Japan's Approaches to Accelerated/Conditional Drug Approval

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New Pharmaceuticals A Virtual Workshop
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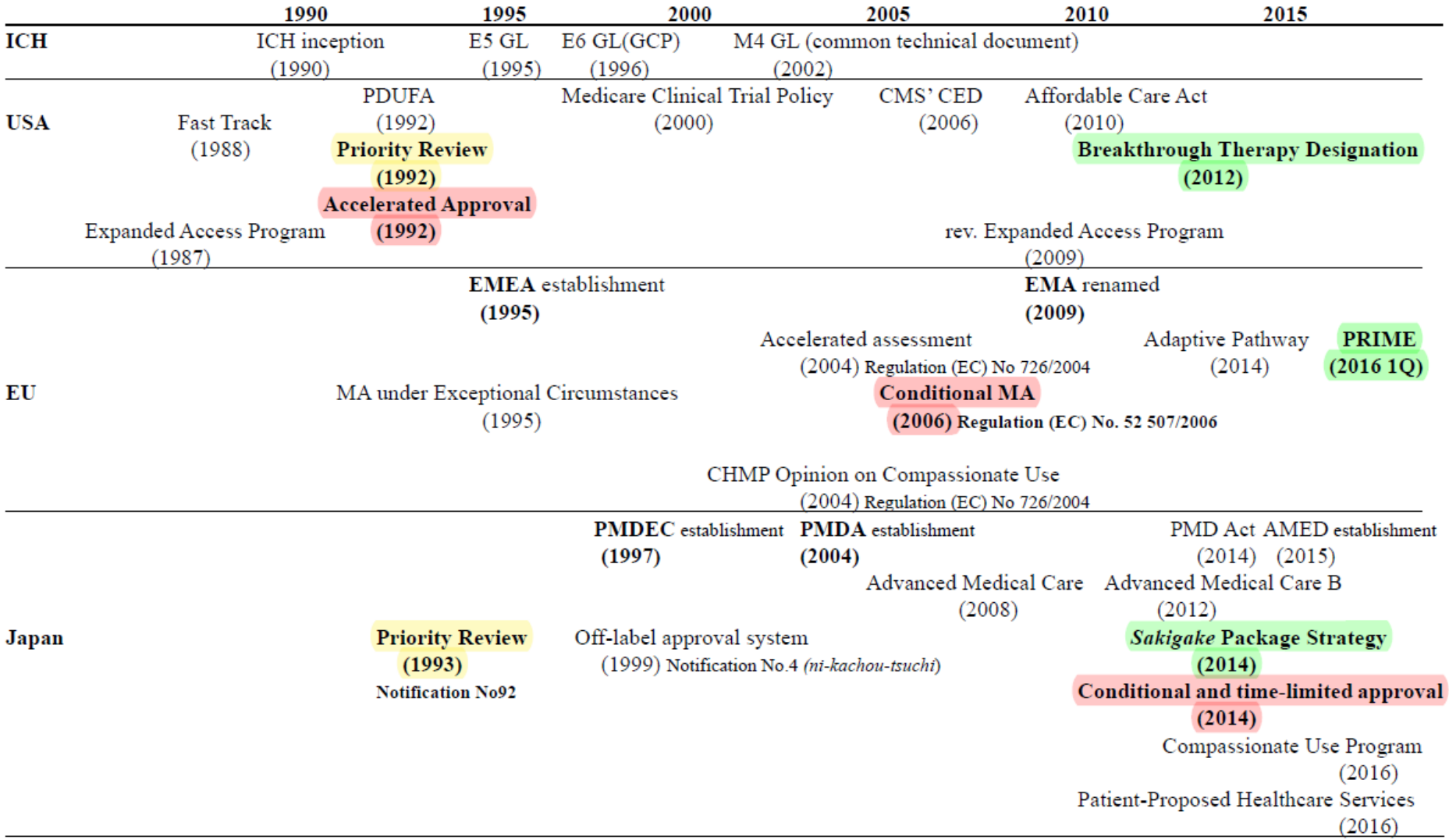
Today's Topics

1. Comparison of Existing Accelerating Pathways
2. Accelerated/Conditional Drug Approval in Japan
3. Conditional Early Approval System (CEAS) for Drugs
4. A Comprehensive Healthcare Framework is Needed

Timeline of Regulatory Actions for Expedited Drug Access in Japan, the EU and the United States



AMED, Japan Agency for Medical Research and Development; **CED**, coverage with evidence development; **CHMP**, Committee for Medicinal Products for Human Use; **CMS**, Centers for Medicare and Medicaid Services; **EMEA**, European Agency for the Evaluation of Medicinal Products; **EMA**, European Medicines Agency; **GL**, guideline; **ICH**, The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; **MA**, marketing authorization; **PDUFA**, the Prescription Drug User Fee Act; **PMDA**, Pharmaceuticals and Medical Devices Agency, Japan; **PMD Act**, the Pharmaceuticals and Medical Devices Act; **PMDEC**, Pharmaceuticals and Medical Devices Evaluation Center of the National Institute of Health Sciences, Japan; **PRIME**, priority medicines scheme of the EMA

Fujiwara Y. Nature Rev Drug Discov 15:293-294, 2016 Table S2

2017

Conditional Early Approval System (CEAS)

Comparison of Existing Accelerating Pathways

	FDA(Breakthrough)	EMA(PRIME)	Japan PMDA(SAKIGAKE)
Establishment	2012	2016	2015
Requirements/Criteria	● Treatment for serious or life-threatening conditions ● Preliminary clinical evidence that demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy	● May offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. ● Show its potential to benefit patients with unmet medical needs based on early clinical data	● Innovative medical products ● For serious diseases ● Development & NDA in Japan: being world's first or simultaneous with other countries ● Prominent effectiveness expected on non-clinical and early phase clinical studies
Number of designated products	502 (264 has been approved) (as of 30 Sept 2022)	109 (23 has been approved) (as of 17 Oct 2022)	23 (13 has been approved) (as of 28 Mar 2022)
Designation	Concurrently with, or at any time after, the submission	At the time of application	At any time

◆ Common points among Breakthrough/PRIME/SAKIGAKE
- ➢ Clear criteria
- ➢ Rolling process
- ➢ Facilitating communication between Regulators and MAHs prior to submission

Accelerated/Conditional Drug Approval in Japan

Type	Area	Product Features
Expedited review	Any product categories	In a particular situation requiring expedited review
Priority review		Designated as: 1. Orphan 2. Apparent improvement of medical care and for severe diseases
SAKIGAKE (Forerunner designation)		• Innovative medical products • For serious diseases • Development & NDA in Japan: being world's first or simultaneous with other countries • Prominent effectiveness expected on non-clinical and early phase clinical studies
Conditional Early Approval	Drugs	Early application through confirmation of a certain degree of efficacy and safety in clinical trials other than confirmatory clinical trials
	Medical Devices	• High clinical needs • Balancing the pre- and post-market requirements
Conditional and Time-limited Approval	Regenerative Medical Products	• Based on the clinical data from a limited number of patients, efficacy is predicted in a shorter time compared with the conventional process. • Acute-phase adverse reactions etc., can be evaluated for safety in a short period of time.

Conditional Early Approval System (CEAS) for Drugs

【Qualifying criteria】 Drugs that meet all of the criteria below:

 # The indicated disease is regarded as severe based on comprehensive evaluation using criteria ①－③ below:

① The indicated disease presents a substantial risk to patient survival (life threatening).
② The indicated disease is irreversible and significantly hinders daily activities.
③ Other serious conditions

 # The drug is considered to have high clinical utility based on comprehensive evaluation using criteria ①and ② below:

① No other treatments, prophylactic measures, or diagnostic methods currently exist.
② The product offers superior clinical utility compared to existing treatments, prophylactic measures, or diagnostic methods in terms of efficacy, safety, and the physical/psychological burden on patients

 # Conducting confirmatory clinical trial is believed to be impracticable, or, if deemed feasible, execution is anticipated to require considerable time due to a small subject population.

 # Results of clinical trials, excluding those that are confirmatory in nature, suggest a certain level of efficacy and safety.

Fujiwara Y et al. Clincal Parmacol Ther 109:1182-1185, 2021 Table S1

CEAS for Drugs contd.

【Post-marketing safety measures】

One of the conditions for approval is the requirement for post-marketing surveillance to reconfirm the efficacy and safety of the product.

Requirements for medical institutions where the drug is used may be added as necessary

【Required reports and other procedures after approval】

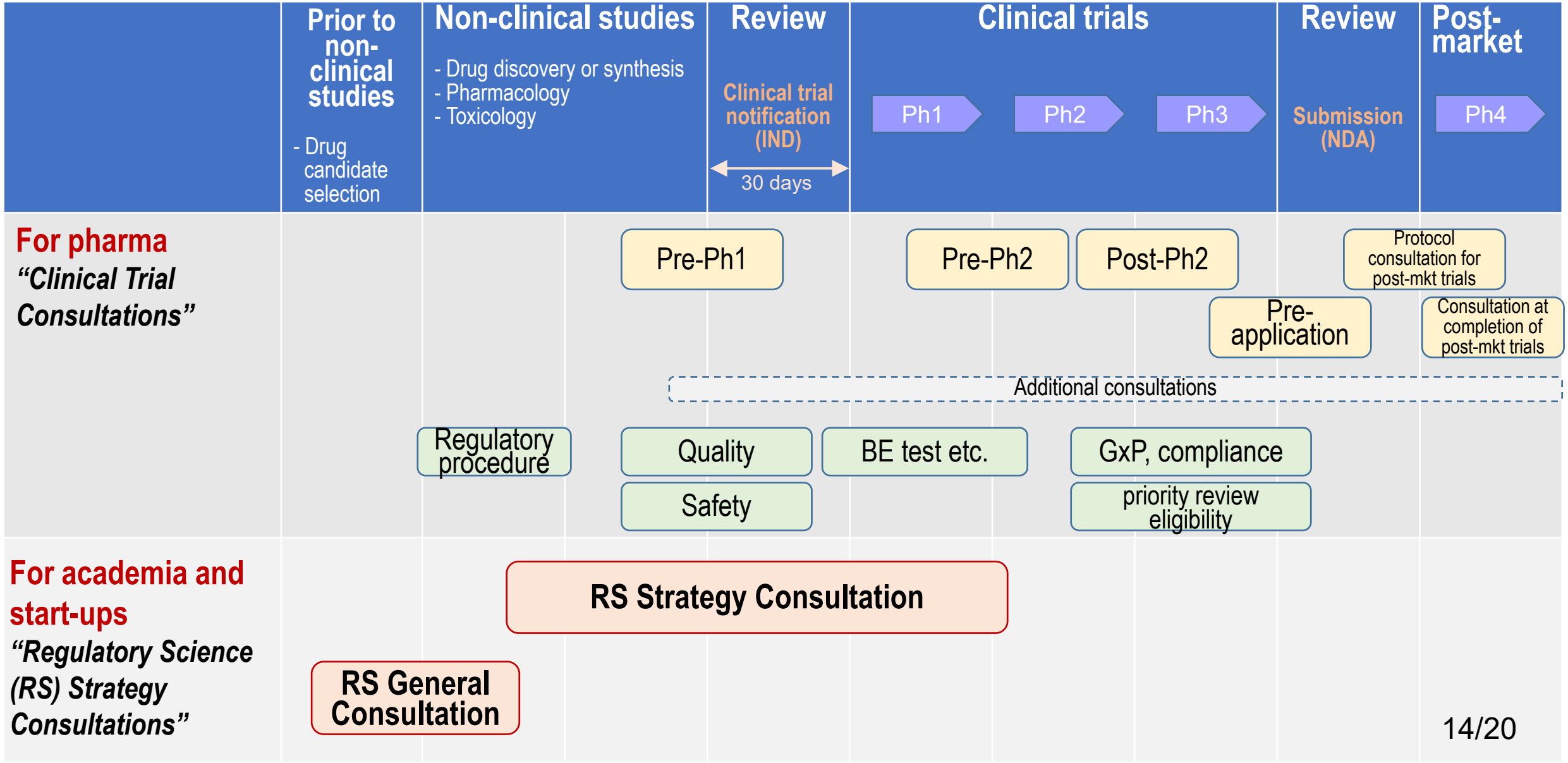
As with the regular approval system, application for "re-examination" and routine reporting are necessary during the period in which re-examination is required.

Pharmaceuticals approved under Conditional early approval system

(As of Dec. 31, 2022)

Bland name (N-proprietary Name)	Applicant	Indication	Application data package ;Clinical trial(Endpoints)	Conditions for approval
Lorbrena Tablets (Lorlatinib)	Pfizer Japan Inc.	ALK-positive NSCLC	Global I/II (ORR), etc.	Communicate New findings from global III and other sources to healthcare professionals. <DONE>
Keytruda Injection (Pembrolizumab)	MSD K.K.	MSI-High solid tumors (for use only if refractory or intolerant to standard therapies)	Global I/II (ORR)	Communicate New findings from two global II's and other sources to healthcare professionals.
Enhertu IV Infusion (Trastuzumab deruxtecan)	Daiichi Sankyo Co., Ltd.	HER2-positive breast (for use only if refractory or intolerant to standard therapies)	Global I/II (ORR), etc.	Communicate New findings from global III and other sources to healthcare professionals. <DONE>
Viltepso Intravenous Infusion (Viltolarsen)	Nippon Shinyaku Co., Ltd.	Duchenne muscular dystrophy (DMD) with a confirmed deficiency of the dystrophin gene amenable to exon 53 skipping therapy	- Japanese I/II (dystrophin protein expression, etc.) - Foreign II (dystrophin protein expression, time to walk/run, etc.)	Submit the data and analysis; - the placebo-controlled, global III - a registry-based research
Akalux IV Infusion (Cetuximab sarotalocan sodium)	Rakuten Medical Japan K.K.	Head and neck cancer	-Japanese I (ORR) -Foreign I/II (ORR)	Communicate New findings from global III and other sources to healthcare professionals.

Consultations offered by PMDA

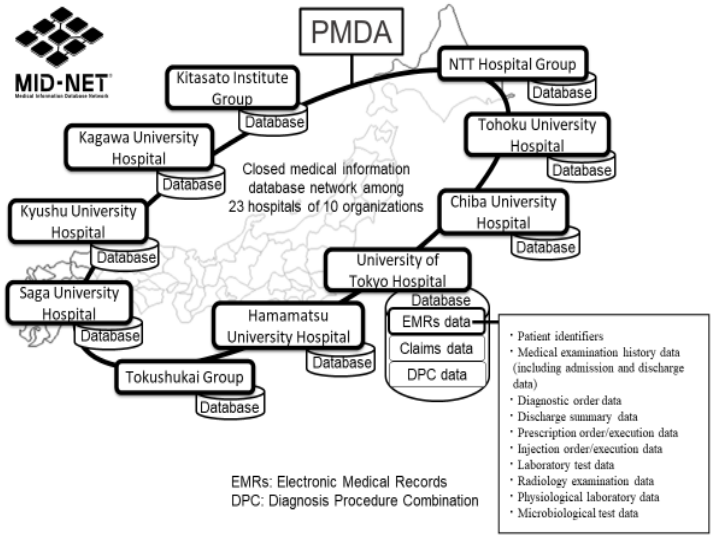


Safety Measures

- ◆Development of Risk Management Plan based on product's characteristics
- ◆Development of Guidelines in collaboration with academia
  （Setting requirement for lecture/training, physician and institution）
- ◆Appropriate provision of study results of continued clinical trial (Phase II and III)
- ◆Use-results surveys for all use cases
- ◆Surveys using registry in collaboration with academia
- ◆Surveys using Real World Data
- ◆the early post-marketing phase vigilance(EPPV)

Post-Marketing *Safety Signal Monitoring* utilizing MID-NET® for Ensitrelvir Fumaric Acid approved for COVID-19 under Emergency Approval Process

- Safety data of this drug were limited at the time of approval, because the drug was approved under emergency approval process
- To ensure the proper benefit/risk balance of the drug, safety data should be quickly accumulated at post-marketing stage in Japan.



Pharmacoepidemiol Drug Saf 28, 1395-404 (2019). 10.1002/pds.4879

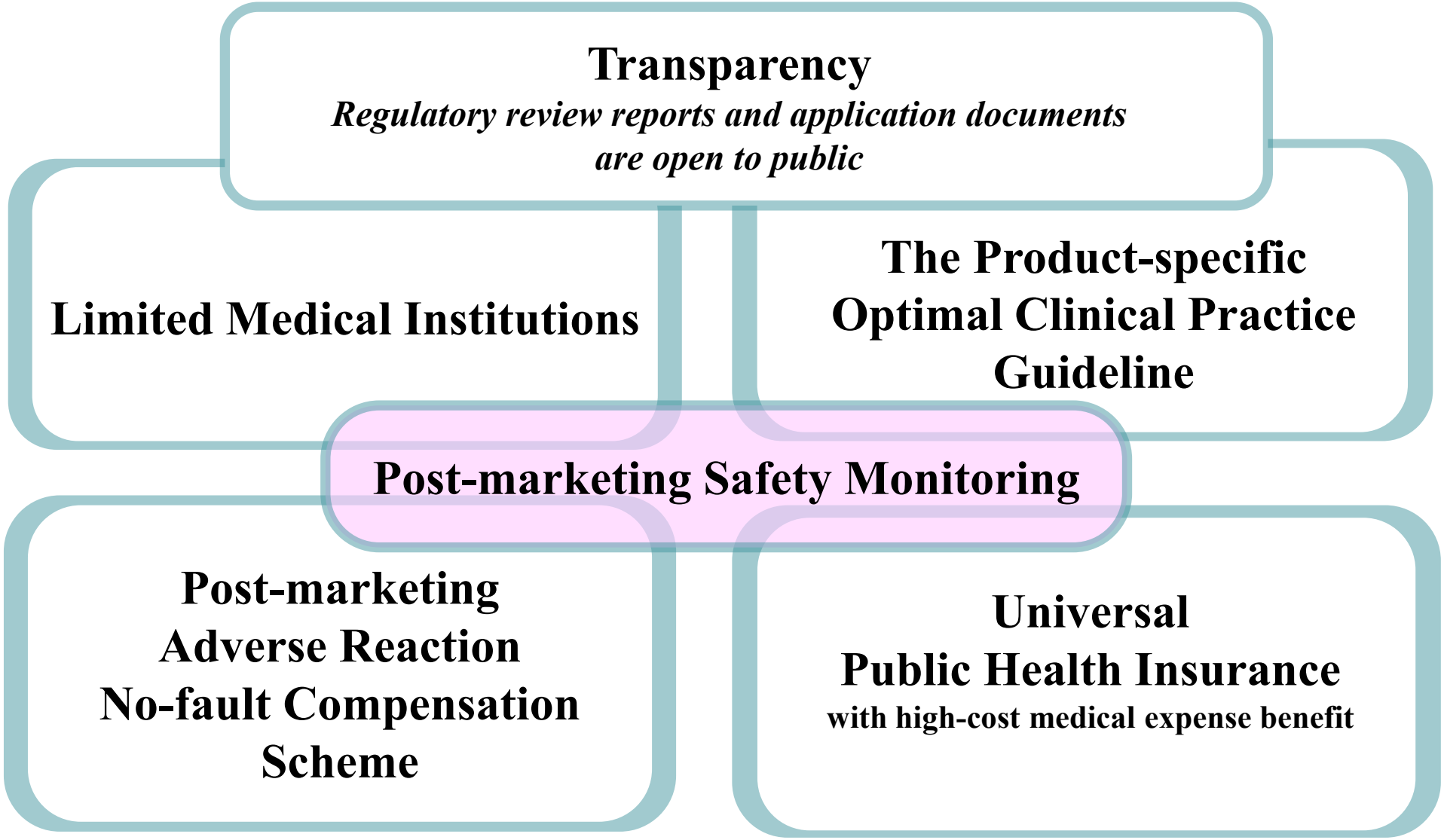
MID-NET®(Medical Information Database NETwork) is used to provide ***real-world evidence*** on safety of the drug.

<Clinical Indexes>

Liver AST, ALT、ALP, T−Bil	**Hemocyte** Leukocyte, Erythrocyte, Platelet
Kidney Cr, e−GFR	**Others** SP−A, SP−D, KL−6

Analyzing data on laboratory tests allow to reveal drug safety profile objectively and efficiently

A Comprehensive Healthcare Framework is Needed



Thank you for your attention

Back-up slides

Conditional and Time-limited Approval (regenerative medicine products)

【Qualifying criteria】

Regenerative Medical Products (RMPs) that meet all of the criteria below:

 # The quality of the proposed product is variable.

 # The clinical data on the proposed product are likely to predict efficacy.

 # It is predicted that the product is worthy of being used as a regenerative medical product because it does not exhibit significant adverse results in terms of efficacy, effectiveness, or performance.

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Conditional and Time-limited Approval contd.

【Post-marketing safety measures】

 # One of the conditions for approval is that post-marketing surveillance must be conducted to confirm the efficacy and safety of the product.

 # Requirements for medical institutions where the product is used may be added as necessary

【Required reports and other procedures after approval】

 # Re-examination does not apply to products that have received conditional and time-limited approval.

 # Application for regular approval is required by a date specified at the time of conditional and time-limited approval (within 7 years; this period can be extended by up to 3 years.)

 # Periodic reporting is required until application for regular approval is submitted.

Sakigake Designation

【Qualifying criteria】All of the following four criteria must be met:

Breakthrough product (the mechanism of action must be different than those of existing drugs)
The target disease is serious and life-threatening or be characterized by chronic symptoms (difficulties in daily life) with no curative therapy
No prior approved product or one anticipated to be markedly more efficacious than existing products or therapies (including a marked increase in safety)
Intent for early development and initial approval in Japan.

【Key performance features】

Applicable to drugs, devices, and IVD
Priority PMDA consultation waiting time; one month
Rolling review
English documents are permitted
Priority review; review time is six months
Concierge (PMDA review partner) support

This individual is involved in discussions of the product ‘s development and progress and facilitates communication between the applicant and the PMDA review team

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Accelerating Pathways during Pandemic in Japan

Type	Area	Features
Special Approval for Emergency	Pharmaceutical Products	• An emergency situation requires an unapproved medical product to be used to prevent damage to the public health caused by the spread of diseases • Such emergency situation cannot be managed appropriately by any means other than the use of the unapproved product • Legally available in a country with a regulatory system for medical products that is equivalent to Japan
Emergency Approval	Pharmaceutical Products	• An emergency situation requires an unapproved medical product to be used to prevent damage to the public health caused by the spread of diseases • Such emergency situation cannot be managed appropriately by any means other than the use of the unapproved product • Confirmed safety feasibility based on estimated efficacy