PMDA's Efforts in Medicinal Area

Takao Yamori, Ph.D.

Director of Center for Product Evaluation and

Deputy Director General of the Office of Review Innovation

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
5. New Approval System to Introduce Regenerative medicines

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Innovative Medicinal seeds from Academia in Japan

POTELIGEO® Injection (Mogamulizumab (r-INN))

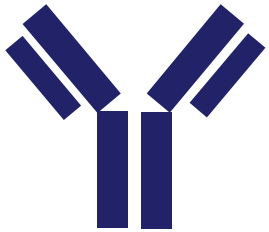
Approved in JAPAN; March 2012
(First marketing authorization)

- 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).



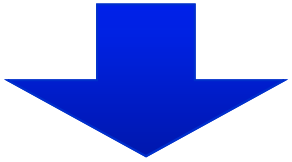
Innovative Medicinal seeds from Academia in Japan

XALKORI® capsules (Crizotinib(INN))

Approved in JAPAN; May 2012
(International Birth Date: Aug. 2011)

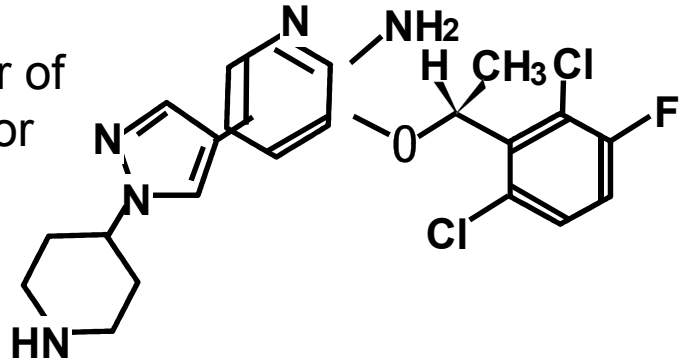
- Target Identification / Target Validation

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.



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Pharmaceutical Affairs Consultation on R&D Strategy

Valley of Death

-Shortage of funds, Knowledge on Regulation and developmental strategy

pmda

Strategic Consultation

Basic Research

Pharmaceuticals and Medical Devices candidates

Quality Study

Non-Clinical Study

Clinical Trial
（Up to the level of POC studies）

Practical Use

Innovative Products

* Further studies are handled by the Regular Consultation

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

Consultation on endpoints or sample size of early clinical trial

Flow of R&D Strategy Consultation

Introductory Consultation

- Explain procedure
- No Charge

600 Consultations

Pre-Consultation

- Sort out issues
- 30 minutes
- No Charge
- Not binding

669 Consultations

Face-to-Face Consultation

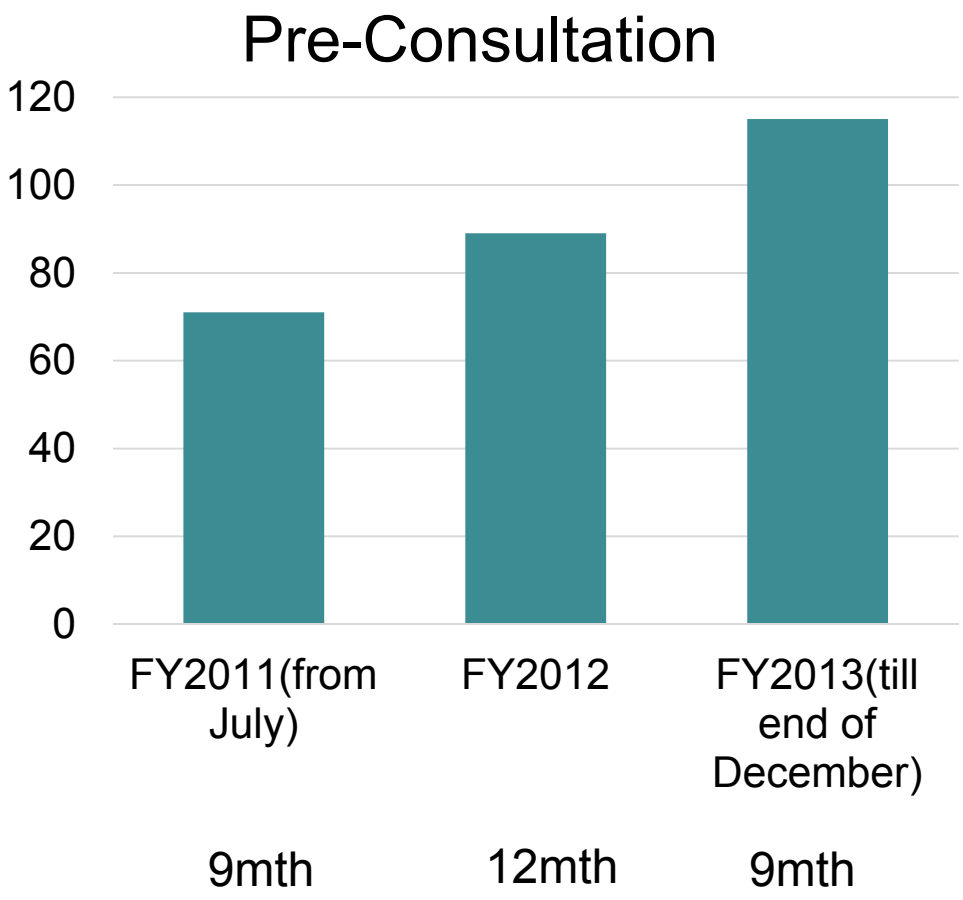
- Scientific discussion
- 2 hours
- Charged
- Binding
- Minutes

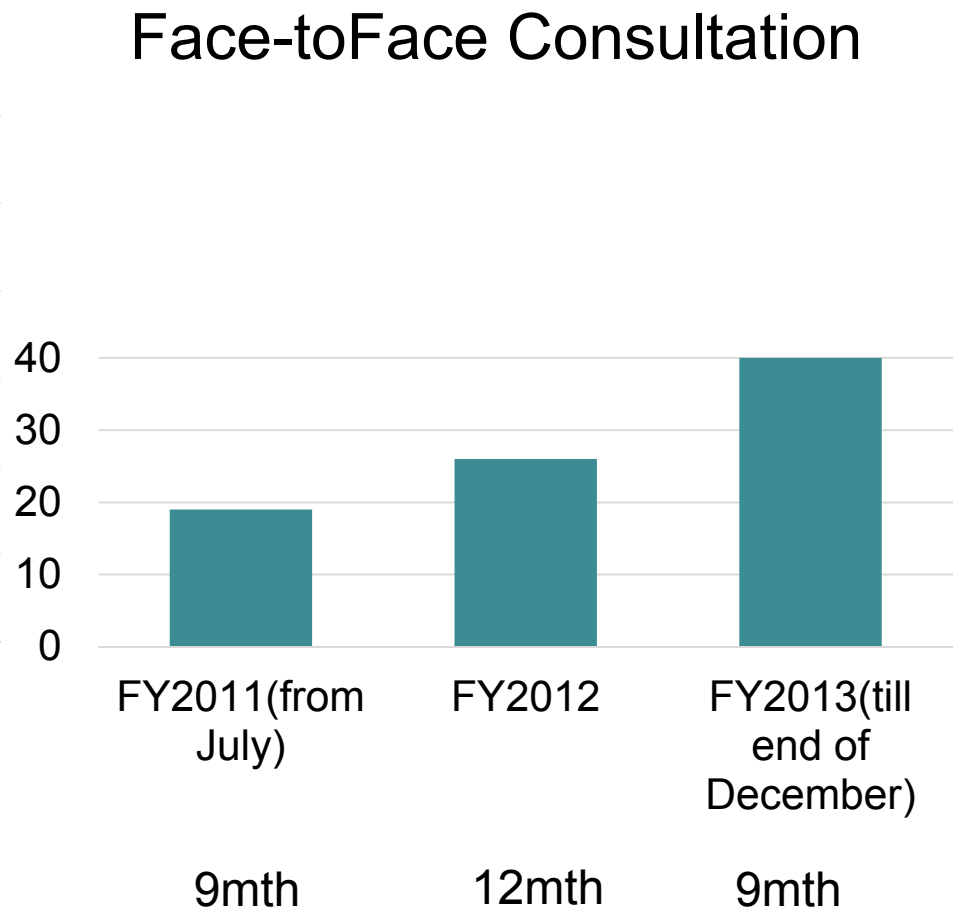
158 Consultations

(7/1/2011 – 12/31/2013)

If needed

Number of R&D strategic consultation for Drugs （except for cellular & tissue-based products）



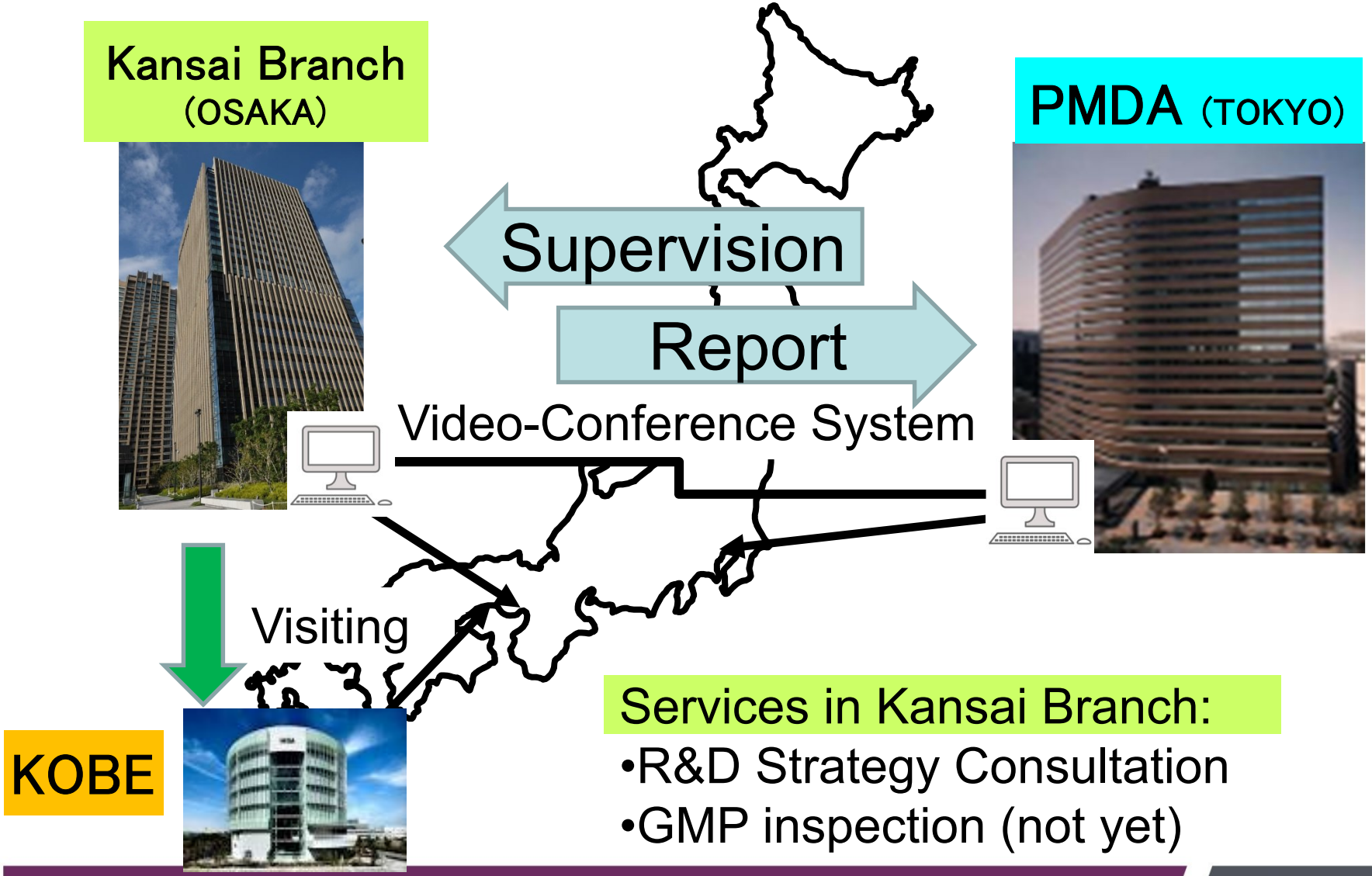


Fiscal Year; Start from April

Case of Face to Face consultation

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

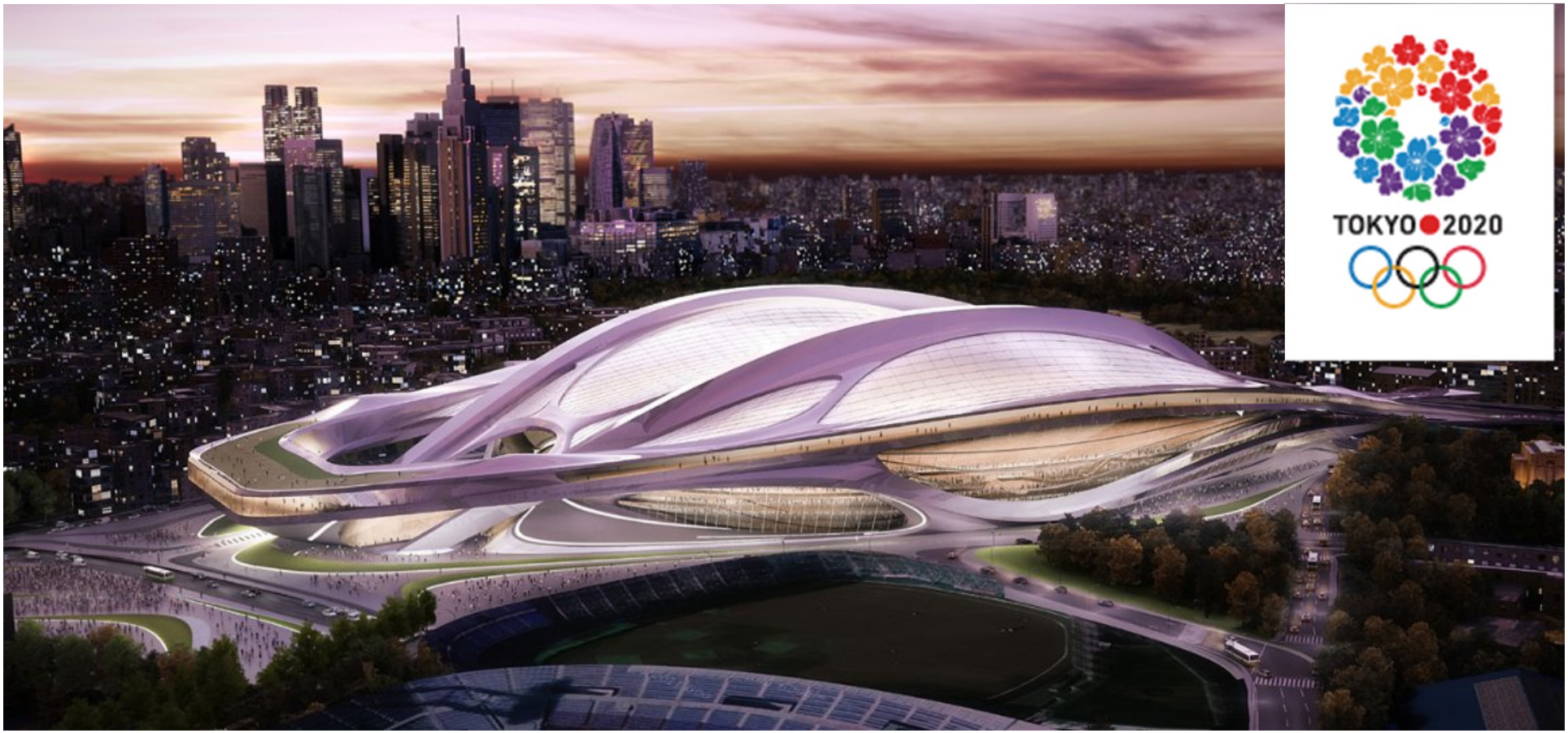
Establishment of the Kansai Branch of PMDA



Services in Kansai Branch:

- R&D Strategy Consultation
- GMP inspection (not yet)

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

Basic Research

Seeds of new drug / medical devices

Quality Tests → Non-clinical tests → Clinical Trial → Review → Approve → Post Marketing

Practical use

Innovative medical products

Pharmaceutical consultation on R&D Strategy | Clinical Trial Consultation | Review | Post Marketing Safety Measure

Offices of Review (Drugs & Medical Devices), Office of Safety

Office of Review Innovation

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 Office of Review Innovation

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

PMDA Office

Review/ Audit/ Inspection

RS

Safety

SGD

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

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

Projects Across Multi-Offices in PMDA

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

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.

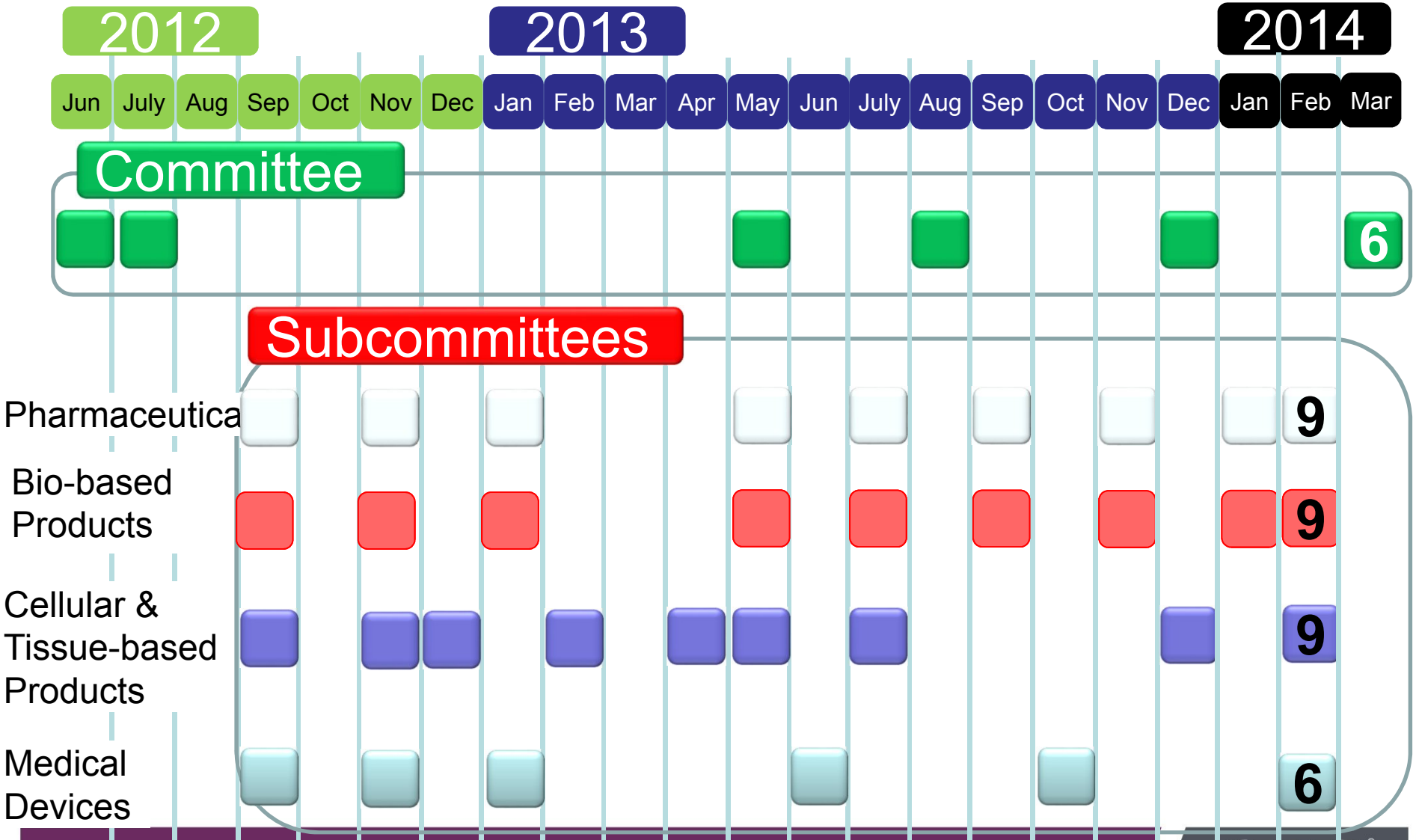
Cellular & Tissue-based Products

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



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)

Cellular & Tissue-based Products

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.

Pharmaceuticals/ Bio-based Products

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

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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.,.

Outcome of the Science Board

平成25年8月20日

iPS 細胞等をもとに製造される細胞組

1. はじめに

独立行政法人医薬品医療機器総合機構
（以下、本専門部会と略）は、細胞組織加工
懸念事項である「造腫瘍性」について、科学

細胞組織加工製品の開発を適切に推進
し、現時点で認識し得る問題をできる限り
れるべきである。ただし、細胞組織加工製
中であり、現時点での知見は限られている
分析と対応を提示するものの、近い将来
必要があることを併せて提言するものであ

「造腫瘍性(tumorigenicity)」とは、動物に

Japanese

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

English（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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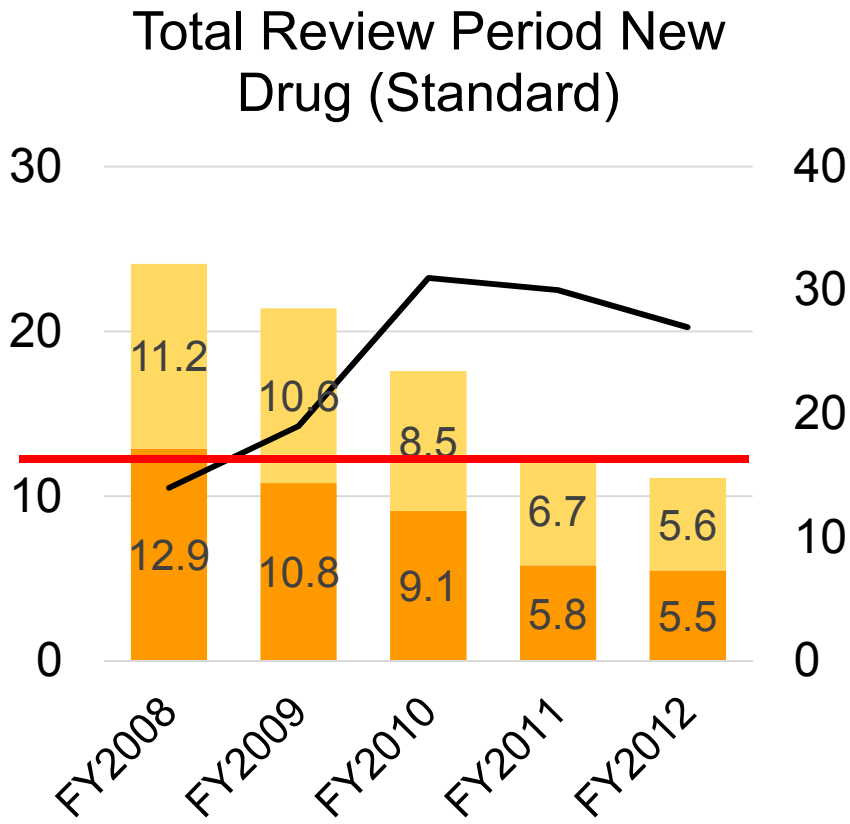
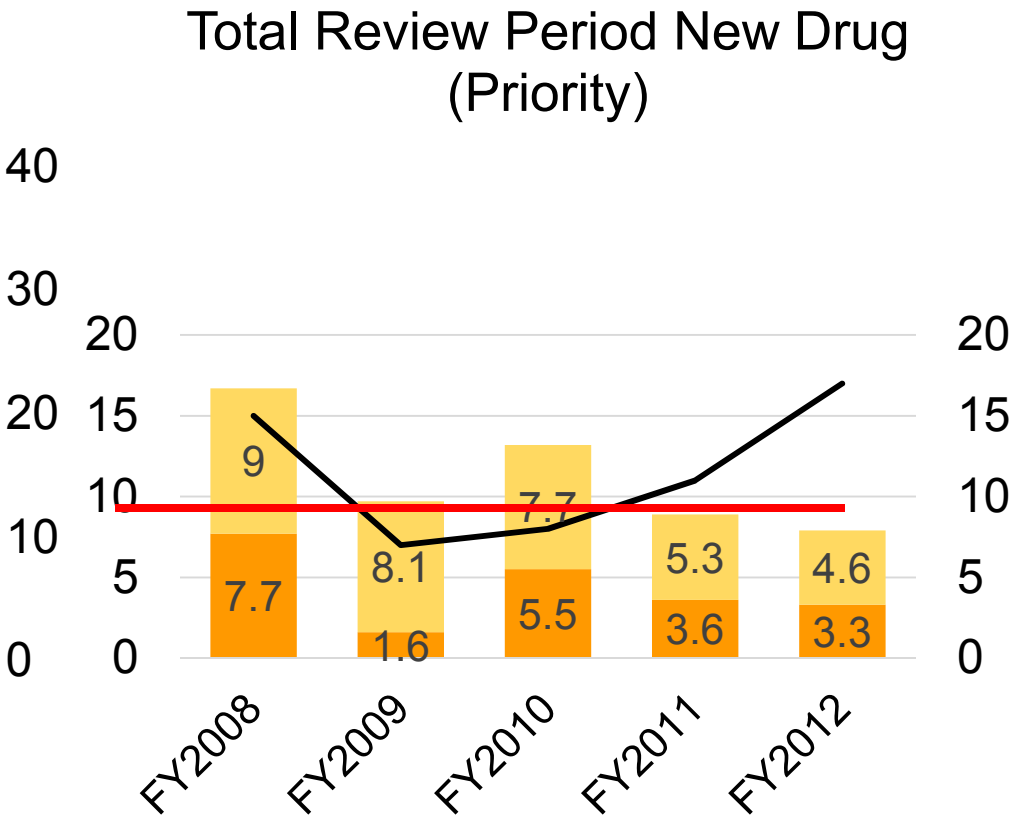
Accelerating Review Period





	Percentile						Total Review Period
	2013	2014	2015	2016	2017	2018	
Standard	50	60	70	70	80	80	12mo.
Priority	50	60	60	70	70	80	9 mo.

Applicant
Regulatory
Number of application
Target Period

Advanced Review/Consultation System

Analysis by PMDA

Giving additional scientific value to submitted data

Cooperation with Academia

Regulatory Science

A rational & effective evaluation process for regulatory decision

Practical use of Innovative Medical Products

NDA etc.

e-Submission of study data

Accumulation data

Database

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

DIA www.diahome.org

Utilization of study data and expected outcomes

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

Subject	Outcome
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

Senior Executive Director

Steering Committee
Relevant board members/executives

Support team
Relevant directors and persons in charge

Task Force for Advanced Review and Consultation with Electronic Data

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

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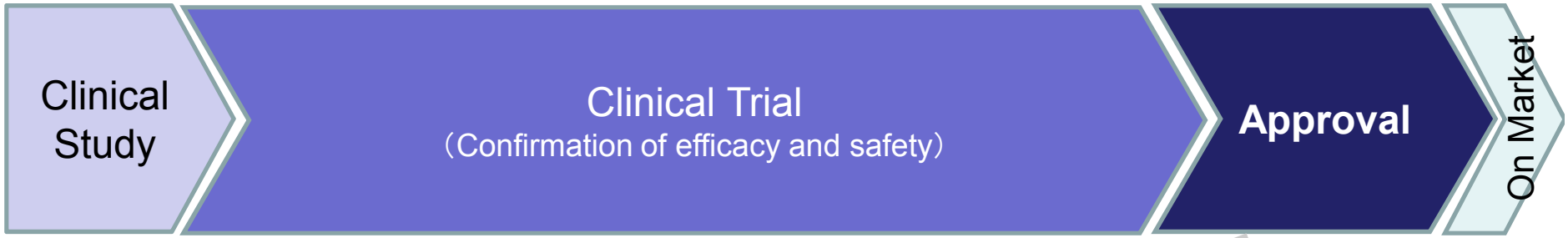
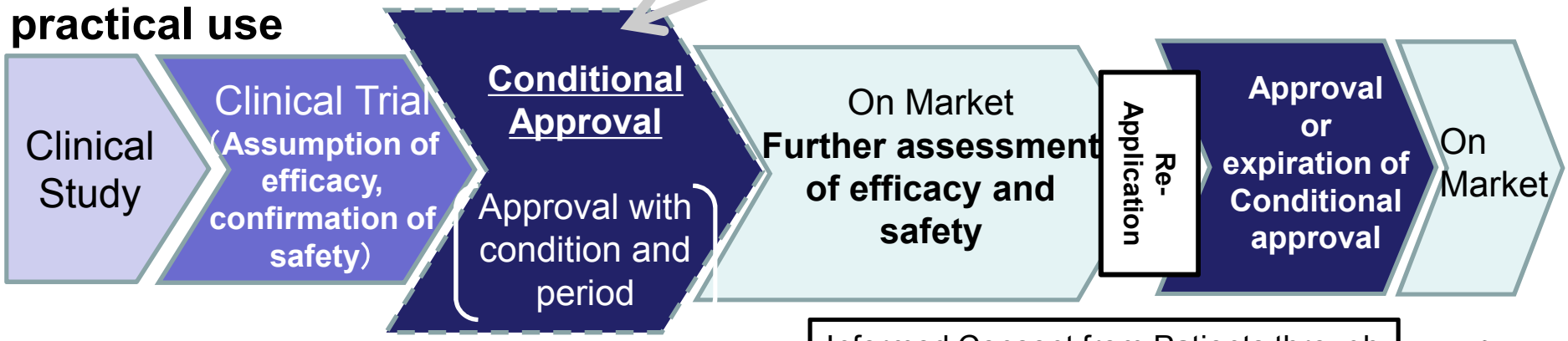
Approval System Corresponding Commercialization of Regenerative Medicines (Conditional Approval)

Previous Pathway of Approval System



Leading to Early-Access!!

New Approval System to Introduce Regenerative medicines in early practical use



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/