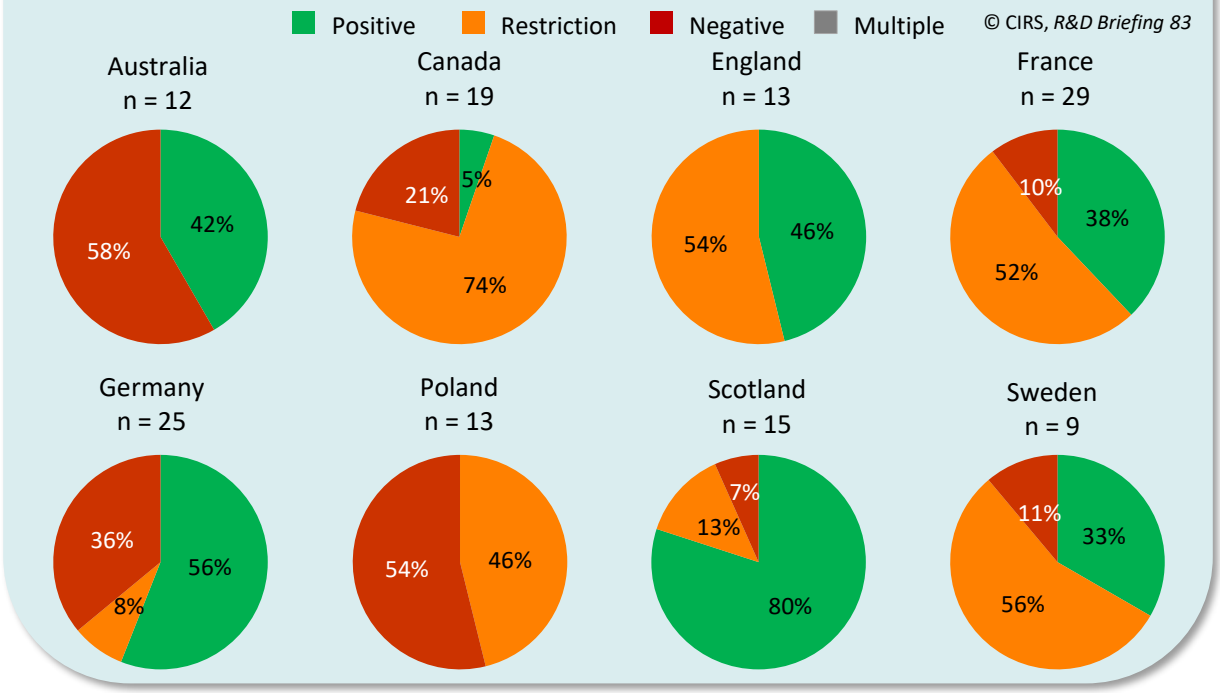
Review of HTA outcomes and timelines in Australia, Canada and Europe 2016-2020

Figure 1: First HTA recommendations: comparisons across key jurisdictions in 2020



Contents

KEY MESSAGES

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 2016 and 2020 by eight HTA agencies, analysing synchronisation between the regulatory decision and first HTA recommendation in timing and outcome.

Recommendations were collected from the **Australian Pharmaceutical Benefits Advisory Committee** (PBAC), **Canadian Agency for Drugs and Technologies in Health** (CADTH; 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 2012-2020 by the respective jurisdictional regulatory agencies, the Australian Therapeutic Goods Administration (TGA), Health Canada and European Medicines Agency (EMA).

Using a methodology outlined on page 14, the HTA recommendations in this report have been classified as *positive, positive with restrictions* or *negative*. Figure 33 illustrates how the specific recommendations by the eight HTA systems are captured within this trichotomous categorisation. In cases where 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

- In 2020, England had the highest proportion (100%) of positive/positive with restrictions recommendations for NASs appraised by HTA agencies, followed by Scotland (93%) (Fig 1).
- For all the studied countries, the number of NAS assessed decreased in 2020 compared to the average number between 2016 to 2019 (Fig 2). This global reduction in the number of NAS had not been observed in previous years from 2016 to 2019 and so may be related to the COVID-19 pandemic.
- Australia had the fastest median rollout time from regulatory submission to first HTA recommendation in 2020 (428 days), followed by Canada (544 days). There were wide variations in the rollout time, Germany showed the least variation in rollout time, which enabled better predictability for companies' marketing strategy (Fig 3).
- The top four therapeutic areas by number approved across all eight HTA agencies made up 68% (191/282) of all products between 2016-2020, with anti-cancer and immunomodulators making up 55% (106/191) of the top therapeutic areas (Fig 10).
- Time taken from regulatory approval to HTA recommendation was marginally faster for anti-cancer and immunomodulators, comparing to other therapeutics in all jurisdictions except Australia and France (Figure 11).
- CIRS analysed NASs rolled out to seven jurisdictions, excluding Poland due to variation, and identified 26 NASs that received a recommendation by all HTA agencies during the period of 2016-2020 (Fig 17). Germany provided the highest number of recommendations as the first country of appraisal (35%), followed by Australia (19%).
- England and Scotland had the highest congruence (81%) of first HTA recommendations (Fig 18).
- In Europe, France assessed the highest number of NASs (148) between 2016-2020, followed by Germany (134). In England, not all NASs undergo the NICE appraisal process, with 108 NASs assessed by NICE in the study cohort, with the lowest percentage of negative recommendation (8%) (Page 13)

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

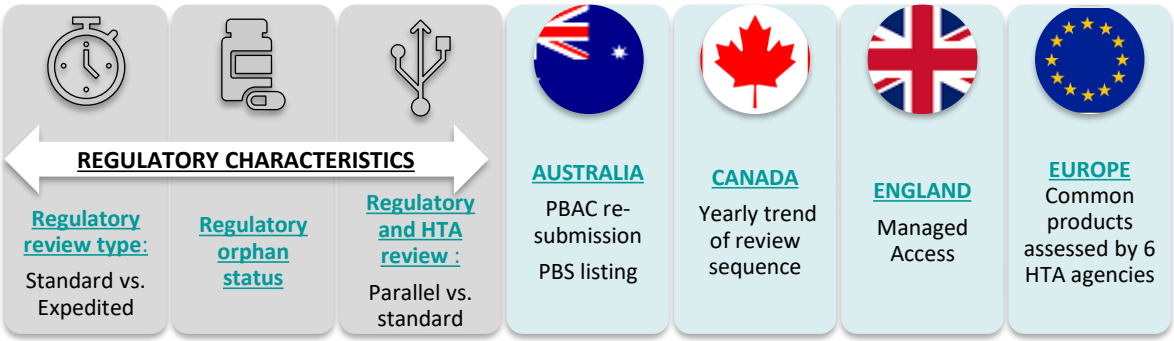
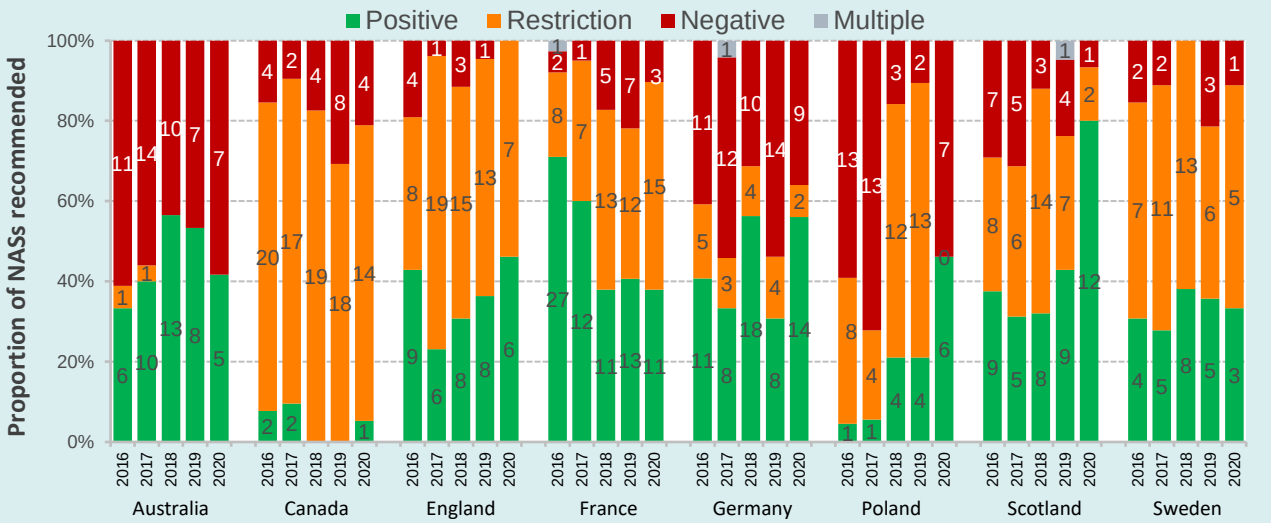


Figure 2: First HTA recommendation comparison across key jurisdictions by year of HTA recommendation Between 2016-2020



N= Number of NASs

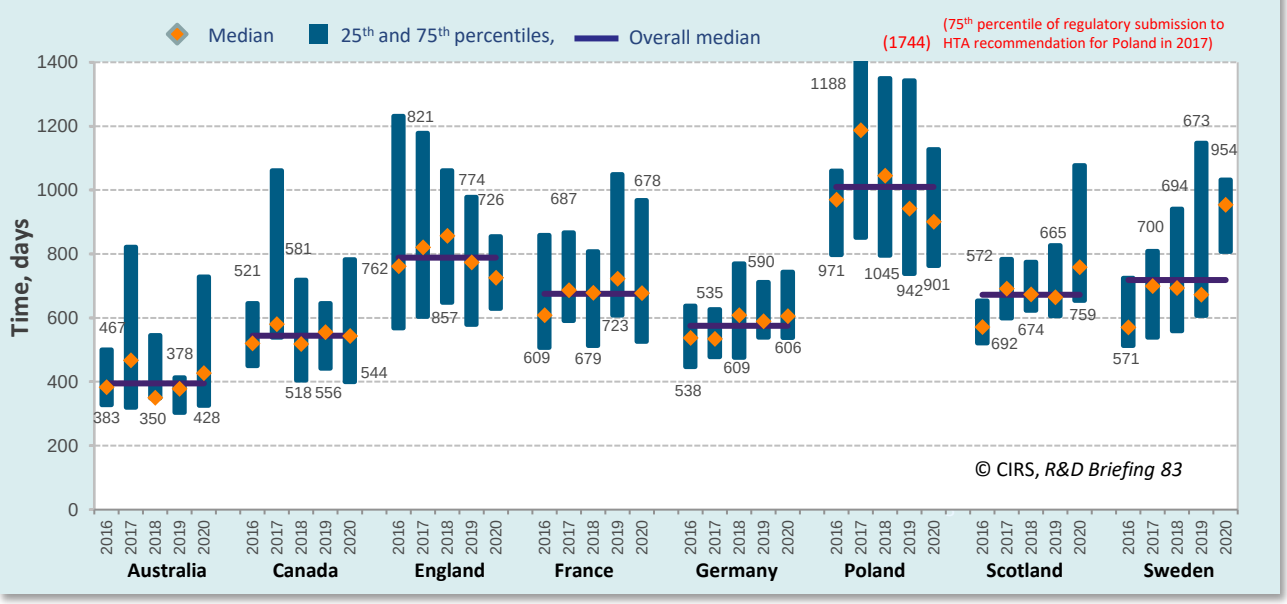
In 2020, England had the highest proportion (100%) of positive/positive with restrictions recommendations for NASs appraised by HTA agencies (Figure 2).

In 2020, France appraised the highest number of NASs (n=29), followed by Germany (n=25), Canada (n=19), Scotland (n=15), England (n=13), Poland (n=13), Australia (n=12) and Sweden (n=9) (Figure 2). For all the studied countries, the number of NAS assessed decreased in 2020 compared to the average number between 2016 to 2019, with the highest reduction found for England in 11 NASs (2016-2019 average 24 NASs vs. 2020 13 NASs). This global reduction in the number of NAS had not been observed in the previous years from 2016 to 2019 and so may be related to the COVID-19 pandemic. Despite the lower number of NASs appraised, the proportion of positive/positive with restriction recommendations remained the same in most jurisdictions, except for Scotland (93% in 2020 vs. 77% in 2016-2019).

Australia had the fastest median rollout time from regulatory submission to first HTA recommendation in 2020 (428 days), followed by Canada (544 days).

Canada showed the highest consistency in the median rollout time from regulatory submission to HTA recommendation over the period 2016-2020, with an overall standard deviation (SD) for the median rollout times of ±28.18 days. **Sweden had** the highest variation, with a SD of ±141.68 days. As noted by the 25th – 75th percentile bars, there were wide variations in the rollout time. Germany showed the least variation in rollout time, which enabled better predictability for companies' marketing strategy.

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



SYNCHRONISATION OF REGULATORY AND HTA RECOMMENDATIONS

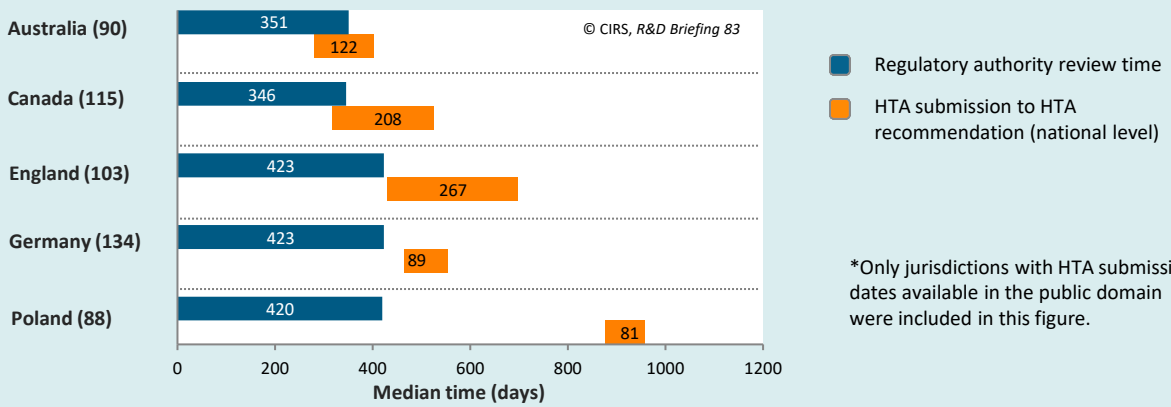
Figure 4: Breakdown of rollout time across all jurisdictions in 2016-2020

Australia (PBAC) had the shortest overall median time between regulatory approval and HTA recommendation (65 days) in 2016-2020 (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.

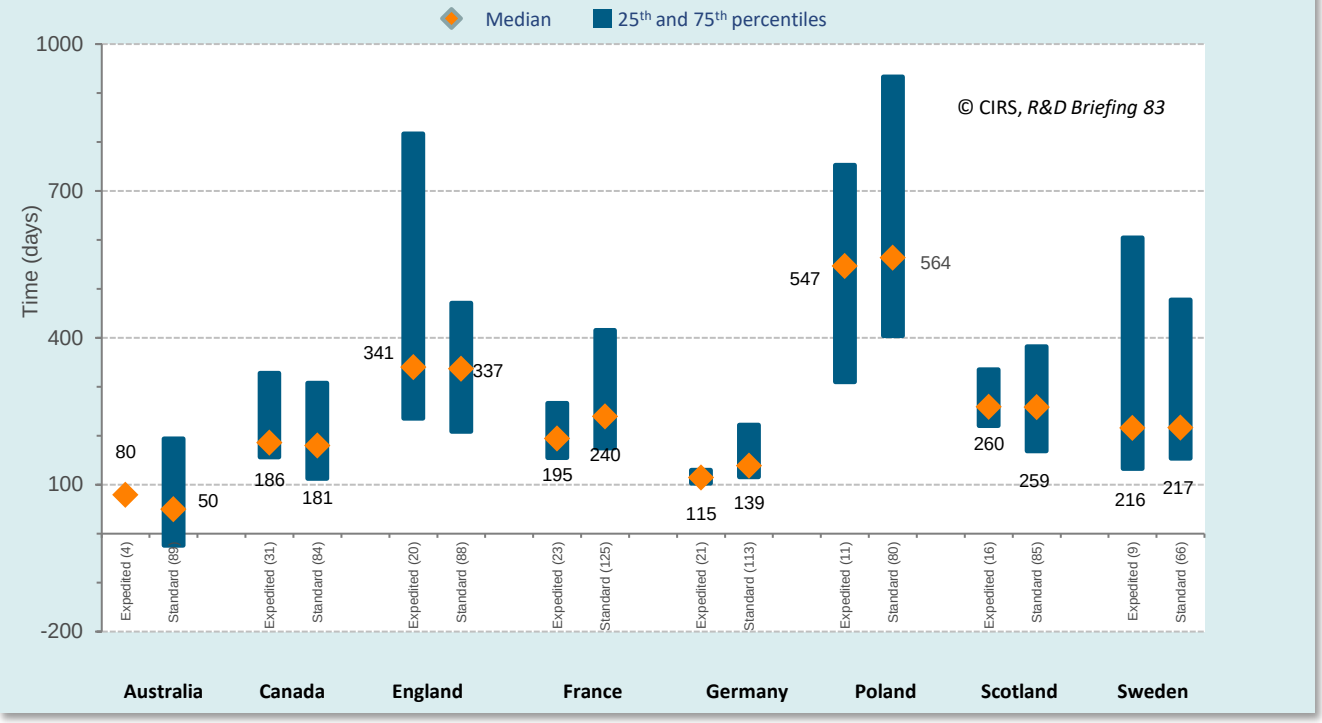
HTA submission dates are only provided in Australia, Canada, England, Germany and Poland (Figure 5). Among these, Australia and Canada are the only countries that allow the HTA process to start before the regulatory approval is granted. In England, not all NASs undergo the NICE appraisal process; scoping is first developed before marketing authorisation is achieved, 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 a 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 a shorter HTA appraisal time (81 days) however it took a longer time for the product to reach patients due to the gap between regulatory approval and HTA submission.

Figure 5 : Breakdown of rollout time in jurisdictions where HTA submission date is provided 2016-2020*



CHARACTERISTICS: REGULATORY REVIEW TYPE

Figure 6: Rollout time from regulatory approval to HTA recommendation (2016-2020) by regulatory review type



All regulatory agencies in Australia, Canada and Europe offer an expedited process designed to hasten the review process of promising NASs (Figure 6).

'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 rollout time from regulatory approval to HTA recommendation was similar for expedited review and standard review in all jurisdictions, except for France, where standard review was 45 days longer than expedited review.

In Europe, the PRIME scheme supports the development of medicines that target an unmet medical need. It is based on enhanced interaction and early dialogue with developers which can involve HTA agencies.

Eight PRIME products were included in the datasets. England appraised four products and recommended with restriction. Seven products were proven to be of "added benefit" by IQWIG in Germany, with one product (Rozlytrek) rated as "less benefit".

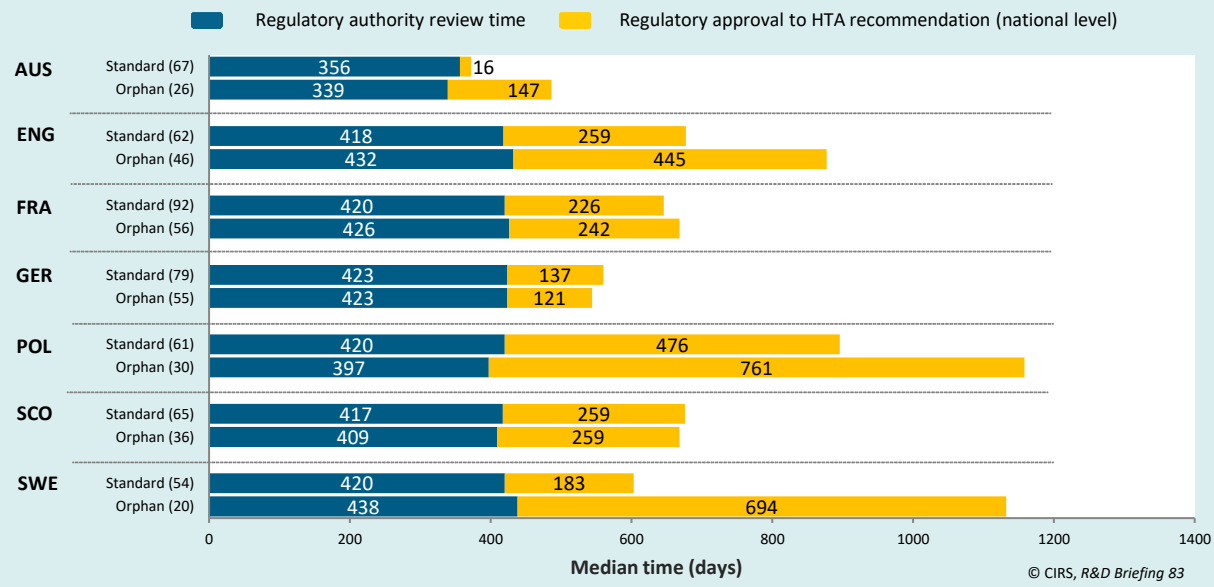
Figure 7: Comparison of HTA recommendations of the EMA PRIME products © CIRS, *R&D Briefing 83*

	EMA PRIME Products Regulatory status				EMA PRIME Products HTA status (1st recommendation)			
Brand Name	**EMA Approval date**	**Orphan status**	**Conditional approval**	**EMA Review pathway**	**England**	**France**	**Germany**	**Scotland**
Kymriah	22/08/2018	Orphan	N	Standard	21/12/2018	12/12/2018	13/12/2018	11/01/2019
Yescarta	23/08/2018	Orphan	N	Standard	23/01/2019	05/12/2018	29/01/2019	11/01/2019
Zynteglo	29/05/2019	Orphan	Conditional	Accelerated	In progress	18/03/2020	12/02/2020	
Givlaari	02/03/2020	Orphan	N	Accelerated	In progress	24/06/2020	10/07/2020	
Zolgensma	18/05/2020	Orphan	Conditional	Standard	07/07/2021*		24/09/2020	03/08/2021 *
Hepcludex	31/07/2020	Orphan	Conditional	Standard	In progress (Suspended)		27/11/2020	
Rozlytrek	31/07/2020	Non-Orphan	Conditional	Standard	12/08/2020		27/11/2020	04/12/2020
Blenrep	25/08/2020	Orphan	Conditional	Accelerated	In progress		10/12/2020	

Positive Restriction Negative

* Recommendation issued in 2021, these products were excluded from the analysis in this report

Figure 8: Breakdown of rollout time of NASs reviewed by HTA in 2016-2020, by regulatory orphan designation

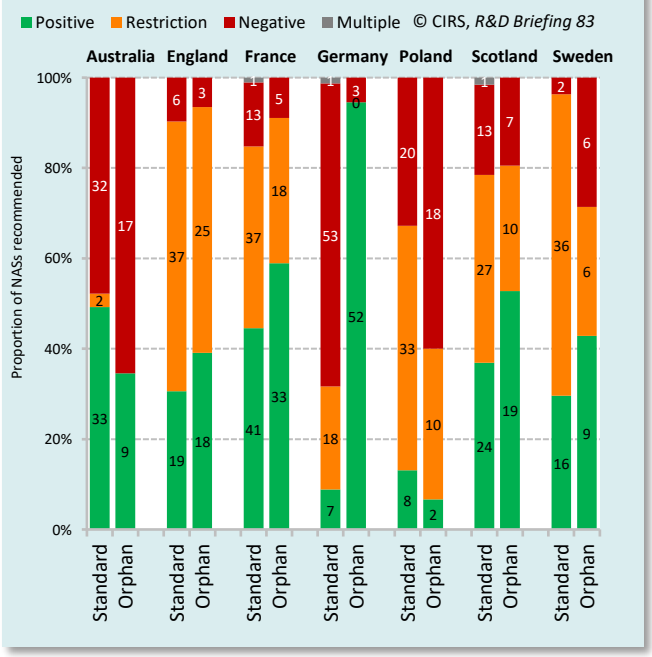


The regulatory orphan designation generally lengthened the time to HTA recommendation (Figure 8) and did not have a considerable effect on the type of HTA recommendation in all jurisdictions except Germany (Figure 9).

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 and Scotland (Figure 8). This finding suggested that further efforts were 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 9). 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 9: First HTA recommendation comparison across key jurisdictions in 2016-2020, by regulatory orphan designation



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

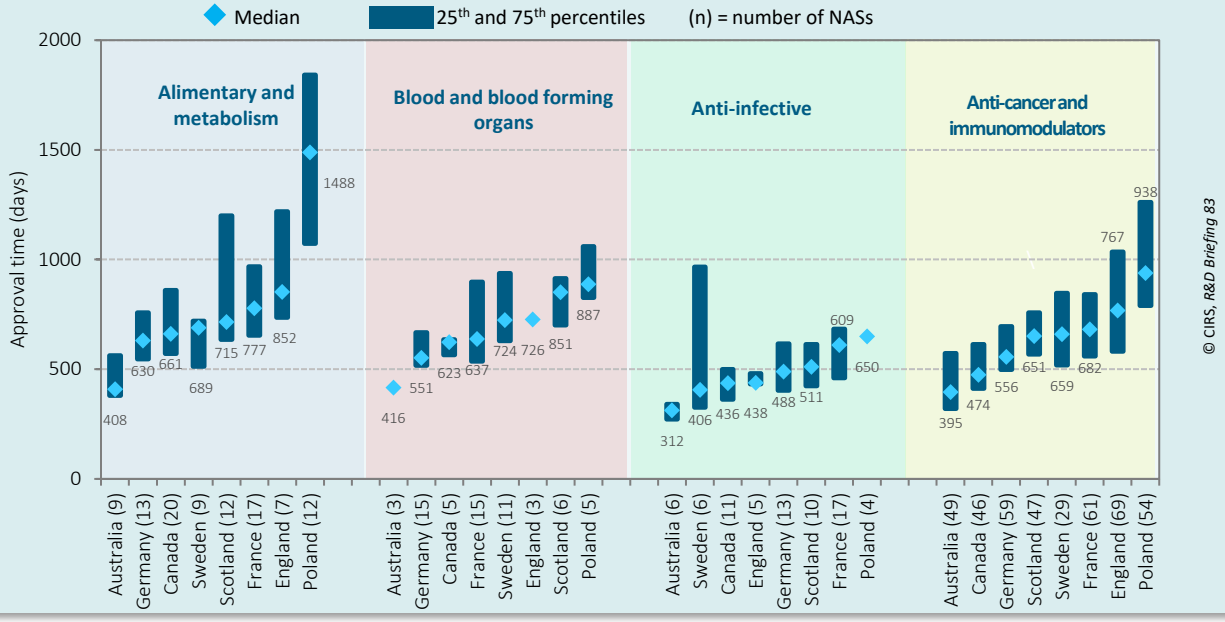
The list of HTA orphan/rare disease-related pathways across all jurisdictions are elaborated in the Appendix (HTA orphan/rare disease-related pathway, Figure 35).

In Germany and Scotland, the majority of the NASs that received a regulatory orphan designation underwent a HTA orphan/ rare disease-related pathway (95% and 86%, respectively), while in Australia and England less than half of the NASs that received a regulatory orphan designation went on to a HTA orphan/ rare disease-related pathway (42% and 24%).

In England and Germany, all the NASs that underwent a HTA orphan/ rare disease-related pathway received a regulatory orphan designation. In these countries, the EMA orphan designation criteria is used in the HTA orphan/ rare disease-related pathways (Figure 35). 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 10: Time taken from regulatory submission to 1st HTA recommendation in 2016-2020, by top therapeutic area



The top four therapeutic areas by number approved across all eight HTA agencies made up 68% (191/282) of all products between 2016-2020, with anti-cancer and immunomodulators making up 55% (106) of the top therapeutic areas (Figure 10).

Australia was fastest for all four therapy areas in term of rollout time from regulatory submission to HTA outcome, while Poland was the slowest country. 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 HTA process.

Time taken from regulatory approval to HTA recommendation was marginally faster for anti-cancer and immunomodulators in all jurisdictions except Australia and France (Figure 11).

As the HTA review time in Australia is consistently around four months, the time difference was mainly due 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, 97% and 90% of submissions, respectively. Although 78% of submissions to Canada were recommended, the HTA recommendations were mostly restricted. 12 anti-cancer and immunomodulators products were assessed in all seven jurisdictions, of which only four products received recommendations for reimbursement (positive or positive with restriction). This reflected the variation of availability of anti-cancer and immunomodulator products at the international level.

Figure 11: Breakdown of rollout time by therapeutic areas (2016-2020)

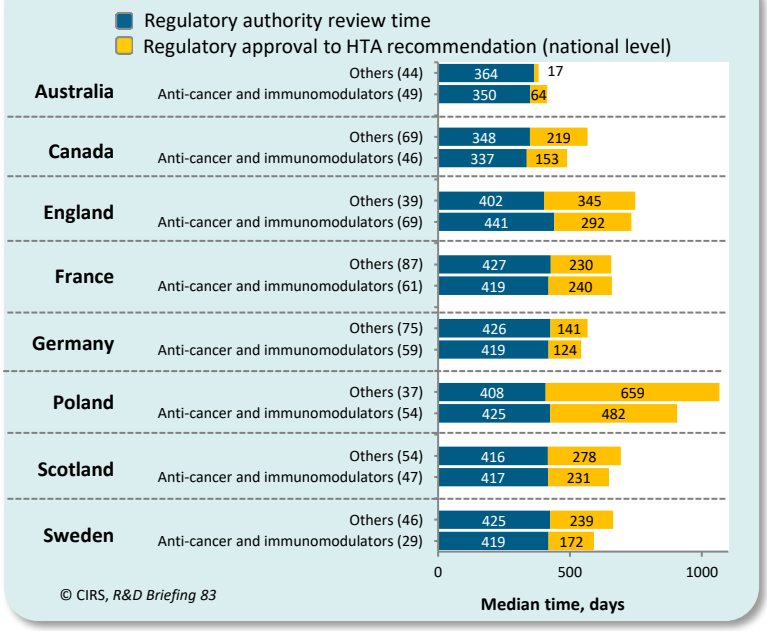
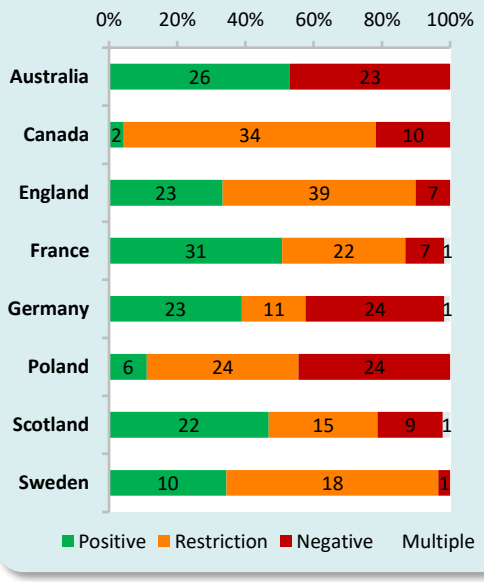


Figure 12: HTA Recommendation for anti-cancer and immunomodulators (2016-2020)



CHARACTERISTICS: REGULATORY AND HTA REVIEW SEQUENCE

Figure 13: Number of NASs assessed by PBAC and CADTH between 2016 and 2020, by HTA submission sequence

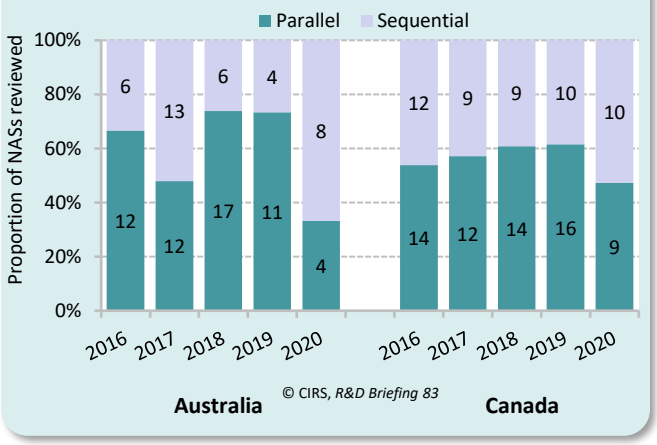


Figure 14: HTA submission sequence by top 5 therapeutic area between 2016-2020

Percentage of NASs	Alimentary and metabolism	Blood and blood forming organs	Anti-infective	Anti-cancer and immuno-modulators	Nervous system
Australia Sequential	44%	75%	0%	45%	22%
Australia Parallel	56%	25%	100%	55%	78%
Canada Sequential	60%	60%	27%	35%	56%
Canada Parallel	40%	40%	73%	65%	44%

In 2020, there was a decrease of parallel submissions in both Australia and Canada (Figure 13).

To receive a 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 2016-2020, 60% products in Australia and 57% products in Canada were submitted under parallel process. 22 products were submitted in parallel in both jurisdictions, of which 12 were anti-cancer and immunomodulators. Looking at the type of products, all anti-infective products were submitted under parallel process in Australia, and a vast majority (73%) in Canada.

Figure 15: Impact of regulatory characteristics on the HTA submission sequence (2016-2020)

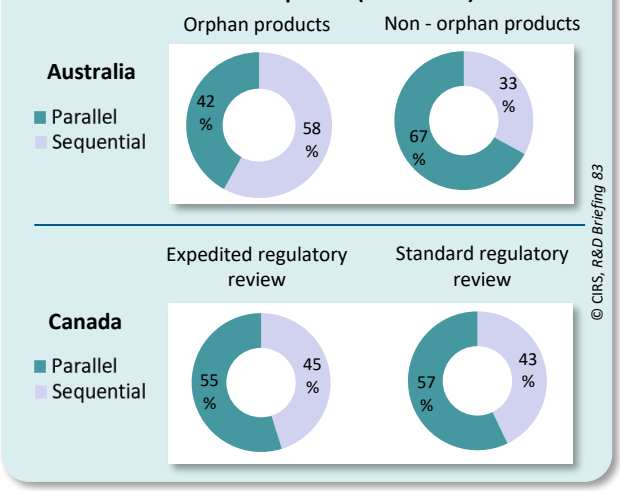
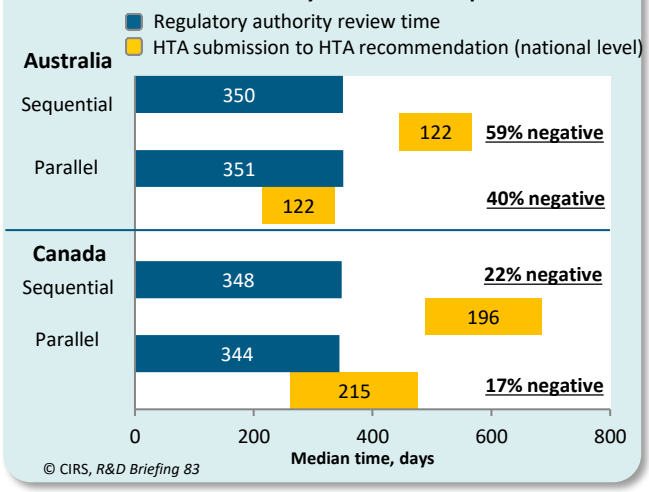


Figure16: Breakdown of rollout time of NASs assessed by HTA 2016-2020 by submission sequence



The parallel process shortened the overall time taken from regulatory submission to HTA recommendation (Figure 16).

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 2016-2020**,** the median submission to PBAC was 136 days prior to TGA approval for parallel review, compared with a 96-day delay in HTA submission with sequential review. 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 141 days for sequential review, which was longer than the sequential process in Australia. Statistical analysis showed that the parallel process in these two jurisdictions significantly decreased the rollout time of NASs between 2016-2020 ($p<0.0001$).

A higher proportion of submissions in Australia received negative decisions (59%) under sequential process, compared to parallel process (40%). However, there was no statistically significant relationship between the review sequence and the HTA outcome, indicating that the HTA outcome was more likely to be associated with the evidence submitted, than the submission sequence. In Australia, products with regulatory orphan designation were more likely to be submitted sequentially (Figure 15). Among four products reviewed by TGA as expedited review, two products were submitted to PBAC in parallel. The expedited regulatory review in Canada showed no impact on the submission sequence.

26 NASs APPRAISED BY SEVEN JURISDICTIONS IN 2016-2020

Figure 17: First HTA recommendation comparison for 26 NASs assessed in all seven jurisdictions

Positive | Restriction | Negative | Multiple

n = Date order of the first HTA recommendation

	AUS	CAN	ENG	FRA	GER	SCO	SWE
abemaciclib	4	7	3	1	2	5	6
alectinib hydrochloride	2	1	7	5	3	6	4
alirocumab	7	5	3	2	1	4	6
baricitinib	6	7	5	2	3	4	1
benralizumab	1	4	6	5	2	7	3
brigatinib	7	5	2	6	3	4	1
daratumumab	4	2	7	5	1	3	6
dupilumab	5	3	6	4	1	7	2
glecaprevir/ pibrentasvir	4	6	7	5	3	2	1
guselkumab	4	2	6	7	3	5	1
ixekizumab	1	4	6	3	7	5	2
lanadelumab	3	6	4	2	1	5	7
letermovir	3	2	6	4	1	5	7
lorlatinib	3	5	7	4	1	6	2
mepolizumab	1	5	7	6	2	3	4
midostaurin	1	2	7	6	3	5	4
migalastat hydrochloride	6	7	5	4	1	2	3
osimertinib mesylate	7	5	3	2	1	4	6
palbociclib	3	1	7	4	2	6	5
ribociclib succinate	1	7	3	5	2	6	4
risankizumab	3	1	4	7	5	6	2
sacubitril / valsartan	2	3	6	7	4	1	5
sarilumab	7	1	2	5	3	6	4
sofosbuvir / velpatasvir	6	5	7	4	3	2	1
trifluridine / tipiracil hydrochloride	5	7	1	3	4	6	2
venetoclax	4	6	5	2	1	3	7

Figure 18: Congruence* of first HTA recommendations for 26 common NASs across seven jurisdictions

≥ 50% and <75% congruence | 75% congruence

	AUS	CAN	ENG	FRA	GER	SCO
CAN	12%					
ENG	19%	58%				
FRA	19%	42%	46%			
GER	23%	30%	27%	46%		
SCO	23%	58%	81%	50%	35%	
SWE	15%	50%	62%	54%	35%	58%

** Congruence is defined as the level of agreement of the HTA outcome between the paired agencies*

England had the highest proportion of positive or positive with restriction recommendations considering the 26 NASs appraised by all seven HTA agencies (100%), followed by France (96%), and with Australia showing the lowest proportion (46%).

CIRS analysed NASs rolled out to seven jurisdictions, excluding Poland due to variation, and identified 26 NASs that received a first HTA recommendation between 2016 and 2020 by all seven HTA agencies, this is defined as "common products".

Figure 17 shows a traffic light system to compare the different HTA outcome across jurisdictions in 2016-2020, 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 recommendation was ranked accordingly.

In England and France, the majority of common NASs received a positive/ positive with restrictions recommendation (100% and 96%, respectively). In comparison, Australia and Germany had the lowest percentages of positive HTA recommendations (46% and 54% of the NASs review, respectively). NASs were mostly likely to receive a restrictive recommendation in Canada (73% of the 26 products). In this cohort, none of the NASs had the same first HTA recommendation.

Germany was usually the first country to give a recommendation (35%), followed by Australia (19%) (Figure 17).

England and Scotland had the highest congruence (81%) of first HTA recommendations, where identical HTA outcomes were provided based on the trichotomous categories of HTA recommendation (Figure 34).

Germany and Australia had the shortest time from first world-wide regulatory submission to jurisdictional HTA recommendation, with a median time of 491 days in both jurisdictions (Figure 19).

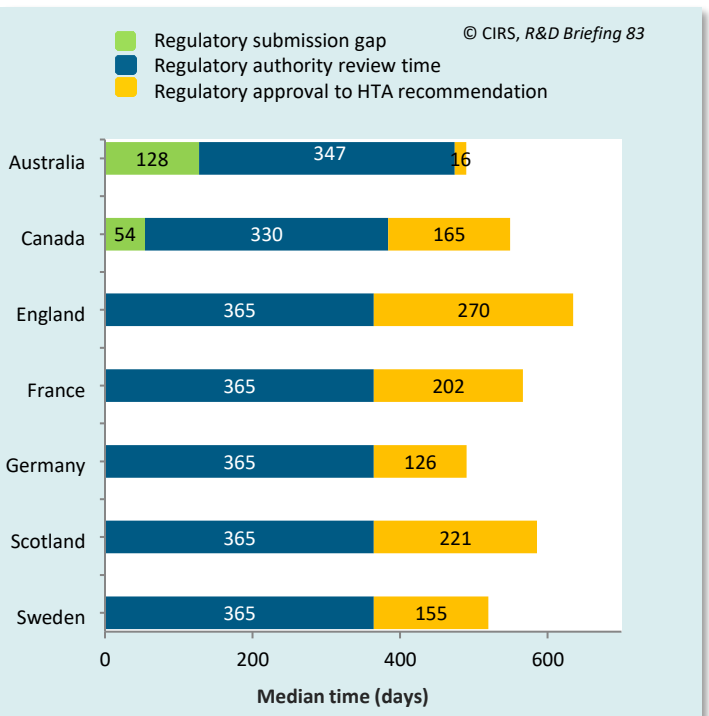


Figure 19: Breakdown of rollout time (days) across 7 jurisdictions for 26 common NASs in 2016-2020

Figure 20: The PBS listing status for NASs reviewed by PBAC between 2016 and 2020

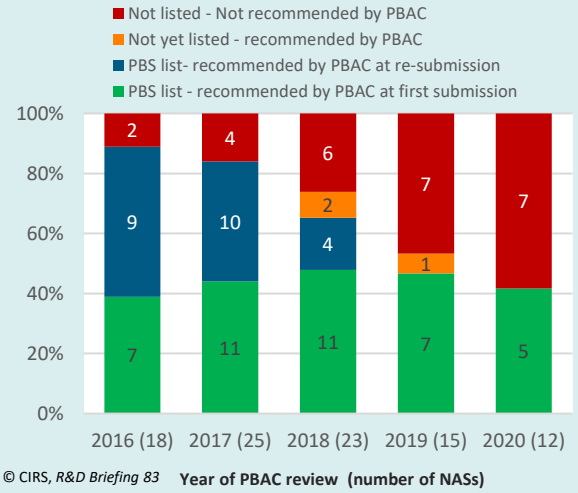
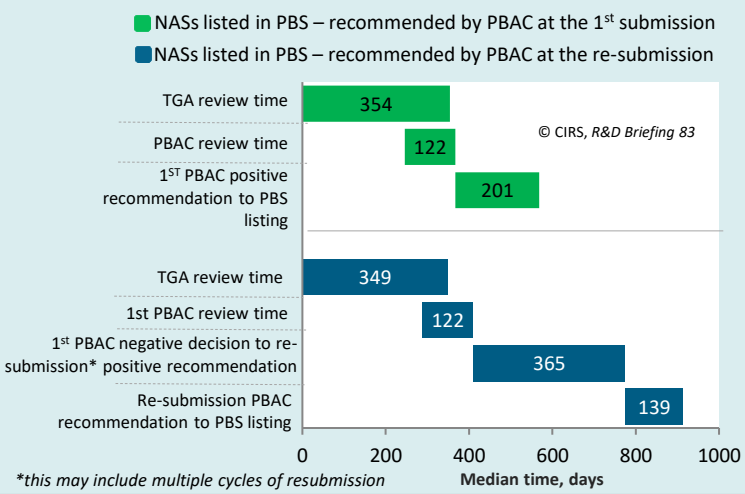


Figure 21: Breakdown of rollout time for NASs from regulatory submission to PBS listing

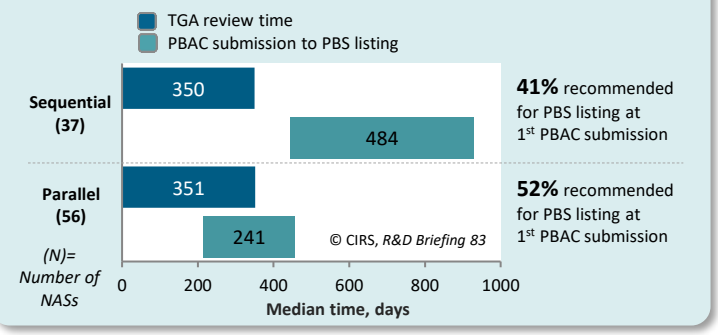


69% of drugs with PBAC recommendations in 2016-2020 were listed in the PBS list in Australia, of which 36% appraised by PBAC took more than one cycle to be listed in the PBS in this cohort (Figure 20).

PBAC makes HTA recommendations for 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 onto 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 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, ranging from 39% in 2016 to 48% in 2018. The proportion of drugs not listed in the PBS list was higher in 2018-2020 compared to previous years as drugs may not be listed yet or have not gone through a re-submission. Multiple review cycles increase the time to be listed in PBS list (Figure 21).

Figure 22 Breakdown of rollout time by review sequence (2016-2020)



The parallel regulatory and HTA review process in Australia shortened the overall time to be listed in PBS, with 60% products going through this process between 2016 and 2020 (Figure 22).

Products that underwent the parallel process were submitted to PBAC approximately four months before TGA approval. 52% of submissions were recommended at the 1st submission, comparing to 41% of products submitted sequentially. The resubmission contributed to the time taken to be listed at PBS, which was longer for sequentially reviewed products (484 days) compared to parallel review (241 days).

Figure 23: HTA recommendation status for products that underwent TGA Priority approval

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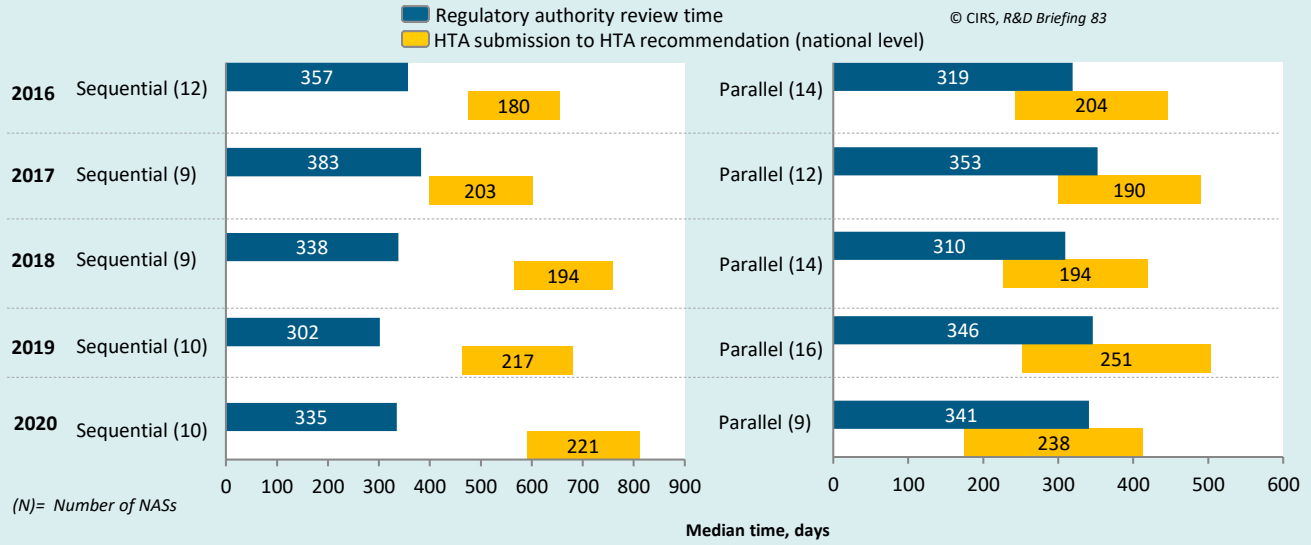
Brand name	Orphan status	TGA Approval	HTA decision date	HTA Committee	First HTA recommendation
Hemlibra	Orphan	Feb-18	Nov-18	MSAC*	Positive with restrictions
Erlyand	Standard	Jul-18	Nov-18	PBAC	Negative
Brineura	Orphan	Aug-18	Jul-18	PBAC	Negative
Takhzyro	Orphan	Jan-19	Jul-19	PBAC	Negative
Polivy	Standard	Oct-19	Nov-19	PBAC	Negative
Qarziba	Orphan	Mar-20	Jul-20	MSAC*	Positive

** 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.*

TGA introduced an expedited review programme from 2017 (Priority review); six products approved with priority review have undergone HTA process (Figure 23).

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 six products included in the study, four products were not recommended by PBAC at the initial submission. Two NASs were assessed by MSAC (medical services advisory committee), the HTA outcome supported the public funding for the two products.

Figure 24: Breakdown of rollout time by review sequence



Submissions to CADTH under parallel process are being made earlier, with 166 days overlap between regulatory and HTA process last year; on the other hand, the submission gap has increased for sequential review in 2020 (Figure 24).

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. From 2 April 2018, CADTH submission criteria were changed to within 180 days before the anticipated NOC from Health Canada. The overlap between regulatory and HTA review has increased since 2018, with the median overlap time being 94 days in 2019 and 166 days in 2020. The submission gap for products reviewed sequentially has increased in 2020, with the time taken from regulatory approval to HTA submission being 255 days.

Products that received a positive CADTH recommendation took the shortest time to be reviewed (178 days), while the negative recommendations took the longest time (243 days).

As noted by the 25th -75th percentile bars in Figure 25, there was also wider variation in HTA review time for negative recommendations. The Canadian Drug Expert Committee (CDEC) is used for drugs that are reviewed through CADTH's Common Drug Review process. The pan-Canadian Oncology Drug Review (pCODR) Expert Review committee (pERC) is used for CADTH pCODR process. Established in 2010, the pCODR is a process operated by CADTH that evaluates oncology drugs and makes recommendations and guides the drug funding recommendations of provinces. The median review time for NASs reviewed through the two processes was similar: 204 days under CDR process and 216 days under pCODR process. In 2016-2020, a higher proportion of NASs under the pCODR process were submitted via parallel review (62%), in comparison the CDR process (54%).

The top therapeutic groups from the 115 NASs assessed by CADTH in 2016-2020 were anti-cancer & immunomodulators (40%), alimentary & metabolism (17%), anti-infectives (10%). Looking at the HTA outcome, all anti-infectives appraised in 2016-2020 received a positive or positive with restrictions CADTH recommendation (Figure 26).

Figure 25: Variation of HTA review time by the recommendation outcome (2016-2020)

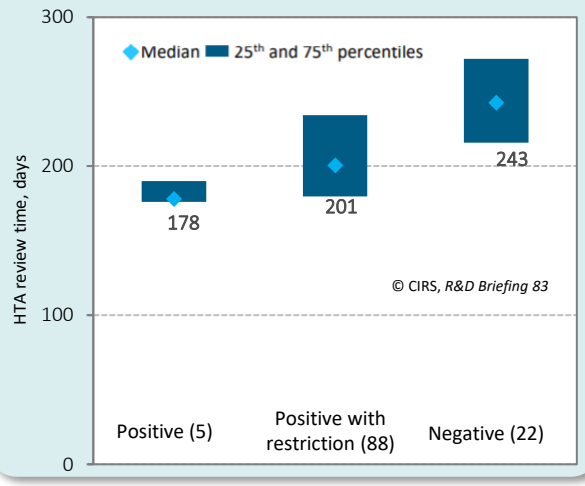


Figure 26: HTA outcome by top 5 therapeutic area reviewed by CADTH between 2016-2020

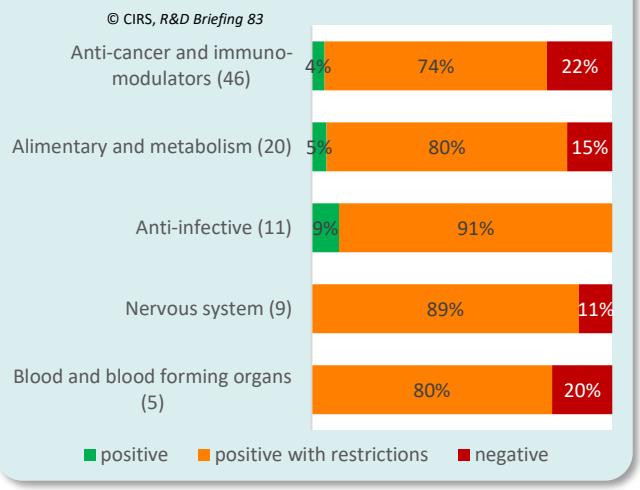
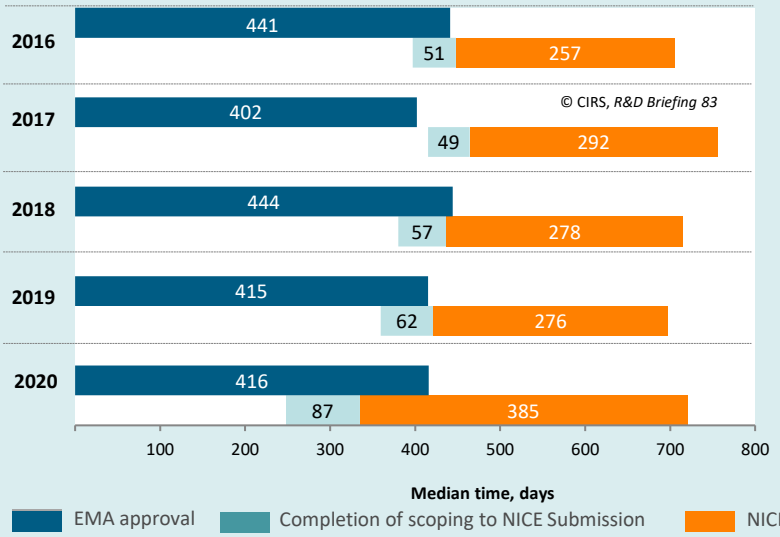


Figure 27: Breakdown of rollout time of NASs appraised by NICE between 2016 and 2020



Median time from EMA approval to NICE recommendation

2016	11.2 months
2017	12.7 months
2018	9.4 months
2019	10.5 months
2020	11.6 months

Time taken from regulatory approval to HTA recommendation includes
- Company submission strategy
- Company time for pre-submission preparation
- HTA agency review time

In England, the scoping process occurs before the NICE appraisal. The scoping process is taking place earlier during regulatory review; the scoping was completed 161 days (median time) before the EMA approval in 2020.

In England, not all NASs undergo the NICE appraisal process. Scopes are first developed before marketing authorisation is achieved. In 2016-2020, the completion of final scoping occurs 61 median days before EMA approval. After the scoping process, the appraisal topic is referred to NICE for development by the Department of Health. In 2018, NICE updated the appraisal process to offer companies the opportunity for recommendations on new drugs to be made close to the granting of the marketing authorization. Earlier scoping and submission to NICE has been observed since 2018 (Figure 27), however, time taken from EMA approval to NICE recommendation increased in 2020 to 11.2 months. Factors not controlled by NICE may have resulted in the increased time, such as pauses due to COVID-19, non-timely referral, and company requests for delay.

In England, drugs can be provided through various funding agreements: Simple discounting; Agreement with Commercial Medicines Unit; Patient Access Scheme (PAS) and Managed Access (MA). PAS allows patients to have a technology when NICE's assessment of value, on the current evidence base, is unlikely to support the list price and can be introduced through simple discounting or complex schemes. MA allows earlier access to drugs while further evidence is collected to address clinical uncertainty. Of the 99 NAS that received a NICE recommendation in 2016-2020, the majority were recommended through the PAS (67%), followed by MA (21%) (Figure 29).

NASs that were recommended under Managed Access (MA) had a shorter time from EMA approval to NICE recommendation.

For MA products, the scoping process was completed earlier than for non-MA products (160 vs. 45 days before EMA approval, respectively). The time from NICE submission to HTA recommendation was longer for MA products (322 vs. 267 days). Due to an earlier NICE submission, the overall rollout process takes less time (Figure 28).

Figure 28: Breakdown of rollout time by Managed Access recommendations

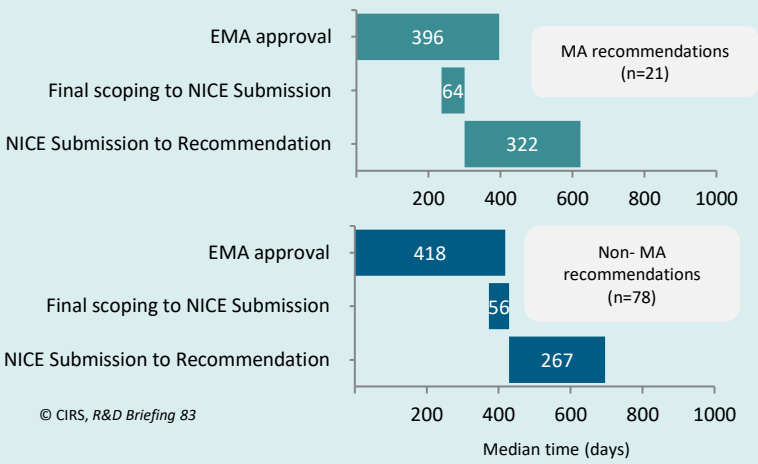
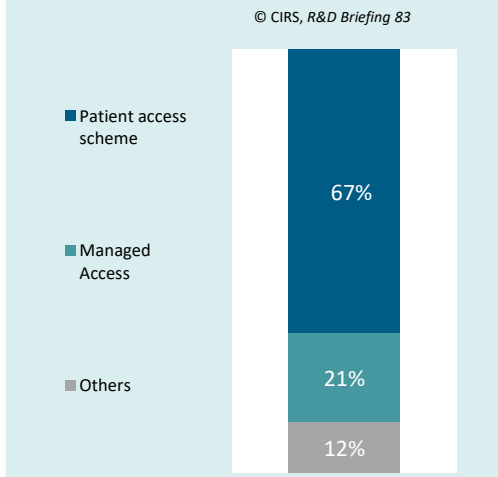


Figure 29: Type of NICE recommendations (n=99)



Features of Europe

ENGLAND
108 NASs assessed, **8%** were not recommended.

FRANCE
148 NASs assessed, **13%** were rated as "lesser benefit".*

GERMANY
134 NASs assessed, **43%** were rated as "no added benefit proven" or "less benefit".*

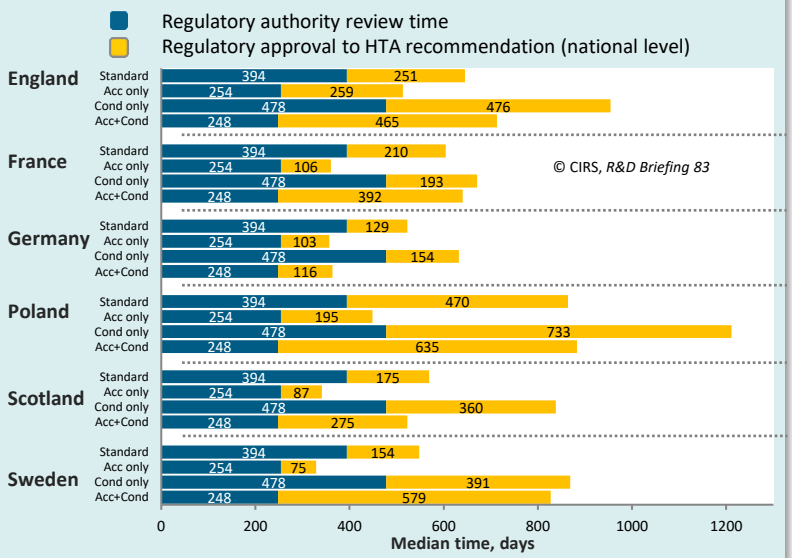
POLAND
91 NASs assessed, **42%** were not recommended.

SCOTLAND
101 NASs assessed, **21%** were not recommended.

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

Between 2016 and 2020

Figure 30: Breakdown of rollout time (days) by EMA approval type for 31 common NASs



Number of Standard = 22; Number of Accelerated = 4; Number of Cond = 3; Number of Acc+Cond = 2

* 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, 31 NASs approved by EMA have been appraised by all six jurisdictions, of which 19 were anti-cancer products and 4 were anti-infectives.

Among the 31 commonly appraised NASs, four were approved as accelerated approval by EMA, three were conditional approvals and two were accelerated and conditional approvals. 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. 19 anti-cancer and immunomodulators NASs had a higher proportion of positive or positive with restrictions recommendation, except for Germany (Figure 31).

Figure 31: First HTA recommendation comparison for 31 common NASs by therapeutic area (2016-2020)

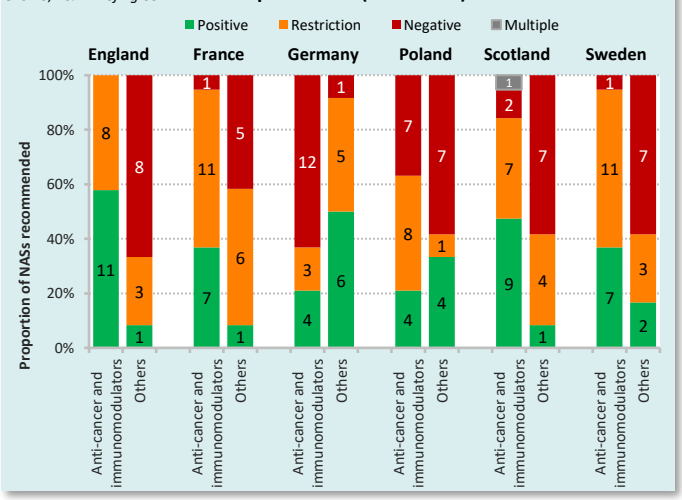
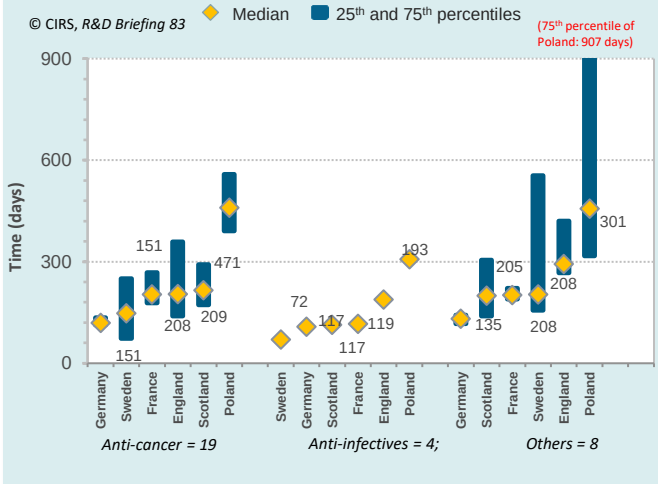


Figure 32: Time taken from regulatory approval to HTA recommendation for 31 common NASs by therapeutic area (2016-2020)



METHODOLOGY

The data on individual NASs appraised by HTA agencies in 2016-2020 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: *positive, positive with restrictions* and *negative*. Figure 33 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 34.

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*.

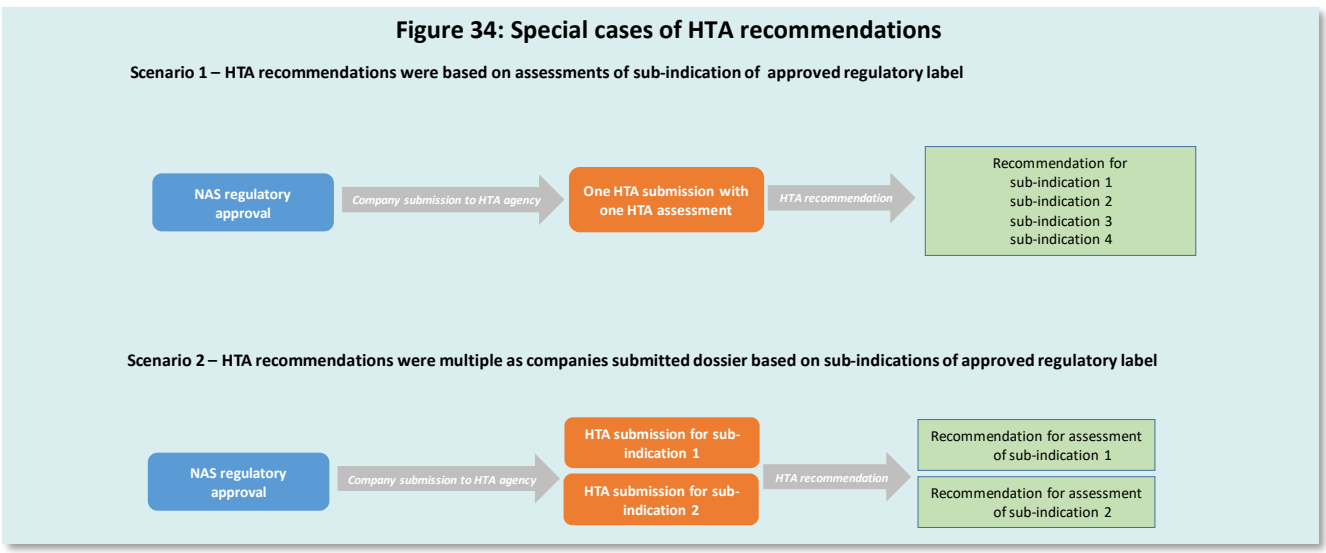
Scenario 2: In the case in which more than one HTA dossier was submitted by companies for the same drug based on different sub-indications of an approved regulatory label and obtained different first HTA recommendations, the final HTA outcome was classified as *multiple*. In this study, this occurrence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

Figure 33 Trichotomous categories of HTA recommendations

	Australia	Canada	England	France	Germany	Poland	Scotland	Sweden
	PBS	CADTH Evidence Driven.	NICE National Institute for Health and Care Excellence	HAS Haute Autorité de Santé Actual benefit (Service Médical Rendu)	IQWiG Institute for Quality and Efficiency in Health Care		Scottish Medicines Consortium	TLV Tandvårds- och läkemedelsförmånsverket
Positive	List	Reimburse	Recommended	Major benefit Important benefit	Major added benefit Considerable added benefit	Recommended	Accepted	General subsidy
Positive with restrictions		Reimburse with conditions	Managed Access Scheme Optimised Indications differ from Market Authorisation	Moderate benefit Minor benefit	Minor added benefit Non-quantifiable added benefit	Recommends with restrictions	Accepted with restrictions	Restricted subsidy
Negative	Do not list	Do not reimburse	Not recommended	Lesser benefit	No added benefit proven Less benefit	Not recommended	Not recommended	No subsidy

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

Figure 34: Special cases of HTA recommendations



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.

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

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.

HTA ORPHAN/RARE DISEASE-RELATED PATHWAYS

Figure 35: 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 categorized 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 has a prevalence of 1 in 50,000 or less in Scotland, • the medicine has an EMA orphan designation for the condition and this is maintained at time of marketing authorisation, • the condition is chronic and severely disabling, and • the condition requires highly specialised management. 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 decision on routine use of the medicine in NHS Scotland. 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 decision 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.

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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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