New Regulation in Japan and Future Direction of PMDA

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<tr>
<th>Type of Financial Interest within last 12 months</th>
<th>Name of Commercial Interest</th>
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<tr>
<td>☐ Grants/Research Funding</td>
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<td>☐ Stock Shareholder</td>
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<td>☐ Consulting Fees</td>
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<td>☐ Employee</td>
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<td>☐ Other (Receipt of Intellectual Property Rights/Patent Holder, Speaker’s Bureau)</td>
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Pharmaceuticals and Medical Devices Agency

Major Services

- Scientific Review for Drugs & Medical Devices
- GCP, GMP Inspection
- Consultation on Clinical Trials
- Safety Measures
- Relief Services

Unique Three-pillar System Securing Nation’s Safety

Review

Japanese citizens

Safety

Relief
3rd 5-year mid-term Plan of PMDA (FY2014-2018)

**Major challenges**

- **Shortening the time to approval**
  - High quality review/consultation services

- **Enhancing safety measures**

- **Globalization**

**Specific measures**

- **Accelerated review process**
  - (Improvement of approval predictability)

- **Improvement of prior assessment**
  - (substantial acceleration of approval review process)

- **Readiness for introduction of RMP**

- **Introduction of approval system with condition/period for Regenerative Medicines**

- **Drastic improvement of consultation service**
  - Improvement of pharmaceutical affairs consultation service on R&D strategy
  - Improvement of clinical trial consultation service

- **Utilization of medical inf. database**

**Advanced Review/Consultation System**

- **Goal**
  - Development of Japan’s original innovative drugs and medical devices
  - Marketing of cellular and tissue-based products
  - Activation of industry
  - Extending health and life span of Japanese people
  - Contribution to global medicine

**Human Resources with excellent skills**

- 751 staffs → 1065 staffs
Japan’s Performance on NDA Review

Reference: The impact of the changing regulatory environment on the approval of new medicines across six major authorities 2004-2013. CIRS (Centre for Innovation in Regulatory Science) R&D 55

http://cirsci.org/node/73
Regenerative medicine & cell therapy in Japan

Medical Care Act (MCA)

Pharmaceuticals and Medical Devices Act (PMD Act)

Academic Research Purpose

Clinical Research using human stem cells (under the Guideline for Human Stem Cell Clinical Research - since 2006)

108 protocols approved (as of November 2014)

Cellular/Tissue based Products

2 marketed products
- JACE (autologous cultured epidermis)
- JACC (autologous cultured cartilage)

18 clinical trials initiated (including 5 gene therapy products) (~January 2015)

Medical care

Cancer immunotherapy

Six types of therapy are currently provided in approved university hospitals as “advanced care”

* Partially covered by national health insurance

Covered by MHLW

Product Marketing Authorization Purpose

Covered by MHLW and PMDA
Two authorized products in Japan

Ref. Japan Tissue Engineering Co., Ltd. (J-TEC), HP

**Autologous Culture Epidermis JACE**

Indication: serious burns treatment (limited to the burns of more than 30% of the body surface area)

Marketing authorization for medical device on 29 October 2007 (submission: 6 October 2004)

**Autologous Cultured Cartilage JACC**

Indication: Relief of symptoms of traumatic cartilage defects and osteochondritis dissecans (exclude osteoarthritis) for knee joints. (limited to a defect area of over 4cm² with no alternative therapy.)

Marketing authorization for medical device on 27 July 2012 (submission: 24 August 2009)
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 Clinical Trial (CT)
- Difficult to conduct **controlled study** to demonstrate “true endpoint” of clinical benefit
- **Heterogeneity** of Quality affected by source materials

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

- Integrated support from basic to clinical research
- Development of infrastructure to promote regenerative medicines
- Support utilizing iPS cells as a drug-discovery tool

Regenerative Medicine Promotion Act (Enacted in May 2013)

Goals for the next 6 years

- Apply new drugs developed by iPS cells technology in clinical trials
- Increase the number of approved cellular therapeutic products
- Expand the target of illness in clinical trials
- Develop equipment or devices related to regenerative medicines

Regulatory reform

- 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
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

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
Revisions of Pharmaceutical Affairs Law

◆ Revisions of Drugs and Medical Devices Articles
  • Relevant party’s obligations are specified to ensure quality, safety, and efficacy of drugs and medical devices.
  • MAH’s obligation to notify labeling and its revision, reflecting the latest findings

◆ Revisions of Medical Devices Articles
  • Independent Chapter for “Medical Devices”
  • Expansion of Third party certification system to higher risk devices
  • Quality Management System (QMS) adherent to ISO 13485
  • Other revisions related to medical devices

◆ Additions for Regenerative Medical Products
  • Definition and independent chapter for Regenerative Medical Products
  • Introduction of conditional/time limited approval system
The Pharmaceuticals and Medical Devices Act (PMD Act)

- **Separate category and definition of “regenerative medical products”**

  Difficult to gather and evaluate the data for efficacy of regenerative medical products in a short time due to heterogeneity of cells

  To secure timely provision of safe regenerative medicines, a new regulatory framework is needed

- **Expedited approval system for regenerative medical products**

  After the safety is confirmed and the results predict likely efficacy, the product will be given conditional, time-limited marketing authorization in order to enable timely provision of the products to patients.
Expedited approval system under PMD Act

[Traditional approval process]

Clinical study → Phased clinical trials (confirmation of efficacy and safety) → Marketing authorization → Marketing

< 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

[New scheme for regenerative medical products]

Clinical study → Clinical trials (likely to predict efficacy, confirming safety) → Conditional /term-limited authorization → Marketing (Further confirmation of efficacy and safety) → Re-application within a period (max. 7 yrs) → Marketing authorization or Revocation → Marketing continues

Post-marketing safety measures must be taken, including prior informed consent of risk to patients
Likely to predict efficacy (clinical benefit)

- To approve products based on the limited data, such as surrogate endpoints in exploratory study.
- Similarity to **accelerated approval of** USFDA * The product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit (ref.)*
- We have experiences in the orphan drug area.

Ref.) USFDA--Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses (57 FR 58958, Dec. 11, 1992)

- It applies to certain new drug products in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments.
- Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.
- The drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.
- Approval will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit (such as OS).
- Postmarketing studies would usually be studies already underway.
- FDA may withdraw approval, if a postmarketing clinical study fails to verify clinical benefit; ................
Japan Approved Member at the 38th PIC/S Committee Meeting

- Japan (MHLW, PMDA, 47 prefectures) GMP Inspectors applied for PIC/S membership on March 2012
- On-site examination on September 9-13, 2013
- Decided to become official membership on July 1st 2014 at the committee meeting on May 15-16, 2014 (Rome)
- 45th member

With PIC/S Chair Dr. Joey Gouws

PIC/S (Pharmaceutical Inspection Convention and Co-operation Scheme)

Cooperative framework between GMP inspectors aimed to achieve harmonized GMP standards within the pharmaceutical area and the international development, enforcement, and conservation of the quality system. PIC/S is emerging to become the world standard in the GMP domain.
### Global Activities

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<th>Abbreviation</th>
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<tr>
<td>Summit</td>
<td>International Summit of Heads of Medicines Regulatory Agencies</td>
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<td>ICH</td>
<td>International Conference on Harmonization</td>
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<td>IMDRF</td>
<td>International Medical Device Regulators Forum</td>
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<td>PIC/S</td>
<td>Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme</td>
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<tr>
<td>HBD</td>
<td>Harmonization By Doing</td>
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<tr>
<td>ICDRA</td>
<td>International Conference of Drug Regulatory Authorities</td>
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<tr>
<td>APEC LSIF RHSC</td>
<td>APEC Life Science Innovation Forum Regulatory Harmonization Steering Committee</td>
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<tr>
<td>OECD MAD</td>
<td>OECD Mutual Acceptance of Data</td>
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<td>PDG</td>
<td>Pharmacopoeial Discussion Group</td>
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<td>IDGRP</td>
<td>International Generic Drug Regulators Pilot</td>
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<tr>
<td>ICMRA</td>
<td>International Coalition of Medicines Regulatory Authorities</td>
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PMDA and the World

- MOU between the Chinese SFDA (present CFDA) and the Japanese MHLW, under which PMDA supports cooperative activities.
- ** MOU concluded between Interchange Association and East Asia Relations Commission, but is being implemented through cooperation of related organizations.
PMDA for the world

-To create society to receive the essential forefront medicines-

Swift approvals of innovative products

Convey Japanese technology to the world

Cooperate with all agencies in the world

Full measures by use and application of medical information

Swift relief for occurred health damage

Contribute to the world’s medicine

Japanese citizens

Regulatory Science
Thank you very much for your attention

(For Win-Win Relationship)