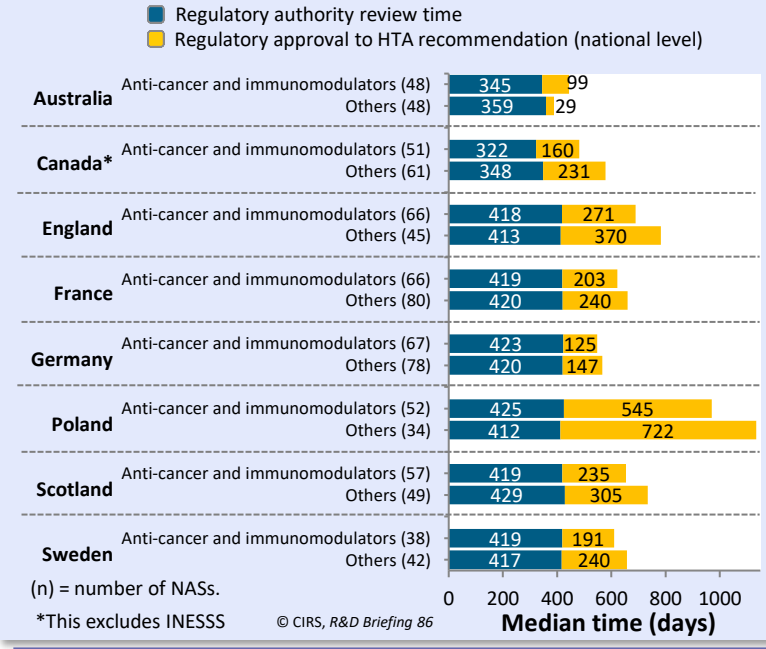


Figure 13: HTA Recommendation for anti-cancer and immunomodulators (2017-2021)

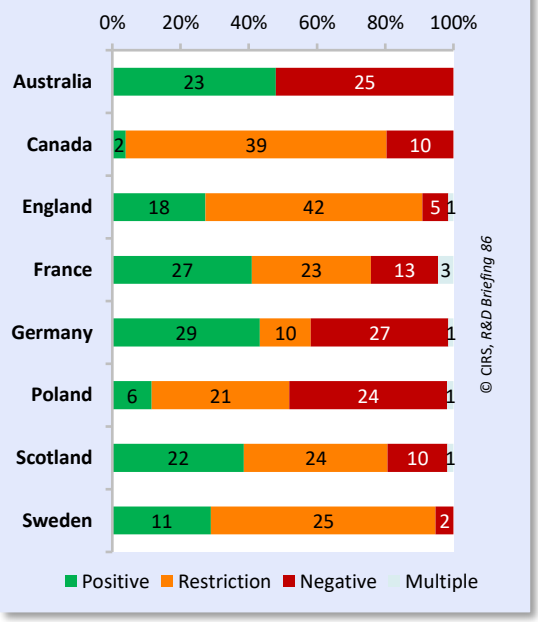
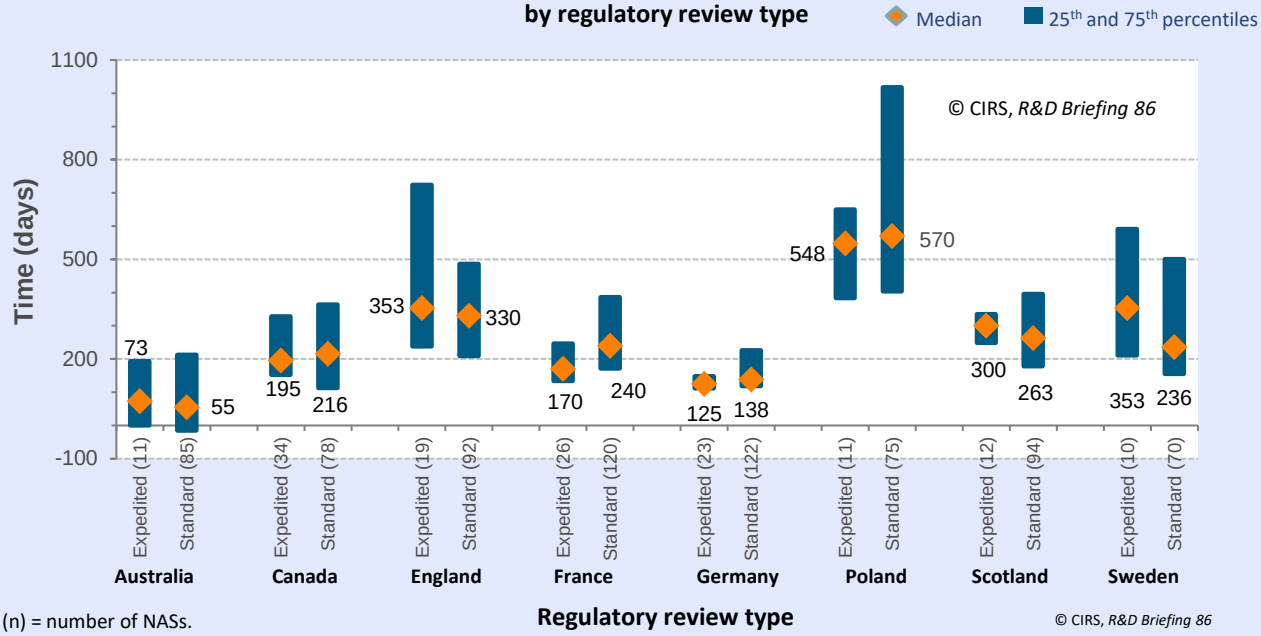


Figure 14: Rollout time from regulatory approval to HTA recommendation (2017-2021) by regulatory review type



The NASs that went through a conditional regulatory pathway consistently presented a longer median time from regulatory approval to HTA recommendation compared to non-conditional (Figure 15).

The list of expedited and conditional regulatory pathways across all jurisdictions is elaborated in the Appendix (Facilitated regulatory pathways, Table 7).

'Expedited review' refers to EMA 'Accelerated Assessment' and Health Canada/TGA 'Priority Review'. TGA introduced an expedited (priority) review programme in 2017. The median overall time from regulatory approval to HTA recommendation was similar for expedited review and standard review in all jurisdictions, except for Sweden, which showed a 117 days longer median time for expedited reviews compared to standard (**Figure 14**).

The regulatory agencies in Australia, Canada and Europe also provide a conditional pathway to facilitate the marketing of promising new medicines where there is limited clinical data. **Figure 15** shows that NASs that went through a conditional regulatory pathway consistently presented a longer median rollout time from regulatory approval to HTA recommendation, except for Germany. **Figure 16** shows the proportion of the HTA outcome by type of regulatory pathway (conditional vs non-conditional), displaying variability across the different jurisdictions.

Figure 15: Breakdown of rollout time comparing the conditional regulatory pathway vs non-conditional between 2017-2021

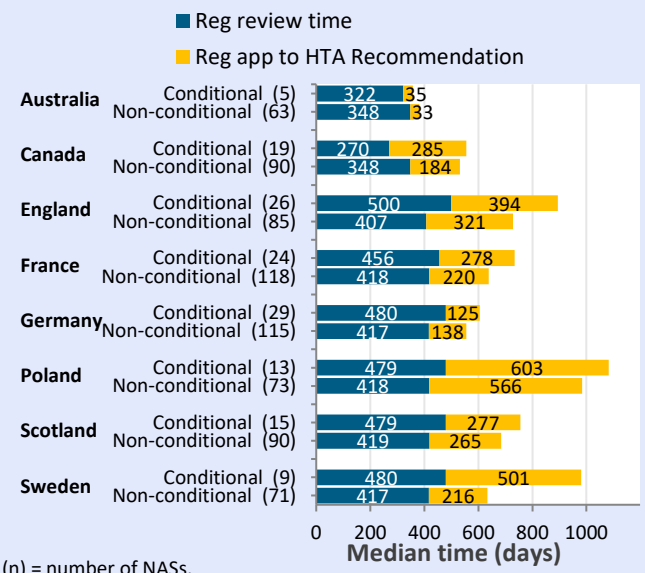


Figure 16: First HTA recommendation type across key jurisdictions comparing the conditional regulatory pathway vs non-conditional between 2017-2021

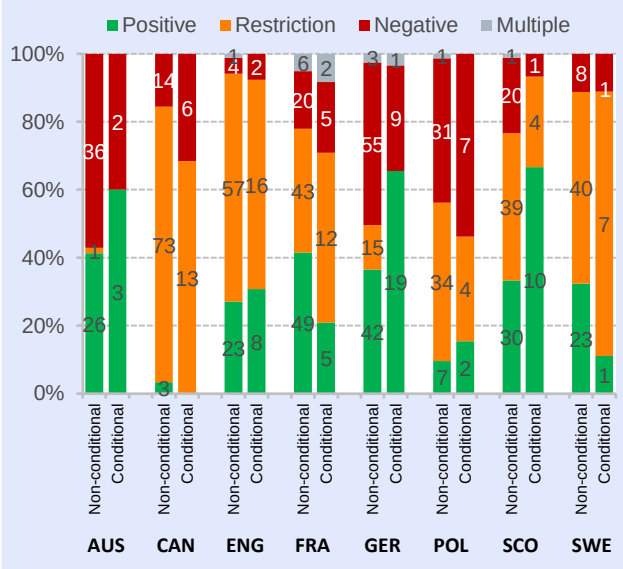
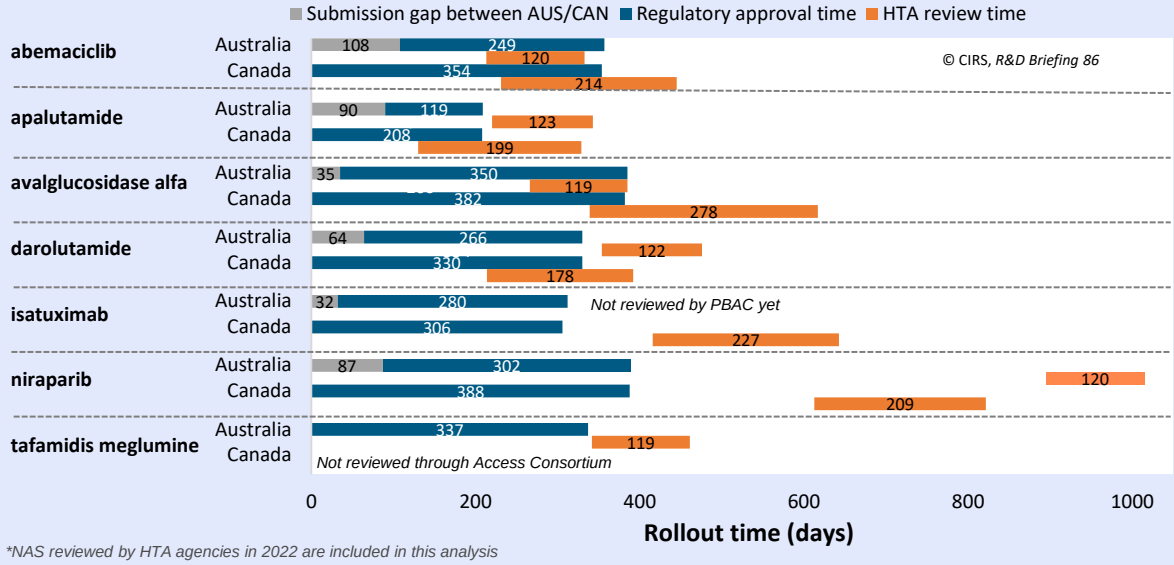


Figure 17: The regulatory approval and HTA recommendation for NASs approved by the Access Consortium between 2018-2021*



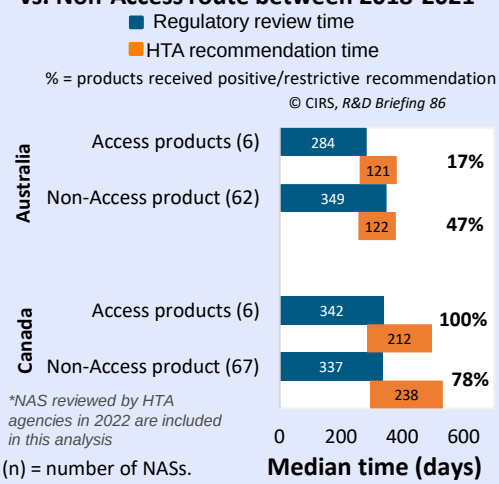
*NAS reviewed by HTA agencies in 2022 are included in this analysis

The Access Consortium is a medium-sized coalition, which was formed by 'like-minded' regulatory agencies to promote greater collaboration and alignment of regulatory requirements. We assessed the Regulatory and HTA recommendation route for the NASs reviewed by Access Consortium.

As part of the work-sharing process, the regulatory agencies review different parts of the dossier. This model of work-sharing is being watched to see if this could be a model for other like-minded agencies to share resources both within and across regions and to streamline company interactions. The following question is how the parallel review in Australia and Canada would be operationalised within the context of Access, and the impact of Access on the HTA time and recommendation.

7 products approved via the Access route were included in the HTADock dataset (**Table 2**). 4 out of 6 products were submitted in parallel to CADTH, while only 2 out of 6 products were submitted to PBAC before regulatory approvals (**Figure 17**). In terms of rollout, the median regulatory time was 65 days faster for Australia for Access NASs compared to all NASs approved between 2018 and 2021 (**Figure 18**). However, the HTA review time is consistent which is related to the fixed frequency of PBAC committee meetings. In Canada, the Access NASs had similar regulatory review times compared with non-Access NASs but were more likely to be submitted in parallel (4/6) in 2018-2021 (**Table 2**). Proportionally, the Access NASs presented a lower percentage of NASs that received a positive/positive with restrictions recommendation by PBAC compared to non-access, but a higher percentage when reviewed by CADTH (**Figure 18**). However, caution needs to be taken when interpreting these results due to the small sample size of the Access products. In January 2021, the UK Medicines and Healthcare products Regulatory Agency (MHRA) started work-sharing applications within this initiative, however, no NASs were approved in that year.

Figure 18: The median time for regulatory approval and HTA recommendation for NASs approved by the Access Consortium vs. Non-Access route between 2018-2021*



*NAS reviewed by HTA agencies in 2022 are included in this analysis

(n) = number of NASs.

Table 2: NASs approved by the Access Consortium between 2018-2021*

Product name	Therapeutic area	TGA-PBAC submission sequence	PBAC initial recommendation	Health Canada – CADTH submission sequence	CADTH initial recommendation
abemaciclib	Anti-cancer and immuno-modulators	Parallel	Positive	Parallel	Positive with restrictions
apalutamide	Anti-cancer and immuno-modulators	Sequential	Negative	Parallel	Positive with restrictions
avalglucosidase alfa	Alimentary and metabolism	Parallel	Negative	Parallel	Positive with restrictions
darolutamide	Anti-cancer and immuno-modulators	Sequential	Negative	Parallel	Positive with restrictions
isatuximab	Anti-cancer and immuno-modulators	Not reviewed as Access	Not reviewed as Access	Sequential	Positive with restrictions
niraparib	Anti-cancer and immuno-modulators	Sequential	Negative	Sequential	Positive with restrictions
tafamidis meglumine	Nervous system	Sequential	Negative	Not reviewed as Access	Not reviewed as Access

*NAS reviewed by HTA agencies in 2022 are included in this table.

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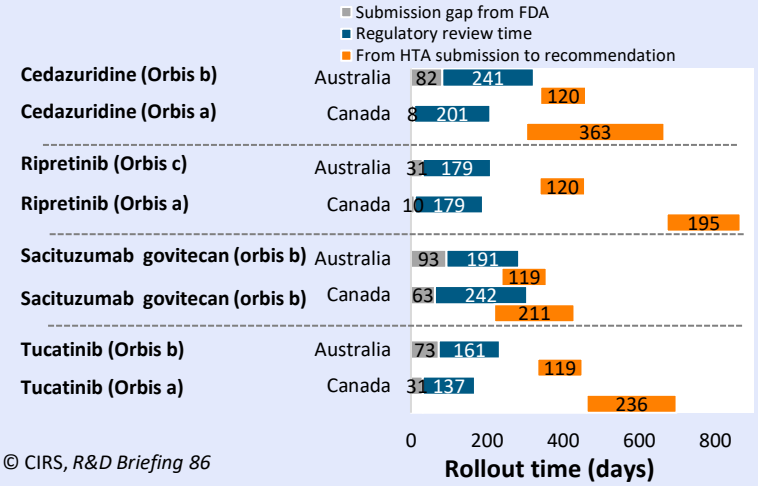
FOCUS: PROJECT ORBIS

Figure 19: The regulatory approval and HTA recommendation for NASs approved by Project Orbis between 2018-2021*



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*NAS reviewed by HTA agencies in 2022 are included in this analysis

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Table 3: NASs approved by Project Orbis that underwent an HTA assessment between 2018-2021*

Product name	cedazuridine	ripretinib	sacituzumab govitecan	tucatinib
Tumour type	Leukemia	Gastrointestinal	Breast	Breast
TGA-PBAC submission sequence	Sequential	Sequential	Parallel	Sequential
PBAC initial recommendation	negative	negative	negative	negative
Health Canada – CADTH submission sequence	Sequential	Sequential	Parallel	Sequential
CADTH initial recommendation	positive with restrictions	positive with restrictions	positive with restrictions	positive with restrictions

*NAS reviewed by HTA agencies in 2022 are included in this analysis

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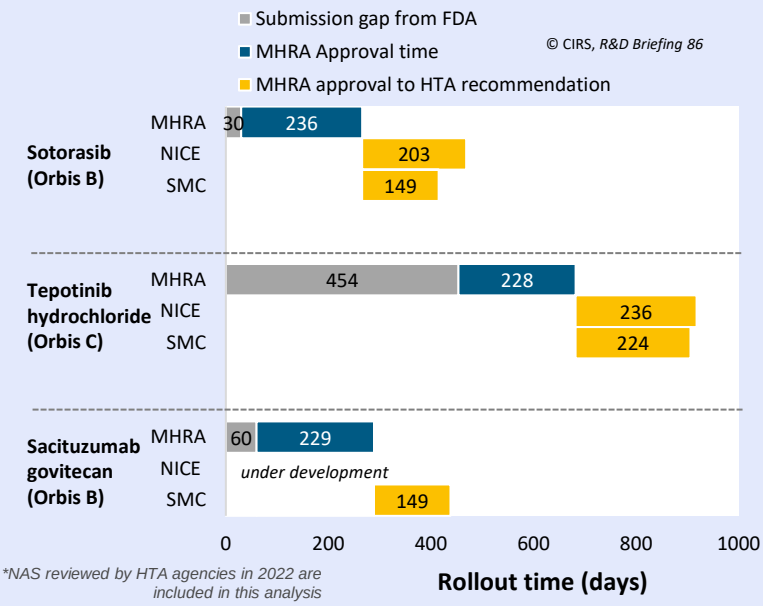
Project Orbis is an initiative of the US FDA Oncology Center of Excellence that aims to give patients faster access to promising cancer treatments across the globe. Project Orbis partners work together on the review of submissions for cancer drugs.

There are 3 types of Project Orbis submissions which are dependent on the timelines between FDA and partners (see definition page for the details of Orbis **A**, **B** and **C** type of reviews). We assessed the regulatory and HTA timing and recommendations for the NASs via the Orbis route in Australia, Canada and the UK.

For NASs approved through Project Orbis between 2018-2021, 4 products were reviewed by HTA agencies in Australia and Canada (**Table 3**). The most commonly used Orbis type was **B** in Australia, where there is a > 30-day delay from FDA to partner submission, while in Canada, Orbis **A** type was used for 3 out of 4 products (**Figure 19**). Although regulatory time was shortened compared to the overall median time, we noticed the longer submission gap to HTA agencies for Cedazuridine and Tucatinib which underwent Orbis type **A**, which may suggest that companies were not ready to submit to HTA agencies when receiving the market authorisation.

Three NASs approved by MHRA were reviewed by Scotland (SMC), and two by England (NICE). As the SMC submission date is not available, we assessed the time from MHRA approval to the HTA recommendation, which SMC was faster than NICE for Sotorasib and Tepotinib (**Figure 20**). Two products went through the SMC Patient and Clinician Engagement (PACE) process, which gives patient groups and clinicians a stronger voice in the SMC recommendation-making (**Table 4**).

Figure 20: The regulatory approval and HTA recommendation for NASs approved by Project Orbis between 2018-2021 in the UK*



*NAS reviewed by HTA agencies in 2022 are included in this analysis

Table 4: NASs approved by Project Orbis between 2018-2021 in the UK*

Product name	sacituzumab govitecan*	sotorasib	tepotinib hydrochloride
Tumour type	Breast	Lung	Lung
NICE Note	NICE appraisal under development	Managed Access Agreement	Simple discount patient access scheme
NICE initial recommendation		Positive	Positive
SMC Note	PACE Meeting	Interim acceptance	PACE Meeting
SMC initial recommendation	Positive	Positive	Negative

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*NAS reviewed by HTA agencies in 2022 are included in this analysis

FOCUS: RESUBMISSION

AUSTRALIA
96 NASs assessed, **56%** had a first negative recommendation.

CANADA
112 NASs assessed, **19%** were not recommended

ENGLAND
111 NASs assessed, **5%** were not recommended.

FRANCE
146 NASs assessed, **17%** were rated as "lesser benefit".*

First HTA recommendation between 2017 and 2021

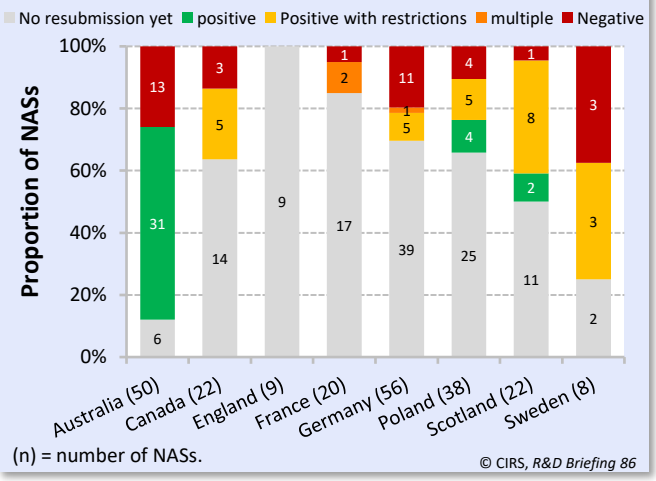
GERMANY
145 NASs assessed, **44%** were rated as "no added benefit proven" or "less benefit".*

POLAND
86 NASs assessed, **44%** were not recommended.

SCOTLAND
106 NASs assessed, **20%** were not recommended.

SWEDEN
80 NASs assessed, **11%** were not recommended.

Figure 21: The resubmission status of NASs that received negative HTA recommendation between 2016-2020



(n) = number of NASs.

* In Germany, products with negative outcome (less benefit proven) will be included in the reference price system within six months of market launch. If a product without additional benefit cannot be allocated to a reference price group, a reimbursement price will also be agreed on.

In France, if the HTA outcome is negative (SMR rate is insufficient) products will not be included on the positive list (not reimbursed).

In 2016-2020, NASs received negative HTA recommendations were followed up to assess the resubmission status by August 2022 (Figure 21).

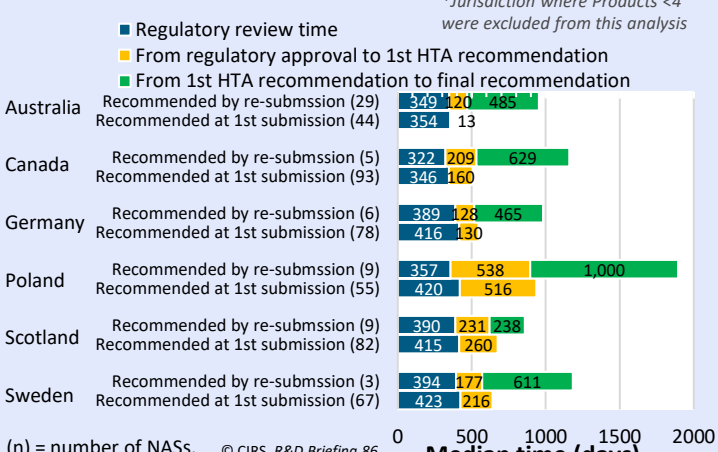
Australia had the highest proportion of negative recommendations in its initial review, however, we observed the biggest resubmission number. The resubmission also led to a high percentage of positive recommendations (62%). All negative recommendations by NICE have not had a re-submission outcome. We focused on resubmissions to HTA agencies within the same regulatory indication; submissions with a new indication or a line extension, or re-evaluation initiated by an HTA agency were not included.

A long rollout time for NASs that received positive/restrictive recommendations at resubmission was observed (Figure 22).

Although products that underwent resubmission had a longer rollout time, when examining the breakdown of the timeline, the major attribute is the resubmission gap (**Figure 23**). The resubmission gap may be related to the time companies need to prepare dossiers, providing additional information for the submission, which was the longest in Poland with a median time of 952 days.

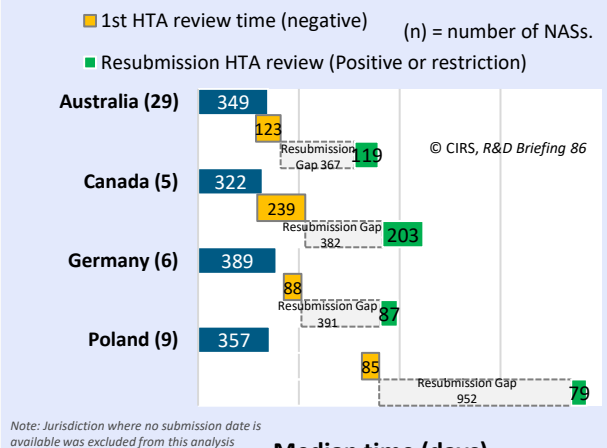
Figure 22: Rollout time for NASs received positive/restrictive recommendations at the 1st submission vs. resubmission (reviewed by HTA agencies 2016-2020)

**Jurisdiction where Products <4 were excluded from this analysis*



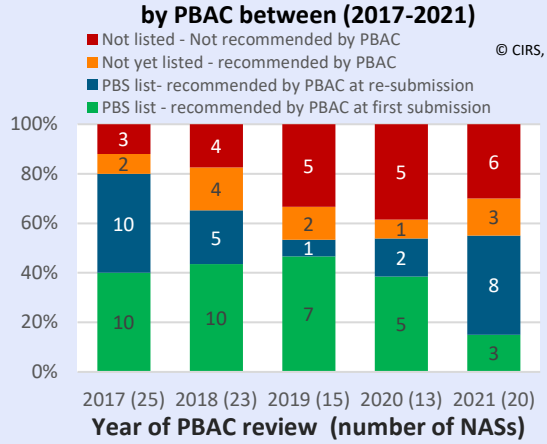
(n) = number of NASs.

Figure 23: Breakdown of resubmission rollout time for NASs received negative recommendation 2016-2020



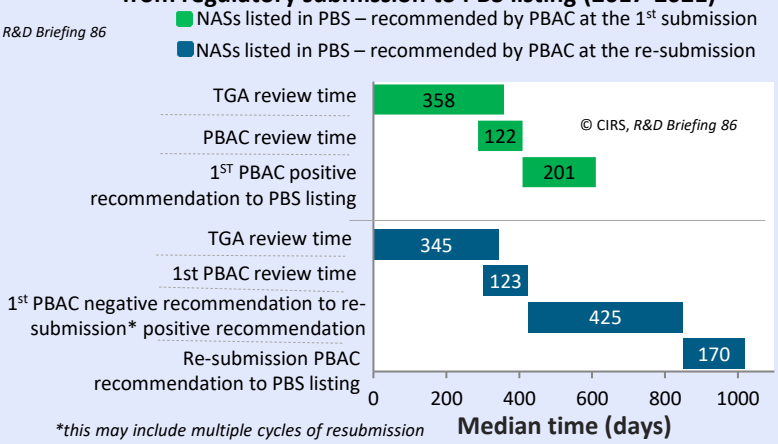
Note: Jurisdiction where no submission date is available was excluded from this analysis

Figure 24: The PBS listing status for NASs reviewed by PBAC between (2017-2021)



(n) = number of NASs.

Figure 25: Breakdown of rollout time for NASs from regulatory submission to PBS listing (2017-2021)



*this may include multiple cycles of resubmission

64% (61/96) of drugs with PBAC recommendations in 2017-2021 were listed in the PBS list in Australia, of which 57% (35/61) appraised by PBAC were listed at the first submission (Figure 24).

PBAC makes HTA recommendations for the listing of medicines on the Pharmaceutical Benefits Scheme (PBS) list that are non-binding and require Ministerial approval. For pharmaceuticals with a projected annual cost of less than AUD$20 million, the Minister of Health (or a delegate) is the decision maker for listing new drugs on the PBS. For pharmaceuticals with a projected annual cost of greater than AUD$20 million, Cabinet consideration is required. These decisions follow the completion of negotiations with the sponsor by officers from the Australian Government Department of Health and Aged Care based on the advice from PBAC.

In Australia, drugs cannot be listed on the PBS without a PBAC recommendation. When the first HTA recommendation does not support listing, 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 listing. The proportion of PBS-listed drugs that were recommended by PBAC at the first submission was similar from 2017-2020, with an average of 42%. However, this dropped to 15% in 2021 (**Figure 24**). Multiple review cycles increase the time to be listed in the PBS list (**Figure 25**).

The parallel regulatory and HTA review process in Australia shortened the overall time to be listed in PBS, with 58% of products going through this process between 2017 and 2021 (Figure 26).

Products that underwent the parallel process were submitted to PBAC approximately four months before TGA approval. 51% of submissions were recommended at the 1st submission, compared to 37% of products submitted sequentially. The time taken to be listed at PBS was longer for sequentially reviewed products (566 days) compared to parallel review (382 days).

TGA introduced an expedited review programme in 2017 (Priority review); 13 products that underwent TGA priority approval have undergone the HTA process (Table 5).

TGA Priority review is a formal expedited mechanism for a faster assessment to address unmet medical needs and where a high therapeutic benefit can be expected. Among the 13 products included in the study, 10 products were not recommended by PBAC at the initial submission. Two NASs were assessed by MSAC* (medical services advisory committee), and the HTA outcome supported the public funding for the two products.

Figure 26 Breakdown of rollout time by review sequence (2017-2021)

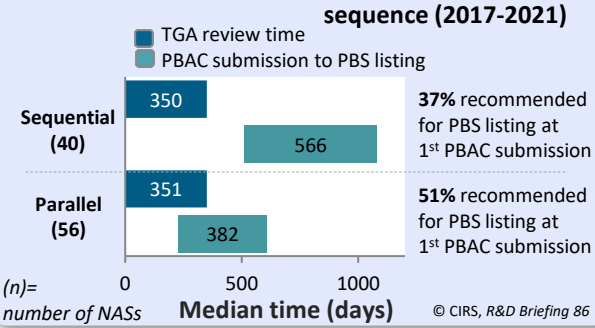
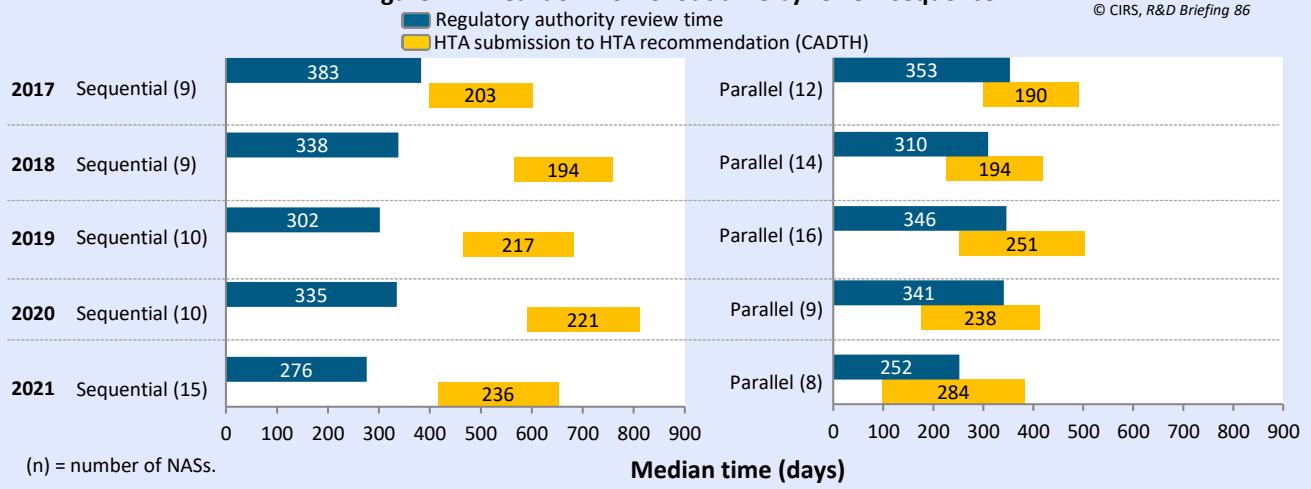


Table 5: HTA recommendation status for products that underwent TGA Priority approval (2017-2021)

Generic Name	Orphan status	TGA Approval	HTA recommendation date	PBAC/ MSAC	First HTA recommendation	Final recommendation if there is a resubmission
Cerliponase alfa	yes	Aug 2018	Jul 2018	PBAC	Negative	No resubmission
Apalutamide	no	Jul 2018	Nov 2018	PBAC	Negative	Positive
Emicizumab	yes	Feb 2018	Nov 2018	MSAC*	Positive with restrictions	NA
Lanadelumab	yes	Jan 2019	Jul 2019	PBAC	Negative	Positive
Polatuzumab vedotin	no	Oct 2019	Nov 2019	PBAC	Negative	No resubmission
Dinutuximab beta	yes	Mar 2020	Jul 2020	MSAC*	Positive	NA
Burosumab	no	Sep 2021	Mar 2021	PBAC	Negative	Not recommended (in 2022)
Risdiplam	no	Jun 2021	Mar 2021	PBAC	Positive with restrictions	NA
Ripretinib	yes	Jul 2021	Mar 2021	PBAC	negative	Positive
Tucatinib	no	Aug 2020	Mar 2021	PBAC	negative	NA
Amifampridine	no	Sep 2021	Nov 2021	PBAC	Negative	Positive (in 2022)
Gilteritinib fumarate	yes	Apr 2020	Nov 2021	PBAC	Negative	Positive (in 2022)
Sacituzumab govitecan	no	Sep 2021	Nov 2021	PBAC	Negative	Positive (in 2022)

** MSAC (medical services advisory committee) was out of scope of this study, was only included in this analysis to compare the funding recommendation of priority products.*

Figure 27: Breakdown of rollout time by review sequence



Submissions to CADTH under parallel process are being made earlier, with 154 days overlap between regulatory and HTA process in 2021.

The Health Canada/CADTH parallel review process, which allows for 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. From 2 April 2018, CADTH submission criteria were changed to within 180 days before the anticipated NOC from Health Canada. The overlap between the median regulatory and HTA reviews increased from 2017 to 2020 and 2020 remained similar to 2021, with the overlap time between the median regulatory and HTA review time being 53, 84, 94, 166 and 154 days in 2017, 2018, 2019, 2020 and 2021, respectively, indicating that the parallel process is being optimised (**Figure 27**). The submission gap for products reviewed sequentially has decreased in 2021 compared to 2020, with the time taken from regulatory approval to HTA submission being 140 and 255 days, respectively.

The companies' request for reconsideration to CADTH extended the median time to the final HTA recommendation.

During the CADTH reimbursement review and after receiving a draft recommendation from CADTH, the sponsor of a drug and the drug programmes may file a request for reconsideration of the recommendation during the feedback period. Every drug application is entitled to one reconsideration and this should be based only on the recommendation not being supported by the evidence provided in the report submitted by the sponsor to CADTH. In the case of a request for reconsideration, a reconsideration meeting will be held by the Expert Committee Meeting and after this, a final recommendation will be issued. If there is no request for reconsideration a final recommendation will be issued after the stakeholder feedback period has ended.

Figure 28 indicates that the request for reconsideration increased the median review time from submission to the recommendation by CADTH compared to no request. During the time period 2020-2021, 41% of the applications that requested a reconsideration received a negative recommendation, 53% a positive with restriction recommendation and 6% a positive recommendation (**data not shown**). In addition, the request for reconsideration extended the median time from the initial to the final recommendation compared to no request: 134 vs 21 and 116 vs 52 days in 2020 and 2021, respectively (**Figure 29**).

Figure 28: Breakdown of rollout time in Canada between 2020-2021 (Requested reconsideration vs standard)

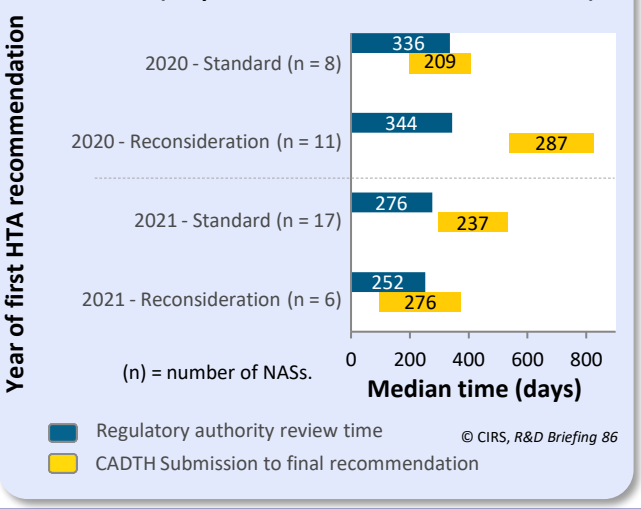


Figure 29: Breakdown of CADTH review time between 2020-2021 (Requested reconsideration vs standard)

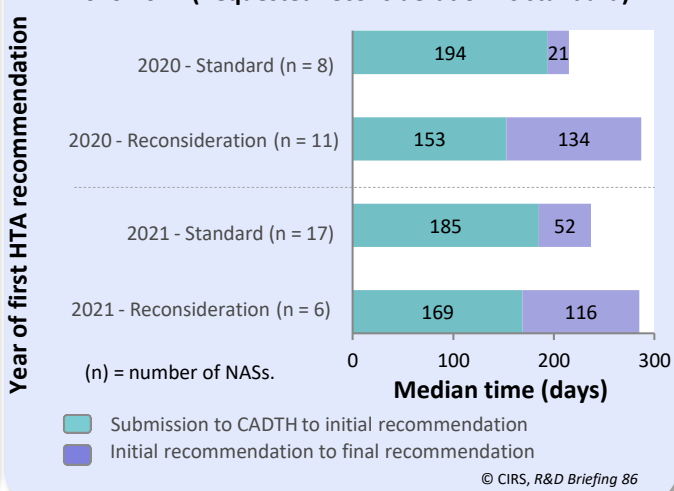
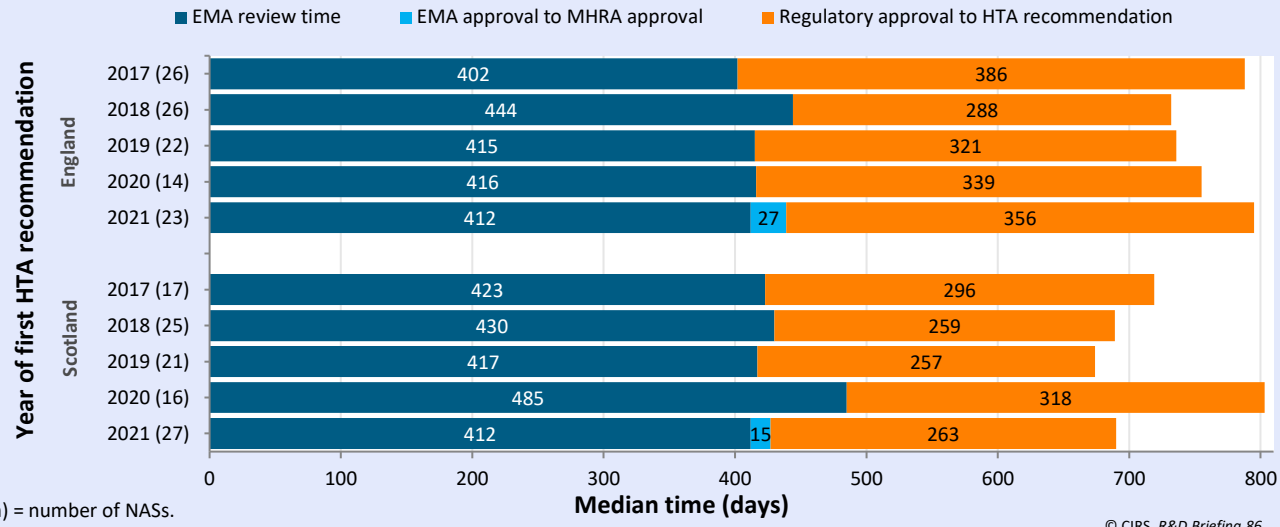


Figure 30: Breakdown of rollout time in the UK 2017-2021



(n) = number of NASs.
Note: the difference in the regulatory timeline is due to the sample size.

Figure 30 displays the breakdown of rollout time in the UK. Considering the changes in the regulatory process after Brexit, the MHRA review time was included in our analysis.

We tracked the EMA approvals and the HTA recommendation in the UK from 2017-2020. Due to Brexit, from the 1st of January of 2021 the Medicines and Healthcare products Regulatory Agency (MHRA) may rely on the decisions taken by the European Commission (EC) on the approval of new marketing authorisations (MAs). Via this route, companies can submit applications to the MHRA after they receive a positive opinion from the Committee for Medicinal Products for Human Use (CHMP). The MHRA will aim to determine the UK authorisation after EC approval, no later than 67 days after the EC decision has been made. **Figure 30** shows that the time from EMA approval to MHRA approval was 27 and 15 days for products reviewed in 2021 at NICE and SMC, falling within the target time range. In addition, the median time from regulatory approval to HTA recommendation remained similar in 2021 compared to the overall median time between 2017-2020: 356 vs 334 and 263 vs 279 days for England and Scotland, respectively. The latter suggests that there has been an effort to align the regulatory and HTA recommendation despite the changes in the regulatory process. This is also reflected in **Figure 31**, where the submission date is available at NICE, we observed an overlap of 148 days between the regulatory and HTA process in 2021.

NICE and SMC displayed a similar time from regulatory approval to HTA recommendation of common NASs between 2017 and 2021.

74 common products were evaluated in both England and Scotland (67 and 70% of England and Scotland products, respectively). Of these common products, the median time from EMA approval to the NICE and SMC recommendation was 297 and 261 days, respectively, during the time period 2017-2021 (**Figure 32**). 51% (38/74) of the common products were recommended by NICE first and 49% recommended by SMC first; 57% of products were recommended by both agencies within 3 months. The median gap between NICE and SMC recommendations is 79 days.

Figure 31: Products roll out time in England (n = 111)

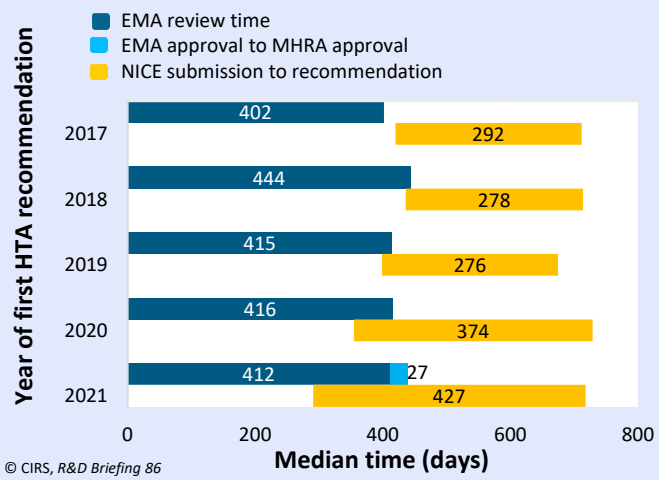


Figure 32: Breakdown of rollout time in UK recommendation common compounds (n=74) across NICE and SMC 2017-2021

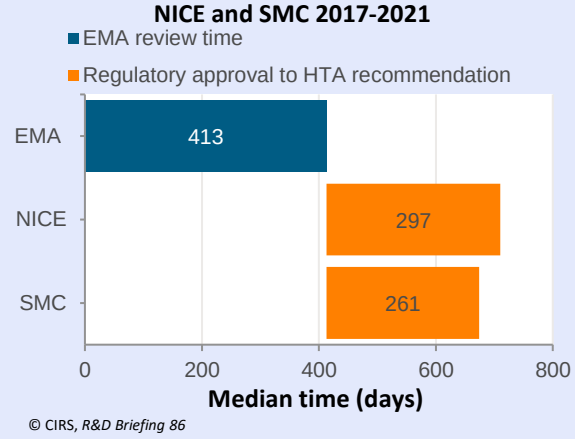


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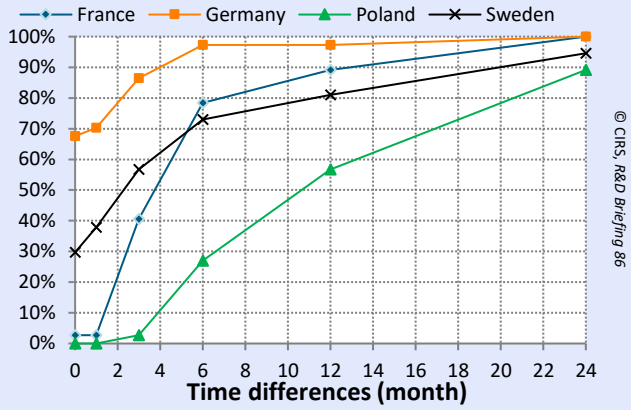
Figure 33: First HTA recommendation comparison for 37 common NASs reviewed by four agencies (2017-2021)

Positive | Restriction | Negative | Multiple

Generic name	France	Germany	Poland	Sweden
Abemaciclib	1	2	4	3
acalabrutinib	3	1	4	2
alectinib hydrochloride	3	1	4	2
alpelisib	2	1	4	3
apalutamide	2	1	3	4
baricitinib	2	3	4	1
benralizumab	3	1	4	2
binimetinib	4	1	3	2
brigatinib	4	2	3	1
dacomitinib	3	2	4	1
encorafenib	4	1	3	2
entrectinib	4	1	2	3
erenumab	3	2	4	1
fremanezumab	4	1	2	3
galcenezumab	2	1	4	3
gilteritinib fumarate	2	1	4	3
glecaprevir / pibrentasvir	3	2	4	1
guselkumab	3	2	4	1
ixazomib	2	1	4	3
lanadelumab	2	1	3	4
larotrectinib	3	1	2	4
letermovir	2	1	3	4
lonoctocog alfa	2	1	4	3
lorlatinib	3	1	4	2
midostaurin	3	1	4	2
ozanimod	2	1	3	4
palbociclib	2	1	4	3
ribociclib succinate	3	1	4	2
risankizumab	4	2	3	1
risdiplam	2	1	4	3
rurioctocog alfa pegol	3	2	4	1
semaglutide	3	2	4	1
siponimod	3	1	4	2
tezacaftor, ivacaftor	3	1	4	2
tofacitinib citrate	3	2	4	1
upadacitinib	2	4	3	1
venetoclax	2	1	3	4

Figure 34: HTA recommendation time gap: 1st HTA recommendation time differences for 37 Common NASs reviewed by four agencies (2017-2021)



Time difference = HTA recommendation date – earliest HTA recommendation date

In 2017-2021, 37 NASs approved by EMA have been appraised by all 4 jurisdictions, of which 25 were anti-cancer products and 2 were anti-infectives.

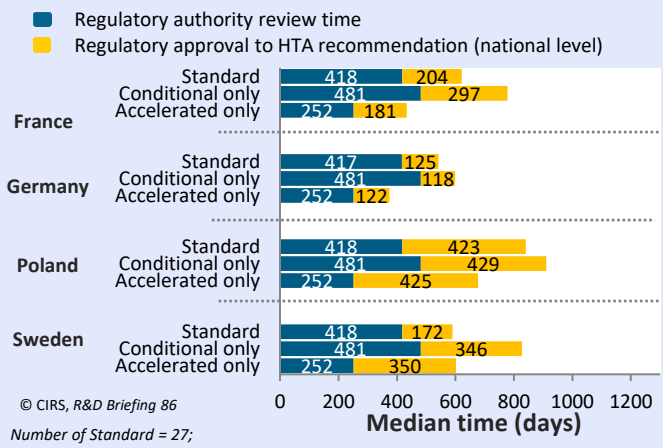
CIRS analysed NASs that rolled out to 4 European jurisdictions and identified 37 NASs that received a first HTA recommendation between 2017 and 2021 by all 4 HTA agencies, referred to as "common products" in this briefing.

Figure 33 shows a traffic light system to compare the different HTA outcomes of these common products, reflecting the diverse perception of the value of these NASs across the compared agencies. The recommendation dates for each product were compared across all 4 agencies and the order of the first HTA recommendation was ranked accordingly.

Figure 34 represents the difference in the time to recommendation for the common products across jurisdictions, and indicates that for this NASs cohort, Germany was the fastest country to reach an HTA recommendation. Also, among the 37 common NASs, 4 were approved as accelerated approval by EMA, 6 were conditional approvals and we identified no common product that was both accelerated and conditional (**Figure 35**). Accelerated products had the fastest median time from regulatory approval to HTA recommendation in all jurisdictions. In particular, in Poland, the median time for accelerated approvals was nearly half that of standard approvals.

The common compounds consisted of 25 anti-cancer and immunomodulators NASs, 2 anti-infectives and 10 belonged to other therapeutic areas (**Figure 36**). For these 3 therapeutic categories, Germany consistently showed the shortest median rollout time from regulatory approval to HTA recommendation.

Figure 35: Breakdown of rollout time in key jurisdictions by EMA regulatory approval type (n=37) (2017-2021)



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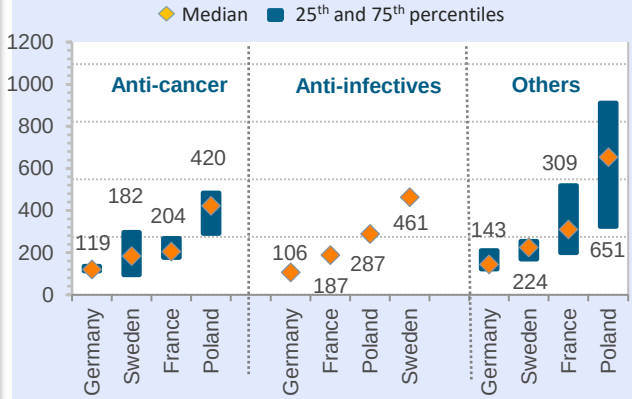
Number of Standard = 27;
Number of Accelerated = 4; Number of Cond = 6;

Figure 36: Time taken from regulatory approval to HTA recommendation for 37 common NASs by therapeutic area (2017-2021)



Anti-cancer = 25 *Anti-infectives = 2* *Others = 10*

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METHODOLOGY

The data on individual NASs appraised by HTA agencies in 2017-2021 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 implemented by the healthcare systems. In Australia, England, Scotland and Sweden, negative HTA recommendations are binding. However, in Canada, France, Germany and Poland, a relevant decision-making agency 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: (i) positive, (ii) positive with restrictions and (iii) negative. **Figure 37** 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 38**.

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 37: Trichotomous categories of HTA recommendations

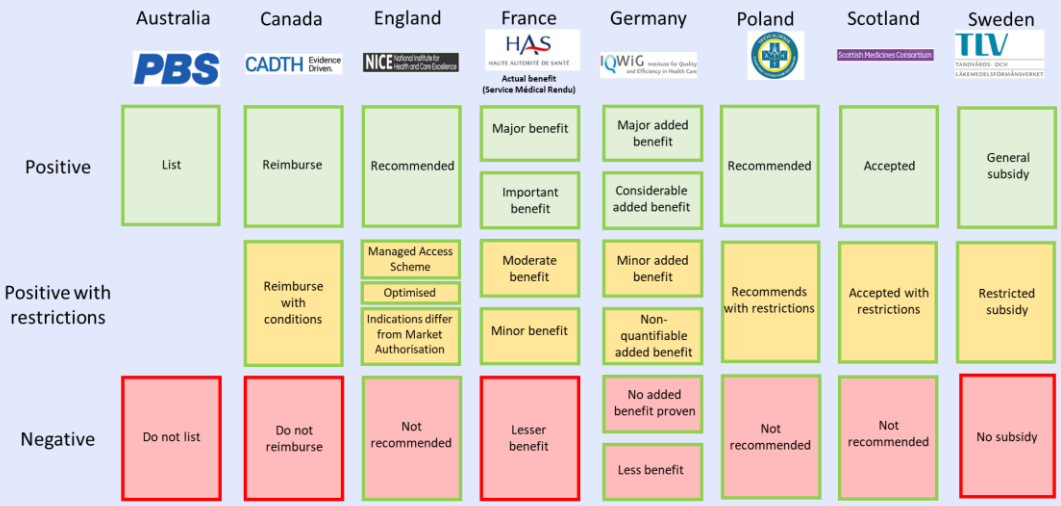

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Figure 38: Special cases of HTA recommendations

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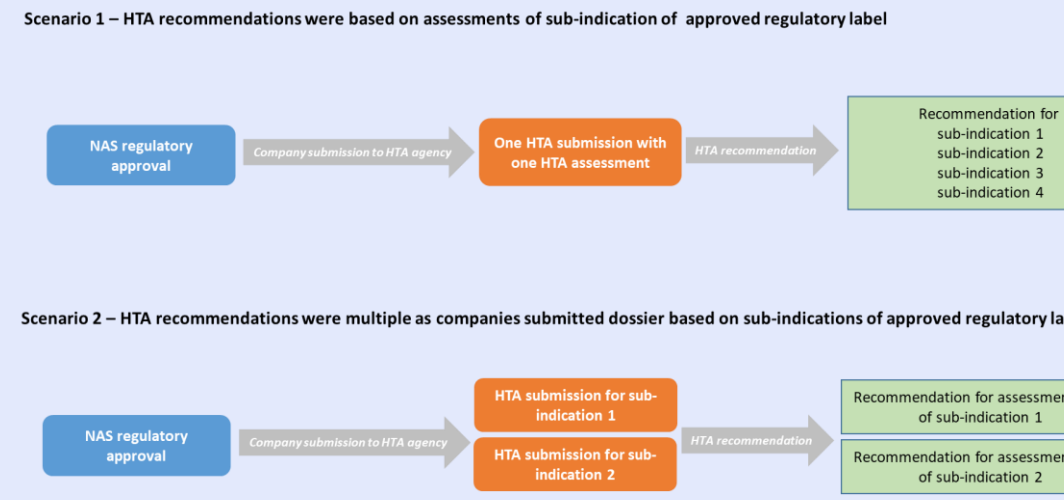

DEFINITIONS

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 international nonproprietary names (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.

Managed entry agreements (MEAs)

Arrangements between companies and HTA agencies that allow early access of new drugs while managing uncertainty around their financial impact or performance.

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.

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.

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

A 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.

Project Orbis

Project Orbis is an initiative of the US FDA Oncology Center of Excellence that aims to give patients faster access to promising cancer treatments across the globe. Project Orbis partners work together on the review of submissions for cancer drugs. There are three types of Project Orbis submissions which are dependent on the timelines between FDA and partners: A, where submission is largely concurrent, compared to B, where there is a > 30-day delay from FDA to partner submission, or C, where submission occurs once FDA has already taken regulatory action.

HTA ORPHAN/RARE DISEASE-RELATED PATHWAYS

Table 6: HTA orphan/ rare disease-related pathways

Country	HTA Orphan/ Rare Disease-Related Pathways
Australia	**Rule of rescue:** A principle that favours listing of medicines with the following circumstances applied concurrently: • No alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction. • The medical condition defined by the requested restriction is severe, progressive and expected to lead to premature death. • The medical condition defined by the requested restriction applies to only a very small number of patients. • The proposed medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition. **Life Saving Drugs Program (LSDP):** LSDP provides fully subsidised access for eligible patients to expensive and life saving drugs for life threatening and rare diseases. The LSDP is separate to the PBS. All LSDP medicines have been considered by PBAC but not recommended for the PBS due in part to the high cost of the medicine. **Highly specialised drugs:** The Highly Specialised Drugs (HSD) Program provides access to specialised Pharmaceutical Benefits Scheme (PBS) medicines for the treatment of chronic conditions which, because of their clinical use and other special features, have restrictions on where they can be prescribed and supplied.
Canada	There is no separate CADTH review process but in March 2016, the standard HTA recommendation Framework was revised to make special consideration drugs for rare diseases. Note: The regulatory agency in Canada (Health Canada) do not currently have an orphan policy.
England	**Highly specialised technologies (HST):** A separate review process for very rare conditions. These evaluations have a higher cost-effectiveness threshold than technology appraisals. Following changes introduced in April 2017, NICE set a maximum additional QALY threshold of £300,000 for highly specialised treatments, under which they will automatically be approved for routine commissioning. This is ten times higher than the standard NICE threshold of £30,000 for non-specialised treatments.
France	There is no separate HAS review process but France offers early access of innovative drugs, including orphan drugs, through the Temporary Licensing System (ATU).
Germany	For orphan drugs, additional therapeutic benefit is considered to be proven at marketing authorisation as long as the annual SHI expenditure for the entire population is below EUR 50 million. IQWiG only assesses information provided by the companies on patient costs and patient numbers. The IQWiG recommendations for orphan drugs are categorised as "positive" within this briefing. Once the EUR 50 million threshold is exceeded, companies are required to submit data on additional therapeutic benefit and orphan drugs are evaluated and prices renegotiated in the same manner as for all other drugs. The assessment of orphan drugs are conducted by G-BA, and the approach for evidence appraisal is similar to the non-orphan assessed by IQWiG. However, the orphan assessment report only determines the extent of additional benefit, and the categories 'no additional benefit' or 'less benefit' are not applicable. Under the GSAV law implemented in July 2019, additional real-world evidence can be requested by G-BA at the initial assessment for drugs with conditional approval and all orphan drugs.
Poland	There is no separate AOTMiT process but there are ongoing plans to introduce a separate procedure for rare and ultra-rare diseases such as the introduction of multi-criteria decision analysis (MCDA) method (Polityka Lekowa Państwa 2018–2022).
Scotland	**Orphan medicine:** A medicine with European Medicines Agency (EMA) designated orphan status (conditions affecting fewer than 2,500 people in a population of 5 million) or a medicine to treat an equivalent size of population irrespective of whether it has orphan status. **Ultra-orphan medicine:** To be considered as an ultra-orphan medicine all criteria listed should be met: • the condition (typically a recognised distinct disease or syndrome) has a prevalence of 1 in 50,000 or less in Scotland • the medicine has a Great Britain (GB) orphan marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) • the condition is chronic and severely disabling, and • the condition requires highly specialised management. SMC uses the description of the orphan condition within the MHRA Orphan Register. Submissions for medicines that are validated as ultra-orphan according to this definition will be assessed by SMC and will then be available to prescribers for a period of up to three years while further clinical effectiveness data are gathered. After this period the company will be asked to provide an updated submission for reassessment and SMC will make a recommendation on the routine use of the medicine in NHSScotland. For medicines used at end of life and for very rare conditions, companies may ask for the medicine to be considered at a Patient and Clinician Engagement (PACE) meeting. This additional step allows SMC to hear more evidence from patient groups and clinicians on the added value of a medicine which may not always be captured in the company's submission. The output from a PACE meeting is a major factor in SMC recommendation-making. Companies can also submit or improve a Patient Access Scheme (PAS), which can help to improve the value for money of the medicine.
Sweden	There is no separate review process in Sweden but TLV can consider a higher cost-effectiveness threshold based on unmet need, severity of condition, and limited budget impact due to small populations.

Facilitated regulatory pathways

Table 7: Facilitated regulatory pathways

Country	Facilitated regulatory pathways
Australia	**TGA Priority**: A formal mechanism for faster assessment of vital and life-saving medicines for severe, debilitating or life-threatening diseases, to address unmet medical needs and where a high therapeutic benefit can be expected. **TGA Provisional Approval:** Time-limited provisional registration for certain promising new medicines where the benefit of early availability of the medicine outweighs the risk inherent in the fact that additional data are still required.
Canada	**Health Canada Priority**: A fast-track status for medicines for severe, debilitating or life-threatening diseases; to address unmet medical needs and where a high therapeutic benefit can be expected. **Health Canada Conditional:** Authorisation to market a new promising drug with the condition that the sponsor undertakes additional studies to verify the clinical benefit.
Europe	**EMA accelerated assessment:** A process designed to expedite products of major interest in terms of public health and therapeutic innovation. **EMA conditional Approval:** Regulation allowing drugs fulfilling unmet medical needs for severe, life-threatening or rare diseases to be approved with limited clinical safety or efficacy data, provided a positive benefit-risk balance

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The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independent UK-based subsidiary of Clarivate plc. Its mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and health technology assessment (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 pharmaceutical products. It is governed and operated by Clarivate 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, special projects and grants.

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