



# Regulatory Interactions with Asia

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Lars Endahl, MSc, PhD, EMM  
Senior Principal Statistician  
Novo Nordisk A/S

# Disclaimer



The views expressed in this presentation represent those of the presenter and not necessarily Novo Nordisk or any regulatory authority

# My experience with regulatory interactions in Asia

- International Project Statistician for various projects
  - Therapeutic areas:
    - diabetes
    - obesity
- Participated in regulatory interactions with regulatory authorities all over Asia
  - e.g. Japan, China, South Korea, India, Taiwan, Malaysia, Singapore, Indonesia etc.
- Most frequent interactions/consultations in Japan and China

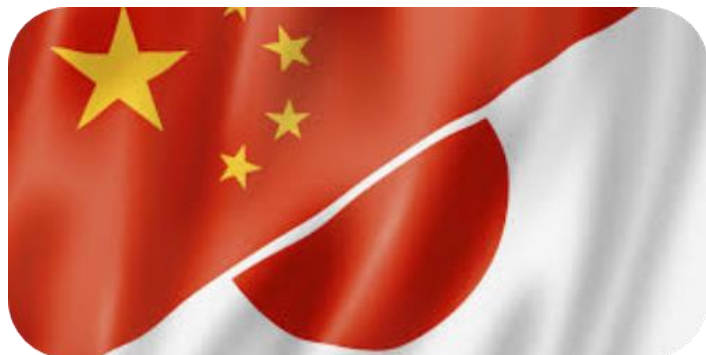


# Regulatory consultations in Japan and China

- Face to face consultations in
  - Tokyo: 2004, 2008, 2009, 2010, 2011, 2014, 2015, 2017
  - Beijing: 2005, 2006, 2014, 2016
  - Some years with more than one consultation



# Scope of the presentation



- Discuss statistical issues in the regulatory interactions with Japan and China
  - Strategy for development program
  - Japan/China as part of a global trial
  - Differences in clinical practice
  - Sample size considerations

# Regulatory authorities in Japan and China



PMDA: Pharmaceuticals and Medical Devices Agency

- Founding member of ICH



CFDA: China Food and Drug Administration

- not yet a member/observer of ICH

# Traditional drug development in China

## Import Drug Licensing (IDL) approach



US/EU program



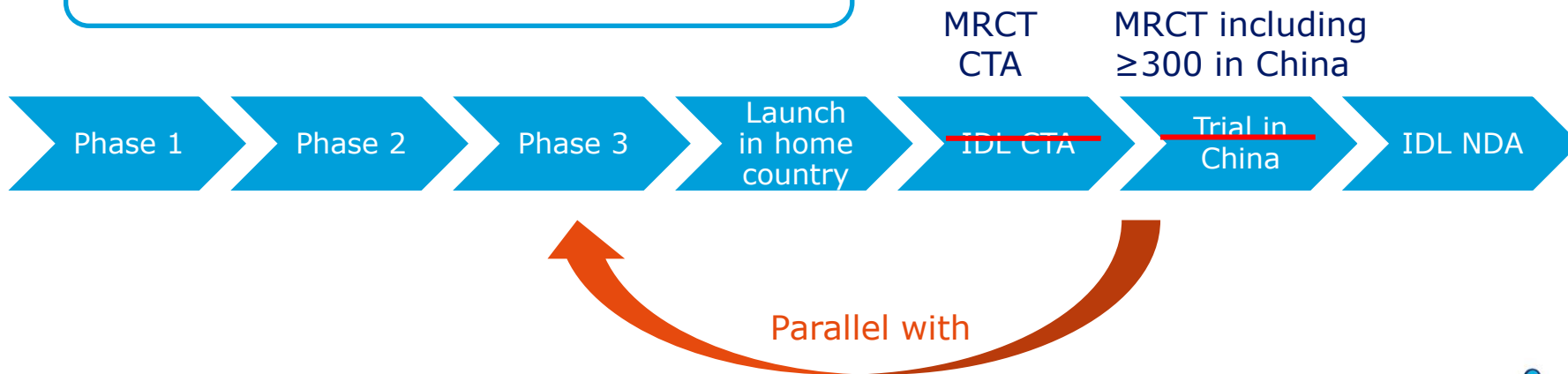
CTA: Clinical Trial Application

# New option in China

## MRCT-backed IDL approach



US/EU program



MRCT: Multi Regional Clinical Trial  
CTA: Clinical Trial Application



## China Healthcare: CFDA proposal to accelerate approval for MNCs' imported drugs

17 March 2017 | 4:06PM HKT

**What's New** - The China Food and Drug Administration (CFDA) today released a proposal regarding a policy to accelerate the approval of imported drugs, aiming to shorten the delay in launching global new drugs in China, and thus to better address Chinese patients' demand for the most advanced therapies available.

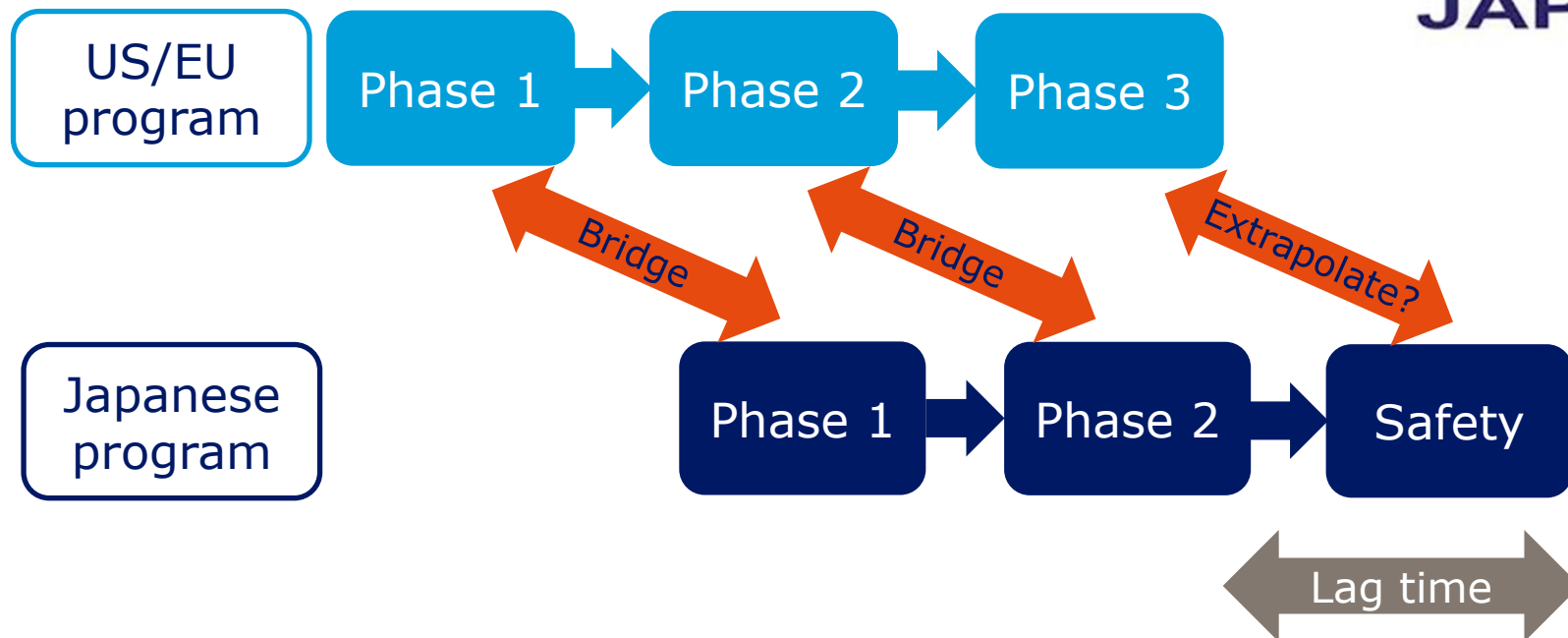
MNC: Multi National Company

For global multi-center clinical trials conducted in China, the investigational drugs don't have to already be registered or at phase 2/3 trials in overseas markets, i.e. more early-stage trials could be conducted in China;

For importing novel drugs, China could be the first market globally for new product launches (previously must be approved in the overseas market first); and

# Traditional drug development in Japan

## Bridging strategy (cf. ICH-E5)



# New option in Japan

## Include Japan as part of the global program



Opportunities	Challenges
Faster approvals	Intrinsic or extrinsic factors may influence effect and safety
May decrease development costs	Determine number of Japanese subjects in global program
Increase diversity in exposure across races	Assessments/clinical practice may differ between regions

# Check list of statistical issues for a regulatory consultation in Japan or China

- Same inclusion criteria as in EU/US?
- Differences in clinical practice?
- Assessments the same in Japan/China as elsewhere?
- Selected comparator relevant in Japan/China?
- Number of Japanese/Chinese subjects for a specific MRCT?
- Exposure in Japan/China across all phase 3 trials ?
- Dealing with missing data?
- Confirmatory endpoints relevant in Japan/China?
  - Confirmatory in the sense of being controlled for multiplicity



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# Differences in clinical practice

## Example: treatment of overweight and obesity

US/EU	Japan	China
Overweight: <ul style="list-style-type: none"><li>BMI &gt; 27 kg/m<sup>2</sup> with comorbidities</li></ul>	Obesity disease: <ul style="list-style-type: none"><li>BMI &gt; 25 kg/m<sup>2</sup> with ≥ 2 comorbidities and visceral fat area (VFA) ≥ 100 cm<sup>2</sup></li></ul>	Overweight: <ul style="list-style-type: none"><li>BMI &gt; 24 kg/m<sup>2</sup> with comorbidities or excess weight circumference (men &gt; 85, women &gt; 80 cm)</li></ul>
Obesity: <ul style="list-style-type: none"><li>BMI &gt; 30 kg/m<sup>2</sup></li></ul>	Advanced obesity disease: <ul style="list-style-type: none"><li>BMI &gt; 35 kg/m<sup>2</sup> with ≥ 1 comorbidities and VFA ≥ 100 cm<sup>2</sup></li></ul>	Obesity: <ul style="list-style-type: none"><li>BMI &gt; 28 kg/m<sup>2</sup></li></ul>

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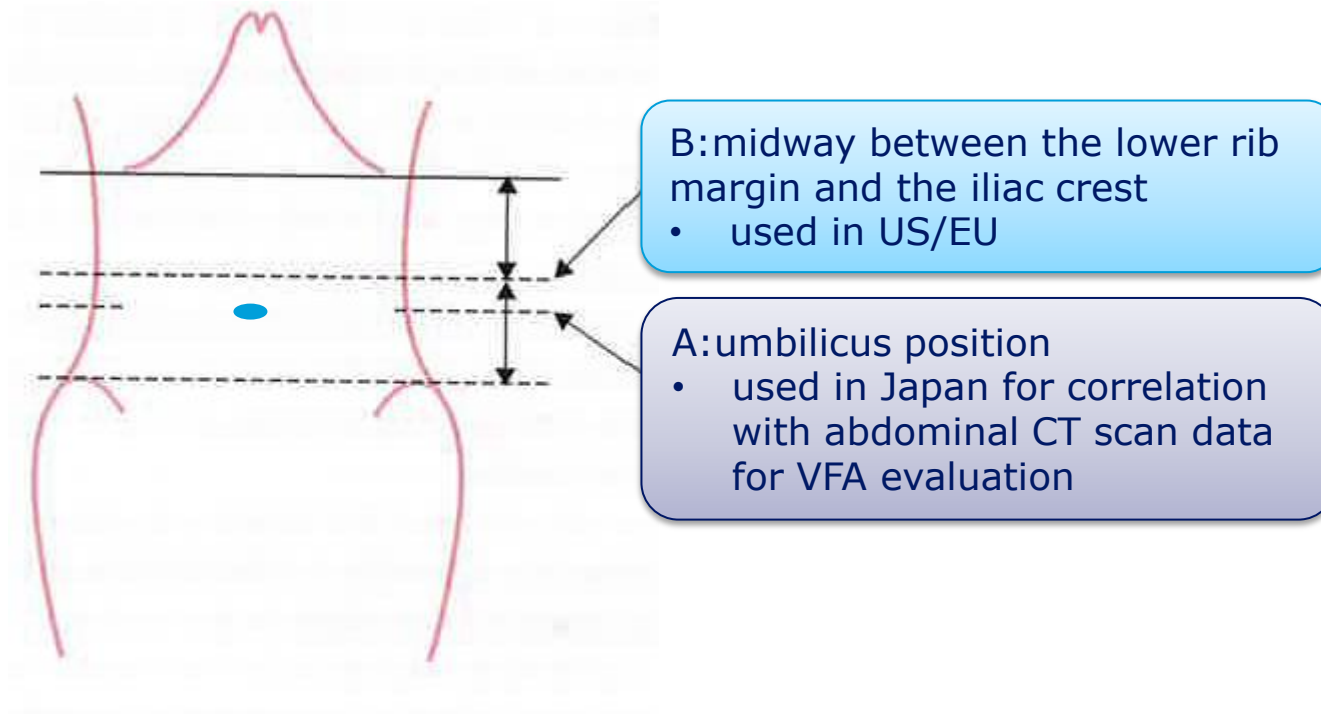
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# Differences in assessments

## Example: waist circumference



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# PMDA guidance 2007

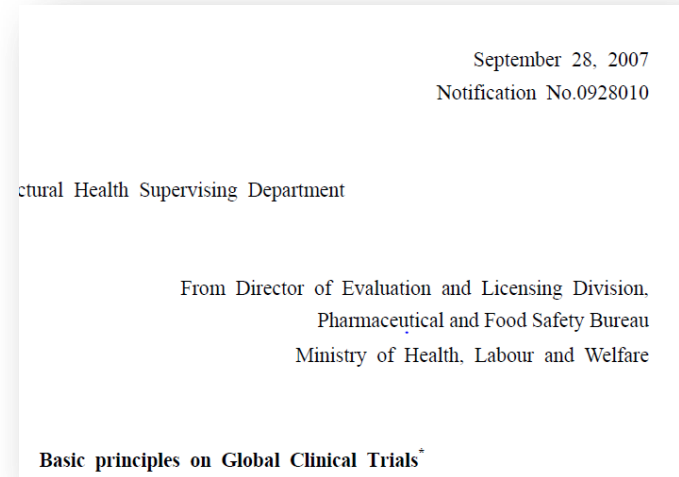
## Basic principles on global clinical trials



An MRCT has at least two main objectives:

- Show a significant benefit in effect of a new drug over placebo in the entire study population
- Demonstrate consistent results between the Japanese subpopulation and the entire population

“sufficient statistical power to detect statistically significant difference should not necessarily be secured within the Japanese subpopulation”



# Sample size considerations in Japan



- Two methods for evaluating number of Japanese subjects in an MRCT
- Not addressed in the guidance:
  - How to apply the two methods in non-inferiority settings
  - Total exposure in Japanese subjects needed for safety evaluation
- References:
  - PMDA (2007): Basic Principles in Global Trials
  - Kawai et al, 2008, Drug Information Journal; pp 139-147
  - Carroll & Le Maulf, 2011, Drug Information Journal; pp 657-677

# Methods for sample size calculations in Japan

## Method 1:

Retain at least half the treatment effect in Japanese subjects compared to entire trial population with more than 80% probability – if, in reality, the treatment effect is the same in Japan as in the entire trial

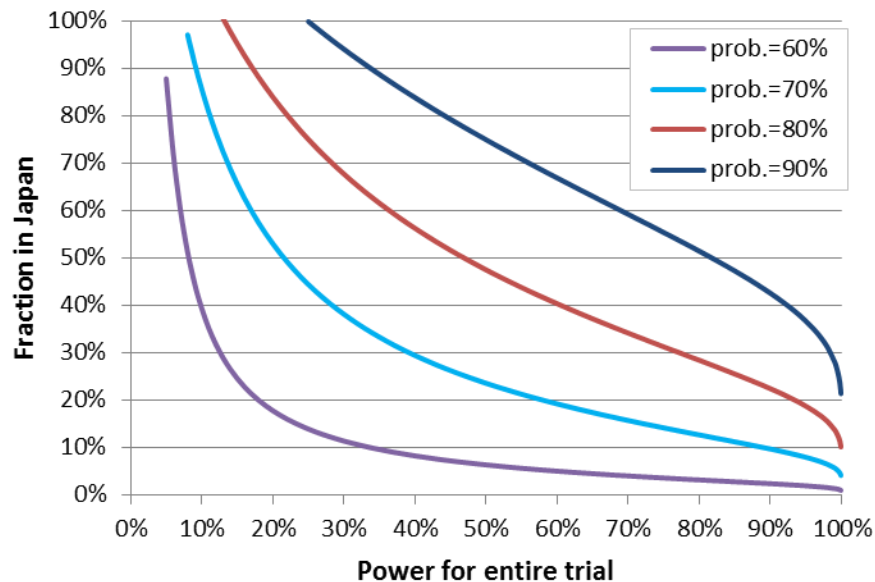
## Method 2:

Ensure that a treatment effect is observed in each geographic region with more than 80% probability – if, in reality, there is a treatment effect in the entire trial population, uniform across regions

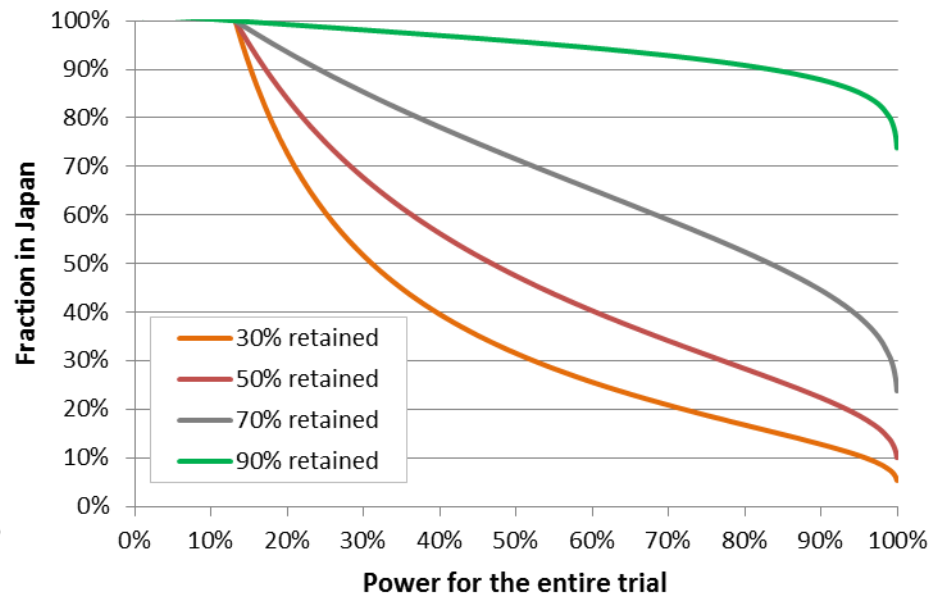
Sometimes the methods includes a condition that a significant effect has been observed in the entire trial, cf. Kawai et al (2008)

# Consequences of method 1 as a function of the power of entire trial

50% retained effect



80% probability

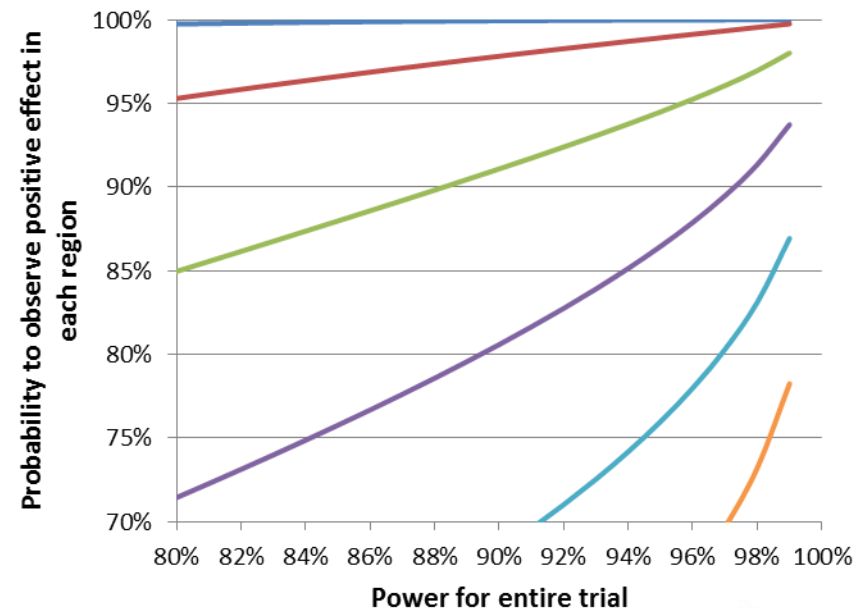
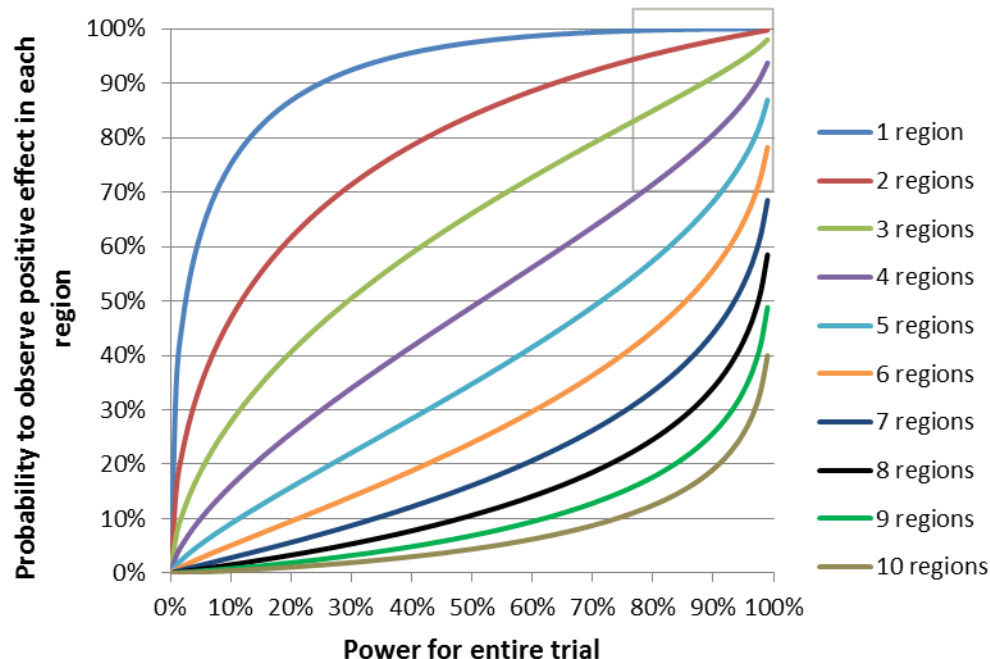


Two-sided significance level: 5%

# Consequences of method 1

- As a minimum the fraction of subjects recruited in must be at least 10% to retain at least 50% of the effect with more than 80% probability
- With 80% power in the entire trial the fraction of Japanese subjects must be at least 28%
- With 90% power in the entire trial the fraction of Japanese subjects must be at least 22%
- With 99.9% power in the entire trial the fraction of Japanese subjects must be at least 10%

# Consequences of method 2 when all regions contains the same number of subjects



Two-sided significance level: 5%



## Consequences of method 2

- Probability to observe treatment effect is maximized when splitting subjects equally between regions
- With 80% power in the entire trial up to 3 regions can be included
  - 33.3% subjects in each region gives a probability of 85.0%
- With 90% power in the entire trial up to 4 regions can be included
  - 25% subjects in each region gives a probability of 80.6%
- With 97% power in the entire trial up to 5 regions can be included
  - 20% subjects in each region gives a probability of 80.3%

# ICH-E17 on multi-regional clinical trials (MRCTs)

- Still in draft
- Discuss design issues for MRCTs
  - Non-inferiority margins
  - Stratification
  - Dose selection
  - etc.

“There are several approaches that could be considered for allocating the overall sample size to regions each with its own limitations, and a few are described...”

INTERNATIONAL CONCIL FOR HARMONISATION OF TECHNICAL  
REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

**GENERAL PRINCIPLES FOR PLANNING AND DESIGN  
OF MULTI-REGIONAL CLINICAL TRIALS**

**E17**

Current *Step 2* version

dated 6 May 2016

# Allocation approaches discussed in ICH-E17

“Determine the regional sample sizes needed to be able to show similar trends in treatment effects across regions”

- “may not be feasible or efficient in terms of enrolment and trial conduct”

“Determine the sample size needed in one or more regions based on the ability to show that the region-specific treatment effect preserves some pre-specified proportion of the overall treatment effect”

- “difficult if all regions have this requirement”

“Size and disease prevalence without adhering to a fixed allocation strategy for regions”

- “insufficient alone to support any evaluation of consistency among region specific effects”

# Allocation approaches discussed in ICH-E17

“Determine the regional sample sizes to be able to achieve significant results within one or more regions”

- “question the reasons for conducting MRCTs and should be discouraged”

“Require a fixed minimum number of subjects in one or more regions”

- “local safety requirement for minimum number of subjects to be exposed to the drug is generally a programme level consideration”

# Allocation approaches discussed in ICH-E17

“Sample size allocation should take into consideration region size, the commonality of enrolled subjects across regions based on intrinsic and extrinsic factors and patterns of disease prevalence, as well as other logistical considerations to ensure enrolment is able to be completed in a timely fashion”

# Final remarks

- Face-to-face consultations with PMDA and CFDA provide an excellent opportunity to discuss strategies for development and statistical issues to be addressed in that connection
- It seems likely that Japan and China by default will be fully integrated into a global clinical development program in the future
- Having Japan and China included in the same MRCT as EU and US (and possibly other countries) will require trials with very high power to allow for evaluation of consistency across regions



