

Sample Size Determination for a Specific Region in a Multi-regional Trial

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Outline

- Regulatory guidance
- Evaluation criteria
- Results

ICH (International Conference on Harmonisation) E5

Ethnic Factors in the Acceptability of Foreign Clinical Data

The purpose of this guidance is to facilitate the registration of medicines among ICH regions by recommending a framework for evaluating the impact of **ethnic factors** upon a medicine's effect, i.e., its efficacy and safety at a particular **dosage** and **dose regimen**.

Objectives of ICH E5

- **To describe the characteristics of foreign clinical data that will facilitate their extrapolation to different populations and support their acceptance as a basis for registration of a medicine in a new region**
- **To describe regulatory strategies that minimize duplication of clinical data and facilitate acceptance of foreign clinical data in the new region**
- **To describe the use of bridging studies, when necessary, to allow extrapolation of foreign clinical data to a new region**
- **To describe development strategies capable of characterizing ethnic factor influences on safety, efficacy, dosage, and dose regimen**

Bridging Study

A bridging study is defined as a supplemental study performed in the **new** region to provide pharmacodynamic or clinical data on efficacy, safety, dosage, and dose regimen in the new region that will allow extrapolation of the foreign clinical data to the new region.

Multi-Regional Trials

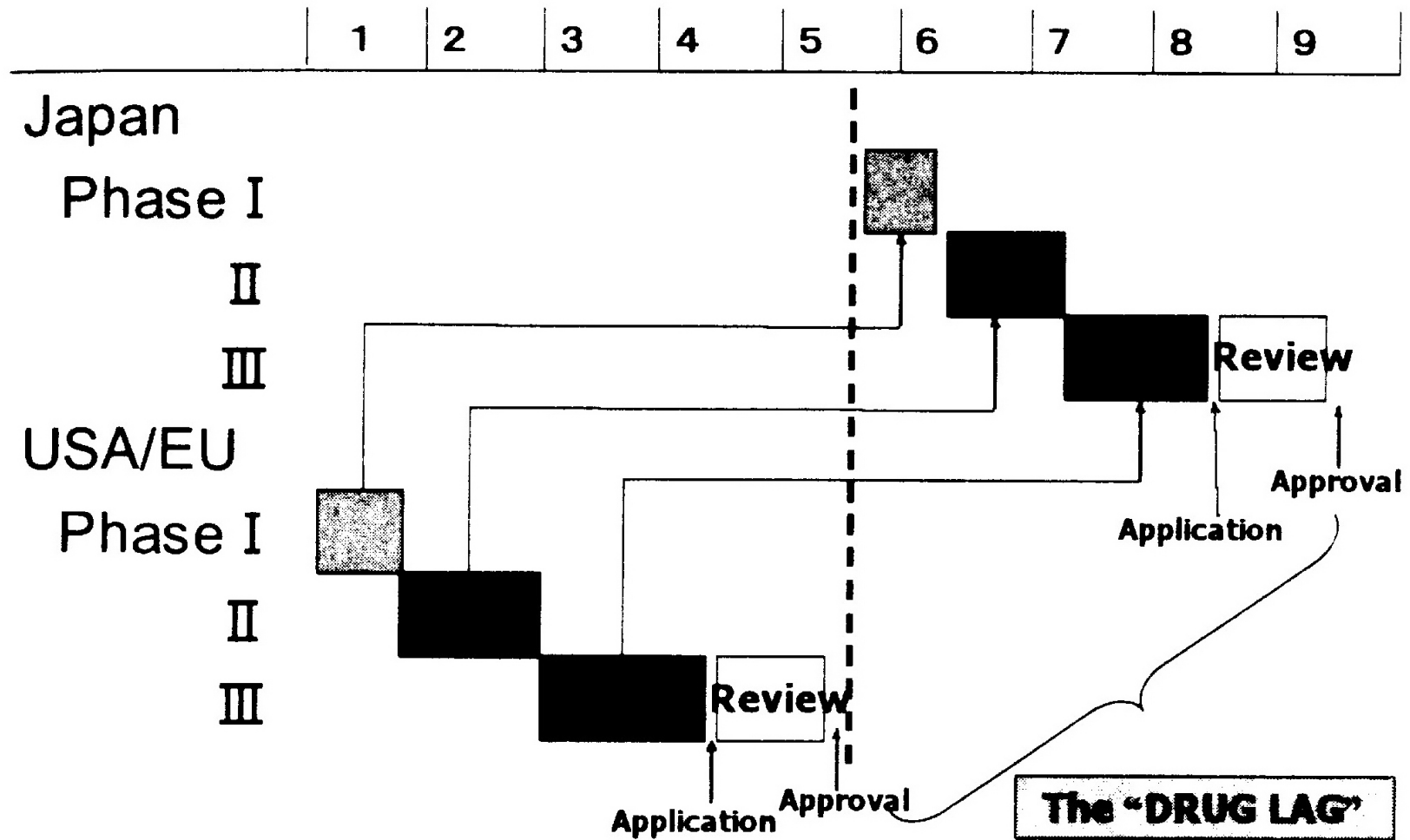
- A bridging study is usually conducted in the new region after the test product has been approved in the original region
- Extensive duplication of clinical evaluation in the new region not only requires valuable development resources but also delay availability of the test product to the needed patients in the new regions
- To shorten the drug lag or the time lag for approval, simultaneous drug development, submission, and approval in the world may be desirable

Drug Lag

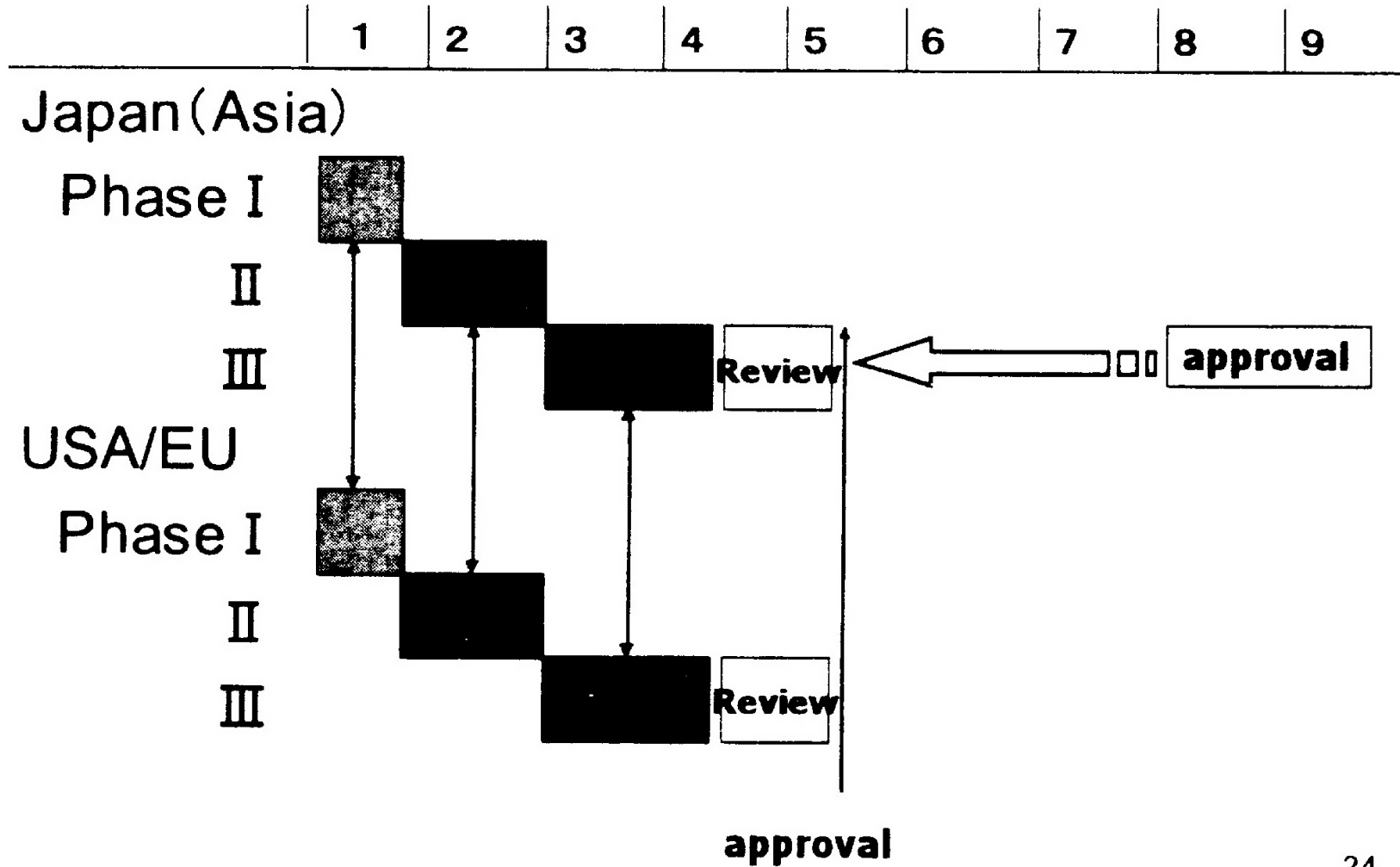
Number of products waiting for marketing among world's top 88 selling-products in 2004

- Japan: 28
- Russia: 27
- Singapore: 22
- **Taiwan: 12**
- France: 9
- Korea: 5
- Germany: 2
- UK: 1
- USA: 0

Full development in each region



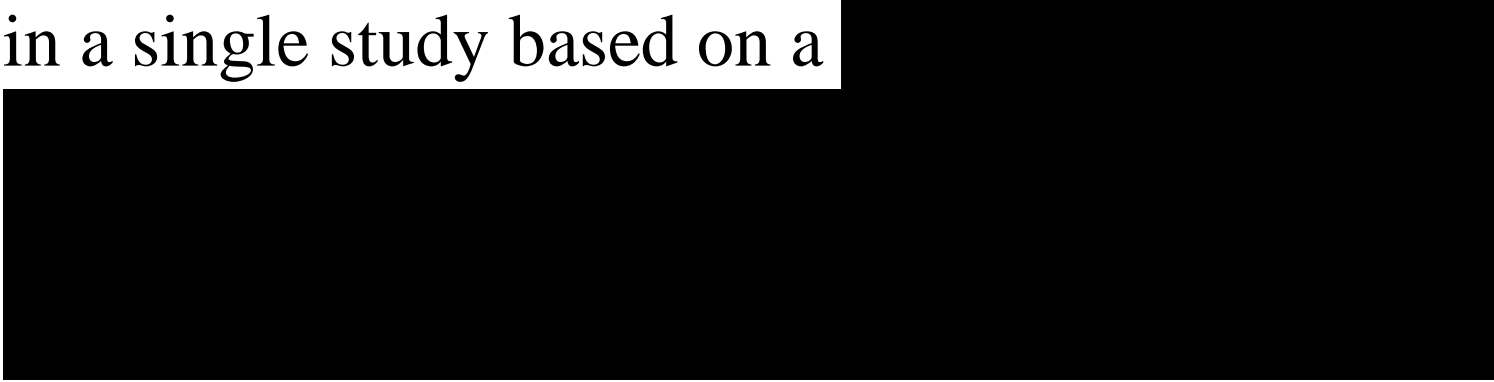
Involvement in Global Clinical Study



Japanese Ministry of Health, Labour and Welfare (MHLW)

The guideline “*Basic Principles on Global Clinical Trials*” in 2007

“global clinical studies refer to studies planned with the objective of world-scale development and approval of new drugs in which study sites of a multiple number of countries and regions participate in a single study based on a



ICH-E5 Q11

It may be desirable in certain situations to achieve the goal of bridging by conducting a multi-regional trial under a common protocol that includes sufficient numbers of patients from each of multiple regions to reach a conclusion about the effect of the drug in all regions...

Multi-regional Trials

- Both guidelines (MHLW and ICH E5) have established a framework on
 - How to demonstrate the efficacy of a drug in *all participating regions*
 - Also evaluating the possibility of *applying the overall trial results to each region*by conducting a multi-regional trial

Questions

- How do we draw inferences concerning the treatment effect in a multi-regional trial?
- How do we assess “consistent trends” or “similarity” between the region of interest and overall regions?
- What is a rational way to determine the minimum sample size for a region?

from Christy Chuang-Stein

Fundamental Promises

- No region should proclaim itself to be the region of interest and demand the treatment to show a statistically significant result at the usual significance level within that region
- The study's primary objective is to demonstrate an overall treatment effect
- Satisfying regional requirement is a key secondary objective

from Christy Chuang-Stein

Multi-Regional Trials

- For clinical trials including patients from a specific region (e.g., Asia), how to assess the similarity of treatment effect between Asia and all regions?
- How large should the sample size be required for Asia region?

Assumption and Notation

- We focus on the trials for comparing a test product and a placebo control
- X and Y are some efficacy responses for patients receiving the test product and the placebo control respectively
- X and Y are normally distributed with known variance σ^2
- μ_T and μ_P are the population means of the test product and placebo, respectively, and let $\Delta = \mu_T - \mu_P$

Assumption and Notation

- Effect size (Δ/σ) is uniform across regions
- Hypothesis: $H_0: \Delta=0$ vs. $H_A: \Delta \neq 0$
- N is the total sample size for each group planned for detecting an expected treatment difference $\Delta=\delta$ at the desired significance level α and with power $1-\beta$.

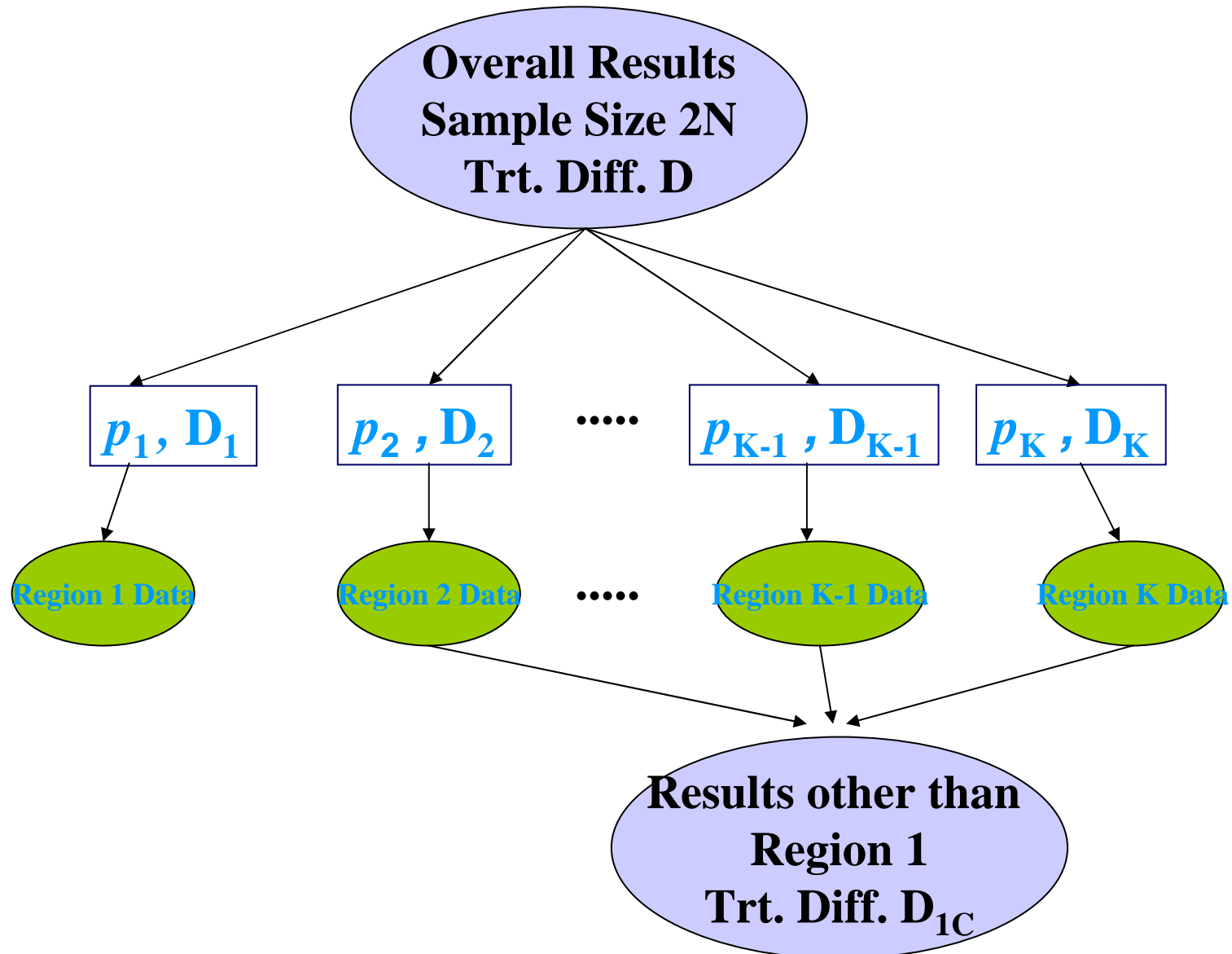
$$N=2\{(z_{1-\alpha}+z_{1-\beta})\sigma/\delta\}^2,$$

where $z_{1-\alpha}$ is the $(1-\alpha)$ th percentile of the standard normal distribution.

Consider a Specific Region

- Suppose that we are interested in judging whether the treatment is effective in a specific region, say Region 1

Multi-Regional Results



Four Criteria

Given that the overall result is significant at α level, we will judge whether the treatment is effective in the Region 1 by the following four criteria.

- (i) $D_1 \geq \rho D_{1c}$, for some $\rho > 0$
- (ii) $D_1 \geq \rho D$, for some $\rho > 0$
- (iii) $\rho \leq D_1 / D_{1c} \leq 1/\rho$, for some $\rho > 0$
- (iv) $\rho \leq D_1 / D \leq 1/\rho$, for some $\rho > 0$

The first two criteria are to assess whether the treatment effect in the region of interest is as large as that of the other regions or of the regions overall, while the last two criteria are to assess the consistency of the treatment effect of the specific region with other regions or the regions overall.

Assurance Probabilities

The assurance probabilities of criteria (i)-(iv) conditioning on the statistical significance of the overall region, given $\Delta = \delta$ are defined as

$$AP_1 = P(D_1 > \rho D_{1c} | Z > Z_{1-\alpha})$$

$$AP_2 = P(D_1 > \rho D | Z > Z_{1-\alpha})$$

$$AP_3 = P(\rho \leq D_1 / D_{1c} \leq 1 / \rho | Z > Z_{1-\alpha})$$

$$AP_4 = P(\rho \leq D_1 / D \leq 1 / \rho | Z > Z_{1-\alpha})$$

Sample Size Determination

- To determine p_1 to ensure that the assurance probabilities of criteria (i)-(iv) given that the overall results are significant are maintained at a desired level, say 80%.

Assurance Probabilities

$$\begin{aligned}
 AP_1 &= P_\delta(D_s > \rho D_{sc} \mid Z > z_{1-\alpha}) \\
 &= \frac{\int_{-z_{1-\beta}}^{\infty} \left(1 - \Phi \left(\left(\frac{\rho \sqrt{p_s}}{1 - p_s + \rho \cdot p_s} \right) u + \left(\frac{\sqrt{p_s} (1 - \rho) (p_s - 1)}{1 - p_s + \rho \cdot p_s} \right) (z_{1-\alpha} + z_{1-\beta}) \right) \right) \phi(u) du}{(1 - \beta)}
 \end{aligned} \tag{1}$$

$$\begin{aligned}
 AP_2 &= P_\delta(D_s > \rho D \mid Z > z_{1-\alpha}) \\
 &= \frac{\int_{-z_{1-\beta}}^{\infty} \left(1 - \Phi \left(\rho \sqrt{p_s} u + \sqrt{p_s} (\rho - 1) (z_{1-\alpha} + z_{1-\beta}) \right) \right) \cdot \phi(u) du}{(1 - \beta)},
 \end{aligned} \tag{2}$$

Assurance Probabilities

$$\begin{aligned}
 AP_3 &= P_\delta \left(\rho < \frac{D_s}{D_{sc}} < \frac{1}{\rho} \mid Z > z_{1-\alpha} \right) \\
 &= \frac{\int_{-z_{1-\beta}}^{\infty} \left(\Phi \left(\left(\frac{\sqrt{p_s}}{\rho(1-p_s) + p_s} \right) u + \left(\frac{\sqrt{p_s}(1-\rho)(1-p_s)}{\rho(1-p_s) + p_s} \right) (z_{1-\alpha} + z_{1-\beta}) \right) \right) \phi(u) du}{(1-\beta)} \\
 &\quad - \frac{\int_{-z_{1-\beta}}^{\infty} \left(\Phi \left(\left(\frac{\rho\sqrt{p_s}}{1-p_s + \rho \cdot p_s} \right) u + \left(\frac{\sqrt{p_s}(1-\rho)(p_s-1)}{1-p_s + \rho \cdot p_s} \right) (z_{1-\alpha} + z_{1-\beta}) \right) \right) \phi(u) du}{(1-\beta)}, \tag{3}
 \end{aligned}$$

$$\begin{aligned}
 AP_4 &= P_\delta \left(\rho < \frac{D_s}{D} < \frac{1}{\rho} \mid Z > z_{1-\alpha} \right) \\
 &= \frac{\int_{-z_{1-\beta}}^{\infty} \left(\Phi \left(\frac{1}{\rho} \sqrt{p_s} u + \sqrt{p_s} \left(\frac{1}{\rho} - 1 \right) (z_{1-\alpha} + z_{1-\beta}) \right) \right) \cdot \phi(u) du}{(1-\beta)} \\
 &\quad - \frac{\int_{-z_{1-\beta}}^{\infty} \left(\Phi \left(\rho \sqrt{p_s} u + \sqrt{p_s} (\rho - 1) (z_{1-\alpha} + z_{1-\beta}) \right) \right) \cdot \phi(u) du}{(1-\beta)}. \tag{4}
 \end{aligned}$$

$\alpha=0.025, \beta=0.1, \text{ and } \rho=0.2$

p_1	AP_1	AP_2	AP_3	AP_4
0.05	0.73	0.73	0.72	0.73
0.10	0.81	0.82	0.80	0.82
0.15	0.86	0.87	0.86	0.87
0.20	0.90	0.91	0.89	0.91
0.25	0.92	0.93	0.91	0.93
0.30	0.94	0.95	0.93	0.95
0.35	0.95	0.97	0.94	0.97
0.40	0.96	0.98	0.95	0.98
0.45	0.97	0.99	0.96	0.99
0.50	0.98	0.99	0.96	0.99
0.55	0.98	0.99	0.95	0.99
0.60	0.99	1.00	0.95	1.00
0.65	0.99	1.00	0.94	1.00
0.70	0.99	1.00	0.93	1.00
0.75	0.99	1.00	0.91	1.00
0.80	1.00	1.00	0.89	1.00
0.85	1.00	1.00	0.85	1.00
0.90	0.99	1.00	0.80	1.00

$\alpha=0.025, \beta=0.1, \text{ and } \rho=0.5$

p_1	AP_1	AP_2	AP_3	AP_4
0.05	0.65	0.65	0.41	0.44
0.10	0.71	0.72	0.52	0.58
0.15	0.74	0.76	0.59	0.68
0.20	0.78	0.80	0.64	0.75
0.25	0.80	0.83	0.67	0.80
0.30	0.82	0.86	0.70	0.84
0.35	0.83	0.89	0.71	0.87
0.40	0.85	0.91	0.72	0.90
0.45	0.86	0.93	0.73	0.92
0.50	0.86	0.94	0.73	0.94
0.55	0.87	0.96	0.73	0.96
0.60	0.88	0.97	0.72	0.97
0.65	0.88	0.98	0.71	0.98
0.70	0.88	0.99	0.69	0.99
0.75	0.87	0.99	0.67	0.99
0.80	0.86	1.00	0.64	1.00
0.85	0.85	1.00	0.59	1.00
0.90	0.82	1.00	0.52	1.00

Discussion

- Selection of the magnitude, ρ , of consistency trend may be critical. It may vary from region to region, and disease to disease.
- The Japanese MHLW suggests that ρ be 0.5 or greater for the second criteria
- The selection of ρ allows flexibility for regulatory agency to make decisions and to negotiate with local and international pharmaceutical industry

Thanks for your attention