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.

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.
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).

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).
All six agencies now offer an expedited priority system (refers to EMA ‘Accelerated Assessment’ and FDA/PMDA/Health Canada/Swissmedic ‘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.

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

<table>
<thead>
<tr>
<th>ID CIRS, R&amp;D Briefing 67</th>
<th>New active substance (NAS) approval type</th>
<th>2017 NAS approvals, number</th>
<th>2017 NASs, % Expeditied, %</th>
<th>2017 median approval time, days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EMA</strong></td>
<td>Overall approvals</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FRP</td>
<td>Accelerated Assessment (referred in Briefing as Expedited)</td>
<td>5</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditional Approval</td>
<td>2</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exceptional Circumstances</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Orphan</td>
<td>10</td>
<td>33%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>FDA</strong></td>
<td>Overall approvals</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FRP</td>
<td>Priority (referred in Briefing as Expedited)</td>
<td>31</td>
<td>62%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Accelerated Approval</td>
<td>6</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breakthrough Designation</td>
<td>20</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fast Track</td>
<td>18</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td>Orphan</td>
<td>21</td>
<td>42%</td>
<td>86%</td>
</tr>
<tr>
<td><strong>PMDA</strong></td>
<td>Overall approvals</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FRP</td>
<td>Priority (referred in this Briefing as Expedited)</td>
<td>8</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sakigake</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Orphan</td>
<td>7</td>
<td>32%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Health Canada</strong></td>
<td>Overall approvals</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FRP</td>
<td>Priority (referred in Briefing as Expedited)</td>
<td>6</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditional (Notice of Compliance with conditions)</td>
<td>7</td>
<td>21%</td>
</tr>
<tr>
<td><strong>Swissmedic</strong></td>
<td>Overall approvals</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FRP</td>
<td>Priority (referred in Briefing as Expedited)</td>
<td>7</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Procedure with prior notification</td>
<td>4</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>Orphan</td>
<td>10</td>
<td>34%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>TGA</strong></td>
<td>Overall approvals</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FRP</td>
<td>Priority (referred in Briefing as Expedited)</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Provisional Approval</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Orphan</td>
<td>7</td>
<td>29%</td>
<td>-</td>
</tr>
</tbody>
</table>

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

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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

<table>
<thead>
<tr>
<th>Agency</th>
<th>Alimentary and metabolism</th>
<th>Cardiovascular</th>
<th>Anti-infective</th>
<th>Anti-cancer and immunomodulators</th>
<th>Nervous system</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMA</td>
<td>458 (10%)</td>
<td>377 (17%)</td>
<td>390 (36%)</td>
<td>428 (16%)</td>
<td>481 (22%)</td>
</tr>
<tr>
<td>FDA</td>
<td>361 (41%)</td>
<td>292 (57%)</td>
<td>243 (83%)</td>
<td>239 (73%)</td>
<td>432 (29%)</td>
</tr>
<tr>
<td>PMDA</td>
<td>311 (37%)</td>
<td>321 (25%)</td>
<td>260 (75%)</td>
<td>288 (75%)</td>
<td>336 (33%)</td>
</tr>
<tr>
<td>Health Canada</td>
<td>403 (29%)</td>
<td>388 (18%)</td>
<td>220 (56%)</td>
<td>348 (23%)</td>
<td>391 (0%)</td>
</tr>
<tr>
<td>Swissmedic</td>
<td>542 (0%)</td>
<td>421 (29%)</td>
<td>447 (44%)</td>
<td>436 (33%)</td>
<td>589 (0%)</td>
</tr>
<tr>
<td>TGA</td>
<td>397 (0%)</td>
<td>368 (0%)</td>
<td>370 (0%)</td>
<td>364 (0%)</td>
<td>402 (0%)</td>
</tr>
</tbody>
</table>

*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.
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 turn 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

<table>
<thead>
<tr>
<th>Agency</th>
<th>2008-2012 (12)</th>
<th>2013-2017 (51)</th>
<th>Submission Gap</th>
<th>Approval Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMA</td>
<td>416</td>
<td>394</td>
<td>17% expedited</td>
<td>25% expedited</td>
</tr>
<tr>
<td>FDA</td>
<td>302</td>
<td>302</td>
<td>58% expedited</td>
<td>57% expedited</td>
</tr>
<tr>
<td>PMDA</td>
<td>525</td>
<td>293</td>
<td>42% expedited</td>
<td>59% expedited</td>
</tr>
<tr>
<td>Health Canada</td>
<td>117</td>
<td>87</td>
<td>8% expedited</td>
<td>24% expedited</td>
</tr>
<tr>
<td>Swissmedic</td>
<td>84</td>
<td>100</td>
<td>25% expedited</td>
<td>29% expedited</td>
</tr>
<tr>
<td>TGA</td>
<td>91</td>
<td>104</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

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

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.

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).
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.

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).
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).

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.
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.

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).
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.

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

<table>
<thead>
<tr>
<th>Approval year</th>
<th>Median time (days)</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>Overall 2015-2017</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Submission Gap</td>
<td>196</td>
<td>223</td>
<td>499</td>
<td>262</td>
</tr>
<tr>
<td></td>
<td>Approval time</td>
<td>373</td>
<td>369</td>
<td>364</td>
<td>371</td>
</tr>
</tbody>
</table>

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).

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

<table>
<thead>
<tr>
<th></th>
<th>Median time (days)</th>
<th>Expedited (based on EMA/FDA designation) (45)</th>
<th>Standard (42)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Submission Gap</td>
<td>225</td>
<td>364</td>
</tr>
<tr>
<td></td>
<td>Approval time</td>
<td>352</td>
<td>386</td>
</tr>
</tbody>
</table>

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.

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

<table>
<thead>
<tr>
<th>Submissio gap (days)</th>
<th>Median</th>
<th>25th and 75th percentiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Top company</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-top company</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Top Company</th>
<th>Non-top Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>2016</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>2017</td>
<td>7</td>
<td>17</td>
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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.

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

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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.

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

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

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

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

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

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.

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

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

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

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.
PMDA approved a total of 22 NASs in 2017, with a median approval time of 333 days.

- 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.

- 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.

- 11 NASs in other therapy areas approved in 2017, with a median approval time of 359 days.

82% of the NASs approved in 2017 by PMDA were approved at EMA, FDA, Health Canada, Swissmedic or TGA first or within one month of their first approval at EMA, FDA, Health Canada, Swissmedic or TGA. 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.
Focus: Health Canada 2017

Health Canada approved a total of 33 NASs in 2017, with a median approval time of 350 days.

- **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.
- **6 Expedited NASs** approved 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.

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.

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

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

10 ORPHAN NASs APPROVED 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

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

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

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

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

10 ORPHAN NASs APPROVED 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

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

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

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

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

100% 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.
TGA APPROVED A TOTAL OF 24 NASs IN 2017, WITH A MEDIAN APPROVAL TIME OF 364 DAYS

- 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
- 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

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.

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Definitions

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

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.
- 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.
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