Current experience with multiplicity issues in PMDA

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Outline

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Introduction

- In Japan, multiplicity is one of the statistical highly-discussed topics along with and relatedto
  - Adaptive designs,
  - Non-inferiority clinical trials,
  - Multi-regional clinical trials,
  - Subgroup analysis.
- However, we have not begun to create guidance document for multiplicity at this time.

Introduction

- Since we have had internal discussion on multiplicity issues, we would like to use this opportunity to share our view.

- In this presentation, we will introduce
  - Current perspective
  - Current case experience

  of multiplicity issues in PMDA.

Current perspective

- There is an ongoing change
  - From - avoiding multiplicity issues by focusing on or restrict to one primary
  - To - consideration of multiple aspect in an appropriate setting.
- Behind this change, there is heightened expectation for
  - More efficient drug development and trial designs,
  - Better characterization of new drugs.
- Multiplicity adjustment methods are necessary.

Efficient development/trial

- Several strategies are considered useful to improve the efficiency of drug development
  - Interim analysis, adaptive designs
    - Decision making during the trial based on the interim results
  - Multi-regional clinical trials
    - Subgroup analysis and consistency of the results among regions
    - Japanese guidance document, "Basic Principles on Global Clinical Trials" and its "Reference Cases"
      - http://www.pmda.go.jp/regulatory/english_guideline.html

Better characterization of drugs

- Investigation and evaluation of
  - Efficacy using several endpoints,
  - Efficacy at several dose levels,
  - Efficacy in various sub-populations,
  - Difference between more than two treatment groups.
- Clinical viewpoint is necessary.
- This aspect is closely related to the drug labeling.

Current perspective

- From the regulatory point of view, overall Type I error must be kept at the certain level in all cases of confirmatory trials.
- We would like to take a cautious but positive approach to multiplicity issues.
  - Discussion on each situation and statistical method at consultation meetings and/or new drug review.
  - Statistical contribution to the provision of information materials and drug labeling.
  - Training of both statisticians and non-statisticians in PMDA, by internal and external statisticians.

Current perspective

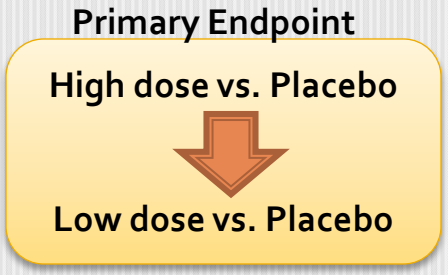
- Real questions of multiplicity may arise in a situation with complex of several aspects
  - e.g. Interim analysis of multiple endpoints in multi-regional clinical trial.
- To answer those questions, it is important to discuss our concerns, experience, and latest statistical methods, between pharmaceutical industry, academia, and regulatory agencies.

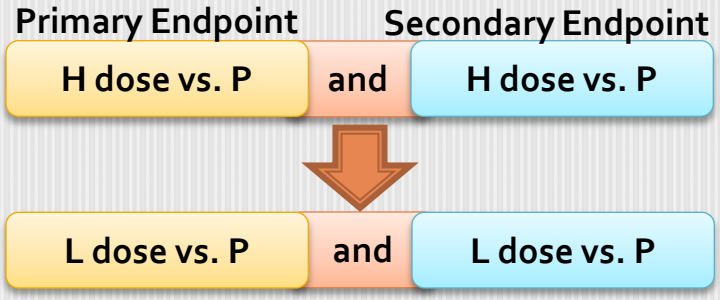
Case experience in PMDA

- Experience in PMDA consultation meetings and new drug review
  - Multiple endpoints
  - Difference between regions

Multiple endpoints

- **Cases of clinical trials with multiple endpoints and multiple dose levels.**
  - **In one case, we would like to focus on the primary endpoint and recommended dose based on the results of primary.**
  - **Company focused on the set of the primary and secondary endpoint at each dose level.**
  - **There may possibly be the disagreement in the order of tests in closed testing procedure**





Multiple endpoints

- To distinguish between multiple endpoints is point of controversy in some cases.
  - Co-primary endpoints which must succeed in all
  - Primary endpoint and secondary endpoint
- Clinical relevance and importance of each endpoint in current medical environment should be reviewed from clinical viewpoints.
- Discussion between statisticians and medical reviewers (non-statisticians) should be important.

Difference between regions

- In some multi-regional clinical trials, different primary analysis methods are planned for different regions without multiplicity adjustment, respectively.
  - Confidence interval of test drug or non-inferiority to the control
  - Different set of primary and secondary endpoint
- Such difference based on the clinical environment may be inevitable and understandable in some situations.

Difference between regions

- They do not seem to have multiplicity issue in the each region, however, it may possibly be controversial.
  - In most of those cases, they did not describe primary analysis method for other regions, PMDA, for example.
  - In Japan, we review them according to our criteria.
  - Which will be the overall results of the trial in the publication?
- Understanding of the situations in the different regions and prior consultation are very important.

Summary

- We believe that multiplicity is one of important statistical issues in the sense that
  - to improve the efficiency of development,
  - to identify the characteristics of the drug,
  - and to provide the appropriate information to patients and healthcare professionals.
- We should continue to share the experience and discuss more with various expertise between pharmaceutical industry, academia, and regulatory agencies.