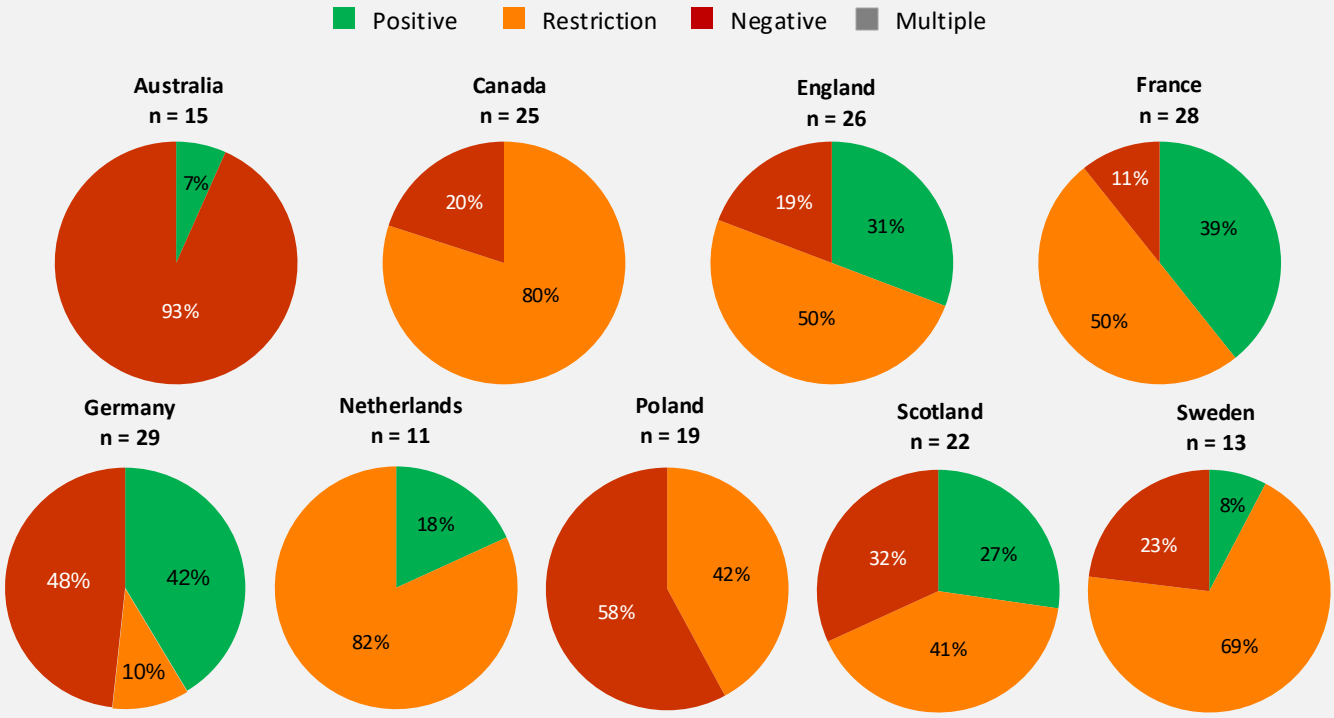
R&D BRIEFING 95

CIRS HTADock Project:

Review of HTA outcomes and timelines in Australia, Canada, Europe and the UK 2019-2023

Figure 1. First HTA recommendations: comparisons of new active substances (NASs) assessed across key jurisdictions in 2023



The 2024 Centre for Innovation in Regulatory Science (CIRS) HTADock Briefing centres on the primary performance metrics of nine health technology assessment (HTA) agencies, with a particular focus on how product characteristics impact the first HTA outcome and its timing.

EXPLORED IN THIS BRIEFING

- Synchronisation of regulatory and HTA outcomes
- HTA outcomes and timelines by regulatory orphan designation
- HTA outcomes and timelines by therapeutic area
- Expedited regulatory pathways and flexible HTA pathways
- HTA outcomes and timelines by conditional regulatory pathways
- International rollout of new active substances

INTRODUCTION

In 2017, CIRS launched the HTADock project as part of its 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 year, the HTADock briefing analyses publicly available data on NASs appraised from 2019 to 2023 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) Canada's Drug Agency (CDA) (formerly Canada's Drug and Health Technology Agency (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) Zorginstituut Nederland (ZIN), (8) the Scottish Medicines Consortium (SMC) and (9) the Swedish Tandvårds & läkemedelsförmånsverket (TLV).

The HTADock study will release three briefings between 2024 and early 2025, with this document being the first in the series. The subsequent sections of this briefing provide a thorough examination of the current HTA landscape in Australia, Canada, Europe, and the UK. The second and third briefings will focus regionally on Australia-Canada-UK and Europe, respectively.

The insights derived from this research form an essential component of CIRS's ongoing commitment to advancing regulatory and HTA policies and processes.

CONTENT

HTADock Methodology

The data on individual NASs appraised by HTA agencies between 2019 and 2023 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 CDA	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	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

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
CDA AMC	Reimburse	Reimburse with conditions	Recommendation for reimbursement	Do not reimburse
England NICE	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 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
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 R&D 95

In 2023, Germany showed the highest number of HTA recommendations across the studied jurisdictions (**Figure 1**). A decrease was observed in the number of HTA recommendations in 2023 compared to the average between 2019 and 2022 in Australia, Canada, France, Germany, the Netherlands and Sweden **(Figure 2).**

Australia presented the shortest median rollout time from regulatory submission to the first HTA recommendation in 2023, which is consistent due to the committee meeting frequency, while Germany maintained the highest consistency in rollout times from 2019 to 2023 (**Figure 3**). Poland presented the shortest median HTA appraisal time for HTA recommendations between 2021 and 2023 (81 days) (Figure 5), but a prolonged overall rollout time delayed the time of HTA recommendation.

In 2022 and 2023., Poland saw a notable increase in the time from regulatory approval to HTA recommendation for products with a regulatory orphan designation compared to previous years, a trend similarly observed in Sweden when comparing 2021, 2022, and 2023 with prior years (Figure 10).

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 country between 2019-2023, with Australia demonstrating the fastest median rollout time from regulatory submission to the 1st HTA outcome for all four areas (**Figure 13**).

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**).

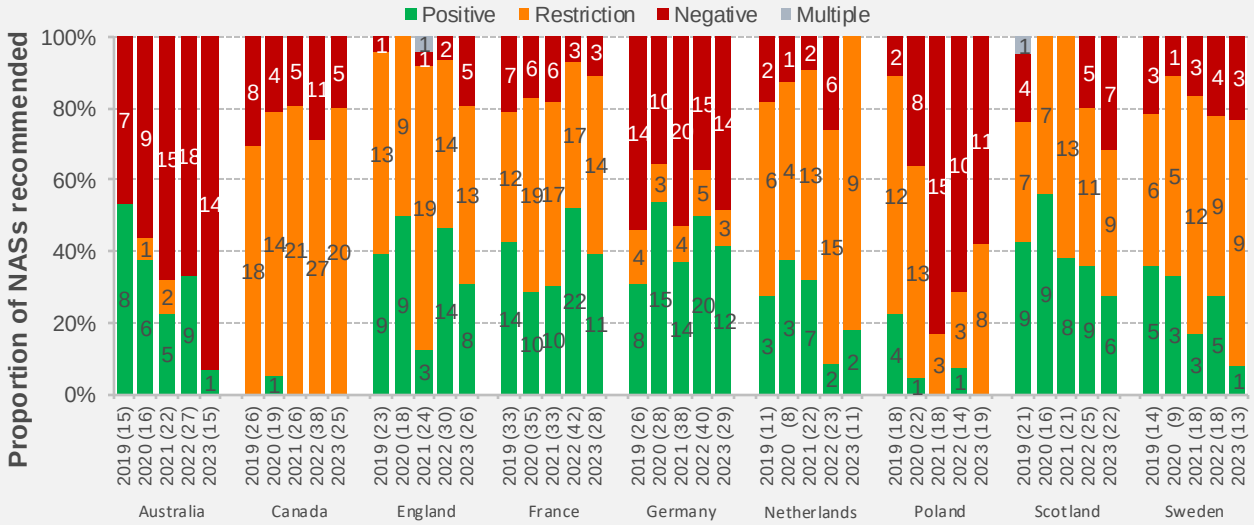
HTA agencies are using flexible HTA approaches to meet the demand for expedited patient access. While the rationale and criteria for these flexible processes vary among HTA agencies, their overarching goal is to enhance capacity and facilitate more efficient decision making in public health (**Figure 18**).

NASs assessed under a conditional regulatory pathway generally displayed a similar or longer median rollout time compared 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 19**). This discrepancy could be influenced by a higher percentage of conditional products undergoing parallel submission compared to non-conditional products.

Between 2019 and 2023, 10 NASs received HTA recommendations in all 9 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 both companies' submission strategies and regulatory and HTA review times (**Figures 21 and 22**)

Overview of new drug recommendations

Figure 2. First HTA recommendation comparison across key jurisdiction by year of HTA recommendation 2019-2023



Year of first HTA recommendation

n = number of NASs

In 2023, Germany showed the highest number of HTA recommendations across the studied jurisdictions.

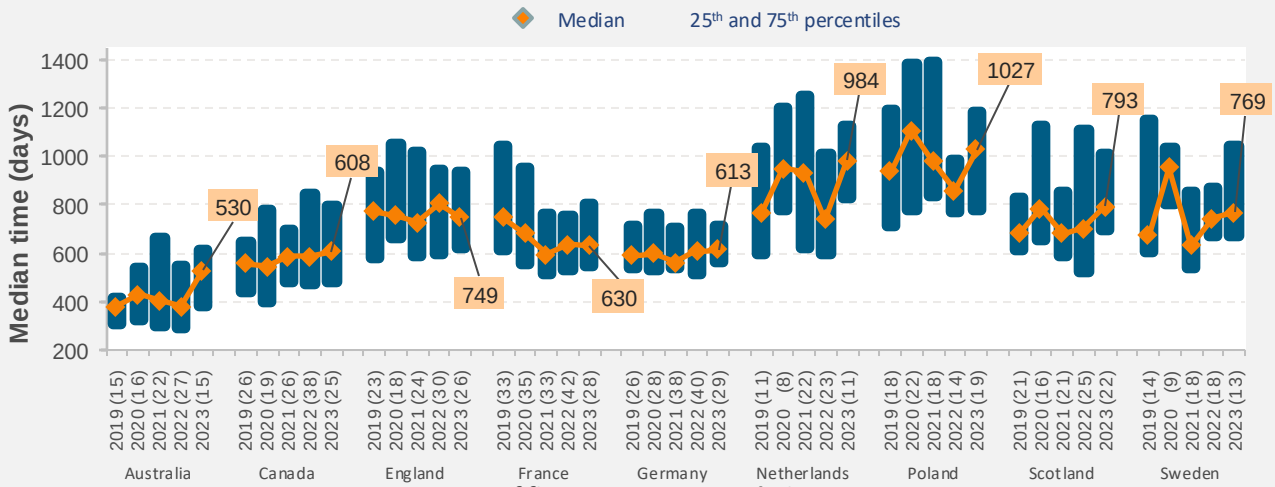
In 2023, Germany appraised the highest number of NASs (n=29), followed by France (n=28), England (n=26), Canada (n=25), Scotland (n=22), Poland (n=19), Australia (n=15), Sweden (n=13) and Netherlands (n=11) (**Figure 1**). The Netherlands presented the highest proportion of positive/positive with restrictions recommendations for NASs appraised by HTA agencies in 2023 (100%).

A decrease was observed in the number of HTA recommendations in 2023 compared to the average between 2019 and 2022 for Australia, Canada, France, Germany, the Netherlands and Sweden (**Figure 2**). The comparative numbers for 2019-2022 and 2023 in each country are as follows: Australia: 20 vs 15, Canada: 27 vs 25, England: 24 vs 26, France: 36 vs 28, Germany: 33 vs 29, Netherlands: 16 vs 11, Poland: 18 vs 19, Scotland: 21 vs 22 and Sweden: 15 vs 13, respectively. This could be influenced partly on a lower number of NASs approved by EMA in 2023 compared to previous years (please, see CIRS RD Briefing 93).

Australia had the shortest median rollout time from regulatory submission to the first HTA recommendation in 2023, while Germany maintained the highest consistency in rollout times from 2019 to 2023.

In 2023, Australia showed the shortest median rollout time from regulatory submission to the first HTA recommendation, completing the process in 530 days (**Figure 3**). This was followed by Canada, Germany and France, which required 608, 613 and 630 days, respectively, to reach the first HTA recommendation. Germany showed the highest consistency in the median time to HTA recommendation over the years 2019-2023, with an overall standard deviation for the median rollout time of ±20 days. Interestingly, there has been a general increase in the time to HTA recommendation in all jurisdictions, except for England and France. Comparing 2022 to 2023, the time to recommendation are: Australia: 379 vs 530 days, Canada: 585 vs 608, England: 806 vs 749, France: 636 vs 630, Germany: 612 vs 613, Netherlands: 739 vs 984, Poland: 860 vs 1027, Scotland: 701 vs 793 and Sweden: 744 vs 769, respectively.

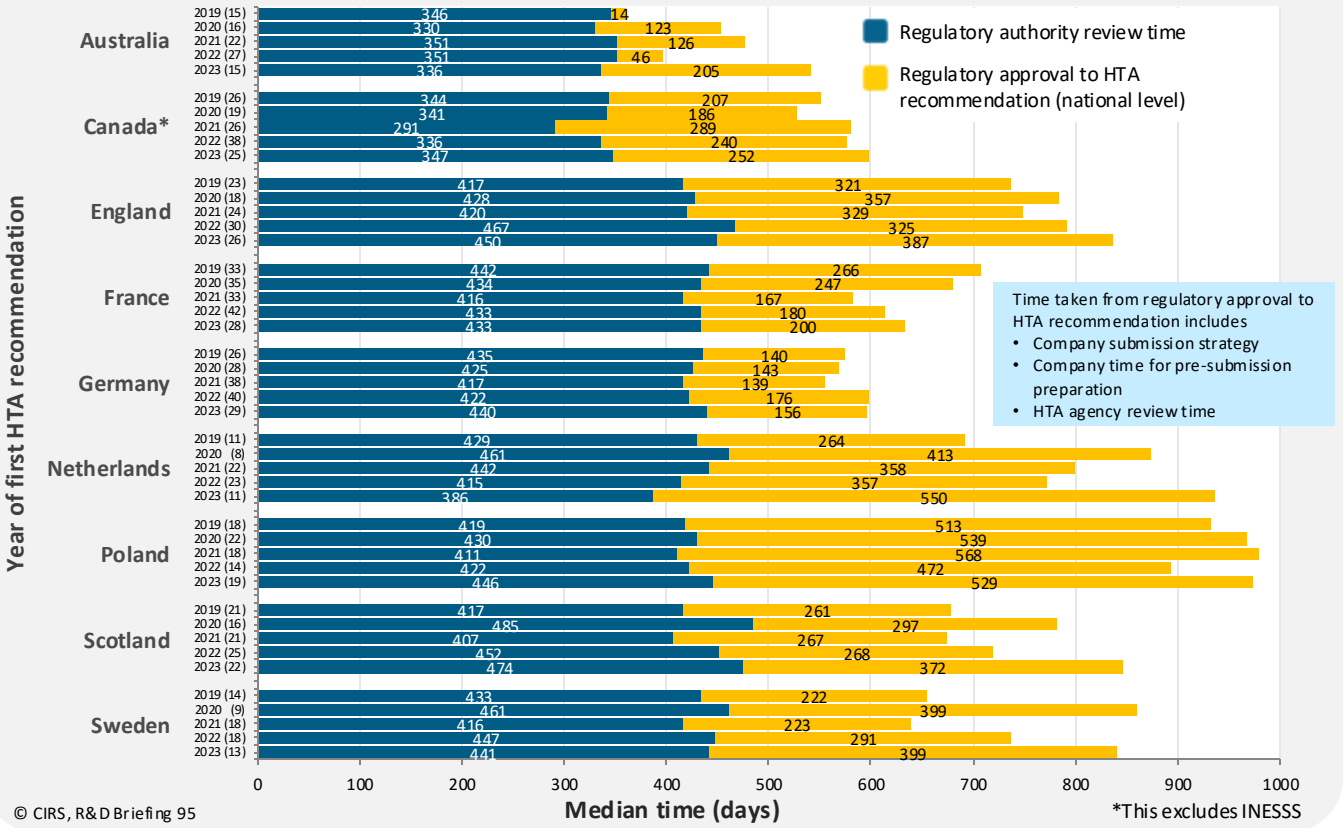
Figure 3. Time taken from regulatory submission to HTA recommendation by year of HTA recommendation 2019-2023



Year of first HTA recommendation

SYNCHRONISATION OF REGULATORY AND HTA OUTCOMES

Figure 4. Breakdown of rollout time across key jurisdictions in 2019-2023



Germany demonstrated the fastest median rollout timeline from regulatory approval to HTA recommendation in 2023.

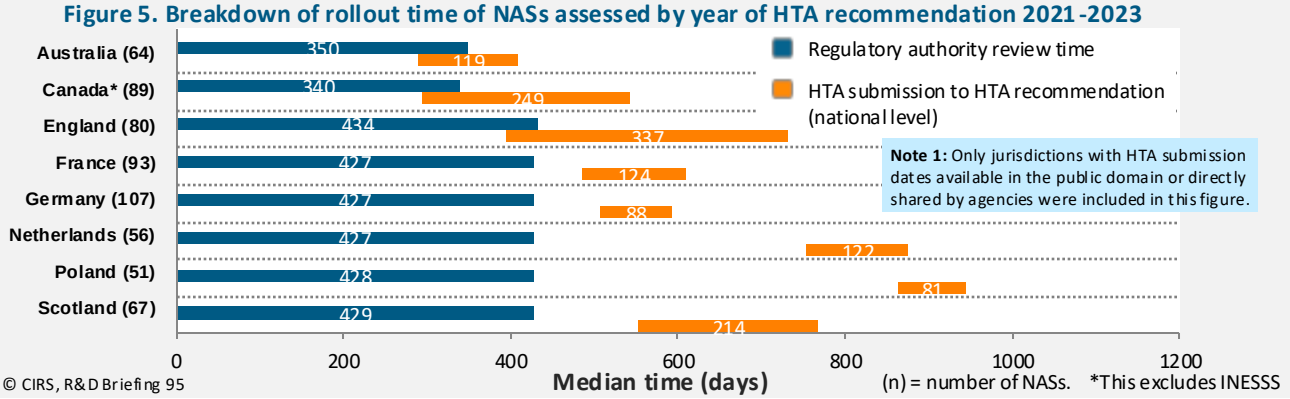
In 2023, Germany exhibited the swiftest rollout duration from regulatory approval to HTA recommendation, achieving this milestone in just 156 days (**Figure 4**). This timeframe maintains consistency with previous years, underscoring Germany's predictable timeline for HTA recommendations. The time taken from regulatory approval to HTA outcome can be attributed to company submission strategy, company time for pre-submission preparation and HTA agency review time. Interestingly, the median time taken from regulatory approval to HTA recommendations in 2023 showed an increase across most jurisdictions compared to 2022, except for Germany: Australia (205 days in 2023 vs 46 days in 2022), Canada (252 vs 240), England (387 vs 325), France (200 vs 180), Germany (156 vs 176), the Netherlands (550 vs 357), Poland (529 vs 472), Scotland (372 vs 268), and Sweden (399 vs 291).

Poland exhibited the faster median HTA review time for HTA recommendations between 2021 and 2023.

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.

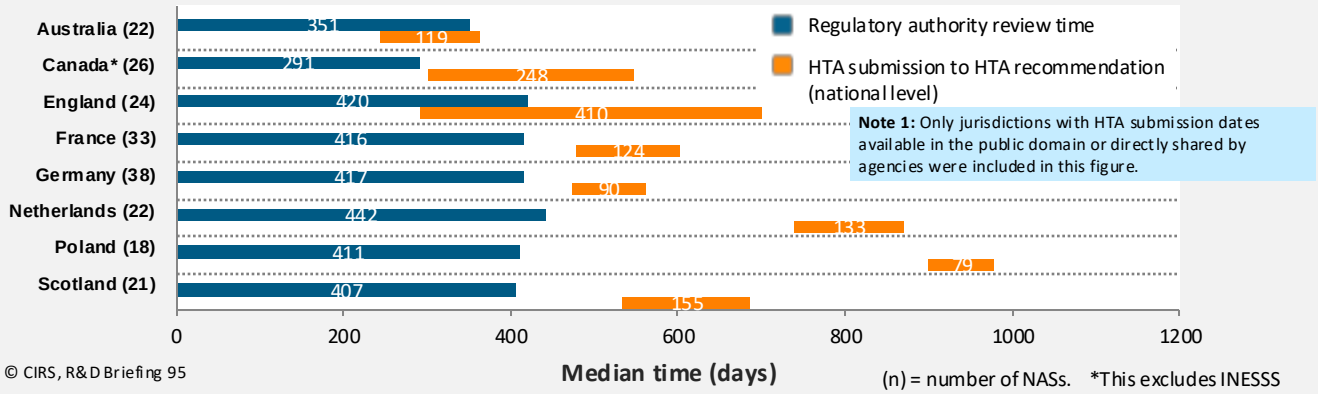
Among the studied jurisdictions, Poland presented the shortest median HTA appraisal time for HTA recommendations between 2021 and 2023 (81 days) (**Figure 5**). However, this expedited process was counterbalanced by a prolonged overall rollout time. This delay could be attributed to the longer gap between regulatory approval and HTA submission (the difference between the median time to regulatory approval and the median time to start of HTA review was 435 days). A similar scenario was observed in the Netherlands (327 days).

Figure 5. Breakdown of rollout time of NASs assessed by year of HTA recommendation 2021-2023



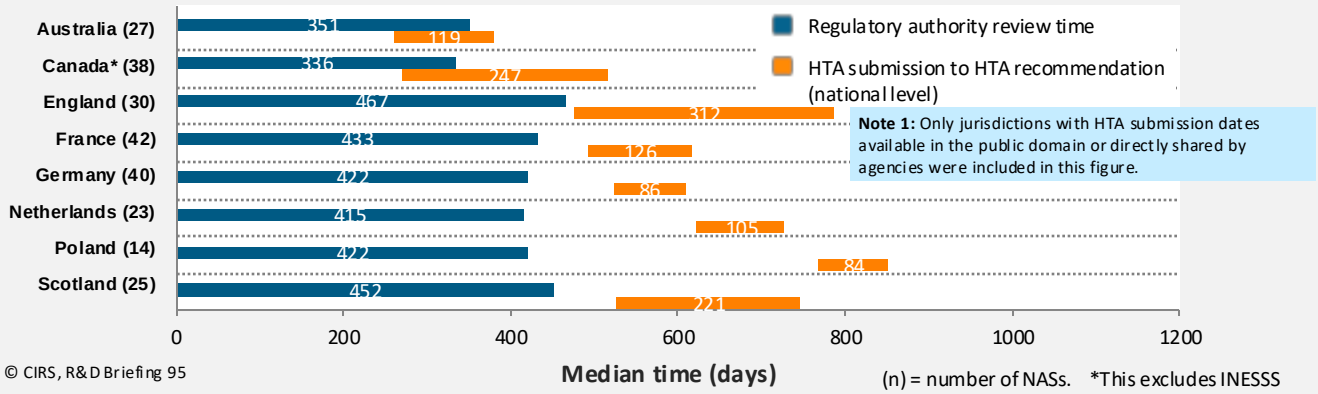
SYNCHRONISATION OF REGULATORY AND HTA OUTCOMES (CONT.)

Figure 6. Breakdown of rollout time of NASs assessed by year of HTA recommendation 2021



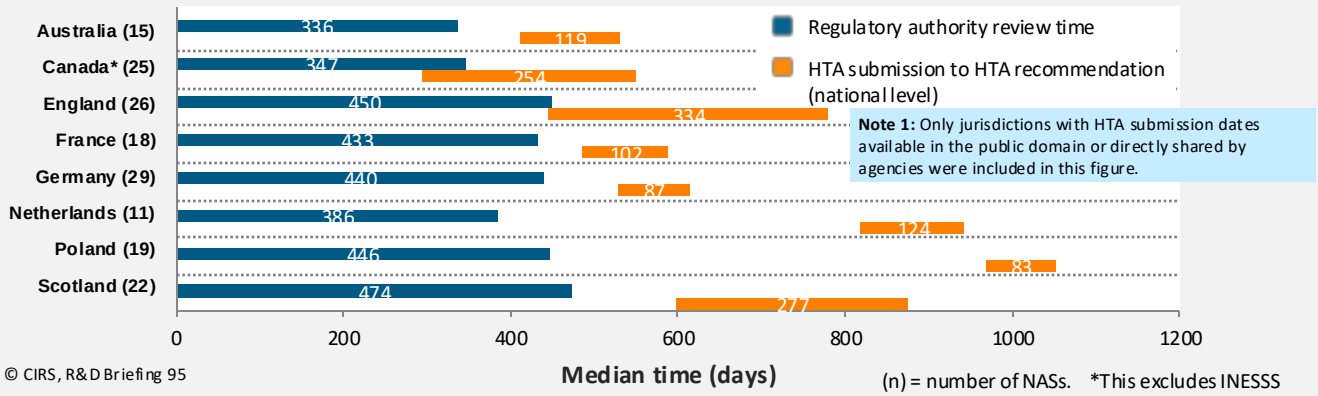
(n) = number of NASs. *This excludes INESSS

Figure 7. Breakdown of rollout time of NASs assessed by year of HTA recommendation 2022



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

Figure 8. Breakdown of rollout time of NASs assessed by year of HTA recommendation 2023



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

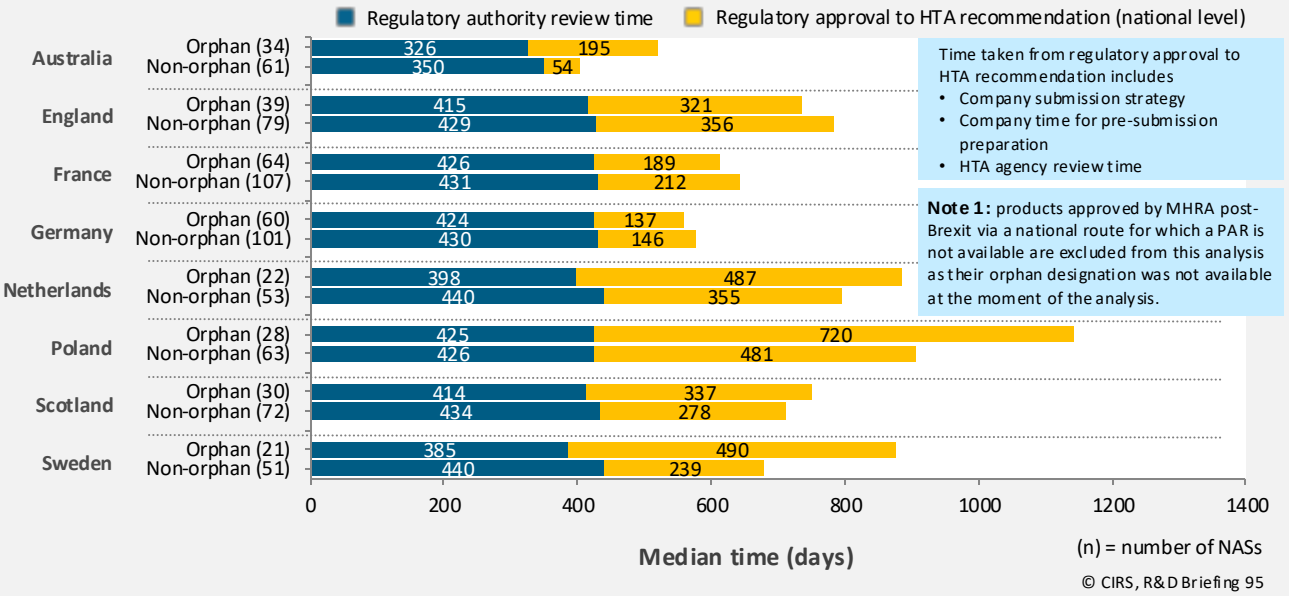
In 2023, Australia's HTA review process started later than in previous years, indicating a shift away from parallel regulatory/HTA reviews.

Continuing the analysis presented in **Figure 5**, a subsequent investigation explored a breakdown of the rollout times for different jurisdictions by the year of HTA recommendation from 2021 to 2023, as illustrated in **Figures 6, 7, and 8**. Notably, a shift in the trend of parallel regulatory and HTA processes was observed for Australia in 2023, contrasting with the preceding years of 2021 and 2022. Specifically, the overlap of the median regulatory and HTA review times was 106 and 91 days in 2021 and 2022, respectively. However, in 2023, the median time from regulatory submission to HTA submission was 75 days longer than the regulatory review process. This finding suggests a reduced use of the TGA/Parallel review process in 2023 compared to previous years.

Analysing the breakdown of rollout time across years, the results indicated an increase in the HTA submission gap for Poland in 2023 compared to previous years. Specifically, the difference between the median time to regulatory approval and the median time to HTA submission was 523 days in 2023, compared to 346 days in 2022 and 489 days in 2021.

CHARACTERISTICS: REGULATORY ORPHAN DESIGNATION

Figure 9. Breakdown of rollout time of NASs reviewed by HTA in 2019-2023, by regulatory orphan designation



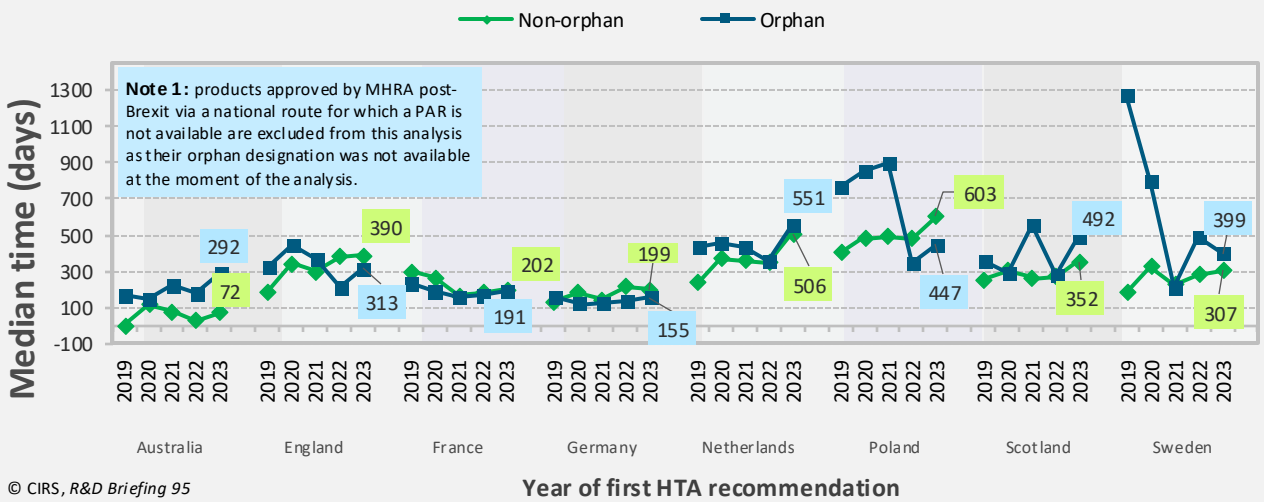
Products with regulatory orphan designations exhibited shorter median regulatory review times across all jurisdictions vs to non-orphan. However, in some jurisdictions, longer median time from regulatory approval to HTA recommendation of orphan products led to a longer time to HTA recommendation.

Regulatory orphan designations are employed by agencies such as the TGA in Australia, the EMA in Europe, and the MHRA in the UK to expedite the approval of drugs aimed at treating serious illnesses or addressing unmet medical needs. In the cases of England and Scotland, if a product was approved via the European Commission Decision Reliance Procedure (ECDRP), 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 noteworthy that Health Canada (HC) does not currently implement an orphan drug policy.

The findings revealed that in all jurisdictions, products with regulatory orphan designations had slightly shorter median regulatory review times compared to non-orphan products (**Figure 9**). However, in jurisdictions such as Australia, the Netherlands, Poland, Scotland, and Sweden, the median time from regulatory approval to HTA recommendation was longer for orphan products. The latter resulted in longer median rollout times for orphan products in these countries. It is important to highlight that the time taken from regulatory approval to HTA recommendation includes companies' submission strategy and HTA review time.

Figure 10 provides a detailed breakdown of the time from regulatory approval to the first HTA recommendation, segmented by the year of HTA recommendation. A notable decrease was observed in the time to recommendation for orphan products in Poland in 2022 and 2023 compared to previous years. A similar trend was observed for Sweden comparing 2021, 2022 and 2023 with previous years. In Australia, non-orphan products typically received HTA recommendations more rapidly than orphan products. This trend may suggest that companies are prepared for expedited submissions for non-orphan products, potentially due to the reduced complexity of their dossiers.

Figure 10. Time taken from regulatory approval to HTA recommendation by year of HTA recommendation and regulatory orphan designation (HTA recommendations between 2019-2023)



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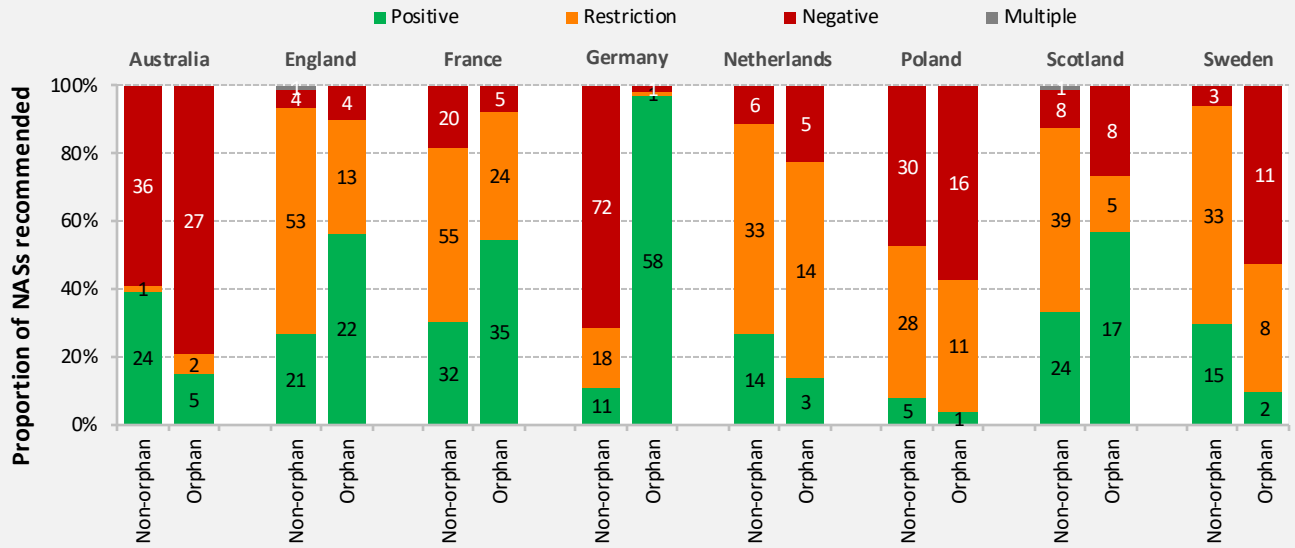
CHARACTERISTICS: REGULATORY ORPHAN DESIGNATION (CONT.)

Figure 11. First HTA recommendation comparison across key jurisdictions in 2019-2023, by regulatory orphan designation



(n) = number of NASs

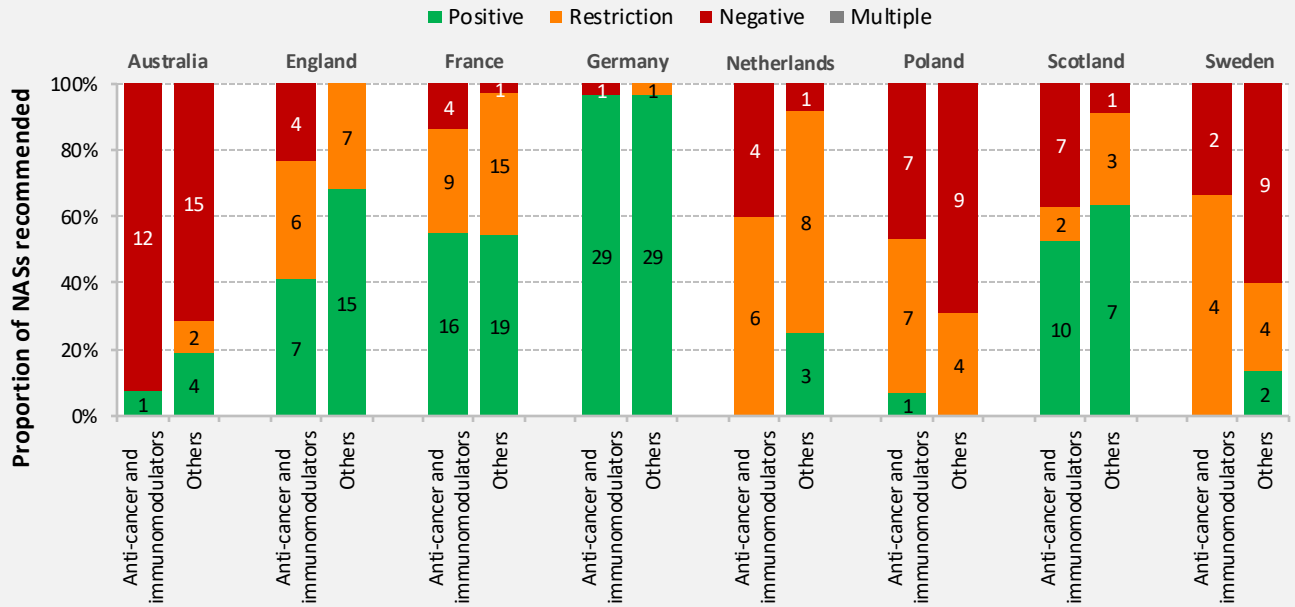
Note 1: products approved by MHRA post-Brexit via a national route for which a PAR is not available are excluded from this analysis as their orphan designation was not available at the moment of the analysis.

Our study showed that non-orphan products exhibited a higher percentage of positive or positive with restrictions recommendations across all jurisdictions, with the exceptions of France and Germany (**Figure 11**).

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 authorization. However, the results in **Figure 11** show one NAS with a positive with restrictions recommendation and one with a negative recommendation. This discrepancy arises because IQWiG evaluated these two compounds as non-orphan drugs, which indicates different criteria in defining orphan products between EMA and IQWIG.

Figure 12 also provides a detailed analysis of the type of HTA recommendations for orphan products, categorised by therapeutic area. The proportion of the different types of HTA recommendations varied across jurisdictions.

Figure 12. First HTA recommendation comparison of orphan products across key jurisdictions in 2019-2023, comparing anti-cancer & immunomodulators vs other therapeutic area

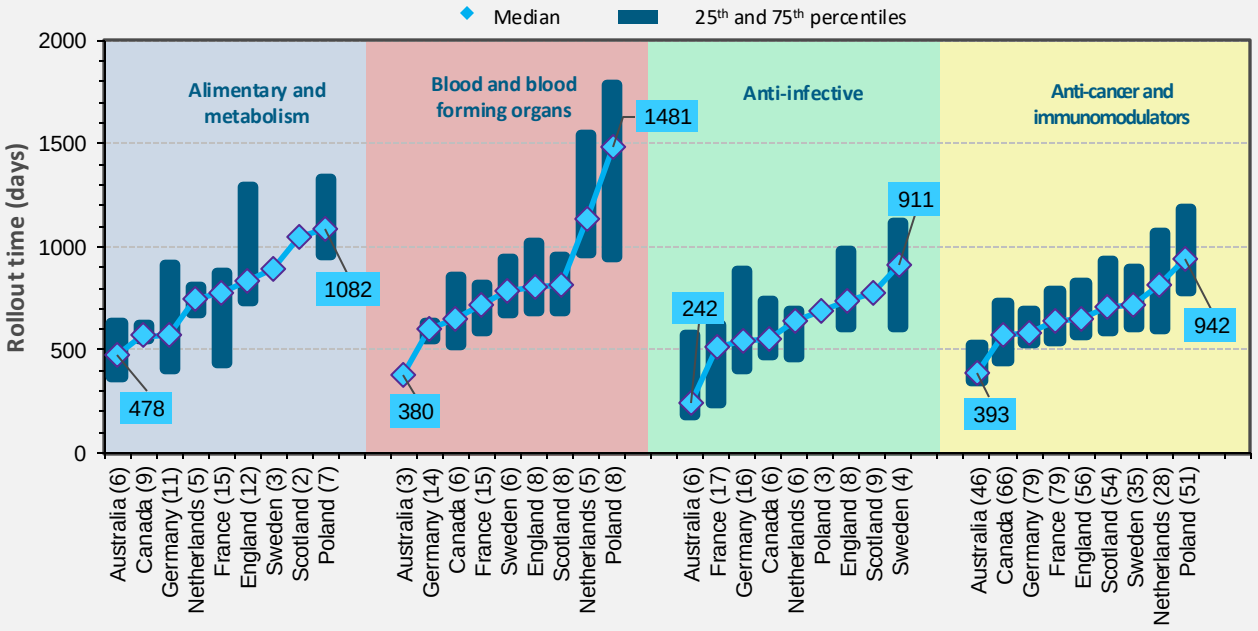


(n) = number of NASs

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

CHARACTERISTICS: THERAPEUTIC AREA

Figure 13. Time taken from regulatory submission to 1st HTA recommendation in 2019-2023, by top therapeutic area



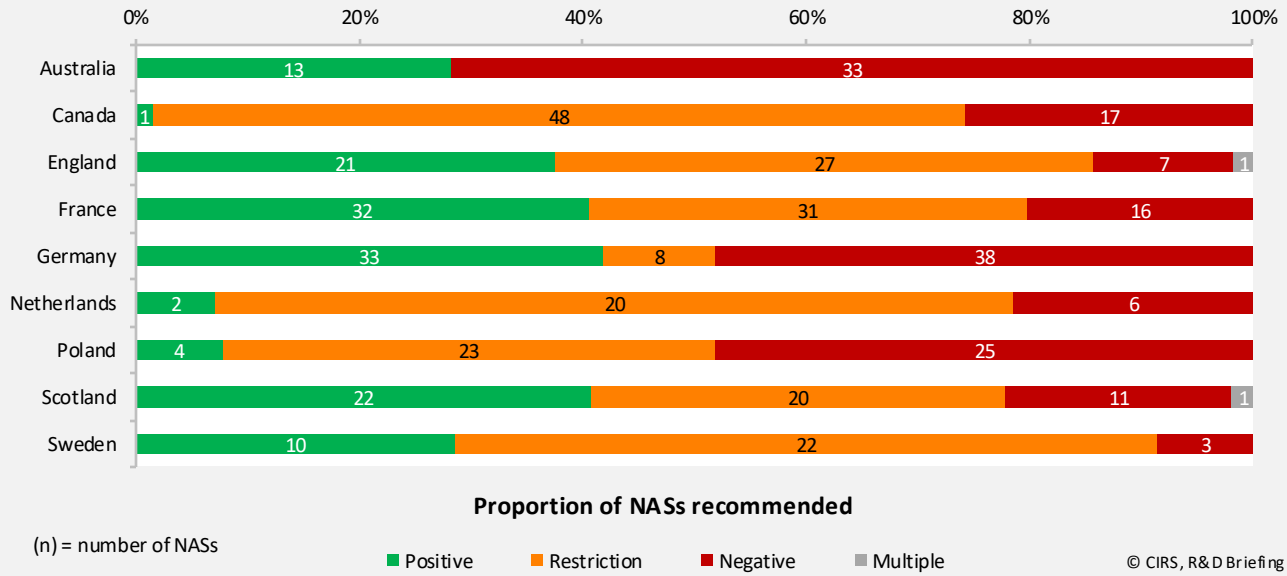
(n) = number of NASs

The top four therapeutic areas constituted 67% of all products assessed by HTA in at least one country between 2019-2023, with Australia demonstrating the fastest median rollout time from regulatory submission to the 1st HTA outcome for all four areas.

The top four therapeutic areas made up 67% (175/261) of the products assessed by HTA in at least one country between 2019-2023, with anti-cancer and immunomodulators making up 63% (110/175) of the top therapeutic areas (**Figure 13**). Australia was the fastest for all four therapy areas in terms of median rollout time from regulatory submission to HTA outcome, while Poland was the slowest country, except for "anti-infectives", where Scotland showed the longest 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 91% and 86% of the recommendations, respectively (**Figure 14**).

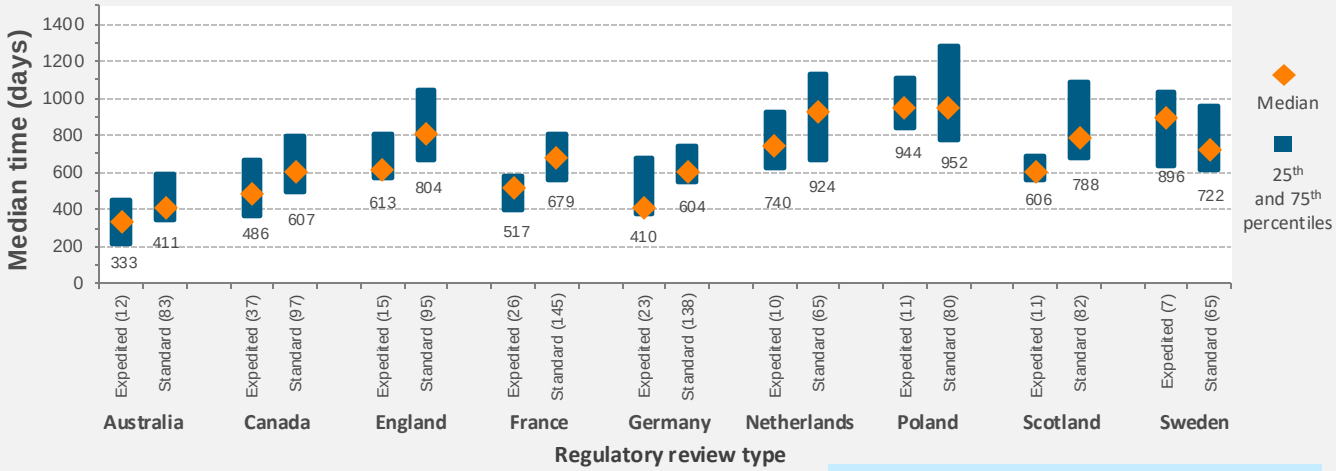
Figure 14. 1st HTA Recommendation for anti-cancer and immunomodulators (2019-2023)



(n) = number of NASs

CHARACTERISTICS: USE OF EXPEDITED AND FLEXIBLE PATHWAYS

Figure 15. Time taken from regulatory submission to HTA recommendation (2019-2023) by regulatory review type



Note 1: 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

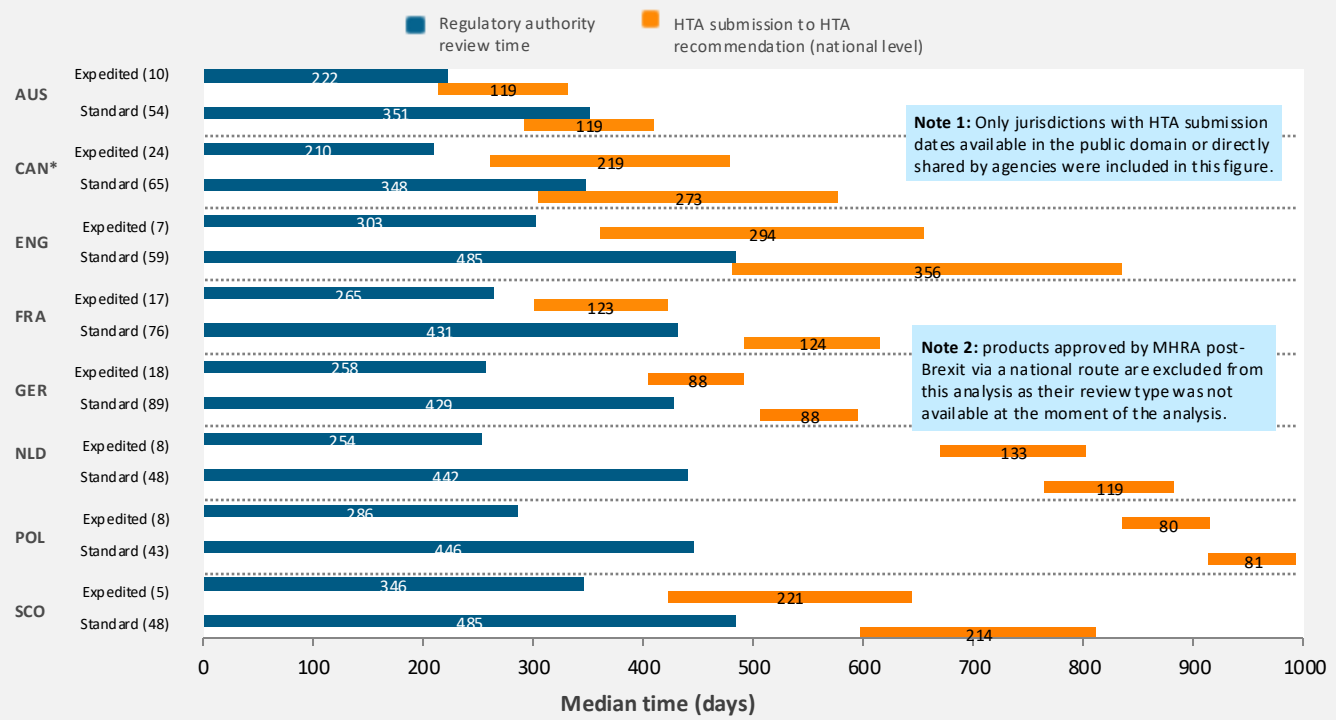
The use of expedited regulatory pathways shortened the median rollout time in all jurisdictions apart from Sweden.

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 (**Figure 16**). Additionally, for all jurisdictions except Scotland and France, the submission gap for expedited products was longer than for those under standard review (Australia: -8 vs -59 days, Canada: 51 vs -43 days, England: 59 vs -5 days, France: 35 vs 61 days, Germany: 147 vs 78 days, Netherlands: 416 vs 322 days, Poland: 550 vs 467 days, and Scotland: 77 vs 113 days) (**Figure 16**)

Figure 16. Breakdown of rollout time of NASs assessed 2021-2023, by regulatory review pathway



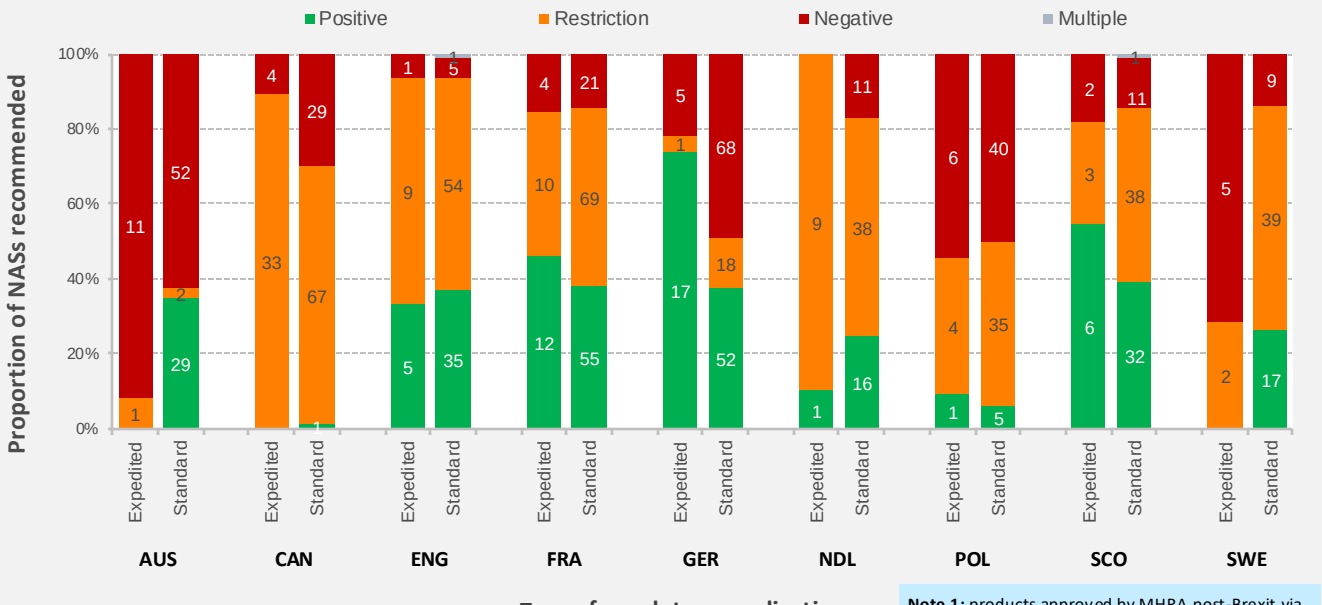
Note 1: Only jurisdictions with HTA submission dates available in the public domain or directly shared by agencies were included in this figure.

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.

 *This excludes INESSS (n) = number of NASs

CHARACTERISTICS: USE OF EXPEDITED AND FLEXIBLE PATHWAYS (CONT.)

Figure 17. First HTA recommendation type across key jurisdictions by review type 2019-2023



(n) = number of NASs

Note 1: 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.

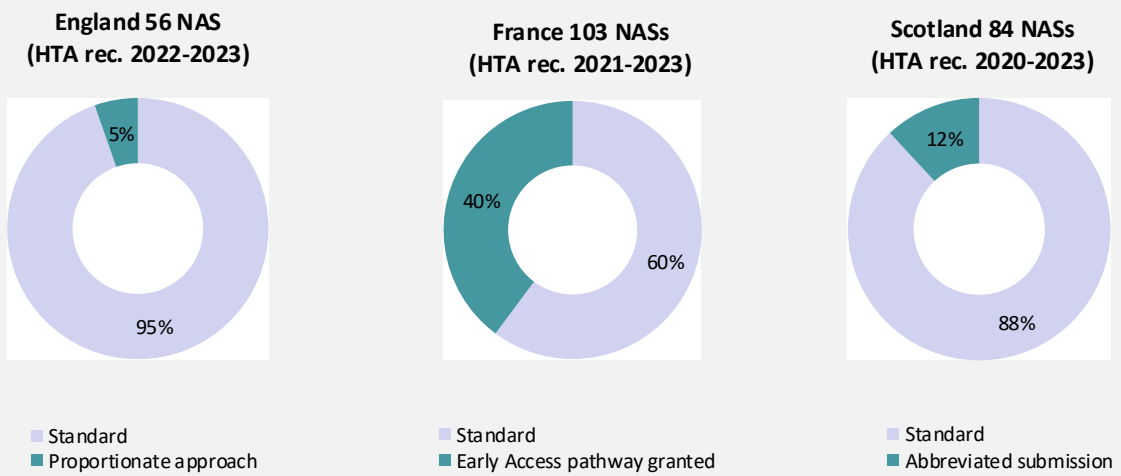
The proportion of positive or positive with restrictions recommendations for products that underwent an expedited review process varied among different jurisdictions.

In several countries, including Canada, Germany, 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 17**). In Australia, only 8% of the products reviewed through an expedited pathway achieved a positive or positive with restrictions as a first HTA recommendation.

Different jurisdictions have implemented various flexible and adaptive HTA process. In England, the Proportionate Approach was introduced in 2022. This approach recognizes 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 authorization 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.

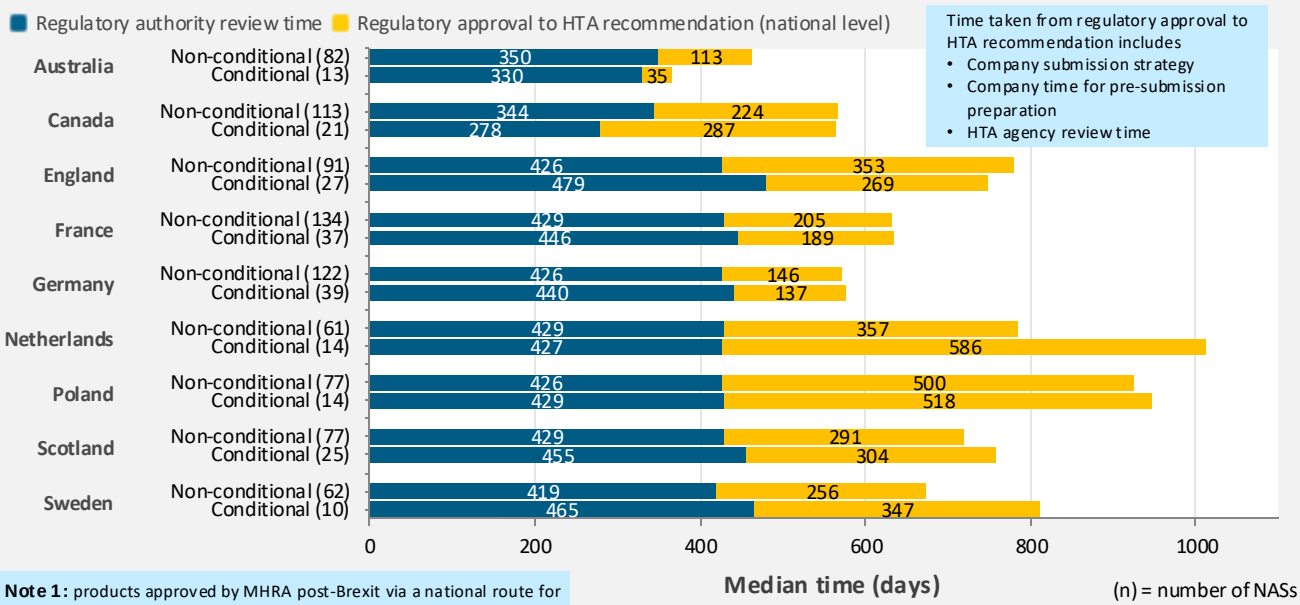
The results indicate that HTA agencies are using these flexible approaches to meet the demand for expedited patient access (**Figure 18**). While the rationale and criteria for these flexible processes vary among HTA agencies, their overarching goal is to enhance capacity and facilitate more efficient decision-making in public health.

Figure 18. Special HTA process: comparison of HTA flexible pathways



CHARACTERISTICS: CONDITIONAL REGULATORY APPROVAL

Figure 19. Breakdown of rollout time of NASs assessed 2019-2023, by regulatory approval conditions



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

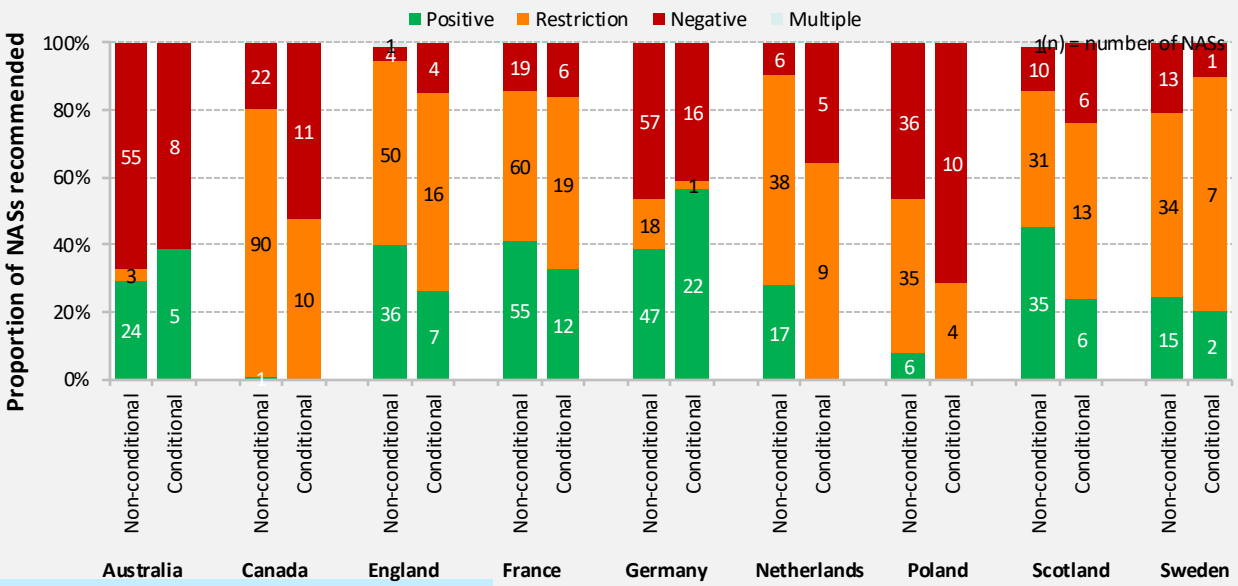
NASs approved through a conditional regulatory pathway generally exhibited a longer median rollout time to HTA recommendation.

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, Table 5).

In France, Germany, the Netherlands, Poland, Scotland, and Sweden, the median time from regulatory approval to HTA recommendation was longer for conditional NASs. The latter resulted in NASs assessed under a conditional regulatory pathway generally displaying a similar or longer median rollout time compared to those evaluated via a non-conditional pathway. Notably, Australia, Canada and England emerged as exceptions to this trend, presenting a shorter median rollout time for conditional products compared to non-conditional ones (**Figure 19**).

The findings in **Figure 20** did not suggest a correlation between a regulatory conditional approval and the likelihood of obtaining an optimal or non-optimal HTA recommendation.

Figure 20. Outcome of 1st HTA recommendation for NASs assessed 2019-2023, by regulatory approval conditions



Note 1: 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.

COMMON COMPOUNDS ACROSS ALL JURISDICTIONS

Figure 21. First HTA recommendation comparison of common NASs (n=10) reviewed by 9 agencies (HTA recommendations between 2019-2023)

Generic name	Australia	Canada	England	France	Germany	Netherlands	Poland	Scotland	Sweden
Acalabrutinib	1	2	5	6	3	9	8	7	4
Darolutamide	2	1	6	4	3	9	7	5	8
Finerenone	2	7	8	6	9	1	4	5	3
Fremanezumab	5	8	6	7	1	9	2	4	3
Galcanezumab	2	9	6	3	1	8	5	7	4
Lanadelumab	3	6	4	2	1	9	7	5	8
Ozanimod	1	9	6	4	2	3	7	5	8
Pegcetacoplan	3	8	2	1	6	7	9	5	4
Risdiplam	1	3	6	4	2	9	7	8	5
Tucatinib	1	4	8	2	3	6	9	5	7

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

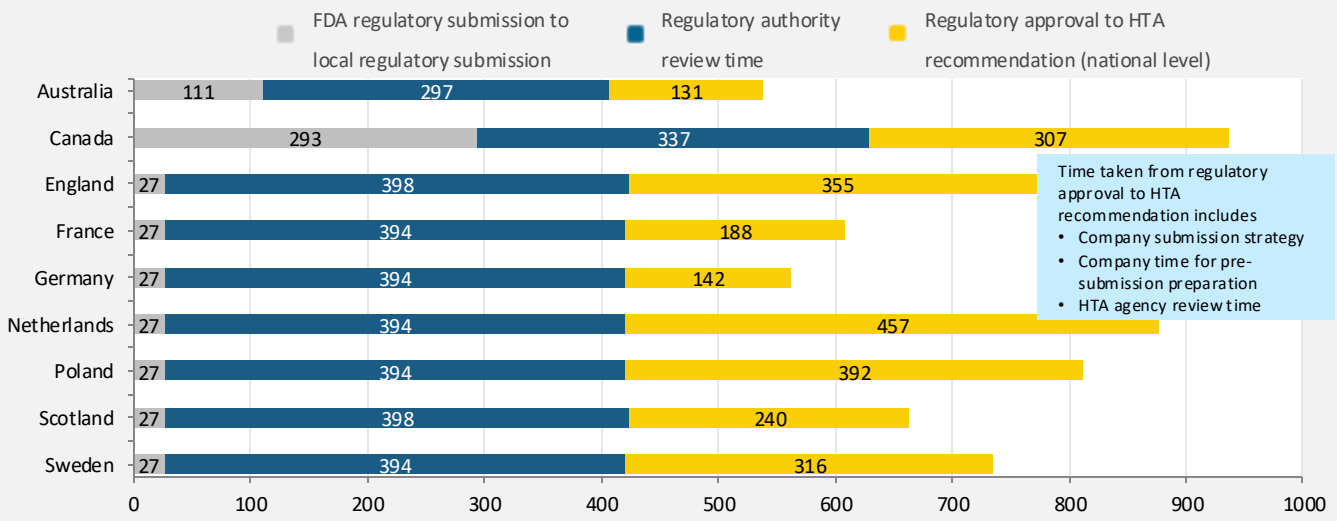
Positive Restriction Negative Multiple

Common NASs received inconsistent HTA recommendations and presented varied timing across nine jurisdictions between 2019 and 2023, leading to potential disparities in patient access to new treatments.

Our study identified 10 NASs that received an HTA recommendation in all nine studied jurisdictions between 2019 and 2023, identified as common compounds, with color-coding by the type of HTA recommendation and inclusion of the timing of the HTA recommendation (**Figure 21**). The data indicate that the same 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, influenced by both companies' submission strategies and regulatory and HTA review times, contributing to unequal access to new treatments as patients in certain regions benefit from earlier availability of therapies.

To further explore the timelines of these common compounds, **Figure 22** presents a breakdown of their rollout times across different jurisdictions, using the submission time to the U.S. Food and Drug Administration (FDA) as a reference point. The results indicate that companies generally prioritised submissions to the US, followed by European and UK countries, with a median submission gap of 27 and 33 days, respectively. Following these, Australia and Canada had median times of 111 days and 293 days, respectively. While the regulatory times were found to be similar, variations in HTA and regulatory submission gaps contributed to differences in rollout times.

Figure 22. Breakdown of rollout time of common NASs (n=10) reviewed by 9 agencies (HTA recommendations between 2019-2023)



Note 1: for England and Scotland, products approved via ECDRP utilise EMA submission date and MHRA approval date.

(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 (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 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.

CDA - 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 CDA 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 CDA 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

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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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