

Biostatistics Summer Workshop 2012

Looking beyond ICH-E9 in the Era of Global Drug Development

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This is not an official PMDA guidance or policy statement.
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Outline

- Impact of ICH-E9 and recent topics
- Adaptive designs
- Multi-regional clinical trials
- Future tasks
- Summary

Impact of ICH-E9 in Japan

- ICH-E9 was issued on November 30, 1998 in Japan
- Impact of E9
 - Active discussion on several related topics at many workshops and conferences during drafting process
 - Quality of design, analysis, and interpretation of clinical trials
 - Quality of materials for new drug applications
 - Ease of discussion on many topics included in ICH-E9
 - Status of biostatisticians, trial statisticians, and statistical reviewers in Japan

Recent topics, beyond ICH-E9?

- Efficient designs for early-phase clinical trials
 - “The principles outlined in this guidance are primarily relevant to clinical trials conducted in the later phases of development, many of which are confirmatory trials of efficacy.”
- Use of biomarkers for patient selection and drug evaluation
- Adaptive designs
- Multi-regional clinical trials (MRCT)
- Post-marketing safety surveillance
- Integrated analysis pre- and post-marketing data

Experience of reviewing adaptive design

- There are more than 30* cases with adaptive design in clinical trial consultation meetings in PMDA
 - Sample size re-estimation
 - Combination of learning and confirm phase
 - Adaptive dose-ranging
- The number of cases is increasing very gradually compared with a few years ago.
- Although oncology area is the key area that adaptive design proposed, the number of cases in other areas is also increasing.

*Not including group sequential trials

Key questions for adaptive design

- Why we need the adaptive design in this situation?
 - Degree of lack of prior information
 - Balance of risk (error, bias) and benefit (efficiency of drug development?)
- Clinical trials with adaptive design in the clinical data package
- Analysis method
- Possibility of introducing bias

Use in adaptive design in Japan

- There seems to be the possible (suitable) situation for using adaptive design
- Appropriate use of adaptive designs with consideration for
 - Characteristics of the disease and drug
 - Sufficiency of prior information for designing clinical trials
 - Sufficiency of safety database
 - Expected clinical data package

Guidance on DMC

- Japanese guidance document on Data Monitoring Committees (DMC) is now under consideration
 - Increasing cases with group sequential trials and large scale trials
 - Importance of safety monitoring and careful implementation

Experience of reviewing MRCT

- Number of the approved NDAs with Multi-regional clinical trials (MRCT) including Japanese patients is rapidly increasing
 - 28 cases as of Aug 1st
 - Both global trials and Asian trials
 - In various therapeutic areas
- There have been many cases with designing or evaluating early phase MRCT, such as MRCTs for dose selection, in consultation meetings in PMDA, but few approved cases.

MRCT of approved cases within Japan 1

	Indication	Date of Approval
Tolterodine tartrate	Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency	Apr. 2006
Losartan potassium	Diabetic nephropathy with proteinuria and hypertension in patients with type 2 diabetes	Apr. 2006
Trastuzumab	Adjuvant therapy for HER2-positive breast cancer	Feb. 2008
Insulin glulisine	Diabetes mellitus	Apr. 2009
Tadalafil	Pulmonary arterial hypertension	Oct. 2009
Peramivir	Type A and Type B Influenza virus infection	Jan. 2010
Everolimus	Metastatic renal cell carcinoma	Jan. 2010
Panitumumab	Metastatic colorectal carcinoma with wild-type KRAS tumors	Apr. 2010
Travoprost/Timolol	Glaucoma	Apr. 2010
Temsirolimus	Advanced renal cell carcinoma	Jul. 2010
Laninamivir	Type A and Type B Influenza virus infection	Sep. 2010
Nilotinib	Newly diagnosed chronic myeloid leukemia in chronic phase	Dec. 2010
Dabigatran	Stroke and systemic embolism in patients with non-valvular atrial fibrillation	Jan. 2011
Trastuzumab	HER-2 positive metastatic gastric cancer	Mar. 2011

MRCT of approved cases within Japan 2

	Indication	Date of Approval
Pramipexole	Parkinson's Disease	Apr. 2011
Edoxaban	Thromboprophylaxis after total hip and knee replacement, hip fracture surgery	Apr. 2011
Dasatinib	Chronic myeloid leukemia	Jun. 2011
Indacaterol	Chronic obstructive pulmonary disease (COPD)	Jul. 2011
Linagliptin	Type 2 diabetes	Jul. 2011
Gefitinib	EGFR-Positive unresectable or metastatic NSCLC	Nov. 2011
Everolimus	Progressive neuroendocrine tumors of pancreatic origin (PNET)	Dec. 2011
Denosumab	Bone complications in patients with multiple myeloma or solid tumour that has spread to the bone	Jan. 2012
Aripiprazole	Manic episodes associated with bipolar disorder	Jan. 2012
Olanzapine	Depression episodes associated with bipolar disorder	Feb. 2012
Exenatide	Type II diabetes	Mar. 2012
Crizotinib	Anaplastic lymphoma kinase (ALK)-positive, advanced or metastatic NSCLC	Mar. 2012
Budesonide/ Formoterol	Asthma (where use of a combination of inhaled corticosteroid and long-acting β_2 adrenoceptor agonist is appropriate)	Jun. 2012
Formoterol	Chronic obstructive pulmonary disease (COPD)	Jun. 2012

MRCT of approved cases

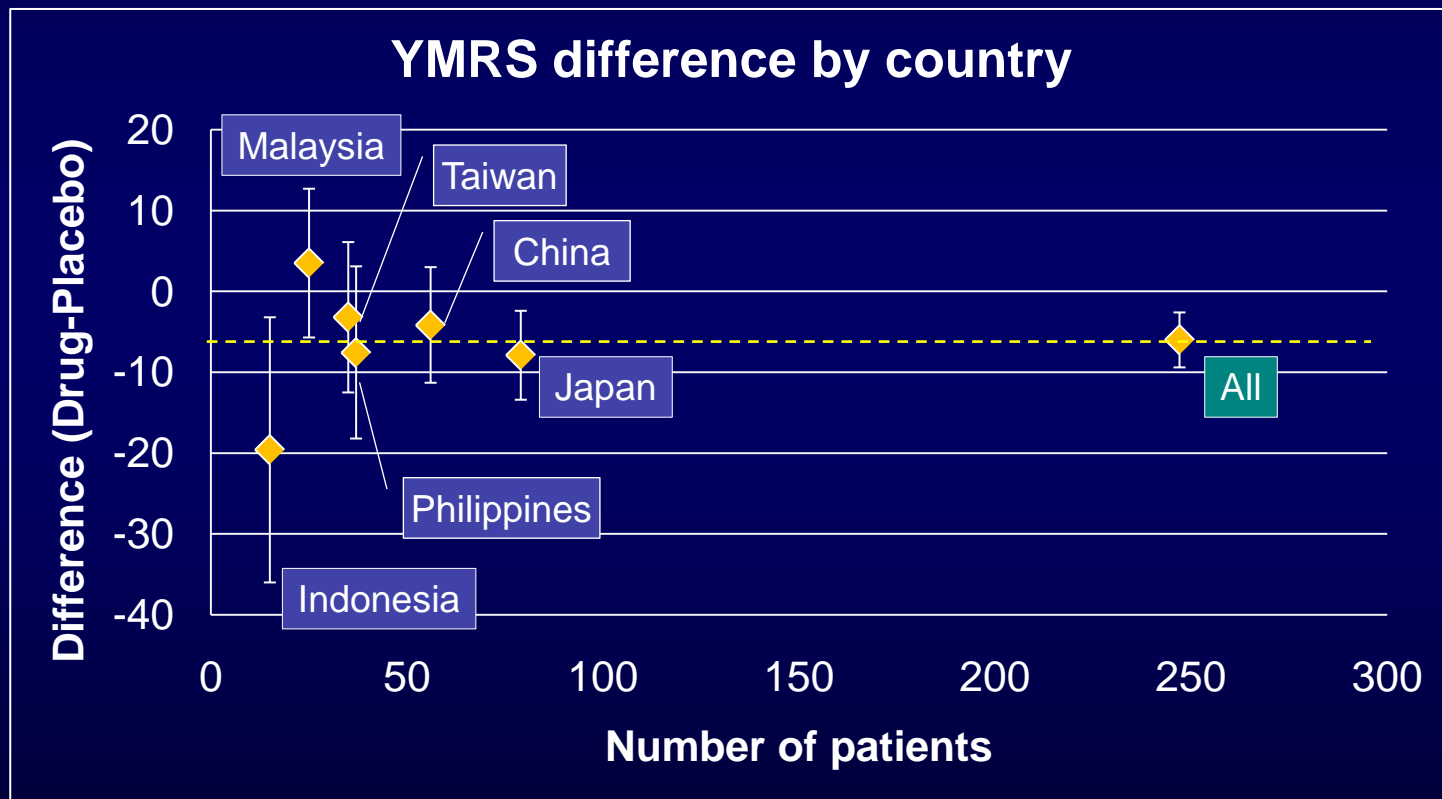
- Our experiences in reviewing MRCTs are rapidly increasing.
 - Most of the cases were approved in the last 2-3 years.
- Oncology area is the main area that actively uses MRCTs for J-NDA.
- The number of Asian trials is increasing.
- MRCT cases for same/similar indications have been approved.
 - Type A and Type B Influenza virus infection
 - Bipolar disorder

Asian trials

- Increasing approved cases with Asian trial as pivotal trial
 - The types and frequency of metabolic enzyme polymorphisms and gene profiles are thought to be similar especially among East Asian ethnicities.
- However, the difference in intrinsic/extrinsic ethnic factors may affect the efficacy and safety of drugs even within East Asia.
 - Prior sufficient evaluation of the effect of ethnic difference is still important
- Further accumulation and review of data and information on Asian populations will lead to easier conduct of Asian trials, and eventually, will facilitate the use of Asian trial data in new drug applications in Japan

Example – Asian trial for Aripiprazole

- Results of primary endpoint by country



Prepared based on

http://www.info.pmda.go.jp/shinyaku/P201200002/18007800_21800AMZ10013000_A100_1.pdf

Large-scale MRCT

- Specifically for cardiovascular drug, a few large-scale MRCT including many regions may be the main confirmatory data in development strategy.
- There are several issues related to such strategies.
 - Investigation and interpretation of drug doses for large-scale MRCT
 - Limited information available in each region at the time point of approval

Lessons learned from recent cases

- Along with the accumulation of the experience, by reviewing cases for same/similar indication, efficient design of MRCT should be well investigated.
- Issues with small proportion of Japanese subjects in large-scale MRCT conducted for rare events
 - Necessity of evaluating several endpoints
 - Sensitivity analysis will be the key in evaluating the variation of Japanese results and relationship of the results between all patients and Japanese patients.
- Limitation of available safety data at pre-approval phase
 - Regionally customized safety consideration and globally prompt feedback of the information is needed in post marketing phase

New guidance document

- “Basic Principles on Global Clinical Trials” was issued in 2007 in Japan.
 - Mainly based on our experience in clinical trial consultation meetings
- “Basic Principles on Global Clinical Trials - Reference Cases-” will be issued soon.
 - Based on recent scientific knowledge, review experience of approved cases, and experience in consultation meetings
 - Focused on both special points to consider for GCTs (MRCTs) in East Asia and general points to consider on GCTs

Topics in the new guidance document

- Points to consider for East Asian GCTs
 - Special points to consider in conducting a global clinical trial in East Asia
 - Possible similarity of gene profiles
 - Recommended therapeutic areas
 - Encouraging drug development for diseases with high morbidity in East Asia
 - Interethnic comparison of pharmacokinetic profiles and global drug development strategy
 - Possibility of a GCT as a bridging study
 - Sufficiency of information of ethnic difference

Topics in the new guidance document

- General points to consider
 - Japanese clinical development strategies and study protocols in the trend of globalization
 - Points to consider in evaluating the results of a global clinical trial
 - Evaluating the data of Japanese subjects living outside of Japan enrolled in foreign studies
 - Comparing PK data between different ethnicities
 - Global clinical trial as a First in Human trial
 - Global clinical trial with different drug exposure between Japanese and non-Japanese

Topics in the new guidance document

- General points to consider (cont.)
 - Unapproved drug as a control
 - Difference of recommended dose of control or concomitant drug between Japan and other regions
 - Points to consider in using a competitive registration system
 - Points to consider in participating in a large-scale global clinical trials with true endpoint such as mortality

Operational errors in clinical trials

- Several cases with operational errors are detected in the era of complex design clinical trials and global drug development
 - Program for statistical analysis
 - Program for randomization or IVRS (Interactive Voice Response System)
 - Information leakage
- Possibility of communication errors in the environment with role specialization and outsourcing
 - On the other hand, a degree of separation will be important in some situations, for example, adaptive design clinical trials

Project across multi-offices in PMDA

- In Vitro companion diagnostic devices project
- Pediatric and orphan drugs project
- QbD assessment project
- Innovative statistical strategies for new drug development project
- Nanomedicine initiative project
- Global clinical study project
- Cardiovascular risk evaluation project
- Omics project

http://www.pmda.go.jp/english/service/projects_am_e.html

Innovative statistical strategies project

- Innovative approaches for efficient and successful new drug development have been discussed also in Japan.
 - Modeling and simulation (Model-based drug development)
 - Adaptive design
- PMDA should play an important role in promoting and supporting the appropriate use of such approaches based on the experience in reviewing study protocols and new drug applications.
 - Providing useful information by investigating submitted information across the drugs
 - Explaining acceptability of the approaches in various situations

Innovative statistical strategies project

- New project team for innovative statistical strategies for drug development was recently established.
- The members are selected from several specialties.
 - Clinical pharmacology
 - Medical/Clinical
 - Biostatistics
 - (Review management, regulatory science, and standards)
- We have just started our research of following topics.
 - Placebo effect in neuropsychiatry drug development
 - Use of PK/PD and Modeling & Simulation for pediatric dose
 - Effects of ethnic factors in multi-regional clinical trials

Summary

- After ICH-E9 guidance was issued, several topics which were not fully covered by ICH-E9 have been actively discussed.
- New statistical approaches will facilitate efficient drug development when they are applied to appropriate situations.
- The role and responsibilities of biostatisticians, trial statisticians, and statistical reviewers become bigger in development and review in this era.
- Information sharing and discussion between industry, academia, and regulatory agency(-ies) is very important in the era of global drug development.

Thank you for your attention.

- Information

- Email: ando-yuki@pmda.go.jp

- PMDA Homepage (English)

- <http://www.pmda.go.jp/english/index.html>

- Selected review reports translated in English

- <http://www.pmda.go.jp/english/service/drugs.html>