Data standardization and advancing regulatory science

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Current Situation
Cost of drug development


Teshirogi I, 11th Kitasato-harvard Symposium, 2011
Stage and Reasons to fail drug development

Figure 1 | Density of actively recruiting clinical sites of biopharmaceutical clinical trials worldwide. Density is in per country inhabitant (in millions; based on 2005 population censuses); darker orange/red denotes a higher density. The trial density and average relative annual growth rate in percent is shown for selected countries. The countries in grey had no actively recruiting biopharmaceutical clinical trial sites as of 12 April 2007. Nature Rev Drug Discovery, 7: 13, 2008
Current Situation of Drug Development

• Huge increase of development cost
  • Failure costs, additional requirements etc.

• Low success rate
  – High failure rate, especially in later stage
  – Scientific limitation (many unknown factors)

• Globalization
  – International harmonization and cooperation

✓ A lack of innovative drug
✓ Delayed development
✓ Unmet-medical needs
✓ A lack of sufficient evidence in a population or a region

Need another approach
Role of Regulatory Science in drug development
Figure 1 The regulatory science “bridge” as a means to introduce products of science to patients and to society. Regulatory science performs three functions: providing tools for data production, a basis for data assessment, and methods for balancing various factors. All three functions are indispensable to a proper introduction of a new product of science (here, “Drug A”).

Details of 3 Factors in Regulatory Science

- **Higher efficiency**
  - Biomarker
  - M&S
  - Adaptive Design
  - and more

- **Data Assessment**
  - Higher quality
    - Objective and Quantitative assessment etc.
      - What is Benefit?
      - What is safety?

- **Better balance**
  - Better methods for benefit/risk assessment
  - Medical and social needs
  - Patients voice

Need alternative approach and more research
Importance of the electronic data standard for advancing regulatory science
Why data standard is important?

- Only limited data are available from one study or one organization
- Wasteful, if expensive clinical data are not utilized effectively
- More effective to analyze data from relevant multiple studies or products

To maximize data value and facilitate proper analysis
- Data should be acquired, submitted, archived in same structure and format
Data in a clinical trial

Out of control, if these data were collected in different standards among studies

- Protocol (eProtocol)
- CRF
- aCRF
- Data Capturing and Processing
- Study Data (SDTM)
- Analysis Data (ADaM)
- Metadata
- Analysis and Reporting
- Annotated CRF
- Submission
CDISC Standards in a clinical trial

Medical Inst

Sponsor

Regulatory Agency

EHR

HL7

Protocol (eProtocol)

CDASH

PRM

CRF

Data Capturing and Processing

SDTM

Study Data Tabulation Model: 臨床試験データ

Define.xml

Analysis Data Model: 統計解析用データ

Study Data (SDTM)

SDTM

Metadata

Analysis Data (ADaM)

Define.xml

Analysis and Reporting

Annotated CRF

CDISC Standards in a clinical trial

Analysis Data Model: 統計解析用データ

Study Data Tabulation Model: 臨床試験データ

Protocol (eProtocol)

CDASH

CRF

Data Capturing and Processing

SDTM

Analysis Data (ADaM)

Annotated CRF

17th Annual Workshop in Japan for Clinical Data Management: BEYOND the Standardization
January 30-31, 2014 | CongresSquare, Nakano, Tokyo
Reinforcement of the PMDA system
-Task force for advanced review and consultation with electronic data-
Background

1. Japan Revitalization Strategy -JAPAN is BACK-
   - Strategic Market Creation Plan
     - Theme 1: Extending the nation’s healthy life expectancy
   - The assessment lag “0” for pharmaceuticals and medical devices by accelerating the assessment process by strengthening the PMDA system

2. 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 Plan
     - Achievement of a healthy, long-lived society
     - Contribution to economic growth
     - Global contribution
   - PMDA-initiated promotion of research and analysis based on clinical data
Task force for advanced review/consultation

- The special task force was formally established on Sept 1st, 2013
  - "Task force for advanced review and consultation with electronic data"  
    http://www.pmda.go.jp/english/service/taskforce.html
Accumulation and Utilization of e-Data

NDA submission

- 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 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
Merit of use of CDISC standards in PMDA

PMDA plans to request patient level clinical trial data in electronic format which complies with CDISC standards

- **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
Relationship between PMDA and 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 introductory lecture of CDISC in PMDA
- Presentation by PMDA in International Interchange and Japan Interchange
Proposed timeline for electronic study data system development

• FY2013
  – Surveys, procurement of hardware/software, pilot*
    *Electronic data viewing and internal analysis

• FY2014 to FY2015
  – Continue the pilot*; to be in full operation after the Lab is open

• FY2016 (prospect)
  – Submission of clinical electronic data for NDA
    – (With transitional period)

• After FY2017
  – Submission of non-clinical electronic data for NDA
    – (To be discussed)
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 will confirm the feasibility of reviewing and analyzing data in CDISC formats, using actual data from clinical trials.
Pilot project updates

• Volunteers for FY2013 pilot
  – more volunteers than expected
  – meetings with sponsor prior to pilot data submission
  – vary in product categories, phases, types, global/domestic
  – datasets
    • compliant with CDISC standards
    • with some additional company-specific variance

• Several volunteers for FY2014 pilot

Thank you for your great support and contribution!!
Pilot project updates

• Tools and training for pilot projects
  – Surveyed and prepared tools/software for data analysis and presentation
    • Feasibility to be tested through the pilots
  – Training on CDISC standards and software
    • ALL new drug reviewers in charge took the trainings
    • To be continuously conducted
Current Activities

• Monthly meeting with pharmaceutical industry association (JPMA, PhRMA Japan, and EFPIA Japan)
  – Japan CRO<clinical research organization> Association just joined to the discussion
  – All procedural and technical issues for data submission have been discussed.
• Information exchange with FDA and EMA
• “Basic principles on e-data submission for NDA” is currently under preparation and will be notified in FY2014
Future
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
  - More predictable efficacy/safety after approval
  - Reduction of applicant’s work load
  - More scientific regulatory decision
  - Epoch-making proposal leading the world
  - Proactive publication of guideline

- **e-Submission of study data**
  - NDA etc.

- **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

- **Practical use of Innovative Medical Products**
  - 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
Regulatory Science Bridge

Products of science
(Substance, Knowledge, Information)

Regulatory Science Bridge

Tools for data production
Data assessment
Balancing of various factors

Drug A

Patients/Society

Stronger & More Complete Regulatory Science Bridge will help us in the future drug developments

Staff Recruitment

Information

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Thank you for your attention