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Regulatory Trends in Regenerative Medicine in Japan

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Daisaku Sato, Ph.D.

Director, Office of Cellular and Tissue-based Products
Pharmaceuticals and Medical Devices Agency, Japan

Background for New Legislations (came into effect on 25 November 2014)

- **The Act on the Safety of Regenerative Medicine**

  New legislation was needed to put regenerative medicine practices (e.g. cancer immunotherapies, cosmetic surgeries) (other than product) under regulatory control to enhance their safety.

- **The Pharmaceuticals, Medical Devices Act (PMD. Act)**

  Revision of the Pharmaceutical Affaires Law (name changed) to accommodate cellular product characteristics.

The goal is to benefit the patients with unmet medical needs

Landscape of Regenerative Medicine in Japan

Medical Care Act (MCA) = The Act on the Safety of Regenerative Medicine.

Pharmaceuticals and Medical Devices Act. (PMD Act.)

Academic Research Purpose

Commercial Product Marketing Authorization Purpose

Medical care

Clinical Research using human stem cells

108 protocols approved

(as of November 2014 - before new legislation)

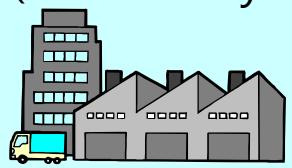
Under the new legislation, as of 31 January 2016:
79 new clinical research plans,
2634 medical care plans
have been notified to MHLW

Cellular/Tissue based Products

4 approved marketed products

22 clinical trials initiated (including 8 gene therapy products)

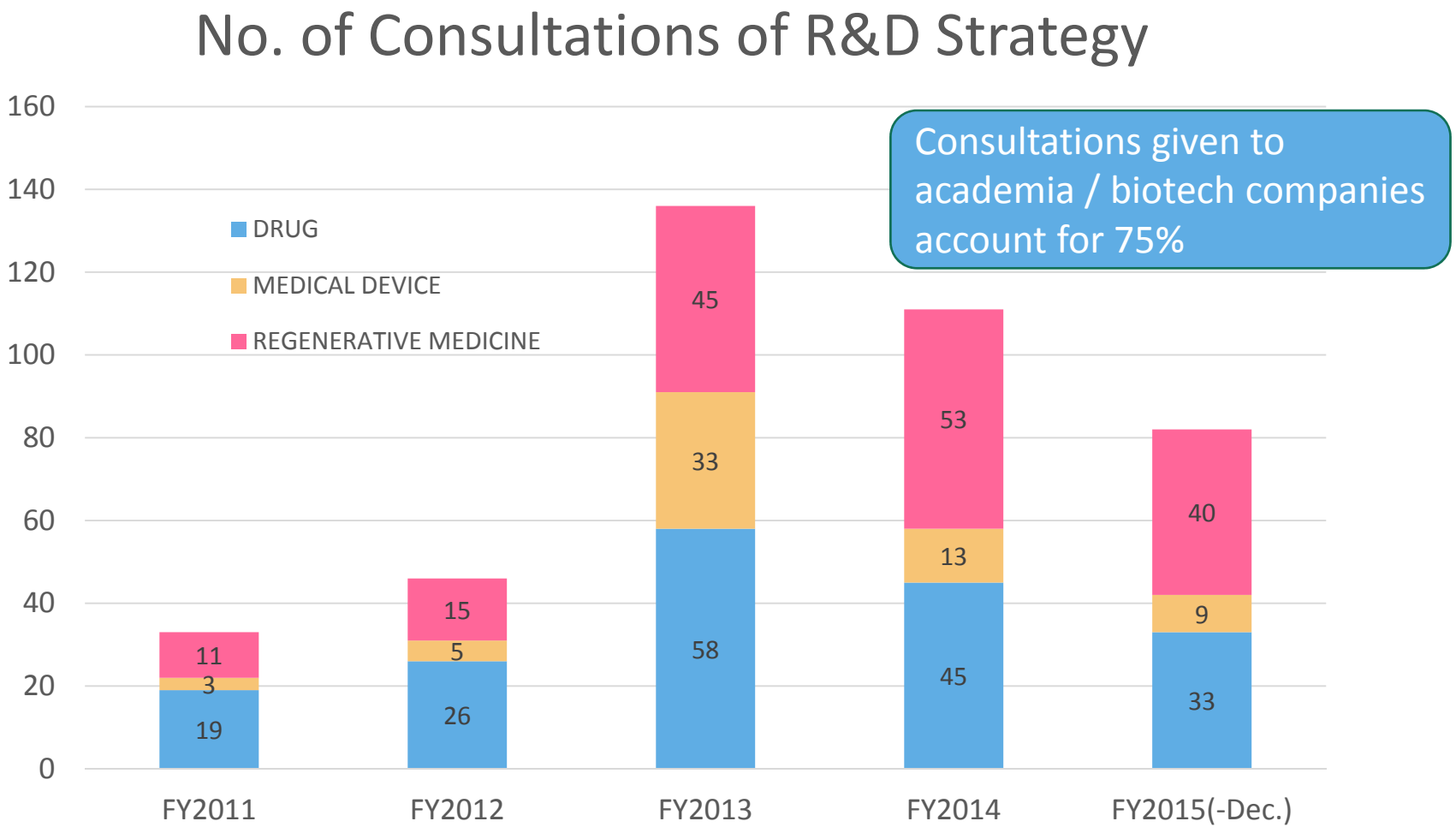
(～February 2016)



Covered by MHLW

Covered by MHLW and PMDA

Pharmaceutical Affairs Consultation on R&D Strategy (face to face)

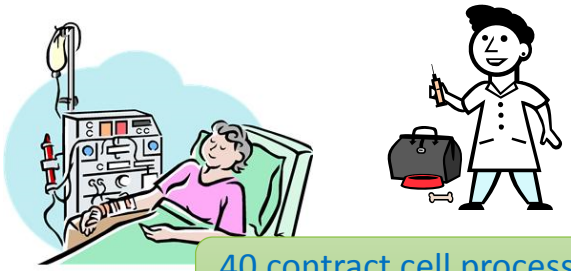


Two acts regulating regenerative medicine & cell therapy

Regenerative Medicine

MHLW process

All **medical technologies** using processed cells which safety and efficacy have not yet been established



40 contract cell processing facilities (CPFs) have been licensed.

The Act on the Safety of Regenerative Medicine

It may be similar to researcher initiated IND or hospital exemption of EU

PMDA process

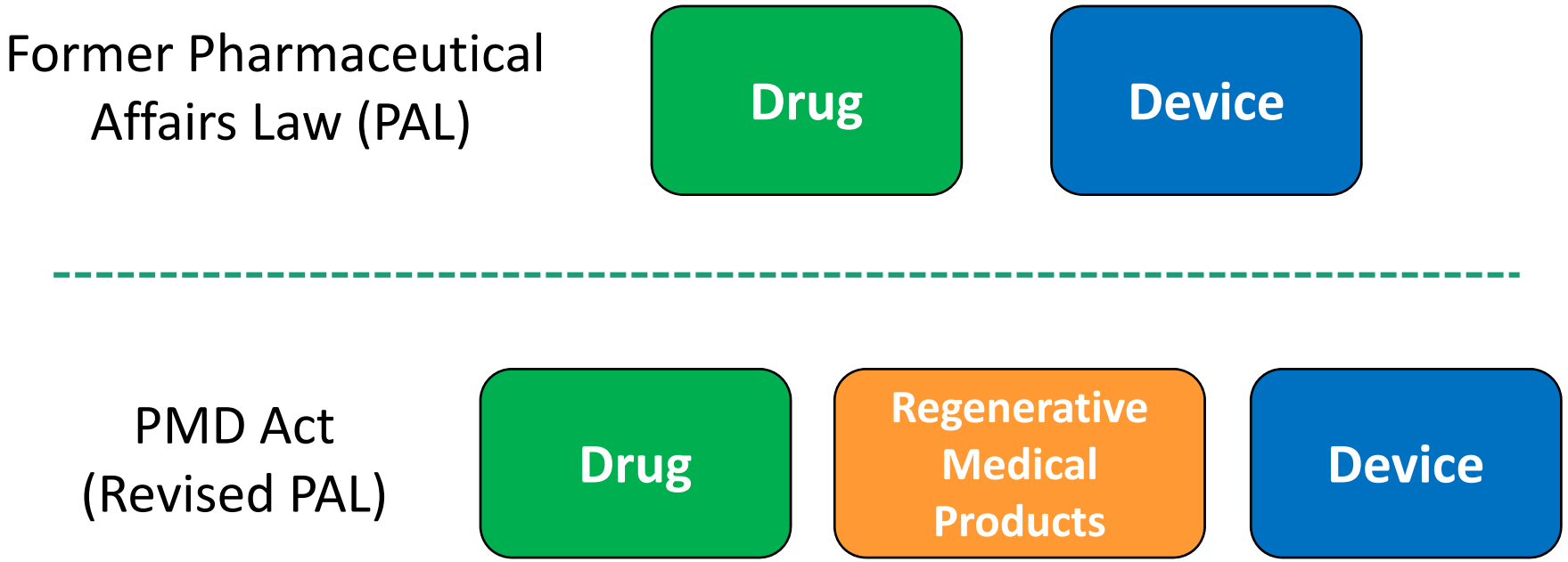
Production and marketing of regenerative and cellular therapeutic **products** by firms

The Act on Pharmaceuticals and Medical Devices (PMD Act)*

* Two laws will be enacted in November 2014

Commercial IND and product approval system

Regenerative Medical Products in the PMD Act



- **Additions for Regenerative Medical Products**
  - Definition and independent chapter for Regenerative Medical Products
  - Introduction of conditional/time limited approval system

How to expedite R&D and review for cellular and tissue based product

- Designed for unmet needs under the present treatment: limited number of patients available for CT
- Difficult to conduct controlled study to demonstrate clinical benefit
- Heterogeneity of Quality affected by source materials

Would it take long time for CTs and review if regulator pursues the conventional drug guidelines too much?

Back ground of conditional and time-limited authorization

To what extent probability of effectiveness is to be pursued before Marketing authorization?

- A new product for life threatening disease, which is affected by the timing of access
- Breakthrough therapeutics for present unmet medical needs, longing for treatment

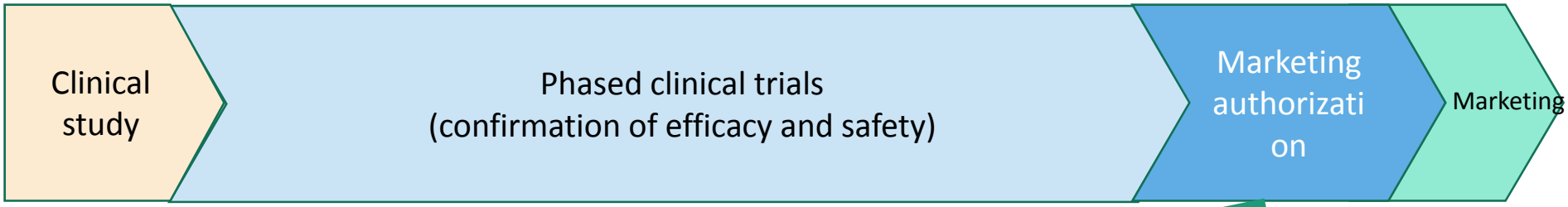
, while paying particular attentions to the safety

- Based on regulatory sciences in terms of social responsibility for pubic health

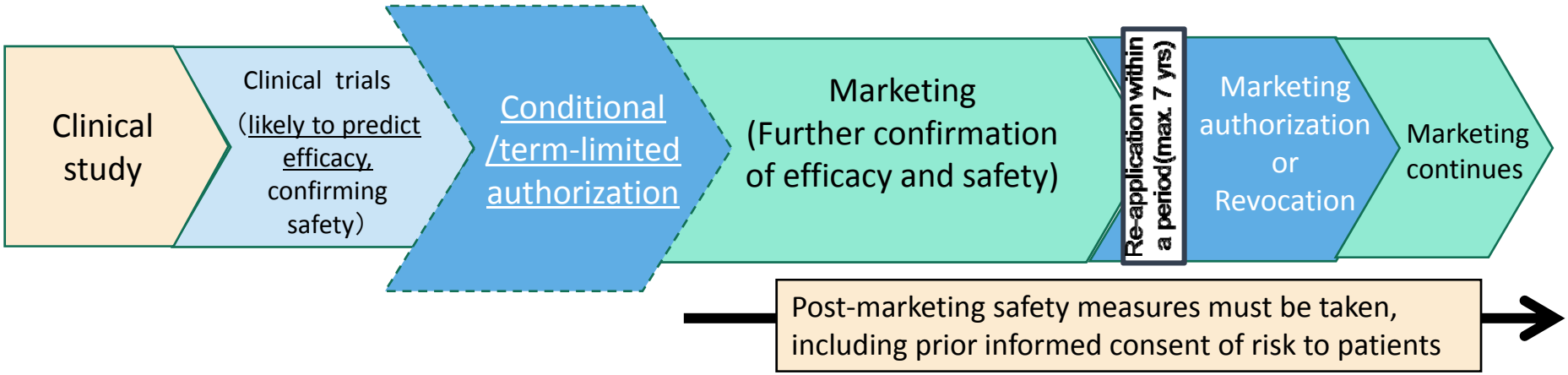
Expedited approval system under PMD Act

< Drawback of traditional PAL approval system >
Long-term data collection and evaluation in clinical trials, due to the characteristics of cellular/tissue-based products, **such as non-uniform quality** reflecting individual heterogeneity of autologous donor patients

[Traditional approval process]



[New scheme for regenerative medical products]



Two of the new product approvals under the new regulation (Update)

- In September and in October 2014, two new product applications for marketing authorization were filed by PMDA.
- They were approved on 18 September 2015.

1. Bone marrow mesenchymal stem cells (MSCs) for GVHD **(normal approval)**

1. Skeletal myoblast sheet for serious heart failure due to ischemic heart disease **(conditional and time-limited authorization** – 5 years, conducting post-marketing efficacy studies**)**

Review Time less than 12 months

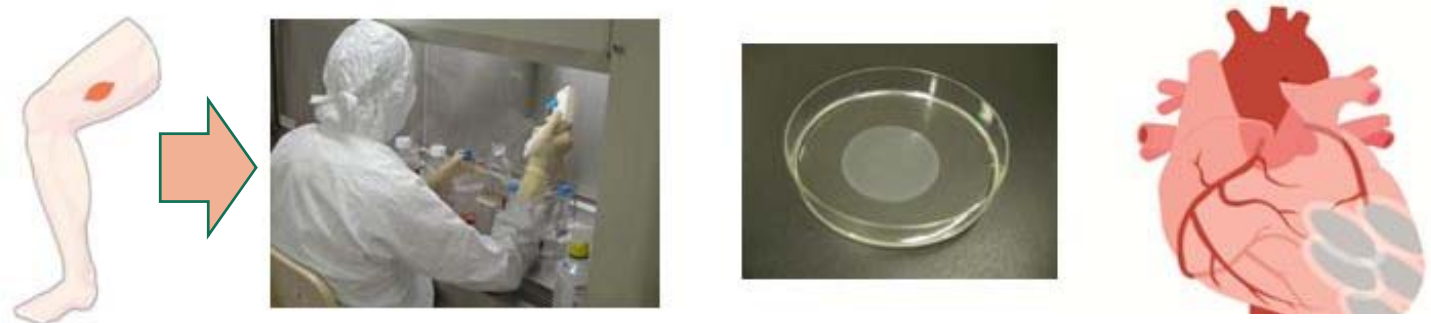
TEMCELL

- Target: Steroid refractory acute GVHD
  - Fatal and Rare disease (approx. 1000-2000/y)
- Product: Allogeneic MSC
- Manufacturer JCR Pharmaceuticals Co., Ltd
- Resources and technology transferred from Mesoblast, Ltd. (Osiris Therapeutics, Inc.)
  - Prochymal® (Brand Name)
    - Conditional approval in Canada and New Zealand

http://www.jcrpharm.co.jp/news/20151126_3991

HeartSheet

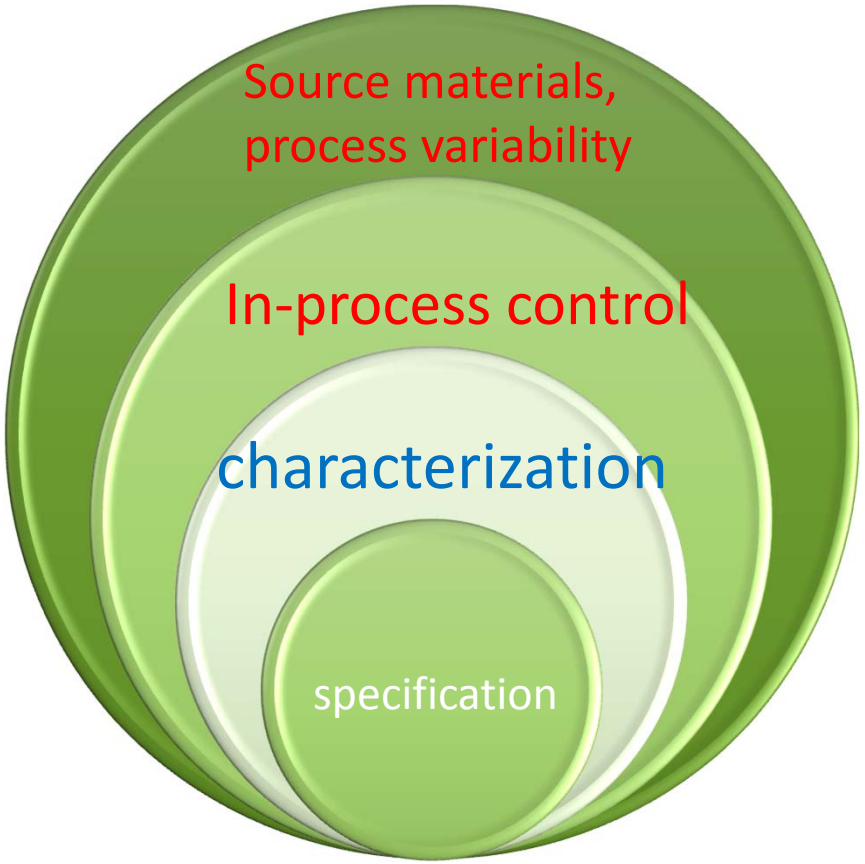
- Target: Serious heart failure due to IHD
  - Chronic and Poor prognosis
- Product: Autologous skeletal myoblast
- Manufacturer: Terumo Corporation
- Manufacturing
  - Biopsy from Quadriceps
  - Final products are cryopreserved vials to be processed sheets using temperature responding culture plates at CPF in hospital



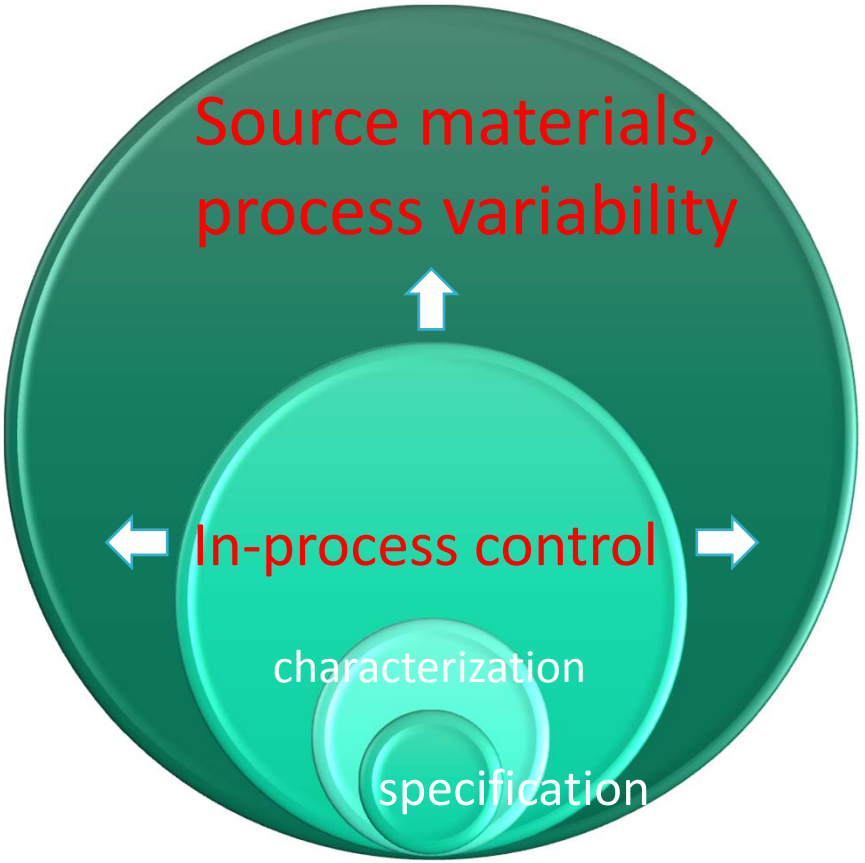
Note: Figures quoted from the company press release docs

Different Quality Concepts in Review process

Bio-pharmaceuticals



hCTPs



- **Difficult to cover every aspect of quality by specification**
- **Limited information can be obtained from characterization and specification**
- **Much more rely on in-process control to control quality →Control Strategy**

Further facilitation and acceleration……

SAKIGAKE Assignment System

– To put innovative products into practice in Japan first in the world –

Assignment Criteria

- Medical products for diseases in dire need of innovative therapy
- Applied for approval firstly or simultaneously in Japan
- Prominent effectiveness can be expected based on non-clinical study and early phase of clinical trials

Assignment Advantage

1. Prioritized Consultation [Waiting time: 2 months→1 month]

2. Substantialized Pre-application Consultation [de facto review before application]

3. Prioritized Review [12 months → 6 months]

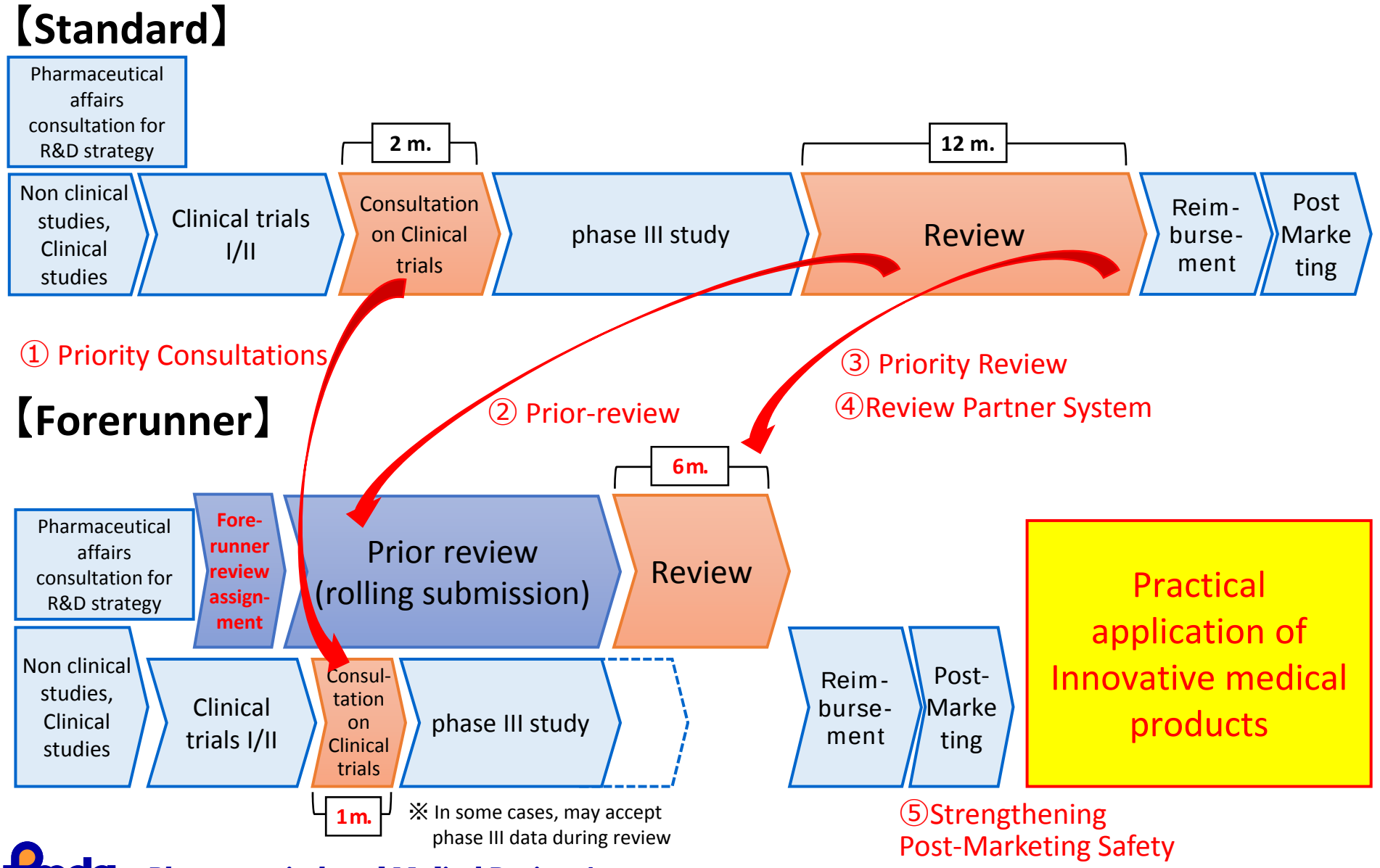
4. Review Partner [PMDA manager as a concierge]

5. Substantial Post-Marketing Safety Measures[Extension of re-examination period]

Procedure

1. Initiation by applicant 2. Initiation by the MHLW

General Timeframe of Forerunner Review Assignment



Assignment on 10 February 2016 regenerative medical products

Name of medical products	Proposed indication	Name of applicant
STR01 (Autologous bone marrow-derived mesenchymal stem cell)	Nerve syndrome and dysfunction caused by spinal cord injury	NIPRO Medical Co., Ltd.
G47Δ (Growth-controlled oncolytic herpes simplex virus type 1)	Malignant glioma	Daiichi Sankyo Co., Ltd. / Institute of Medical Sciences, University of Tokyo
autologous cardiac progenitor/stem cells	Pediatric congenital heart disease (single ventricle physiology)	Japan Regenerative Medicine Co., Ltd.

Challenges of Accelerated Process in general

- Clinical study in post-marketing: RCT may be difficult for confirmation in some cases (single arm study with pre-agreed threshold or observational case / control study) in the postmarketing settings
  - monitoring, collection and use of real-world data, post-authorisation, as a complement to RCT data **(like Adaptive pathway of EU)**
- Reimbursement: Question on consistency with regulatory approval and on acceptance of clinical data for HTA payers
- CMC and quality assurance : limited qualification in early stage and quality control under GMP/GCTP (validation, scalability, comparability)

Sharing of Information, Experience and Knowledge is Valuable !!

World Health Organization

ICH harmonisation for better health

Regulatory Harmonization Steering Committee

APEC Life Sciences Innovation Forum

asean

PANDRH

…Others

Thank You for your attention!

Daisaku Sato, Ph.D.

Director, Office of Cellular and Tissue based Products, PMDA, Japan

sato-daiasku@pmda.go.jp

Thanks to my colleagues of Office of Cellular and Tissue-based Products