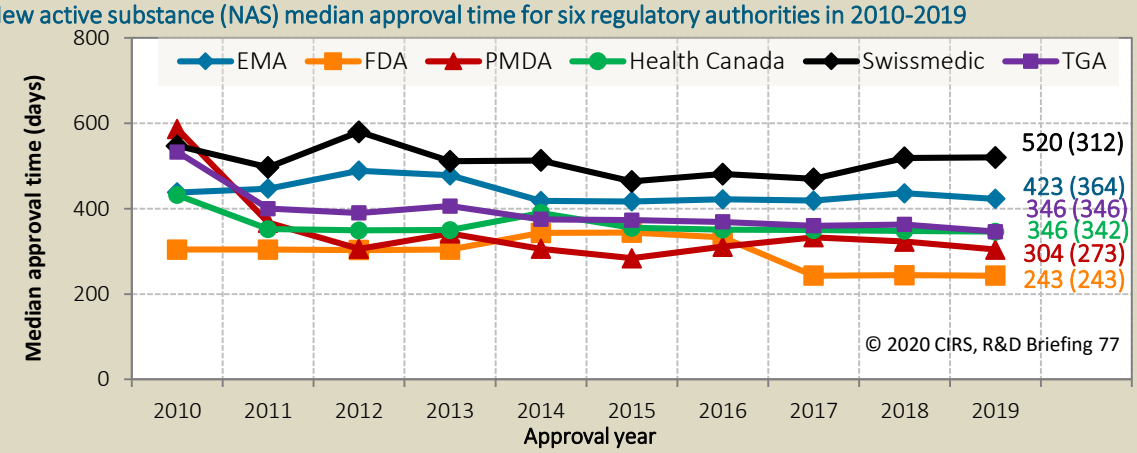
New drug approvals in six major authorities 2010-2019:

Focus on Facilitated Regulatory Pathways and Internationalisation

This 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 2019 as well as looking back at 2010-2019. Although median approval times can be a marker of agency performance and the time it takes to make medicines available to patients, other factors need to be taken into account. This Briefing focuses on two such factors, namely facilitated regulatory pathways (FRPs) and internationalisation based on company strategy to ensure timely availability of medicines globally.

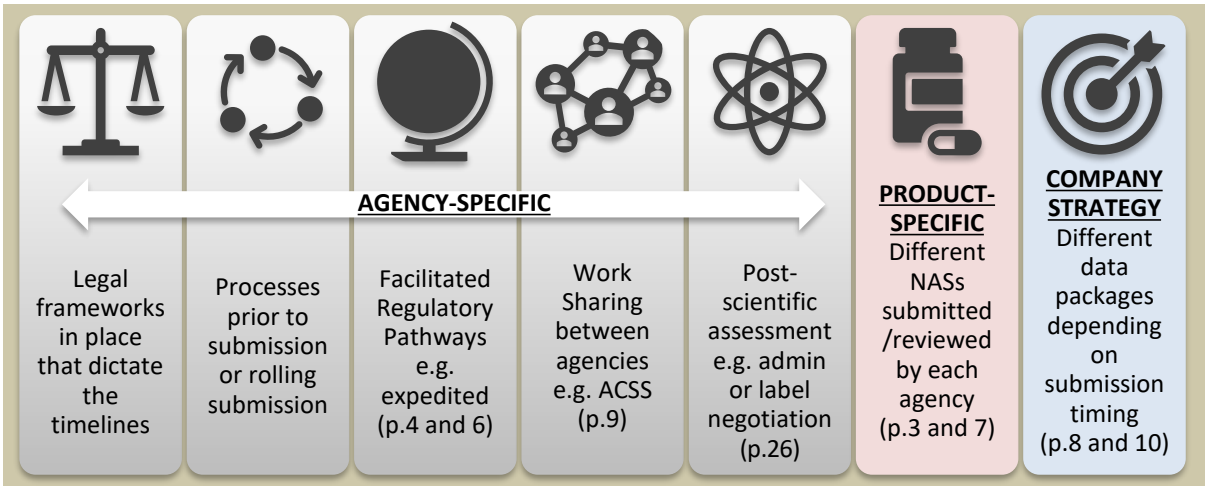
Contents

New active substance (NAS) median approval time for six regulatory authorities in 2010-2019



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 2019; (N2) = median time from submission to the end of scientific assessment (see p.26) for products approved in 2019.

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



Key messages

- In 2019, FDA (CDER and CBER combined) approved the highest number of NASs (Fig. 1). **The overall number of NASs approved by the six agencies** has generally increased over the decade, but has flattened for the past 5 years, except for FDA, which has continued to increase.
- **The total number of NAS approvals between 2015-2019 across the 6 agencies** was 1026, of which FDA had the largest proportion at 22% (230 NASs). Interestingly, of the 182 NASs submitted and approved at FDA from 2015-2019, 112 (62%) came from non-top companies and 70 (38%) from top companies (Fig.14).
- Despite recent **convergence in approval times** over the last 20 years, there were still differences in the median approval times across the six agencies (cover page; for example, 277 days between FDA and Swissmedic). However, this difference was a lot narrower when comparing the median time from submission to end of scientific assessment (for example, 69 days between FDA and Swissmedic).
- FDA was the agency with the shortest **median approval time** (243 days), which is likely due to the extensive use of facilitated regulatory pathways (FRPs), highlighting the importance of those products in addressing unmet medical need. This was followed by PMDA (304 days), Health Canada (346 days), TGA (346 days), EMA (423 days) and Swissmedic (520 days) (Fig. 2).
- All six agencies now offer an **expedited process** designed to hasten the review process of promising NASs (Fig. 3). TGA implemented its priority system in 2017 and three expedited approvals were granted in 2018 as well as in 2019.
- The number of NASs with an **orphan designation** has increased across EMA, FDA, PMDA, Swissmedic and TGA, from 28% in 2010-2014 to 37% in 2015-2019 (Fig. 5). From 2015-2019, the proportion of orphans varied year-on-year but was generally high, which may be due to disease stratification and companies' growing R&D pipelines, and is consistent with increased commitment from agencies to tackle unmet medical needs.
- Between 2015-2019, **the top 5 therapeutic areas (TA)** by number approved across all six agencies, made up 78% of all approvals. Anti-cancer and immunomodulators made up 46% of the top 5 TA approvals (Fig. 10).
- **The number of products approved by all six agencies in a five-year period** increased by 36% from 2010-2014 (30 NASs) to 2015-2019 (41 NASs), which indicates that more products were becoming internationalised. However, when comparing 2009-2013 to 2014-2018 this increase was much larger at 255% (see R&D Briefing 70), suggesting that the pace of internationalisation may now be levelling off (Fig. 11).
- In 2018-2019, 3 NASs were approved by Health Canada and TGA through the **New Chemical Entities Work Sharing Initiative** of the Australia-Canada-Singapore-Switzerland (ACSS) Consortium (Fig. 12). As part of the worksharing process, the agencies review different parts of the dossier.

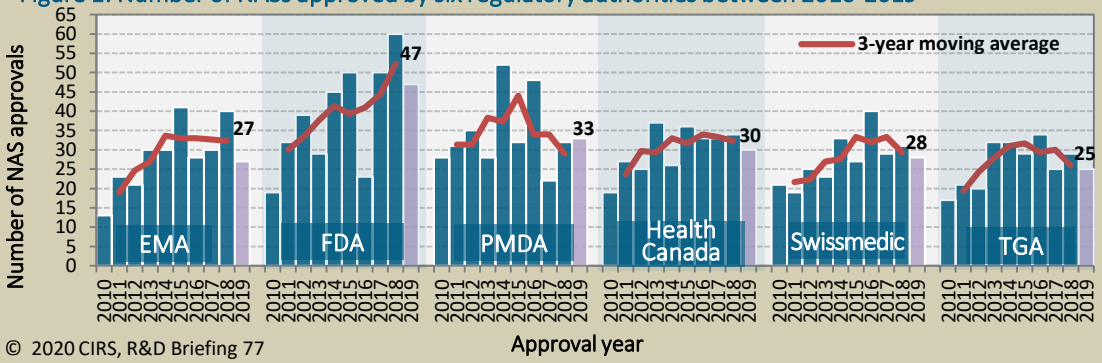
Analyses in the coming years may demonstrate the impact of the COVID-19 pandemic on the NAS approvals in these agencies, as well as changes to the internationalisation of medicines. The availability and use of expedited as well as other facilitated regulatory pathways is key to addressing areas of unmet need and other public health emergencies such as COVID-19 (see CIRS R&D Briefing 75).

See agency-specific infographics for 2019 snapshots:

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

Approval times

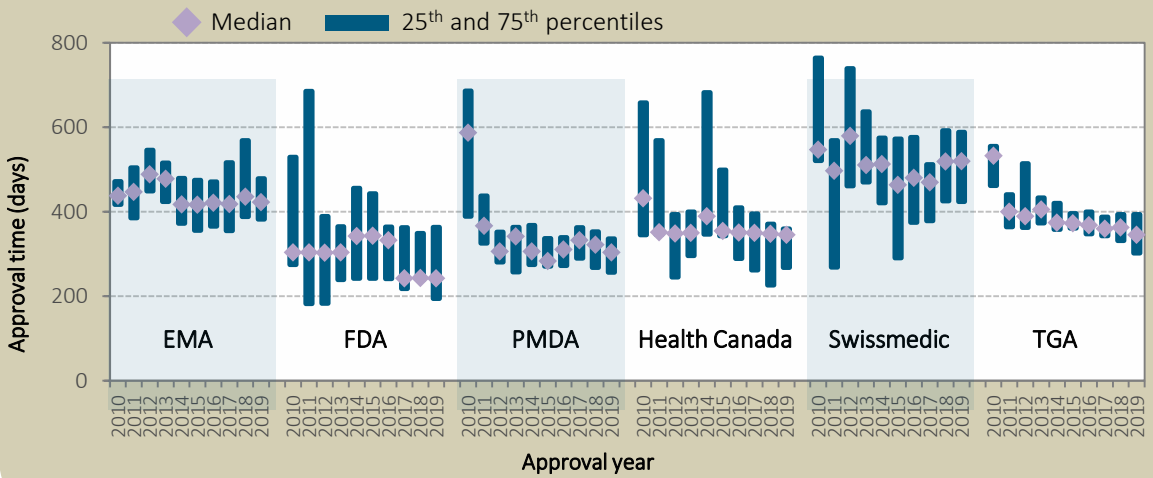
Figure 1: Number of NASs approved by six regulatory authorities between 2010-2019



In 2019, FDA (CDER and CBER combined) approved the highest number of NASs (47) (Fig. 1). The overall number of NASs approved by the six agencies has generally increased over the decade, but has flattened for the past 5 years, except for FDA, which has continued to increase. The rationale for the typically higher number of approvals by FDA compared to other agencies may be the availability of FRPs, or that some of the medicines approved by FDA, particularly from smaller companies, do not become internationalised (p. 10). A comparison of the NAS numbers during the two halves of the decade, 2010-2014 and 2015-2019, revealed that the biggest difference in the number of approvals was seen for EMA, with a 42% increase, followed by FDA (40%), Swissmedic (28%), Health Canada (24%), TGA (16%), whereas for PMDA there was a decrease of 4%. 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 need and review speed.

Analyses in the coming years may also demonstrate the impact of the COVID-19 pandemic on NAS approvals by these agencies.

Figure 2: NAS approval time for six regulatory authorities between 2010-2019

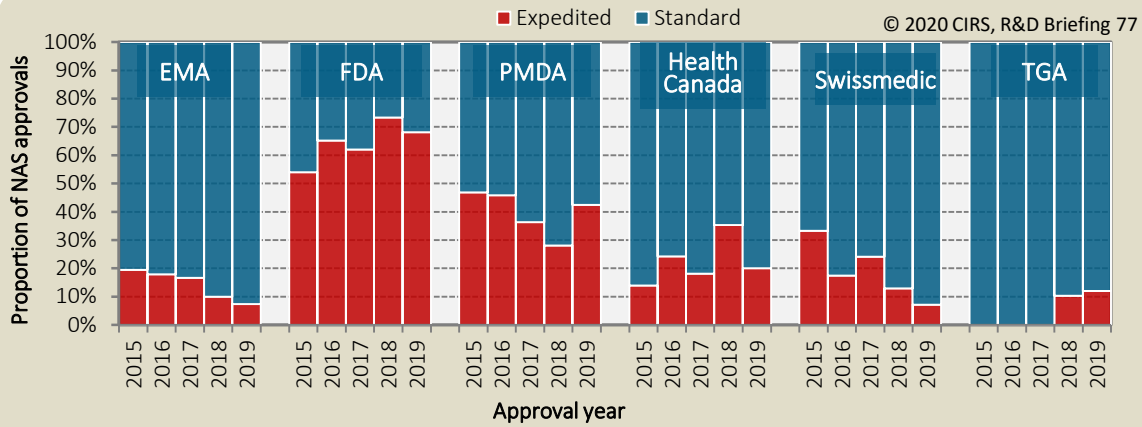


Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time.

In 2019, FDA had the shortest median approval time (243 days), which is likely to be due to the wide use of FRPs. This was followed by PMDA (304 days), Health Canada (346 days), TGA (346 days), EMA (423 days) and Swissmedic (520 days) (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; 277 days between FDA and Swissmedic). However, this difference was a lot narrower when comparing the median time from submission to the end of scientific assessment (69 days between FDA and Swissmedic). For FDA, Health Canada and TGA, the overall approval time and the time to end of scientific assessment were the same or similar, which indicates that there are very few activities that occur after the end of scientific assessment. However, for the other agencies, there are additional steps following the end of scientific assessment (outlined on p. 26), such as administrative activities or additional negotiations with the sponsor, like in the case of Swissmedic to negotiate the label. There were 208, 59 and 31 days between the end of scientific assessment and the date of approval for Swissmedic, EMA and PMDA, respectively.

Characteristics: Review type

Figure 3: Number of NAS approvals by review type for six regulatory authorities between 2015-2019

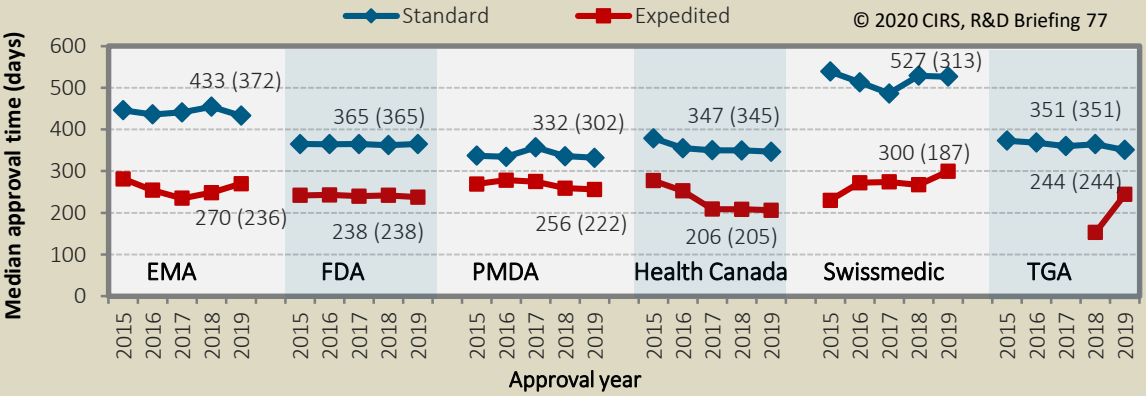


'Expedited review' refers to EMA 'Accelerated Assessment', Swissmedic 'Fast Track' and FDA/PMDA/Health Canada/TGA 'Priority Review'. TGA introduced an expedited (priority) review programme in 2017.

All six agencies offer an expedited process (see definitions above) designed to hasten the review process of promising NASs (Fig. 3). TGA implemented its priority system in 2017 and three expedited approvals were granted in 2018 as well as in 2019. In 2019, the ratio of expedited approvals to standard reviews was highest for FDA (68%), followed by PMDA (42%), Health Canada (20%), TGA (12%), EMA and Swissmedic (7%). The proportion of expedited approvals has been consistently high for FDA and increased from 47% between 2010-2014 (results not shown) to 65% between 2015-2019. For EMA, the number of expedited approvals remains the lowest, which is partially due to the fact that the review type can be reverted back to standard review if timelines cannot be met by the sponsor. In 2019, 4 NASs initially designated by EMA as expedited were reverted. Swissmedic was another agency where the number of expedited approvals was low (2 in 2019), but it should be noted that in 2019, 4 products benefited from the Prior Notification process (20% faster time subject to a fee surcharge).

The availability and use of expedited pathways as well as other FRPs (see p. 6) are key to addressing areas of unmet need and other public health emergencies such as COVID-19.

Figure 4: NAS median approval time by review type for six regulatory authorities between 2015-2019

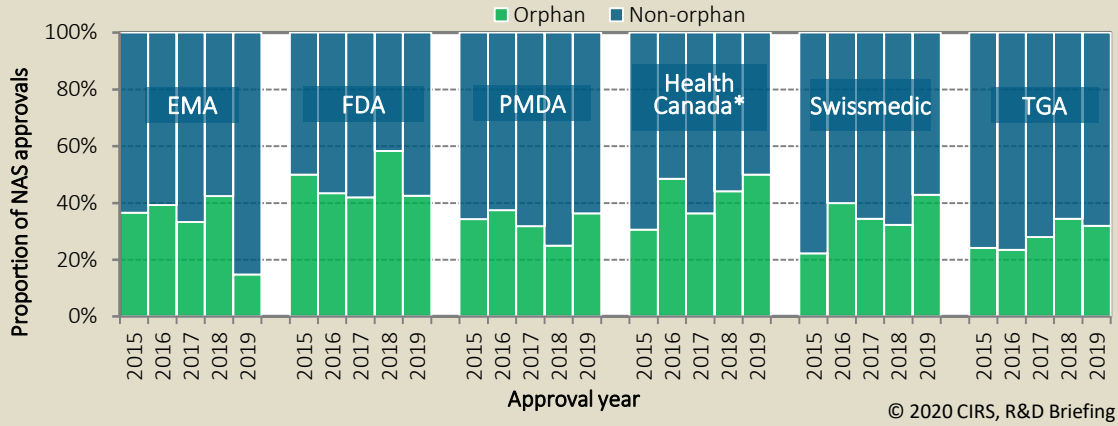


'Expedited review' refers to EMA 'Accelerated Assessment', Swissmedic 'Fast Track' and FDA/PMDA/Health Canada/TGA 'Priority Review'. TGA introduced an expedited (priority) review programme in 2017. Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time. N1 = overall approval time for 2019; (N2) = time from submission until the end of scientific assessment for 2019.

Although Swissmedic had the longest median approval time for standard and expedited NASs in 2019, the median time from submission to end of scientific assessment (see p. 26) was 313 days for standard and 187 days for expedited, which is similar to the other agencies. Interestingly, for EMA and Swissmedic, the additional activities taking place following the end of scientific assessment were taking approximately half the time for products designated as expedited compared to standard (Fig. 4). For EMA, this is due to the European Commission time being expedited, while for Swissmedic, it may be a result of label negotiations and other administrative activities being carried out more quickly for high unmet need products. For the 3 NASs approved through the TGA priority process in 2019, the median approval was 244 days, which is in line with the other agencies.

Characteristics: Orphan designation

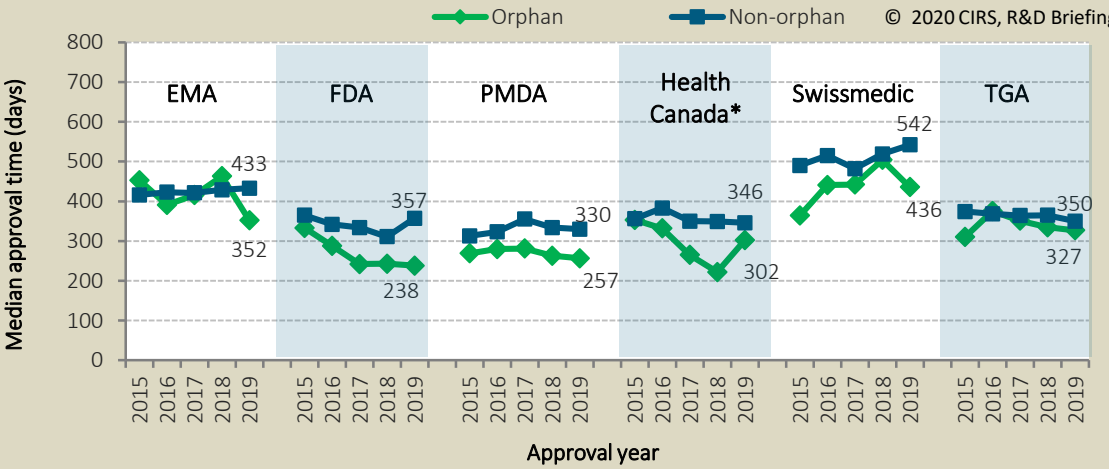
Figure 5: Proportion of NAS approvals by orphan designation for six regulatory authorities between 2015-2019



** 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.*

The number of NASs with an orphan designation has increased across EMA, FDA, PMDA, Swissmedic and TGA, from 28% between 2010-2014 (results not shown) to 37% between 2015-2019. From 2015-2019 (Fig. 5), the proportion of orphans varied year-on-year but was generally high, which may be due to disease stratification and companies' growing R&D pipelines, and is consistent with increased commitment from agencies to tackle unmet medical needs. In 2019, FDA and Swissmedic had the highest amount of orphans approved (43%) while EMA had the lowest (15%), which may be due to the types of products submitted to each agency. Nevertheless, in 2019, 20 of the 23 non-orphans approved by EMA were also approved by one of the other five agencies, and of those 20 products, 7 were approved as an orphan by at least one other agency. This may be due to the differences in orphan designation criteria across the agencies, as well as the indication submitted by the sponsor. Although Health Canada does not currently have an orphan policy, 50% of the NASs approved by the agency in 2019 were classified as orphan by either FDA, EMA or TGA.

Figure 6: NAS median approval time by orphan designation for six regulatory authorities between 2015-2019



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 2015-2019 (Fig. 6). All of the orphan NASs approved in Japan over the past five years have been through expedited review, as an incentive from PMDA to fill the gap of unmet needs, and their median approval time in 2019 was 257 days. FDA had the fastest median approval time for orphans in 2019 (238 days), as 95% of these products have been approved through expedited review. Health Canada does not currently have an orphan policy; however, for the 15 NASs approved by Health Canada in 2019 that were classified as orphan by either FDA, EMA or TGA, the median approval time was 302 days. For the 4 orphans approved by EMA in 2019, the median approval time was 352 days, where 2 (50%) of the NASs were expedited by the agency. 25% of orphan drugs approved by TGA in 2019 were approved with the newly introduced priority review and their median approval time was slightly faster than that for non-orphans.

Characteristics: Facilitated Regulatory Pathways (FRPs)

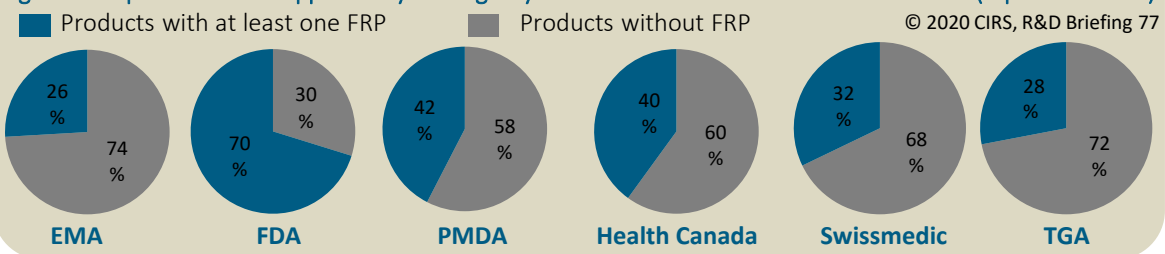
Of the six agencies, FDA approved the highest number of NASs through FRPs to enable the availability, review and/or approval of medicines for unmet need (Fig. 7 and 8).

Figure 7: Facilitated regulatory pathway (FRP) and orphan status timelines across six agencies; focus on 2019

© 2020 CIRS, R&D Briefing 77	New Active Substance (NAS) approval type		2019 NAS approvals, number	2019 NASs, %	Expedited, % of 2019 approvals	2019 median approval time, days
EMA	**Overall approvals**		27			423
	FRP	Accelerated Assessment (referred to in this Briefing as Expedited)	2	7%		270
		Conditional Approval	6	22%	17%	481
		Exceptional Circumstances	0	N/A	N/A	N/A
		PRIME	1	4%	100%	281
	Orphan		4	15%	50%	352
FDA	**Overall approvals**		47			243
	FRP	Priority (referred to in this Briefing as Expedited)	32	68%		238
		Accelerated Approval	9	19%	100%	173
		Breakthrough Designation	15	32%	100%	182
		Fast Track	19	40%	95%	243
	Orphan		20	43%	95%	238
PMDA	**Overall approvals**		33			304
	FRP	Priority (referred to in this Briefing as Expedited)	14	42%		256
		Sakigake	1	3%	100%	181
		Conditional Early Approval	0	N/A	N/A	N/A
	Orphan		12	36%	100%	257
Health Canada	**Overall approvals**		30			346
	FRP	Priority (referred to in this Briefing as Expedited)	6	20%		206
		Conditional Approval (Notice of Compliance with Conditions)	5	17%	20%	259
		ACSS work-sharing	2	7%	0%	371
Swissmedic	**Overall approvals**		28			520
	FRP	Fast-Track (referred to in this Briefing as Expedited)	2	7%		300
		Procedure with prior notification	4	14%		430
		Conditional Approval	0	N/A	N/A	N/A
		Art.13 TPA	3	11%	0%	271
		ACSS work-sharing	0	N/A	N/A	N/A
	Orphan		12	43%	17%	436
TGA	**Overall approvals**		25			346
	FRP	Priority (referred to in this Briefing as Expedited)	3	12%		244
		Provisional Approval (Conditional)	2	8%	0%	224
		ACSS work-sharing	2	8%	0%	276
	Orphan		8	32%	25%	327

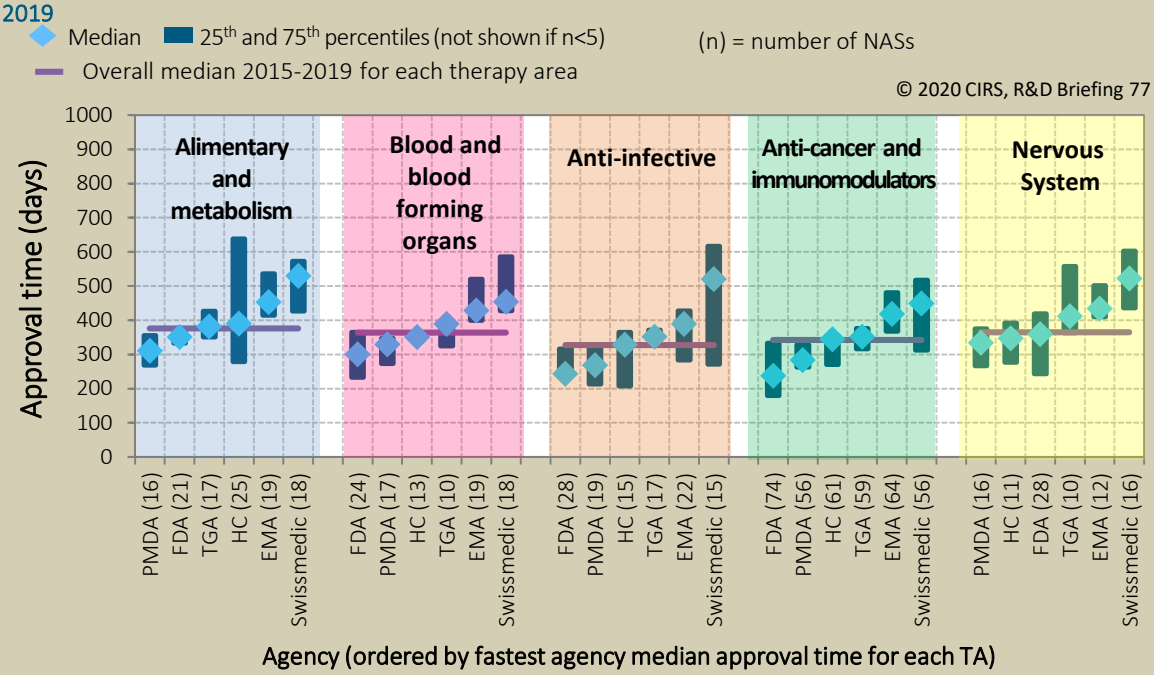
TGA introduced an expedited (priority) review and provisional approval programme in 2017, with first decisions in 2018/2019. Health Canada does not currently have an orphan policy. Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time.

Figure 8: Proportion of NASs approved by each agency in 2019 that benefited from at least one FRP (orphan excluded)



Characteristics: Therapeutic area

Figure 9: NAS median approval time by top 5 therapeutic areas (TA) for six regulatory authorities between 2015-2019



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 5 TAs by number approved across all six agencies made up 78% (796/1026) of all approvals between 2015-2019, with anti-cancer and immunomodulators making up 46% (370) of the top 5 TAs approvals (Fig. 9). Anti-infective therapies were approved marginally faster with an overall median of 327 days, compared with 342 days for anti-cancer and immunomodulators, 364 days for blood and blood forming organs, 365 days for nervous system and 376 days for alimentary and metabolism NASs. PMDA and FDA had the fastest approval times across 4 of the 5 therapy areas. Nevertheless, as noted by the 25th-75th percentile bars, there were also wide variations for certain jurisdictions across therapy areas. This may reflect the more frequent use of expedited review pathways by agencies across the 5 therapy areas (Fig. 10).

Analysis in the coming years might show the impact of COVID-19 on approval times across these therapeutic areas.

Figure 10: NAS overall median approval time by top 5 therapeutic areas in relation to expedited approvals for six regulatory authorities between 2015-2019

© 2020 CIRS, R&D Briefing 77	Alimentary and metabolism		Blood and blood forming organs		Anti-infective		Anti-cancer and immuno-modulators		Nervous system	
Approval time, days (proportion of expedited approvals – for TGA captures 2018 and 2019 only)										
EMA	453	(11%)	429	(16%)	390	(23%)	419	(13%)	435	(17%)
FDA	351	(52%)	301	(54%)	244	(82%)	239	(77%)	360	(46%)
PMDA	311	(44%)	330	(29%)	269	(63%)	284	(64%)	334	(25%)
Health Canada	391	(28%)	351	(23%)	329	(40%)	345	(20%)	348	(27%)
Swissmedic	530	(0%)	455	(0%)	521	(40%)	450	(32%)	523	(0%)
TGA	382	(6%)	390	(20%)	352	(0%)	352	(3%)	412	(0%)

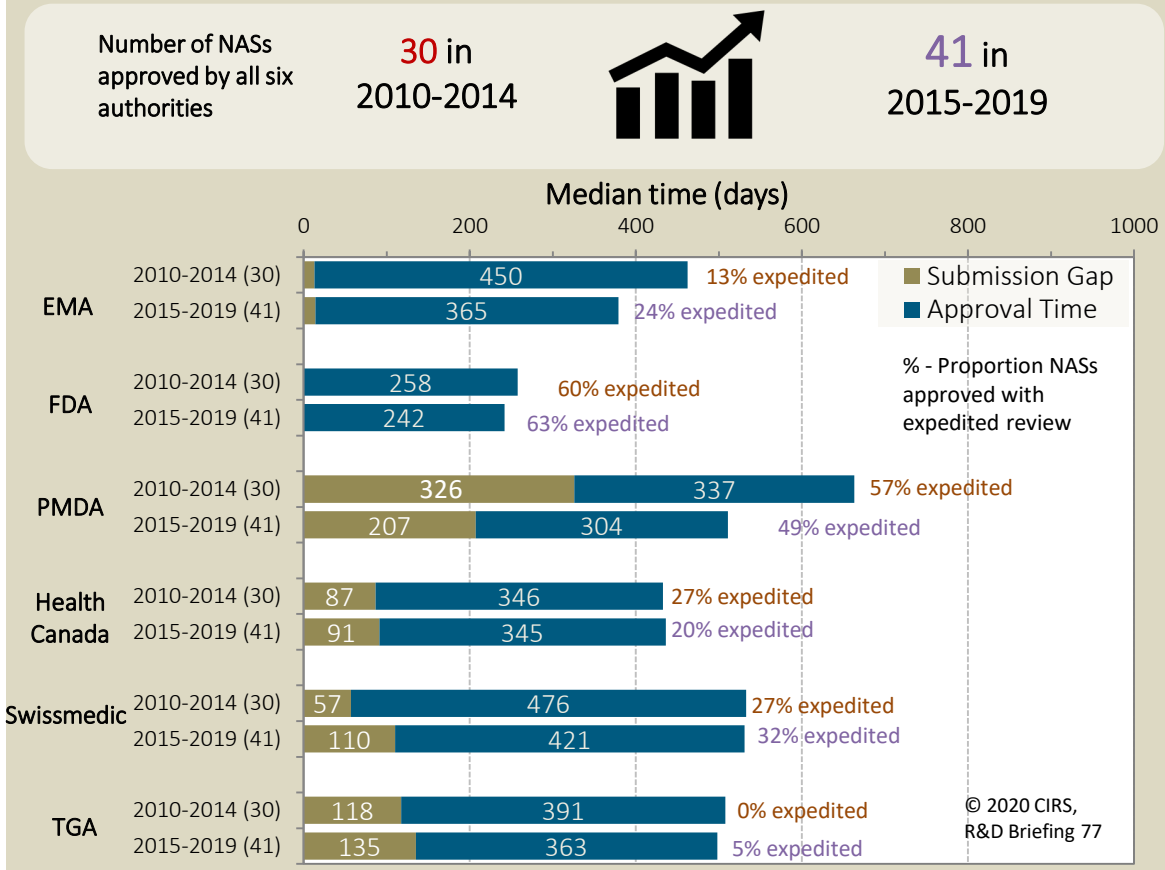
Therapeutic areas relate to the WHO ATC codes. 'Expedited review' refers to EMA 'Accelerated Assessment', Swissmedic 'Fast Track' and FDA/PMDA/Health Canada/TGA 'Priority Review'. TGA introduced an expedited (priority) review programme in 2017, therefore the numbers in parentheses only relate to 2018 and 2019 approvals. 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.

Common approvals: six regulatory agencies

A true comparison of regulatory performance can be derived from studying the review of compounds that were approved by all six agencies. This comparison was carried out for two time cohorts in the last decade, namely 2010-2014 and 2015-2019, to determine whether any trends could be identified. The number of products approved by all six agencies in a five-year period increased by 36% from 2010-2014 (30 NASs) to 2015-2019 (41 NASs), which indicates that more products were becoming internationalised. However, this increase was much larger (255%) when comparing 2009-2013 to 2014-2018 (see R&D Briefing 70), suggesting that the pace of internationalisation may now be levelling off. The overall length of time to registration, consisting of the submission gap and approval time (Fig. 11), may be a result of potential factors that impact registration of NASs. This may include company strategy to submit as well as the use of expedited pathways within agencies to address unmet medical need for promising medicines. This Briefing, as in past Briefings, shows there is no change in the waves of submission to agencies: first to EMA and FDA, then to Health Canada, Swissmedic and TGA, and finally to PMDA. The quickest time to registration was at FDA for both cohorts, as a result of companies submitting there first and quick regulatory review times. Submissions to EMA occurred almost simultaneously with FDA, and the overall time to registration decreased, which may reflect the increased use of expedited pathways by EMA. For the other four agencies, the submission gap was generally similar for Health Canada and TGA, with a slight increase between the two time frames for Swissmedic. However, for PMDA the submission gap was reduced by over 100 days between the two time frames. When looking across the agencies in terms of total time to approval from 1st Submission to the 1st agency, the difference between the two cohorts show that for EMA and PMDA time has decreased, but for FDA, Health Canada, TGA and Swissmedic there were little differences in total time between the two cohorts.

COVID-19 may have an impact on the internationalisation of medicines in the coming years.

Figure 11: Median submission gap and median approval time for NASs approved by all six authorities in 2010-2014 (30) compared with 2015-2019 (41), as well as the proportion of NASs approved as expedited

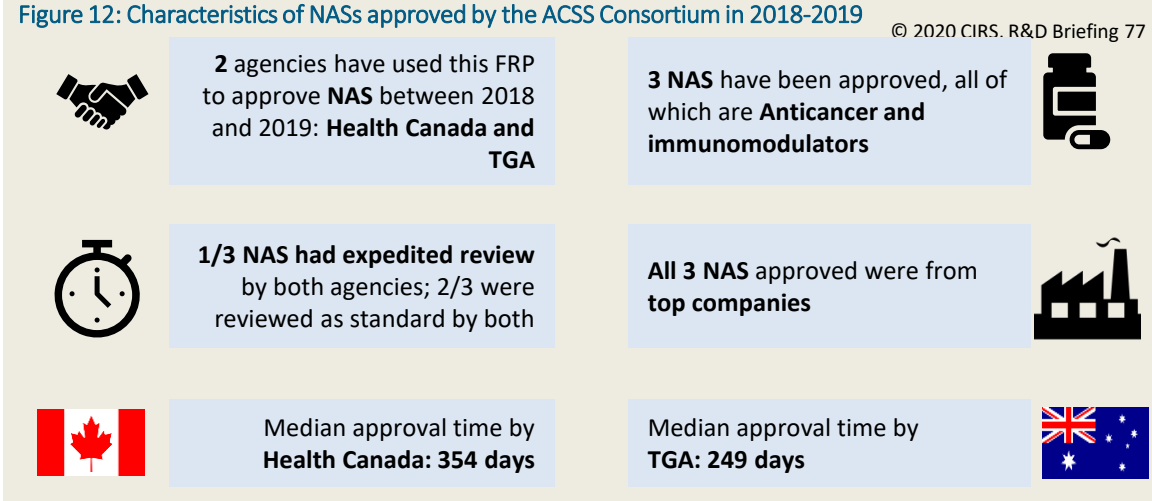


Submission gap is calculated as the time from date of submission at the first regulatory agency to the date of regulatory submission to the target agency. Expedited review' refers to EMA 'Accelerated Assessment', Swissmedic 'Fast Track' and FDA/PMDA/Health Canada/TGA 'Priority Review'. TGA introduced an expedited (priority) review programme in 2017, therefore the numbers for 2015-2019 only relate to 2018-2019 approvals. 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: ACSS Worksharing Consortium

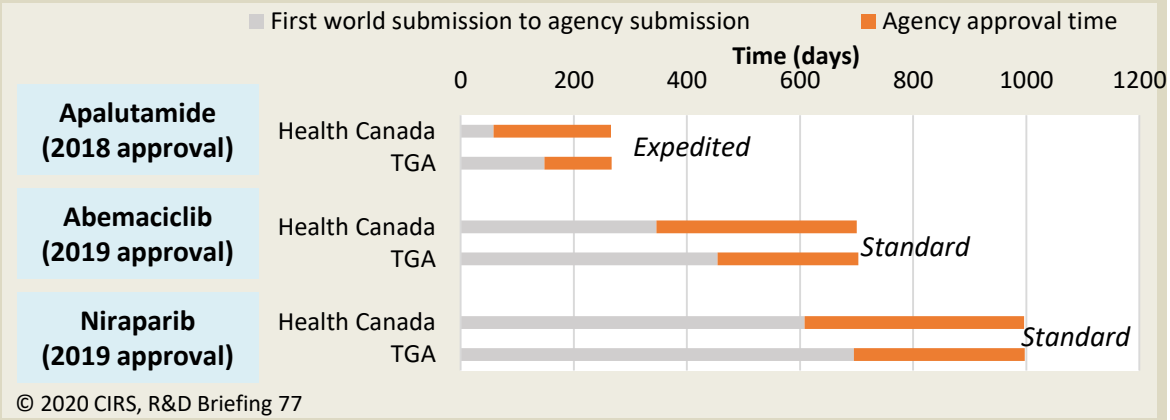
The Australia – Canada – Singapore – Switzerland (ACSS) Consortium is a medium-sized coalition, which was formed in 2007 by 'like-minded' regulatory authorities to promote greater regulatory collaboration and alignment of regulatory requirements. Its goal is to maximise international cooperation, reduce duplication, and increase each agency's capacity to ensure consumers have timely access to high quality, safe and effective therapeutic products.

Figure 12: Characteristics of NASs approved by the ACSS Consortium in 2018-2019



In 2018-2019, 3 NASs were approved through the New Chemical Entities Work Sharing Initiative by Health Canada and TGA (Fig. 12). Although there were differences in median approval times, this can be accounted for by the pilot nature of the initiative, where candidates were retrospectively identified by TGA and Health Canada based on common submissions that had already been received by both agencies. Since that time the process has been formalised and sponsors are required to submit an expression of interest 3 to 6 months before their proposed submission. Applications should be submitted to each participating agency simultaneously, ideally within 15 calendar days. Thus, even accounting for the Pre-submission planning form, the submission and approval times will be virtually simultaneous. In the future, it is likely that there will be no submission gap, though some may remain due to differences in agency processes.

Figure 13: Submission lag and approval times for NASs approved by the ACSS Consortium between 2018-2019



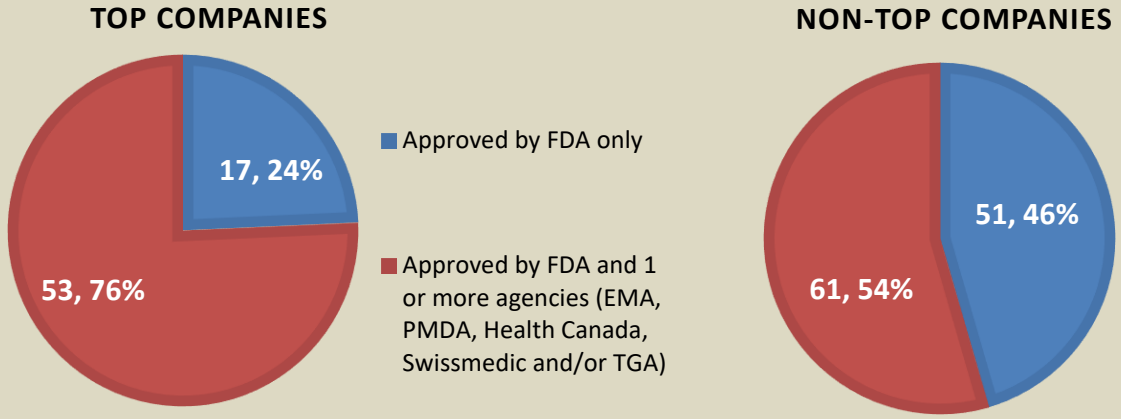
Submission gap is calculated as the time from date of submission at the first regulatory agency to the date of regulatory submission to the target agency. 'Expedited review' refers to Health Canada/TGA 'Priority Review'. Approval time is calculated from the date of submission to the date of approval by the agency.

As part of the worksharing process, the agencies review different parts of the dossier. In the case of Niraparib, Health Canada completed the clinical and quality reviews while TGA completed the non-clinical review. For Abemaciclib, Health Canada completed the clinical review while TGA completed the quality and non-clinical reviews. Interestingly, Health Canada also consulted quality review reports from Swissmedic, who was not involved in this particular workshare but was involved in the approval of baloxavir marboxil in 2020 where Swissmedic, Health Canada and TGA workshared. Although the review is shared, each regulator makes an independent decision regarding approval (market authorisation) of the new medicine. This model of worksharing is being watched to see if this could be a model for other like minded agencies to share resource both within and across regions and to streamline company interactions.

Internationalisation of NAS submitted to FDA 2015-2019

The total number of approvals of NAS 2015-2019 across the 6 agencies was 1026. FDA had the largest proportion of NASs approved at 22% (230 NASs), which compared to 14-16% for the other agencies. Is this difference just a timing issue, or is there a cohort of medicines approved by FDA which do not get internationalised? To look at this question, NASs submitted to FDA between 2015-2019 and approved in that time period were evaluated in terms of how many were approved by FDA only or had been approved by FDA and one of the other agencies. As submission is largely a product of company strategy, we looked at company size to determine whether this has an impact on the internationalisation of medicines.

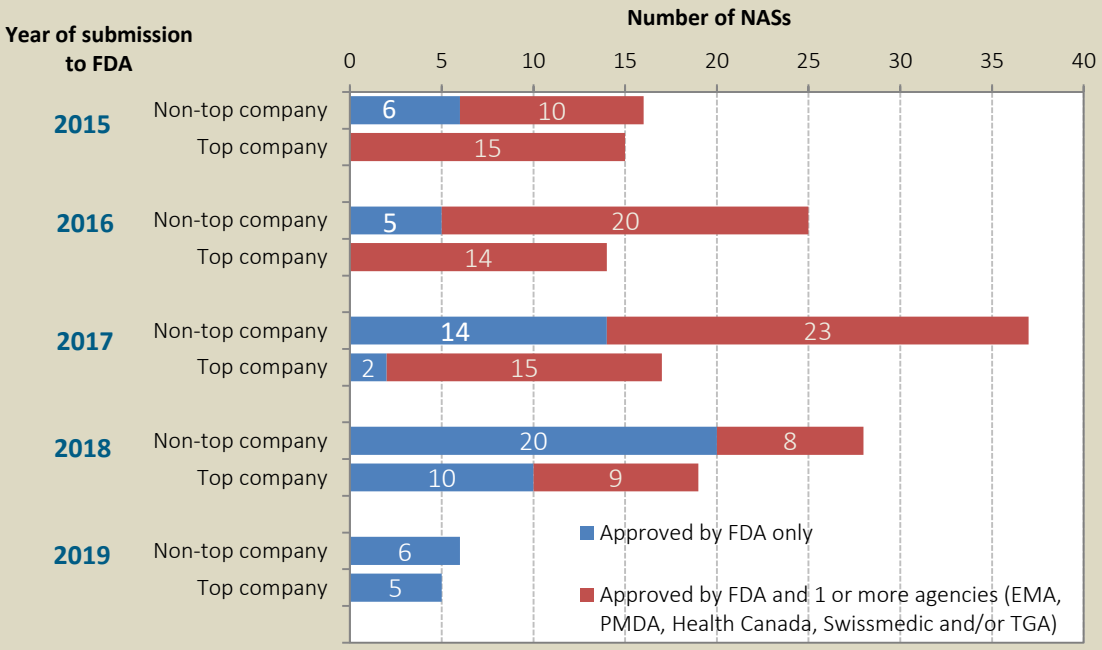
Figure 14: NASs submitted to FDA between 2015-2019 and their internationalisation, by company size



Top company is defined as having R&D budget>3 billion USD in 2019.

Of the 182 NASs submitted and approved at FDA from 2015-2019, 112 (62%) came from non-top companies and 70 (38%) from top companies. Of the 182 NASs, 68 (37%) NASs were approved by FDA only, of which 51 (75%) were from non-top companies. Although timing will be an important component, with 60% (41/68 NASs) of those only approved by FDA being submitted to FDA between 2018-2019, size of company will also play a role in the likelihood of a product being internationalised quickly. Of the 124 NASs submitted between 2015-2017 to FDA, 22% (27) were approved only at FDA, of which 93% (25) were from non-top companies (Fig 15). This data suggest that the majority of medicines approved by FDA will be internationalised, although this may take more time for medicines developed by non-top companies.

Figure 15: NASs submitted to FDA between 2015-2019 and their internationalisation, by company size and submission year



Top company is defined as having R&D budget>3 billion USD in 2019.

Figure 16: Median time of review process for NASs approved by EMA between 2015-2019, by approval year and CHMP decision-making process (majority vs. consensus)

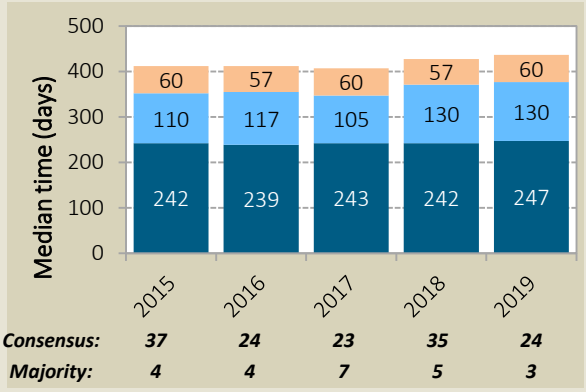
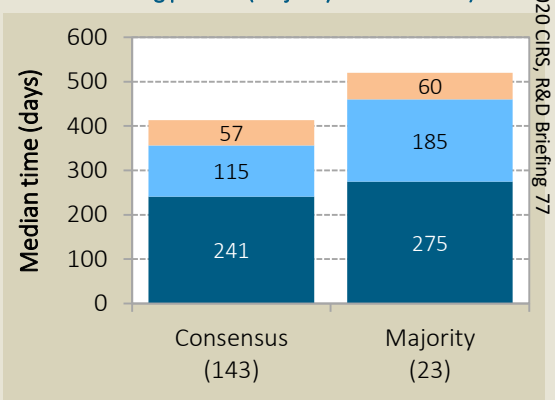


Figure 17: Median time of review process for NASs approved between 2015-2019, according to the CHMP decision making process (majority vs. consensus)



EU Commission time Company response time EMA review time

Expedited review refers to EMA Accelerated Assessment. The EMA approval time includes the EU Commission time.

Over the last two years (2018-2019) the EMA median company or clock stop time shows an increase by about 1 month of extra company time compared to 2015-2017 (Fig. 16)**.** What is driving this increase in company time has not been explored in detail, but could relate to an increase in quantity or complexity of questions raised by the agency, or more non-top companies submitting where their experience and resource may be limited, leading to an increase in time to answer the questions raised. Interestingly, the proportion of non-top companies made up around 49% of all approvals from 2015-2017 but that increased to 57% for 2018-2019. Whether a product is approved by consensus or by majority (this is when some CHMP members have a divergent opinion), seemed to have an effect on the length of the review process. Products approved by a majority were characterised by an increase of around 14% in median agency and 61% in company time compared to those approved by consensus (Fig. 17). However, this is unlikely to be the sole driver for the increased company time, as the proportion of majority to consensus is larger for the products approved between 2015-2017 (15%) than 2018-2019 (12%).

Figure 18: EMA conditional authorisation 2015-2019

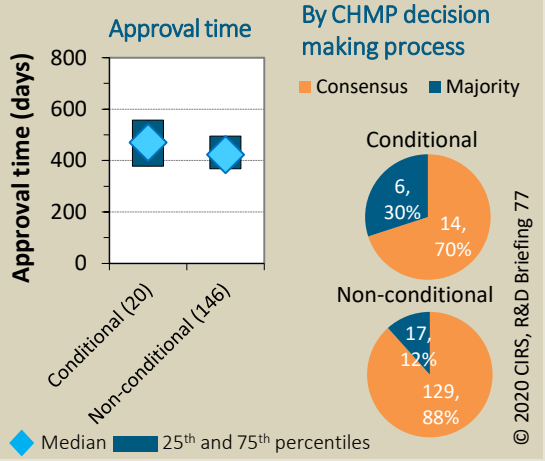
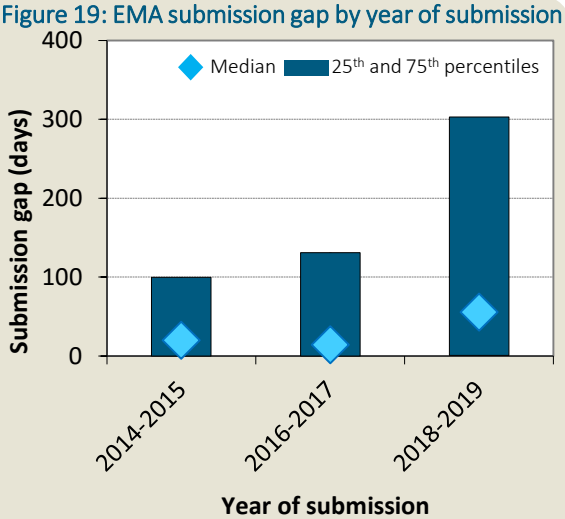


Figure 19: EMA submission gap by year of submission



EMA approval time includes the EU Commission time. Submission gap is calculated as the time from date of submission at the first regulatory agency to the date of regulatory submission to the target agency. The gap is an absolute difference between the EMA and FDA time submission date.

A comparative analysis evaluating conditional versus non-conditional approvals between 2015-2019 at EMA revealed that for the 20 NASs approved through the conditional route, the median approval time was longer (470 days) compared to non-conditional approvals (420 days), with a higher proportion approved by majority (30% versus 12%) (Fig 18). The conditional approval route has in the past been used as a rescue route; only 3 of the 20 conditional approvals between 2015-2019 were proposed by the CHMP with the rest being requested by the sponsor. Interestingly, on evaluating any change in submission gap between first regulatory agency submission to submission to the EMA, the data shows an increase in median time, as well as a larger variation for submissions in 2018/2019 compared to the previous two year cohorts (Fig.19). The reason for this has not been evaluated.

Figure 20: Proportion of NASs approved by FDA CDER, by number of review cycles and approval year, n=number of NASs

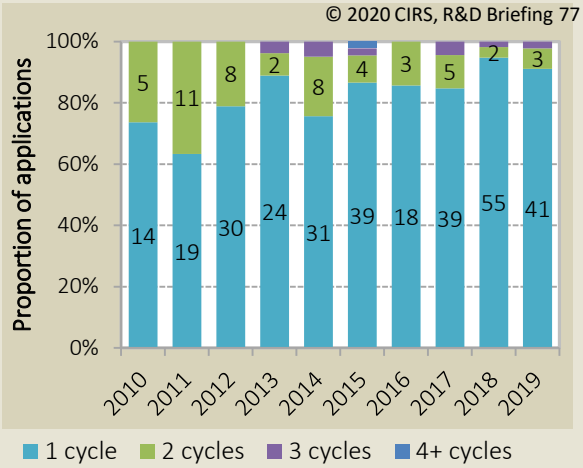
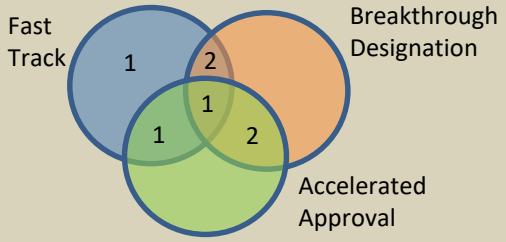


Figure 21: Personalised medicines snapshot for 2019

8 of 47 (17%) NASs approved in 2019 by FDA were **personalised medicines** with median approval time: **221 days**

FACILITATED REGULATORY PATHWAY

All 8 personalised medicines reviewed as priority. In addition, 7 had other combinations of FRPs associated:



The proportion of NASs approved by FDA CDER after one cycle increased from 76% between 2010-2014 to 89% between 2015-2019 (Fig. 20). An improvement in the number of one-cycle reviews may suggest better quality of dossiers, which in turn has a positive impact on review efficiency. However, it is important to note that this analysis only includes approvals; inclusion of compounds that have not been approved may generate a different perspective. **Eight of NASs approved by FDA in 2019 were personalised medicines (Fig. 21).** All of them were reviewed as priority and 7 combined at least one other FRP, which shows that these medicines are promising and are addressing unmet medical needs, therefore qualifying for these tools.

Figure 22: FDA Breakthrough Designation snapshot

In 2019, 15 NASs with Breakthrough Designation (BTD) were approved

FACILITATED REGULATORY PATHWAY (2019)

All 15 BTD reviewed as Expedited:

5 BTD with Expedited only

5 Accelerated Approval (AA)

3 Fast Track (FT)

2 FT and AA

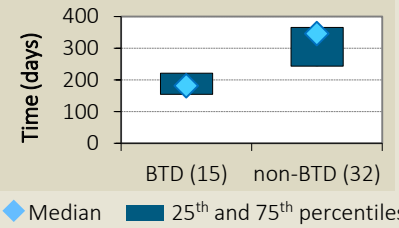
THERAPY AREA (2019)

7/15 BTD were anti-cancer and immunomodulators (ATC = L), compared to 7/32 non-BTD

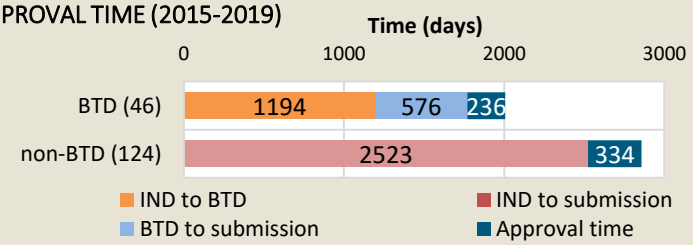
SPONSOR SIZE (2019)

8/15 BTD were from top companies, compared with 13/32 non-BTD

APPROVAL TIME (2019)



INFLUENCE OF BREAKTHROUGH DESIGNATION ON DEVELOPMENT AND APPROVAL TIME (2015-2019)



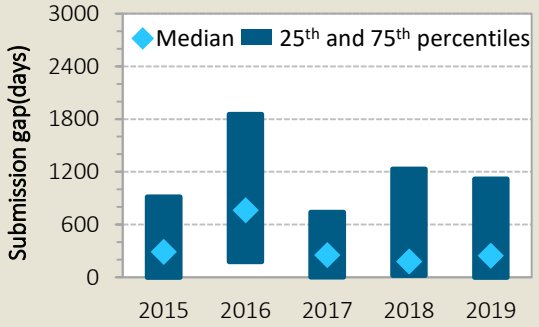
Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. Top company is defined as having R&D budget>3 billion USD in 2019. Not all IND/BTD submission dates were identified for the 67 BTD and 163 non-BTD NASs approved in 2015-2019, thereby resulting in different N numbers.

In 2019, FDA approved 15 BTD NASs, all of them reviewed as expedited (priority) and 53% of which were submitted by top companies compared to 13% in 2018 (Fig. 22). 7 of the 15 BTD NASs were approved using the Accelerated Approval programme, which shows that they were approved using a surrogate marker, and of these, 6 were anti-cancer and immunomodulators. 2015-2019 BTD approvals had reduced development time from IND to application submission, in alignment with the expected benefit for BTD.

Figure 23: Number of NASs approved by PMDA according to month and year of approval, by calendar year (Jan-Dec) and fiscal year (Apr-Apr)

Year	Jan	Feb	Mar	Jun	Jul	Sep	Dec	NAS, N Jan-Dec	NAS, N Apr-Apr
2015			10		10	12		32	39
2016	3		14	1	6	16	8	48	37
2017			6		6	10		22	35
2018	9	1	9		5	8		32	31
2019	11		7	6		9		33	

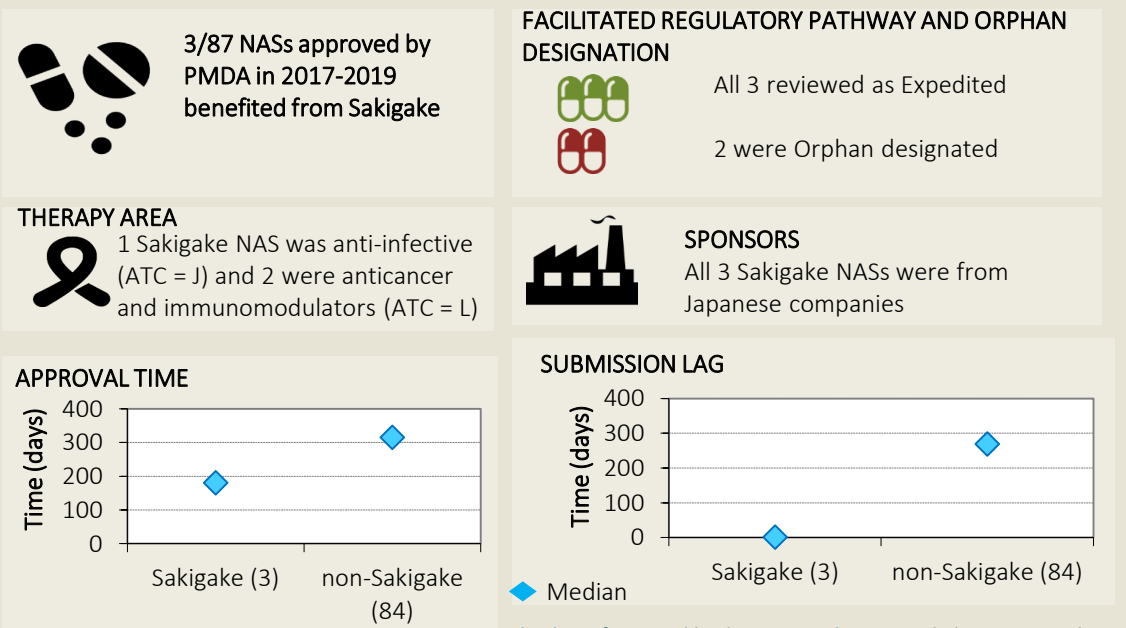
Figure 24: Submission gap for NASs approved by PMDA, by year of approval



Submission gap is defined as date of submission at the first regulatory agency (EMA or FDA) to the date of submission at PMDA.

PMDA generally approves medicines 4 times per fiscal year, between April and April, and consequently, analysis by calendar year may result in year-on-year fluctuations in the total numbers approved, compared with other agencies such as FDA, where the approvals can occur at any time of the year. Interestingly, PMDA approval numbers based on fiscal year decreased year-on-year between 2015-2018 (Fig. 23). In 2019, the PMDA median submission gap was 248 days, which is 67 days longer than the previous year. Nevertheless, the variance is similar between the two years. This may be a result of companies' changing strategies for submission to Japan (Fig. 24). Indeed, the availability of older products to Japanese patients was facilitated in recent years through government programmes, as well as through issues in local development rights amongst sponsors (domestic versus foreign).

Figure 25: PMDA Sakigake snapshot for 2017-2019



Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. Submission gap is calculated as the time from date of submission at the first regulatory agency (EMA or FDA) to the date of regulatory submission to PMDA.

Three NASs approved by PMDA between 2017-2019 benefited from Sakigake, a designation that enables development and approval of novel medicines. The median approval time for the 3 Sakigake NASs was 181 days, which is 135 days faster than non-Sakigake, and there was no median submission gap for the Sakigake NASs (Fig. 25).

All 3 Sakigake NASs were also approved by FDA, whereas 1 of 3 was approved by EMA. They were all approved as expedited by both agencies. 2 of 3 Sakigake NASs were anti-cancer and immunomodulators, and 2 were orphan designated.

Features of the Health Canada approval process

Figure 26: Median submission gap and approval time for NASs approved by Health Canada

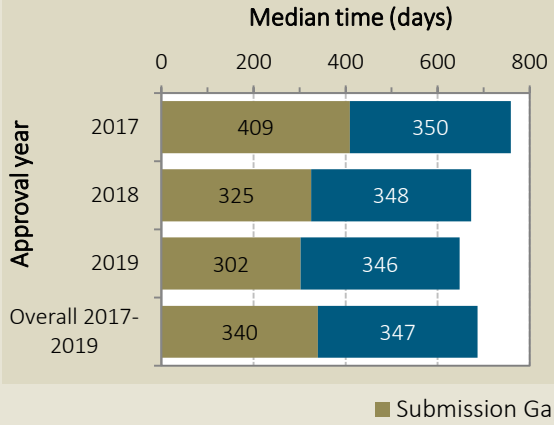
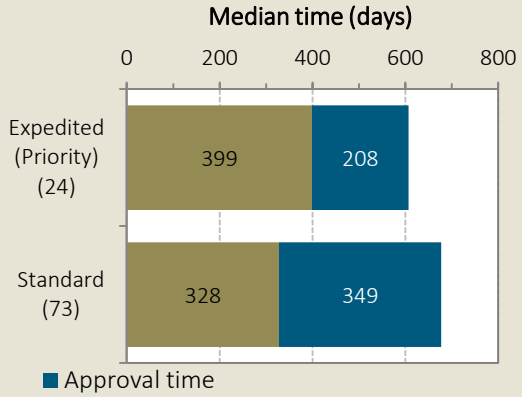


Figure 27: Median submission gap and approval time for NASs approved by Health Canada between 2017-2019, by review type



'Expedited review' refers to Health Canada 'Priority Review'. Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. Submission gap is calculated as the time from date of submission at the first regulatory agency to the date of regulatory submission to Health Canada.

The median submission gap to Health Canada decreased year-on-year from 2017, with a difference in median submission gap of 107 days for 2019 compared to 2017 (Fig. 26). The overall submission gap and approval time between 2017-2019 were also analysed according to review type (Fig. 27). The median approval time was shorter for NASs designated as expedited (priority), but the same was not true for median submission gap. This suggests that for these products (standard vs. priority), there was little difference in company strategy to submit the dossier to Health Canada.

Figure 28: Health Canada FRPs snapshot for 2019

12/30 NASs approved by Health Canada in 2019 benefited from at least 1 FRP

FACILITATED REGULATORY PATHWAY

5 reviewed as Expedited
4 Conditional Approval
2 ACSS worksharing
1 Expedited and Conditional

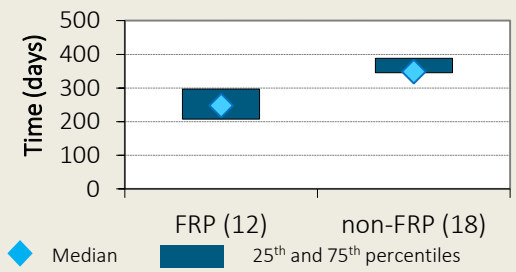
THERAPY AREA

9/12 FRP products were anti-cancer and immunomodulators (ATC = L), compared to 9/18 non-FRP

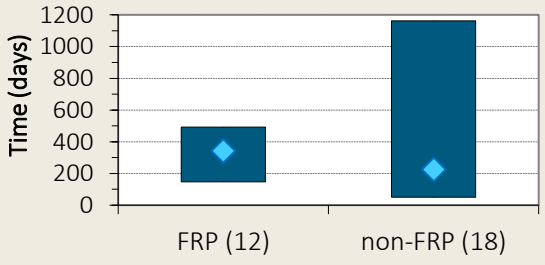
SPONSOR SIZE

7/12 FRP products were from top companies, compared with 9/18 non-FRP

APPROVAL TIME



SUBMISSION LAG



Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. Submission gap is calculated as the time from date of submission at the first regulatory agency to the date of regulatory submission to Health Canada. Top company is defined as having R&D budget>3 billion USD in 2019. 'Expedited review' refers to Health Canada 'Priority Review'.

40% of NASs approved in 2019 by Health Canada benefited from at least one FRP, and they were approved 101 days faster than other NASs. Of these 12 NASs, 75% were anti-cancer and immunomodulators and 58% originated from top companies (Fig. 28). Health Canada also approved 2 NASs in 2019 as part of the recently introduced ACSS Consortium worksharing.

Features of the Swissmedic approval process

Figure 29: Median submission gap and approval time for NASs approved by Swissmedic

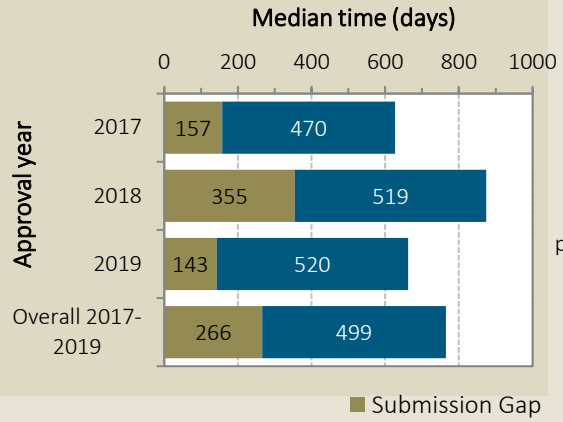
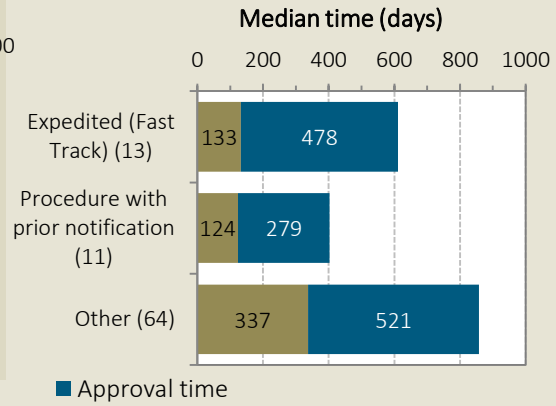


Figure 30: Median submission gap and approval time for NASs approved by Swissmedic between 2017-2019, by review type



'Expedited review' refers to Swissmedic 'Fast-Track'. Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. Submission gap is calculated as the time from date of submission at the first regulatory agency to the date of regulatory submission to Swissmedic.

The median submission gap to Swissmedic decreased in 2019 to 143 days, compared with 355 days in 2018. Conversely, the median approval time remained almost the same (Fig. 29). The overall median submission gap and median approval time between 2017-2019 were also analysed according to review type; both were faster for NASs designated as expedited (Fast Track) or for NASs using the Procedure with prior notification (Fig. 30).

Figure 31: Swissmedic FRPs snapshot for 2019

9/28 NASs approved by Swissmedic in 2019 benefited from at least 1 FRP

FACILITATED REGULATORY PATHWAY

2 reviewed as Expedited

3 Art.13 TPA

4 Procedure with prior notification

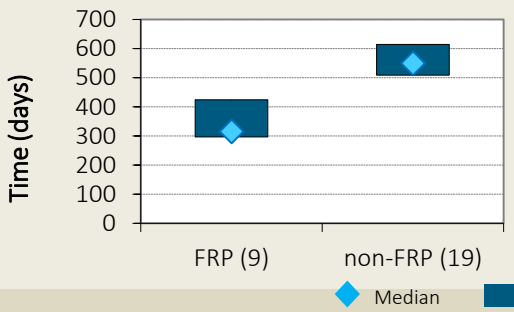
THERAPY AREA

3/9 FRP products were anti-cancer and immunomodulators (ATC = L), compared to 7/19 non-FRP

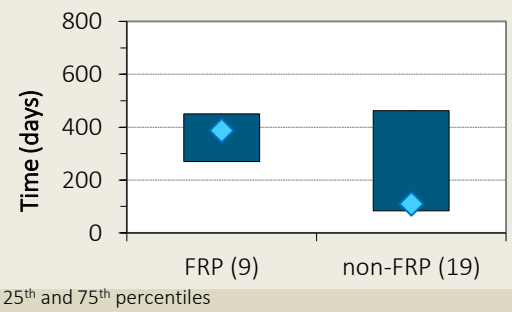
SPONSOR SIZE

4/9 FRP products were from top companies, compared with 11/19 non-FRP

APPROVAL TIME



SUBMISSION LAG



Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. Submission gap is calculated as the time from date of submission at the first regulatory agency to the date of regulatory submission to Swissmedic. Top company is defined as having R&D budget>3 billion USD in 2019. 'Expedited review' refers to Swissmedic 'Fast-Track procedure'.

In 2019, the 9 NASs approved with at least one FRP were approved a median 234 days faster than the non-FRP NASs, but the submission lag for FRP NASs was longer compared to non-FRP, which may be due to company strategy (Fig.31). In 2019, 3 NASs were approved using Art.13 TPA, through which Swissmedic takes into account results of assessments carried out by comparable foreign regulatory agencies. Submission lag was 278 days higher for NASs approved with at least 1 FRP compared to non-FRP NASs.

Figure 32: Median submission gap and approval time for NASs approved by TGA from 2017-2019

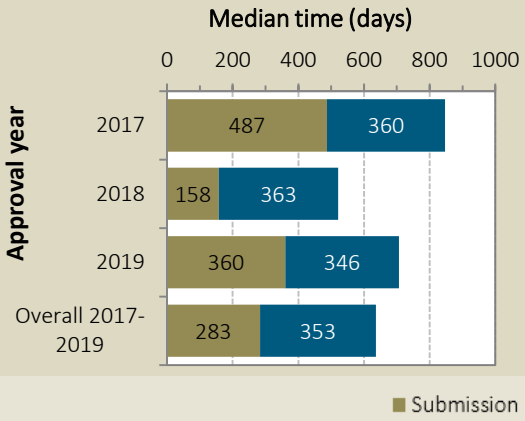
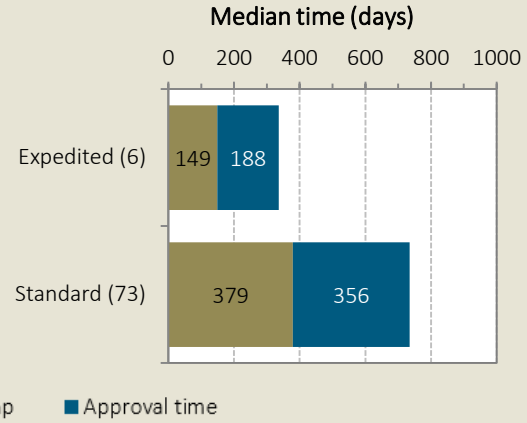


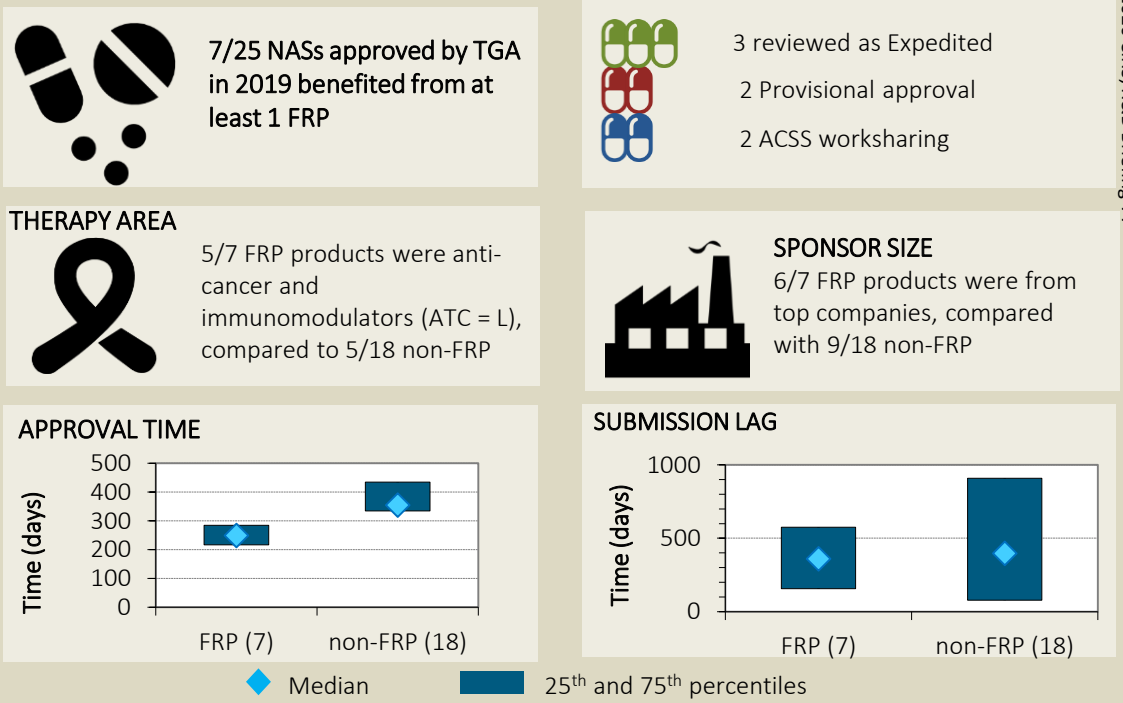
Figure 33: Median submission gap and approval time for NASs approved by TGA between 2017-2019, by review type



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

The median submission gap to TGA increased in 2019 to 360 days, compared with 158 days in 2018. On the contrary, the median approval time was similar, with a slight decrease by 17 days (Fig. 32). Six NASs were approved by TGA between 2017-2019 using the expedited review (priority) introduced in 2017, with a median approval time of 188 days, which was 168 days faster than the median standard approval time. The median submission gap for expedited NASs was 149 days, which was 230 days shorter than for standard products (Fig. 33).

Figure 34: TGA FRPs snapshot for 2019



Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. Submission gap is calculated as the time from date of submission at the first regulatory agency to the date of regulatory submission to TGA. Top company is defined as having R&D budget>3 billion USD in 2019. Expedited review' refers to TGA 'Priority Review' introduced in 2017.

Seven NASs approved by TGA in 2019 benefited from at least one FRP, and were approved 106 days faster than the non-FRP NASs. The median submission gap for FRP NASs was 37 days shorter than for medicines without an FRP, and the variance was lower (Fig. 34). TGA approved two NASs in 2019 with the newly introduced ACSS worksharing, where the review for these products was also undertaken by Health Canada.

Summary of NAS approved in 2019 by the 6 agencies

This table summarises approval times for NAS approved in 2019 by the 6 agencies, broken down by product type, review type and major therapeutic area.

Agency median 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	27	47	33	31	28	25
NAS overall Approval time (days)	423	243	304	346	520	346
By Biologics (days)	440	239	288	345	447	347
By Chemicals (days)	418	243	304	346	531	346
By Standard review (days)	433	365	332	347	557	351
By Expedited review (days)	270	238	256	206	300	244
By Orphans (days)	352	238	257	302*	436	327
By Anticancer and Immuno-modulators (days)	417	220	263	344	540	310

** Health Canada does not have an orphan policy; however, 15 NASs that were classified as orphan by either FDA, EMA or TGA were approved by Health Canada in 2019, with a median approval time of 302 days.*

Approval at EMA 2019

EMA **APPROVED A TOTAL OF 27 NASs IN 2019,** WITH A MEDIAN APPROVAL TIME OF **423 DAYS**

Type of Medicine

11 BIOLOGIC NASs APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **440 DAYS**

16 CHEMICAL NASs APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **418 DAYS**

11 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **417 DAYS**

16 NASs IN OTHER THERAPY AREAS APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **437 DAYS**

Designation and Review Type

2 EXPEDITED NAS APPROVALS IN 2019, WITH A MEDIAN APPROVAL TIME OF **270 DAYS;** THIS IS **163 DAYS FASTER** THAN THE MEDIAN OF THE **25 STANDARD NAS APPROVALS IN 2019**

4 ORPHAN NAS APPROVALS IN 2019, WITH A MEDIAN APPROVAL TIME OF **352 DAYS;** THIS IS **81 DAYS FASTER** THAN THE MEDIAN OF THE **23 NON-ORPHAN NAS APPROVALS IN 2019**

Availability by EMA

30% OF THE NASs APPROVED IN 2019 BY EMA WERE APPROVED BY EMA **FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL BY FDA, PMDA, HEALTH CANADA, SWISSMEDIC OR TGA**

70% OF THE NASs APPROVED IN 2019 BY EMA WERE APPROVED BY FDA, PMDA, HEALTH CANADA, SWISSMEDIC OR TGA **FIRST OR MORE THAN ONE MONTH BEFORE BEING APPROVED BY EMA**

THE MEDIAN **SUBMISSION GAP** TO EMA FOR THESE NASs WAS **249 DAYS**

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.

Approval at FDA 2019

FDA (CDER AND CBER) **APPROVED A TOTAL OF 47 NASs IN 2019,** WITH A MEDIAN APPROVAL TIME OF **243 DAYS**

Type of Medicine

12 BIOLOGIC NASs APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **239 DAYS**

35 CHEMICAL NASs APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **243 DAYS**

14 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **216 DAYS**

33 NASs IN OTHER THERAPY AREAS APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **334 DAYS**

Designation and Review Type

32 EXPEDITED NAS APPROVALS IN 2019, WITH A MEDIAN APPROVAL TIME OF **238 DAYS;** THIS IS **127 DAYS FASTER** THAN THE MEDIAN OF THE **15 STANDARD NAS APPROVALS IN 2019**

20 ORPHAN NAS APPROVALS IN 2019, WITH A MEDIAN APPROVAL TIME OF **238 DAYS;** THIS IS **119 DAYS FASTER** THAN THE MEDIAN OF THE **27 NON-ORPHAN NAS APPROVALS IN 2019**

Availability by FDA

85% OF THE NASs APPROVED IN 2019 BY FDA WERE APPROVED BY FDA **FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL BY EMA, PMDA, HEALTH CANADA , SWISSMEDIC OR TGA**

15% OF THE NASs APPROVED IN 2019 BY FDA WERE APPROVED BY EMA, PMDA, HEALTH CANADA, SWISSMEDIC OR TGA **FIRST OR MORE THAN ONE MONTH BEFORE BEING APPROVED BY FDA**

THE MEDIAN **SUBMISSION GAP** TO FDA FOR THESE NASs WAS **0 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.

Approval at PMDA 2019

PMDA **APPROVED A TOTAL OF 33 NASs IN 2019,** WITH A MEDIAN APPROVAL TIME OF **304 DAYS**

Type of Medicine

10 BIOLOGIC NASs APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **288 DAYS**

23 CHEMICAL NASs APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **304 DAYS**

11 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **263 DAYS**

22 NASs IN OTHER THERAPY AREAS APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **315 DAYS**

Designation and Review Type

14 EXPEDITED NAS APPROVALS IN 2019, WITH A MEDIAN APPROVAL TIME OF **256 DAYS;** THIS IS **76 DAYS FASTER** THAN THE MEDIAN OF THE **19 STANDARD NAS APPROVALS IN 2019**

12 ORPHAN NAS APPROVALS IN 2019, WITH A MEDIAN APPROVAL TIME OF **257 DAYS;** THIS IS **73 DAYS FASTER** THAN THE MEDIAN OF THE **21 NON-ORPHAN NAS APPROVALS IN 2019**

Availability by PMDA

36% OF THE NASs APPROVED IN 2019 BY PMDA WERE APPROVED BY PMDA **FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL BY EMA, FDA, HEALTH CANADA , SWISSMEDIC OR TGA**

64% OF THE NASs APPROVED IN 2019 BY PMDA WERE APPROVED BY EMA, FDA, HEALTH CANADA, SWISSMEDIC OR TGA **FIRST OR MORE THAN ONE MONTH BEFORE BEING APPROVED BY PMDA**

THE MEDIAN **SUBMISSION GAP** TO PMDA FOR THESE NASs WAS **930 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.

Approval at Health Canada 2019

HEALTH CANADA **APPROVED A TOTAL OF 30 NASs IN 2019,** WITH A MEDIAN APPROVAL TIME OF **346 DAYS**

Type of Medicine

9 BIOLOGIC NASs APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **345 DAYS**

21 CHEMICAL NASs APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **346 DAYS**

18 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **344 DAYS**

12 NASs IN OTHER THERAPY AREAS APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **346 DAYS**

Designation and Review Type

6 EXPEDITED NAS APPROVALS IN 2019 WITH A MEDIAN APPROVAL TIME OF **206 DAYS;** THIS IS **141 DAYS FASTER** THAN THE MEDIAN OF THE **24 STANDARD NAS APPROVALS IN 2019**

HEALTH CANADA DOES NOT HAVE AN ORPHAN POLICY; HOWEVER, **15 NASs THAT WERE CLASSIFIED AS ORPHAN BY EITHER FDA, EMA OR TGA WERE APPROVED BY HEALTH CANADA IN 2019,** WITH A MEDIAN APPROVAL TIME OF **302 DAYS**

Availability by Health Canada

10% OF THE NASs APPROVED IN 2019 BY HEALTH CANADA WERE APPROVED BY HEALTH CANADA **FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL BY EMA, FDA, PMDA, SWISSMEDIC OR TGA**

90% OF THE NASs APPROVED IN 2019 BY HEALTH CANADA WERE APPROVED BY EMA, FDA, PMDA, SWISSMEDIC OR TGA **FIRST OR MORE THAN ONE MONTH BEFORE BEING APPROVED BY HEALTH CANADA**

THE MEDIAN **SUBMISSION GAP** TO HEALTH CANADA FOR THESE NASs WAS **338 DAYS**

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

Approval at Swissmedic 2019

SWISSMEDIC **APPROVED A TOTAL OF 28 NASs IN 2019** ,WITH A MEDIAN APPROVAL TIME OF **520 DAYS (TIME TO SCIENTIFIC ASSESSMENT: 312 DAYS)**

Type of Medicine

11 BIOLOGIC NASs APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **447 DAYS**

17 CHEMICAL NASs APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **531 DAYS**

10 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **540 DAYS**

18 NASs IN OTHER THERAPY AREAS APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **482 DAYS**

Designation and Review Type

2 EXPEDITED NAS APPROVALS IN 2019, WITH A MEDIAN APPROVAL TIME OF **300 DAYS;** THIS IS **227 DAYS FASTER** THAN THE MEDIAN OF THE **26 STANDARD NAS APPROVALS IN 2019**

12 ORPHAN NAS APPROVALS IN 2019, WITH A MEDIAN APPROVAL TIME OF **436 DAYS;** THIS IS **106 DAYS FASTER** THAN THE MEDIAN OF THE **16 NON-ORPHAN NAS APPROVALS IN 2019**

Availability by Swissmedic

11% OF THE NASs APPROVED IN 2019 BY SWISSMEDIC WERE APPROVED BY SWISSMEDIC **FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL BY FDA, EMA, PMDA, HEALTH CANADA OR TGA**

89% OF THE NASs APPROVED IN 2019 BY SWISSMEDIC WERE APPROVED BY FDA, EMA, PMDA, HEALTH CANADA OR TGA **FIRST OR MORE THAN ONE MONTH BEFORE BEING APPROVED BY SWISSMEDIC**

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

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

Approval at TGA 2019

TGA **APPROVED A TOTAL OF 25 NASs IN 2019** , WITH A MEDIAN APPROVAL TIME OF **346 DAYS**

Type of Medicine

10 BIOLOGIC NASs APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **347 DAYS**

15 CHEMICAL NASs APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **346 DAYS**

10 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **310 DAYS**

15 NASs IN OTHER THERAPY AREAS APPROVED IN 2019, WITH A MEDIAN APPROVAL TIME OF **356 DAYS**

Designation and Review Type

3 EXPEDITED NAS APPROVALS IN 2019 WITH A MEDIAN APPROVAL TIME OF **244 DAYS;** THIS IS **107 DAYS FASTER** THAN THE MEDIAN OF THE **22 STANDARD NAS APPROVALS IN 2019**

8 ORPHAN NAS APPROVALS IN 2019, WITH A MEDIAN APPROVAL TIME OF **327 DAYS;** THIS IS **23 DAYS FASTER** THAN THE MEDIAN OF THE **17 NON-ORPHAN NAS APPROVALS IN 2019**

Availability in TGA

16% OF THE NASs APPROVED IN 2019 BY TGA WERE APPROVED BY TGA **FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL BY FDA, EMA, PMDA, HEALTH CANADA OR SWISSMEDIC**

84% OF THE NASs APPROVED IN 2019 BY TGA WERE APPROVED BY FDA, EMA, PMDA, HEALTH CANADA OR SWISSMEDIC **FIRST OR MORE THAN ONE MONTH BEFORE BEING APPROVED BY TGA**

THE MEDIAN **SUBMISSION GAP** TO TGA FOR THESE NASs WAS **535 DAYS**

'Expedited review' refers to TGA 'Priority Review' 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.

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
EMA Accelerated Assessment	A process designed to expedite products of major interest in terms of public health and therapeutic innovation	• 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

Facilitated Regulatory Pathways in ICH

	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 comparable medicinal product control system, taking account of the results of the trials conducted for this purpose provided the 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)
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)
ACSS Worksharing	Medium-sized coalition to promote greater regulatory collaboration and alignment of regulatory requirements between Australia-Canada-Singapore-Switzerland (ACSS)	• 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

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.

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.
- 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).

Personalised medicines
Therapeutic products for which the label includes reference to specific biological markers that help guide decisions and/or procedures for their use in individual patients.

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

Submission gap
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 6 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.

• 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.

Continued: see next page

*The full list of NASs approved by each jurisdiction in 2019 will be made available on the CIRS website. Applications that are excluded from the study.

• 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 2019.

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.

*The full list of NASs approved by each jurisdiction in 2019 will be made available on the CIRS website.

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About CIRS

The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independently managed UK-based subsidiary company, forming part of the Clarivate Analytics group. CIRS' mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and 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 medical products through these activities. This is CIRS' purpose. CIRS is operated solely for the promotion of its purpose. 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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