Amended Pharmaceutical Affairs Law and Regenerative Medicine

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Shinji MIYAKE, Ph.D.
Professor, Keio Center for Clinical Research, School of Medicine, Keio University
Disclaimer

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Present environment of research and development of cell-tissue products in Japan

1. Number of cell tissue products approved in Japan are still 2.

2. Comparison between GCP clinical trials and non-GCP clinical research.

3. iPS cell product clinical research will start soon.

4. Reform of Pharmaceutical affairs Law

5. New law for cell therapy using non approved cell-tissue products: The Act on the Safety of Regenerative Medicine
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”

Several hundred clinics are providing cancer cell immunotherapy outside of national health insurance scheme as hospital exemption.

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 February 2014.
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Development of Cell/Tissue-based Products

**Pharmaceuticals/Medical devices**

- Review of clinical trial protocol (30 days-IND review)
- Application for Marketing Authorization

**Quality**

- Non-clinical
- Clinical trial

**Development**

- Application for confirmation “Kakunin-Shinsei”
- Confirmation “Kakunin”

**ADD-ON for cell/tissue-based products**

Removed and substituted by Pre IND consultation in July 2011.
<table>
<thead>
<tr>
<th>Year</th>
<th>Disease</th>
<th>Cell/Tissue</th>
<th>Auto/Allo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Prostate Cancer</td>
<td>Dendritic Cell</td>
<td>Autologous</td>
</tr>
<tr>
<td></td>
<td>Multiple Myeloma</td>
<td>Dendritic Cell</td>
<td>Autologous</td>
</tr>
<tr>
<td>2002</td>
<td><strong>Severe Burns</strong></td>
<td><strong>Epidermal Cell</strong></td>
<td><strong>Autologous</strong></td>
</tr>
<tr>
<td>2004</td>
<td>Cartilage Defect</td>
<td>Cartilage*</td>
<td>Autologous</td>
</tr>
<tr>
<td>2006</td>
<td>Coronary Infarction</td>
<td>Skeletal Myoblast</td>
<td>Autologous</td>
</tr>
<tr>
<td>2007</td>
<td>GVHD</td>
<td>Mesenchymal Stem Cell</td>
<td>Allogeneic</td>
</tr>
<tr>
<td></td>
<td>Severe Burns</td>
<td>Epidermal cell and Fibroblast</td>
<td>Autologous</td>
</tr>
<tr>
<td>2009</td>
<td>Severe Ocular Surface Diseases</td>
<td>Corneal Epithelial Cell and Amnion</td>
<td>Allogeneic</td>
</tr>
<tr>
<td>2011</td>
<td>severe heart failure</td>
<td>Skeletal Myoblast Sheet</td>
<td>Autologous</td>
</tr>
</tbody>
</table>

*Approved for Marketing in 2007
*Approved for Marketing in 2012
# Second Product approved in Japan

<table>
<thead>
<tr>
<th>Approval Date</th>
<th>July 27, 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic Name</td>
<td>Human Autologous Tissue for Transplantation</td>
</tr>
<tr>
<td>Product Name</td>
<td>JACC®</td>
</tr>
<tr>
<td><strong>Structure, Principle</strong></td>
<td>This product is autologous cultured cartilage created by sampling the patient’s own cartilage tissue, culturing separated cartilage cells in atelocollagen, for use by the same patient.</td>
</tr>
<tr>
<td><strong>Purpose, Indications</strong></td>
<td>Relief of symptoms of traumatic cartilage defects and osteochondritis dissecans (exclude osteoarthritis) for knee joints. The use of this product is limited to patients with a defect area of over 4cm² with no alternative therapy.</td>
</tr>
</tbody>
</table>

Clinical Trial data of JACC

1) GCP study of 30 human subjects
2) Single arm test
3) MRI Image (1.5 T)
   prosthesis were observed in 13 case / 30 case
4) symptomatic states of subjects improved
   Lysholm Knee Score, Mayo Clinic Performance Index

Condition for approval:
Due to the very limited number of patients treated in the clinical study, use-results surveys in all patients treated with JACC should be conducted for fixed period (until the end of the re-examination period) as a rule, efficacy and safety information on the product should be collected early after market launch, and the results should be reported periodically.
Present environment of research and development of cell-tissue products in Japan

1. Number of cell tissue products approved in Japan are still 2.

2. Comparison between GCP clinical trials and non-GCP clinical research.

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Positioning of Clinical Trial (CHIKEN) in Clinical Research

Clinical Test to get approval as Drug or MD based on Pharmaceutical Affairs Law Under GCP (Good Clinical Practice)
# Two Tracks for Clinical Study in Japan

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Clinical Trial (CHIKEN)</th>
<th>Clinical Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose</td>
<td>Application for Marketing Authorization</td>
<td>Not for Marketing Authorization (publication of research papers, medical treatment)</td>
</tr>
<tr>
<td>Regulatory</td>
<td>Pharmaceutical Affairs Law</td>
<td></td>
</tr>
<tr>
<td>Framework</td>
<td>Required</td>
<td></td>
</tr>
<tr>
<td>GCP compliance</td>
<td>Required</td>
<td>Not Required</td>
</tr>
<tr>
<td>IND-Review</td>
<td>PMDA/MHLW</td>
<td>IRB, MHLW (for stem cell-based products and gene therapy products)</td>
</tr>
</tbody>
</table>
Non GCP clinical research guidelines in Japan

Ethical Guidelines for Clinical Studies”
In addition, medical advances will ultimately and inevitably depend on clinical studies, and therefore appropriate implementation of clinical studies needs to be promoted through obtaining social understanding and cooperation and with human dignity and human rights fully respected.

Because of the above reasons the Ministry of Health, Labour and Welfare (MHLW) formulated the “Ethical Guidelines for Clinical Studies” (MHLW Notification No. 255 in 2003) in July 2003, which cover all clinical studies, in thus promoting their appropriate implementation.

<table>
<thead>
<tr>
<th>GCP</th>
<th>Ethical Guidelines for Clinical Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>protection of human rights as a subject in clinical trial.</td>
<td>O</td>
</tr>
<tr>
<td>assurance of the safety and efficacy of the newly developed compounds</td>
<td>O</td>
</tr>
<tr>
<td>Data quality control to assure data reliability : monitoring, etc.</td>
<td>O</td>
</tr>
</tbody>
</table>

(voluntary standard)
Medical university study in Kyoto manipulated data on blood pressure medicine Diovan

Jul 12, 2013

An investigation team at the Kyoto Prefectural University of Medicine disclosed that the results of a study of a drug to treat high blood pressure may contain errors due to manipulation. The team found discrepancies in the patients’ medical records for a study on the drug Diovan from Novartis Pharma.

[ via NHK ]
Example: JACOG(Japan Clinical Oncology Group)

Responsible for JCOG’s core functions, the Data Center and Operations Office conduct patient registration, data management, data analysis, protocol development, site visits and audits, investigator roster management, and so on. The JCOG Data Center and Operations Office are located in the National Cancer Center, Tokyo.
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“Guidelines for Clinical Studies using Human Stem Cells”
Clinical studies on human stem cells play an important role in maintaining public health and preventing, diagnosing, and treating diseases through organ function regeneration, etc.
Because of the above reasons the Ministry of Health, Labour and Welfare (MHLW) formulated “Guidelines for Clinical Studies using Human Stem Cells” (MHLW Notification No. 425 in 2006) in July 2006 in thereby ensuring that all clinical studies involving human stem cells are appropriately implemented/promoted through obtaining the understanding of society and get implemented with human dignity and human rights fully respected, and effectiveness and safety secured based on scientific knowledge.
In order to respond to these changes in the environment surrounding clinical studies involving human stem cells an overall review of the Guidelines took place in November 2010 (MHLW Notification No. 380 of 2010) to newly cover human ES cells and human iPS cells, etc. in addition to somatic stem cells.
This guideline includes the procedure to get the authorization from the Minister of MHLW.
June 28, 2013

Key regulatory hurdle cleared in planned iPS cell clinical research

Human iPS cells

A key panel of the Japanese Ministry of Health, Labor and Welfare has given a conditional green light to clinical research involving induced pluripotent stem (iPS) cells. The research, to be conducted by Masayo Takahashi of the RIKEN Center for Developmental Biology in Kobe, will investigate the use of iPS cells in patients suffering from age-related macular degeneration, a common disease in elderly people that can ultimately lead to loss of vision. It is estimated that up to 700,000 people suffer from the disease in Japan.

The group plans to create autologous iPS cells using skin cells taken from a small number of patients, and then induce retinal pigment epithelium cells, or RPE cells, from each patient’s iPS cells. The RPE cells will be transplanted into the patients’ retinas in the form of a cell sheet, initially to gauge the safety of the therapy.

The research will be carried out in close collaboration between RIKEN and the Institute of Biomedical Research and Innovation, also in Kobe.

The plan will now go two more panels and then to the Minister of Health, Labor and Welfare, who is expected to give his official endorsement. The transplantation, which may begin next year at earliest, promises to be the first clinical application of iPS cells. iPS cell therapy gained international fame in 2012, when Kyoto University Professor Shinya Yamanaka, who discovered the process for creating iPS cells, was awarded the Nobel Prize in Medicine and Physiology. The Japanese government has made research on iPS cells a key priority in its science budget for FY2013.
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This clinical research will be done under the “Guidelines for Clinical Studies using Human Stem Cells”
Amendment bill of Pharmaceutical affairs Law was decided in September 2013, will come into force in September 2014.

Outlines of Revision 1

1. To tighten security measure for Pharmaceuticals and Medical Devices

2. To establish the proper regulation based on characteristics of Medical Devices.

3. To establish the proper regulation based on characteristics of cell/Tissue based products. (regenerative medicine products)
Simplification of the regulation for Cell-Tissue Based products

Today
Classification of Products in Pharmaceutical Affairs Law
1) Pharmaceuticals
2) Medical Devices
3) Cosmetics and Quasi-Drugs

Example of classification of Cell-Tissue Based products
◆ Pharmaceuticals
  Skeletal Myoblast Sheet for severe heart failure
◆ Medical Devices
  Epidermal Cell for Severe Burns
  Cartilage for Cartilage Defect
Future after the revision of Pharmaceutical Affairs Law (expectation)

1) Pharmaceuticals
2) **Cell-Tissue Based products**
3) Medical Devices
4) Cosmetics and Quasi-Drugs
Out lines of Revision 2
3 To establish the proper regulation based on characteristics of cell/Tissue based products.
  ■ To give new definition to the cell/tissue products.
    To establish the proper safety measure regulation based on the characteristics.

■ To establish the temporary and conditional Approval system for cell/tissue products which meets all following condition:
  a) Not homogeneous product (autogenous products?)
  b) The cell/tissue products in application is presumed to possess indications and effects indicated in the application.
  c) The cell/tissue products in application is not presumed to possess harmful action which outweighs its indications and effects indicated in the application.
Grounds for denial of application

A. The drug, quasi-drug or medical device in application is not shown to possess indications and effects or performance indicated in the application.

B. The drug, quasi-drug or medical device in application is found to have no value as a drug, quasi-drug or medical device since it has harmful action which outweighs its indications and effects or performance.

C. In addition to the cases indicated in A or B above, the drug, quasi-drug, cosmetic or medical device in application is specified in MHLW ministerial Ordinance as being inappropriate as a drug, quasi-drug, cosmetic or medical device in application.
Amended Pharmaceutical Affairs Law

Expedited approval system under PMD Law

[Traditional approval process]

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

[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
Outlines of Revision 3

4. Change of the title of the Law:

Pharmaceutical Affairs Law

Pharmaceuticals and Medical Devices Law
PMD Law
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Counter measure for non regulated cell therapy in Japan

On the other hand, in Japan there are hundreds of clinics which provide unlicensed cell-tissue products therapy as a kind of hospital exemption.

In order to keep the safety of patients, Japanese Government planed to establish the new law which regulates the unlicensed cell-tissue products therapies.

The Act on the Safety of Regenerative Medicine was decided in September 2013, will come into force in September 2014.

Outlines of the Act:
1. To establish 3 Classification of cell therapies (Regenerative Medicines) based on risks to lives and health of patients.
   1st class cell therapies : High Risk cell therapies
     For example ; cell therapy using iPS Cell products.
   2nd class intermediate risk
   3rd class comparatively low risk
To establish the proper regulation or requirement for each class.
2 To establish necessary procedure to start providing cell therapy

- 1st class
  Provider of cell therapies shall seek beforehand the certification of special committee for regenerative medicine and shall submit the plan of providing cell therapy to the Minister of MHLW 90 days before start of providing cell therapy.
  In this fixed period, Minister may order the provider to change the plan, if the plan has problem of risk or non-conformity to the guidelines.

- 2nd class
  Provider of cell therapies shall seek beforehand the certification of special committee for regenerative medicine and shall submit the plan of providing cell therapy to Minister of MHLW and may start providing.

- 3rd class
  Provider of cell therapies shall seek beforehand the certification of committee for regenerative medicine and shall submit the plan of providing cell therapy to Minister of MHLW and may start providing.
The Act on the Safety of Regenerative Medicine

3 To establish the proper regulation to information providing and exchange

1) Informed consent, protection of private information
2) Adverse reaction reporting system
3) To establish the power and authority of Minister to issue an order to improve or to issue an order to suspend operation.

4. To establish the license system to manufacturing cell/tissue products which are not approved on pharmaceutical Affairs Law (Pharmaceuticals and Medical Devices Law)

The license system of cell/tissue products for contract manufacturers (not hospitals) will be established.
• Thank you for your attention.

• ありがとうございました