Strategy of SAKIGAKE & Medical Innovation

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Dramatic change in developmental strategy of NEW DRUG

The NEW ENGLAND JOURNAL of MEDICINE

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Perspective

The Demise of the Blockbuster?

David M. Cutler, Ph.D.

N Engl J Med 2007; 356:1292-1293 | March 29, 2007 | DOI: 10.1056/NEJMp078020

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Article | References | Citing Articles (13)

When Pfizer announced that it was halting clinical testing of its new cholesterol drug, torcetrapib, the company's market value fell by $21 billion overnight. Ten thousand job cuts followed. The ongoing promise of nearly $3 billion in annual sales vanished when Merck pulled Vioxx (rofecoxib) from the shelves, and the company's market value fell by $25 billion. For decades, blockbuster drugs have nourished Big Pharma, but it is increasingly uncertain whether they can be counted on to support the industry in the future.

US New National Strategy

Perspective

A New Initiative on Precision Medicine

Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

N Engl J Med 2015; 372:793-795 | February 26, 2015 | DOI: 10.1056/NEJMp1500523

Published in NEJM Feb. 26th 2015

Comments open through March 4, 2015

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Article | References | Comments (6)

> "Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier."
>
> — President Barack Obama, State of the Union Address, January 20, 2015

President Obama has long expressed a strong conviction that science offers great potential for improving health. Now, the President has announced a research initiative that aims to accelerate progress toward a new era of precision medicine (www.whitehouse.gov/precisionmedicine). We believe that the time is right for this visionary initiative, and the National

Audio Interview

Interview with Dr. Francis Collins on what to expect from the recently announced

FDA approved 41 NME in 2014

CDER's 2014 Novel New Drugs

41 Novel New Drugs

In calendar year 2014, FDA's Center for Drug Evaluation and Research (CDER) approved 41 novel new drugs, approved as new molecular entities (NMEs) under New Drug Applications (NDAs) or as new therapeutic biologics under Biologics License Applications (BLAs).[1] Below lists CDER's novel new drugs of 2014.

IN

2014

CDER APPROVED

41

NOVEL NEW DRUGS

Novel new drugs are often innovative products that serve previously unmet medical needs or otherwise significantly help to advance patient care and public health. In some cases, while categorized as novel for technical and/or administrative purposes, a particular novel new drug may not necessarily offer unique clinical advantages over existing therapies. This report summarizes all of the 2014 novel new drug approvals, emphasizing those that offer new and innovative treatments to patients in need.

The vertical bars in the chart on the next page indicate the number of novel new drugs approved by CDER in each year of the past decade. CDER approved 41 novel new drugs in 2014, more than in any other year during this time. From 2005 through 2013, CDER has averaged about 25 novel new drug approvals per year.

Applications For New Approvals Remain Steady

CDER approved a higher than average number of novel new drugs in 2014; however, the number of applications for these drugs that sponsors have submitted over time has remained relatively stable.

The purple portion of the graph on the next page indicates the number of new NDA and BLA applications for new molecular entities and new therapeutic biologics CDER has received and filed for approval during the last 10 years. From 2005 through 2013, CDER filed an average of about 34 applications for novel new drugs per year. CDER projects 41 filings for 2014, which is consistent with previous years in this decade.

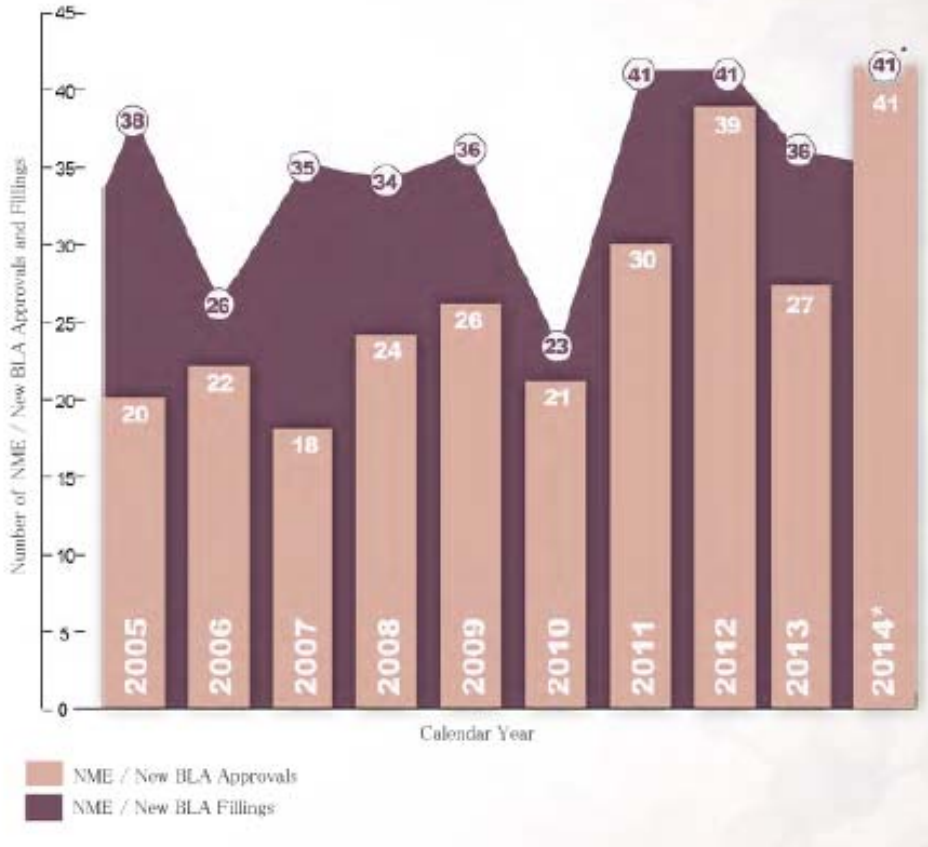
Novel New Drugs Approved by CDER in Calendar Year 2014 (see pages 14–16 for their non-proprietary names, approval dates, and what these drugs are used for.)

Akynzeo	Dalvance	Imprivo	Lynparza	Opdivo	Striverdi Respimat	Xtoro
Beleodaq	Entyvio	Jardiance	Movantik	Orbactiv	Sylvant	Zerbaxa
Belsomra	Esbriet	Jublia	Myalept	Otezla	Tanzeum	Zontivity
Blincyto	Farxiga	Kerydin	Neuraceq	Plegridy	Trulicity	Zydelig
Cerdelga	Harvoni	Keytruda	Northera	Rapivab	Viekira Pak[2]	Zykadia
Cyramza	Heplisav	Lumason	Ofev	Sivextro	Vimizim	

1. This total includes only novel new drugs approved by FDA's CDER. It does not include approvals by FDA's Center for Biologics Evaluation and Research (CBER).
2. One novel new drug comprised of four active ingredients - ritonavir (previously approved), and three novel new molecules - dasabuvir, ombitasvir, and paritaprevir.

41 NOVEL NEW DRUG APPROVALS IN CY 2014 IS MORE THAN THE AVERAGE NUMBER APPROVED ANNUALLY DURING THE PAST DECADE

FROM 2005 THROUGH 2013 CDER HAS AVERAGED **25** NOVEL NEW DRUG APPROVALS PER YEAR



* - The 2014 filed numbers include those filed in CY 2014 plus those currently pending filing (i.e., within their 60 day filing period) in CY 2014.
- Receipts that received a "Refuse to File" (RTF) or "Withdrawn before filing" (WF) identifier are excluded.
- Multiple submissions (multiple or split originals) pertaining to a single new molecular/biologic entity are only counted once.
- The filed number is not indicative of workload in the PDUFA V Program.

(Ref) Novel New Drugs 2014 SUMMARY, January 2015, U.S. FDA CDER

22% was Breakthrough Therapy

INNOVATION

METHODS FOR EXPEDITING INNOVATIVE NOVEL NEW DRUGS TO MARKET

CDER used a number of regulatory methods to expedite the approval of novel new drugs in 2014. These involved the following four expedited development and review pathways: Fast Track, Breakthrough, Priority Review, and Accelerated Approval.

FAST TRACK

Seventeen of the 2014 novel new drugs (41%) were designated by CDER as Fast Track, meaning drugs with the potential to address unmet medical needs. Fast Track speeds new drug development and review, for instance, by increasing the level of communication FDA allocates to drug developers and by enabling CDER to review portions of a drug application ahead of the submission of the complete application.

1. BELEODAQ
2. CYRAMZA
3. DALVANCE
4. ENTYVIO
5. ESBRIET
6. HARVONI
7. IMPAVIDO
8. MYALEPT
9. NORTHERA
10. OFEV
11. OPDIVO
12. RAPIVAB
13. VIEKIRA PAK
14. VIMIZIM
15. ZERBAXA
16. ZONTIVITY
17. ZYDELIG*.

BREAKTHROUGH

CDER designated nine of the 2014 novel new drugs (22%) as Breakthrough therapies, meaning drugs with preliminary clinical evidence demonstrating that the drug may result in substantial improvement on at least one clinically significant endpoint (i.e., study result) over other available therapies. A breakthrough therapy designation includes all of the Fast Track program features, as well as more intensive FDA guidance on an efficient drug development program. Breakthrough status is designed to help shorten the development time of a promising new therapy.

1. BLINCYTO
2. ESBRIET
3. HARVONI
4. KEYTRUDA
5. OFEV
6. OPDIVO
7. VIEKIRA PAK
8. ZYDELIG*
9. ZYKADIA

PRIORITY REVIEW

Twenty-five of the 2014 novel new drugs (61%) were designated Priority Review, in which CDER determined the drug to potentially provide a significant advance in medical care and set a target to review the drug within six months instead of the standard 10 months.

1. BELEODAQ
2. BLINCYTO
3. CERDELGA
4. CYRAMZA
5. DALVANCE
6. ENTYVIO
7. ESBRIET
8. HARVONI
9. HETLIOZ
10. IMPAVIDO
11. KEYTRUDA
12. LYNPARZA
13. MYALEPT
14. NORTHERA
15. OFEV
16. OPDIVO
17. ORBACTIV
18. SIVEXTRO
19. SYLVANT
20. VIEKIRA PAK
21. VIMIZIM
22. XTORO
23. ZERBAXA
24. ZYDELIG*
25. ZYKADIA

ACCELERATED APPROVAL

CDER approved eight of the 2014 novel new drugs (20%) under FDA's Accelerated Approval program, which allows early approval of a drug for a serious or life-threatening illness that offers a benefit over current treatments. This approval is based on a "surrogate endpoint" (e.g., a laboratory measure) or other clinical measure that we consider reasonably likely to predict a clinical benefit of the drug. Once Accelerated Approval is granted, the drug must undergo additional testing to confirm that benefit; this speeds the availability of the drug to patients who need it.

1. BELEODAQ
2. BLINCYTO
3. KEYTRUDA
4. LYNPARZA
5. NORTHERA
6. OPDIVO
7. ZYDELIG*
8. ZYKADIA

* ZYDELIG was submitted with two indications of which one of the indications was granted a Breakthrough Therapy, Fast Track and Priority Review; the other was granted Accelerated Approval.

One or more expedited development and review method **66%**

OVERALL USE OF EXPEDITED DEVELOPMENT AND REVIEW METHODS

Two-thirds of the 2014 novel new drugs (27 of 41 or 66%) were designated in one or more categories of Fast Track, Breakthrough, Priority Review, and/or Accelerated Approval. Each of these designations helps expedite the speed of the development and/or approval process and is designed to help bring important medications to the market as quickly as possible.

1. BELEODAQ
2. BLINCYTO
3. CERDELGA
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5. DALVANCE
6. ENTYVIO
7. ESBRIET
8. HARVONI
9. HETLIOZ
10. IMPAVIDO
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18. RAPIVAB
19. SIVEXTRO
20. SYLVANT
21. VIEKIRA PAK
22. VIMIZIM
23. XTORO
24. ZERBAXA
25. ZONTIVITY
26. ZYDELIG
27. ZYKADIA

Fast Track **41%**

Priority Review **61%**

Breakthrough **22%**

Accelerated Approval **20%**

QUALIFIED INFECTIOUS DISEASE PROGRAM DESIGNATIONS

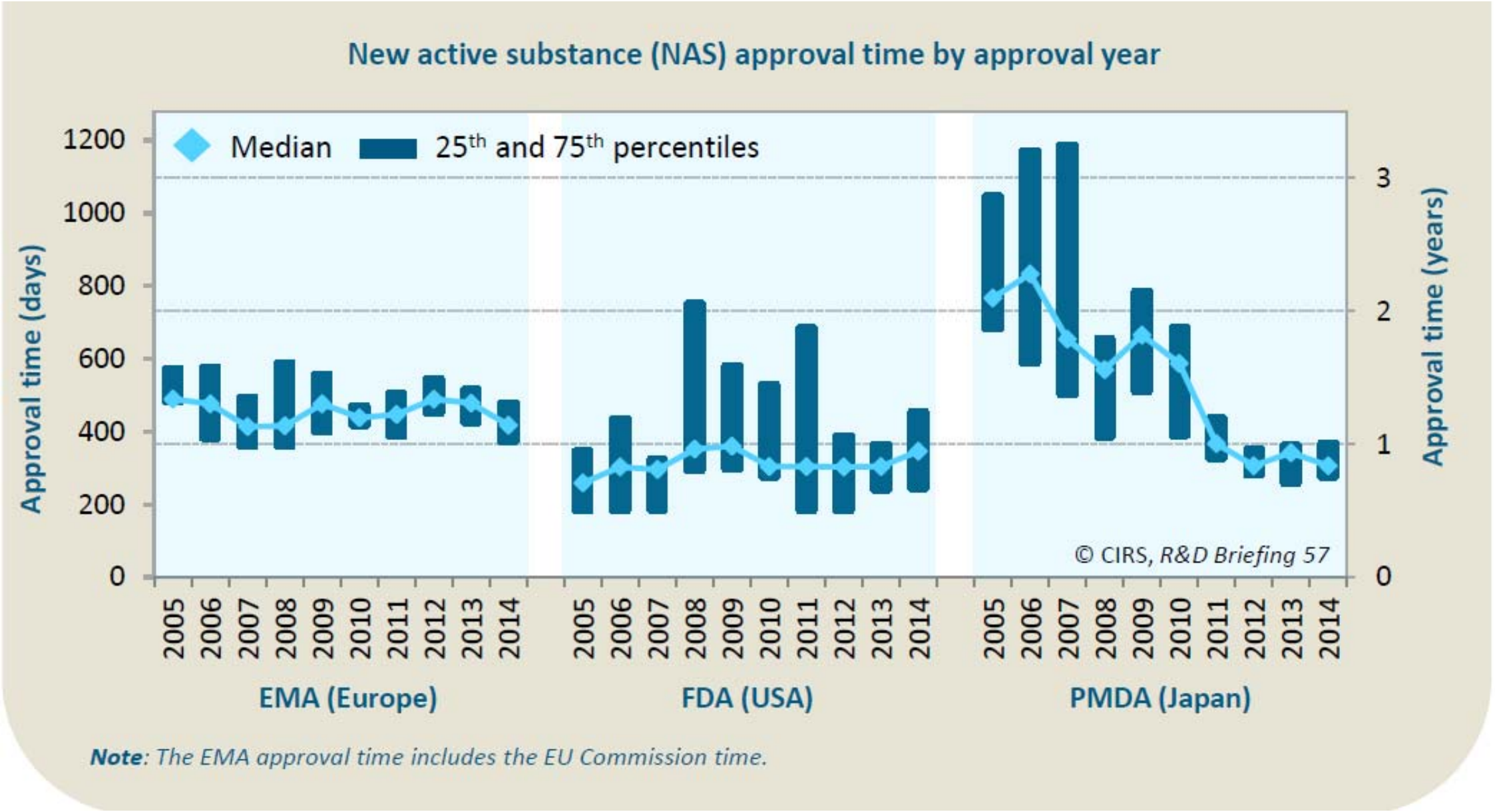
1. DALVANCE
2. ORBACTIV
3. SIVEXTRO
4. ZERBAXA

The Generating Antibiotics Incentives Now Act (GAIN Act) provides incentives to help bring new antibiotics and other antimicrobials to market. A drug with particular promise can be designated as a Qualified Infectious Disease Product (QIDP) by authority of the GAIN Act. In 2014, CDER approved four new antibiotics with this designation, the first four QIDP-designated novel new drugs approved by FDA.

(Ref) Novel New Drugs 2014 SUMMARY, January 2015, U.S. FDA CDER

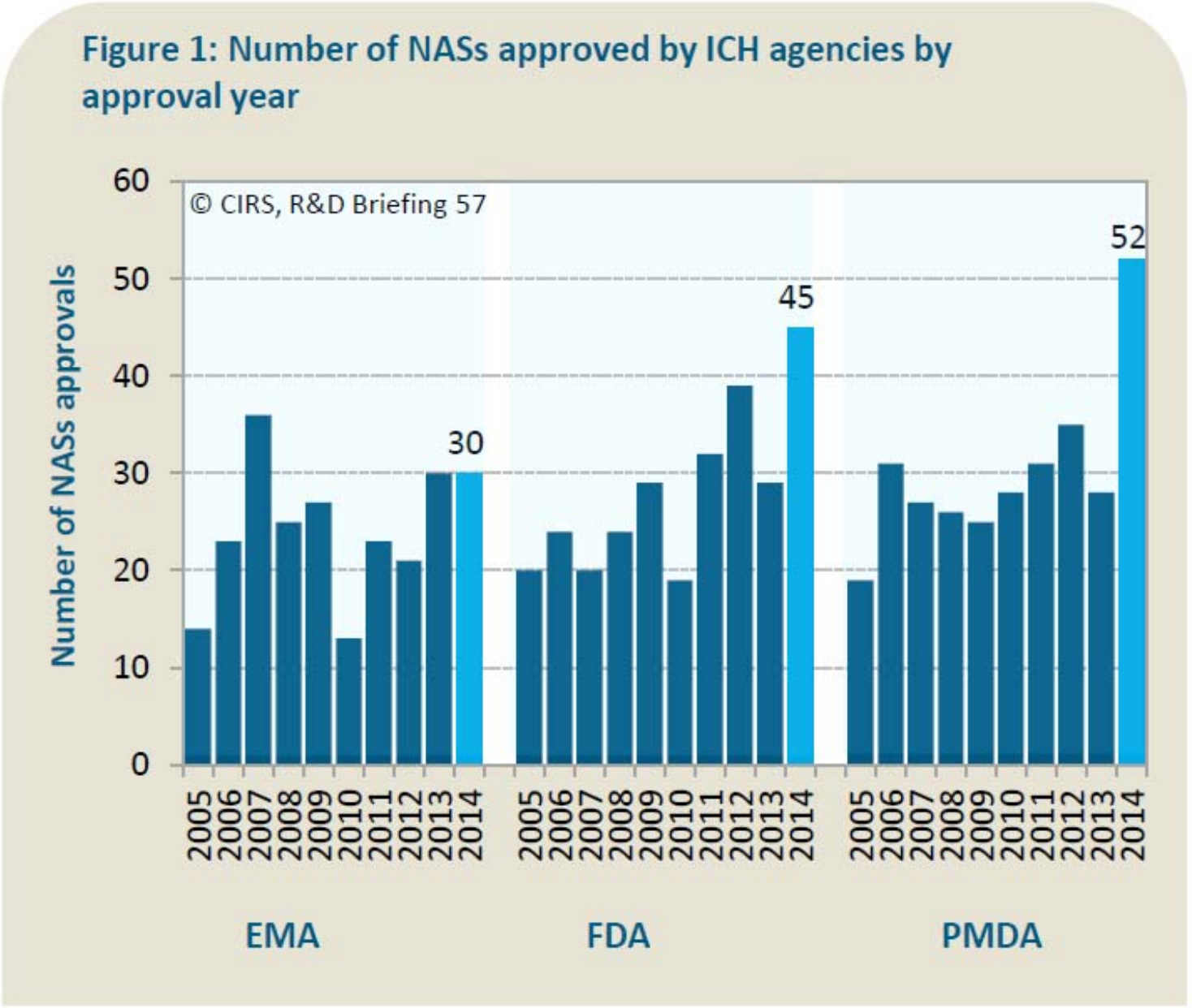
New drug approvals in ICH countries 2005 – 2014

R&D Briefing 57, July 2015, © Centre for Innovation in Regulatory Science, Ltd.



http://cirsci.org/sites/default/files/CIRS_R&D_57_ICH_%20approval_%20times_2005-2014_%2006072015.pdf

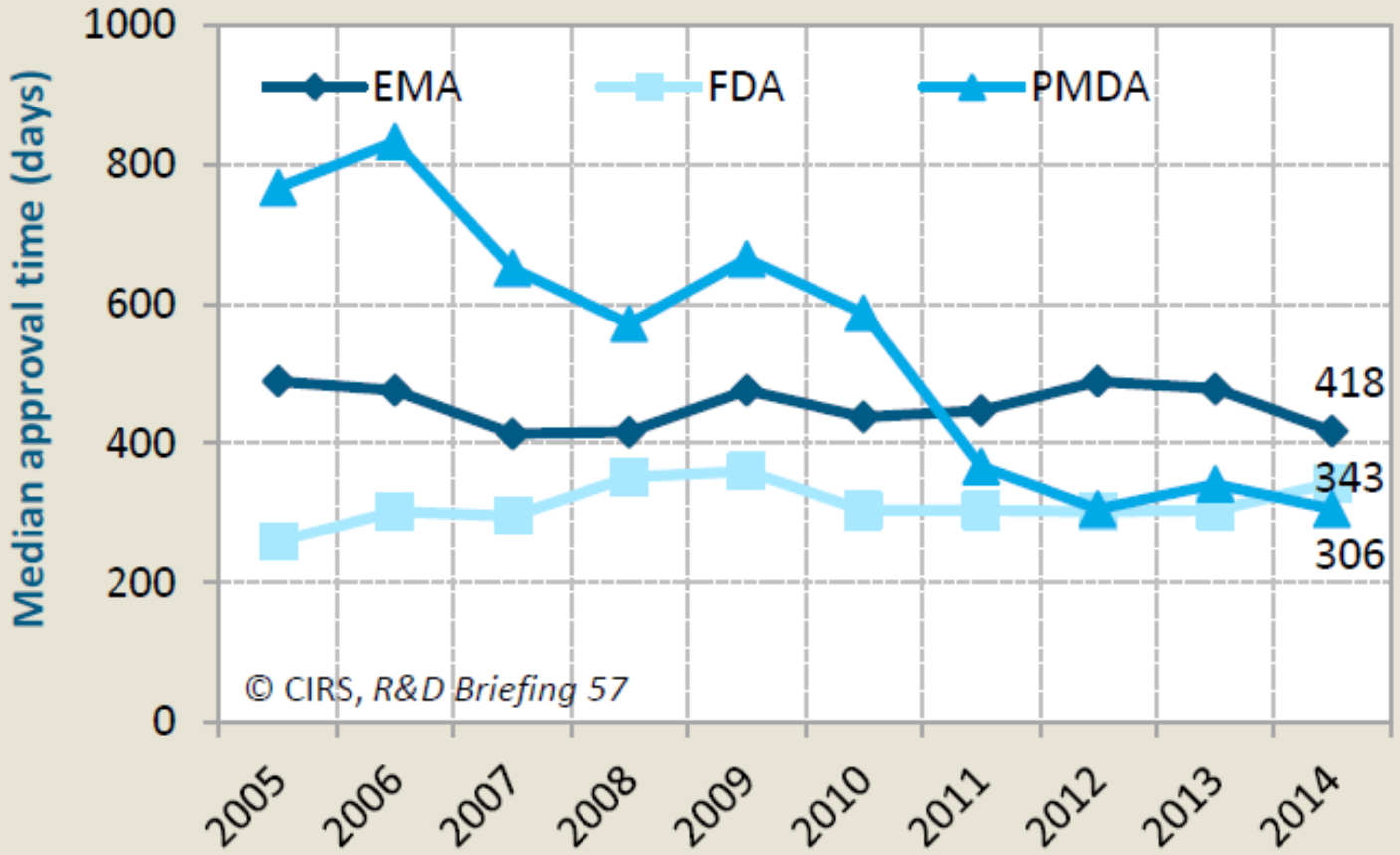
High performance in amount of business



http://cirsci.org/sites/default/files/CIRS_R&D_57_ICH_%20approval_%20times_2005-2014_%2006072015.pdf

High performance at review speed

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



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

http://cirsci.org/sites/default/files/CIRS_R&D_57_ICH_%20approval_%20times_2005-2014_%2006072015.pdf

Japan Revitalization Strategy Revised in 2014

– Japan's challenge for the future –

June 24th, 2014

Section 2 Three Action Plans II. Strategic Market Creation Plan

Theme 1: Extending the nation's "healthy life expectancy"

(3) Specific new measures to be taken

v) Others

2) Promoting world-leading commercialization of innovative drugs and medical devices ("Strategy of SAKIGAKE as a Package")

The Government will promote a package of measures, including the creation of a "priority examination designation system" that would halve the approval examination period before commercialization (from 12 months to 6 months) for drugs identified in the early clinical trial phase as being likely to be remarkably effective. Through these measures, the Government will aim to ensure that Japan leads the world in commercializing innovative drugs, medical devices, regenerative medicine products, and other items targeting fatal diseases (including orphan cancers, intractable diseases, and other serious conditions) for which effective remedies do not currently exist.

Strategy of SAKIFAGE as a Package

～Lead the world in the practical application of innovative medical products～

Promote the strategy package facilitating all the process from R&D, clinical research/trials, pre- and post- marketing safety, insurance coverage, through globalization of innovative products which are to be put into practical use. Specifically, this package is targeting innovative pharmaceuticals/medical devices/regenerative medicine which can cure serious illnesses (such as rare cancer etc.) without established therapy.

Prioritized Policy I — ***SAKIGAKE***

Prioritized Policy II — **Scheme to rapid authorization of unapproved drug**

Pre-Clinical Research → **Clinical Research /Trial** → **Approval** → **NHI* Price Listing** → **facilitate the environment for industry activities** → **International Deployment**

*:National Health Insurance

Accelerate R&D through supporting each stage

- Coalition between “Network for Drug Discovery” and “Pharmaceutical Affairs Consultation on Research and Development (R&D) Strategy”
- Support of Drug-Repositioning (DR) and development of off-label use
- Development of safety assessment technique for iPS followed by international standardization
- R&D through public-private joint project

- High-quality clinical trials by Clinical Trial Core Hospital・ NC and coalition with research group for rare diseases
- Support for orphan drug R&D
  Support for ultra-orphan through the R&D to Early designation
- Support for Drug Development through Medical Information and Communication Technology (MICT)
  - DB of Medical Information
  - Rapid and effective Clinical Trials
  - Incorporation into review for approval

- Analysis on Modeling and Simulation (M&S) conducted by PMDA
- Utilizing Pre-application Consultation
- Strengthening measures on post-marketing safety
  Development of system of patient registry
  Research on biomarker

- Improve the predictability of NHI drug price
  - Discussion on Premium to promote the development of new drugs and eliminate off-label use

- Strengthening industry competitiveness
  - tax incentive
  - HR Development
- Support for SME and venture
  - Discussion on funding system for review user fee to be implemented
- Utilization of the data from clinical research of rare disease / cancer for post-marketing surveillance

- Mutual understanding of the process from R&D to approval with the trading partner, to promote export

Strengthen the structure of PMDA (consultation, review, safety measures in terms of quality and quantity)

Promotion of Regulatory Science (Developing guidelines/assessment for the state-of-the-art technology)

SAKIGAKE Designation System

SAKIGAKE is a strategy to put innovative medicines/medical devices/regenerative medicines into practice.

Designation Criteria

Medical products for diseases in dire need of innovative therapy and satisfies the following two conditions:

1. Applied for approvals firstly in Japan or simultaneously in Japan and other countries (desirable to have PMDA consultation from the beginning of R&D)
2. Prominent effectiveness (i.e. radical improvement compared to existing therapy), can be expected based on the data of mechanism of action from non-clinical study and early phase of clinical trials (phase I to II)

Designation Advantage

: To shorten the time to approval

: To facilitate R&D

①Prioritized Consultation
[Waiting time: 2 months→1 month]
Shortening a waiting time for a clinical trial consultation from the submission of materials.

② Substantial Pre-application Consultation
[de facto review before application]
Accepting materials in English

③Prioritized Review
[12 months → 6 months]
Striving to conclude review within 6 months
* Accept the result of phase III study after the application on a case-by-case basis to shorten the time from R&D to approval

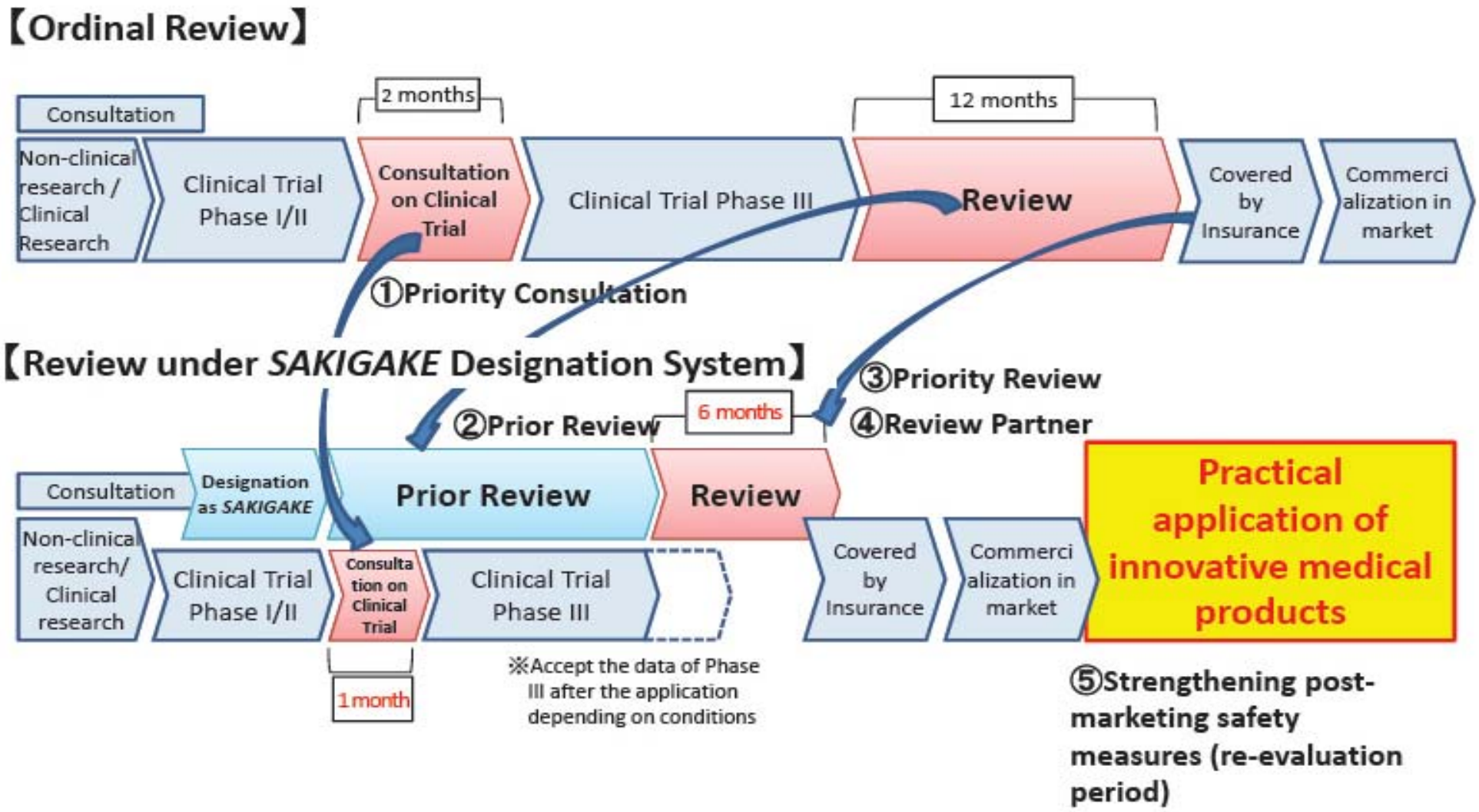
④Review Partner
[PMDA manager as a concierge]
Assign a manager as a concierge to take on overall management for the whole process toward approval including conformity assurance, quality management, safety measures, and review

⑤Substantial Post-Marketing Safety Measures
[Extension of re-examination period]
Strengthening post-marketing safety measures such as extension of re-examination period as well as facilitating coalition with scientific societies, and transmission of information globally.

Designation Procedure

1. **Initiation by applicant:** Application is to be submitted to the Evaluation and Licensing Division (ELD) and to be reviewed at the PMDA. The result is to be notified within 60 days.
2. **Initiation by the ELD:** the ELD is to approach a potential applicant. The result is to be notified within 30 days after the submission, if agreed by the applicant.

General Timeframe of SAKIGAKE



Criteria for designation

[1] Innovativeness of the product

In principle, the product should have a novel mechanism of action that is different from those of approved drugs (including a drug with a mechanism of action indicated for the target medical condition for the first time, even though the mechanism of action is the same as that of approved drugs, or a drug that is expected to produce a radical improvement in efficacy by means of an innovative drug delivery system, for example)

[2] Treatment for which the earliest commercialization is required for target diseases

The target medical condition should be one of the following:

- Serious or life-threatening medical condition
- Medical condition with persistent symptoms (conditions interfering with normal activities of daily living) for which there is no other curative treatment

[3] Highly effective treatment against the target medical condition

There is no approved drug for treating the target medical condition, or the symptoms of patients are expected to be significantly improved through use of the product as compared to the efficacy of existing drugs or therapies (including the case where safety is expected to be improved significantly).

[4] Develop the product rapidly and file an application for approval in Japan, ahead of other countries

The sponsor of the product should be planning to file an initial application in Japan, ahead of any other country (including the case where simultaneous applications are planned to be made in both Japan and other countries), focusing on starting development at an early stage in Japan. It is desirable for the product to be at least one of the following therapeutic drugs in order to confirm the fact that development in Japan is progressing steadily:

- Product for which FIH study was conducted in Japan
- Product for which POC study was conducted in Japan

* If it is confirmed that the aim is to file an initial application for the product in Japan, ahead of any other country at the time of designation, there should be no problem with other preferential systems applied in other countries.

Schedule for the Future until the First Designation

Step1：Trial operation beginning and public advertisement

◆ The notification is made public to the start in 2015 fiscal year, and it advertises for the candidate products after a well-known period of about one month.

Step2：Hearing and preliminary selection on candidate products

◆ The Evaluation and Licensing Division conducts hearing on the candidate products to be applied, and the potential candidates meeting specified criteria are selected as candidates of the preparatory phase.

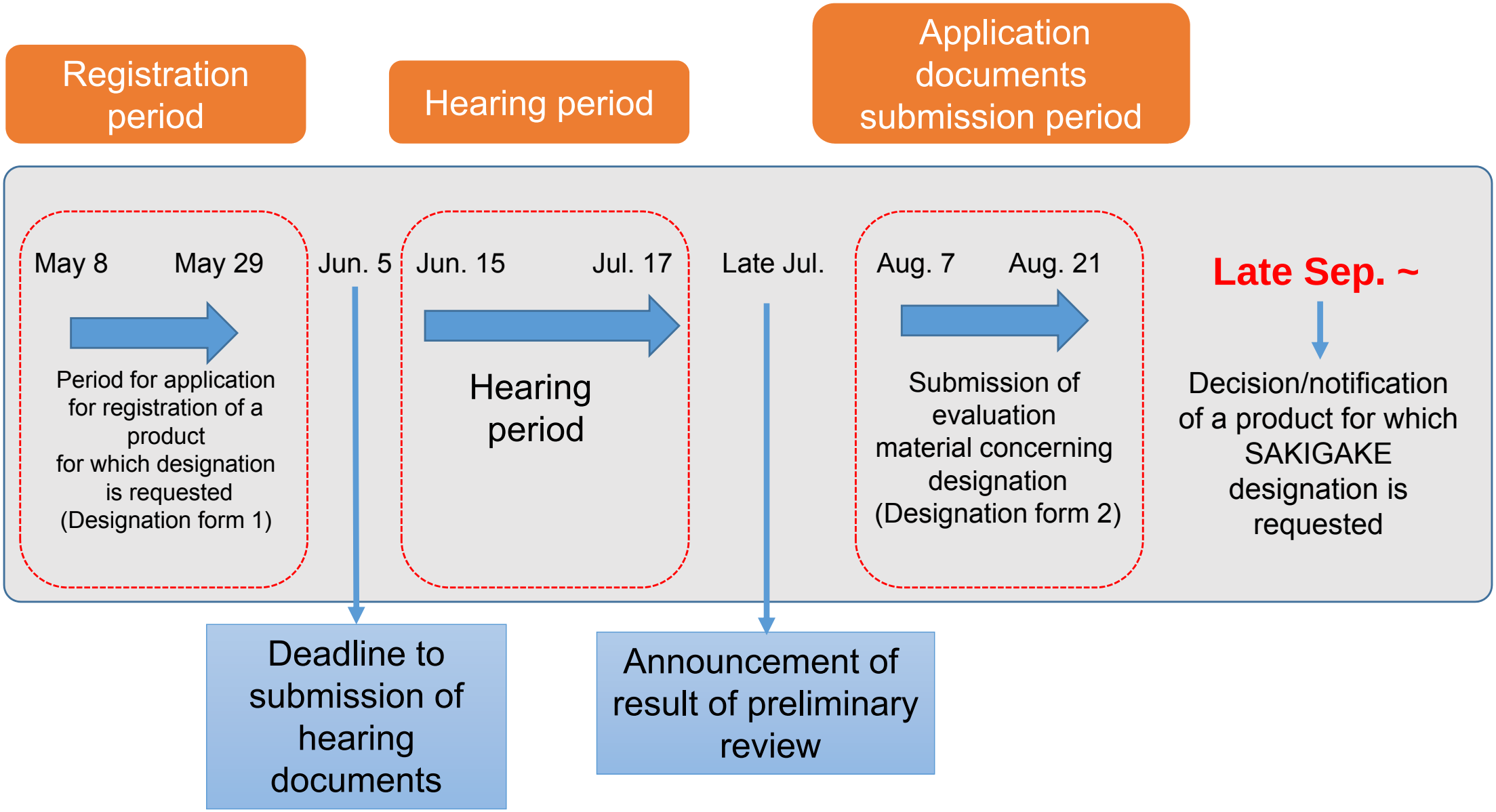
Step3：Evaluation and prioritization

◆ The New Drug Review Division of PMDA evaluates the applied products on each area in charge, and it sets priorities. Especially, the product judged to be excellent is selected.

Step4：Specification and report to subcommittee meeting

◆ Excellent products are specified as SAKIGAKE designated products based on the evaluation results, and the designation results are made public. The PMDA promptly reports the designation results to the Pharmaceutical Affairs and Food Sanitation Council.

Pilot scheme for FY2015 review under SAKIGAKE designation system



厚生労働省

Ministry of Health, Labour and Welfare

Thank you for your attention !

SAKIGAKE in English:
http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/140729-01.html