Marketing Authorizations for Earlier Patient Access:

Regulatory Challenges in Japan

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Introduction of PMDA

Pharmaceuticals and Medical Devices Agency (PMDA)

◆ an Incorporated Administrative Agency (IAA)
Japan’s Performance on NDA Review

New active substance (NAS) median approval time for six regulatory authorities in 2004-2013

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

4 Major challenges

◆ Shortening the time from early development to approval
  Measures: improvement in consultation system, accelerated review process, etc.

◆ High quality review/consultation services
  Measures: promotion of regulatory science research, etc.

◆ Enhancing safety measures
  Measures: utilization of medical information database

◆ Globalization
  Measures: information transfer with the world
PMDA Staff Size

- Administrative part
- Safety Department
- Review Department
- Planned


- 2004: 256
- 2005: 291
- 2006: 319
- 2007: 341
- 2008: 426
- 2009: 521
- 2010: 605
- 2011: 648
- 2012: 678
- 2013: 708
- 2014: 753
- 2018: 1065
ADAPTIVE PATHWAYS
The Basic Concept on Regulatory Science in PMDA

For further improvement of the quality of the three services such as Reviewing, Conducting Safety and Providing relief, PMDA needs to make exact prediction, assessment, and judgment based on convincing evidence adopting the latest scientific knowledge, and so, promotion of regulatory science research does become important.

(The Basic Concept on Regulatory Science in PMDA, Aug 10, 2011)
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 in terms of social responsibility for public health
More comprehensive and stronger “Regulatory Science Bridge” will help us develop a drug in the future.

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

Question is “What is the socially and scientifically acceptable level of effectiveness for approval?”

For:

- 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
Concept of Adaptive Licensing

- Expand access of the new drug to the patient population in a staged approach

The goal of this concept is to expedite access
Pre-clinical Data

Clinical Data (No. of Patients)

CT NDA Marketing authorization

Unknown Adverse Event

Drugs for chronic disease

Unknown Adverse Event

Adaptive licensing model

e.g. VIOXX

Unknown Adverse Event
# Early Access schemes of ICH 3 parties

<table>
<thead>
<tr>
<th>US</th>
<th>EU</th>
<th>JAPAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Priority Review</td>
<td></td>
<td>Priority review</td>
</tr>
<tr>
<td>Accelerated approval for serious or life-threatening illnesses</td>
<td>Conditional MA MA under exceptional circumstances</td>
<td>Approval for Oncology drug, Orphan drug Conditional &amp; Time-limited approval for regenerative medicine</td>
</tr>
<tr>
<td>Break through therapy &amp; Fast Track designation</td>
<td>Pilot Project on Adaptive Licensing</td>
<td>Forerunner Review Assignment</td>
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</table>

Various agencies have various approaches to accommodate patient access.
HUMAN CELL AND GENE THERAPY UPDATES IN JAPAN
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

Government policy

- 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)
Definition of “Regenerative Medical Products” in Japanese Legislation

Regenerative medical products are defined as processed human/animal cells that are intended to be used 1) for either (1) the reconstruction, repair, or formation of structures or functions of the human body or (2) the treatment or prevention of human diseases, or 2) for gene therapy.

Cellular and Tissue based Products and Gene therapy Products

Advanced-therapy medicinal products (ATMPs)

Regulation (EC) No 1394/2007
Regenerative medicine & cell therapy in Japan

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

Pharmaceuticals and Medical Devices Act. (PMD Act.)

Commercial Product Marketing Authorization Purpose

Cellular/Tissue based Products
2 marketed products
- JACE (autologous cultured epidermis)
- JACC (autologous cultured cartilage)

19 clinical trials initiated (including 6 gene therapy products) (~March 2015)

Cancer immunotherapy
Six types of therapy are currently provided in approved university hospitals as “advanced care”.
- Partially covered by national health insurance

Clinical Research using human stem cells
108 protocols approved
(as of November 2014 - before new legislation)

Academic Research Purpose

Medical care

Covered by MHLW

Covered by MHLW and PMDA

19 clinical trials initiated (including 6 gene therapy products) (~March 2015)
## Approved Cellular/Tissue based Products

<table>
<thead>
<tr>
<th>Category</th>
<th>Brand Name (Company)</th>
<th>Approval Date</th>
<th>Target Organ</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous cultured epidermis</td>
<td>JACE (Japan Tissue Engineering Co.,Ltd.)</td>
<td>Oct. 29, 2007 (submitted on Oct. 6, 2004)</td>
<td>Skin</td>
<td>Autologous cultured keratinocytes using Green’s technique in which keratinocytes derived from the patient’s own skin tissue are co-cultured with irradiated 3T3-J2 cells derived from mouse fetuses as a feeder to form a sheet in approximately three to seven layers thick. This is indicated for the treatment of serious large burns that cannot be provided with a sufficient area of donor skin for autologous skin grafting, and of burns in which the total area of deep second-degree (deep dermal) and third-degree (full-thickness) burn is 30% or more of the total body surface area.</td>
</tr>
<tr>
<td>Autologous cultured cartilage</td>
<td>JACC (Japan Tissue Engineering Co.,Ltd.)</td>
<td>Jul. 27, 2012 (submitted on Aug. 24, 2009)</td>
<td>Bone/Cartilage</td>
<td>An autologous cultured cartilage to alleviate clinical symptoms by implanting it in the affected site of traumatic cartilage efficiency and osteochondritis dissecans (excluding knee osteoarthritis) in knee joints with a cartilage defective area of 4 cm² or more for which there are no other treatment options. Chondrocytes isolated from the non-load-bearing site of a knee joint of patients by taking a small amount of cartilage tissue are three-dimensionally cultured in atelocollagen gel to obtain this product. Clinical studies were conducted to evaluate the efficacy and safety of this product for patients with traumatic cartilage deficiency, osteochondritis dissecans, and knee osteoarthritis.</td>
</tr>
</tbody>
</table>
Two of the new products application under the new regulation

According to the news released by the sponsor companies, in September and in October 2014, two new product applications for marketing authorization were filed by PMDA.

On-going review process to be goaled in 2015 ????

1. Bone marrow mesenchymal stem cells for GVHD
2. Skeletal myoblast sheet for serious heart failure due to ischemic heart disease

Note: Figures quoted from the company press release docs
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 “**true end point**” 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?
Quality concept of hCTPs

Bio-pharmaceuticals

- Source materials, process variability
- In-process control
- Characterization
- Specification

hCTPs

- Source materials, process variability
- In-process control
- Characterization
- Specification

- 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
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.

New regulation will be effective on 25 November 2014
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]

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

[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 years)
- Marketing authorization or Revocation
- Marketing continues

Post-marketing safety measures must be taken, including prior informed consent of risk to patients

May limit distribution to HCPs/hospitals with expertise and skills to handle the new technology
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)
Evidence level of efficacy: Drug (normal) vs. HCT/P

If there is no effective treatment available for the target population of the disease

Drug (normal)

PMD Act. (Regenerative medical products)

Confirmation study

Exploratory study

Conditional and time-limited approval

Marketing authorization

Orphan level

Evidence level of efficacy
Pharmaceutical Affairs Consultation on R&D Strategy

Valley of Death
- Shortage of funds, Knowledge on Regulation and developmental strategy

Consultation on quality and battery of pre-clinical, including examining tumorigenicity, biological ingredient safety

Consultation on endpoints or sample size of early clinical trial

Further studies are handled by the Regular Consultation

Flow of Strategy Consultation
- Introductory Consultation (744)
- Pre-Consultation (900)
- Face-to-Face Consultation (258)

(7/1/2011 – 9/30/2014)
CHALLENGES OF EARLY ACCESS SCHEME
Conversion of the business model of pharmaceutical companies

Traditional

- Development target: “blockbuster” for disease with large number of patients (chronic disease)
- Major development resources: company in-house R&D

Current Trends

- Development target: “Unmet medical needs” with more targeted patients
- Major development resources: Open innovation – alliance with biotech companies and academic research organisations

Enhance the probability of successful R&D with more targeted patients

- Diversify the sources of promising seeds outside the company
- Apply new design to clinical trials such as enrichment using “companion diagnostics” toward tailor-made medicine, adaptive design trials, etc.
- Apply iPS technology for assessing pre-clinical safety and efficacy
Safety and Efficacy evaluation of limited number of subjects in the trial for conditional approval

- Challenge on new designs and statistical methodologies for small population
- How to secure evidence level
  - Design: controlled? / blinded? possibility?
  - Clinical endpoint (efficacy): clinical significance, objectiveness, surrogacy, etc.
- At least, Maximize the information from a single subject in terms of safety and efficacy.
- Post-marketing study?
What is an orphan disease/drug? How will an adaptive pathway progress?

Orphan disease?

Orphan disease?

Orphan disease?

Lever XX mutation Positive

Melanoma XX mutation Positive

Adaptive strategy?

Lung XX mutation Positive

Adaptive strategy?
Small scale R&D for adaptive pathway whatever

More targeted be the patient, pharma business should become more global

- Enroll patients to **multi-national trials** to keep analizable scale, due to **fragmentation of patients**
- Adaptive licensing phenomena has already begun, hasn’t it?
- More international regulatory collaboration is needed?
Increasing trend in Multi-national trial based on Clinical Trial Notifications (CTNs)

Source: PMDA
Further expansion?

- **Pilot Project on Adaptive Pathway (EU):** “The aim of AL is timely access for patients to treatments that promise to address serious conditions where there is an unmet medical need, especially when there are no satisfactory alternative therapies”

- **Conditional, time-limited marketing authorization:**

  Regenerative Medicine (so-far, for the time being)
  
  Treatment for patients with serious or life-threatening condition without existing effective therapy (unmet needs)

  Regenerative Medicine (future ?)
  
  Could be a treatment for chronic disease, plastic surgery? (RCT would be requested?)

We will have to have careful discussion to expand adaptive license and other access scheme in the future.
Regulatory Challenges

- **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 *(Adaptive pathway)*

- **Reimbursement**: Question on consistency with regulatory approval and on acceptance of clinical data for HTA (predicted effectiveness vs. confirmed effectiveness)

- **Quality data**: limited characterization of bio-products in early stage and quality control under GMP/GCTP (validation, scale)
Overall picture of CMC development

【Typical Development】

Non-Clinical Study

Phase 1

Phase 2

Clinical Study

Early access review timeline

Approval

Post-Approval

Target product Profile

Establishment of Design Quality and Product Quality by CMC study

Control strategy

Control strategy

Control strategy

Process Parameters

Quality Attributes

CQA

CPP

Consistency

Equivalency

Knowledge Control/Quality Risk Management

Investigational Product GMP

GMP
SAKIGAKE PACKAGE 2015
MHLW drew up a new strategy to lead the world in the practical application of innovative medical products in 2014.

Forerunner Review Assignment System is a system to put innovative medicines/medical devices/regenerative medicines originated from Japan into practice.

**Designation Criteria**

Medical products for diseases in dire need of innovative therapy and satisfies the following two conditions:

1. Having developed firstly in Japan and anticipating an application for approvals (desirable to have PMDA consultation from the beginning of R&D)
2. Prominent effectiveness (i.e. radical improvement compared to existing therapy), can be expected based on the data of mechanism of action from non-clinical study and early phase of clinical trials (phase I to II)

Not limited to life-threatening and regenerative medicine
General Timeframe of Forerunner Review Assignment

【Standard】
- Pharmaceutical affairs consultation for R&D strategy
- Non clinical studies, Clinical studies
- Clinical trials I/II
- Consultation on Clinical trials
- phase III study
- Review
- Reimbursement
- Post Marketing

【Forerunner】
- Priority Consultations
- Prior review (rolling submission)
- Clinical trials I/II
- Consultation on Clinical trials
- phase III study
- Review
- Reimbursement
- Post Marketing

① Priority Consultations
② Prior-review
③ Priority Review
④ Review Partner System
⑤ Strengthening Post-Marketing Safety

Practical application of Innovative medical products

※ In some cases, may accept phase III data during review

Around 60 drug applications for the assignment have come to MHLW/PMDA

General Timeframe of Forerunner Review Assignment

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Summary

Mission of regulatory science itself is to regulate progress of technology in harmony with the society. That is “ethics”.

PMDA pursues updating its regulatory science capability for more scientifically effective review, supported by the Science Board

For example, PMDA is aimed at improving access of new therapy in a timely manner through introducing various schemes, supported by up-to-date regulatory science view points.

- Conditional and time limited authorization for regenerative products,
- SAKIGAKE review assignment scheme

PMDA encourages active use of consultations from the early stages of development.
Thank You for your attention!

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

Literature available in English:
