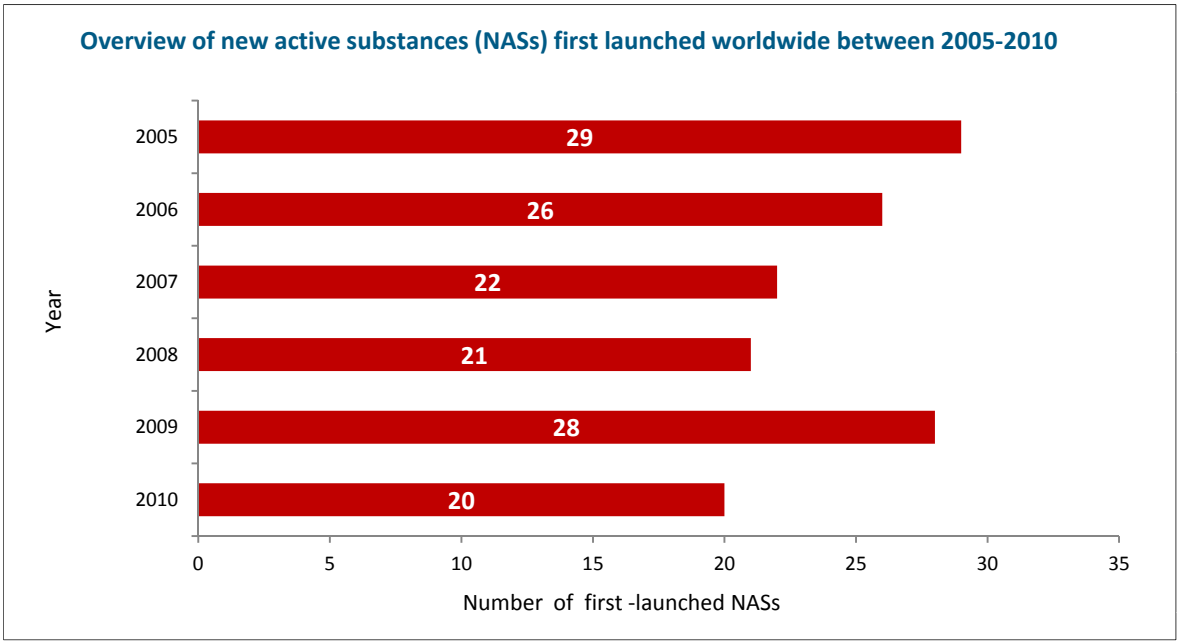
AVAILABILITY OF NEW MEDICINES

CHARACTERISING THE FACTORS INFLUENCING DRUG ROLL OUT TO SIX MATURE MARKETS



Contents

Introduction and Objective	1
Methods	2
Results	3
Overview of first-launched NASs	3
Availability of first-launched NASs	4
Internationalisation of NASs	5
Comparison of regulatory performance in six jurisdictions	6
Comparison of time taken to submit and be approved in six jurisdictions	7
Drug availability by company size	8
Drug availability by therapeutic area	9
47 first launched NASs available in all six jurisdictions	10
Jurisdiction -specific analysis	11
Conclusions	17

CIRS Centre for Innovation in Regulatory Science

R&D BRIEFING 53

R&D Briefing 53 Availability of new medicines

Introduction

Every marketed medicine undergoes a rigorous evaluation from a regulatory agency to ensure that the benefits of the medicine outweigh the risks and as such can become a valuable asset in the treatment of diseases. The development of new medicines is time-consuming, expensive and risky with only around 10% of new active substances (NASs) that enter man making it to its first market (1).

Today, companies are interested in the integration of worldwide drug development and global registration is the goal of most pharmaceutical companies, in order to make their products available to patients globally in a timely, ideally simultaneous fashion. However, this can be impeded by a number of factors both company driven and those that relate to the needs of countries (2). Such factors include long approval times, requests for further clinical data and an increasingly divergent landscape with regard to pricing and reimbursement.

Over the last decade there has been an increasing number of NASs that are first launched by small-to-medium companies and the questions is, are these products only available to patients in the country of first market or do these NASs benefit a wider patient population.

This Briefing describes a study that investigates the NASs first launched (available for sale, in any market) between 2005-2010. For this cohort of medicines, we analysed their regulatory approval status as of 31 December 2012 in six mature markets (USA, Europe, Japan, Canada, Switzerland and Australia) to identify in each market, what proportion of first-launched NASs are subsequently approved and the time taken to reach each of these markets.

Objective

To review NASs first launched between 2005-2010 and to determine their regulatory status as of 31 December 2012 in USA, Europe, Japan, Canada, Switzerland and Australia to identify the characteristics of these products.

CIRS Centre for Innovation in Regulatory Science

Methods

146 NASs were identified that were first launched between 2005-2010, from the CMR International First Launch database. The date and country of first launch was also identified from this database. The first launch date is defined as "The first ever date on which the active substance was available for sale, in any market."

Each NAS was then identified in the CIRS Regulatory Review Times Database to assess its regulatory status as of 31 December 2012 in USA, Europe, Japan, Canada, Switzerland and Australia.

Detailed data regarding submission and approval dates, approval route, company size and therapeutic area were collated to evaluate and characterise the factors impacting international drug roll out across the six jurisdictions. The types of company were categorised as Top companies (n = 13, 2010 R&D spend greater than 3 billion USD) and others (2010 R&D spend less than 3 billion USD).

Analyse for drug roll out times across jurisdictions were calculated as below (Figure 1):

- **Submission gap:** Time from submission to the first regulatory agency to the date of regulatory submission to the target market
- **Approval gap:** Time from approval from the first regulatory agency to the date the license at the target market was granted
- **Regulatory review time:** Time from submission for market authorisation to the date the licence to market was granted
- **International medicine:** An NAS that has been granted market authorisation by US FDA, European EMA, and at least two other target jurisdictions (Japan, Canada, Switzerland or Australia)
- **Time to internationalisation:** Time from the first submission for market authorisation to the date of licence by the fourth target jurisdiction in the study
- **Drug roll out time**: Time from the first submission for market authorisation to the date the licence was granted to the last target market in the study

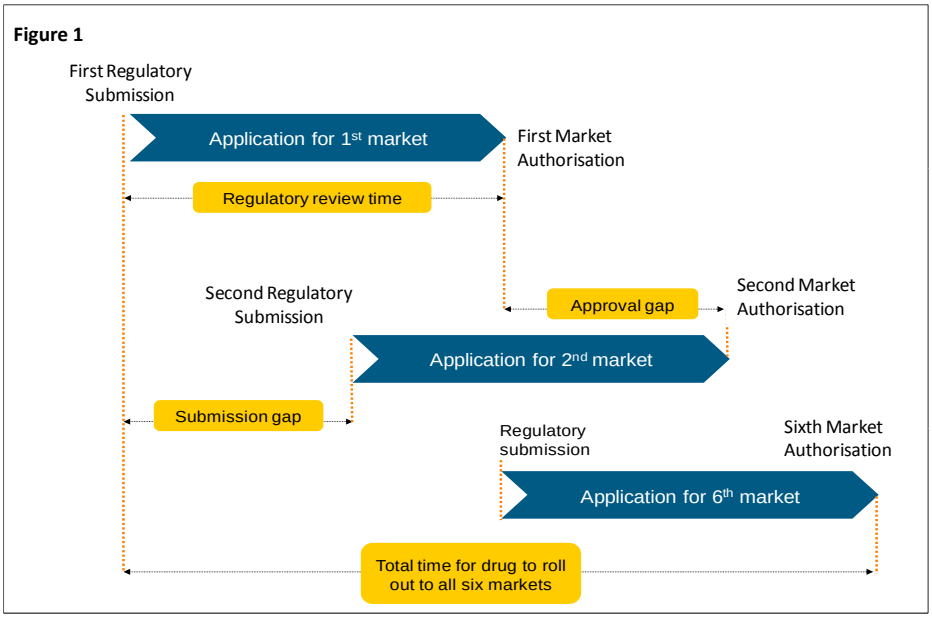


Figure 1. Schematic outline of timeline analysis,

Results

Overview of NASs first launched between 2005-2010

The majority of 146 NASs first launched between 2005-2010 were first launched in US (51%), with 24% first launched in Europe and 14% in Japan. Canada and Switzerland had 2% and 3% of first launches respectively, with the remaining 6% first launched in other countries (Figure 2).

By 2012,72% of first launched medicines were approved in USA, compared with only 53% in Australia (Figure 3).

Figure 2. Proportion of NASs by first launched jurisdiction.

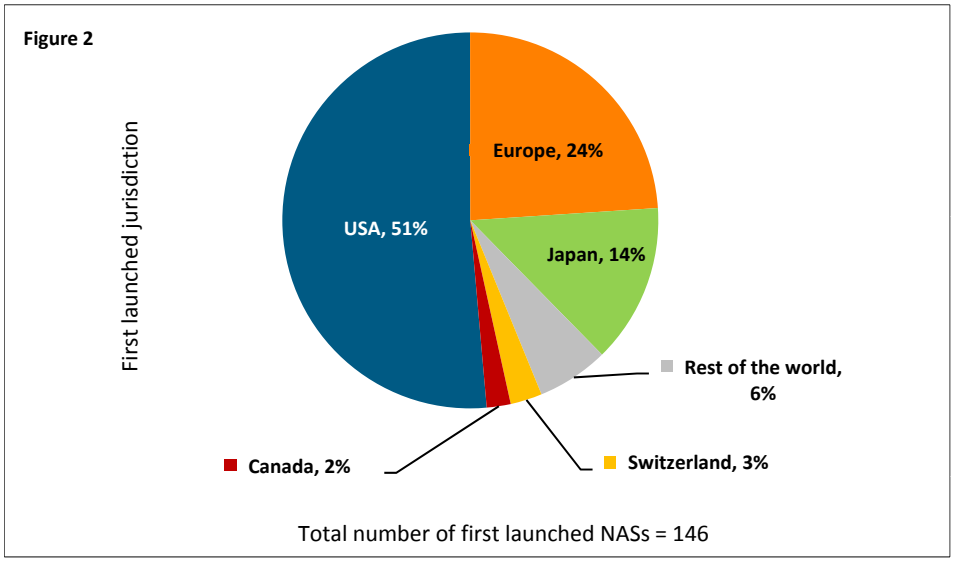
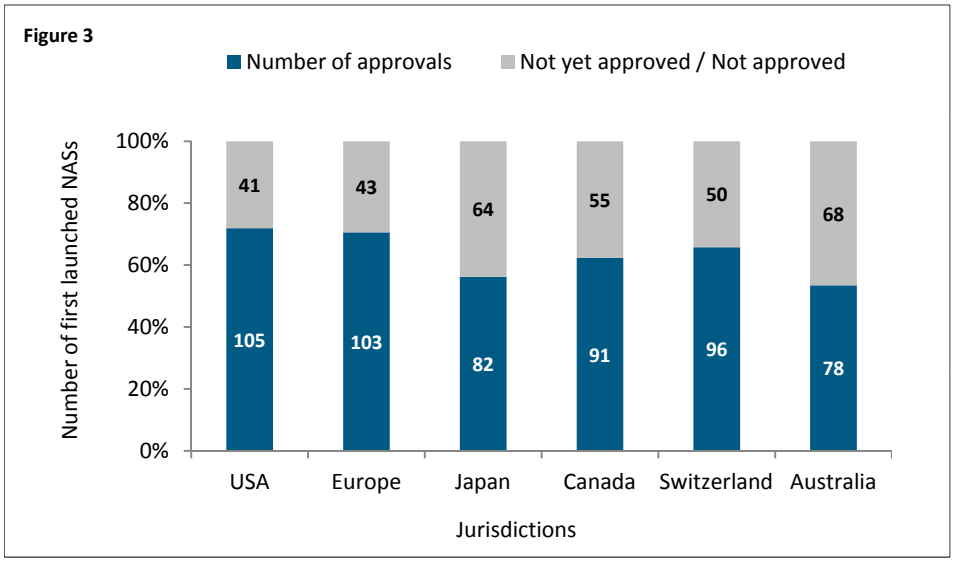


Figure 3. A comparison of approval status of first launched NASs in six jurisdictions.



CIRS Centre for Innovation in Regulatory Science

Availability of first launched NASs in target jurisdictions

By the end of 2012, 20% of medicines first launched between 2005-2010 were approved in only one jurisdiction whilst 34% (47 NASs) were approved in all six jurisdictions (Figure 4).

Figure 4

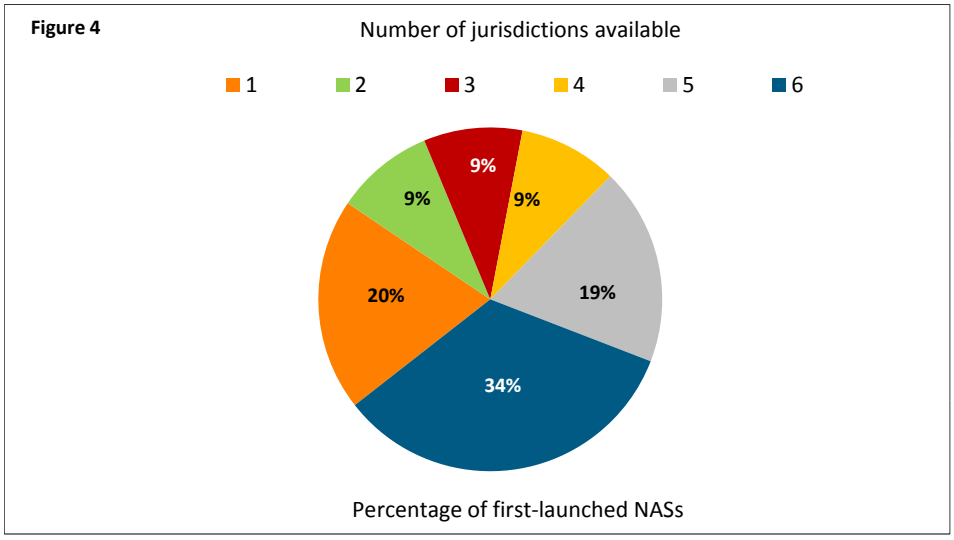


Figure 4.Availability of 1st launched NASs in six markets (USA, Europe, Japan, Canada, Switzerland, Australia)

Fifty-four NASs were designated by FDA for a priority review, of which 42 (78%) were approved in five or more jurisdictions, compared with 61% of those NASs designated by FDA for a standard review (Figure 5).

Forty-six percent of the total NASs were from top companies but made up 74% of the 47 NASs approved in all six jurisdictions (Figure 6).

Figure 5

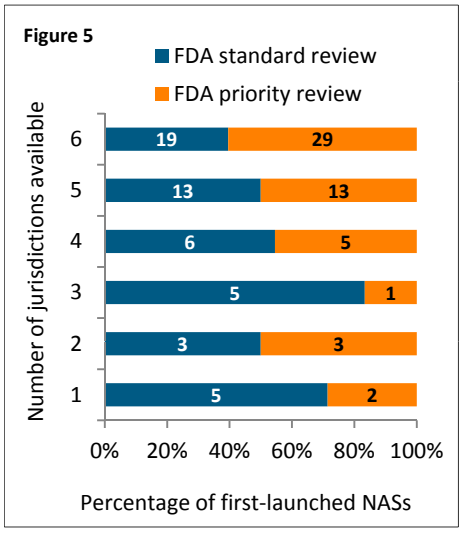


Figure 5. Availability of first-launched NASs in six markets, breakdown by the FDA review type.

Figure 6

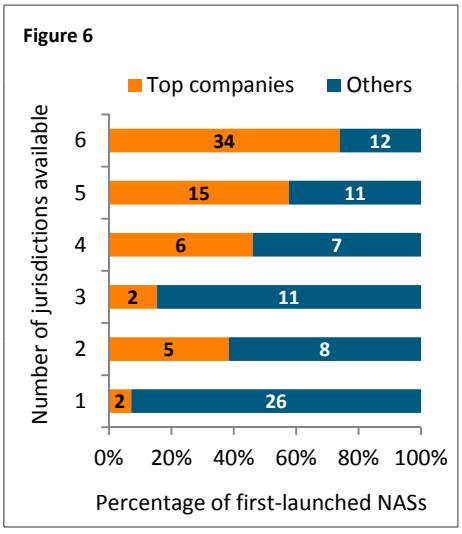


Figure 6. Availability of first-launched NASs in six markets, break down by the company size (top vs. others).

Internationalisation of NASs

Seventy-nine first-launched NASs were indentified as "international medicines", which had been granted market authorisation by US FDA, European EMA and at least two other target jurisdictions (Japan, Canada, Switzerland or Australia). When categorised by therapeutic area, the greatest number of products to roll out internationally were anti-cancer products (30%) (Figure 7). Approximately two thirds of the internationalised NASs were developed by top companies (Figure 8).

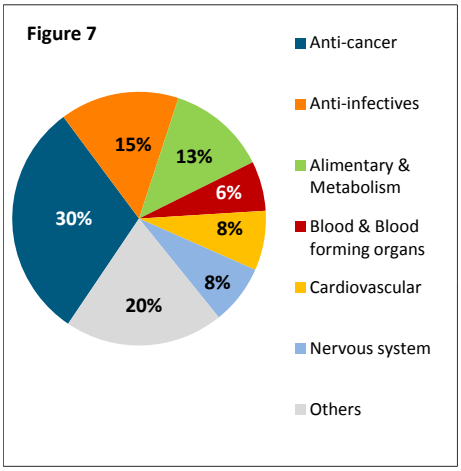


Figure 7. Percentage breakdown of the 79 internationalised NASs by therapeutic area.

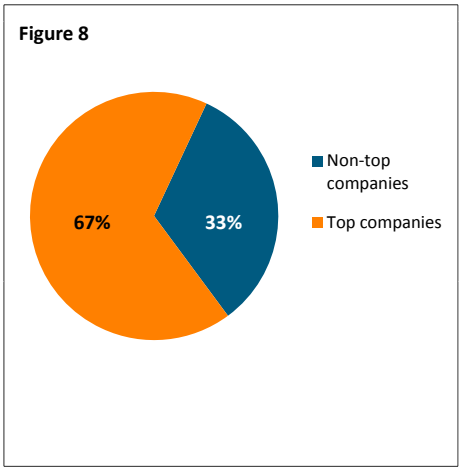


Figure 8. Percentage split of the 79 internationalised NASs by company size.

Median time for NASs from submission to first market to being approved in the fourth target market are displayed by therapeutic area and company size (Figure 9). It took approximately 600 days (median time) longer for non-top companies to roll their products out internationally, compared with top companies.

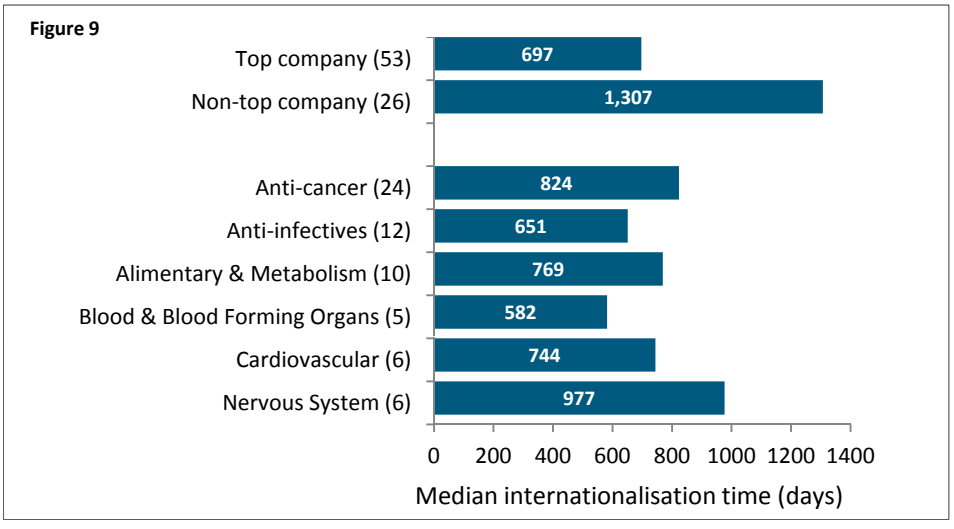


Figure 9. Timeline analysis of internationalised NASs (n=79).

Comparison of regulatory performance in six jurisdictions

For the cohort of first-launched NASs approved in each jurisdiction, the median approval time was shortest in the USA (302 days) although the variability in time was much greater at FDA compared with the other agencies (Figure 10).

For the cohort of 47 NASs approved in all six jurisdictions, the median approval time for the same products across the agencies was quickest for FDA (273 days); PMDA had the next quickest review (367 days) then Canada (392 days), with the EMA, TGA and Swissmedic taking 414, 434 and 485 days respectively. Interestingly, the 47 products had marginally quicker median approval times than the total cohort, except for PMDA where the difference was over 100 days quicker and for Canada where the cohort of 47 NASs took slightly longer.

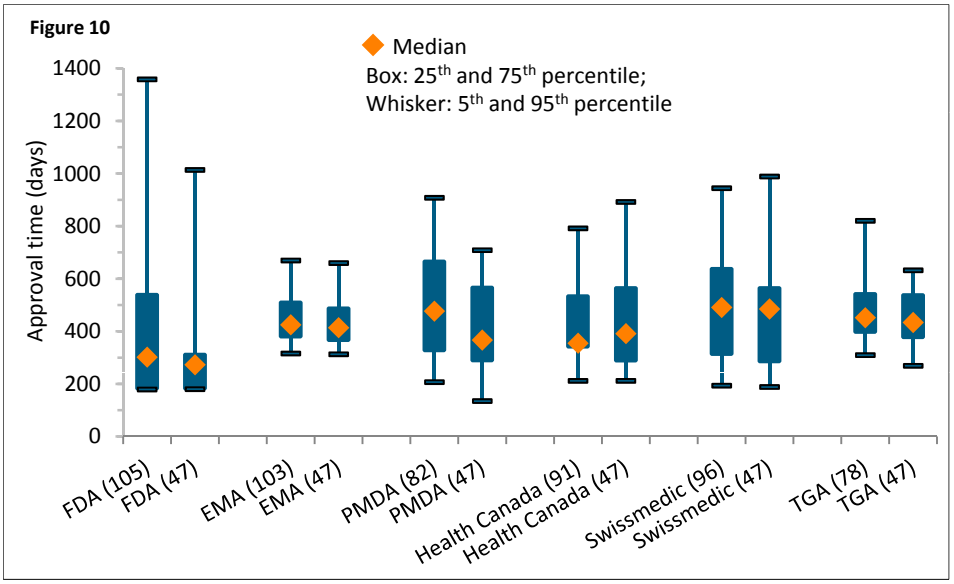


Figure 10. Comparison of review time of all approvals vs 47 products that are available in six jurisdictions.

Time taken for a new medicines to be licensed is made up of the time it takes for the company to submit the dossier to that country and the time taken by the authority to approve the medicine, this includes both company time to answer questions and agency time to review the NAS. As all these countries have adopted the ICH guidelines, a company could technically submit a dossier simultaneously to each of these countries, although there are some nuances based on different approval pathways used and in Japan, the need for local data.

An analysis has been undertaken in which the date of the first submission to the first country out of the six jurisdictions has been taken as the start date to measure the submission gap between this date and the date the NAS is actually submitted to each of the six jurisdictions. This has been plotted against the approval time of that NAS in the specific jurisdiction.

This analysis was undertaken to give insight into whether the time taken for a medicine to become licensed in a country is primarily due to the time that companies take to submit to each of the jurisdictions or relates primarily to the time taken to approve the medicine.

For the US and EU, which are usually the countries of first submission or where submission is made very quickly after the first submission, the time taken to get a license relates primarily to the approval time. Although the time taken to submit to Swissmedic, Health Canada and TGA after the date of first submission was usually longer than that to EMA or US, for the majority of products the approval time as a proportion of the total time (submission gap plus approval time) was longer than the submission gap proportion in each of these jurisdictions. However, for this cohort of NASs, at the PMDA, this result is reversed.

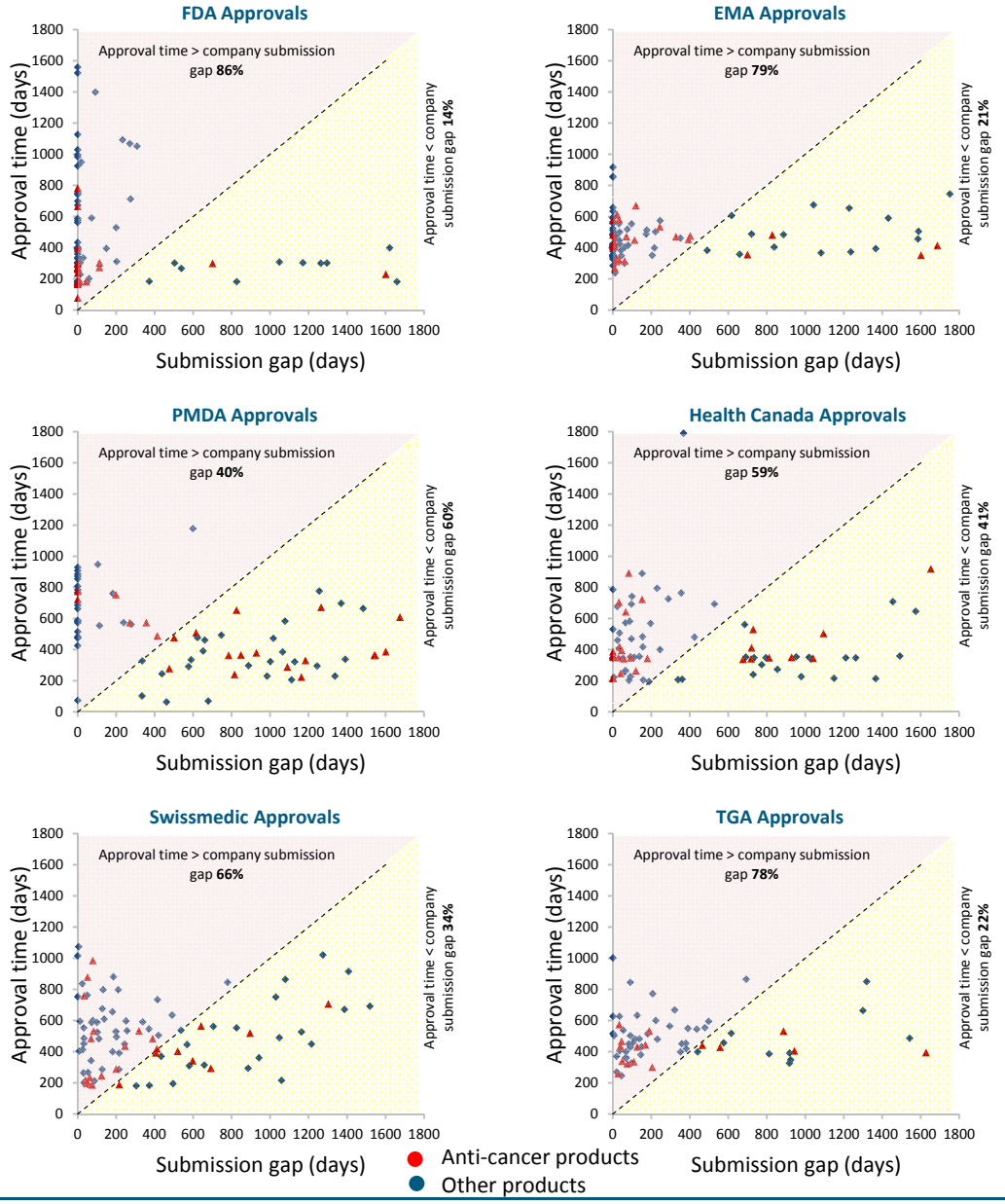


Figure 11. Comparison of agency time vs company submission time for NASs approved at six jurisdictions.

Company size

Median approval times for NASs developed by top companies (R&D spend >3 billion USD 2010) was similar compared with smaller companies, however, the variation in approval time was greater for non-top companies in USA.

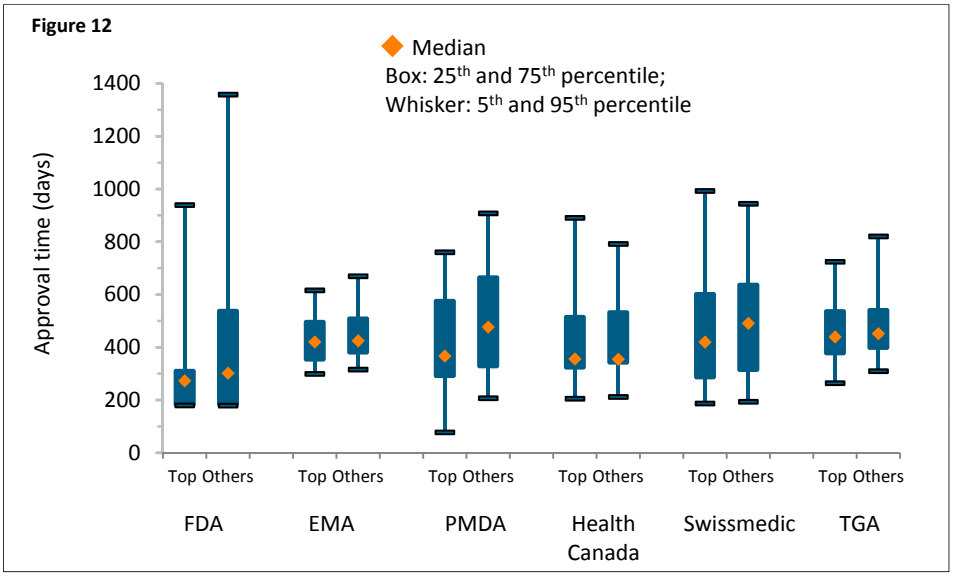


Figure 12. Regulatory agency approval time by the size of company.

Submission gap was calculated as "time from submission to the first regulatory agency to the date of regulatory submission to the target market", which was a measurement of the companies' strategy in terms of submission timing. Twenty-eight percent of first-launched NASs developed by non-top companies were submitted to Japan within a year of first submission, compared with 15% of these by top companies. Also a higher proportion of non-top companies products had not been submitted/not approved across all jurisdictions. (Figure 13).

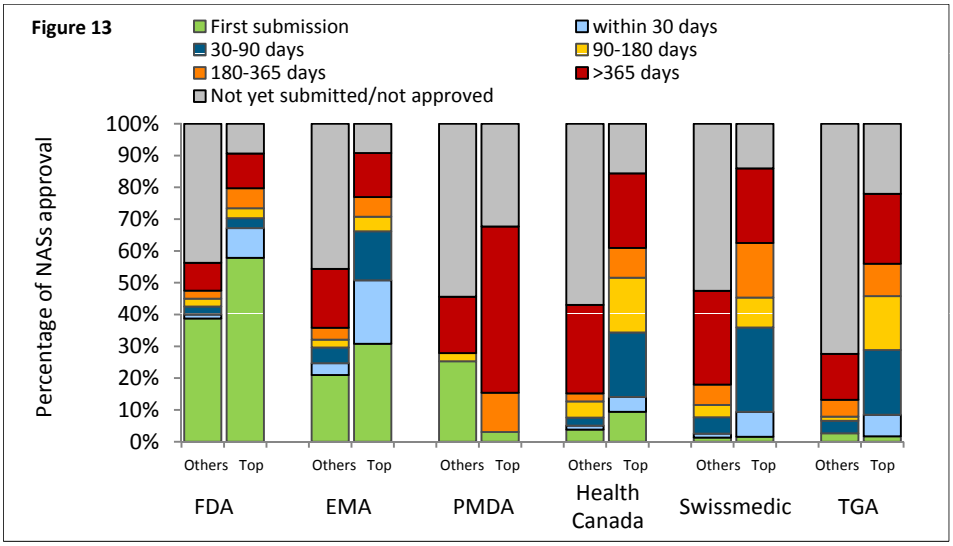


Figure 13. A comparison of submission timing strategy by company size.

Therapeutic area

Three therapeutic areas made up 48% of first launches (anti-cancer 22%, anti-infective 14%, alimentary and metabolism 12%), and 72% of the cohort of 47 NASs approved in all six jurisdictions (anti-cancer 38%, anti-infective 15% and alimentary and metabolism 19%)(Figure14).

Number of jurisdictions available (Number of NASs)	1 (28)	2 (13)	3 (13)	4 (13)	5 (26)	6 (47)
Anti-cancer	11%	23%	15%	15%	19%	38%
Anti-infective	18%	0%	8%	15%	15%	15%
Alimentary & Metabolism	11%	8%	15%	8%	4%	19%
Blood & Blood forming organs	14%	8%	0%	0%	4%	8%
Cardiovascular	4%	23%	23%	0%	19%	4%
Nervous system	7%	15%	8%	8%	15%	4%
Other	35%	23%	31%	54%	24%	13%

Figure 14. Availability of first-launched NASs in six markets by therapeutic area.

For anti-cancer and cardiovascular products, the majority of these were launched first in the USA (79% and 71% respectively), compared with only 40% first launched in USA for blood & blood forming organs products.

Figure 15

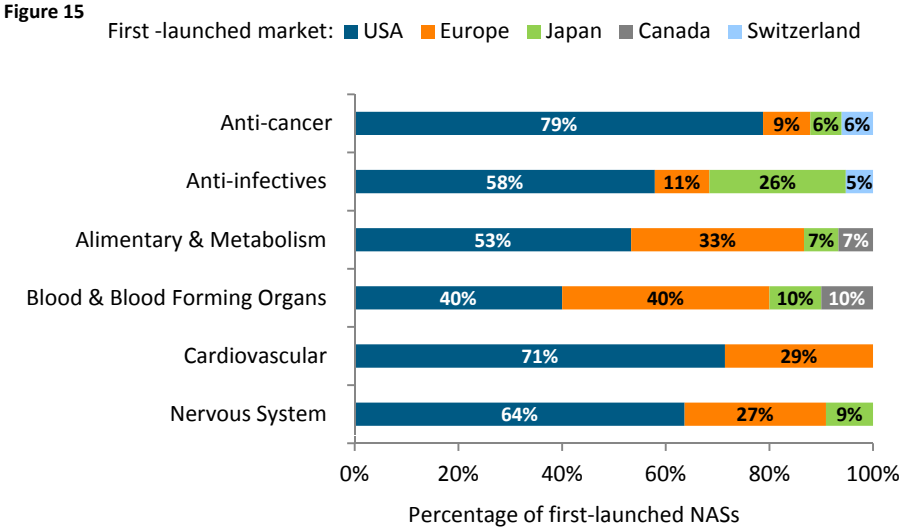


Figure 15. A comparison of first-launched market by six therapeutic areas.

Forty-seven first-launched NASs available at all six jurisdictions

For the cohort of 47 NASs approved in all six jurisdictions, the median delay from first submission to the first country out of the six jurisdictions to the date of submission to each of the six jurisdictions was USA (0 days), Europe (31 days), Switzerland (129 days), Australia (154 days), Canada (201 days) and Japan (825 days). The fastest median approval times were seen at the FDA (273 days), compared with the longest times at Swissmedic (485 days; Figure 16).

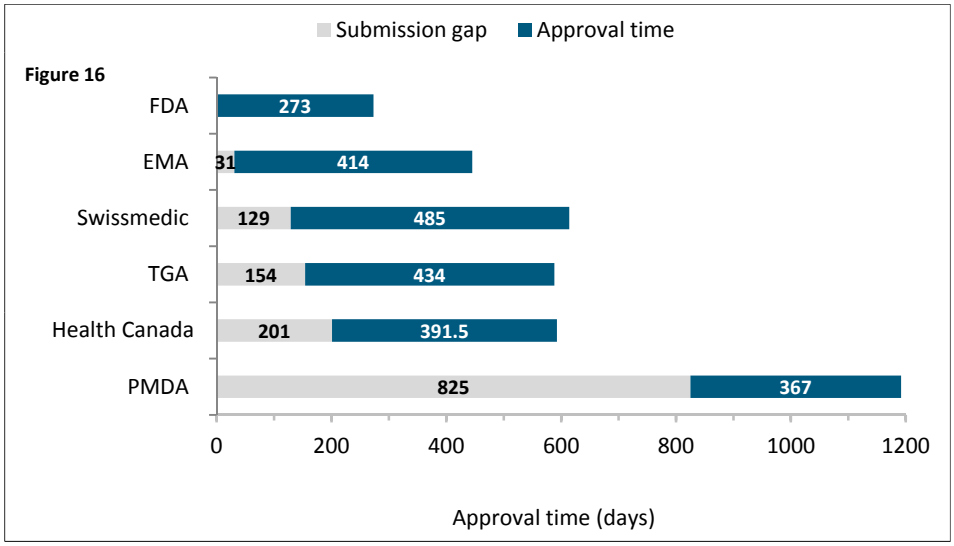


Figure 16. Regulatory agency review time for 47 NASs approved by all six jurisdictions.

For the cohort of 47 NASs, the median time for a product to be approved in all countries (time taken from submission to the first market to the date of approval in the last market) was around 4 years. The median time was longer (5.6 years) for non-top companies, compared with top companies (3.8 years; Figure 17).

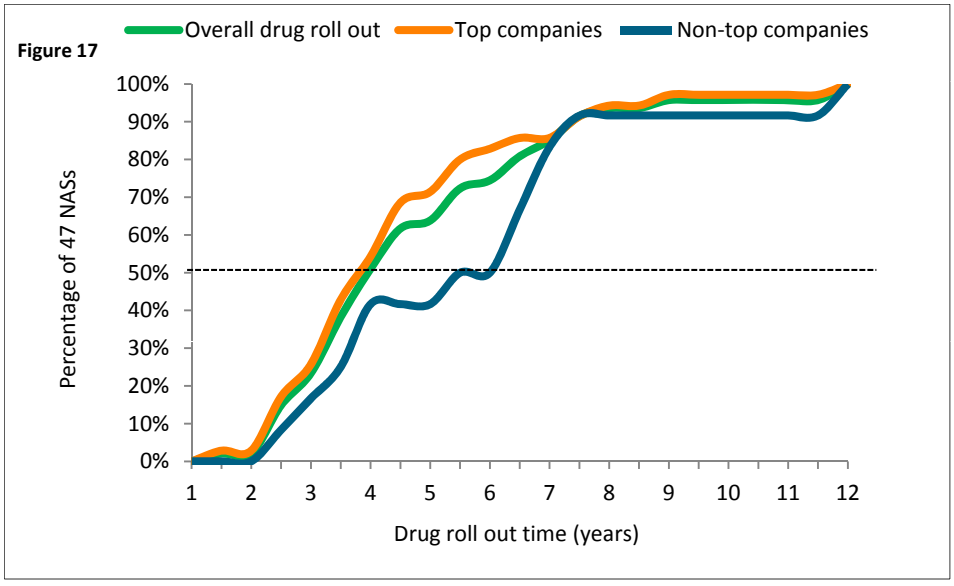


Figure 17. Drug roll out time to all six markets by the size of company.

USA Profile

Figure 18 illustrates the number of first-launched products approved in the USA by company size and therapeutic area.

Figure 18

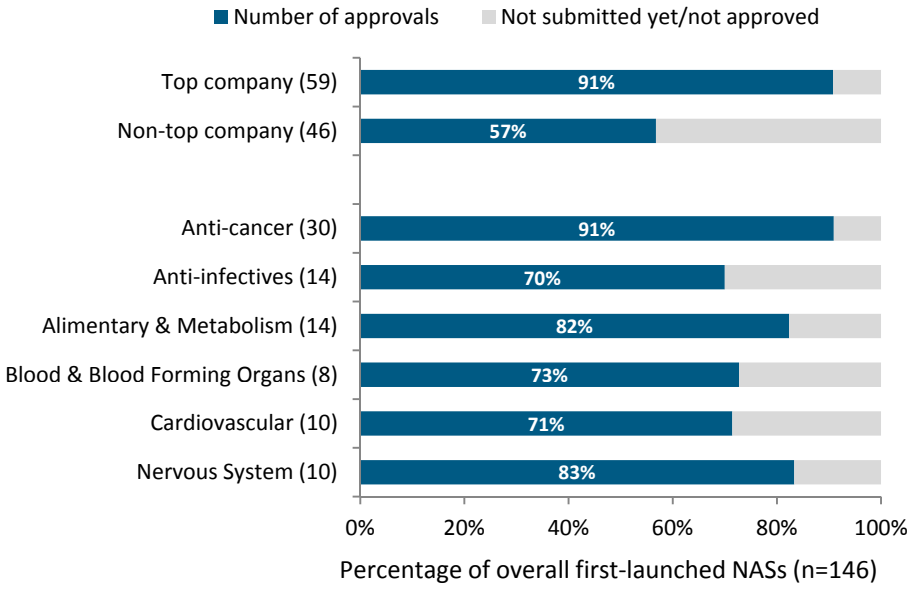


Figure 18. Number of first-launched NASs approved in USA (n=105).

Figure 19 shows the FDA median review time, breaking down FDA review type, company size and therapeutic area.

Figure 19

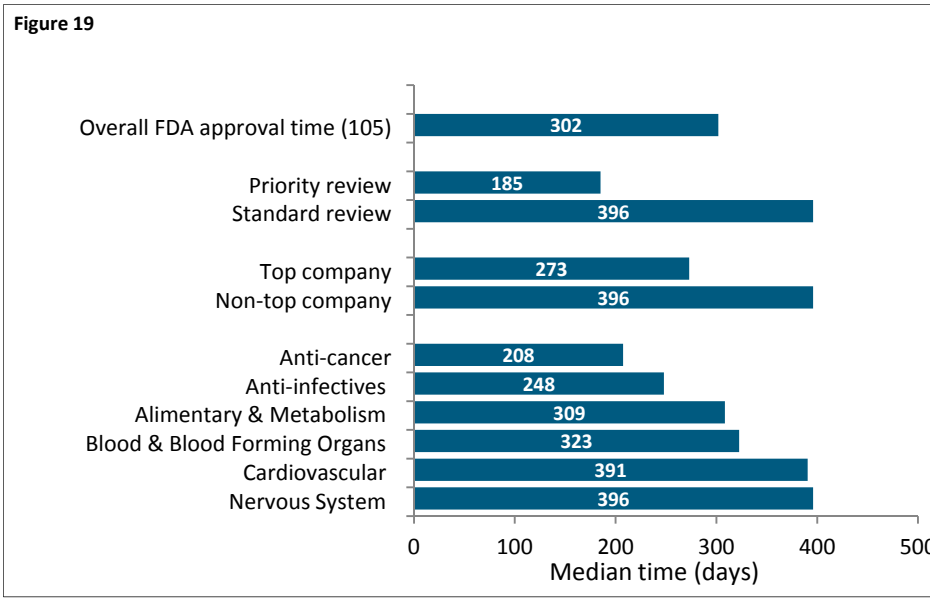


Figure 19. Timeline analysis of NASs approved by FDA (n=105).

EU Profile

Figure 20 illustrates the number of first-launched products approved in the EU by company size and therapeutic area.

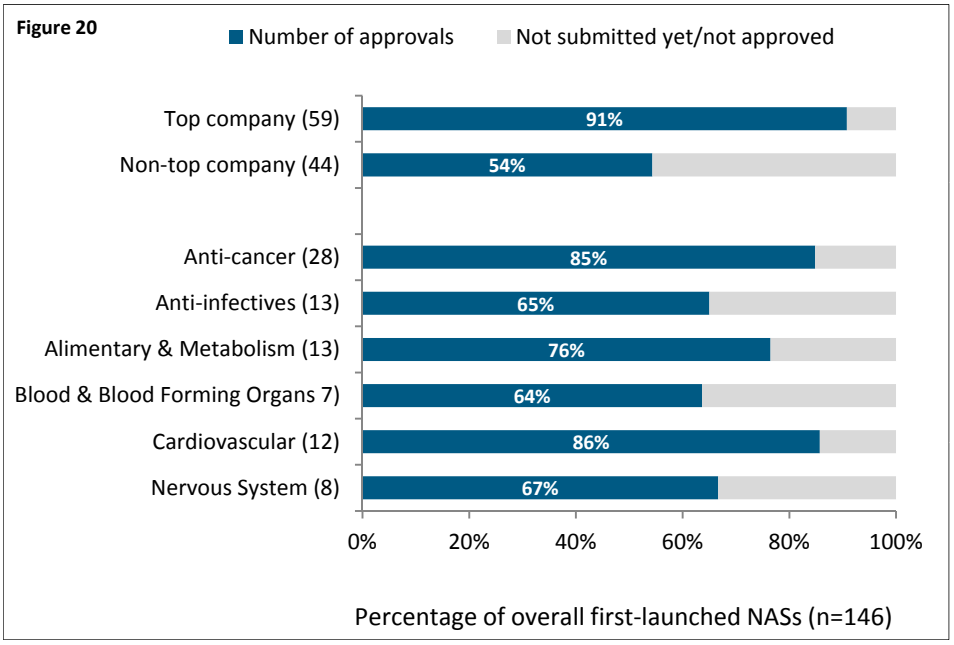


Figure 20. Number of first-launched NASs approved in EU (n=103).

Figure 21 shows the EMA median review time, breaking down company size and therapeutic area. The submission gap was analysed as time taken from submission to the first regulatory agency in the six jurisdictions to the date of regulatory submission to EMA.

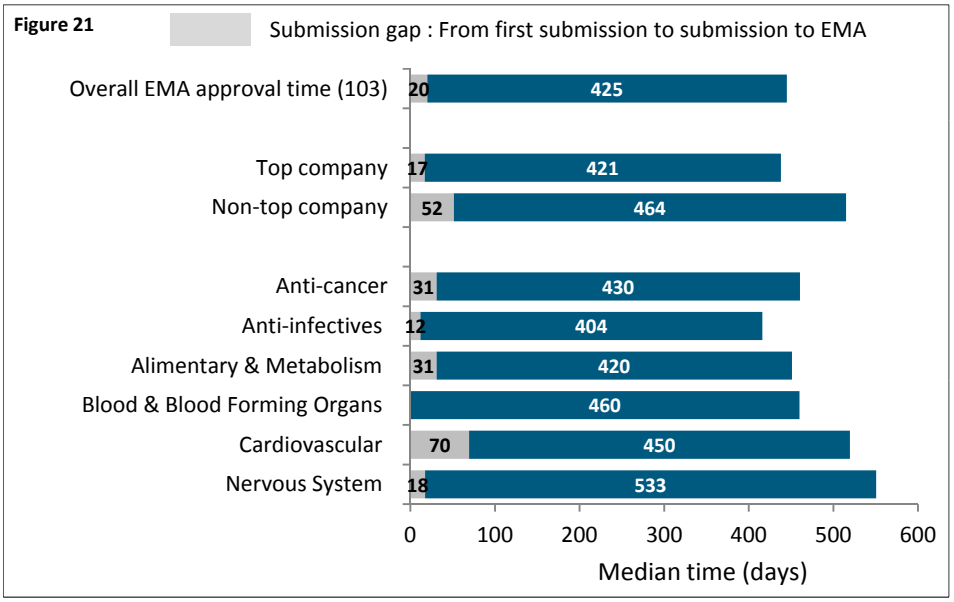


Figure 21. Timeline analysis of NASs approved by EMA (n=103).

Japan Profile

Figure 22 illustrates the number of first-launched products approved in Japan by company size and therapeutic area.

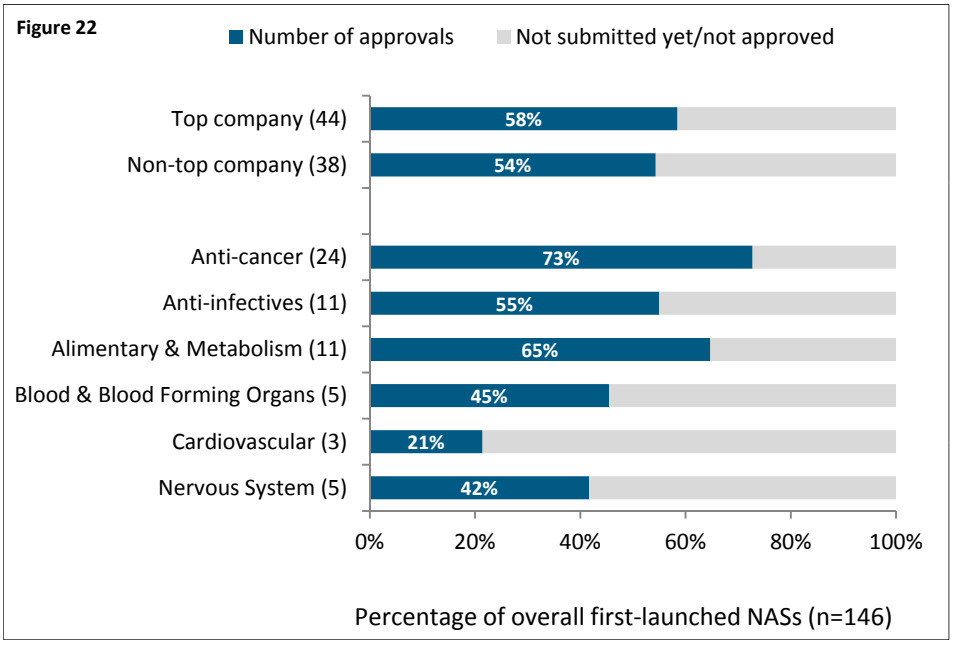


Figure 22. Number of first-launched NASs approved in Japan (n=82).

Figure 23 shows the PMDA median review time, breaking down company size and therapeutic area. The submission gap was analysed as time taken from submission to the first regulatory agency in the six jurisdictions to the date of regulatory submission to PMDA.

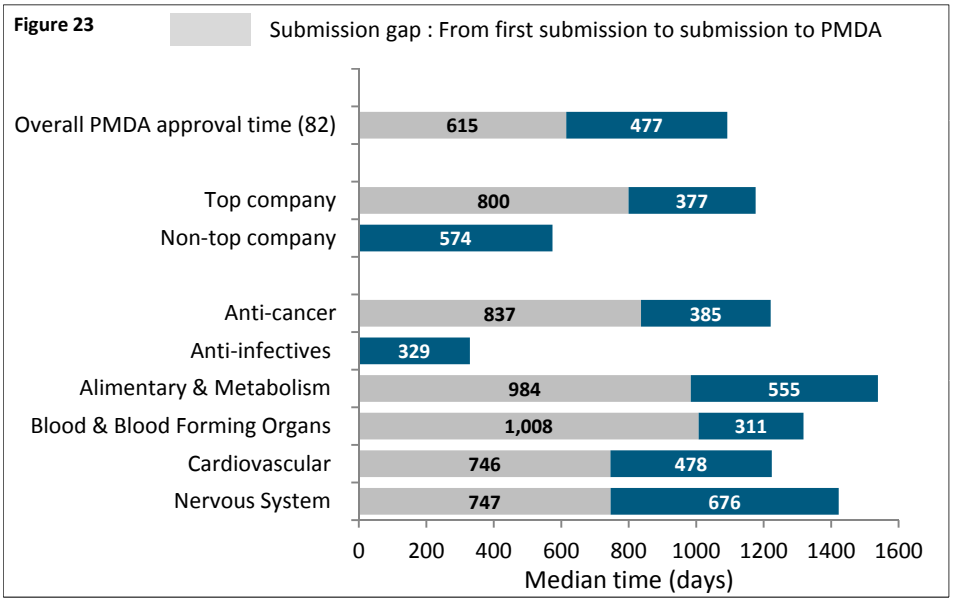


Figure 23. Timeline analysis of NASs approved by PMDA (n=82).

Canada Profile

Figure 24 illustrates the number of first-launched products approved in Canada by company size and therapeutic area.

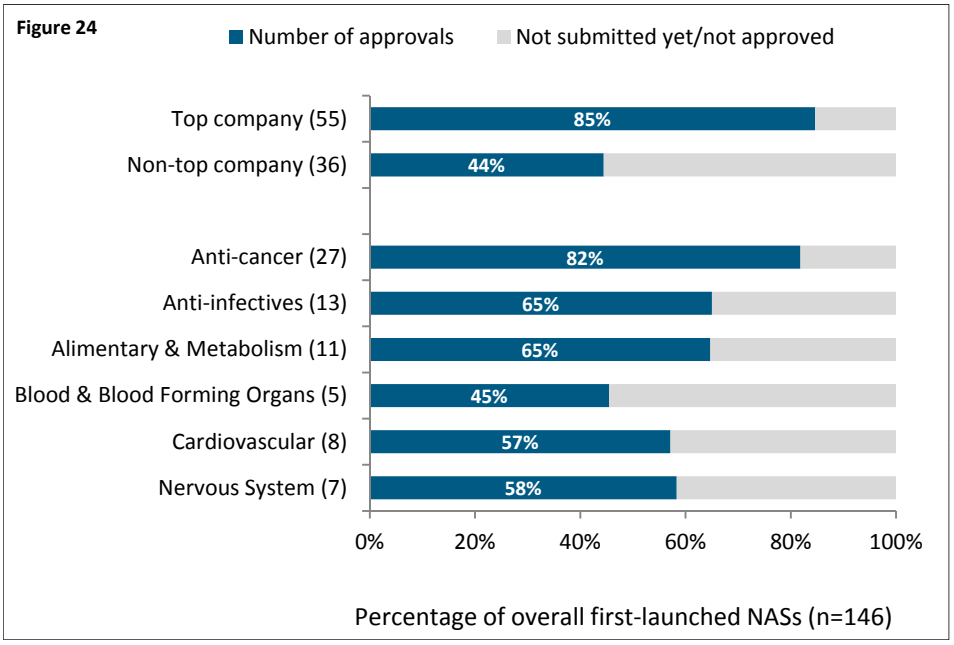


Figure 24. Number of first-launched NASs approved in Canada (n=91).

Figure 25 shows the Health Canada median review time, breaking down company size and therapeutic area. The submission gap was analysed as time taken from submission to the first regulatory agency in the six jurisdictions to the date of regulatory submission to Health Canada.

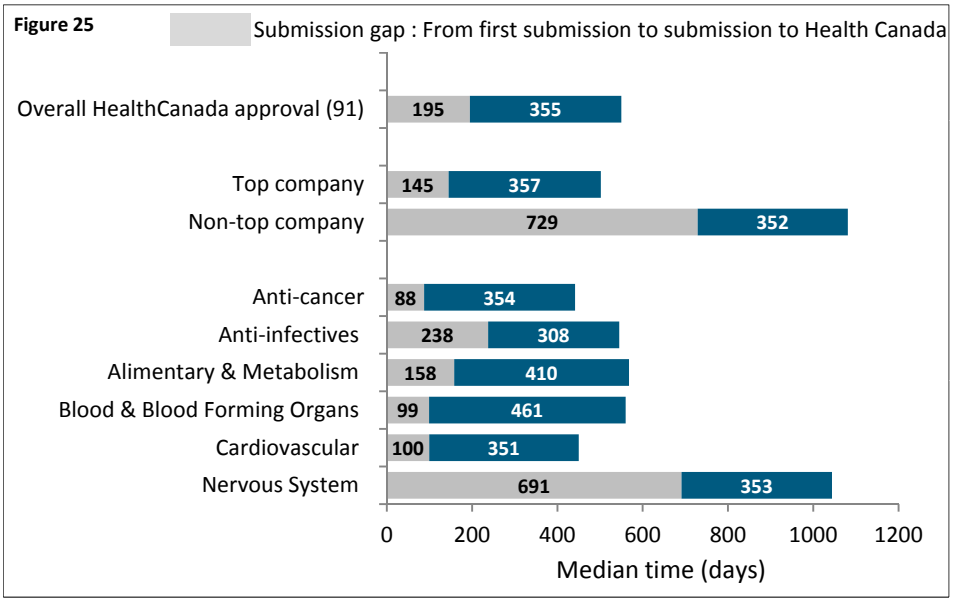


Figure 25. Timeline analysis of NASs approved by Health Canada (n=91).

Switzerland Profile

Figure 26 illustrates the number of first-launched products approved in Switzerland by company size and therapeutic area.

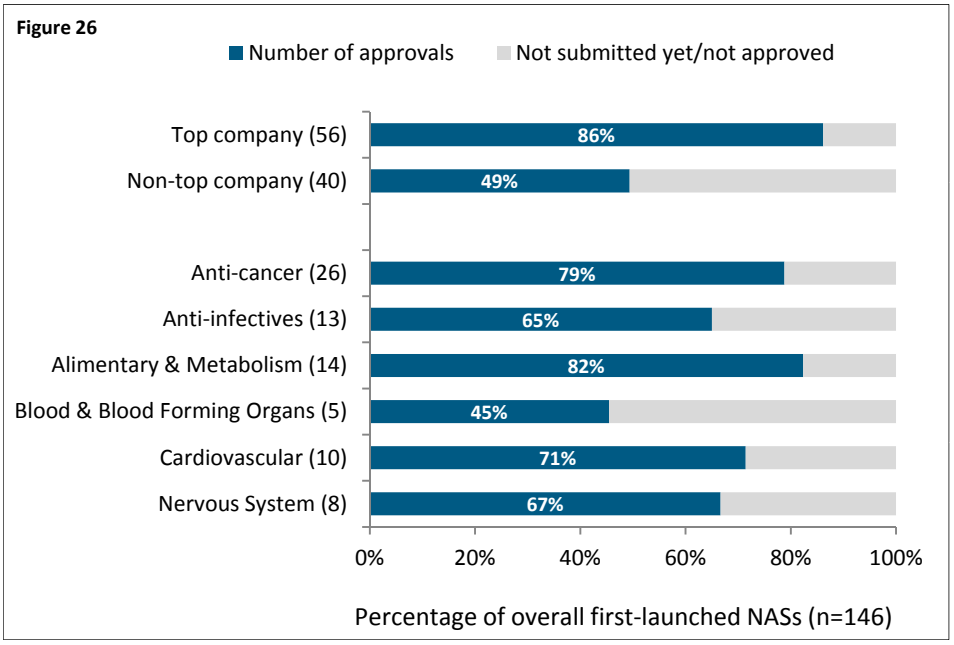


Figure 26. Number of first-launched NASs approved in Switzerland (n=96)

Figure 27 shows the Swissmedic median review time, breaking down company size and therapeutic area. The submission gap was analysed as time taken from submission to the first regulatory agency in the six jurisdictions to the date of regulatory submission to Swissmedic.

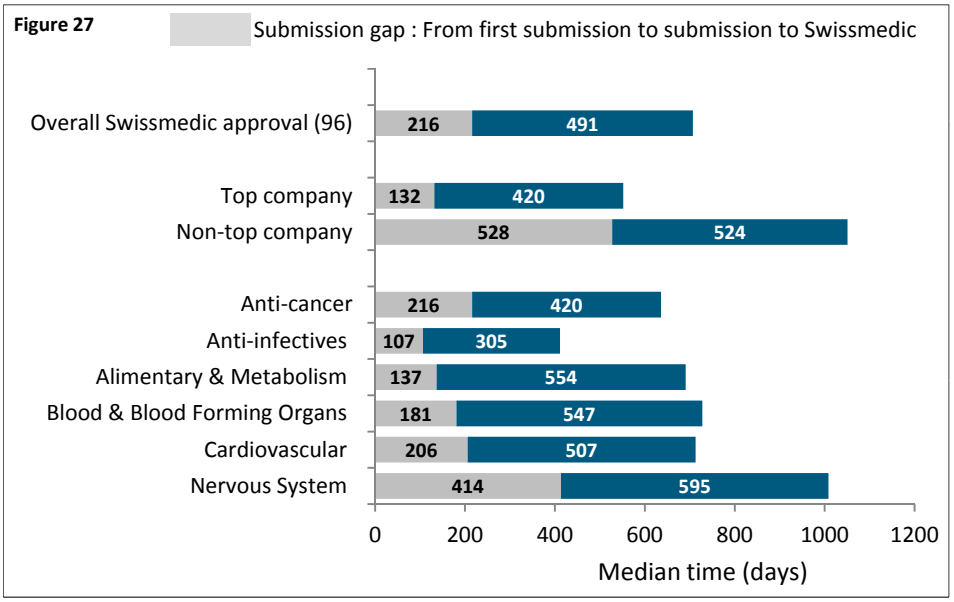


Figure 27. Timeline analysis of NASs approved by Swissmedic (n=96).

Australia Profile

Figure 28 illustrates the number of first-launched products approved in Australia by company size and therapeutic area.

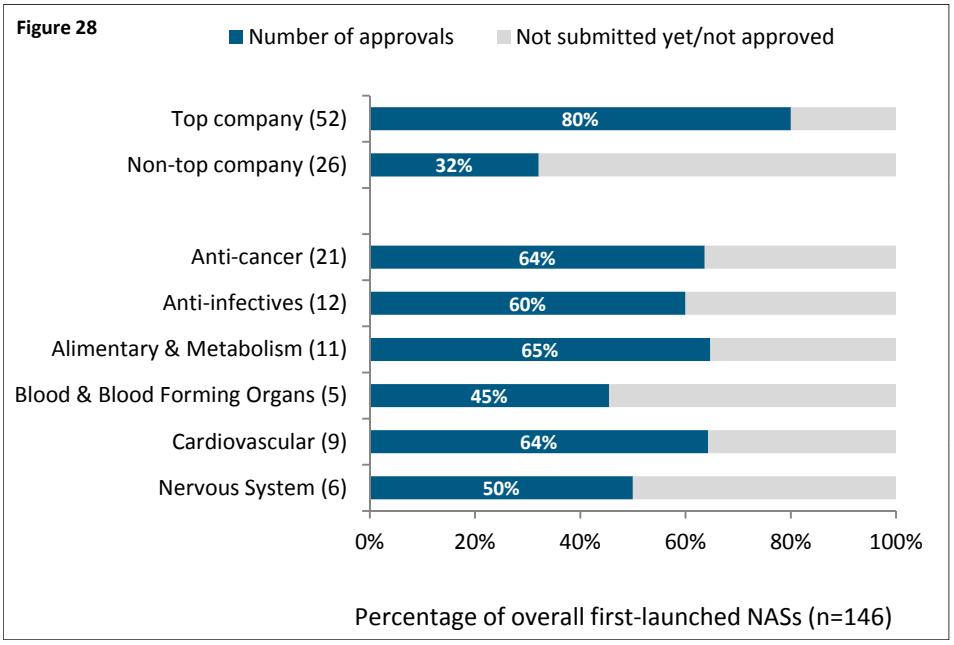


Figure 28. Number of first-launched NASs approved in Australia.

Figure 29 showed the TGA median review time, breaking down company size and therapeutic area. Submission gap is analyzed as time taken from submission to the first regulatory agency in the six jurisdictions to the date of regulatory submission to TGA

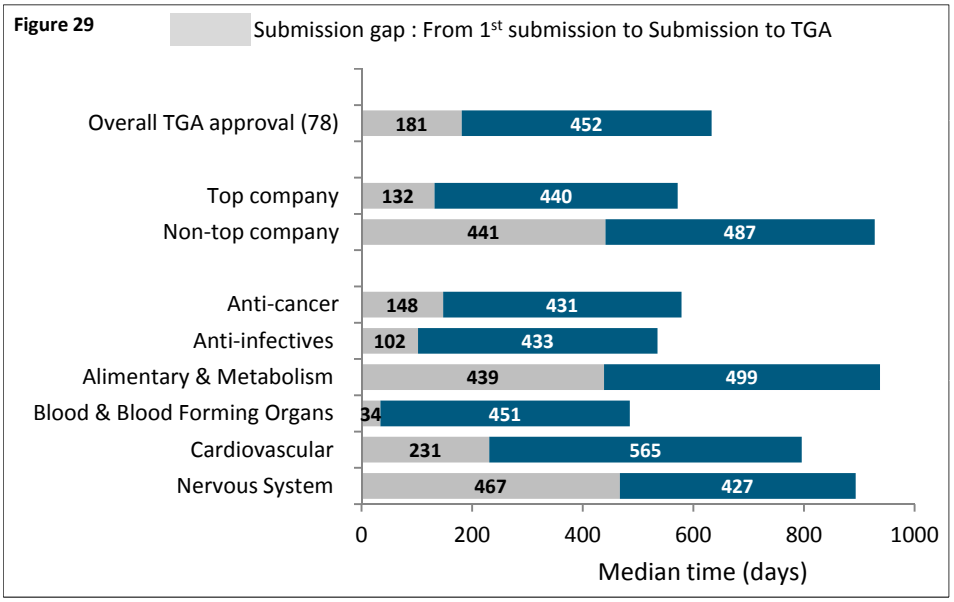


Figure 29. Timeline analysis of NASs approved by TGA (n=78).

Conclusions

Only 47 (32%) of new medicines first launched between 2005-2010 were licensed across all six jurisdictions in the study by the end of 2012 and the median time for a product to be approved in all countries was around 4 years.

A number of factors can influence both the number of products licensed and the time it takes to achieve licensing across these jurisdictions. These include the therapy area, with anti-cancer making up only 22% of the total numbers first launched but 38% of the cohort of medicines found in all six jurisdictions. Timing to the point of achieving a regulatory approval can be influenced by not only the company strategy in terms of submission timing, which can be driven by market size, need for new data to be generate for the jurisdiction, but also by the time it takes the agencies to review a new medicine.

This study reflects these factors in that the US has both the greatest number of first launches and also the most rapid approval times; overall, medicines were licensed 172 days earlier in the USA than in the EU.

In terms of roll out time to the last market, Japan was the market with the longest time to submission by about 600 days, suggesting the need for a different development strategy for this market.

However, results from this study indicate that the key influencer for submission and management of a regulatory dossier for a new medicine across these six markets relates to the size of the company. Companies with large R&D budgets are more likely to have the resources to undertake the submission of dossiers and to support their review in multiple jurisdictions.

These findings suggest that smaller companies should investigate mechanisms to supplement their ability to offer their products for assessment in multiple jurisdictions, thereby finding opportunities for their novel products to quickly reach patients.

References

1. Hirako M, McAuslane N, Salek S, Anderson C, Walker S. A Comparison of the Drug Review Process at Five International Regulatory Agencies. *Drug Info J*.2007; 41:291–308.

2. McAuslane N, Anderson C, Walker S. *The Changing Regulatory Environment: Reality and Perception. Epsom, UK: CMR International; 2004. R&D Briefing 42.* Available at http://213.120.141.158/node/73. Accessed February 2014.

R&D Briefing 53 Availability of new medicines

Report prepared by:

Tina Wang, MSc, Portfolio Manager, HTA Programme

Neil McAuslane, PhD, Director, CIRS

Acknowledgements

We are most grateful to Magdalena Bujar (CIRS) for extracting first-launched datasets that we have used in order to generate the analyses.

CIRS – The Centre for Innovation in Regulatory Science – is a neutral, independent UK-based subsidiary company, forming part of the Intellectual Property and Science business of Thomson Reuters.

The mission of CIRS is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science. It is governed and operated for the sole support of its members' activities.

The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities and grants.

Centre for Innovation in Regulatory Science (CIRS)
The Johnson Building, 77 Hatton Garden
London
EC1N 8JS
UK

Email: cirs@cirsci.org
Website: www.cirsci.org

CIRS Centre for Innovation in Regulatory Science