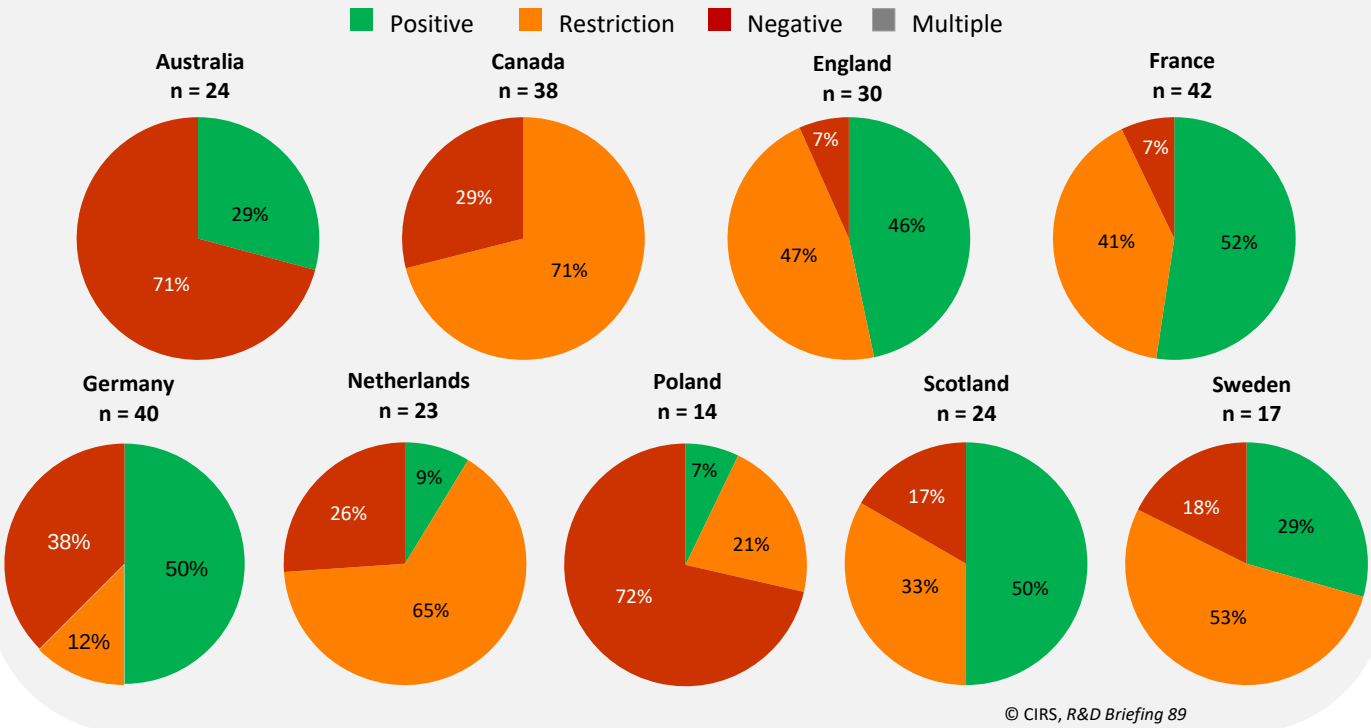
R&D BRIEFING 89

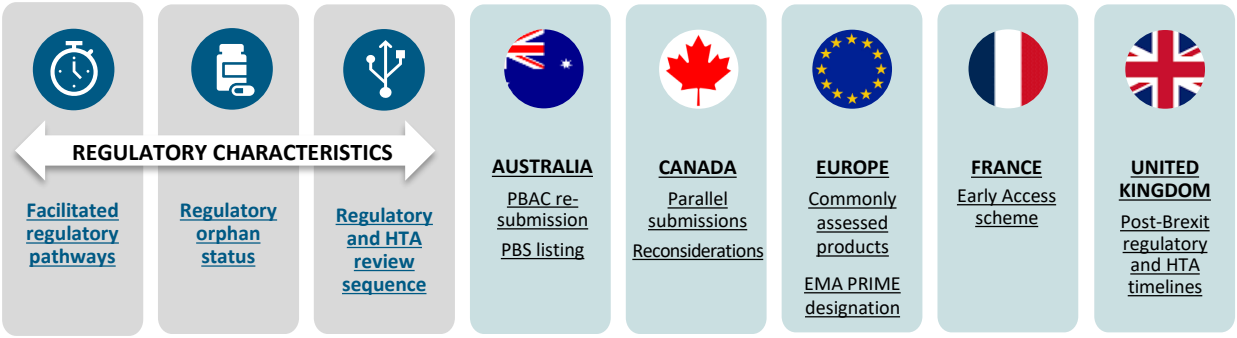
CIRS HTADock Project:

Review of HTA outcomes and timelines in Australia, Canada, Europe and the UK 2018-2022

Figure 1. First HTA recommendations: comparisons of NASs assessed across key jurisdictions in 2022



The 2023 HTADock Briefing focuses on the key performance metrics of nine HTA agencies, placing special emphasis the influence of product characteristics on the first HTA outcome and its timing. Furthermore, an investigation of jurisdictional features has been conducted to provide further insights into the local context.



INTRODUCTION

In 2017, The Centre for Innovation in Regulatory Science (CIRS) launched the HTADock project as part of its HTA programme. This project explores the synchronization between the regulatory and HTA landscapes, aiming to increase the transparency of the outcomes and timelines of HTA assessments. It also seeks to facilitate the enhancement of performance within HTA agencies.

This year, the HTADock briefing analyses publicly available data on new active substances (NASs) appraised from 2018 to 2022 by key international HTA agencies, each with unique perspectives and methodologies. The agencies involved in this comprehensive study include: (1) the Australian Pharmaceutical Benefits Advisory Committee (PBAC), (2) the Canadian Agency for Drugs and Technologies in Health (CADTH), (3) the English National Institute for Health and Care Excellence (NICE), (4) the French Haute Autorité de Santé (HAS), (5) the German Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), (6) the Polish Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT), (7) the National Health Care Institute in Netherlands (ZIN), (8) the Scottish Medicines Consortium (SMC) and (9) the Swedish Tandvårds & läkemedelsförmånsverket (TLV).

In the following sections of this HTADock briefing, a comprehensive examination of the current landscape of HTA in Australia, Canada, Europe and the UK is presented. The insights derived from this research form an essential component of CIRS's ongoing commitment to advancing regulatory and HTA policies and processes.

CONTENTS

HTADock Methodology

The data on individual NASs appraised by HTA agencies between the years 2018 and 2022 were systematically collected from the respective agencies' official websites. Only the first HTA recommendation, derived from the initial assessment, was included in the analysis, unless specified. The figures below describe the research methodology, designed to enable robust benchmarking between agencies.

Regulatory and HTA process

	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 MHRA/ EMA (ECDRP)	Approval issued by MHRA	Company evidence submission date	Technology appraisal guidance publication
France	Submission to EMA	Approval issued by EU Commission	Date de validation administrative	Publication of Commission de la transparence review
Germany	Submission to EMA	Approval issued by EU Commission	Datum des Auftrags at IQWIG	Publication of Dossierbewertung
Netherlands	Submission to EMA	Approval issued by EU Commission	Letter dated by Minister of health to ZIN	Date of Summary of recommendation by ZIN
Poland	Submission to EMA	Approval issued by EU Commission	Order of the Minister of Health publication	Publication of Rekomendacja Prezesa
Scotland	Submission to MHRA/ EMA (ECDRP)	Approval issued by MHRA	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

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
Zorginstituut Nederland	To include	To include + restrictions	Recommendation for inclusion in the national health system	Not to include
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 NHS Scotland	Not recommended for use within NHS Scotland
Sweden TLV	Ngå i läkemedelsförmånerna	Begränsningar	Include in pharmaceutical benefits scheme	Avslår

Note: The terminology used here is based on the individual agency's guidance on the official website.

KEY FINDINGS OF HTADOCK 2023

• In 2022, France showed the highest number of HTA recommendations across the studied jurisdiction (Figure 1); a general increase was observed in 2022 compared to the average between 2018 and 2021 in all the studied countries, except Poland (Figure 2).

• Australia presented the shortest median rollout time from regulatory submission to the first HTA recommendation in 2022, while Germany maintained the highest consistency in rollout times from 2018 to 2022 (Figure 3).

• SMC is the only HTA agency examined in this briefing that has a designated orphan pathway. In Scotland, 83% of the NASs with a regulatory orphan designation followed an HTA orphan/rare disease-related pathway (Figure 11).

• In all jurisdictions, except for Sweden, the median overall time from regulatory submission to HTA recommendation was shorter for products undergoing an expedited review in comparison to those following the standard review process (Figure 15).

• NASs assessed under a conditional regulatory pathway generally displayed a longer median rollout time (or a similar time, in the case of France) in comparison to those evaluated via a non-conditional pathway (Figure 18).

• Between 2018 and 2022, 13 products approved via the Access route received an HTA recommendation (Table 1), and all four studied jurisdictions showed a shorter median review time for Access products (Figure 20).

• 16 Orbis products obtained an HTA recommendation in Australia, Canada, England, or Scotland between 2018-2022 (Table 2).

• Since 2021, 12 products have benefited from the early re-entry pathway in Australia (Figure 26)

• Among the NASs assessed by SMC between 2018-2022, 74% implemented a patient access scheme (PAS). In England, out of the NASs evaluated, 59 incorporated a PAS while 19 products were made accessible under a Managed Access Agreement by NICE (Figure 41).

A total of 53% (52/98) of the drugs with PBAC recommendations in 2018-2022 were listed in the PBS list in Australia, of which 65% (34/52) appraised by PBAC were listed at the first submission (Figure 25).

Parallel submissions expedite the rollout process, with a median rollout time of 446 days for parallel submissions vs 743 days for sequential submissions (Figure 28).

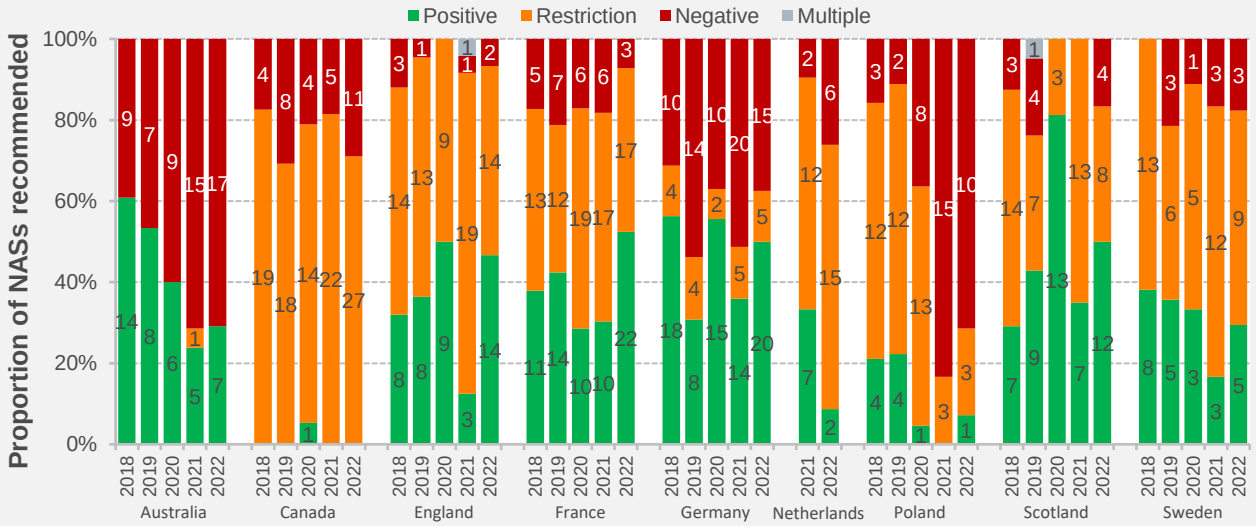
Between 2018 and 2022, 20 PRIME products were assessed by HTA in at least the jurisdictions of France, Germany, Poland or Sweden, and there were heterogeneous perceptions regarding the value of the PRIME products across agencies (Table 3).

From July 1st, 2021, HAS has undertaken the responsibility of evaluating and granting authorization for medications that are being considered for coverage under the "Early Access" framework. Notably, in 2022, 57% of NASs that underwent evaluation by HAS had been granted Early Access (Figure 34). In addition, a faster rollout time was measured for products that had received an Early access designation (Figure 36).

A total of 82 common products were evaluated in both England and Scotland between 2018 and 2022, and the pattern of rollout time was found to be comparable in both jurisdictions (Figure 44).

Overview of new drug recommendations

Figure 2. First HTA recommendation comparison across key jurisdiction by year of HTA recommendation 2018-2022



Year of first HTA recommendation

n = number of NASs

In 2022, France showed the highest number of HTA recommendations across the studied jurisdiction.

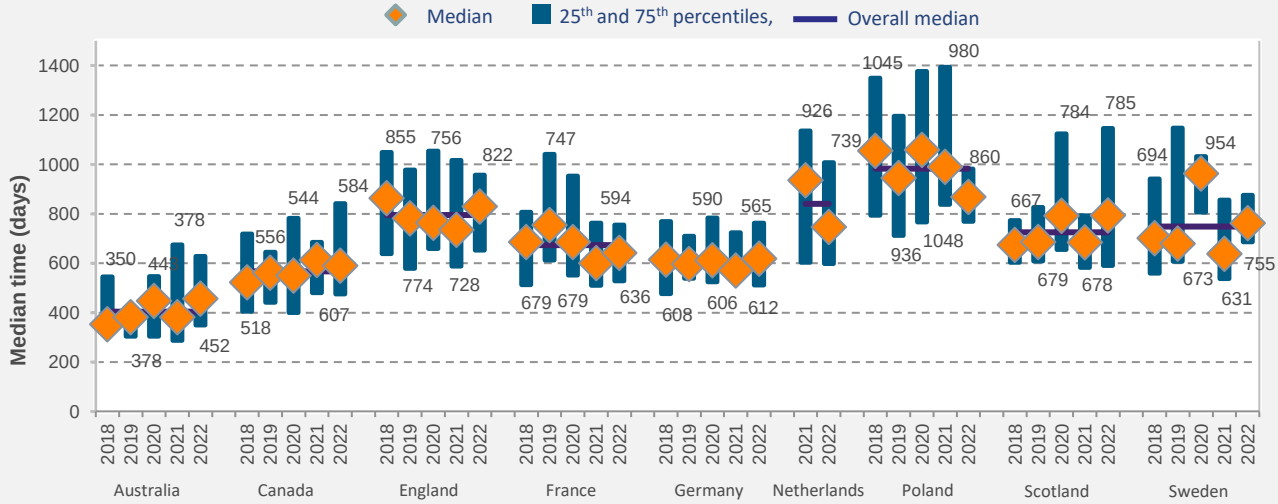
In 2022, France appraised the highest number of NASs (n=42), followed by Germany (n=40), Canada (n=38), England (n=30), Australia (n=24), Scotland (n=24), Netherlands (n=23), Sweden (n=17) and Poland (n=14) (**Figure 1**). France and England presented the highest proportion of positive/positive with restrictions recommendations for NASs appraised by HTA agencies (93%).

A general increase was observed in the number of HTA recommendations in 2022 compared to the average between 2018 and 2021 in all the studied countries, except Poland (**Figure 2**). The comparative numbers for 2018-2021 and 2022 in each country are as follows: Australia: 19 vs 24, Canada: 24 vs 38, England: 22 vs 30, France: 33 vs 42, Germany: 31 vs 40, Netherlands: 21 vs 23 (this only includes 2021 vs 2022), Poland: 19 vs 14, Scotland: 20 vs 24 and Sweden: 16 vs 17, respectively. Notably, Canada showed the highest growth, with a 58% increase in the number of appraisals.

Australia has the shortest median rollout time from regulatory submission to the first HTA recommendation in 2022, while Germany maintained the highest consistency in rollout times from 2018 to 2022.

In 2022, Australia showed the shortest median rollout time from regulatory submission to the first HTA recommendation, completing the process in 452 days. This was followed by Canada and Germany, which required 584 and 612 days, respectively, to reach the first HTA recommendation (**Figure 3**). Germany showed the highest consistency in the median rollout time from regulatory submission to HTA recommendation over the years 2018-2022, with an overall standard deviation (SD) for the median rollout times of ±19 days. The latter enabled better predictability for companies' market access strategies. Interestingly, the rollout time to Poland has consistently decreased since 2020, suggesting an optimization of the rollout process. In addition, a decrease in the median rollout time was also observed when comparing 2021 vs 2022 for Canada (607 vs 584) and the Netherlands (926 vs 739).

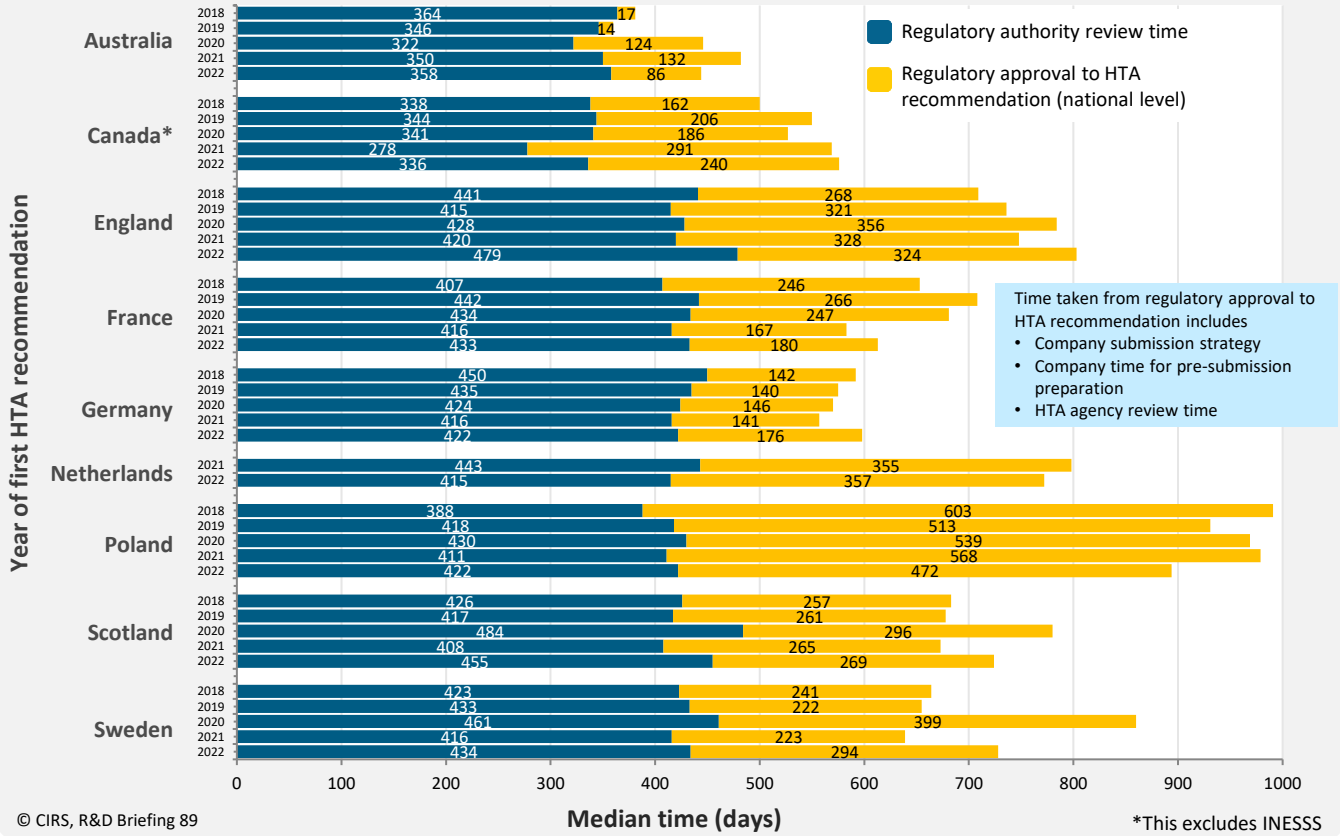
Figure 3. Time taken from regulatory submission to HTA recommendation by year of HTA recommendation 2018-2022



Year of first HTA recommendation

SYNCHRONISATION OF REGULATORY AND HTA RECOMMENDATIONS

Figure 4. Breakdown of rollout time across key jurisdictions in 2018-2022



*This excludes INESSS

Australia demonstrated the fastest median rollout timeline from regulatory approval to HTA recommendation in 2022.

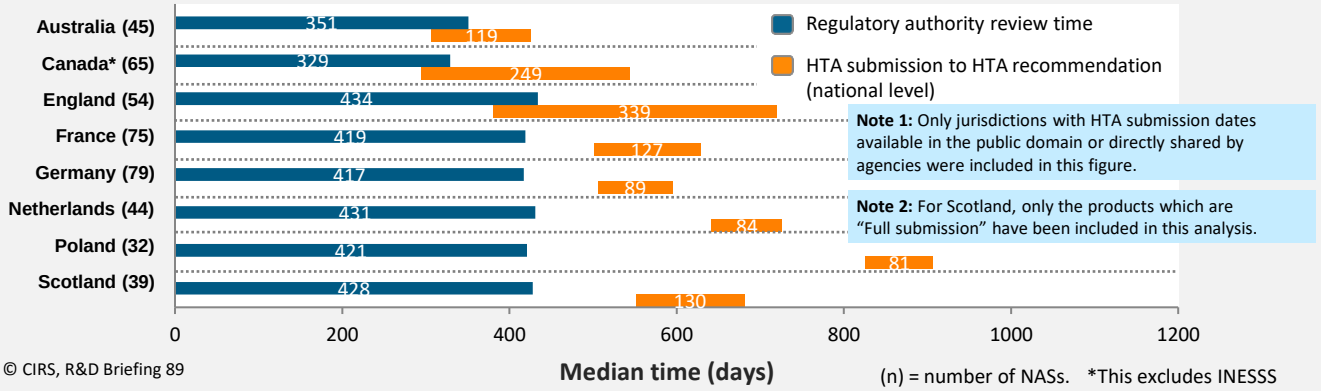
In 2022, Australia demonstrated the fastest median rollout timeline from regulatory approval to HTA recommendation, taking only 86 days (**Figure 4**). These results suggest that the proactive approach within Australia to move toward synchronising the timing of HTA and regulatory review is achieving 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 2022 compared to the median from 2018 to 2021 for France and Poland (180 vs 234 days, and 472 vs 564 days, respectively).

Poland exhibited the faster median review HTA time for HTA recommendations between 2021 and 2022.

The HTA process varies across different jurisdictions. 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. Initially, a scoping phase takes place before marketing authorisation is achieved. Subsequently, companies are invited to submit HTA dossiers to NICE. In Germany, companies can set 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.

Among the studied jurisdictions, Poland presented the shortest median HTA appraisal time for HTA recommendations between 2021 and 2022 (81 days) (**Figure 5**). However, this expedited process was counterbalanced by a prolonged overall rollout time. This delay could be attributed to the longer gap between regulatory approval and HTA submission. A similar scenario was observed in the Netherlands.

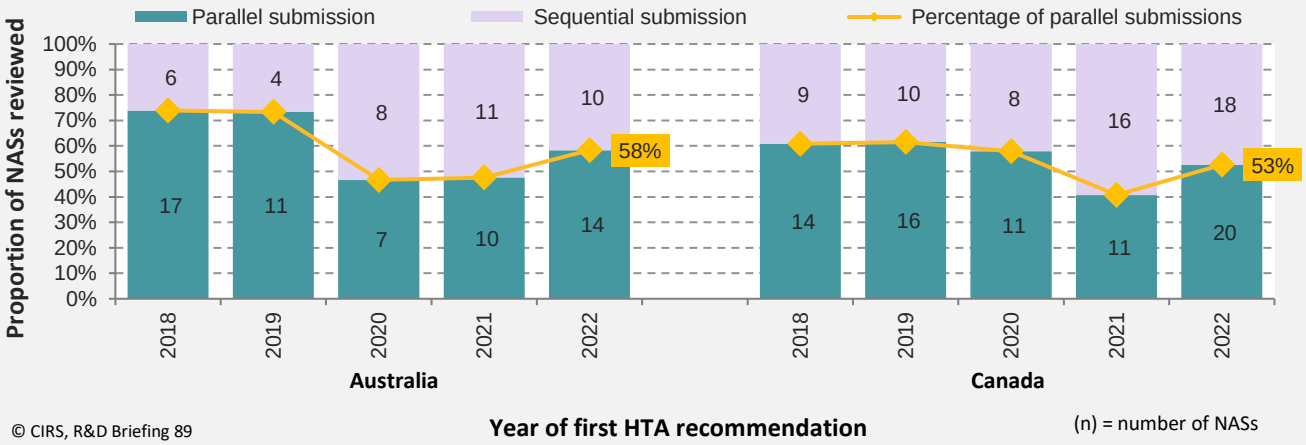
Figure 5. Breakdown of rollout time of NASs assessed by year of HTA recommendation 2021-2022



(n) = number of NASs. *This excludes INESSS

CHARACTERISTICS: REGULATORY AND HTA REVIEW SEQUENCE

Figure 6. Number of NASs assessed in Australia (PBAC) and Canada (CADTH) 2018-2022 by HTA submission routes



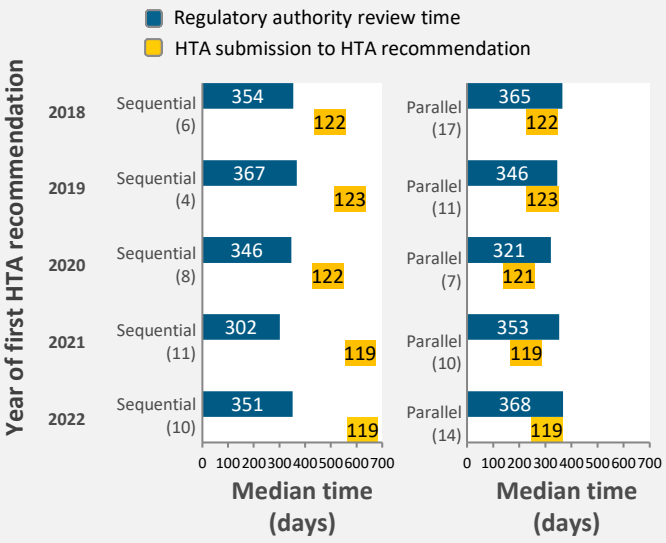
(n) = number of NASs

In 2022, the number of parallel submissions in both Australia and Canada increased compared to 2021.

In Australia and Canada, companies can submit dossiers to the HTA agency during the regulatory review process, 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 in order to facilitate timely access to new medicines.

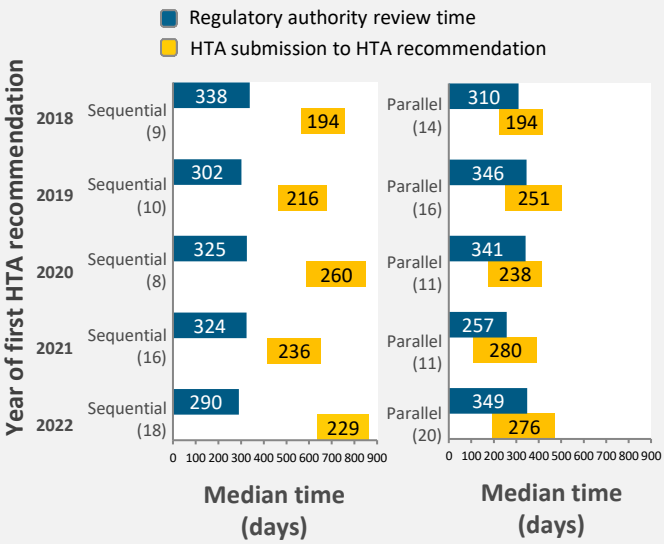
In 2022, data revealed that the percentage of parallel submissions are 58% for Australia and 53% for Canada, as indicated in **Figure 6**. Although the number of parallel submissions rose in both countries in 2022 compared to 2021, the proportion of parallel submissions has maintained an average of 60% for Australia and 55% for Canada over the period from 2018 to 2021.

Figure 7. Breakdown of rollout time by review sequence in Australia (2018-2022)



(n) = number of NASs

Figure 8. Breakdown of rollout time by review sequence in Canada (2018-2022)



(n) = number of NASs

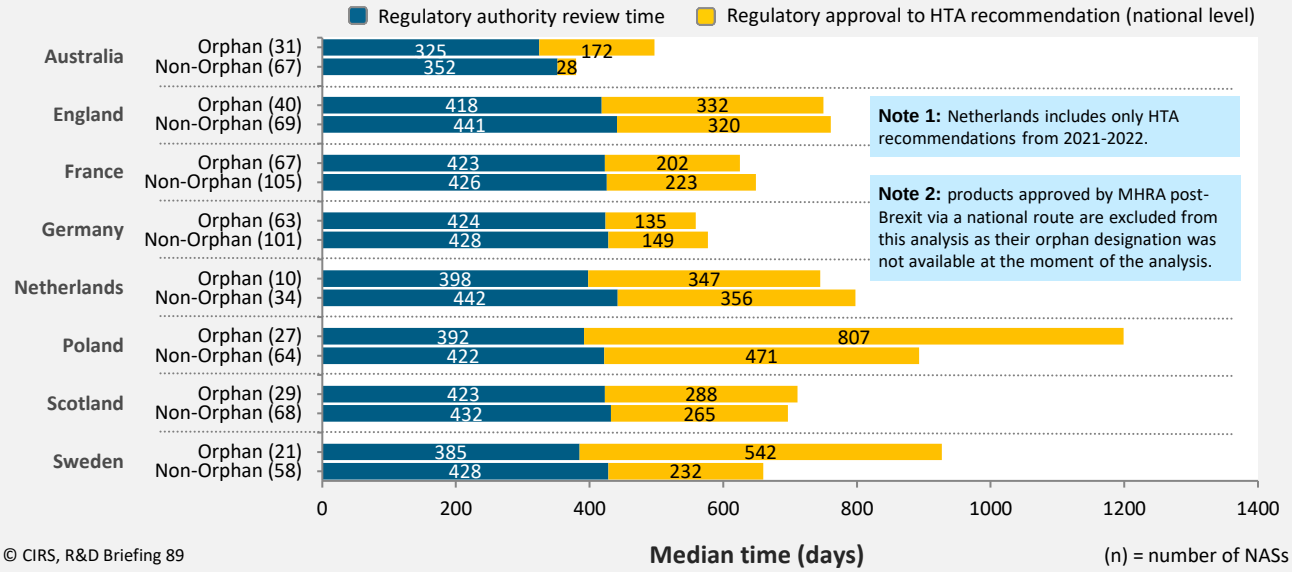
The parallel process shortened the overall time taken from regulatory submission to HTA recommendation in both Australia and Canada.

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 2018-2022, the median time for submission to PBAC was 121 days prior to TGA approval for parallel submissions. This contrasts with a 133-day delay in HTA submission with the sequential review (**Figure 7**).

For the parallel review process in Canada, HTA submissions must be made within 180 days before the anticipated Notice of Compliance (NOC) date from Health Canada (HC). Our analysis displayed that the median submission time to CADTH for NASs recommended between 2018-2022 was 123 days prior to the NOC for parallel submissions, as opposed to a 179-day delay in HTA submissions following the sequential review process (**Figure 8**).

CHARACTERISTICS: REGULATORY ORPHAN DESIGNATION

Figure 9. Breakdown of rollout time of NASs reviewed by HTA in 2018-2022, by regulatory orphan designation

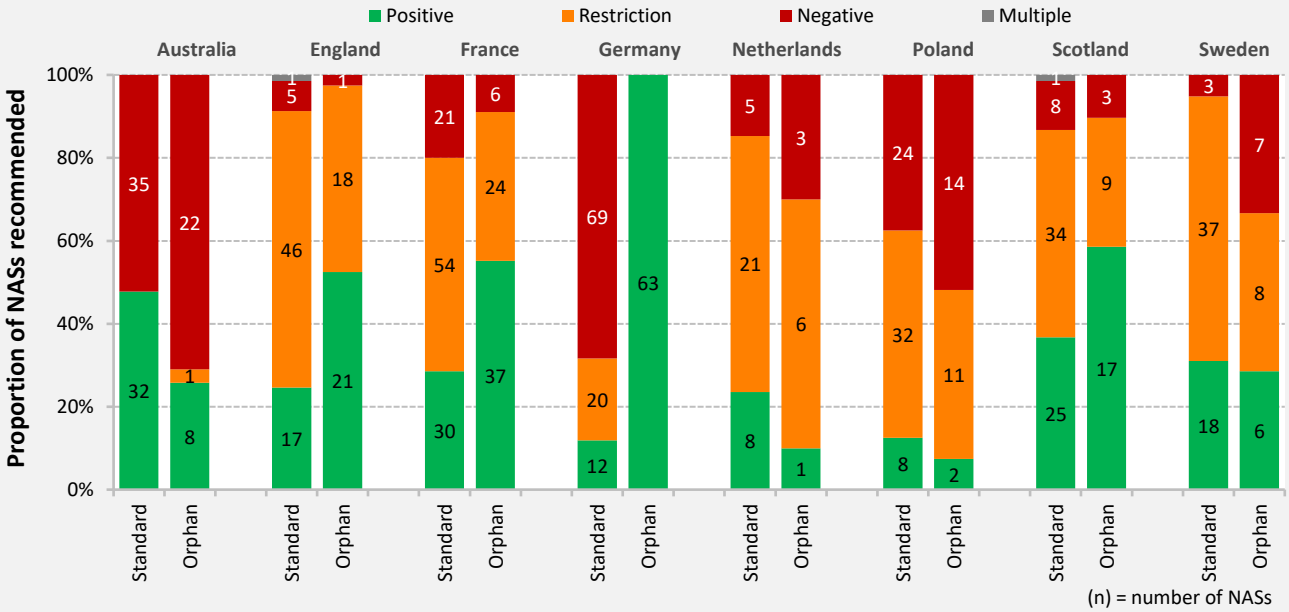


Products that received a regulatory orphan designation generally took longer to go from regulatory approval to their 1st HTA recommendation compared to non-orphan products.

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. HC does not currently have an orphan policy. The results showed that NASs with regulatory orphan designation had a slightly longer median time from regulatory approval to HTA recommendation compared to non-orphan in all jurisdictions, except France and Germany (**Figure 9**). The time taken from regulatory approval to HTA recommendation includes company strategy and HTA review time. The findings suggest that further efforts are needed by all stakeholders to accelerate time to HTA decision.

In addition, regulatory orphan designation did lead to 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 positive because the 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 2018-2022, by regulatory orphan designation

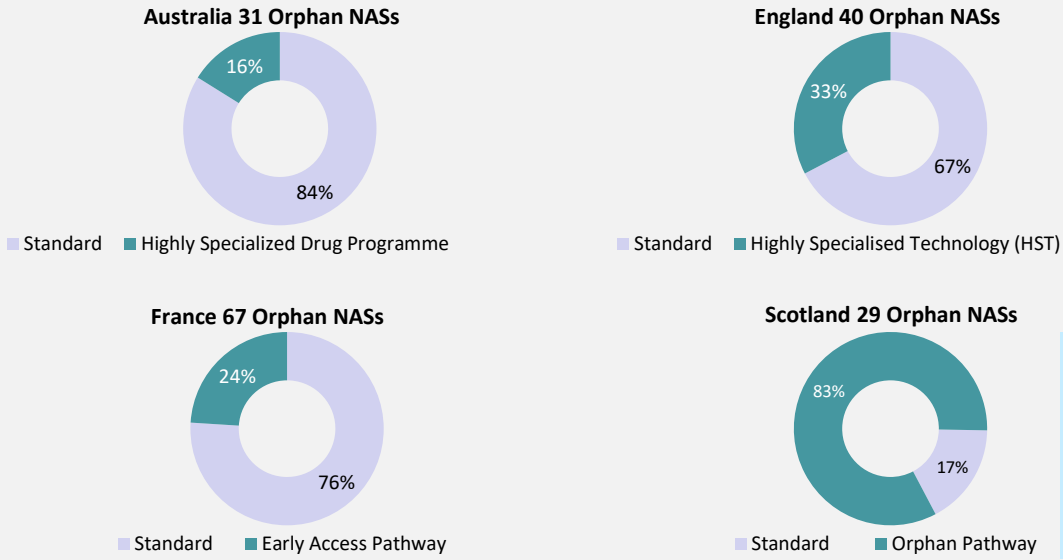


Note 1: Netherlands includes only HTA recommendations from 2021-2022.

Note 2: products approved by MHRA post-Brexit via a national route are excluded from this analysis as their orphan designation was not available at the moment of the analysis.

CHARACTERISTICS: REGULATORY ORPHAN DESIGNATION (CONT.)

Figure 11. Orphan products assessed 2018-2022, by the HTA pathway



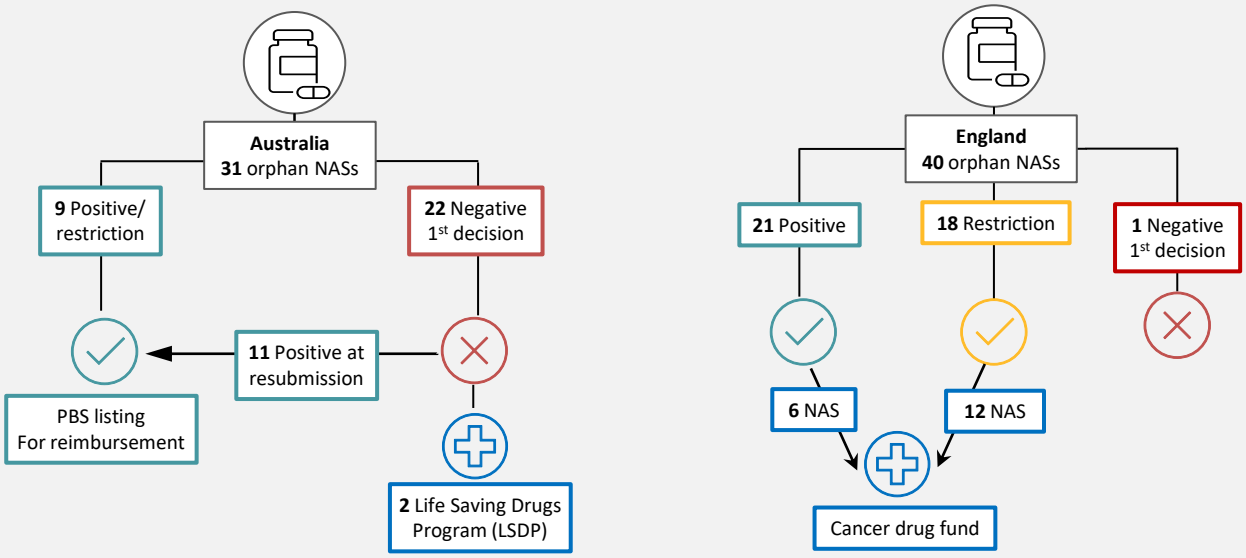
Note: In Scotland, medicines for extremely rare conditions are now assessed via the ultra-orphan pathway.

Scotland SMC has a designated pathway to assess orphan products, where 83% of NASs with a regulatory orphan designation underwent an HTA orphan/rare disease-related pathway

In this briefing, we examined the HTA pathways that orphan products have undergone (see Table 4 in the Appendix). Among all jurisdictions, only Scotland's SMC has an orphan pathway, with 83% of regulatory-approved orphan products undergoing this process (**Figure 11**). In other jurisdictions, non-standard pathways are in place and have been utilized for orphan products where applicable. However, these pathways are not utilized for all orphan products, with only 16% in Australia, 33% in England, and 24% in France using them, respectively (**Figure 11**).

In addition to the assessment process, orphan products can also be reimbursed via alternative funding mechanisms. In Australia, 65% of the compounds appraised by PBAC between 2018-2022 were recommended to be covered under Public Benefit Scheme (PBS), while the PBAC decisions were negative, 2 products were financially supported through the Life-Saving Drugs Programme (LSDP). An observation conducted simultaneously in England revealed that the majority (98%) of orphan drugs were recommended by NICE. Of these, 55% were reimbursed by NHS funding, and 45% were covered by the Cancer Drugs Fund (CDF) (**Figure 12**).

Figure 12. Orphan products HTA outcome, by funding mechanism

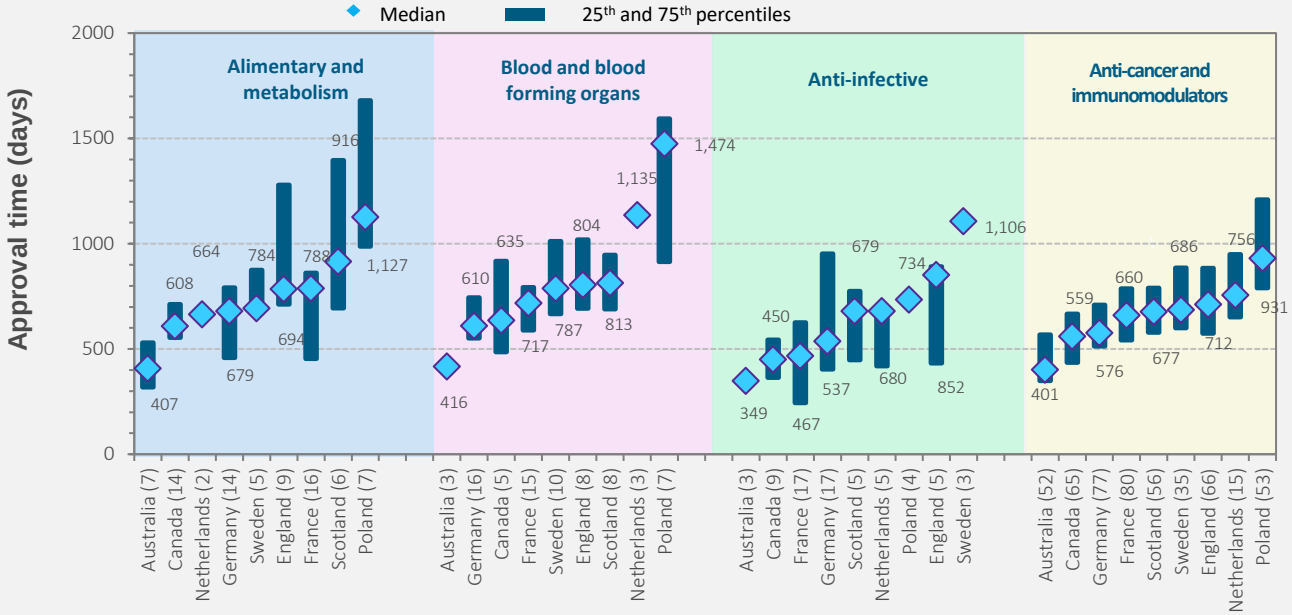


65% of orphan NASs were listed
6% covered by LSDP

98% of orphan NASs recommended
45% covered by cancer drug fund

CHARACTERISTICS: THERAPEUTIC AREA

Figure 13. Time taken from regulatory submission to 1st HTA recommendation in 2018-2022, by top therapeutic area



Note: Netherlands includes only HTA recommendations from 2021-2022.

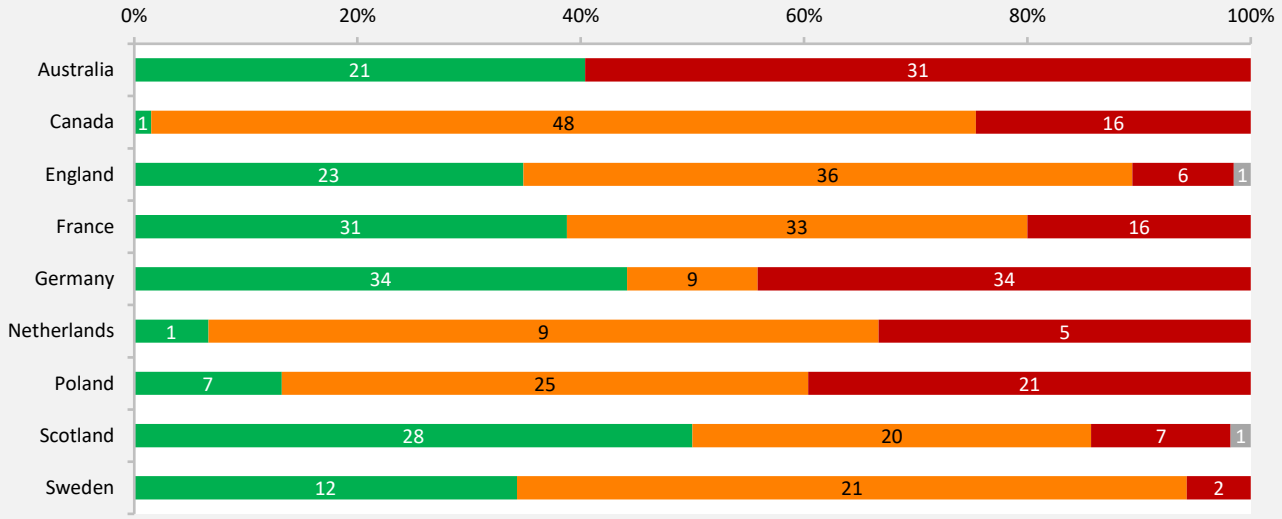
(n) = number of NASs

The top four therapeutic areas constituted 70% of all products assessed by HTA in at least one country between 2018-2022, with Australia demonstrating the fastest rollout time from regulatory submission to the 1st HTA outcome for all four areas.

The top four therapeutic areas made up 70% (188/270) of all the products assessed by at least one country between 2018-2022, with anti-cancer and immunomodulators making up 62% (113/182) of the top therapeutic areas (**Figure 13**). 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 13**). As noted by the 25th-75th percentile bars, there were also wide variations for certain jurisdictions across therapy areas. The variation in rollout time may be attributed to expedited review pathways by regulatory agencies, companies' submission strategy (parallel vs. sequential), and time taken during the HTA process.

Sweden and England recommended (including both positive and restriction recommendations) the highest percentage of anti-cancer and immunomodulators for reimbursement, with 98% and 93% of the recommendations, respectively (**Figure 14**).

Figure 14. 1st HTA Recommendation for anti-cancer and immunomodulators (2018-2022)



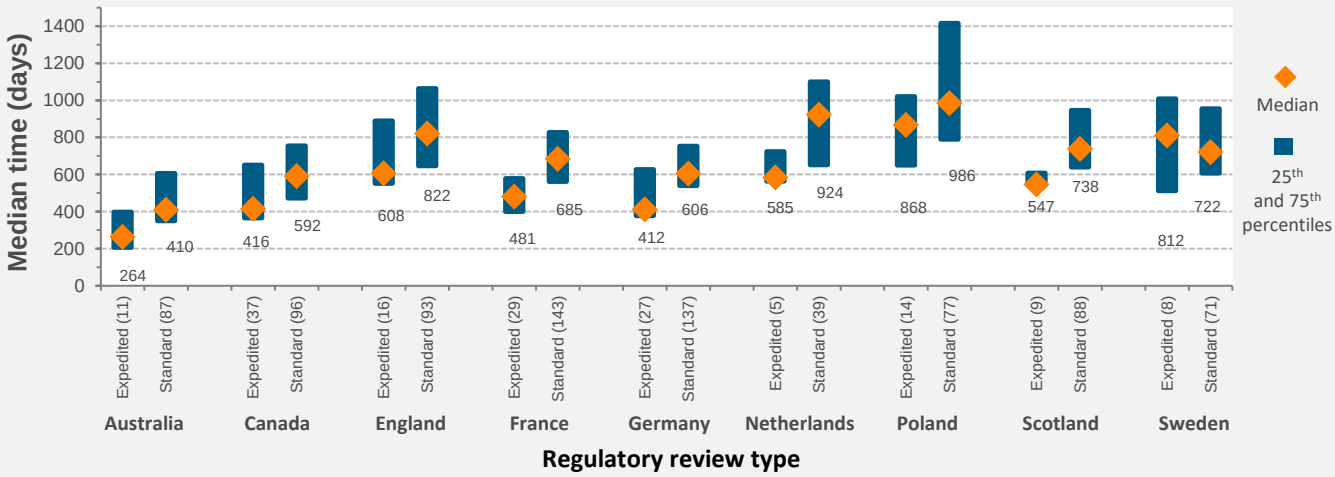
(n) = number of NASs

Positive Restriction Negative Multiple

Note: Netherlands includes only HTA recommendations from 2021-2022.

Characteristics: Use of Expedited Regulatory Pathways

Figure 15. Time taken from regulatory submission to HTA recommendation (2018-2022) by regulatory review type



Note 1: Netherlands includes only HTA recommendations from 2021-2022.

Note 2: products approved by MHRA post-Brexit via a national route are excluded from this analysis as their review type was not available at the moment of the analysis.

(n) = number of NASs

The use of expedited regulatory pathways shortened the rollout time in all jurisdictions apart from Sweden.

Expedited regulatory pathways are mechanisms designed to accelerate the review process of innovative products that are intended to address unmet medical needs or serving significant concerns related to public health. The list of expedited regulatory pathways across all jurisdictions is elaborated in the Appendix (Facilitated regulatory pathways, Table 5). 'Expedited review' refers to EMA 'Accelerated Assessment' and HC/TGA 'Priority Review'. TGA introduced an expedited (priority) review program in 2017.

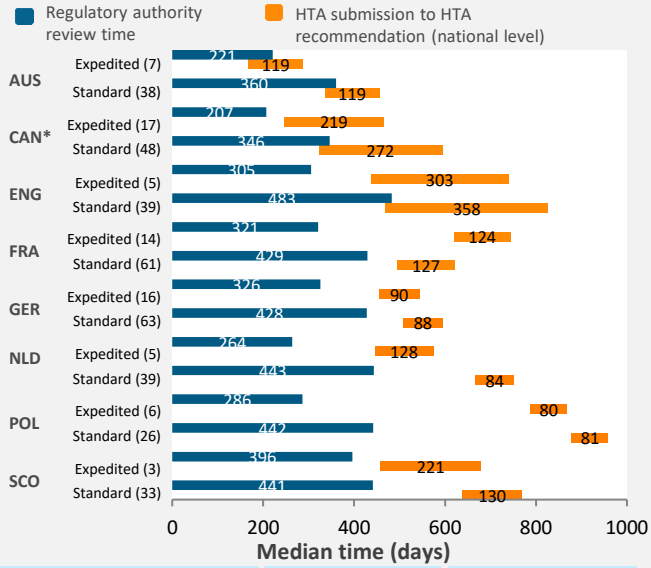
In all jurisdictions, except for Sweden (**Figure 15**), the median overall time from regulatory submission to HTA recommendation was shorter for products undergoing an expedited review in comparison to those following the standard review process.

A further breakdown of rollout time suggests that the HTA review time was not influenced by the use of an expedited pathway. The overall shorter rollout time could primarily be attributed to faster regulatory timelines (**Figure 16**).

The proportion of positive or positive with restrictions recommendations for products that underwent an expedited review process varied among different jurisdictions.

In several countries, including Canada, England, France, Germany, the Netherlands and Scotland, products that underwent an expedited review process presented a higher proportion of positive or positive with restrictions recommendations than those subjected to a standard review process (**Figure 17**). However, in Australia, only 9% of the products reviewed through an expedited pathway achieved a positive or positive with restrictions as a first HTA recommendation.

Figure 16. Breakdown of rollout time of NASs assessed 2021-2022, by regulatory review pathway*



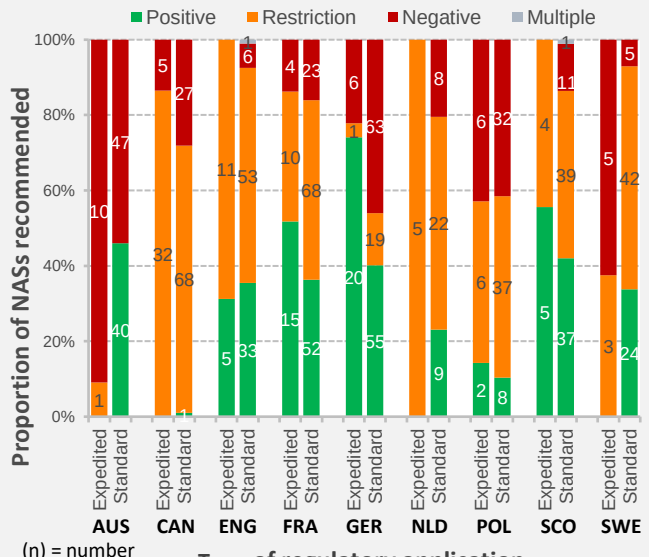
Note 1: products approved by MHRA post-Brexit via a national route are excluded from this analysis as their review type designation was not available at the moment of the analysis.

Note 2: For Scotland, only the products which are "Full submission" have been included in this analysis.

Note 3: Sweden is not included in this analysis because its HTA submission date

*This excludes INESSS (n) = number of NASs

Figure 17. First HTA recommendation type across key jurisdictions by review type 2018-2022

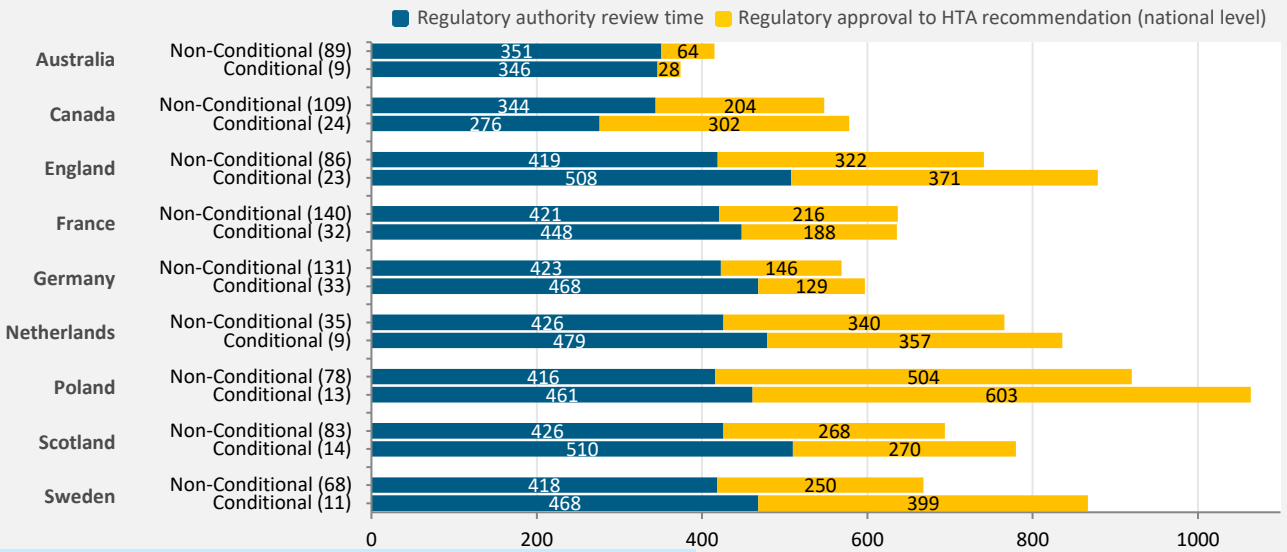


Note 1: Netherlands includes only HTA recommendations from 2021-2022.

Note 2: products approved by MHRA post-Brexit via a national route are excluded from this analysis as their review type designation was not available at the moment of the analysis.

CHARACTERISTICS: CONDITIONAL REGULATORY APPROVAL

Figure 18. Breakdown of rollout time of NASs assessed 2018-2022, by regulatory approval conditions



Note 1: Netherlands includes only HTA recommendations from 2021-2022.
Note 2: products approved by MHRA post-Brexit via a national route are excluded from this analysis as their Conditional/Non-conditional designation was not available at the moment of the analysis.

Generally, NASs approved through a conditional regulatory pathway exhibited a longer median rollout time.

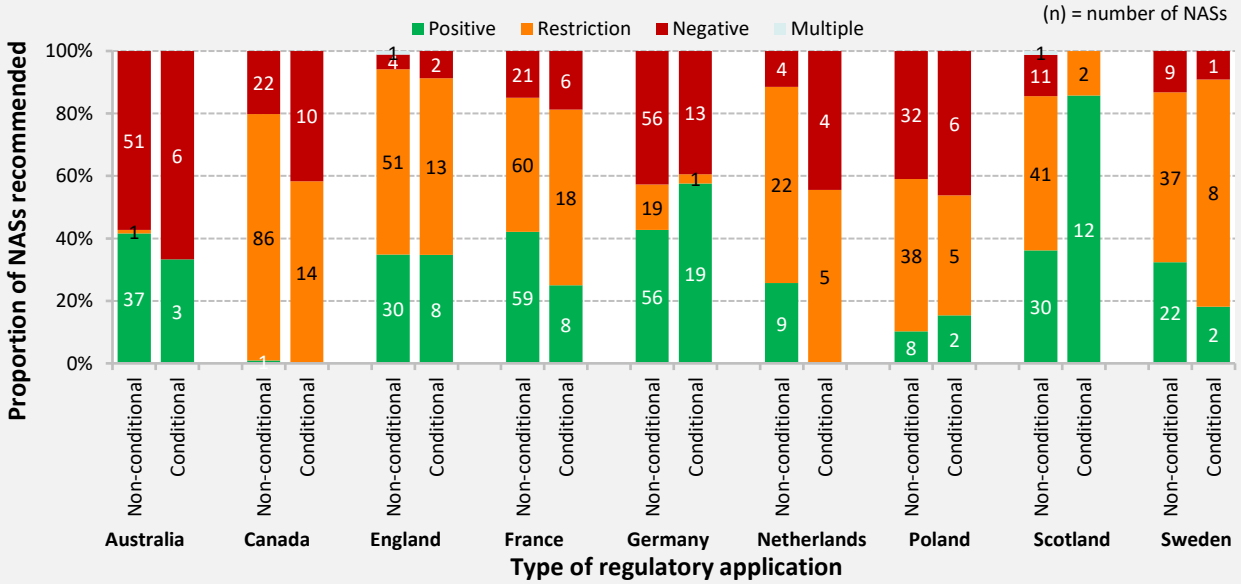
Regulatory agencies in Australia, Canada and Europe have implemented a conditional pathway to facilitate the marketing of promising new medicines in situations where clinical evidence is limited. The list of conditional regulatory pathways across the studied jurisdictions is elaborated in the Appendix (Facilitated regulatory pathways, Table 5).

For all the jurisdictions under the European Medicines Agency (EMA), the median review time for conditionally approved products was found to be consistently longer compared to the time taken for evaluations under non-conditional approval (**Figure 18**). In contrast, both Australia and Canada exhibited a shorter median regulatory review time for conditional approval. Nevertheless, a longer median HTA review time was found for conditional products in Canada. The latter led to the observation that, overall, NASs assessed under a conditional regulatory pathway generally displayed a longer median rollout time (or a similar time, in the case of France) in comparison to those evaluated via a non-conditional pathway. Notably, Australia emerged as an exception to this trend, presenting a shorter median rollout time for conditional products compared to non-conditional ones (**Figure 18**).

The regulatory conditional pathway may not affect the HTA outcome.

The findings in **Figure 19** did not suggest any correlation between a regulatory conditional approval and the likelihood of obtaining an optimal or non-optimal HTA recommendation. This could suggest that the conditional pathway does not influence HTA outcome. However, it is worth noting that in Scotland, all products that received conditional approval were granted either a positive or positive with restriction HTA recommendation.

Figure 19. Outcome of 1st HTA recommendation for NASs assessed 2018-2022, by regulatory approval conditions



Note 1: Netherlands includes only HTA recommendations from 2021-2022.

Note 2: products approved by MHRA post-Brexit via a national route are excluded from this analysis as conditional status was not available at the moment of the analysis.

FOCUS: ACCESS WORK-SHARING CONSORTIUM

Table 1. NASs approved and assessed by the Access Consortium 2018-2022

Generic name	Therapeutic area	First regulatory approval	HTA outcome			
			Australia	Canada	England*	Scotland*
Niraparib	Anti-cancer and immuno-modulators	16/11/2017	Negative	Positive with restrictions		
Apalutamide	Anti-cancer and immuno-modulators	03/07/2018	Negative	Positive with restrictions		
Abemaciclib	Anti-cancer and immuno-modulators	26/09/2018	Positive	Positive with restrictions		
Tafamidis meglumine	Nervous system	20/01/2020	Negative	Not approved as Access		
Darolutamide	Anti-cancer and immuno-modulators	20/02/2020	Negative	Positive with restrictions		
Isatuximab	Anti-cancer and immuno-modulators	29/04/2020		Positive with restrictions		
Inclisiran	Cardiovascular system	09/12/2020	Assessed in 2023, excluded in this report	Negative		
Somatrogon	Systemic hormonal preparations	26/10/2021	Positive	Positive with restrictions		
Vericiguat	Cardiovascular system	10/11/2021	Negative			
Avalglucosidase alfa	Alimentary tract and metabolism	12/11/2021	Negative	Positive with restrictions		
Finerenone	Cardiovascular system	18/11/2021	Negative	Assessed in 2023, excluded in this report		
Faricimab	Sensory organs	27/05/2022	Positive	Positive with restrictions	Positive with restrictions	Positive with restrictions
Asciminib	Anti-cancer and immuno-modulators	22/06/2022	Negative	Positive with restrictions	Positive	Positive

Positive
Restriction
Negative
Multiple

*MHRA joined the Access Consortium in 2021

Among the products that received a 1st HTA recommendation between 2018-2022, 13 were approved via the Access Consortium.

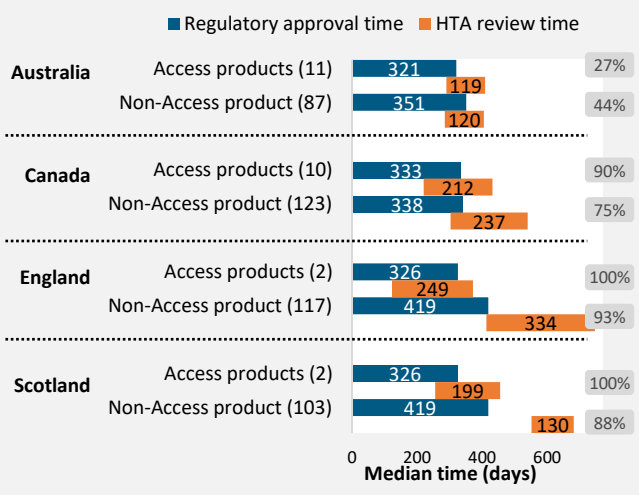
The Access Consortium is a medium-sized coalition, comprising 'like-minded' regulatory agencies from various international jurisdictions. It was formed with the aim of promoting greater collaboration and alignment of regulatory requirements. As part of the work-sharing process, the regulatory agencies review different sections of the dossier. By sharing resources between partners, the consortium seeks to facilitate a more efficient and harmonized approach to the regulatory evaluation and approval of medical products. This collaboration aims to expedite access to high-quality, safe and effective therapeutic products.

A total of 13 products approved via the Access route, which received a 1st HTA recommendation between 2018 and 2022, were identified in this briefing (**Table 1**). Among these Access products, those that rolled out to Canada, England or Scotland received either a positive or positive with restrictions recommendation. In the case of the Access products rolled out to Australia, 73% received a negative 1st HTA recommendation, with the remaining 27% obtaining a positive recommendation. It is worth noting that the low number of NASs appraised by either NICE or SMC can be attributed to the fact that the MHRA only joined these work-sharing applications in 2021.

Access products presented a shorter median regulatory review time compared to non-Access products.

All four studied jurisdictions presented a shorter median regulatory review time for Access products compared to non-Access products (**Figure 20**). The HTA review time varied across jurisdictions, not displaying a clear general trend. Within Canada, England and Scotland, Access products were observed to have a higher percentage of either positive or positive with restrictions recommendations compared to non-Access products (**Figure 20**). Conversely, Access products presented a lower percentage of positive or positive recommendations compared to non-Access products in Australia. However, caution needs to be taken when interpreting these results, as the small sample size of the Access products may limit their interpretability. **Figure 21** includes two case studies of Access products that rolled out to all 4 studied jurisdictions.

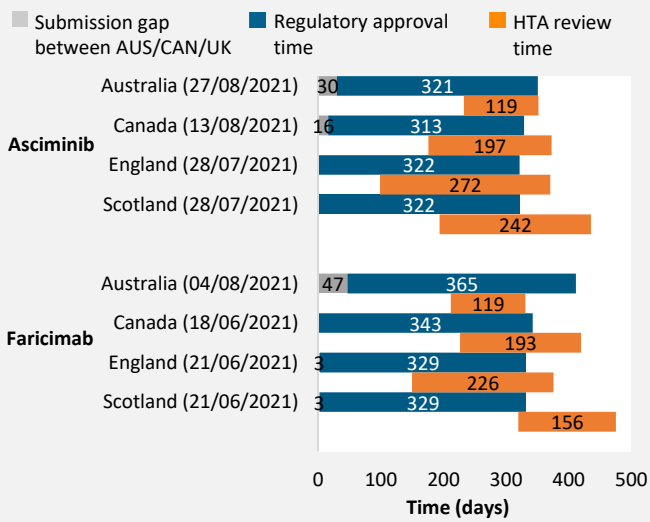
Figure 20. Rollout time of NASs assessed 2018-2022 approved by the Access Consortium vs. Non-Access route



% = products received positive/restrictive recommendation

(n) = number of NASs

Figure 21. Case studies of NASs approved by the Access Consortium and received HTA decisions in four jurisdictions



(n) = Regulatory submission date

FOCUS: PROJECT ORBIS

Table 2. 1st HTA recommendation for NASs assessed in key jurisdictions 2018-2022, approved via Project Orbis

Generic Name	Australia	Canada	England	Scotland
Amivantamab			(Orbis C) Standard, Conditional	
Cedazuridine	(Orbis B) Standard	(Orbis A) Standard		
Enfortumab Vedotin	(Orbis C) Standard	(Orbis B) Expedited		
Lurbinectedin		(Orbis C) Standard, Conditional		
Mobocertinib	(Orbis B) Standard, Conditional			
Nivolumab / Relatlimab	(Orbis B) Standard			
Pralsetinib		(Orbis C) Standard, Conditional		
Ripretinib	(Orbis A) Expedited	(Orbis A) Expedited		
Sacituzumab Govitecan	(Orbis B) Expedited	(Orbis B) Expedited	(Orbis B) Expedited	(Orbis B) Expedited
Selpercatinib		(Orbis C) Standard, Conditional		
Selumetinib	(Orbis C) Standard			
Sotorasib	(Orbis B) Standard, Conditional		(Orbis B) Standard, Conditional	(Orbis B) Standard, Conditional
Tafasitamab		(Orbis C) Standard, Conditional		
Tepotinib		(Orbis A) Standard, Conditional	(Orbis C) Standard	
Trastuzumab Deruxtecan	(Orbis C) Standard, Conditional	(Orbis C) Standard, Conditional		
Tucatinib	(Orbis B) Expedited	(Orbis A) Expedited		

Positive
Restriction
Negative

*__Note__: a grey fill denotes that the NASs is either under review, has not yet been submitted, was assessed in 2023, or was assessed by HTA but not under the project Orbis.

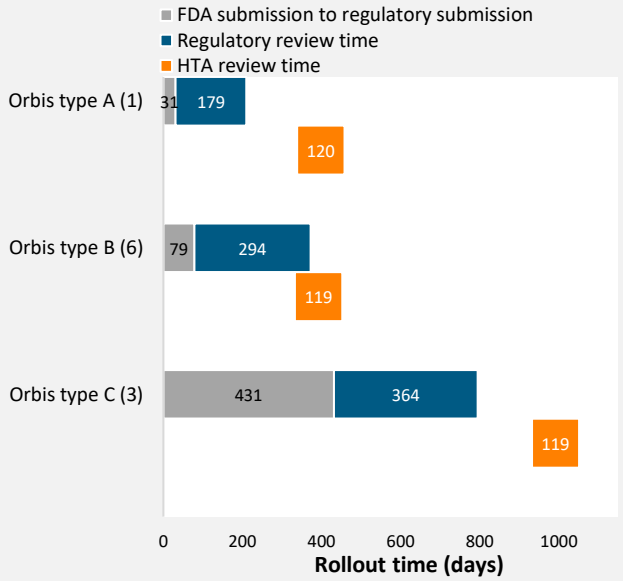
Between 2018 and 2022, 16 Orbis products received HTA recommendations in Australia, Canada, England or Scotland.

Project Orbis is an initiative of the US FDA Oncology Center of Excellence. It is coordinated by the FDA and provides a framework for the concurrent submission and review of oncology products among international partners. It aims to deliver faster patient access to innovative cancer treatments with potential benefits over existing therapies. Within the scope of Project Orbis, there are three distinct types of submissions - These differ on the timelines between the FDA and its international partners (please see the Facilitated Regulatory Pathways page for detailed descriptions of these types).

Table 2 displays the 16 Orbis products that obtained an HTA recommendation in at least one of the following jurisdictions: Australia, Canada, England or Scotland, during the period from 2018 to 2022. In Australia, the most common Orbis category was type B, with delays over 30 days from FDA to partner submission. In Canada, 5 out of 11 NASs were categorized as Orbis type C, followed by 4 classified as type A, and 2 as type B. Nice had a 50% split between types B and C, while SMC had both products evaluated as type B. The limited number of Orbis products appraised by both NICE and SMC is due to MHRA only joining the scheme in January 2021. All Orbis products that rolled out to Australia received a negative 1st recommendation.

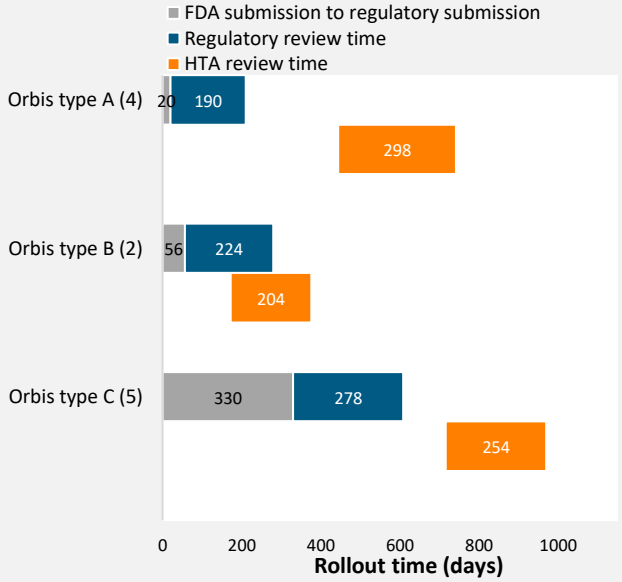
Figure 22 and **Figure 23** illustrate the breakdown of rollout time for NASs approved through the Orbis route that received an HTA recommendation in either Australia or Canada, respectively. The data is organised according to the specific type of Orbis submission. Results suggest that companies were more prepared for parallel HTA submission for Orbis B products, while Orbis A and C were presented through a sequential submission.

Figure 22. Breakdown of rollout time for Orbis products in Australia (HTA recommendation 2018-2022)



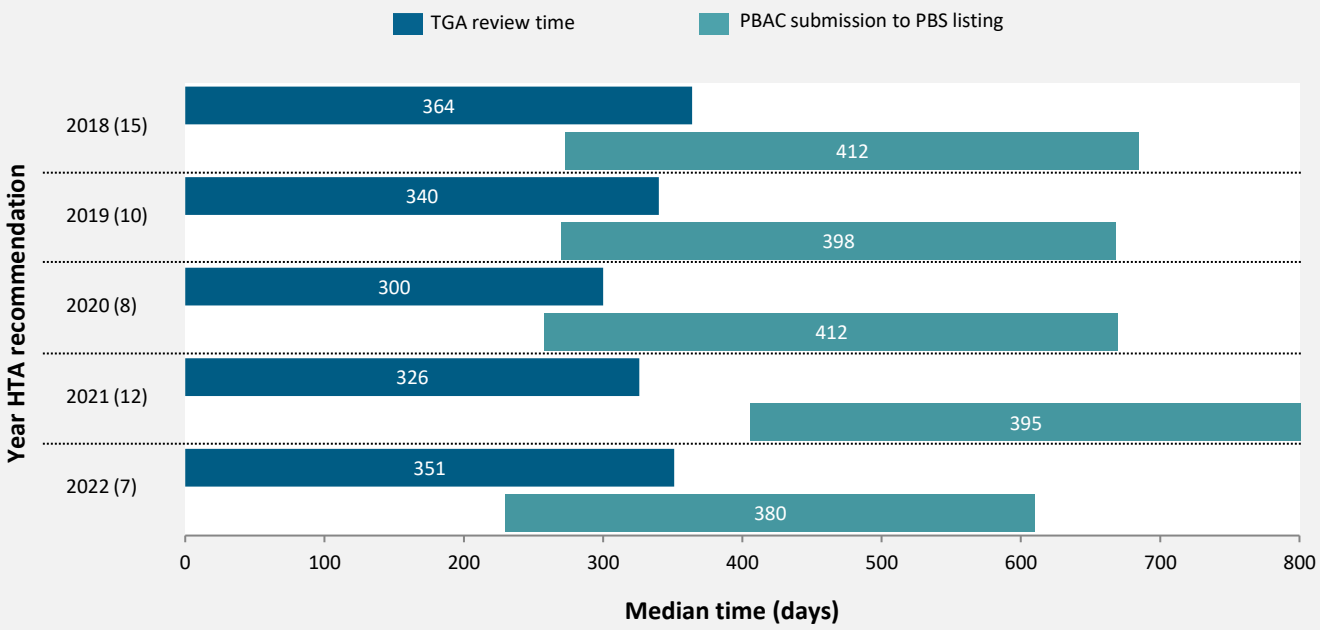
(n) = number of NASs

Figure 23. Breakdown of rollout time for Orbis products in Canada (HTA recommendation 2018-2022)



(n) = number of NASs

Figure 24. Breakdown of rollout time by PBAC 1st recommendation year

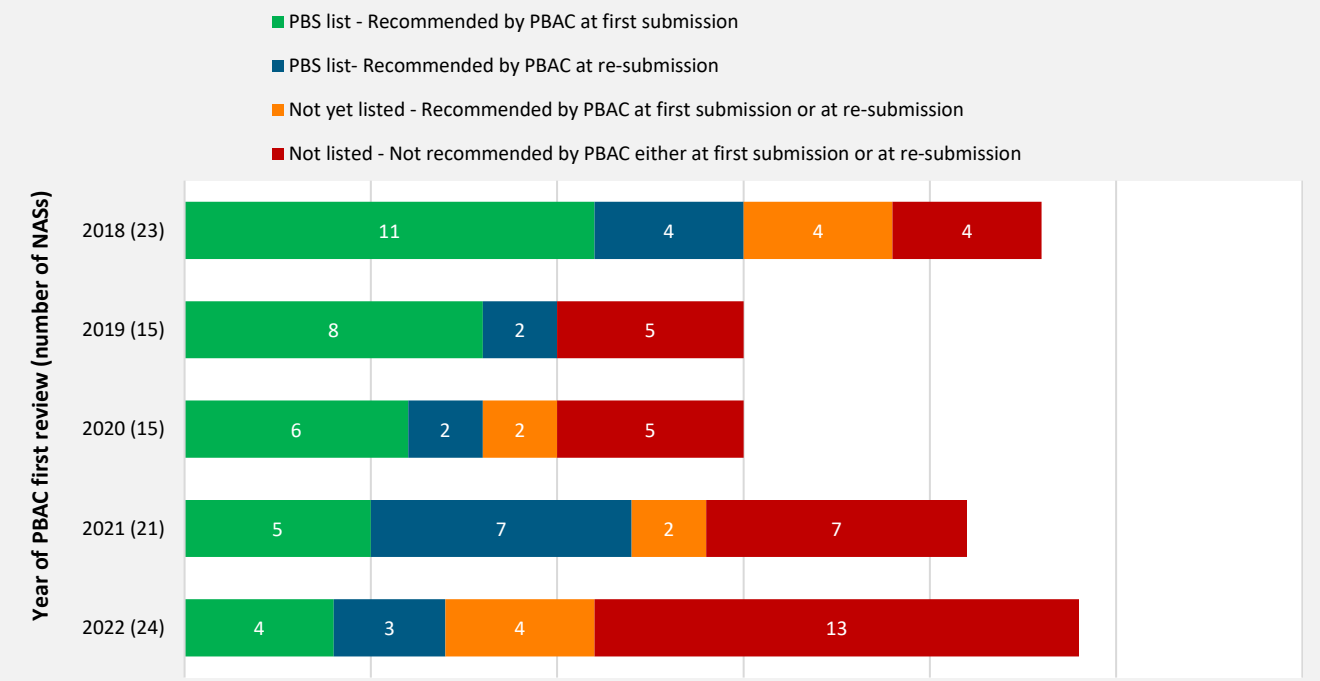


(n) = number of NASs

Generally, there has been a consistent decrease in the median time to PBS listing from 2018 to 2022, with the exception of 2021.

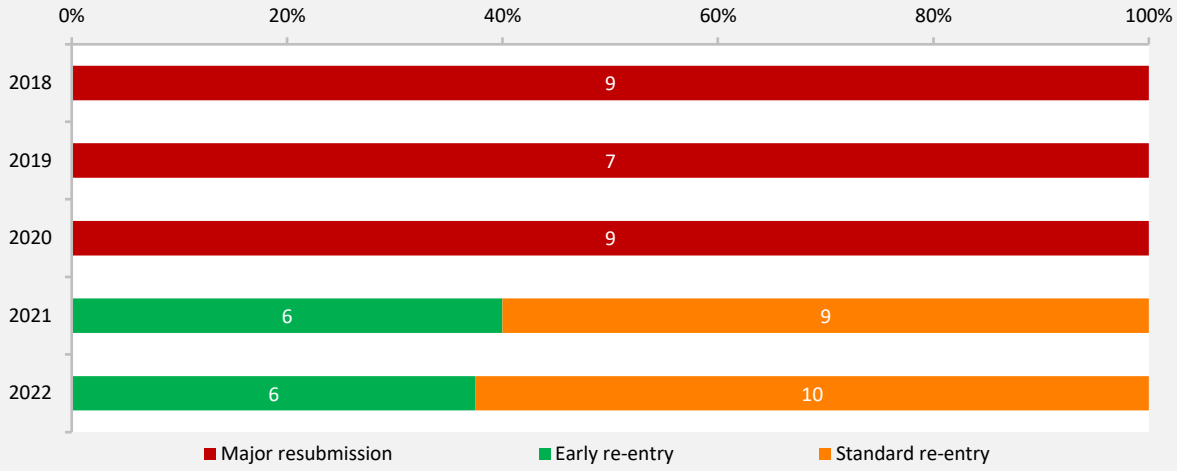
PBAC makes HTA recommendations for the listing of medicines on the Pharmaceutical Benefits Scheme (PBS) list that are non-binding and require Ministerial approval. **Figure 24** displays the breakdown of rollout time until PBS listing for the NASs appraised by PBAC from 2018 to 2022. The results demonstrate that the median time for the dossier submission to PBAC has been progressively occurring earlier across the studied years, with the exception of 2021. In line with these findings, the analysis also indicates a consistent decrease in the median PBS listing time over the specified timeframe. A total of 53% (52/98) of drugs with PBAC recommendations in 2018-2022 were listed in the PBS list in Australia, of which 65% (34/52) appraised by PBAC were listed at the first submission (**Figure 25**).

Figure 25. The PBS listing status for NASs reviewed by PBAC 2018-2022



(n) = number of NASs

Figure 26. Proportion of type of resubmissions in Australia (2018-2022)



Note: when the resubmission type was not specified in the PBS document, these were classified as "Standard re-entry". "Facilitated resolutions" were not included in this analysis.

(n) = number of NASs

If the initial PBAC recommendation does not support PBS listing, companies may resubmit the dossier until a positive or restrictive recommendation is granted for listing.

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. More specifically, following a 'not recommended' PBAC outcome, there are four different resubmission pathways available to applicants: Standard Re-entry, Early Re-entry, Early Resolution and Facilitated Resolution.

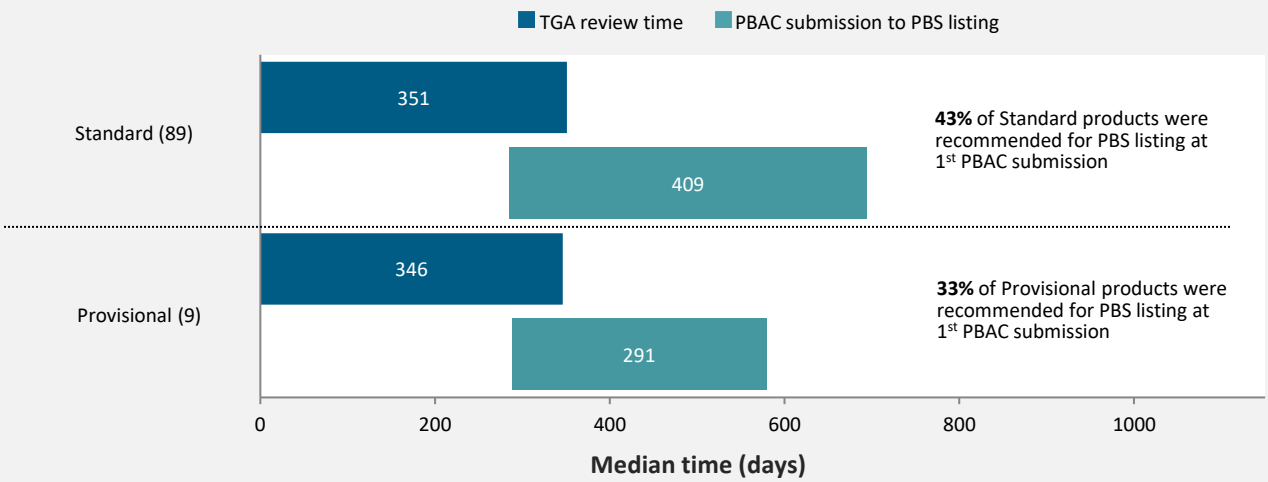
The early re-entry pathway can be nominated by PBAC since 2021 and may be nominated when the PBAC considers that the remaining issues could be easily resolved. Applicants who accept this pathway are eligible for PBAC consideration at the immediately subsequent meeting, thus potentially facilitating a faster listing.

Figure 26 illustrates the type of resubmission followed by NASs that received a negative recommendation by PBAC during the time period 2018-2022. Since 2021, 12 products have benefited from the early re-entry pathway.

For HTA recommendations between 2018 and 2022, 33% of the 9 NASs that received a TGA provisional approval were recommended for PBS listing at the 1st submission.

In 2018, TGA introduced the provisional approval pathway, a mechanism that provides access to certain promising new medicines where TGA assesses that the benefit of early availability of the medicine outweighs the risk inherent in the fact that additional data are still required. Between 2018 and 2022, 9 NASs that received TGA provisional approval obtained an HTA recommendation by PBAC. Among the 9 provisional products, 33% were recommended for PBS listing at the 1st HTA recommendation (**Figure 27**).

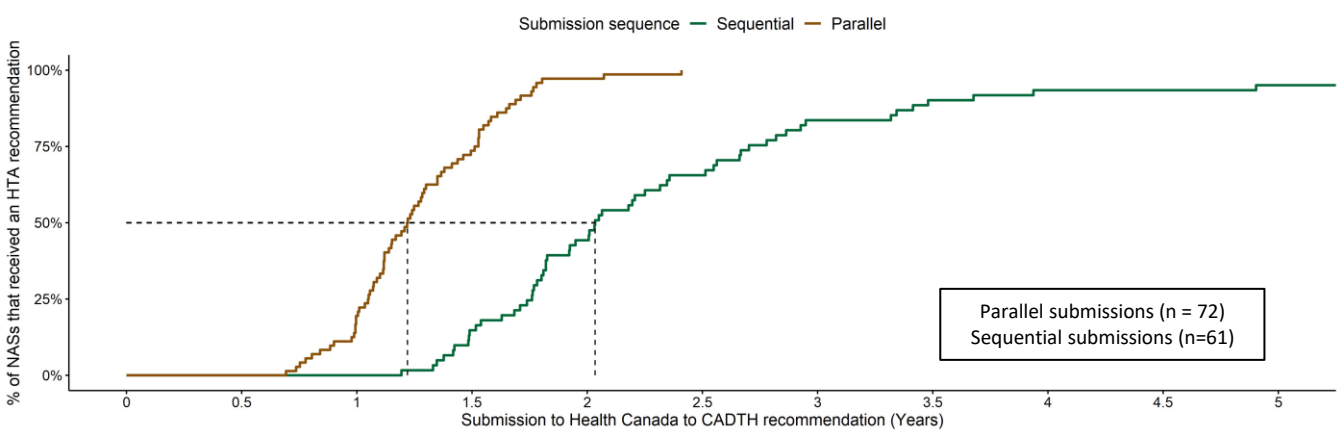
Figure 27. Breakdown of rollout time by Provisional vs Standard (2018-2022)



Note: "Recommended" includes positive and positive with restrictions recommendations.

(n) = number of NASs

Figure 28. Cumulative percentage of HTA recommendations of NASs appraised in Canada by submission sequence (HTA recommendation 2018-2022)



Parallel submissions were found to expedite the rollout process for NASs that received an HTA recommendation by CADTH between 2018 and 2022.

The HC/CADTH parallel review process, which allows for submission to CADTH within 90 days before the date of the anticipated Notice of Compliance (NOC) from HC, had been available for companies since 2012. From 2 April 2018, CADTH submission criteria were changed to within 180 days before the anticipated NOC from HC.

Figure 28 displays a cumulative analysis of NASs appraised by CADTH from 2018 to 2022 comparing two distinct groups: (Sequential) the NASs that were evaluated through a sequential submission and (Parallel) the NASs that followed a parallel submission. The cumulative analysis illustrates the proportion of NASs that received an HTA recommendation over time (from submission to HC to HTA recommendation by CADTH) in each group. The graphical representation clearly highlights the advantage of parallel submission **over** sequential. Specifically, the parallel approach appears to expedite the rollout process.

In the evaluation of parallel submissions, we observed an increase in the median overlap between the regulatory and HTA reviews from 2018 to 2020 (**Figure 29**). Following this increase, the overlap has remained generally constant from 2020 to 2022. Conversely, for sequential submissions, the time from regulatory approval to HTA submission has exhibited fluctuations from 2018 to 2022, not revealing any clear trend.

The request for reconsideration by companies led to an increase in the median time required for a recommendation by CADTH.

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, 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 30 suggests that the request for reconsideration extended the median time from the initial draft recommendation to the final recommendation by CADTH compared to no request: 112 vs 21, 84 vs 52 and 143 vs 37 days in 2020, 2021 and 2022, respectively. The latter may have resulted also in the request for reconsideration increasing the median time from the company submission to the recommendation by CADTH compared to no request.

Figure 29. Time difference between regulatory approval and HTA submission
Parallel submission vs sequential submission

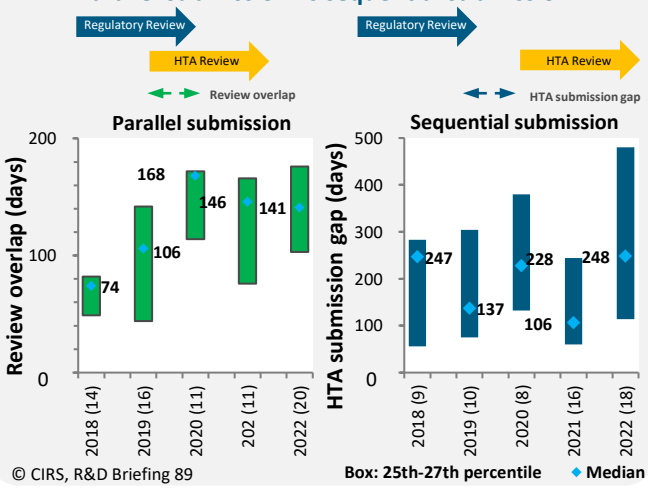
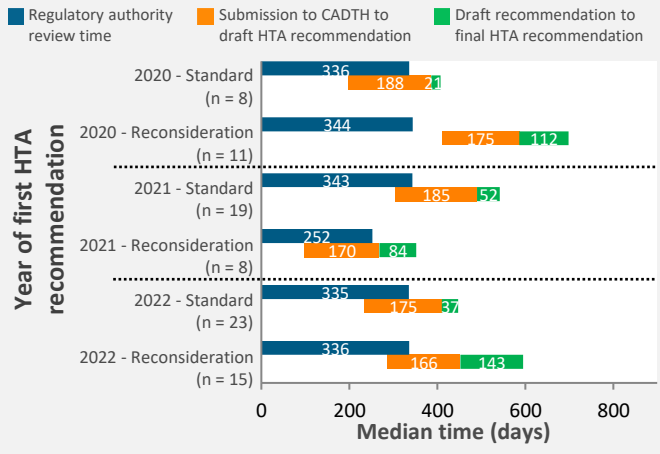


Figure 30. Breakdown of rollout time in Canada between 2020-2022 (Requested reconsideration vs standard)



(n) = number of NASs

Figure 31. First HTA recommendation comparison for 44 common NASs reviewed by four agencies (2018-2022)

Generic name	France	Germany	Poland	Sweden
abemaciclib	1	2	4	3
abrocitinib	1	2	4	3
acalabrutinib	3	1	4	2
alpelisib	2	1	4	3
apalutamide	2	1	3	4
avatrombopag	1	3	4	2
benralizumab	3	1	4	2
bimekizumab	2	3	4	1
binimetinib	4	1	3	2
brigatinib	4	2	3	1
cariprazine	3	2	4	1
cenobamate	2	1	4	3
dacomitinib	3	2	4	1
darolutamide	2	1	3	4
dupilumab	3	1	4	2
elexacaftor/ ivacaftor/tezacaftor	1	2	4	3
encorafenib	4	1	3	2
entrectinib	4	1	2	3
erenumab	3	2	4	1
fedratinib	3	1	4	2
filgotinib	2	1	4	3
fremanezumab	4	1	2	3
galcanezumab	2	1	4	3
gilteritinib fumarate	2	1	4	3
guselkumab	3	2	4	1
lanadelumab	2	1	3	4
larotrectinib	3	1	2	4
letermovir	2	1	3	4
lorlatinib	3	1	4	2
midostaurin	3	1	4	2
neratinib	3	2	4	1
niraparib	2	1	4	3
ozanimod	2	1	3	4
ponesimod	1	2	4	3
risankizumab	4	2	3	1
risdiplam	2	1	4	3
roxadustat	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
tildrakizumab	2	1	3	4
tivozanib	3	1	4	2
upadacitinib	2	4	3	1

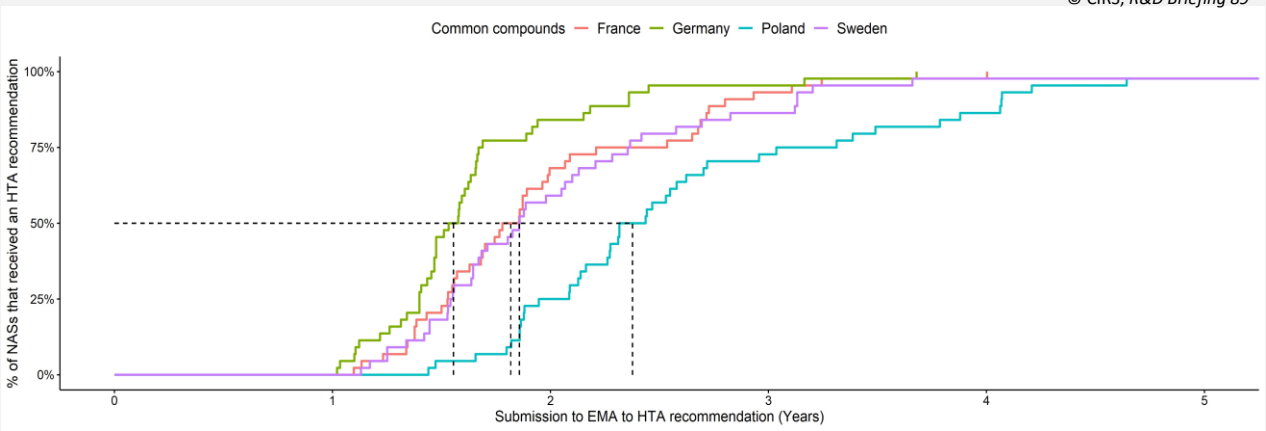
Positive
Restriction
Negative
Multiple

Note: Netherlands has not been included in this analysis as only HTA recommendations from 2021-2022 are available in our database.

A total of 44 common products were rolled out to France, Germany, Poland and Sweden between 2018 and 2022, and their HTA outcome varied across jurisdictions.

Between 2018 and 2022, 44 NASs were identified that received a first HTA recommendation from HTA agencies in France, Germany, Poland and Sweden. These were referred to as "common products" in this briefing. **Figure 31** displays a traffic light system to compare the different HTA outcomes associated with these common products. This visualization reflects the varied perceptions concerning the value of the NASs across the compared agencies. The recommendation dates for each product were also compared across all 4 agencies and the order of the first HTA recommendation was ranked from earliest recommendation (1) to last (4). **Figure 32** displays a cumulative analysis of the common NASs appraised by HTA agencies in France, Germany, Poland and Sweden from 2018 to 2022. The analysis illustrates the proportion of NASs that received an HTA recommendation over time (from submission to EMA to HTA recommendation by the respective agency). The results suggests the quickest rollout of compounds in Germany, as opposed to the slowest rollout in Poland. As depicted previously in **Figure 17**, this delay could potentially be attributed to the lag in company submission to HTA compared to the other agencies.

Figure 32. Cumulative percentage of HTA recommendations of common NASs appraised in Europe (HTA recommendation 2018-2022)



FEATURES OF EUROPE (CONT.)

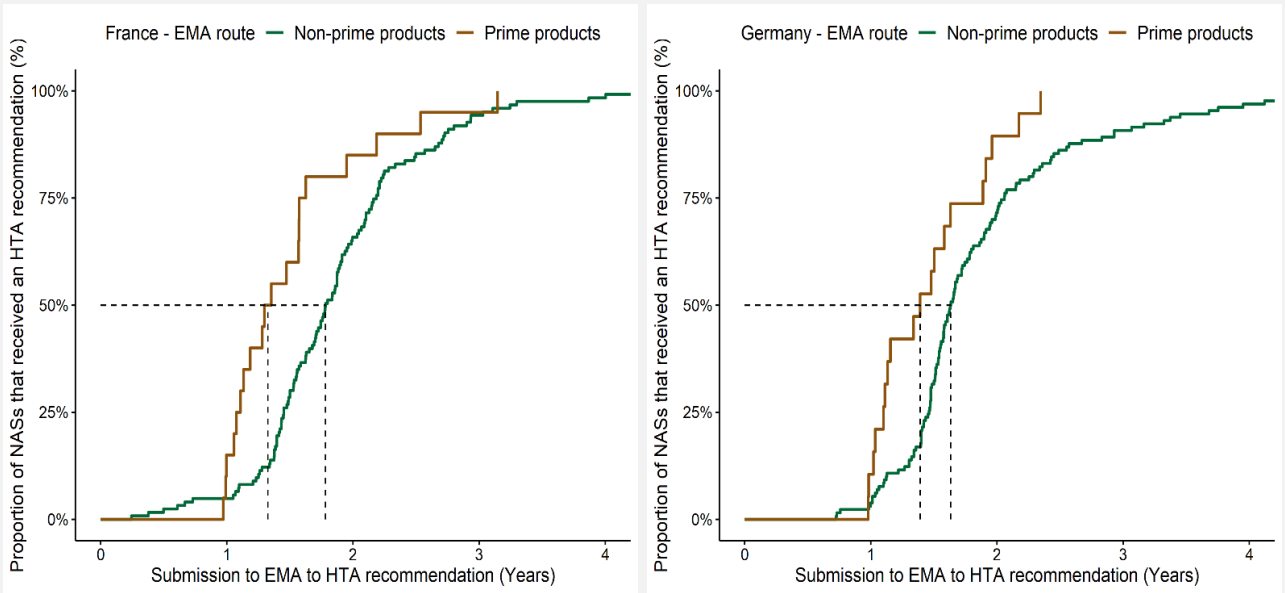
Table 3. PRIME Products assessed by HTA 2018-2023

PRIME ProductsR	EMA approval year	France	Germany	The Netherlands	Poland	Sweden
tisagenlecleucel	2018	positive	positive	positive with restrictions	negative	
axicabtagene ciloleucel	2018	positive	positive	positive with restrictions	negative	
betibeglogene autotemcel	2019	positive with restrictions	positive	Applicant withdrawn		
polatuzumab vedotin	2020	negative	positive	positive with restrictions	positive with restrictions	
givosiran	2020	positive with restr ictions	positive	positive with restrictions		positive with restrictions
onasemnogene abeparvovec	2020	positive with restrictions	positive	positive with restrictions		
bulevirtide	2020	positive with restrictions	positive			positive with restrictions
entrectinib	2020	negative	negative	negative	negative	positive with restrictions
belantamab mafodotin	2020	positive	positive			
imlifidase	2020	positive	positive			
lumasiran	2020	positive	positive			
brexucabtagene autoleucel	2020	positive	positive	negative		
risdiplam	2021	positive with restrictions	positive with restrictions	positive with restrictions	positive with restrictions	negative
odevixibat	2021	positive with restrictions	positive	positive with restrictions		
setmelanotide	2021	positive	positive	positive with restrictions		negative
idecabtagene vicleucel	2021	positive	positive			
avacopan	2022	positive	positive	negative		
voxelotor	2022	positive with restrictions	positive			
ciltacabtagene autoleucel	2022	positive		negative		
olipudase alfa	2022	positive	positive			

Among France, Germany, the Netherlands, Poland, and Sweden, 20 PRIME products were assessed by HTA in at least one of these jurisdictions between 2018 and 2022.

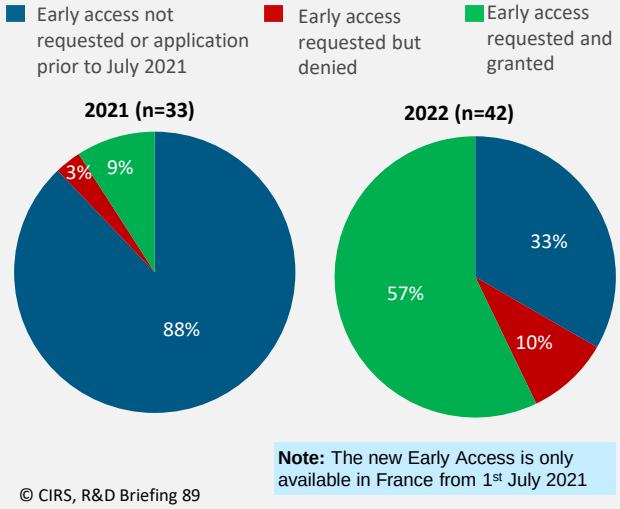
Table 3 contains the PRIME products that have been assessed by HTA in at least the jurisdictions of France, Germany, the Netherlands, Poland or Sweden. Similar to the observations in **Figure 31, Table 3** displays the heterogeneous perceptions regarding the value of the PRIME products across the agencies being compared. In addition, the cumulative analysis in **Figure 33** suggests the faster rollout of PRIME products in both France and Germany.

Figure 33. Time taken from EMA submission to 1st HTA recommendation by PRIME designation (HTA recommendation 2018-2022)



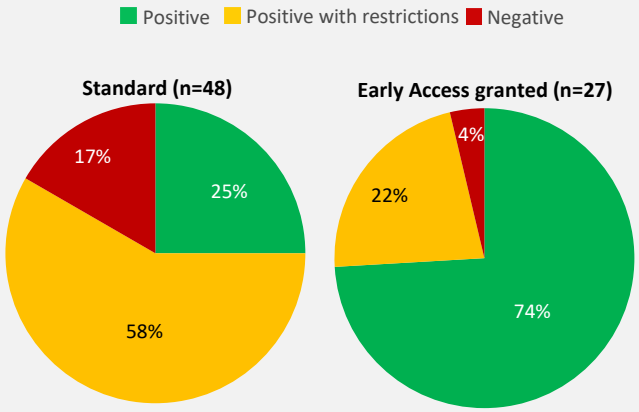
FEATURES OF FRANCE

Figure 34. Proportion of NASs that received an HTA recommendation by type of Early Access application (2021-2022)



Note: The new Early Access is only available in France from 1st July 2021

Figure 35. Proportion of HTA outcomes where Early Access was granted (2021-2022)



In France, there has been a growing utilization of the Early Access mechanism since its implementation on the 1st of July 2021.

As of the 1st of July 2021, the HAS evaluates and authorises medicines that are the subject of a request for coverage in the context of "Early Access". Overall, Early access is a mechanism that allows patients to benefit exceptionally and temporarily from certain drugs not yet recommended for reimbursement yet in a specific therapeutic indication.

For a NAS to be considered eligible for Early Access, the following four conditions must be met: (i) The drug must be intended to treat serious, rare or disabling diseases, (ii) There is no appropriate treatment available, (iii) The implementation of the treatment cannot be postponed, (iv) the medicinal product is presumed to be innovative, in particular with regard to a possible clinically relevant comparator. Furthermore, Early Access can be requested for either a medicine with already a marketing authorisation or medicinal products that do not have a marketing authorisation, and these are referred to as post-approval early access and pre-approval early access, respectively.

Figure 34 illustrates that 57% of the NASs appraised by the HAS in 2022 had received an Early Access designation. In addition, **Figure 35** indicates that NASs that were granted Early Access presented a higher proportion of positive recommendations from HAS compared to standard. The latter could be indicative of the unique therapeutic value of Early Access products.

Products with an Early Access designation displayed a faster rollout time, potentially reflecting their underlying therapeutic urgency.

Figure 36 displays a faster rollout time for products that received an Early access designation. This may reflect the underlying therapeutic urgency associated with these products. **Figure 37** provides a more granular analysis, suggesting that products granted pre-approval Early Access eventually received an HTA recommendation by the HAS faster than those receiving post-approval early access.

Figure 36. Rollout time where Early Access granted vs other (2021-2022)

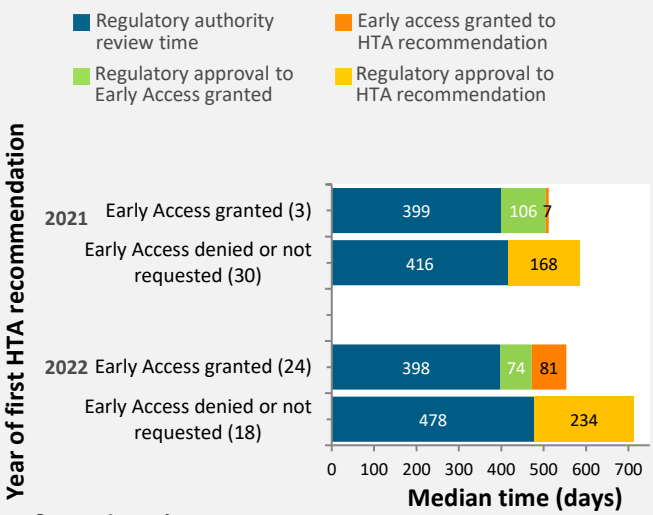


Figure 37. Rollout time where Early Access was granted: Pre- vs Post-approval (2021-2022)

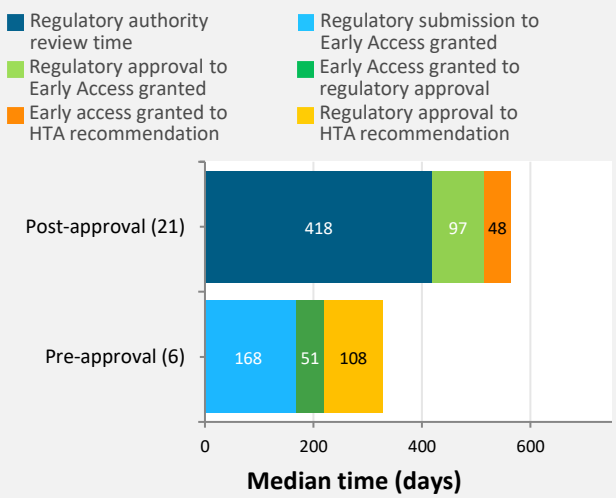
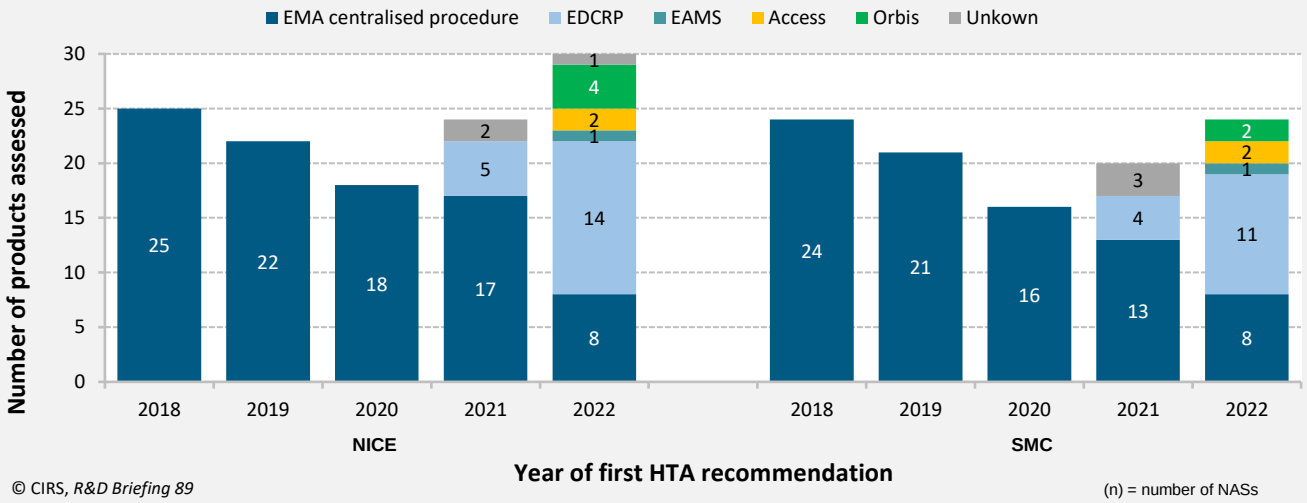


Figure 38. Number of NICE/SMC recommendations by year, and the route of regulatory approval



(n) = number of NASs

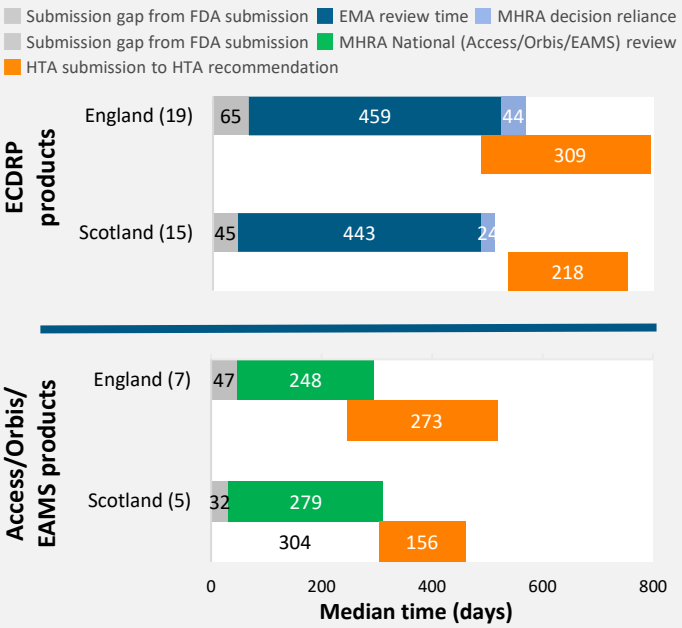
Post-Brexit, products can be approved in the UK at the national level by MHRA, or through the EC decision reliance procedures (ECDRP). In 2021 and 2022, NICE and SMC assessments consisted primarily of ECDRP products.

Following Brexit, a transitional regulatory mechanism began on 1 January 2021. Under this, the MHRA can rely on EC decisions for marketing authorisation in Great Britain through ECDRP, available to NASs approved centrally by EMA. The MHRA aims to authorize within the UK no later than 67 days after an EC decision. Additionally, the MHRA is part of other initiatives like the Orbis project and the Access consortium.

Figure 38 displays the number of NASs that received a recommendation by either NICE or SMC from 2018 to 2022. Up until 2020, all NASs evaluated by HTA had received regulatory approval through the centralised procedure. Post-Brexit, products approved via the centralised procedure continued reaching HTA assessment. From 2021 onwards, products from the ECDRP, as well as those from Orbis and Access, reached HTA evaluation. In particular, the number of ECDRP products evaluated by both NICE and SMC increased considerably from 2021 to 2022. Despite the MHRA formally joining both the Orbis project and the Access consortium in 2021, NASs evaluated through these routes only reached HTA in 2022.

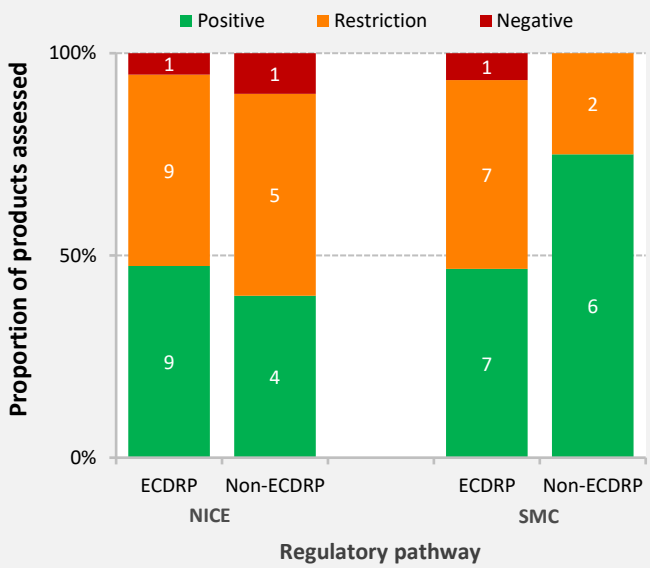
In a comparative analysis of the timelines of ECDRP products versus national MHRA route (EAMS, Orbis and ACCESS), the results generally indicate a faster rollout time for the cohort of nationally approved products as opposed to ECDRP products (**Figure 39**). Interestingly, the HTA review of ECDRP products also exhibited a longer median HTA review time compared to the products evaluated through these national pathways for both NICE (309 vs 273 days) and SMC (218 vs 156 days). **Figure 40** indicates that the type of HTA recommendation was generally equally distributed among the different regulatory pathway.

Figure 39. Products roll out time in the UK 2021-2022



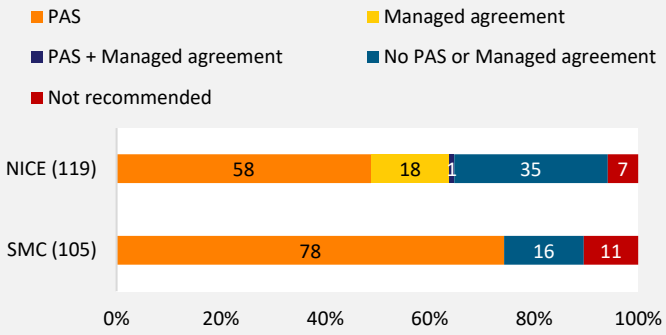
(n) = number of NASs

Figure 40. HTA first recommendation 2021-2022 by regulatory route



(n) = number of NASs

Figure 41. NICE/SMC recommendation via patient access scheme/managed entry agreements 2018-2022



(n) = number of NASs

NICE and SMC have implemented mechanisms, including Managed Access Agreements and patient access schemes (PAS), to enable patient access to medicines that might not be found to be cost-effective, facilitating access to promising new treatments.

Both NICE and SMC have implemented different mechanisms to enable patient access to medicines that might not be found to be cost-effective. More particularly, NICE implements a Managed Access Agreement that gives people faster access to promising new treatments. Without the managed access, they might not be recommended because of uncertainties about their clinical or cost-effectiveness. During managed access, more evidence is collected to address any uncertainties about a treatment using a managed access agreement. In addition, both NICE and SMC have patient access schemes (PAS) in place which include cost reduction mechanisms.

Figure 41 illustrates the proportion of NASs evaluated by NICE and the SMC from 2018 to 2022 for which either a Managed Access Agreement or a PAS was implemented. The data shows that among the NASs assessed by SMC, 74% implemented a PAS. In England, out of the NASs evaluated, 59 were incorporated into a PAS while 19 products were made accessible under a Managed Access Agreement by NICE.

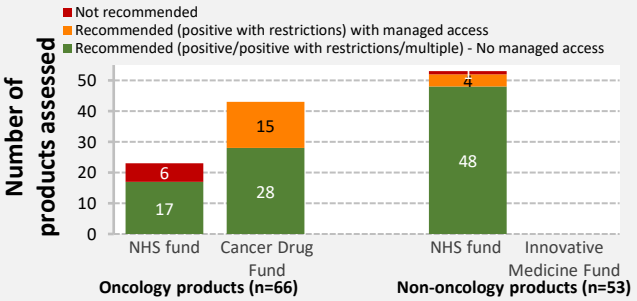
In England, there are two funding sources to pay for treatments in managed access: NHS England's Cancer Drugs Fund (CDF) and NHS England's Innovative Medicines Fund (IDF). We identified 15 NASs with managed access agreements that were funded by the CDF between 2018 and 2022. while the IDF was only established in 2022, no products were reimbursed under this fund yet. (**Figure 42**).

In addition, the SMC provides submitting companies with the opportunity to request a Patient and Clinician Engagement (PACE) meeting. This mechanism serves to amplify the voices of patient groups and clinicians in SMC's decision-making process, specifically for medicines utilized in the treatment of end-of-life and/or rare conditions. As illustrated in **Figure 43**, oncology products presented a higher number of PACE meetings. While PACE meetings have also been utilized for non-oncology products, the data indicates that they were less commonly implemented. This discrepancy could potentially be attributed to the lower proportion of end-of-life, orphan, or ultra-orphan medicines in the non-oncology category compared to oncology.

A total of 82 common products were evaluated in both England and Scotland between 2018 and 2022, and the rollout time was comparable in both jurisdictions.

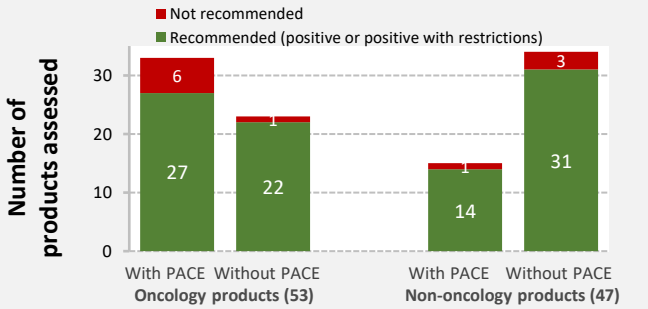
Finally, between 2018 and 2022, a total of 82 common products were evaluated in both England and Scotland (**Figure 44**). Among these common products, 51% (44/82) were first recommended by SMC, while the remaining 49% received an earlier recommendation by NICE. A cumulative analysis including only these common compounds, graphically reveals that the rollout time, from regulatory submission to HTA recommendation, was comparable in both jurisdictions (**Figure 44**).

Figure 42. NICE Recommendations by funding mechanism 2018-2022



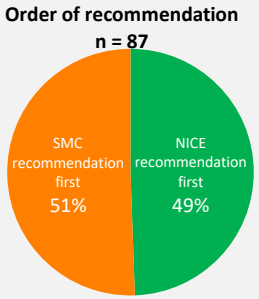
(n) = number of NASs

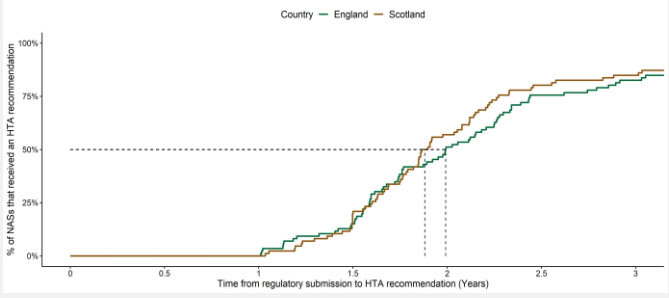
Figure 43. SMC Recommendation by HTA route 2018-2022



(n) = number of NASs

Figure 44. 82 common NASs were assessed by NICE and SMC between 2018-2022





Note: the regulatory submission is submission to MHRA for Orbis and Access products and submission to EMA for ECDRP products.

(n) = number of NASs

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 access agreement (MAA) - NICE

A time-limited agreement that sets out: (I) the conditions under which people will be able to have NHS-funded treatment and (II) how data will be collected to address the uncertainties in the clinical- or cost-effectiveness data.

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.

European Commission Decision Reliance Procedure (ECDRP)

From 1 January 2021, for a period of 3 years, the MHRA may rely on a decision made by the European Commission regarding the approval of a new Marketing Authorisation in the centralised procedure when evaluating an application for a Great Britain marketing authorisation.

DEFINITIONS

PBAC early re-entry pathway

It is one of the four type of resubmission pathways available to applicants following a 'not recommended' PBAC outcome. The Early Re-entry Pathway may be designated by the PBAC if the committee deems that any remaining issues can be easily resolved, and the medicine or vaccine does not qualify as High Added Therapeutic Value (HATV) for the intended population.

CADTH - Request for reconsideration

The sponsor of a drug that is the subject of a draft recommendation and the drug programs may file a request for reconsideration of the recommendation during the feedback period. The sponsor and drug programs are entitled to have the draft recommendation reconsidered one time (this does not include situations where a revised draft recommendation has been issued after a request for reconsideration).

A request for reconsideration can be made only on the grounds that the recommendation is not supported by the evidence that had been submitted or the evidence identified in the CADTH review report(s).

SMC Patient and Clinician Engagement (PACE)

For medicines used to treat end of life and/or rare conditions, the SMC offers the submitting company the opportunity to request a PACE meeting which gives patient groups and clinicians a stronger voice in SMC decision-making.

Cancer Drugs Fund (CDF) – NHS England

The CDF is a source of funding for cancer drugs in England. This new approach provides: (I) Access to promising new treatments, via managed access arrangement, while further evidence is collected to address clinical uncertainty, (II) Interim funding for all newly recommended cancer drugs, giving patients access to these treatments many months earlier than before.

Innovative Medicines Fund (IMF) – NHS England

The IMF provides a consistent and transparent managed access process for companies offering promising non-cancer medicines at a responsible price. The Innovative Medicines Fund supports faster access to non-cancer drugs.

EMA PRIME: priority medicines

PRIME is a scheme run by the European Medicines Agency to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier.

HTA ORPHAN/RARE DISEASE-RELATED PATHWAYS

Table 4: 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	**Early Access:** Starting from 1st July 2021, the HAS now evaluates and authorizes medicines that are requested for coverage under the "early access" provision. "Early access" is a mechanism that allows patients in a therapeutic impasse to benefit, on an exceptional and temporary basis, from certain drugs not authorized for a specific therapeutic indication. The following four conditions must be met: 1. The drug must be intended to treat serious, rare, or disabling diseases. 2. No appropriate treatment must be available. 3. Implementation of the treatment cannot be postponed. 4. The medicinal product must be presumed to be innovative, especially in comparison to a possibly clinically relevant comparator. Early access applies to drugs either awaiting reimbursement approval or lacking marketing authorization. In this scenario, the ANSM must assent to its efficacy and safety based on the results of therapeutic trials before the HAS makes a decision.
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 5: 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
Access Consortium	Medium-sized coalition to promote greater regulatory collaboration and alignment of regulatory requirements between Australia-Canada-Singapore-Switzerland-UK
Project Orbis	An initiative of the FDA Oncology Center of Excellence (OCE), provides a framework for concurrent submission and review of oncology products among international partners – Australia – Brazil – Canada – Singapore – Switzerland – UK - US. 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.

- Maximises international cooperation, reduce duplication, and increase each agency's capacity to ensure consumers have timely access to high quality, safe and effective therapeutic products.
- Maximises the use of up-to-date technical expertise, and ensures a consistent, contemporary approach to assessing the benefits and risks associated with the use of therapeutic product

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About CIRS

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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