Advanced Review/Consultation in PMDA

September 10, 2013
Tower Hall Funabori

Health and Medical Care Strategy

(Agreement of Chief Cabinet Secretary, Minister of Health, Labour and Welfare and other concerned Ministers; June 14, 2013)

Three Basic Principles

- Achievement of a healthy, long-lived society
- Contribution to economic growth
- Global contribution

Specific strategy

Enhancing the PMDA

- Enhancement of the Pharmaceutical Affairs Consultation on R&D Strategy
- Organizing and enhancing the consultation service in close coordination with the Drug Discovery Support Network
- **PMDA-initiated promotion of research and analysis based on clinical data**
- Increase of the quantity and quality of the large-scale medical information database for early achievement of the 10-million data set
- Identification of an appropriate financial base for the PMDA's tasks and necessary measures
  * Including more proactive proposals than those made for the Japan Reconstruction Strategy and matters not discussed therein.

Direction of enhancement for the third mid-term plan

(Major matters concerning new drug review)

Enhancement required for fast marketing of effective and safe drugs, medical devices, and cellular and tissue-based products

—Enhancing the quantity and quality of the PMDA's system—

- ○ "Zero" review time lag
  - ➢ Further acceleration of the review process (aim to keep 80-percentile total review time for new drugs for 12 months [in general])
  - ➢ Enhancement of prior assessment consultation (substantial acceleration of the review process)
  - ➢ Enhancement of overseas inspection (ex. GMP inspection)
- ○ Support for elimination of development time lag
  - ➢ Improvement of pharmaceutical affairs consultation on R&D strategy
  - ➢ Improvement of clinical trial consultation
- ○ Review/consultation quality improvement and enhancement of basic regulatory science research and human resources development
  - ➢ **Development of a review/consultation framework using an innovative assessment techniques**
  - ➢ Enhancement of regulatory science research and human resources development through active use of the Science Board
- ○ Response to further globalization
  - ➢ Promotion of enhanced human resources development and information transmission by achieving a Road map for the PMDA international vision
  - ➢ Promotion of harmonization with the US and EU regulatory authorities and enhancement of cooperation
  - ➢ Receiving more trainees from the Asian countries and enhancement of cooperation with the Asian regulatory authorities
- ○ Response to the revision of the Pharmaceutical Affairs Act
  - ➢ Responding to the increased consultation/approval requests after the introduction of review system with approval conditions and fixed-term for cellular and tissue-based products

Prerequisite: US/EU-equivalent system and human resources with excellent skills

[Reference] International comparison of manpower for review and safety assurance at drug and medical device regulatory authorities[Note 1)]

Japan	US	EU		
PMDA[Note 2)]/MHLW[Note 2)] 636 [Apr. 2013]	FDA About 5,400 [2010]	EMA About 750 [2011]	Major EU member authorities	
			UK	Germany
			About 900	About 1,050

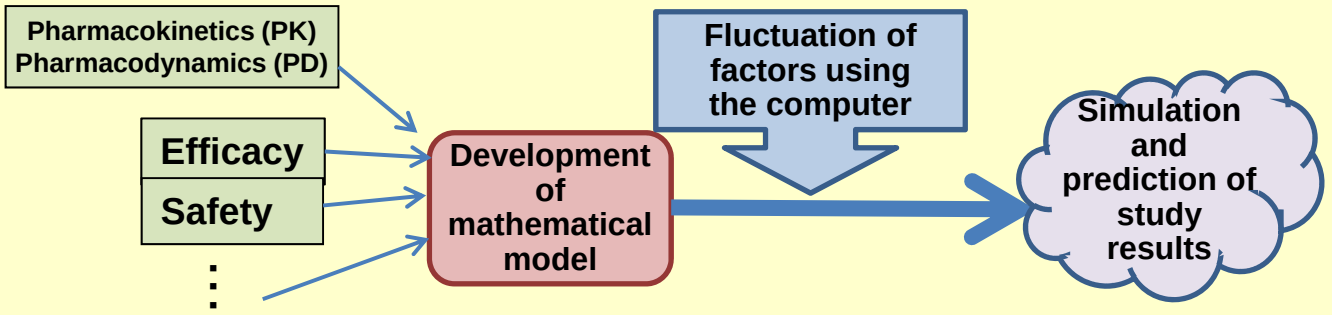
Note 1) Limitation in simple comparison due to different jurisdiction of the organization

Note 2) Total number of PMDA staff, 708 (Apr. 2013)

Innovative assessment techniques

Example: Modeling and Simulation (M&S)

Develop a mathematical model based on a variety of data and information to predict the result after mathematical/statistical data processing



Example of utilization and expected outcomes

Predict the study success rate ➞ **Avoid unnecessary investment by early discontinuation of product development**

Enhance development efficiency

- Predict human PK based on nonclinical PK to determine the dose for phase I study
- Predict the scope of study design factors (ex. patient inclusion criteria, sample size, study duration) for a successful study
- Predict drug interactions and optimal dose for children/the elderly… etc.

➞ **Improve the development success rate; shorten the development time**

Faster marketing of new drugs

In the regulatory review process
- Determine the best usage
- Improve the predictability of post-marketing efficacy and safety

➞ **Maximize the benefit/risk ratio**

Improve public health benefits

Accumulation and Utilization of Data

NDA submission

e-Submission of data

- Submission of electronic data from clinical and nonclinical studies

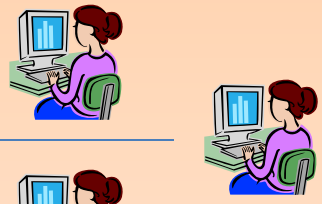
Storage of electronic data in the dedicated server and registration in the database

Visualization and analysis of data, supported by browsing software

Regulatory Review

Use of electronic data

- Accessible, visualized electronic data for each reviewer
- Easy to identify individual clinical case data, drilling down of data
- Operation of various analyses - simple, subgroup analysis for the present



Scientific discussion and decision making on the basis of internal analysis result

Utilization of Accumulated Data

Integration of cross-products information

- Utilization of exhaustive information by therapeutic category for review/consultation
- Internal review on particular theme – e.g.) active utilization of M&S
  - Review on pediatric dosage
  - Preparation of disease model
  - Development of evaluation indicator
- Utilization in preparation of guideline

What the review authority can do with the information of all products.

Contribution to efficient development through review/consultation and GL publication based on further analyses by dry-lab

Advanced workflow of review/consultation using innovative assessment techniques

Analysis by PMDA

Giving additional scientific value to submitted data

Cooperation with Academia

Regulatory Science

More rational & effective evaluation process for regulatory decision

Practical use of Innovative Medical Products

NDA etc.

e-Submission of study data

Sophisticated NDA review

- Each reviewer utilizes innovative assessment techniques

Effective and High Quality Review

- More predictable efficacy/safety after approval
- Reduction of applicant's work load
- More scientific regulatory decision

Accumulation data

Database

Cross-Products Analysis

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

Sophisticated Consultation

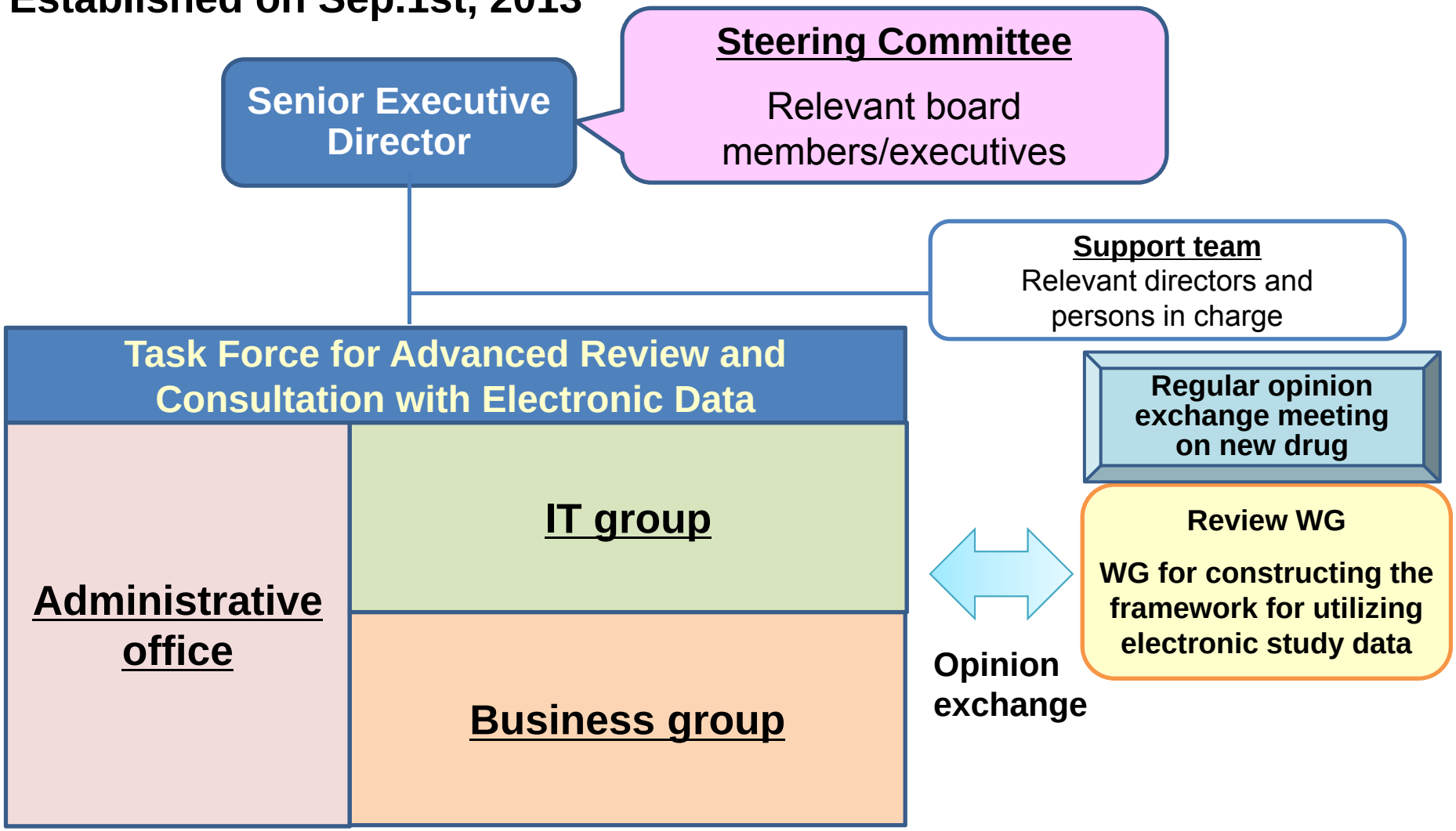
- More evidence-based consultation

More efficient and Successful Development

- Epoch-making proposal leading the world
- Proactive publication of guideline

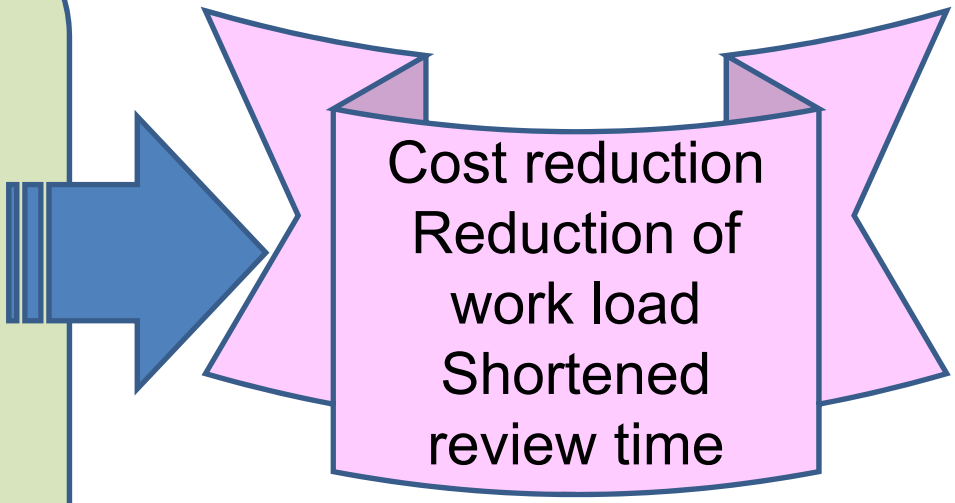
Task Force for Advanced Review/Consultation

Established on Sep.1st, 2013



Advantages for the industry

- Preparation of submitted data
  - No paper-based documents required
- Review
  - Accelerated access to the submitted data kept by PMDA
  - Decreased inquiries (ex. request for reanalysis)



- In future:
  Increased development efficiency by utilization of cross-products analysis results

Project for Constructing the Framework for Utilizing Electronic Study Data
- Future goals -

- Make proposals leading the world
- Development of guideline
- Increase of development success rate

↓

Effective and Successful Development
(Shortened development time, cost reduction)

Analysis by PMDA → Additional scientific value to submitted data

Regulatory science = Science of prediction and verification

A rational & effective evaluation process for regulatory decision

- Cooperation with academia?

- More predictable efficacy/safety after approval
- Reduction of applicant's work load
- More scientific discussion and regulatory decision

↓

Effective and High Quality Review

Development of Japan's original innovative drugs and medical devices

To be the world's best regulatory agency

To promote medical innovation

Major challenges

- **Shortening the time from early development to approval**
  - "Zero" review time lag
  - Support for elimination of development time lag
- **High quality review/consultation services**
- **Enhancing safety measures**
- **Globalization**

Specific measures

- **Accelerated review process** (Improvement of approval predictability)
- **Improvement of prior assessment** (substantial acceleration of approval review process)
- **Enhanced overseas inspection system**
- **Drastic improvement of consultation service**
  Active involvement from the early development phase
  - Improvement of pharmaceutical affairs consultation service on R&D strategy
  - Improvement of clinical trial consultation service
- **Enhancement of regulatory science research and human resource development**
  - Development of advanced review/consultation framework using innovative assessment techniques
  - Cross-products analysis of accumulated large data sets by PMDA using innovative techniques
  - Utilization of Science Board (cooperation with the academia)
- **Utilization of medical information database**
- **Readiness for introduction of risk management plan**

Goal

- Development of Japan's original innovative drugs and medical devices
- Marketing of cellular and tissue-based products

→ Activation of the industry

→ Extending health and life span of Japanese people

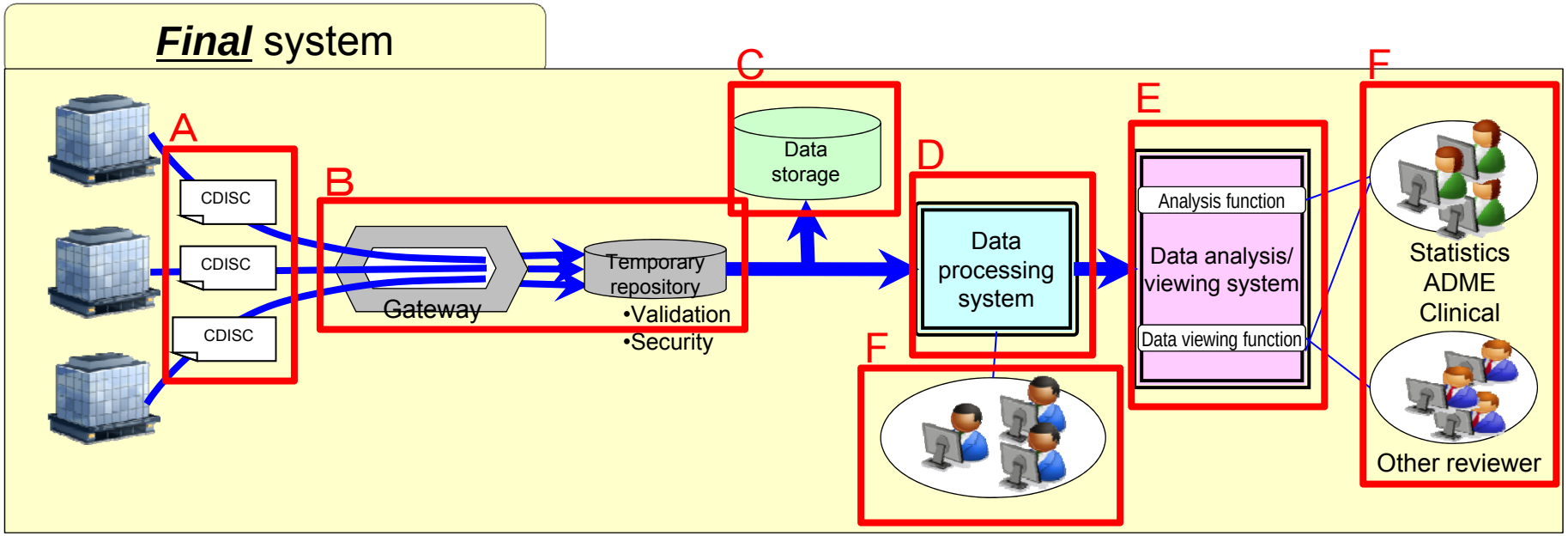
→ Contribution to global medicine

Appropriately accommodate the most advanced technologies including personalized medicine and regenerative medicine

Prerequisites:
US/EU-equivalent system and human resources with excellent skills

Responding to social needs such as Japan Reconstruction Strategy and Health/Medical Care Strategy

Overview of utilization of electronic study data within PMDA



Objective

- Improvement of regulatory review/ consultation quality
- Support to increase drug development efficiency

○ Factors involved in the “final system”

A) Study data in standardized format (CDISC)

B) Evaluation of electronically submitted data (Gateway + validation)

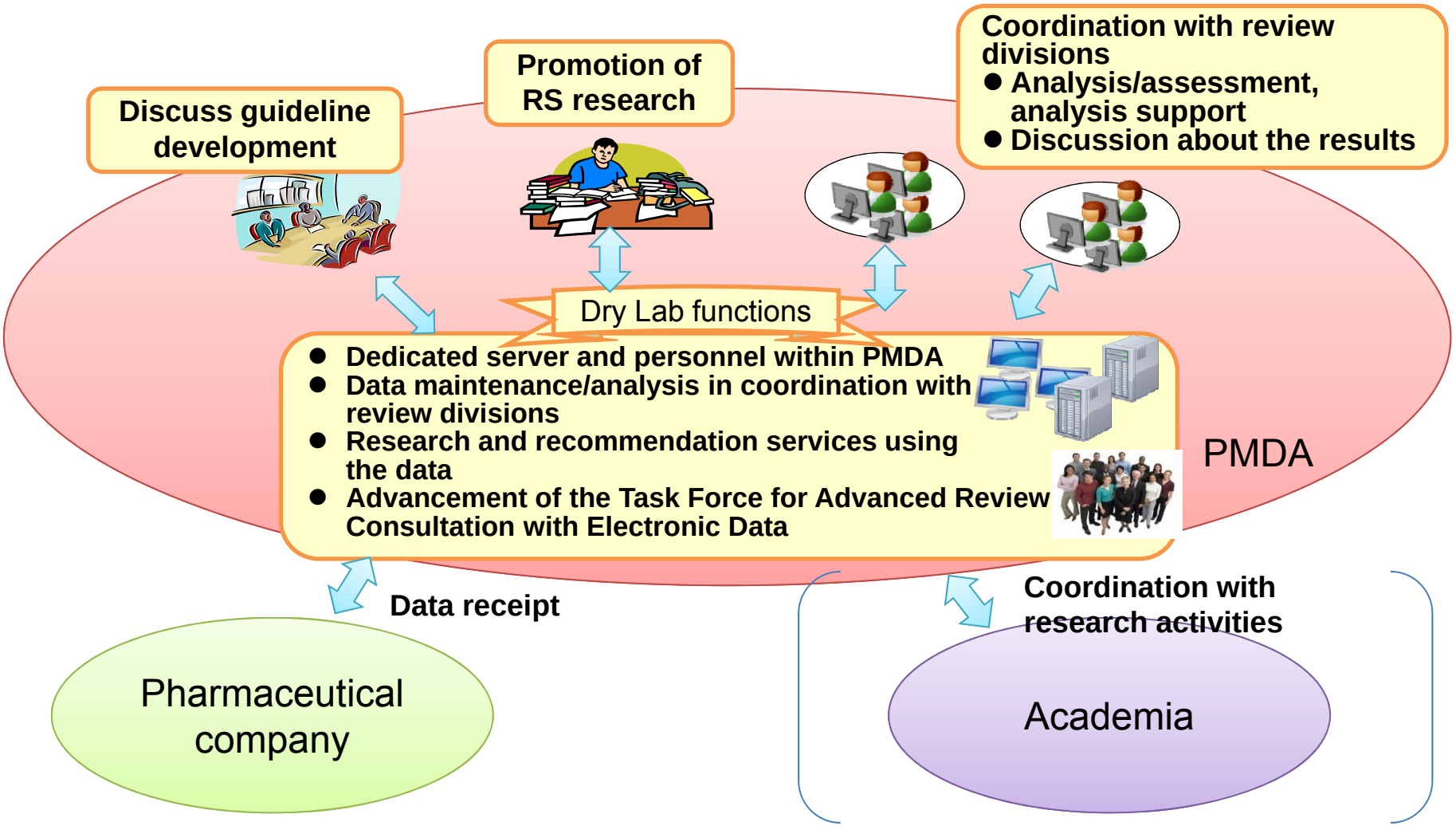
C) Storage of original data in one place (storage)

D) Data processing for easy analysis (data reduction system)

E) Analysis (data analysis/viewing system)

F) Effective use of the “final system” (trained experts)

Concept for future Dry Lab



Expect an increase of Lab personnel as part of the PMDA system enhancement process

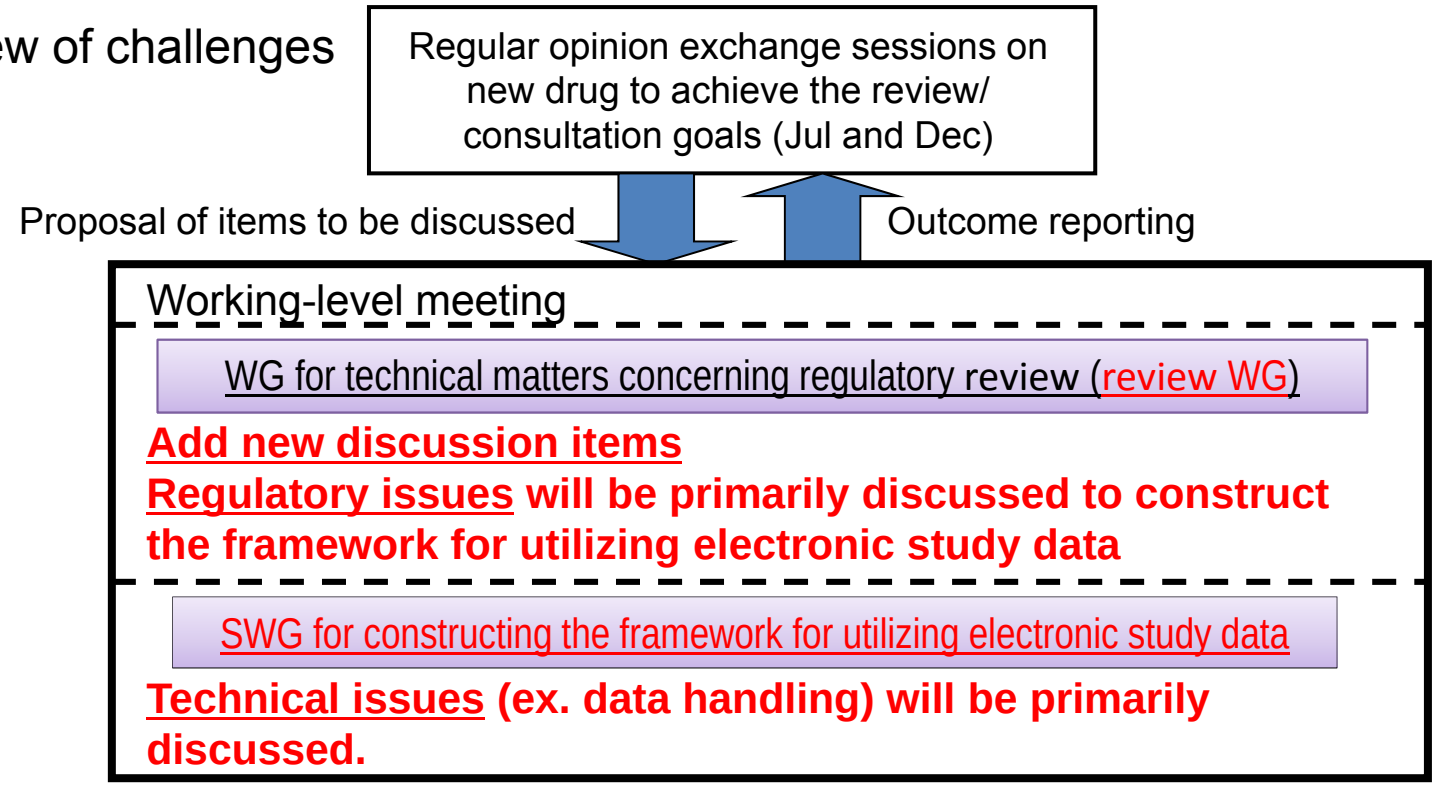
Proposed timeline for constructing the framework for utilizing electronic study data

TENTATIVE; Currently under discussion

- FY 2013
  - Surveys, procurement of hardware/software, test run
    <Test run; Electronic data viewing and internal analysis>
- FY 2014 to 2015
  - Continue the test run; to be in full-scale operation after the Lab is open
- FY 2016 (prospect)
  - Submission of electronic clinical data for NDA
  - (With transitional period)
- After FY 2017
  - Submission of electronic non-clinical data for NDA
  - (To be discussed)

Discussion with the industry on constructing the framework for utilizing electronic study data

1. Review of challenges



2. Informing the industry

System organization will be required at individual companies since the ongoing (planned) clinical study data collection will be affected.

Advanced review/consultation in PMDA
Future policies and discussion status was explained to the industry
13:00 to 16:00, Tuesday, September 10; Tower Hall Funabori

2013 pilot project (request)

Provisional Translation (as of September 2013) *

PMDA/CPE Notification No. 0902001
September 2, 2013

To: As specified in the Appendix separately

From: Takao Yamori, Ph.D.
Director, Center for Product Evaluation of
Pharmaceuticals and Medical Devices Agency

Re: Request for Electronic Clinical Study Data for Pilot Project

First, we would like to express our gratitude to all of your support.

In recent drug development, the use of data-based quantitative information such as those using modeling and simulation (M&S) methods has been proactively promoted in decision-making process. Under such circumstances, the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as PMDA) recognizes the need for accumulating electronic study data, analyzing the data by advanced methods, and making use of the data in the process of its reviews and consultations. The use of such accumulated data is expected to reduce the workload of regulatory submission for sponsors, improve PMDA's evidence-based reviews and consultations, and lead to development of new guidelines, which will eventually result in the rise of the success rate of drug development.

In order to promote utilization of submitted electronic study data in the future, PMDA internally set up the Project for Constructing the Framework for Utilizing Electronic Study Data, and organized a joint working group with the industry to discuss regulatory and technical issues. It is planned to develop a basic system and confirm the feasibility of the system by the end of this fiscal year.

In this regard, your member companies are kindly requested to provide electronic clinical study data to PMDA so that the Agency may test the feasibility of the system. Participation in this pilot project is not mandatory and the details will be informed later, but PMDA will need, for example, the data that meet the following three criteria for this feasibility test:

1. data of drug products that are under regulatory review or going to be filed to PMDA;
2. data amassed and summarized according to the CDISC standards (prepared because of planned submission to the US Food and Drug Administration, or other reasons), and;
3. clinical study data including those of Japanese subjects

Please note that the electronic data provided for this pilot project is used only for the purpose of testing the system feasibility (check of the system's operational capability, data compatibility with software tools, etc.) and there will be no influence on regulatory review of the concerned products.

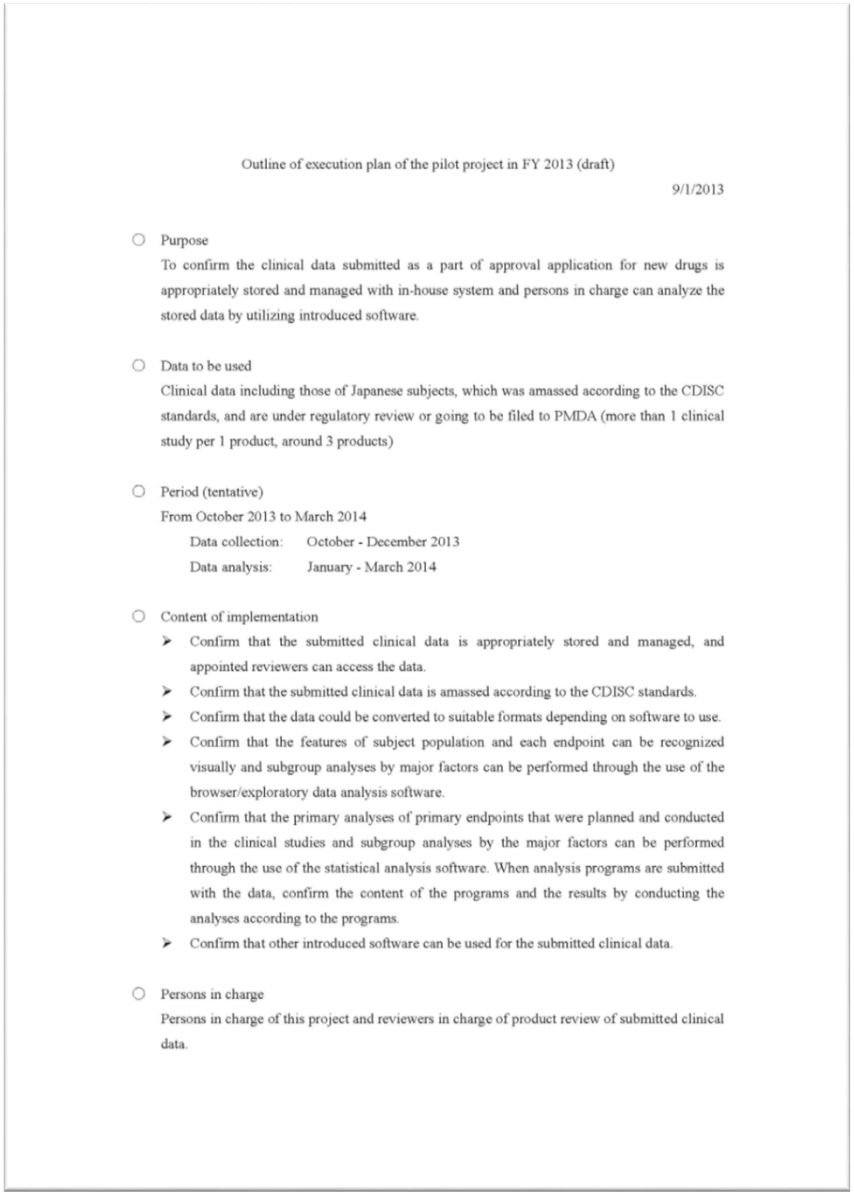
PMDA will contact your member companies individually with more specific plan at a later date to ask for cooperation on this pilot project. However, your member companies that are willing to participate in this pilot project, even before PMDA contacts them individually, are encouraged to contact us at the e-mail address stated below by the end of September 2013. Also, if you have any inquiries on this pilot project, please contact us at the e-mail address below.

It would be appreciated very much if you could understand this matter and take time in your busy schedule to ask for cooperation from your member companies. Thank you very much again for your cooperation in advance.

Please contact:
E-mail: electronicdata@pmda.go.jp
Task Force for Advanced Review and Consultation with Electronic Data
Pharmaceuticals and Medical Devices Agency

* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

2013 pilot project (outline)



Outline of execution plan of the pilot project in FY 2013 (draft)

9/1/2013

- Purpose

  To confirm the clinical data submitted as a part of approval application for new drugs is appropriately stored and managed with in-house system and persons in charge can analyze the stored data by utilizing introduced software.

- Data to be used

  Clinical data including those of Japanese subjects, which was amassed according to the CDISC standards, and are under regulatory review or going to be filed to PMDA (more than 1 clinical study per 1 product, around 3 products)

- Period (tentative)

  From October 2013 to March 2014

  Data collection: October - December 2013

  Data analysis: January - March 2014

- Content of implementation
  - Confirm that the submitted clinical data is appropriately stored and managed, and appointed reviewers can access the data.
  - Confirm that the submitted clinical data is amassed according to the CDISC standards.
  - Confirm that the data could be converted to suitable formats depending on software to use.
  - Confirm that the features of subject population and each endpoint can be recognized visually and subgroup analyses by major factors can be performed through the use of the browser/exploratory data analysis software.
  - Confirm that the primary analyses of primary endpoints that were planned and conducted in the clinical studies and subgroup analyses by the major factors can be performed through the use of the statistical analysis software. When analysis programs are submitted with the data, confirm the content of the programs and the results by conducting the analyses according to the programs.
  - Confirm that other introduced software can be used for the submitted clinical data.

- Persons in charge

  Persons in charge of this project and reviewers in charge of product review of submitted clinical data.