New drug approvals in six major authorities 2008 -2017:

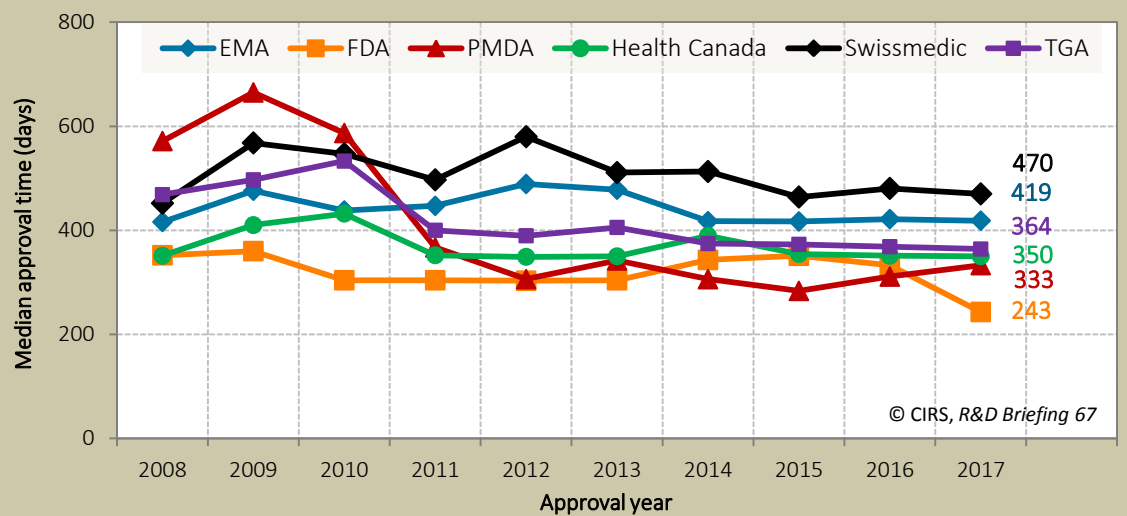
Focus on the availability of medicines and company size

Major improvements in the regulatory environment as well as changes in strategies of multinational companies have led to a decrease in the time to marketing authorisation as well as an increase in the number of medicines that have become available over the last decade, 2008-2017, across six major regulatory agencies, namely 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). More specifically, the number of common products approved by all six agencies increased from 12 in 2008-2012 to 51 in 2013-2017.

Contents

Underlying factors influencing the overall time it takes for a new medicine to be submitted and then approved by an agency include company strategy, the conduct and the type of the review process, the type of the product and its therapeutic area; these aspects are analysed and discussed in this study. Nevertheless, one of the key factors that may determine the likelihood and timing of submission is the size of the sponsor, which will be a focus of this Briefing, where a medicine may be less likely to become internationalised beyond the first country of submission if it is developed by a smaller company.

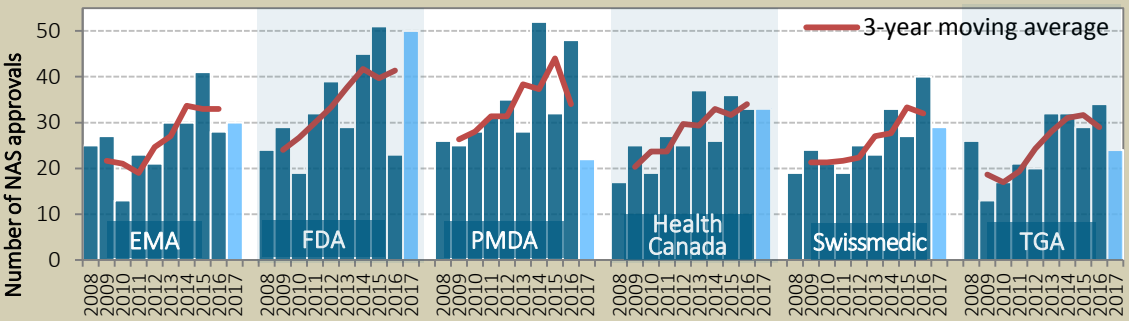
New active substance (NAS) median approval time for six regulatory authorities in 2008-2017



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.

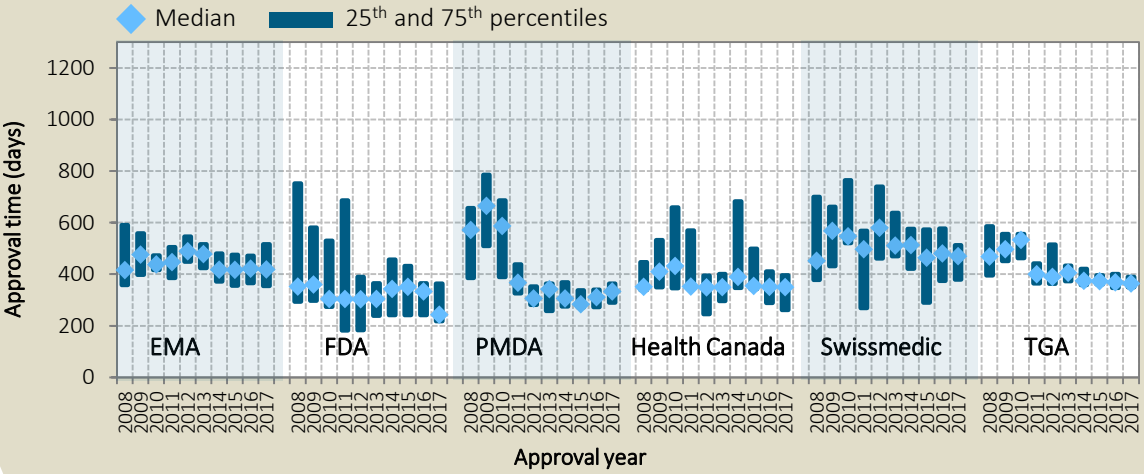
Approval times

Figure 1: Number of NASs approved by six regulatory authorities by approval year 2008-2017



In 2017, FDA approved the highest number of NASs (50), followed by Health Canada (30), EMA (30), Swissmedic (29) , TGA (24) and PMDA (22) (Fig. 1). Despite these numbers varying on an annual basis, the overall number of NASs approved by the six agencies has increased, as shown by the three-year moving average. A comparison of numbers of NASs approved by each agency during the two parts of the decade, 2008-2012 and 2013-2017, revealed that the biggest difference in the number of approvals was seen for TGA, with a 56% increase, followed by Health Canada and EMA (46%), Swissmedic (41%), FDA (38%) and PMDA (26%). The year-on-year variance across countries 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, which varies according to company size and unmet medical need (pp. 6-14), as well as agency review speed. Another factor is the review timing, where certain agencies, such as the FDA, approve NASs throughout the year on ongoing basis, whereas others approve in batches at specific points in the year, such as PMDA (p. 17).

Figure 2: NAS approval time for six regulatory authorities in 2008-2017

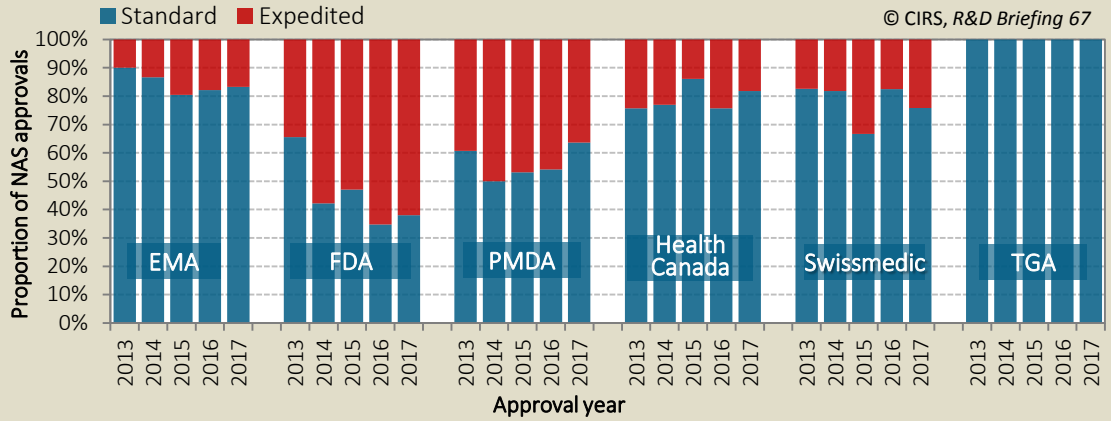


Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time.

In 2017, FDA was the agency with the shortest median approval time (243 days), which is likely due to the wide use of facilitated regulatory pathways (FRPs) that year, where 40% of NAS approvals were designated as Breakthrough, highlighting the importance of those products in addressing unmet medical need. The fastest median approval time for FDA was followed by PMDA (333), Health Canada (350), TGA (364), EMA (419) and Swissmedic (470). In general, the median approval times were similar across the six agencies, where the difference between the fastest and slowest agency (excluding FDA) was 137 days, which is in line with the convergence in median times observed in the past (*R&D Briefing* 59 and 65). Recent years have also seen low variation in approval time (25th - 75th percentile) especially for TGA, FDA, EMA and PMDA (Fig. 2), which established even more consistency in review timing. This may be a result of a number of factors, such as the legislation of approval procedures and processes within EMA and TGA, improving quality of submissions from companies, as well as implementation of various quality measures by agencies, such as pre-submission activities in order to verify the quality of the dossier ahead of the review and to ultimately improve process consistency and timeliness. Where there is variance, this may be due to the use of standard or expedited pathways by the agency in order to prioritise the review of certain NASs (see page 3).

Characteristics: Review type

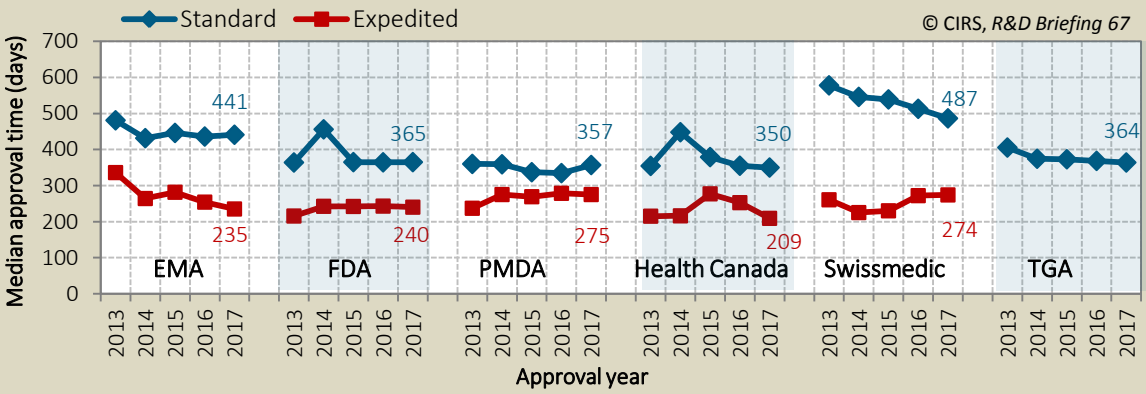
Figure 3: Number of NAS approvals by review type for six regulatory authorities in 2013-2017



'Expedited review' refers to EMA 'Accelerated Assessment' and FDA/PMDA/Health Canada/ Swissmedic 'Priority Review'. TGA introduced an expedited (priority) review programme in 2017, with first decisions expected in 2018.

All six agencies now offer an expedited priority system (refers to EMA 'Accelerated Assessment' and FDA/PMDA/Health Canada/Swissmedic /TGA 'Priority Review') designed to hasten the review process of promising NASs (Figure 3). TGA implemented its priority system in 2017 but no expedited approvals were granted that year. Nevertheless, the agency has been accepting applications, with first decisions expected in 2018. In 2016, the ratio of expedited approvals to standard reviews was highest for FDA (62%), followed by PMDA (36%), Swissmedic (24%), Health Canada(18%) and EMA (17%). The proportion of expedited approvals has been consistently high for FDA and PMDA in the last few years, but has in fact increased when comparing 2008-2012 (results not shown) to 2013-2017 for all five agencies. EMA experienced the most notable increase from 7% in 2008-2012 to 16% in 2013-2017, followed by Swissmedic (10% to 22%), PMDA (22% to 45%), FDA (43% to 55%) and Health Canada (18% to 21%). The large increase within EMA is likely a result of the revision of the guidelines for Accelerated Assessment by the agency in 2015, where the updated guidelines are expected to optimise the use of this tool by companies. Nevertheless, more time is needed to see whether a further increase will take place in the use of the priority pathways, particularly with the launch of the PRIority MEdicines (PRIME)scheme in 2016 at EMA, which is specifically designed to promote the use of accelerated assessment for medicines that aim to address unmet medical need.

Figure 4: NAS median approval time by review type for six regulatory authorities in 2013-2017



'Expedited review' refers to EMA 'Accelerated Assessment' and FDA/PMDA/Health Canada/ Swissmedic 'Priority Review'. TGA introduced an expedited (priority) review programme in 2017, with first decisions expected in 2018. 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 2017, the median approval time for standard NASs continued to decrease for the fifth year in a row for Swissmedic, dropping by 91 days since 2013. Swissmedic was also the agency with the greatest difference in median approval time between expedited and standard review in 2017, with a difference of 213 days (Figure 4), whereas the smallest difference was for PMDA, with 82 days; the gap for other agencies was 206 days for EMA, 141 for Health Canada and 125 days for FDA. The priority system introduced under TGA in 2017 has a review target timeline of 150 days (agency time only), which is the same as EMA and should result in a similar opportunity to accelerate review of important products in line with the other agencies.

Characteristics: facilitated regulatory pathways

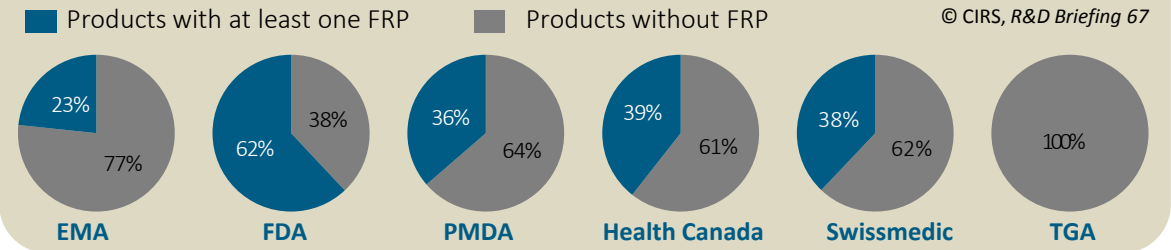
Figure 5: Facilitated regulatory pathway (FRP) and orphan status timelines across six agencies; focus on 2017

© CIRS, *R&D Briefing 67*	New active substance (NAS) approval type		2017 NAS approvals, number	2017 NASs, %	Expedited, %	2017 median approval time, days
EMA	**Overall approvals**		**30**			**419**
	FRP	Accelerated Assessment (referred in Briefing as Expedited)	5	17%		235
		Conditional Approval	2	7%	0%	437
		Exceptional Circumstances	1	3%	100%	368
	Orphan		10	33%	30%	416
FDA	**Overall approvals**		**50**			**243**
	FRP	Priority (referred in Briefing as Expedited)	31	62%		240
		Accelerated Approval	6	12%	100%	191
		Breakthrough Designation	20	40%	100%	220
		Fast Track	18	36%	100%	242
	Orphan		21	42%	86%	242
PMDA	**Overall approvals**		**22**			**333**
	FRP	Priority (referred in this Briefing as Expedited)	8	36%		275
		Sakigake	0	0%	-	-
	Orphan		7	32%	100%	281
Health Canada	**Overall approvals**		**33**			**350**
	FRP	Priority (referred in Briefing as Expedited)	6	18%		209
		Conditional (Notice of Compliance with conditions)	7	21%	0%	262
Swiss-medic	**Overall approvals**		**29**			**470**
	FRP	Priority (referred in Briefing as Expedited)	7	24%		274
		Procedure with prior notification	4	14%	0%	398
	Orphan		10	34%	40%	442
TGA	**Overall approvals**		**24**			**364**
	FRP	Priority (referred in Briefing as Expedited)	0	0%		-
		Provisional Approval	0	0%	-	-
	Orphan		7	29%	-	351

TGA introduced an expedited (priority) review and provisional approval programme in 2017, with first decisions expected in 2018. 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.

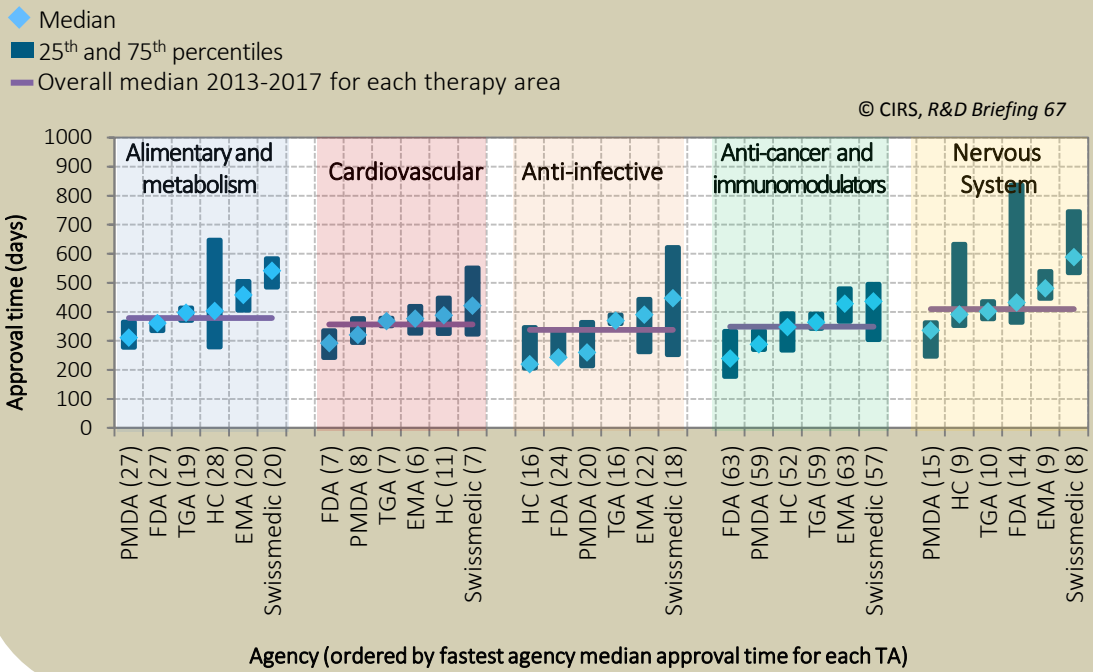
Out of the six agencies, FDA offered (or made available) the greatest number of facilitated regulatory pathways (FRPs) to enable the availability, review and/or approval of medicines where there is an unmet medical need (Fig. 5). In 2017, 62% of NASs approved by FDA benefitted from at least one of the available FRPs, compared with ~20-40% in other agencies (Fig. 6). Across the various FRPs for the five agencies, compounds reviewed through FDA Accelerated Assessment had the fastest median approval time in 2017 (191 days). Nevertheless, it should be noted that many compounds reviewed by FDA often take advantage of multiple FRPs, which generally results in a faster approval time (*R&D Briefing 57*). TGA has also introduced this year a Provisional Approval pathway, which will provide a process for the registration of promising medicines on the basis of early clinical data.

Figure 6: Proportion of NASs approved by each agency in 2017 that benefitted from at least one FRP



Characteristics: Therapeutic area

Figure 7: NAS approval time by therapeutic area (TA) for six regulatory authorities in 2013-2017, ordered by fastest agency median approval time within each TA



In 2013-2017, anti-infective therapies were approved marginally faster across all six agencies, with an overall median of 338 days, compared with 349 days for anti-cancer and immunomodulators, 357 days for cardiovascular, 379 days for alimentary and metabolism and 409 days for nervous system NASs. PMDA and FDA had the fastest approval times across three out of the five therapy areas (Fig. 7), namely alimentary and metabolism, cardiovascular, and anti-cancer and immunomodulators. This may reflect the more frequent use of expedited review pathways for those therapy areas (Fig. 8). Nevertheless, as noted by the 25th - 75th percentile bars, there were also wide variations for certain jurisdictions across therapy areas; for example, Health Canada and FDA approval timing for nervous system NASs was highly variable compared with low timing variability for approval of anti-infective, cardiovascular and anti-cancer and immunomodulators therapies. There were also variations within therapy areas for the six agencies; for example, the anti-infective and anti-cancer and immunomodulator areas, which is likely due to the differences in the use of expedited pathways across the six agencies (Fig. 7).

Figure 8: NAS overall median approval time by therapeutic area for six regulatory authorities in 2013-2017

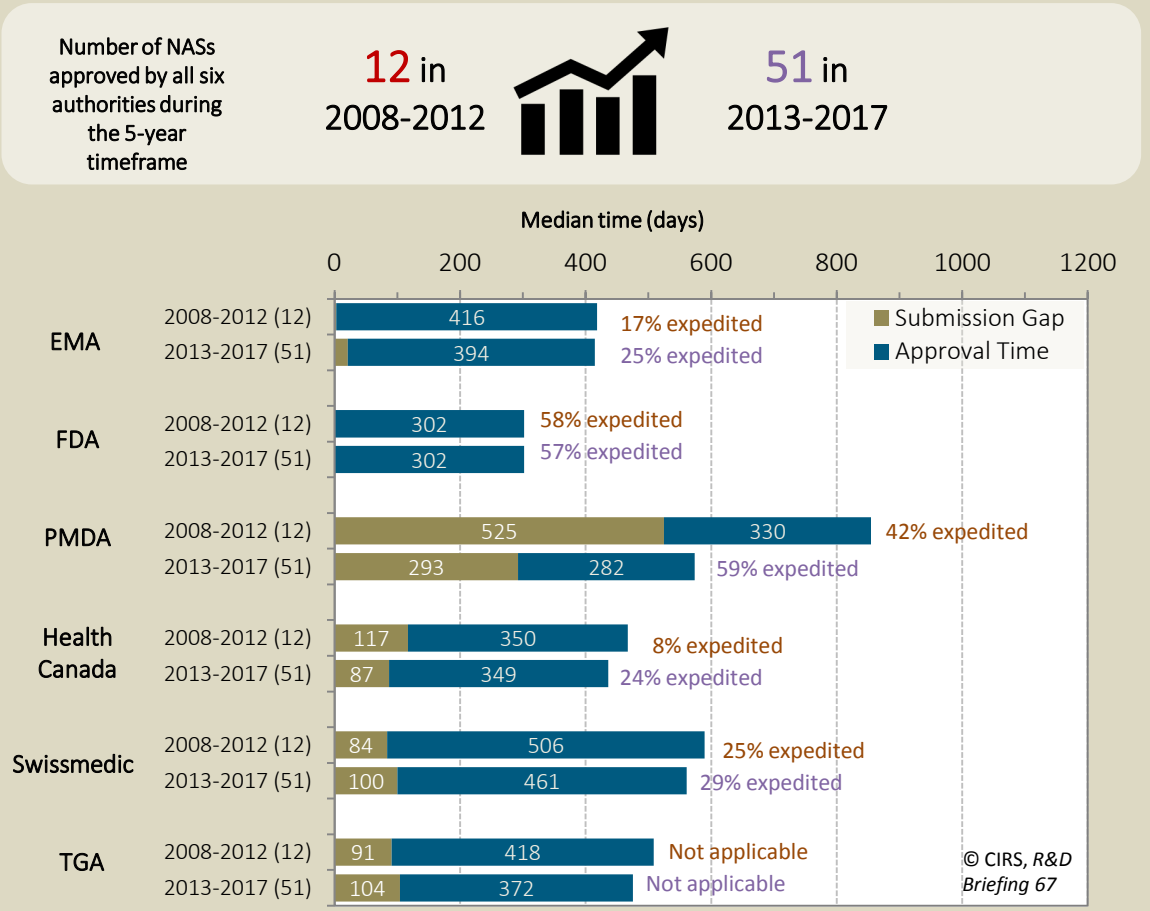
© CIRS, *R&D Briefing 67*	Alimentary and metabolism	Cardiovascular	Anti-infective	Anti-cancer and immuno-modulators	Nervous system
	Approval time, days (proportion of expedited approvals)				
EMA	458 (10%)	377 (17%)	390 (36%)	428 (16%)	481 (22%)
FDA	361 (41%)	292 (57%)	243 (83%)	239 (73%)	432 (29%)
PMDA	311 (37%)	321 (25%)	260 (75%)	288 (75%)	336 (33%)
Health Canada	403 (29%)	388 (18%)	220 (56%)	348 (23%)	391 (0%)
Swissmedic	542 (0%)	421 (29%)	447 (44%)	436 (33%)	589 (0%)
TGA	397 (0%)	368 (0%)	370 (0%)	364 (0%)	402 (0%)

'Expedited review' refers to EMA 'Accelerated Assessment' and FDA/PMDA/Health Canada/ Swissmedic '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.

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 ten years, namely 2008-2012 and 2013-2017 to determine whether any trends could be identified. Interestingly, the number of products approved by all six agencies in a two-year period increased from 12 NASs in 2008-2012 to 51 NASs in 2013-2017, which indicates that more products are becoming internationalised within the same time frame. The overall length of time to registration, consisting of the submission gap and approval time (Fig. 9) may be a result of potential factors that impact registration of NASs. This may include company strategy to submit or target approval times at a particular agency, which is in turned influenced by the type of NASs as well as the use of expedited pathways within agencies to address unmet medical need for promising medicines. The quickest time to registration was at FDA for both time frames, as a result of companies submitting there first as well as quick regulatory review times by the agency. Submissions to EMA occurred almost simultaneously with FDA, and the overall time to registration decreased, which may reflect the increased use of expedited pathways for important products by EMA. Following EMA and FDA submissions, the submission gap to Health Canada, Swissmedic and TGA was approximately 80-100 days, which varied for the two time periods. Although the longest submission gap occurred to PMDA, the submission gap decreased by approximately one half and the approval time also decreased considerably, which may reflect the wider use of expedited review by the agency in 2013-2017 compared with 2008-2012. This demonstrates PMDA efforts to speed up the review of medicines, where the most notable changes made by the agency included an increase in resources, the introduction of prior-evaluation meetings to discuss clinical trial study results, as well as the prior-assessment consultations approximately 6 months before submission of a new drug application.

Figure 9: Median submission gap and median approval time for NASs approved in all six authorities in 2008-2012 (12) compared with 2013-2017 (51) as well as the % 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' and FDA/PMDA/Health Canada/ Swissmedic 'Priority Review'. TGA introduced an expedited (priority) review programme in 2017, with first decisions expected in 2018. 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.

Features of the EMA approval process

Figure 10: Median time of review process for NASs approved by EMA by approval year 2008-2017

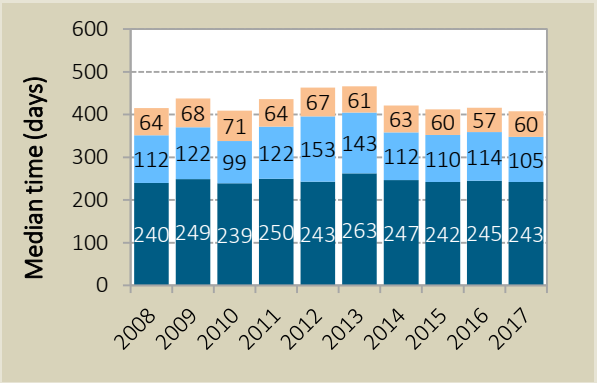
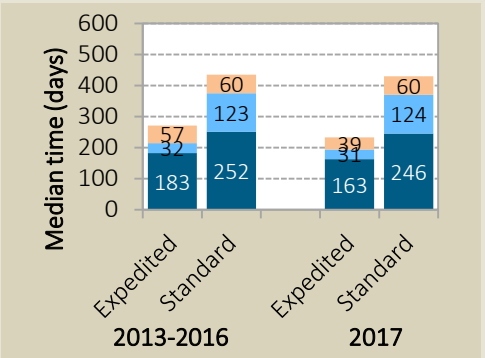


Figure 11: Median time of review process for NASs approved by EMA by review type for approval period 2013-2016 and 2017



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.

The decrease in the overall median approval time for EMA from 2012 onwards was driven largely by the decrease in company response time (Fig. 10). Furthermore, an important difference between expedited and standard NAS median approval times was the decrease in the EU Commission time, as was discussed in R&D Briefing 62, of 57 days in 2013-2016 compared with 39 days in 2017 (Fig. 11). Furthermore, a comparison of 2012 and 2017 (Fig.10) revealed that overall, the median company response time decreased by 48 days; the median EMA review time remained the same at 243 days in 2017 and 2012 (though some variation occurred over 2013-2016) and the EU Commission time decreased slightly by 7 days from 2012 to 2017. In general, the EMA review time was approximately 1.4-1.5x faster for expedited review, owing to a shorter clock for Committee for Medicinal Products for Human Use (CHMP) opinion (150 days instead of 210 days). The expedited review was also characterised by an approximately four-times-faster company response time for both time periods (Fig. 11). This is due to the fact that the company clock stop is legislated and if it exceeds one month, EMA may decide to revert the assessment back to a standard review.

Figure 12: Submission gap between EMA and FDA, months (number of products); NASs approved initially 2014-2016 and status tracked until 2017

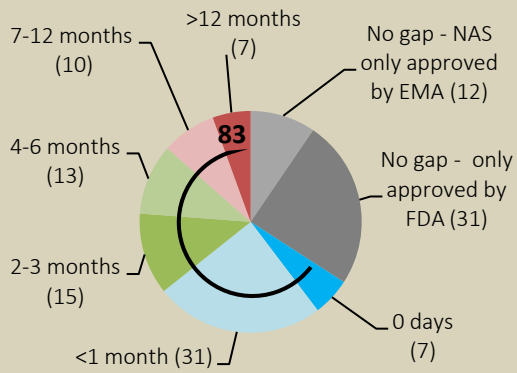
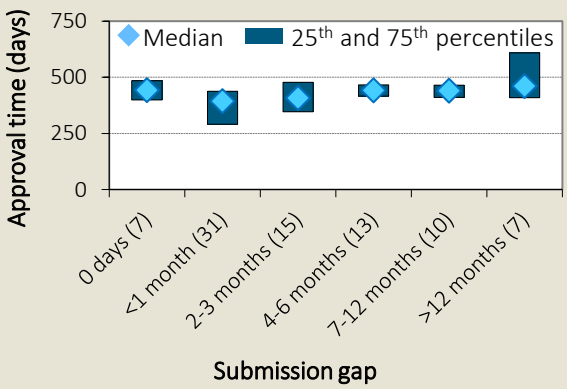


Figure 13: Approval time in EMA for the 83 NASs that were approved by both agencies, according to the submission gap between EMA and FDA



'NAS only approved by EMA/FDA', may be due : no submission, review not finalised, withdrawal by sponsor, rejection by the agency . 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.

An analysis of products approved by either EMA, FDA or both revealed that 31 NASs approved by FDA in 2014-2016 had not been approved by EMA (due to lack of submission, review not finalised, sponsor withdrawal or rejection by EMA) by the end of 2017. Similarly, 12 NASs initially approved by EMA in 2014-2016 had not been approved by FDA by the end of 2017. Eighty-three common NASs were identified, where the most common submission gap was 1 month (Fig.12). Interestingly, the median approval times at EMA were similar across the different submission gap groups (Fig. 13). Nevertheless, the 75th percentile was the longest for products submitted with a gap of longer than 12 months compared with FDA. Interestingly, the submission gap to EMA was 91 days in 2017 compared with 34 in 2016, for NASs approved more than one month following the other agencies (p. 15).

Features of the FDA approval process

Figure 14: Proportion of NASs approved by FDA CDER by number of review cycles by approval year, n=number of NASs

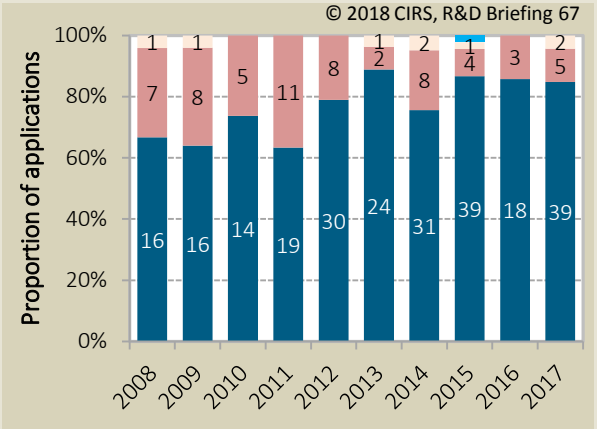
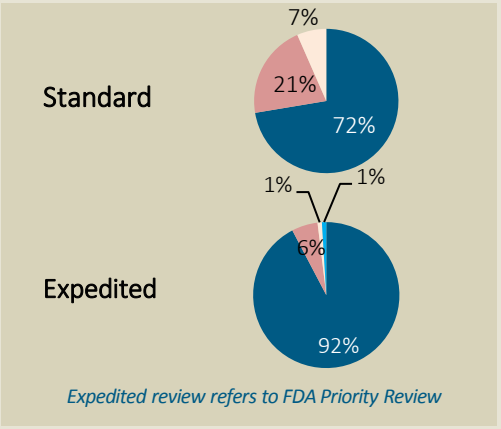
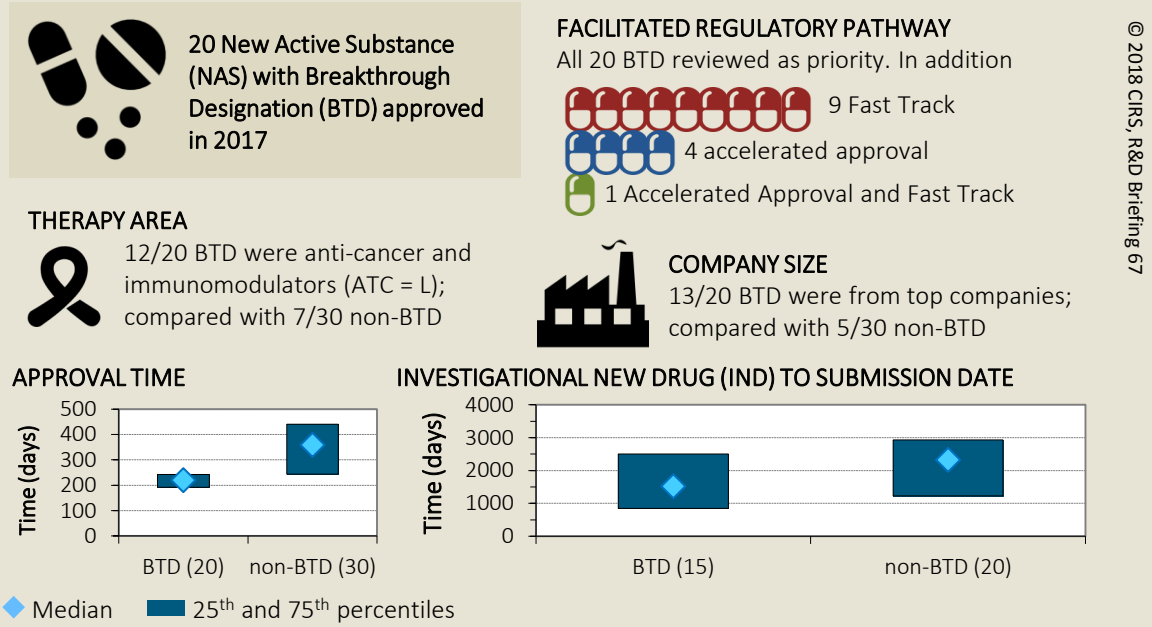


Figure 15: Proportion of NASs approved by FDA CDER by number of review cycles and review type for approval period 2013-2017



The number of the FDA Center for Drug Evaluation and Research (CDER)NASs approved after one cycle increased from 70% in 2008-2012 to 84% in 2013-2017 (Fig. 14). In addition, the proportion of one-cycle reviews was higher for expedited compared with standard reviews 2013-2017 (Fig. 15). This reflects CDER efforts to further optimise its review process, particularly by increasing the number of one-cycle approvals. 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 but it is important to note that this analysis (Fig. 14) only includes approvals and inclusion of compounds that have not been approved may generate a different perspective.

Figure 16: FDA Breakthrough Designation snapshot for 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. Top company is defined as having R&D budget>3 billion USD in 2016. Not all IND dates were identified for the 50 NASs (15/20 for BTD; 20/30 for non-BTD) thereby resulting in different N numbers.

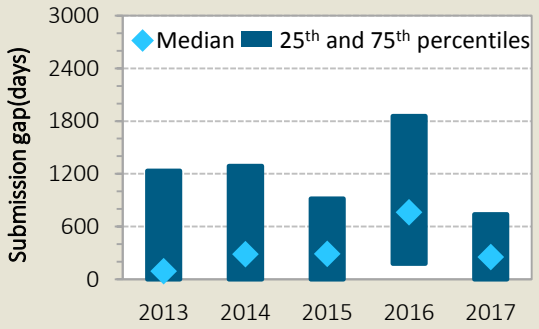
In 2017, FDA approved a record number of BTD NASs, with 20 medicines, representing 41% of all BTD NASs approved by FDA since the initiation of the pathway in 2013 (Fig. 16). The BTD NASs generally had other FRPs in place (Priority Review, Fast Track and Accelerated), and were generally anti-cancer and immunomodulator NASs from major (top) companies. Importantly, the BTD designation shortened both the approval time as well as the development time (IND to submission).

Features of the PMDA approval process

Figure 17: Number of NASs approved by PMDA according to month and year of approval; by calendar year (Jan-Dec) and fiscal year (Apr-Apr)

Approval year	Jan	Mar	Jun	Jul	Sep	Dec	NAS, N Jan-Dec	NAS, N Apr-Apr
2013		14	5		9		28	33
2014	8	11		16	9	8	52	43
2015		10		10	12		32	39
2016	3	14	1	6	16	8	48	37
2017		6		6	10		22	36
2018 (provisional)	10	10	-	-	-	-		-

Figure 18: 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

In 2017 (January-December), PMDA approved the lowest number of NASs in a decade, 22, compared with 48 in 2016. Nevertheless, an analysis of approval numbers by fiscal year revealed that the numbers were stable over the last two years at 37 and 36. Indeed, PMDA generally approves medicines four 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.

In 2017, the PMDA submission gap was 254 days, which was a large decrease from the 2016 spike of 763 days. This may be a result of companies' changing strategies for submission to Japan as well as the decreasing impact of the legacy product gap (Fig. 18). Indeed the availability of older products to Japanese patients was facilitated in recent years through government programmes as well as through issues in the local development rights amongst sponsors (domestic versus foreign).

Figure 19: Submission gap to PMDA, years (number of products); for NASs approved 2013 -2017

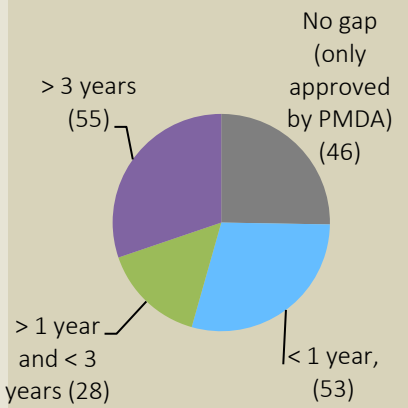


Figure 20: Submission gap to PMDA and various characteristics for NASs approved 2013 -2017 (red = >50%)

Sub-mission gap	Anti-cancer /immuno-modulator, % NAS	Top sponsor company, % NAS	Japanese sponsor company, % NAS	Expedited (priority), % NAS	Orphan, % NAS
No gap	7%	22%	72%	20%	11%
<1 year	42%	57%	26%	49%	30%
>1 and <3 years	50%	61%	25%	71%	57%
>3 years	36%	31%	49%	49%	47%

'Only approved by PMDA', may be due to : no submission, review not finalised, withdrawal by sponsor, rejection by the agency. Submission gap is defined as date of submission at the first regulatory agency to the date of submission at PMDA. Top company is defined as having R&D budget>3 billion USD in 2016.

NASs approved by PMDA 2013-2017 were analysed according to submission gap length, where 25% products are unique to PMDA (no gap; only approved by PMDA) (Fig. 19) which are developed primarily by Japanese companies (Fig. 20). A large proportion of medicines had a submission gap of less than a year (29%) and between 1-3 years (15%), and these were primarily high need products, i.e. expedited, orphan or anti-cancer and immunomodulator NASs, from major pharmaceutical companies. Nevertheless, 30% of NASs had a submission gap of more than 3 years, thereby highlighting that, in particular, smaller companies (non-top), as well as multinational companies that go to a local Japanese sponsor to develop their product, may delay their submission to PMDA for strategic reasons.

Features of the Health Canada approval process

Figure 21: Median submission gap and approval time for NASs approved by Health Canada

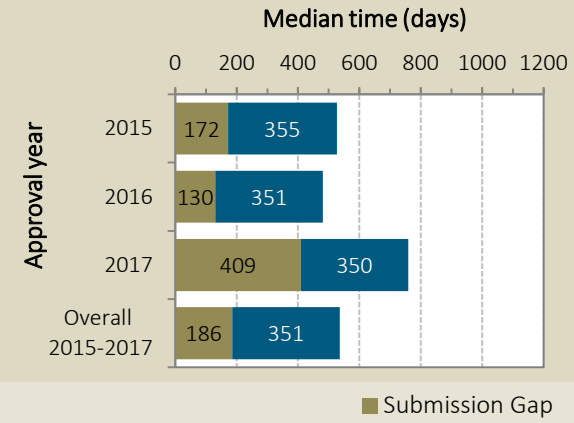
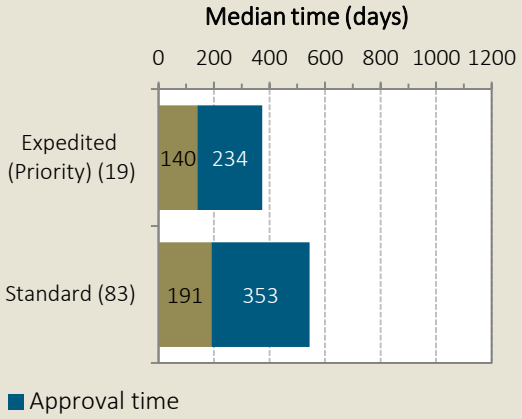


Figure 22: Median submission gap and approval time in Health Canada, for NASs approved 2015-2017, by review type



'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 doubled in 2017 to 409 days compared with 172 days and 130 days in 2015 and 2016 respectively. Conversely, the median approval time stayed very similar (Fig. 21). The overall submission gap and approval time 2015-2017 were also analysed according to review type, where both the median approval time, as well as the submission gap were shorter for NASs designated as expedited (priority). This indicates that companies as well as the agency respectively fast-track the submission and approval of important products that address high unmet medical need.

Figure 23: NAS Submission gap to Health Canada according to sponsor company size

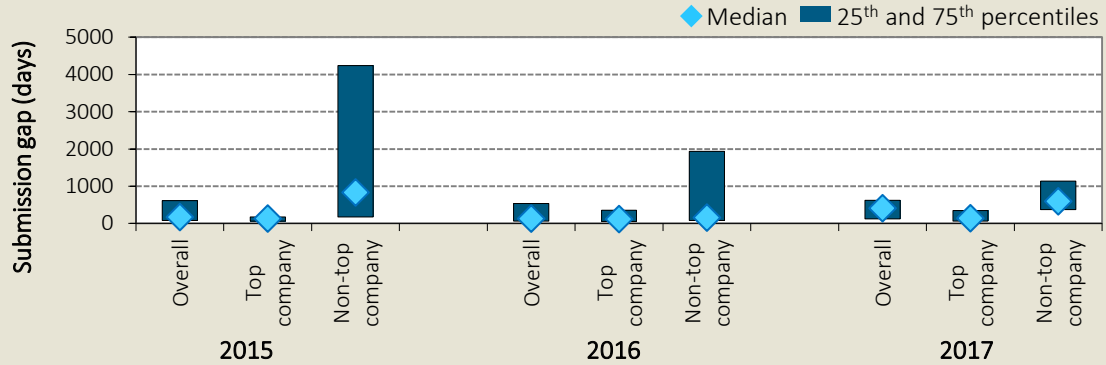
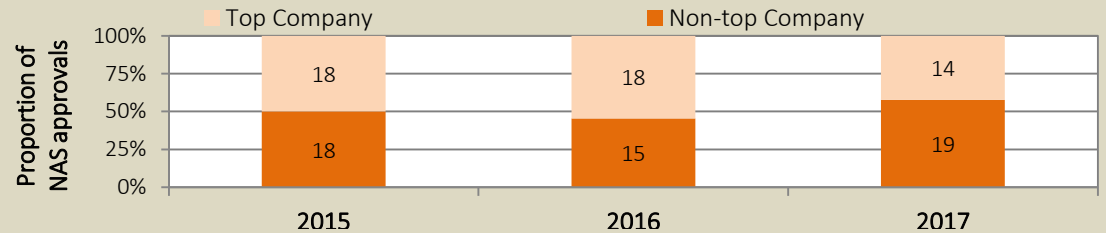


Figure 24: Number of NAS approvals 2015-2017 by Health Canada according to sponsor company size



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 2016.

Although the median submission gap increased considerably in 2017 for Health Canada, the variance (25th-75th percentile) for the overall gap was similar compared to 2015 and 2016, approximately 450-550 days. The submission gap to Health Canada varied according to the size of the sponsor, where either the median or the variance or both were larger in the case of non-top companies (Fig. 23). In 2017, the median submission gap from non-top companies was 595 days compared to 157 in 2016 and 833 in 2015. Finally, the proportion of NASs from non companies was slightly higher this year, at 58%, compared to 45% and 50% in 2016 and 2015 (Fig. 24).

Features of the Swissmedic approval process

Figure 25: Median submission gap and approval time for NASs approved by Swissmedic

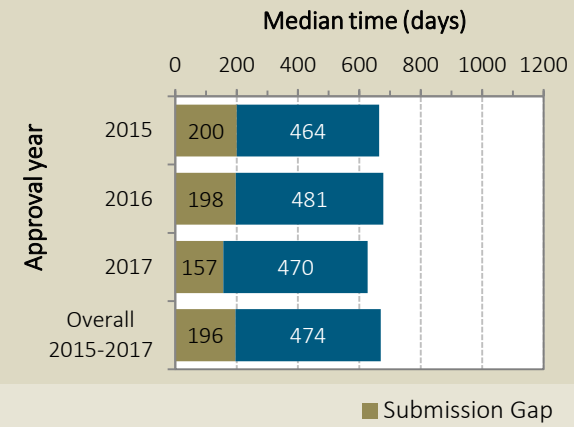
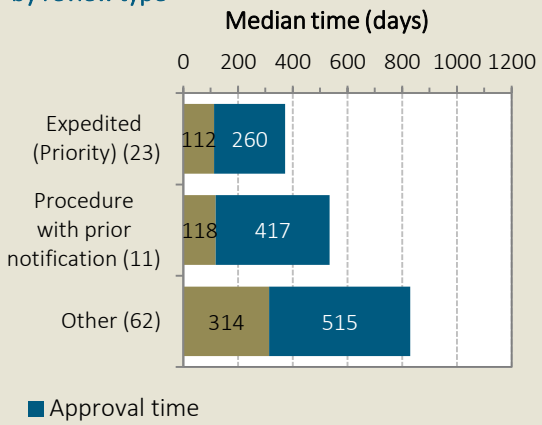


Figure 26: Median submission gap and approval time in Swissmedic, for NASs approved 2015-2017, by review type



Submission Gap Approval time

'Expedited review' refers to Swissmedic '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 Swissmedic.

The median submission gap to Swissmedic decreased in 2017 to 157 days, compared with 200 days and 198 days in 2015 and 2016, whereas the median approval time stayed relatively similar (Fig. 25). The overall submission gap and approval time 2015-2017 were also analysed according to review type, where both the median approval time, as well as the submission gap were shorter for NASs designated as expedited (priority) or using the procedure with prior notification (PPN), which offers a 20% faster review for a 100% surcharge in user fees (Fig. 26). Interestingly, the agency has now introduced a system where sponsors not granted expedited (priority) can automatically switch to PPN to speed up the review.

Figure 27: NAS submission gap to Swissmedic according to sponsor company size

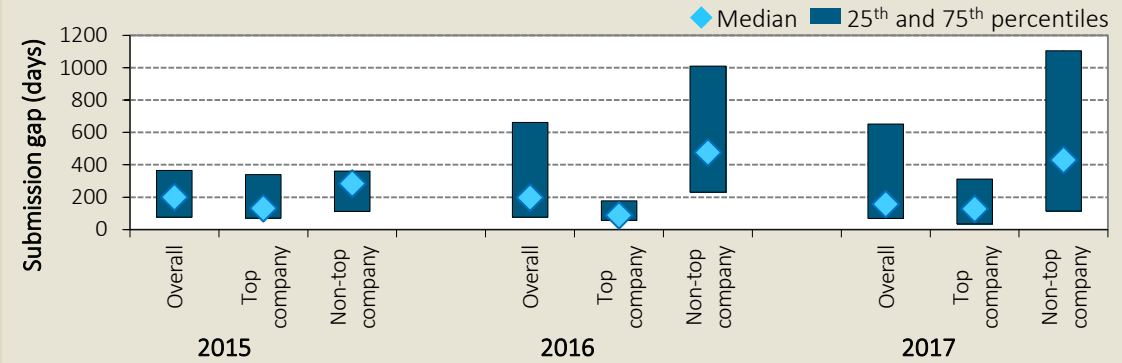
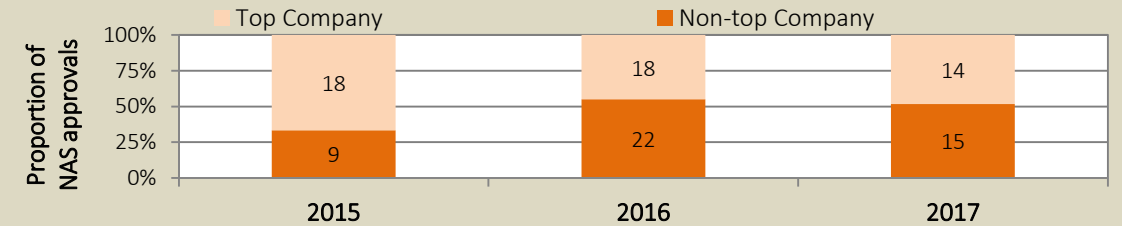


Figure 28: Number of NAS approvals 2015-2017 by Swissmedic according to sponsor company size



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 2016.

Although the median submission gap decreased in 2017 for Swissmedic, the variance (25th-75th percentile) for the overall gap was 586 days and 583 days in 2016 and 2017 respectively, compared with 288 in 2015 (Fig. 27). This may be as a result of more NASs being approved from non-top companies in the last two years, approximately one half in 2016 and 2017 compared with one third in 2015 (Fig. 27). Similarly to Health Canada (p.10) and TGA (p.12), the submission gap from non-top sponsors was longer in terms of median and/or had larger variance compared with top companies.

Features of the TGA approval process

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

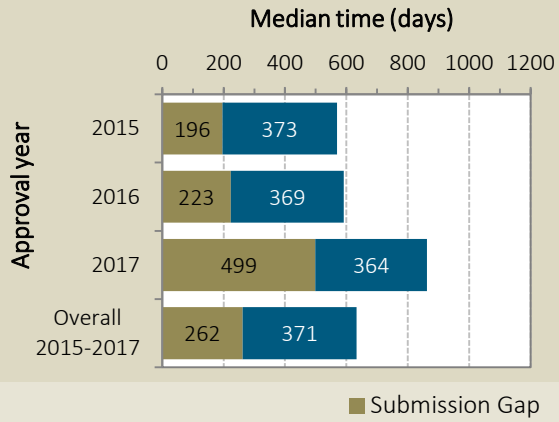
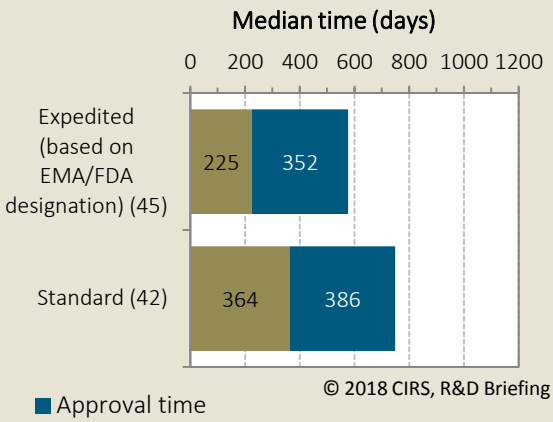


Figure 30: Median submission gap and approval time in TGA, for NASs approved 2015-2017, based on 'expedited' status in EMA/FDA



TGA introduced an expedited (priority) review programme in 2017, with first decisions expected in 2018. 'Expedited review' here refers therefore to NASs which were expedited (EMA Accelerated Assessment; FDA Priority). 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 doubled in 2017 to 499 days compared with 196 days and 223 days in 2015 and 2016 respectively. Conversely, the median approval time stayed very similar (Fig. 29). Although no NASs were approved by TGA in 2017 under the newly introduced priority (expedited) pathway an analysis of NASs approved by TGA 2015-2017 according to their expedited designation by FDA/EMA revealed that products prioritised by EMA or FDA had shorter submission gap as well as median approval time compared with standard NASs within TGA (Fig. 30). The priority system introduced by TGA in 2017 has a target timeline of 150 days (excluding company time) and should result in an even faster review of important medicines.

Figure 31: NAS Submission gap to TGA according to sponsor company size

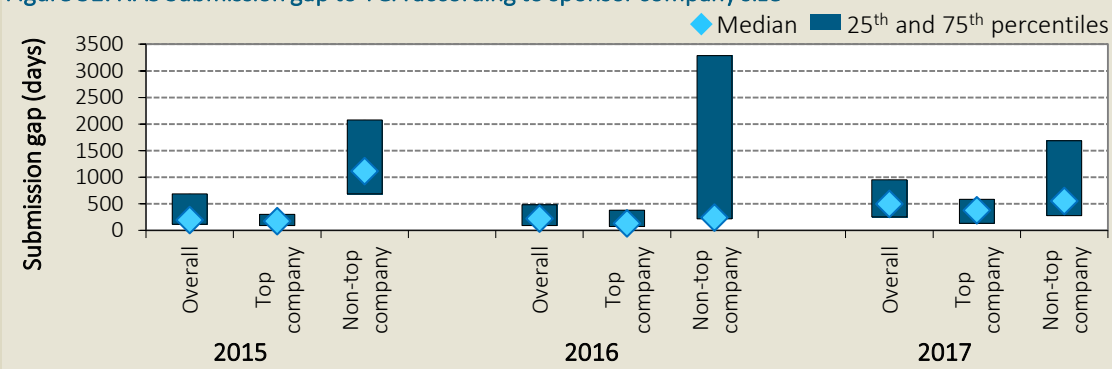
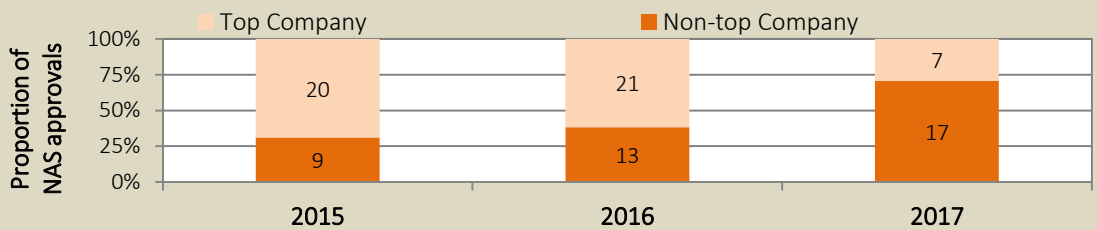


Figure 32: Number of NAS approvals 2015-2017 by TGA according to sponsor company size



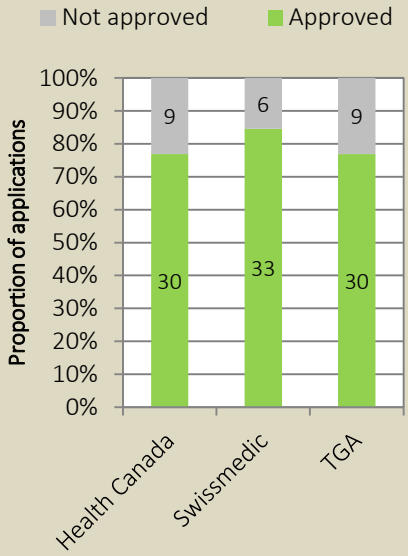
Submission gap is calculated as the time from date of submission at the first regulatory agency to the date of regulatory submission to TGA. Top company is defined as having R&D budget>3 billion USD in 2016.

Similarly to Health Canada and Swissmedic, the submission gap to TGA varied according to sponsor size, where NASs developed by non-top companies had longer median times and/or larger variance (Fig. 31). Finally, the proportion of approvals from non-top companies was very high in 2017, at 71%, compared with 31% and 38% in 2015 and 2016, which may partially explain the spike in median submission gap in 2017.

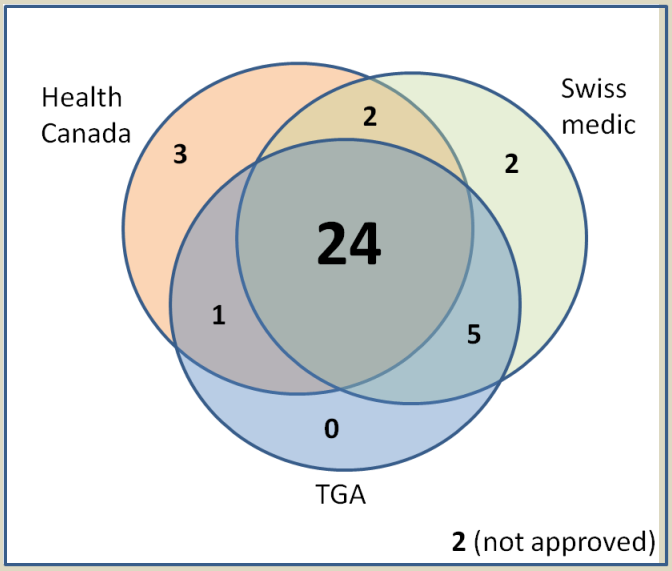
Availability of medicines in Health Canada, Swissmedic and TGA

Figure 33: NASs approved by Health Canada, Swissmedic and TGA by the end of 2017, for NASs approved by both EMA and FDA 2015-2016 (39)

a) Proportion of NASs



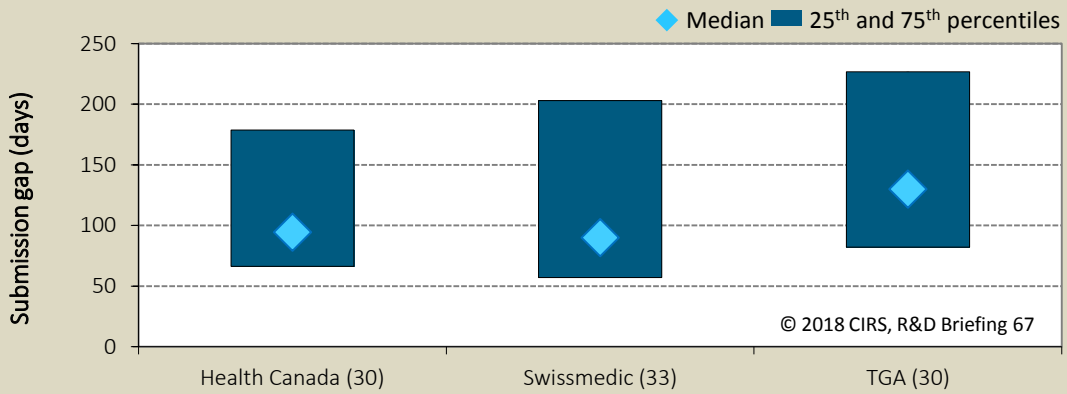
b) Venn diagram



'Not approved' includes no submission, review not finalised, withdrawal by sponsor, rejection by the agency.

In 2015-2016, there were 39 NASs that were approved by both EMA and FDA. An analysis of availability of those NASs in Health Canada, Swissmedic and TGA revealed that 15 of the NASs (38%) had not been approved by all three jurisdictions (Fig. 33). Health Canada approved 30/39 NASs, Swissmedic 33/39 and TGA 30/39. Out of the 39 NASs, 24 were approved by all three agencies, and some compounds were approved by 1-2 agencies as noted in the Venn diagram. TGA did not approve any compounds that were unique to that agency, whereas Health Canada and Swissmedic approved 3 and 2 respectively. Interestingly, the greatest overlap in terms of common NASs was for Swissmedic and TGA, where 5 NASs were approved by both agencies but not approved by Health Canada. Two NASs approved both by EMA and FDA were not approved by any of the three agencies.

Figure 34: Submission gap to Health Canada, Swissmedic and TGA from EMA/FDA; for NASs approved by both EMA and FDA in 2015-2016 (39) and approved by the other three agencies by 2017

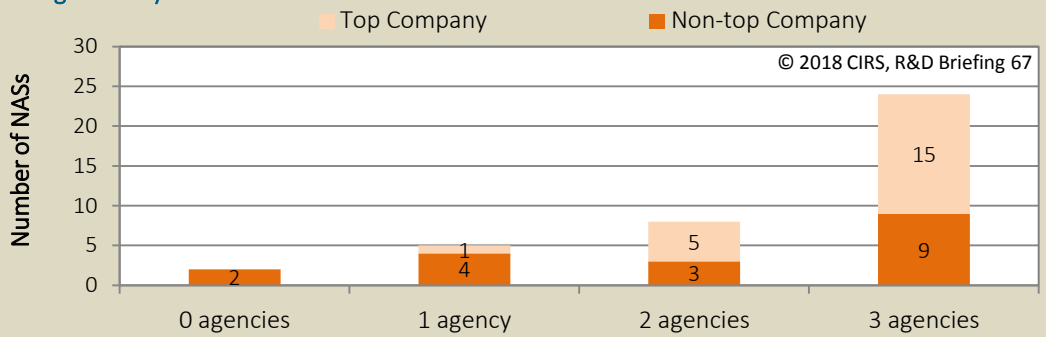


Submission gap is calculated as the time from date of submission at the first regulatory agency (EMA or FDA) to the date of regulatory submission to the target agency.

The median submission gap was 90 days for Swissmedic, 95 days for Health Canada and 130 days for TGA (Fig. 34) across the compounds approved by each agency from those initially approved by EMA/FDA in 2015-2016. On the other hand, there was considerable variance around each of the medians, where the difference between 25th and 75th percentile was the smallest for Health Canada (113 days), followed by TGA (145) and Swissmedic (146).

Availability of medicines in Health Canada, Swissmedic and TGA

Figure 35: Number of NASs approved by 0-3 agencies (Health Canada/Swissmedic/TGA) according to company size; for NASs approved by both EMA and FDA 2015-2016 (39) and approved by the other three agencies by 2017



'Not approved' includes no submission, review not finalised, withdrawal by sponsor, rejection by the agency. Top company is defined as having R&D budget>3 billion USD in 2016.

Analysis of NASs initially approved by both EMA and FDA in 2015-2016 uncovered that the internationalisation of the NASs to the three agencies (Health Canada, Swissmedic and TGA) depended on the size of company, where out of the 7 NASs approved by 0-1 agencies, only 1 NAS was developed by a top company, whereas for NASs approved by 2-3 agencies, 63% were from top companies (Fig. 35). In addition, the products that were not approved by the three agencies (either due to lack of submission, rejection or withdrawal) were primarily from non-top companies (Fig. 36). Finally, analysis of the NASs that were approved by each of the three agencies demonstrated that the submission gap to the three agencies was larger when the sponsor was a non-top company (Fig. 37). The variance was also generally larger for non-top companies, where the 75th percentile was close to (or over) 1 year for Health Canada, Swissmedic and TGA, suggesting that certain products 'not approved' (Fig 36) from smaller companies may reach the three agencies in the coming year.

Figure 36: Proportion of NASs approved by Health Canada, Swissmedic and TGA by the end of 2017 by company size; for NASs approved by both EMA and FDA 2015-2016; n, 39

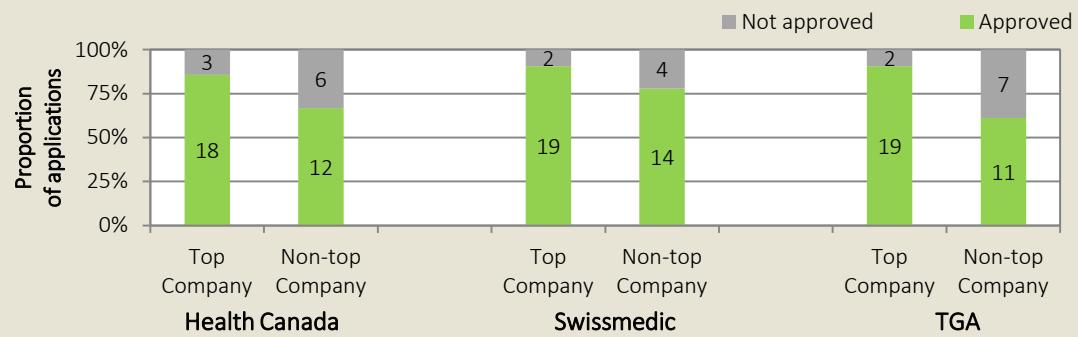
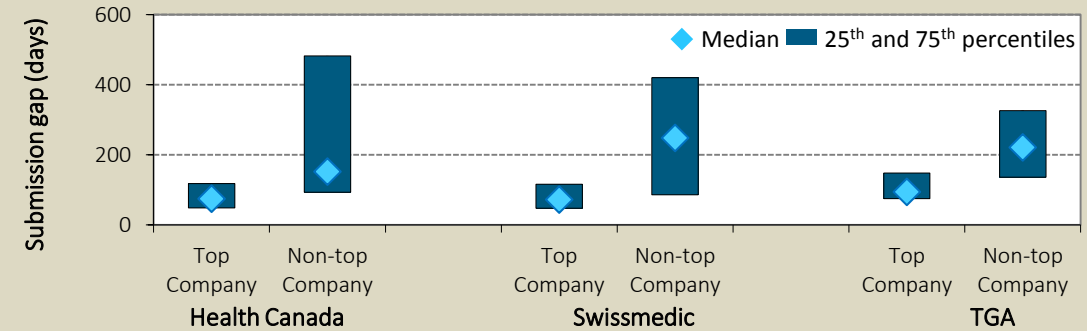


Figure 37: Submission gap to Health Canada, Swissmedic and TGA from EMA/FDA by company size; for NASs approved by both EMA and FDA 2015-2016 (39) and approved by the other three agencies by 2017



'Not approved' includes no submission, review not finalised, withdrawal by sponsor, rejection by the agency. 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 the target agency. Top company is defined as having R&D budget>3 billion USD in 2016.

Approval at EMA 2017

EMA **APPROVED A TOTAL OF 30 NASs IN 2017,** WITH A MEDIAN APPROVAL TIME OF **419 DAYS**

Type of Medicine

13 BIOLOGIC NASs APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **397 DAYS**

17 CHEMICAL NASs APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **423 DAYS**

14 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **416 DAYS**

16 NASs IN OTHER THERAPY AREAS APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **421 DAYS**

Designation and Review Type

5 EXPEDITED NAS APPROVALS IN 2017, WITH A MEDIAN APPROVAL TIME OF **235 DAYS;** THIS IS A MEDIAN **206 DAYS FASTER** THAN THE **25 STANDARD NAS APPROVALS IN 2017**

10 ORPHAN NAS APPROVALS IN 2017, WITH A MEDIAN APPROVAL TIME OF **416 DAYS;** THIS IS A MEDIAN **5 DAYS FASTER** THAN THE **20 NON-ORPHAN NAS APPROVALS IN 2017**

Availability in EMA

33% OF THE NASs APPROVED IN 2017 BY EMA WERE APPROVED BY EMA **FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL AT FDA, PMDA, HEALTH CANADA, SWISSMEDIC OR TGA**

67% OF THE NASs APPROVED IN 2017 BY EMA WERE APPROVED AT FDA, PMDA, HEALTH CANADA, SWISSMEDIC OR TGA **FIRST OR MORE THAN ONE MONTH BEFORE BEING APPROVED IN EMA**

THE MEDIAN **SUBMISSION GAP** TO EMA FOR THESE NASs WAS **91 DAYS**

EMA approval time includes the EU Commission time.
'Expedited review' refers to EMA 'Accelerated Assessment and FDA/PMDA/Health Canada/Swissmedic '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 FDA 2017

FDA *(CDER AND CBER)* **APPROVED A TOTAL OF 50 NASs IN 2017,** WITH A MEDIAN APPROVAL TIME OF **243 DAYS**

Type of Medicine

16 BIOLOGIC NASs APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **241 DAYS**

34 CHEMICAL NASs APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **244 DAYS**

19 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **214 DAYS**

31 NASs IN OTHER THERAPY AREAS APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **293 DAYS**

Designation and Review Type

31 EXPEDITED NAS APPROVALS IN 2017, WITH A MEDIAN APPROVAL TIME OF **240 DAYS;** THIS IS A MEDIAN **125 DAYS FASTER** THAN THE **19 STANDARD NAS APPROVALS IN 2017**

21 ORPHAN NAS APPROVALS IN 2017, WITH A MEDIAN APPROVAL TIME OF **242 DAYS;** THIS IS A MEDIAN **92 DAYS FASTER** THAN THE **29 NON-ORPHAN NAS APPROVALS IN 2017**

Availability in FDA

86% OF THE NASs APPROVED IN 2017 BY FDA WERE APPROVED BY FDA **FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL AT EMA, PMDA, HEALTH CANADA, SWISSMEDIC OR TGA**

14% OF THE NASs APPROVED IN 2017 BY FDA WERE APPROVED AT EMA, PMDA, HEALTH CANADA, SWISSMEDIC OR TGA **FIRST OR MORE THAN ONE MONTH BEFORE BEING APPROVED IN FDA**

THE MEDIAN **SUBMISSION GAP** TO FDA FOR THESE NASs WAS **175 DAYS**

'Expedited review' refers to EMA 'Accelerated Assessment and FDA/PMDA/Health Canada/Swissmedic '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 2017

PMDA **APPROVED A TOTAL OF 22 NASs IN 2017,** WITH A MEDIAN APPROVAL TIME OF **333 DAYS**

Type of Medicine

7 BIOLOGIC NASs APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **331 DAYS**

15 CHEMICAL NASs APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **343 DAYS**

11 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **304 DAYS**

11 NASs IN OTHER THERAPY AREAS APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **359 DAYS**

Designation and Review Type

8 EXPEDITED NAS APPROVALS IN 2017, WITH A MEDIAN APPROVAL TIME OF **275 DAYS;** THIS IS A MEDIAN **82 DAYS FASTER** THAN THE **14 STANDARD NAS APPROVALS IN 2017**

7 ORPHAN NAS APPROVALS IN 2017, WITH A MEDIAN APPROVAL TIME OF **281 DAYS;** THIS IS A MEDIAN **74 DAYS FASTER** THAN THE **15 NON-ORPHAN NAS APPROVALS IN 2017**

Availability in PMDA

18% OF THE NASs APPROVED IN 2017 BY PMDA WERE APPROVED IN PMDA **FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL AT EMA, FDA, HEALTH CANADA, SWISSMEDIC OR TGA**

82% OF THE NASs APPROVED IN 2017 BY PMDA WERE APPROVED AT EMA, FDA, HEALTH CANADA, SWISSMEDIC OR TGA **FIRST OR MORE THAN ONE MONTH BEFORE BEING APPROVED IN PMDA**

THE MEDIAN **SUBMISSION GAP** TO PMDA FOR THESE NASs WAS **524 DAYS**

'Expedited review' refers to EMA 'Accelerated Assessment and FDA/PMDA/Health Canada/Swissmedic '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 2017

HEALTH CANADA **APPROVED A TOTAL OF 33 NASs IN 2017,** WITH A MEDIAN APPROVAL TIME OF **350 DAYS**

Type of Medicine

13 BIOLOGIC NASs APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **332 DAYS**

20 CHEMICAL NASs APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **359 DAYS**

9 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **270 DAYS**

24 NASs IN OTHER THERAPY AREAS APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **354 DAYS**

Designation and Review Type

6 EXPEDITED NAS APPROVALS IN 2017 WITH A MEDIAN APPROVAL TIME OF **209 DAYS;** THIS IS A MEDIAN **141 DAYS FASTER** THAN THE **27 STANDARD NAS APPROVALS IN 2017**

HEALTH CANADA DOES NOT HAVE AN ORPHAN POLICY; HOWEVER, **12 NASs THAT WERE CLASSIFIED AS ORPHAN BY EITHER FDA, EMA OR TGA WERE APPROVED BY HEALTH CANADA IN 2017,** WITH A MEDIAN APPROVAL TIME OF **265 DAYS**

Availability in Health Canada

15% OF THE NASs APPROVED IN 2017 BY HEALTH CANADA WERE APPROVED BY HEALTH CANADA **FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL AT EMA, FDA, PMDA, SWISSMEDIC OR TGA**

85% OF THE NASs APPROVED IN 2017 BY HEALTH CANADA WERE APPROVED AT EMA, FDA, PMDA, SWISSMEDIC OR TGA **FIRST OR MORE THAN ONE MONTH BEFORE BEING APPROVED IN HEALTH CANADA**

THE MEDIAN **SUBMISSION GAP** TO HEALTH CANADA FOR THESE NASs WAS **491 DAYS**

'Expedited review' refers to EMA 'Accelerated Assessment and FDA/PMDA/Health Canada/Swissmedic '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 2017

SWISSMEDIC **APPROVED A TOTAL OF 29 NASs IN 2017** ,WITH A MEDIAN APPROVAL TIME OF **470 DAYS**

Type of Medicine

10 BIOLOGIC NASs APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **419 DAYS**

19 CHEMICAL NASs APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **483 DAYS**

14 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **433 DAYS**

15 NASs IN OTHER THERAPY AREAS APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **507 DAYS**

Designation and Review Type

7 EXPEDITED NAS APPROVALS IN 2017, WITH A MEDIAN APPROVAL TIME OF **274 DAYS;** THIS IS A MEDIAN **213 DAYS FASTER** THAN THE **22 STANDARD NAS APPROVALS IN 2017**

10 ORPHAN NAS APPROVALS IN 2017, WITH A MEDIAN APPROVAL TIME OF **442 DAYS;** THIS IS A MEDIAN **40 DAYS FASTER** THAN THE **19 NON-ORPHAN NAS APPROVALS IN 2017**

Availability in Swissmedic

10% OF THE NASs APPROVED IN 2017 BY SWISSMEDIC WERE APPROVED BY SWISSMEDIC **FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL AT FDA, EMA, PMDA, HEALTH CANADA OR TGA**

90% OF THE NASs APPROVED IN 2017 BY SWISSMEDIC WERE APPROVED AT FDA, EMA, PMDA, HEALTH CANADA OR TGA **FIRST OR MORE THAN ONE MONTH BEFORE BEING APPROVED IN SWISSMEDIC**

THE MEDIAN **SUBMISSION GAP** TO SWISSMEDIC FOR THESE NASs WAS **272 DAYS**

'Expedited review' refers to EMA 'Accelerated Assessment and FDA/PMDA/Health Canada/Swissmedic '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 TGA 2017

TGA **APPROVED A TOTAL OF 24 NASs IN 2017** , WITH A MEDIAN APPROVAL TIME OF **364 DAYS**

Type of Medicine

10 BIOLOGIC NASs APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **352 DAYS**

14 CHEMICAL NASs APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **383 DAYS**

8 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **357 DAYS**

16 NASs IN OTHER THERAPY AREAS APPROVED IN 2017, WITH A MEDIAN APPROVAL TIME OF **383 DAYS**

Designation and Review Type

0 EXPEDITED NAS APPROVALS IN 2017; TGA DID NOT APPROVE ANY NASs IN 2017 UNDER ITS RECENTLY INTRODUCED PRIORITY REVIEW PROGRAMME

7 ORPHAN NAS APPROVALS IN 2017, WITH A MEDIAN APPROVAL TIME OF **351 DAYS;** THIS IS A MEDIAN **17 DAYS FASTER** THAN THE **17 NON-ORPHAN NAS APPROVALS IN 2017**

Availability in TGA

8% OF THE NASs APPROVED IN 2017 BY TGA WERE APPROVED BY TGA **FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL BY FDA, EMA, PMDA, HEALTH CANADA OR SWISSMEDIC**

92% OF THE NASs APPROVED IN 2017 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 **532 DAYS**

Submission gap is the date of submission at the first regulatory agency to the date of regulatory submission to the target agency.

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

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)

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

Top company
Pharmaceutical company with R&D spending >3 billion USD in 2016 (http://www.pharmexec.com/2016-pharm -exec-50).

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
- C - Cardiovascular: Cardiac therapy, antihypertensives, beta blocking agents, calcium channel blockers, agents acting on the renin-angiotensin system, serum lipid reducing 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 2017 will be made available on the CIRS website.

R&D Briefing 67

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