Science-based Initiatives of PMDA

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<table>
<thead>
<tr>
<th>Type of Financial Interest within last 12 months</th>
<th>Name of Commercial Interest</th>
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<tbody>
<tr>
<td>☐ Grants/Research Funding</td>
<td></td>
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<tr>
<td>☐ Stock Shareholder</td>
<td></td>
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<tr>
<td>☐ Consulting Fees</td>
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<td>☐ Employee</td>
<td></td>
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<tr>
<td>☐ Other (Receipt of Intellectual Property Rights/Patent Holder, Speaker’s Bureau)</td>
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1. Introduction: Products from Japan
2. Current Status of Pharmaceutical Affairs Consultation on R&D Strategy
3. Updates of Science Board
4. Advanced Review/Consultation System
Today’s Presentation

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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).
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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 POC studies)

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

Non-Clinical Study
Consultation on endpoints or sample size of early clinical trial

Clinical Trial

Practical Use
Innovative Products

* Further studies are handled by the Regular Consultation

Flow of Strategy Consultation
Introductory Consultation (775)
Pre-Consultation (937)
Face-to-Face Consultation (236)

(7/1/2011 – 10/31/2014)
## Case of Face to Face consultation

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

Board members
Academia
Working policy of discussion on Subcommittees (1st Stage: Jul. 2012-Mar. 2014)

**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.
Outcomes of the Science Board (1st Stage)

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 related to development and review (Mar. 11, 2014)
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
Subcommittees on 2nd Stage (Apr. 2014 -) and Their Activities

**Category of Drugs**
a. Subcommittee on Placebo-controlled Trials (held 2 times till end of Feb. 2015)
b. Subcommittee on Non-clinical Studies (held 3 times till end of Feb. 2015)

**Category of Medical Devices**
c. Subcommittee on Application of Numerical Analysis to Non-clinical Evaluation (held 3 times till end of Feb. 2015)
d. Subcommittee on Evaluation of Medical Devices for Pediatric Use (held 2 times till end of Feb. 2015)

**Category of Cellular & Tissue-based Products**
e. Subcommittee on CPC (Cell Processing Center) (held 4 times till end of Feb. 2015)
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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

Regulatory Science

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

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
Utilization of study data and expected outcomes

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

<table>
<thead>
<tr>
<th>Subject</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Prediction of drug interaction using a model</td>
<td>• Increase of study success rate</td>
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<tr>
<td></td>
<td>• Avoidance of unnecessary studies</td>
</tr>
<tr>
<td>Development of a dose-response model and prediction of optimal dose</td>
<td>• Confirmation of model appropriateness in the review process, decrease of regulatory inquiries</td>
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<tr>
<td>Development of a new evaluation indicator for disorders with no appropriate indicator</td>
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<tr>
<td>Identification of factors affecting efficacy or safety</td>
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<tr>
<td>Evaluation of class effect in rare adverse events</td>
<td>• Enhanced safety prediction, etc.</td>
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<tr>
<td>Prediction of QT prolongation based on simulated blood concentration-QT relationship</td>
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Task Force for Advanced Review / Consultation

Established on Sep. 1st, 2013

Senior Executive Director

Steering Committee
Relevant board members/executives

Support team
Relevant directors and persons in charge

Advanced Review with Electronic Data Promotion Group

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 MAA

After FY 2017
Submission of electronic non-clinical data for MAA
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.
Thank you for your attention!

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Ask