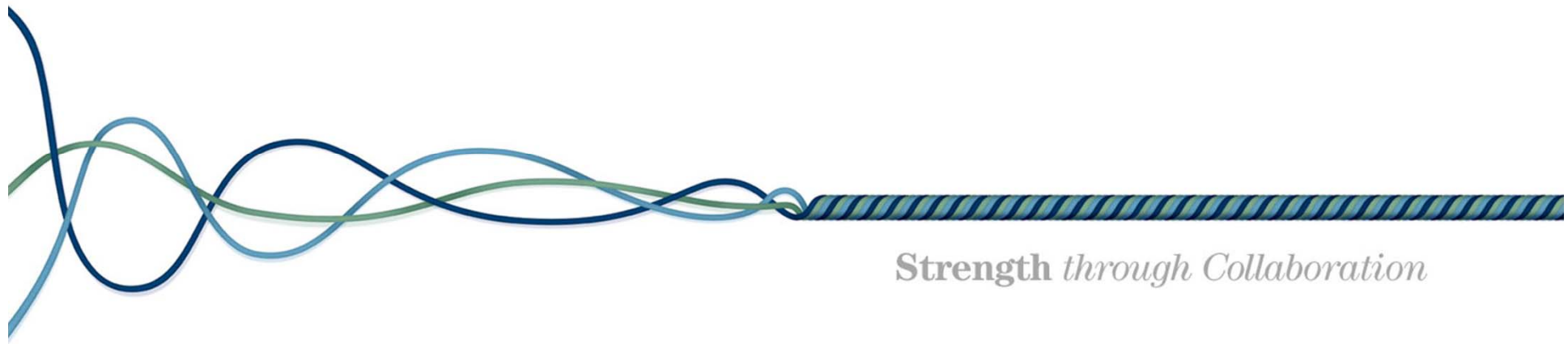


Overview of CDISC Implementation at PMDA

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Strength through Collaboration

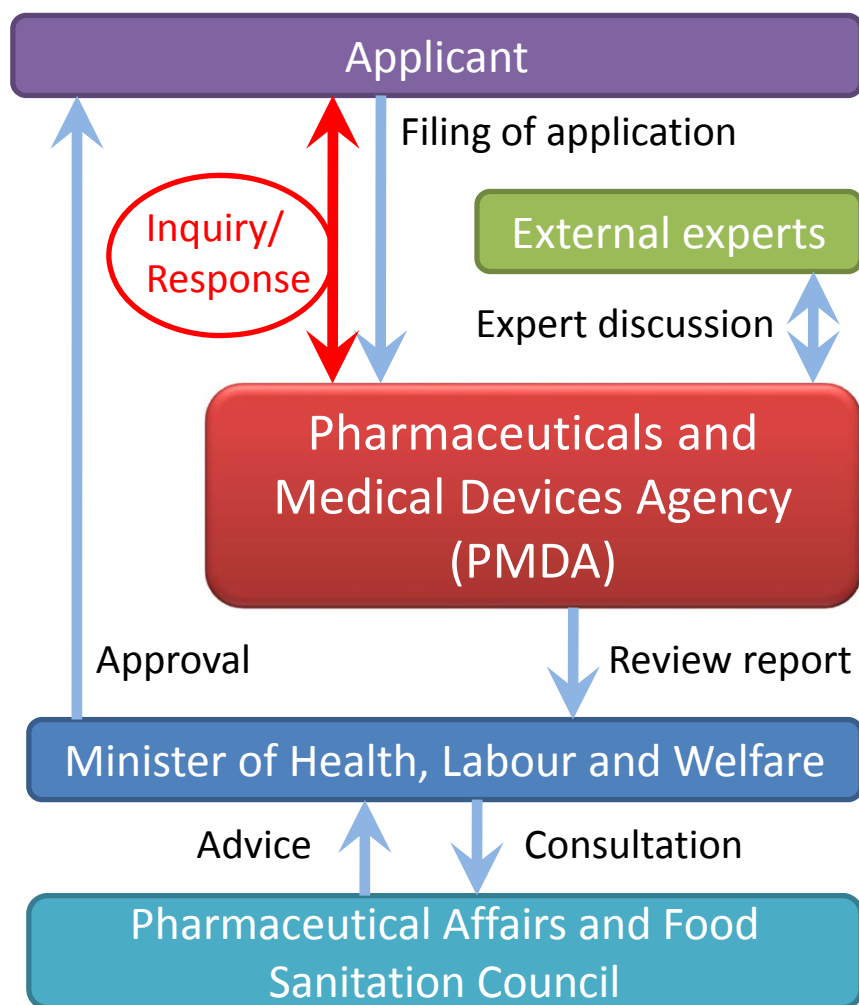
Outline

- Introduction
- Update of PMDA activity
- CDISC implementation in PMDA

What we do in PMDA

- PMDA (Pharmaceuticals and Medical Devices Agency), established in 2004, is Japanese regulatory agency, working together with Ministry of Health, Labour and Welfare.
- Our obligation is to protect the public health by assuring safety, efficacy and quality of pharmaceuticals and medical devices.
- Services of PMDA
 - Relief services for adverse health effects
 - Drug and medical device reviews
 - Post-marketing safety measures

New drug review process in Japan



- So far, patient level clinical trial data are not required in new drug application in Japan.
- Since PMDA does not have data to analyze, applicants must re-analyze the data to answer the inquiries from PMDA during the new drug review.
- Exchange of the inquiries and responses may be very frequent.

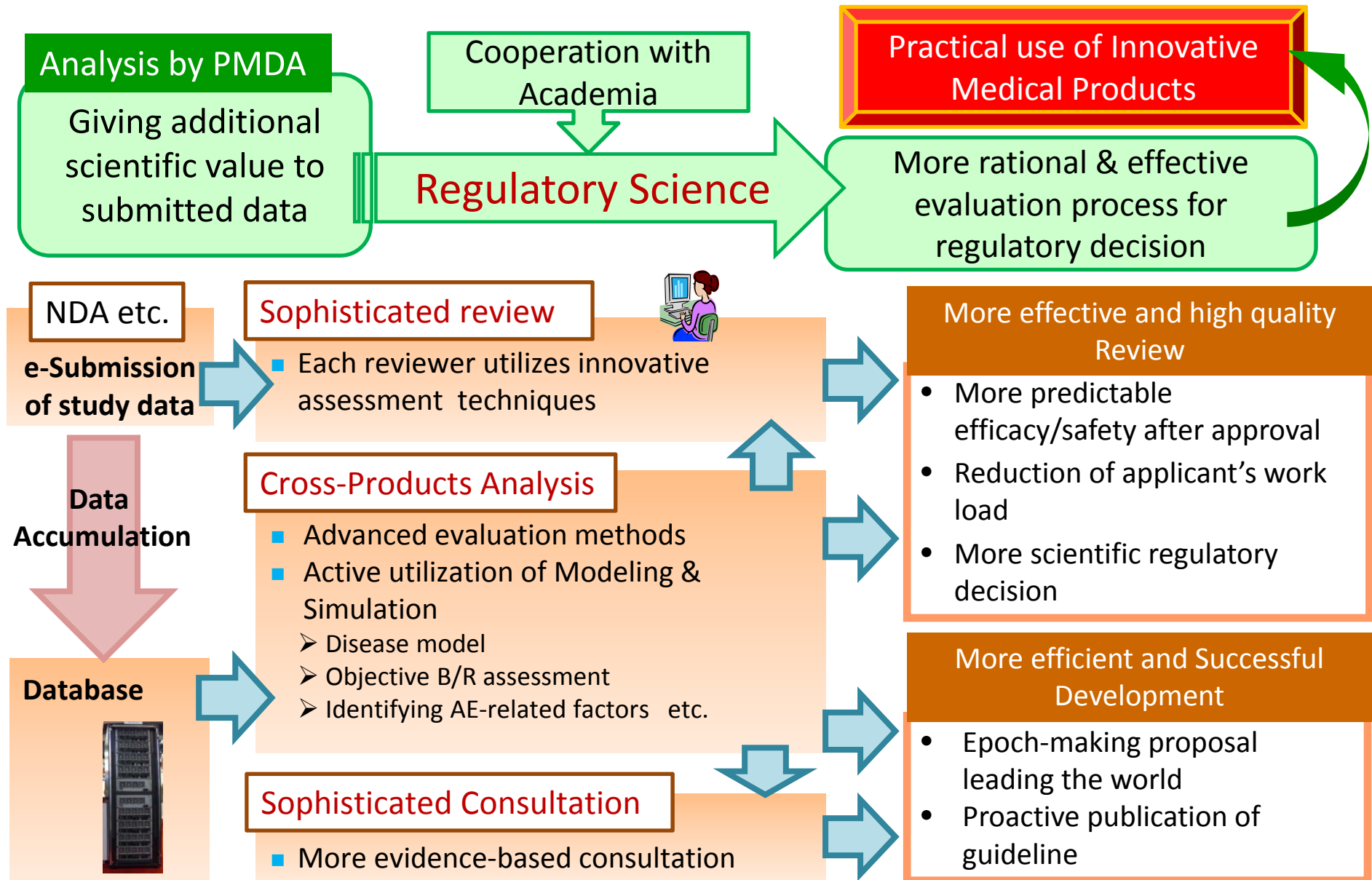
Task force for advanced review/consultation

- PMDA started a discussion in the view of mandating electronic submissions in the future, and internally established "Task force for advanced review and consultation with electronic data" on Sept 1st, 2013
 - <http://www.pmda.go.jp/english/service/taskforce.html>



- On April 1st, 2014, the Task Force was reorganized as “Advanced Review with Electronic Data Promotion Group”, which is more established body.

Advanced workflow of review/consultation



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



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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 Modeling & Simulation
 - 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

Outline of Implementation Process (Draft)

Year	Main implementation contents	Purpose
FY2013	<p><u>Establishment of 'the Task force for advanced review and consultation with electronic data'</u></p> <p>Investigation & Survey (FDA/EMA, Industry) Procurement of storage servers Assessment of data standards, selection of validation rules Selection and procurement of software for visualizing and analyzing data, education and training of reviewers</p> <p>FY2013 Pilot Project for confirmation of feasibility</p>	<p>Development of Fundamental system Feasibility confirmation of the system Extraction of problems and confirmation of its handling</p>
FY2014	<p><u>Establishment of 'the Advanced Review with Electronic Data Promotion Group'</u></p> <p><u>Release notice of the basic policy for submitting of the electronic clinical study data</u></p> <p>Decision of how to accept the electronic data</p> <p>FY2014 Pilot Project for analyzing study data on a trial basis</p> <p>Consultation for Electronic Data Submission Plan (tentative) on a trial basis</p>	<p>Improvement of operation system Consideration of new review process with data analysis</p>
FY2015	<p><u>Release of technical notice for the electronic data submission</u></p> <p>Establishment of data processing system</p> <p>FY2015 Pilot Project for analyzing study data intended for actual review</p> <p>Start of the Consultation for Electronic Data Submission Plan (tentative)</p>	<p>Establishment of new review process</p>
FY2016	<p><u>Obligation for submission of electronic clinical study data for NDA (with a certain transitional period)</u></p>	<p>Implementation of electronic data view and analysis for NDA review</p>
FY2017	<p>Continues consideration for expanding the scope of submission (e.g.; non-clinical study data)</p> <p>Consideration of internal data analysis for clinical trial consultation meeting</p> <p>Conducting cross-product analysis on a trial basis</p>	<p>Consideration of using data analysis for clinical trial consultation meeting</p> <p>Consideration of using cross-product analysis</p>
FY2018	<p><u>Obligation for submission of electronic clinical study data for all NDA (to be discussed)</u></p> <p>Consideration of the relationship with academia</p>	<p>Construction of cooperative relationship with academia</p>

Update of PMDA activity

FY2013 pilot project (outline)

- Purpose
 - To confirm that the clinical data submitted as a part of approval application for new drugs is appropriately stored and managed with in-house system, and that 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)

Through the pilot project, PMDA confirmed the feasibility of reviewing and analyzing data in CDISC formats, using actual data from clinical trials.

Results of FY2013 pilot project (outline)

- Submission of clinical study data
 - Upon the request for electronic clinical study data for pilot project, **clinical study data on five drug products** were submitted from the five companies that offered to cooperate, by December 2013.
 - Before submission of data, PMDA sent inquiries about the data, such as the products considered for data submission, details of clinical studies and datasets, and conformance to standards. Then **interviews were conducted with the companies** based on the information.

Results of FY2013 pilot project (outline)

- Implementation details
 - Data visualization and analysis were conducted from January to February 2014
 - Around 100 persons in charge
 - About 80 reviewers from new drug review offices, including clinical reviewers, clinical pharmacologists, and statistical reviewers
 - About 20 staff from the Task Force for Advanced Review and Consultation with Electronic Data
 - PMDA introduced and used software for
 - Data visualization/exploratory analysis
 - Analyzing CDISC compliant study data
 - Statistical analysis
 - Pharmacokinetic analysis

Results of FY2013 pilot project (outline)

- Confirmation of feasibility
 - There were no problems regarding data storage and management within PMDA.
 - Analysis of actual clinical trial data was confirmed to be feasible by the reviewers who possess a certain level of knowledge regarding datasets and software.
- Future and ongoing tasks
 - Improvement and enhancement of the training for the reviewers
 - Consideration of the new review process with clinical data analysis
 - Preparation of basic and technical notices to keep high level of conformance to the data standards

Data standards = CDISC is the key in handling the clinical study data of a lot of products at the PMDA

The Basic Policy for electronic data submission (Draft)

- The draft basic policy for electronic data submission is in the process of development
 - Based on the PMDA's future plan of review and data use, and also based on the discussion with industry
- Will be published in FY2014

Contents of the Basic Policy for electronic data submission (Draft)

- Background
- Application types and future schedule
- Scope of clinical study for data submission
- How to submit the data
- Relationship between electronic data submission and eCTD
- Consultation process for electronic data submission plan
- Information management
- Association between electronic data submission and conformity audit
- Glossary

Application types and scope of clinical study

- New drug applications
 - including follow-on biologics
 - except OTCs
- Data of Phase 2 and 3 study including long-term studies which are major bases of efficacy and safety as well as dosage
- Data of Phase 1 study of anti-cancer drugs, Phase 1 studies in global drug development, and Thorough QT study according to ICH-E14
- ISS/ISE may be required in some cases

How to submit the data

- Data standards to be used
 - The clinical study data should be CDISC compliant
- Types of data
 - SDTM datasets with metadata (e.g. Define.XML)
 - ADaM datasets with metadata (e.g. Define.XML) and programs for generating ADaM dataset
 - ADaM datasets for ISS/ISE
 - The variables which have controlled terminology or codelists recommended by CDISC should be described in English
- Analysis programs
 - The program for the primary analysis of primary endpoint should be submitted
- Version of the standards, coding, units
 - Acceptable multiple versions of CDISC and MedDRA will be noticed
 - Although the details will be noticed in the near future based on further discussion, basically the controlled terminology and coding recommended by CDISC and SI units should be used

Consultation process

- Since there may be several case-by-case basis issues in the electronic data submission in each NDA, PMDA plans to offer the Consultation for Electronic Data Submission Plan (tentative) .
- The issues should be discussed between the sponsor and PMDA at the consultation meeting before the data submission for the NDA.
- The details of the consultation such as timing for the start, scope, and process will be noticed later.

Major points to be confirmed at Consultation for Electronic Data Submission Plan

- Clinical data package and summary of clinical studies
- Information about individual CDISC-compliant study data
 - Clinical study design
 - Dataset to be submitted
 - SDTM : Source of SDTM datasets (i.e. use of CDASH), version of SDTM and IG, datasets (domains) to be submitted, metadata
 - ADaM: Source of ADaM datasets, version of ADaM and IG, datasets to be submitted, metadata
 - Other information, such as Annotated CRF
 - Information about CDISC conformity
 - Analysis programs
 - Submission of programs, software and system requirement

The Basic Policy (Draft) and future Pilot Project

- After the mandating of electronic data submission, the data complying the Basic Policy will be submitted.
- Future pilot projects should be proceeded with the data complying the Basic Policy whenever possible.
 - On the other hand, analysis datasets for the particular purposes such as pharmacological investigations using special software should be acceptable, even if they are not compliant to CDISC standards.

In FY2014 pilot project, electronic study data complying the Basic Policy, **especially regarding the CDISC standards**, will be used. (Analysis datasets for particular purposes will be separately collected for confirmation of feasibility.)

FY2014 pilot project

- Purpose

- To confirm that the analysis of the submitted clinical data using introduced software enables the reviewers to obtain the necessary results for the review
- And to consider the utilization of the analysis results in the new drug review process
- To confirm that the data for population pharmacokinetic analysis is appropriately stored and managed with in-house system, and that persons in charge can analyze the stored data by utilizing introduced software.



CDISC
Data

FY2014 pilot project

- Scope regarding CDISC compliant data
 - Clinical studies (phases II and III) of new drugs (including follow-on biologics) that include data of Japanese subjects and that are either approved, currently under regulatory review, or scheduled to be reviewed in Japan by September 30, 2014.
 - One or more than one study per one application.

The request was posted on March 27.

FY2014 pilot project

- Implementation details for CDISC compliant data
 - Confirm CDISC conformance of the submitted clinical study data
 - Confirm that by using the data visualizing/exploratory analysis software, certain study results which are generally reported in application can be reviewed
 - Confirm that by using the statistical analysis software, the results of primary analysis of primary endpoints and other results useful for the review can be obtained
 - Examine the extent of analysis feasible in the review process, estimated workload, and utilization of analysis results in the future review process

FY2014 pilot project

- CDISC compliant data to be submitted
 - Data standards to be used
 - The clinical study data should be CDISC compliant
 - Basically the controlled terminology and coding recommended by CDISC and SI units should be used
 - Target datasets and programs
 - SDTM datasets with metadata (e.g. Define.XML)
 - ADaM datasets with metadata (e.g. Define.XML)
 - Programs for ADaM datasets to obtain the results of the primary analysis of primary endpoint
 - Programs for generating ADaM dataset, if ADaM datasets were generated from the SDTM

Very close to the description in the draft Basic Policy

CDISC implementation in PMDA

Experiences in FY 2013 pilot project

- There are a certain degree of differences in datasets between the companies.
 - Variables used
 - Use of Japanese characters
 - Availability of software
 - Formats and contents of metadata
 - Relationship to clinical study protocol and CRF

We reaffirm that it is critical to understand

- possible inter-company or inter-product difference
- when and where the difference may be exist

Tasks based on the experiences in FY 2013 pilot project

- Improvement of the compliance with CDISC
 - The basic policy and the technical notice may standardize the data to be submitted
- Handling of Japanese characters
 - Detecting variables which need to be described in Japanese and considering the methods to submit those data
- Effort to make the dataset easier to understand
 - Contents of metadata
 - Information of the data for the Consultation for Electronic Data Submission Plan (tentative)

Data standards and variability of the data

- It is unavoidable to have a certain degree of inter-company or inter-product variability of the formats of submitted data
 - The flexibility of the standards themselves to be applied for various applications
 - Difference in understanding and experience of using the standards
 - Difference in characteristics of the drug
- By sharing our knowledge, it may be possible to
 - Understand the standards further
 - Find recommendable solutions
 - Know the patterns of the variability of a certain part of the standards

Discussion with the industry

Periodic new drug opinion exchange meetings to achieve the review/consultation goals (Jul and Dec)

Reformed
2014.3.7

Proposal of items to be discussed

Outcome reporting

Working-level meeting

WG for technical matters concerning regulatory review (Review WG)

(Add new discussion items
Systematic issues will be primarily discussed to develop an electronic NDA data system)

SWG for electronic NDA data system development

(Technological issues (ex. Data handling) will be primarily discussed)

Including the members from J3C, CJUG

CDISC Technical Team (NEW)

In order to avoid misunderstanding or misuse of the CDISC standards, provide explanation for particular issues
Also consider the measure to submit the data which is not compliant to the CDISC

Clinical Pharmacology Team (NEW)

Consider standardized format of the electronic data for clinical pharmacology review

Relationship between PMDA and CDISC

- Information exchange with CDISC
- PMDA regularly attend the meetings of CDISC in Japan as observer since July 2013.
 - Japan CDISC Coordinating Committee (J3C)
 - CDISC Japan Users Group (CJUG) SDTM, ADaM
- Contribution of CJUG members to the first introductory lecture of CDISC in PMDA
- Presentation by PMDA representatives in International, Japan, and Europe Interchange as well as CJUG workshop
- Participation in the official CDISC training (SDTM, ADaM, and CDASH)

We plan to enhance CDISC training for reviewers

Summary

- The Task Force was reorganized as “Advanced Review with Electronic Data Promotion Group” and we proceed our project at a rapid pace.
- Based on the experience of FY2013 pilot project, we think that the conformance of the study data with the CDISC standards and understanding of the CDISC standards will be the key for the new drug review after the electronic data submission is mandated.
- PMDA will make an effort to promote the CDISC standards, and in order to make our requests clear, PMDA will issue the series of the notices based on the discussion with the industry.

Thank you for your attention

- PMDA Homepage
 - <http://www.pmda.go.jp/english/index.html>
- Drug and Medical Device Reviews
 - http://www.pmda.go.jp/english/service/outline_s.html
- “Task force for advanced review and consultation with electronic data” Homepage
 - <http://www.pmda.go.jp/english/service/taskforce.html>