Current Challenges of Regulation in Japan
- Amendment of Pharmaceutical Affairs Act

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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
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

Concrete Measures

- Amendment of Pharmaceutical Affairs Act
- Draft of Medical Devices Act
- Regenerative Medicines Promotion Act (already passed)

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

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

Basic framework
Based on Lawmaker-initiated Acts

Amended PAA

- Strengthen Safety Measures regarding Drugs, Medical Devices
  - Obligation to submit revised Package insert (notification)
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Concrete Measures (Passed on 20th Nov. 2013)

- 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.
The notification of PI before marketing is now mandatory. The draft PI and its supporting document should be submitted together with application materials. MAH shall develop the PI based on the latest scientific knowledge.

In case of non-compliance, the following penalties may be applied:
- Order to improve (Article 72-4)
- Prevention of hazard (Article 77-4)
- Emergency Orders (Article 69-3)
- Punitive Clause (Articles 84, 86, and 90)
### Regulation Relating to Package Insert (For Revision)

<table>
<thead>
<tr>
<th>Current System</th>
<th>Revised System</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consideration to revise PI</strong></td>
<td><strong>Consideration to revise PI</strong></td>
</tr>
<tr>
<td>Based on Article 77-4 etc., MAH is responsible to verify the contents of PI</td>
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</tr>
<tr>
<td>ADR (Adverse Drug Reactions) reporting</td>
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<tr>
<td>Periodic Safety Report</td>
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</tr>
<tr>
<td>GVP etc.</td>
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<tr>
<td>The procedure should be based on the administrative circular “The flow of standard procedure to revise PI”</td>
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</tr>
<tr>
<td><strong>Consultation prior to revision</strong></td>
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</tr>
<tr>
<td><strong>Revision of PI</strong></td>
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</tr>
<tr>
<td>Mandatory contents to be described in PI (Article 52)</td>
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</tr>
<tr>
<td>Prohibition on Entries (Article 54)</td>
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</tr>
<tr>
<td><strong>Revision of PI</strong></td>
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</tr>
<tr>
<td><strong>Notification of PI</strong></td>
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</tr>
<tr>
<td><strong>In case of non-compliance</strong></td>
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<td>Prevention of hazard (Article 77-4)</td>
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<td>Order to improve management (Article 72-4)</td>
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<tr>
<td><strong>Order to Improve</strong></td>
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</tr>
<tr>
<td><strong>Penalty</strong></td>
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<tr>
<td>Punitive Clause (Articles 84, 86, and 90)</td>
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</tbody>
</table>

**The notification of PI before marketing is now mandatory**

**Check of compliance with the regulation**

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

MEDICAL DEVICES
## GHTF Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A</td>
<td>extremely low risk</td>
</tr>
<tr>
<td></td>
<td>X-Ray film</td>
</tr>
<tr>
<td>Class B</td>
<td>low risk</td>
</tr>
<tr>
<td></td>
<td>MRI, digestive catheters</td>
</tr>
<tr>
<td>Class C</td>
<td>medium risk</td>
</tr>
<tr>
<td></td>
<td>artificial bones, dialyzer</td>
</tr>
<tr>
<td>Class D</td>
<td>high risk</td>
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<tr>
<td></td>
<td>pacemaker, artificial heart valves</td>
</tr>
</tbody>
</table>

## PAL classification

<table>
<thead>
<tr>
<th>Category</th>
<th>Pre-market regulation</th>
<th>Japanese MD Nomenclature</th>
</tr>
</thead>
<tbody>
<tr>
<td>General MDs</td>
<td>Self declaration</td>
<td>1,195</td>
</tr>
<tr>
<td>Controlled MDs</td>
<td>Third party Certification</td>
<td>1,799 (1,367 for 3rd Party)</td>
</tr>
</tbody>
</table>
| Specially Controlled MDs | Minister’s Approval (Review by PMDA) | 756 | 342

Scope of third party certification will be expanded!
It processes, stores and displays image data from CT, MRI etc.

Processing by program

Data from CT scanning

3D image of skull

Current PAA

Only combination of hardware and software is regulated.

Future

SMDS

Software will be independently regulated

Example of Medical Device with program in the current PAL

Image Diagnostic Apparatus

Standalone Medical Device Software (SMDS) will be regulated in revised PAL
Cellular and tissue therapeutic product will be newly categorized

[Current]
- Drug
- Quasi Drug
- Cosmetic
- Medical Device
  - RCTP
  - GTP

[Future]
- Drug
- Quasi Drug
- Cosmetic
- Medical Device
  - Regenerative and Cellular Therapy Products
  - Gene Therapy Products
Third Pillar of the New PAA

REGENERATIVE MEDICINE
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**

1. **Clinical Study**
2. **Clinical Trial** (Confirmation of efficacy and safety)
3. **Approval**
4. **On Market**

**New Approval System to Introduce Regenerative medicines in early practical use**

1. **Clinical Study**
2. **Clinical Trial** (Assumption of efficacy, confirmation of safety)
3. **Conditional Approval** (Approval with condition and period)
4. **On Market**
5. **Further assessment of efficacy and safety**
6. **Approval or expiration of Conditional approval**
7. **On Market**

**Leading to Early-Access!!**

- 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)

New Act for Ensuring Regenerative Medicine

Ensuring safety by implementing measures for collecting cells, processing cells and providing regenerative medicine.

Amended Pharmaceutical Affairs Act (PAA)

Securing efficacy and safety of Regenerative and Cell Therapy Product and Gene Therapy Product by implementing measures for manufacturers.

Clinical Research/Private Practice

Regenerative Medicine Product

Firms*

*Licensed firms

Hospitals/Clinics*

*Notified hospitals/clinics

Cell Harvest

Provision/Transplant

Outsource

Firms*

*Licensed firms

Cell processing/Preservation

Cell processing/Preservation

Purchase approved products

Scope

Regenerative Medicine Act

Pharmaceutical Affairs Act

Clinical Research/Private Practice

Regenerative Medicine Product

Firms*

*Licensed firms

Hospitals/Clinics*

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Cell Harvest

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Cell processing/Preservation

Cell processing/Preservation

Purchase approved products

Scope

Regenerative Medicine Act

Pharmaceutical Affairs Act

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

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Example of cells used for regenerative medicine</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Category (High risk)</td>
<td>iPS cells and ES cells</td>
<td>Transplantation of retinal pigment epithelium sheets derived from autologous iPS cells in patients with age-related macular degeneration</td>
</tr>
<tr>
<td>Second Category (Medium risk)</td>
<td>Somatic stem cells</td>
<td>Autologous bone marrow cell infusion therapy for liver cirrhosis</td>
</tr>
<tr>
<td>Third Category (Low risk)</td>
<td>Somatic cells</td>
<td>Activated lymphocyte therapy</td>
</tr>
</tbody>
</table>
Registry system of patient treated with cellular therapy product etc. is under consideration

1. Registration of information on patient treated with cellular therapy product
2. Registration of follow-up information on the patient

MHLW/PMDA
- Establishment and management
- Utilization of registered information for safety measures

Collaboration with academia
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

<table>
<thead>
<tr>
<th>Country/Region Name (date and city)</th>
<th>Main Topics</th>
</tr>
</thead>
<tbody>
<tr>
<td>China (2012/3/22, Beijing)</td>
<td>Current Status of Global Clinical Trials &amp; Utilization of Clinical Data, and Clinical Trial Consultation System</td>
</tr>
<tr>
<td>Indonesia (2013/2/13, Jakarta)</td>
<td>Pharmacovigilance and Good Distribution Practice (GDP)</td>
</tr>
<tr>
<td>Thailand (2013/10/24–25, Bangkok)</td>
<td>Risk Management Plan, Pharmacovigilance, GMP, Pharmacopoeia</td>
</tr>
</tbody>
</table>
Thank you for your attention!