CIRS Centre for Innovation in Regulatory Science

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Review of HTA Outcomes and Timelines in Australia, Canada, Europe, and the UK 2020-2024

CIRS HTADock Project | R&D Briefing 103

Introduction

In 2017, CIRS launched the HTADock project as part of its health technology assessment (HTA) programme. This project explores the synchronisation 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 HTADock briefing analyses publicly available data on new active substances (NASs) reviewed from 2020 to 2024 by key international HTA agencies, each with unique perspectives and methodologies. The agencies involved in this comprehensive study include:

1. Australian Pharmaceutical Benefits Advisory Committee (PBAC)
2. Canada's Drug Agency (CDA-AMC) (formerly Canada's Drug and Health Technology Agency (CADTH))
3. Institut national d'excellence en santé et en services sociaux (INESSS)
4. English National Institute for Health and Care Excellence (NICE)
5. French Haute Autorité de Santé (HAS)
6. German Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)
7. Irish National Centre for Pharmacoeconomics (NCPE)
8. Zorginstituut Nederland (ZIN)
9. Polish Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT)
10. Portuguese Autoridade Nacional do Medicamento e Produtos de Saude (INFARMED)
11. Scottish Medicines Consortium (SMC)
12. Swedish Tandvårds & läkemedelsförmånsverket (TLV).

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 reviewed by HTA agencies between 2020 and 2024 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 next figures describe the research methodology, designed to enable robust benchmarking between agencies.

First HTA recommendations: Trichotomous categories

	Positive	Positive with restrictions	*Implication for "positive" or "positive with restrictions"*	Negative
PBS	List	List with conditions	Listing in the Pharmaceutical Benefits Scheme	Do not list
CDA AMC	Reimburse	Reimburse with conditions	Recommendation for reimbursement	Do not reimburse
INESSS	Inscription	Inscription - Avec conditions	Recommendation for reimbursement	Refus d'inscription - Valeur thérapeutique/ Ensemble des aspects
NICE	Recommended	Recommended + restrictions	NHS Implementation of NICE guidance	Not recommended
HAS	Majeur/Important	Modéré ou faible	The NHI defines the reimbursement rate accordingly	Insufficient
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
NCPE National Centre for Pharmacoeconomics, Ireland	NAS is considered for reimbursement	NAS is considered for reimbursement with conditions	The HSE considers the NCPE recommendations and make decisions on reimbursement.	NAS not recommended for reimbursement
Zorginstituut Nederland	To include	To include + restrictions	Recommendation for inclusion in the national health system	Not to include
Prezes Agencji	Prezes Agencji rekomenduje	Prezes Agencji rekomenduje+restrictions	Agency's president's recommendation	Prezes Agencji nie rekomenduje
Infarmed	Deferido	Deferido + restrições	The MoH decides on reimbursement based on the Infarmed report	Indeferido
Healthcare Improvement Scotland SMC	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
TLV TANDVÅRDS- OCH LÄKEMEDELSFÖRMÅNSVERKET	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. . Green outline indicates that drug reimbursement is possible while red outline indicates that drug reimbursement is not possible.

HTADock Methodology (Cont.)

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 (CDA-AMC)	Submission to Health Canada	Approval by Health Canada	Submission received by CDA-AMC	Final recommendation issued to sponsor and drug plans
Canada (INESSS)	Submission to Health Canada	Approval by Health Canada	Provided by INESSS	Avist transmis au minister
England	Submission to MHRA/ EMA (ECDRP/IRP)	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
Ireland	Submission to EMA	Approval issued by EU Commission	Rapid review commissioned	Rapid Review completed/ NCPE (full) assessment completed
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
Portugal	Submission to EMA	Approval issued by EU Commission	Not available in the public domain	Data decisão
Scotland	Submission to MHRA/ EMA (ECDRP/IRP)	Approval issued by MHRA	Provided by SMC	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

Key Findings of R&D Briefing 103

In 2024, Germany showed the highest number of 1st HTA recommendations across the studied jurisdictions (**Figure 1**). In Australia, the proportion of positive HTA outcomes in 2024 increased to 67%, a considerable rise from the 28% recorded between 2020 and 2023 **(Figure 2).**

CDA-AMC (Canada) presented the shortest median rollout time from regulatory submission to HTA recommendation in 2024, followed by INESSS (Canada) (**Figure 3**). Germany demonstrated the fastest HTA review time, completing the process in 87 days. Poland followed closely, with 94 days **(Figure 4)**

Companies' submission strategies varied across jurisdictions: while countries like Australia, Canada, England, France, and Germany received more than 60% of their HTA submissions less than 3 months after regulatory approval, others such as the Netherlands and Poland often experienced longer delays (**Figure 7**).

The top four therapeutic areas (alimentary and metabolism, blood and blood forming organs, anti-infective, and anti-cancer and immunomodulators) constituted 67% of all products assessed by HTA in at least one jurisdiction between 2020-2024 (**Figure 10**).

In all jurisdictions, except for the Netherlands and Sweden, the median overall time from regulatory submission to HTA recommendation was shorter for products undergoing an expedited review compared to those following the standard review process (**Figure 12**).

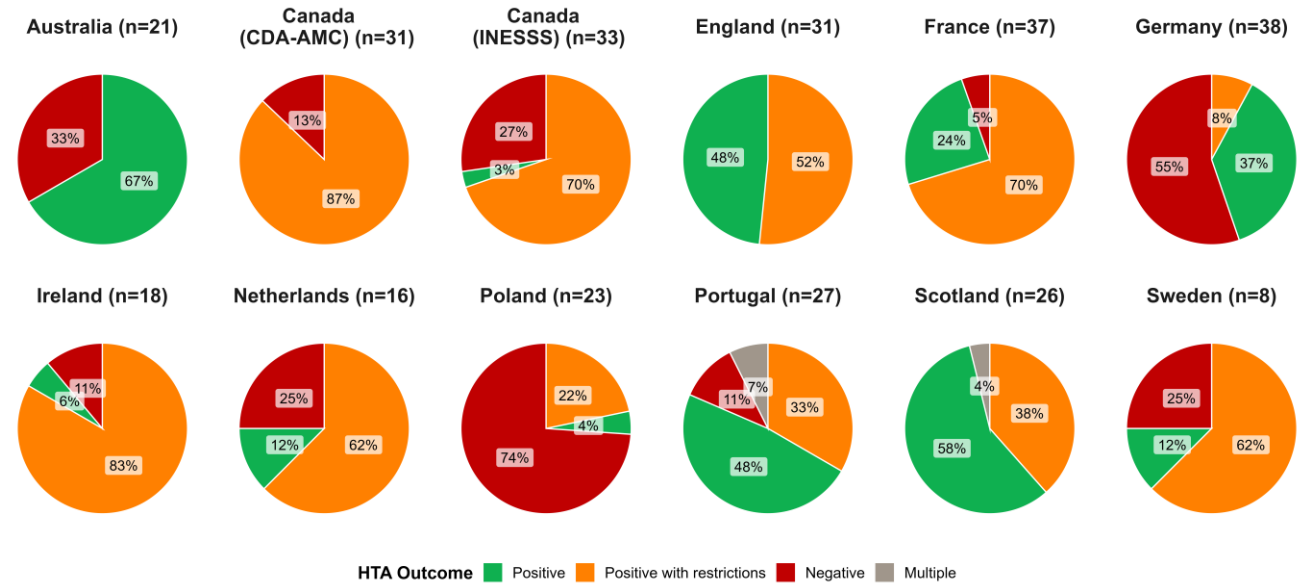
Between 2020 and 2024, 26 Project Orbis products received an HTA recommendation in at least one of the four studied countries: Australia, Canada, England, or Scotland (**Figure 17**)

Between 2022 and 2024, both the proportion of NASs applying for and being granted Early Access by HAS declined, suggesting reduced industry interest and stricter eligibility criteria (**Figure 36**).

Between 2020 and 2024, 8 NASs received a 1st HTA recommendation in all 12 studied jurisdictions. These NAS often received different HTA recommendations across different jurisdictions, suggesting potential disparities in patient access to new treatments. Additionally, the chronological order of HTA recommendations varied across jurisdictions, potentially influenced by companies' submission strategies and regulatory and HTA review times (**Figures 42**)

Overview of New Drug Recommendations

Figure 1. First HTA Recommendation for NASs Across Key Jurisdictions (HTA Recommendations in 2024)



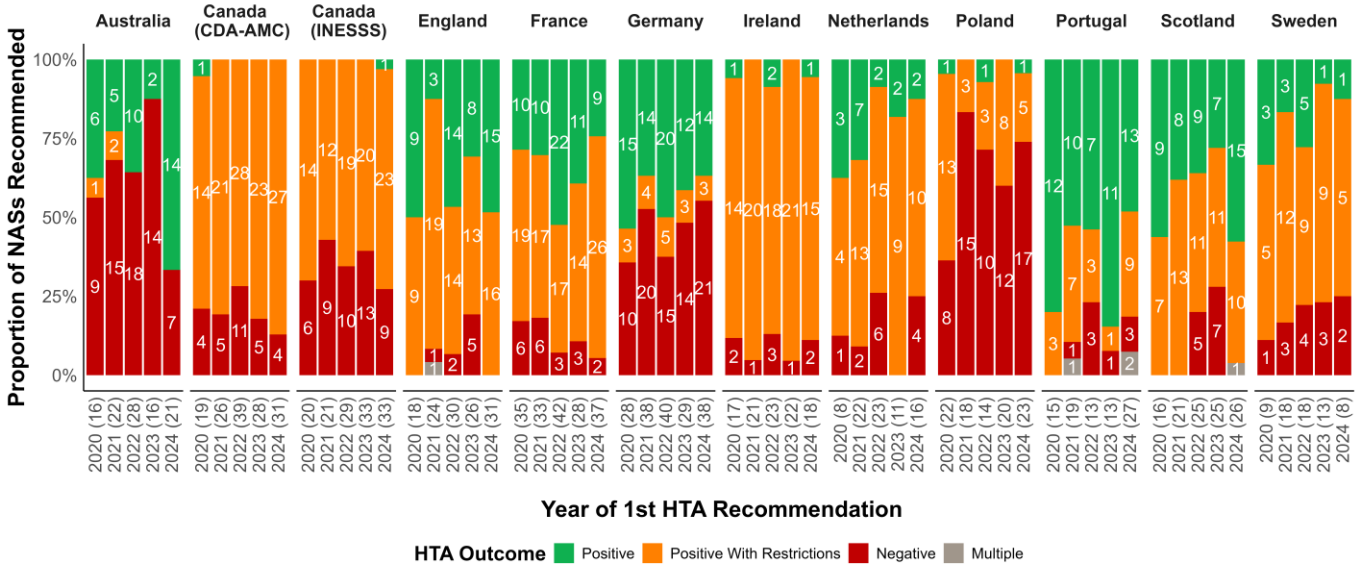
Note: Please note that some countries may include price negotiation as part of their HTA process

In 2024, Germany published the highest number of HTA recommendations across the studied jurisdictions.

In 2024, Germany reviewed the highest number of NASs (n=38), followed by France (n=37), Canada (INESSS) (n=33) and Canada (CDA-AMC) (n=31), England (n=31). Among these, England and Scotland presented the highest proportion of positive/positive with restrictions recommendations for NASs reviewed by HTA agencies in 2024 (100% and 94%, respectively).

In 2024, several countries experienced an increase in the number of HTA recommendations compared to the average from 2020 to 2023, including Canada (CDA-AMC and INESSS), England, France, Germany, Poland, Portugal, and Scotland (**Figure 2**). For example, Canada (INESSS) rose from 26 on average to 33 recommendations in 2024, while Portugal nearly doubled its output from 15 on average to 27. Other countries such as England and Scotland also saw notable growth, with England increasing from 25 to 31 and Scotland from 22 to 26. In contrast, some countries like Ireland and Sweden observed a decline, with Sweden dropping from 15 on average to 8 recommendations. It is important to note here that TLV only assesses outpatient medicines, as in-patient medicines follow different routes. Interestingly, Australia maintained a consistent number of recommendations at 21, but the proportion of positive HTA outcomes in 2024 increased to 67% (14 out of 21), a considerable rise from the 28% recorded between 2020 and 2023.

Figure 2. First HTA Recommendation Across Key Jurisdictions (HTA Recommendations Between 2020–2024)

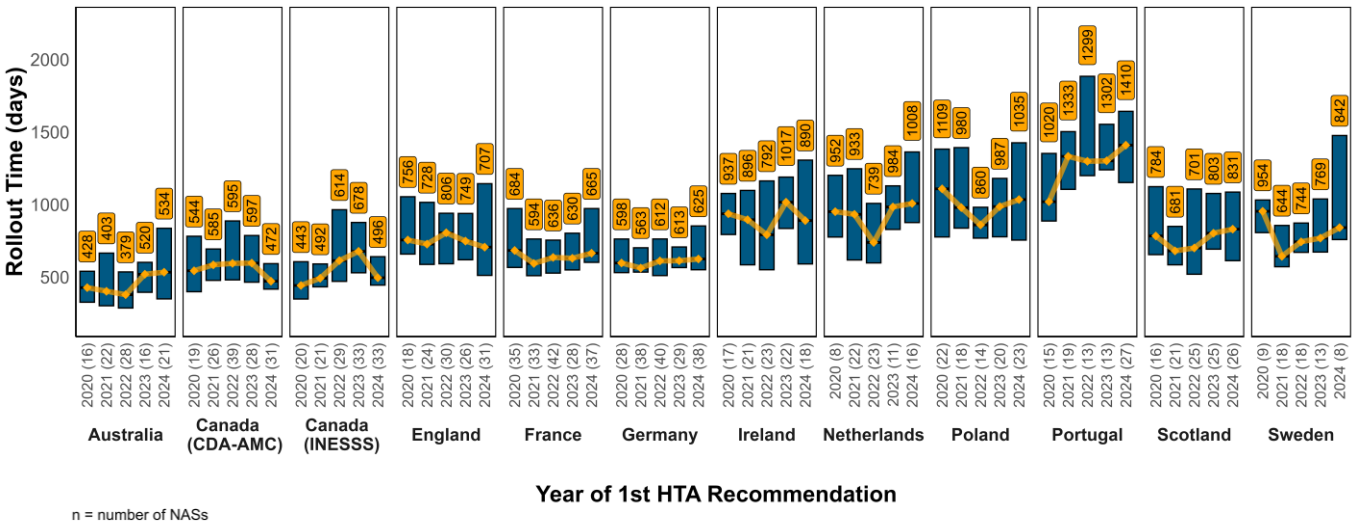


Note: Please note that some countries may include price negotiation as part of their HTA process

n = number of NASs

Synchronisation of Regulatory and HTA Processes

Figure 3. Regulatory Submission to HTA Recommendation (HTA Recommendations Between 2020–2024)



n = number of NASs

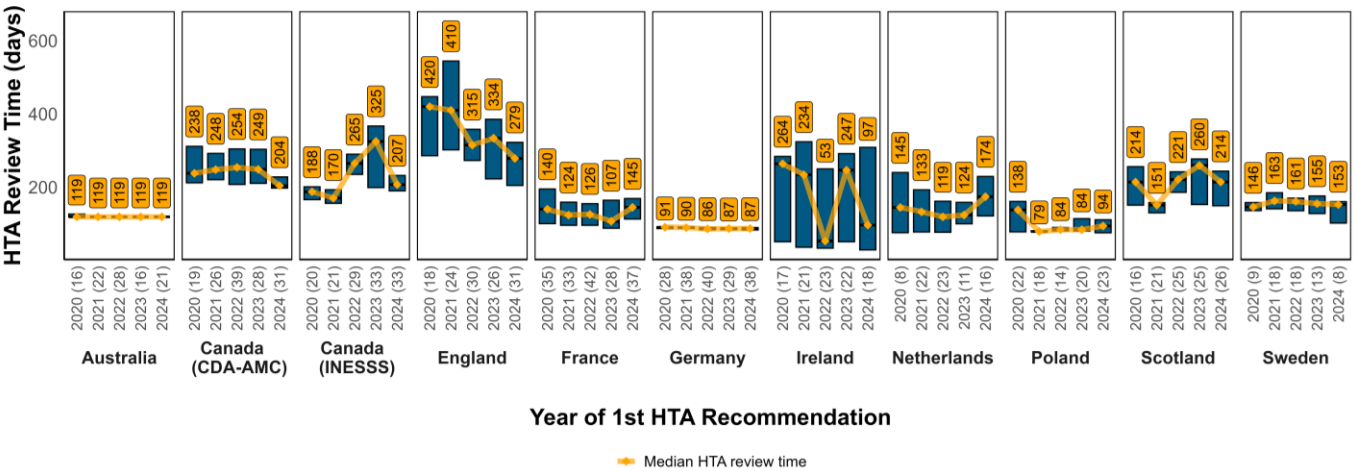
The box represents the interquartile range (from the 1st to the 3rd quartile), and the line inside the box indicates the median

Among the 12 studied agencies, CDA-AMC (Canada) presented the shortest median rollout time from regulatory submission to HTA recommendation in 2024, followed by INESSS (Canada). Germany had the highest consistency in rollout times from 2020 to 2024.

In 2024, Canada (CDA-AMC) showed the shortest median rollout time from regulatory submission to the first HTA recommendation, completing the process in 472 days (**Figure 3**). This was followed by Canada (INESSS), Australia, Germany and France, which required 496, 534, 625 and 665 days, respectively, to reach the first HTA recommendation. Notably, INESSS experienced an increase in median rollout time from 2020 to 2023, indicating a backlog of HTA reviews. This trend reversed in 2024, positioning INESSS among the fastest agencies that year. Germany showed the highest consistency in the median time to HTA recommendation between 2020-2024, with an overall standard deviation for the median rollout times of ±24 days.

In 2024, Germany demonstrated the fastest HTA review time, completing the process in 87 days. Poland followed closely, with 94 days (**Figure 4**). The longitudinal data indicated a strong consistency in HTA review times for both Australia and Germany throughout the studied years. In Germany, this predictability is derived from the AMNOG process, which indicates that IQWiG should assess the added therapeutic benefit of a new drug compared to an appropriate comparator within three months of dossier submission. Similarly, Australia's consistency is supported by its formalised HTA procedures, in which PBAC operates under a 17-week timeframe to assess and decide on applications, based on the frequency of its committee meetings. Interestingly, the data indicate a decreasing trend in HTA review time for England (NICE) over the past five years.

Figure 4. HTA Review Time by Year of HTA Recommendation (HTA Recommendations Between 2020–2024)



n = number of NASs

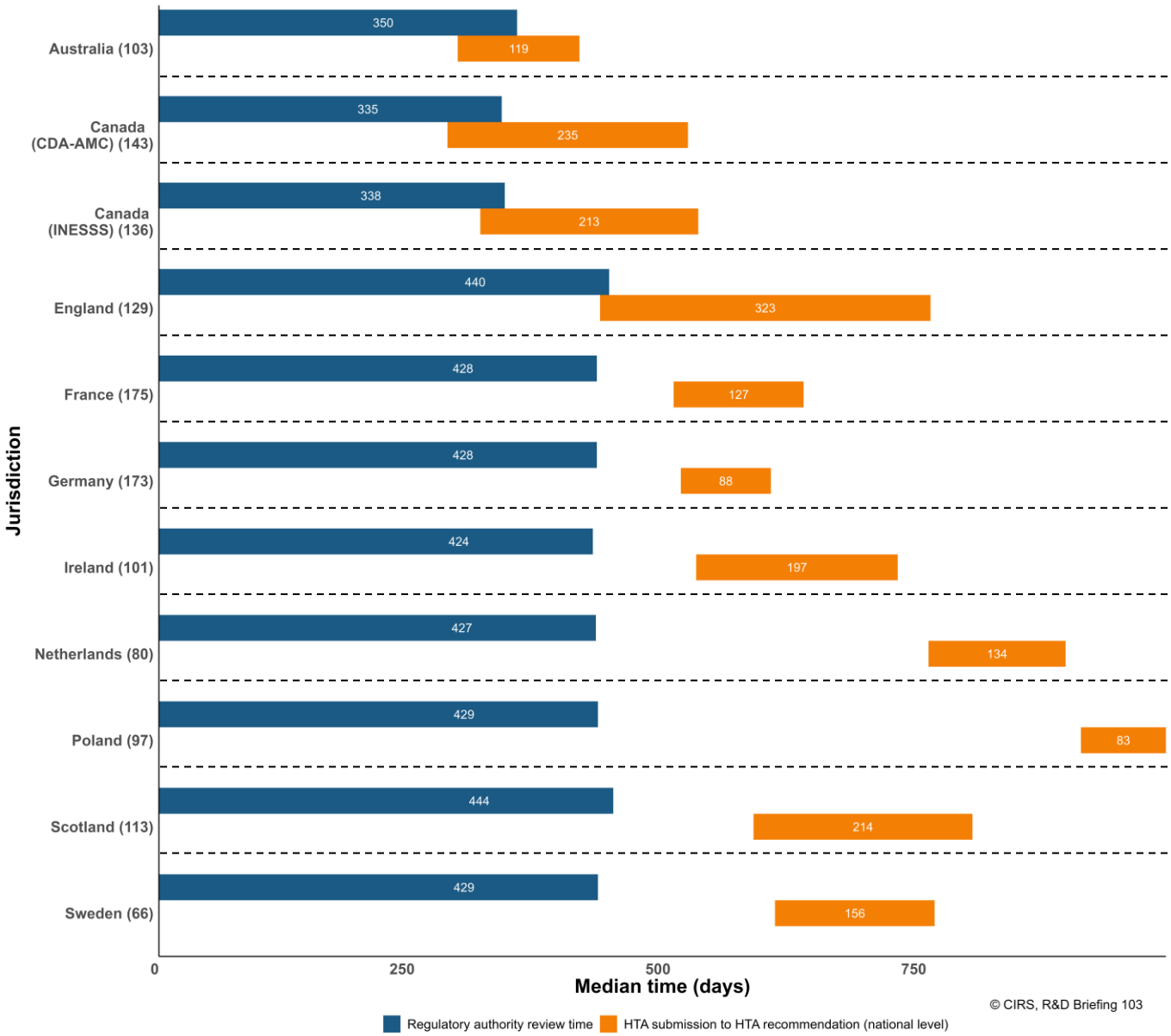
The box represents the interquartile range (from the 1st to the 3rd quartile), and the line inside the box indicates the median

Note 1: Portugal is excluded from this analysis due to the unavailability of their HTA submission dates in the public domain.

Note 2: For Ireland, both rapid and full reviews are included in this analysis. In addition, the HTA review for Ireland time is calculated as (Rapid Review completed - Rapid Review commissioned) + (NCPE assessment completed - Full submission received from applicant).

Synchronisation of Regulatory and HTA Processes (Cont.)

Figure 5. Breakdown of Rollout Time for NASs by Jurisdiction (HTA Recommendations Between 2020–2024)



n = number of NASs

Note 1: Portugal is excluded from this analysis due to the unavailability of their HTA submission dates in the public domain.

Note 2: For Ireland, both rapid and full reviews are included in this analysis. In addition, the HTA review for Ireland time is calculated as (Rapid Review completed - Rapid Review commissioned) + (NCPE assessment completed - Full submission received from applicant).

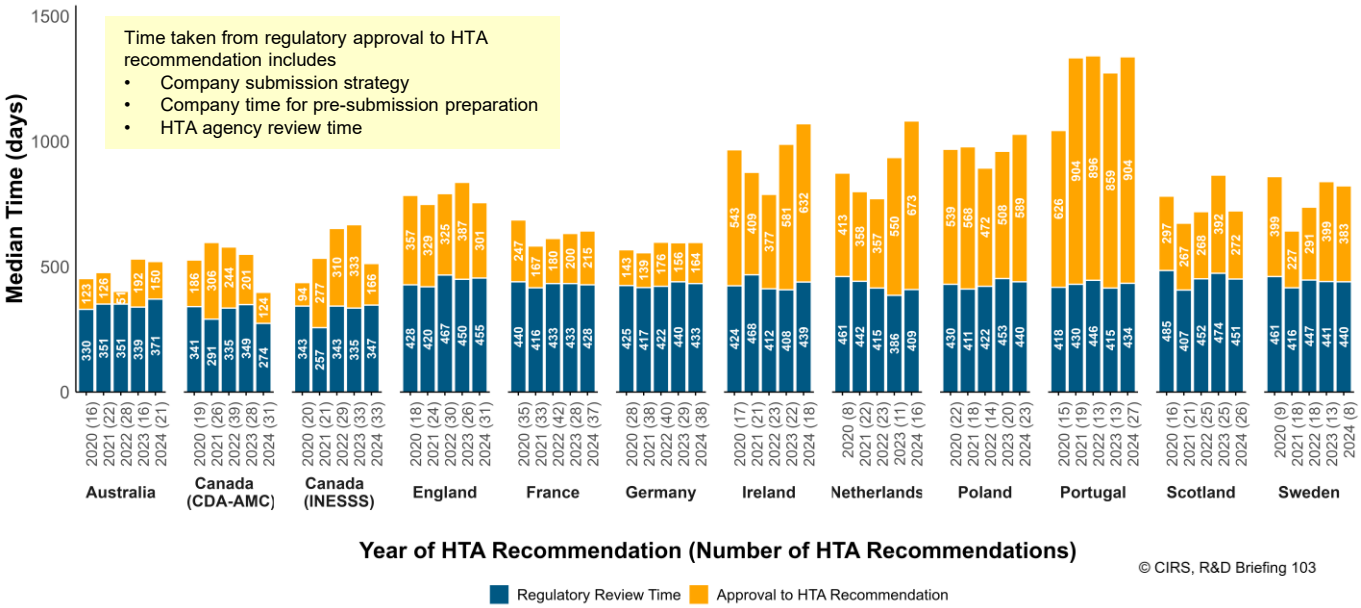
Poland exhibited the faster median HTA review time for HTA recommendations between 2020 and 2024.

The HTA process varies across different jurisdictions. Australia and Canada (both CDA-AMC and INESSS) allow the HTA process to start before the regulatory approval is granted. In England, not all NASs undergo the NICE review 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 review time for HTA recommendations between 2020 and 2024 (83 days) (**Figure 5**). However, this expedited process was counterbalanced by a prolonged overall rollout time. This delay is attributed to the longer gap between regulatory approval and HTA submission. England demonstrated an overlap between its HTA and regulatory processes, as companies are permitted to submit evidence to NICE prior to marketing authorisation.

Synchronisation of Regulatory and HTA Processes (Cont.)

Figure 6. Breakdown of Rollout Time Across Key Jurisdictions by Year of HTA Recommendation (HTA Recommendations Between 2020–2024)

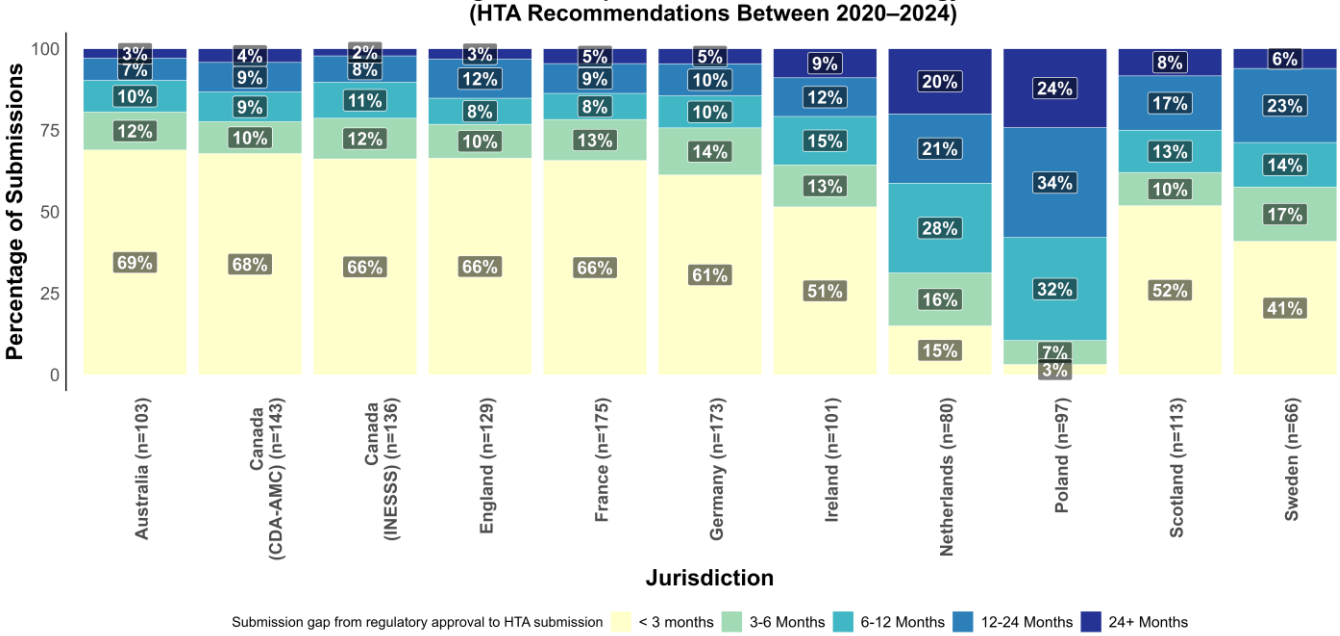


Companies' submission strategies were heterogenous among the studied jurisdictions.

Figure 6 shows a breakdown of the rollout time across key jurisdictions from 2020 to 2024 with two main components: the regulatory review time and the time from regulatory approval to HTA recommendation. This highlights that some jurisdictions face extensive timelines after regulatory approval. The time from approval to HTA recommendation is attributed to company submission strategy, company time for pre-submission preparation and HTA agency review times.

Figure 7 shows the timing of HTA submissions in relation to regulatory approval across eleven jurisdictions. In Australia, Canada (CDA-AMC and INESSS), England, France, and Germany, most HTA submissions occur early - over 60% are submitted no later than three months after regulatory approval. In contrast, the Netherlands and Poland display a different pattern: only 15% or fewer submissions take place no later than three months after approval. Instead, a large proportion of submissions in these countries occur between three and twelve months post-approval, with 20% in the Netherlands and 24% in Poland submitted as late as 24 months after approval. These differences underscore the heterogeneity in submission timing across jurisdictions, likely reflecting variation in national HTA requirements, company prioritisation, and resource allocation.

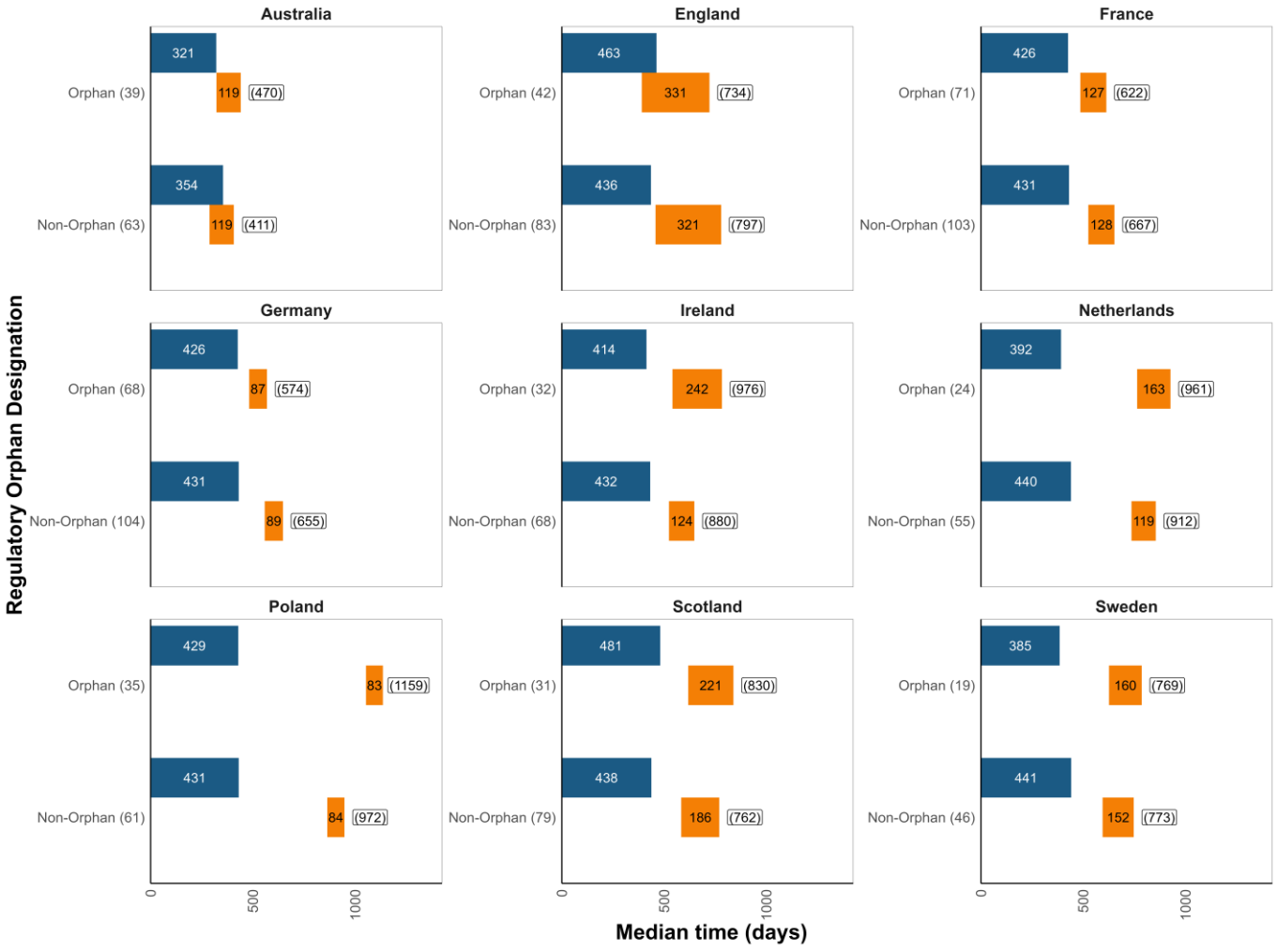
Figure 7. Companies' HTA Submission Strategy (HTA Recommendations Between 2020–2024)



Note: Products for which the HTA submission date is not available in the public domain have been removed from this analysis

Characteristics: Regulatory Orphan Designation

Figure 8. Breakdown of Rollout Time for NASs by Orphan Designation (HTA Recommendations Between 2020–2024)



n = number of NASs

Note 1: Canada is excluded from this analysis because Health Canada does not have an orphan designation. Portugal is also excluded from this analysis due to the unavailability of their HTA submission dates in the public domain.

Note 2: Numbers in white boxes represent the overall median rollout time (days).

Note 3: Evrysdi was removed from this analysis as EMA evaluated this product as an orphan drug, but the orphan designation was later withdrawn.

Note 4: For Ireland, both rapid and full reviews are included in this analysis. In addition, the HTA review for Ireland time is calculated as (Rapid Review completed - Rapid Review commissioned) + (NCPE assessment completed - Full submission received from applicant).

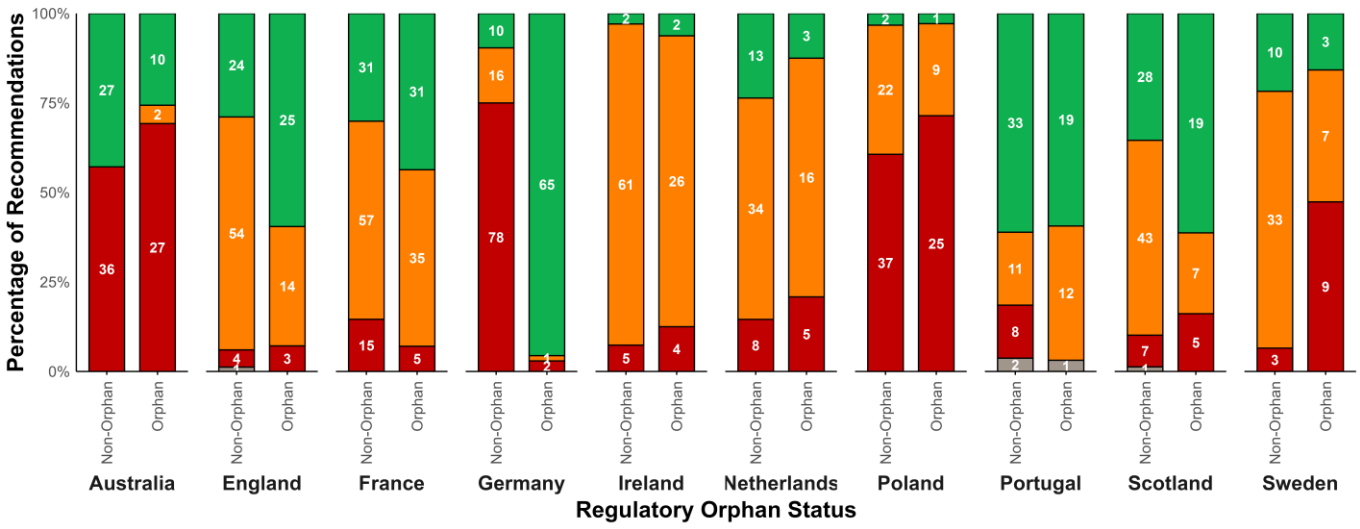
Products with regulatory orphan designations exhibited slightly shorter median regulatory review times across all jurisdictions compared to non-orphan products, except in the UK. However, in some jurisdictions, longer submission gaps for orphan products may have led to longer overall rollout times.

The orphan designation is employed by regulatory agencies such as the Australian Therapeutic Goods Administration (TGA), European Medicines Agency (EMA), and UK Medicines and Healthcare products Regulatory Agency (MHRA) to expedite the approval of drugs aimed at treating serious illnesses or addressing unmet medical needs. In our analysis of England and Scotland, if a product was approved via a reliance mechanism on the EMA decision (e.g. through the European Commission Decision Reliance Procedure (ECDRP) or the International Recognition Procedure (IRP)), the EMA orphan designation was applied. Alternatively, if the product was approved through a national route by the MHRA, the MHRA orphan designation was used. It is worth noting that Health Canada does not have an orphan drug policy.

Across most jurisdictions, products with a regulatory orphan designation exhibited slightly shorter median regulatory review times compared to non-orphan products (**Figure 8**). This trend was consistent in countries such as Australia, France, Germany, Ireland, and Sweden, but not in the UK, where orphan products had slightly longer review times. However, shorter regulatory review times did not consistently translate into faster overall rollout. In jurisdictions like Australia, Ireland, the Netherlands, Poland, and Scotland, while the median regulatory review time was shorter, orphan products experienced longer median rollout times. These delays may be attributed to longer submission gaps (the time between regulatory approval and HTA submission) as well as HTA review timelines and company-specific market access strategies.

Characteristics: Regulatory Orphan Designation (Cont.)

Figure 9. First HTA Recommendation Outcomes by Regulatory Orphan Designation (HTA Recommendations Between 2020–2024)



Note: Evrysdi was removed from this analysis as EMA evaluated this product as an orphan drug, but the orphan designation was later withdrawn.

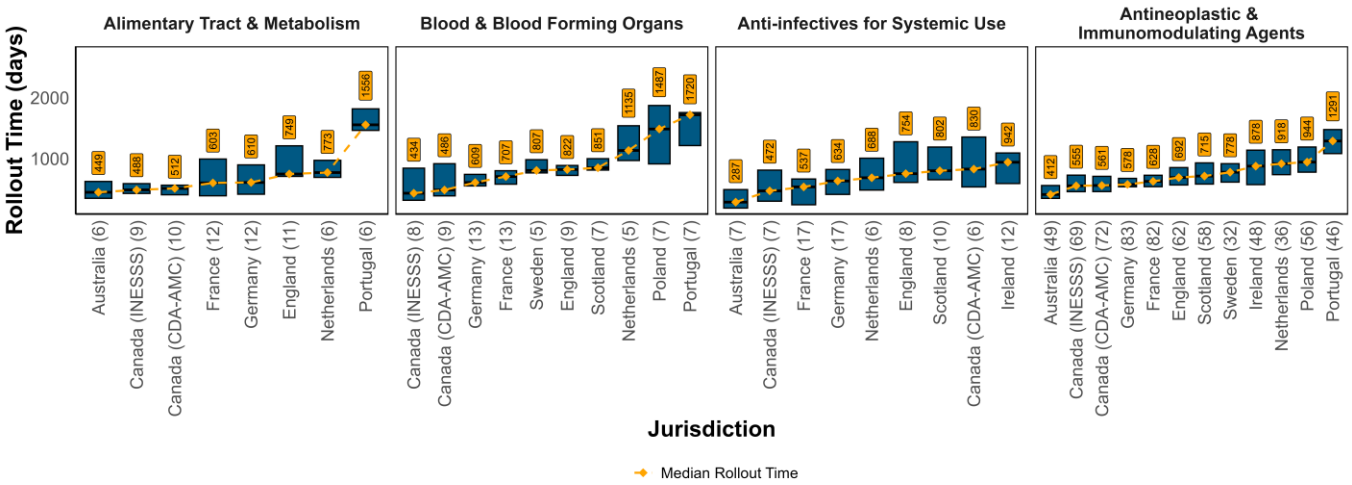
Orphan drugs faced more negative HTA recommendations than non-orphan drugs in most studied countries.

Figure 9 presents a comparative analysis of HTA outcomes for orphan versus non-orphan drugs across ten jurisdictions. The distribution of HTA recommendation types (positive, positive with restrictions, and negative) varied between countries. Notably, in 7 out of 10 countries (Australia, England, Ireland, the Netherlands, Poland, Scotland, and Sweden) orphan drugs presented a higher proportion of negative HTA recommendations compared to non-orphan drugs. This trend indicates that obtaining regulatory orphan designation does not guarantee HTA success, and these products may still encounter significant challenges in securing favorable reimbursement decisions.

In Germany, IQWiG generally issues positive recommendations for orphan drugs because the additional therapeutic benefit is considered to be proven at the time of marketing authorisation. However, the results in **Figure 9** show one NAS with a positive with restrictions recommendation and two with a negative recommendation. This discrepancy arises because IQWiG evaluated these three compounds as non-orphan drugs.

Characteristics: Therapeutic Area

Figure 10. Regulatory Submission to 1st HTA Recommendation by Therapeutic Area (HTA Recommendations Between 2020–2024)



n = number of NASs

The box represents the interquartile range (from the 1st to the 3rd quartile), and the line inside the box indicates the median

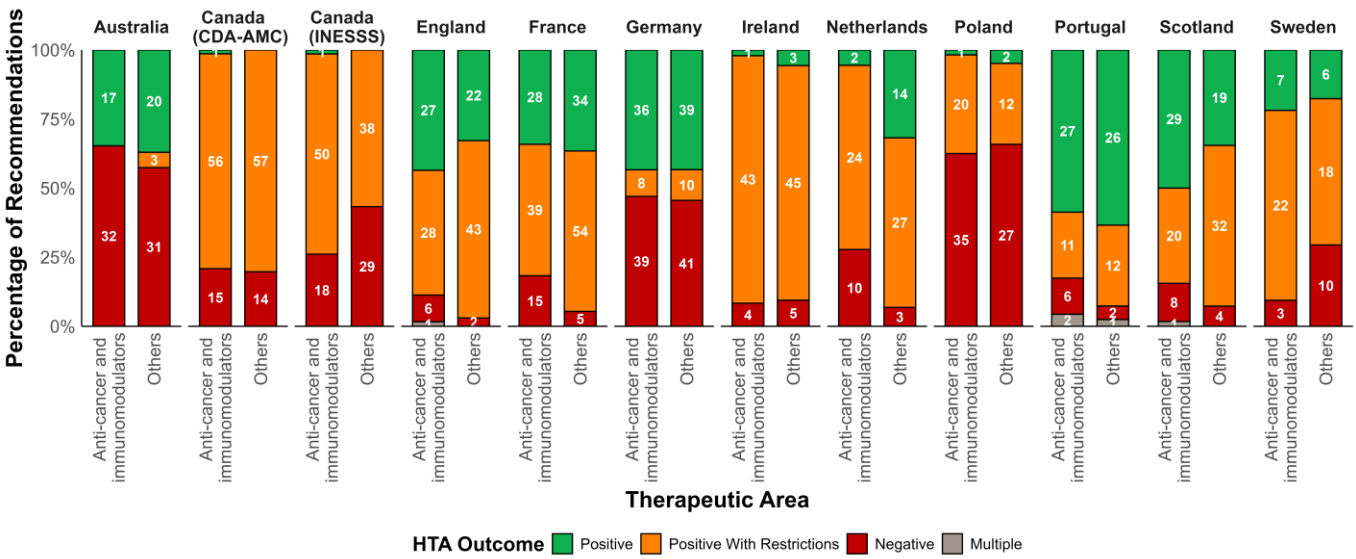
Note: entries where n<5 have been removed

Australia demonstrated the fastest median rollout time from regulatory submission to the 1st HTA outcome for all four top therapeutic areas.

The top four therapeutic areas made up 67% (189/283) of the unique products assessed by HTA in at least one country between 2020-2024, with anti-cancer and immunomodulators making up 63% (120/189) of the top therapeutic areas (**Figure 10**). Australia was the fastest for Alimentary tract and metabolism, Anti-infectives for systemic use, and Antineoplastic and immunomodulators in terms of median rollout time from regulatory submission to HTA outcome (**Figure 10**). 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.

Ireland and Sweden recommended (including both positive and restriction recommendations) the highest percentage of anti-cancer and immunomodulators for reimbursement, with 92% and 91% of the recommendations, respectively (**Figure 11**).

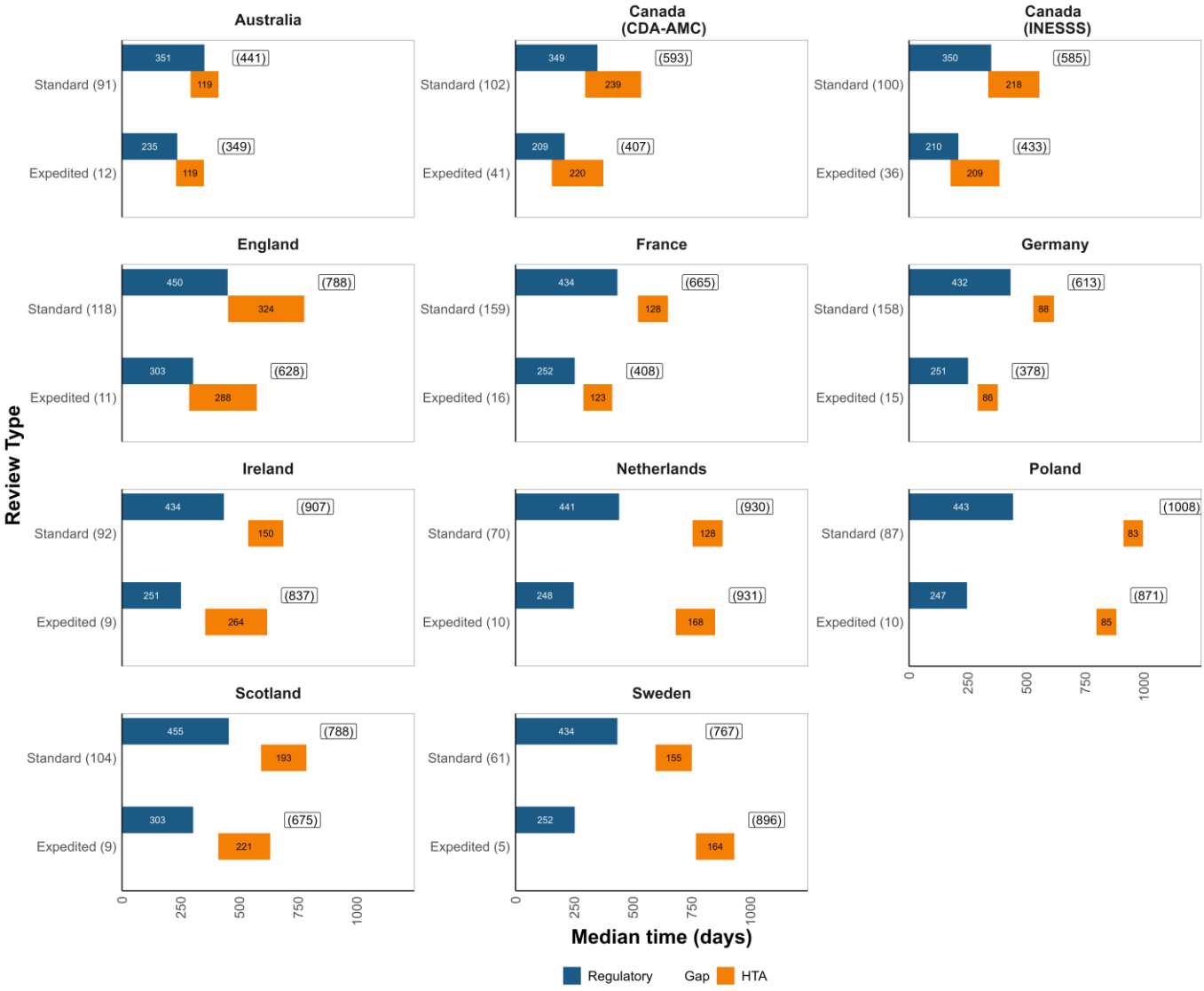
Figure 11. 1st HTA Recommendation: Anti-Cancer and Immunomodulators vs. Other (HTA Recommendations Between 2020–2024)



Note: 'others' include all atc code different from ('Anti-cancer and immunomodulators').

Characteristics: Expedited and Flexible Pathways

Figure 12. Breakdown of Rollout Time for NASs by Regulatory Review Type (HTA Recommendations Between 2020–2024)



n = number of NASs

Note 1: Portugal is excluded from this analysis due to the unavailability of their HTA submission dates in the public domain.
Note 2: Numbers in white boxes represent the overall median rollout time (days).

Note 3: For Ireland, both rapid and full reviews are included in this analysis. In addition, the HTA review for Ireland time is calculated as (Rapid Review completed - Rapid Review commissioned) + (NCPE assessment completed - Full submission received from applicant).

Products reviewed through expedited regulatory pathways presented shorter overall rollout times in all countries, except for the Netherlands and Sweden.

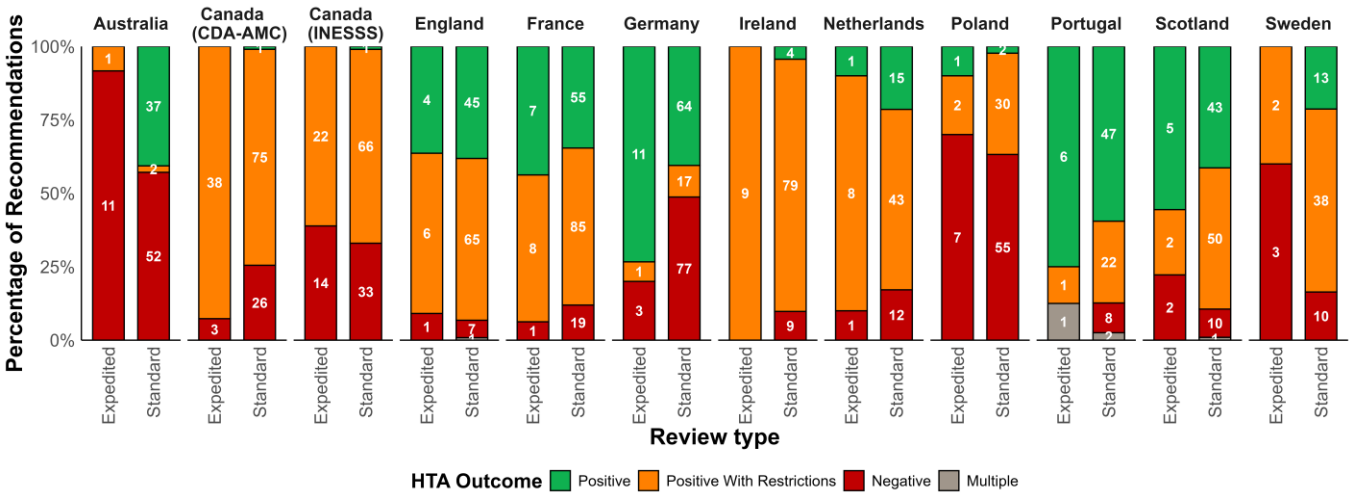
Expedited regulatory pathways are mechanisms designed to accelerate the review process of innovative products that are intended to address unmet medical needs or significant concerns related to public health. The list of expedited regulatory pathways across all jurisdictions is elaborated in the Appendix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

In all jurisdictions except the Netherlands and Sweden (**Figure 12**), the median time from regulatory submission to HTA recommendation was shorter for products undergoing expedited review compared to those following the standard process. The data suggest this trend is driven by the shorter regulatory review times of expedited pathways, which may have generally enabled an earlier start of the HTA review process.

However, shorter regulatory review times did not always translate to shorter overall rollout times. In the Netherlands and Sweden, although expedited products presented quicker regulatory reviews, delayed submissions for HTA assessment may have contributed to longer overall rollout times.

Characteristics: Expedited and Flexible Pathways (Cont.)

Figure 13. First HTA Recommendation Outcomes by Regulatory Review Type (HTA Recommendations Between 2020–2024)



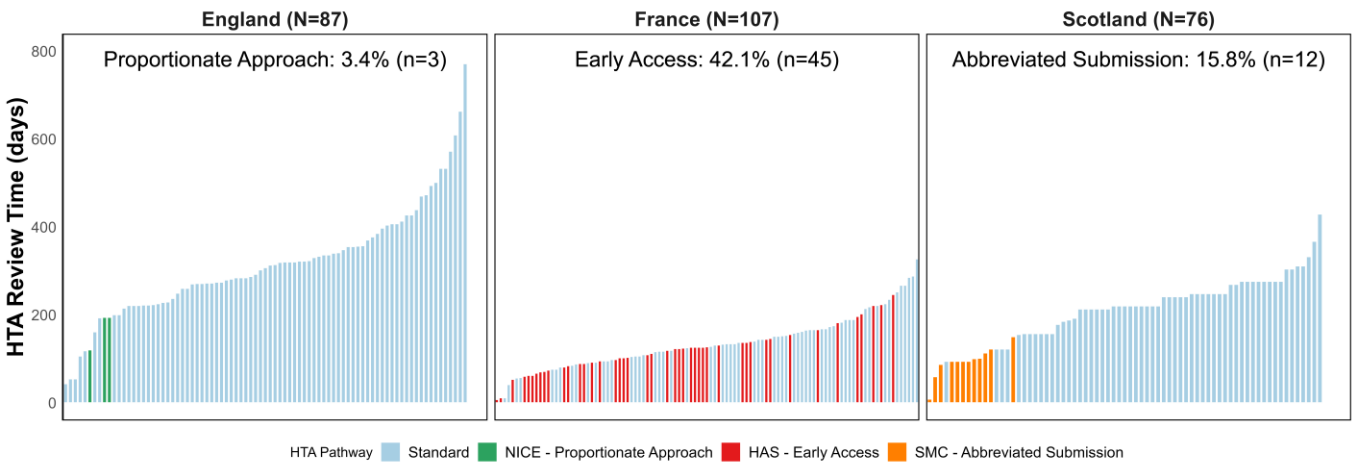
The proportion of positive or positive with restrictions recommendations for products that underwent an expedited review process varied among different jurisdictions.

In several jurisdictions, including Canada (CDA-AMC), France, Germany, Ireland, and the Netherlands, 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 13**). In Australia, only 8% (1/12) of the products reviewed through an expedited pathway achieved a first HTA recommendation that was positive or positive with restrictions.

Different jurisdictions have implemented various flexible and adaptive HTA processes. In England, the Proportionate Approach was introduced in 2022. This approach recognises that not all treatments require the same level of scrutiny, allowing simpler submissions to benefit from a 'light-touch' evaluation process. France's Early Access Pathway, introduced in 2021, enables the early availability and reimbursement of medicinal products indicated for severe, rare, or incapacitating diseases before either a marketing authorisation is granted or an HTA recommendation is issued. Since 2020, Scotland has allowed abbreviated submissions for new medicines where alternatives within the same therapeutic class have previously been accepted for use (or restricted use) by the SMC.

The results in **Figure 14** indicate that HTA agencies are using these flexible approaches to meet the demand for expedited patient access. While the rationale and criteria for these flexible processes vary among HTA agencies, their overarching goal is to enhance capacity and facilitate more efficient decision making in public health.

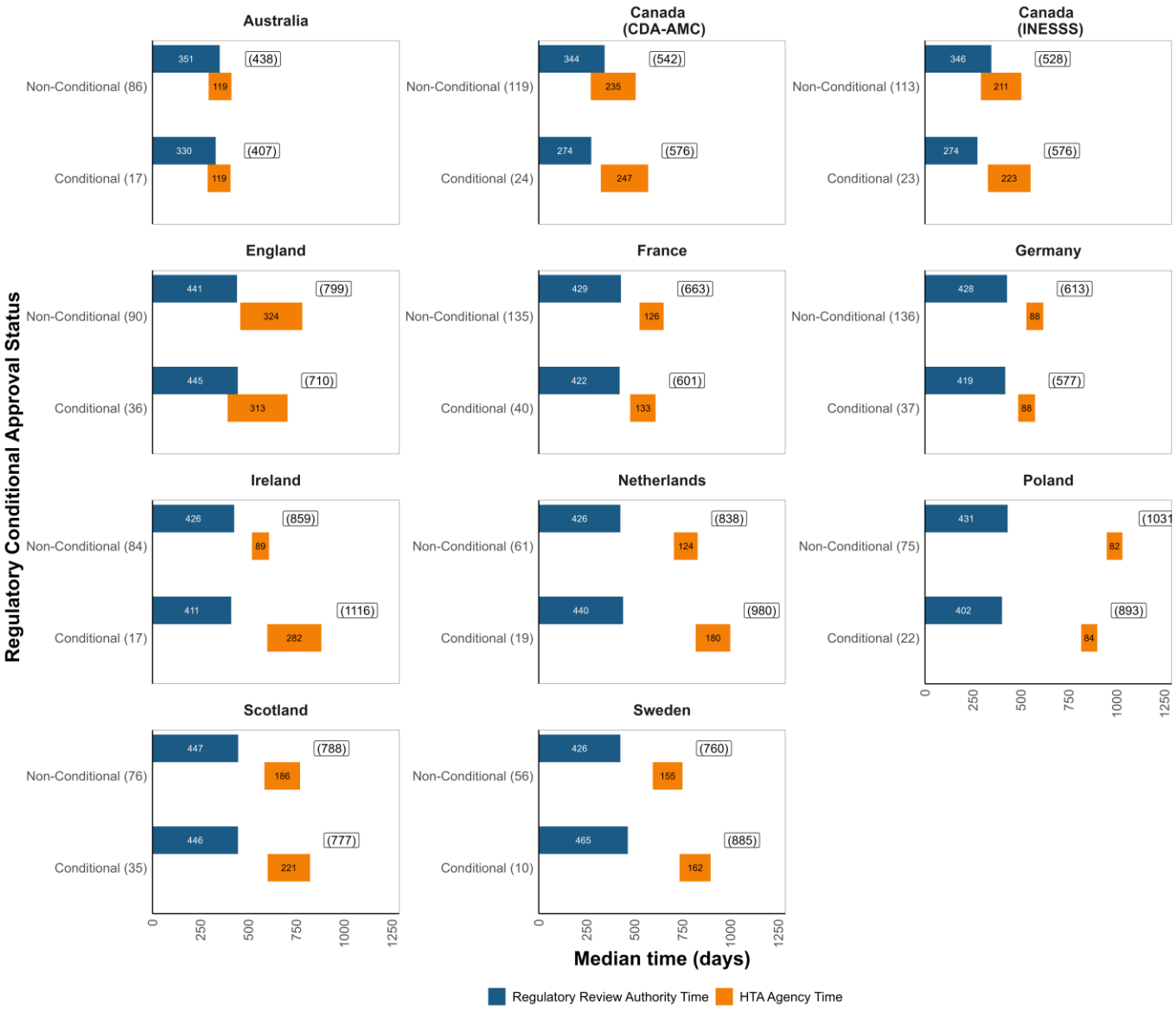
Figure 14. Proportion of Special Pathways in England, France, and Scotland (HTA Recommendations Between 2022–2024)



Note: Each bar represents a NAS

Characteristics: Conditional Regulatory Approval

Figure 15. Breakdown of Rollout Time for NASs by Conditional Status (HTA Recommendations Between 2020–2024)



n = number of NASs

Note 1: Portugal is excluded from this analysis due to the unavailability of their HTA submission dates in the public domain.

Note 2: Numbers in white boxes represent the overall median rollout time (days).

Note 3: For Ireland, both rapid and full reviews are included in this analysis. In addition, the HTA review for Ireland time is calculated as (Rapid Review completed - Rapid Review commissioned) + (NCPE assessment completed - Full submission received from applicant).

In nearly half of the studied countries, the conditional pathway presented a longer median time to HTA recommendation.

Regulatory agencies in Australia, Canada, Europe and the UK have implemented conditional pathways 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).

In 5 out of 11 studied jurisdictions, NASs approved through a conditional regulatory pathway exhibited longer median rollout times to HTA recommendation compared to those that followed non-conditional pathways (**Figure 15**). This trend was observed in Canada (both CDA-AMC and INESSS), Ireland, the Netherlands, and Sweden.

Characteristics: Conditional Regulatory Approval (Cont.)

Figure 16. First HTA Recommendation by Regulatory Conditional Status (HTA Recommendations Between 2020–2024)

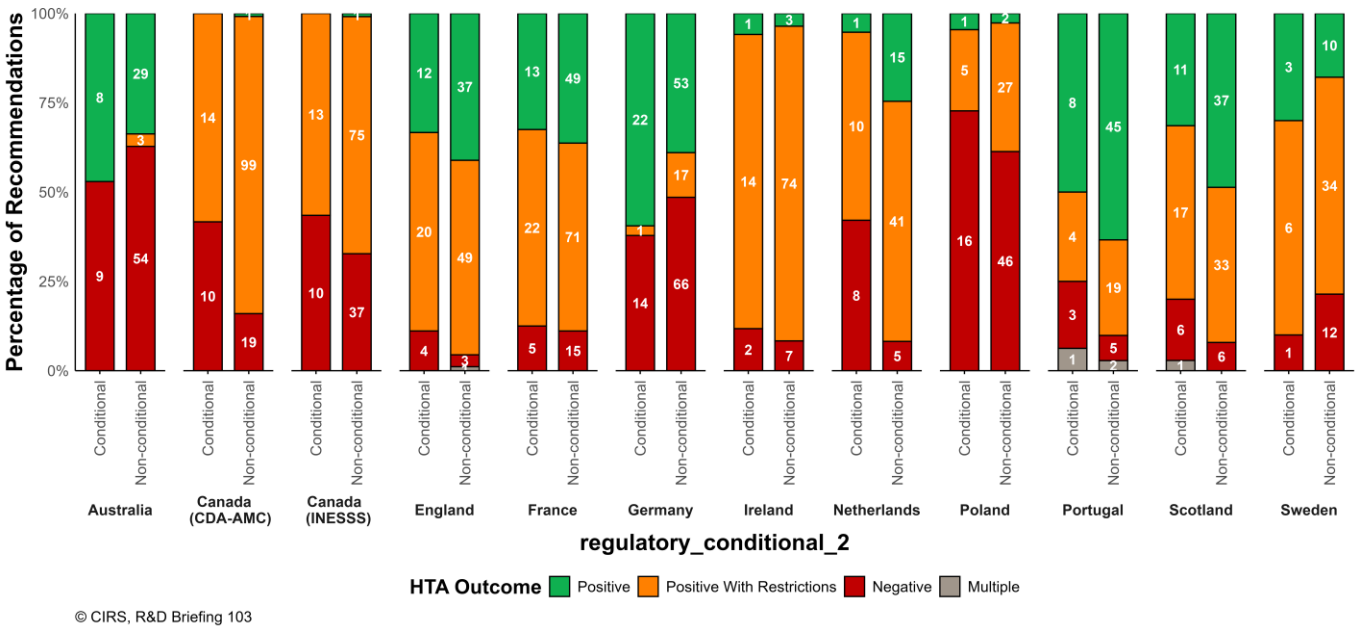
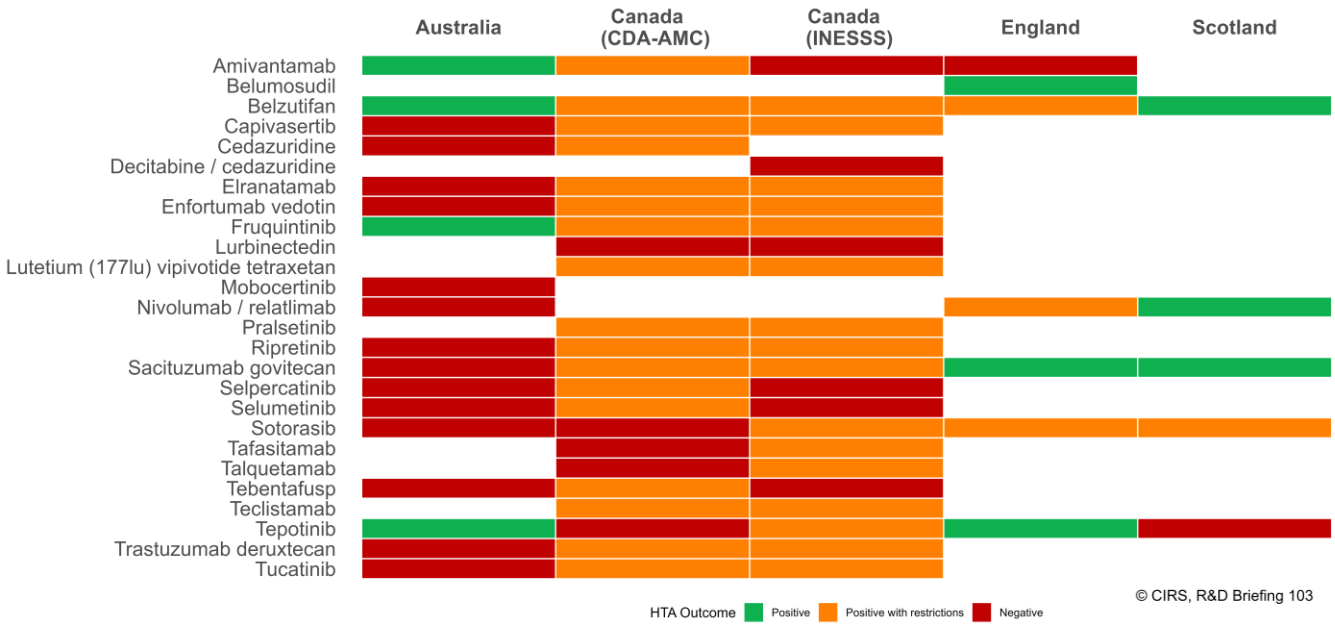


Figure 16 compares the distribution of first HTA recommendations for NASs across 12 jurisdictions, segmented by regulatory conditional status: Conditional vs. Non-Conditional approvals. The findings in **Figure 16** did not suggest a trend between a regulatory conditional approval and obtaining an optimal or non-optimal HTA recommendation.

Focus: Project Orbis

Figure 17. 1st HTA Recommendation for NASs Approved via Project Orbis (HTA Recommendations Between 2020–2024)



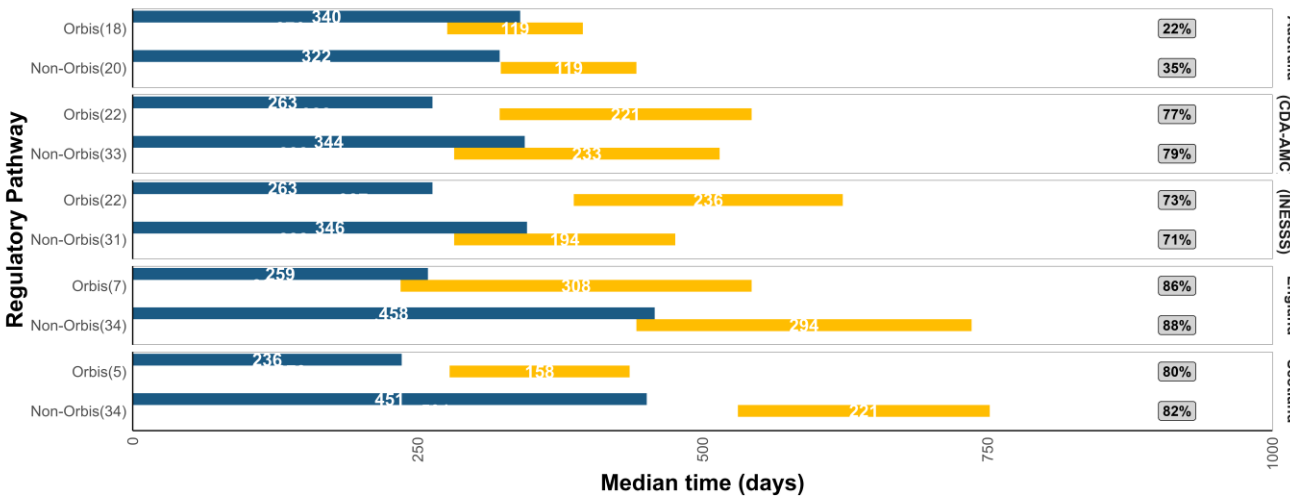
Note 1: Products in white indicate that there is currently no HTA recommendation between 2020 and 2024 from the studied agencies within Project Orbis; however, products may have followed alternative patient access routes.

Note 2: The UK joined Project Orbis in 2021.

Between 2020 and 2024, 26 Orbis products received 1st HTA recommendations in Australia, Canada, England or Scotland.

Project Orbis, initiated by the US Food and Drug Administration (FDA) Oncology Center of Excellence, establishes a framework for the simultaneous submission and review of oncology products by international regulatory agencies. Its primary goal is to expedite patient access to innovative cancer therapies that may offer advantages over current treatments. The FDA oversees the selection of applications for Project Orbis and requests that sponsors include their global submission timelines and plans. The FDA then shares the proposal with the relevant Project Orbis Partners (POPs) to confirm their interest and capacity to participate. **Figure 17** displays the 26 Orbis products that obtained an HTA recommendation in at least one of the following jurisdictions: Australia, Canada (CDA-AMC), Canada (INESSS), England or Scotland, from 2020 to 2024. The limited number of Orbis products reviewed by both NICE and SMC is due to MHRA only joining the scheme in January 2021. For products that received an HTA recommendation between 2020 and 2024, Orbis products exhibited a shorter median regulatory review time in all jurisdictions, except in Australia (**Figure 18**).

Figure 18. Breakdown of Rollout Time for NASs Approved via Orbis vs. Non-Orbis (HTA Recommendations Between 2020–2024)



Non-Orbis NASs: ATC L01 NASs approved outside Project Orbis.

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Focus: Access Consortium

Figure 19. 1st HTA Recommendation for NASs Approved via the Access Consortium (HTA Recommendations Between 2020–2024)

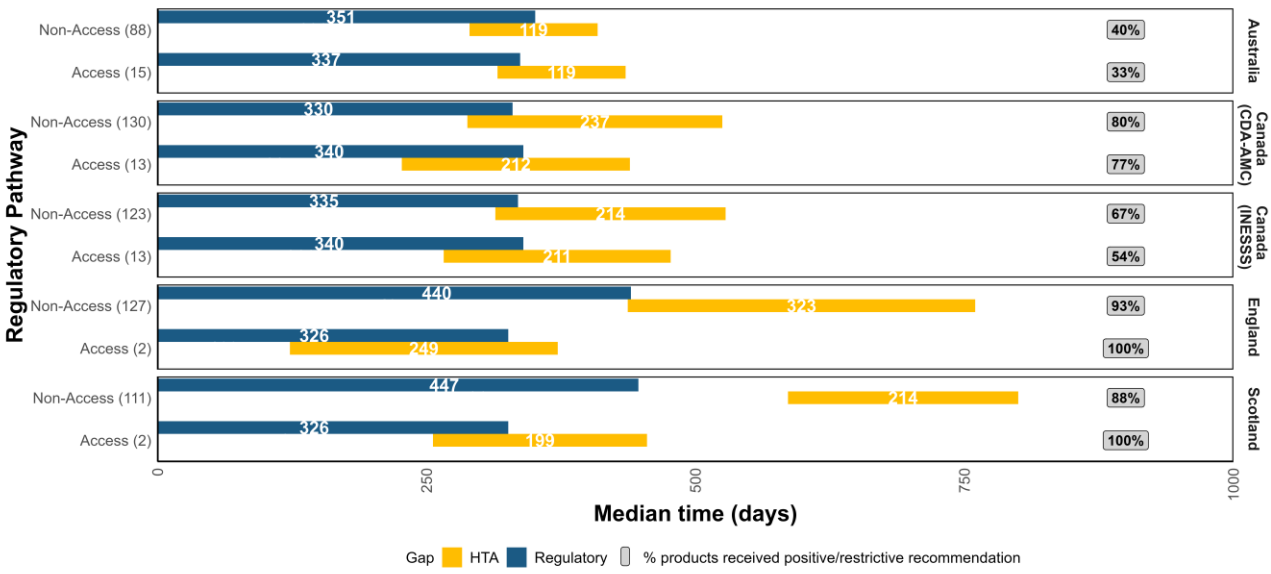
Note 1: Products in white indicate that there is currently no HTA recommendation between 2020 and 2024 from the studied agencies within the Access Consortium; however, products may have followed alternative patient access routes.

Between 2020 and 2024, 19 NASs approved via the Access Consortium were assessed by HTA in at least one of the studied jurisdictions: Australia, Canada or the UK.

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.

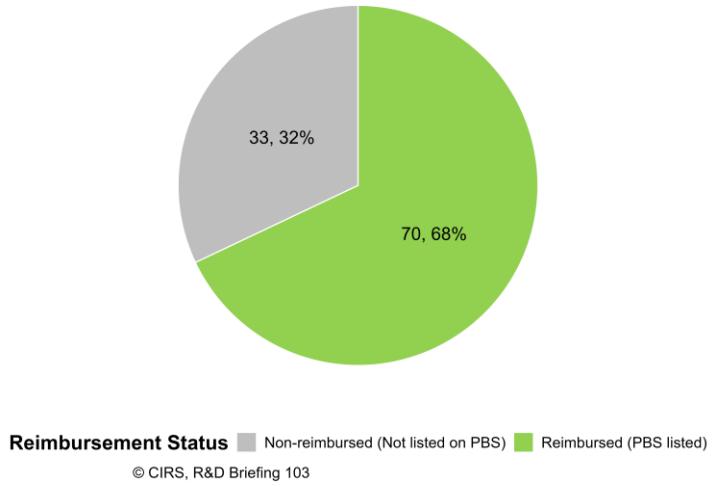
A total of 19 products approved via the Access route received a 1st HTA recommendation in Australia, Canada or the UK between 2020 and 2024 (**Figure 19**). All studied jurisdictions presented a shorter or similar median regulatory review time for Access products compared to non-Access products (**Figure 20**). Access products also presented a shorter overall rollout time, except in Australia.

Figure 20. Breakdown of Rollout Time for NASs Approved via the Access vs. Non-Access (HTA Recommendations Between 2020–2024)



Features of Australia

Figure 21. Proportion of Products Assesed by PBAC That Received Reimbursement in Australia (Reviewed by PBAC Between 2020–2024)

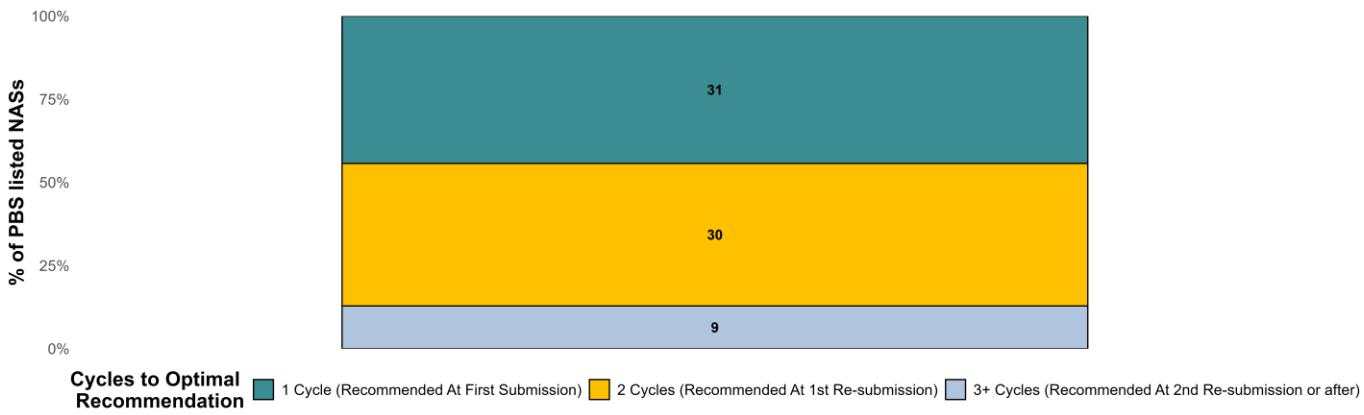


Of the 103 NASs reviewed by the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia between 2020-2024, 68% have been listed on the Pharmaceutical Benefits Scheme (PBS). Of these listed products, 56% required more than one cycle of submission to PBAC to obtain a recommendation for reimbursement.

In Australia, under the PBS, the government subsidises the cost of medicine for most medical conditions. PBAC is an independent expert body appointed by the Australian Government, consisting of doctors and health professionals, among others. Its primary role is to recommend new medicines for listing on the PBS. No new medicine can be listed without a positive or positive with restrictions recommendation from the committee. 68% of the NASs that were assessed by PBAC between 2020 and 2024 have been PBS-listed (**Figure 21**). The remaining 32% are NASs that either have been recommended for reimbursement by PBAC but have not been PBS-listed yet, or NASs that have not been recommended for reimbursement by PBAC (i.e. they have received a negative HTA recommendation).

When PBAC's initial HTA recommendation is negative, companies may resubmit an application with an improved dossier. As a result, several review cycles may be required before a positive (or positive with restrictions) recommendation is achieved. Currently, there are four pathways for companies to resubmit to PBAC: the early re-entry pathway, early resolution pathway, facilitated resolution pathway, and standard re-entry pathway. Achieving a positive recommendation can require multiple cycles (**Figure 22**). Overall, 44% (31/70) of NASs received a positive or positive with restrictions recommendation within a single cycle. These NASs had a median time to PBS listing of 200 days following receipt of their HTA recommendation. Among the cases where the initial recommendation was negative, 43% (30/70) required two submission cycles, and 13% (9/70) required three or more cycles to secure a positive reimbursement recommendation. For these cases where the initial recommendation was negative, the median time from the first negative PBAC recommendation to a subsequent positive recommendation via resubmissions was 243 days, followed by a median of 170 days from that positive recommendation to PBS listing.

Figure 22. Number of NASs Reviewed by PBAC Listed on the PBS (Reviewed by PBAC Between 2020–2024)



Note 1: The products represented include those recommended for listing by PBAC at first submission ("1 cycle") or at resubmission ("2 cycles" or "3 or more cycles"), and that have been PBS listed.

Note 2: The optimal recommendations include both positive and positive with restrictions recommendations.

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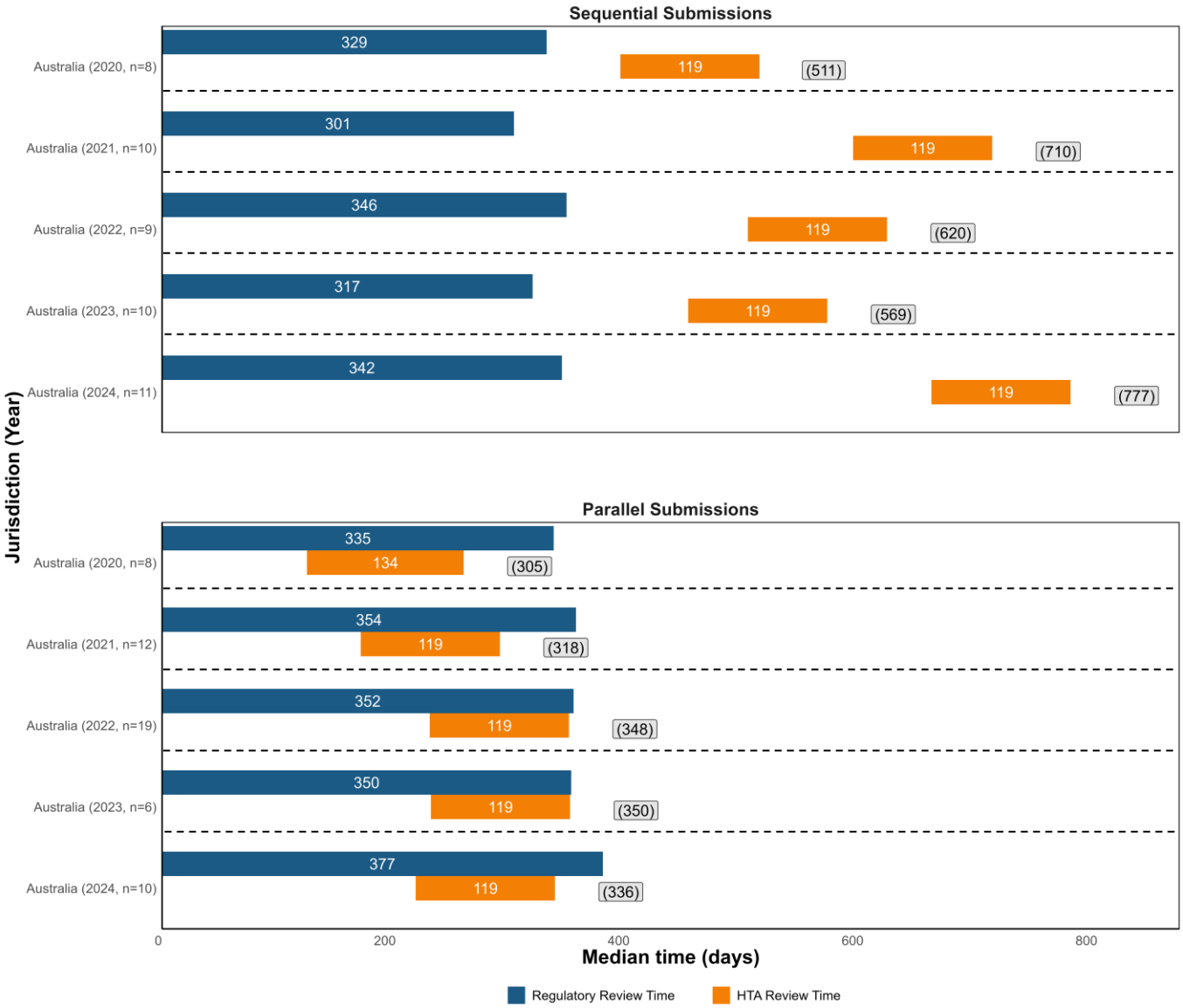
Features of Australia (Cont.)

Figure 23. Breakdown of Rollout Time by Review Sequence in Australia (Reviewed by PBAC Between 2020–2024)



n = number of NASs

Note: Numbers in grey boxes represent the overall median rollout time (days).

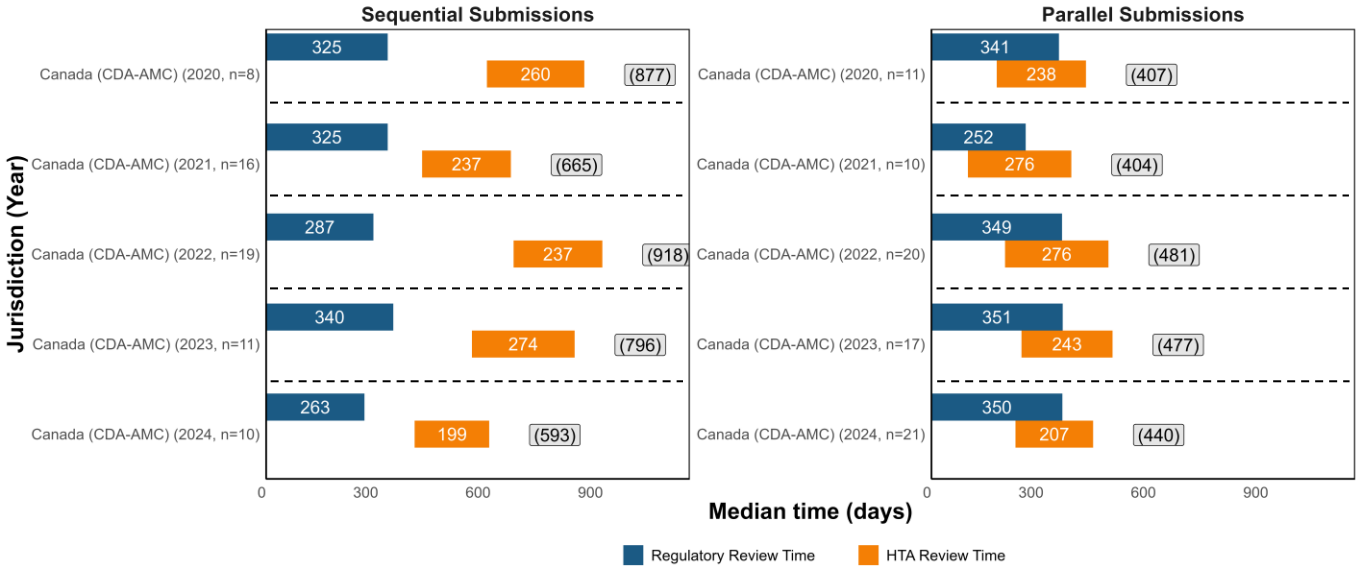
Parallel submissions consistently present faster median rollout times compared to those products submitted sequentially.

In Australia, companies can submit the HTA dossier to PBAC either before TGA approval, known as the parallel process, or after TGA approval, known as the sequential process. Under the TGA/PBAC parallel process, the TGA Delegate's Overview informs the PBAC's review of a drug, and companies may submit the Delegate's Overview up to one week before the PBAC meeting.

The parallel process has consistently presented a shorter overall median time from regulatory submission to HTA recommendation in Australia (**Figure 23**). In 2020, the median time was 511 days for sequential submissions compared with 305 days for parallel submissions. In 2021, the times were 710 days versus 318 days, in 2022 they were 620 versus 348 days, in 2023 they were 569 versus 350 days, and in 2024 they were 777 versus 336 days.

In 2023, only six products were submitted through the parallel process, followed by ten in 2024. This is in contrast to earlier years, when 19 products were submitted in 2022 and 12 in 2021 through the parallel pathway. In addition, 2024 presented a longer submission gap compared to previous years.

Figure 24. Breakdown of Rollout Time by Review Sequence in Canada (CDA-AMC) (Reviewed by CDA-AMC Between 2020–2024)



n = number of NASs

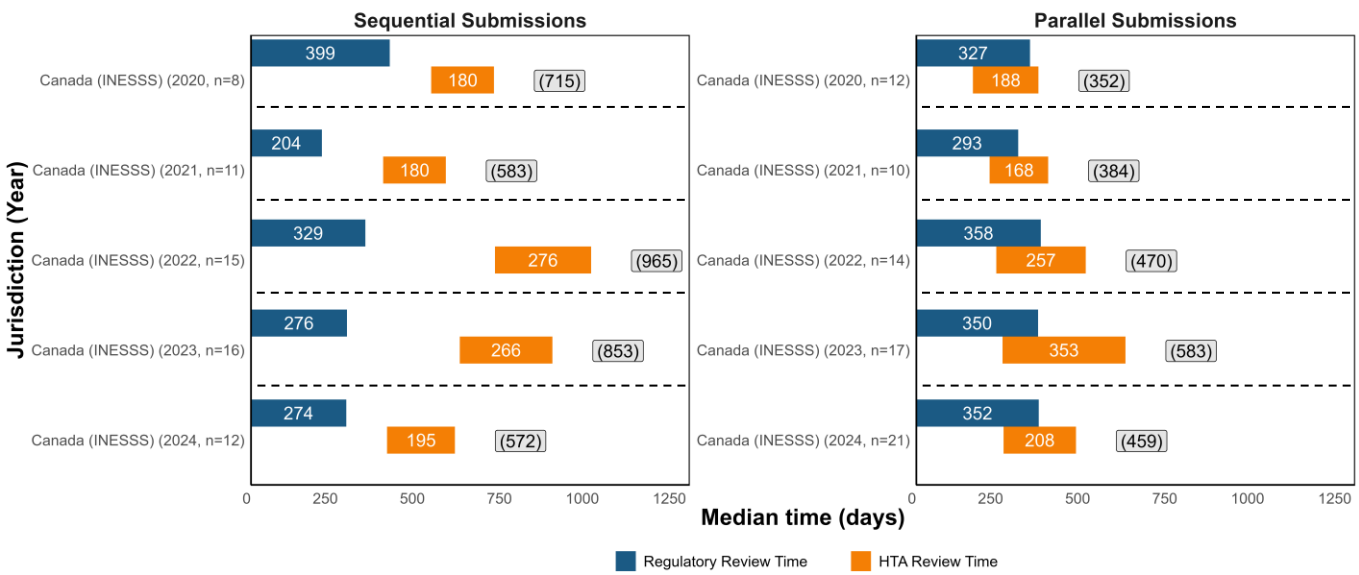
Note: Numbers in grey boxes represent the overall median rollout time (days).

Products submitted to either CDA-AMC or INESSS through the parallel regulatory/HTA process had a faster median rollout time than those submitted sequentially. 2024 had the highest number of parallel submissions in the past five years across both agencies.

A parallel regulatory/HTA review pathway is available for submissions to CDA-AMC and INESSS. This process allows companies to submit to either HTA agency up to 180 days prior to the anticipated Notice of Compliance (NOC) from Health Canada. For both CDA-AMC and INESSS, NASs submitted via the parallel process consistently showed a shorter median rollout time from regulatory submission to HTA recommendation each year (**see Figures 27** and **28**, respectively).

Interestingly, both agencies have shown a similar trend over the past three years (2022–2024), with sequential submissions being made increasingly closer to the date of regulatory approval (**Figure 24, 25 and 26**). Likewise, 2024 saw the highest number of parallel submissions in five years, with 21 submissions each to CDA-AMC and INESSS.

Figure 25. Breakdown of Rollout Time by Review Sequence in Canada (INESSS) (Reviewed by INESSS Between 2020–2024)

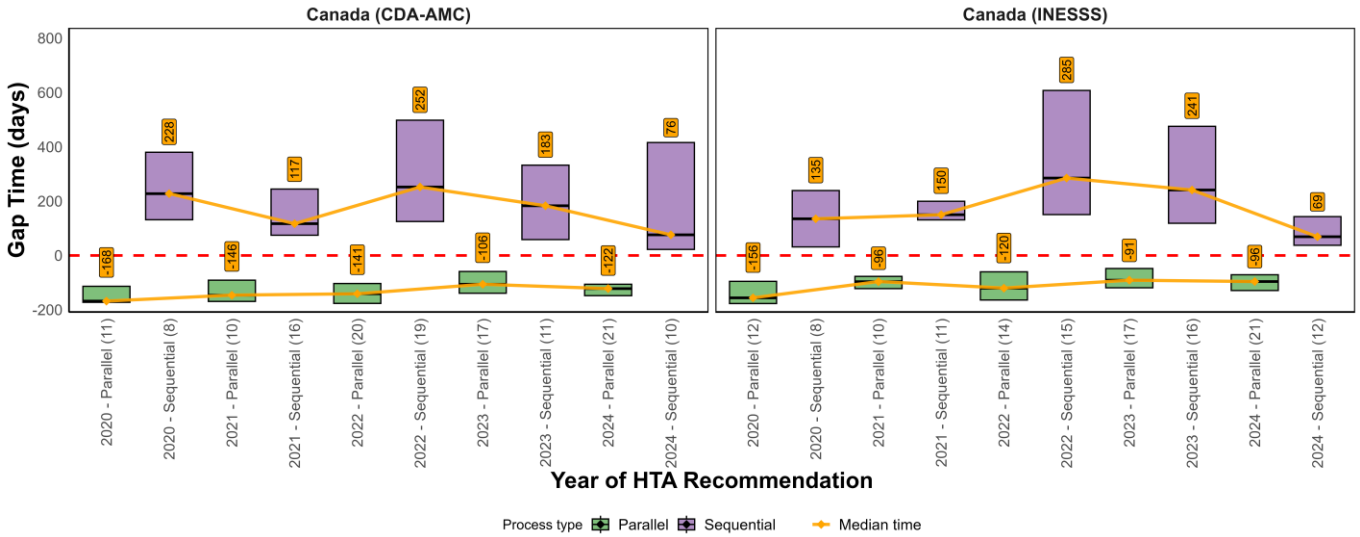


n = number of NASs

Note: Numbers in grey boxes represent the overall median rollout time (days).

Features of Canada (Cont.)

Figure 26. Regulatory Approval to HTA Submission Gap Time by Submission Sequence Type (Canada: CDA-AMC and INESS (HTA Recommendations Between 2020–2024)



n = number of NASs
The box represents the interquartile range (from the 1st to the 3rd quartile), and the line inside the box indicates the median

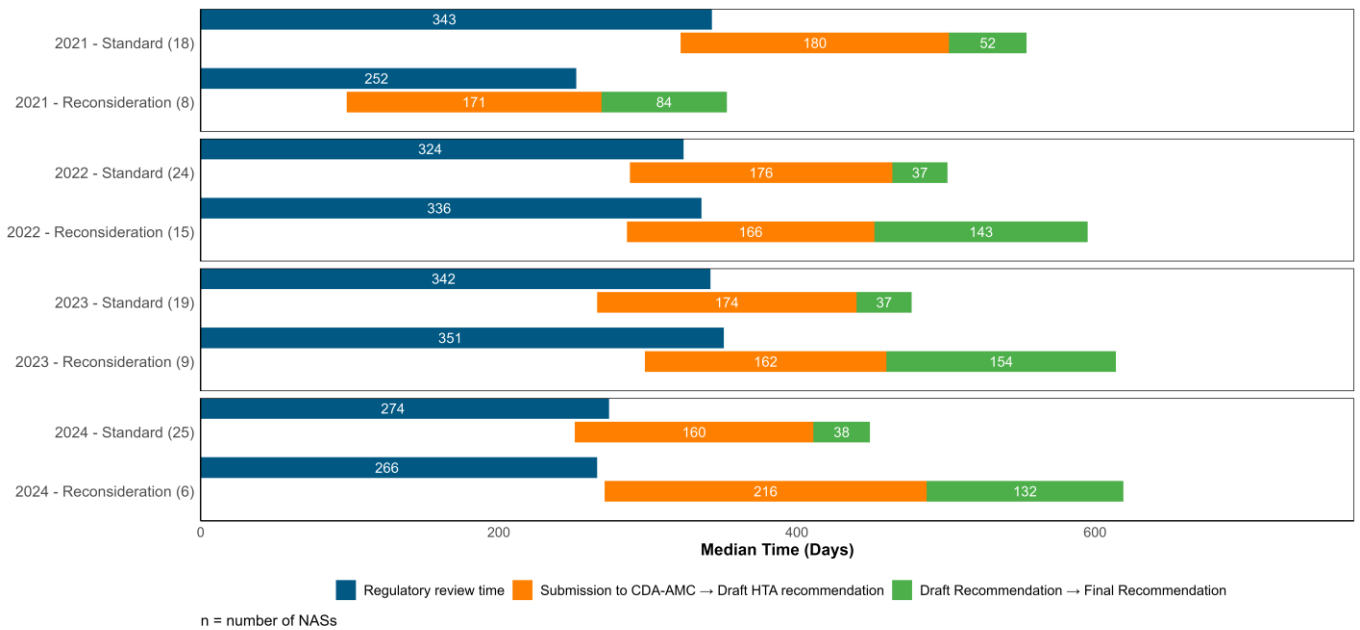
From 2020 to 2024, 34% (49/143) of CDA-AMC recommendations were requested for reconsideration by companies.

For Canada, the proportion of parallel submissions has increased over the past three years. At INESSS, parallel submissions rose from 48% in 2022 to 52% in 2023 and reached 64% in 2024. Similarly, at CDA-AMC, the proportion increased from 51% in 2022 to 61% in 2023 and peaked at 68% in 2024, reflecting a consistent upward trend.

The company applicant for a drug with a draft recommendation may file a request to CDA-AMC for reconsideration of the recommendation during the feedback period. Such a request can be made only on the grounds that the recommendation is not supported by the evidence that had been submitted or by the evidence identified in the review report. Parallel and sequential submissions presented similar percentages of requests for reconsideration (33% (26/79) and 36% (23/64), respectively).

Figure 27 shows that requests for reconsideration extended the median time from the initial draft recommendation to the final recommendation by CDA-AMC compared to no request.

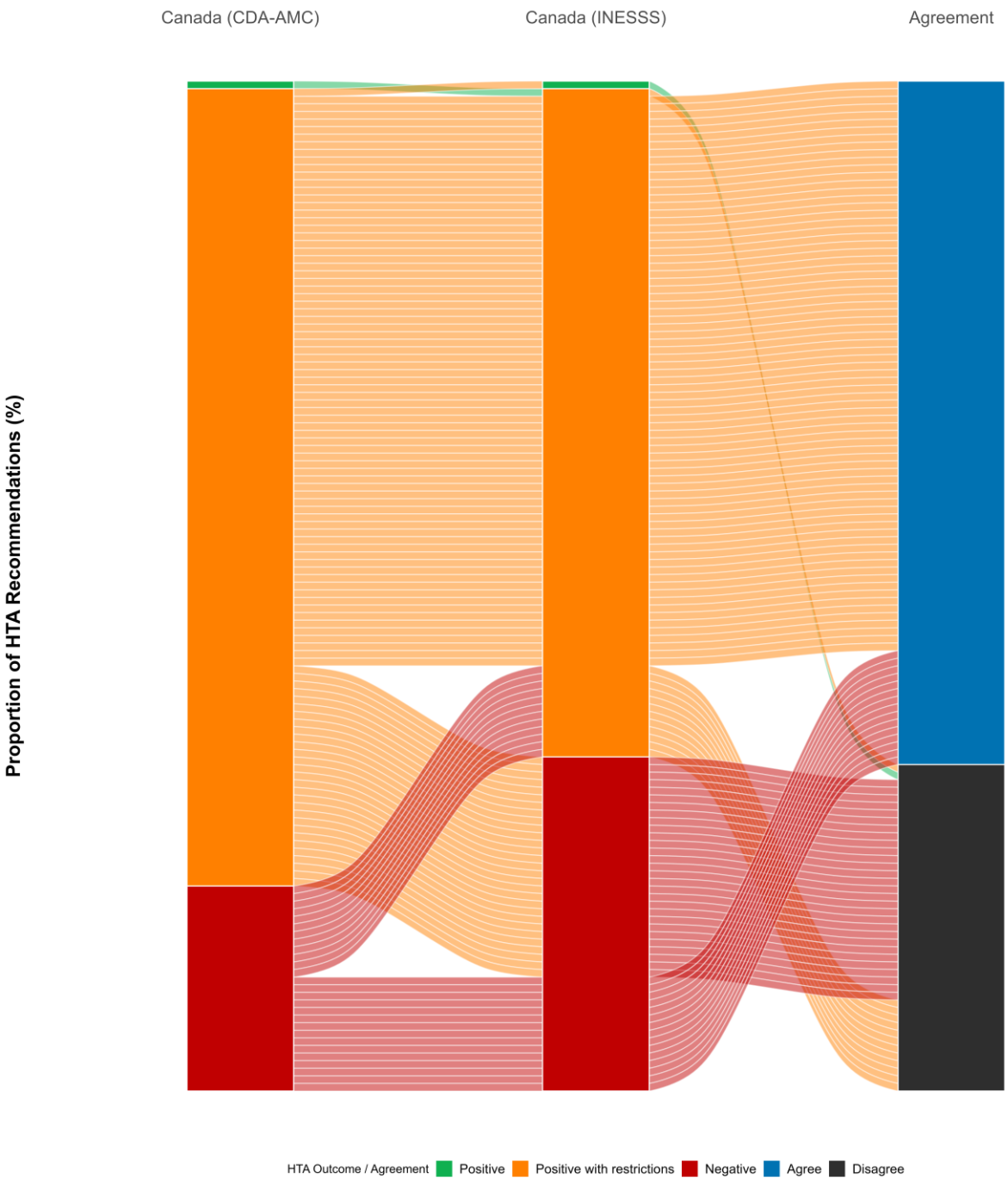
Figure 27. Breakdown of rollout time in CDA between 2021-2024 (Requested Reconsideration vs Standard)



n = number of NASs

Features of Canada (Cont.)

Figure 28. First HTA recommendation comparison of common NASs (n=133) reviewed in Canada (HTA Recommendations Between 2020-2024)



Agreement between CDA-AMC and INESSS: 68%; Disagreement: 32%

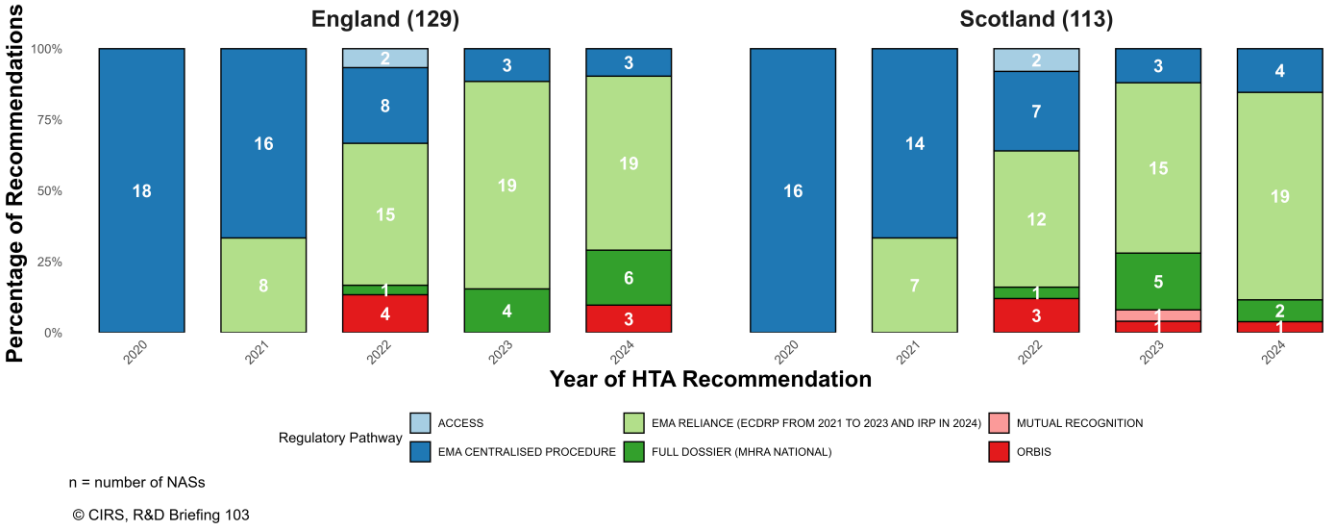
Note: each flow represents one HTA recommendation for one NAS

CDA-AMC and INESSS assessed 133 common compounds in 2024. They agreed on the HTA recommendation in 68% of cases.

A total of 133 NASs received HTA recommendations from both CDA-AMC and INESSS between 2020 and 2024 (**Figure 28**). Of these, 88% (117/133) were first submitted to CDA-AMC, 9% (12/133) were submitted to INESSS first, and 3% (4/133) where submitted to both agencies at the same time. A 59% were first recommended by CDA-AMC. Both jurisdictions agreed on the type of HTA recommendation for 68% (90/133) of the common compounds and published different recommendations for the remaining 32%. Such discrepancies may be attributed to differences in their evaluation frameworks. HTA recommendations influence the next step in the reimbursement process: price negotiations. Divergent HTA outcomes can potentially result in variations in access to new medicines across Canadian provinces.

Features of the UK

Figure 29. Number of NICE/SMC Recommendations by Year and the Route of Regulatory Approval (HTA Recommendation Between 2020–2024)



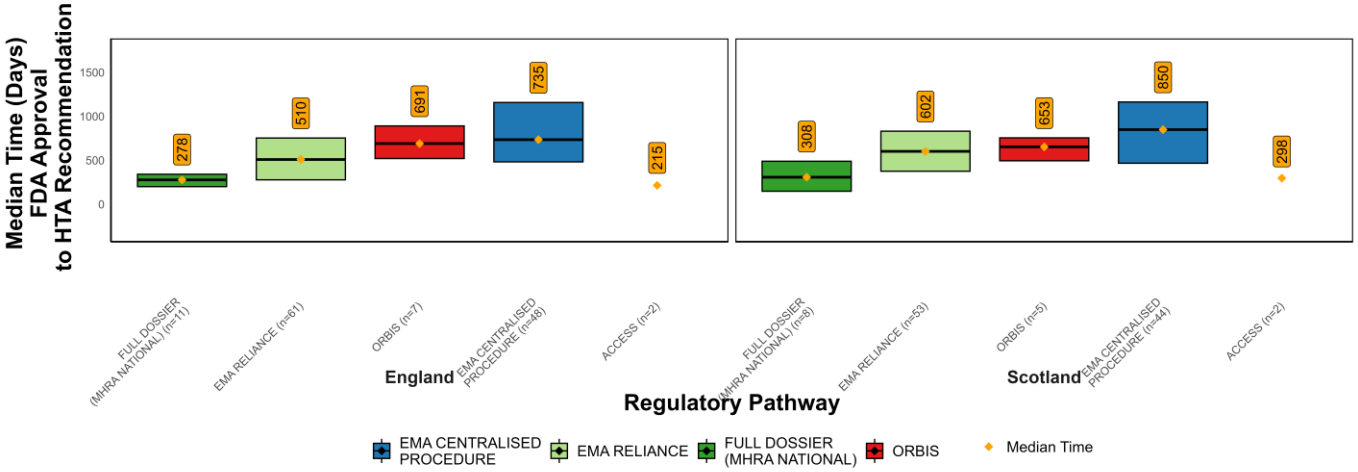
n = number of NASs

In 2024, 61% and 73% of reviews by NICE and SMC, respectively, were approved via reliance on EMA decisions (Figure 29).

Following Brexit, a transitional regulatory mechanism began on 1 January 2021. Under this system, MHRA could review national submissions or rely on European Commission (EC) decisions to grant marketing authorisations in Great Britain through the EC Decision Reliance Procedure (ECDRP), which applied to NASs approved centrally by the EMA. In January 2024, MHRA introduced a new International Recognition Procedure (IRP), allowing the reliance on existing approvals not only from the EU, but also from Australia, Canada, Japan, Switzerland, Singapore, and the US. This new pathway complements MHRA's national procedures. MHRA also participates in international initiatives such as Project Orbis and the Access Consortium.

Figure 30 shows a comparative analysis of rollout times for NASs receiving HTA recommendations in the UK, across different regulatory pathways. Products approved via the Access Consortium had the fastest median rollout time; however, this should be interpreted cautiously due to the small sample size (n=2). These were followed by products approved through national procedures, with median rollout times of 278 days in England and 308 days in Scotland. Next were products approved through EMA reliance pathways (ECDRP and IRP), with median rollout times of 510 days in England and 602 days in Scotland. Products approved via Project Orbis followed, with median rollout times of 691 days in England and 653 days in Scotland. Interestingly, products approved through the EMA centralised procedure had the longest rollout times. This may be due to the fact that the EMA centralised procedure has not been available in the UK since before 2021.

Figure 30. Products Rollout Time in the UK by Regulatory Pathway (HTA Recommendation Between 2020–2024)

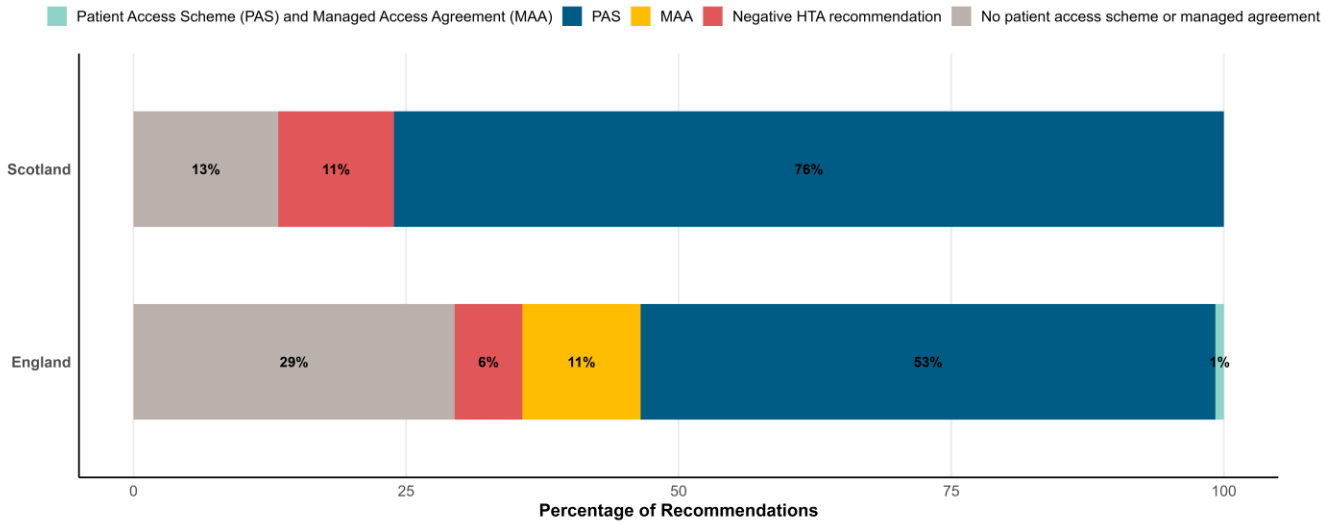


The box represents the interquartile range (from the 1st to the 3rd quartile), and the line inside the box indicates the median

Note: entries where n<3 only display median time

Features of the UK (Cont.)

Figure 31. NICE/SMC Recommendations via Patient Access Scheme/Managed Entry Agreements (HTA Recommendation Between 2020–2024)



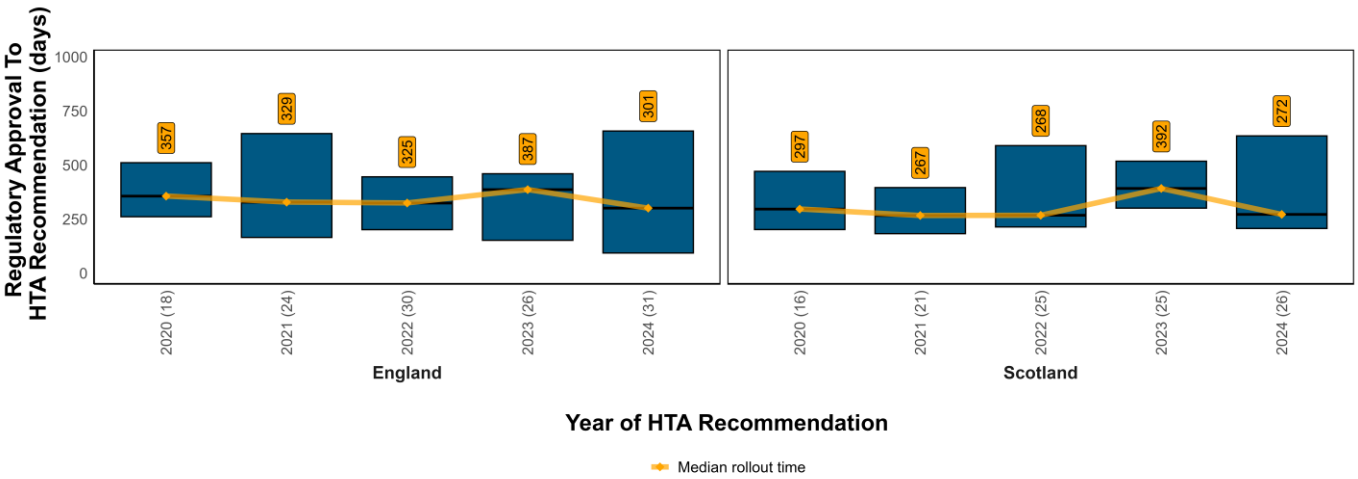
For NASs reviewed by NICE and SMC, 53% and 76%, respectively, were recommended under patient access schemes (PAS) (Figure 31).

NICE and SMC have introduced mechanisms such as Managed Access Agreements (MAAs) and PAS to improve access to medicines that may not initially meet cost-effectiveness criteria. NICE's MAAs enable earlier access to promising treatments while uncertainties around clinical or cost-effectiveness are addressed through additional evidence collection. PAS, used by both NICE and SMC, typically involve cost-reduction strategies that make treatments more affordable and accessible. These mechanisms play a critical role in balancing timely patient access with financial sustainability.

The utilisation of these schemes is notable. PAS were included in 53% (68 out of 129) of NICE's HTA recommendations and in 76% (86 out of 113) of SMC's recommendations, as shown in **Figure 31**. MAAs were also a key pathway for NICE, accounting for 11% (14 out of 129) of NAS recommendations. **Figure 32** examines the time from regulatory approval to HTA recommendation in England and Scotland between 2020 and 2024, indicating a relatively consistent timeline across the years.

In addition, NICE and SMC reviewed 98 common compounds between 2020 and 2024. Of these, 51% (50/98) received a recommendation from NICE before SMC.

Figure 32. Regulatory Approval to HTA Recommendation (HTA Recommendations Between 2020–2024)

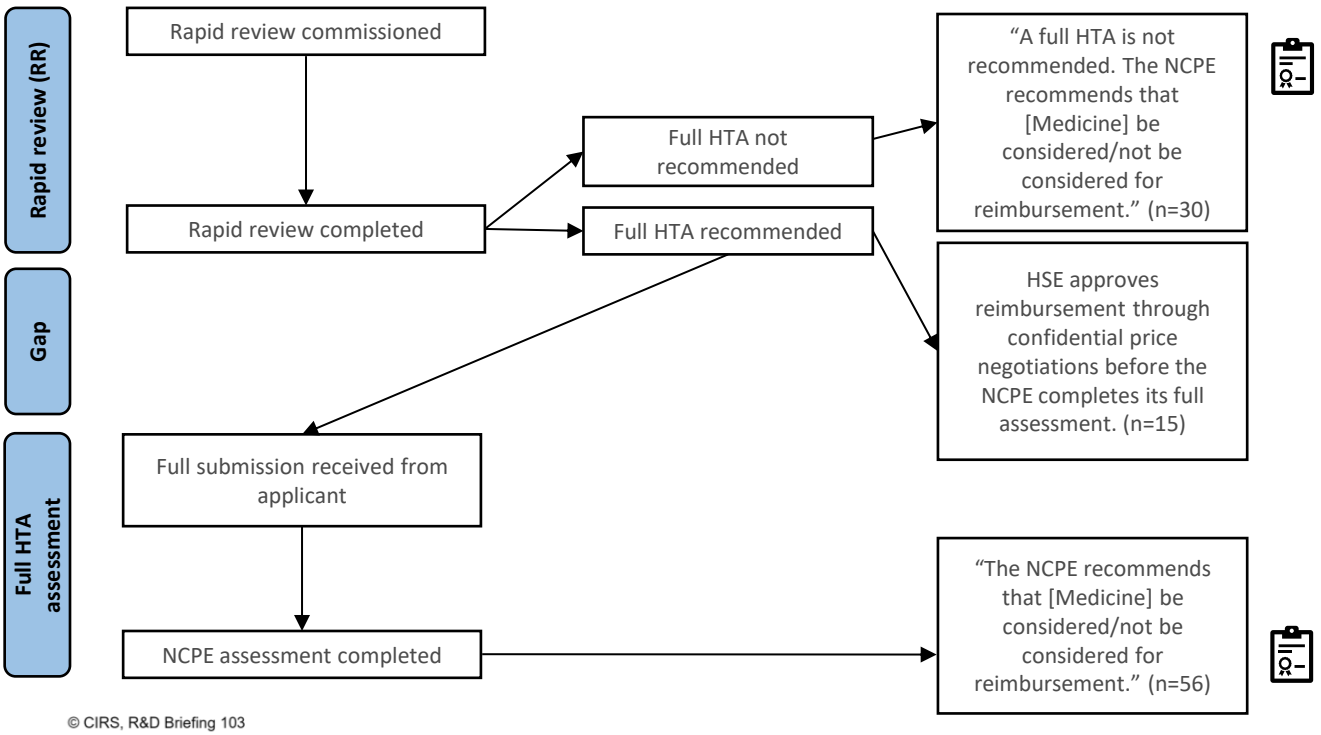


n = number of NASs

The box represents the interquartile range (from the 1st to the 3rd quartile), and the line inside the box indicates the median

Features of Ireland

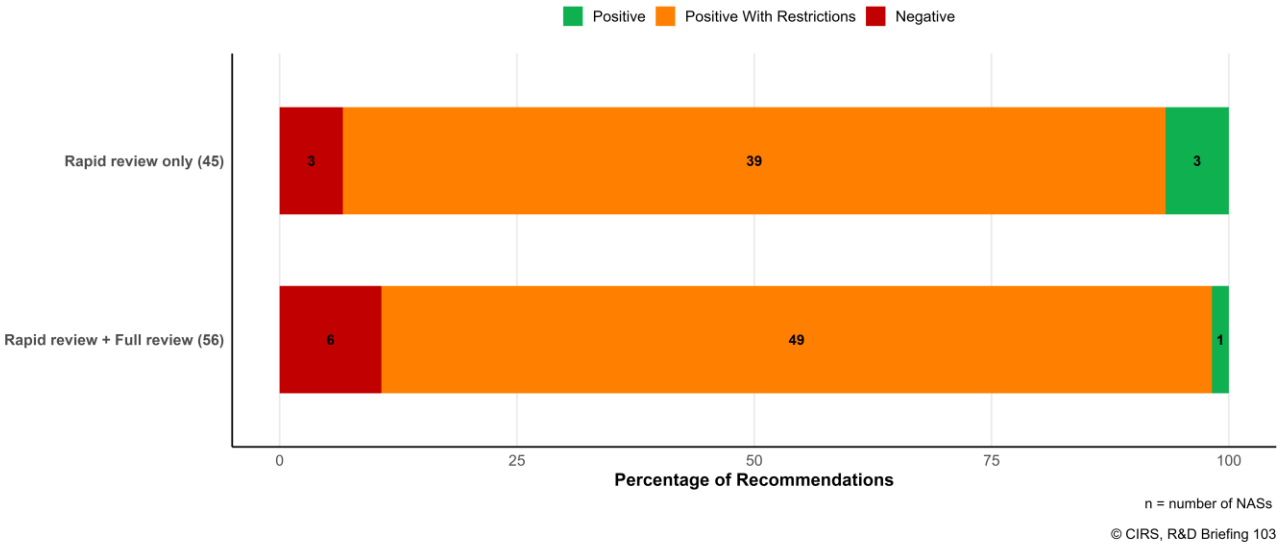
Figure 33. NCPE Recommendation Process (Simplified Schematic)
(HTA Recommendations Between 2020–2024)



The primary objective of Rapid Reviews (RR) is to assess new medicines to determine if they require a more comprehensive evaluation through a full HTA (**Figure 33**). If a full HTA is not needed, the RR provides a recommendation on reimbursement. The NCPE aims to complete a RR within four weeks, and in order to do this, some aspects of the full review are not part of the RR, such as evidence synthesis analyses and formal cost-effectiveness analyses. Following the RR, a full HTA may subsequently be recommended for those drugs for which additional information and/or analysis is required to inform a reimbursement recommendation. In some cases, a full HTA may not be needed if the Health Service Executive (HSE) can agree a suitable price reduction with the pharmaceutical company via confidential price negotiations. Between 2020 and 2024, 15 out of 71 products that were recommended for full HTA were approved for reimbursement via confidential price negotiations (**Figure 33**).

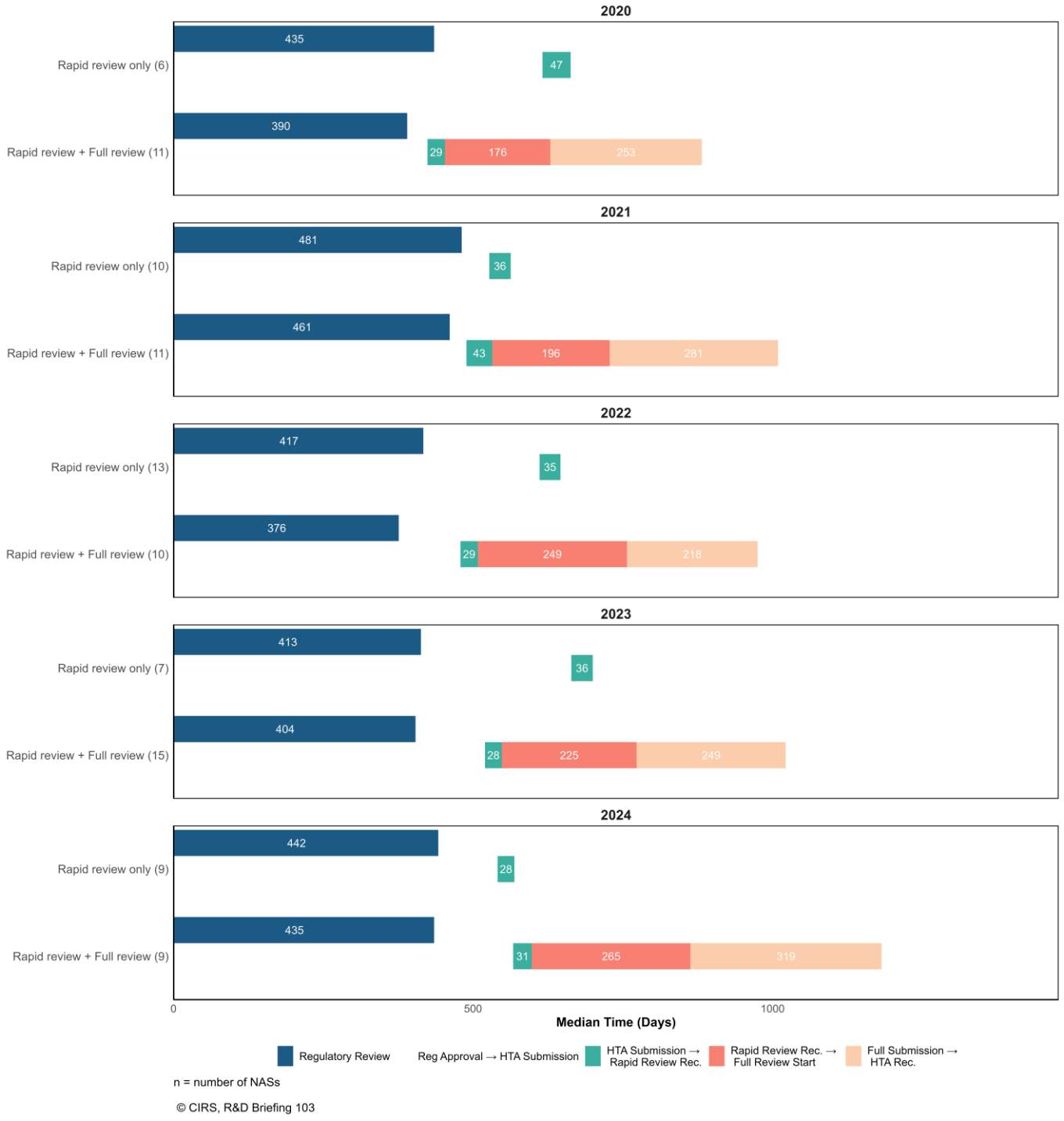
Figure 34 illustrates the proportion of HTA recommendations published by NCPE that were reached either through an RR only or through an RR followed by a full HTA review between 2020 and 2024. The data indicate that a similar proportion of positive or positive with restrictions recommendations was observed for applications following an RR only and those undergoing an RR plus a full review.

Figure 34. Type of HTA Recommendation in Ireland: Rapid Reviews vs Full Reviews
(HTA Recommendation Between 2020 and 2024)



Features of Ireland (Cont.)

Figure 35. Breakdown of Rollout Time for NASs Recommendations in Ireland (Rapid vs Full HTA Reviews) (HTA Recommendation Between 2020 and 2024)



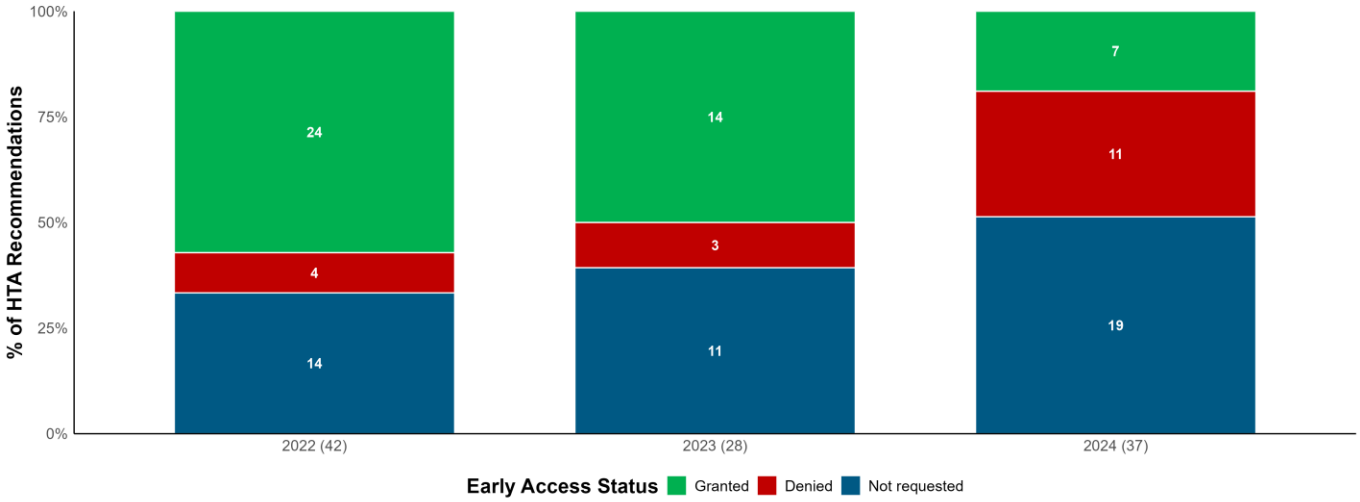
n = number of NASs

Rapid Reviews reduced the time to 1st HTA recommendation by the NCPE in Ireland.

Figure 35 shows the breakdown of rollout time of NASs that received an HTA recommendation from NCPE between 2020 and 2024. The data indicated that the median time for the completion of RRs ranged from 28 to 47 days. For those applications that needed a subsequent full HTA review, the gap between rapid and full presented a median time between 176 and 265 days, and the full HTA review was completed in between 218 and 319 days. Overall, the analysis showcases that NASs undergoing only RR presented a faster time to HTA recommendation compared to RR + full reviews. In particular, 2024 presented the fastest median time for RRs between 2020 and 2024.

Features of France

Figure 36. Proportion of NASs That Received an HTA Recommendation by Type of Early Access Application (HTA Recommendation Between 2022 and 2024)



n = number of NASs

There was a decrease in the number of NASs granted Early Access in France in 2024.

Since 1st July 2021, HAS has evaluated and authorised 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 with unmet medical needs to benefit exceptionally and temporarily from certain drugs not recommended for reimbursement yet in a specific therapeutic indication.

Analysis of NASs reviewed by HAS highlights two trends (**Figure 36**). First, the proportion of NASs evaluated by HAS between 2020 and 2024 that applied for Early Access has decreased over the past three years: 67% (28/42) in 2022, 61% (17/28) in 2023, and 49% (18/37) in 2024. Second, the proportion of NASs evaluated by HAS that were granted Early Access has also declined, with 57% (24/42) granted in 2022, 50% (14/28) in 2023, and only 19% (7/37) in 2024. This shift may reflect a reduced interest from pharmaceutical companies in pursuing Early Access and/or a more stringent application of eligibility criteria by HAS.

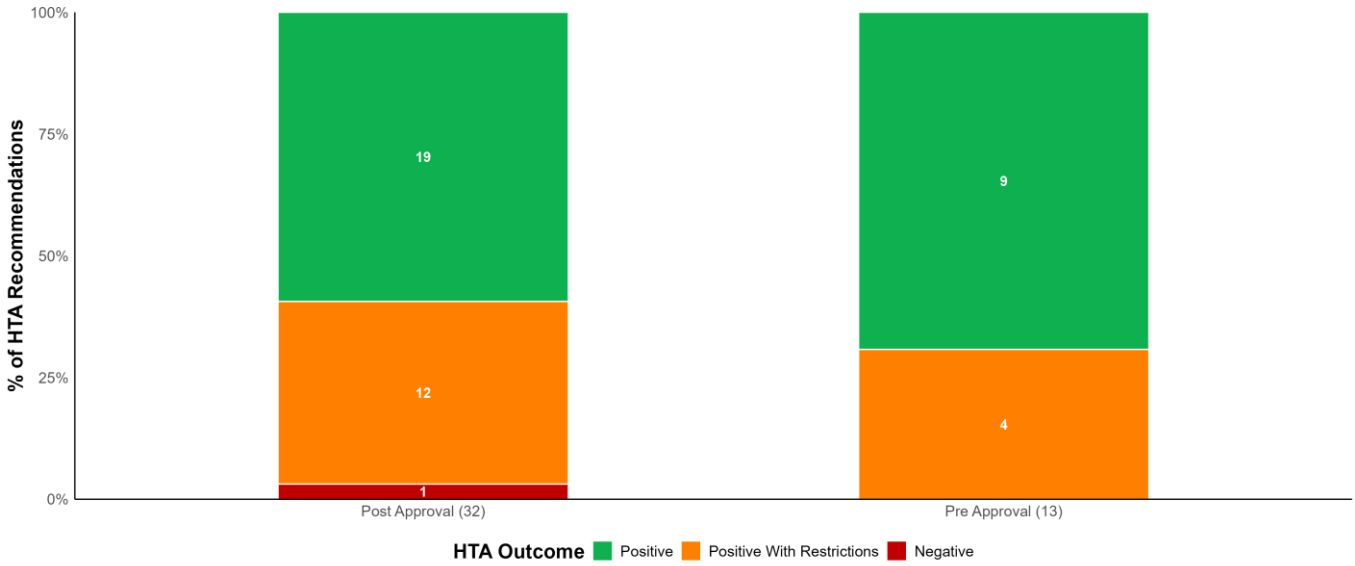
Figure 37 shows that NASs granted Early Access between 2022 and 2024 presented a higher proportion of positive recommendations from HAS compared with standard NASs (62% [28/45] vs. 23% [14/62], respectively). The latter could be indicative of the unique therapeutic value of Early Access products.

Figure 37. Proportion of NASs That Received an HTA Recommendation by Early Access Status (HTA Recommendation Between 2022 and 2024)

n = number of NASs

Features of France (Cont.)

Figure 38. Proportion of HTA Outcomes Where Early Access Was Granted (n=35) Comparing Pre-Marketing Authorisation and Post-Marketing Authorisation Early Access (HTA Recommendation Between 2022 and 2024)

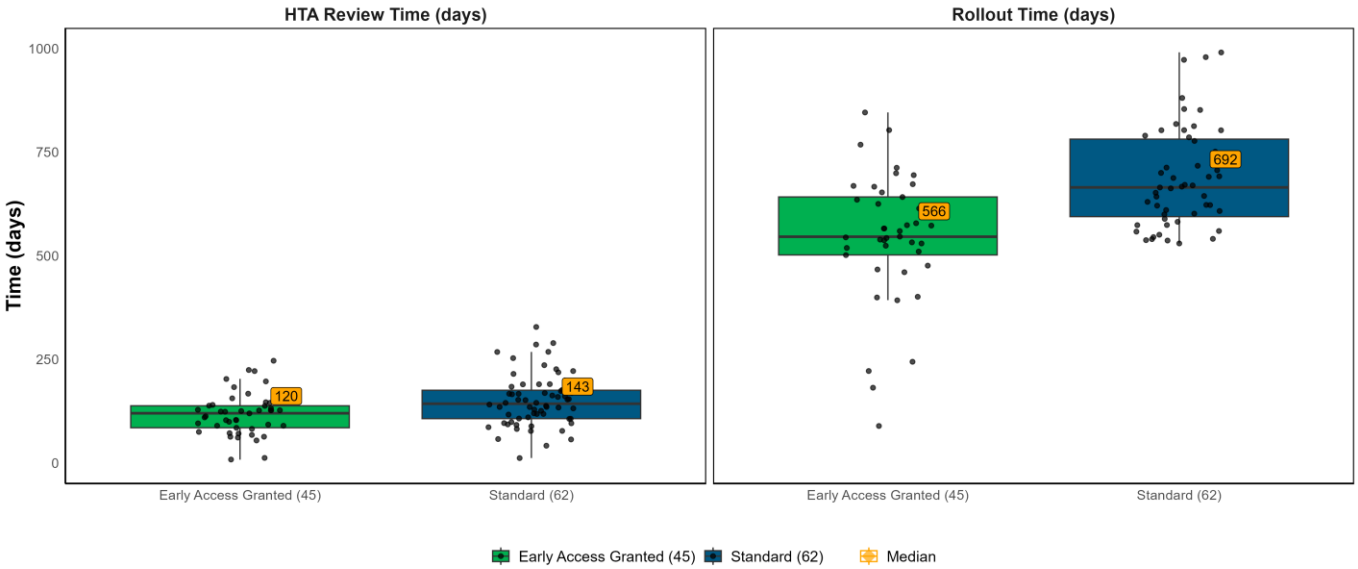


n = number of NASs

Figure 38 provides a comparative analysis of HTA outcomes for products that received Early Access, distinguishing between those granted Early Access before and after marketing authorisation. The data show that 59% (19 out of 32) of products granted Early Access post-authorisation received a positive HTA recommendation (without restrictions). In contrast, 69% (9 out of 13) of products granted Early Access prior to authorisation were positively recommended.

Figure 39 evaluates both the HTA review time and the rollout time for NASs that received an HTA recommendation in France, comparing products granted Early Access with those assessed through the standard pathway. The findings indicate that products with Early Access experienced shorter median HTA review times and faster rollout to market compared to standard NASs.

Figure 39. Rollout Time of NASs in France (Early Access Granted vs. Standard) (HTA Recommendation Between 2022 and 2024)

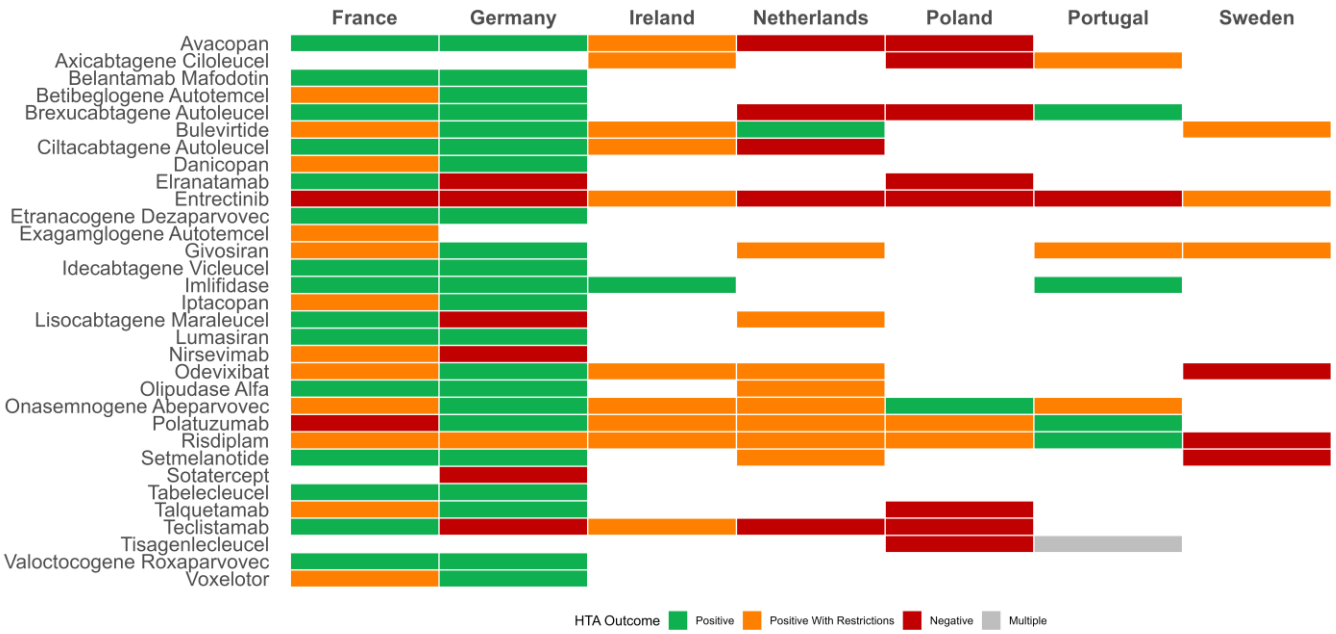


The box represents the interquartile range (from the 1st to the 3rd quartile), and the line inside the box indicates the median

n = number of NASs

Features of Europe: PRIME Products

Figure 40. PRIME Products Assessed by HTA (n = 32)
(HTA Recommendation Between 2020 and 2024)



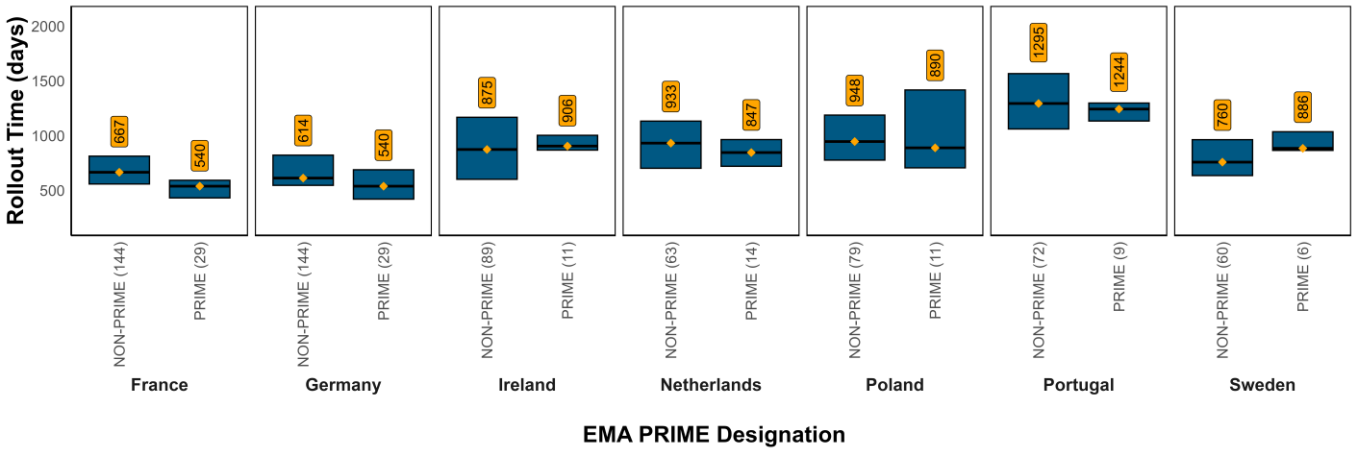
Note: Products in white indicate that there is currently no HTA recommendation for the product; however, alternative mechanisms for patient access may be available.

Among France, Germany, Ireland, the Netherlands, Poland, Portugal and Sweden, 32 PRIME products were assessed by HTA in at least one of these jurisdictions between 2020 and 2024.

PRIME is an initiative established by the EMA to strengthen support for the development of medicines that target unmet medical needs. **Figure 40** shows the heterogeneity of recommendations for PRIME products that have been assessed by HTA in at least one of the European countries included in this study. Among these, Germany presented the higher percentage of positive HTA recommendations for assessed PRIME products (76% (22/29)), while Poland presented the higher proportion of negative recommendations (73% (8/11)).

Figure 41 compares the median rollout time from regulatory submission to HTA recommendation in all European jurisdictions of PRIME products vs non-PRIME products. The data shows that for all countries, expect for Ireland and Sweden, PRIME products presented a faster median time from regulatory submission to HTA recommendation.

Figure 41. Regulatory Submission to HTA Recommendation by EMA PRIME Designation
(HTA Recommendations Between 2020–2024)

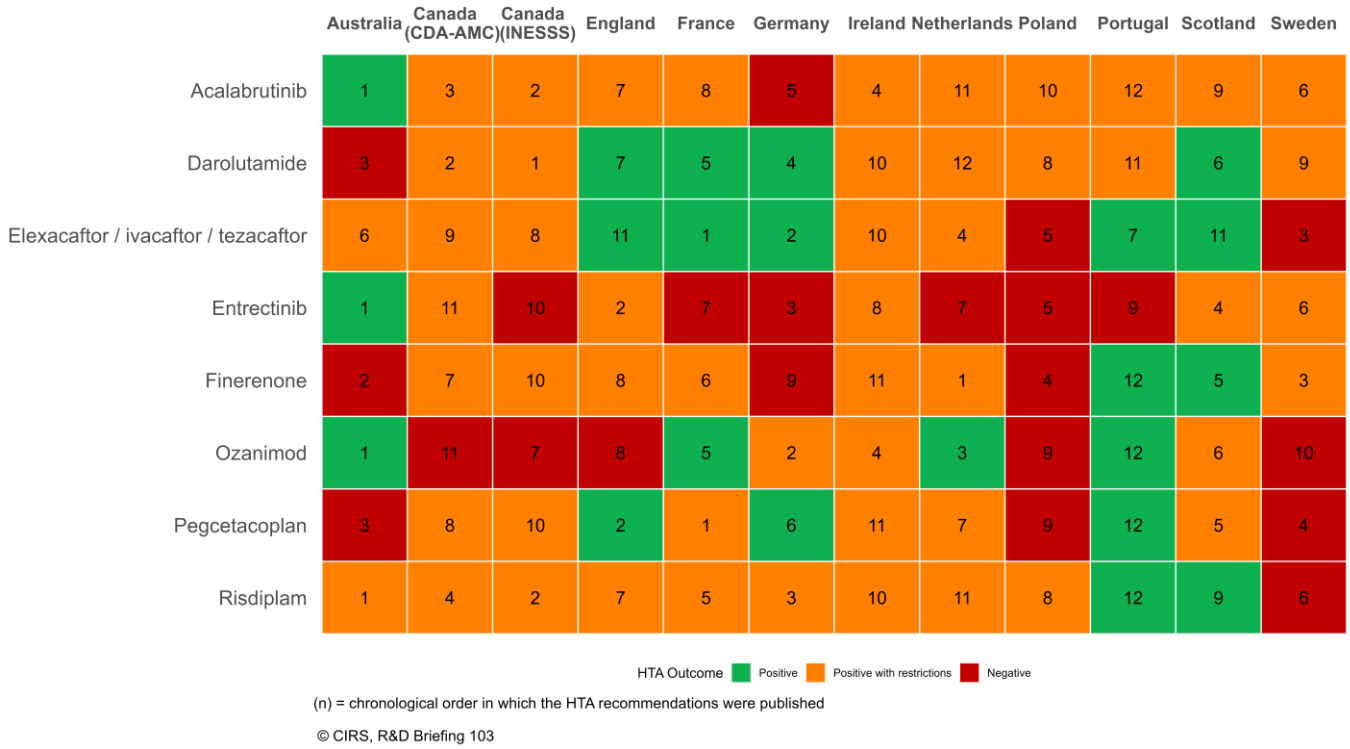


Note 1: The box represents the interquartile range (from the 1st to the 3rd quartile), and the line inside the box indicates the median

Note 2: EMA approvals before 2018 are excluded from this analysis

Common Compounds Across 12 Jurisdictions

Figure 42. First HTA Recommendation Comparison of Common NASs (n=8) Reviewed by 12 Agencies (HTA Recommendations Between 2020-2024)

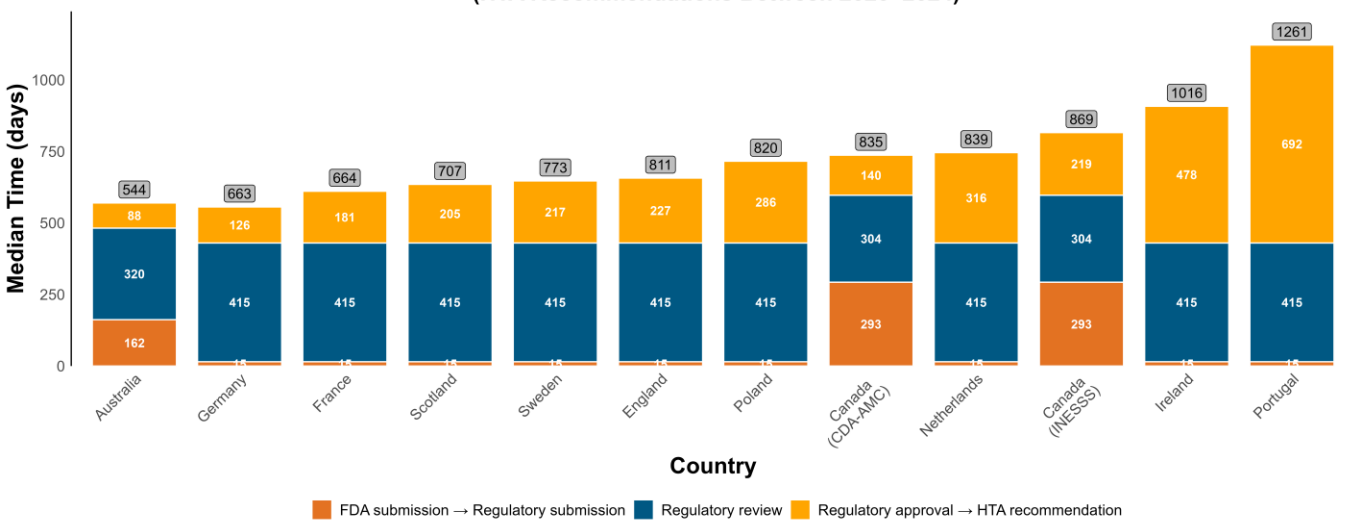


(n) = chronological order in which the HTA recommendations were published

Between 2020 and 2024, eight NASs received their first HTA recommendation in all 12 jurisdictions studied. We refer to these as "common compounds". **Figure 42** lists these eight compounds and uses a traffic light system to compare the HTA outcomes across the different jurisdictions. This visualisation highlights the variation in recommendations among the agencies. We also analysed the timing of the first HTA recommendation for each compound across seven agencies, ranking them from the earliest (1) to the latest (7). Notably, Australia issued the first recommendation for four of the 12 common compounds.

Figure 43 presents the international rollout timeline for these common compounds, using the FDA submission date as a reference point. The data shows that regulatory approval submissions were typically first made to the EMA, followed by Australia and Canada. However, post-approval processes extended the time to HTA recommendations in some European countries, such as the Netherlands, Poland, Ireland, and Portugal. Conversely, despite later regulatory submissions, Australia and Canada issued HTA recommendations sooner than some European jurisdictions due to faster post-approval timelines.

Figure 43. Breakdown of Rollout Time of Common NASs (n=8) Reviewed by 12 Agencies (HTA Recommendations Between 2020–2024)



Note: Numbers in grey boxes represent the overall median rollout time (days).

Definitions

Anti-cancer drugs

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

Exclusion criteria (HTADock study)

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 the national level.

New active substance (NAS)

A chemical, biological, biotechnology or radiopharmaceutical substance that has not been previously available for therapeutic use in humans and is destined to be made available as a 'prescription-only medicine', to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans; the term NAS also includes:

- An isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously available as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously available.
- A biological or biotech substance previously available as a medicinal product, but differing in molecular structure, nature of source material or manufacturing process and which will require clinical investigation.
- A radiopharmaceutical substance that is a radionuclide or a ligand not previously available as a medicinal product. Alternatively, the coupling mechanism linking the molecule and the radionuclide has not been previously available.

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 briefing, a drug is identified as parallel if the 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 EMA is followed by jurisdictional HTA recommendations by member states.

Definitions

(Agency specific)

CDA-AMC - Request for reconsideration

The sponsor of a drug that is the subject of a draft recommendation and the drug programmes may file a request for reconsideration of the recommendation during the feedback period. The sponsor and drug programmes 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 CDA-AMC review report(s).

EMA PRIME: priority medicines

PRIME is a scheme run by the EMA 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.

MHRA - 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 by the centralised procedure when evaluating an application for a Great Britain marketing authorisation.

MHRA - International Recognition Procedure (IRP)

The International Recognition Procedure (IRP) is a regulatory route introduced by the UK's MHRA on 1 January 2024, allowing marketing authorisation applications in the UK to rely on prior approvals from trusted reference regulators (such as the FDA, EMA, Health Canada, etc.). It aims to streamline the authorisation process by enabling a targeted MHRA assessment while maintaining regulatory independence. IRP has replaced the ECDRP.

NICE - Managed access agreement (MAA)

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.

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 CDA-AMC review process for drugs for rare diseases but in March 2016, the standard HTA recommendation framework was revised to make special consideration for these drugs. Note: The regulatory agency in Canada (Health Canada) does 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 Quality-Adjusted Life Year (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:** Since 1st July 2021, HAS can evaluate and authorise medicines that are requested for coverage under the "early access" provision. "Early access" is a mechanism that allows patients to benefit on an exceptional and temporary basis from certain drugs not authorised 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 authorisation. In this scenario, the French National Agency for Medicines and Health Products Safety (ANSM) must assent to its efficacy and safety based on the results of therapeutic trials before HAS makes a decision.
Germany	For orphan drugs, additional therapeutic benefit is considered to be proven at marketing authorisation as long as the annual statutory health insurance (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 the multi-criteria decision analysis (MCDA) method (Polityka Lekowa Państwa 2018–2022).
Scotland	**Orphan medicine:** A medicine with 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

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

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The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independent UK-based subsidiary of Clarivate plc. Its mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and health technology assessment (HTA) policies and processes.

CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science and to facilitate access to pharmaceutical products. It is governed and operated by Clarivate for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities, special projects and grants.

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