Introduction of the Conditional Early Approval (CEA) System in Japan

7th APAC RA-EWG Session Part 2

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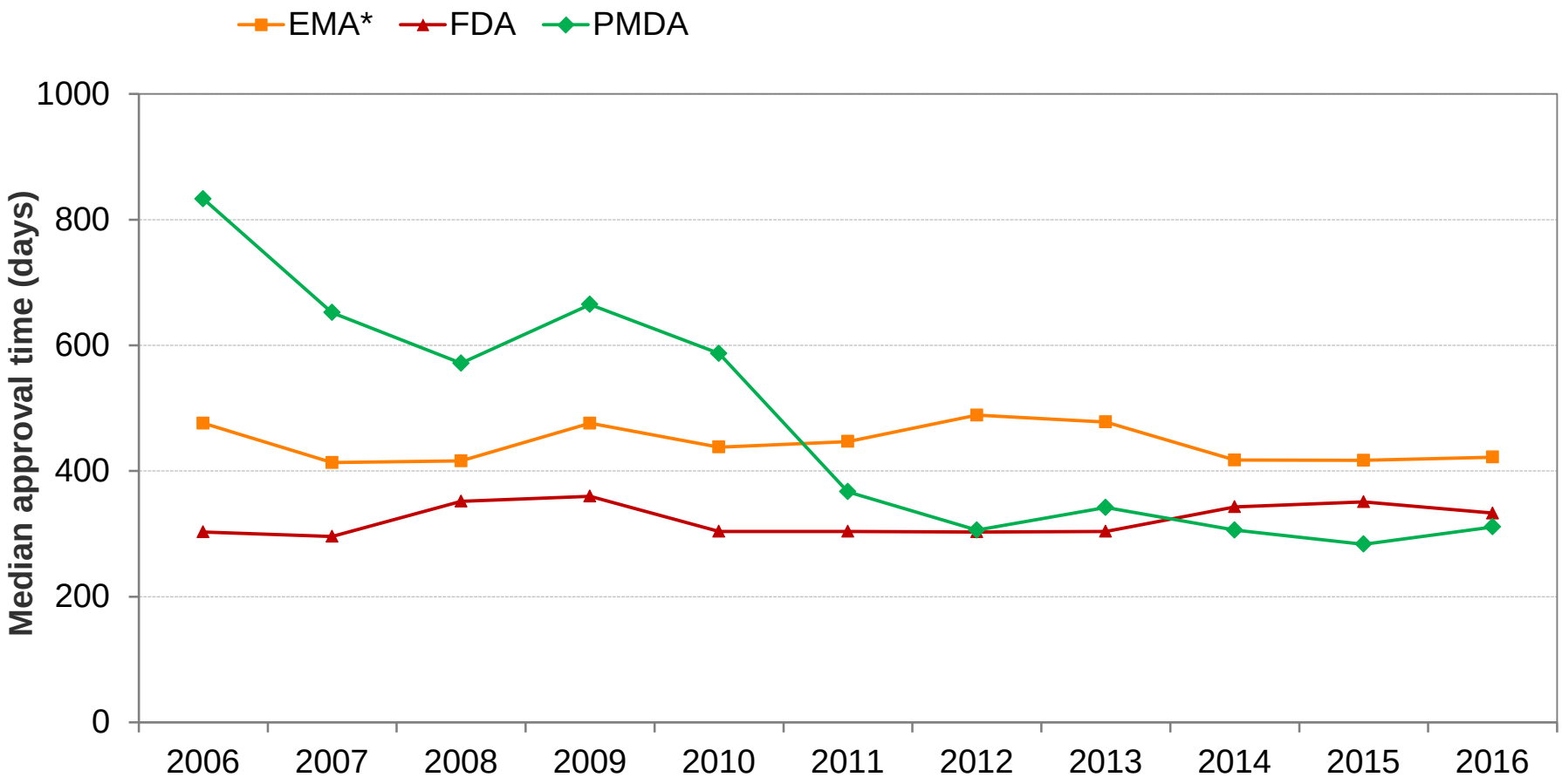
New active substance median approval time for three regulatory authorities in 2006-2016



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The Center for Innovation in Regulatory Science 2016 and 2017

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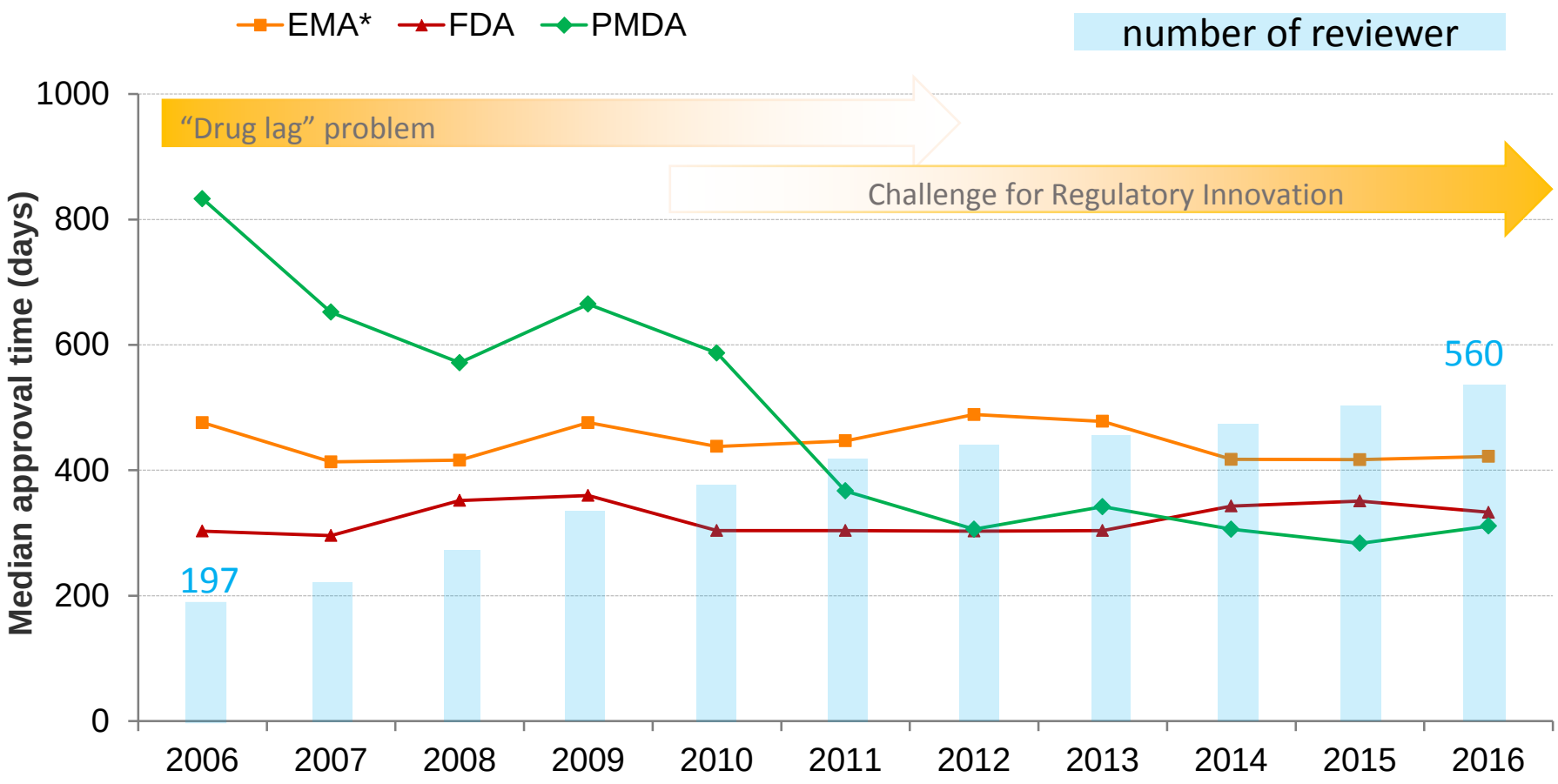

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The Center for Innovation in Regulatory Science 2016 and 2017

Lead the regulatory science innovation

Stage	Agendas for PMDA	Activity
Development	○Support for promising seeds to forward the development	→ Pharmaceutical Affairs Consultation on R&D Strategy(July 2011)
Review	○Approaches to cutting-edge technologies (by collaboration with Academia)	→ Science Board (June 2012)
	○Support for early practical use of regenerative medical products	→ Conditional time-limited Authorization for Regenerative Medical Products(Nov. 2014)
	○Encourage Japan-first development and approvals	→ SAKIGAKE Designation System (FY2015) → Conditional Early Approval System for Pharmaceuticals(FY2017)
	○Improve efficiency of development and review process by utilizing electronic data	→ Advanced review system (Oct. 2016)
Post-marketing	○Utilize medical information database to develop more sophisticated safety measures	→ MIHARI project (FY 2009) MID-NET project (FY2018)

SAKIGAKE designation system

SAKIGAKE is a strategy by MHLW to put innovative medicines/medical devices/regenerative medicines into practice by promoting R&D.

Designation Criteria

1. Innovative medical products
2. For serious diseases
3. Development & NDA in Japan being world's first or simultaneous with other countries
4. Prominent effectiveness expected on non-clinical and early phase clinical studies

Advantage for Designated Products

Prioritized Consultation
[Waiting time: 2 →1 month]

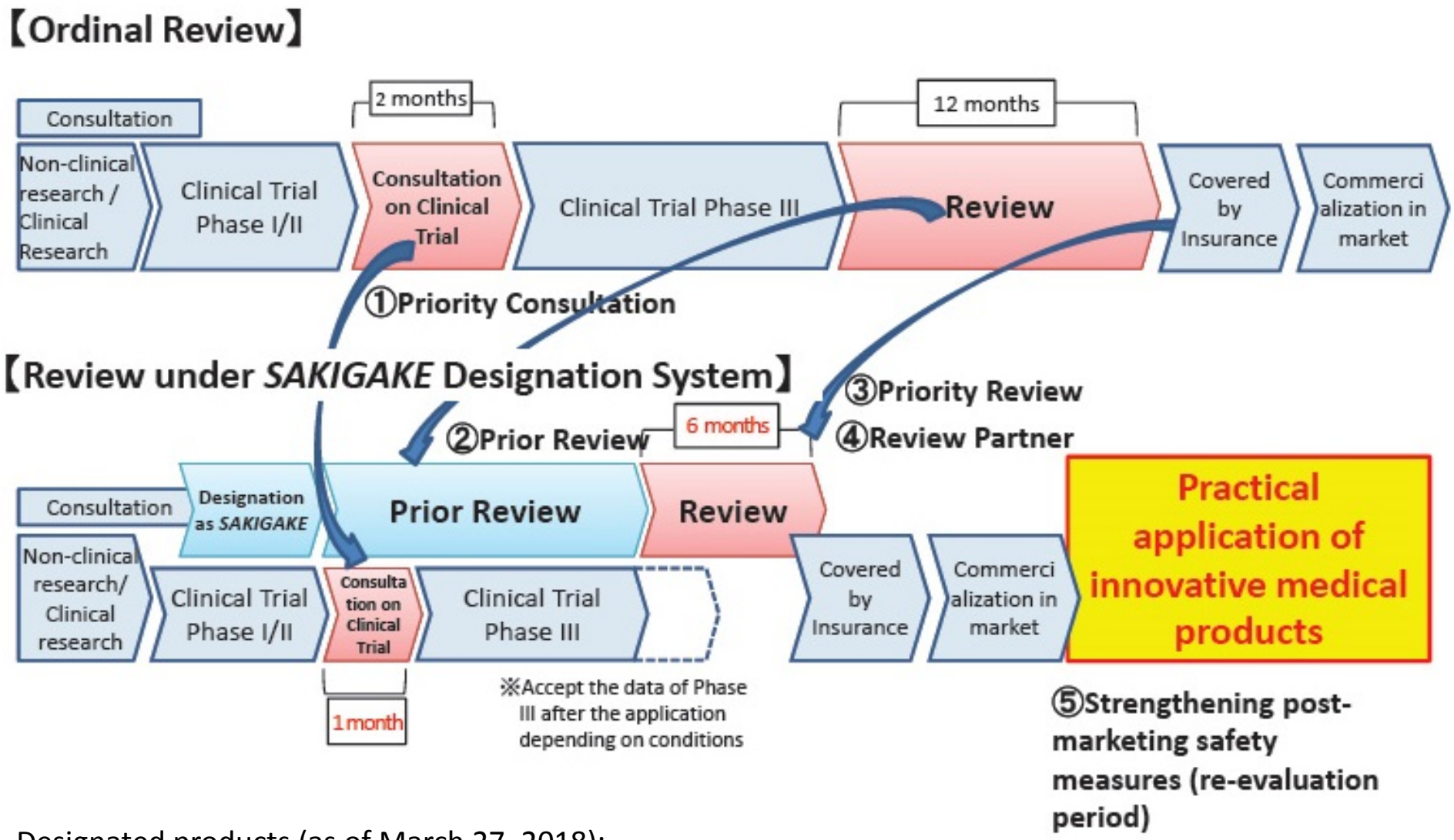
Prior-Review Consul.
(Rolling Review)

Prioritized Review
[12 → 6 months]

Review Partner
[PMDA manager as concierge]

Post Market Measures
[Extension of re-examination period considered]

SAKIGAKE general timeframe



Designated products (as of March 27, 2018):
16 Pharmaceuticals, 5 Medical Devices, 9 Regenerative Products and 1 IVD

1st Round SAKIGAKE Products

(Pharmaceuticals, designated Oct. 2015)

Name of drug	Proposed indication	Applicant
Sirolimus (NPC-12G)	Angiofibroma associated with tuberous sclerosis Approved	Nobelpharma Co., Ltd.
NS-065/NCNP-01	Duchenne muscular dystrophy (DMD)	Nippon Shinyaku Co., Ltd
S-033188	Influenza A or B virus infection Approved	Shionogi & Co., Ltd.
BCX7353	Management of angioedema attacks in patients with hereditary angioedema (HAE)	Integrated Development Associates Co., Ltd.
ASP2215	First-relapsed or treatment-resistant FLT3 mutation-positive acute myeloid leukaemia	Astellas Pharma Inc.
Pembrolizumab (genetical recombination)	Unresectable, advanced and recurrent gastric cancer Withdrawn SAKIGAKE designation	MSD K.K.

2nd Round SAKIGAKE Products

(Pharmaceuticals, designated Apr. 2017)

Name of drug	Proposed indication	Applicant
Olipudase alfa (genetical recombination)	Acid Sphingomyelinase Deficiency (Niemann-Pick Disease)	Sanofi K.K.
Aducanumab	Alzheimer disease	Biogen Japan, Ltd.
DS-5141b	Duchenne muscular dystrophy (DMD) who has a mutation of the dystrophin gene that is amenable to exon 45 skipping	Daiichi Sankyo Co., Ltd.
SPM-011/ for Boron neutron capture therapy(BNCT) system*	Recurrent malignant glioma Unresectable local recurred H&N cancer / local advanced H&N cancer (non squamous)	Stella Pharma Corp. Kyoto University Sumitomo Heavy Industries, Ltd.
Nivolumab (genetical recombination)	Biliary tract cancer	Ono Pharmaceutical Co.,Ltd.

*BNCT system is designated as a SAKIGAKE product on Feb. 2017

3rd Round SAKIGAKE Products

(Pharmaceuticals, designated Mar. 2018)

Name of drug	Proposed indication	Applicant
RTA402	Diabetic kidney disease	Kyowa Hakko Kirin Co., Ltd.
JR-141	Mucopolysaccharidosis Ⅱ (Hunter syndrome)	JCR Pharmaceuticals Co., Ltd.
Tafamidis Meglumine	Transthyretin Cardiac Amyloidosis (TTR-CM)	Pfizer Japan Inc.
MSC2156119J	*MET* positive Locally Advanced or Metastatic NSCLC	Merck Serono Co., Ltd.
Trastuzumab deruxtecan	Unresectable, advanced and recurrent Gastric Cancer with *HER2* overexpression	DAIICHI SANKYO Co., Ltd.
Entrectinib	Adult and child solid tumors harboring *NTRK* gene rearrangement	Ignyta Inc.

Conditional Early Approval System for Pharmaceuticals

The purpose of the Conditional Early Approval System for Pharmaceutical Products is to facilitate faster patient access to drugs offering high clinical utility with respect to severe diseases. Eligible drugs are those indicated for severe diseases with few effective treatments, for which confirmatory clinical trial execution is time-consuming or impracticable due reasons such as a small subject population. By requiring applicants to conduct post-marketing surveys as a condition for approval, this system enables swifter approvals of products demonstrating the necessary levels of efficacy and safety based on nonconfirmatory clinical study results. Conditionally approved product efficacy and safety will be re-examined through post-marketing vigilance activities.

Usual application review

Exploratory clinical studies*1, etc. → Confirmatory clinical studies*2 → Application Submission and Review → Approval → Adverse drug reaction reporting Post-marketing surveillance

*1 Small-scale, dose-finding clinical studies investigating drug efficacy and safety
*2 Large-scale clinical studies investigating the efficacy and safety of an established dosing regimen

Conditional early approval system

Exploratory clinical studies*1, etc. → Application review → Approval → Adverse drug reaction reporting Post-marketing surveillance

- Early approval enabled by ensuring a certain level of efficacy and safety in nonconfirmatory clinical studies
- Shorter review time through priority review product designation

Examples of conditions for approval:
- **Re-confirming product efficacy/safety during the post-marketing phase (Use of Real-World Data permitted)**
- **Establishing policies to ensure optimal product use by medical institutions, as necessary**

Pharmaceutical products eligible for the system

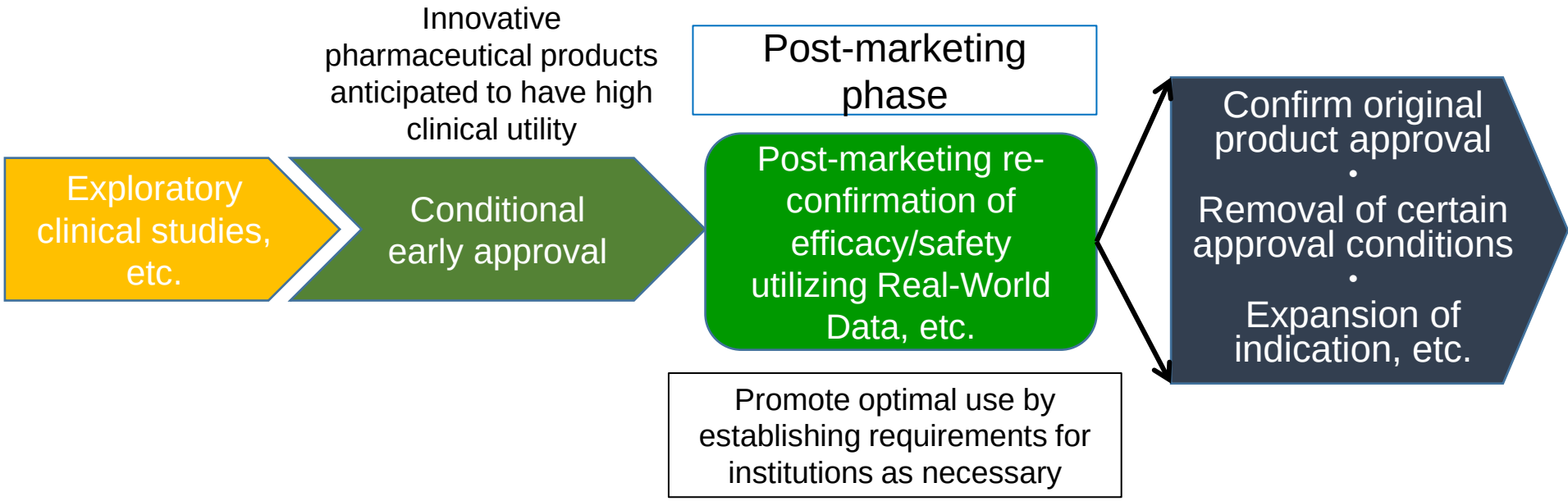
Pharmaceutical products that meet each of the following criteria

* Current requirement for priority review product classification

1. Disease severity
   - The condition presents a substantial risk to patient survival (life-threatening)
   - The condition is irreversible and presents a significant hindrance on daily activities
   - Other serious conditions
2. Clinical utility
   - No treatments, prophylactic measures, or diagnostics currently exist
   - The product offers superior clinical utility over existing treatments, prophylactic measures, or diagnostics in terms of efficacy, safety, and physical/psychological burden on patients
3. Conducting confirmatory clinical studies is believed to be impracticable, or, if deemed feasible, execution is anticipated to require considerable time due to a small subject population
4. Results of clinical studies other than confirmatory clinical studies suggest a certain level of efficacy and safety

* "Outlook on priority review" (PSEHB/PED notification No. 0122-12, PSEHB/MDED notification No. 0122-2, dated January 22, 2016)

Requirements for Conditional Early Approval



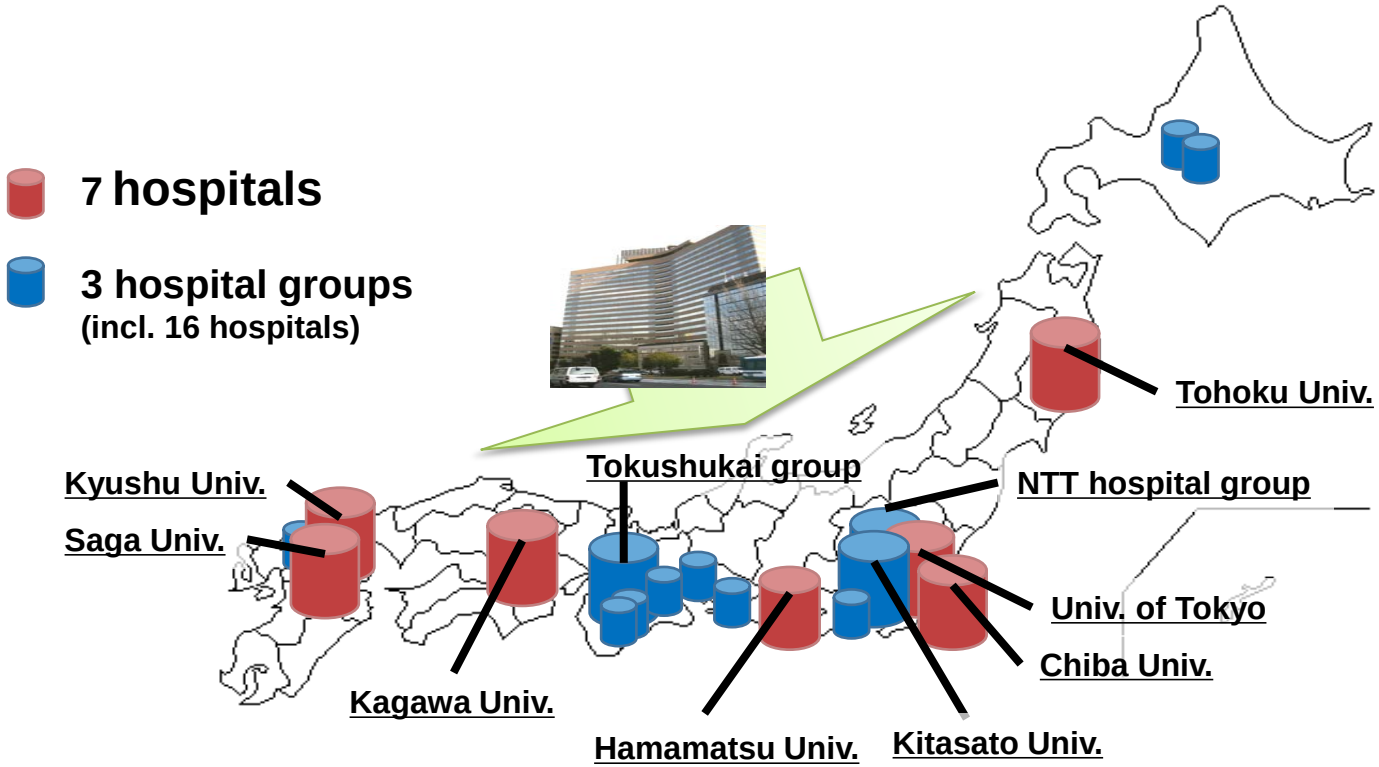
- Results of clinical studies other than confirmatory clinical studies suggest a certain level of efficacy and safety (e.g., exploratory clinical studies or non-clinical studies) at the time of review.
- Approval requirements include confirmation of efficacy/safety by collecting data that demonstrates the rationale and medical significance of the product. Such post-marketing data may include Real-World Data, etc*.

*Includes utilization of the Medical Information Database-Network (MID-NET) project and patient registry data maintained by the Clinical Innovation Network.

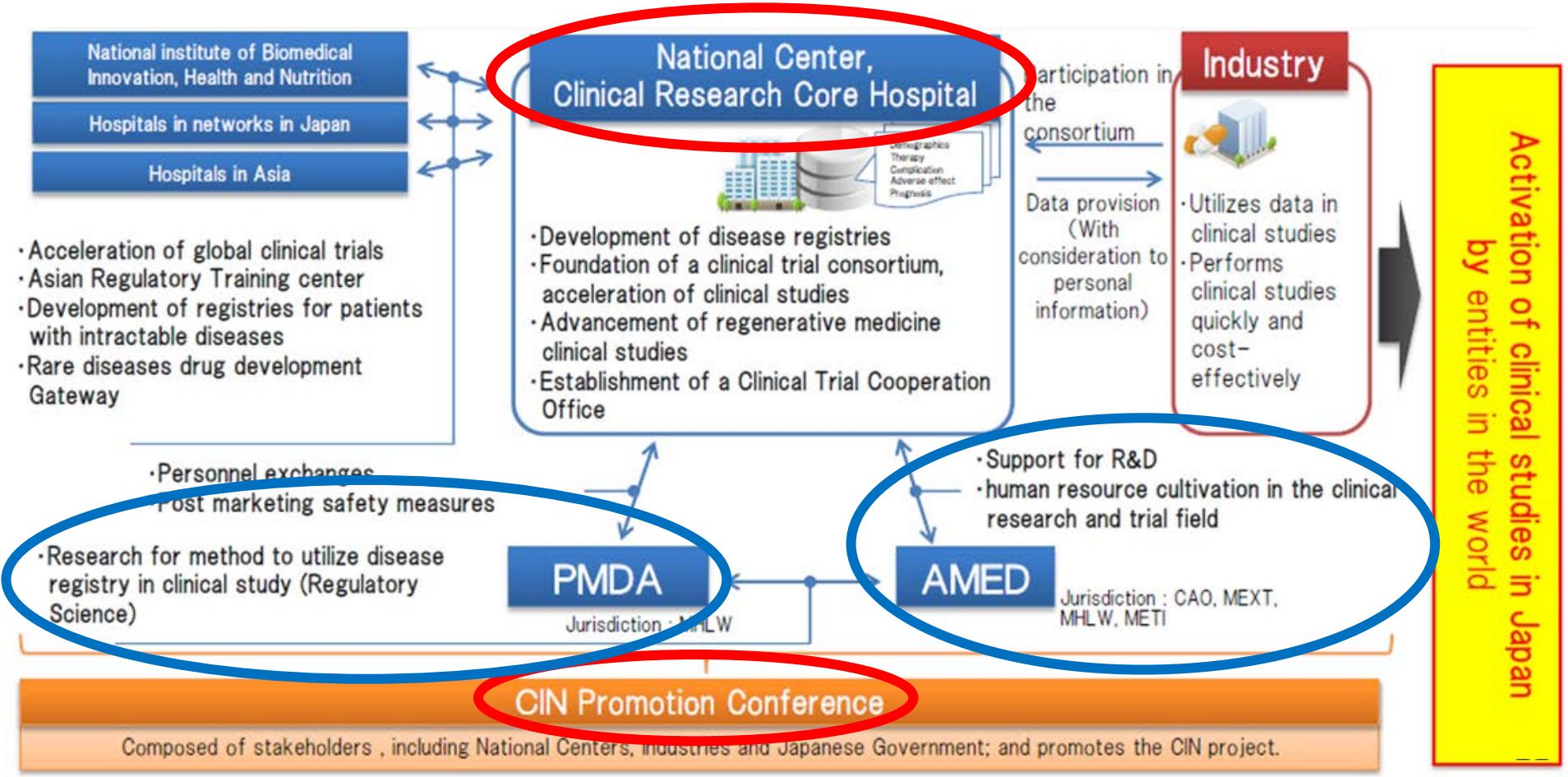
- Requirements for institutions will be established as necessary according to the characteristics of the target disease or the pharmaceutical product in order to promote optimal use.
- Authorization requirements may be waived according to the results of the post-approval evaluation. Expansions of indications based on such evaluation may be considered, once sufficient data is collected.

Ongoing projects for the application of “Real World Data” -MID-NET-

MID-NET（Medical Information Database Network） is a national project initiated by MHLW to establish the DB network for MIHARI Project to utilize electronic healthcare data for drug safety.



Ongoing projects for the application of “Real World Data” -Clinical Innovation Network (CIN)-



http://pari.u-tokyo.ac.jp/eng/event/smp150818_mori.pdf

Process flow for determining eligibility for “Conditional Early Approval”

Based on the result of exploratory clinical studies (phase II studies, etc.), the following information should be prepared in conjunction with use of PMDA’s consultation services:

- Conditional early approval system eligibility
- Required application materials
- Overview of anticipated approval conditions

To be evaluated in reference to data and summary documents indicating the product’s clinical significance

Upon the implementation of this system, the PMDA will begin offering consultation services specifically to assess eligibility under the Conditional Early Approval system for pharmaceutical products.

PMDA will prepare an assessment report regarding System Eligibility while ensuring the agreement by the applicant on its content.

Applicant will file an application with the assessment report.

The Ministry of Health, Labour and Welfare will report the results of its consideration concerning System Eligibility to the Pharmaceutical Affairs and Food Sanitation Council for endorsement.

The product will be reviewed under the Conditional Early Approval system.

Approved anticancer agent in Japan without confirmatory clinical trial (2015-2016)

Brand Name / INN	Indication	Pivotal Study	Primary EP	Remarks
Yondelis® I.V.infusion (Trabectedin)	Malignant Soft Tissue Sarcoma	Phase Ⅱ (J, 2arm)	PFS	Orphan drug designation
Targretin® cap. (Bexarotene)	Cutaneous T-cell Lymphoma (CTCL)	Phase Ⅰ/Ⅱ (J)	ORR	Orphan drug designation
Zykadia® cap. (Ceritinib)	Crizotinib resistant *ALK* positive Non Small Cell Lung Cancer (NSCLC)	Phase Ⅱ (MRCT)	ORR	Orphan drug designation
Tagrisso® tab. （Osimertinib）	*EGFR* T790M positive NSCLC	Phase Ⅱ (MRCT)	ORR	Priority review
Iclusig® tab. (Ponatinib)	Chronic Myelogenous Leukemia (CML) Ph+ Acute Lymphoblastic Leukemia (Ph+ALL)	Phase Ⅱ (Oversea)	Cumulative MCyR / MaHR	Orphan drug designation
Opdivo® I.V. infusion (Nivolumab)	classical Hodgkin's Lymphoma (cHL)	Phase Ⅱ (J) Phase Ⅱ (Oversea)	ORR	Orphan drug designation
Erwinase® lyophilisate for injection (Crisantaspase)	Acute Leukemia and Malignant Lymphoma patients receiving treatment with L-asparaginase from *E.coli*, and who develop hypersensitivity to that enzyme	Phase Ⅱ (J)	Serum L-asparaginase activity	Request from MHLW Unapproved/ Off-labeled Drug Committee
Revlimid® cap. (Lenalidomide)	Adult T-cell Leukemia / Lymphoma (ATLL)	Phase Ⅱ (J)	ORR	Orphan drug designation
Mundesine® cap. (Forodesine)	Peripheral T-cell Lymphoma (PTCL)	Phase Ⅱ (J)	ORR	Orphan drug designation

Source: PMDA Science Board rare cancer subcommittee

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Orphan drug designation vs SAKIGAKE vs CEA
-Timeframe of various review categories-