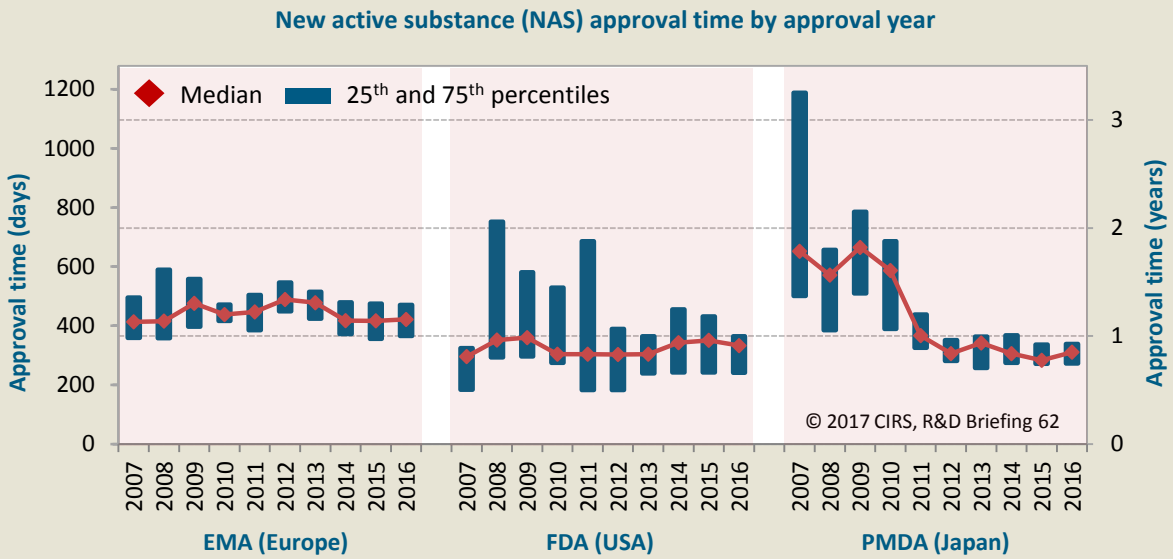
New drug approvals in ICH countries 2007 – 2016



***Note**: Time calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. 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 led to a decrease in the time to approval as well as an increase in the number of medicines that become available. Furthermore, the introduction and wider use of special 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 2007-2016 for three regulatory authorities; the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), the European Medicines Agency (EMA) and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA).

For the purposes of this Briefing, **facilitated regulatory pathways (FRP) 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 (CA), EMA Exceptional Circumstances (EC), FDA Fast Track (FT), FDA Breakthrough Therapy Designation (BTD), FDA Accelerated Approval (AA)**

Key findings from this Briefing

- **In 2016, PMDA approved the greatest number of NASs (48) of the three ICH agencies (Fig. 1), approximately double the NASs compared with EMA (28) and FDA (22). FDA and PMDA NAS median approval times converged in 2007-2016, with PMDA the fastest of the three agencies for a third year in a row (Fig. 2).**
- **Expedited reviews (EMA Accelerated Assessment and FDA/PMDA Priority Reviews) made up 68% and 46% of all NAS approvals at FDA and PMDA in 2014, and 18% 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 2016 (Fig. 4).**
- **Out of the three agencies, FDA had the greatest number of FRPs to enable the availability, review and/or approval of medicines where there is unmet medical need (Figure 6).**
- **The proportion of orphan NASs increased in the past decade across all three agencies, and hit a decade high for 2015-2016, with 38% at EMA, 49% at FDA and 36% at PMDA (Figure 8).**
- **The anti-cancer and immunomodulator therapy area represented the largest proportion of NAS approvals in 2016 for EMA, FDA and PMDA compared with the other major therapy groups, namely anti-infective and nervous system (Fig. 9).**
- **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).**
- **During 2012-2016, there were 64 NAS common approvals amongst the three ICH agencies, but the submission gap, as well as the approval type varied across the agencies relative to FDA (Fig. 13). Of the 64 common approvals, 15 were approved in 2015-2016 (Fig. 14). EMA, FDA and PMDA assigned the same review type for the majority of the products, with 5 expedited and 4 standard.**
- **The decrease in the overall median approval time for EMA from 2014 onwards compared with 2012-2013 was driven largely by the decrease in company response time (Fig. 15). When comparing these numbers for expedited versus standard review during the approval period 2012-2016 (Fig. 16), the expedited review was characterised by an almost four-times-faster company response time. A comparison of 2007-2011 and 2012-2016 revealed both an increase in the number of CA NASs as well as a difference in how the CA was requested (Fig. 17). In 2016, 14% of the products approved by EMA were based on a CHMP majority vote, compared with 86% that were adopted through consensus (Fig. 18).**
- **The number of the FDA CDER NASs approved after one cycle has increased from 68% to 83% from 2007-2011 to 2012-2016 (Fig. 19). The proportion of one-cycle reviews was higher for expedited compared with standard reviews 2012-2016 (Fig. 20). The median time difference between the date an NAS was designated as either FDA FT or BTD and the NASs submission date (Fig. 21) demonstrated that FT was given almost 2 years before NAS submission (537 days in 2013-2014 and 705 days in 2015-2016), whereas the BTD timing increased between 2012-2014 (designation given 32 median days before submission) compared with 2015-2016 (447 days). This reflects the maturity of the BTD programme, which was introduced in 2012 and is now being used more prospectively in order to enable not only the review but also the development of medicines.**
- **The overall rollout time to Japan doubled in 2016 compared with 2012-2015 (Fig. 23), which is due to an increase in the submission gap to Japan in 2016 (Fig. 24). Submission gaps also appeared to be related to company origin, with NASs from Japanese companies having experienced the longest submission gap in 2016 (Fig. 25). In addition, compounds that were designated as orphan experienced the longest submission gap during 2012-2016, which may related to sponsor size where "large Japanese companies are developing orphan drugs after initial approval or at a later stage of development than in the USA or EU" (Fig.26). Interestingly, PMDA approved the highest number of orphan medicines in 2016, which may also partially explain the increase in lag time in 2016.**

Overview of ICH agencies' approvals

In 2016, PMDA approved the greatest number of NASs (48) of the three ICH agencies (Fig. 1), approximately double the NASs compared with EMA (28) and FDA (22).

Following a spike in approval numbers in 2014 and 2015 for the three agencies, where 2014 marked a record year in the decade for FDA and PMDA and 2015 for EMA, in 2016 22 NASs were approved by FDA and 28 by EMA. According to the FDA, this drop occurred for several reasons, including natural fluctuation of the timing of application submissions which meant there was a smaller pool of novel drug applications to review, as well as a large number of deficiencies, as a result of which FDA issued a higher number of complete response letters for novel drugs in 2016.[1]

However, although PMDA approved the largest number of NASs of the three agencies in 2016, 71% of these NASs had been approved by the FDA or EMA previously prior to PMDA submission (Figure 5).

NAS approvals increased from 2007-2011 to 2012-2016 across all three agencies; a 50% increase for FDA, 42% for PMDA and 21% for EMA.

FDA and PMDA NAS median approval times converged in 2007-2016, with PMDA the fastest of the three agencies for a third year in a row (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 2016, the FDA overall median approval times decreased slightly from 2015 by 14 days. Nevertheless, when comparing 2007-2011 with 2012-2016, the median FDA approval times increased by 29 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, EMA approval times have been consistently lower for the last three years, by approximately 70 days compared with 2012-2013.

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

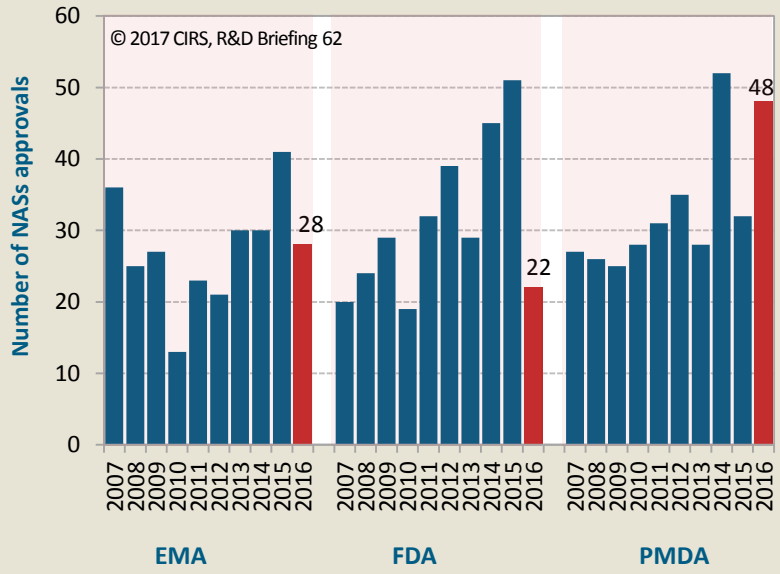
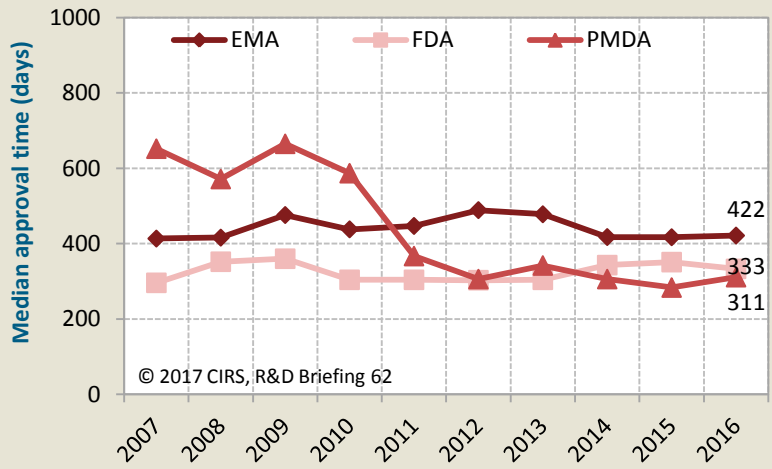


Figure 2: Median approval time for NASs approved by ICH agencies by approval year



***Note**: Time calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. The EMA approval time includes the EU Commission time*

[1]Jenkins J. 2017. A Review of CDER's Novel Drug Approvals for 2016. FDA Voice. Available at: *https://blogs.fda.gov/fdavoice/index.php/2017/01/a-review-of-cders-novel-drug-approvals-for-2016/ [Accessed 6 April 2017]*

ICH approvals – Review type

Expedited reviews (EMA Accelerated Assessment and FDA/PMDA Priority Reviews) made up 68% and 46% of all NAS approvals at FDA and PMDA in 2014, and 18% at EMA (Fig. 3).

The expedited review FRP played an important role at FDA and PMDA in accelerating the approval of innovative medicines over the last decade. The proportion of expedited reviews was consistent when comparing 2012-2015 to 2016 for PMDA, but there was a considerable increase for both FDA (48% to 68%) and EMA (13% to 18%), despite the fact that three NASs approved in 2016 which had been originally designated for expedited review by EMA, were reverted during the process back to standard. It is not certain whether this increase in expedited reviews reflects a long-term trend at EMA, which has been revising its guidelines on accelerated assessment and has introduced a new scheme, PRIME (PRIority MEdicines).

Despite differences in the use of expedited review, median approval times for these reviews were similar across the ICH agencies in 2016 (Fig. 4).

Although the number of EMA expedited NASs was considerably lower than those of FDA and PMDA, the 2016 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.

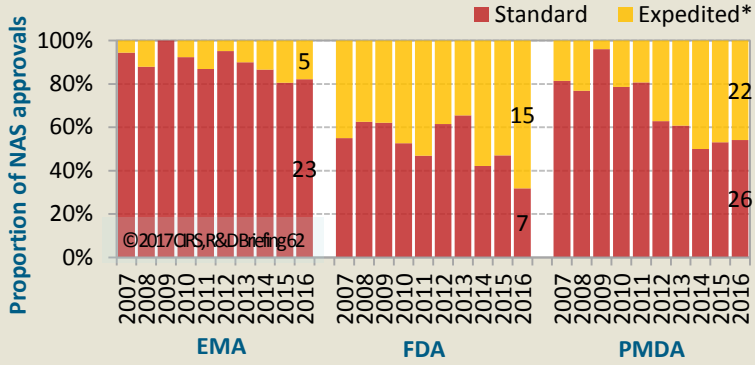
Looking at the difference between approval time for standard and expedited, there was a bigger median gap for EMA (182 days) and FDA (122), whereas for PMDA there is less difference (56).

The timing of approval varied across the three agencies in 2016 and was affected by type of approval (Fig. 5).

Looking the overall number of NASs, the majority of EMA reviews were concurrent with another ICH agency, at 64% (18 out of 28 NASs). Conversely, the majority of FDA approvals were first-in-ICH (approved only in that jurisdiction) at 55% (12 out of 22); whereas PMDA approved mostly follow-on products at 71% (34 out of 48).

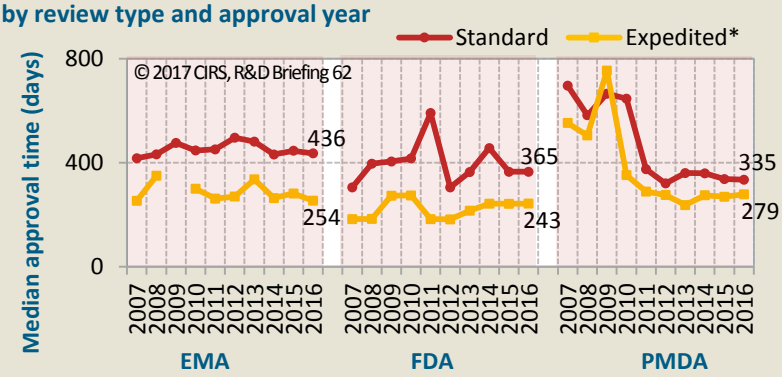
Differences in timing were seen according to review type. None of the expedited approvals were a "follow-on" for EMA or FDA, reflecting the high unmet need for NASs with that designation. Moreover, for FDA the majority of expedited NASs had not yet been approved by PMDA or EMA by 2016. For PMDA, the opposite was true, where the majority of expedited were follow-on NASs, likely due to the fact that these are legacy products whose availability is being prioritised.

Figure 3: Proportion of NASs approved by ICH agencies by review type and approval year (n=number of NASs)



**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



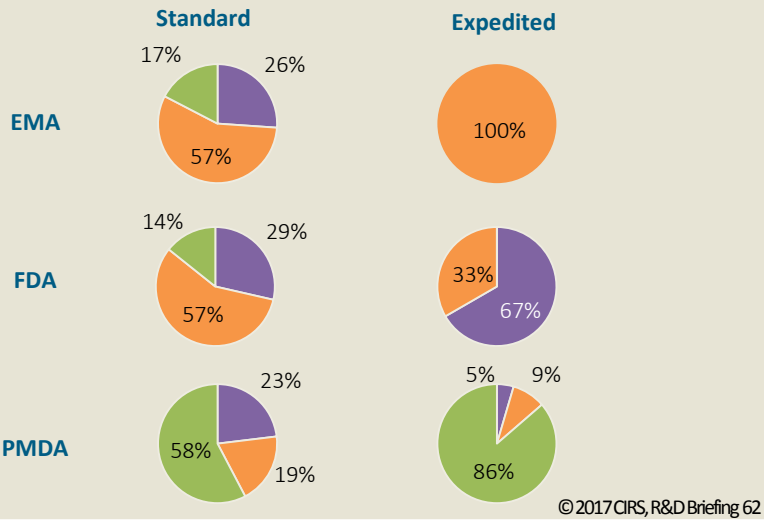
**Expedited review refers to EMA Accelerated Assessment and FDA/PMDA Priority Review*

Figure 5: Approval timing for NASs approved by each ICH agency in 2016 by review type

No previous submission/approval (NAS approved only in the jurisdiction)

Concurrent review with another ICH agency (submission to agency occurs prior to first-in-world approval)

Follow-on approval (submission to agency following first-in-ICH approval)



ICH approvals – FRP and orphan status

Figure 6: Facilitated Regulatory Pathway (FRP) and orphan status; focus on 2016

	NAS type		2016 NAS approval number	% of 2016 NASs	% Expedited**	2016 median approval time (days)
EMA	**Overall approvals**		**28**			**422**
	FRP*	Accelerated Assessment (referred in this Briefing as Expedited)	5	18%	100%	254
		Conditional Approval (CA)	7	25%	43%	388
		Exceptional Circumstances (EC)	0	-	-	-
	Orphan		11	39%	18%	391
FDA	**Overall approvals**		**22**			**333**
	FRP*	Priority (referred in this Briefing as Expedited)	15	68%	100%	243
		Accelerated Approval (AA)	6	27%	100%	209
		Breakthrough Therapy (BTD)	7	32%	100%	238
		Fast Track (FT)	8	36%	88%	289
	Orphan		10	45%	80%	288
PMDA	**Overall approvals**		**48**		-	**311**
	FRP*	Priority (referred in this Briefing as Expedited)	22	46%	100%	279
		Sakigake	0	-	-	-
	Orphan		18	38%	100%	280

** Each NAS can have more than one FRP. **Expedited review refers to EMA Accelerated Assessment and FDA/PMDA Priority Review*

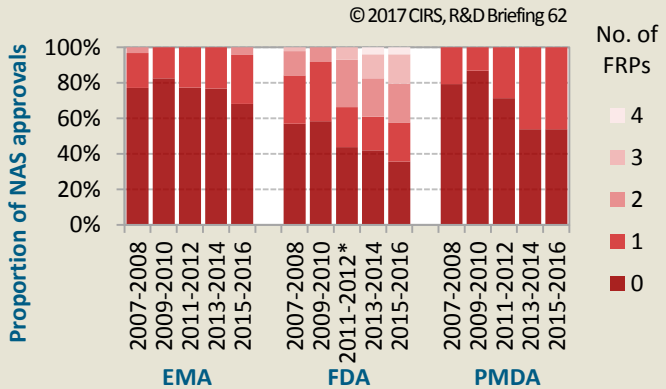
Out of the three agencies, FDA had the greatest number of FRPs to enable the availability, review and/or approval of medicines where there is unmet medical need (Figure 6).

Moreover , the overall number of NASs that benefited from at least one FRP increased across all three agencies (Figure 7); in 2015-2016, 32% of NASs at EMA, 46% at PMDA and 64% at FDA received at least one FRP. This wider use of diverse regulatory pathways and designations reflects both the unmet need of products submitted by companies, as well as introduction and formalisation of new pathways such as the FDA BTD in 2012. Moreover, the number of NASs approved by EMA through CA has increased, with the largest number approved in 2016 compared with the rest of the decade 2007-2015.

The proportion of orphan NASs increased in the past decade across all three agencies, and hit a decade high for 2015-2016, with 38% at EMA, 49% at FDA and 36% at PMDA (Figure 8).

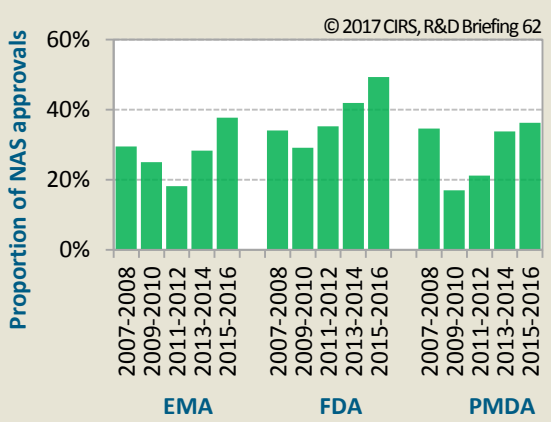
In addition, the majority of these orphan NASs benefited from an expedited review at FDA (80%) and PMDA (100%), whereas for EMA only 18% NASs were reviewed as expedited.

Figure 7: Proportion of NASs approved by ICH agencies by number of FRPs and approval year rage



**FDA introduced its 4th FRP (breakthrough designation) in 2012*

Figure 8: Proportion of orphan NASs approved by ICH agencies by approval year range



ICH approvals – Therapeutic area

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

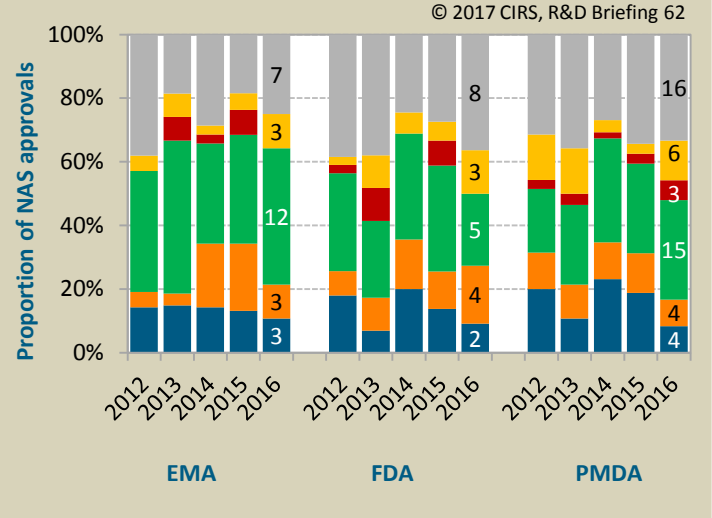
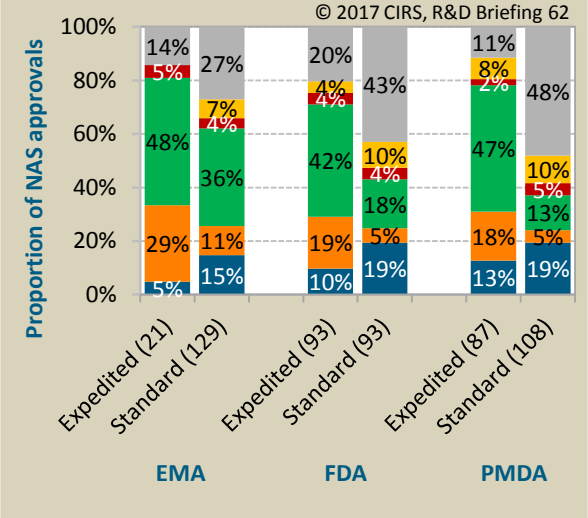


Figure 10: Proportion of NASs approved by ICH agencies by therapeutic area and review type for approval period 2012-2016



The anti-cancer and immunomodulator therapy area represented the largest proportion of NAS approvals in 2016 for EMA, FDA and PMDA compared with the other major therapy groups, namely anti-infective and nervous system (Fig. 9).

In terms of review type, the expedited versus standard patterns by therapeutic area looked almost identical when comparing FDA and PMDA. The pattern for EMA was different, with the review of only 10/57 (18%) anti-cancer NASs expedited over the last 5 years, compared with 39/56 (70%) and 41/55 (75%) for FDA and PMDA; and 6/20 (30%) anti-infective NASs expedited by EMA, in comparison to 18/23 (78%) and 16/21 (76%) 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 2012-2016

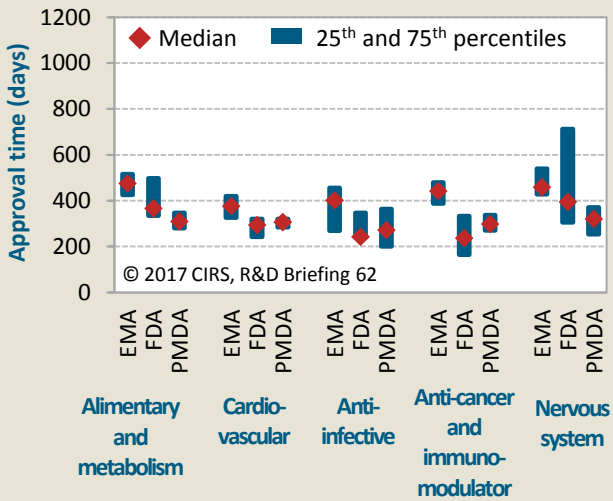
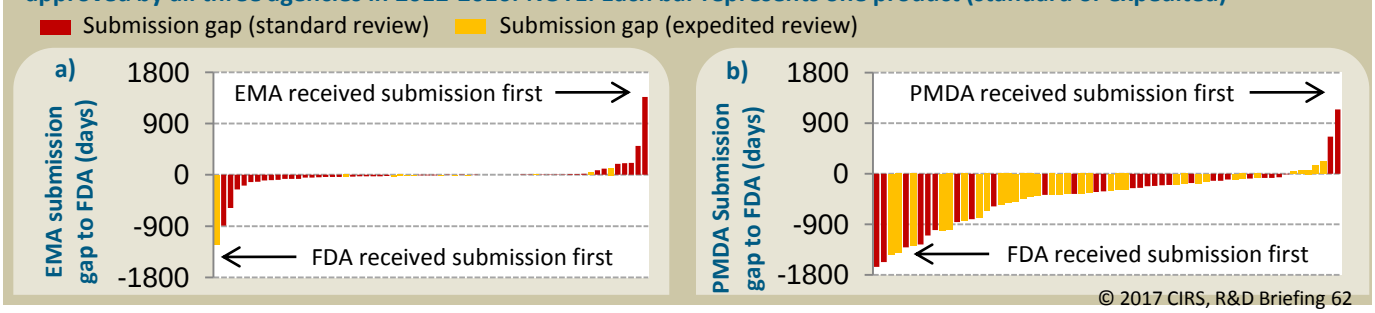


Figure 12: Median approval time (days) for NASs approved by ICH agencies in 2012-2016 by review type

© 2017 CIRS, R&D Briefing 62	EMA		FDA		PMDA	
	Standard	Expedited	Standard	Expedited	Standard	Expedited
Alimentary and metabolism	483	277	387	334	337	269
Cardio-vascular	415	338	335	242	308	255
Anti-infective	433	258	364	242	364	238
Anti-cancer and immuno-modulator	449	288	304	182	354	279
Nervous system	458	-	409	243	363	248

ICH approvals – Common approvals

Figure 13: Time difference between submission to FDA and either a) EMA or b) PMDA for the 64 common NASs approved by all three agencies in 2012-2016. NOTE: Each bar represents one product (standard or expedited)



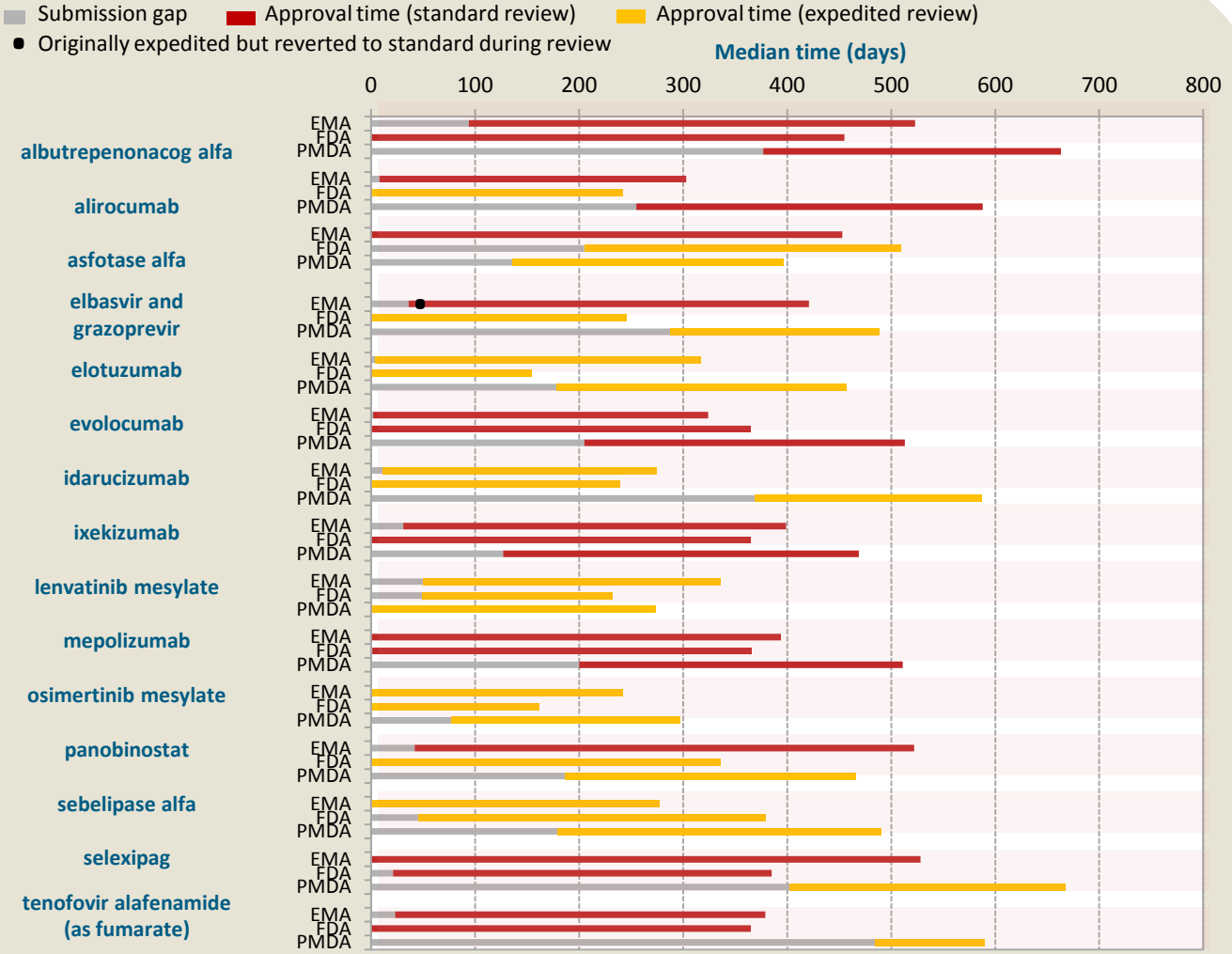
During 2012-2016, there were 64 NAS common approvals amongst the three ICH agencies, but the submission gap, as well as the approval type varied across the agencies relative to FDA (Fig. 13).

Submission occurred more or less simultaneously at EMA and FDA, but almost a year later at PMDA, with a median submission gap of 7 days for EMA and 307 days for PMDA relative to FDA submission. PMDA was the fastest to approve the 64 NASs (284 median approval days) followed by FDA (302) and EMA (407). Expedited reviews were used for 53%, 45% and 20% at FDA, PMDA and EMA, respectively.

Of the 64 common approvals, 15 were approved in 2015-2016 (Fig. 14). EMA, FDA and PMDA assigned the same review type for the majority of the products, with 5 expedited and 4 standard.

Although the PMDA median approval time was the shortest at 279 days compared with EMA (356) and FDA (334), the median submission gap of 200 days meant that PMDA was the last agency to approve 12/15 of the compounds.

Figure 14: Individual compound plot for 15 NASs approved by all ICH agencies between 2015-2016



Features of the EMA approval process

Figure 15: Median time of review process for NASs approved by EMA by approval year

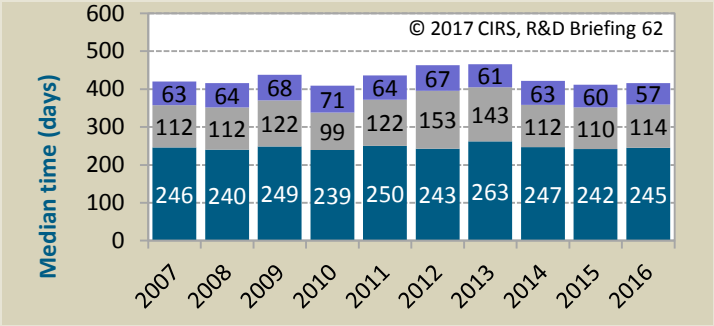
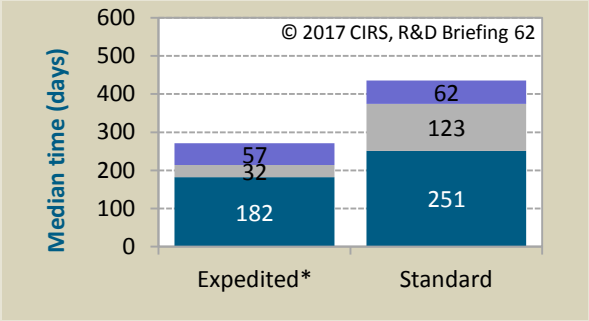


Figure 16: Median time of review process for NASs approved by EMA by review type for approval period 2012-2016



EU Commission time | Company response time | EMA review time

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

The decrease in the overall median approval time for EMA from 2014 onwards compared with 2012-2013 was driven largely by the decrease in company response time (Fig. 15).

Overall, the median company response time decreased by 39 days in 2016 compared with 2012; the median EMA review time remained the same with 245 days in 2016 compared with 243 in 2012; and the European Commission time decreased by 10 days for the same time period with 57 days in 2016, which is the lowest in the decade.

When comparing these numbers for expedited versus standard review during the approval period 2012-2016 (Fig. 16), the expedited review was characterised by an almost four-times-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 approximately 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.

A comparison of 2007-2011 and 2012-2016 revealed both an increase in the number of CA NASs as well as a difference in how the CA was requested (Fig. 17).

More CA NASs have been requested by applicants (and accepted) as opposed to being suggested by the CHMP during the review in 2012-2016 (70%) compared with 2007-2011 (40%), which may reflect a change in the way this pathways is being utilised. Moreover, an evaluation of median approval time in 2012-2016 indicated that CA NASs had longer approval compared with non-CA (523 vs. 436 days).

In 2016, 14% of the products approved by EMA were based on a CHMP majority vote, compared with 86% that were adopted through consensus (Fig. 18).

Interestingly, there was a difference between the approval time depending on the decision-making process through which the CHMP opinion was adopted, with NASs approved through majority vote being a median 94 days longer compared with consensus. This difference may reflect the difficult nature of the product and the dossier, which may lead to divergent opinions.

Figure 17: Number of NASs approved by EMA through Conditional Approval (CA) in 2007-2011 and 2012-2016 according to who requested the CA

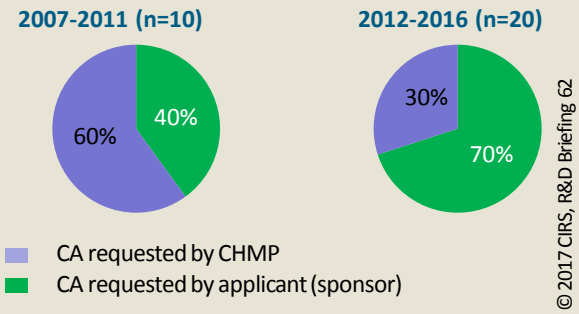
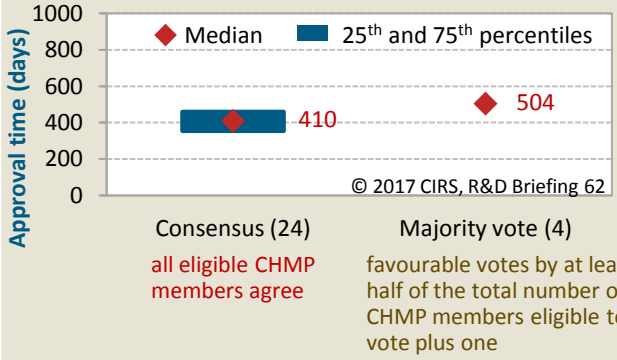


Figure 18: NAS approval time by type of decision-making process undertaken by the CHMP in 2016



Features of the FDA approval process

Figure 19: Proportion of NASs approved by CDER by number of review cycles by approval year (n=number of NASs)

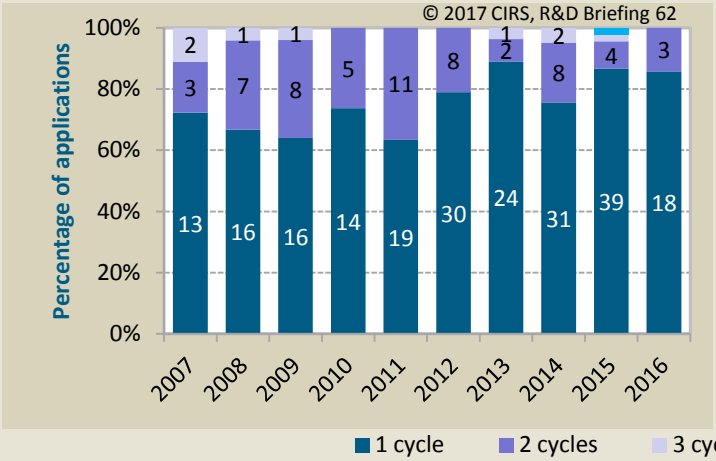
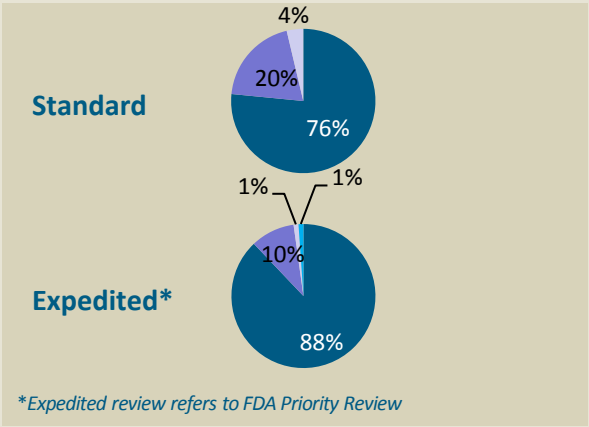


Figure 20: Proportion of NASs approved by CDER by number of review cycles and review type for approval period 2012-2016



**Expedited review refers to FDA Priority Review*

The number of the FDA CDER NASs approved after one cycle has increased from 68% to 83% from 2007-2011 to 2012-2016 (Fig. 19). The proportion of one-cycle reviews was higher for expedited compared with standard reviews 2012-2016 (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, particularly as noted by FDA that CDER issued 14 complete response deficiency letters for novel drugs in 2016, which is higher than in the recent years, and may be consequently reflected in he number of review cycles in the coming years.

The median time difference between the date an NAS was designated as either FDA FT or BTD and the NASs submission date (Fig. 21) demonstrated that FT was given almost 2 years before NAS submission (537 days in 2013-2014 and 705 days in 2015-2016), whereas the BTD timing increased between 2012-2014 (designation given 32 median days before submission) compared with 2015-2016 (447 days). This reflects the maturity of the BTD programme, which was introduced in 2012 and is now being used more prospectively in order to enable not only the review but also the development of medicines.

Of the 17 products that were approved under the BTD by FDA in 2015-2016, not all had been reviewed or approved by EMA and PMDA by 2016. Nevertheless, EMA approved 12 (71%) of those products by 2016 compared with 7 (41%) for PMDA.

Figure 21: Median time between the designation date as either FDA fast track (FT) or breakthrough (BTD) and NAS submission date by year of approval range**

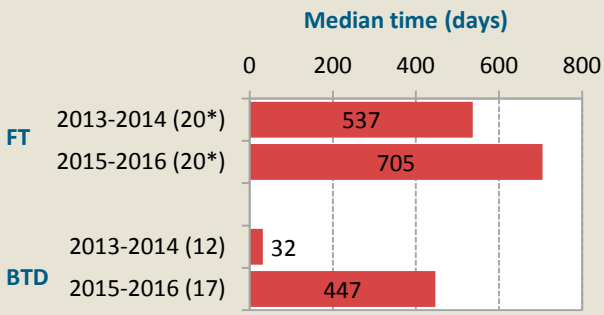
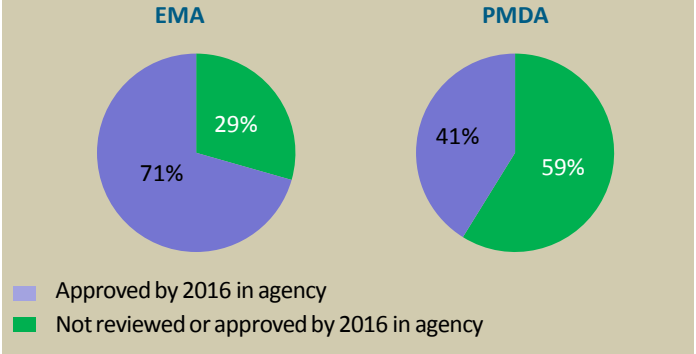


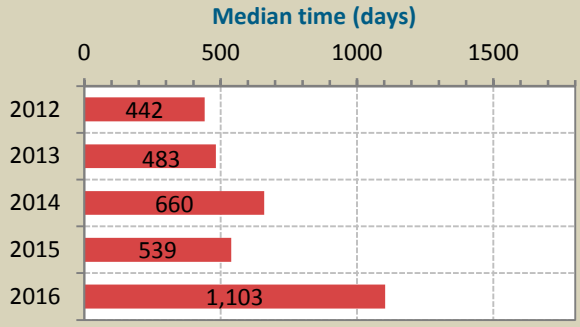
Figure 22: Approval status by 2016 for EMA and PMDA for 17 NASs approved by FDA in 2015-2016 under the BTD.**



**** FDA introduced breakthrough designation in 2012**

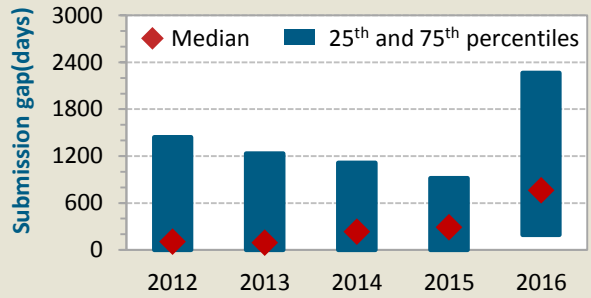
Features of the PMDA approval process

Figure 23: Rollout time* for NASs approved in Japan by year of approval



**Date of submission at the first regulatory agency to the date of regulatory approval at PMDA*

Figure 24: Submission gap for NASs approved in Japan by year of approval**



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

The overall rollout time to Japan doubled in 2016 compared with 2012-2015 (Fig. 23), which is due to an increase in the submission gap to Japan in 2016 (Fig. 24).

This may reflect the fact a number of products approved in 2016 were legacy products whose availability to Japanese patients was facilitated through government programmes as well as issues in the local development rights amongst sponsors (domestic versus foreign).

Submission gaps also appeared to be related to company origin, with NASs from Japanese companies having experienced the longest submission gap in 2016 (Fig. 25). In addition, compounds that were designated as orphan experienced the longest submission gap during 2012-2016, which may related to sponsor size where "large Japanese companies are developing orphan drugs after initial approval or at a later stage of development than in the USA or EU" [1] (Fig.26). Interestingly, PMDA approved the highest number of orphan medicines in 2016, which may also partially explain the increase in lag time in 2016.

Figure 25: Submission gap and approval time for NASs approved in Japan by the origin of the sponsoring company and approval year

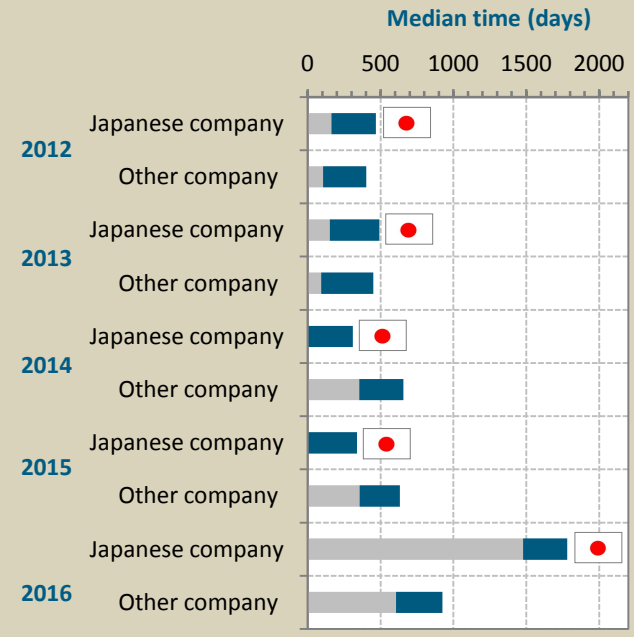
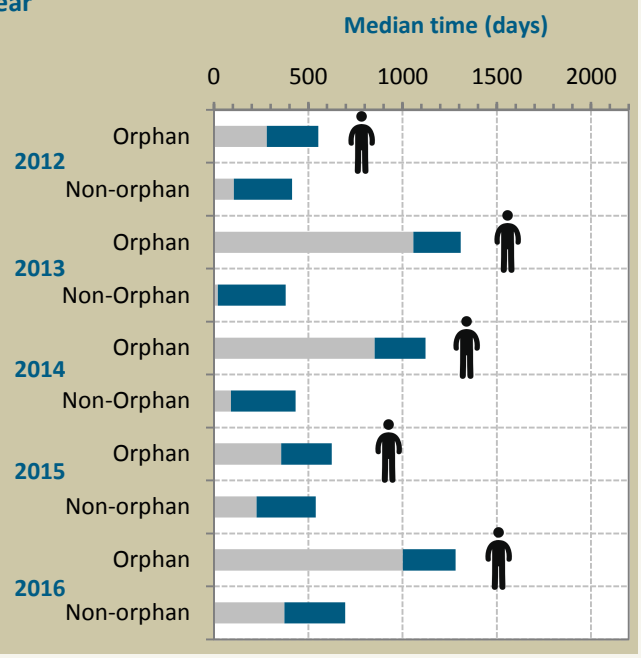


Figure 26: Submission gap and approval time for NASs approved in Japan by orphan designation and approval year



Submission Gap Approval time

[1]Murakami M, Narkuawa M. 2016. Matched analysis on orphan drug designations and approvals: cross regional analysis in the United States, the European Union, and Japan. *Drug Discov Today. 2016;21:544-549. doi: 10.1016/j.drudis.2016.02.016.*

2016 Regulatory Metrics Snapshots

Approval in EMA 2016

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

Type of Medicine

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

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

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

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

Designation and Review Type

5 EXPEDITED NAS APPROVALS IN 2016** WITH A MEDIAN APPROVAL TIME OF **254 DAYS**

11 ORPHAN NASs APPROVALS IN 2016 WITH A MEDIAN APPROVAL TIME OF **391 DAYS**

23 STANDARD NAS APPROVALS IN 2016 WITH A MEDIAN APPROVAL TIME OF **436 DAYS**

17 NON-ORPHAN NAS APPROVALS IN 2016 WITH A MEDIAN APPROVAL TIME OF **423 DAYS**

Availability in EMA

36% OF THE NASs APPROVED IN 2016 BY EMA WERE **APPROVED BY EMA FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL IN ICH**

64% OF THE NASs APPROVED IN 2016 BY EMA WERE **APPROVED MORE THAN ONE MONTH FOLLOWING APPROVAL IN ANOTHER ICH COUNTRY**

THE MEDIAN **SUBMISSION GAP** TO EMA FOR THESE NASs WAS **34 DAYS**

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

2016 Regulatory Metrics Snapshots

Approval in FDA 2016

FDA HAD **A TOTAL OF 22 NASs APPROVED IN 2016,** WITH A MEDIAN APPROVAL TIME OF **333 DAYS**

7 BIOLOGIC NASs APPROVED IN 2016 WITH A MEDIAN APPROVAL TIME OF **359 DAYS**

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

Type of Medicine

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

17 NASs IN OTHER THERAPY AREAS APPROVED IN 2016 WITH A MEDIAN APPROVAL TIME OF **336 DAYS**

Designation and Review Type

15 EXPEDITED* NASs APPROVALS IN 2016 WITH A MEDIAN APPROVAL TIME OF **243 DAYS**

10 ORPHAN NASs APPROVALS IN 2016 WITH A MEDIAN APPROVAL TIME OF **288 DAYS**

7 STANDARD NAS APPROVALS IN 2016 WITH A MEDIAN APPROVAL TIME OF **365 DAYS**

12 NON-ORPHAN NAS APPROVALS IN 2016 WITH A MEDIAN APPROVAL TIME OF **338 DAYS**

Availability in FDA

91% OF THE NASs APPROVED IN 2016 BY FDA WERE **APPROVED BY FDA FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL IN ICH**

9% OF THE NASs APPROVED IN 2016 BY FDA WERE **APPROVED MORE THAN ONE MONTH FOLLOWING APPROVAL IN ANOTHER ICH COUNTRY**

THE MEDIAN **SUBMISSION GAP** TO FDA FOR THESE NASs WAS **685 DAYS**

** Expedited review refers to FDA Priority Review*

2016 Regulatory Metrics Snapshots

Approval in PMDA 2016

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

Type of Medicine

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

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

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

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

Designation and Review Type

22 EXPEDITED* NASs APPROVALS IN 2016 WITH A MEDIAN APPROVAL TIME OF **279 DAYS**

18 ORPHAN NASs APPROVALS IN 2016 WITH A MEDIAN APPROVAL TIME OF **280 DAYS**

26 STANDARD NAS APPROVALS IN 2016 WITH A MEDIAN APPROVAL TIME OF **335 DAYS**

30 NON-ORPHAN NAS APPROVALS IN 2016 WITH A MEDIAN APPROVAL TIME OF **323 DAYS**

Availability in PMDA

15% OF THE NASs APPROVED IN 2016 BY PMDA WERE **APPROVED BY PMDA FIRST OR WITHIN ONE MONTH OF THEIR FIRST APPROVAL IN ICH**

85% OF THE NASs APPROVED IN 2016 BY PMDA WERE **APPROVED MORE THAN ONE MONTH FOLLOWING APPROVAL IN ANOTHER ICH COUNTRY**

THE MEDIAN **SUBMISSION GAP** TO PMDA FOR THESE NASs WAS **1007 DAYS**

** Expedited review refers to PMDA Priority Review*

EMA NAS approvals in 2016

Brand Name	Generic Name	Marketing Authorisation Holder	Approval Date	Expedited Review*	Orphan	Exceptional Circumstances	Conditional Approval
Episalvan	betulae cortex dry extract (5-10 : 1); extraction solvent: n-heptane 95% (w/w)	Birken AG	14/01/2016				
Briviact	brivaracetam	UCB Pharma SA	14/01/2016				
Tagrisso	osimertinib mesylate	AstraZeneca AB	02/02/2016				
Portrazza	necitumumab	Eli Lilly Nederland B.V.	15/02/2016				
Zurampic	lesinurad	Grünenthal GmbH	18/02/2016				
Wakix	pitolisant	Bioprojet Pharma	31/03/2016				
Taltz	ixekizumab	Eli Lilly Nederland B.V.	25/04/2016				
Lonsurf	trifluridine / tipiracil hydrochloride	Les Laboratoires Servier	25/04/2016				
Idelvion	albutrepenonacog alfa	CSL Behring GmbH	11/05/2016				
Empliciti	elotuzumab	Bristol-Myers Squibb	11/05/2016				
Alprolix	eftrenonacog alfa	Swedish Orphan Biovitrum AB (publ)	12/05/2016				
Uptravi	selexipag	Actelion Registration Ltd	12/05/2016				
Darzalex	daratumumab	Janssen-Cilag International N.V.	20/05/2016				
Strimvelis	autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence from human haematopoietic stem/progenitor (CD34+) cells	GlaxoSmithKline Trading Services Limited	26/05/2016				

**Expedited review refers to EMA Accelerated Assessment*

EMA NAS approvals in 2016

Brand Name	Generic Name	Marketing Authorisation Holder	Approval Date	Expedited Review*	Orphan	Exceptional Circumstances	Conditional Approval
Galafold	migalastat hydrochloride	Amicus Therapeutics UK Ltd	26/05/2016	**			
Zavicefta	ceftazidime / avibactam	AstraZeneca AB	24/06/2016				
Ongentys	opicapone	Bial - Portela & Cª, S.A.	24/06/2016				
Epclusa	sofosbuvir / velpatasvir	Gilead Sciences International Ltd	06/07/2016				
Zepatier	elbasvir / grazoprevir	Merck Sharp & Dohme Limited	22/07/2016	**			
Cinqaero	reslizumab	Teva Pharmaceuticals Limited	16/08/2016				
Zalmoxis	Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (LNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)	MolMed SpA	18/08/2016				
Truberzi	eluxadoline	Allergan	19/09/2016				
Lartruvo	olaratumab	Eli Lilly Nederland B.V.	09/11/2016				
Ibrance	palbociclib	Pfizer Limited	09/11/2016				
Parsabiv	etelcalcetide hydrochloride	Amgen Europe B.V.	11/11/2016				
Ninlaro	ixazomib citrate	Takeda Pharma A/S	21/11/2016	**			
Venclyxto	venetoclax	AbbVie Ltd	05/12/2016				
Ocaliva	obeticholic acid	Intercept Pharma Ltd	12/12/2016				

**Expedited review refers to EMA Accelerated Assessment*
***Originally expedited but reverted to standard during review*

FDA NAS approvals in 2016

Brand Name	Generic Name	Marketing Authorisation Holder	Approval Date	Expedited Review*	Orphan	Fast Track	Break-through	Accelerated Approval
ZEPATIER NDA #208261	ELBASVIR; GRAZOPREVIR	MERCK SHARP DOHME	28/01/2016					
BRIVIACT NDA #205836	BRIVARACETAM	UCB INC	18/02/2016					
IDELVION	Coagulation Factor IX (Recombinant), Albumin Fusion Protein	CSL Behring Recombinant Facility AG	04/03/2016					
ANTHIM BLA #125509	OBILTOXAXIMAB	ELUSYS THERAPEUTICS INC	18/03/2016					
TALTZ BLA #125521	IXEKIZUMAB	ELI LILLY AND CO	22/03/2016					
CINQAIR BLA #761033	RESLIZUMAB	TEVA RESPIRATORY LLC	23/03/2016					
DEFITELIO NDA #208114	DEFIBROTIDE SODIUM	JAZZ PHARMS INC	30/03/2016					
VENCLEXTA NDA #208573	VENETOCLAX	ABBVIE INC	11/04/2016					
NUPLAZID NDA #207318	PIMAVANSERIN TARTRATE	ACADIA PHARMS INC	29/04/2016					
TECENTRIQ BLA #761034	ATEZOLIZUMAB	GENENTECH INC	18/05/2016					
AXUMIN NDA #208054	FLUCICLOVINE F-18	BLUE EARTH	27/05/2016					
OCALIVA NDA #207999	OBETICHOLIC ACID	INTERCEPT PHARMS INC	27/05/2016					
NETSPOT NDA #208547	GALLIUM DOTATATE GA-68	AAA USA INC	01/06/2016					
EPCLUSA NDA #208341	SOFOSBUVIR; VELPATASVIR	GILEAD SCIENCES INC	28/06/2016					

** Expedited review refers to FDA Priority Review*

FDA NAS approvals in 2016

Brand Name	Generic Name	Marketing Authorisation Holder	Approval Date	Expedited Review*	Orphan	Fast Track	Break-through	Accelerated Approval
XIIDRA NDA #208073	LIFITEGRAST	SHIRE DEV LLC	11/07/2016					
ADLYXIN NDA #208471	LIXISENATIDE	SANOFI-AVENTIS US	27/07/2016					
EXONDYS 51 NDA #206488	ETEPLIRSEN	SAREPTA THERAPS INC	19/09/2016					
LARTRUVO BLA #761038	OLARATUMAB	ELI LILLY AND CO	19/10/2016					
ZINPLAVA BLA #761046	BEZLOTOXUMAB	MERCK SHARP DOHME	21/10/2016					
EUCRISA NDA #207695	CRISABOROLE	ANACOR PHARMS INC	14/12/2016					
RUBRACA NDA #209115	RUCAPARIB CAMSYLATE	CLOVIS ONCOLOGY INC	19/12/2016					
SPINRAZA NDA #209531	NUSINERSEN SODIUM	BIOGEN IDEC	23/12/2016					

** Expedited review refers to FDA Priority Review*

PMDA NAS approvals in 2016

Brand Name	Generic Name	Marketing Authorisation Holder	Approval Date	Expedited Review*	Orphan	Sakigake
Repatha	Evolocumab	Amgen Astellas BioPharma K.K	22/01/2016			
Provocholine/ Kenbran	Methacholine chloride	Sanwa Kagaku Kenkyusho/Santen Pharmaceutical	22/01/2016			
Targretin	Bexarotene	Minophagen	22/01/2016			
Sabril	Vigabatrin	Sanofi	28/03/2016			
Sycrest	Asenapine maleate	Meiji Seika Pharma	28/03/2016			
Fycompa	Perampanel hydrate	Eisai	28/03/2016			
Nucala	Mepolizumab	GlaxoSmithKline	28/03/2016			
Kanuma	Sebelipase alfa	Alexion	28/03/2016			
Tafinlar	Dabrafenib mesilate	Novartis	28/03/2016			
Mekinist	Trametinib dimethyl sulfoxide	Novartis	28/03/2016			
Xofigo	Radium （223Ra） dichloride	Bayer	28/03/2016			
Zykadia	Ceritinib	Novartis	28/03/2016			
Tagrisso	Osimertinib mesilate	AstraZeneca	28/03/2016			
Imbruvica	Ibrutinib	Janssen	28/03/2016			
Adynovate	Rurioctocog alfa pegol	Baxter Limited	28/03/2016			
Primaquine	Primaquine phosphate	Sanofi	28/03/2016			
Kovaltry	Octocog beta	Bayer	28/03/2016			
Genvoya	elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide	Japan Tobacco	17/06/2016			
Okinobel	Oxcarbazepine	Nobel Pharma	04/07/2016			
Kyprolis	Carfilzomib	ONO	04/07/2016			
Vimpat	lacosamide	UCB	04/07/2016			
Praluent	alirocumab	Sanofi Aventis	04/07/2016			
Taltz	Ixekizumab	Eli Lilly	04/07/2016			
Lumicef	brodalumab	Kyowa Hakko Kirin	04/07/2016			

** Expedited review refers to PMDA Priority Review*

PMDA NAS approvals in 2016

Brand Name	Generic Name	Marketing Authorisation Holder	Approval Date	Expedited Review*	Orphan	Sakigake
Signifor	Pasireotide	Novartis	28/09/2016			
Brilinta	Ticagrelor	AstraZeneca	28/09/2016			
Ovidrel	choriogonadotropin alfa	Merck Serono	28/09/2016			
Deselex	desloratadine	MSD	28/09/2016			
Bilanoa	Bilastine	Taiho Pharmaceutical	28/09/2016			
Idelvion	Albutrepenonacog alfa	CSL	28/09/2016			
Keytruda	Pembrolizumab	MSD	28/09/2016			**
Emplicity	ELOTUZUMAB	BRISTOL MYERS SQUIBB	28/09/2016			
Xifaxan	Rifaximin	Asuka Pharmaceutical	28/09/2016			
Uptravi	selexipag	Nippon Shinyaku	28/09/2016			
Juxtapid	Lomitapide	AEGERION PHARMACEUTICALS	28/09/2016			
Iclusig	ponatinib hydrochloride	Otsuka Pharmaceutical	28/09/2016			
Carbaglu	Carglumic acid	Pola Pharma	28/09/2016			
PRAXBIND	Idarucizumab	Japan Boehringer Ingelheim	28/09/2016			
Grazyna	grazoprevir	MSD	28/09/2016			
Erelsa	elbasavir	MSD	28/09/2016			
Ximency	Daclatasvir,asunaprevir, beclabuvir hydrochloride	Bristol-Myers Squibb	19/12/2016			
Parsabiv	Etelcalcetide hydrochloride	Ono pharmaceutical	19/12/2016			
Mozobil	Plerixafor	Sanofi	19/12/2016			
Amyvid	Florbetapir F-18	Fujifilm RI Pharma	19/12/2016			
Linzess	Linaclotide	Astellas Pharma	19/12/2016			
Riamet	Artemether, lumefantrine mixt	Novartis Pharma	19/12/2016			
Otezla	Apremilast	Celgene	19/12/2016			
Tecfidera	Dimethyl fumarate	Biogen	19/12/2016			

** Expedited review refers to PMDA Priority Review*

*** Keytruda received Sakigake designation, but for a follow-on indication of advanced/recurrent unresectable gastric cancer, whereas the NAS listed is for unresectable melanoma*

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 fulfil 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 fulfil 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 (calendar days) 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 (calendar days).

Rollout time
Date of submission at the first regulatory agency to the date of regulatory approval at the target agency (calendar days).

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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CIRS - The Centre for Innovation in Regulatory Science - is a neutral, independent UK-based subsidiary company, forming part of Clarivate Analytics. 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.

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