Late Clinical Development in Asia

Acceptance of Clinical Data - The Challenge of Generalizability -

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AHC APEC Harmonization Center
DIA www.diahome.org
IFPMA International Federation of Pharmaceutical Manufacturers & Associations

Outline

- Introduction
- Efficient process for simultaneous drug development
- Japan's experience in the evaluation of multi-regional clinical trials
- Statistical consideration
- Ongoing and future tasks
- Summary

Simultaneous drug development

- Objectives
  - To avoid drug lag and enable rapid access to new drugs in many regions
  - To minimize duplication of clinical data in the development program

Simultaneous drug development

- Challenges
  - To plan the new drug development program so that the data package acceptable to all regions
  - To collect sufficient data for efficacy and safety for each region
  - To meet regulatory requirements in each region

Implementation of efficient development

- Importance of step-by-step development and building-up of evidence
  - Prior information, collected data, interpretation, and decision making for next step
  - Investigation of factors which affect the efficacy and safety of the drug from the beginning stage of its development
  - Collection of information on possible intrinsic and extrinsic ethnic factors

Implementation of efficient development

- Planning of data collection in major population at every stage based on the prior information
  - Possibility of the ethnic factors
  - Quantitative relationship among PK, PD and clinical efficacy and safety

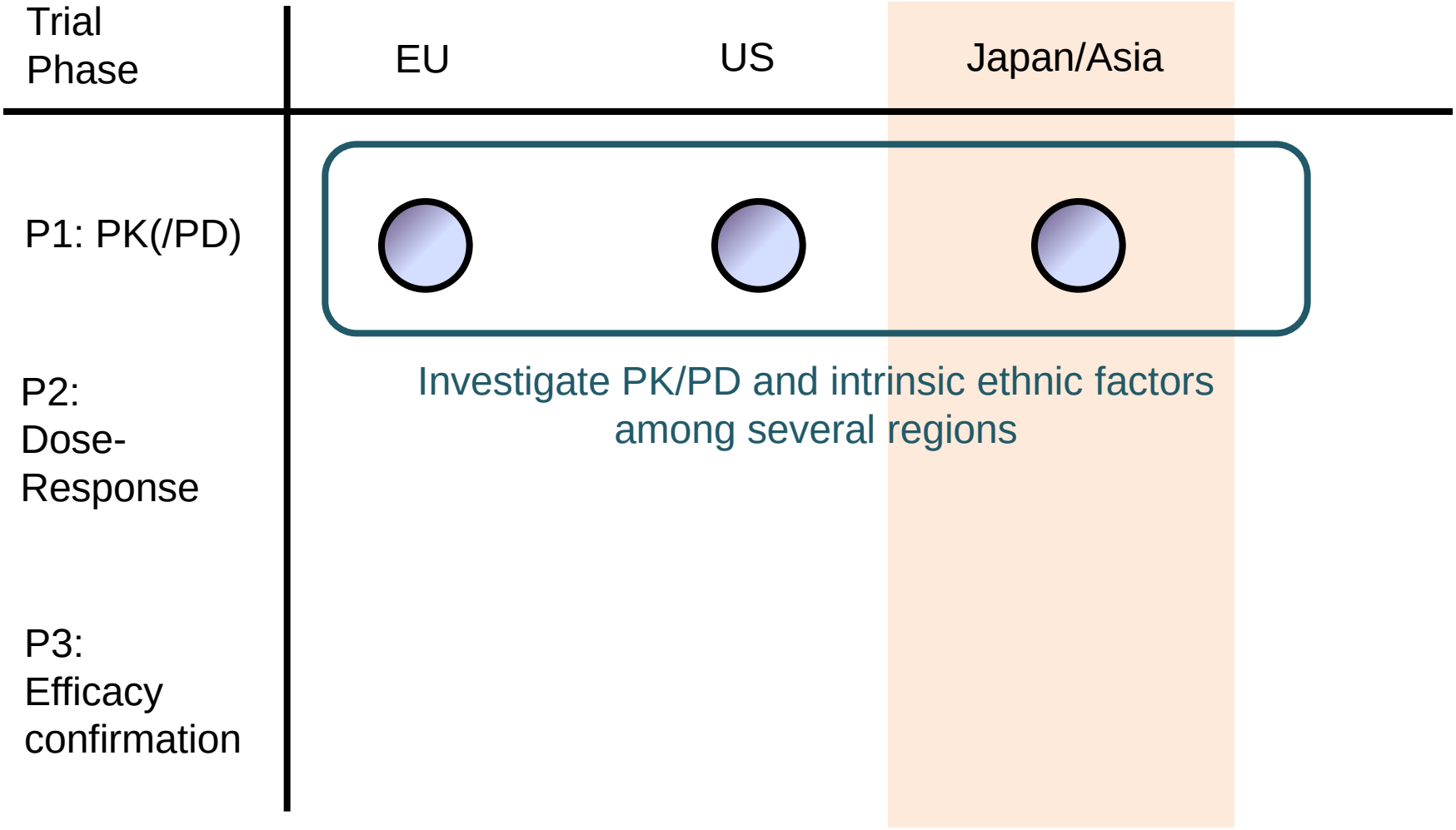
Regional data in global development

- In Japanese new drug review, the information on efficacy and safety in Japanese subjects is considered important.
- Why are we interested in regional results in Japan?
  - There were many cases approved with different recommended dose compared to other regions.
  - In some cases, dose-response relationship shown in the bridging study was different from that in the corresponding study.
- These experiences and ideas are also useful in other East Asian regions.

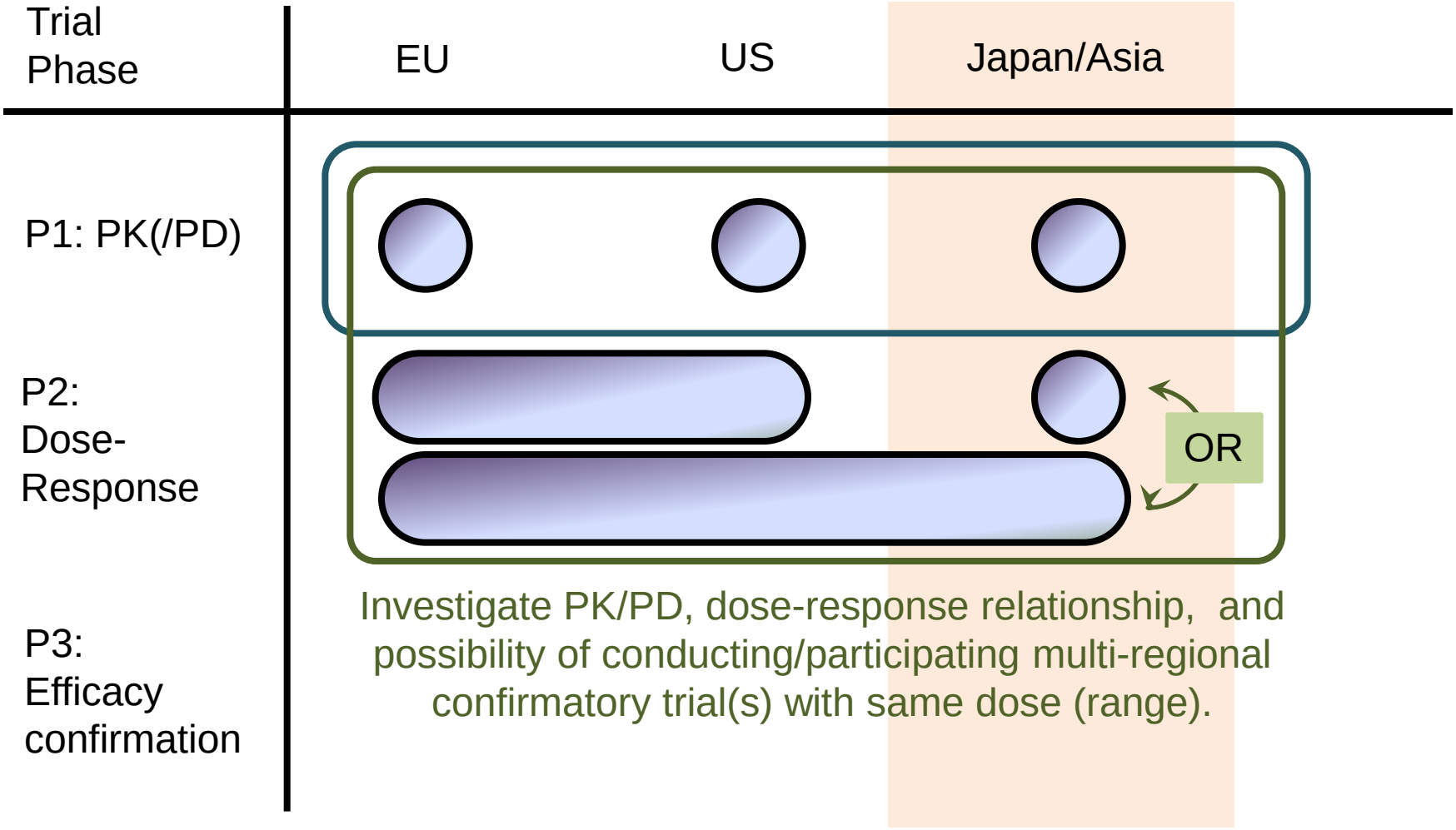
Regional data in global development

- How should we handle the possibility of regional difference in global simultaneous drug development?

A model of global drug development



A model of global drug development



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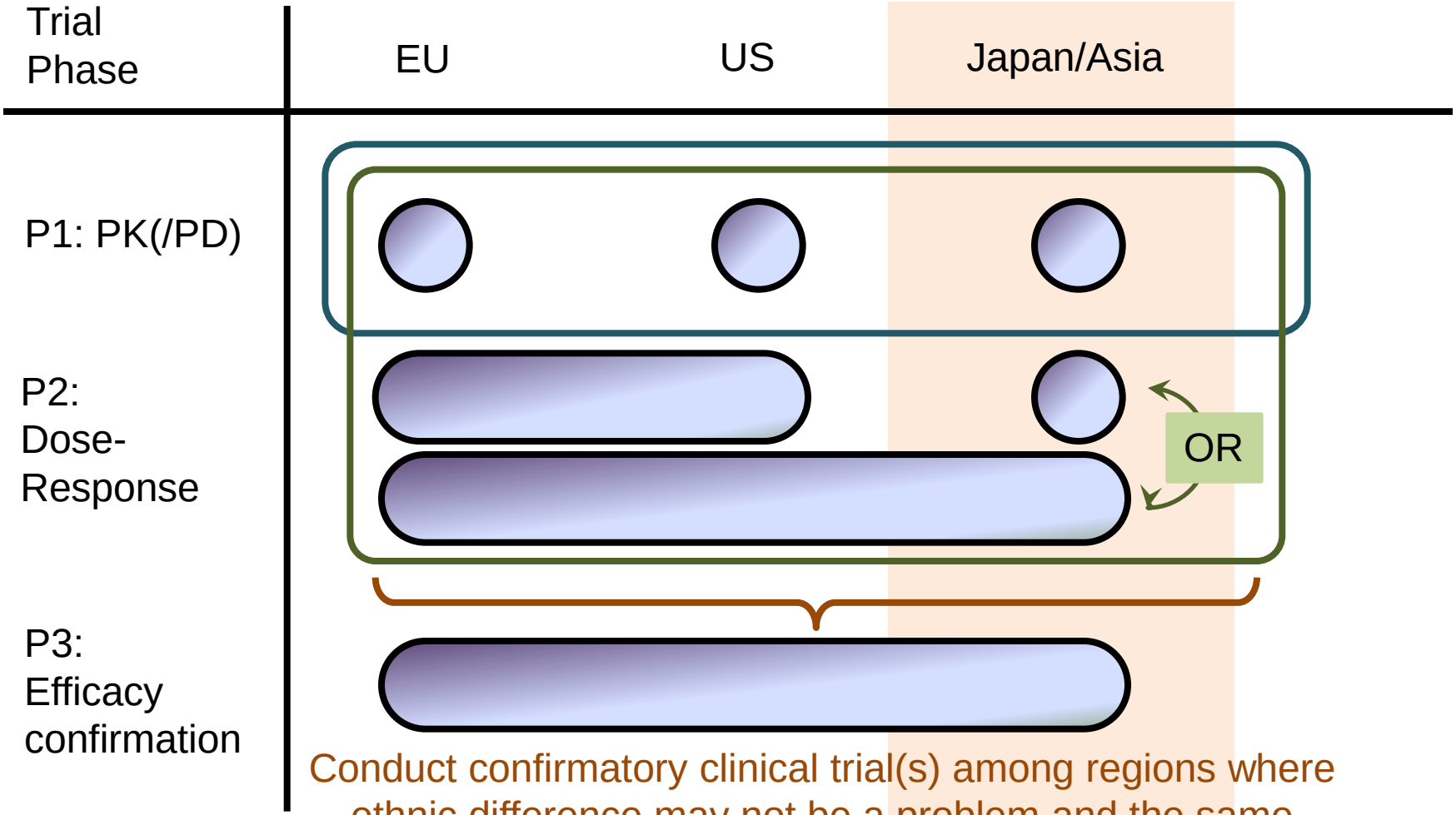
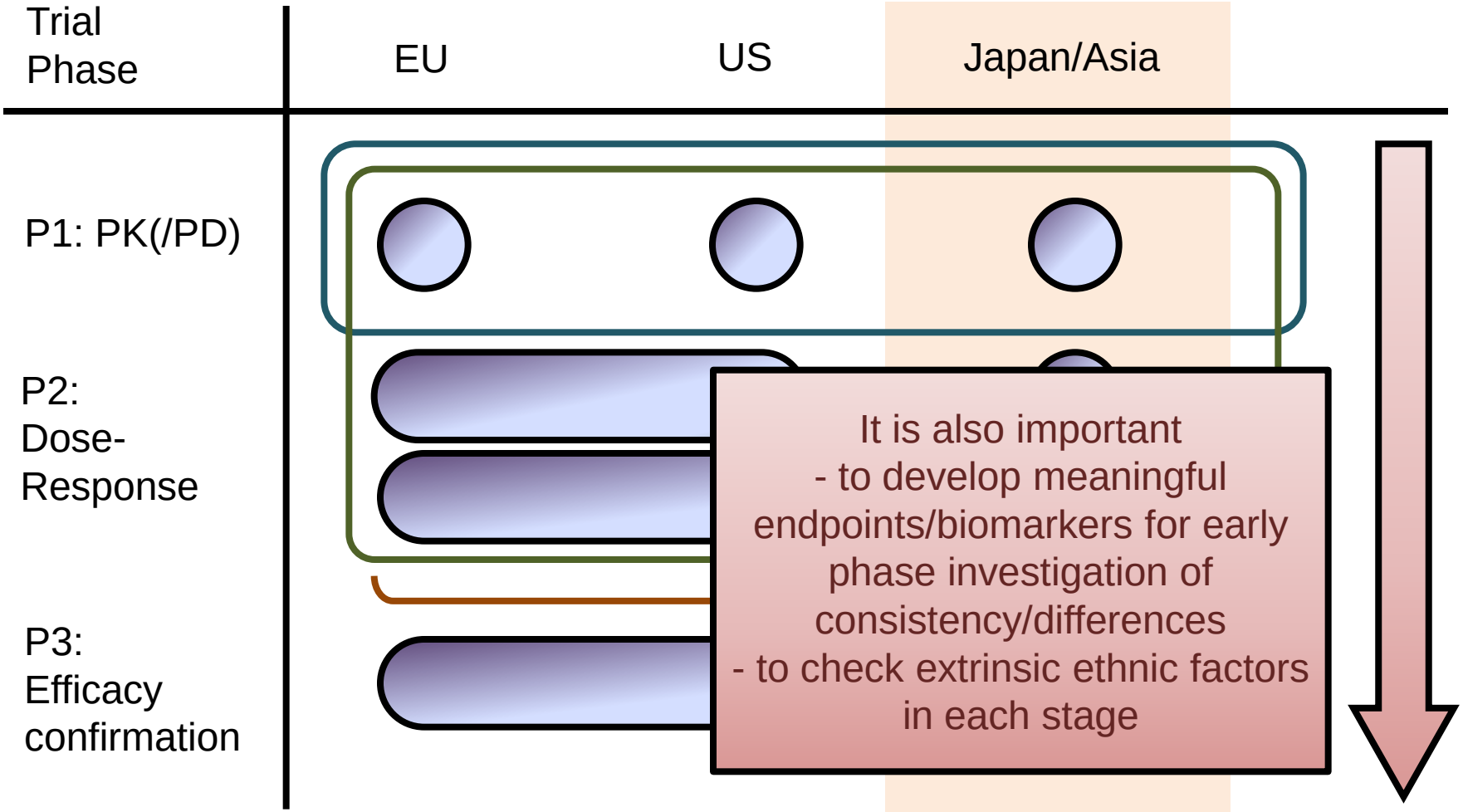


Conduct confirmatory clinical trial(s) among regions where ethnic difference may not be a problem and the same dose (range) can be used

A model of global drug development



Expectation for global development

- Step-by-step consideration is important
  - To select the best way to have sufficient data for all regions under the possibility of regional differences
  - To avoid eventual duplication of clinical data based on the evidence
- Investigating East Asian data may be the key in confirming appropriate doses for Asian population and to establishing good foundation of global study including Asian regions.

Japan's experience

- In Japan, we use foreign data based on the ICH E5 guidance document, its supplemental Q&A, and "Basic Principles on Global Clinical Trials" by MHLW
  - Conducting bridging study in Japan
  - Participating in multi-regional clinical trials (MRCTs)
- We have more than ten cases of approved new drug applications with multi-regional clinical trials as confirmatory trials

Approved cases with MRCTs

Name of Drug	Indication	Approval
Tolterodine	Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency	Apr. 2006
Losartan	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
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	Nov. 2010
Dabigatran	Stroke and systemic embolism in patients with non-valvular atrial fibrillation	Jan. 2011
Trastuzumab	HER-2 positive metastatic gastric cancer	Feb. 2011

Evaluation of MRCTs

- Results of late stage MRCTs are evaluated basically according to the standard procedure.
  - Checking prior information
  - Checking subject characteristics
  - Evaluation of the results
    - Results of primary analysis
    - Results of secondary analyses
- However, the regional results and the factor “region” are focused on.

Evaluation of late phase MRCTs -1

- Checking prior information
  - Information on the possibility of ethnic difference
    - Disease characteristics
    - Mechanism of the drug and information on similar drugs
  - Information from the early-phase clinical trials
    - PK/PD, dose-response
  - Relationship between the endpoints in each phase

Evaluation of late phase MRCTs -2

- Checking subject characteristics
  - Distribution of factors
- Evaluation of the results for all subjects
  - Whether the primary objective was achieved
- Evaluation of subgroup analyses
  - By region = Evaluation of the results for Japanese subjects (in Japan) and the consistency of the results among regions
  - By other factors

Evaluation of late phase MRCTs -3

- Comparison of results for Japanese subjects against results for all subjects
  - Sample size and variability of the results for the subgroup
  - Differences in patient characteristics
  - Possibility of regional differences
  - Implications of differences

  Whether the results of the MRCT can be regarded as the evidence for Japanese population?

Statistical consideration

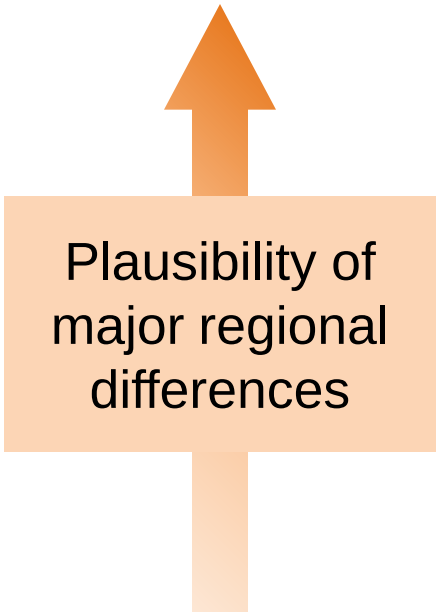
- We need a statistical aspect to the evaluation of the study plan and the results of late-stage multi-regional clinical trials.
  - Sample size estimation for one region
  - Statistical analysis of the results of one region
- Two methods for sample size estimation are mentioned in Japanese guidance as examples.
  - However, there is no generally recommended statistical methods.

Statistical consideration

- Basically, late stage MRCTs are planned on the assumption that there are no major ethnic difference among the participating regions.
- The selection of the statistical methods may possibly depend on the plausibility of regional differences and sufficiency of the early clinical data.

Selection of analysis methods

- Analysis methods
  - A certain level of statistical test for the results of one region
  - (Comparison of point estimates of the results among regions)
  - Evaluation of the impact of the results of one region in the trial
  - Checking possible variability of the results of one region



- The methods for sample size estimation basically correspond to the analysis methods

Emerging topics

- Model-based drug development
  - MBDD may be useful for planning efficient development program that takes the possibility of ethnic differences into consideration
- Interim analysis and adaptive design
  - Patient recruitment speed by regions and timing of interim analysis should be considered

Ongoing and future tasks

- China-Japan-Korea tripartite project
  - To investigate ethnic difference/similarity within East Asia
  - To make a solid foundation for the possibility of extrapolating data from one region to others in East Asia
- Recommendation of efficient global drug development in PMDA consultation meetings
  - To select efficient combination of regional and multi-regional data from early stage of the development

Summary

- For efficient global drug development,
  - It is important to collect sufficient data about ethnic sensitivity and evidence of the efficacy and safety of the drug.
  - There are many options for development strategy, such as multi-regional clinical trials, and it is important to choose one of them based on the accumulated data.
  - Step-by-step generalization of the data is reasonable.
  - East Asian collaboration may accelerate generalization of clinical data and lead to more efficient development.

Thank you for your attention!

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  - Dr. Yoshiaki Uyama

- Information
  - Email: ando-yuki@pmda.go.jp
  - PMDA Homepage (English)
    - http://www.pmda.go.jp/english/index.html
  - PMDA Drug Information (Japanese)
    - http://www.info.pmda.go.jp/