New drug approvals in six major authorities 2007 – 2016:

Focus on the internationalisation of medicines

Over the last decade, 2007-2016, convergence in approval times as well as changes in strategies of multinational pharmaceutical companies have resulted in more new active substances (NASs) being internationalised, referring here to receiving marketing authorisation in 6 major regulatory agencies, namely the European Medicines Agency (EMA), the US Food and Drug Authority (FDA), the Japan Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada, Swissmedic and the Australian Therapeutic Goods Administration (TGA). More specifically, the number of products approved by all the six agencies increased from 4 NASs in 2011-2012 to 13 NASs in 2015-2016.

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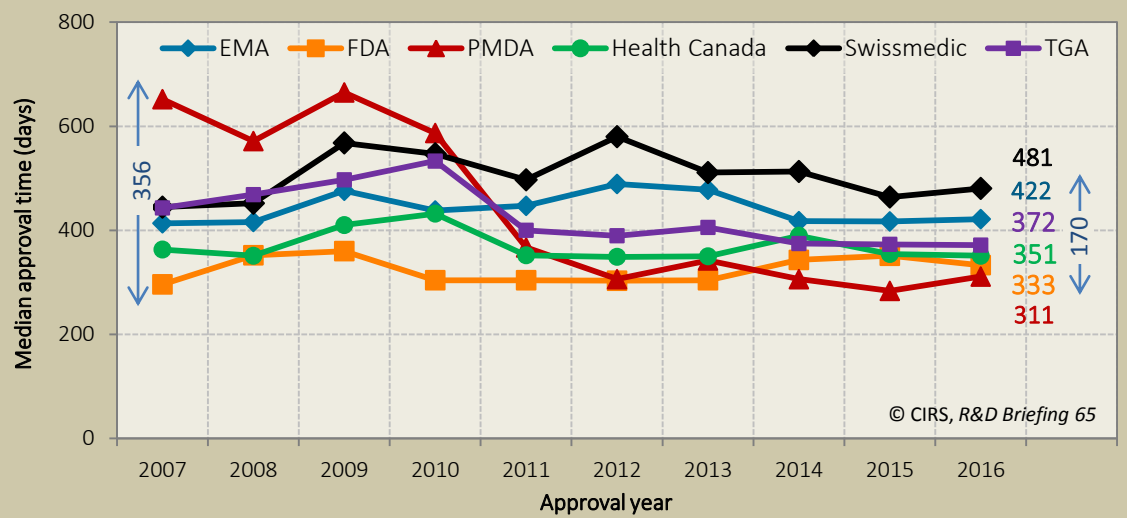
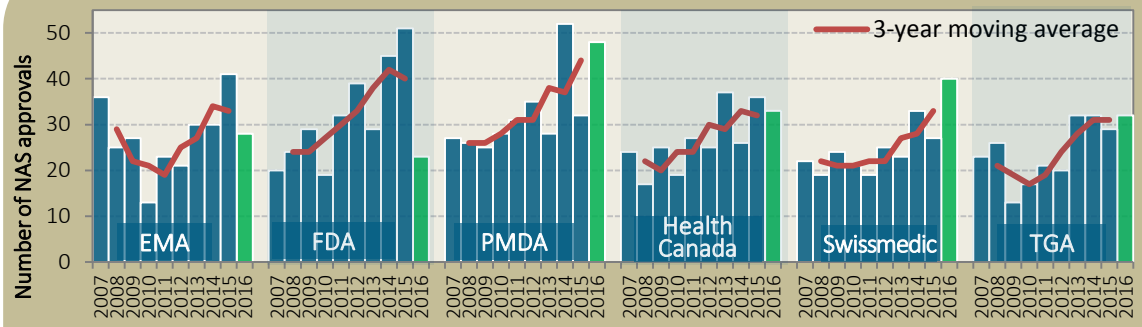
High-unmet need was seen as one of the key drivers for internationalisation. A greater proportion of anti-cancer and immunomodulating NASs and, in particular, products given a Breakthrough Designation by FDA, obtained marketing authorisation in the six agencies compared with the rest of NASs. The size of sponsor also had an effect; companies with large R&D budgets (>3 billion USD) were more likely to internationalise their products and also submitted to the six agencies earlier. Such integration of worldwide drug development and registration by companies, as well as more efficient reviews within agencies, enable NASs to be made available to wider patient populations globally in a timely manner.

New active substance (NAS) median approval time for six regulatory authorities in 2007-2016



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 1: Number of NASs approved by six regulatory authorities by approval year 2007-2016.



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In 2016, PMDA approved the highest number of NASs (48), followed by Swissmedic (40), Health Canada (33), TGA (32), EMA (28) and FDA (23) (Figure 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, 2007-2011 and 2012-2016, revealed that the biggest difference in the number of approvals was seen for FDA, with a 51% increase, followed by TGA (45%), PMDA (42%), Swissmedic (41%) Health Canada (40%) and EMA (21%). 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 in turn varies according to sponsor R&D budget size and unmet medical need (see pages 7-12), as well as agency review speed that can also vary according to therapeutic area (page 5) and the use of expedited pathways (pages 3-4).

Figure 2: NAS approval time for six regulatory authorities in 2007-2016.

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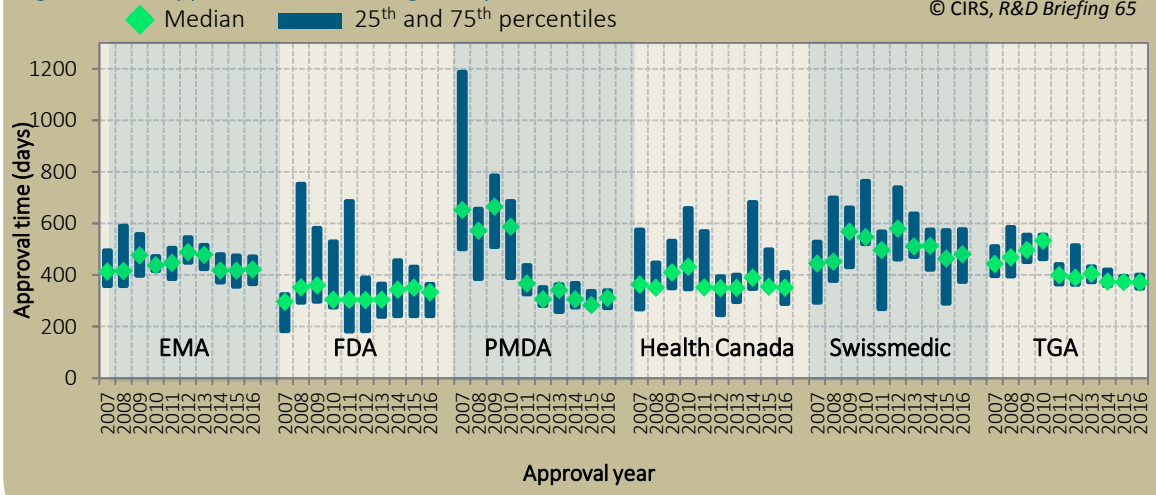
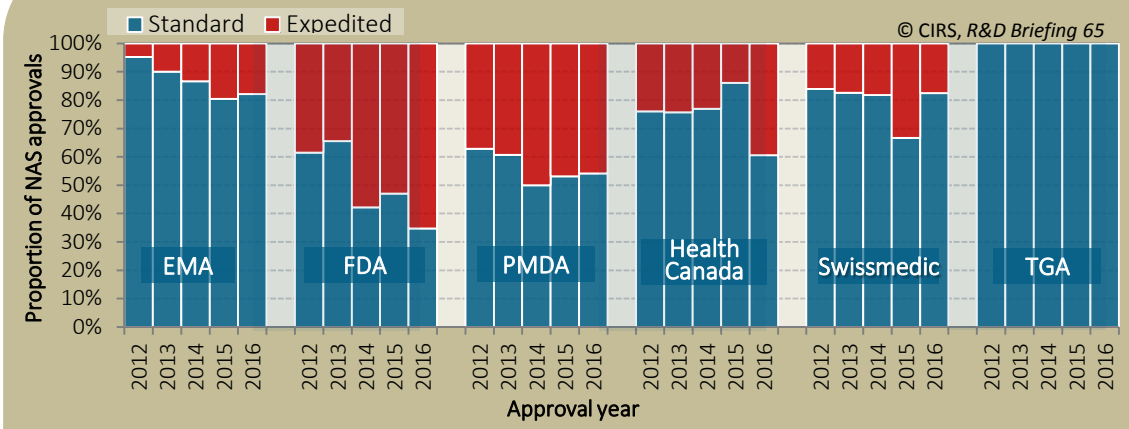


Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time.

The convergence in median approval time observed in the previous years (*R&D Briefing 55* and 59) continued in 2016, when the difference in the median approval time between the fastest and the slowest agency decreased from 356 days in 2007 to 170 days in 2016 (cover page Figure). In 2016, PMDA was the agency with the shortest median approval time (311 days), followed by FDA (333), Health Canada (351), TGA (372), EMA (422) and Swissmedic (481). Besides a decrease in variability in approval times across the six agencies, the past years have also seen a decrease in variation in approval time (25^{th} - 75^{th} percentile) within the six agencies, especially for TGA, EMA, and PMDA (Figure 2), which has established even more consistency in review timing in the last five years. 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).

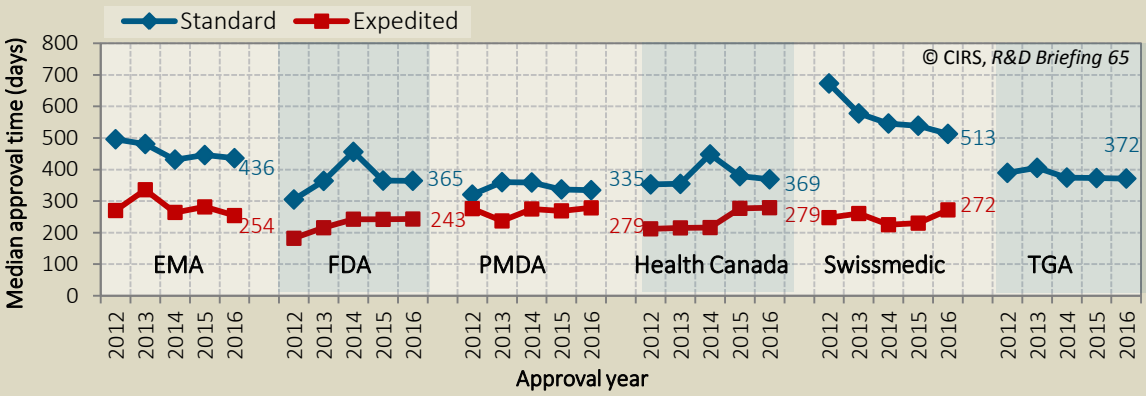
Figure 3: Number of NAS approvals by review type for six regulatory authorities in 2012-2016.



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

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, and therefore no expedited approvals were granted in 2012-2016. Nevertheless, the agency is now accepting applications, with first decisions expected later in 2017. In 2016, the ratio of expedited approvals to standard reviews was highest for FDA (65%), followed by PMDA (46%), Health Canada (39%), Swissmedic (18%) and EMA (18%). The proportion of expedited approvals has been consistently high for FDA and PMDA in the last few years, but has increased when comparing 2012-2014 to 2015-2016 for all five agencies. EMA experienced the most notable increase from 10% in 2012-2014 to 19% in 2015-2016, followed by Swissmedic (17% to 24%), FDA (45% to 57%), Health Canada (24% to 26%) and PMDA (43% to 46%). 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 PRIME (PRIority MEdicines) scheme in 2016 at EMA, which is specifically designed to promote the usage 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 2012-2016.



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

For 2016, the overall median approval time across the five agencies for standard review was 390 days, compared with 269 days for expedited review. In 2016, the agency with the greatest difference in median approval time between expedited and standard review was Swissmedic with a difference of 241 days (Figure 4), whereas the smallest difference was for PMDA with 56 days; the gap for other agencies was 182 days for EMA, 122 for FDA and 90 days for Health Canada. 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 5 agencies.

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Figure 5: Facilitated regulatory pathway (FRP) and orphan status timelines across six agencies; focus on 2016.

© CIRS, *R&D Briefing 65*	NAS approval type		2016 NAS approvals, number	2016 NASs, %	Expedited, %	2016 median approval time, days
EMA	**Overall approvals**		**28**			**422**
	FRP	Accelerated (referred in Briefing as Expedited)	5	18%		254
		Conditional	7	25%	43%	388
		Exceptional	0	0%	-	-
	Orphan		11	39%	18%	391
FDA	**Overall approvals**		**23**			**333**
	FRP	Priority (referred in Briefing as Expedited)	15	65%		243
		Accelerated	6	26%	100%	209
		Breakthrough Designation	7	30%	100%	238
		Fast Track	8	35%	88%	289
	Orphan		10	43%	80%	288
PMDA	**Overall approvals**		**48**			**311**
	FRP	Priority (referred in this Briefing as Expedited)	22	46%		279
		Sakigake	0	0%	-	-
	Orphan		18	38%	100%	280
Health Canada	**Overall approvals**		**33**			**351**
	FRP	Priority (referred in Briefing as Expedited)	13	39%		279
		Conditional (Notice of Compliance with conditions)	7	21%	71%	322
Swiss-medic	**Overall approvals**		**40**			**481**
	FRP	Priority (referred in Briefing as Expedited)	7	18%		272
		Procedure with prior notification	4	10%	0%	472
	Orphan		16	40%	13%	441
TGA	**Overall approvals**		**32**			**372**
	Orphan		8	25%	0%	376

TGA has introduced an expedited (priority) review programme in 2017. 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 used 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 (Figure 5). In 2016, 70% of NASs approved by FDA benefitted from at least one of the available FRPs, compared with 46% at PMDA, 45% at Health Canada, 32% at EMA and 28% at Swissmedic (Figure 6). Across the various FRPs for the five agencies, compounds which included FDA Accelerated Assessment had the fastest median approval time in 2016 (209 days), followed by the FDA Breakthrough Designation (238 days). Nevertheless, it should be noted that many compounds reviewed at FDA often take advantage of multiple FRPs, which generally results in a faster approval time (*R&D Briefing 57*). In addition to a priority FRP added to the TGA toolbox in 2017, the agency is planning to introduce in 2018 a Provisional Approval pathway, which will provide a formal process for the registration of promising medicines on the basis of early clinical data.

Figure 6: Proportion of NASs approved by each agency in 2016 that benefitted from at least one FRP.

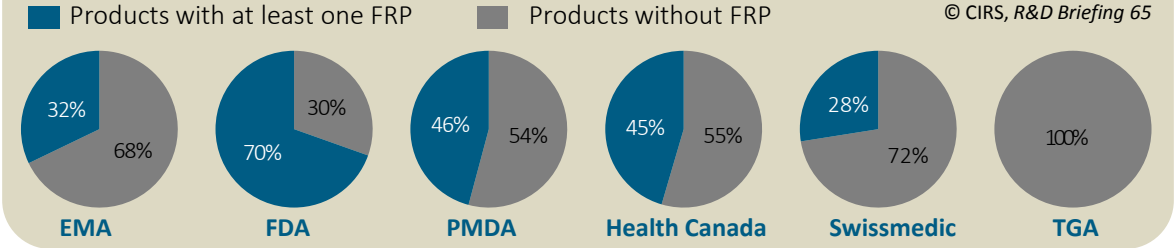
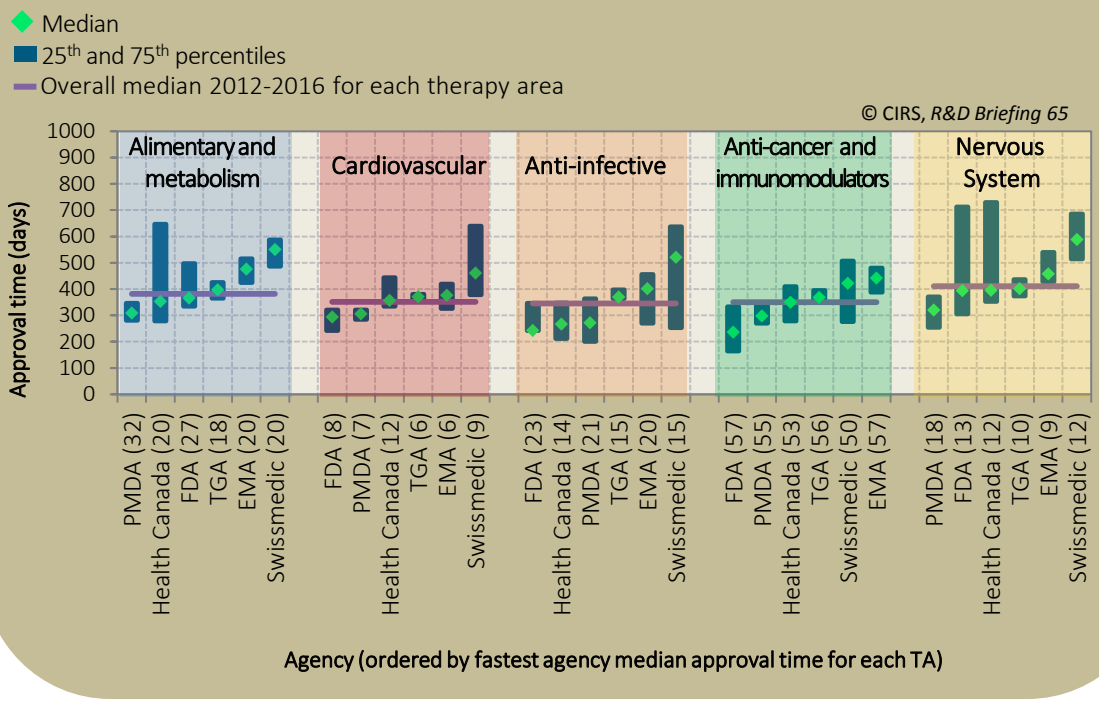


Figure 7: NAS approval time by therapeutic area (TA) for six regulatory authorities in 2012-2016, ordered by fastest agency median approval time within each TA.



In 2012-2016, anti-infective therapies were approved marginally faster across all six agencies, with overall median of 345 days, compared with 350 days for anti-cancer and immunomodulators, 352 days for cardiovascular, 382 days for alimentary and metabolism and 412 days for nervous system NASs. PMDA, Health Canada and FDA had the fastest approval times across all five therapy areas (Figure 7), with median approval times at or below the overall median. This may reflect the more frequent use of expedited review pathways for certain therapy areas with short approval times (Figure 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's and FDA's 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 (Figure 8).

Figure 8: NAS overall median approval time (days) by therapeutic area for six regulatory authorities in 2012-2016. (%)=proportion of expedited approvals

© CIRS, *R&D Briefing 65*	Alimentary and metabolism	Cardiovascular	Anti-infective	Anti-cancer and immuno-modulators	Nervous system
EMA	476 (5%)	377 (17%)	402 (30%)	442 (18%)	458 (0%)
FDA	366 (33%)	294 (50%)	243 (78%)	238 (68%)	394 (31%)
PMDA	308 (36%)	306 (29%)	272 (76%)	298 (75%)	321 (39%)
Health Canada	353 (35%)	357 (17%)	267 (50%)	350 (34%)	396 (0%)
Swissmedic	551 (0%)	461 (22%)	521 (40%)	422 (38%)	589 (0%)
TGA	398 (0%)	371 (0%)	370 (0%)	369 (0%)	402 (0%)

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

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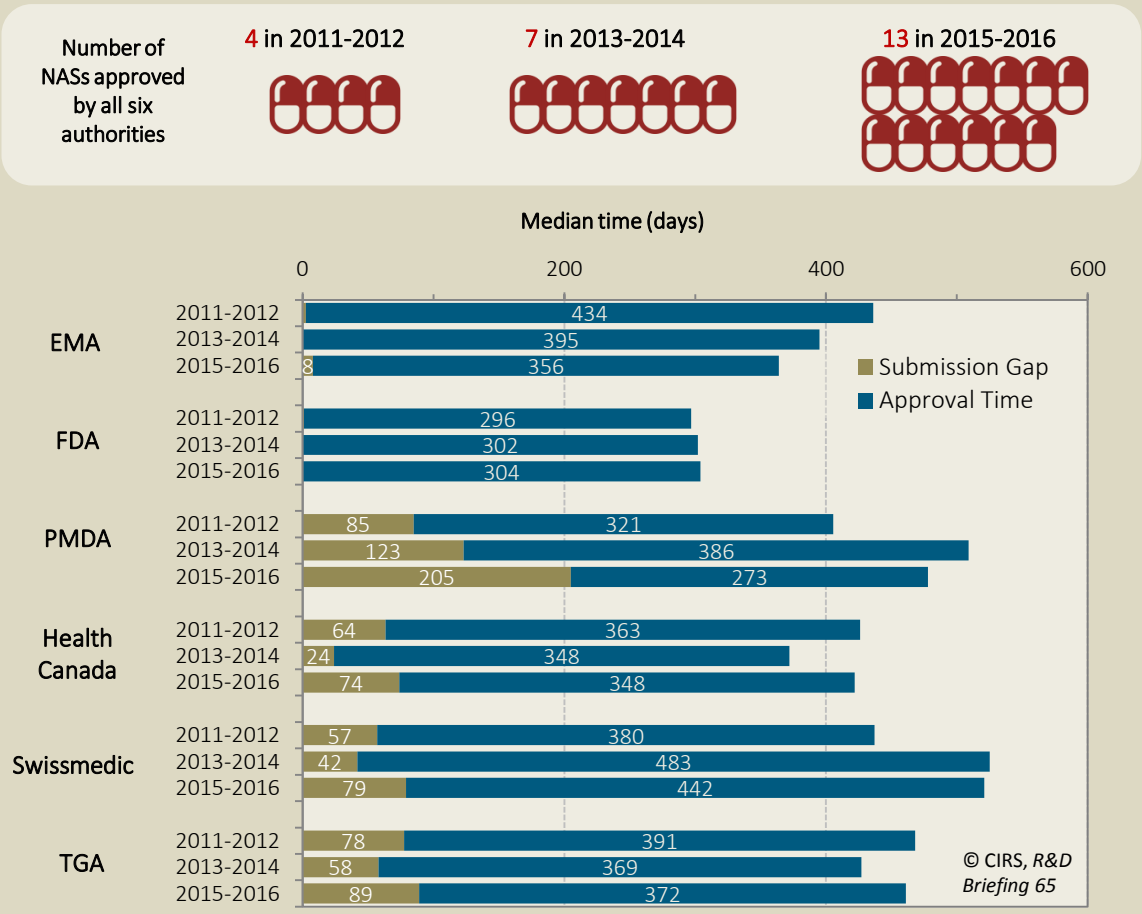
A true comparison of regulatory performance can be derived from studying the review of compounds that were approved by all six agencies. This comparison was carried out for three time cohorts in the last six years, namely 2011-2012, 2013-2014 and 2015-2016 to determine whether any trends could be identified. Interestingly, the number of products approved by all six agencies in a two-year period increased from 4 NASs in 2011-2012 to 13 NASs in 2015-2016, which indicates that more products are becoming internationalised within the same time frame. The breakdown of the overall time to registration into submission gap and approval time (Figure 9) uncovered potential limiting factors for registration of NASs. This may include company strategy to submit later or long approval times at a particular agency. The quickest time to registration was at FDA for all three 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 over the last six years for those common products, as a result of shorter median EMA approval times. This reflects increased use of expedited pathways for important products by EMA, particularly in 2015-2016. Following EMA and FDA submissions, the submission gap to Health Canada, Swissmedic and TGA was around ~60 days. This gap varied for the three time periods but the longest submission gap occurred in 2015-2016 for all three agencies. Although the longest submission gap occurred to PMDA and has increased steadily over the last few years (as discussed in more detail in R&D Briefing 62), the overall time to registration was quicker for Japan compared with Switzerland as a result of faster approval time at PMDA. This reflects 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 prior to submission of a new drug application.

Figure 9: Median submission gap and median approval time for NASs approved in all six authorities in 2011-2012 (4), 2013-2014 (7) and 2015-2016 (13).



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. 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.

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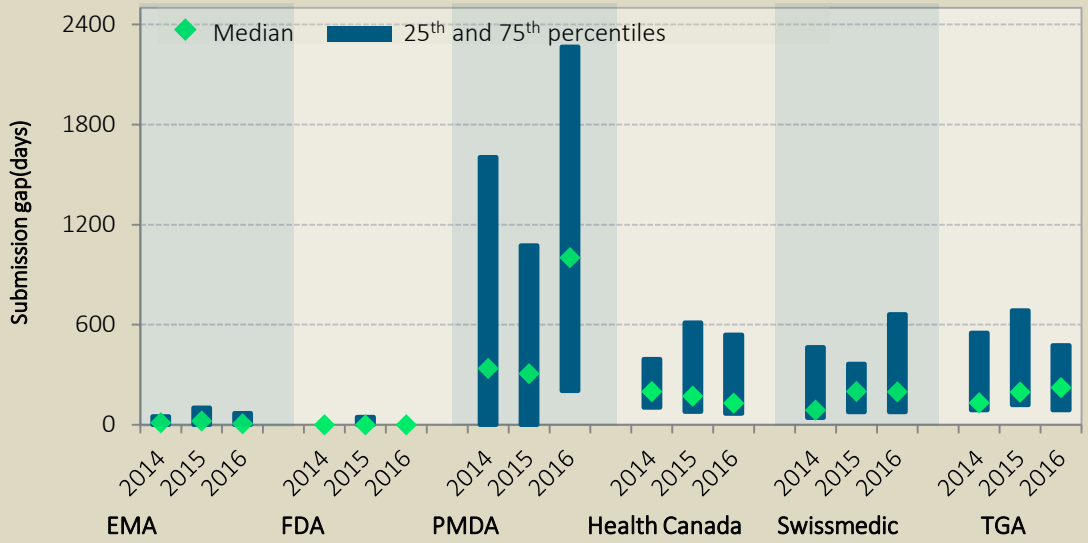
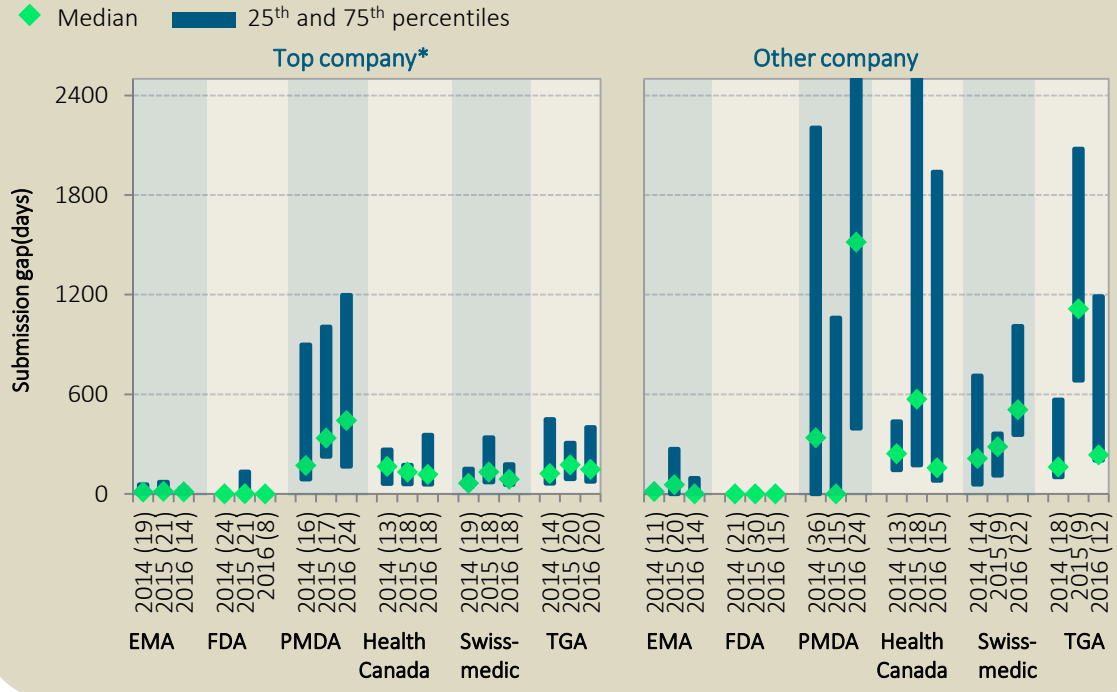
Figure 10: Submission gap for NASs approved by each agency in 2014, 2015 and 2016.



The submission gap (Figure 10) to the six agencies was evaluated for 2014-2016 and subsequently broken down according to company R&D budget size (Figure 11). It was found that although the submission gap did not vary for EMA and FDA (both within each year and when comparing 2014, 2015 and 2016) the median submission gap to PMDA, Swissmedic and TGA increased, whereas the gap to Health Canada decreased. The submission gap varied the most for PMDA, both within each year and when comparing the three years. For compounds approved in 2016, the median submission gap was shortest for FDA (0 days), followed by EMA (7 days), Health Canada (130), TGA (223), Swissmedic (274) and PMDA (930). In addition, the submission gap was evaluated according to company 2016 R&D budget size (Figure 11). The median submission gap was shorter and much less variable for top pharmaceutical companies compared with other companies, which suggests that this factor has major influence on the overall time to registration.

Figure 11: Submission gap by company 2016 R&D budget size for NASs approved by each agency in 2014, 2015 and 2016.



**Top company is defined as having R&D budget>3 billion USD in 2016.*
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. Y-axis limited to 2400 days.

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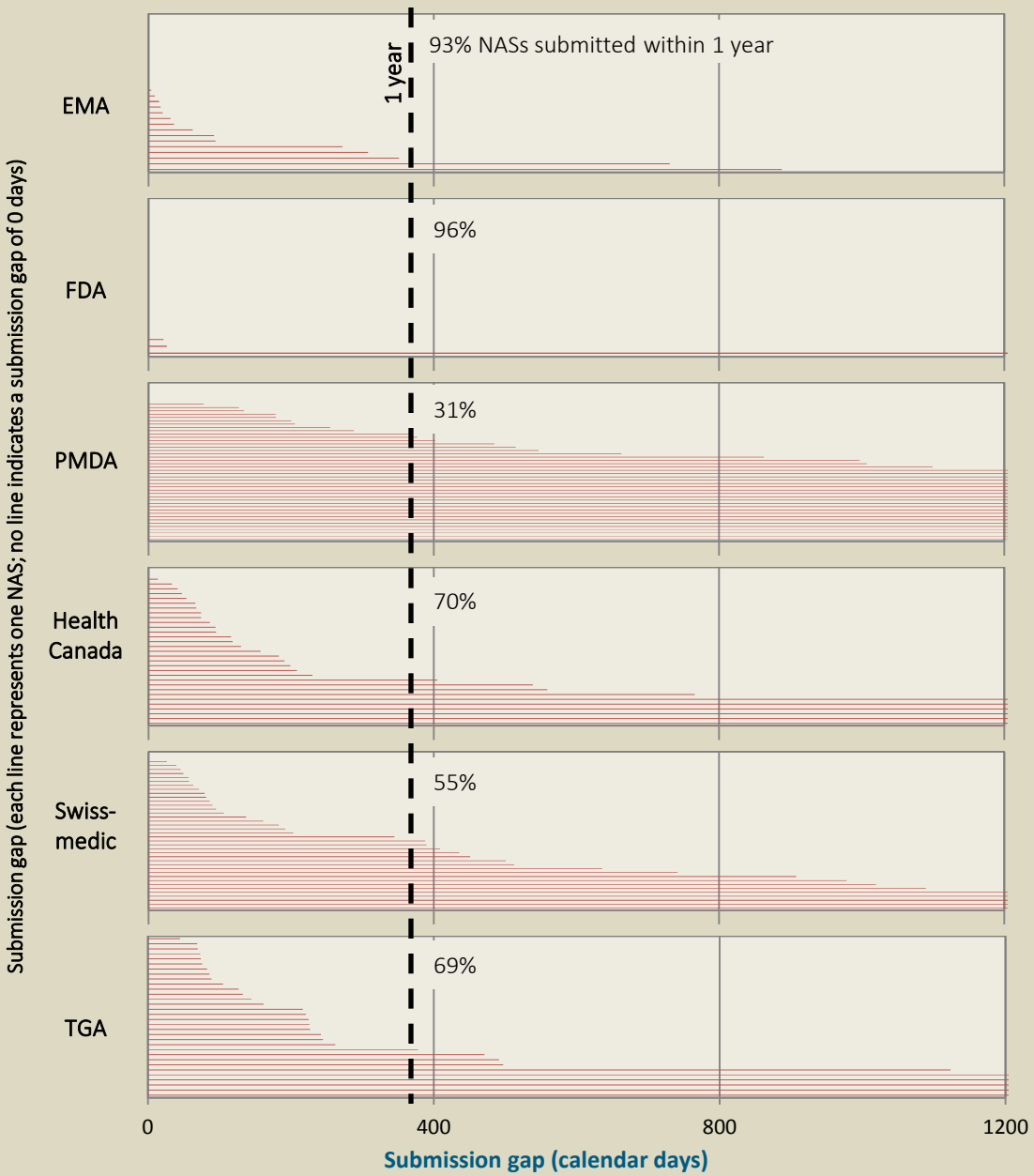
Figure 12: Submission gap for individual NASs approved by each agency in 2016.
%=proportion of products submitted within 1 year



Submission gap is calculated as the time from date of submission to the first regulatory agency to the date of regulatory submission to the target agency. X-axis limited to 1200 days.

The submission gap for individual NASs to the six agencies was illustrated for approval year 2016 (Figure 12). This analysis demonstrated the differences in the pattern of the submission gap between the six agencies as well as the difference in the percentage of products with a submission gap of less than a year. It should be noted nevertheless, that similar to the overall submission gap, this pattern varies on an annual basis as a result of a complex mix of factors such as type of compound as well as company R&D budget size and strategy and is therefore only a snapshot of the specific year. The 2016 submission gap pattern to FDA was reflective of the fact that most companies submitted to the agency first, followed by EMA. A stepwise submission gap pattern was observed for Health Canada, Swissmedic and TGA in 2016, which suggests that companies waited for completion of certain milestones within other agencies (e.g., receiving first round of questions from EMA or FDA), before submitting to Health Canada, Swissmedic or TGA. The submission gap pattern for PMDA, where only 31% NASs were submitted within a year to the agency in 2016, is reflective of the long submission gap to the agency in 2016, as discussed in more detail in R&D Briefing 62.

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Figure 13: Number of NASs approved in 1-6 agencies by the end of 2016 for all NASs approved initially in 2012-2014; N=162.

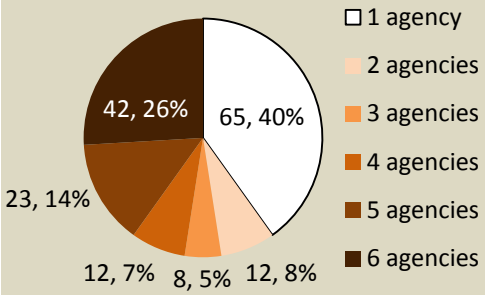
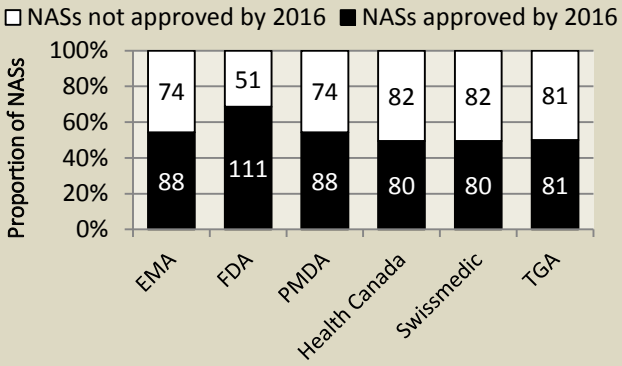


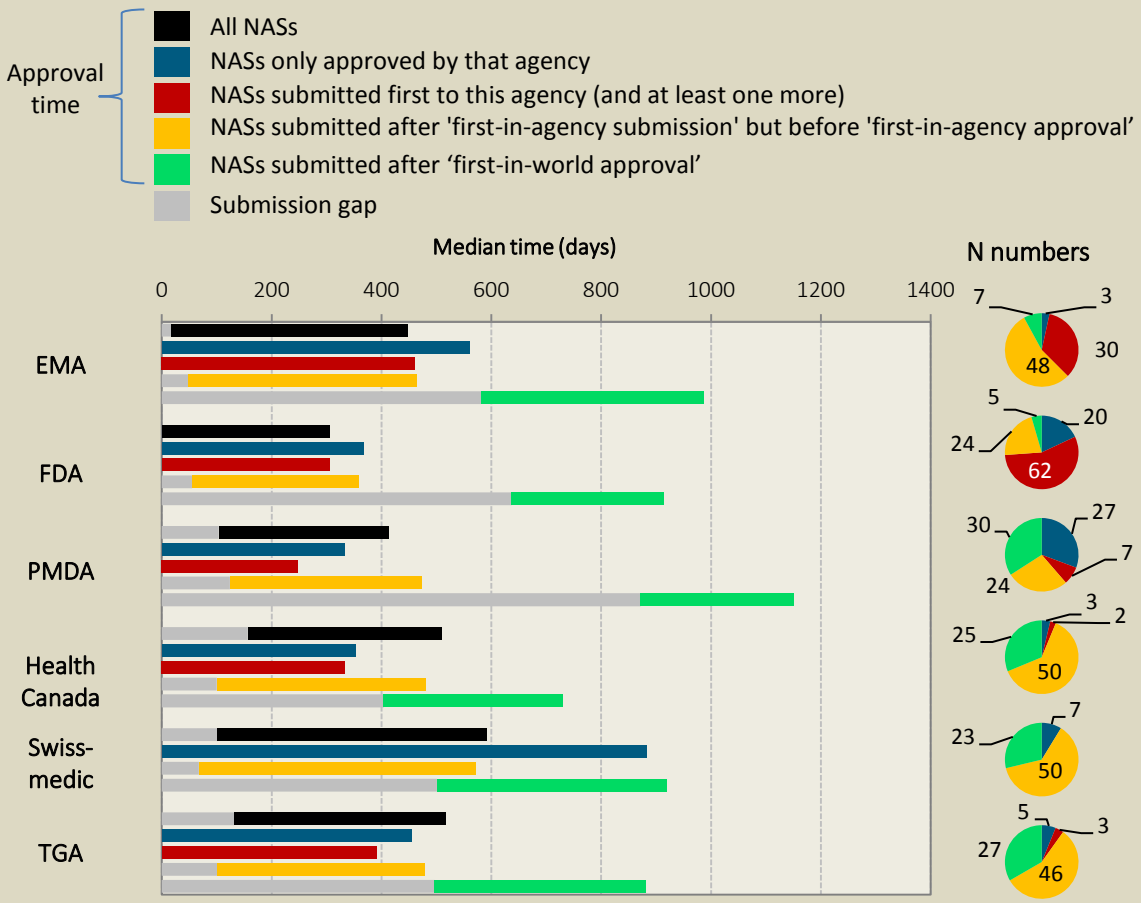
Figure 14: Proportion of NASs approved in each agency by the end of 2016 for all NASs approved initially in 2012-2014; N=162.



'Not approved', may be due to no submission, review not finalised, withdrawal by sponsor or rejection by the agency

In order to further evaluate the level of internationalisation in the six agencies, NASs approved initially by one of the six agencies in 2012-2014 were identified (N=162) and their approval in the agencies tracked until 2016. Only 26% NASs were approved by all six agencies and 40% of NASs were approved only in one agency (Figure 13). FDA approved the largest proportion of the 162 NASs (Figure 14). Interestingly, products from top companies (R&D budget> 3 billion USD in 2016) were more likely to be internationalised in agencies compared with smaller companies (results not shown). The submission gap and approval time were also evaluated (Figure 15) by timing of review.

Figure 15: Submission gap and approval time by timing of review in each agency for all NASs approved initially in 2012-2014 (approval status tracked until 2016 for remaining 5 agencies); N=162.



Submission gap is calculated as the time from date of submission to the first regulatory agency to the date of regulatory submission to the target agency. Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time.

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Figure 16: Number of anti-cancer and immunomodulating NASs approved in 1-6 agencies by the end of 2016 for NASs approved initially in 2012-2014; N=42.

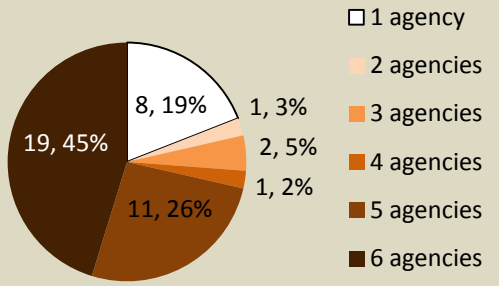
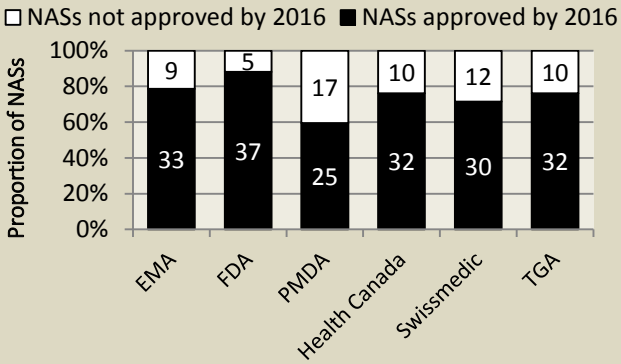


Figure 17: Proportion of anti-cancer and immuno-modulating NASs approved in each agency by the end of 2016 for NASs approved initially in 2012-2014; N=42.



NOTE: 'Not approved', may be due : no submission, review not finalised, withdrawal by sponsor, rejection by the agency

The internationalisation analysis on page 9 was subsequently repeated for anti-cancer and immunomodulating NASs (WHO ATC classification 'L'), which represents a therapy area with high unmet medical need (Figure 16 and 17). Such compounds often benefit from expedited approval pathways within agencies (page 5) and consequently, these products had faster overall approval times (Figure 18) compared with the overall cohort for the majority of agencies (page 9). Nevertheless, despite these products being internationalised across more agencies compared with the overall cohort, the submission gap was similar or slightly longer for most agencies.

Figure 18: Submission gap and approval time by timing of review in each agency for anti-cancer and immunomo-dulating NASs approved initially in 2012-2014 (approval status tracked until 2016 for remaining 5 agencies); N=42.

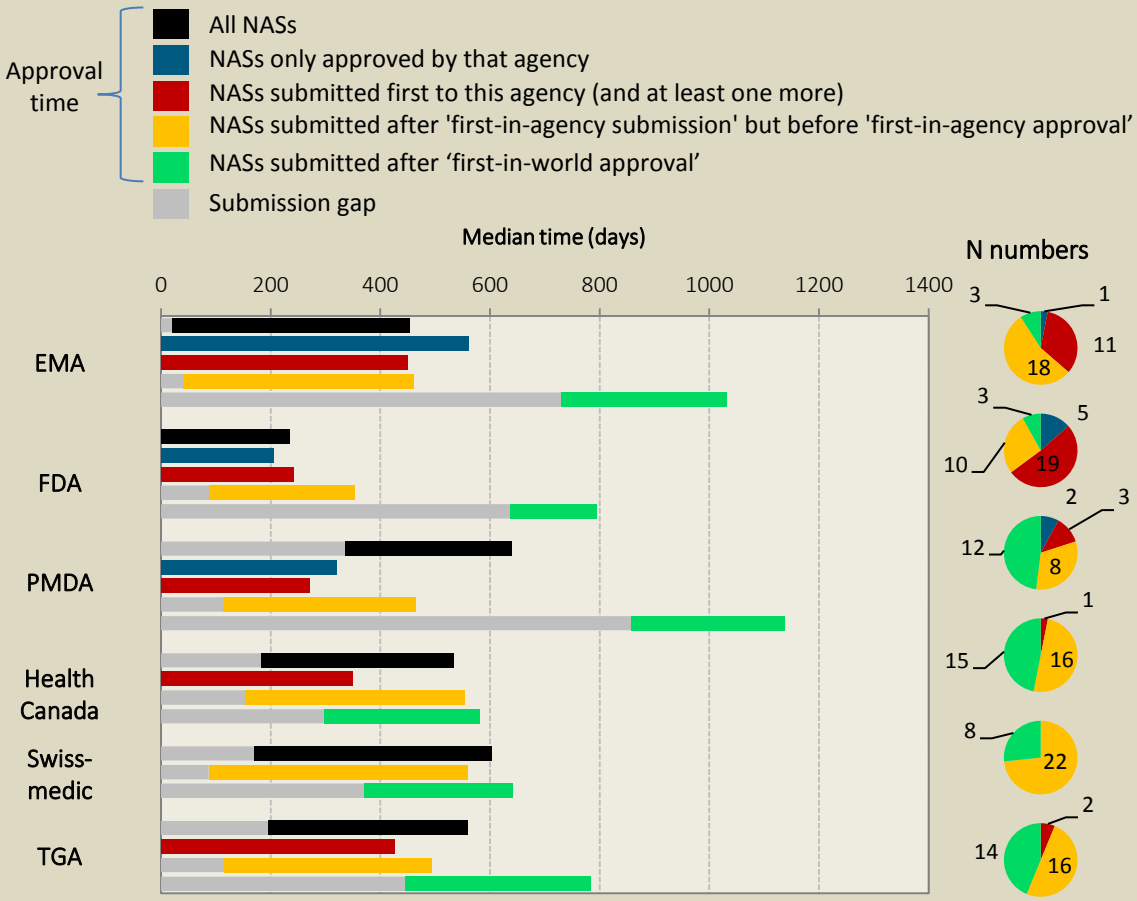


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Figure 19: Number of NASs with FDA Breakthrough Designation approved in 1-6 agencies by the end of 2016 for NASs approved initially in 2012-2014; N=12.

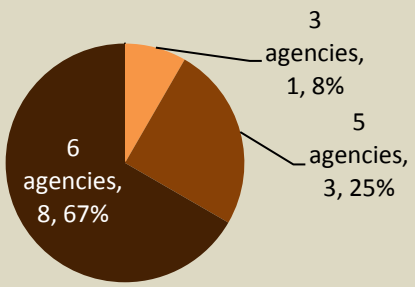
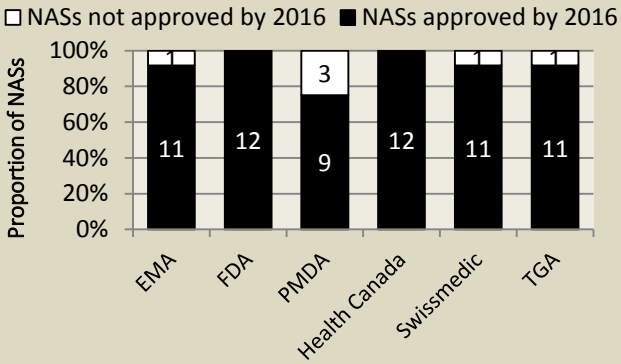


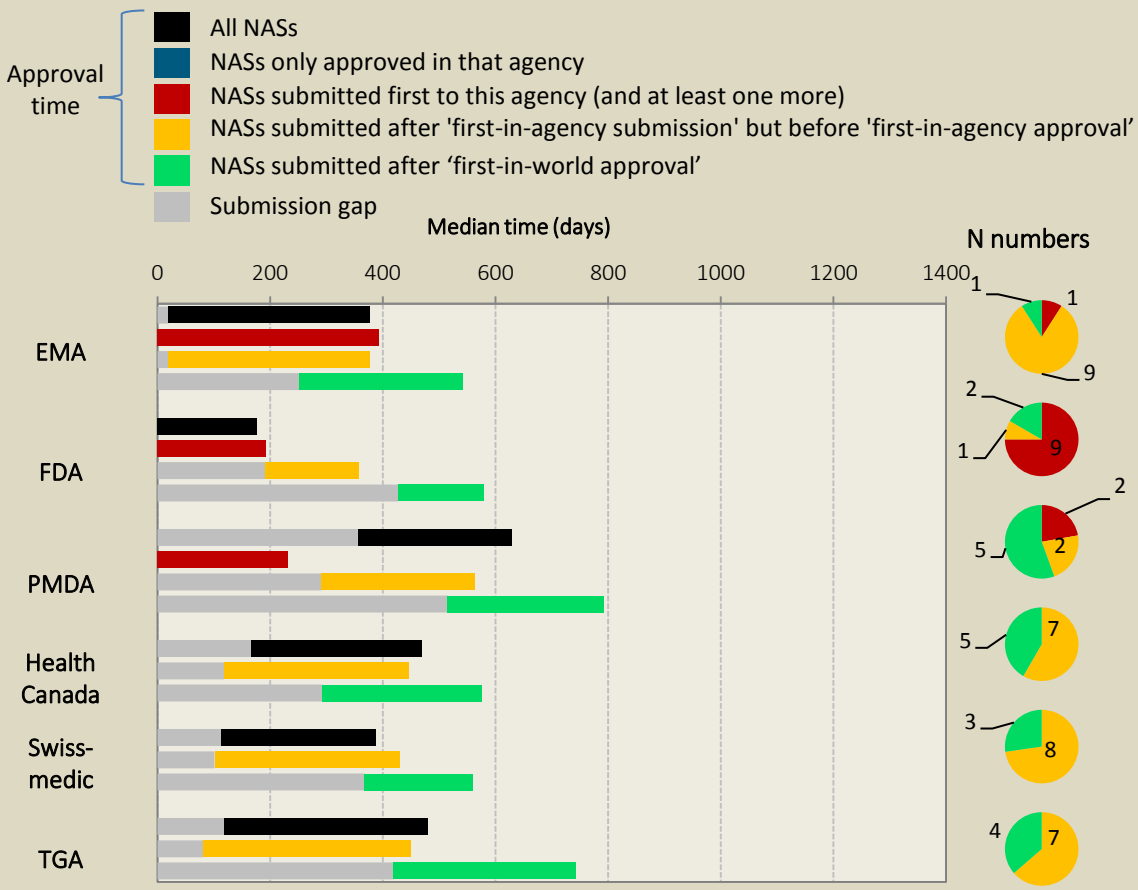
Figure 20: Proportion of NASs with FDA Breakthrough Designation approved in each agency by the end of 2016 for NASs approved initially in 2012-2014 ; N=12.



NOTE: 'Not approved', may be due : no submission, review not finalised, withdrawal by sponsor, rejection by the agency

The internationalisation analysis on page 9 was repeated for products which received FDA Breakthrough Designation, which is a process designed to expedite the development and review of important drugs. Out of the 12 NASs, all were internationalised across more than three agencies. (Figure 19). In addition, the approval times as well as the submission gap for those NASs were also generally much shorter (Figure 21) compared to the overall cohort on page 9. These findings may reflect the fact that 75% of the 12 FDA Breakthrough Designation NASs were submitted by top companies (R&D budget>3 billion USD in 2016), compared with 55% for anti-cancer and immunomodulators (page 10) and 39% for overall products (page 9) (results not shown).

Figure 21: Submission gap and approval time by timing of review in each agency for NASs with FDA Breakthrough Designation approved initially in 2012-2014 (approval status tracked until 2016 for remaining 5 agencies); N=12.



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. 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.

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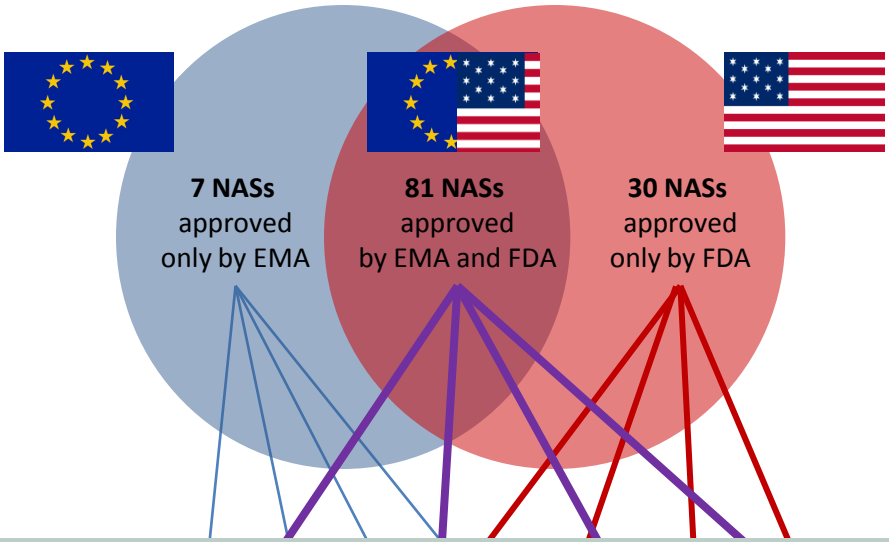
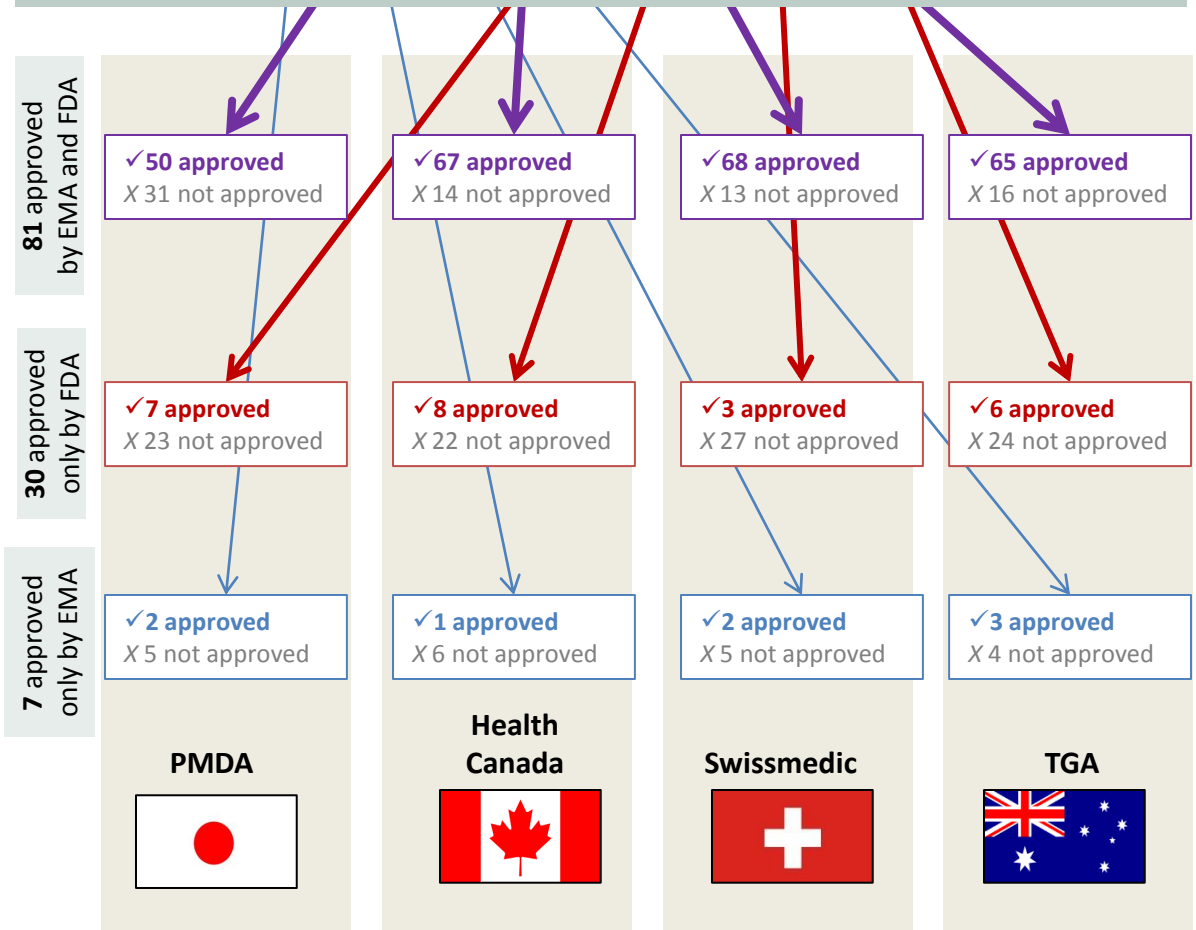
INTERNATIONALISATION – FOCUS ON EMA AND FDA

In 2012-2014, there were 118 NASs approved either by EMA or FDA or both.



These **were internationalised in PMDA, Health Canada, Swissmedic and TGA as follows (approval status tracked until 2016)**.



In general, **NASs from a top companies** (R&D budget> 3 billion USD in 2016) initially approved by EMA and FDA, had a **higher proportion of approval in the other 4 agencies** (~50-60%), compared with those approved by non-top companies (~20-30%)

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Approval at EMA 2016

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EMA **APPROVED A TOTAL OF 28 NASs IN 2016**, WITH A MEDIAN APPROVAL TIME OF **422 DAYS***

Type of Medicine

10 BIOLOGIC NASs APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **380 DAYS**

18 CHEMICAL NASs APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **447 DAYS**

12 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **390 DAYS**

16 NASs IN OTHER THERAPY AREAS APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **433 DAYS**

Designation and Review Type

5 EXPEDITED NAS APPROVALS IN 2016,** WITH A MEDIAN APPROVAL TIME OF **254 DAYS;** THIS IS A MEDIAN **182 DAYS FASTER** THAN THE **23 STANDARD NAS APPROVALS IN 2016**

11 ORPHAN NAS APPROVALS IN 2016, WITH A MEDIAN APPROVAL TIME OF **391 DAYS;** THIS IS A MEDIAN **32 DAYS FASTER** THAN THE **17 NON-ORPHAN NAS APPROVALS IN 2016**

Availability in EMA

36% OF THE NASs APPROVED IN 2016 BY EMA WERE APPROVED BY EMA **FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL AT FDA, PMDA, HEALTH CANADA, SWISSMEDIC OR TGA**

64% OF THE NASs APPROVED IN 2016 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 **34 DAYS**

*EMA approval time includes the EU Commission time.

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

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

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Approval at FDA 2016

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FDA *(CDER AND CBER)* **APPROVED A TOTAL OF 23 NASs IN 2016,** WITH A MEDIAN APPROVAL TIME OF **333 DAYS**

Type of Medicine

8 BIOLOGIC NASs APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **361 DAYS**

15 CHEMICAL NASs APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **245 DAYS**

5 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **179 DAYS**

18 NASs IN OTHER THERAPY AREAS APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **339 DAYS**

Designation and Review Type

15 EXPEDITED* NAS APPROVALS IN 2016, WITH A MEDIAN APPROVAL TIME OF **243 DAYS;** THIS IS A MEDIAN **122 DAYS FASTER** THAN THE **8 STANDARD NAS APPROVALS IN 2016**

10 ORPHAN NAS APPROVALS IN 2016, WITH A MEDIAN APPROVAL TIME OF **288 DAYS;** THIS IS A MEDIAN **54 DAYS FASTER** THAN THE **13 NON-ORPHAN NAS APPROVALS IN 2016**

Availability in FDA

87% OF THE NASs APPROVED IN 2016 BY FDA WERE APPROVED BY FDA **FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL AT EMA, PMDA, HEALTH CANADA, SWISSMEDIC OR TGA**

13% OF THE NASs APPROVED IN 2016 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 **0 DAYS**

*'Expedited review' refers to EMA 'Accelerated Assessment and FDA/PMDA/Health Canada/Swissmedic 'Priority Review'.
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Approval at PMDA 2016

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PMDA **APPROVED A TOTAL OF 48 NASs IN 2016,** WITH A MEDIAN APPROVAL TIME OF **311 DAYS**

Type of Medicine

13 BIOLOGIC NASs APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **311 DAYS**

35 CHEMICAL NASs APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **312 DAYS**

15 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **312 DAYS**

33 NASs IN OTHER THERAPY AREAS APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **308 DAYS**

Designation and Review Type

22 EXPEDITED* NAS APPROVALS IN 2016, WITH A MEDIAN APPROVAL TIME OF **279 DAYS;** THIS IS A MEDIAN **56 DAYS FASTER** THAN THE **26 STANDARD NAS APPROVALS IN 2016**

18 ORPHAN NAS APPROVALS IN 2016, WITH A MEDIAN APPROVAL TIME OF **280 DAYS;** THIS IS A MEDIAN **43 DAYS FASTER** THAN THE **30 NON-ORPHAN NAS APPROVALS IN 2016**

Availability in PMDA

12.5% OF THE NASs APPROVED IN 2016 BY PMDA WERE APPROVED IN PMDA **FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL AT EMA, FDA, HEALTH CANADA, SWISSMEDIC OR TGA**

87.5% OF THE NASs APPROVED IN 2016 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 **1333 DAYS**

*'Expedited review' refers to EMA 'Accelerated Assessment and FDA/PMDA/Health Canada/Swissmedic 'Priority Review'.
**Date of submission at the first regulatory agency to the date of regulatory submission to the target agency.

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Approval at Health Canada 2016

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HEALTH CANADA **APPROVED A TOTAL OF 33 NASs IN 2016,** WITH A MEDIAN APPROVAL TIME OF **351 DAYS**

Type of Medicine

9 BIOLOGIC NASs APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **355 DAYS**

24 CHEMICAL NASs APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **347 DAYS**

11 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **289 DAYS**

22 NASs IN OTHER THERAPY AREAS APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **358 DAYS**

Designation and Review Type

13 EXPEDITED* NAS APPROVALS IN 2016 WITH A MEDIAN APPROVAL TIME OF **279 DAYS;** THIS IS A MEDIAN **90 DAYS FASTER** THAN THE **20 STANDARD NAS APPROVALS IN 2016**

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 2016,** WITH A MEDIAN APPROVAL TIME OF **322 DAYS**

Availability in Health Canada

15% OF THE NASs APPROVED IN 2016 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 2016 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 **187 DAYS**

*'Expedited review' refers to EMA 'Accelerated Assessment and FDA/PMDA/Health Canada/Swissmedic 'Priority Review'.
**Date of submission at the first regulatory agency to the date of regulatory submission to the target agency.

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Approval at Swissmedic 2016

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SWISSMEDIC **APPROVED A TOTAL OF 40 NASs IN 2016** ,WITH A MEDIAN APPROVAL TIME OF **481 DAYS**

Type of Medicine

19 BIOLOGIC NASs APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **460 DAYS**

21 CHEMICAL NASs APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **521 DAYS**

8 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **438 DAYS**

32 NASs IN OTHER THERAPY AREAS APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **506 DAYS**

Designation and Review Type

7 EXPEDITED* NAS APPROVALS IN 2016, WITH A MEDIAN APPROVAL TIME OF **272 DAYS;** THIS IS A MEDIAN **241 DAYS FASTER** THAN THE **33 STANDARD NAS APPROVALS IN 2016**

16 ORPHAN NAS APPROVALS IN 2016, WITH A MEDIAN APPROVAL TIME OF **441 DAYS;** THIS IS A MEDIAN **74 DAYS FASTER** THAN THE **24 NON-ORPHAN NAS APPROVALS IN 2016**

Availability in Swissmedic

5% OF THE NASs APPROVED IN 2016 BY SWISSMEDIC WERE APPROVED BY SWISSMEDIC **FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL AT FDA, EMA, PMDA, HEALTH CANADA OR TGA**

95% OF THE NASs APPROVED IN 2016 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 **274 DAYS**

*'Expedited review' refers to EMA 'Accelerated Assessment and FDA/PMDA/Health Canada/Swissmedic 'Priority Review'.
**Date of submission at the first regulatory agency to the date of regulatory submission to the target agency.

Approval at TGA 2016

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TGA **APPROVED A TOTAL OF 32 NASs IN 2016**, WITH A MEDIAN APPROVAL TIME OF **372 DAYS**

Type of Medicine

10 BIOLOGIC NASs APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **383 DAYS**

22 CHEMICAL NASs APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **351 DAYS**

13 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **352 DAYS**

19 NASs IN OTHER THERAPY AREAS APPROVED IN 2016, WITH A MEDIAN APPROVAL TIME OF **377 DAYS**

Designation and Review Type

0 EXPEDITED NAS APPROVALS IN 2016; TGA DID NOT APPROVE ANY NASs IN 2016 UNDER ITS RECENTLY INTRODUCED PRIORITY PROGRAMME

8 ORPHAN NAS APPROVALS IN 2016, WITH A MEDIAN APPROVAL TIME OF **376 DAYS;** THIS IS A MEDIAN **4 DAYS SLOWER** THAN THE **24 NON-ORPHAN NAS APPROVALS IN 2016**

Availability in TGA

0% OF THE NASs APPROVED IN 2016 BY TGA WERE APPROVED BY TGA **FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL BY FDA, EMA, PMDA, HEALTH CANADA OR SWISSMEDIC**

100% OF THE NASs APPROVED IN 2016 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 **223 DAYS**

*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, 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
- 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 2016 will be made available on the CIRS website.

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R&D Briefing 65

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