PMDA’s Efforts in Medicinal Area

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Today’s Presentation

1. Introduction: Products from Japan
2. Current Status of Pharmaceutical Affairs Consultation on R&D Strategy
3. Establishment of the Science Board
4. Advanced Review/Consultation System
5. New Approval System to Introduce Regenerative medicines
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Innovative Medicinal seeds from Academia in Japan

POTELIGEO® Injection (Mogamulizumab (r-INN))

Approved in JAPAN; March 2012
(First marketing authorization)

● Target Identification / Target Validation

Professor Ryuzo Ueda (Nagoya City University, Japan) discovered CCR4 as the pathogenic factor of Adult T-cell leukemia (ATL) (Clinical Cancer Res 2003; Sep 1; 9(10 Pt 1):3625-34)

● Extensive research & Development

POTELIGEO® (Mogamulizumab) is a humanized monoclonal antibody targeting CCR4 developed by Kyowa-kirin Co., Ltd. It is considered to bind with CCR4, suppressing tumor growth by antibody-dependent cellular cytotoxicity (ADCC).
Innovative Medicinal seeds from Academia in Japan

XALKORI® capsules (Crizotinib(INN))

- Target Identification / Target Validation
  Professor Hiroyuki Mano (Jichi Medical University, Japan) discovered EML4-ALK fusion oncogene in non-small-cell-lung cancer (Nature 2007; 448:561-6 etc.,)

- Extensive research & Development
  XALKORI® (Crizotinib) is the ATP competitive inhibitor of tyrosine kinase of the Hepatocyte growth factor receptor developed by Pfizer Inc.

Approved in JAPAN; May 2012
(International Birth Date: Aug. 2011)
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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 the level of POC studies)

Consultation on quality or toxicity study of biologics, cellular and tissue-based products

Consultation on endpoints or sample size of early clinical trial

Practical Use
- Innovative Products

* Further studies are handled by the Regular Consultation
Flow of R&D Strategy Consultation

**Introductory Consultation**
- Explain procedure
- No Charge

**Pre-Consultation**
- Sort out issues
- 30 minutes
- No Charge
- Not binding

**Face-to-Face Consultation**
- Scientific discussion
- 2 hours
- Charged
- Binding
- Minutes

**Consultations**
- Introductory Consultation: 600 Consultations
- Pre-Consultation: 669 Consultations
- Face-to-Face Consultation: 158 Consultations

*(7/1/2011 – 12/31/2013)*
Number of R&D strategic consultation for Drugs (except for cellular & tissue-based products)

Pre-Consultation

Face-toFace Consultation

Fiscal Year; Start from April
# Case of Face to Face consultation

<table>
<thead>
<tr>
<th>Consulter</th>
<th>Product under development</th>
<th>Intended performance, Intended use, Indications</th>
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<tbody>
<tr>
<td>National Institute of Neuroscience, NCNP Department of Molecular Therapy Shin’ich Takeda</td>
<td><strong>Morpholino oligos</strong> <em>(Antisense)</em></td>
<td>Remedy for Duchenne muscular dystrophy (DMD)</td>
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<td>Molecular Medicine and Therapy, Medicine (ART), Tohoku University School of Medicine, Toshio Miyata</td>
<td><strong>PAI-1 Inhibitor</strong> <em>(TM5509)</em></td>
<td>Hematogenic recovery of cord blood transplantation</td>
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<tr>
<td>Center for iPS Cell Research and Application (CiRA), Kyoto University, Shinya Yamanaka</td>
<td><strong>iPS Cell (Allo)</strong></td>
<td>Starting Materials for cellular &amp; tissue based products derived from iPS Cells</td>
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<tr>
<td>Sapporo Medical University, Osamu Honmou</td>
<td><strong>Mesenchymal Stem Cell (Auto)</strong></td>
<td>Improvement of neurological sign, activities of daily living disorders in daily activities, and dysfunction associated with Stroke</td>
</tr>
<tr>
<td>CYBERDYNE INC.</td>
<td><strong>ROBOT SUIT HAL</strong> <em>(Hybrid Assistive Limb®)</em> and partial Equipment for the subset of function of HAL used for movement training</td>
<td>Devices for assistive movement within patients. Planed to introduce models which differ in intended use or indications.</td>
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Establishment of the Kansai Branch of PMDA

Kansai Branch (OSAKA)

PMDA (TOKYO)

Supervision Report

Video-Conference System

Services in Kansai Branch:
- R&D Strategy Consultation
- GMP inspection (not yet)

KOBE
Ready for the next stage
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Issues of PMDA

1. Conducting review and consultation understanding of the research activities in state-of-the-art technologies,

2. Conducting review and consultation in the state of the art technologies from early stage of development,

3. Training reviewers to catch up on the accelerating innovative technologies and contributing in the establishment of practical use of state of the art technologies.

Science Board
For PMDA To Be More Science-Based

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.
Science Board and Office of Review Innovation

Science Board

- Committee members: External experts from Academia
- Declare Conflicts of Interest
- Not involved in the Review Process of individual products

Committee
- Recommendation on PMDA tasks
- Improvements in the scientific aspects of review

Subcommittee
- Deliberation on problems in each field
- Collaboration with PMDA working team

PMDA Office

Review/Audit/Inspection

RS: Office of Regulatory Science
SGD: Office of Standards and Guidelines Development

Office of Review Innovation

Director General

Secretariat Director

Associate Director General

Mission
Reform PMDA review system and related services based on science with consideration of actual medical practices

Projects Across Multi-Offices in PMDA

- Pharmaceuticals
- Medical Devices
- Bio-based Products
- Cellular & Tissue-based products

RS: Office of Regulatory Science
SGD: Office of Standards and Guidelines Development

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Working policy of discussion on Subcommittee

Pharmaceuticals  Bio-based Products

Aiming at summary of “Recommendation for the review policy of the pharmaceuticals regarding personalized medicine” and discuss needed items in order of priority.

Cellular & Tissue-based Products

Discussing how to ensure the safety of cellular and tissue-based products and aiming at revealing the predictable risks in the products as possible.

Medical Devices

Starting from discussion about the common issues as many kind of medical devices as possible because of big differences among product attributes of the medical devices.
Science Board Activities

**Committee**

- Pharmaceuticals
- Medical Devices
- Bio-based Products
- Cellular & Tissue-based Products

**Subcommittees**

- Pharmaceuticals: 9
- Bio-based Products: 9
- Cellular & Tissue-based Products: 9
- Medical Devices: 6

*26th Annual EuroMeeting Vienna 2014*
Outcome of the Science Board

Cellular & Tissue-based Products

➢ Current Perspective on Evaluation of Tumorigenicity of Cellular and Tissue-based Products Derived from iPSCs and iPSCs as Their Starting Materials (Aug. 21, 2013)

Pharmaceuticals, Bio-based Products

➢ Summary of Discussion on Non-clinical Pharmacology Studies of Anticancer Drugs (Dec. 10, 2013)

➢ Summary of the discussion on assessment of the current status of personalized medicine relating to drug development and review (Mar. 11, 2014)
Theme: Scientific methods for examining tumorigenicity regarding the capabilities and limits of each test method, and presented the points for consideration.

- Discussed assay for appearing undifferentiated cells/tumorigenic cell contaminants as a cause of “tumorigenicity” in the products.
  - Undifferentiated pluripotent cells are assessed by cell culture or animal model
    - The methods have to be more sensitive or quantified.

- Genetic abnormality that induces persistent cell proliferation
  - Validate that the pluripotency inducing transgenes used for generation of iPSCs are not inserted into the host genome regardless of the approach used for transgene delivery.

- Genomic instability
  - Confirm that the genomic mutation rate is not increased in iPSCs
Theme: Appropriateness of submitting published literature as application data instead of non-clinical pharmacology with reliability assurance.

➢ Not necessary for conducting non-clinical pharmacology for target cancers merely for applications.

➢ It is possible under the following conditions.

✓ Efficacy for target cancers has already been confirmed by clinical studies.

✓ Literature is peer-reviewed one.

✓ Raw data, detailed study conditions, etc. can be shown as necessary.
Pharmaceuticals/ Bio-based Products

Theme: Assessment of the current status of Personalized Medicine relating to Drug Development / Review

The subcommittee discuss

- the impact of drug development and utilization in human of emphasis of personalized medicine

- fundamental technology of personalized medicine such as development of CoDx, the issues of utilization, the role of biomarker regarding evaluation for drugs etc.,.
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

Tatsutoshi Nakahata, Chair, Cellular and Tissue-based Products Subcommittee
Hideyuki Okano, Vice-chair, Cellular and Tissue-based Products Subcommittee

1. Introduction

The Cellular and Tissue-based Products Subcommittee (hereinafter, the subcommittee) of the Science Board to Pharmaceuticals and Medical Devices Agency (PMDA) has held multiple discussions from the scientific point of view on “tumorigenicity” that is the major safety concern of induced pluripotent stem cells (iPSCs) for cellular and tissue-based products, and come to conclusion at present of
Immediate Issue in Science Board

1. Drugs
   - Placebo-controlled trials
   - Utilization of non-clinical testing

2. Medical Devices
   - Application of numerical analysis for non-clinical testing
   - Evaluation of medical devices for pediatric use (including application of non-clinical testing)

3. Cellular & tissue-based products
   - CPC (Cell Processing Center)
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### Accelerating Review Period

#### Total Review Period New Drug (Standard)

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#### Total Review Period New Drug (Priority)

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<td>7.7</td>
<td>5.3</td>
<td>3.6</td>
<td>3.3</td>
<td>9 mo.</td>
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**Legend:**
- Applicant
- Regulatory
- Number of application
- Target Period
Advanced Review/Consultation System

Analysis by PMDA
- Giving additional scientific value to submitted data

Cooperation with Academia

Practical use of Innovative Medical Products
- A rational & effective evaluation process for regulatory decision

Sophisticated NDA review
- Each reviewer utilizes innovative assessment techniques

Cross-Products Analysis
- Innovative evaluation methods
- Active utilization of Modeling & Simulation
  - Disease model
  - Objective B/R assessment
  - Identifying AE-related factors etc.

Sophisticated Consultation
- More evidence-based consultation

NDA etc.
- e-Submission of study data

Database
- Accumulation of data

Effective and High Quality Review
- More predictable efficacy/safety after approval
- Reduction of applicant’s work load
- More scientific regulatory decision

Effective and Successful Development
- Epoch-making proposal leading the world
- Proactive publication of guideline

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## Utilization of study data and expected outcomes

Clinical: evaluation of data from Japanese subjects, comparison with those from non-Japanese subjects, etc.

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<th>Subject</th>
<th>Outcome</th>
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| Prediction of drug interaction using a model (eg. in vitro and in vivo PK prediction) | • Increase of study success rate  
• Avoidance of unnecessary studies  
• Confirmation of model appropriateness in the review process, decrease of regulatory inquiries |
| Development of a dose-response model and prediction of optimal dose (Eg. optimal pediatric dose, optimal dose for Japanese patients in a global clinical trial) |                                                                                           |
| Development of a new evaluation indicator for disorders with no appropriate indicator (Eg. Alzheimer’s disease) |                                                                                           |
| Identification of factors affecting efficacy or safety (Eg. placebo reaction of antidepressant users) |                                                                                           |
| Evaluation of class effect in rare adverse events (Eg. heart failure, suicide) | • Enhanced safety prediction, etc.                                                        |
| Prediction of QT prolongation based on simulated blood concentration-QT relationship |                                                                                           |
Task Force for Advanced Review / Consultation

Established on Sep.1st, 2013

Steering Committee
Relevant board members/executives

Support team
Relevant directors and persons in charge

Senior Executive Director

Task Force for Advanced Review and Consultation with Electronic Data

Opinion exchange

Regular opinion exchange meeting on new drug

Review WG
WG for constructing the framework for utilizing electronic study data

Administrative office
IT group
Business group

FY 2016
Submission of electronic clinical data for NDA
After FY 2017
Submission of electronic non-clinical data for NDA

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Approval System Corresponding Commercialization of Regenerative Medicines (Conditional Approval)

Previous Pathway of Approval System

- **Clinical Study**
- **Clinical Trial** (Confirmation of efficacy and safety)
- **Approval**
- **On Market**

Leading to Early-Access!!

New Approval System to Introduce Regenerative medicines in early practical use

- **Clinical Study**
- **Clinical Trial** (Assumption of efficacy, confirmation of safety)
- **Conditional Approval**
  - Approval with condition and period
- **On Market**
  - Further assessment of efficacy and safety
- **On Market**
- **Approval or expiration of Conditional approval**
- **Re-Application**

Informed Consent from Patients through the explanation of possible risk with taking post-market measures.
Summary

- *Pharmaceutical Affairs Consultation on R&D Strategy* is offering consultation for innovative products developed by academia/venture businesses.

- *Science board* was established for review/consultation in PMDA to become more science based.

- New systems for introducing Regenerative medicine
Thank you for your attention!

http://www.pmda.go.jp/