Current Challenges of Regulation in Japan

- Amendment of Pharmaceutical Affairs Act

Hiroshi Yamamoto, MS

Chief Safety Officer

Pharmaceuticals and Medical Devices Agency (PMDA), Japan

26th Annual EuroMeeting

25-27 March 2014

ACV, Vienna

Austria

www.diahome.org

Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. (“DIA”), its directors, officers, employees, volunteers, members, chapters, councils, Special Interest Area Communities or affiliates, or any organization with which the presenter is employed or affiliated.

Agenda

- Concept of New Pharmaceutical Affairs Act(PAA)
- Three Pillars of New PAA
  - Safety Measures: Package insert
  - Medical Devices
  - Regenerative Medicine
- Dissemination of ICH Outcomes to Asian Countries

Background of the New PAA

CONCEPT OF NEW PAA

Amendment of Pharmaceutical Affairs Act As of 7th June, 2013

Basic framework Based on Lawmaker-initiated Acts

Based on 2 Lawmaker-initiated Acts, prepare concrete implementation

Concrete Measures

Draft of Medical Devices Act

Progress the measures comprehensively and planned regarding R&D and Promotion on Medical devices

- •Basic Plan
- •Basic measures
- •Measures on legislation, finance, tax
- •Measures on related people's cooperation/coalition

Regenerative Medicines Promotion Act (already passed)

Promotion the measures comprehensively from R&D to practical use on Regenerative Medicines

- • Basic Plan
- • Basic Measures (Measures on legislation, environments)
- • Consideration from safety and ethics aspects

Amended PAA

○ **Strengthen Safety Measures regarding Drugs, Medical Devices**

- •Obligation to submit revised Package insert (notification)
- •Electronic Package insert of Medical Devices in some conditions

○ **Regulation considering Medical Devices Character**

- •Independent Chapter for "Medical Devices"
- •Third party certification system
- •Quality Management System (QMS)
- •Other revisions related to medical devices
- •Regenerative and Cellular Therapy Products, and Gene Therapy Products

○ **Regulation considering Regenerative Medicines Character**

- •Creation for Regenerative Medicines regulations
- •Introduction of approval system with condition/period

New Act for Ensuring Regenerative Medicines Safety

Regulation on the measures for Regenerative Medicines treated as Medical care

- ・Procedure for collections etc
- ・Standard on Medical Facilities to use
- ・Standard on Facilities to culture, processing

Amendment of Pharmaceutical Affairs Act

As of 2nd Dec, 2013

Basic framework Based on Lawmaker-initiated Acts

Based on 2 Lawmaker-initiated Acts, prepare concrete implementation

Concrete Measures (Passed on 20th Nov. 2013)

Amended PAA

○ **Strengthen Safety Measures regarding Drugs, Medical Devices**
- Obligation to submit revised Package insert (notification)
- Electronic Package insert of Medical Devices in some conditions

○ **Regulation considering Medical Devices Character**
- Independent Chapter for "Medical Devices"
- Third party certification system
- Quality Management System (QMS)
- Other revisions related to medical devices
- Regenerative and Cellular Therapy Products, and Gene Therapy Products

○ **Regulation considering Regenerative Medicines Character**
- Creation for Regenerative Medicines regulations
- Introduction of approval system with condition/period

Regenerative Medicines Promotion Act (already passed)

Promotion the measures comprehensively from R&D to practical use on Regenerative Medicines
- Basic Plan
- Basic Measures (Measures on legislation, environments)
- Consideration from safety and ethics aspects

New Act for Ensuring Regenerative Medicines Safety

Regulation on the measures for Regenerative Medicines treated as Medical care
- Procedure for collections etc
- Standard on Medical Facilities to use
- Standard on Facilities to culture, processing

Amendment of Pharmaceutical Affairs Act

- **Strengthen Safety Measures regarding Drugs, Medical Devices**
  - Specify relevant party's obligation to ensure quality, safety, and efficacy of drugs and medical devices.
  - MAH's obligation to notify revised Package insert reflecting the latest findings
- **Regulation considering Medical Devices Character**
  - Independent Chapter for "Medical Devices"
  - Third party certification system
  - Quality Management System (QMS)
  - Other revisions related to medical devices
  - Regenerative and Cellular Therapy Products, and Gene Therapy Products
- **Regulation considering Regenerative Medicines Character**
  - Creation for Regenerative Medicines regulations
  - Introduction of approval system with condition/period

First Pillar of New PAA

SAFETY MEASURES: PACKAGE INSERT

Regulations on Package Insert (PI)

1. Contents of package insert should be notified to MHLW on the time of approval and revision.
2. Package insert notified will be uploaded in a web-site.
3. Paper package insert of any medical devices will be able to be omitted under certain conditions.

Regulation Relating to Package Insert (For New Drug Application)

Current System

Draft of PI

○Mandatory contents to be described in PI (Article 52)
○Prohibition on Entries (Article 54)

Submission of draft PI

The draft PI is to be submitted by the administrative direction

Approval

In case of non-compliance

Order to Improve

- ○ Prevention of hazard (Article 77-4)
- ○ Order to improve management (Article 72-4)
- ○ Emergency Orders (Article 69-3)

Penalty

○Punitive Clause（Articles 84, 86, and 90)

Revised System

Draft of PI

○Mandatory contents to be described in PI (Article 52)
○Prohibition on Entries (Article 54)

MAH shall develop the PI based on the latest scientific knowledge

Submission of draft PI

The draft PI and its supporting document should be submitted together with application materials

Approval

Notificati on of PI

The notification of PI before marketing is now mandatory

Check of compliance with the regulation

In case of non-compliance

Order to Improve

- ○ Prevention of hazard (Article 77-4)
- ○ Order to improve management (Article 72-4)
- ○ Emergency Orders (Article 69-3)

Penalty

○Punitive Clause（Articles 84, 86, and 90)

Regulation Relating to Package Insert (For Revision)

Current System

Consideration to revise PI

- Based on Article 77-4 etc., MAH is responsible to verify the contents of PI
  - ADR (Adverse Drug Reactions) reporting
  - Periodic Safety Report
  - GVP etc.

Consultation prior to revision

- The procedure should be based on the administrative circular "The flow of standard procedure to revise PII

Revision of PI

- Mandatory contents to be described in PI (Article 52)
- Prohibition on Entries (Article 54)

In case of non-compliance

Order to Improve

- Prevention of hazard (Article 77-4)
- Order to improve management (Article 72-4)
- Emergency Orders (Article 69-3)

Penalty

- Punitive Clause (Articles 84, 86, and 90)

Revised System

Consideration to revise PI

- Based on Article 77-4 etc., MAH is responsible to verify the contents of PI
  - ADR (Adverse Drug Reactions) reporting
  - Periodic Safety Report
  - GVP etc.

Consultation prior to revision

- The procedure should be based on the administrative circular "The flow of standard procedure to revise PII

The recipient of ADR report is to be unified to PMDA (leading to enhancement of collection of ADR report and enforcement of PhV)

Revision of PI

- Mandatory contents to be described in PI (Article 52)
- Prohibition on Entries (Article 54)

MAH should draft/revise PI based on the latest scientific knowledge

Notification of PI

The notification of PI before marketing is now mandatory

Check of compliance with the regulation

In case of non-compliance

Order to Improve

- Prevention of hazard (Article 77-4)
- Order to improve management (Article 72-4)
- Emergency Orders (Article 69-3)

Penalty

- Punitive Clause (Articles 84, 86, and 90)

Second Pillar of New PAA

MEDICAL DEVICES

Scope of third party certification will be expanded

GHTF Classification	
Class A	**extremely low risk** X-Ray film
Class B	**low risk** MRI, digestive catheters
Class C	**medium risk** artificial bones, dialyzer
Class D	**high risk** pacemaker, artificial heart valves

PAL classification		
Category	**Pre-market regulation**	Japanese MD Nomenclature
General MDs (Class I)	**Self declaration**	**1,195**
Controlled MDs (class II)	**Third party Certification**	**1,799 (1,367 for 3rd Party)**
Specially Controlled MDs (class III & IV)	**Minister's Approval (Review by PMDA)**	**756**
		342

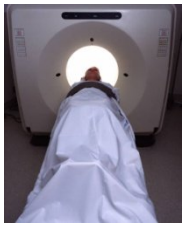
Expanded!

Standalone Medical Device Software (SMDS) will be regulated in revised PAL

Example of Medical Device with program in the current PAL

Image Diagnostic Apparatus

It processes, stores and displays image data from CT, MRI etc.



Data from CT scanning

Processing by program

3D image of skull

Current PAA

Software (program)

Hardware

Only combination of hardware and software is regulated.

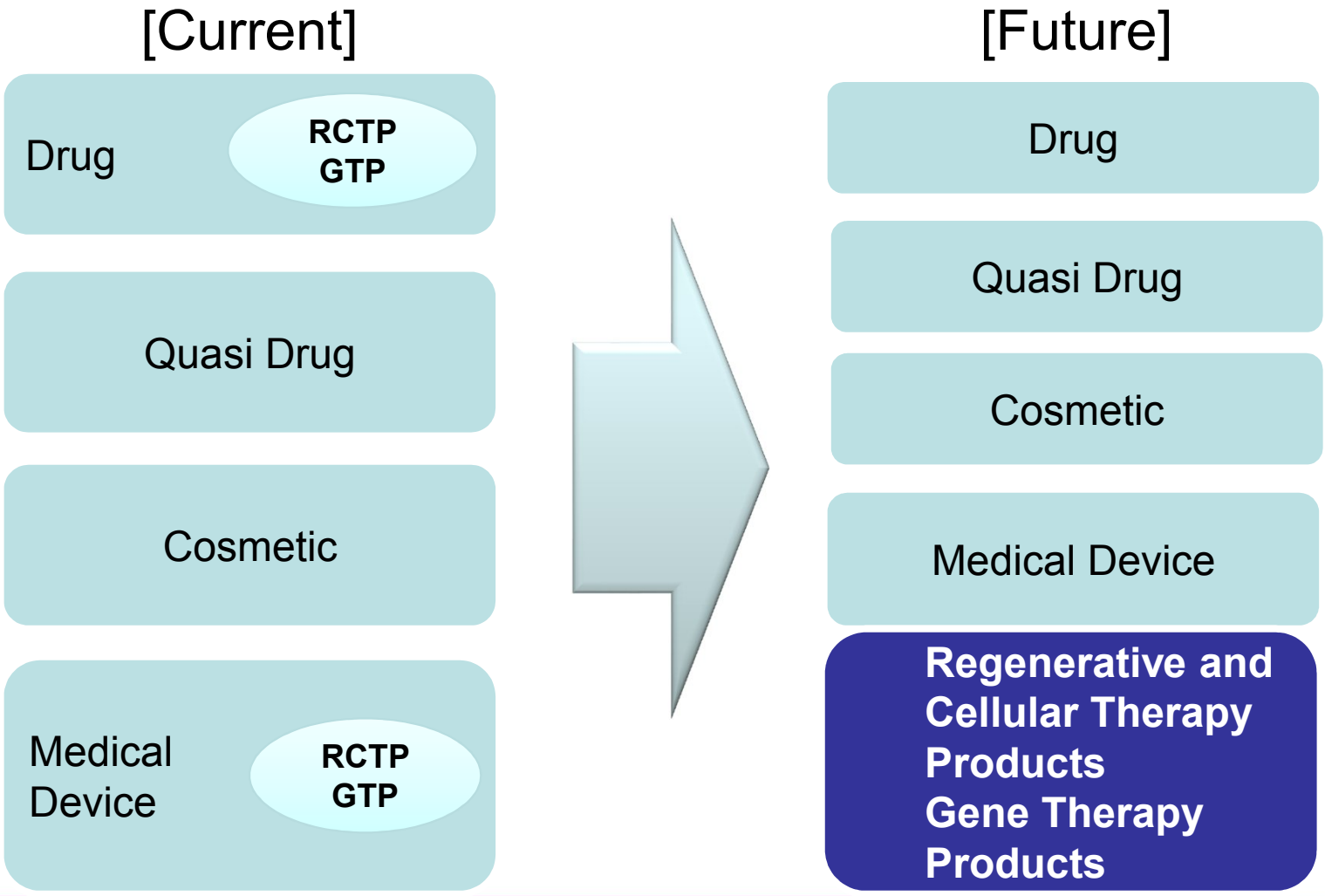
Future

SMDS

Software (program)

Software will be independently regulated

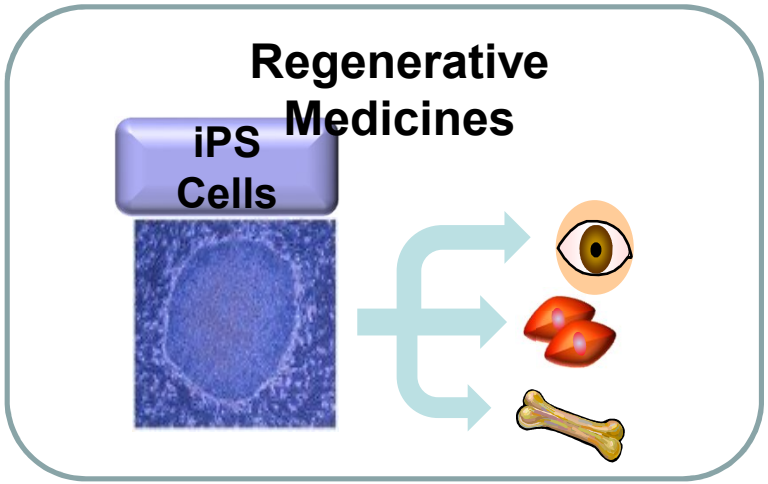
Cellular and tissue therapeutic product will be newly categorized



Third Pillar of the New PAA

REGENERATIVE MEDICINE

2 Acts Regulating Regenerative Medicines



Providing regenerative medicines within hospitals and clinics

.The Act on the Safety of Regenerative Medicine

Producing regenerative and cellular therapeutic products in firms

Amendment of Pharmaceuticals Affairs Act (PAA)*

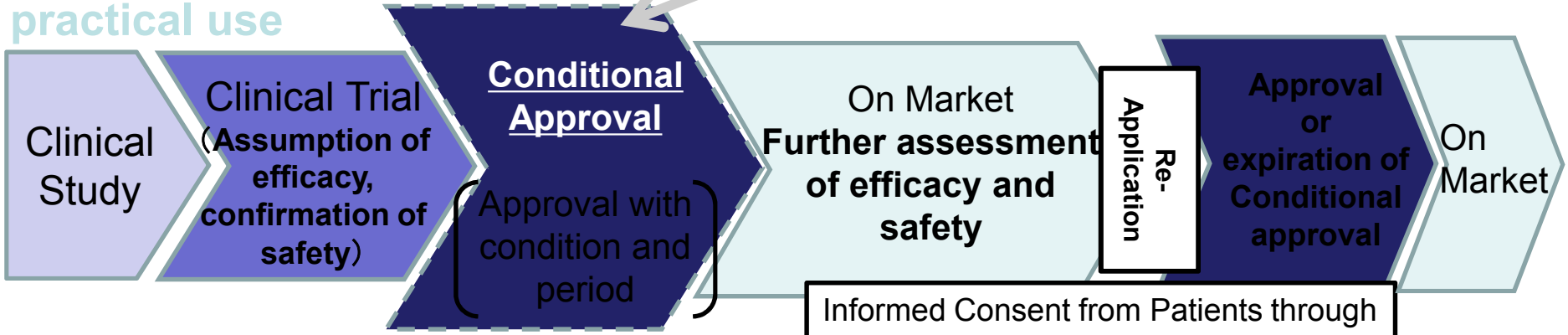
- The Amended Pharmaceutical Affairs Act and the Act on the Safety of Regenerative Medicine were enacted in November 2013, and will be enforced within 1 year

Approval System Corresponding Commercialization of Regenerative Medicines (Conditional Approval)

Previous Pathway of Approval System

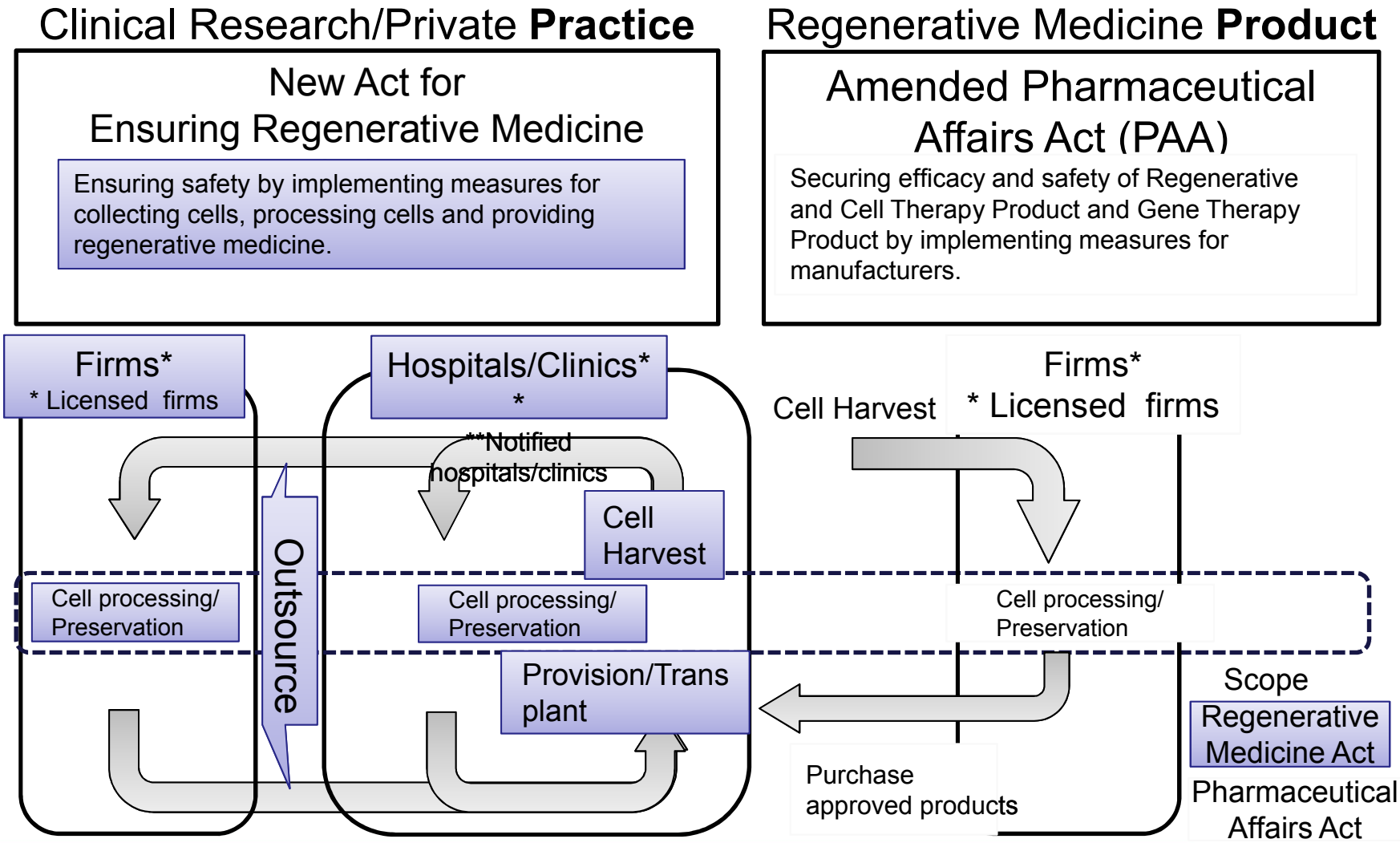
Leading to Early-Access!!

New Approval System to Introduce Regenerative medicines in early practical use



Informed Consent from Patients through the explanation of possible risk with taking post-market measures.

Outsourcing System of Processed Cells under New Act for Ensuring Regenerative Medicine Safety and Amended Pharmaceutical Affairs Act (PAA)



Rules of practice in hospitals and clinics

・Hospitals and clinics are required to

a) Prepare the plan of provision

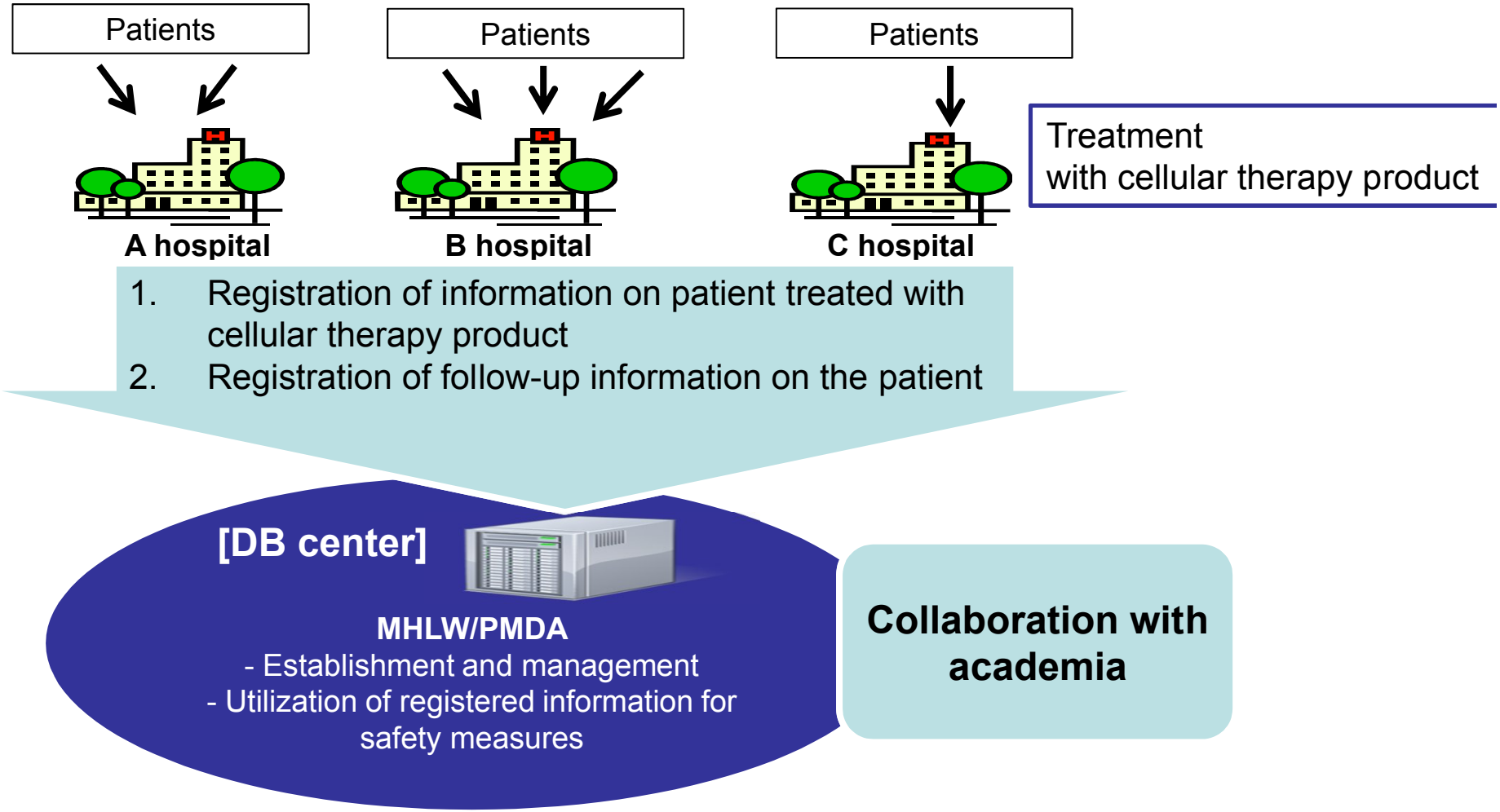
b) Receive evaluation by certified committee for regenerative medicir

c) Submit the plan to Minister of Health, Labour and Welfare

・The plan shall be prepared according to the risk categories of regenerative medicine

Category	Example of cells used for regenerative medicine	Example
First Category (High risk)	iPS cells and ES cells	Transplantation of retinal pigment epithelium sheets derived from autologous iPS cells in patients with age-related macular degeneration
Second Category (Medium risk)	Somatic stem cells	Autologous bone marrow cell infusion therapy for liver cirrhosis
Third Category (Low risk)	Somatic cells	Activated lymphocyte therapy

Registry system of patient treated with cellular therapy product etc. is under consideration



Dissemination of ICH Outcomes to Asian Countries

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

History and Goal

In April 1990, steering committee of ICH launched to rationalize and standardize the pharmaceutical review system of Japan, US, and EU for faster delivery of safe and effectual new drugs to the patient in urgent need.

Steering Committee (SC)

SC is responsible for the governance and decision making of ICH. The SC meeting is held every 6 months, with 2 representatives from each member organization.

Member Organization

JAPAN: MHLW, PMDA, and JPMA

US: FDA and PhRMA

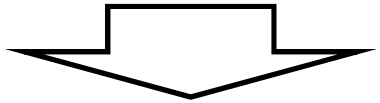
EU: EC, EFPLA

Working Group (WG)

WG is established for each technical topic to be harmonized by making the guidelines and relevant materials. The WG meeting is held every 6 months with experts from organizers and stakeholder organization.

Outcomes of ICH

- ICH have harmonized over 80 guidelines regarding technical elements about the evaluation of quality, efficacy and safety, as well as the format of application form and the post-market safety measures.



- Preventing duplication of clinical trials and reducing research resources
- Reducing International barriers
- Facilitating the dissemination and communication of information on harmonized guidelines and their use for non-member countries

Outreach activity of ICH

Global corporation (GC)

- The purpose of the GC is dissemination of ICH guidelines
- Participating organization: ICH members, plus DRA(Drug Regulation Authorities), DoH (Department of Health), RHI (Regional Harmonization Initiative)
- It has been held independently as Global Corporation Group (GCG), but classified regular SC session from the 2013 meeting.
- GC invites one participant of each RHI.
- GC deals with requests of training from DRA/DoH and RHI.

International Pharmaceutical Regulators Forum (IPRF)

Former ICH Regulators Forum

- Voluntary party of regulators participating ICH
- Updating each activity, sharing domestic issues, discussing common topics.
- Paperwork regarding GCP inspection for E6 Discussion Group

IPRF

- No big changes of activity per se from the former RF
- Assigned the chair, Co-chair and secretariat
- Enhancement the management system by Terms of Reference(ToR)
- Will publish manuals for the establishment of Working/Discussion group

Bilateral Cooperated activities: Recent Joint Symposia

Country/Region Name (date and city)	Main Topics
China (2012/3/22, Beijing)	Current Status of Global Clinical Trials & Utilization of Clinical Data, and Clinical Trial Consultation System
Indonesia (2013/2/13, Jakarta)	Pharmacovigilance and Good Distribution Practice (GDP)
Thailand (2013/10/24–25, Bangkok)	Risk Management Plan, Pharmacovigilance, GMP, Pharmacopoeia

Thank you for your attention!