New drug approvals in six major authorities 2013-2022:

Focus on orphan designation and facilitated regulatory pathways

This R&D Briefing presents the results from the Centre for Innovation in Regulatory Science (CIRS) annual analysis of new active substance (NAS) approvals by six major regulatory agencies: the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), the Japan Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada, Swissmedic and the Australian Therapeutic Goods Administration (TGA). The analysis focuses on 2022 as well as looking back at 2013-2022. Although median approval times can be a marker of agency performance and the time it takes to make medicines available to patients, other factors must be considered. More specifically, facilitated regulatory pathways (FRPs) and orphan drug designation are major elements of the submission and approval strategies. This R&D Briefing focuses on such factors in detail.

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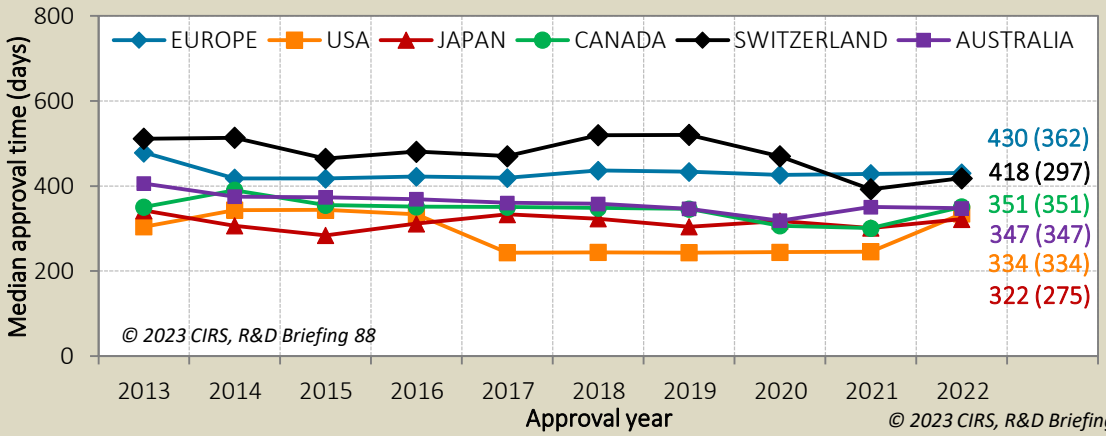
New active substance (NAS) median approval time for six regulatory authorities in 2013-2022



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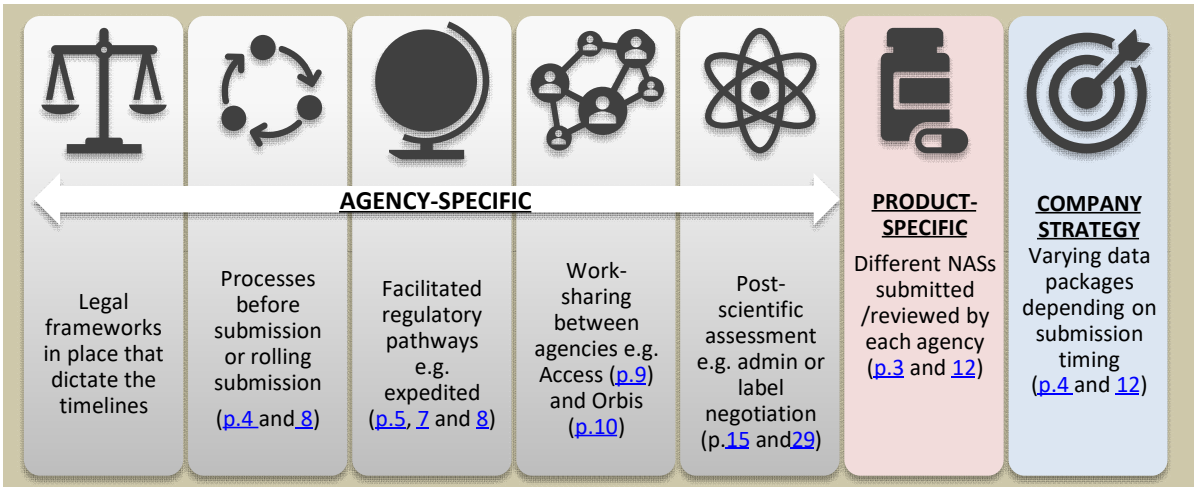
Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time. N1 = median approval time for products approved in 2022; (N2) = median time from submission to the end of scientific assessment (see p.28) for products approved in 2022.

Differences in median time to marketing authorisation can be attributed to several factors that are agency-specific, or related to company strategy, as detailed in the infographic below.



Key messages

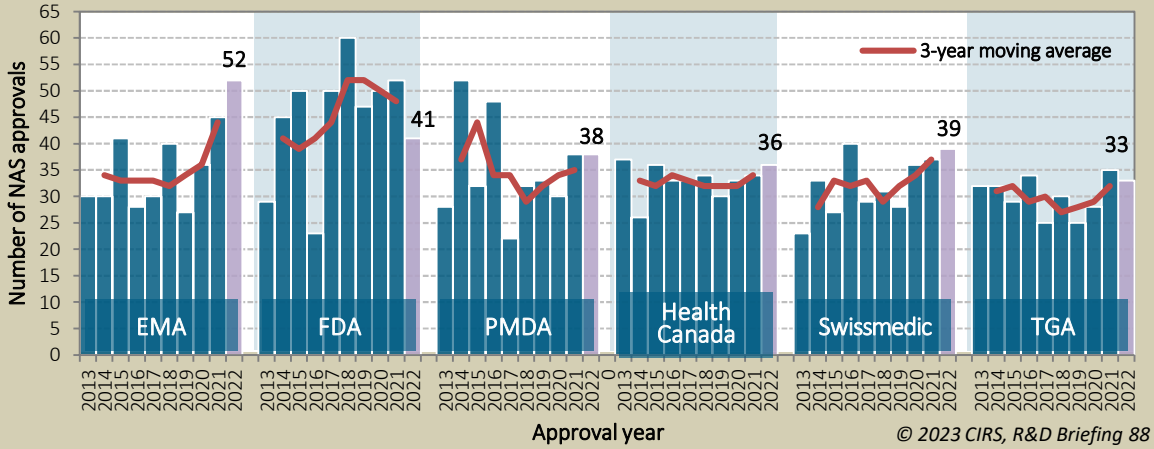
- In 2022, EMA approved the highest number of NASs (52) (Fig. 1). When looking at the 3-year moving average across the last four years, the number of approvals increased for EMA, PMDA, Health Canada, Swissmedic and TGA, whereas for FDA there was a decrease.
- PMDA had the shortest median approval time (322 days) and the shortest interquartile range (IQR) of 99 days. FDA followed this with 334 days (IQR of 213), TGA with 347 days (IQR of 123), Health Canada with 351 days (IQR of 132), Swissmedic with 418 days (IQR of 196) and EMA with 430 days (IQR of 107) (Fig. 2).
- In 2022, FDA had the shortest median submission gap (0 days) followed by EMA with 66 days, PMDA with 71 days, Health Canada with 205 days, TGA with 229 days and Swissmedic with 270 days (Fig. 3).
- All six agencies offer an expedited process designed to hasten the review process of promising NASs (Fig. 5). In 2022, the ratio of expedited approvals to standard reviews was highest for FDA (71%), followed by PMDA (39%), Health Canada (22%), EMA (10%), Swissmedic (8%), and TGA (6%).
- EMA had the greatest difference in median approval time between expedited and standard review in 2022, with 183 days, whereas the smallest difference was for PMDA, with 57 days. The difference between standard and expedited review was 132 days for Health Canada, 117 days for TGA, 113 days for Swissmedic, and 94 days for FDA (Fig. 6).
- The top five therapeutic areas (TAs) by number of NASs approved across all six agencies made up 76% (849/1110) of all approvals between 2018-2022, with anti-cancer and immunomodulators making up 53% (454/1110) of the top five TAs approvals (Fig. 7).
- Between 2018-2022, the usage of facilitated regulatory pathways (FRPs) has increased for most agencies versus 2013-2017 period (Fig. 9). For instance, for Swissmedic and TGA, the proportion of conditional/accelerated/provisional approvals has been steadily increasing and was the highest in 2022 with 33% and 30% of NASs, respectively (Fig. 10).
- For all agencies, the median submission gap and median approval time were faster for NASs approved via Access Consortium compared to all NASs approved between 2018 and 2022 (Fig. 13), suggesting that these work-sharing activities are reducing the rollout time (submission gap + approval time).
- The median rollout times for NASs approved by Project Orbis were shorter compared to Non-Orbis NASs approvals based on shorter submission gap and approval time (Fig. 15), thereby demonstrating that global regulatory collaboration is attainable and can deliver faster access to new therapies for patients with cancer.
- In 2022, the proportion of approved orphan NASs was high with 56% for FDA, 42% for EMA, 39% for PMDA, 38% for Swissmedic and 33% for TGA (Fig. 16). However, the median submission gap was longer for orphan NASs compared to non-Orphan NAS for all agencies except for EMA and FDA (Fig. 18).
- Between 2018-2022, besides anti-cancer and immunomodulators NASs, the NASs that were more commonly designated as orphans were alimentary and metabolism as well as blood and blood forming orphans (Fig. 19). Additionally, the NASs approved by all five agencies (except Health Canada) were analysed to identify commonalities and differences in the designation across the agencies. 25 out of 44 NASs approved were designated as orphans in at least one agency. Out of these 25 NASs, 88% were designated orphans in FDA as well as in PMDA, 56% in TGA and 48% in EMA as well as in Swissmedic. Only 24% of the 25 NASs were approved with an orphan designation by all five agencies, whereas 28% by four agencies (Fig. 20).
- The number of products approved by all six agencies in a five-year period decreased from 53 NASs in 2013-2017 to 42 NASs in 2018-2022, suggesting that the pace of internationalisation may be levelling off (Fig. 21).
- EMA timelines were divided into their constituents (EMA review time, company time and EU Commission). Consistent medians and IQRs were seen for all timelines across 2018-2022, which reflects the legislated timelines that EMA stipulates (Fig. 22 &23).
- FDA approvals were divided according to the type of regulatory outcome (first cycle, first cycle with major amendments, more than one cycle and more than one cycle with major amendments). In 2022, the proportion of the approvals that went through any of the last three types of regulatory outcome increased compared to previous years, which may explain the increase in last year's median approval time and its IQR compared to 2021 (Fig. 24 & 25).

See agency-specific infographics for 2022 snapshots:

EMA	FDA	PMDA	Health Canada	Swissmedic	TGA
p.18	p.19	p.20	p.21	p.22	p.23

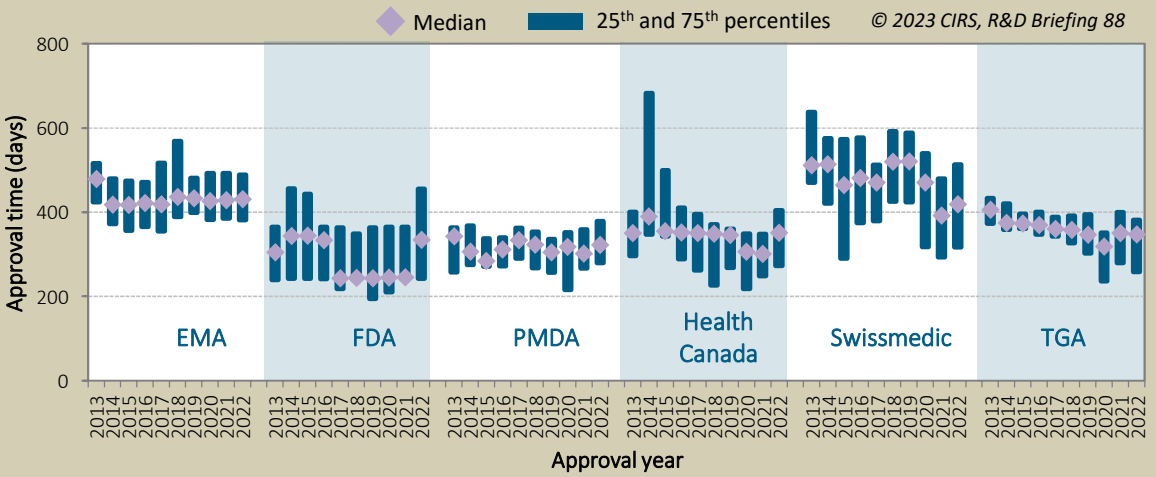
Overall approvals

Figure 1: Number of NASs approved by six regulatory authorities between 2013-2022



In 2022, EMA approved the highest number of NASs (52) (Fig. 1). When looking at the 3-year moving average across the last four years, the number of approvals increased for EMA, PMDA, Health Canada, Swissmedic and TGA, whereas for FDA there was a decrease. Comparing the number of NAS approvals during the two halves of the decade, 2013-2017 and 2018-2022, revealed that the biggest change was seen for FDA, with a 27% increase, followed by EMA (26%), Swissmedic (13%), and Health Canada (1%), whereas the number of TGA and PMDA approvals decreased by 1% and 6% respectively. The variance in the number of products approved by each agency may be explained by a number of factors, such as different submission strategies to each agency, depending on company size, unmet medical needs, review speed as well as the use of risk-based pathways and collaborative/work-sharing reviews.

Figure 2: NAS approval time for six regulatory authorities between 2013-2022

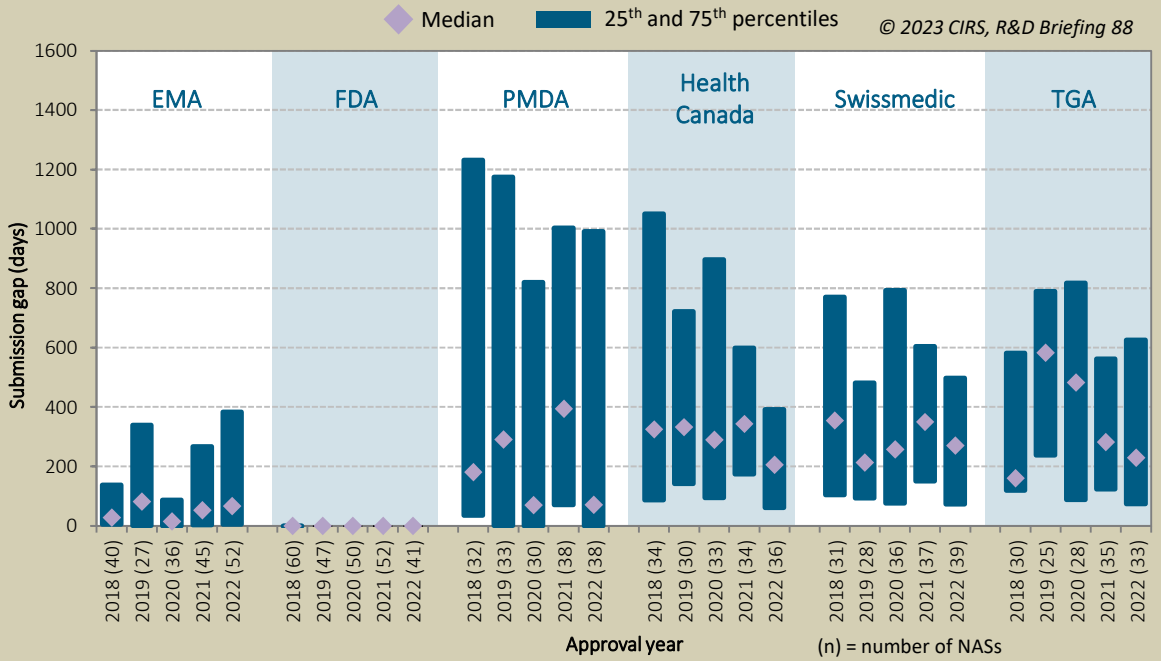


Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time.

In 2022, PMDA had the shortest median approval time (322 days) as well as the shortest interquartile range (IQR) of 99 days. FDA followed this with 334 days (IQR of 213), TGA with 347 days (IQR of 123), Health Canada with 351 days (IQR of 132), Swissmedic with 418 days (IQR of 196) and EMA with 430 days (IQR of 107) (Fig.2). Despite convergence in approval times over the last 20 years (data not shown), there were still differences in median approval times across the six agencies (cover page; 108 days between PMDA and EMA). Additionally, this difference was narrower when comparing the median time from submission to the end of the scientific assessment (87 days between PMDA and EMA). For FDA, Health Canada and TGA, the overall approval time and the time to end of the scientific assessment were the same or similar, which indicates that very few activities occur after the scientific assessment compared to EMA (see p.15) or Swissmedic (as defined on p.28). The biggest difference in median approval time between 2021 and 2022 was for FDA, which increased by 89 days, mainly as a result of the increase in the proportion of NASs approved via a first cycle with major amendments, a resubmission or a resubmission with major amendments (described in p.16).

Submission gap

Figure 3: NAS submission gap for six regulatory authorities between 2018-2022



Submission gap is calculated as the time from the date of submission at the first regulatory agency to the date of regulatory submission to the target agency.

In 2022, FDA had the shortest median submission gap (0 days) followed by EMA with 66 days, PMDA with 71 days, Health Canada with 205 days, TGA with 229 days and Swissmedic with 270 days (Fig. 3). Compared with 2021, the median submission gap for PMDA has decreased by 325 days, followed by Health Canada with 138 days, Swissmedic with 80 days, TGA with 53 days and was similar for EMA. The submission gap was also analysed in terms of the variance around the median and IQR. For EMA, the 75th percentile for the submission gap has increased from 267 to 384 days. The decrease in Health Canada and Swissmedic median submission gap was also reflected in a decrease in the 25th and 75th percentile. PMDA had the widest IQR compared to the other five agencies across 2018-2022. In 2022, the 25th percentile of 0 days likely reflects the submission strategy of local companies that only submit to Japan, whereas the high 75th percentile of 992 days may be a result of certain, particularly smaller international companies, submitting to Japan later due to resource constraints.

Figure 4: Proportion of NASs approved by more than one agency between 2018-2022

	% of NASs approved by more than one agency				
Agency	**2018**	**2019**	**2020**	**2021**	**2022**
EMA	100%	93%	92%	98%	90%
FDA	77%	85%	76%	71%	61%
PMDA	88%	82%	73%	79%	79%
Health Canada	100%	97%	100%	100%	94%
Swissmedic	87%	96%	100%	97%	100%
TGA	97%	100%	96%	100%	91%

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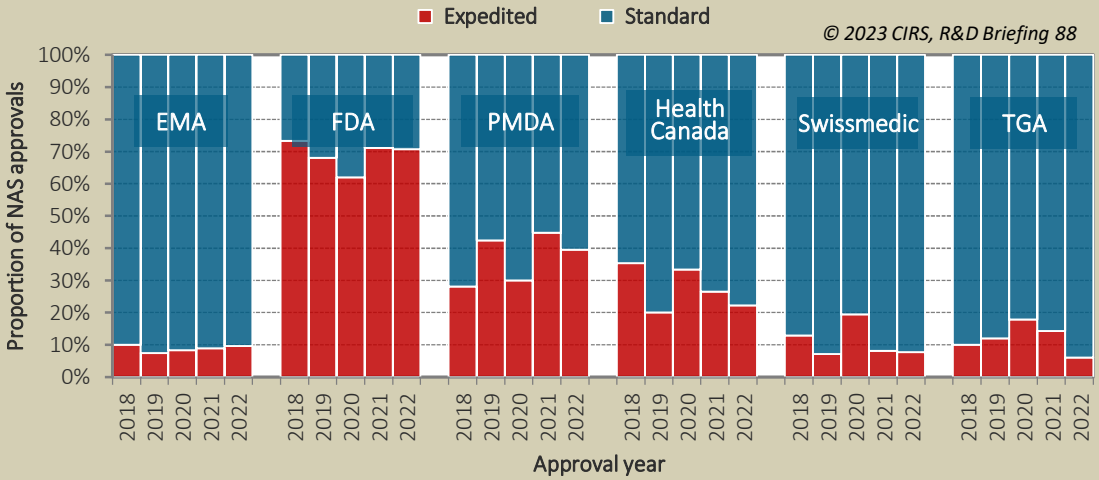
The internationalisation of products was studied by comparing whether the NASs were approved by more than one agency. For FDA, in 2022, 39% of NASs were just approved in US, although given this % was lower in 2018-2021, some of those products are likely to reach the other agencies at a later stage. For PMDA, in 2022, 21% of NASs were approved only in Japan, and were mostly developed by local Japanese companies that do not submit to other markets.

Characteristics: Review type

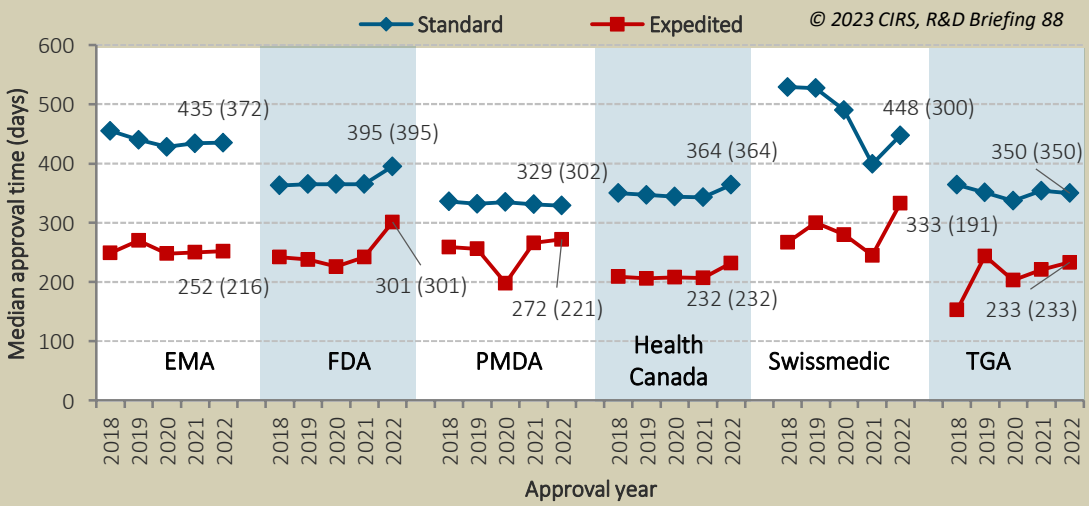
Figure 5: Number of NAS approvals by review type for six regulatory authorities between 2018-2022



'Expedited review' refers to EMA 'Accelerated Assessment', Swissmedic 'Fast Track' and FDA/PMDA/Health Canada/TGA 'Priority Review'. TGA introduced an expedited (priority) review programme in 2017.

All six agencies offer an expedited process designed to hasten the review process of promising NASs (Fig. 5). In 2022, the ratio of expedited approvals to standard reviews was highest for FDA (71%), followed by PMDA (39%), Health Canada (22%), EMA (10%), Swissmedic (8%), and TGA (6%). The proportion of expedited approvals was similar in 2022 compared to 2021 for the six agencies, the biggest difference being TGA, where the percentage decreased by eight percentage points. In the last year, EMA approved only five expedited approvals, partially because the review type can be reverted to standard review if the legislated timelines can not be met. For instance, in 2022, seven NASs initially designated by EMA as expedited were reverted, whereas, for 11 NASs, the applicant requested expedited review, but these requests were not granted by EMA.

Figure 6: NAS median approval time by review type for six regulatory authorities between 2018-2022

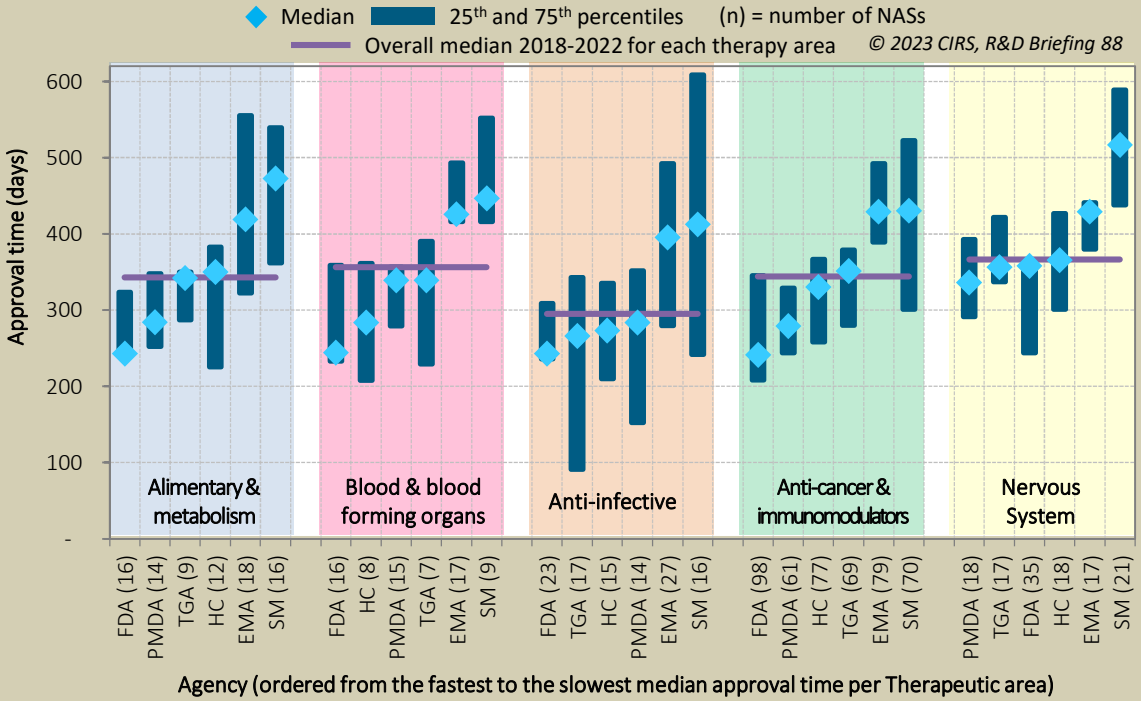


'Expedited review' refers to EMA 'Accelerated Assessment', Swissmedic 'Fast Track' and FDA/PMDA/Health Canada/TGA 'Priority Review'. TGA introduced an expedited (priority) review programme in 2017. Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time. N1 = overall approval time for 2021; (N2) = time from submission until the end of scientific assessment (see p.28) for 2022.

EMA was the agency with the greatest difference in median approval time between expedited and standard review in 2022, with a difference of 183 days, whereas the smallest difference was for PMDA, with 57 days. The difference between standard and expedited review was 132 days for Health Canada, 117 days for TGA, 113 days for Swissmedic, and 94 days for FDA (Fig.6). For EMA, in 2022, the expedited median time was 216 days when analysing the time until the end of scientific assessment, and so the authorisation process (European Commission) took 36 days, compared to 60 days for standard. Although the Swissmedic median time from submission until the end of scientific assessment was 191 for expedited, an additional 142 days were needed to receive marketing authorisation as a result of a labelling process. Both EMA and Swissmedic have recently been implementing measures to accelerate the authorisation processes further.

Characteristics: Therapeutic area

Figure 7: NAS median approval time by top five therapeutic areas (TAs) for six regulatory authorities between 2018-2022



Therapy areas relate to the WHO ATC codes. Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time.

The top five TAs by number of NASs approved across all six agencies made up 76% (849/1110) of all approvals between 2018-2022, with anti-cancer and immunomodulators making up 53% (454/1110) of the top five TAs approvals (Fig. 7). Anti-infective therapies obtained the fastest median global approval of the top five therapeutic areas with 295 days. When comparing the overall median approval times reported in previous briefings (R&D 77, 81 and 85), it appears that the gap between the overall median approval time of anti-infective therapies versus other therapeutic areas has widened, which may be due to products approved for COVID. On the other hand, alimentary and metabolism therapies are now in second place together with anti-cancer and immunomodulator therapies, with an overall median approval time of 343 and 344 days, respectively, which might be due to the use of expedited review pathways in these areas as well as a shift in unmet medical need.

Figure 8: NAS overall median approval time by top five therapeutic areas in relation to expedited approvals for six regulatory authorities between 2018-2022

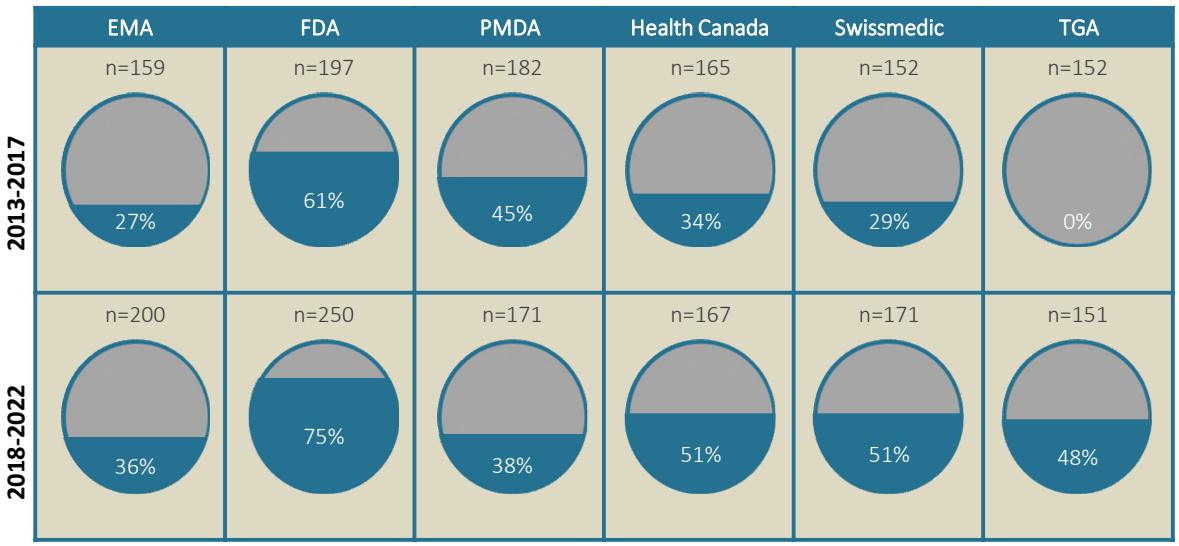
© 2023 CIRS, R&D Briefing 88	Alimentary and metabolism	Blood and blood forming organs	Anti-infective	Anti-cancer and immuno-modulators	Nervous system
	Approval time in days (proportion of expedited approvals)				
EMA	419 (22%)	426 (18%)	395 (4%)	429 (9%)	429 (12%)
FDA	243 (81%)	244 (69%)	243 (91%)	241 (77%)	358 (49%)
PMDA	284 (57%)	339 (47%)	284 (57%)	279 (51%)	336 (11%)
Health Canada	350 (33%)	284 (50%)	273 (33%)	330 (23%)	366 (28%)
Swissmedic	473 (0%)	447 (0%)	413 (6%)	431 (16%)	517 (14%)
TGA	342 (11%)	339 (29%)	266 (6%)	351 (12%)	356 (6%)

Therapeutic areas relate to the WHO ATC codes. 'Expedited review' refers to EMA 'Accelerated Assessment', Swissmedic 'Fast Track' and FDA/PMDA/Health Canada/TGA 'Priority Review'. TGA introduced an expedited (priority) review programme in 2017. Therefore, the numbers in parentheses only relate to approvals from 2018 to 2022. Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time.

Focus on facilitated regulatory pathways (FRPs)

Over the last five years (2018-2022), the usage of facilitated regulatory pathways (FRPs) has increased for most of the agencies compared with the beginning of the decade (2013-2017) (Fig. 9). FDA was the agency that mostly used FRPs, with 75% of NASs that had at least one FRP, followed by Health Canada (51%), Swissmedic (51%), TGA (48%), PMDA (38%) and EMA (36%). TGA was the agency that has seen the biggest increase in terms of the percentage of NAS approvals with FRPs, which demonstrates the recent implementation of the five FRPs by TGA (Priority review, Provisional approvals, Comparable overseas regulators (COR) review, Access Work-sharing Consortium, and Project Orbis). PMDA was the only agency where the proportion of NASs approved with an FRP decreased (by seven percentage points) when comparing 2013-2017 and 2018-2022.

Figure 9: Proportion of NAS approved by each agency between 2013-2017 vs 2018-2022 that benefited from an FRP



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The number of conditional/accelerated/provisional approvals has generally increased in the last five years across the six agencies. For Swissmedic and TGA, the proportion of conditional/accelerated/provisional approvals has been steadily increasing and was the highest in 2022 with 33% and 30% of NASs respectively (Fig. 10). On the other hand, for EMA, FDA and Health Canada, the proportion of conditional/accelerated approvals decreased by seven, ten and 21 percentage points, respectively. Despite these differences in the last year, in general, these types of approval pathways were faster than the overall median approval time for all six regulatory agencies (Fig. 11).

Figure 10: Number of NAS approved through a conditional/accelerated/provisional approval pathway by the six regulatory authorities between 2018-2022

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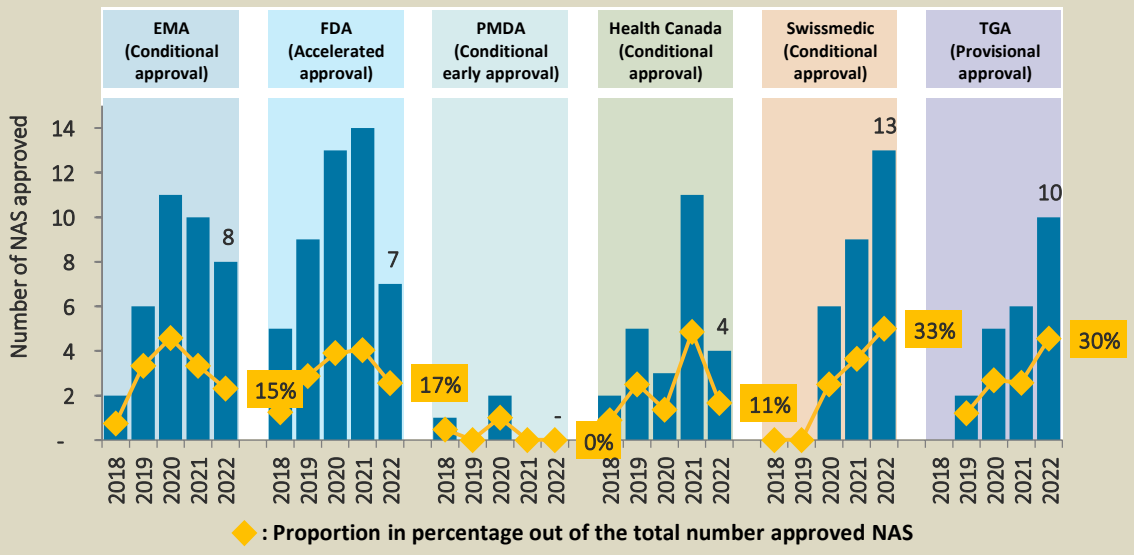
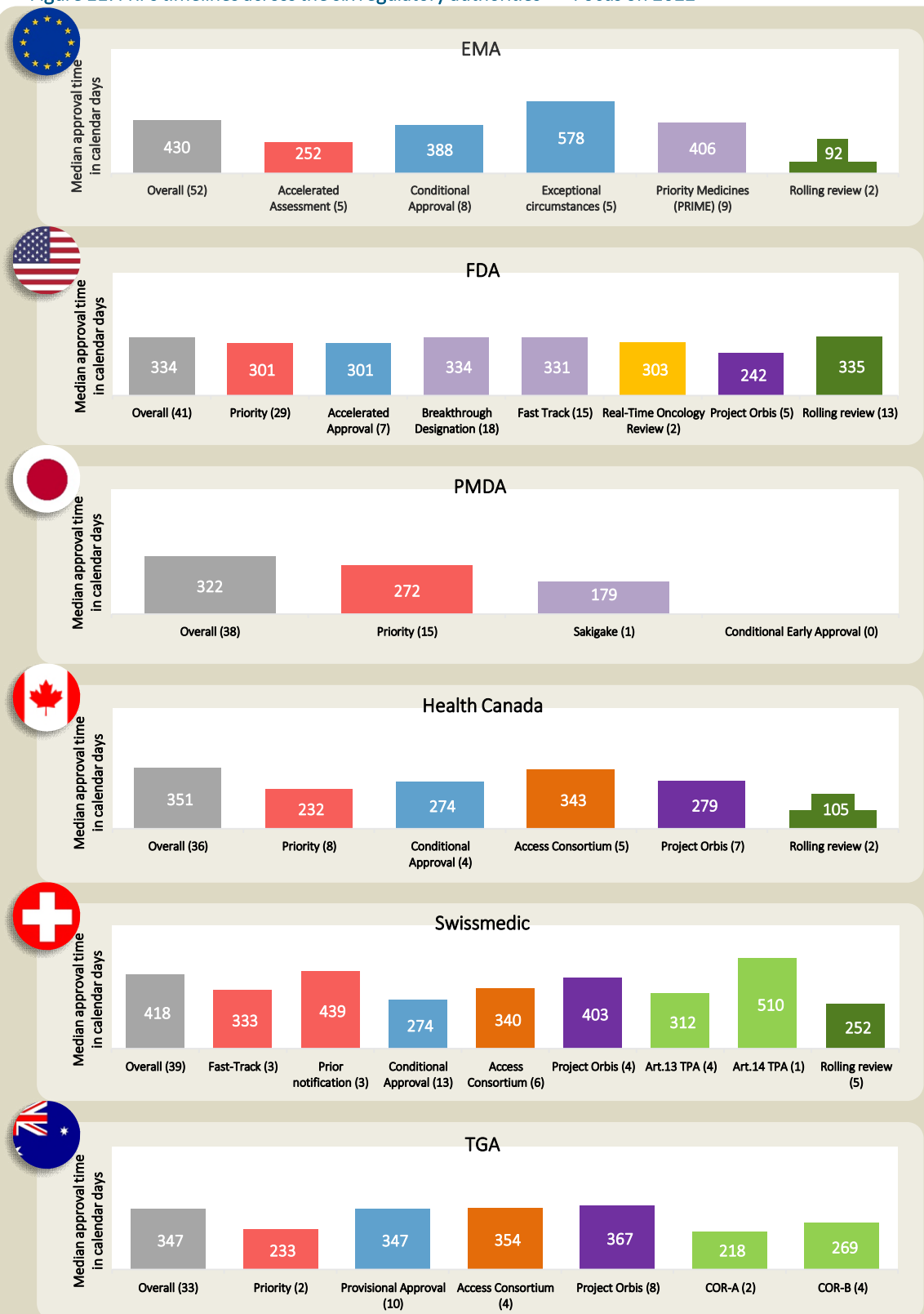


The 2022 NAS median approval times for the different FRPs are illustrated on the next page (Fig. 11).

Focus on facilitated regulatory pathways (FRPs) *(cont.)*

Figure 11: FRPs timelines across the six regulatory authorities — Focus on 2022



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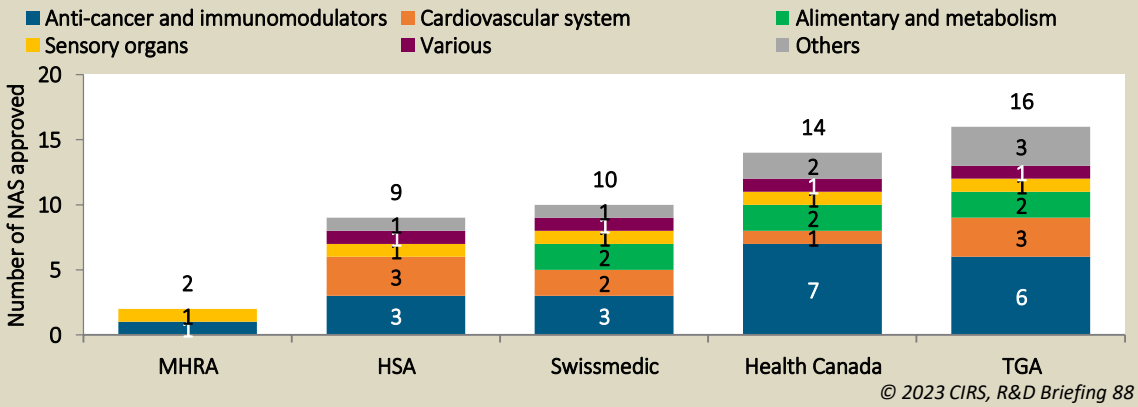
(n) = number of NASs

For FRP definitions go to p.26 of this R&D Briefing.

Focus on Access Consortium

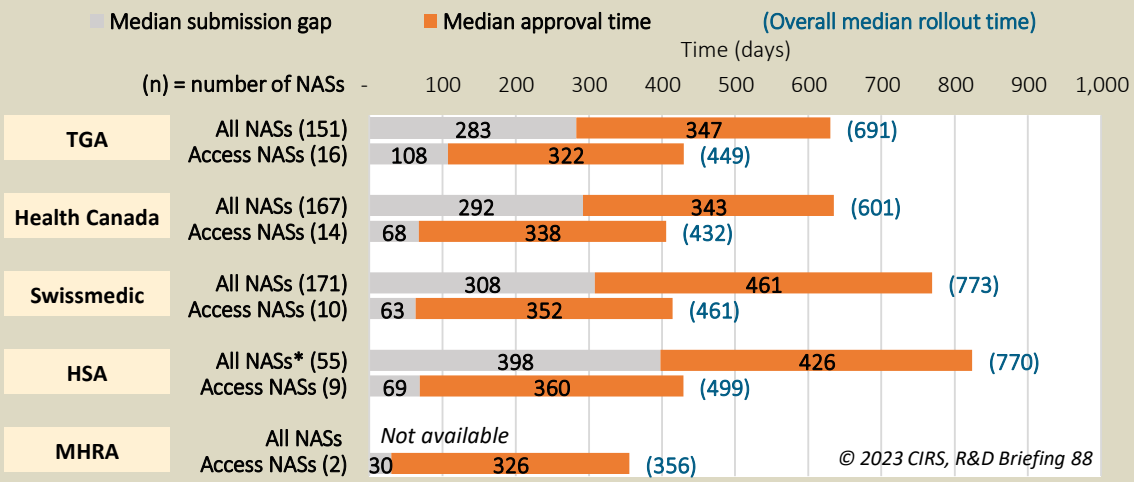
The Access Consortium is a medium-sized coalition which was formed in 2007 by 'like-minded' regulatory agencies to promote greater collaboration and alignment of regulatory requirements. Its goal is to maximise international cooperation, reduce duplication, and increase each agency's capacity ensuring timely access to high-quality, safe and effective medicines to patients. As part of the work-sharing process, the agencies review different parts of the dossier. Although the review is shared, each regulator makes an independent decision regarding approval (market authorisation) of the new medicine. TGA was the agency that participated the most, approving 16 NASs, followed by Health Canada with 14 NASs, Swissmedic with 10 NASs, HSA with nine NASs and MHRA with two NASs. In general, anti-cancer and immunomodulators and cardiovascular therapies account for the majority of the approvals (Fig.12).

Figure 12: Number of NAS approved through the Access Consortium between 2018-2022 by type of therapeutic indication



For all the assessed agencies, median submission gap and median approval time were faster for NASs approved via Access Consortium compared to all NASs approved between 2018 and 2022 (Fig. 13), suggesting that these work-sharing activities are reducing the rollout time (submission gap + approval time). In terms of reduction in the overall median rollout time for Access NASs compared to all NASs, the biggest differences were seen for Swissmedic, HSA, and TGA, where Access NAS median rollout times were 312 days, 271 days and 242 days faster, respectively when compared to all NASs approved between 2018 and 2022. The median submission gap was the metric most affected by this type of work-sharing initiative and it was between 170 to 330 days shorter across the agencies, representing a reduction in submission time between 62 to 83%.

Figure 13: Median submission gap and median approval time for all NASs approved compared to those approved via the Access Consortium between 2018-2022

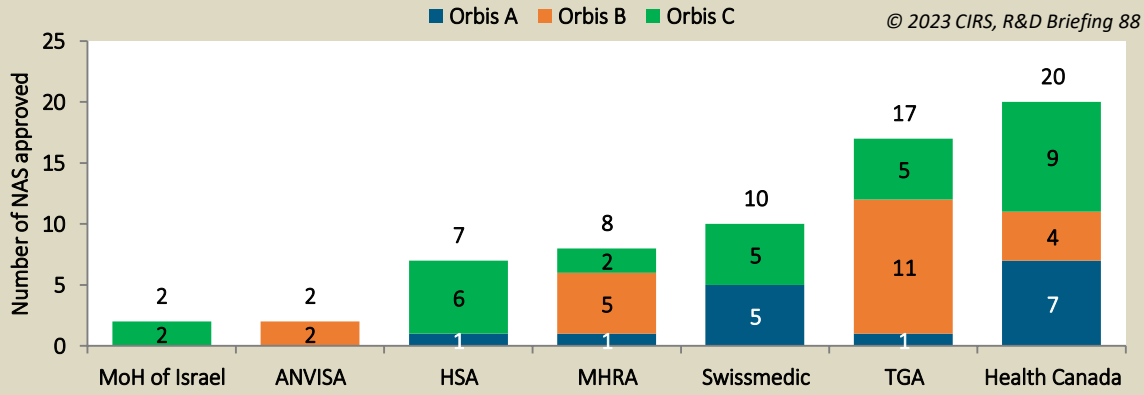


Submission gap is calculated as the time from the date of submission at the first regulatory agency (out of EMA, FDA, PMDA, Health Canada, Swissmedic and TGA) to the date of regulatory submission to the target agency. Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. Rollout time is calculated from the date of submission at the first regulatory agency to the date of regulatory approval at the target agency.
**The timelines for other NASs were obtained from Industry via the CIRS Growth and Emerging Markets Programme.*

Focus on Project Orbis

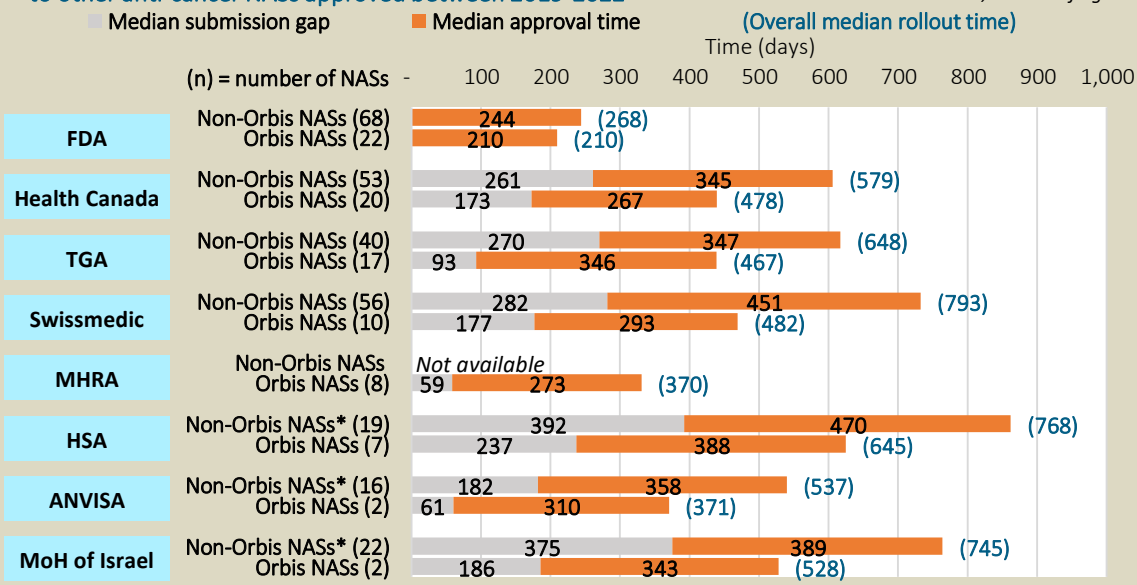
Project Orbis is an initiative of the US FDA Oncology Center of Excellence that aims to give patients faster access to promising cancer treatments across the globe. Project Orbis partners work together on the review of submissions for cancer drugs. There are three types of Project Orbis submissions which 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. For NASs approved through Project Orbis between 2019-2022 (Fig.14), the highest number was by Health Canada (20), followed by TGA (17), Swissmedic (10), MHRA (8), HSA (7), ANVISA (2) and the Ministry of Health of Israel (2) which joined the partnership in 2021.

Figure 14: Number of NAS approved through Project Orbis between 2019-2022 by Orbis type



The median rollout times for NASs approved by Project Orbis were shorter compared to Non-Orbis NASs approvals based on shorter submission gap and approval time (Fig. 15), thereby demonstrating that global regulatory collaboration is attainable and can deliver faster access to new therapies for patients with cancer. Regarding the reduction of median submission gap, this was 189 days shorter for Orbis NASs compared to non-Orbis NASs for the Israeli MoH, followed by HSA with 155 days, TGA with 177, ANVISA with 121, Swissmedic with 105, and Health Canada with 88 days. In addition, median approval times were 158 days shorter for Orbis NASs compared to non-Orbis NASs for Swissmedic, followed by HSA with 82 days, Health Canada with 78, ANVISA with 48, the MoH of Israel with 46, FDA with 34, and TGA with one day.

Figure 15: Median submission gap and median approval time for NASs approved by Project Orbis compared to other anti-cancer NASs approved between 2019-2022

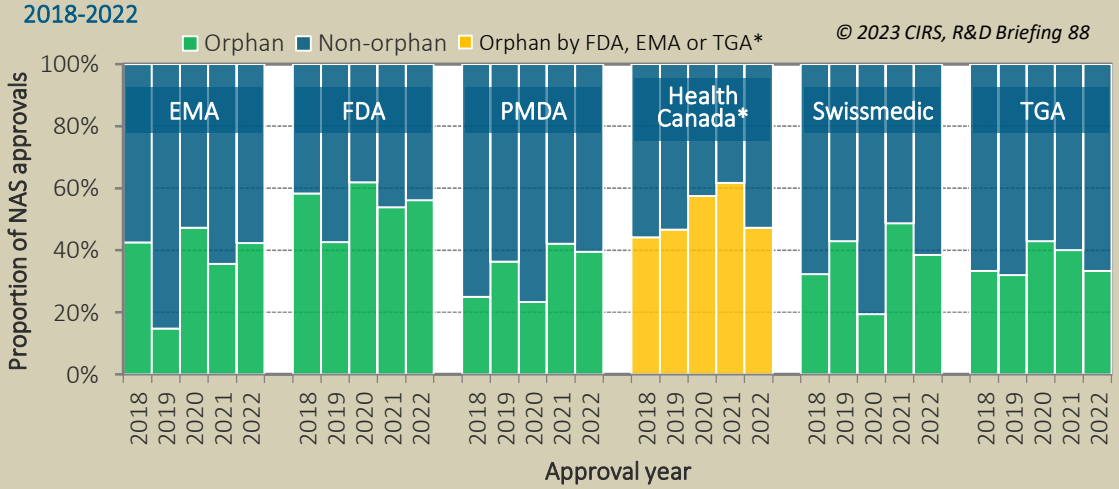


Submission gap is calculated as the time from the date of submission at the first regulatory agency to the date of regulatory submission to the target agency. Four products were considered MLEs to FDA and considered NAS to other agencies within the Project Orbis initiative, for these cases, the FDA submission date was used instead of the date of submission at the first regulatory agency. Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. Rollout time is calculated from the date of submission at the first regulatory agency to the date of regulatory approval at the target agency.

**The timelines for other Non-Orbis NASs were obtained from Industry via the CIRS Growth and Emerging Markets Programme*

Focus on orphan designations

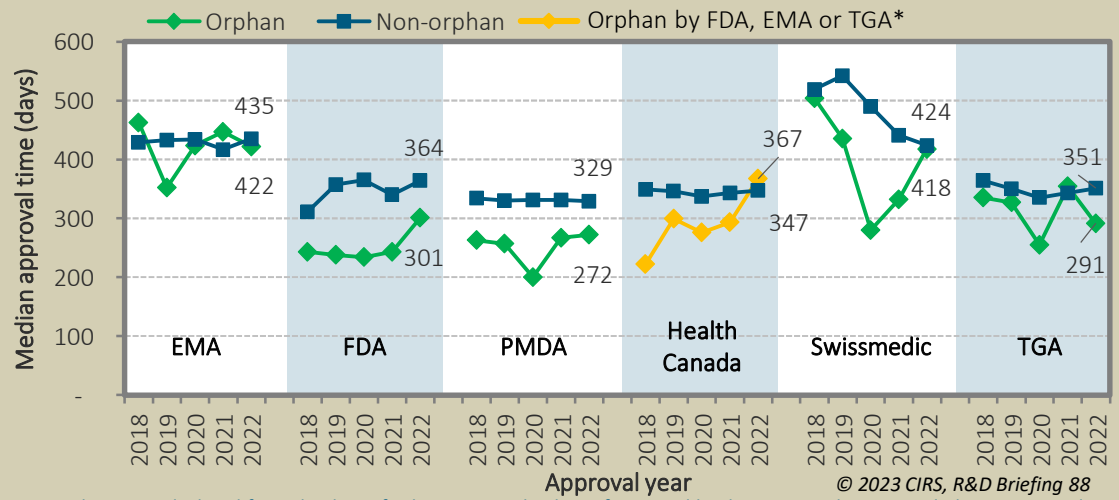
Figure 16: Proportion of NAS approvals by orphan designation for six regulatory authorities between 2018-2022



** Health Canada does not currently have an orphan policy; this data shows the number of medicines that were approved by Health Canada that were classified as orphan by either FDA, EMA or TGA.*

In 2022, the proportion of approved NASs with an orphan designation was high across the agencies with 56% for FDA, 42% for EMA, 39% for PMDA, 38% for Swissmedic and 33% for TGA (Fig.16).
From 2018-2022, the proportion of orphans varied year-on-year but generally increased compared to 2013-2017 where the proportion of NASs approved with an orphan designation was 44% for FDA, 41% for Health Canada*, 35% for PMDA, 33% for EMA, 29% for TGA and 28% for Swissmedic. This may also be due to disease stratification and companies' growing R&D pipelines and is consistent with increased commitment from agencies to tackle unmet medical needs. The variance across agencies may be due to a variety of factors, such as differences in orphan designation criteria across the agencies or the indication submitted by the sponsor, which is analysed on p.13.

Figure 17: NAS median approval time by review type for six regulatory authorities between 2018-2022



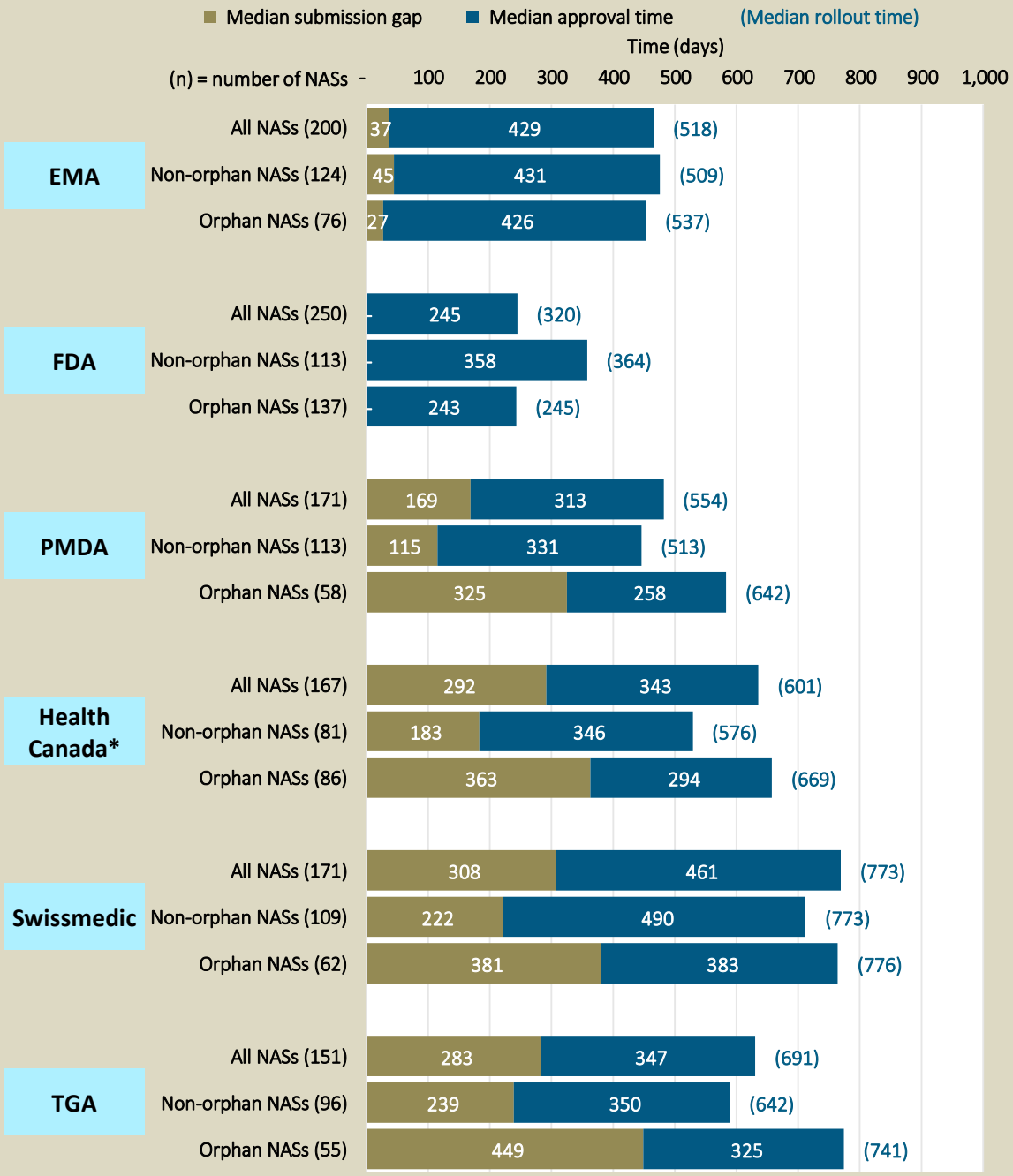
Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time.
**Health Canada does not currently have an orphan policy; this data shows the number of medicines that were approved by Health Canada that were classified as orphan by either FDA, EMA or TGA.*

Approval timelines for orphans and non-orphans were compared across the six agencies between 2018-2022 (Fig. 17). PMDA had the fastest median approval time for orphans in 2022 (272 days), as all these products were approved through expedited review, due to an incentive from PMDA to address unmet need. TGA had the second fastest median approval time for orphans in 2022 (291 days). Health Canada does not currently have an orphan policy; however, for the 17 NASs approved by Health Canada in 2022 that were classified as orphan by either FDA, EMA or TGA, the median approval time was 367 days.

Focus on orphan designations *(cont.)*

The median submission gap was longer for orphan NASs compared to non-orphan NAS for all agencies except for EMA and FDA (Fig.18). Although the median approval time was shorter for NASs approved with an orphan designation compared to non-orphan NASs for all agencies, the longer time to submission resulted in a longer overall rollout time for NASs approved with an orphan designation across the four agencies. The median submission gap for orphan NASs was 210 days longer for PMDA and TGA, 180 longer days for Health Canada, and 159 days for Swissmedic.

Figure 18: Median submission gap and median approval time for NASs approved with an orphan designation compared to other approved NASs between 2018-2022



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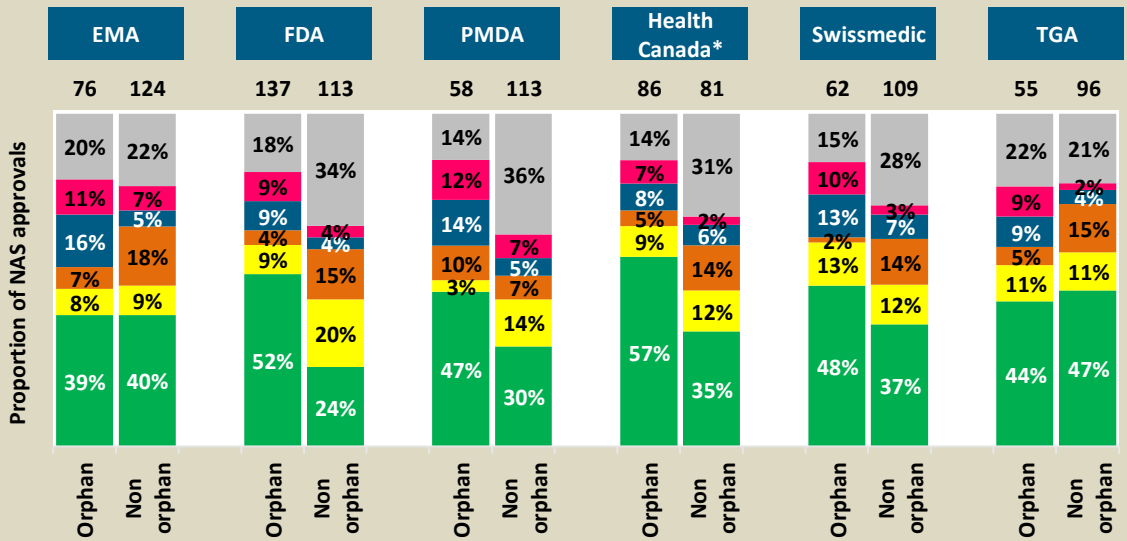
Submission gap is calculated as the time from the date of submission at the first regulatory agency to the date of regulatory submission to the target agency. Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time. Rollout time is calculated from the date of submission at the first regulatory agency to the date of regulatory approval at the target agency.
** Health Canada does not currently have an orphan policy; this data shows the number of medicines that were approved by Health Canada that were classified as orphan by either FDA, EMA or TGA.*

Focus on orphan designations *(cont.)*

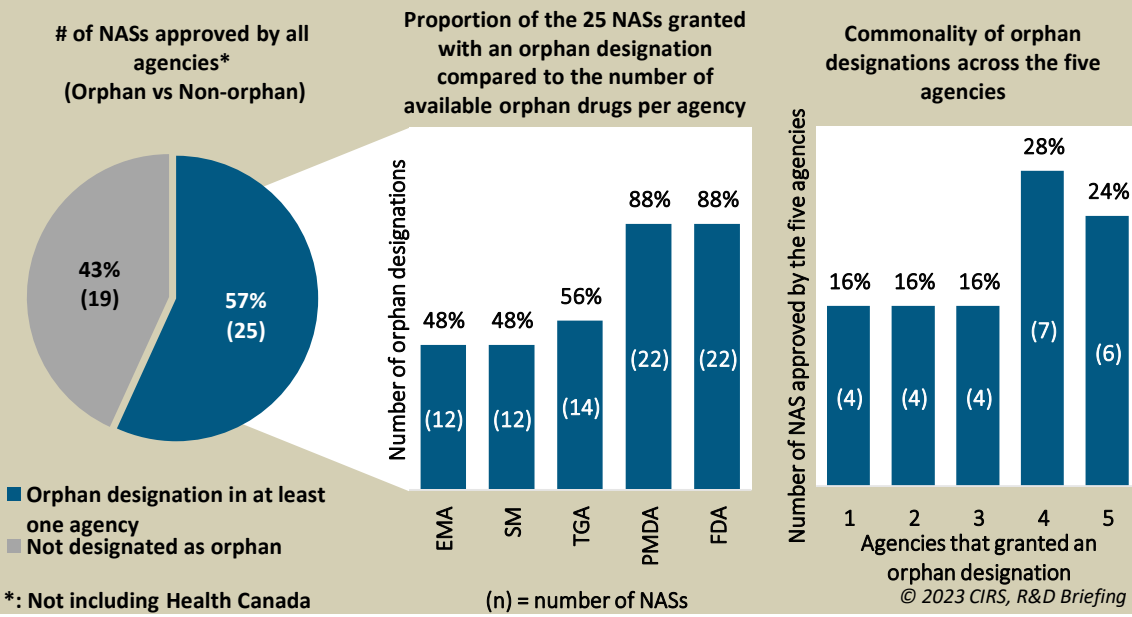
The therapeutic area was compared for orphan and non-orphan NASs, demonstrating that most of the orphan products approved are anti-cancer and immunomodulators. In addition, the NASs that were more commonly designated as orphans compared to non-orphans were alimentary and metabolism as well as blood and blood forming orphans (Fig.19).

Figure 19: Distribution in the therapeutic area for orphan NASs vs non-orphans approved by the six regulatory authorities between 2018-2022



Compounds approved by all five of the agencies (except Health Canada, which does not currently have an orphan policy) were analysed to identify commonalities and differences in the designation across the agencies. In 2018-2022, 25 out of 44 NASs approved by all agencies were designated as an orphan in at least one agency (Fig.20). Out of these 25 NASs, 88% were designated orphans in FDA as well as in PMDA, 56% in TGA and 48% in EMA as well as in Swissmedic. Only 24% of the NASs were approved with an orphan designation by all five agencies and 28% by four agencies. This landscape may be a result of several factors such as company strategy, the higher proportion of small domestic pharmaceutical companies developing orphan drugs in the US and Japan, the difference in the definition of what constitutes an orphan drug, e.g., epidemiology and severity of the rare disease for each jurisdiction. See the *Appendix* for more detail.

Figure 20: Orphan designation of NASs approved by all five agencies between 2018-2022



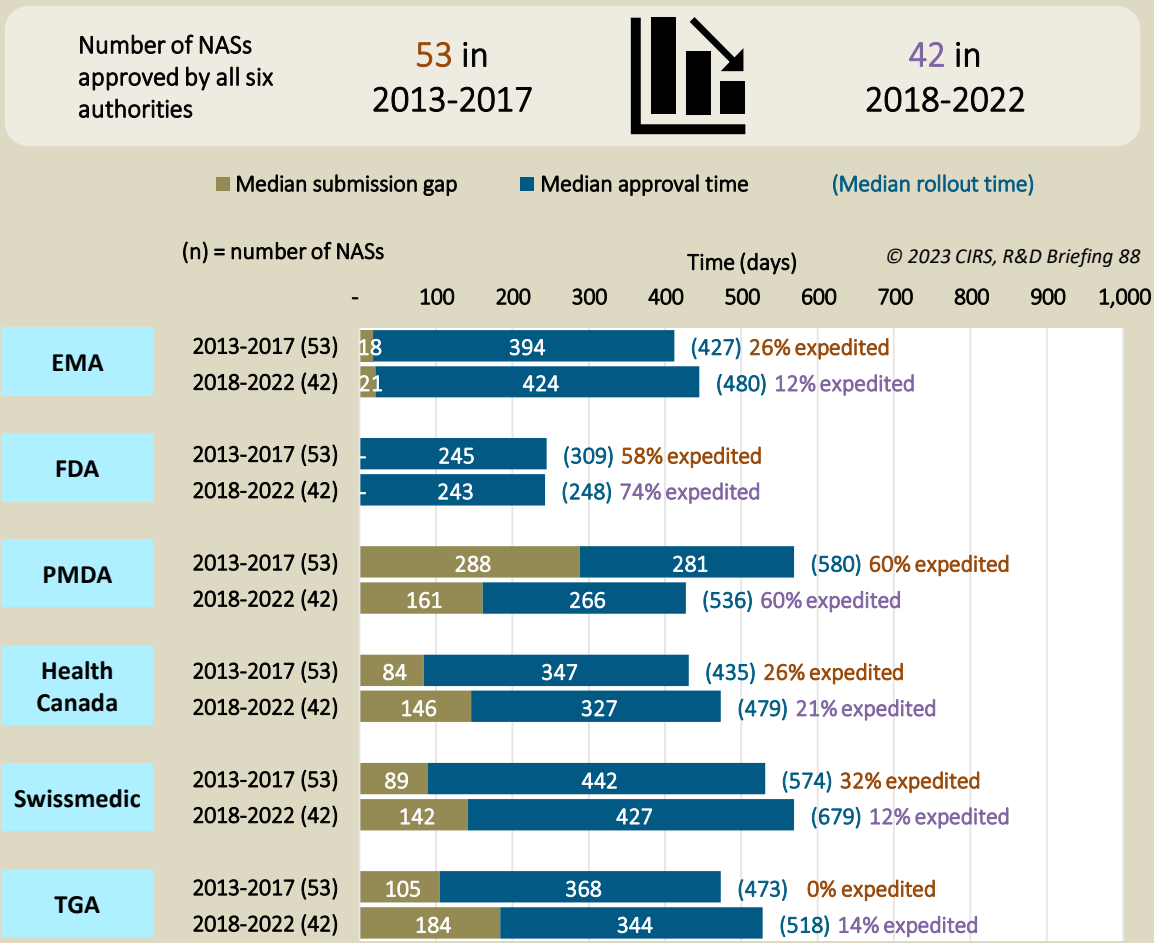
Common approvals across the six regulatory agencies

In order to have a true regulatory performance benchmark assessment, it is important to review the compounds that were approved by all six agencies. This assessment was carried out for the two time cohorts in the last decade (2013-2017 and 2018-2022) to identify trends. The number of products approved by all six agencies in a five-year period decreased from 53 NASs in 2013-2017 to 42 NASs in 2018-2022, compared to analyses in the past years where there was an increase (see R&D Briefing 70 and 77), suggesting that the pace of internationalisation may be levelling off.

The rollout time, consisting of the submission gap and approval time (Fig. 21), can be influenced by a number of factors such as company submission strategy and the use of expedited pathways to address unmet medical need. The fastest overall median rollout time for the 2018-2022 cohort was for FDA with 248 days, as a result of companies submitting there first and quick regulatory review times due the wider use of expedited reviews (74%), followed by Health Canada with 479 days, EMA with 480 days, TGA with 518 days, PMDA with 536 days, and Swissmedic with 679 days.

Submission to EMA occurred almost simultaneously with FDA, followed by Swissmedic, Health Canada, PMDA and TGA. Compared to past R&D Briefings, this Briefing suggests that there has been a change in the waves of submission to agencies, where submission to PMDA was previously found to be later than the submission to Health Canada, Swissmedic, and TGA, but it is now more in line with those agencies. Indeed, the median submission gap to PMDA was almost halved from 288 days in 2013-2017 to 161 days in 2018-2022.

Figure 21: Median submission gap and median approval time for NASs approved by all six authorities in 2013-2017 (53) compared with 2018-2022 (42), as well as their expedited review proportion



Submission gap is calculated as the time from the date of submission at the first regulatory agency to the date of regulatory submission to the target agency. Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time. Rollout time is calculated from the date of submission at the first regulatory agency to the date of regulatory approval at the target agency. 'Expedited review' refers to EMA 'Accelerated Assessment', Swissmedic 'Fast Track' and FDA/PMDA/Health Canada/TGA 'Priority Review'.

Figure 22: Median EMA review time, company response time and EU commission time for NASs approved by EMA between 2018-2022

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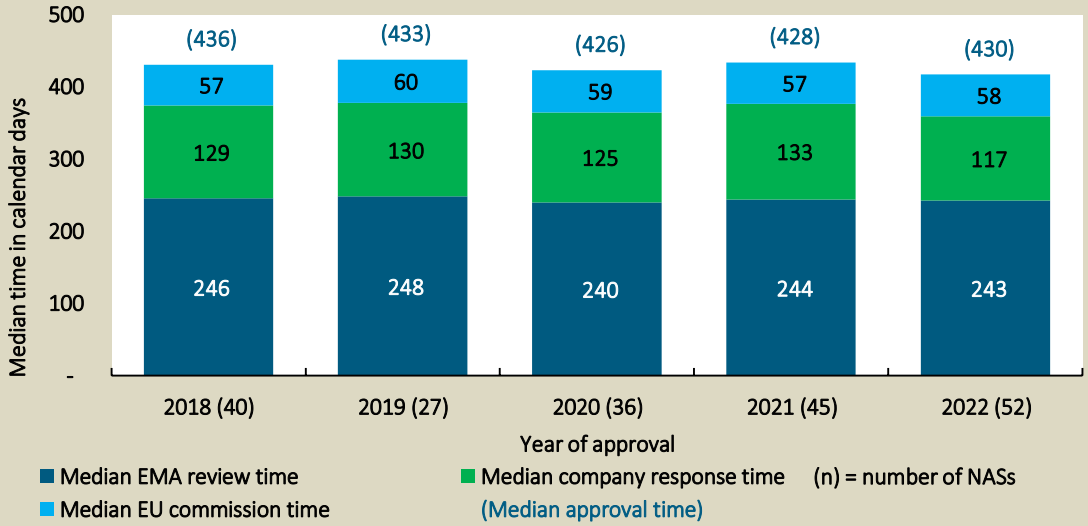
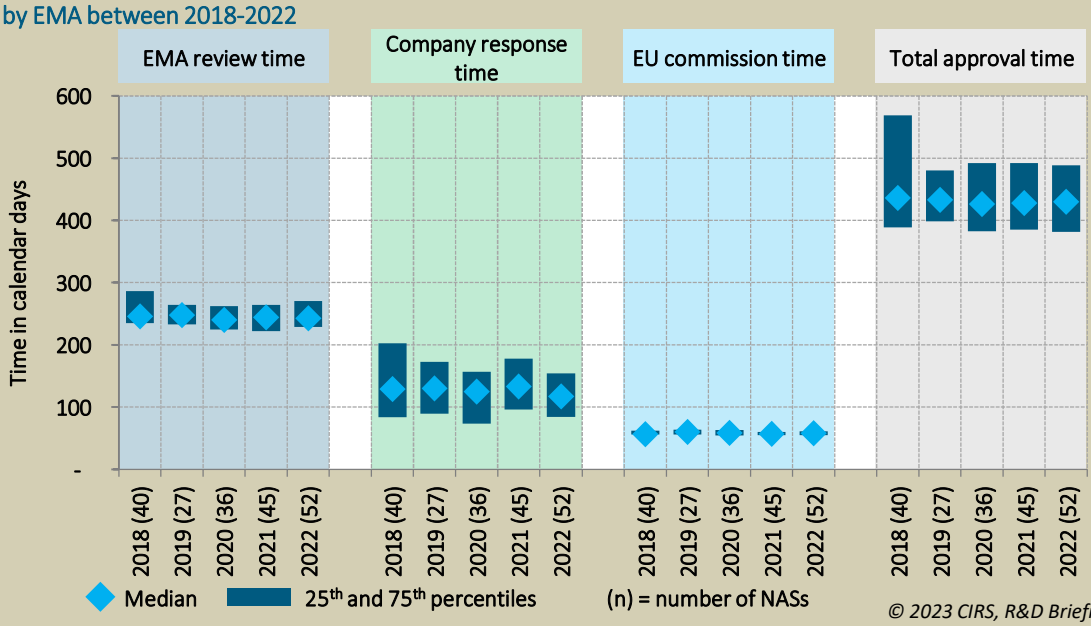


EMA timelines were subsequently broken down into their constituents, namely the EMA review time during validation and scientific assessment, the company time and the European Commission time to obtain final marketing authorisation. The results demonstrate the consistency in those timelines regarding the median and IQR across 2018-2022, which reflects the legislated timelines that EMA stipulates (Fig. 22 & 23). EMA's overall median approval time ranged from 426 to 436 days across the five years, median EMA review time ranged from 240 to 248 days (57% out of the median approval time in 2022), whereas the median company response time ranged between 117 and 133 days (27% out of the median approval time in 2022) and the median EU commission time ranged between 57 and 60 days (13% out of the median approval time in 2022). In addition, the IQR of the overall EMA approval time decreased from 180 days in 2018 to 107 in 2022, the IQR of the EMA review time decreased from 51 days in 2018 to 42 in 2022, the IQR of the company response time decreased from 119 days in 2018 to 70 in 2022, and the IQR of the EU commission time stayed similar with 7 days in 2018 and 6 days in 2022.

Figure 23: Variance in EMA review time, company response time and EU commission time for NASs approved by EMA between 2018-2022



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Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time. Company response time is calculated as the sum of periods between the date the CHMP agrees on the consolidated List of Questions/ List of Outstanding Issues to be sent to the applicant and the date in which the applicant submits the responses. EU commission time is calculated from the date of end of scientific assessment to the date of approval by the EU commission. EMA review time is calculated as the difference among the approval time minus the sum of the company time and the EU commission time (see p.29).

Focus on types of regulatory outcome of FDA

Figure 24: Distribution of NASs approved by FDA based on the type of regulatory outcome between 2018-2022

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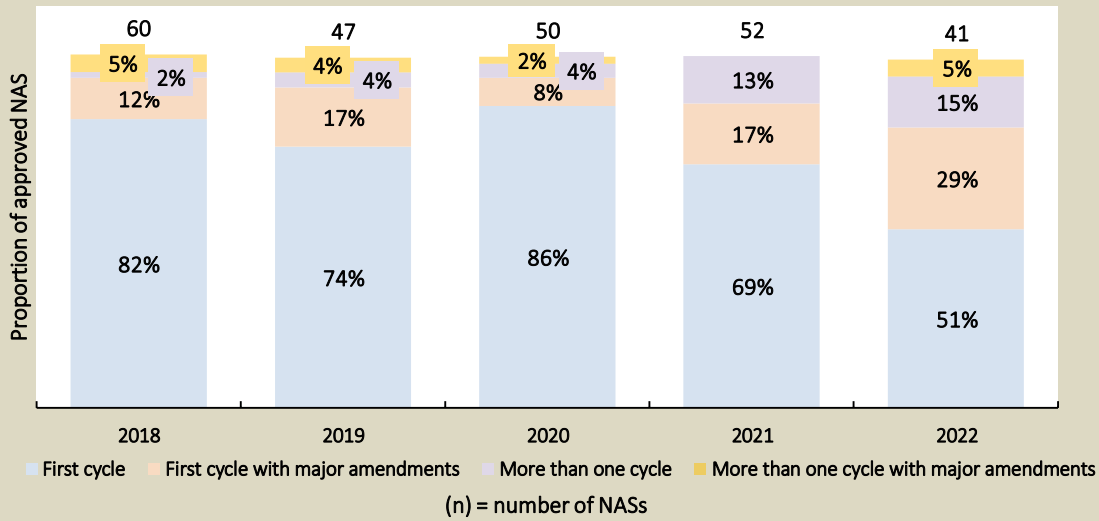
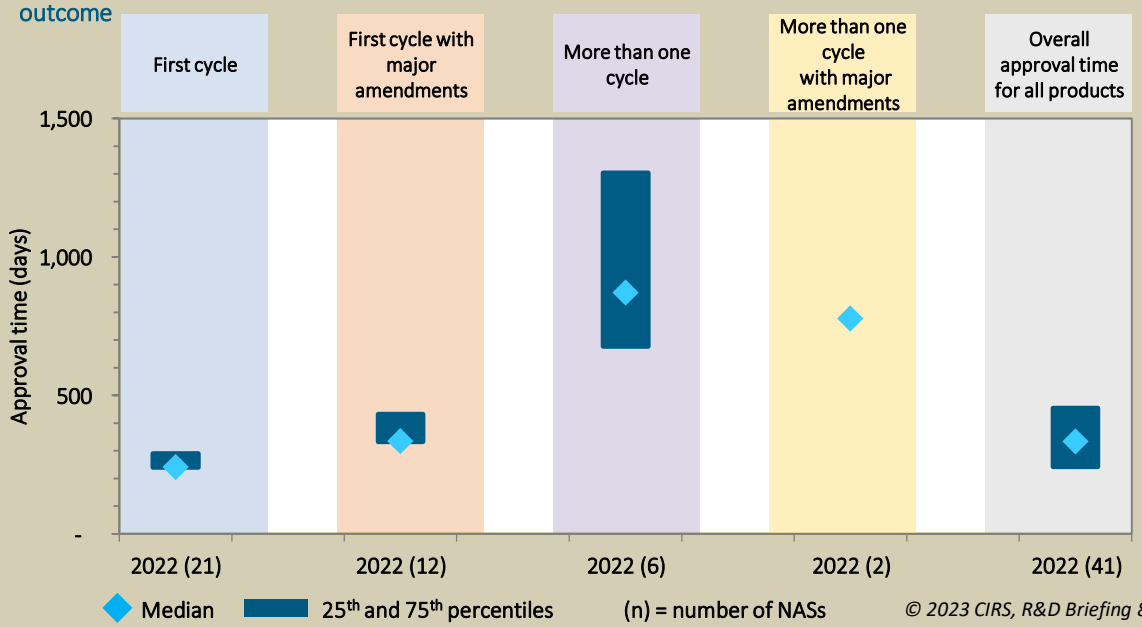


FDA approvals were broken down according to the type of regulatory outcome (first cycle, first cycle with major amendments, more than one cycle and more than one cycle with major amendments). In 2022, the proportion of the approvals that went through any of the last three types of regulatory outcome increased compared to previous years, which may explain the increase in last year's median approval time and its IQR compared to 2021 (Fig. 24 & 25).

In addition to the increase in the above-mentioned proportion of approvals with a regulatory outcome other than a first cycle approval, the NASs that went through more than one cycle review had a longer median approval. The median approval time for NASs approved through a first cycle with major amendments was 93 days longer compared to first cycle only (242 days vs 335 days) and NASs approved through more than one cycle had a median approval time 630 days longer compared to first cycle only (242 days vs 872 days). In addition, the NASs that went through more than a single cycle review showed a higher IQR (669 days) compared to the IQR from the NASs that were approved through only one cycle (49 days).

Figure 25: Variance in approval time for NASs approved by FDA in 2022 based on the type of regulatory outcome



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Approval time is calculated from the date of submission to the date of approval by the agency. Only the median is shown when (n) is lower than three

Summary of NAS approved in 2022 by the six agencies

This table summarises approval times for NAS approved in 2022 by the six agencies, broken down by product type, review type and major therapeutic area.

Agency Median approval time in calendar days	EMA  p.18	FDA  p.19	PMDA  p.20	Health Canada  p.21	Swissmedic  p.22	TGA  p.23
Number of NAS approved	52	41	38	36	39	33
NAS overall approval time (days)	430	334	322	351	418	347
By biologics (days)	425	316	343	343	388	365
By chemicals (days)	435	335	303	355	457	344
By standard review (days)	435	364	329	392	515	381
By expedited review (days)	252	301	272	232	333	233
By orphans (days)	422	301	272	367*	418	291
By anticancer and immuno-modulators (days)	429	334	293	367	444	370

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Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time.

** Health Canada does not have an orphan policy; however, 17 NASs that were classified as orphan by either FDA, EMA or TGA were approved by Health Canada in 2022, with a median approval time of 367 days.*

Focus: Approval at EMA 2022

EMA **APPROVED A TOTAL OF 52 NASs IN 2022,** WITH A MEDIAN APPROVAL TIME OF **430 DAYS AND A MEDIAN TIME TO END OF SCIENTIFIC ASSESSMENT OF 362 DAYS**

THE MEDIAN EU COMMISSION TIME WAS 58 DAYS, THE EMA REVIEW TIME 243 DAYS AND THE COMPANY TIME 117 DAYS

Type of Medicine

25 BIOLOGIC NASs APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **425 DAYS**

27 CHEMICAL NASs APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **435 DAYS**

19 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **429 DAYS**

33 NASs IN OTHER THERAPY AREAS APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **435 DAYS**

Designation and Review Type

5 EXPEDITED NAS APPROVALS IN 2022, WITH A MEDIAN APPROVAL TIME OF **252 DAYS;** THIS IS **183 DAYS FASTER** THAN THE MEDIAN OF THE **47 STANDARD NAS APPROVALS IN 2022**

22 ORPHAN NAS APPROVALS IN 2022, WITH A MEDIAN APPROVAL TIME OF **422 DAYS;** THIS IS **13 DAYS FASTER** THAN THE MEDIAN OF THE 30 **NON-ORPHAN NAS APPROVALS IN 2022**

Availability by EMA

19% OF THE NASs APPROVED IN 2022 BY EMA WERE APPROVED FIRST BY THE AGENCY OR WITHIN ONE MONTH WHEN COMPARED WITH THE FIRST APPROVAL BY ANY OF THE OTHER AGENCIES

81% OF THE NASs APPROVED IN 2022 BY EMA WERE APPROVED BY ANY OF THE OTHER AGENCIES **FIRST OR MORE THAN ONE MONTH BEFORE BEING APPROVED BY THE AGENCY**

THE MEDIAN **SUBMISSION GAP** TO EMA FOR THESE NASs WAS **85 DAYS**

Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time.'Expedited review' refers to EMA 'Accelerated Assessment. Submission gap is the date of submission at the first regulatory agency to the date of regulatory submission to the target agency.

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FDA (CDER AND CBER) **APPROVED A TOTAL OF 41 NASs IN 2022,** WITH A MEDIAN APPROVAL TIME OF **334 DAYS**

FOR THE NASs APPROVED, 80% WERE 1-CYCLE REVIEWS, 17% 2-CYCLE REVIEWS

Type of Medicine

18 BIOLOGIC NASs APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **316 DAYS**

23 CHEMICAL NASs APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **335 DAYS**

17 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **334 DAYS**

24 NASs IN OTHER THERAPY AREAS APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **334 DAYS**

Designation and Review Type

29 EXPEDITED NAS APPROVALS IN 2022, WITH A MEDIAN APPROVAL TIME OF **301 DAYS;** THIS IS **94 DAYS FASTER** THAN THE MEDIAN OF THE **12 STANDARD NAS APPROVALS IN 2022**

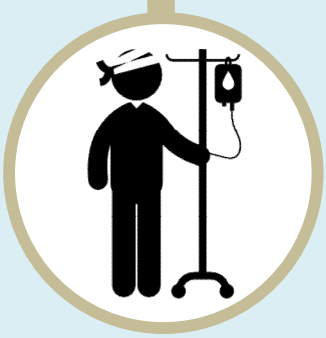
23 ORPHAN NAS APPROVALS IN 2022, WITH A MEDIAN APPROVAL TIME OF **301 DAYS;** THIS IS **63 DAYS FASTER** THAN THE MEDIAN OF THE **18 NON-ORPHAN NAS APPROVALS IN 2022**

Availability by FDA

73% OF THE NASs APPROVED IN 2022 BY FDA WERE APPROVED FIRST BY THE AGENCY OR WITHIN ONE MONTH WHEN COMPARED WITH THE FIRST APPROVAL BY ANY OF THE OTHER AGENCIES

27% OF THE NASs APPROVED IN 2022 BY FDA WERE APPROVED BY ANY OF THE OTHER AGENCIES **FIRST OR MORE THAN ONE MONTH BEFORE BEING APPROVED BY THE AGENCY**

THE MEDIAN **SUBMISSION GAP** FOR THESE NASs WAS **144 DAYS**



'Expedited review' refers to FDA 'Priority Review'. Submission gap is the date of submission at the first regulatory agency to the date of regulatory submission to the target agency.

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PMDA **APPROVED A TOTAL OF 38 NASs IN 2022,** WITH A MEDIAN APPROVAL TIME OF **322 DAYS AND A MEDIAN TIME TO END OF SCIENTIFIC ASSESSMENT OF 275 DAYS**

Type of Medicine

18 BIOLOGIC NASs APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **343 DAYS**

20 CHEMICAL NASs APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **303 DAYS**

10 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **293 DAYS**

28 NASs IN OTHER THERAPY AREAS APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **329 DAYS**

Designation and Review Type

15 EXPEDITED NAS APPROVALS IN 2022, WITH A MEDIAN APPROVAL TIME OF **272 DAYS;** THIS IS **57 DAYS FASTER** THAN THE MEDIAN OF THE **23 STANDARD NAS APPROVALS IN 2022**

15 ORPHAN NAS APPROVALS IN 2022, WITH A MEDIAN APPROVAL TIME OF **272 DAYS;** THIS IS **57 DAYS FASTER** THAN THE MEDIAN OF THE **23 NON-ORPHAN NAS APPROVALS IN 2022**

Availability by PMDA

32% OF THE NASs APPROVED IN 2022 BY PMDA WERE APPROVED FIRST BY THE AGENCY OR WITHIN ONE MONTH WHEN COMPARED WITH THE FIRST APPROVAL BY ANY OF THE OTHER AGENCIES

68% OF THE NASs APPROVED IN 2022 BY PMDA WERE APPROVED BY ANY OF THE OTHER AGENCIES **FIRST OR MORE THAN ONE MONTH BEFORE BEING APPROVED BY THE AGENCY**

THE MEDIAN **SUBMISSION GAP** FOR THESE NASs WAS **537 DAYS**

'Expedited review' refers to PMDA 'Priority Review'. Submission gap is the date of submission at the first regulatory agency to the date of regulatory submission to the target agency.

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HEALTH CANADA **APPROVED A TOTAL OF 36 NASs IN 2022,** WITH A MEDIAN APPROVAL TIME OF **351 DAYS AND A MEDIAN TIME TO END OF SCIENTIFIC ASSESSMENT OF 351 DAYS**

Type of Medicine

9 BIOLOGIC NASs APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **343 DAYS**

27 CHEMICAL NASs APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **355 DAYS**

14 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **367 DAYS**

22 NASs IN OTHER THERAPY AREAS APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **348 DAYS**

Designation and Review Type

8 EXPEDITED NAS APPROVALS IN 2022, WITH A MEDIAN APPROVAL TIME OF **232 DAYS;** THIS IS **132 DAYS FASTER** THAN THE MEDIAN OF THE **28 STANDARD NAS APPROVALS IN 2022**

HEALTH CANADA DOES NOT HAVE AN ORPHAN POLICY; HOWEVER, **17 NASs THAT WERE CLASSIFIED AS ORPHAN BY EITHER FDA, EMA OR TGA WERE APPROVED BY HEALTH CANADA IN 2022,** WITH A MEDIAN APPROVAL TIME OF **367 DAYS**

Availability by Health Canada

11% OF THE NASs APPROVED IN 2022 BY HEALTH CANADA WERE APPROVED FIRST BY THE AGENCY OR WITHIN ONE MONTH WHEN COMPARED WITH THE FIRST APPROVAL BY ANY OF THE OTHER AGENCIES

89% OF THE NASs APPROVED IN 2022 BY HEALTH CANADA WERE APPROVED BY ANY OF THE OTHER AGENCIES **FIRST OR MORE THAN ONE MONTH BEFORE BEING APPROVED BY THE AGENCY**

THE MEDIAN **SUBMISSION GAP** FOR THESE NASs WAS **265 DAYS**

'Expedited review' refers to Health Canada's 'Priority Review'. Submission gap is the date of submission at the first regulatory agency to the date of regulatory submission to the target agency.

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SWISSMEDIC **APPROVED A TOTAL OF 39 NASs IN 2022,** WITH A MEDIAN APPROVAL TIME OF **418 DAYS AND A MEDIAN TIME TO END OF SCIENTIFIC ASSESSMENT OF 297 DAYS**

Type of Medicine

19 BIOLOGIC NASs APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **388 DAYS**

20 CHEMICAL NASs APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **457 DAYS**

16 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **444 DAYS**

23 NASs IN OTHER THERAPY AREAS APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **408 DAYS**

Designation and Review Type

3 EXPEDITED NAS APPROVALS IN 2022, WITH A MEDIAN APPROVAL TIME OF **333 DAYS;** THIS IS **115 DAYS FASTER** THAN THE MEDIAN OF THE **36 STANDARD NAS APPROVALS IN 2022**

15 ORPHAN NAS APPROVALS IN 2022, WITH A MEDIAN APPROVAL TIME OF **418 DAYS;** THIS IS **6 DAYS FASTER** THAN THE MEDIAN OF THE **24 NON-ORPHAN NAS APPROVALS IN 2022**

Availability by Swissmedic

0% OF THE NASs APPROVED IN 2022 BY SWISSMEDIC WERE APPROVED FIRST BY THE AGENCY OR WITHIN ONE MONTH WHEN COMPARED WITH THE FIRST APPROVAL BY ANY OF THE OTHER AGENCIES

100% OF THE NASs APPROVED IN 2022 BY SWISSMEDIC WERE APPROVED BY ANY OF THE OTHER AGENCIES **FIRST OR MORE THAN ONE MONTH BEFORE BEING APPROVED BY THE AGENCY**

THE MEDIAN **SUBMISSION GAP** FOR THESE NASs WAS **270 DAYS**

'Expedited review' refers to the 'Fast-Track procedure' of Swissmedic. Submission gap is the date of submission at the first regulatory agency to the date of regulatory submission to the target agency.

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TGA **APPROVED A TOTAL OF 33 NASs IN 2022,** WITH A MEDIAN APPROVAL TIME OF **347 DAYS AND A MEDIAN TIME TO END OF SCIENTIFIC ASSESSMENT OF 347 DAYS**

Type of Medicine

11 BIOLOGIC NASs APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **365 DAYS**

22 CHEMICAL NASs APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **344 DAYS**

19 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **370 DAYS**

14 NASs IN OTHER THERAPY AREAS APPROVED IN 2022, WITH A MEDIAN APPROVAL TIME OF **269 DAYS**

Designation and Review Type

2 EXPEDITED NAS APPROVALS IN 2022, WITH A MEDIAN APPROVAL TIME OF **233 DAYS;** THIS IS **117 DAYS FASTER** THAN THE MEDIAN OF THE **31 STANDARD NAS APPROVALS IN 2022**

11 ORPHAN NAS APPROVALS IN 2022, WITH A MEDIAN APPROVAL TIME OF **291 DAYS;** THIS IS **60 DAYS FASTER** THAN THE MEDIAN OF THE **22 NON-ORPHAN NAS APPROVALS IN 2022**

Availability by TGA

15% OF THE NASs APPROVED IN 2022 BY TGA WERE APPROVED FIRST BY THE AGENCY OR WITHIN ONE MONTH WHEN COMPARED WITH THE FIRST APPROVAL BY ANY OF THE OTHER AGENCIES

85% OF THE NASs APPROVED IN 2022 BY TGA WERE APPROVED BY ANY OF THE OTHER AGENCIES **FIRST OR MORE THAN ONE MONTH BEFORE BEING APPROVED BY THE AGENCY**

THE MEDIAN **SUBMISSION GAP** FOR THESE NASs WAS **301 DAYS**

'Expedited review' refers to the 'Priority Review' of TGA introduced in 2017. Submission gap is the date of submission at the first regulatory agency to the date of regulatory submission to the target agency.

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Comparison of review timelines, FRPs and other features for orphan vs non-orphan NASs

EMA				
	Orphan		Non-Orphans	
	Number of NAS		Number of NAS	
Overall	76		124	
Type of FRP	Proportion of NASs	Median approval time	Proportion of NASs	Median approval time
Non-FRPs	38%	426	80%	435
Accelerated Assessment	17%	251	4%	246
Conditional approval	28%	451	13%	424
Exceptional circumstances	14%	570	1%	329
Priority medicines (PRIME)	29%	363	3%	424
Rolling review	0%	-	8%	33
Other features	Orphan		Non-Orphans	
ATMP	18%	406	1%	644

FDA				
	Orphan		Non-Orphans	
	Number of NAS		Number of NAS	
Overall	137		113	
Type of FRP	Proportion of NASs	Median approval time	Proportion of NASs	Median approval time
Non-FRPs	8%	365	46%	365
Priority	85%	242	50%	242
Accelerated approval	29%	240	7%	214
Breakthrough	51%	241	16%	240
Fast-track	46%	243	27%	243
RTOR	8%	210	2%	324
Project Orbis	14%	210	3%	178
Rolling review	23%	244	7%	413
Other features	Orphan		Non-Orphans	
First-in-class	47%	245	40%	335
Patient experience data	38%	245	34%	364

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Comparison of review timelines, FRPs and other features for orphan vs non-orphan NASs *(cont.)*

PMDA				
	Orphan		Non-Orphans	
	Number of NAS		Number of NAS	
Overall	58		113	
Type of FRP	Proportion of NASs	Median approval time	Proportion of NASs	Median approval time
Non-FRPs	0%	-	94%	334
Priority	100%	258	5%	199
Sakigake	12%	181	2%	142
Conditional early approval	2%	181	2%	216

Swissmedic				
	Orphan		Non-Orphans	
	Number of NAS		Number of NAS	
Overall	62		109	
Type of FRP	Proportion of NASs	Median approval time	Proportion of NASs	Median approval time
Non-FRPs	34%	525	57%	530
Fast-track	23%	282	5%	254
Prior notification	2%	305	13%	448
Conditional approval	21%	304	14%	258
Access Consortium	5%	392	6%	343
Project Orbis	8%	300	5%	264
Art. 13 TPA	23%	309	2%	370
Art. 14 TPA	2%	510	3%	527
Rolling review	3%	315	6%	241

TGA				
	Orphan		Non-Orphans	
	Number of NAS		Number of NAS	
Overall	55		96	
Type of FRP	Proportion of NASs	Median approval time	Proportion of NASs	Median approval time
Non-FRPs	40%	367	59%	364
Priority	24%	223	5%	189
Provisional approval	13%	379	17%	238
Access Consortium	5%	337	14%	321
Project Orbis	18%	331	8%	342
COR-A	4%	213	1%	224
COR-B	9%	280	4%	257

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Definitions: Facilitated regulatory pathways

	What is it?	Advantage
FDA Priority Review	A process that directs resources to the evaluation of drugs that represent significant improvements in safety or effectiveness compared with standard applications	• Review time shortened from 10 to 6 months
FDA Accelerated Approval	Regulation allowing drugs for serious conditions that fulfil an unmet medical need to be approved based on a surrogate endpoint	• Conditional approval granted using surrogate endpoint(s) from phase 2 trials or interim phase 3 data; confirmatory trials with hard clinical endpoints required
FDA Fast Track	A process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fulfil an unmet medical need	• More frequent meetings with FDA to discuss drug development plan • More frequent communication on clinical trials design • Option for rolling data submission
FDA Breakthrough Therapy	A process designed to expedite the development and review of drugs that may demonstrate substantial improvement over available therapy	• All Fast Track designation features • Intensive guidance on an efficient drug development program from phase 1 • Organisational commitment with senior managers • Option for priority review
Real-Time Oncology Review (RTOR)	A programme launched by the FDA Oncology Center of Excellence (OCE), it allows FDA to access and review key data ahead of time, prior to official submission	• RTOR allows the FDA to review much of the data earlier, before the applicant formally submits the complete application.
EMA Accelerated Assessment	A process designed to expedite products of major interest in terms of public health and therapeutic innovation	• Committee for Medicinal Products for Human Use (CHMP) opinion shortened from 210 days to 150 days
EMA Conditional Approval	Regulation allowing drugs fulfilling unmet medical need for severe, life-threatening or rare diseases to be approved with limited clinical safety or efficacy data, provided a positive benefit-risk balance	• Conditional approval is granted before all data are available (valid for one year, on a renewable basis; once pending studies are provided, it can become a “normal” marketing authorisation)
EMA Exceptional Circum-stances	Regulation allowing drugs fulfilling unmet medical need for severe, life-threatening or rare diseases to be approved without comprehensive efficacy and safety data	• Conditional approval is granted before all data are available (reviewed annually to re-assess the risk-benefit balance)
EMA PRIME (Priority Medicines)	A scheme to enhance support for the development of medicines that target an unmet medical need. It is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development and speed evaluation.	• Early dialogue with EMA (appointed rapporteur) • Provision of scientific advice, involving additional stakeholders (e.g. HTA) • Dedicated point of contact from EMA • Option of Accelerated Assessment
PMDA Priority Review	A process that provides faster access to new therapies responding to high medical needs; includes products such as orphans, HIV medicines	• Review time shortened from 9 to 6 months
PMDA Conditional Early Approval	A system to put highly useful and effective drugs for treating serious diseases into practical use as early as possible	• Early application through confirmation of a certain degree of efficacy and safety • Shorten overall review times for priority review products
PMDA Sakigake (pioneer)	A system to put highly useful and effective drugs for treating serious diseases into practical use as early as possible	• All Priority Review designation features • Prioritised clinical trial and pre-application consultation • Assigned PMDA manager as a concierge • Post-marketing safety measures

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Definitions: Facilitated regulatory pathways *(cont.)*

	What is it?	Advantage
Health Canada Priority	A fast-track status for medicines for severe, debilitating or life-threatening disease; to address unmet medical need and where a high therapeutic benefit can be expected	• Review time shortened from 300 to 180 days
Health Canada Conditional (NOC/c)	Authorisation to market a new promising drug with the condition that the sponsor undertakes additional studies to verify the clinical benefit	• Earlier marketing of promising drugs for serious conditions before the drugs have definitively demonstrated clinical efficacy
Swissmedic Fast-Track	A rapid review of applications for severe, debilitating or life-threatening disease; to address unmet medical need and where a high therapeutic benefit can be expected	• Review time shortened from 330 to 140 days
Swissmedic Prior Notification	A process to enable applicants to notify their submission date at an early stage, so that Swissmedic can draw up a streamlined and precise schedule for the review	• 20% faster processing time and fixed planning offered by this procedure are subject to a fee surcharge of 100%
Art.13 TPA	A process to authorise medicinal products that have already been approved in a country with a comparable medicinal product control system, taking account of the results of the trials conducted for this purpose provided that some requirements are satisfied	• In justified cases Swissmedic may reduce the scale of scientific assessments, either on request or ex officio, based on the result of the corresponding assessment by the foreign authority (e.g. USA FDA or EMA)
Art.14 TPA	An authorisation procedure for medicinal products with active substances that has been authorised in an EU or EFTA country for at least 10 years	• A simplified procedure where a review of original clinical documentation is generally only admissible for bioequivalence studies, e.g. where the pharmaceutical forms differ
TGA Priority	A formal mechanism for faster assessment of vital and life-saving medicines for severe, debilitating or life-threatening disease, to address unmet medical need and where a high therapeutic benefit can be expected	• Review time shortened from 220 to 150 working days • Dynamic process with rolling questions and more flexible arrangements for accessing advice
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	• Conditional approval is granted based on preliminary clinical data (valid for a maximum of 6 years)
Comparable overseas regulators (CORs)	The TGA makes use of assessments from comparable overseas regulators (CORs), where possible, in the regulation of prescription medicines.	Shortened evaluation and decision timeframe for prescription medicines that have already been approved by a COR partner: • For COR-A the timeframe is 120 working days • For COR-B the timeframe is 175 working days
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 products
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	

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Approval time
Time calculated from the date of submission to the date of approval by the agency. This time includes agency and company time.

Biological/Biotechnology product
A substance isolated from animal tissues or product produced by recombinant DNA or hybridoma technology and expressed in cell lines, transgenic animals or transgenic plants) for therapeutic, prophylactic or in vivo diagnostic use in humans.

Chemical entity
An entity produced by chemical synthesis.

Development time
Time calculated from the date of approval/ submission of the Investigational New Drug (IND) application to the date of submission of the NAS application in FDA

Expedited review
Refers to EMA 'Accelerated Assessment' and FDA/PMDA/Health Canada/Swissmedic/TGA 'Priority Review'.

Facilitated regulatory pathway
Regulatory pathway designed to facilitate availability, review and/or approval of medicines where there is an unmet medical need by providing alternatives to standard regulatory review routes.

New active substances (NASs)*
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 through changes to the 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.

Applications that are excluded from the study:

- Vaccines
- Biosimilars
- 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).
- Emergency use or Special authorisations derived from an emergency (e.g. COVID-19 pandemic)

*The full list of NASs approved by each jurisdiction in 2022 will be available on the CIRS website.

Real-world data (FDA definition)
Real-world data are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. RWD can come from a number of sources, for example:

- Electronic health records
- Claims and billing activities
- Product and disease registries
- Patient-generated data including in home-use settings
- Data gathered from other sources that can inform on health status, such as mobile devices

Submission gap
Time calculated from date of submission at the first regulatory agency to the date of regulatory submission to the target agency.

Time from submission to the end of Scientific Assessment
Time from submission to the end of Scientific Assessment has been defined as follows for the six agencies. It includes agency and company time and is calculated as time from acceptance of the submission for evaluation submission until:

- EMA: The CHMP issues an opinion for granting a marketing authorisation. Excluded is the time from CHMP opinion to final decision by the European Commission.

Continued: see next page

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- FDA: The FDA action letter to approve is signed (FDA action date). This is equivalent to the regulatory approval, and therefore for FDA, time from acceptance of submission to end scientific assessment and time from acceptance of submission to approval are the same.
- PMDA: The First/Second Committee on New Drugs' meeting, when it is concluded that a marketing authorisation can be granted. Excluded is the time from New Drugs meeting to MHLW final decision.
- Health Canada: The last review stream is completed and the outcome letter is sent. Excluded is further time to ensure the information on file is complete and properly filed, generate drug identification numbers, prepare an executive summary and prepare the Notice of Compliance (NOC) package for routing and sign off as well as time to check that requirements are met with respect to the Patented Medicines (NOC) Regulations and the data protection provisions .
- Swissmedic: The advisory committee review and decision is made and the outcome letter (preliminary decision) is sent. Excluded is the negotiation time with the sponsor regarding the label following the end of the scientific review.
- TGA: The delegate decision is made and the decision (outcome letter) is sent to the sponsor. This is equivalent to the regulatory approval, and therefore for TGA, time from acceptance of submission to end scientific assessment and time from acceptance of submission to approval are the same.

Top company
Pharmaceutical company with R&D spending >3 billion USD in 2020.

World Health Organisation (WHO) ATC classification
- A - Alimentary and metabolism: Drugs for acid related disorders, gastrointestinal disorders, antiemetics and antinauseants, bile and liver therapy, laxatives, antidiarrheals, intestinal antiinflammatory/antiinfective agents, drugs used in diabetes
- B – Blood and blood forming organs: antithrombotic agents, antihemorrhagics, antianemic preparations, blood substitutes and perfusion solutions, other hematological agents
- J - Anti-infectives: Antibacterials for systemic use, antimycotics for systemic use, antimycobacterials, antivirals for systemic use, immune sera and immunoglobulins, vaccines
- L - Anticancer and immunomodulators: Antineoplastic agents, endocrine therapy, immunostimulants, immunosuppressive agents
- N - Nervous system: Anesthetics, analgesics, antiepileptics, anti-parkinson drugs, psycholeptics, psychoanaleptics, other nervous system.

Rollout time
Time calculated from date of submission at the first regulatory agency to the date of regulatory approval at the target agency.

Company response time
Time calculated as the sum of periods between the date the CHMP agrees on the consolidated List of Questions/ List of Outstanding Issues to be sent to the applicant and the date in which the applicant submits the responses.

EU commission time
Time calculated from the date of end of scientific assessment to the date of approval by the EU commission.

EMA review time
Time calculated as the difference among the approval time minus the sum of the company time and the EU commission time.

Interquartile range (IQR)
The interquartile range is calculated as the difference between the 75th percentile and the 25th percentile of a distribution of measurements.

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About CIRS

The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independent UK-based subsidiary of Clarivate plc. CIRS provides an international forum for industry, regulators, Health Technology Assessment (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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