



Regulatory frameworks of regenerative medicines and products review in Japan

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1. Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD Act)

New Legislative Framework

These two acts were promulgated in November 2013 by the Japanese Diet (Parliament) in line with the **Regenerative Medicine Promotion Act**, in order to reform the pharmaceutical and medical regulation related to regenerative medicine

- **Revision of the Pharmaceutical Affairs Law: The Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD Act)**
- **The Act on the Safety of Regenerative Medicine**

These two acts were enacted on 25 November 2014

Other related governmental policy:

- **Healthcare and Medical Strategy Promotion Act (2014.5)**
- **Japan Medical Research Development Institution Act (2014.5)**

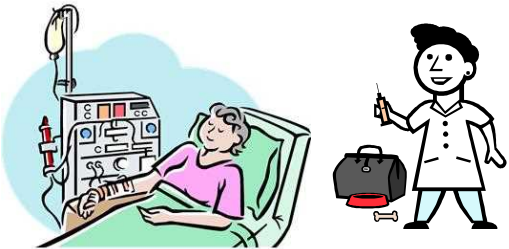
Two acts regulating regenerative medicine & cell therapy

MHLW process

Regenerative Medicine

PMDA process

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



The Act on the Safety of Regenerative Medicine (ASRM)

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



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

* Two laws were enacted in November 2014

Commercial IND and product approval system

Outsourcing Cell Culturing and Processing under the Act on the Safety of Regenerative Medicine (ASRM and PMD Act)

Clinical study, private practice

Regenerative medical products

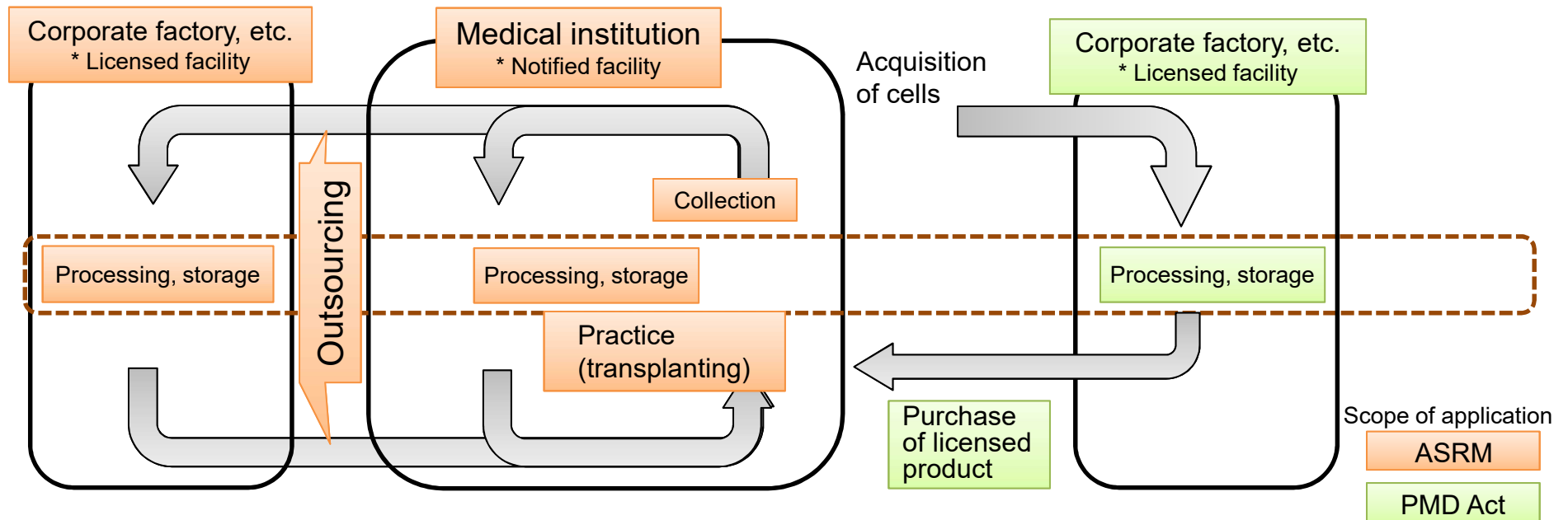
ASRM

The safety, etc., of regenerative medicine provided as a medical service is ensured by stipulating the practical procedures of, for instance, sampling, standards for medical institutions that provide regenerative medicine and standards for facilities that culture and process cells.

PMD Act (Revised PAL)

The efficacy and safety of regenerative medical products are ensured by stipulating standards for manufactory of regenerative medical products.

* Outsourcing of cell culturing and processing carried out under the responsibility of physicians based on the Regenerative Medicine Safety Assurance Act is exempt from the application of the Pharmaceutical and Medical Device Act.



regenerative medicine products in the PMD Act

Former Pharmaceutical
Affairs Law (PAL)

Drug

Device

PMD Act
(Revised PAL)

Drug

Regenerative
Medical
Products

Device

◆ Additions for regenerative medicine products

- Definition and independent chapter for regenerative medicine products
- Introduction of conditional/time limited approval system

Limitations of Clinical Trials of Regenerative Medicine to satisfy unmet medical needs

There are some specific limitations for cell therapy products

- ▶ Designed for unmet needs under the present treatment (e.g. last line therapy): **limited number of patients** available for clinical trials
- ▶ Difficult to conduct **controlled study** to demonstrate clinical benefit, in the Japanese medical environment, due to:
 - highly invasive surgical intervention
 - autologous cell collection
- ▶ Clinical trial design affected by **heterogeneity** of quality derived from source materials (including autologous collection and culture procedures)

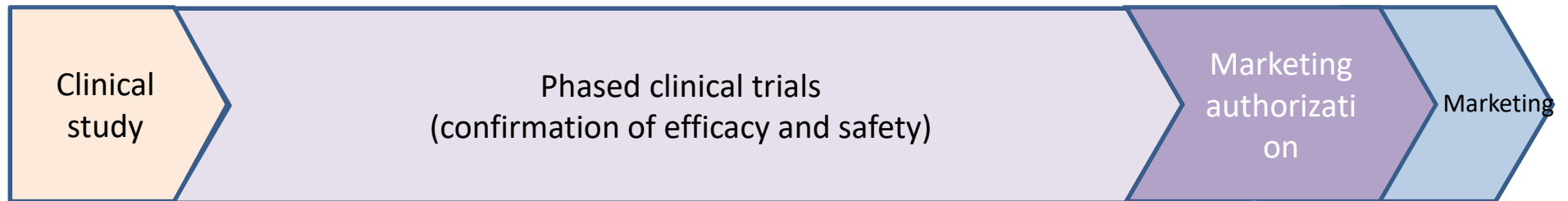
2. Conditional/Time-limited Authorization System

Expedited approval system under PMD Act

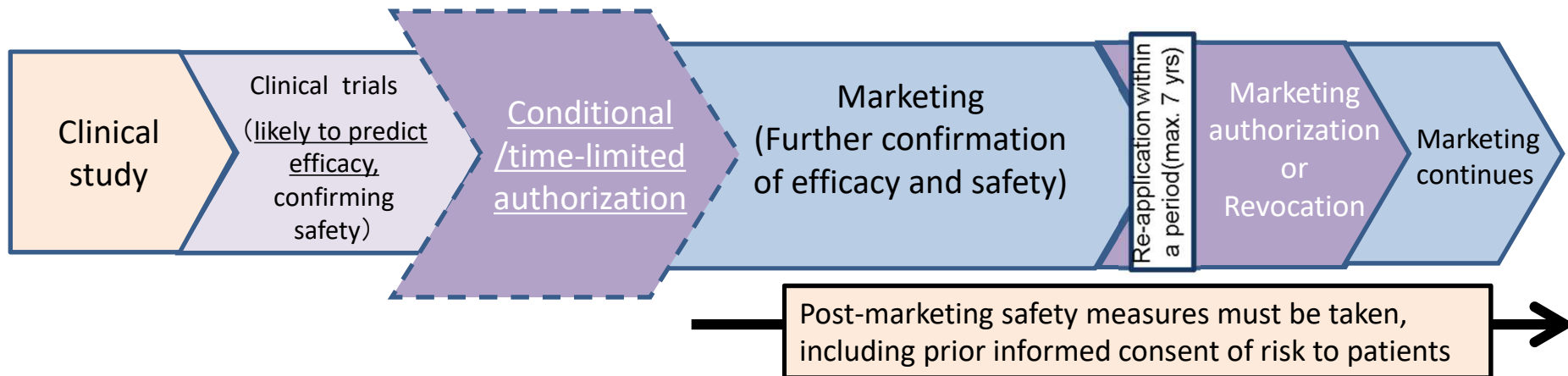
< Drawback of traditional PAL approval system >

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 medicine products]



Comparison of Expedited and ordinal approval system

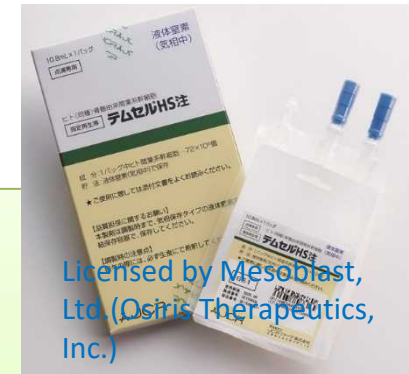
- Expedited approval system also requires CT under the GCP, therefore, regarding of securing evidence of efficacy, it is the same level as for review for orphan drugs,
- The revision of law just clearly defined it as “estimation of efficacy” under the law.

	CT	Evidence	Post-market measures
Drug	<ul style="list-style-type: none"> ○ Evaluate with appropriate size of Clinical trials according to the product's features 	<ul style="list-style-type: none"> ○ Usually, statistically significant difference is proven by controlled CTs 	<ul style="list-style-type: none"> ○ Post-market use survey
Orphan drug	<ul style="list-style-type: none"> ○ In most cases, only small size CTs are available due to scarcity of patients ○ Controlled CTs are usually difficult to conduct 	<ul style="list-style-type: none"> ○ Sometimes strict statistically evaluation are difficult 	<ul style="list-style-type: none"> ○ Post-market use surveillance for all cases or post-market CTs ○ Limitation of clinical institutes which can use the drug for secure proper use
regenerative medicine products	<ul style="list-style-type: none"> ○ In most cases, only small size CTs are available due to scarcity of patients ○ <u>Heterogeneity of the products makes it difficult to evaluate with limited size of CTs</u> ○ Controlled CTs are usually difficult to conduct 	<ul style="list-style-type: none"> ○ Sometimes strict statistically evaluation are difficult 	<ul style="list-style-type: none"> ○ Post-market use surveillance for all cases or post-market CTs ○ Limitation of clinical institutes which can use the drug for secure proper use ○ <u>The approval expires in seven years</u>

Two of the new product approvals under the new regulation

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



Conditional approval in Canada and New Zealand

Review Time (less than 12 months)



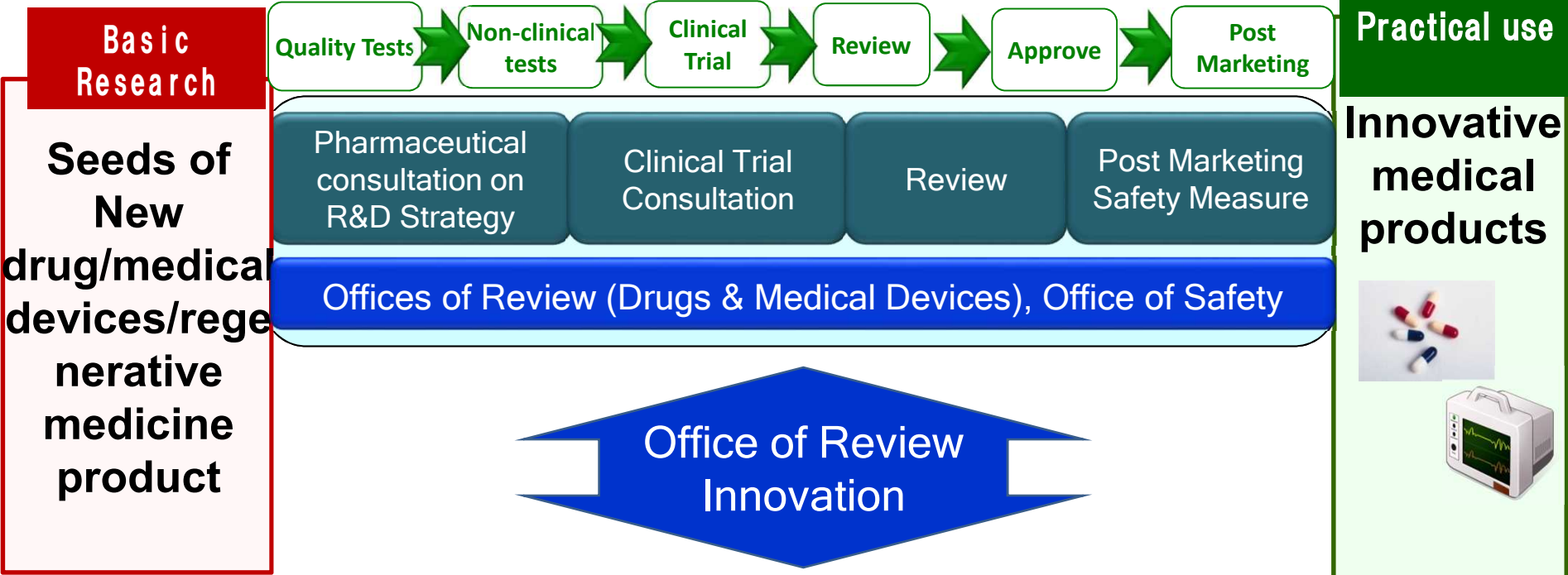
Note: Figures quoted from the company press release docs¹¹

Benefit and Risk Balance Assessment

- Discussion of acceptable level of clinical effectiveness vs. patient access to the new therapy
- Weighing acceptable risk against expected benefit
- Based on **regulatory sciences**

3. Foundation for Regenerative Medicines

Establishment of the Science-Based Board



Establishment of the Science Board

The Science Board was established in May 2012 to discuss how PMDA can better cope with products with advanced science & technology, in each developmental stage such as basic research, development support, product review, and post market safety measures.



Board members

Academia

平成25年8月20日

iPS 細胞等をもとに製造される細胞組織加工

細胞
細胞

1. はじめに

独立行政法人医薬品医療機器総合機構(PMDA) (以下、本専門部会と略)は、細胞組織加工製品に関する懸念事項である「造腫瘍性」について、科学的

細胞組織加工製品の開発を適切に推進するため、現時点で認識し得る問題をできる限り整理されるべきである。ただし、細胞組織加工製品の開発の中であり、現時点での知見は限られている。科学的分析と対応を提示するもの、近い将来関連する必要があることを併せて提言するものである。

「造腫瘍性(tumorigenicity)」とは、動物に移

Provisional Translation (as of September 30, 2013)†

August 20, 2013

Current Perspective on Evaluation of Tumorigenicity of Cellular and Tissue-based Products Derived from induced Pluripotent Stem Cells (iPSCs)* and iPSCs as Their Starting Materials

Tatsutoshi Nakahata, Chair, Cellular and Tissue-based Products Subcommittee

Hideyuki Okano, Vice-chair, Cellular and Tissue-based Products Subcommittee

1. Introduction

The Cellular and Tissue-based Products Subcommittee (hereinafter, the subcommittee) of the Science Board to Pharmaceuticals and Medical Devices Agency (PMDA) has held multiple discussions from the scientific point of view on “tumorigenicity” that is the major safety concern of induced pluripotent stem cells (iPSCs)* for cellular and tissue-based products, and come to conclusion at present of

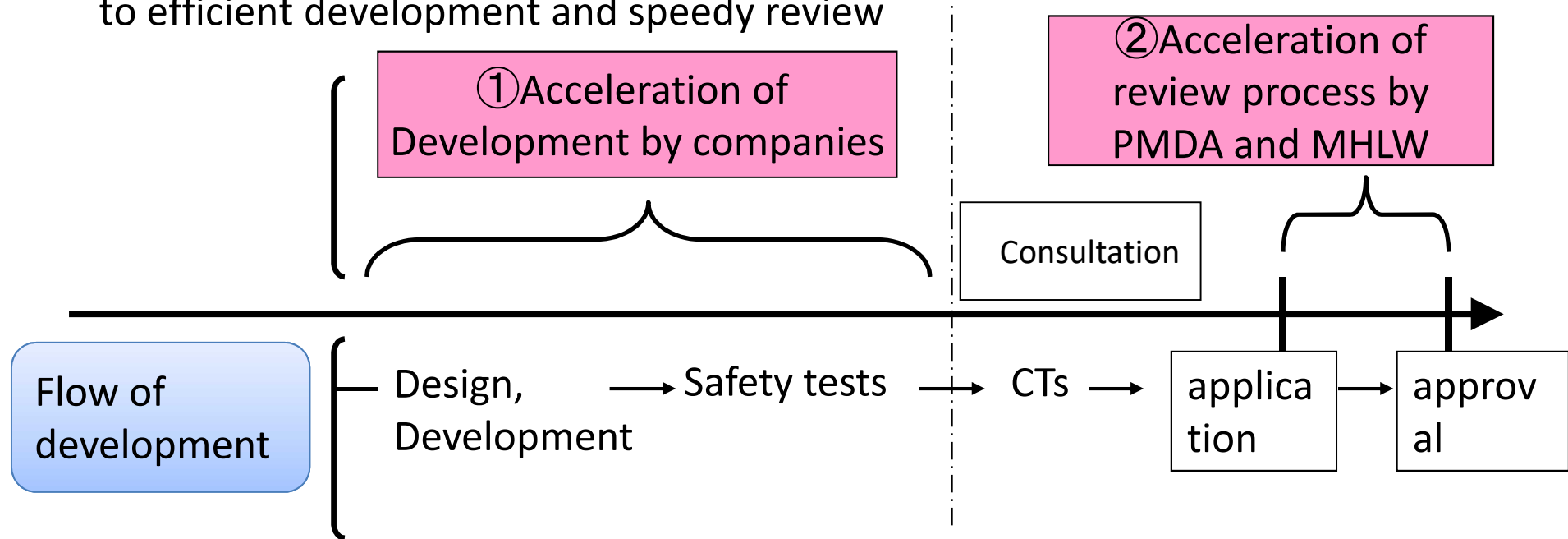
Japanese

English (Provisional Translation)

Review guidance for Next-generation regenerative medicine products

[Purpose]

To facilitate development of diverse innovative regenerative medicine products, publishing review guidance for regenerative medicine products with extensive medical needs and practicability, which is expected to enable to efficient development and speedy review



[Results]

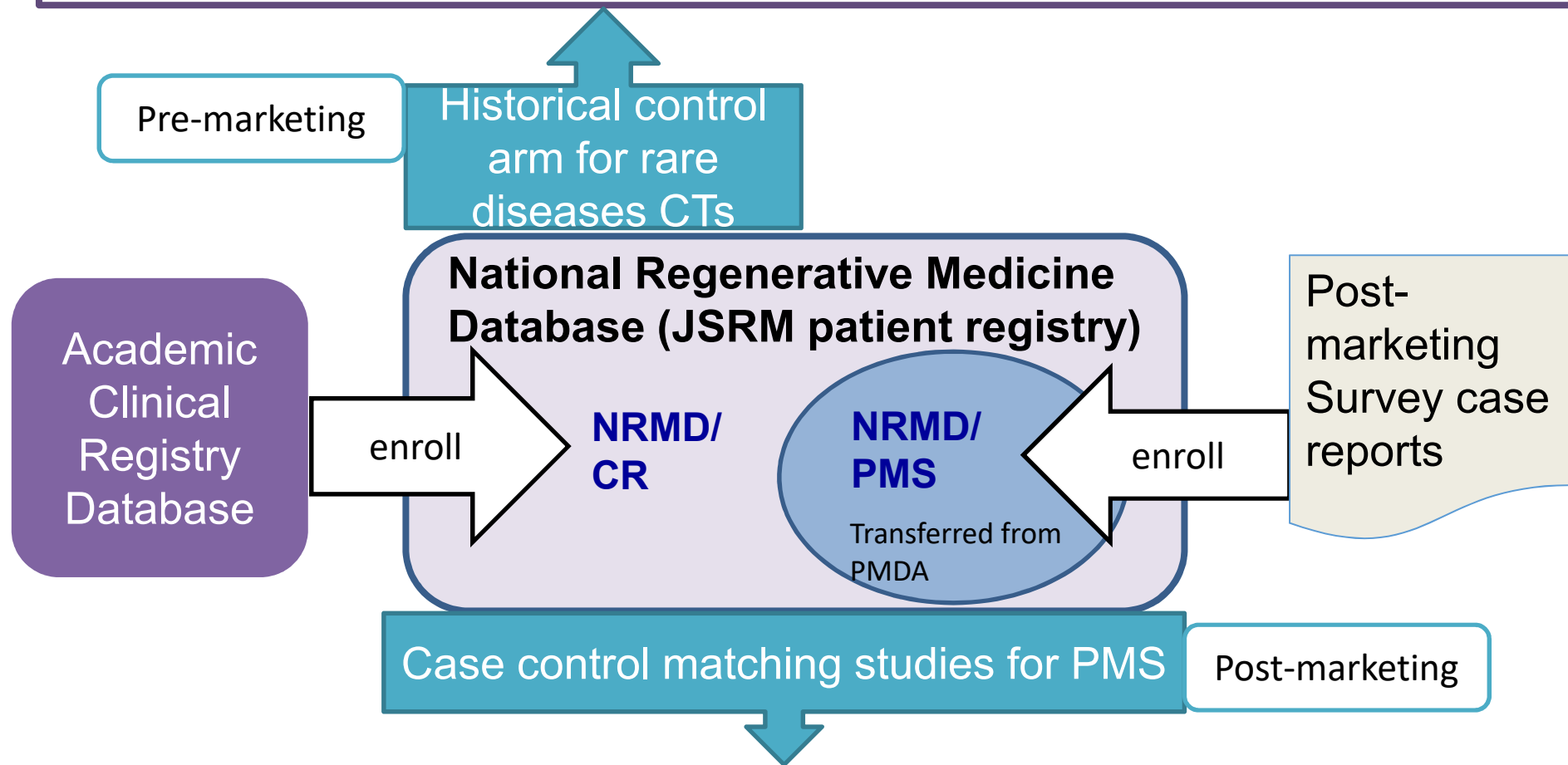
more than 10 review concepts for cell sheets, regenerative cartilage and iPS have been published

4. For Practical Use

- Patient Registry Database -

RM patient registry initiatives (with JSRM) in a product lifecycle management

- The patient registry database has been in place for facilitating regenerative medicine studies (pre- and post- marketing)



5. Harmonization on the regulations for Regenerative Medicines



Summit of Heads of Medicines Regulatory Agencies Symposium

October 27, 2017 | Kyoto International Conference Center, Japan

**Host: Ministry of Health, Labour and Welfare,
Pharmaceuticals & Medical Devices Agency,
Kyoto Prefecture and DIA Japan**

Endorsement: JPMA and JFMDA

Website: <http://www.c-linkage.co.jp/12th-summit-symposium/en/>

Outcome of Kyoto Summit

- Regulatory convergence on regenerative medicines.
 - National regulations may need to evolve in order to better reflect the characteristics of the products.
 - International regulatory convergence at existing organizations (WHO, ICH, IPRF) is called for.

Sharing of Information, Experience and Knowledge is Valuable !!



Regulatory Harmonization
Steering Committee



Life Sciences
Innovation Forum



...Others



***Thank you for your
attention***