Biostatistical review of new drug applications in Japan
-Current and future activity-

Yuki Ando, PhD
Senior Scientist for Biostatistics
Pharmaceuticals and Medical Devices Agency (PMDA)
Outline

• Background of biostatistical review in PMDA
• Statistical topics in new drug review
• Future new drug review in Japan
• Summary
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
History and related guidance


1997: Establishment of Pharmaceuticals and Medical Devices Evaluation Center

1998: ICH-E9 “Statistical Principles for Clinical Trials”
2002: ICH-E10 “Choice of Control Group and Related Issues in Clinical Trials”

2004: Establishment of Pharmaceuticals and Medical Devices Agency (PMDA)

2007: “Basic Principles on Global Clinical Trials”
2012: “Basic Principles on Global Clinical Trials Reference Cases”
2013: “Guidance on Data Monitoring Committee (in Japanese)”
2014: Discussion of ICH-E9(R1) “Choosing Appropriate Estimands and Defining Sensitivity Analyses”
Organization Chart


- Review Management
- International Affairs
- New Drug Review
- New Device Review
- Safety
- IT
- Relief Funds
- Administration
Review offices and review team

- New drug review offices

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<tr>
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</thead>
<tbody>
<tr>
<td>Office of Cellular and Tissue-based Products</td>
<td>Office of Vaccines and Blood Products</td>
<td>CMC</td>
<td>Pharmacology</td>
<td>Pharmacokinetics</td>
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</tbody>
</table>
Review offices and review team

- New drug review team for each therapeutic area
  - The same review team is involved in the clinical trial consultation and new drug review for the area

<table>
<thead>
<tr>
<th>Office Director</th>
<th>Review Director</th>
<th>Team Leader</th>
<th>Deputy Team Leader</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>CMC</td>
<td>Pharmacology</td>
<td>Pharmacokinetics</td>
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<tr>
<td></td>
<td>Toxicology</td>
<td>Clinical/Medical</td>
<td>Biostatistics</td>
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</tbody>
</table>
New drug review process in Japan

- So far, patient-level clinical trial data in electronic format 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.
Biostatistics reviewers in PMDA

• 9 biostatistics reviewers are distributed between 7 new drug review offices.
  – They are working also for Offices of Medical Devices, Office of In Vitro Diagnostics, and Office of OTC/Quasi-Drugs if need arises.

• Responsibilities
  – Statistical aspects of new drug review and clinical trial consultation meetings
    • Design, conduct, analysis, and interpretation of clinical trials
    • Non-clinical, clinical pharmacological consideration
  – Development of related guidance
    • Projects Across Multi-Offices in PMDA
  – Training of design and analysis of clinical trials for non-statisticians
Data Science Round Table Discussion

• Presentations and group discussions mainly by young biostatisticians between industry, academia, and PMDA
  – 1st: February 14, 2014
    • Small clinical trials
    • Missing data
    • Multi-regional clinical trials
  – 2nd: March 4, 2015
    • Adaptive designs
    • Missing data
    • Bayesian approach
Statistical topics in new drug review

• Multi-regional clinical trials
• Complex clinical trial designs - adaptive design
Multi-regional clinical trials – Trends in Japan

Preliminary results for FY2014
Case example - perutuzumab

• Indication: HER2 positive inoperable or recurrent breast cancer

• Trial design: Randomized, double-blinded, parallel-group study
  – Comparison groups
    • Pertuzumab + trastuzumab + docetaxel
    • Plasebo + trastuzumab + docetaxel
  – Stratification factors: pretreatment, region
  – Primary endpoint: PFS(IRF)
  – Secondary endpoints: OS, PFS, response rate
**All subjects**

<table>
<thead>
<tr>
<th></th>
<th>pertuzumab</th>
<th>placebo</th>
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<tbody>
<tr>
<td>N</td>
<td>402</td>
<td>406</td>
</tr>
<tr>
<td>Event(%)</td>
<td>119 (47.5%)</td>
<td>242 (59.6%)</td>
</tr>
<tr>
<td>Median survival</td>
<td>18.5 [14.6, 22.8]</td>
<td>12.4 [10.4, 13.2]</td>
</tr>
<tr>
<td>[95%CI]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>[95%CI]</td>
<td>[0.51, 0.75]</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
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</table>

**Japanese subgroup**

<table>
<thead>
<tr>
<th></th>
<th>pertuzumab</th>
<th>placebo</th>
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<tbody>
<tr>
<td>N</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>Event(%)</td>
<td>18 (69.2%)</td>
<td>13 (48.1%)</td>
</tr>
<tr>
<td>[95%CI]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>1.92</td>
<td></td>
</tr>
<tr>
<td>[95%CI]</td>
<td>[0.91, 4.04]</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.0871</td>
<td></td>
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http://www.info.pmda.go.jp/shinyaku/P201300075/450045000_22500AMX01001000_A100_1.pdf
Multi-regional clinical trials

• Prior consideration on possible factors and interpretation of the difference between regions are important.
• Evaluation based on the interaction between region and drug effects seems to have a limitation because of the sample size for each region.
  – In pertuzumab case, the reason of difference was not suggested by model-based analysis, investigations of heterogeneity between countries and influences of prognostic factors
• Although Japanese guidance focused on the subgroup analysis for sample size estimation, evaluation only of the point estimates in subgroup compared to that in all subjects is not sufficient for explaining the consistency.
  – Watch the discussion of ICH-E17
• Trial design used for the submission to multiple regions will be also considered.
Adaptive designs

• Since 2004, PMDA has had many consultation meetings including adaptive design as the design of proposed trial.
  – For both exploratory and confirmatory phase, for all type of region (Japanese/foreign/multi-regional)
  – Major types of modifications are sample size re-estimation, seamless phase II/III designs.

• Some applications were approved based on the clinical trial using adaptive design.

• Guidance on DMC was issued in 2013, for the preparation for active use of adaptive designs.
Major discussion points

• Efficiency
  – Motivation
  – Disease area, drug properties, states of the clinical trial (exploratory/confirmatory)
  – Advantage and disadvantage compared to traditional study design
• Mathematical validity
  – Theoretical consideration
  – Operation characteristics
• Integrity
  – Operation system for clinical trial to ensure independency of unblinded persons in charge
  – Appropriate documentation, such as IDMC charter and minutes
  – Consistency of results before and after adaptation
Future new drug review in Japan

• Advanced review with electronic data
• PMDA International Strategic Strategic Plan 2015
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

Strengthening the PMDA
- System enhancement for 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

Specific Strategy
Advanced workflow of review/consultation

Analysis by PMDA

- Giving additional scientific value to submitted data

Cooperation with Academia

- More predictable efficacy/safety after approval
- Reduction of applicant’s workload
- More scientific regulatory decision

Practical use of Innovative Medical Products

- More rational & effective evaluation process for regulatory decision

Regulatory Science

- 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

NDA etc.

e-Submission of study data

Data Accumulation

Database

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**
- Submission of electronic data from clinical and nonclinical studies

**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

**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

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

Visualization and analysis of data, supported by browsing software

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

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

What the review authority can do with the information of all products.
Importance of data 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/Medical institutes
  – For efficient and qualified process to make submission materials
  – For promotion of participating global development and using Japanese clinical trial data for submission to foreign regulatory authorities
  – For efficient use of medical records of medical institutes for clinical trials in the future
Data standard - CDISC

• PMDA will request patient level clinical trial data in electronic format which complies CDISC standards
  – CDISC (Clinical Data Interchange Standards Consortium, http://www.cdisc.org/)
  – PMDA will request clinical study dataset in SDTM, analysis dataset in ADaM, and definition files for both in Define-XML.
  – Also the formats by PhUSE (Pharmaceutical Users Software Exchange, http://www.phuse.eu/) will be used for the related documents
# Timeline for implementation of e-study data submission

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<td>5 6 7 8 9 10 11 12 1 2 3</td>
<td>4 5 6 7 8 9 10 11 12 1 2 3</td>
<td>4 5 6 7 8 9 10 11 12 1 2 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.5 years of Transitional period</td>
</tr>
<tr>
<td>Review</td>
<td>2014 1st Pilot</td>
<td>2015 Pilot</td>
<td>Initiation of e-study data submission</td>
</tr>
<tr>
<td></td>
<td>2014 2nd Pilot</td>
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<tr>
<td>Consultation for e-study data submission</td>
<td>Pilot</td>
<td>New Consultation framework</td>
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<tr>
<td>System Development</td>
<td>System Development</td>
<td>Pilot for data submission</td>
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Today
Overview of the Pilot Projects

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<tr>
<td><strong>Purpose</strong></td>
<td>Feasibility</td>
<td>Feasibility &amp; utilization of study data in review process</td>
<td>Utilization of study data in review process</td>
<td>Utilization of study data for actual review</td>
</tr>
<tr>
<td><strong>Target studies</strong></td>
<td>5 drugs</td>
<td>CDISC: 4 drugs CP: 3 PPK datasets</td>
<td>CDISC: 3 drugs CP: 3 PPK/PD datasets</td>
<td>CDISC: 13 drugs CP: Standard Two-Stage Approach: 4 datasets Population Approach: 7 datasets (As of May 29,2015)</td>
</tr>
<tr>
<td><strong>Persons in charge</strong></td>
<td>Around 80 reviewers + 20 from promotion group</td>
<td>Around 180 reviewers + 20 from promotion group</td>
<td>Around 190 reviewers + 20 from promotion group</td>
<td>Around 190 reviewers + 20 from promotion group (tentative)</td>
</tr>
<tr>
<td><strong>Details</strong></td>
<td>All the reviewers try to reproduce the several analysis results in CTD</td>
<td>All the reviewers try to replicate the main analysis results in CTD Team meetings for the discussion on the review process with data analysis</td>
<td>Some reviewers including biostatisticians in each review team are assigned mainly handle the data analysis Team meetings for the discussion on the necessary analyses for the review and the review process with data analysis</td>
<td>Pilot project which is almost parallel with actual new drug review The pilot project will NOT affect the actual regulatory review of the drug</td>
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Prospect of e-Study Data Utilization in Japan

Prospect As of June 2015 (Subject to Change)

- e-study data can be received and managed appropriately
- e-study data can be utilized in the review
- Industries’ workload is reduced gradually while keeping the same review period

**Present** J-FY2015

**J-FY2016**

Setup e-data management and utilization

**J-FY2018**

Ordinary utilization of e-data in the product review

**J-FY2019 - 2021**

Starting earnest cross-product analysis

**J-FY2020 - 2021**

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

**J-FY2022 -**

First-class review authority

- Establishment of disease models
- Publication of disease-specific guidelines

**Transitional period are taken until March 31st, 2020**

- Establishment of disease models
- Publication of disease-specific guidelines

- Earnest on cross-product analysis and development of disease models

**Preparations of guidelines and related documents**

**Setup e-data management and utilization**

- Ordinance and regulations
- Promotion of paperless operation

Start e-study data submission for NDA* from Oct 1st, 2016

Present J-FY2015

**Ordinary utilization of e-data in the product review**

**Start e-study data submission for NDA**

* NDA=New Drug Application

**E.g. guidelines and disease models based on data on Asian population**

**2015/06/30 ISBS/DIA Symposium on Biopharmaceutical Statistics**
Biostatistical review in the future

• More collaborative work with Medical/Clinical Reviewers and Clinical Pharmacologists in the review team
  – Review meeting with the results of internal analyses

• More frequent provision of information about the knowledge based on the cross-product analyses to industry and academia
  – Guidance development
  – Clinical trial consultation meetings
PMDA International Strategic Plan 2015

1. Establish the “Regulatory Science Center” for conducting first-in-the-world product reviews, implementing safety measures, and undertaking other activities, as well as publishing the outcomes.

2. Launch the “Asian Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs” to share PMDA’s accumulated knowledge and experience in product reviews, implementation of safety measures, and provision of relief services with Asian and overseas regulatory authorities.

3. Cooperate with overseas regulatory authorities for expansion of harmonization activities (e.g., ICH, IMDRF) and work-sharing (e.g., GMP/QMS inspections)

June 26, 2015.

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3. Cooperate with overseas regulatory authorities for expansion of harmonization activities (e.g., ICH, IMDRF) and work-sharing (e.g., GMP/QMS inspections).

“In the Center, in close collaboration with relevant academics, societies and industry around the globe, activities such as identification of safety risks using electronic medical records, simulation and model building based on clinical trial data across products will be conducted.”

June 26, 2015.

Summary

• Biostatistics reviewers in PMDA are now in the new phase of new drug review in Japan.
  – Biostatisticians will be the key in new drug review/development collaborating with experts in other areas.
  – We re-realized the importance of data standards and operating system of clinical trials including data managers, and CROs.

• Biostatistics reviewers are working on the statistical topics including MRCTs and adaptive designs continuously.

• We will be pleased to have discussion with industry and academia about our new drug review and future use of clinical study data.