DISCLAIMER

I attend this conference as an individual expert and do not represent the ACTO nor PMDA/JMHLW/CFDA.

The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of or reflecting the position of the ACTO.

Official regulations are written in Chinese and Japanese. Translation is only my personal use.
Situation around Asia Medical Tourism

Patients from USA, Europe and Middle East are visiting Asian countries for cellular therapy as well as from patients in Asia countries.

Especially China or Japan to receive cellular therapy where autologous cellular therapy is regulated as part of medical practice. There were no direct regulations for autologous cellular therapy.
Differences in Regulation

• Some autologous cellular therapy is regulated as part of medical practice, not by drug or medical device law in China and Japan. Korea, Singapore and Taiwan regulation are regulating as drug following USA and EU.

• Recently, China proposed new regulation for cellular therapy which try to regulate autologous cellular therapy but not by drug law. New regulation Japan require manufacturing license for cellular products. Japanese new regulation require clinical benefit data within few years after manufacturing license.

• Temporary conditional approval followed by Phase III/IV study by KFDA will accelerate development and help small company. Japanese new regulation also give conditional approval.
Specific to cellular therapy

In general, cellular therapy is developed by small company and/or academy and financially very weak. Cannot conduct large clinical trials. Conditional approval will help small company and accelerate development.

• Cellular therapy is not a simple drug/device but therapy with various elements needed for medical practice

• Who will own product license if you need approval as a drug. Autologus cells are different from patient to patient ➔ Need new regulation based on new concept.
Regulations for Cellular Therapies in Asia

Japanese new regulation on cellular therapy is fully enforcing from November 25, 2014.

China proposed new regulations for cellular therapy some years ago. But this is not yet effective. Just this month, National Health and Family Planning Commission of the People’s Republic of China (NHFPC) and CFDA announced the new rules on autologus cellular therapy. Autologus cellular therapy can be given only at the Level 3, Class A (第三級甲) hospital and CFDA has right to audit those hospitals to confirm the safety of cellular products. This idea is similar to Japanese new regulation.
How to speed up regulatory process

*The best solution is to make it possible for patient to receive wished therapy in home country.*

What we can do?

- In some country, need speedy approval of already approved drug/device/therapy in other country
- Propose Conditioned approval for new therapy
- Introduce regulation and its philosophy from other country for setting up new regulation
干细胞临床试验研究管理办法（试行）
（征求意见稿）

第一章 总则
第一条 为保证干细胞临床试验研究过程规范，结果科学可靠，保护受试者的权益并保障其安全，根据《中华人民共和国药品管理法》、《医疗机构管理条例》和《药物临床试验质量管理规范》等相关法律法规，制定本办法。
干细胞临床试验研究基地管理办法（试行）
（征求意见稿）

第一章 总则
第一条 为加强干细胞临床试验研究的监督管理，根据《药物临床试验质量管理规范》、《药物临床试验机构资格认定办法（试行）》和《干细胞临床试验研究管理办法（试行）》，制定本办法。
干细胞制剂质量控制及临床前研究指导原则（试行）
（征求意见稿）

一、前言
二、干细胞制剂的质量控制
（一）干细胞的采集、分离及干细胞（系）的建立
（二）干细胞制剂的制备
（三）干细胞制剂的检验
（四）干细胞制剂的质量研究

三、干细胞制剂的临床前研究
（一）安全性评价
（二）有效性评价
1. Chinese Background

➢ Technique development pushing & highly unmet medicinal need.
➢ Lead the healthy development of the industry.
➢ Working group is set up and is responsible for making the relevant policy.

✓ Cooperation of National Health and Family Planning Commission of the People’s Republic of China (NHFPC) and China Food and Drug Administration (CFDA).
✓ Based on “Drug Administration Law”, scientific principles and technique requirements.
2. Status

Two provisions and One guideline

1. Clinical Trial Provisions for Stem Cell-based Medicinal Products (draft)

2. Clinical Trial Institution Provisions for Stem Cell-based Medicinal Products (draft)

3. Guideline on Quality Control and Pre-clinical Study of Stem Cell-based Medicinal Products (draft)

Post on the NHFPC website for comments since March, 2013
3. Main Content

3.1 Clinical Trial Provisions for Stem Cell-based Medicinal Products (draft)

7 chapters 38 items and 2 appendixes

Chapter 1 General Principles
Chapter 2 Application and Registration
Chapter 3 Clinical Trial
Chapter 4 Protection for Donors’ and Subjects’ Rights
Chapter 5 Reports
Chapter 6 Supervision and Punishment
Chapter 7 Appendix
3. Main Content

3.2 Clinical Trial Institution Provisions for Stem Cell-based Medicinal Products (draft)

6 chapters 19 items and 2 appendixes

Chapter 1 General Principles
Chapter 2 Mission and Qualification of Clinical Trial Institution
Chapter 3 Designation Procedures for Clinical Trial Institution
Chapter 4 Management of Clinical Trial Institution
Chapter 5 Supervision and Punishment
Chapter 6 Appendix
3. Main Content

3.3 Guideline on Quality Control and Pre-clinical study of Stem Cell-based Medicinal Products (draft)

1. Preface
2. Quality control
3. Pre-Clinical study
4. Glossary
5. Reference
II. Review Perspectives

1. Quality Control and Manufacturing
2. Pre-Clinical Study
3. Clinical Trial
II. Review Perspectives

CDE Organization

- Office of Management and Communication
- Office of TCM Clinical Evaluation
- Office of Traditional Chinese Medicines
- Office of Pharmacology and Toxicology
- Office of Clinical Evaluation I
- Office of Clinical Evaluation II
- Office of New Drug Pharmaceutical Science
- Office of Biostatistics
- Office of Generic Drug Pharmaceutical Science
- Office of HR and Information
- Office of Compliance and Development
- Office of Logistics
- Office of Biological Products
II. Review Perspectives

1. Quality Control and Manufacturing

1.1 Starting materials

1.2 Manufacturing

1.3 Characterization and Quality control

1.4 Stability

……
II. Review Perspectives

2. Pre-Clinical Study

2.1 Pharmacology

2.2 Toxicology

......
II. Review Perspectives

3. Clinical Trial

3.1 Protocol
3.2 Clinical Trial Institution
3.3 Qualification of Principle Investigator
3.4 Adverse event monitoring

......
II. Review Perspectives

- Quality Control and Manufacturing
- Pre-Clinical Study
- Clinical Trial
- Risk and Benefit Assessment
- Decision Making
2. Japan has lagged its peers in bringing products to market

【The Number of Marketed Products & Products under Clinical Trials】

As of Dec. 2012

**U.S. (9 products)**
- Under Clinical Trials: 88 products
  - Epicel (Autologous, cultured skin)
  - Dermagraft (Allogenic cultured derma)
  - OrCel (Allogenic composition of cellular matrix)
  - Carticel (Autologous, cultured cartilage)

**Europe (20 products)**
- Under Clinical Trials: 42 products
  - Bioseed-S (Autologous cultured derma)
  - Chondrotrelplant (Autologous cultured cartilage)
  - Cellactive (Autologous cultured cartilage)
  - ChondroCelect (Autologous cultured cartilage)
  - Hyalograft (Autologous cultured cartilage)

**Korea (14 products)**
- Under Clinical Trials: 42 products
  - Holoderm (Autologous cultured derma)
  - Articell (Autologous cultured cartilage)
  - Ossron (Autologous cultured bones)

**Japan (2 products)**
- Under Clinical Trials: 4 products
  - JACE (Autologous cultured skin)
  - JACC (Autologous cultured cartilage)

**Other Markets (6 products)**
- Under Clinical Trials: 23 products
  - Chondrotrelplant (Autologous cultured cartilage)
  - Cartogen (Autologous cultured cartilage)

**Comparison By Market**

**[Disease Types]**
- Nerve: for Parkinson’s disease
- Heart: ischemic cardiac disease
- Vessel: arteriosclerotic obliteration
- Pancreas: Type I diabetes
- cartilage/skin/bone
- vessel/heart/nerve/pancreas/eye
- cancer immunity
- others

**[Market] Comparison**
- U.S.
- Europe
- Japan
- Korea
- Others
3. Regenerative Medicine and Conventional Medical Care

Raw Materials Considerations

- Autologous (own) HCTs
  - Transplantation
  - Isolation
  - Genetic Manipulation
  - Cultivation

- Allogenic (donor’s) HCTs
  - Transplantation
  - Isolation
  - Genetic Manipulation
  - Cultivation

Affinity to Patients

- No immune response?
- No cancer risk?
- No allergic?
  - Immune response
  - Cancer risk
  - Allergic risk

Regenerative Medicine

- Autologous Stem Cell
- Autologous iPS Cells
- Allogenic ES/iPS Stem Cell

Treatment

- Reconstructive Medicine
- Aesthetic Surgery
- Immune Cell Therapy
- Organ Transplant
- Bone marrow Transplant
- Blood Transfusion

Medical Practitioner Act / Medical Service Act

- Toxicity risk
  - risk

Pharmaceutical Affairs Law

- Medication
4. New Legal Framework Conductive to Regenerative Medicine

<table>
<thead>
<tr>
<th>Target Areas</th>
<th>Medical Practitioner Act / Medical Service Act</th>
<th>Pharmaceutical Affairs Law</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aesthetic Surgery</td>
<td>Medical treatment at own expense</td>
<td>Clinical research</td>
</tr>
<tr>
<td>Immune Cell Therapy</td>
<td>Clinical trials</td>
<td>Clinical trials</td>
</tr>
<tr>
<td>Regenerative medicine</td>
<td></td>
<td>Regenerative medicine products</td>
</tr>
<tr>
<td>for clinical use</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Promotion Act for Regenerative Medicine**
- Responsibility for each player
- Organize security and other standards
- **Organize a system that allows medical institutions to outsource cells / tissue processing operation to external businesses**
- Introduction of an Early Approval System

**Safety Act for Regenerative Medicine**
- Introduce safety guaranteed systems related to each risks of regenerative medicine (introduce approval / notification system)
- **Organize a system that allows medical institutions to outsource cell / tissue processing operation to external businesses**

**Revised Pharmaceutical Affairs Law**
- Define “regenerative medicine”
- **Introduce Early Approval System**
- Post-marketing monitoring
Safety Act for Regenerative Medicine
Enables medical institutions to outsource cell / tissue processing

Safety Act / Revised Pharmaceutical Affairs Law
Sets security and other standards suitable for regenerative medicine

Early approval system
Introduction of an early approval system

Procurement of Cells/Tissues
Patient

Cultivation

Cultivation

Cultivation

Revised Pharmaceutical Affairs Law

Allogenic Human Cells
6. Direction of Japan's Regulatory Reform

Current

National insurance coverage

Reviewed
Nov.2014 ~

Function

Revised Pharmaceutical Affairs Law

Early Approval System

Shorten approval period

Speedy Approval

Safety Act

1. Medical Treatment Service

(Medical Practitioner Act / Medical Service Act)

After data is gathered, the process will move to clinical trials under Revised Pharmaceutical Affairs Law.

- only inside of hospital / Medical Institution
- operated only by medical doctor

2. Regenerative Medicine Products

(Pharmaceutical Affairs Law)

Medical Institution A

Medical Institution B

Cell Processing Organization (outsourcing)

Auto cells

Allo cells

Medical Institution A

Medical Institution B

Cell Processing Organization (outsourcing)

Auto cells

Allo cells

MAHs

PMDA / MHLW

Medical Institution

MAHs

Auto cells

Allo cells

Medical Institution

MAHs

Allo cells

Auto cells
Introduction of PMDA

Pharmaceuticals and Medical Devices Agency (PMDA)

- an Incorporated Administrative Agency (IAA)

PMDA’s Safety Triangle

- Securing Safety and Efficacy
- Review: Reduction in risk
- Three-pillar System Unique to Japan

Japanese citizens

Safety
Continuous risk mitigation efforts

Relief
Relief measures for health damage caused by risk factors
Two Japanese Regulatory Authorities

- **Ministry of Health, Labor and Welfare (MHLW)**
  Planning basic policy, enforcement of administrative measures based on the law
  - Marketing authorization of pharmaceuticals and medical devices
  - Issue emergency safety information and direct product withdrawal
  - Safety measures for emergent and significant cases

- **Pharmaceuticals and Medical Devices Agency (PMDA)**
  Review, examination and data analysis
  - Scientific review, GMP/GLP/GCP inspection and consultation on the development of pharmaceuticals and medical devices for marketing authorization
  - Collection, analysis and dissemination of information relating to quality, efficacy and safety of pharmaceuticals and medical devices
Health research regulations in Japan

- **Health Research**
  - **Clinical Trials**
    - **Sponsor-Investigator CTs**
    - **Company-sponsor CTs**
  - **Clinical Trials under PAL**

**Academic Purpose (other than MA)**
- Observational studies
- Interventional studies
- Human Genome Analysis

**Product Marketing Authorization Purpose**
- Interventional studies intended for application for MA of drugs and medical devices under **Pharmaceutical Affairs Law (PAL)**

Covered by MHLW itself

Covered by PMDA
Regenerative medicine & cell therapy in Japan

Clinical trials using human stem cells (non-PAL) (under the Guideline for Human Stem Cell Clinical Trials)

90 clinical trials have been approved as of February 2014

Cancer immunotherapy

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

No statistics available for those provided outside of national health insurance scheme

Regenerative medical products (under Pharmaceutical Affairs Law)

Number of marketed products: 2
  (JACE (autologous cultured epidermis), JACC (autologous cultured cartilage))

Number of clinical trials initiated: 11 (including 2 gene therapy products)  
As of May 2014
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 7 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
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 are scheduled to be 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)
Background for new legislations

1. Needing legal basis for the guideline to secure safety of stem cell therapies
2. Growing need for collaboration between medical institutions and industry from the early stage of development

New legislation is needed for prompt and safe regenerative medicine.
→ Act on the Safety of Regenerative Medicine

3. The existing framework in Pharmaceutical Affairs Law does not fit for the characteristics of regenerative and cellular therapeutic products

Definition of regenerative and cellular therapeutic products and establishment of new framework are needed
→ Revised Pharmaceutical Affairs Law (name change to PMD. Act)
Two Acts regulating regenerative medicine & cell therapy

Regenerative Medicine

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 will be enacted on 25 November 2014
Overview of the Act on the Safety of Regenerative Medicine

I. Obligate hospitals and clinics to submit plans

II. Enable commissioning cell processing to licensed enterprises

III. Obligate CPCs to notify or obtain license

Provision of regenerative medicine

Hospitals / Clinics

Certification

Minister of Health

Cell processing

Cell processors

Notification (Hospitals / Clinics) or Application for a license (Firms)
Rules for hospitals and clinics

High Risk (class I)
- Hospitals / Clinics
- Plan
- Submission
  - Certified special committee for regenerative medicine*
  - Evaluation
  - MHLW
  - Health Science Council
  - Provision (Within 90 days)
  - Change order (Within 90 days)

Middle Risk (class II)
- Hospitals / Clinics
- Plan
- Submission
  - Certified special committee for regenerative medicine*
  - Evaluation
  - MHLW
  - Provision

Low Risk (class III)
- Hospitals / Clinics
- Plan
- Submission
  - Certified committee for regenerative medicine
  - Evaluation
  - MHLW
  - Provision

*Certified special committee for regenerative medicine is required to have highly specialized screening expertise and third-party characteristics (roughly 10 to 15 certified special committees for regenerative medicine across the country)
Common part of the two Acts

Medical technologies using processed cells (except clinical trials under PMD Act.)

The Act on the Safety of Regenerative Medicine

- Manufacturer (Licensed)
- Hospital
- Cell collection
- Cell processing
- Transplant

PMD Act. (revised PAL)

- Obtaining Cell
- GCTP
- Cell Processing
- Delivery of cell product

Regenerative Medical Products
Two acts regulating regenerative medicine & cell therapy

Regenerative Medicine

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

Production and marketing of regenerative and cellular therapeutic products by firms

The Act on the Safety of Regenerative Medicine

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

* Two laws were enacted in November 2014

Company driven IND and product 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.
Phased clinical trials (confirmation of efficacy and safety)

Marketing authorization

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

< 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

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)

Marketing authorization or Revocation

Marketing continues
Pharmaceutical Affairs Consultation on R&D Strategy

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

Basic Research
- Pharmaceuticals and Medical Devices candidates

Strategic Consultation
- Quality Study
- Non-Clinical Study
- Clinical Trial (Up to POC studies)

Consulation 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 (684)
- Pre-Consultation (813)
- Face-to-Face Consultation (209)

(7/1/2011 – 6/30/2014)
## Related Guidelines for Products Evaluation

### Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell/Tissue

- **Autologous** (2008)
- **Allogeneic** (2008)

### Guidelines on Ensuring the Quality and Safety of Products Derived from Processed Human Stem

- **Autologous Somatic Stem Cells** (2012)
- **Autologous iPS-like Cells** (2012)
- **Allogeneic Somatic Stem Cells** (2012)
- **Allogeneic iPS-like Cells** (2012)
- **Embryonic Stem Cells** (2012)

### Points to Consider for the Evaluation of Specific Products

- Cell sheet for heart failure (2010)  
- Corneal epithelial cell sheet (2010)  
- Corneal endothelial cell sheet (2010)  
- Articular cartilage repair (2010)  
- Cell sheet for periodontal tissue regeneration (2011)  
- Autologous induced pluripotent stem cells-derived retinal pigment epithelial cells (2013)  
- Allogeneic induced pluripotent stem cells-derived retinal pigment epithelial cells (2014)

### The Science Board Report. PMDA.

- 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 (2013)
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.
Purpose of Japanese new regulation

• Encourage scientist-industry for challenging clinical development for patients. Cellular therapy is regulated as 3\textsuperscript{rd} category product, \textit{Cellular Product} not a drug, not a device.

• First step is to confirm safety of cellular products used for patient treatment. => GMP level manufacturing to guarantee safe and reproducible product quality

• Then start clinical investigation

• Outcome of the study has to be reported annually and Efficacy has to be proved within few years

• Once efficacy is suggested, then conditional approval will be given. Institute/small company need not run huge study.
ACTO is an Organization for Academy, Industry and Regulatory Authorities to Collaborate for patients

- Provide opportunity for exchange information/opinion internationally among academy, industry and government authority together for the development of cellular therapy in Asia
- Work together for the acceleration of research and development for cellular therapy based on collaboration among three players
- Not just in the country but also international collaboration for research and development among Asian countries
- Activate Translational Research
- Create new business opportunity
- *Simple warnings or stop therapy are not enough!*

*In collaboration with ISCT*
The 6th ACTO meeting on August 20-22, 2015
ISCT-ACTO joint session on August 21
Gwangju, KOREA
Gwangju

- Location: The Center of Southwestern part of Korea
- Area: 501.18㎢
- Population: 1,484,000 people
Thank you

Learn More

Please Visit

www.asianct.org