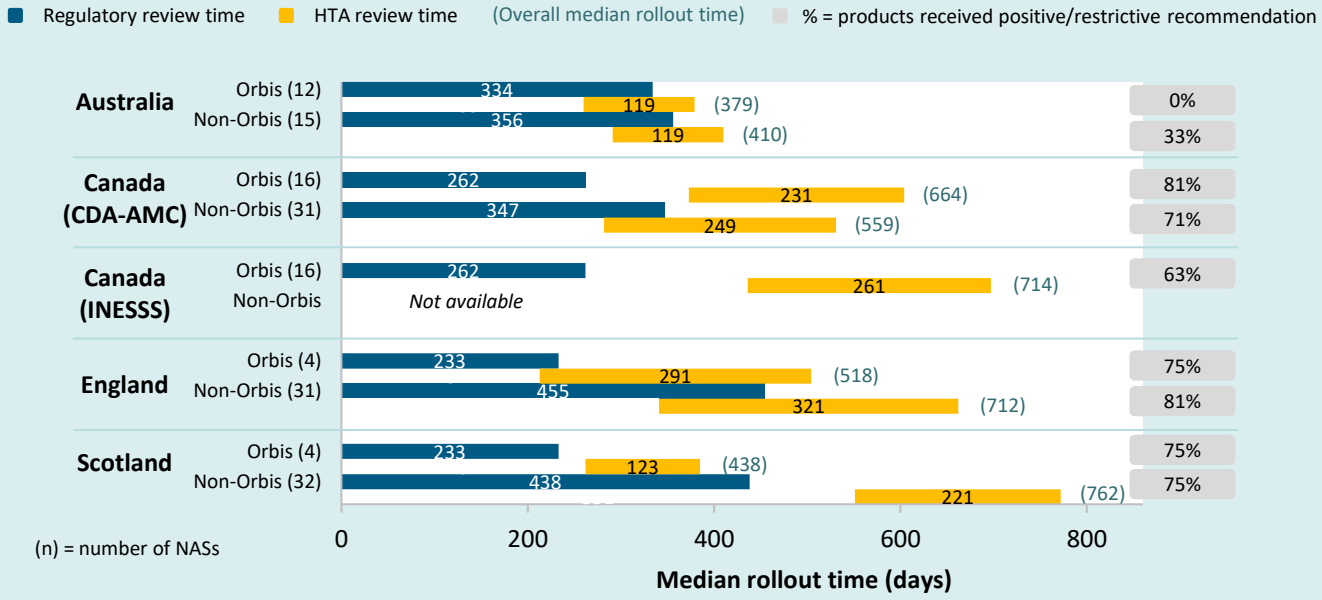
R&D BRIEFING 96

CIRS HTADock Project

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

Figure 1. Breakdown of rollout time of oncology products approved by Orbis vs Non- Orbis route, in Australia, Canada and the UK (1st HTA recommendation between 2021-2023)



Note 1: For Canada (INESSS), only ACCESS and Orbis products have been included in this briefing.

Note 2: Non-Orbis products are defined as those products where their ATC code is equal to "L" (Antineoplastic and Immunomodulating Agents), "V09" (Diagnostic Radiopharmaceuticals) or "V10" (Therapeutic Radiopharmaceuticals) and are not part of the Orbis project.

The 2024 Centre for Innovation in Regulatory Science (CIRS) HTADock R&D Briefing 96 centres on the primary performance metrics of four 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

- **HTA outcomes and timelines of Project Orbis products**
- **HTA outcomes and timelines of Access Consortium products**
- **Comparison of common products appraised by 4 HTA agencies**
- **Pathways and timelines of orphan products**
- **Regulatory and HTA review sequence**
- **In-depth analysis of the HTA landscape in Australia, Canada, and the UK**

INTRODUCTION

In 2018, the Centre for Innovation in Regulatory Science (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 document is the second in a series of three briefings released in 2024. The first briefing is a broader exploration of the HTA landscape in Australia, Canada, Europe, and the UK. This briefing, HTADock 2, provides a more in-depth analysis of Australia, Canada and the UK, while the third briefing will focus on Europe.

CIRS has analysed publicly available data on new active substances (NASs) appraised between 2019 and 2023 by four HTA agencies: the Australian Pharmaceutical Benefits Advisory Committee (PBAC), Canada's Drug Agency (CDA-AMC) (formerly Canada's Drug and Health Technology Agency (CADTH)), the English National Institute for Health and Care Excellence (NICE), and the Scottish Medicines Consortium (SMC). The Institut national d'excellence en santé et en services sociaux (INESSS) was included in this briefing for analyses of the Access Consortium and Project Orbis. The Medical Services Advisory Committee (MSAC) was included for an analysis on TGA priority review.

Using a methodology outlined on page 3, the HTA recommendations in this report have been classified as positive, positive with restrictions or negative. The methodology page illustrates how the specific recommendations by the HTA systems are captured within this trichotomous categorisation. In cases where more than one HTA dossier was submitted by a company for the same drug based on different sub-indications within an approved regulatory label and the final HTA outcome for these individual sub-indications differed, the outcome was classified as multiple.

CONTENTS

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. Additionally, data from INESSS and MSAC were incorporated in the sections "Focus: Project Orbis", "Focus: Access Work-sharing Consortium", and "Features of Australia".

Regulatory and HTA process

	Regulatory submission	Regulatory approval	HTA submission	HTA Recommendation
Australia	Submission to TGA	Approval to 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	Submission to INESSS*	Notice sent to the Minister
England	Submission to MHRA/ EMA (ECDRP)	Approval issued by MHRA	Company evidence submission date	Technology appraisal guidance publication
Scotland	Submission to MHRA/ EMA (ECDRP)	Approval issued by MHRA	Submission to SMC*	The first statement of advice by SMC

*Not available from the public domain, provided directly by agencies.

The first HTA recommendations: Trichotomous categories

	Positive	Positive with restrictions	*Implication for "positive" or "positive with restrictions"*	Negative
Australia PBS	List	List with conditions	Listing in the Pharmaceutical Benefits Scheme	Do not list
Canada (CDA-AMC) CDA AMC	Reimburse	Reimburse with conditions	Recommendation for reimbursement	Do not reimburse
Canada (INESSS) INESSS	Recommended	Recommended + restrictions	Recommendation for reimbursement	Not recommended
England NICE National Institute for Health and Care Excellence	Recommended	Recommended + restrictions	NHS Implementation of NICE guidance	Not recommended
Scotland Scottish Medicines Consortium	Accepted for use within NHS Scotland	Accepted for restricted use within NHS Scotland	Accepted for use within NHS Scotland	Not recommended for use within NHS Scotland

KEY FINDINGS OF HTADOCK 2024 – BRIEFING 96

Between 2021 and 2023, 19 Orbis products received an HTA recommendation in at least one of the four studied countries: Australia, Canada, England, or Scotland. The most common category in Australia was Orbis type B, while in Canada (in both CDA-AMC and INESSS) it was type C (Table 1)

A total of 17 products were approved through the Access Consortium and received their first HTA recommendation in at least one of the four studied jurisdictions between 2019 and 2023 (Table 2). All studied jurisdictions demonstrated a shorter median regulatory review time for Access products compared to non-Access products (Figure 6); however, the overall median rollout time for Access versus non-Access products varied across jurisdictions.

Between 2019 and 2023, 40 NASs received HTA recommendations from PBAC, CDA-AMC, NICE, and SMC, with varied HTA recommendation types across agencies (Table 3). Despite NICE having the longest review time, its parallel submission strategy led to faster HTA recommendations, while SMC experienced delays primarily due to a longer company-driven submission gap (Figure 9).

Scotland's SMC is the only jurisdiction with a designated orphan pathway, with 68% of regulatory-approved orphan NASs with HTA recommendations between 2019 and 2023 undergoing this process (Figure 12). Other countries also utilise non-standard pathways for orphan products.

In 2023, the proportion of parallel submissions in Australia decreased compared to previous years, whereas Canada maintained a similar rate (Figure 15).

In Australia, between 2019 and 2023, out of the 44 NASs that have been listed on the PBS, 39% required more than one cycle of resubmission to PBAC for PBS listing (Figure 20).

From 2021 to 2023, the median overlap between regulatory and HTA reviews in Canada's parallel review process has decreased (Figure 27). Additionally, requests for reconsideration of CDA-AMC recommendations extended the timeline from draft to final recommendation (Figure 28).

In 2023, 73% and 64% of appraisals by NICE and SMC were approved under the European Commission Decision Reliance Procedure (ECDRP) route (Figure 29). The HTA review of ECDRP products exhibited a longer median review time compared to products evaluated through national pathways for both NICE and SMC, which may be related to the type of product undergoing the different regulatory review pathways.

FOCUS: PROJECT ORBIS

Table 1. 1st HTA recommendation (2021-2023) for NASs assessed in key jurisdictions approved via Project Orbis

Generic name	Australia	Canada (CDA-AMC)	Canada (INESSS)	England	Scotland
amivantamab	Orbis approved but no recommendation	(Orbis C) Standard, Conditional	(Orbis C) Standard, Conditional	(Orbis C) Review type and Conditional status unknown	Orbis approved but no recommendation
belzutifan	Orbis approved but HTA recommendation in 2024*	(Orbis B) Standard	(Orbis B) Standard	Orbis approved but HTA recommendation in 2024*	(Orbis B) Review type unknown
cedazuridine	(Orbis B) Standard	(Orbis A) Standard	(Orbis A) Standard	MHRA approved in 2023 and not part of Orbis	MHRA approved in 2023 and not part of Orbis
enfortumab vedotin	(Orbis C) Standard	(Orbis B) Expedited	(Orbis B) Expedited	MHRA approved in 2022 and not part of Orbis	MHRA approved in 2022 and not part of Orbis
lurbinectedin	Orbis approved but no recommendation	(Orbis C) Standard, Conditional	(Orbis C) Standard, Conditional	Not approved by MHRA	Not approved by MHRA
lutetium (177lu) vipivotide tetraxetan	TGA approved in 2024* and not part of Orbis	(Orbis C) Expedited	(Orbis C) Expedited	MHRA approved in 2022 and not part of Orbis	MHRA approved in 2022 and not part of Orbis
mobocertinib	(Orbis B) Standard, Conditional	Not approved by HC	Not approved by HC	MA withdrawn	MA withdrawn
nivolumab / relatlimab	(Orbis B) Standard	HC approved in 2023 but not part of Orbis	HC approved in 2023 but not part of Orbis	Orbis approved but HTA recommendation in 2024*	Orbis approved but HTA recommendation in 2024*
pralsetinib	Orbis approved but no recommendation	(Orbis C) Standard, Conditional	(Orbis C) Standard, Conditional	Approved via ECDRP	Approved via ECDRP
ripretinib	(Orbis A) Expedited	(Orbis A) Expedited	(Orbis A) Expedited	Approved via ECDRP	Approved via ECDRP
sacituzumab govitecan	(Orbis B) Expedited	(Orbis B) Expedited	(Orbis B) Expedited	(Orbis B) Review type unknown	(Orbis B) Review type unknown
selpercatinib	(Orbis C) Standard, Conditional	(Orbis C) Standard, Conditional	(Orbis C) Standard, Conditional	Transition**	Transition**
selumetinib	(Orbis C) Standard	(Orbis C) Standard	(Orbis C) Standard	Approved via ECDRP	Approved via ECDRP
sotorasib	(Orbis B) Standard, Conditional	Orbis approved but HTA recommendation in 2024*	Orbis approved but HTA recommendation in 2024*	(Orbis B) Review type unknown, Conditional	(Orbis B) Review type unknown, Conditional
tafasitamab	Orbis approved but no recommendation	(Orbis C) Standard, Conditional	(Orbis C) Standard, Conditional	Approved via ECDRP	Approved via ECDRP
tebentafusp	(Orbis B) Expedited	(Orbis B) Expedited	(Orbis B) Expedited	Orbis approved but no HTA recommendation	Orbis approved but no HTA recommendation
tepotinib	Orbis approved but no recommendation	(Orbis A) Standard, Conditional	(Orbis A) Standard, Conditional	(Orbis C) Review type unknown, Conditional	(Orbis C) Review type unknown, Conditional
trastuzumab deruxtecan	(Orbis C) Standard, Conditional	(Orbis C) Standard, Conditional	(Orbis C) Standard, Conditional	Transition**	Transition**
tucatinib	(Orbis B) Expedited	(Orbis A) Expedited	(Orbis A) Expedited	Transition**	Transition**

*Recommendation is out of scope of this briefing

** Products received an opinion from the Committee for Medicinal Products for Human Use (CHMP) in December 2020 and were subsequently granted marketing authorisation by the EMA in 2021 (Brexit commencing period)

Positive Restriction Negative

Between 2021 and 2023, 19 Orbis products received 1st HTA recommendations in Australia, Canada, England or Scotland.

Project Orbis, initiated by the US 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. Sponsors can also choose the number of POPs involved (with a minimum of two, including the FDA). Criteria for consideration includes but is not limited to high impact, clinically significant applications, that should generally qualify for priority review because of improvement in safety/efficacy.

There are 3 types of Project Orbis submissions. In a Type A Orbis submission, the marketing application must be submitted to the POP < 30 days after the FDA submission, which allows the possibility of concurrent action with FDA. If the submission > 30 days and/or the regulatory action takes more than three months after the FDA's decision, it is referred to as a Type B Orbis. Type B allows the possibility of concurrent review with FDA but no concurrent action. Lastly, in Type C Orbis submissions, where the FDA has already taken regulatory action, the FDA shares its completed review documents with the POP but there is no concurrent review or action with FDA.

For products that received an HTA recommendation between 2021 and 2023, Orbis products exhibited a shorter median regulatory review time in all 4 jurisdictions (**Figure 1**). All HTA agencies showed shorter review times for Orbis products compared to non-Orbis except for PBAC, as the timeline is aligned with the frequency of the committee meetings.

Table 1 displays 19 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 2021 to 2023. In Australia, the most common Orbis category was type B (7/12). In Canada (CDA-AMC and INESSS), 8 out of 16 NASs were categorised as Orbis type C, followed by 4 classified as type A, and 4 as type B. NICE had a 50% split between types B and C, while SMC had 75% of products evaluated as type B and the remaining 25% as type C. The limited number of Orbis products appraised by both NICE and SMC is due to MHRA only joining the scheme in January 2021. All Orbis products that rolled out to Australia received a negative 1st recommendation.

FOCUS: PROJECT ORBIS (CONT.)

Figure 2, 3 and 4 illustrate the breakdown of rollout time for NASs approved through the Orbis route that received an HTA recommendation in either Australia, the UK or Canada, respectively.

Results show that, in Australia and Canada, the submission gap from FDA submission to regulatory submission and the regulatory review time of Orbis A products was the shortest compared to Orbis B and C. However, these compounds showed a longer gap between regulatory approval and HTA submission.

In the UK, both NICE and SMC have published a 1st HTA recommendation for 4 Orbis products (**Figure 3**). The median HTA review time for Orbis products was longer in NICE compared to SMC, but this could be related to differences in the products assessed.

Figure 2. Breakdown of rollout time for Orbis products assessed in Australia (1st HTA recommendation 2021-2023)

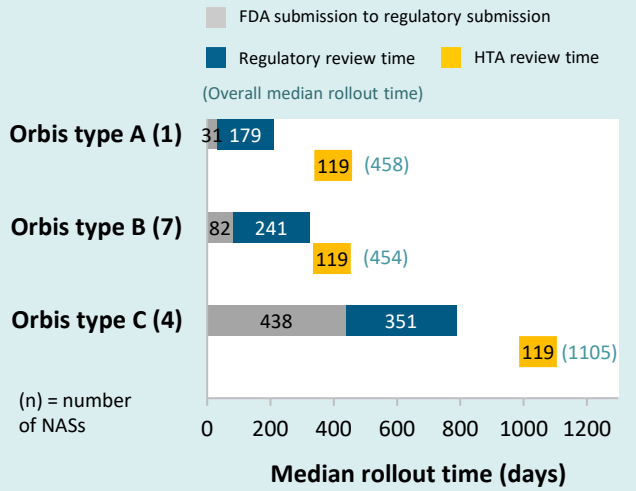
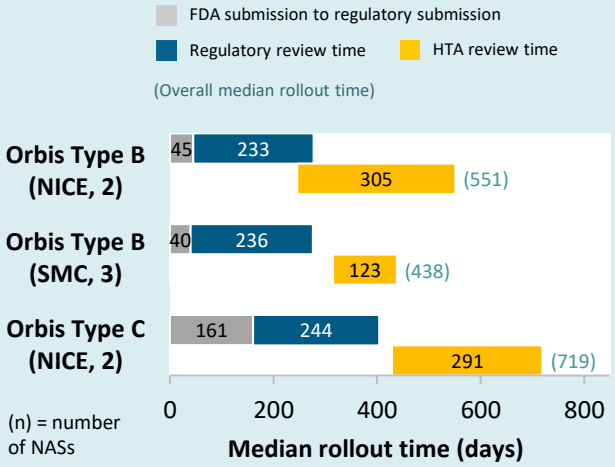


Figure 3. Breakdown of rollout time for Orbis products assessed in the UK (1st HTA recommendation 2021-2023)



Note: this analysis includes Orbis products approved by MHRA which have received recommendation from either NICE or SMC

Products can be submitted for HTA review to CDA-AMC up to 180 days prior to the anticipated Notice of Compliance (NOC) from Health Canada. In **Figure 5** the submission trend of CDA-AMC and INESSS shows that Orbis products are submitted to CDA-AMC 93 days after the NOC release and 68 days later to INESSS.

Figure 4. Breakdown of rollout time for Orbis products in Canada (1st HTA recommendation 2021-2023)

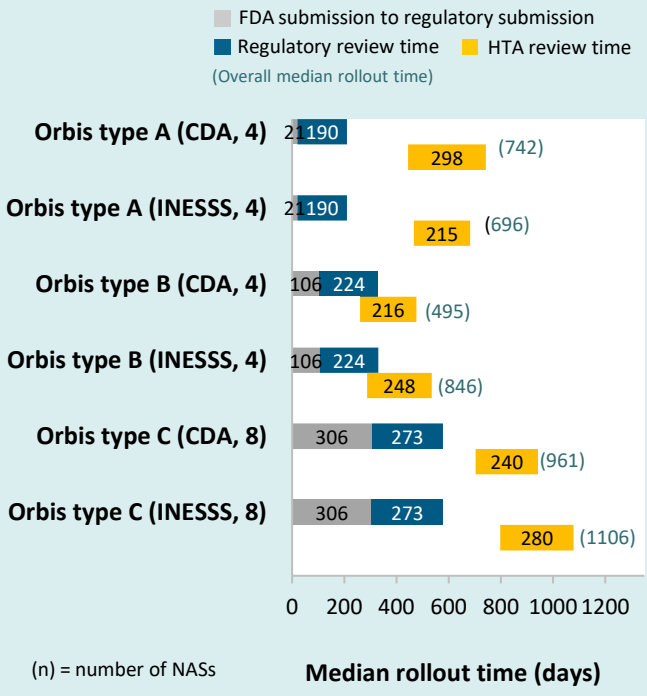
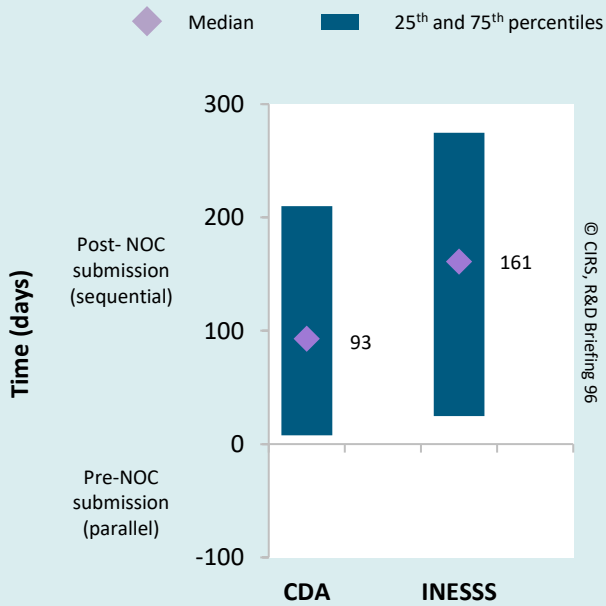


Figure 5. Submission trend of NASs approved via Orbis project in Canada (1st HTA recommendation 2021-2023)



- 4 of 16 Orbis products were submitted to CDA-AMC in parallel (25%)
- 3 of 16 Orbis products were submitted to INESSS in parallel (19%)

FOCUS: ACCESS WORK-SHARING CONSORTIUM

Table 2. NASs approved and assessed by the Access Consortium (1st HTA recommendation 2019-2023)

Generic name	ATC-short	1st regulatory approval*	Australia	Canada (CDA-AMC)	Canada (INESSS)	England	Scotland
abemaciclib	L	05/04/2019				Regulatory approval prior to 2021	Regulatory approval prior to 2021
niraparib	L	27/06/2019				Regulatory approval prior to 2021	Regulatory approval prior to 2021
darolutamide	L	20/02/2020				Regulatory approval prior to 2021	Regulatory approval prior to 2021
tafamidis meglumine	N	13/03/2020		Approved by HC but not through Access	Approved by HC but not through Access	Regulatory approval prior to 2021	Regulatory approval prior to 2021
isatuximab	L	29/04/2020	Approved by TGA through Access but no PBAC recommendation yet			Regulatory approval prior to 2021	Regulatory approval prior to 2021
inclisiran	C	26/07/2021				Regulatory approval prior to 2021	Regulatory approval prior to 2021
somatrogon	H	26/10/2021				Approved via ECDRP	Approved via ECDRP
vericiguat	C	10/11/2021		Approved by HC but not through Access	Approved by HC but not through Access	Approved via ECDRP	Approved via ECDRP
avalglucosidase alfa	A	12/11/2021				Approved via ECDRP	Approved via ECDRP
finerenone	C	18/11/2021		Approved by HC but not through Access	Approved by HC but not through Access	Approved via ECDRP	Approved via ECDRP
molnupiravir	J	18/01/2022		No HC approval yet	No HC approval yet	Approved by MHRA but not though Access	Approved by MHRA but not though Access
avacopan	L	14/04/2022	Approved by TGA but not through Access		Reviewed by INESSS in 2024 (out of scope from this report)	Approved via ECDRP	Approved via ECDRP
faricimab	S	16/05/2022					
asciminib	L	15/06/2022					
difelikefalin	V	16/08/2022			Reviewed by INESSS in 2024 (out of scope from this report)	Approved via ECDRP	Approved via ECDRP
tirzepatide	A	22/12/2022		Approved by HC through Access but no CDA-AMC recommendation	Approved by HC through Access but no INESSS recommendation	Approved via ECDRP	Approved via ECDRP
mirikizumab	L	26/09/2023		Approved by HC but not through Access	Approved by HC but not through Access	Approved via ECDRP	Approved via ECDRP

* Earliest regulatory approval among the jurisdictions where the NAS was approved through Access and received a recommendation between 2019 and 2023

Positive Restriction Negative Multiple

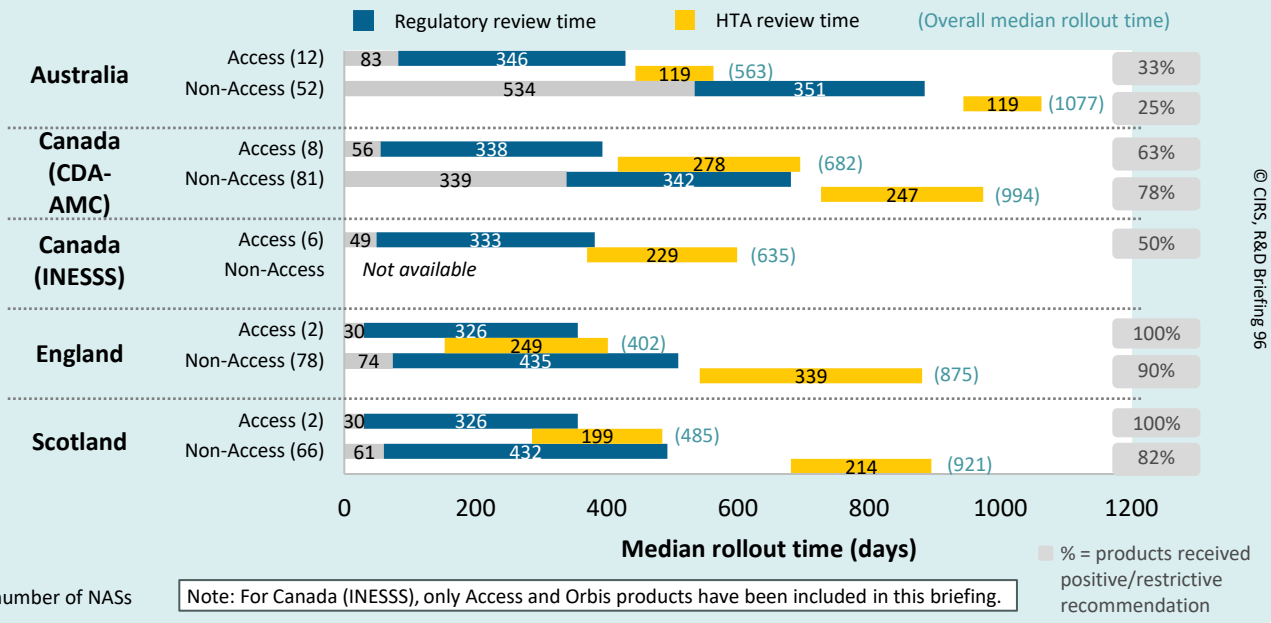
Among the products that received a 1st HTA recommendation between 2019-2023, 17 were approved via the Access Consortium.

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

A total of 17 products approved via the Access route, which received a 1st HTA recommendation between 2019 and 2023, were identified in this briefing (**Table 2**). Of the Access products rolled out to Australia, 67% received a negative 1st HTA recommendation, while the remaining obtained a positive recommendation. In Canada, 73% and 67% received a positive with restrictions or multiple recommendation by CDA-AMC and INESSS, respectively, and the rest received a negative recommendation. In the case of the Access products rolled out to England or Scotland, these received either a positive or positive with restrictions recommendation. It is worth noting that the low number of NASs appraised by either NICE or SMC can be attributed to the fact that the MHRA only joined these work-sharing applications in 2021.

FOCUS: ACCESS WORK-SHARING CONSORTIUM (CONT.)

Figure 6. Rollout time of NASs approved by the Access Consortium vs. Non-Access route (1st HTA recommendation between 2021-2023)



(n) = number of NASs

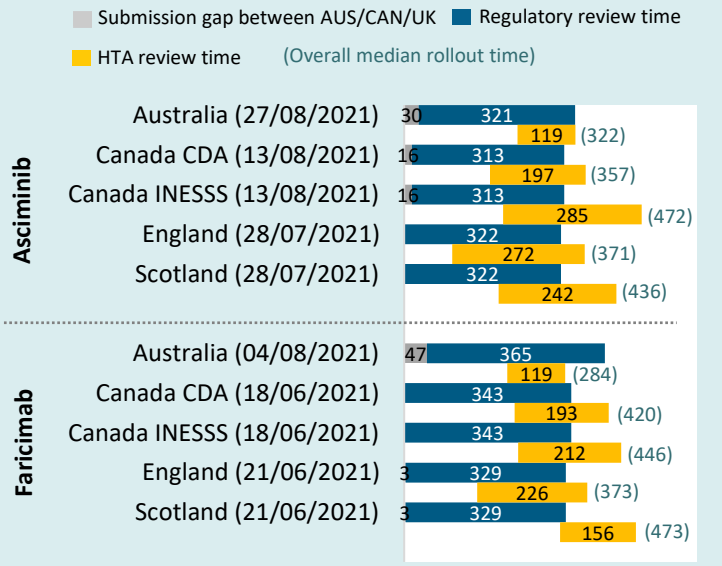
Note: For Canada (INESSS), only Access and Orbis products have been included in this briefing.

For HTA recommendations between 2021 and 2023, Access products presented a shorter median regulatory review time compared to non-Access products.

All studied jurisdictions presented a shorter median regulatory review and overall rollout time for Access products compared to non-Access products (**Figure 6**). Only one jurisdiction, CDA-AMC, showed a longer HTA review time for Access compared to non-Access products. Within Australia, England and Scotland, Access products were observed to have a higher percentage of either positive or positive with restrictions recommendations compared to non-Access products (**Figure 6**). Conversely, Access products presented a lower percentage of positive or positive recommendations compared to non-Access products in Canada. However, caution needs to be taken when interpreting these results, as the sample size of the Access products is small.

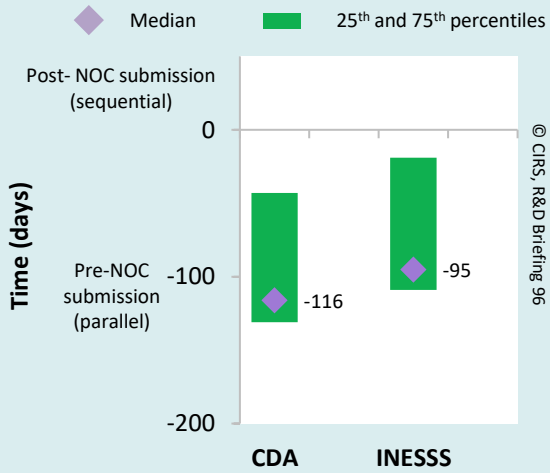
Figure 7 includes two case studies of Access products that rolled out to all 5 studied jurisdictions. The figure shows parallel submissions in all jurisdictions. The median time of days in which Access products were submitted to CDA-AMC and INESSS prior to NOC release was similar but it shows a small delay for INESSS (116 days for CDA-AMC versus 95 days for INESSS) (**Figure 8**).

Figure 7. Case studies of common NASs approved by the Access Consortium that received a 1st HTA recommendation



(n) = Regulatory submission date

Figure 8. Submission trend of NASs approved via Access project in Canada (1st HTA recommendation 2019-2023)



- ❑ 7 of 9 Access products were submitted to CDA-AMC in parallel (78%)
- ❑ 7 of 9 Access products were submitted to INESSS in parallel (78%)

COMMON NASS APPRAISED BY ALL HTA AGENCIES

Table 3. First HTA recommendation comparison for 40 common NASs reviewed by four agencies (2019-2023)

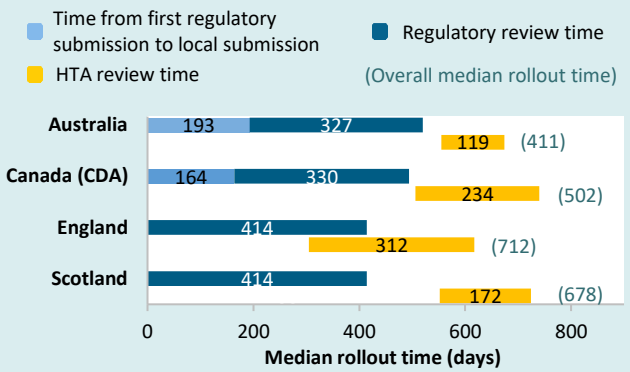
Generic name	Australia	Canada (CDA-AMC)	England	Scotland
abemaciclib	2	4	1	3
acalabrutinib	1	2	3	4
asciminib	1	3	2	4
avacopan	2	3	1	4
avalglucosidase alfa	1	2	3	4
bimekizumab	3	4	1	2
brigatinib	4	3	1	2
brolucizumab	1	2	4	3
cabotegravir	3	1	4	2
caplacizumab	1	2	4	3
cemiplimab	4	3	1	2
darolutamide	2	1	4	3
dostarlimab	2	4	3	1
eptinezumab	1	2	4	3
faricimab	1	3	2	4
finerenone	1	3	4	2
fremanezumab	2	4	3	1
galcanezumab	1	4	2	3
gilteritinib	4	1	3	2
inclisiran	4	3	2	1
lanadelumab	1	4	2	3
lorlatinib	1	2	4	3
maribavir	4	1	2	3
mogamulizumab	1	4	3	2
neratinib	1	3	2	4
onasemnogene abeparvovec	4	2	3	1
ozanimod	1	4	3	2
patisiran	4	2	3	1
pegcetacoplan	2	4	1	3
polatuzumab	1	4	3	2
ravulizumab	1	4	3	2
risankizumab	2	1	3	4
risdiplam	1	2	3	4
sacituzumab govitecan	1	2	4	3
selpercatinib	4	3	2	1
selumetinib	2	3	1	4
somatrogon	2	1	4	3
trastuzumab deruxtecan	3	4	1	2
tucatinib	1	2	4	3
upadacitinib	1	2	3	4

Positive
Restriction
Negative
Multiple

Between 2019 and 2023, 40 NASs were identified as having received their HTA recommendation from PBAC, CDA-AMC, NICE, and SMC.

These NASs are referred to as "common products" in this briefing. **Table 3** presents a traffic light system to compare the HTA outcomes for these common products, illustrating the diverse evaluations of their value by the different agencies. The dates of the first HTA recommendation for each product were compared across all four agencies, with rankings assigned from earliest (1) to latest (4).

Figure 9. Breakdown of rollout time of common NASs (n=40) reviewed by 4 agencies (2019-2023)



Note: SMC submission dates only available for recommendations after 2020 (n=24)

Figure 9 illustrates the rollout times of these common products across the jurisdictions. NASs were submitted first in the UK for regulatory review, followed by Canada and Australia with 193 and 164 days gap, respectively. Although NICE exhibited the longest median review time, its parallel submission resulted in the fastest recommendation compared to other HTA agencies. Nevertheless, products reviewed by SMC, which undergo the same regulatory review time as England and had a shorter HTA review, took a longer rollout time, primarily due to a submission gap of 552 days driven by company strategy, which was not observed in the other three jurisdictions.

Figure 10 examines the submission order to the three jurisdictions. Of the 24 common NASs reviewed in the past three years, the majority (70%) were submitted to NICE first, followed by PBAC. Half of the common NASs were submitted to all HTA agencies within 8 months, indicating a well-synchronised submission trend. **Figure 11** further analyses the overall process from regulatory submission to HTA recommendation for NASs reviewed over the past five years.

Figure 10. HTA submission time differences for 24 common NASs reviewed by Australia (PBAC), Canada (CDA-AMC), England (NICE) and Scotland (SMC) (2021-2023)

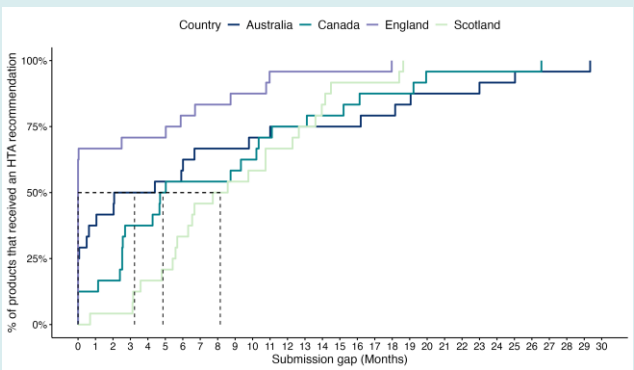
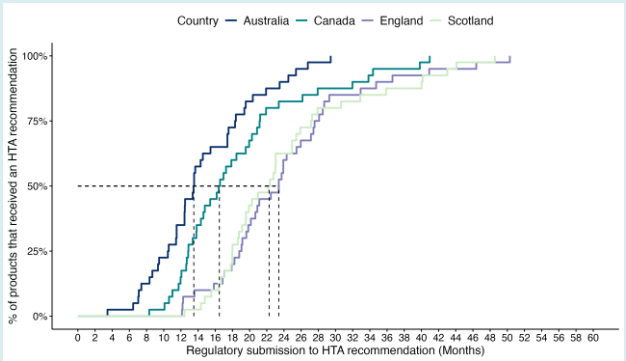
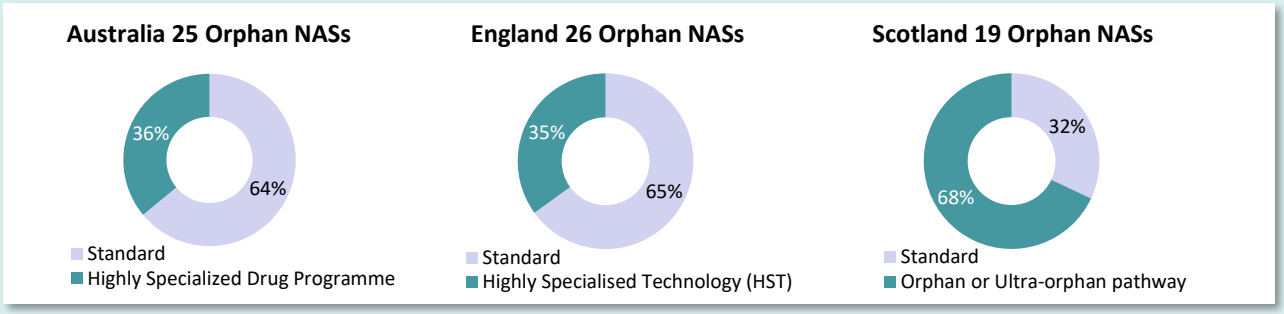


Figure 11. Regulatory submission to HTA recommendation for 40 common NASs reviewed by Australia (PBAC), Canada (CDA-AMC), England (NICE) and Scotland (SMC) (2019-2023)



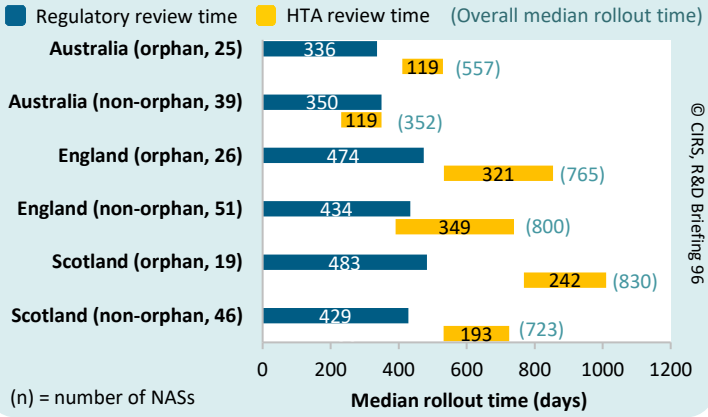
FOCUS: ORPHAN APPROVALS

Figure 12. Orphan products assessed by HTA between 2021-2023, by the HTA pathway (1st HTA recommendation 2021-2023)



Note: Since 2018, SMC has developed a framework for assessing ultra-orphan medicines for very rare conditions.

Figure 13. Breakdown of rollout time for orphan products vs. non orphan products (1st HTA recommendation 2021-2023)



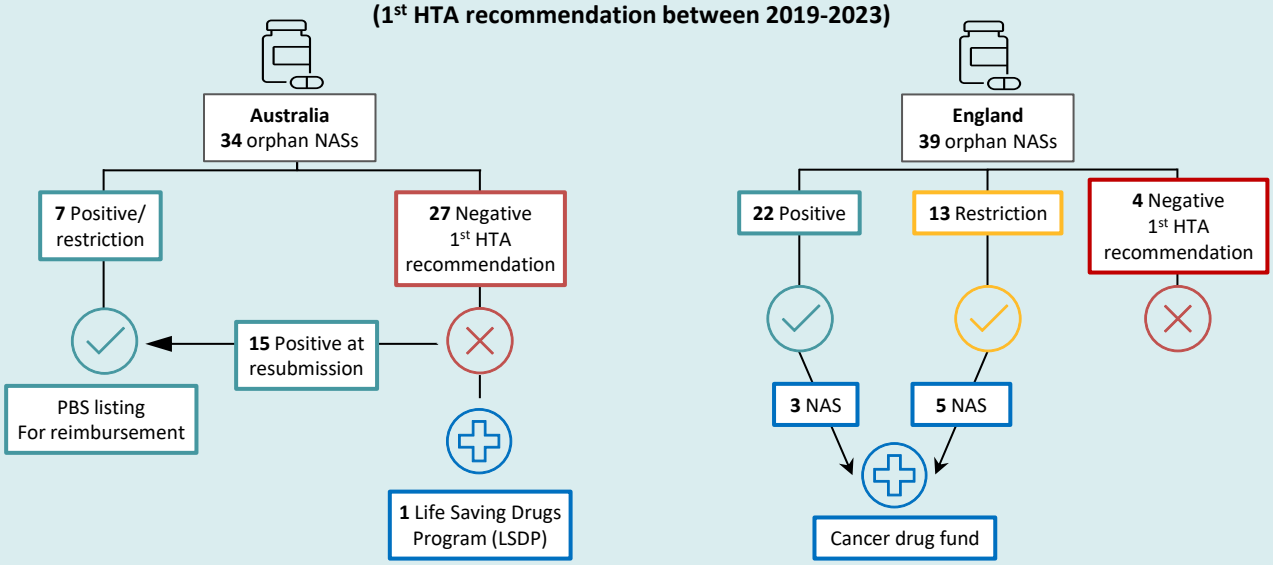
SMC has a designated pathway to assess orphan products, where 68% of NASs with a regulatory orphan designation underwent an HTA orphan/rare disease-related pathway.

In this briefing, we examined the HTA pathways that orphan products have undergone (see Table 5 in the Appendix). Among all jurisdictions, only Scotland's SMC has a designated orphan pathway, with 68% of regulatory-approved orphan products that received an HTA recommendation by SMC undergoing this process (**Figure 12**). In other jurisdictions, non-standard pathways are in place and have been utilised for orphan products where applicable. However, these pathways are not utilised for all orphan products, with only 36% in Australia and 35% in England, respectively.

The rollout time for orphan products was longer in all three jurisdictions compared to non-orphan products (**Figure 13**). In Australia, 64% of orphan products and 31% of non-orphan product that received a recommendation between 2021 and 2023 were submitted sequentially.

In addition to the assessment process, orphan products can also be reimbursed via alternative funding mechanisms. In Australia, 65% of the orphan compounds appraised by PBAC between 2019-2023 were recommended to be covered under Public Benefit Scheme (PBS) at first submission or resubmission. For PBAC negative recommendations, 1 product was financially supported through the Life-Saving Drugs Programme (LSDP). An observation conducted simultaneously in England revealed that 90% of orphan drugs were recommended for reimbursement by NICE, and 21% were covered by the Cancer Drugs Fund (CDF) (**Figure 14**).

Figure 14. Orphan products HTA outcome, by funding mechanism (1st HTA recommendation between 2019-2023)

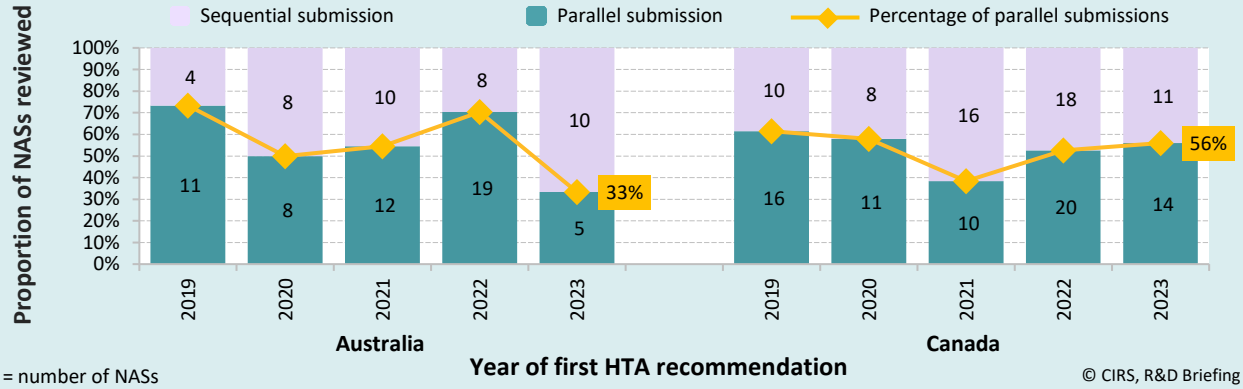


65% of orphan NASs were recommended for listing
3% covered by LSDP

90% of orphan NASs were reimbursed
21% covered by cancer drug fund

CHARACTERISTICS: REGULATORY AND HTA REVIEW SEQUENCE

Figure 15. Number of NASs assessed in Australia (PBAC) and Canada (CDA-AMC) by HTA submission timing (2019-2023)

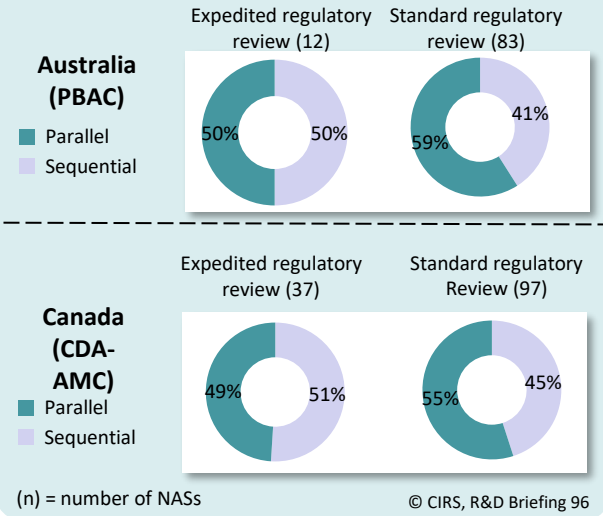


(n) = number of NASs

In 2023, the proportion of parallel submissions in Australia decreased to 33%, whereas Canada maintained a similar rate with 56% of its total appraisals conducted in parallel (Figure 15).

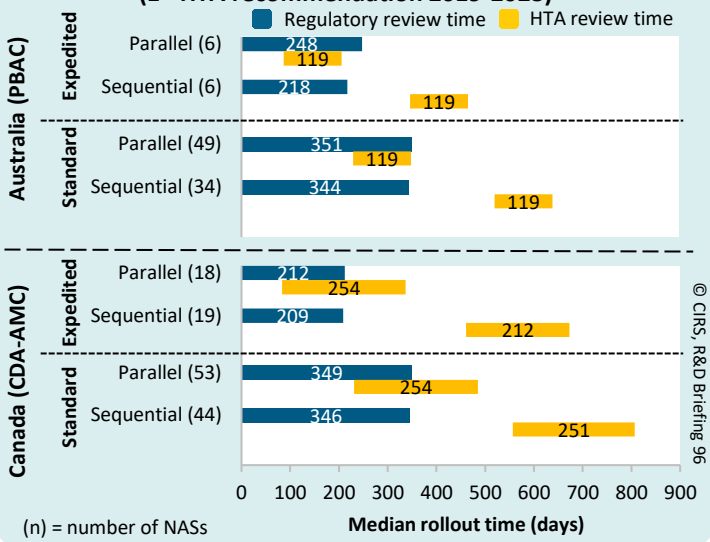
The submission sequence depends on the company's submission strategy and readiness. Further analysis assessed how different types of regulatory approval routes (conditional, expedited) influence the submission sequence and timelines (**Figure 16-19**) .

Figure 16. Impact of expedited regulatory review on the HTA submission sequence (2019-2023)



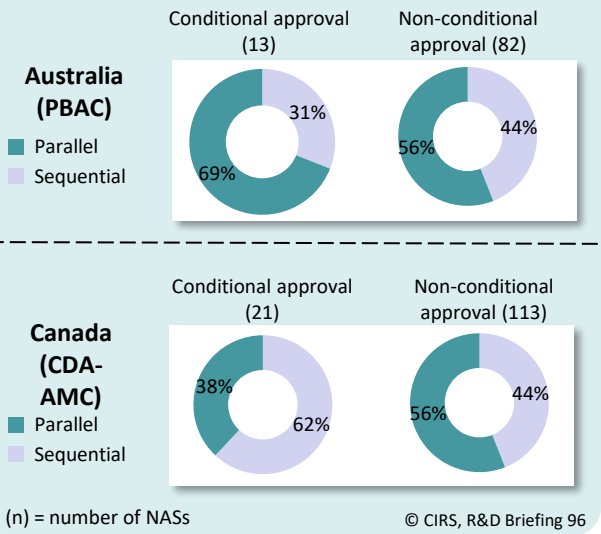
(n) = number of NASs

Figure 17. Comparison of rollout times by review type (1st HTA recommendation 2019-2023)



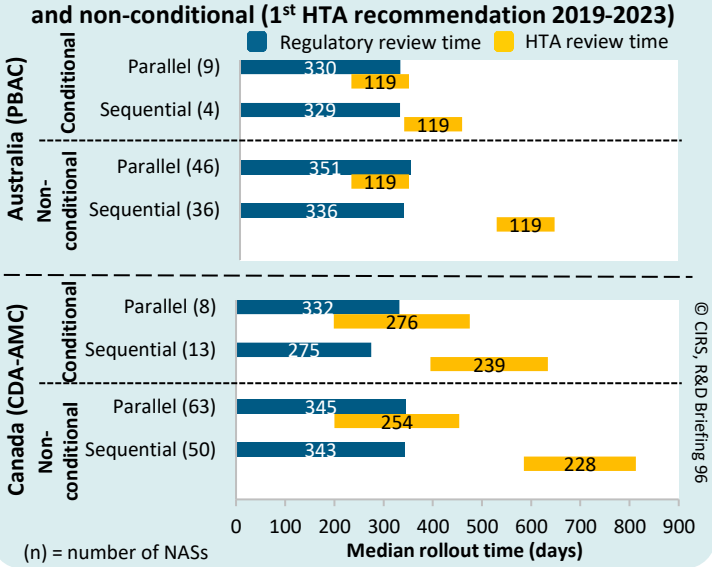
(n) = number of NASs

Figure 18. Impact of conditional approval on the HTA submission sequence (2019-2023)



(n) = number of NASs

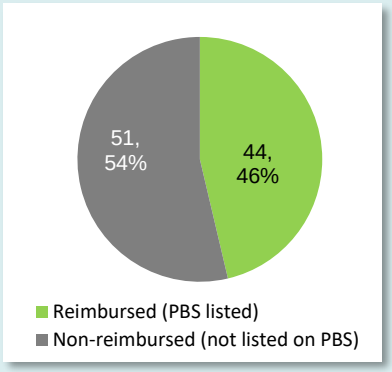
Figure 19. Comparison of rollout times comparing conditional and non-conditional (1st HTA recommendation 2019-2023)



(n) = number of NASs

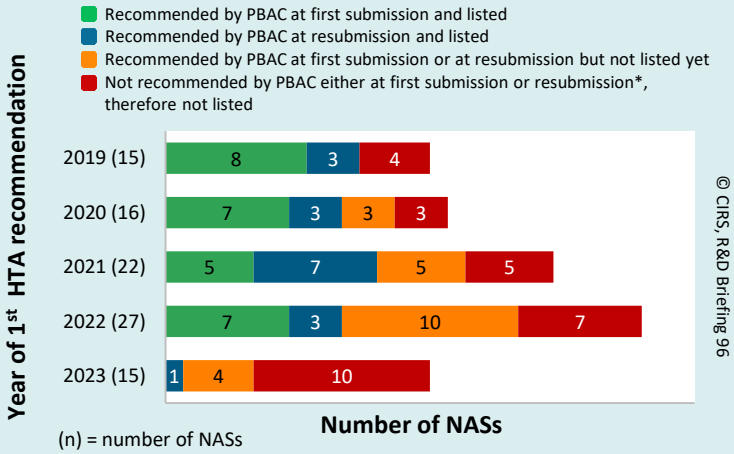
FEATURES OF AUSTRALIA

Figure 20. Proportion of products that received reimbursement in Australia (1st HTA recommendation 2019-2023)



Reviewed by PBAC between 2019-2023

Figure 21. The PBS listing status for NASs reviewed by PBAC between 2019 to 2023



(n) = number of NASs

* Including products not resubmitted by companies

Out of the 95 NASs reviewed by the PBAC between 2019-2023, 44 have been listed on the PBS in Australia. Of these, 39% required more than one cycle to resubmit to the PBAC for PBS listing (Figure 20).

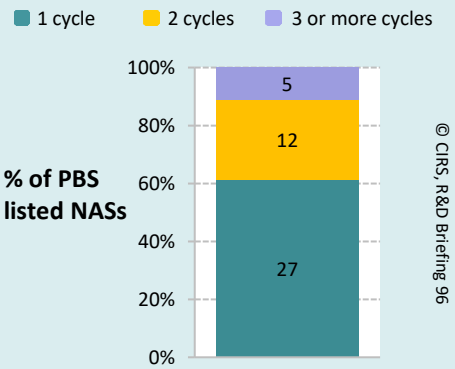
In Australia, under the Pharmaceutical Benefits Scheme (PBS), the government subsidises the cost of medicine for most medical conditions. The Pharmaceutical Benefits Advisory Committee (PBAC) is an independent expert body appointed by the Australian Government, consisting of doctors, health professionals, health economists, and consumer representatives. 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. When the PBAC's first HTA recommendation is negative, companies can resubmit an application with an improved dossier. Consequently, several review cycles may occur until a positive or positive with restriction recommendation is achieved.

The proportion of PBS-listed drugs recommended by the PBAC at the first submission was 53% in 2019 and 44% in 2020. However, from 2021 onwards, this proportion declined as some drugs have not yet been listed or resubmitted (**Figure 21**).

Currently, there are four pathways for companies to resubmit to PBAC: the early re-entry pathway, the early resolution pathway, the facilitated resolution pathway, and the standard re-entry pathway. Achieving a positive recommendation can require multiple cycles (**Figure 22**). The majority of NASs were recommended within two cycles, while 11% of listed products required more than two submissions to gain a positive or positive with restrictions recommendation.

Despite regular meetings by the PBAC, which ensure consistency in review times, resubmissions extend the time required for a drug to be listed on the PBS (**Figure 23**). The median time taken from the first PBAC negative recommendation to receiving a positive recommendation is 123 days. However, this time ranged from 122 days (25th percentile) to 365 days (75th percentile), influenced by the number of cycles needed and the time companies take to prepare additional evidence for an enhanced submission.

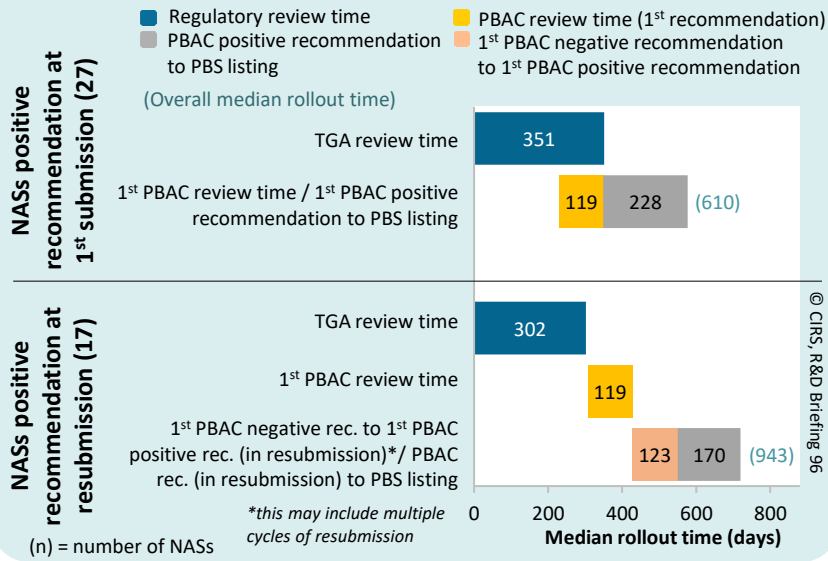
Figure 22. Number of NASs reviewed by PBAC listed on the PBS (reviewed by PBAC between 2019-2023)



Reviewed by PBAC between 2019-2023

Note: 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.

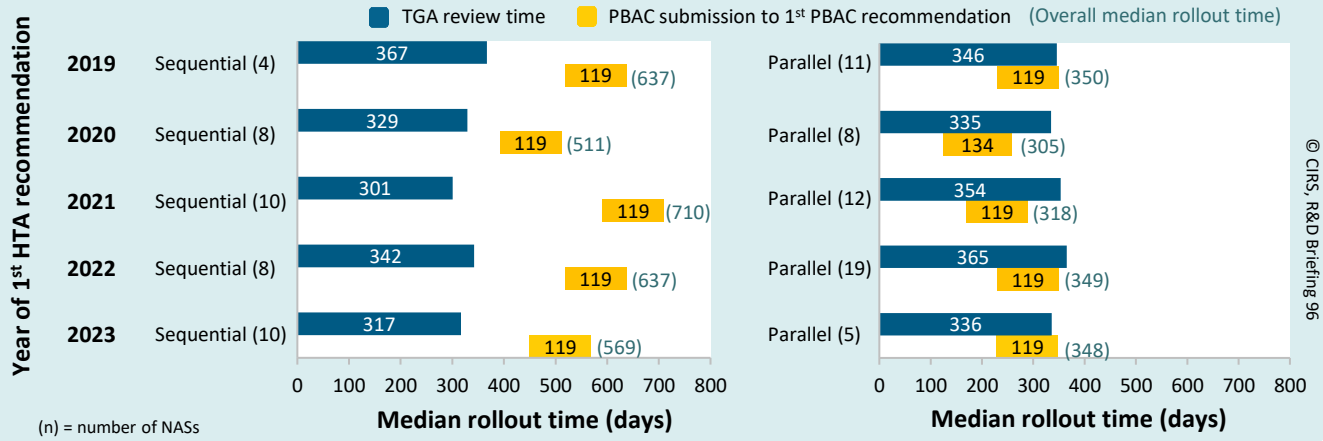
Figure 23. Breakdown of rollout time for NASs from TGA submission to PBS listing (reviewed by PBAC between 2019-2023)



(n) = number of NASs

FEATURES OF AUSTRALIA (CONT.)

Figure 24: Breakdown of rollout time by submission sequence (reviewed by PBAC 2019-2023)



In 2023, the median time for submission to PBAC was 107 days before TGA approval for parallel submissions. This contrasts with a 133-day gap in HTA submission with the sequential review.

In Australia, companies can submit the HTA dossier to the PBAC either before TGA approval (parallel process) or after TGA approval (sequential process). Under the TGA/PBAC parallel process, the TGA delegate's overview informs PBAC's consideration for appraising a drug. Companies can submit the regulatory delegate overview up to a week before the PBAC meeting. The parallel process shortened the overall time from regulatory submission to HTA recommendation in Australia.

However, in 2023, only five products were submitted through the parallel process, compared to an average of 13 from 2019 to 2022. Interestingly, for products submitted sequentially, a trend of decreasing gap from regulatory submission to HTA submission was observed from 2021 to 2023, with a median time of 591 days in 2021, 518 days in 2022, and 450 days in 2023 (**Figure 24**).

Table 4. HTA recommendation status for products that underwent TGA Priority approval (reviewed by PBAC 2019-2023)

Brand name	Orphan status	TGA approval	HTA recommendation date	PBAC/ MSAC	First HTA recommendation	Listing status/ resubmission status
Takhzyro	Orphan	Jan-19	Jul-19	PBAC	Negative	PBS listed
Polivy	Standard	Oct-19	Nov-19	PBAC	Negative	Not listed/Resubmission negative
Qarziba	Orphan	Mar-20	Jul-20	MSAC	Positive	Not PBS listed
Xospata	Orphan	Apr-20	Nov-21	PBAC	Negative	PBS listed
Qinlock	Orphan	Jul-20	Mar-21	PBAC	Negative	PBS listed
Tukysa	Standard	Aug-20	Mar-21	PBAC	Negative	Not listed/No resubmission
Evrysdi	Orphan	Jun-21	Mar-21	PBAC	Positive with restrictions	PBS listed
Crysvita	Standard	Sep-21	Mar-21	PBAC	Negative	Not listed/Resubmission positive
Trodelvy	Standard	Sep-21	Nov-21	PBAC	Negative	Not listed/Resubmission positive
Ruzurgi	Standard	Sep-21	Nov-21	PBAC	Negative	PBS listed
Kimmtrak	Orphan	May-22	Mar-23	PBAC	Negative	Not listed/Resubmission positive
Livtencity	Orphan	Sep-22	Nov-23	PBAC	Negative	No resubmission
Sunlenca	Standard	Mar-23	Nov-22	PBAC	Negative	Not listed/Resubmission positive

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

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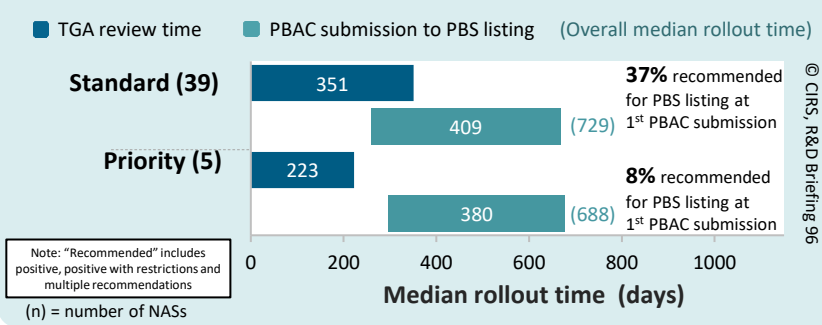
TGA introduced an expedited review programme from 2017 (Priority review); 13 products approved with priority review have undergone the HTA process between 2019 and 2023 (Table 4).

TGA Priority review is a formal expedited mechanism for a faster assessment to address unmet medical needs and where a high therapeutic benefit can be expected. Among the 13 products included in the study, 11 products were not recommended by PBAC at the initial submission. However, following the resubmissions, 5 were listed.

1 NAS was assessed by MSAC; the HTA outcome supported the public funding for the product but as of 2023 it had not been listed yet.

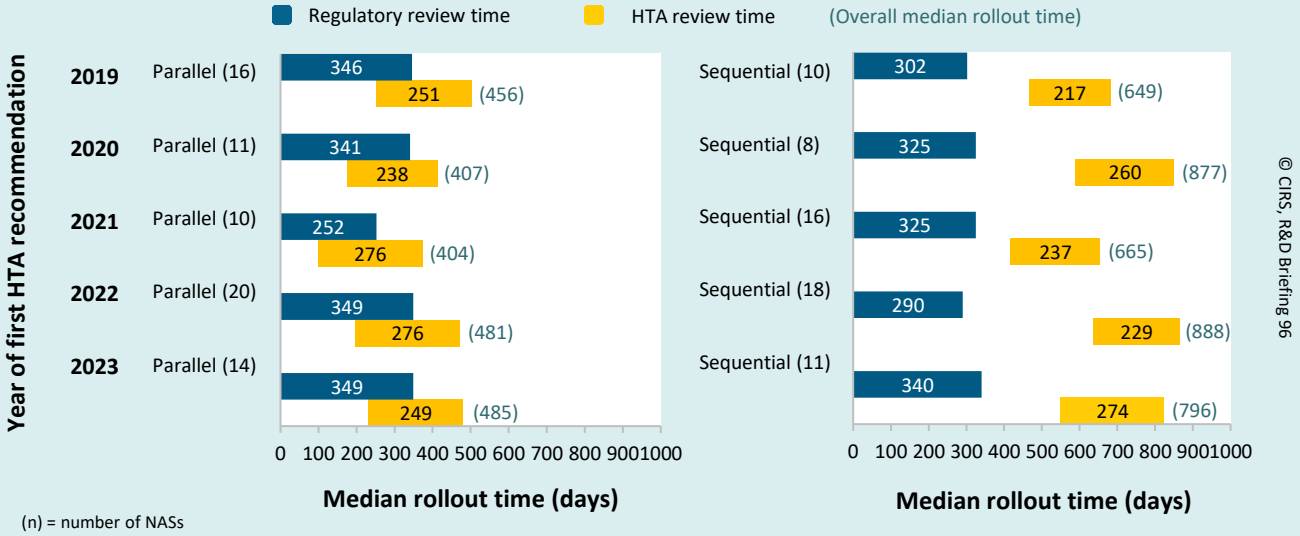
Figure 25. Breakdown of rollout time by Priority vs Standard (1st HTA recommendation 2019-2023)



For products approved under priority review by TGA, the overall time to be listed on the PBS is similar to those undergoing standard TGA review (Figure 25).

The priority review leads to a shorter TGA review period (351 days for standard vs. 223 days for priority), however, the HTA submission trend for the priority review products was sequential rather than parallel. This meant that even though the TGA review time and time from PBAC submission to PBS were shorter, the overall rollout time was similar (729 for standard vs. 688 for priority).

Figure 26. Breakdown of rollout time by review sequence in Canada (CDA-AMC) (1st HTA recommendation between 2019-2023)



(n) = number of NASs

Since 2021, data indicates that submissions to CDA-AMC under the parallel process are being made later during the regulatory process (Figure 26), and the median overlap between the regulatory and HTA processes is also decreasing (Figure 27).

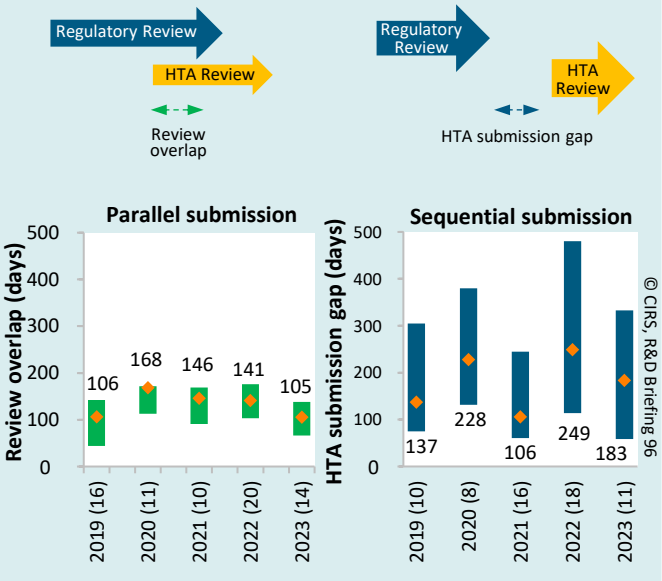
The Health Canada/CDA-AMC parallel review process allows for a submission to CDA-AMC up to 180 days before the anticipated Notice of Compliance (NOC) from Health Canada. For parallel reviews, submissions to CDA-AMC under the parallel process are being made later, with a median overlap between regulatory and HTA review of 146 days in 2021, 141 days in 2022 and 105 days in 2023 (**Figure 27**). The submission gap for products reviewed sequentially has decreased in 2023 compared to 2022 (183 days in 2023 versus 249 days in 2022) (**Figure 27**).

From 2021 to 2023, 36% of CDA-AMC recommendations were requested for reconsideration by companies.

The company applicant for a drug that is the subject of a draft recommendation may file a request 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.

Figure 28 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: 84 vs. 52 days in 2021, 143 vs. 37 days in 2022, and 154 vs. 37 days in 2023.

Figure 27. Time difference between regulatory approval and HTA submission (2019-2023) Parallel submission vs sequential submission

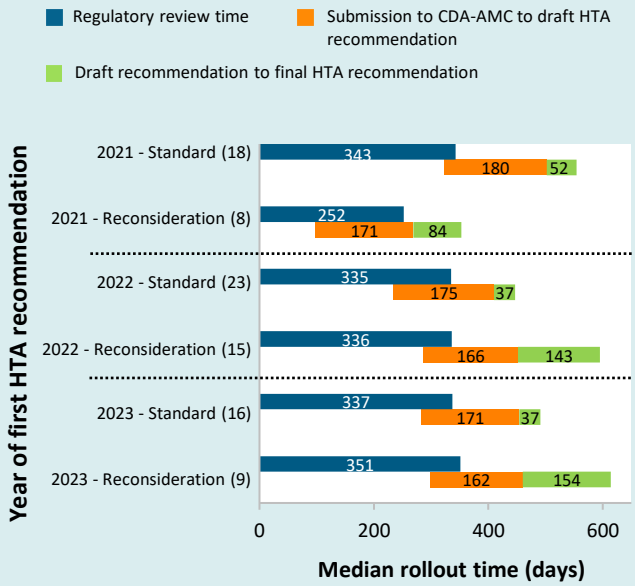


(n) = number of NASs

Median

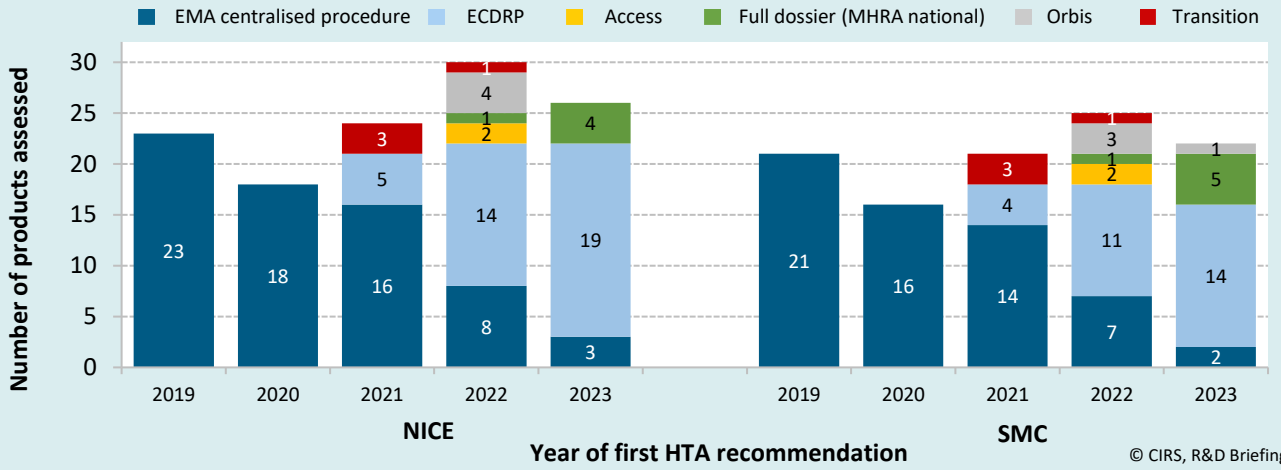
25th and 75th percentiles

Figure 28. Breakdown of rollout time in Canada between 2021-2023 (Requested reconsideration vs standard)



(n) = number of NASs

Figure 29. Number of NICE/SMC recommendations by year and the route of regulatory approval (1st HTA recommendation between 2019-2023)



Note: "Transition" refers to products approved during the Brexit commencing period. These products received an opinion from the Committee for Medicinal Products for Human Use (CHMP) in December 2020 and were subsequently granted marketing authorisation by the EMA in 2021

In 2023, 73% and 64% of appraisals by NICE and SMC, respectively, were approved under the ECDRP (Figure 29).

Following Brexit, a transitional regulatory mechanism began on 1 January 2021. Under this, the MHRA can rely on European Commission decisions for marketing authorisation in Great Britain through the ECDRP, which is available for NASs approved centrally by EMA. Additionally, MHRA has created a new international recognition route for medicines using pre-existing approvals from Australia, Canada, the EU, Japan, Switzerland, Singapore, and the US. This framework, available from 1 January 2024 (no products that underwent this route were included in this briefing), complements MHRA's current national procedures. MHRA also participates in other initiatives like Project Orbis and the Access Consortium.

A comparative analysis of the timelines for ECDRP products versus the national MHRA route (including Orbis, Access and EAMS) indicates a generally faster rollout time for nationally approved products compared to ECDRP products (**Figure 30**). Interestingly, the HTA review of ECDRP products exhibited a longer median review time compared to products evaluated through national pathways for both NICE (321 vs. 273 days) and SMC (249 vs. 157 days), which may be related to the type of product undergoing the different review pathways.

Further analysis explored the proportion of different types of HTA recommendation by the approval route (**Figure 31**). Comparing the MHRA national route (including Orbis and Access) with the EMA/ECDRP route, the data suggested no association between the approval route and the HTA recommendation for NICE and SMC.

Figure 30. Products rollout time in the UK (1st HTA recommendation 2022-2023)

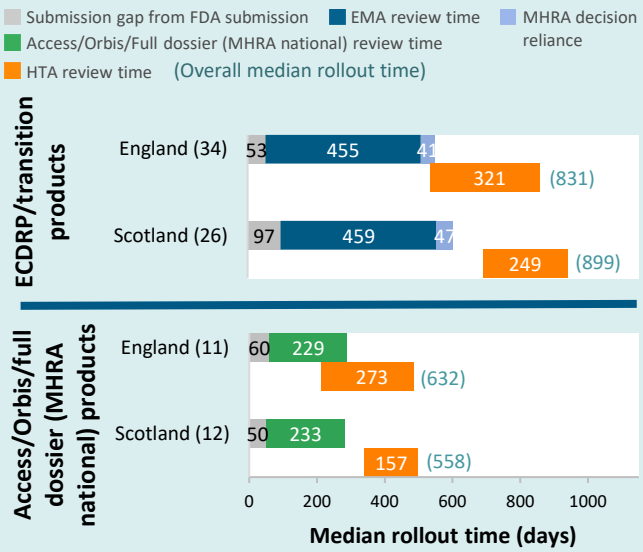


Figure 31. HTA first recommendation by regulatory route (1st HTA recommendation between 2022-2023)

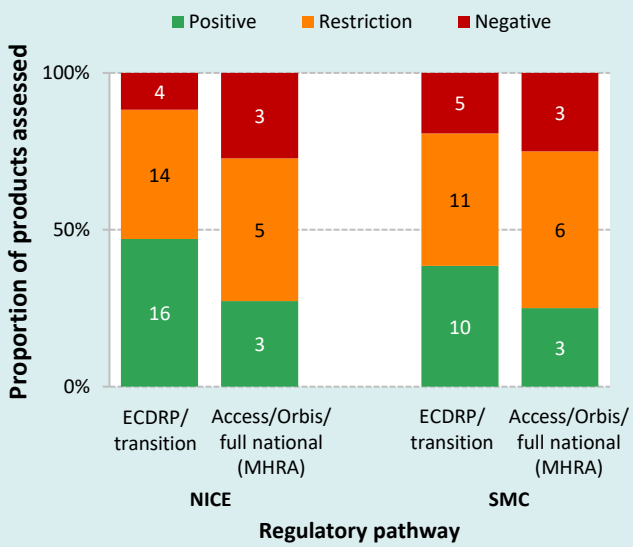
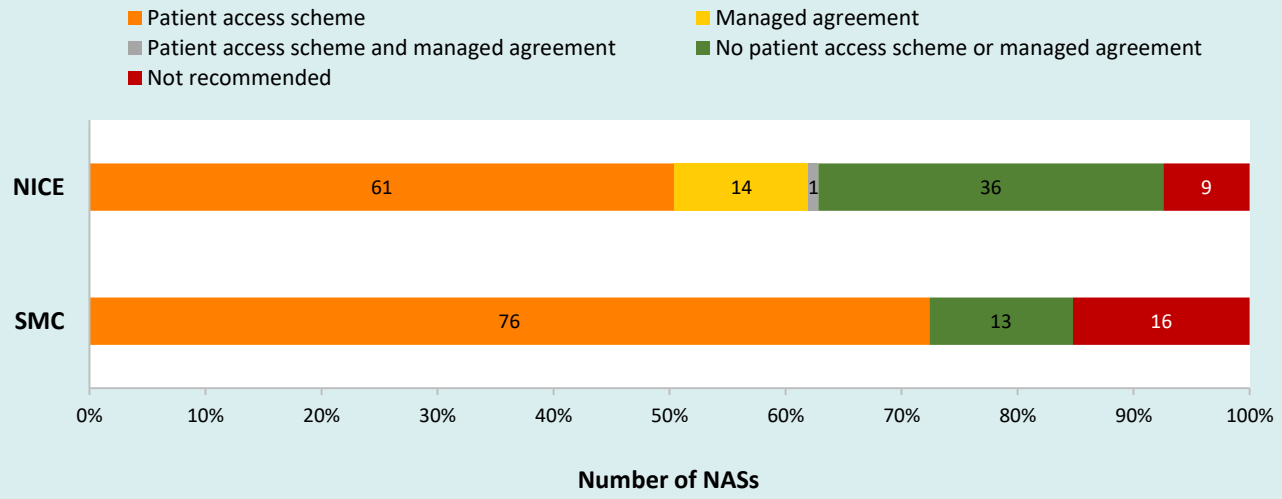


Figure 32. NICE/SMC recommendations via patient access scheme/managed entry agreements (1st HTA recommendation between 2019-2023)



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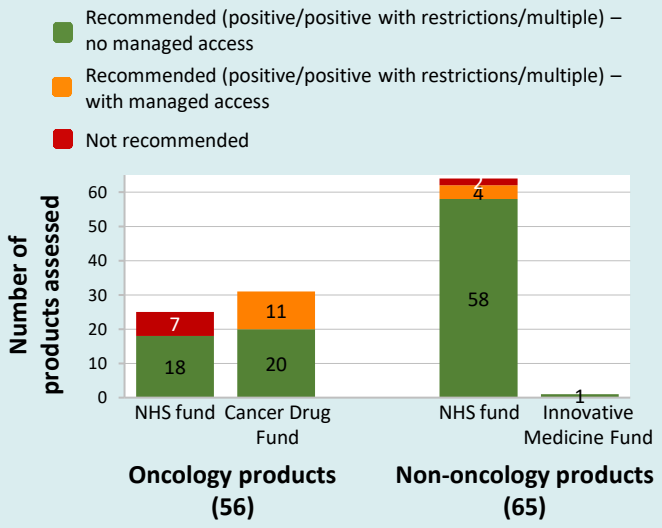
For NASs appraised by NICE and SMC, 50% and 72%, respectively, were recommended under patient access schemes (PAS) (Figure 32).

NICE and SMC have implemented mechanisms such as Managed Access Agreements and PAS to facilitate access to medicines that might not initially be deemed cost-effective. NICE's Managed Access Agreement provides faster access to promising new treatments despite uncertainties about their clinical or cost-effectiveness. During this period, additional evidence is gathered to address these uncertainties. Similarly, both NICE and SMC use PAS, which include cost reduction mechanisms to make treatments more accessible.

Figure 33. NICE Recommendations by funding mechanism (1st HTA recommendation between 2019-2023)



(n) = number of NASs

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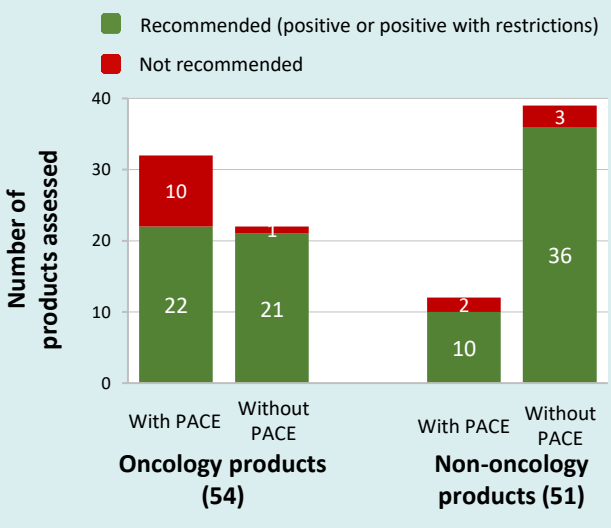
Figure 34. SMC Recommendation by HTA route (1st HTA recommendation between 2019-2023)



(n) = number of NASs

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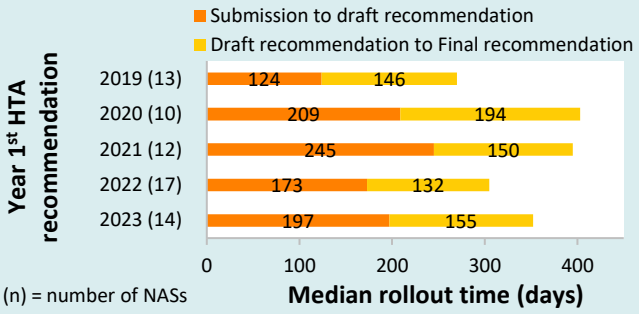
In England, there are two funding sources to pay for treatments in managed access: NHS England's Cancer Drugs Fund (CDF) and NHS England's Innovative Medicines Fund (IDF). We identified 11 NASs with managed access agreements that were funded by the CDF between 2019 and 2023, while the IDF was only established in 2022 and 1 product was reimbursed under this fund (**Figure 33**).

In addition, the SMC provides submitting companies with the opportunity to request a Patient and Clinician Engagement (PACE) meeting. This mechanism serves to amplify the voices of patient groups and clinicians in SMC's recommendation-making process, specifically for medicines utilised in the treatment of end-of-life and/or rare conditions. As illustrated in **Figure 34**, oncology products presented a higher number of PACE meetings. While PACE meetings have also been utilised for non-oncology products, the data indicates that they were less commonly implemented. This discrepancy could potentially be attributed to the lower proportion of end-of-life, orphan, or ultra-orphan medicines in the non-oncology (24%) versus the oncology group (65%).

FEATURES OF THE UK (CONT.)

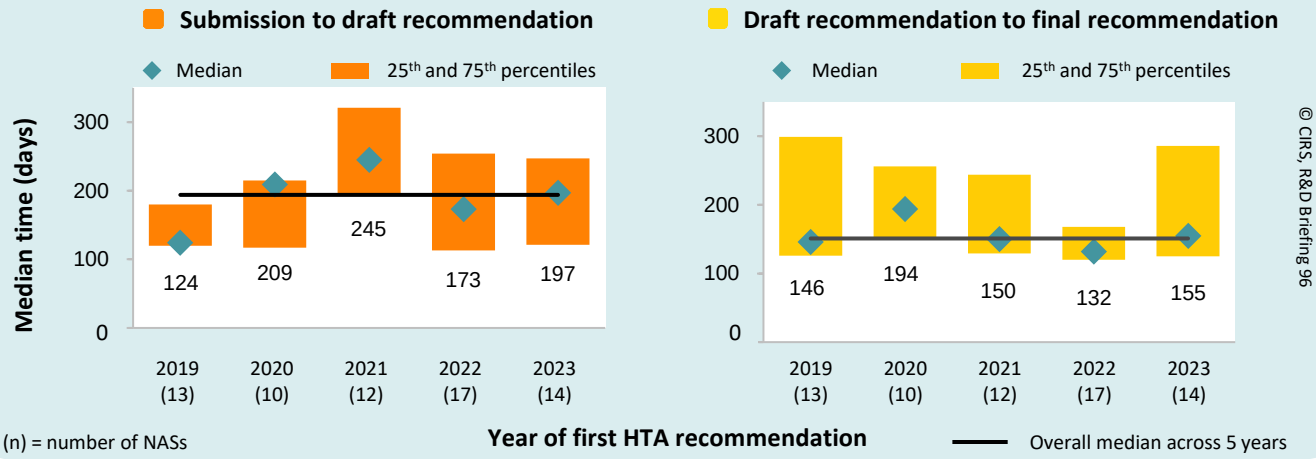
Figure 35. NICE breakdown of review time by year of HTA recommendation (1st HTA recommendation 2019-2023)



The NICE appraisal process begins with the submission of evidence by the company applicant. Following the evaluation by the Evidence Review Group, the Appraisal Committee then drafts guidance, and stakeholders have four weeks to provide comments. The committee considers these comments before issuing the final recommendations on reimbursement.

Figure 35 presents an analysis of the time taken from company submission to draft recommendation, as well as the time from draft to final recommendation. The draft recommendation to final recommendation time, which includes review time and company time, is generally longer than the submission to draft recommendation time, apart from 2019. The overall median across 5 years from submission to draft recommendation was 194 days, and from draft recommendation to final recommendation was 151 days (**Figure 36**).

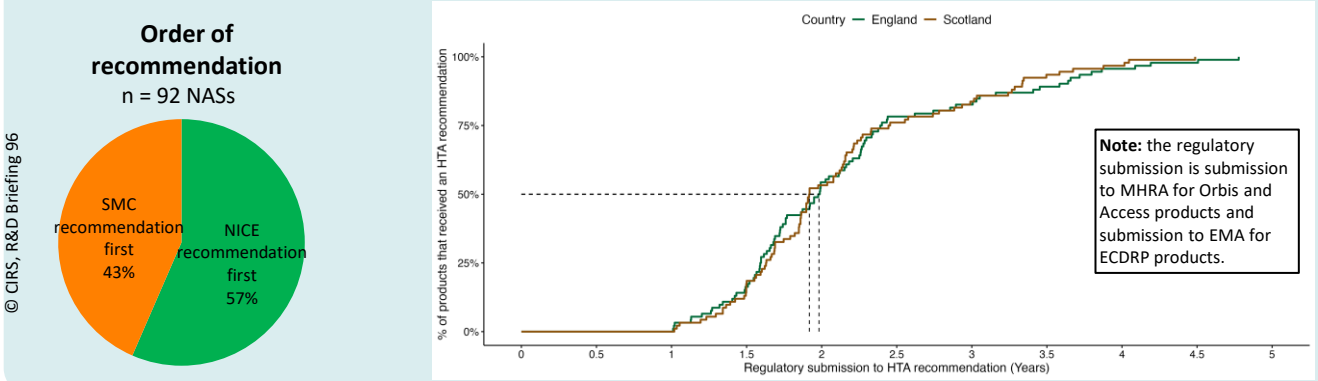
Figure 36. Variation of NICE review time (1st HTA recommendation between 2019-2023)



The SMC introduced the abbreviated process as an interim measure in October 2020. This process applies to medicines where alternatives within the same therapeutic class are already available for the same indication. It was part of SMC's strategy to resume operations following the COVID-19 pandemic. The goal was to reduce the workload on committee members by streamlining decisions for certain medicines. Following a positive stakeholder evaluation, this process has become permanent.

Among the NASs appraised by SMC between 2021 and 2023, 10 out of 68 were recommended via this route. The median time from regulatory approval to HTA recommendation for the abbreviated process was 322 days compared to 298 days for the standard process. However, it is noted that the submission gap from regulatory approval to SMC submission was longer due to company strategies (data not shown).

Figure 37. 92 common NASs were assessed by NICE and SMC between 2019-2023



A total of 92 common products were evaluated in both England and Scotland between 2019 and 2023, and the rollout time was comparable in both jurisdictions.

Finally, between 2019 and 2023, a total of 92 common products were evaluated in both England and Scotland (**Figure 37**). Among these common products, 57% (52/92) were first recommended by NICE, while the remaining 43% received an earlier recommendation by SMC.

A cumulative analysis including only these common compounds, graphically reveals that the rollout time, from regulatory submission to HTA recommendation, was comparable in both jurisdictions.

DEFINITIONS

Anti-cancer drugs

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

Exclusion criteria

Applications that are excluded from the study:

- Vaccines
- Any other application, where new clinical data were submitted
- Generic applications
- Those applications where a completely new dossier was submitted from a new company for the same indications as already approved for another company
- Applications for a new or additional name, or a change of name, for an existing compound (i.e. a 'cloned' application)

First assessment report

The first assessment report is the earliest assessment available. Note that for some drugs; for example, those with the same INN, strength and presentation, are listed more than one time. The reasons may be twofold – consideration of the drug in more than one indication or re-assessment of the drug by the agency.

Health technology assessment (HTA)

For the purpose of this project, HTA refers to the assessment and appraisal of pharmaceuticals prior to reimbursement. The HTA process includes clinical assessment, economic assessment and an appraisal that results in either a coverage recommendation or recommendation.

HTA review time

Time (calendar days) calculated from the date of submission to the date of recommendation by the HTA agency. Note: The HTA recommendation refers to the recommendation at national level.

Managed entry agreements (MEAs)

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

New active substance (NAS)

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

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

Parallel review

Pharmaceutical companies submit evidence to the regulatory agency that prove the efficacy, safety, quality of the product. However, during the regulatory review process, companies submit dossiers to HTA bodies so that the two review steps can occur in parallel. Following the regulatory approval, HTA recommendation will be provided to companies for drug reimbursement. This sequence is available in Australia and Canada. In this report, a drug is identified as parallel if HTA recommendation is earlier than regulatory approval.

Regulatory submission gap

Date of submission at the first regulatory agency to the date of regulatory submission to the target agency.

Regulatory review time

Time (calendar days) calculated from the date of submission to the date of approval by the agency; this time includes agency and company time. Note: The EMA approval time includes the EU Commission time.

Rollout time

Date of submission at the regulatory agency to the date of HTA recommendation at the target jurisdiction (calendar days).

Sequential review

Regulatory review is conducted first to determine the benefit-risk profile of a new medicine, followed by the HTA review to assess the value of the medicine for a reimbursement decision. The regulatory-HTA sequence is seen at a national level in many countries, and also at a super-national level in Europe where a centralised regulatory decision made by the European Medicines Agency is followed by jurisdictional HTA recommendations by member states.

DEFINITIONS

Jurisdictional pathways and processes

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.

CDA-AMC - 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-AMC review report(s).

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.

Innovative Medicines Fund (IMF) – NHS England

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

PBAC early re-entry pathway

The early re-entry pathway is one of the four types of resubmission pathways available to applicants following a 'not recommended' PBAC outcome. It 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.

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.

Transition

Term for products approved during the Brexit commencing period. These products received an opinion from the Committee for Medicinal Products for Human Use (CHMP) in December 2020 and were subsequently granted marketing authorisation by the EMA in 2021.

HTA ORPHAN/RARE DISEASE-RELATED PATHWAYS

Table 5. 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 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.
Scotland	**Orphan medicine:** A medicine with European Medicines Agency (EMA) designated orphan status (conditions affecting fewer than 2,500 people in a population of 5 million) or a medicine to treat an equivalent size of population irrespective of whether it has orphan status. **Ultra-orphan medicine:** To be considered as an ultra-orphan medicine all criteria listed should be met: • the condition has a prevalence of 1 in 50,000 or less in Scotland, • the medicine has an EMA orphan designation for the condition and this is maintained at time of marketing authorisation, • the condition is chronic and severely disabling, and • the condition requires highly specialised management. Submissions for medicines that are validated as ultra-orphan according to this definition will be assessed by SMC and will then be available to prescribers for a period of up to three years while further clinical effectiveness data are gathered. After this period the company will be asked to provide an updated submission for reassessment and SMC will make a decision on routine use of the medicine in NHS Scotland. For medicines used at end of life and for very rare conditions, companies may ask for the medicine to be considered at a Patient and Clinician Engagement (PACE) meeting. This additional step allows SMC to hear more evidence from patient groups and clinicians on the added value of a medicine which may not always be captured in the company's submission. The output from a PACE meeting is a major factor in SMC decision making. Companies can also submit or improve a Patient Access Scheme (PAS), which can help to improve the value for money of the medicine. **Abbreviated submissions:** this process was introduced by SMC as an interim measure in October 2020 for medicines where alternatives within the same therapeutic class are already available for the same indication. It was part of SMC's strategy to resume business following the pause due to the COVID pandemic. The aim was to reduce demand on committee members by streamlining decisions on certain medicines. Following a positive stakeholder evaluation, it is now a permanent process.

FACILITATED REGULATORY PATHWAYS

Table 6. 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.

Access Consortium	Medium-sized coalition to promote greater regulatory collaboration and alignment of regulatory requirements between Australia-Canada-Singapore-Switzerland-UK	• Maximises international cooperation, reduce duplication, and increase each agency's capacity to ensure consumers have timely access to high quality, safe and effective therapeutic products. • Maximises the use of up-to-date technical expertise, and ensures a consistent, contemporary approach to assessing the benefits and risks associated with the use of therapeutic product
Project Orbis	An initiative of the FDA Oncology Center of Excellence (OCE), provides a framework for concurrent submission and review of oncology products among international partners – Australia – Brazil – Canada – Singapore – Switzerland – UK - US. There are three types of Project Orbis submissions which are dependent on the timelines between FDA and partners: A, where submission is largely concurrent, compared to B, where there is a > 30-day delay from FDA to partner submission, or C, where submission occurs once FDA has already taken regulatory action.	

Report prepared by

Penelope Cervelo, MRes, Research Analyst
Tina Wang, PhD, Associate Director, HTA Programme and strategic partnership
Belen Sola, PhD, Research Analyst
Neil McAuslane, PhD, Director

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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.

Centre for Innovation in Regulatory Science (CIRS)

Email: cirs@cirsci.org
Website: www.cirsci.org
Follow us on LinkedIn

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