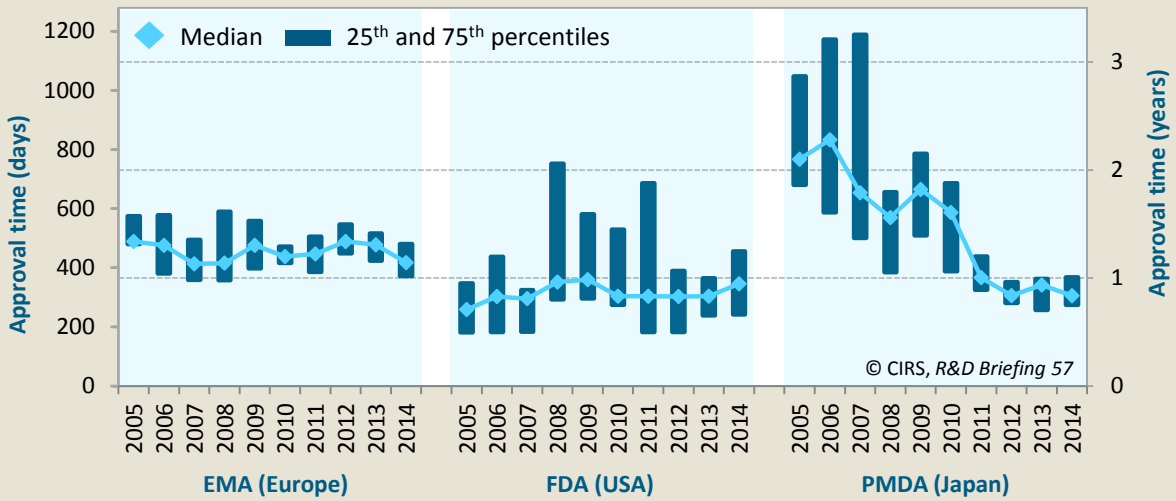
New drug approvals in ICH countries 2005 – 2014

Focus on facilitated regulatory pathways and orphan designations



***Note**: The EMA approval time includes the EU Commission time.*

Contents

Key points

There have been **major improvements** in the regulatory environment in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (**ICH) countries over the last decade,** which have lead to a **decrease in the time it takes to bring new drugs to market as well as an increase in the number of medicines that become available**. Furthermore, the introduction, formalisation and wider use of **diverse regulatory pathways and designations have played a major role in this process**, particularly for medicines developed in response to unmet medical need.

As part of an ongoing study to monitor regulatory performance, **CIRS has analysed the trends in new medicines' approval between 2005 and 2014 by three regulatory authorities;** the US Food and Drug Authority **(FDA),** the European Medicines Agency **(EMA)** and the Japanese Pharmaceuticals and Medical Devices Agency **(PMDA), focusing on the use of:**

- **Facilitated regulatory pathways (FRP).** FRPs for the purposes of this briefing specifically **include:**
  - ❖ **Expedited review** to accelerate regulatory assessment**:** in this report refers to **EMA Accelerated Assessment, FDA Priority Review, PMDA Priority Review**
  - ❖ **Other pathways** to enable the availability, review and/or approval of medicines; in this report include **EMA Conditional Approval, EMA Exceptional Circumstances, FDA Fast Track, FDA Breakthrough Therapy, FDA Accelerated Approval**
- **Orphan designations** within each of the three agencies

Key findings from this Briefing

- In 2014, the highest number of NASs were approved in a decade, with PMDA approving the greatest number of NASs out of the three ICH agencies (Fig. 1) . FDA and PMDA NAS median approval times converged in 2005-2014, with PMDA the fastest in 2014 (Fig. 2).
- Expedited reviews (EMA Accelerated Assessment and FDA/PMDA Priority Reviews) made up 58% and 50% of all NAS approvals at FDA and PMDA in 2014, and 13% at EMA (Fig. 3). Despite differences in the use of expedited review, median approval times for these reviews were similar across the ICH agencies in 2014 (Fig. 4).
- For all NASs approved by each agency in 2014, FDA had the highest percentage of first-in-ICH approvals compared with EMA and PMDA (Fig. 5).
- In 2014, a record number of orphan NASs were approved in a decade in all three ICH countries (Fig. 6). Expedited review was used for 14%, 69% and 100% of orphan NASs respectively at EMA, FDA and PMDA between 2010-2014 (Fig. 7). Over the decade, the median approval times for orphan medicines were consistently quicker than non-orphans at FDA and PMDA whilst at EMA there was very little difference between the two groups (Fig. 8).
- For FDA and PMDA, anti-cancer and immunomodulator NASs made up the largest proportion of expedited reviews compared with anti-infective NASs for EMA in 2010-2014 (Fig. 10).
- During 2010-2014, there were 35 NAS common approvals amongst the three ICH agencies, but the submission gap, as well as the approval type and speed varied across the agencies (Fig. 13 and Fig. 14). Of the 35 common approvals, nine were approved in 2013-2014 (where the last ICH agency granted approval in 2014). Five of the products were assigned an expedited review by FDA, of which four were also assigned expedited by PMDA, and one by EMA, although this assignment was reverted back to a standard review during the review process. This points to the criteria or the process limits of the use of this FRP within the EMA approval system (Fig. 15).
- The 2014 decrease in the overall median approval time for EMA was driven largely by the decrease in company response time (Fig. 16). In 2010-2014, 35% of approved NASs (41/117) benefited from at least one of the three FRPs or an orphan designation at EMA to facilitate the availability, review and/or approval of medicines (Fig. 18).
- The number of the FDA Center for Drug Evaluation and Research (CDER) NASs approved after one cycle has increased from 68% to 76% from 2005-2009 to 2010-2014 (Fig. 19). The proportion of one-cycle reviews was higher for expedited compared with standard reviews 2010-2014 (Fig. 20). In 2010-2014, of the three agencies, FDA used the greatest number of FRPs to facilitate the availability, review and/or approval of medicines where there is an unmet medical need; 62% of NASs (101/164) benefitted from at least one of the four FRPs or an orphan designation at FDA (Fig.21).
- The submission gap to Japan sharply decreased 2010-2014 although the submission gap increased by 2.5 times in 2014 compared with 2013 (Fig. 22). This appears to be related to company origin as well as review type, with orphan NASs from non-Japanese companies having experienced the longest submission gap in 2014 (Fig. 23-25). In addition, a number of products approved in Japan in 2014 were legacy products whose availability to Japanese patients was facilitated through government programmes.

Overview of ICH agencies' approvals

In 2014, the highest number of NASs were approved in a decade, with PMDA approving the greatest number of NASs out of the three ICH agencies (Fig. 1)

Following a 2013 drop in approval numbers, 2014 marked a record year in the decade 2005-2014 for FDA and PMDA , with the agencies having approved 55% and 86% more NASs respectively compared with 2013. However, although PMDA approved more NASs than FDA in 2014, 63% of these compounds had been approved by the FDA or EMA previously (Figure 5).

FDA and PMDA approvals increased from 2005-2009 to 2010-2014 by 40% and 36%. EMA numbers were consistent over the decade, but lower than FDA's. A number of NASs that were approved by FDA in 2014 are still being reviewed by EMA or have been approved in 2015.

FDA and PMDA NAS median approval times converged in 2005-2014, with PMDA the fastest in 2014 (Fig. 2).

Although Japan historically had the longest regulatory approval times, this has decreased following the creation of PMDA, and with its increase in resource and commitment PMDA review timing is now equivalent to FDA.

In 2014, the FDA overall median approval times increased for the first time in five years (by about 40 days) which is likely due to the process changes introduced under the Prescription Drug User Fee Act (PDUFA) V legislation. Europe, within the confines of its legislative approval procedures and processes, has had the slowest approval times out of the three countries since 2011. Nevertheless, in 2014, EMA approval times were one of its shortest in a decade.

Figure 1: Number of NASs approved by ICH agencies by approval year

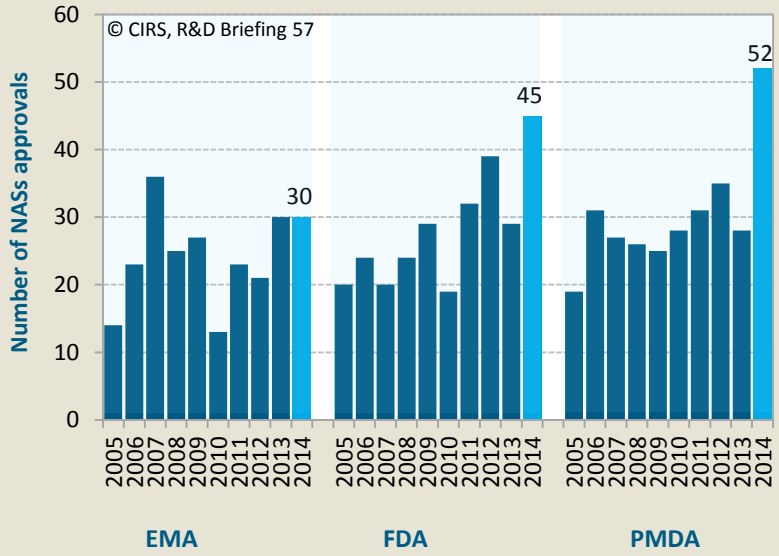
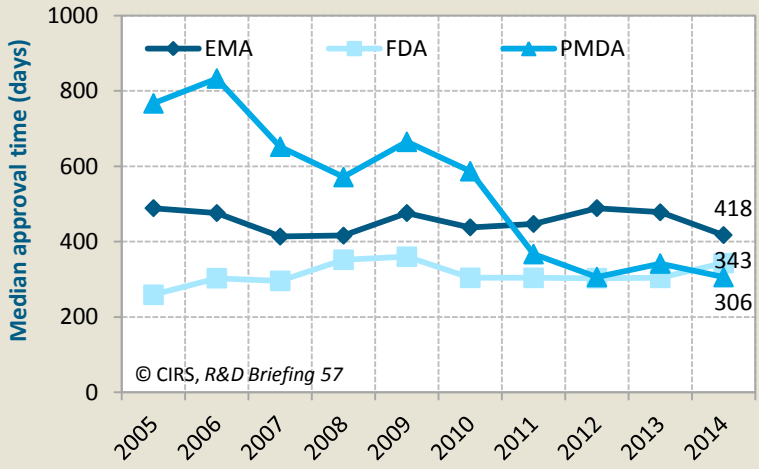


Figure 2: Median approval time for NASs approved by ICH agencies by approval year



***Note**: The EMA approval time includes the EU Commission time*

ICH approvals – Review type

Expedited reviews (EMA Accelerated Assessment and FDA/PMDA Priority Reviews) made up 58% and 50% of all NAS approvals at FDA and PMDA in 2014, and 13% at EMA (Fig. 3)

The expedited review FRP played an important role in FDA and PMDA in accelerating the approval of innovative medicines over the last decade. The proportion of expedited reviews was consistent throughout the decade for FDA at around 47%, but PMDA doubled its proportion of expedited NASs during this time. This relates mainly to a change at PMDA, enabling the use of an expedited process for NASs to meet the needs of Japanese patients.

The limited use of the EMA expedited review suggests that either the criteria for expedited review are much stricter for EMA than FDA and PMDA or that aspects of the process limit its use by companies or its designation by the agency. Indeed, in 2014, three NASs which had been originally designated for expedited review, were reverted during the process back to standard.

Despite differences in the use of expedited review, median approval times for these reviews were similar across the ICH agencies in 2014 (Fig. 4).

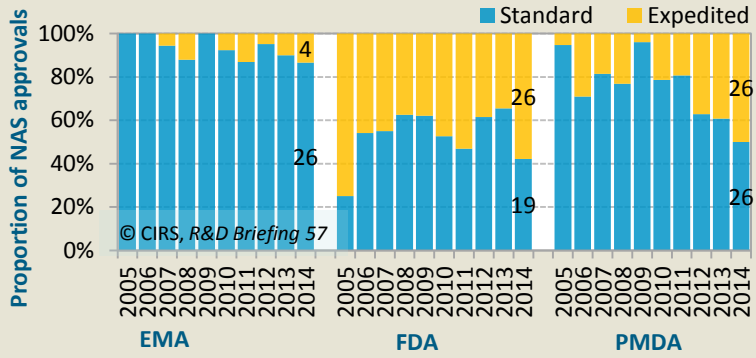
Although the number of EMA expedited NASs was considerably lower than those of FDA and PMDA, the 2014 expedited approval times for EMA were similar to expedited times at the other two agencies, emphasising that the EMA expedited review meets the goal of decreasing approval time, but is not used as frequently.

When comparing the difference in median approval times, since 2012, there was an increase of about 150 days in the standard review of NASs at FDA compared with an increase of around 60 days for expedited reviews, which may in part be due to an additional two-month period added to the review timeline under PDUFA V.

For all NASs approved by each agency in 2014, FDA had the highest percentage of first-in-ICH approvals compared with EMA and PMDA (Fig. 5).

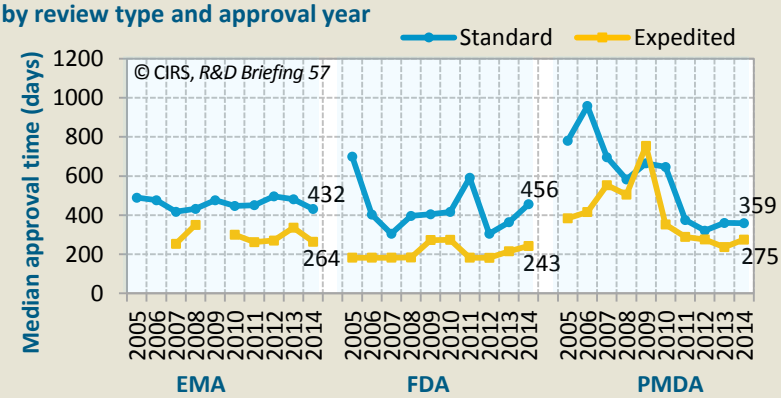
In 2014, 78% of FDA approvals were NASs that were approved first across the three ICH agencies, compared with 30% and 37% at EMA and PMDA.* For FDA, the first-in-ICH approvals consisted of a larger proportion of expedited reviews compared with compounds that were not first-in-ICH, but the opposite was true for EMA and PMDA.

Figure 3: Proportion of NASs approved by ICH agencies by review type and approval year



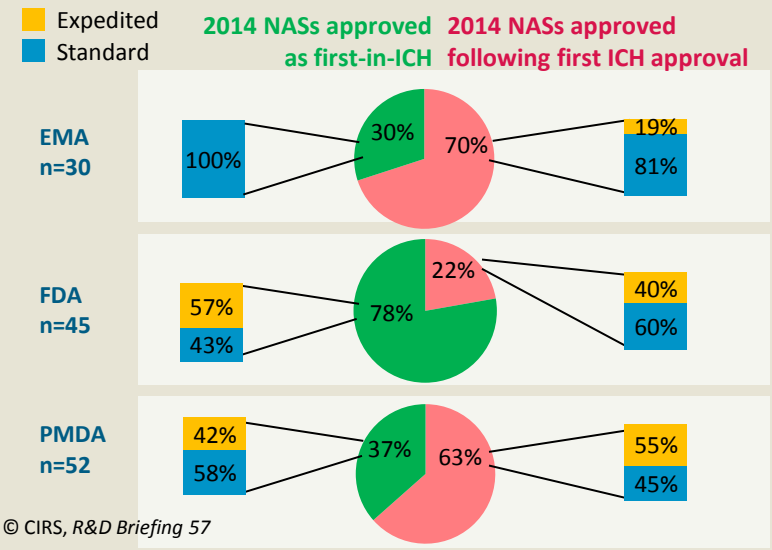
Note: *Expedited review refers to EMA Accelerated Assessment and FDA/PMDA Priority Review*

Figure 4: Median approval time for NASs approved by ICH agencies by review type and approval year



Note: *Expedited review refers to EMA Accelerated Assessment and FDA/PMDA Priority Review*

Figure 5: Approval timing in ICH agencies for NASs approved by each agency in 2014 by review type*



Note: *Expedited review refers to EMA Accelerated Assessment and FDA/PMDA Priority Review*
**Please note that this analysis included products which have only been approved by one agency and may not have been intended to be submitted to another ICH agency.*

ICH approvals – Orphan status

In 2014, a record number of orphan NASs were approved in a decade in all three ICH countries (Fig. 6)

Orphan NASs approvals constituted 43%, 47% and 37% of all NAS approvals in 2014 for EMA, FDA and PMDA respectively. Nevertheless, when comparing 2005-2009 to 2010-2015, the proportion of orphan NASs has remained relatively constant, having decreased by 5% at EMA and increased at both FDA and PMDA by 5% and 2% respectively. More time is needed to see whether the exceptionally high number of orphan approvals in 2014 compared to prior year was just a one-off occurrence or a long-term trend towards increasing numbers of orphan medicines.

Expedited review was used for 14%, 69% and 100% of orphan NASs respectively at EMA, FDA and PMDA between 2010-2014 (Fig. 7).

In addition to the expedited review of orphan NASs, the wider usage of other FRPs (exceptional circumstances and conditional approval for EMA; fast track, accelerated approval and breakthrough for FDA), has also contributed to the availability of orphan drugs for patients with no other treatment options.

Looking at all FRPs available at each agency between 2010-2014, 43% of orphan NASs benefited from at least one of the three FRPs available at EMA compared with 17% non-orphans (Fig. 17). For FDA, 85% of orphans benefited from at least one of the four FRPs compared with 39% non-orphans (Fig.20). For PMDA, all orphans automatically undergo expedited review.

Over the decade, the median approval times for orphan medicines were consistently quicker than non-orphans at FDA and PMDA whilst at EMA there was very little difference between the two groups (Fig. 8)

The 2014 median approval times for orphan drugs compared with non-orphans was shorter by 46 and 73 days for FDA and PMDA respectively. This is likely related to the wide usage of expedited reviews for orphan NASs at the two agencies. For EMA, orphans were 60 days slower to approve than non-orphans in 2014.

Figure 6: Proportion of NASs approved by ICH agencies by orphan status and approval year

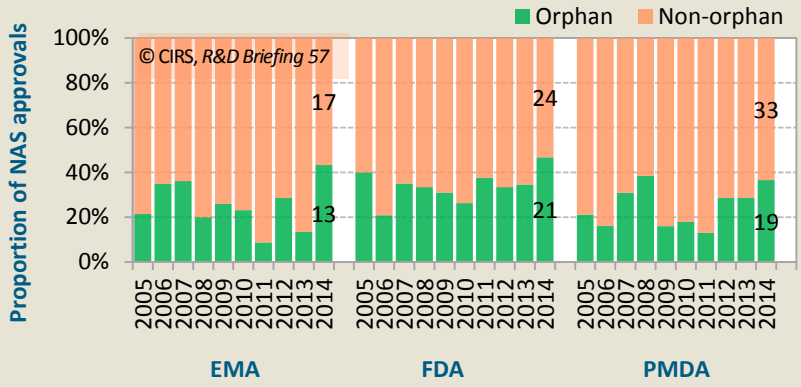
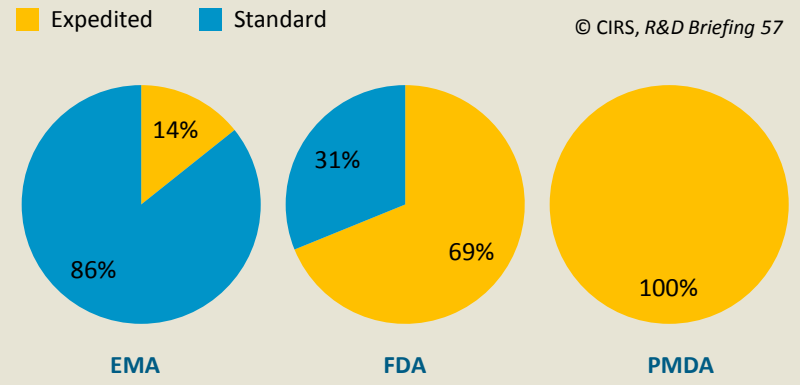
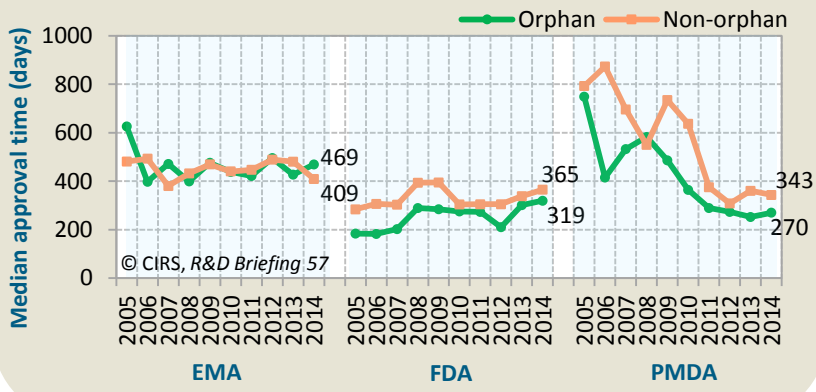


Figure 7: Proportion of orphan NASs by review type for approval period 2010-2014



***Note**: Expedited review refers to EMA Accelerated Assessment and FDA/PMDA Priority Review*

Figure 8: Median approval time for NASs approved by ICH agencies by orphan status by approval year



ICH approvals – Therapeutic area

Figure 9: Proportion of NASs approved by ICH agencies by therapeutic area and year of approval

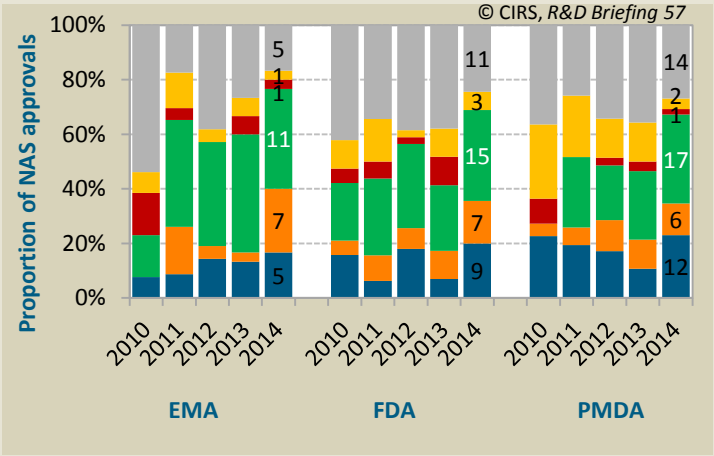
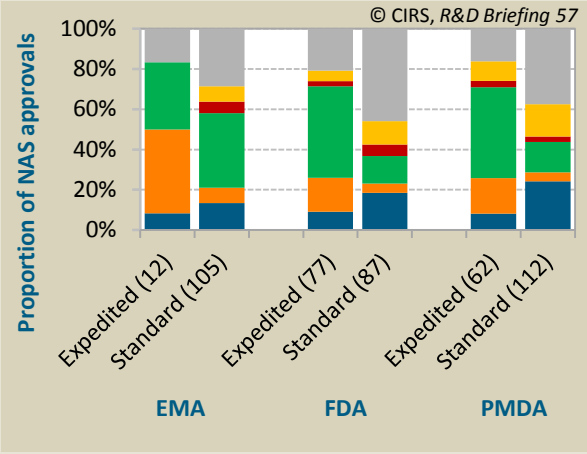


Figure 10: Proportion of NASs approved by ICH agencies by therapeutic area and review type for approval period 2010-2014



For FDA and PMDA, anti-cancer and immunomodulator NASs made up the largest proportion of expedited reviews compared with anti-infective NASs for EMA in 2010-2014 (Fig. 10).

Alimentary and metabolism, anti-infective, and anti-cancer and immunomodulator therapy areas had the greatest number of NAS approvals in 2014 (Fig. 9). In terms of review type, the expedited vs. standard patterns by therapeutic area looked almost identical when comparing FDA and PMDA. The pattern for EMA was different, with the review of only 4/43 anti-cancer NASs expedited over the last 5 years, compared with 35/47 and 28/45 for FDA and PMDA.

For FDA and PMDA, the high proportion of anti-infective and anti-cancer and immunomodulator products that underwent an expedited review was reflected in the faster median approval times when comparing therapy areas within and across agencies (Fig. 11 and Fig. 12).

Figure 11: NAS approval time by therapeutic area for approval period 2010-2014

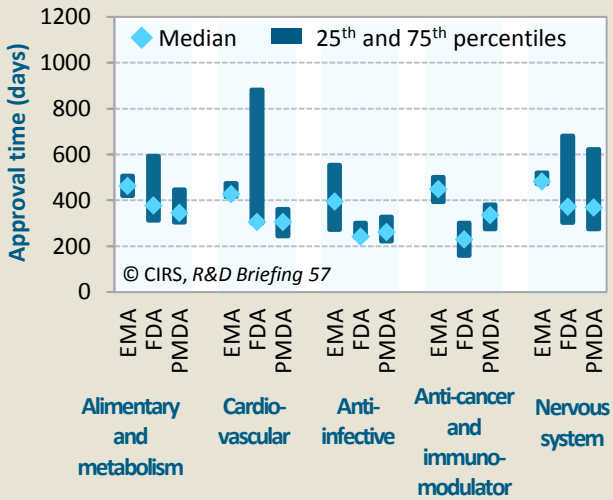


Figure 12: Median approval time (days) for NASs approved by ICH agencies in 2010-2014 by review type

© CIRS, *R&D Briefing 57*	EMA		FDA		PMDA	
	Standard	Expedited	Standard	Expedited	Standard	Expedited
Alimentary and metabolism	466	300	422	322	367	275
Cardio-vascular	428	-	306	821	361	226
Anti-infective	551	262	305	242	317	248
Anti-cancer and immuno-modulator	450	286	304	183	391	285
Nervous system	483	-	379	329	417	234

ICH approvals – Common approvals

Figure 13: Median submission gap for 35 NASs approved by all ICH agencies during approval period 2010-2014

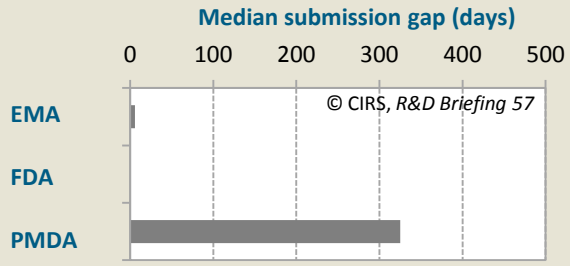
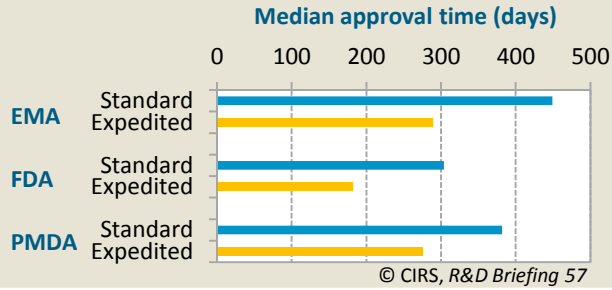


Figure 14: Median approval time for 35 NASs approved by all ICH agencies in 2010-2014 by review type



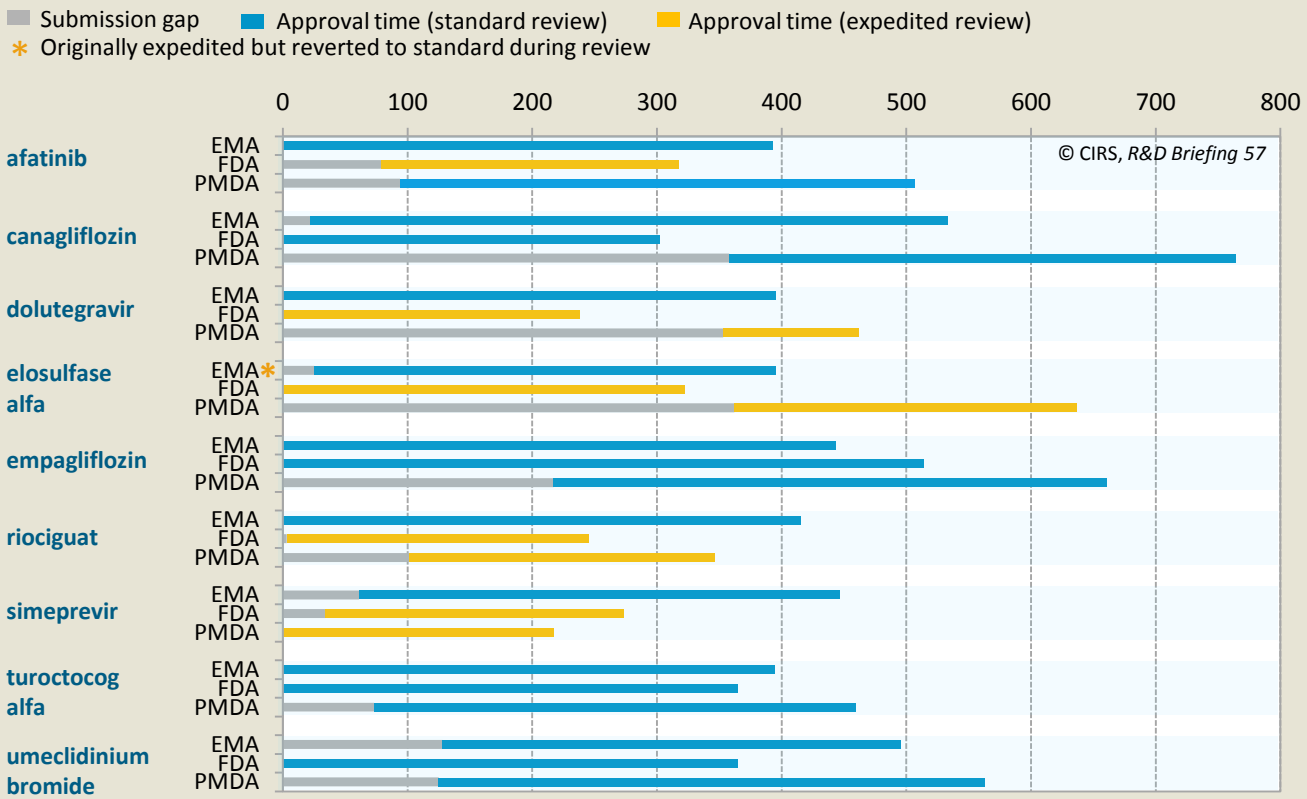
During 2010-2014, there were 35 NAS common approvals amongst the three ICH agencies, but the submission gap, as well as the approval type and speed varied across the agencies (Fig. 13 and Fig. 14).

Submission occurred more or less simultaneously at EMA and FDA, but almost a year later at PMDA. FDA was the fastest to approve the 35 NASs, followed by PMDA and EMA. Expedited reviews were used for 57%, 54% and 11% reviews at FDA, PMDA and EMA, respectively.

Of the 35 common approvals, nine were approved in 2013-2014 (where the last ICH agency granted approval in 2014). Five of the products were assigned an expedited review by FDA, of which four were also assigned expedited by PMDA, and one by EMA, although this assignment was reverted back to a standard review during the review process. This again points to the criteria or the process limits of the use of this FRP within the EMA approval system (Fig. 15).

For the nine products approved, seven were submitted to EMA and FDA more or less simultaneously (within 30 days). Although one of the nine NASs (simprevir) was submitted to Japan first, (34 days before FDA) for the remaining eight NASs , PMDA was the last agency for submission , with a median submission gap of 171 days. This suggests that a submission delay to Japan still exists, although the submission gap has decreased since approval period 2010-2011 (Fig. 22).

Figure 15: Individual compound plot for 10 NASs approved by all ICH agencies between 2013-2014, where the final ICH approval occurred in 2014



Features of the EMA approval process

Figure 16: Median time of review process for NASs approved by EMA by approval year

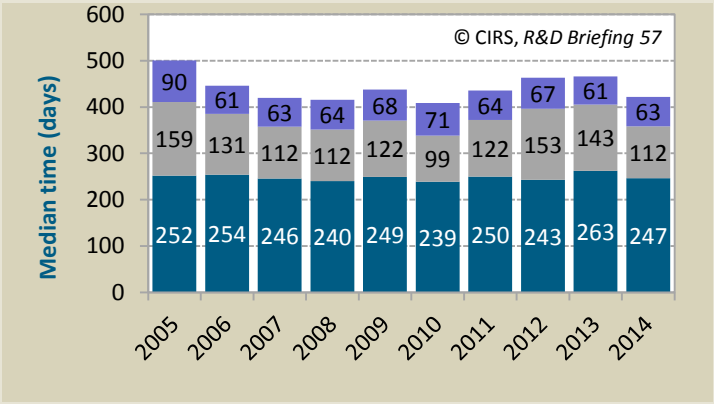
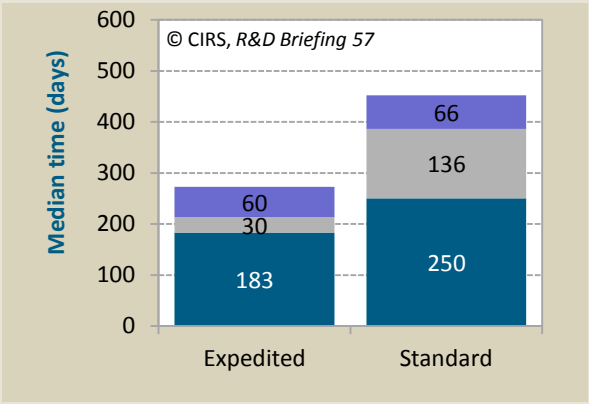


Figure 17: Median time of review process for NASs approved by EMA by review type for approval period 2010-2014



The 2014 decrease in the overall median approval time for EMA was driven largely by the decrease in company response time (Fig. 16).

The median company response time decreased by 31 days in 2014 compared with 2013; the median EMA review time decreased by 11 days and the European Commission time stayed essentially the same. When comparing these numbers for expedited vs. standard review during the approval period 2010-2014 (Fig. 17), the expedited review was characterised by 4.5x faster company response time. 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. The EMA review time was 1.4x faster for expedited review, owing to a shorter clock for CHMP opinion (150 days instead of 210 days). Nevertheless, the European Commission time was similar regardless of the type of review and presents an opportunity for possible acceleration of the European Commission time for expedited products.

In 2010-2014, 35% of approved NASs (41/117) benefited from at least one of the three FRPs or an orphan designation at EMA to facilitate the availability, review and/or approval of medicines (Fig. 18).

Besides expedited review (referring to Accelerated Assessment at EMA) there currently are two other FRPs that facilitate availability of NASs, Conditional Approval (CA) and Exceptional Circumstances (EC). However, for products designated for CA, the approval times have been around 100 days longer than the overall median time for standard EMA review, potentially because, as has been noted in the *2014 Escher Report* the route is perceived as a "rescue route" for compounds that are not able to be approved via a standard review, rather than as a "prospectively planned pathway to provide early access". The EC designation was only used in the review of two NASs 2010-2014. It is nevertheless important to note that EMA is currently exploring new routes for early availability through pilot projects.

Figure 18: EMA orphan designation and FRPs that can be used to facilitate the availability, review and/or approval of medicines for approval period 2010-2014; where n1 = median approval time (days), (n2) = number of NASs approved

© CIRS, *R&D Briefing 57*		No other FRP	Conditional Approval (CA)	Exceptional Circumstances (EC)	CA and EC
Orphan 458 (28)	**Standard** 473 (24)	452 (16)	554 (7)	476 (1)	-
	Expedited* 285 (4)	285 (4)	-	-	-
Non-orphan 453 (89)	**Standard** 459 (81)	454 (74)	547 (6)	517 (1)	-
	Expedited* 267 (8)	267 (8)	-	-	-

Note: **Expedited review refers to EMA Accelerated Assessment; The EMA approval time includes the EU Commission time.*

Features of the FDA approval process

Figure 19: Proportion of NASs approved by CDER by number of review cycles by approval year

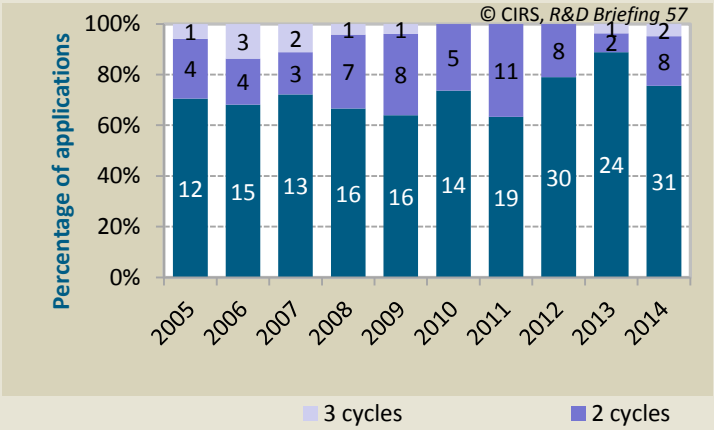
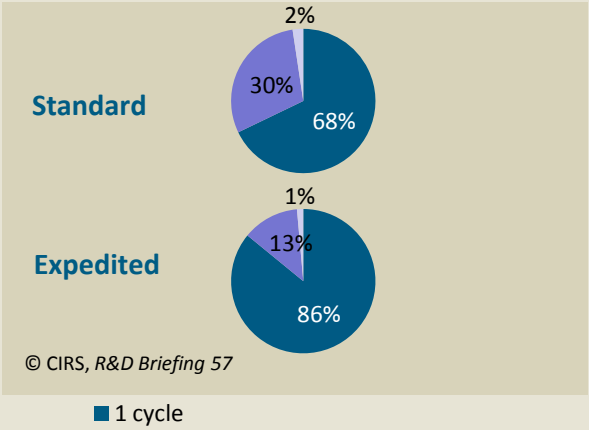


Figure 20: Proportion of NASs approved by CDER by number of review cycles and review type for approval period 2010-2014



The number of the FDA Center for Drug Evaluation and Research (CDER) NASs approved after one cycle has increased from 68% to 76% from 2005-2009 to 2010-2014 (Fig. 19).The proportion of one-cycle reviews was higher for expedited compared with standard reviews 2010-2014 (Fig. 20).

CDER has been seeking 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. 19) only includes approvals, and inclusion of compounds that have not (yet) been approved, may generate a different perspective.

In 2010-2014, of the three agencies, FDA used the greatest number of FRPs to facilitate the availability, review and/or approval of medicines where there is an unmet medical need; 62% of NASs (101/164) benefitted from at least one of the four FRPs or an orphan designation at FDA (Fig.21).

Besides expedited review (referring to FDA Priority Review), FDA offers three other FRPs; these are referred to as Fast Track designation (FT), Accelerated Approval pathway (AA), and Breakthrough Therapy designation (BT) introduced in 2012. Although FT and AA did not by themselves lead to a faster review, when used in conjunction with expedited review, these NASs benefitted from an approval which was often even faster than for NASs which only met the criteria for expedited. For example, orphan compounds which took advantage of multiple FRPs had generally faster approval times. This may be due to the fact that some of these FRPs also facilitate a more frequent and earlier agency-sponsor dialogue in development (which may result in less questions asked later at the review stage) as well as offer the possibility for a rolling submission.

Figure 21: FDA orphan designation and FRPs that can be used to facilitate the availability, review and/or approval of medicines for approval period 2010-2014; where n1 = median approval time (days), (n2) = number of NASs approved

© CIRS, *R&D Briefing 57*		No other FRP	Fast Track (FT)	Breakthrough Therapy (BT)	Accelerated Approval (AA)	FT and AA	FT and BT	BT and AA	FT and AA and BT
Orphan 292 (61)	**Standard** 306 (19)	306 (9)	455 (5)	-	622 (2)	304 (3)	-	-	-
	Expedited* 237 (42)	275 (9)	257 (16)	193 (1)	319 (1)	182 (7)	986** (2)	126 (3)	145 (3)
Non-orphan 338 (103)	**Standard** 380 (68)	387 (63)	361 (5)	-	-	-	-	-	-
	Expedited* 238 (35)	230 (17)	238 (15)	-	-	-	242 (3)	-	-

Note: **Expedited review refers to FDA Priority Review*
***One of the compounds (pirifenidone) required additional clinical data and underwent 3 review cycles, which have been captured when calculating approval time*

Features of the PMDA approval process

Figure 22: Submission gap* and approval time for NASs approved in Japan by year of approval

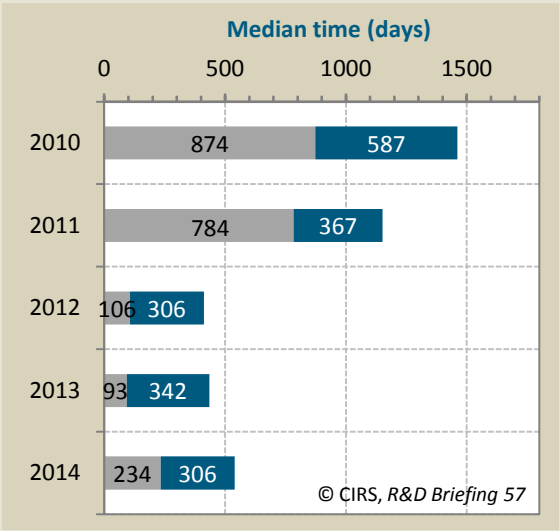
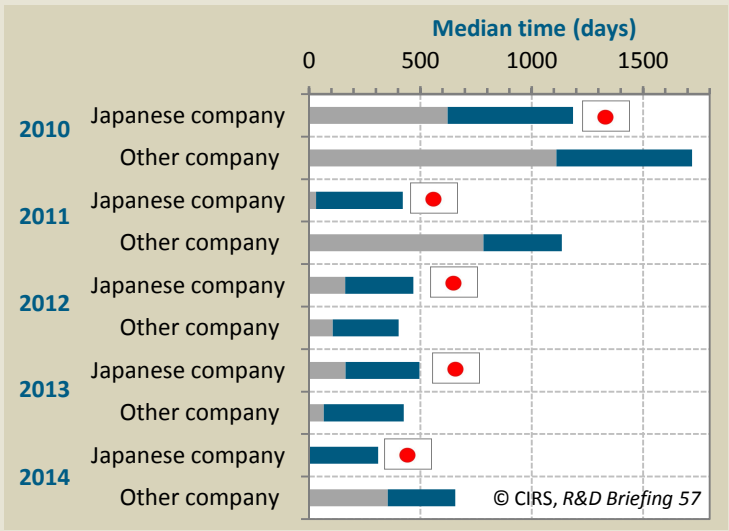


Figure 23: Submission gap* and approval time for NASs approved in Japan by company origin and year of approval



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

The submission gap to Japan sharply decreased 2010-2014 although the submission gap increased by 2.5 times in 2014 compared with 2013 (Fig. 22). This appears to be related to company origin as well as review type, with orphan NASs from non-Japanese companies having experienced the longest submission gap in 2014 (Fig. 23-25). In addition, a number of products approved in Japan in 2014 were legacy products whose availability to Japanese patients was facilitated through government programmes.

When comparing 2005-2009 and 2010-2014, the number of NAS approvals from Japanese companies has increased from 39% to 51%. These companies often develop NASs primarily for the Japanese population and consequently the submission gap is considerably lower compared to that for products from non-Japanese companies, which seek approval in EMA and FDA first. Besides company origin, review type (and orphan status) also influence the submission gap, with orphan NASs having a longer submission gap compared to non-orphan, regardless of company origin.

Fig 24: Submission gap* and approval time for NASs approved in Japan 2014 by company origin by review type

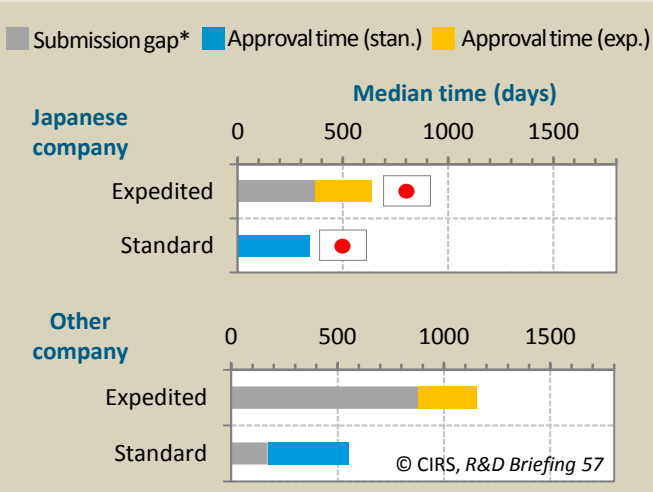
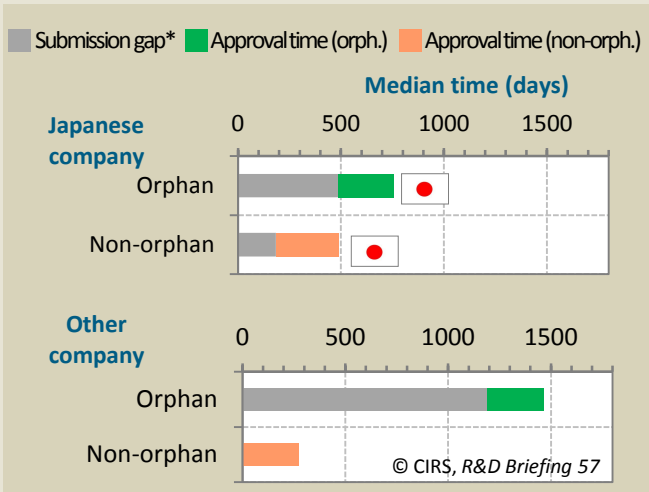


Fig 25: Submission gap* and approval time for expedited NASs approved in Japan 2014 by company origin by orphan status



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

2014 Regulatory Metrics Snapshots

Approval in EMA 2014

EMA HAD **A TOTAL OF 30 NASs APPROVED IN 2014**, WITH A MEDIAN APPROVAL TIME OF **418 DAYS***

Type of Medicine

9 BIOLOGIC NASs APPROVED IN 2014 WITH A MEDIAN APPROVAL TIME OF **420 DAYS**

21 CHEMICAL NASs APPROVED IN 2014 WITH A MEDIAN APPROVAL TIME OF **415 DAYS**

11 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2014 WITH A MEDIAN APPROVAL TIME OF **442 DAYS**

19 NASs IN OTHER THERAPY AREAS APPROVED IN 2014 WITH A MEDIAN APPROVAL TIME OF **415 DAYS**

Designation and Review Type

4 EXPEDITED NAS APPROVALS IN 2014** WITH A MEDIAN APPROVAL TIME OF **264 DAYS**

26 STANDARD NAS APPROVALS IN 2014 WITH A MEDIAN APPROVAL TIME OF **432 DAYS**

13 ORPHAN NASs APPROVALS IN 2014 WITH A MEDIAN APPROVAL TIME OF **469 DAYS,**

17 NON-ORPHAN NAS APPROVALS IN 2014 WITH A MEDIAN APPROVAL TIME OF **409 DAYS,**

Availability in EMA

37% OF THE NASs APPROVED IN 2014 BY EMA WERE **APPROVED BY EMA FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL IN ICH**

63% OF THE NASs APPROVED IN 2014 BY EMA WERE **APPROVED MORE THAN ONE MONTH FOLLOWING APPROVAL IN ANOTHER ICH COUNTRY**

THE MEDIAN **SUBMISSION GAP** TO EMA FOR THESE NASs WAS **25 DAYS**

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

2014 Regulatory Metrics Snapshots

Approval in FDA 2014

FDA HAD **A TOTAL OF 45 NASs APPROVED IN 2014**, WITH A MEDIAN APPROVAL TIME OF **343 DAYS**

15 BIOLOGIC NASs APPROVED IN 2014 WITH A MEDIAN APPROVAL TIME OF **334 DAYS**

30 CHEMICAL NASs APPROVED IN 2014 WITH A MEDIAN APPROVAL TIME OF **362 DAYS**

Type of Medicine

15 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2014 WITH A MEDIAN APPROVAL TIME OF **241 DAYS**

30 NASs IN OTHER THERAPY AREAS APPROVED IN 2014 WITH A MEDIAN APPROVAL TIME OF **365 DAYS**

Designation and Review Type

26 EXPEDITED* NASs APPROVALS IN 2014 WITH A MEDIAN APPROVAL TIME OF **243 DAYS**

19 STANDARD NAS APPROVALS IN 2014 WITH A MEDIAN APPROVAL TIME OF **456 DAYS**

21 ORPHAN NASs APPROVALS IN 2014 WITH A MEDIAN APPROVAL TIME OF **319 DAYS**

24 NON-ORPHAN NAS APPROVALS IN 2014 WITH A MEDIAN APPROVAL TIME OF **365 DAYS**

Availability in FDA

87% OF THE NASs APPROVED IN 2014 BY FDA WERE **APPROVED BY FDA FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL IN ICH**

13% OF THE NASs APPROVED IN 2014 BY FDA WERE **APPROVED MORE THAN ONE MONTH FOLLOWING APPROVAL IN ANOTHER ICH COUNTRY**

THE MEDIAN **SUBMISSION GAP** TO FDA FOR THESE NASs WAS **231 DAYS**

***Note**: Expedited review refers to FDA Priority Review*

2014 Regulatory Metrics Snapshots

Approval in PMDA 2014

PMDA HAD **A TOTAL OF 52 NASs APPROVED IN 2014**, WITH A MEDIAN APPROVAL TIME OF **306DAYS**

12 BIOLOGIC NASs APPROVED IN 2014 WITH A MEDIAN APPROVAL TIME OF **300 DAYS**

40 CHEMICAL NASs APPROVED IN 2014 WITH A MEDIAN APPROVAL TIME OF **321 DAYS**

Type of Medicine

17 ANTI-CANCER AND IMMUNOMODULATOR NASs APPROVED IN 2014 WITH A MEDIAN APPROVAL TIME OF **298 DAYS**

35 NASs IN OTHER THERAPY AREAS APPROVED IN 2014 WITH A MEDIAN APPROVAL TIME OF **332 DAYS**

Designation and Review Type

26 EXPEDITED* NASs APPROVALS IN 2014 WITH A MEDIAN APPROVAL TIME OF **275 DAYS**

19 ORPHAN NASs APPROVALS IN 2014 WITH A MEDIAN APPROVAL TIME OF **270 DAYS**

26 STANDARD NAS APPROVALS IN 2014 WITH A MEDIAN APPROVAL TIME OF **359 DAYS**

33 NON-ORPHAN NAS APPROVALS IN 2014 WITH A MEDIAN APPROVAL TIME OF **343 DAYS**

Availability in PMDA

38% OF THE NASs APPROVED IN 2014 BY PMDA WERE **APPROVED BY PMDA FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL IN ICH**

62% OF THE NASs APPROVED IN 2014 BY PMDA WERE **APPROVED MORE THAN ONE MONTH FOLLOWING APPROVAL IN ANOTHER ICH COUNTRY**

THE MEDIAN **SUBMISSION GAP** TO PMDA FOR THESE NASs WAS **867 DAYS**

***Note**: Expedited review refers to PMDA Priority Review*

EMA NAS approvals in 2014

Brand Name	Generic Name	Marketing Authorisation Holder	Approval Date	Expedited Review*	Orphan	Exceptional Circumstances	Conditional Approval
Sovaldi	sofosbuvir	Gilead Sciences International Ltd	16/01/2014				
Tivicay	dolutegravir	ViiV Healthcare	16/01/2014				
Neuraceq	florbetaben (18F)	Piramal Imaging Limited	20/02/2014				
Sirturo	bedaquiline fumarate	Janssen-Cilag International N.V.	05/03/2014				
Eperzan	albiglutide	GlaxoSmithKline Trading Services	21/03/2014				
Latuda	lurasidone	Takeda Pharma A/S	21/03/2014				
Cometriq	cabozantinib	TMC Pharma Services Ltd	21/03/2014				
Adempas	riociguat	Bayer Pharma AG	27/03/2014				
Vimizim	recombinant human n-acetylgalactosamine-6-sulfatase	BioMarin Europe Ltd	28/04/2014				
Incruse	umeclidinium bromide	Glaxo Group Ltd	28/04/2014				
Deltyba	delamanid	Otsuka Novel Products GmbH	28/04/2014				
Olysio	simeprevir	Janssen-Cilag International N.V.	14/05/2014				
Jardiance	empagliflozin	Boehringer Ingelheim Internat.	22/05/2014				
Sylvant	siltuximab	Janssen-Cilag International NV	22/05/2014				
Entyvio	vedolizumab	Takeda Pharma A/S	22/05/2014				
Mekinist	trametinib	Glaxo Group Ltd	30/06/2014				
Plegridy	peginterferon beta-1a	Biogen Idec Ltd	18/07/2014				
Gazyvaro	obinutuzumab	Roche Registration Ltd	23/07/2014				
Nuwiq	simoctocog alfa	Octapharma AB	24/07/2014				
Translarna	ataluren	PTC Therapeutics International Limited	31/07/2014				

***Note**: Expedited review refers to EMA Accelerated Assessment*

EMA NAS approvals in 2014

Brand Name	Generic Name	Marketing Authorisation Holder	Approval Date	Expedited Review*	Orphan	Exceptional Circumstances	Conditional Approval
Daklinza	daclatasvir dihydrochloride	Bristol-Myers Squibb Pharma EEIG	22/08/2014				
Vizamyl	flutemetamol (18F)	GE Healthcare Ltd	22/08/2014				
Zydelig	idelalisib	Gilead Sciences International Ltd	18/09/2014				
Imbruvica	ibrutinib	Janssen-Cilag International NV	21/10/2014				
Harvoni	sofosbuvir / ledipasvir	Gilead Sciences International Ltd	17/11/2014				
Vargatef	nintedanib	Boehringer Ingelheim Internat.	21/11/2014				
Trulicity	dulaglutide	Eli Lilly Nederland B.V.	21/11/2014				
Moventig	naloxegol	AstraZeneca AB	08/12/2014				
Lynparza	olaparib	AstraZeneca AB	16/12/2014				
Cyramza	ramucirumab	Eli Lilly Nederland B.V.	19/12/2014				

***Note**: Expedited review refers to EMA Accelerated Assessment*

FDA NAS approvals in 2014

Brand Name	Generic Name	Marketing Authorisation Holder	Approval Date	Expedited Review*	Orphan	Fast Track	Break-through	Accelerated Approval
Farxiga	dapagliflozin	Astrazeneca Ab	08/01/2014					
Hetlioz	tasimelteon	Vanda Pharms Inc	31/01/2014					
Vimizim	elosulfase alfa	Biomarin Pharm	14/02/2014					
Northera	droxidopa	Lundbeck Na Ltd	18/02/2014					
Myalept	metreleptin	Amylin Pharms Llc	24/02/2014					
Impavido	miltefosine	Knight Theraps	19/03/2014					
Neuraceq	florbetaben f-18	Piramal Imaging	19/03/2014					
Otezla	apremilast	Celgene Corp	21/03/2014					
Alprolix	coagulation factor ix (recombinant), fc fusion protein	Biogen Idec Inc.	28/03/2014					
Tanzeum	albiglutide	Glaxosmithkline Llc	15/04/2014					
Cyramza	ramucirumab	Eli Lilly and Co	21/04/2014					
Sylvant	siltuximab	Janssen Biotech	22/04/2014					
Zykadia	ceritinib	Novartis Pharms Corp	29/04/2014					
Zontivity	vorapaxar sulfate	Merck Sharp Dohme	08/05/2014					
Entyvio	vedolizumab	Takeda Pharms Usa	20/05/2014					
Dalvance	dalbavancin hydrochloride	Durata Theraps Intl	23/05/2014					
Eloctate	antihemophilic factor (recombinant), fc fusion protein	Biogen Idec Inc.	06/06/2014					
Jublia	efinaconazole	Dow Pharm	06/06/2014					
Sivextro	tedizolid phosphate	Cubist Pharms Inc	20/06/2014					
Beleodaq	belinostat	Spectrum Pharms	03/07/2014					
Kerydin	tavaborole	Anacor Pharms Inc	07/07/2014					
Ruconest	c1 esterase inhibitor (recombinant)	Pharming Group Nv	16/07/2014					
Zydelig	idelalisib	Gilead Sciences Inc	23/07/2014					

***Note**: Expedited review refers to FDA Priority Review*

FDA NAS approvals in 2014

Brand Name	Generic Name	Marketing Authorisation Holder	Approval Date	Expedited Review*	Orphan	Fast Track	Break-through	Accelerated Approval
Striverdi Respimat	olodaterol hydrochloride	Boehringer Ingelheim	31/07/2014					
Jardiance	empagliflozin	Boehringer Ingelheim	01/08/2014					
Orbactiv	oritavancin diphosphate	Medicines Co	06/08/2014					
Belsomra	suvorexant	Merck Sharp Dohme	13/08/2014					
Plegridy	peginterferon beta-1a	Biogen Idec inc	15/08/2014					
Cerdelga	eliglustat tartrate	Genzyme Corp	19/08/2014					
Keytruda	pembrolizumab	Merck Sharp Dohme	04/09/2014					
Movantik	naloxegol oxalate	Astrazeneca Pharms	16/09/2014					
Trulicity	dulaglutide	Eli Lilly and Co	18/09/2014					
Akynzeo	netupitant; palonosetron hydrochloride	Helsinn Hlthcare	10/10/2014					
Harvoni	ledipasvir; sofosbuvir	Gilead Sciences inc	10/10/2014					
Lumason	sulfur hexafluoride lipid-type a microspheres	Bracco	10/10/2014					
Esbriet	pirfenidone	Intermune inc	15/10/2014					
Ofev	nintedanib	Boehringer Ingelheim	15/10/2014					
Obizur	antihemophilic factor (recombinant), porcine sequence	Baxter Healthcare Corporation	23/10/2014					
Blincyto	blinatumomab	Amgen	03/12/2014					
Xtoro	finafloxacin	Alcon Res ltd	17/12/2014					
Lynparza	olaparib	Astrazeneca lp	19/12/2014					
Rapivab	peramivir	Biocryst Pharmaceuticals	19/12/2014					
Viekira Pak	ombitasivr; paritaprevir; ritonavir; dasabuvir	Abbvie inc	19/12/2014					
Zerbaxa	Ceftolozane; tazobactam	Cubist Pharms inc	19/12/2014					
Opdivo	nivolumab	Bristol Myers Squibb	22/12/2014					

***Note**: Expedited review refers to FDA Priority Review*

PMDA NAS approvals in 2014

Brand Name	Generic Name	Marketing Authorisation Holder	Approval Date	Expedited Review*	Orphan
Giotrif	afatinib maleate	Nippon Boehringer Ingelheim Co., Ltd.	17/01/2014		
Cystadane	betaine	ReqMed Company, Ltd	17/01/2014		
Adcetris	brentuximab vedotin (genetical recombination)	Takeda Pharmaceutical Company Limited	17/01/2014		
Savene	dexrazoxane	Kissei Pharmaceutical Co., Ltd.	17/01/2014		
Riona	ferric citrate hydrate	Japan Tobacco Inc.	17/01/2014		
Suglat	ipragliflozin l-proline	Astellas Pharma Inc.	17/01/2014		
Adempas	riociguat	Bayer Yakuhin, Ltd	17/01/2014		
NovoEight	turoctocog alpha (genetical recombination)	Novo Nordisk Pharma Ltd.	17/01/2014		
Forxiga	dapagliflozin propylene glycolate hydrate	Bristol-Myers K.K	24/03/2014		
Tivicay	dolutegravir sodium	ViiV Healthcare K.K	24/03/2014		
Xtandi	enzalutamide	Astellas Pharma Inc.	24/03/2014		
Avigan	favipiravir	Toyama Chemical Co., Ltd.	24/03/2014		
Lusefi	luseogliflozin hydrate	Taisho Pharmaceutical Co., Ltd	24/03/2014		
Tysabri	natalizumab (genetical recombination)	Biogen Idec Japan Ltd.	24/03/2014		
Efient	prasugrel hydrochloride	Daiichi Sankyo Company, Limited	24/03/2014		
Tapenta	tapentadol hydrochloride	Janssen Pharmaceutical K.K.	24/03/2014		
Deberza	tofogliflozin hydrate	Kowa Company, Ltd/Sanofi K.K.	24/03/2014		
Treprost	treprostinil	Mochida Pharmaceutical Co., Ltd	24/03/2014		
Lonsurf	trifluridine/tipiracil hydrochloride	Taiho Pharmaceutical Co., Ltd.	24/03/2014		
Zytiga	abiraterone acetate	Janssen Pharmaceutical Co., Ltd.	04/07/2014		
Alecensa	alectinib hydrochloride	Chugai Pharmaceutical Co., Ltd.	04/07/2014		
Sunvepra	asunaprevir	Bristol-Myers Co., Ltd.	04/07/2014		
Jevtana	cabazitaxel	Sanofi (Ltd.)	04/07/2014		
Canaglu	canagliflozin hydrate	Mitsubishi Tanabe Pharma Co., Ltd.	04/07/2014		
Nicystagon	cysteamine bitartrate capsule	Mylan Pharmaceuticals Ltd.	04/07/2014		
Daklinza	daclatasvir	Bristol-Myers Co., Ltd.	04/07/2014		

**Note*: *Expedited review refers to PMDA Priority Review*

PMDA NAS approvals in 2014

Brand Name	Generic Name	Marketing Authorisation Holder	Approval Date	Expedited Review*	Orphan
Deltyba	delamanid	Otsuka Pharmaceutical Co., Ltd.	04/07/2014		
Byclot	drying concentrated human blood coagulation factor x pressurized activated factor vii	Kaketsuken The Chemo-Sero-Therapeutic Research Institute	04/07/2014		
Clenafin	efinaconazole	Kaken Pharmaceutical Co., Ltd.	04/07/2014		
Alprolix	eftrenonacog alfa (genetical recombination)	Biogen Idec Japan Co., Ltd.	04/07/2014		
Opdivo	nivolumab (genetical recombination)	Ono Pharmaceutical Co., Ltd.	04/07/2014		
Jakavi	ruxolitinib	Novartis Pharma Co., Ltd.	04/07/2014		
Rapalimus	sirolimus	Nobel Pharma Co., Ltd.	04/07/2014		
Anoro Ellipta	umeclidinium/vilanterol	GlaxoSmithKline Inc.	04/07/2014		
Vpriv	velaglucerase alfa (genetical recombination)	Shire Japan Co., Ltd.	04/07/2014		
MabCampath	alemtuzumab	Sanofi (Ltd.)	26/09/2014		
Agrylin capsules	anagrelide hydrochloride	Shire Japan Co., Ltd.	26/09/2014		
Bosulif	bosutinib hydrate	Pfizer Inc.	26/09/2014		
Fomepizole	fomepizole	Takeda Pharmaceutical Co., Ltd.	26/09/2014		
G-Lasta	pegfilgrastim (genetical recombination)	Kyowa Hakko Kirin Co., Ltd.	26/09/2014		
Glanatec	ripasudil hydrochloride hydrate	Kowa Co., Ltd.	26/09/2014		
Zanosar	streptozotocin	Nobel Pharma Co., Ltd.	26/09/2014		
Belsomra	suvorexant	MSD (Ltd.)	26/09/2014		
Vanihep	vaniprevir	MSD (Ltd.)	26/09/2014		
Bepio	benzoyl peroxide	Maruho Co., Ltd.	26/12/2014		
Eloctate	efraloctocog alfa（genetical recombination)	Biogen Idec	26/12/2014		
Vimizim	elosulfase alfa (genetical recombination)	BioMarin Pharmaceutical Japan (Ltd.)	26/12/2014		
Jardiance	empagliflozin	Nippon Boehringer Ingelheim Co., Ltd.	26/12/2014		
Orfadin	nitisinone	Astellas Pharma Co., Ltd.	26/12/2014		
Cosentyx	secukinumab（genetical recombination）	Novartis Pharma Co., Ltd.	26/12/2014		
Zelboraf	Vemurafenib	Chugai Pharmaceutical Co., Ltd.	26/12/2014		
Takecab	vonoprazan fumarate	Takeda Pharmaceutical Co., Ltd.	26/12/2014		

***Note**: Expedited review refers to PMDA Priority Review*

Facilitated Regulatory Pathways in ICH

	What is it?	Advantage
FDA Fast Track	A process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need	• More frequent meetings with FDA to discuss drug development plan • More frequent communication on clinical trials design • Option for rolling data submission
FDA Breakthrough Therapy	A process designed to expedite the development and review of drugs that may demonstrate substantial improvement over available therapy	• All Fast Track designation features • Intensive guidance on an efficient drug development program from phase 1 • Organisational commitment with senior managers • Option for priority review
FDA Accelerated Approval	Regulation allowing drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint	• Conditional approval granted using surrogate endpoint(s) from phase 2 trials or interim phase 3 data; confirmatory trials with hard clinical endpoints required
FDA Priority Review	A process that directs resources to the evaluation of drugs that represent significant improvements in safety or effectiveness compared with standard applications	• Review time shortened from 10 to 6 months
EMA Conditional Approval	Regulation allowing drugs fulfilling unmet medical need for severe, life-threatening or rare diseases to be approved with limited clinical safety or efficacy data, provided a positive benefit-risk balance	• Conditional approval is granted before all data are available (valid for one year, on a renewable basis; once pending studies are provided, it can become a "normal" marketing authorisation)
EMA Exceptional Circum-stances	Regulation allowing drugs fulfilling unmet medical need for severe, life-threatening or rare diseases to be approved without comprehensive efficacy and safety data	• Conditional approval is granted before all data are available (reviewed annually to re-assess the risk-benefit balance)
EMA Accelerated Assessment	A process designed to expedite products of major interest in terms of public health and therapeutic innovation	• CHMP opinion shortened from 210 days to 150 days
PMDA Priority Review	A process that provides faster access to new therapies responding to high medical needs; includes products such as orphans, HIV medicines and products given "Extraordinary Approval"	• Review time shortened from 9 to 6 months
PMDA Sakigake (pioneer)	A system to put into practice innovative medicines/medical devices, regenerative medicines initially developed in Japan	• All Priority Review designation features • Prioritised clinical trial and pre-application consultation • Assigned PMDA manager as a concierge • Post-marketing safety measures

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.

Note: The EMA approval time includes the EU Commission 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
In this Briefing, expedited review refers to EMA Accelerated Assessment and FDA/PMDA 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 (NAS)
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.

Applications that are excluded from the study

- 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).

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

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.

R&D Briefing

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