PMDA’s Efforts in Medicinal Area

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PMDA, Japan
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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
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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

Strategic Consultation

Basic Research
- Pharmaceuticals and Medical Devices candidates

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

Non-Clinical Study

Clinical Trial
- (Up to the level of POC studies)

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
- If needed
  - 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

600 Consultations
669 Consultations
158 Consultations
(7/1/2011 – 12/31/2014)
Number of R&D strategic consultation for Drugs (except for cellular & tissue-based products)

Pre-Consultation

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>9mth</th>
<th>12mth</th>
<th>9mth</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY2011(from July)</td>
<td>60</td>
<td>80</td>
<td>120</td>
</tr>
<tr>
<td>FY2012</td>
<td>80</td>
<td>100</td>
<td>150</td>
</tr>
<tr>
<td>FY2013(till end of December)</td>
<td>120</td>
<td>120</td>
<td>180</td>
</tr>
</tbody>
</table>

Face-to-Face Consultation

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>9mth</th>
<th>12mth</th>
<th>9mth</th>
</tr>
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<tr>
<td>FY2011(from July)</td>
<td>10</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>FY2012</td>
<td>20</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>FY2013(till end of December)</td>
<td>30</td>
<td>40</td>
<td>60</td>
</tr>
</tbody>
</table>

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>
</tr>
</thead>
<tbody>
<tr>
<td>National Institute of Neuroscience, NCNP Department of Molecular Therapy</td>
<td>Morpholino oligos (Antisense)</td>
<td>Remedy for Duchenne muscular dystrophy (DMD)</td>
</tr>
<tr>
<td>Shin’ich Takeda</td>
<td></td>
<td></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</td>
<td>Devices for assistive movement with in patients. Planed to introduce models which differ in intended use or indications.</td>
</tr>
</tbody>
</table>
Establishment of the Kansai Branch of PMDA

Kansai Branch (OSAKA)

PMDA (TOKYO)

Supervision

Report

Video-Conference System

Visiting

KOBE

Services in Kansai Branch:
• R&D Strategy Consultation
• GMP inspection
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.

Board members

Academia
Science Board and Its Management Office

Science Board Management Office
- Director General
- Secretariat Director
- Associate Director General

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

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
  - Safety
  - SGD

RS: Office of Regulatory Science
SGD: Office of Standards and Guidelines Development
Working policy of discussion on Subcommittee (1st Stage)

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

**Bio-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.

**Cellular & Tissue-based Products**

**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.
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
Pharmaceuticals/ Bio-based Products

**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.
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.,.
Provisional Translation (as of September 30, 2013)†

August 20, 2013

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

* include preliminary translation
† provisional translation
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)

Total Review Period New Drug (Priority)

<table>
<thead>
<tr>
<th>Year</th>
<th>Standard</th>
<th>Priority</th>
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<tbody>
<tr>
<td>2013</td>
<td>50</td>
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<tr>
<td>2014</td>
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<td>2015</td>
<td>70</td>
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<tr>
<td>2016</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>2017</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>2018</td>
<td>80</td>
<td>80</td>
</tr>
</tbody>
</table>

12mo. Target Period

9 mo. Target Period

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

Regulatory Science

NDA etc.
e-Submission of study data

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 (eg. in vitro and in vivo PK prediction)</td>
<td>• Increase of study success rate</td>
</tr>
<tr>
<td>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)</td>
<td>• Avoidance of unnecessary studies</td>
</tr>
<tr>
<td>Development of a new evaluation indicator for disorders with no appropriate indicator (Eg. Alzheimer's disease)</td>
<td>• Confirmation of model appropriateness in the review process, decrease of regulatory inquiries</td>
</tr>
<tr>
<td>Identification of factors affecting efficacy or safety (Eg. placebo reaction of antidepressant users)</td>
<td></td>
</tr>
<tr>
<td>Evaluation of class effect in rare adverse events (Eg. heart failure, suicide)</td>
<td>• Enhanced safety prediction, etc.</td>
</tr>
<tr>
<td>Prediction of QT prolongation based on simulated blood concentration-QT relationship</td>
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</table>
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

Administrative office
IT group
Business group

Opinion exchange

Regular opinion exchange meeting on new drug

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

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

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