Regulatory perspective to review MRCT data for drug approval: Focusing on ethnic factor evaluation

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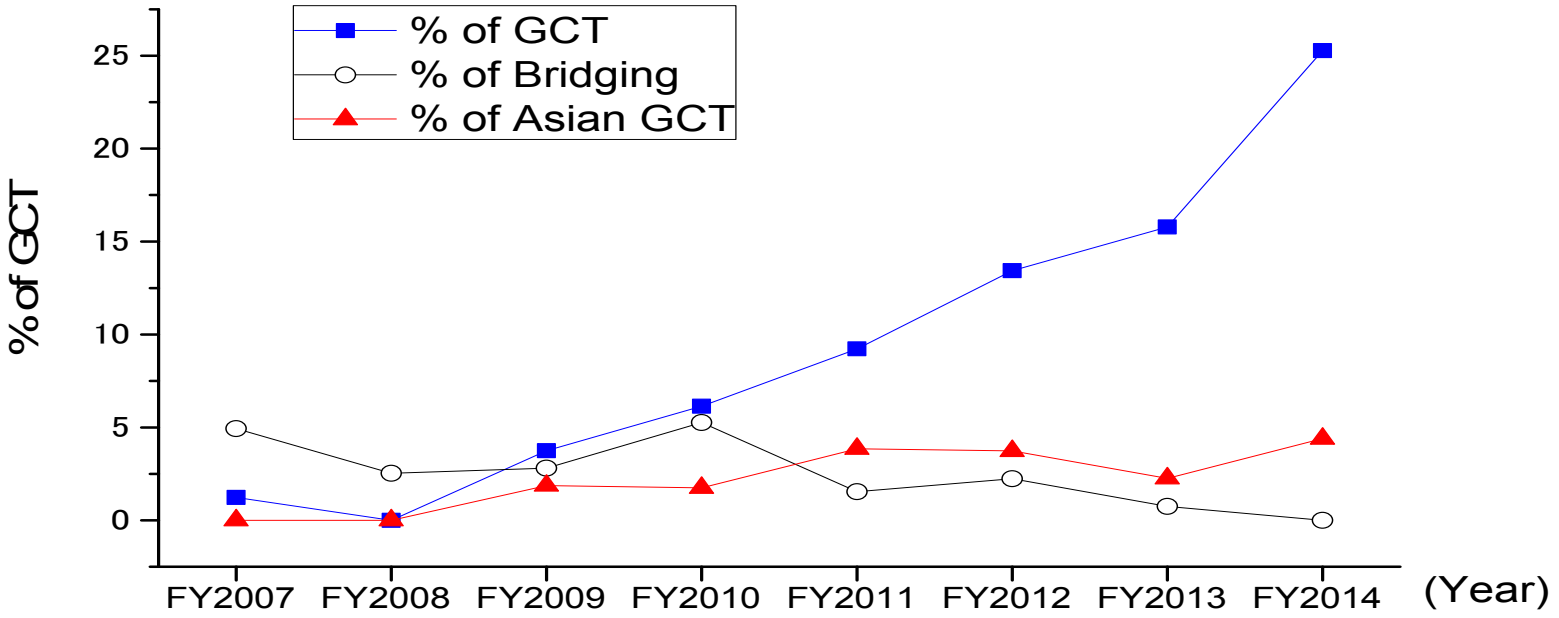
Drug Approval Based on Global Clinical Trials



As of Dec

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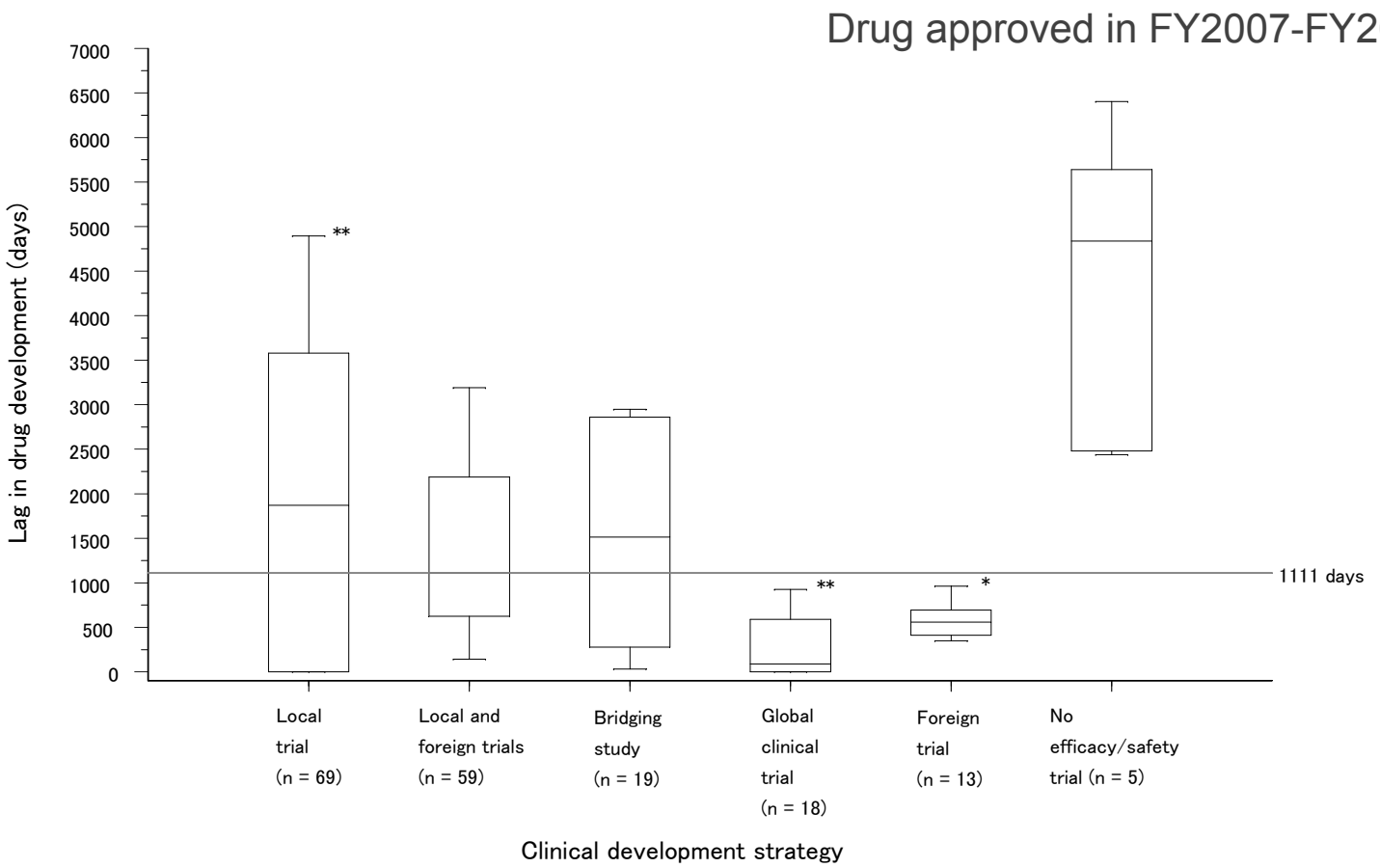
Conduct of MRCT has contributed to decreasing “Drug Lag”



Ueno T et al, Clin Pharmacol Ther, 95, 533-41 (2014)

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Recent experiences to review MRCT data for regulatory approval

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Suvorexant: Product Overview

- Approval: September 2014
- New active ingredient (an orexin receptor antagonist) indicated for the treatment of insomnia
- Phase II and Phase III was conducted as GCT
  - Phase II:
    - Japan and US, n=254
  - Phase III:
    - 16 countries (Japan, US , Australia, Brazil, Canada, France, Denmark, Germany, Spain etc.)
    - n=1022

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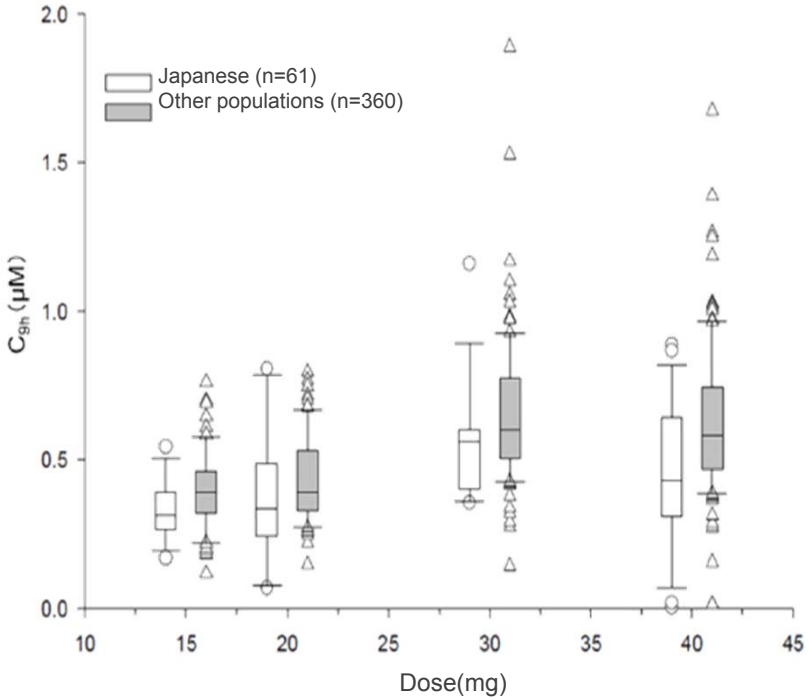
Pre-consideration about ethnic factors



- Intrinsic factors
  - There was no major differences in PK data between Japanese and other populations
- Extrinsic factors
  - Common diagnostic criteria in all regions
  - No major differences on medical treatment for insomnia
  - Training to ensure inter-rater reliability

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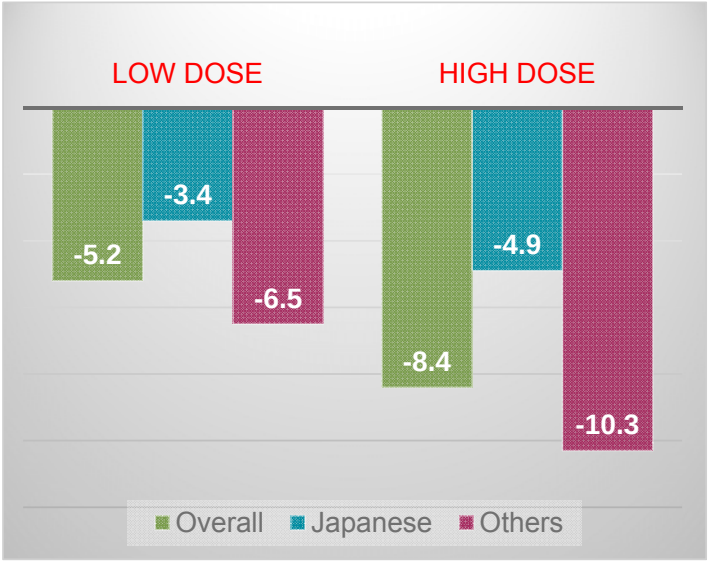
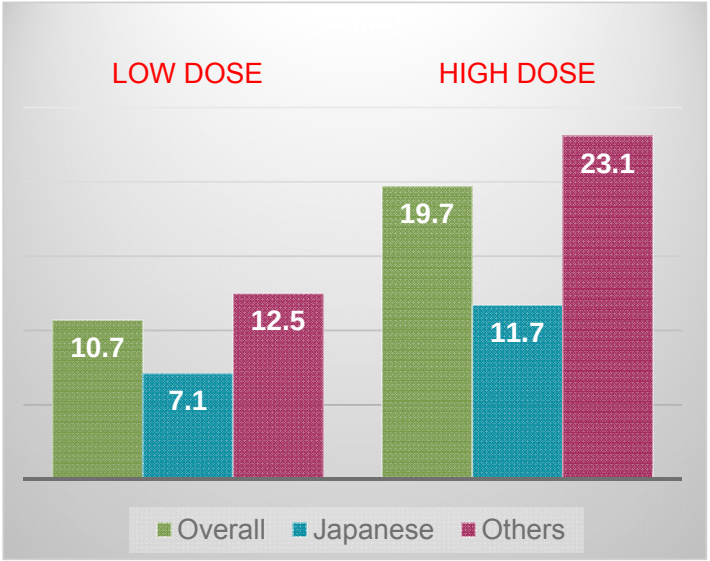
Efficacy: Phase III trial

sTSOm (3M)
Differences from placebo



sTSTm (3M)
Differences from placebo



Overall: n=915
Japanese: n=226

sTSOm: Subjective time to sleep onset (min.)
sTSTm: Subjective total sleep time (min.)

Relatively small effects in Japanese,
but improvement tendency was consistently found in all conditions

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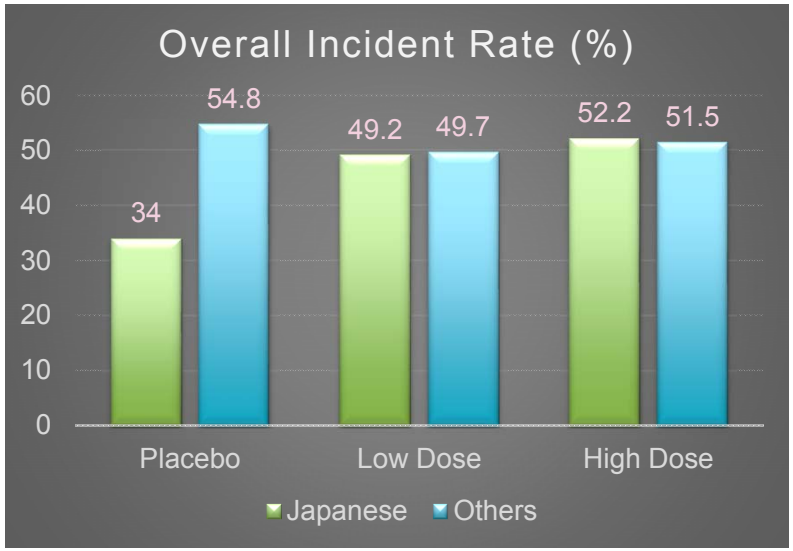
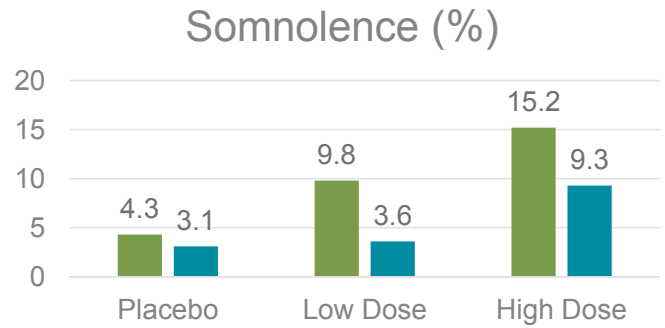
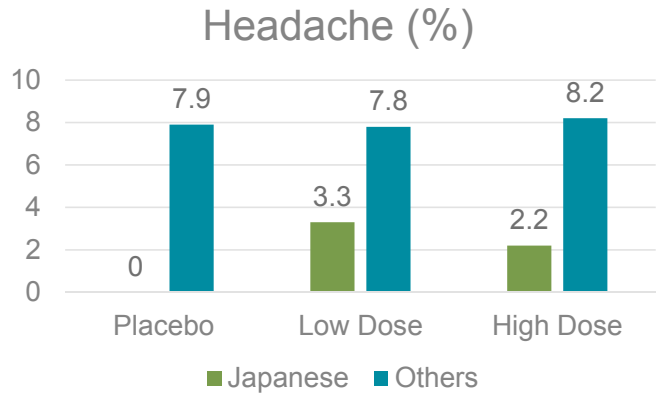
Safety







- Similar safety profiles
- Different incident rate was observed in some events, but most of them were mild

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MRCT Data Review Experiences

- Extrinsic ethnic factors such as concomitant therapies sometimes have impacts on data evaluation
- PPK data are useful for ethnic factor consideration
- Consistency evaluation approach following to confirming efficacy in overall population is beneficial.
  - limitation in evaluating data when sample size was small
- Differences in adverse event rate are not uncommon; partly due to difference on categorization or data collection process of adverse events in GCTs
- Ethnic factor consideration is important even in Asian GCTs

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Recent scientific advances on impacts of ethnic factors in drug responses

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Ethnic Similarities

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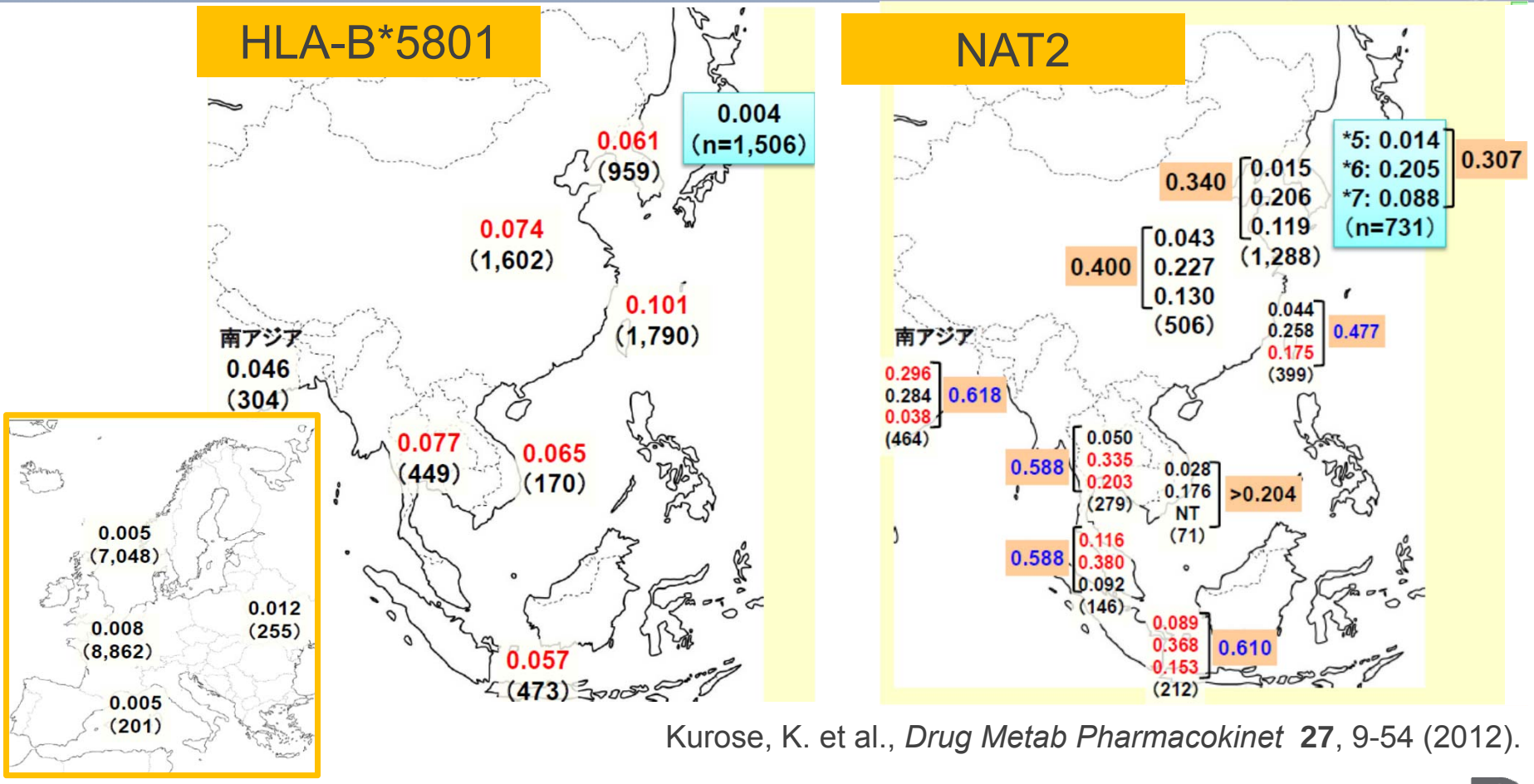
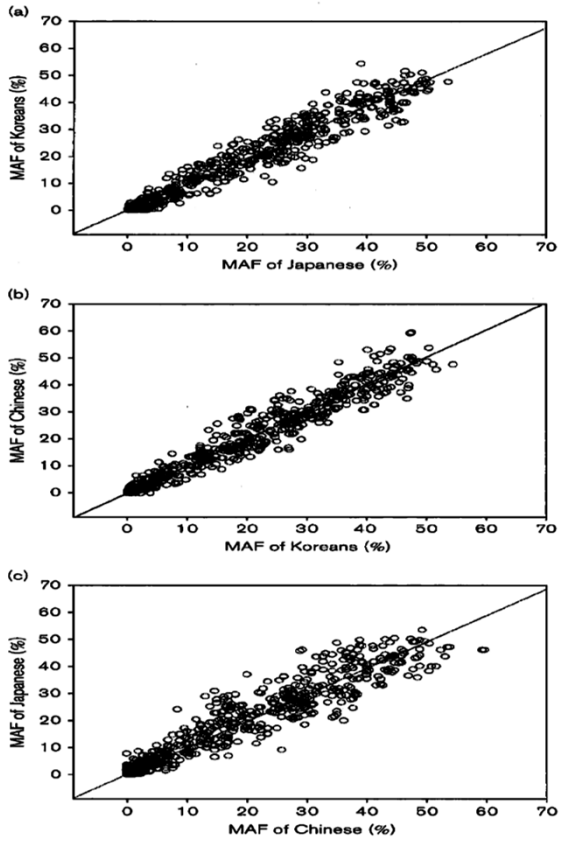
Genetic similarities/differences among Asian populations



Kurose, K. et al., *Drug Metab Pharmacokinet* **27**, 9-54 (2012).

Genetic similarities among East-Asian populations



Correlation of minor allele frequencies between population

- The frequencies of 1936 variants representing 225 genes encoding drug-metabolizing enzymes and transporters were determined from 786 healthy participants (448 Korean, 208 Japanese, and 130 Chinese)
- No major ethnic differences among Chinese, Korean and Japanese populations

Yi, S. et al. Pharmacogenetics and Genomics 24, 477-85 (2014).

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Ethnic differences

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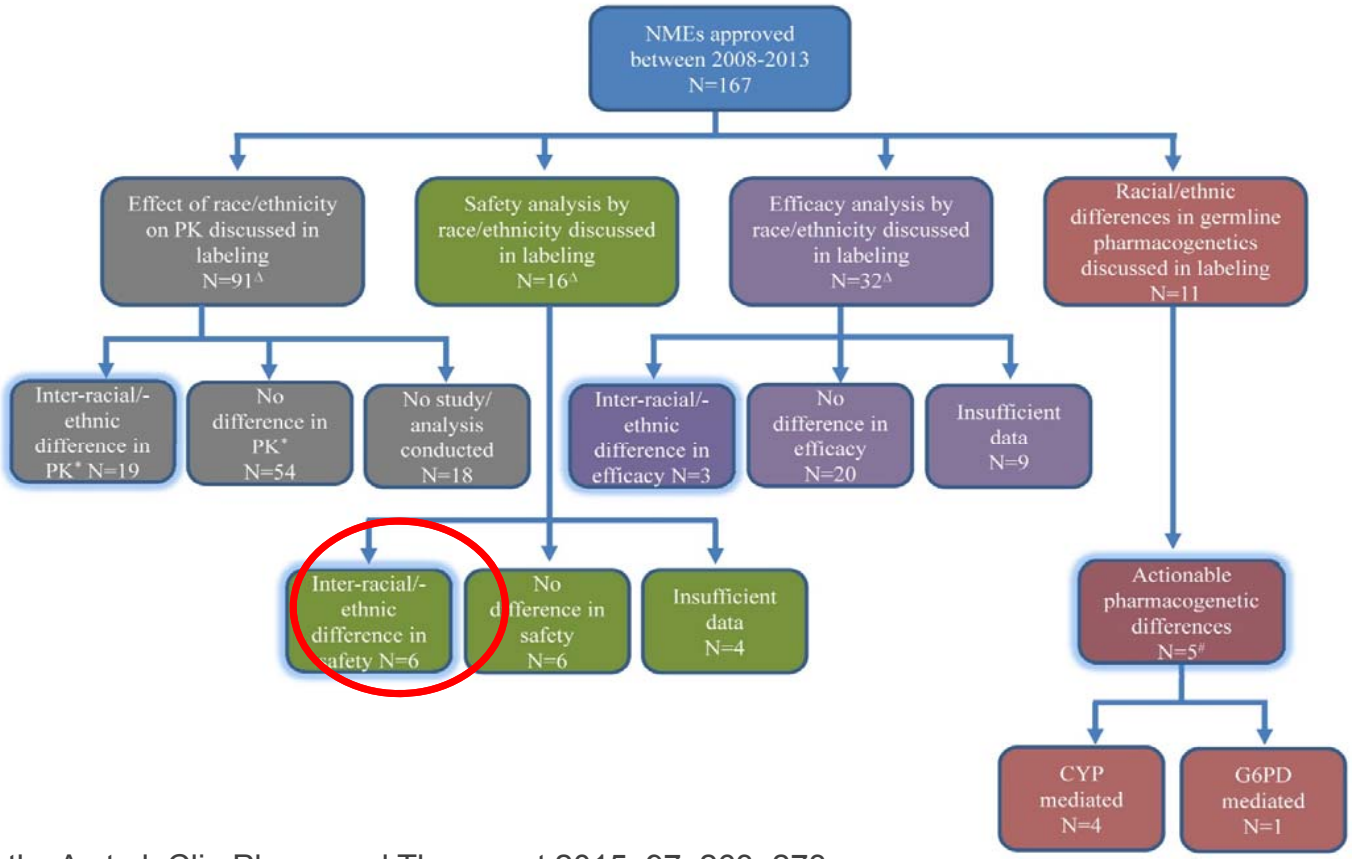
Ethnic sensitivities on US-approved drugs



Ramamoorthy A et al. Clin Pharmacol Therapeut 2015; 97: 263–273

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Example; Ethnic difference on PK and safety -US drug label-

Generic name	PK	Efficacy/Safety	Approved dose: US/Japan
Afatinib (NSCLC)	No major difference on PK	Incidence of interstitial lung disease Asian (2.1%) > non-Asians (1.2%).	40mg/40mg
Eltrombopag olamine (thrombocytopenia)	East Asian 50-55% higher > non-East Asian	A reduction in the initial dose is recommended for East Asian patients More reduced dose in East Asian patients with hepatic impairment.	50mg/12.5mg
Simeprevir (Anti-viral, HCV infection)	Asian 3.4-fold higher > Caucasians.	Higher simeprevir exposures have been associated with increased frequency of adverse reactions, including rash and photosensitivity.	150mg/100mg

Modified from the article by Ramamoorthy A et al. Clin Pharmacol Therapeut 2015; 97: 263–273

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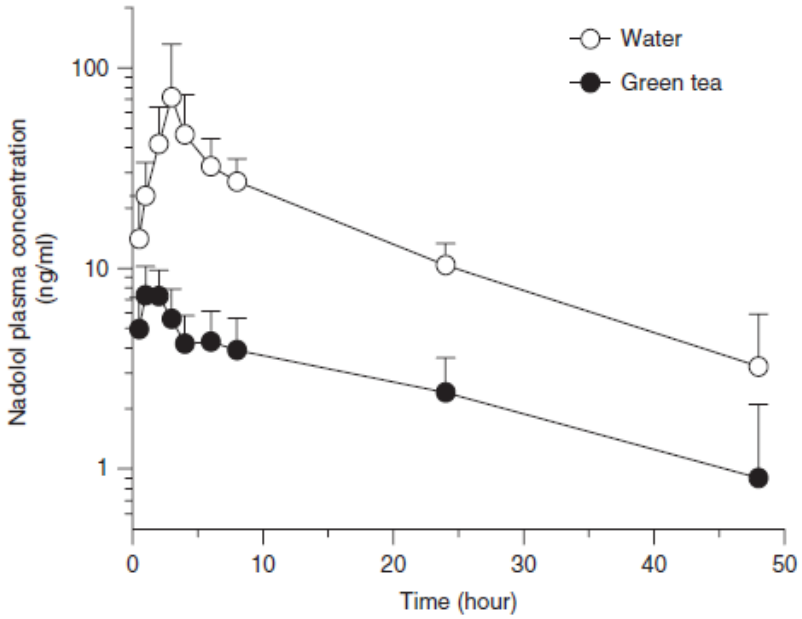
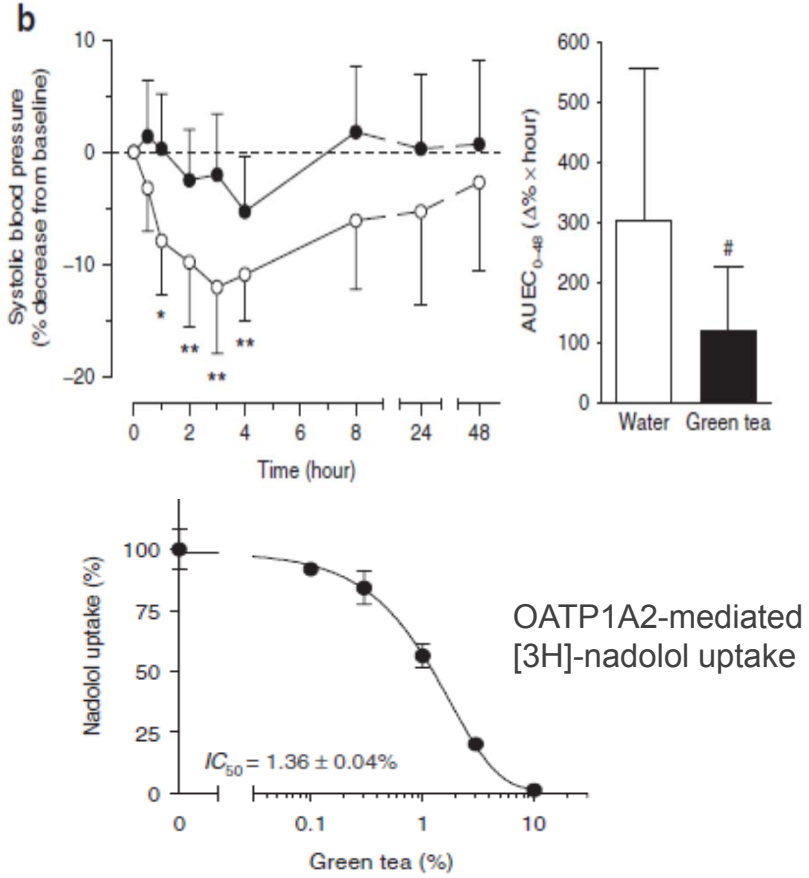
Effects of Green Tea on β-blocker, nadolol responses





OATP1A2-mediated [3H]-nadolol uptake

Misaka, S. et al. Clin Pharmacol Ther 95, 432-8 (2014).

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Toward Regulatory Harmonization
-ICH E17 guideline-

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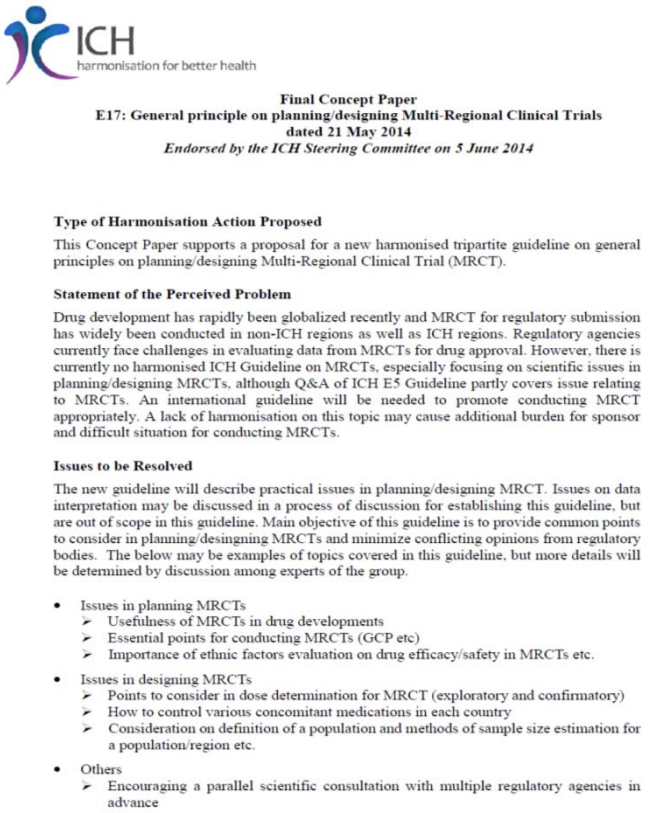
ICH E17 Guideline: MRCTs

General principle on planning/designing Multi-Regional Clinical Trials



ICH
harmonisation for better health

Final Concept Paper
E17: General principle on planning/designing Multi-Regional Clinical Trials
dated 21 May 2014
Endorsed by the ICH Steering Committee on 5 June 2014

Type of Harmonisation Action Proposed

This Concept Paper supports a proposal for a new harmonised tripartite guideline on general principles on planning/designing Multi-Regional Clinical Trial (MRCT).

Statement of the Perceived Problem

Drug development has rapidly been globalized recently and MRCT for regulatory submission has widely been conducted in non-ICH regions as well as ICH regions. Regulatory agencies currently face challenges in evaluating data from MRCTs for drug approval. However, there is currently no harmonised ICH Guideline on MRCTs, especially focusing on scientific issues in planning/designing MRCTs, although Q&A of ICH E5 Guideline partly covers issue relating to MRCTs. An international guideline will be needed to promote conducting MRCT appropriately. A lack of harmonisation on this topic may cause additional burden for sponsor and difficult situation for conducting MRCTs.

Issues to be Resolved

The new guideline will describe practical issues in planning/designing MRCT. Issues on data interpretation may be discussed in a process of discussion for establishing this guideline, but are out of scope in this guideline. Main objective of this guideline is to provide common points to consider in planning/desingning MRCTs and minimize conflicting opinions from regulatory bodies. The below may be examples of topics covered in this guideline, but more details will be determined by discussion among experts of the group.

- Issues in planning MRCTs
  - Usefulness of MRCTs in drug developments
  - Essential points for conducting MRCTs (GCP etc)
  - Importance of ethnic factors evaluation on drug efficacy/safety in MRCTs etc.
- Issues in designing MRCTs
  - Points to consider in dose determination for MRCT (exploratory and confirmatory)
  - How to control various concomitant medications in each country
  - Consideration on definition of a population and methods of sample size estimation for a population/region etc.
- Others
  - Encouraging a parallel scientific consultation with multiple regulatory agencies in advance

- ✓ E17 EWG: established in June 2014
  - ✓ Rapporteur: PMDA
- ✓ Provide common points to consider in planning/designing MRCTs and minimize conflicting opinions from regulatory bodies.

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Current table of contents (E17)

1. INTRODUCTION
   - 1.1 Objective(s) of the Guideline
   - 1.2 Background
   - 1.3 Scope of the Guideline
   - 1.4 General Principles
2. General recommendations in planning/designing MRCT
   - 2.1 Strategy-related points
     - 2.1.1 The value of MRCTs in drug development and regulatory approval
     - 2.1.2 The basic requirements to conduct a MRCT
     - 2.1.3 Scientific consultation meeting with regulatory agencies

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Current table of contents (E17)

2. General recommendations in planning/designing MRCT
   - 2.2 Clinical trial design and protocol-related points
     - 2.2.1 Pre-consideration of regional variability on efficacy/safety
     - 2.2.2 Subject selection
     - 2.2.3 Selection of doses in MRCTs
     - 2.2.4 Choice of endpoint/index
     - 2.2.5 Estimation of a sample size and a proportion of each regional subjects in an MRCT
     - 2.2.6 Collecting and handling efficacy/safety information in MRCTs
     - 2.2.7 Statistical analysis plans that specifically address the features of MRCTs
     - 2.2.8 Selection of comparator (where applicable)
     - 2.2.9 Handling concomitant medications or therapies in a MRCT
3. GLOSSARY

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Current Timeline of the E17 guideline

- First face-to-face EWG Meeting in November 2014 in Lisbon
- Discussion by e-mail and web-based conference: 4Q 2014 - 1Q 2015
- Second F2F EWG Meeting in 2Q 2015 for coordinating opinions of all parties and delivering Step 1 document
- Third F2F EWG meeting in 4Q 2015 for adaption of *Step 2* document
- Public consultation: 4Q 2015 - 2Q 2016
- Revision of the guideline based on comments: 2Q 2016 - 4Q 2016 (depending on contents of comments recieved)
- Fourth face-to-face EWG Meeting for adaption of *Step 4* document in 4Q 2016 or 2Q 2017

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Conclusion

- More regulatory experiences to review MRCT data facilitate our understanding regarding impacts of ethnic factors on drug efficacy/safety

- More scientific data promote international harmonization on regulatory requirements for drug approval based on MRCT data

International cooperation for providing more drugs earlier to patients

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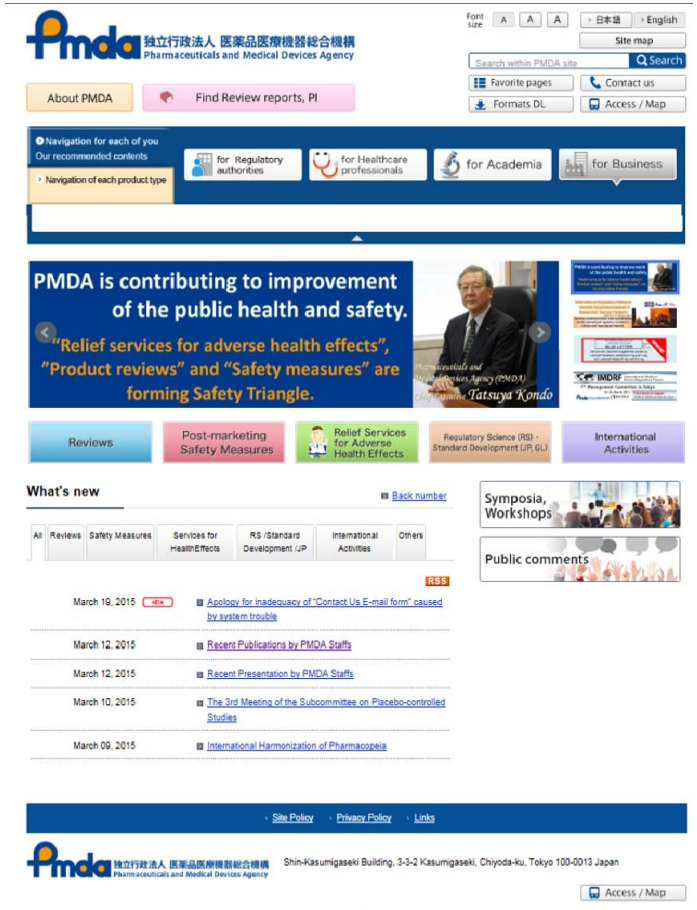
Information



all new!

- **PMDA web site (English)**
  http://www.pmda.go.jp/english/index.html
- **E-mail:**
  uyama-yoshiaki@pmda.go.jp

Thank you for your attention

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Ask