PhUSE Single Day Event
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Advanced Review with Electronic Data and Use of CDISC Standards in PMDA

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Pharmaceuticals and Medical Devices Agency (PMDA)

Outline

- Outline of Advanced Review with Electronic Data and progress
- Technical notification and guide
- Pilot projects

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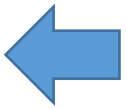


Advanced workflow of review/consultation

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

Data Accumulation

Database

Sophisticated review

- Each reviewer utilizes innovative assessment techniques

Cross-Products Analysis

- Advanced 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 effective and high quality Review

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

More efficient and Successful Development

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

Accumulation and Utilization of Data

NDA submission

e-Submission of data

- Submission of electronic data from clinical and nonclinical studies

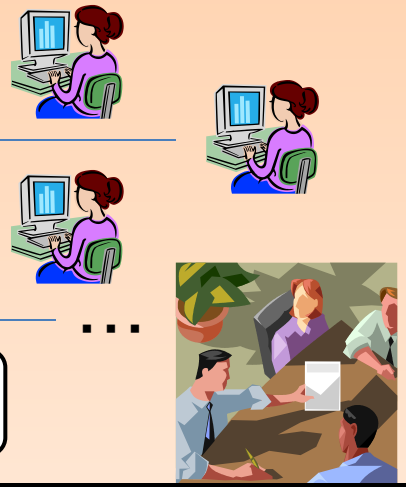
Storage of electronic data in the dedicated server and registration in the database

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

Medium- and long-term Prospect

Tentative assumption and expectation

Present
FY2014

- e-data can be received and managed appropriately
- e-data can be utilized in the review
- without extension of review period, industries' workload would decrease gradually

FY2016

Setup e-data management and utilization

FY2018

Ordinary utilization of e-data in the product review

- More predictable efficacy/safety
- Consideration of expanding scope to toxicological study and post-approval clinical study

Promotion of paperless

FY2019 - 2021

Starting earnest cross-product analysis

- Develop guidance and related documents
- Earnest cross-product analysis, development of disease models

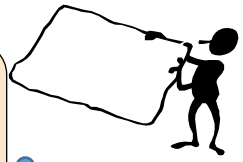
FY2022 - 2023

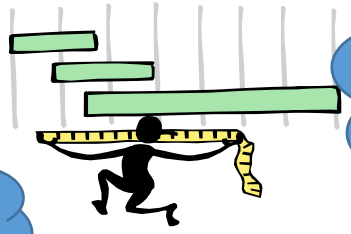
Publication of guidance to contribute to drug development

- Establishment of disease model
- Publication of disease-specific guidance

First-class review authority

e.g. guidance and disease models based on data on Asian population





Importance of data standard

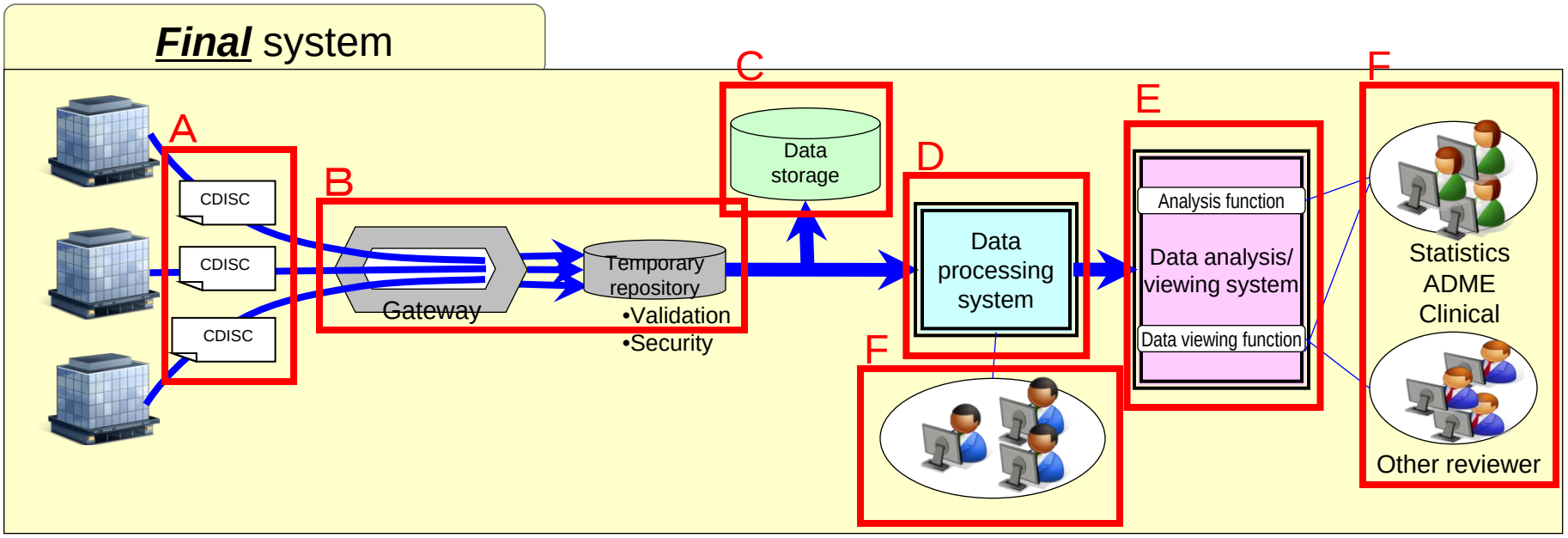
- PMDA
  - For fast access and easy handling of submitted clinical trial data in many new drug applications
  - For future use of accumulated clinical trial data for cross-products analysis
- Industry/Sponsor
  - For efficient and qualified process to make submission materials
  - For efficient use of medical records of medical institutes for clinical trials
  - For promotion of participating global development and using Japanese clinical trial data for submission to foreign regulatory authorities

PMDA will request patient level clinical trial data in electronic format which complies CDISC standards

Using submitted electronic data for drug review

- CDISC conformant data
  - SDTM
    - Data visualization and analysis by using software for standardized data
    - Statistical analysis by using analysis software
  - ADaM
    - Primary analysis and its sensitivity analysis
    - Other analysis by using analysis software
- Analysis program
  - Confirmation of analysis algorism
  - Utilization for sensitivity analysis and subgroup analysis if possible
- Programs for creating ADaM
  - Understanding of variables in the datasets
- Definition files
  - Understanding of variables in the datasets

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)

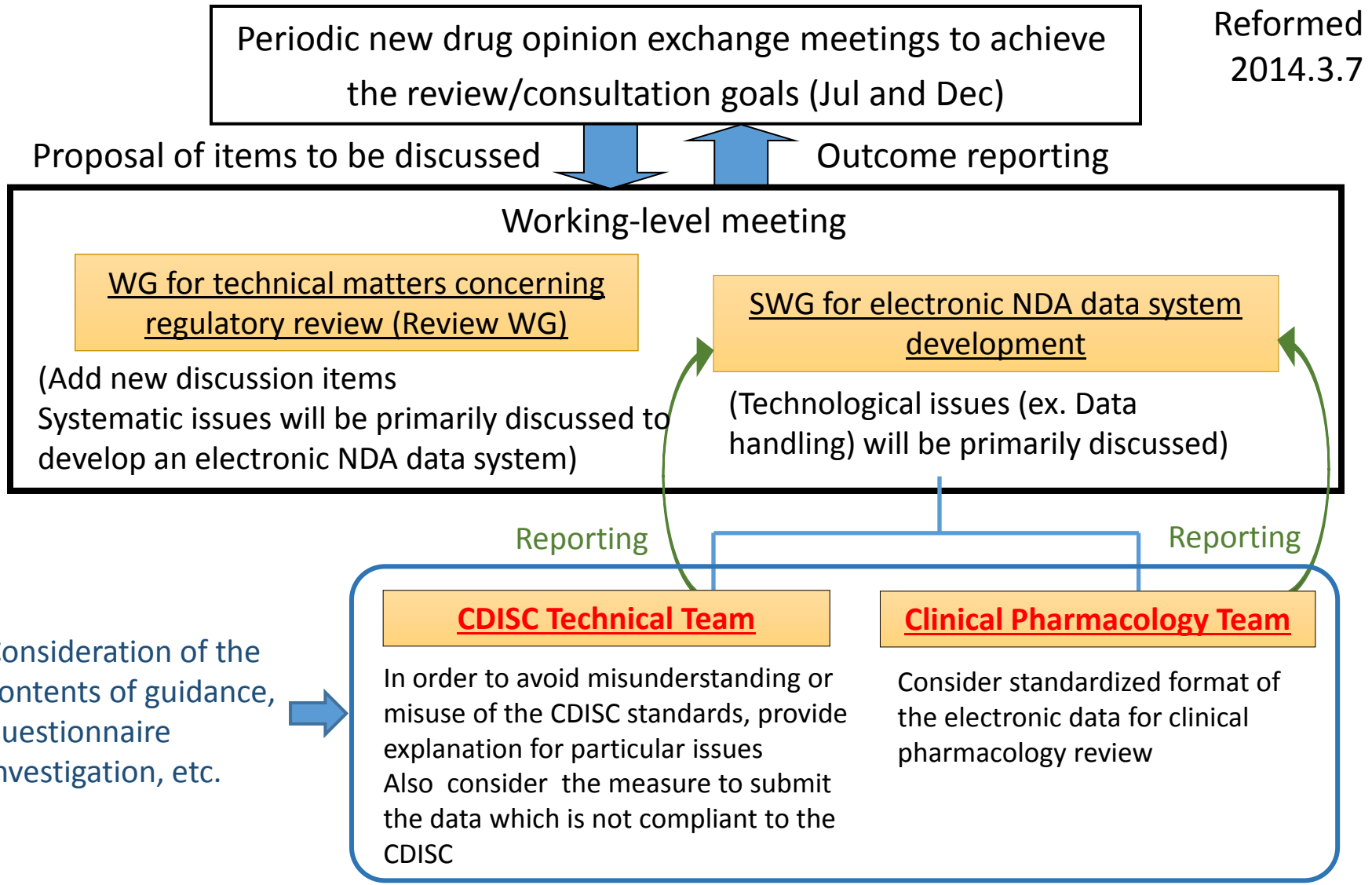
F) Effective use of the “final system” (trained experts)

Outline of Implementation Process (Draft)

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

FY2013*: April 2013 – March 2014

Discussion with the industry



CDISC Technical Team

- 14 experts from industry and CROs
- Several key items are investigated and discussed based on their experiences in the team meetings, and the outcome are sent to SWG.
  - Points to be considered in organizing SDTM and ADaM datasets
  - CDISC validation rules
  - Management of datasets including Japanese character
- Most of the outcome will be reflected in the contents of the technical guide or data management system.

Outline

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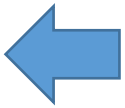
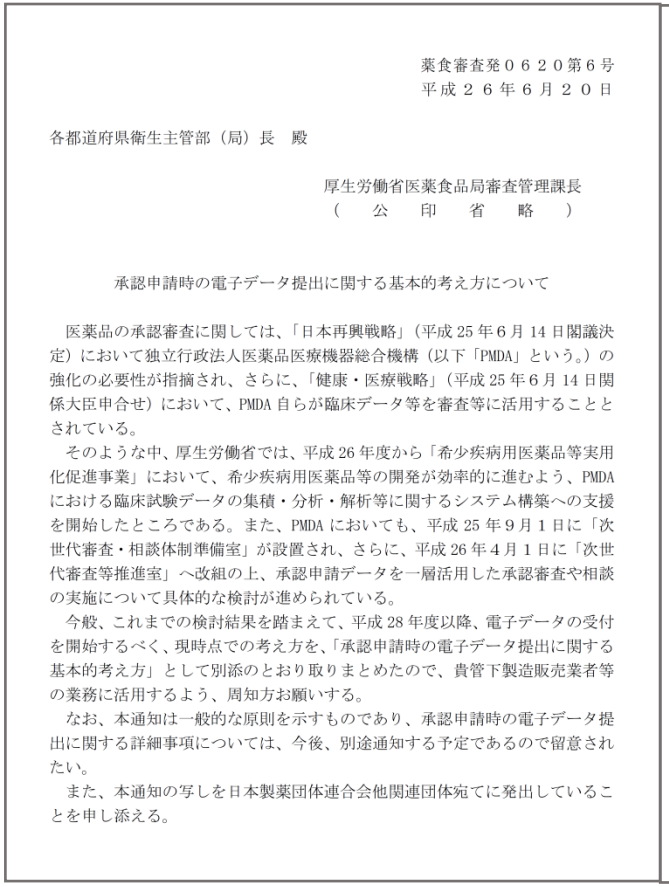


Basic principles on electronic submission of study data



薬食審査発０６２０第６号
平成２６年６月２０日

各都道府県衛生主管部（局）長　殿

厚生労働省医薬食品局審査管理課長
（　公　印　省　略　）

承認申請時の電子データ提出に関する基本的考え方について

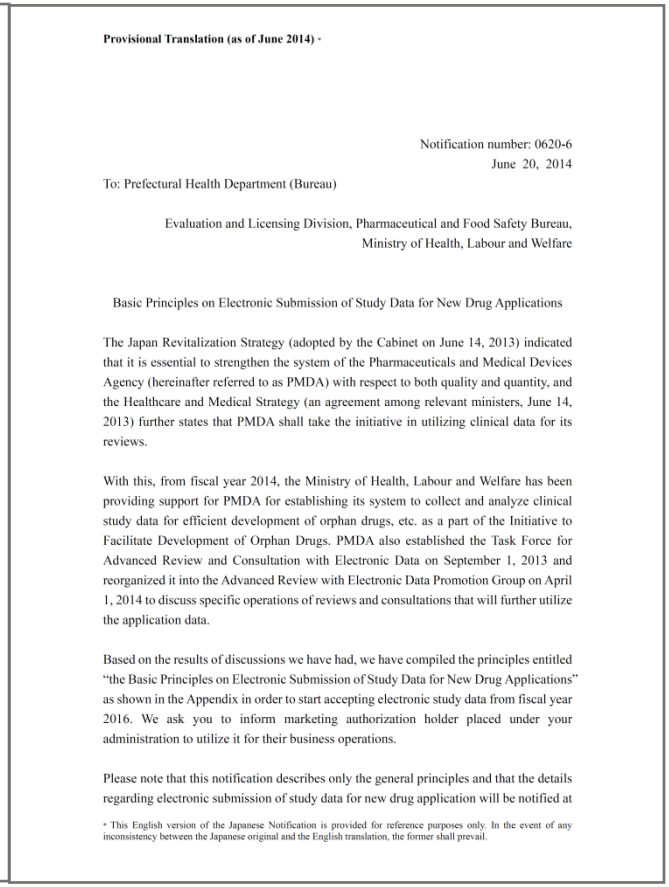
医薬品の承認審査に関しては、「日本再興戦略」（平成25年6月14日閣議決定）において独立行政法人医薬品医療機器総合機構（以下「PMDA」という。）の強化の必要性が指摘され、さらに、「健康・医療戦略」（平成25年6月14日関係大臣申合せ）において、PMDA自らが臨床データ等を審査等に活用することとされている。

そのような中、厚生労働省では、平成26年度から「希少疾病用医薬品等実用化促進事業」において、希少疾病用医薬品等の開発が効率的に進むよう、PMDAにおける臨床試験データの集積・分析・解析等に関するシステム構築への支援を開始したところである。また、PMDAにおいても、平成25年9月1日に「次世代審査・相談体制準備室」が設置され、さらに、平成26年4月1日に「次世代審査等推進室」へ改組の上、承認申請データを一層活用した承認審査や相談の実施について具体的な検討が進められている。

今般、これまでの検討結果を踏まえて、平成28年度以降、電子データの受付を開始するべく、現時点での考え方を、「承認申請時の電子データ提出に関する基本的考え方」として別添のとおり取りまとめたので、貴管下製造販売業者等の業務に活用するよう、周知方お願いする。

なお、本通知は一般的な原則を示すものであり、承認申請時の電子データ提出に関する詳細事項については、今後、別途通知する予定であるので留意されたい。

また、本通知の写しを日本製薬団体連合会他関連団体宛てに発出していることを申し添える。



Provisional Translation (as of June 2014) *

Notification number: 0620-6
June 20, 2014

To: Prefectural Health Department (Bureau)

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Basic Principles on Electronic Submission of Study Data for New Drug Applications

The Japan Revitalization Strategy (adopted by the Cabinet on June 14, 2013) indicated that it is essential to strengthen the system of the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as PMDA) with respect to both quality and quantity, and the Healthcare and Medical Strategy (an agreement among relevant ministers, June 14, 2013) further states that PMDA shall take the initiative in utilizing clinical data for its reviews.

With this, from fiscal year 2014, the Ministry of Health, Labour and Welfare has been providing support for PMDA for establishing its system to collect and analyze clinical study data for efficient development of orphan drugs, etc. as a part of the Initiative to Facilitate Development of Orphan Drugs. PMDA also established the Task Force for Advanced Review and Consultation with Electronic Data on September 1, 2013 and reorganized it into the Advanced Review with Electronic Data Promotion Group on April 1, 2014 to discuss specific operations of reviews and consultations that will further utilize the application data.

Based on the results of discussions we have had, we have compiled the principles entitled "the Basic Principles on Electronic Submission of Study Data for New Drug Applications" as shown in the Appendix in order to start accepting electronic study data from fiscal year 2016. We ask you to inform marketing authorization holder placed under your administration to utilize it for their business operations.

Please note that this notification describes only the general principles and that the details regarding electronic submission of study data for new drug application will be notified at

* 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.

June 20, 2014

Notification Number0620-6

Notification of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau,

Ministry of Health, Labour and Welfare

Both Japanese and English versions are available at our webpage

Japanese : http://www.pmda.go.jp/operations/shonin/info/iyaku/jisedai/file/140620-tsuchi.pdf
English : http://www.pmda.go.jp/operations/shonin/info/iyaku/jisedai/file/140620-tsuchi_e.pdf

Contents of the “Basic principles”

1. Background
2. Products and data subject to electronic submission
3. Electronic data and its method of submission
4. Relationship of eCTD and e-data submission
5. Consultation process regarding e-data
6. Information management regarding e-data submission
7. Relationship between e-data submission and conformity inspection
8. Initiation timing of e-data submission
9. Glossary

Basic principles, technical notification, and guide

- The details of data submission is described as “will be notified at a later date based on future discussion” in the basic policy.
- The details of electronic submission of study data will be issued as technical notification, guide, and Q&As, based on the system development, the experience of pilot projects and other considerations.
- Currently we are vigorously drafting those documents through discussion with the industry.

Possible contents of technical notification and guide -1

Draft

- Method of data submission
  - Use of Gateway, process of submission
  - Electronic submission format and procedure
  - CDISC and other validation rules
  - Data submission of supplemental NDA and situation of withdrawal
  - Data analysis environment in PMDA such as software
- Clinical trials subject to electronic submission
  - Clinical trial other than Phase II or III
  - Data submission of ISS/ISE
  - Additional electronic data submission after application, such as submission with interim analysis results

Possible contents of technical notification and guide -2

Draft

- Data and programs to be submitted
  - CDISC conformant data
    - Details of datasets (SDTM, ADaM) to be submitted
    - Handling dataset with Japanese characters
    - File format of the datasets
    - Terminology and codelists
    - Versions of standards
    - Points to be considered in organizing CDISC datasets
  - Programs to be submitted
  - Documents accompanied by the data, such as Annotated CRF and data guides
  - Analysis datasets and programs for clinical pharmacological investigation
- Start date for e-data submission and transitional period

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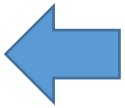
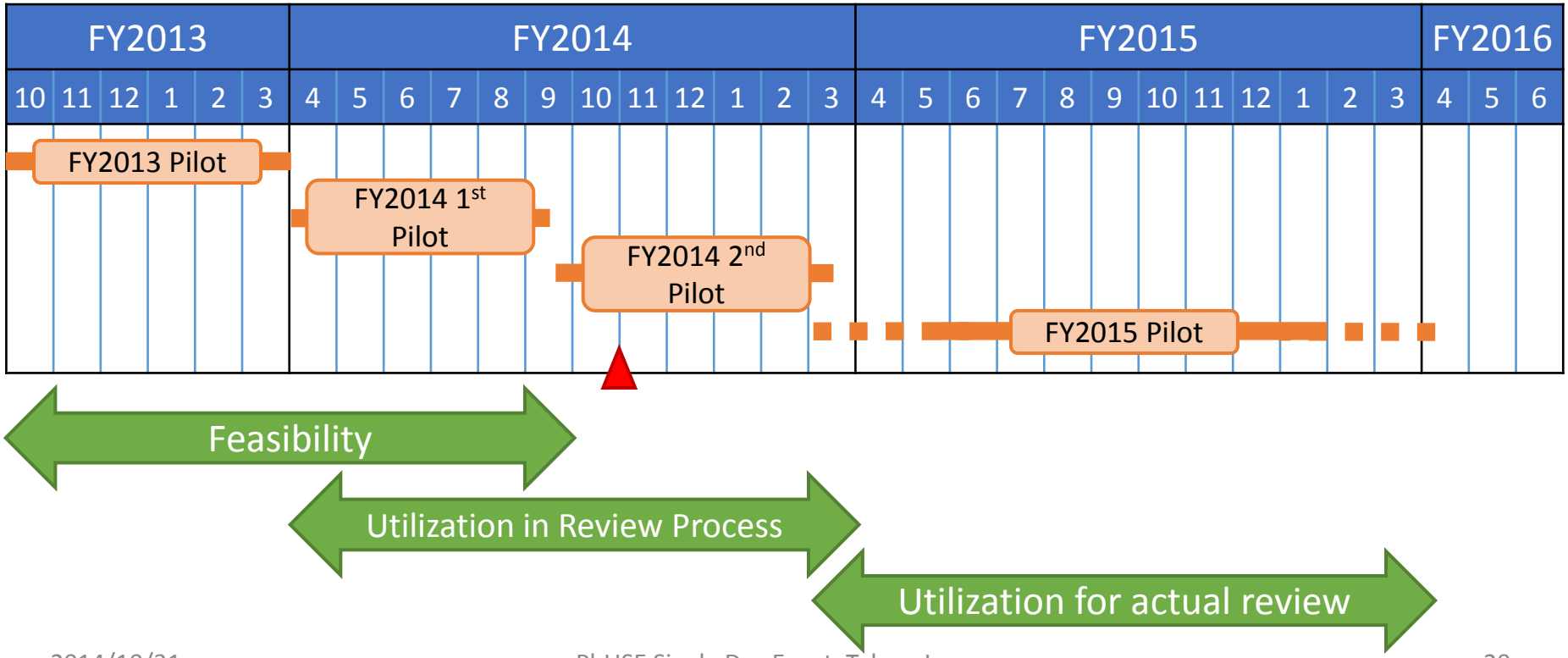


Pilot projects for utilization of electronic data

- Step-by-step implementation of pilot projects
  - Confirmation of feasibility
  - Consideration of data utilization in the review process
  - Pilot intended for actual new drug review



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

Results of FY2013 pilot project (outline)

- Implementation
  - Clinical study data on five drug products were submitted from the five companies.
  - Before submission of data, interviews were conducted with the companies based on the information of the drug, clinical trials and data.
  - Around 100 reviewers analyzed the data with using a software for CDISC compliant data, from January to February 2014
  - Other software were also used by statistical and pharmacological reviewers
- Results
  - 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 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

Analysis datasets for clinical pharmacology

- Analyses of clinical pharmacology data will be conducted for particular purposes with using datasets from multiple clinical trials.
  - Population PK/PD analysis
  - Modeling & simulation
- Although these datasets will not be compliant with CDISC, they will be useful for the particular pharmacological analysis
- Pilot for the utilization of clinical pharmacological (non-CDISC) data is included in FY2014 pilot project.

Pilot project in the first half of FY2014 (outline)

- Purpose
  - To confirm that the analysis of the submitted clinical study data for new drugs using
  - introduced software enables the reviewers to obtain the necessary 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 can be stored and managed appropriately with in-house system, and that persons in charge are able to analyze the stored data by utilizing introduced software.

- Target studies
  - CDISC compliant data: Clinical studies (phases II and III) of new drugs (including follow-on biologics) that include those of Japanese subjects
  - Data for population pharmacokinetic analysis: Datasets for population pharmacokinetic analysis of blood concentration data that include those of Japanese subjects obtained from one or more clinical studies on new drugs (including follow-on biologics)

Pilot project in the first half of FY2014 (outline)

- Period
  - Data collection: April – May 2014
  - Analysis: June – September 2014
- Implementation details: 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 (distribution of background factors, results of primary and secondary efficacy endpoints, occurrence of adverse events, etc.) can be obtained.
  - Confirm that by using the statistical analysis software, the results of primary endpoints and other useful results for the review can be obtained. Confirm the details of the analysis program, if submitted, and conduct analysis based on those details to confirm the results.
  - Examine the extent of analysis feasible in the review process; estimated workload; and utilization of the analysis results for future review process.

Results of the Pilot project in the first half of FY2014

- Provided data and persons in charge
  - CDISC-compliant clinical study datasets for four drug products, one from each of four companies, were provided voluntarily.
  - Before submission of data, interviews were conducted with the companies based on the information of the drug, clinical trials and data.
  - The pilot project was conducted from June to August 2014 by about 180 reviewers and about 20 staff from the Advanced Review with Electronic Data Promotion Group.

Results of the Pilot project in the first half of FY2014

- Results and future tasks
  - More than half of the reviewers could reproduce the results described in CTD using the provided data. A part of the reviewers could conduct their own data analyses to obtain information necessary for review.
  - It seems that the role, necessity and appropriate timing of data analyses will vary depend on the content of the each application, and the variation should be considered in the discussion on the future review process.
  - We plan to solve issues likely caused by commercial software specifications, such as through inquiring with vendors.
  - We will continue to provide various training options (CDISC, software) to reviewers.

Current and future pilot projects

- We have just started the pilot project in the last half of FY2014.
  - Although the plan of the pilot project is similar to that of the pilot project in the first half of FY2014, the roles of persons in charge are different from those of previous pilot project.
- We already announced the pilot project in FY2015.
  - The purpose of the pilot project is examining the future use of submitted data under the actual regulatory review.
  - The pilot will be carried in parallel with, but NOT affecting the actual regulatory review of the product.

Experiences based on the pilot projects

- Experiences of analyzing CDISC conformant data in the pilot projects
  - There are differences in datasets between the companies.
    - Variables used
    - Use of Japanese characters
    - Version of the standards
    - Formats and contents of metadata
  - We reaffirm that it is critical to understand possible inter-company or inter-product difference and in which situation the difference may exist
    - Difference in conformance for CDISC standards
    - Contents of metadata
    - Usefulness of analysis results metadata, annotated CRF, and data guides

Experiences based on the pilot projects

- The depth of understanding of the data will be increased
  - Careful checkup on study data
    - Relationship between analysis sets, exclusion criteria, and missing data
    - Individual patient profile
    - Calculation of values of primary endpoint
  - Interest not only in the analyzed results, but also in the data and the variables

New drug reviewers will get more interested in the data and data management process.
Communication with the persons in charge of data management and data analysis may be enhanced.

Summary

- Advanced Review with Electronic Data Project being executed successfully so far, and our experience of reviewing and analyzing CDISC-conformant data is accumulating through multiple pilot projects
- We work on drafting the technical notification and guide, and the details of the electronic submission will be provided in the near future.
- Compliance with the data standards, quality of the submitted electronic data and documentation will be the key in future review process.
- Effective utilization of submitted electronic data will lead to more efficient drug development and more predictable efficacy/safety evaluation, and finally benefit the public.
- We appreciate your understanding and cooperation.

Thank you for your attention!

- PMDA Advanced Review with Electronic Data Promotion Group HP
  - http://www.pmda.go.jp/english/service/taskforce.html
- Secretariat of PMDA Advanced Review with Electronic Data Promotion Group
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