Study on statistical analysis planning and procedures based on differences in regulations between Japan and the United States in global drug development

グローバル医薬品開発における日米の規制の違いをふまえた統計解析計画と手順に関する研究

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TABLE OF CONTENTS

DEFINITION AND TERMINOLOGY USED IN THIS RESEARCH

This research uses the definitions as described below.

Global drug development

Global drug development, including global and overseas trials will be submitted to Pharmaceuticals and Medical Devices Agency (PMDA).

Statistical analyses for clinical trials

The statistical analyses of clinical trials are divided into three steps. The first is developing the statistical analysis plan, the second is the creation of the dataset used for the analysis, and the third is the output of the results of the statistical analyses.

List of terms and abbreviations

The terms and abbreviations in this dissertation are listed as below.

Term/Abbreviation	Non-abbreviated	Details
ADaM	Analysis Data Model	Fundamental standards for analysis datasets and associated metadata of clinical studies.
AE	adverse events	Medical occurrence temporally associated with the use of a medicinal product.
Biosimilar	-	Biological product highly similar to another approved biologic.
CDISC	Clinical Data Interchange Standards Consortium	A non-profit organization that has established standards to support the acquisition, exchange, submission and maintenance of an archive of clinical research data and metadata.
CI	confidence interval	A range of values that is likely to include a population value with a certain degree of confidence. It is often expressed as a % whereby a population mean lies between an upper and lower interval.
CSR	clinical study report	Description and analyses of the results of a clinical trial according to the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Guideline E3, Structure and Content of Clinical Study Reports (ICH E3).

Term/Abbreviation	Non-abbreviated	Details
CTD	common technical document	Consolidated documents including clinical study reports to be submitted to regulatory authorities.
e-Data	electronic data	-
EQ (study design)	equivalence (study design)	A study design to demonstrate equivalence between two treatments or interventions.
EU	European Union	-
FDA	Food and Drug Administration	A health authority in the United States for the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices.
FTE	full-time equivalent	A unit of measurement equivalent to an individual full-time worker.
ICH	International Council for Harmonisation	Council for regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and develop guidelines.
ISE	integrated summary of effectiveness	Integrated data of effectiveness in CTD.
ISS	integrated summary of safety	Integrated data of safety in CTD.
MHLW	Ministry of Health, Labor, and Welfare	A ministry of the Japanese government to provide services on health, labor and welfare.
MRCT	multiregional clinical trial	Clinical trials including multiple regions.
NDA	new drug application	A comprehensive document to be submitted to a health authority in order to request approval for marketing a new drug.
NI (study design)	non-inferiority (study design)	A study design to demonstrate non-inferiority of a new drug or intervention to an existing one.

Term/Abbreviation	Non-abbreviated	Details
PMDA	Pharmaceuticals and Medical Device Agency	Japanese regulatory agency, subsidiary of the Ministry of Health, Labor and Welfare.
RBP	reference biological product	An already licensed, biotechnology medicinal product.
RD	response difference	Absolute risk difference.
RR	response ratio	Relative risk.
SAP	statistical analysis plan	A document to describe the planned analysis of clinical trials.
SDTM	Study Data Tabulation Model	Fundamental standards for study datasets and associated metadata of clinical studies
TLF	tables, listings, and figures	Analysis results of clinical trials. Tables usually include summary statistics and frequencies. Listings are printouts of raw data of individual subjects (e.g a listing of all adverse events).
TOST	two one-sided tests	-
US	United States	-

1. INTRODUCTION

1. INTRODUCTION

1.1 Background

The Ministry of Health, Labour, and Welfare (MHLW) issued "Basic Principles on Global Clinical Trials" in 2007[1], which has encouraged Japanese participation in multi-regional clinical trials (MRCTs). For globalization of drug development, multiple pharmaceutical companies and/or geographical regions [e.g., Japan, the United States (US), and the European Union (EU)] might be involved in development and global submissions. Data from MRCTs and overseas clinical trials are often submitted to the Pharmaceuticals and Medical Devices Agency (PMDA) in addition to data from Japan local clinical trials for supporting marketing approval of drugs. When using data and conducting statistical analyses of data from MRCTs and overseas clinical trials for PMDA submissions, there are several difficulties and issues described as below.

1.1.1 Statistical analysis for Biosimilar development

In general, similar to FDA and other health authorities, the PMDA requires clinical efficacy study(ies) to evaluate equivalence between a reference biological product and a Biosimilar product for new drug applications. Even if an identical clinical efficacy study is included in both of PMDA and FDA submissions, the coefficients of confidence interval (CI) used for comparison with the equivalence margins could differ between the two submissions (e.g., 95% CI vs. 90% CI).

1.1.2 Non-inferiority analysis

In the FDA non-inferiority (NI) guidance, two margins are described for ensuring, respectively: a) a greater effect for the test drug than for the placebo; and b) preservation of a specified portion of the control effect. The two margins are called M1 and M2; the M1 is the entire effect size of the active control, the M2 is the largest loss of effect that would be clinically acceptable. The guidance states that the synthesis method can be used for M2. For M2, the fraction preservation of the control effect is specified in advance, but the quantity is not specified because it synthesizes data from historical studies and the NI study to be conducted. The synthesis method with an appropriately chosen value of preservation rate is always more efficient than a fixed-margin approach that achieves the same control of the type 1 error rate. However, another argument posits that a fixed-margin method is easier to understand than the synthesis method. Particularly in Japan, even if the synthesis method is used, the NI margin should be specified in advance according to guidelines.

1.1.3 Statistical analysis procedure

While conducting statistical analyses of MRCTs and overseas clinical trials in global drug development, statisticians and programmers across regions may face challenges due to the differences in regulation, language, and geographic region. Especially, PMDA requires Japan specific analysis outputs, and it might cause delays of PMDA submissions.

1.2 Objectives

According to regulatory guidance which will be mentioned in later sections, there are several differences of the statistical planning and procedures required for clinical trials between PMDA and other regulatory agencies such as the Food and Drug Administration (FDA). Several committees [i.e., the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and Japan Pharmaceutical Manufacturers Association (JPMA)] have been discussing problems between regulatory bodies and the pharmaceutical industry to fill the gaps and resolve issues caused by the differences. . JPMA consists of representatives from pharma in Japan and has continued discussions with PMDA, however, there are still several differences in regulations regarding statistical analyses.

In general, a clinical trial would follow the steps below (Figure 1-1).

1. Collecting data from patients who participate in a clinical trial
2. Conducting statistical analyses using the collected data
3. Documenting a report of a clinical trial based on the results of the analyses
4. Consolidating reports and analyses from multiple trials of a new drug and submitting it to regulatory authorities (FDA, PMDA/MHLW)

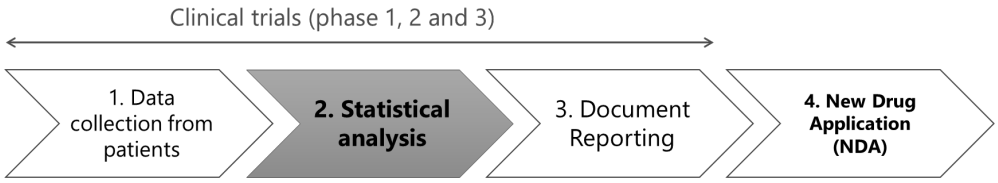


Figure 1-1. Overall steps for clinical trials

Figure 1-2 is a schematic representation of clinical trials in global drug development. In general, a New Drug Application (NDA) would include Phase 1 study(ies) to evaluate the safety and pharmacokinetics of drugs in a small number of healthy volunteers, Phase 2 study(ies) to confirm dose response in a small number of patients and Phase 3 study(ies) to confirm the efficacy and safety in a large number of patients. The results of statistical analyses of these studies will be summarized in Clinical Study Reports (CSRs) and consolidated as Common Technical Document (CTD) to be submitted to regulatory authorities such as MHLW/PMDA. This research will target global drug development including global and overseas trials and to be submitted to PMDA (Example 1 and 2 in Figure 1-2).

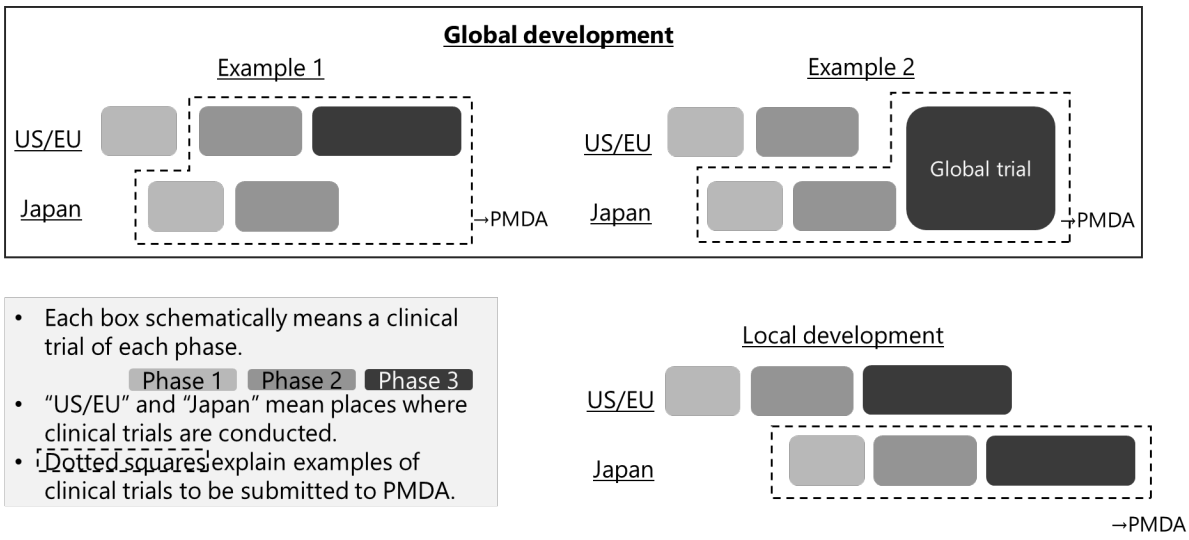


Figure 1-2. Schema of global drug development in this research

Table 1-1 explains the outline of the statistical analysis steps of clinical trials. The statistical analysis of clinical trials would be divided into three steps. The first is the statistical analysis plan, the second is the creation of the dataset used for the analysis, and the third is the output of the statistical analysis results. The first step includes determining statistical analysis methods, significance levels and confidence interval coefficients. These items must be determined before conducting the clinical trial and cannot be changed at later step. In the second step, the data collected in clinical trials are converted into a format that can be statistically analyzed. At the third step, statistical analyses are conducted using computer programming with the analysis datasets.

We identified five elements of differences in regulations between Japan and the EU/US within the three processes. Because there seems not to be a large difference between US and EU regarding the five elements, we will focus on the differences between Japan and US. In the first step, there were two differences regarding the confidence interval coefficients used for the equivalence design of Biosimilar development and statistical methods for non-inferiority design such as the synthesis method. In the second step, there were difference in data format and documentation regarding data quality. In the third step, there were tables and listings additionally required by PMDA. In summary, the five elements of differences were identified which could cause delays in NDA to PMDA.

Table 1-1. Statistical analysis steps and differences in regulation

	1. Statistical analysis plan		2. Analysis datasets		3. Analysis results
Step	To be planned before conducting a clinical trial about statistical methods, significance level, coefficient for confidence interval, etc.		To be created for statistical analysis using collected data from subjects in a clinical trial		To be conducted by computer programming with analysis datasets
Diff. of regulations between Japan and US/EU	Diff-1. Equivalence Study design for Biosimilars	Diff-2. Non-inferiority Study design	Diff-3. Format of datasets	Diff-4. Data validation document	Diff-5. Additional tables and listings only for Japan

Abbreviation: Diff, difference.

Note: Equivalence Study= To declare the equivalency of efficacy between two drugs; Non-inferiority Study= To declare that a new drug is not inferior to a standard drug.

The objectives of this research are to sort out the differences and the impact on NDA in Japan and propose statistical solutions and a global standard procedure for global drug development. Table 1-2 explains the proposed solutions for the five elements. Sections 2 and 3 provide the solutions for the differences of 1 and 2. Section 4 proposes a solution for the differences of 3, 4 and 5.

Table 1-2. Statistical analysis steps and differences of regulation

	1. Statistical analysis plan		2. Analysis datasets		3. Analysis results
Diff.	Diff-1.	Diff-2.	Diff-3.	Diff-4.	Diff-5.
Proposed solution	To provide interpret PMDA guidance documents and provide statistical solutions		To establish a global standard procedure of statistical analysis in order to reduce the time and efforts for the additional work specific to PMDA		

Abbreviation: Diff, difference.

1.3 Previous research and the positioning of this research

As mentioned previously, there are several difficulties and issues in the statistical analyses of MRCTs and overseas clinical trials used for PMDA submissions. There are some publications on statistical analysis of MRCTs, however, these are mainly specific to the Japanese sample size of MRCTs[2] and few investigations on how differences in regulatory authority, language, and the region could impact operations, processes, and implementation of statistical analyses. For Biosimilar development and the synthesis method for non-inferiority design, there are research mainly about FDA and EU submissions[3,4]. Since these related guidance documents were released in 2007, 2009 and 2010[5,6], the relevant research might have just started.

Table 1-3. Previous research on the statistical analysis of MRCT, Biosimilar development and the synthesis method for non-inferiority design

Previous research	Limitation	Background	Positioning of this research
Publications on statistical analysis of MRCT	Mainly about the statistical consideration on the Japanese sample size	MRCT guidance was released in 2007 and very limited research on the general statistical analyses	General statistical analysis procedure for MRCT
Publications on statistical analyses on Biosimilar development	Only about the statistical analyses to be used for US and EU submissions	Biosimilar guidance in Japan was released in 2009 and very limited research on the statistical analyses of Biosimilar development in Japan	Japan-specific analysis plan for Biosimilar
Publications on the synthesis method of non-inferiority	Only about the method to be used for US and EU submissions	FDA non-inferiority guidance was released in 2016 and no guidance in Japan	Japan-specific analysis plan for Non-inferiority

Consequently, this research focuses on the three aspects below.

Firstly, we will focus on the clinical efficacy studies of Biosimilar products and provide an overview of the two one-sided tests (TOST) and the type I error rate for equivalence design. Then, we summarize published PMDA review reports of Biosimilar products in terms of the coefficients of CI and other elements of the primary endpoints, and explain some Japanese guidelines of Biosimilar and Statistics behind the difference between PMDA and FDA submissions. Additionally, we discuss how to use statistical methods correctly and efficiently for PMDA submissions.

Secondly, we explain how to obtain and visualize the back-calculated margin for the synthesis method for a time-to-event endpoint without data from an NI study to fulfill the Japanese guidelines. The proposed method allows simple calculation and visualization of the NI margin for the synthesis method. This proposal facilitates the use of the synthesis method for NI studies for PMDA submissions.

Thirdly, we propose a procedure that facilitates the appropriate and timely implementation of statistical analyses and regulatory responses. Based on the experience of the US and Japanese pharmaceutical companies in conducting global clinical trials and submitting new drug applications, we propose a process for implementing statistical analyses and regulatory responses irrespective of the locations of study team members. The process is based on gap analyses of regulations and practices regarding statistical analyses between regions, including considering different requirements for tables, listings, and figures between the PMDA and FDA. Through

efficient resource utilization and early planning, Japanese and US teams were able to successfully deliver datasets and analyses for both PMDA and FDA submissions in a timely manner with high quality based on the proposed process. A well-defined process improves the efficiency and quality of PMDA submissions using global clinical trials. The current proposal facilitates the appropriate and timely conduct of statistical analyses using the Clinical Data Interchange Standards Consortium standards for global clinical trials and new drug applications.

1.4 Structure of this research

This research is organized as follows.

- Section 2. Japan-specific analysis plan for Biosimilars: this section focuses on statistical considerations regarding Biosimilar development and proposes a solution for the PMDA submissions, corresponding to the difference 1 in Table 1-1.
- Section 3. Japan-specific analysis plan for non-inferiority: this section explains the FDA and the PMDA guidance for non-inferiority and proposes a solution to use the synthesis method for the PMDA submissions, corresponding to the difference 2 in Table 1-1.
- Section 4. Development of a statistical analysis procedure for global submission and Japan-specific preparations for e-Data submission to the PMDA: this section proposes a statistical analysis procedure for global drug development and PMDA submissions, corresponding to the difference 3,4 and 5 in Table 1-1.
- Section 5. Overall discussion: this section summarizes the discussions on the objectives of this research through Section 2, 3 and 4.
- Section 6. Conclusion: this section focuses on the conclusion of this research.

2. JAPAN-SPECIFIC ANALYSIS PLAN FOR BIOSIMILAR

2. JAPAN-SPECIFIC ANALYSIS PLAN FOR BIOSIMILAR

2.1 Background

Biosimilar (i.e., follow-on biological medicinal product in Japanese guidelines) is defined as a new biotechnological medicinal product developed to be similar in terms of quality, safety and efficacy to an already licensed, biotechnology medicinal product (hereinafter referred to as reference biological product or RBP) developed by a different marketer-manufacturer in Japan[5].

In general, clinical pharmacokinetic (PK) study(s) (or pharmacodynamic (PD) study(s), PK/PD study(s)) and clinical efficacy study(ies) are required to evaluate equivalence (EQ) between a RBP and a Biosimilar product for new drug applications (NDAs) to Pharmaceuticals and Medical Devices Agency (PMDA), similarly to the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

2.2 Related regulations

2.2.1 PMDA review reports of Biosimilar products

A clinical efficacy study of Biosimilar needs to define the primary endpoint to evaluate EQ at a planning stage. To simplify the explanation, we categorize the primary endpoint into three elements, a) endpoint (narrow sense), b) metric and c) coefficient of confidential interval (CI) to be compared with the EQ margin in this manuscript.

As of June 2019, 18 Biosimilar products have been approved for 10 RBPs in Japan. Table 2-1 shows elements of the primary endpoints for PMDA submissions of clinical efficacy studies of Biosimilar products that two or more Biosimilar products for a reference biological product have been approved in Japan, referring to the published review reports[7]. In addition, if the same information of the FDA submission is available from the published review report, it is also included[8]. As results, 8 Biosimilar products are listed with the information of the PMDA submission, and 4 of 8 products have the information of the FDA submissions as well.

Regarding a) endpoint (narrow sense), even if it may differ within a group of Biosimilar products for a reference biological product, it is the same between the PMDA submission and the FDA submission for a Biosimilar product. As for b) metric of the Biosimilar products with binary outcomes, 5 of 6 PMDA submissions used response difference (RD), while 3 of 4 FDA submissions used response ratio (RR). RD and RR are defined as below:

$$\text{RD} = P_t - P_c$$

$$\text{RR} = \frac{P_t}{P_c}$$

P_t: Response rate in a test drug group (Biosimilar product)

P_c: Response rate in a control group (RBP)

Regarding c) coefficient of CI, all of the 8 PMDA submissions used the two-sided 95% CIs, while two of four FDA submissions used the two-sided 90% CIs and other two FDA submissions commented that biosimilar comparative clinical studies use a two-sided 90% CI in the primary analysis in general in order to control the type I error rate ≤ 0.05[9].

Table 2-1. Elements of the primary endpoints in clinical efficacy studies of Biosimilar for PMDA submissions (as of June 2019)

Product name in Japan[*1]	**PMDA review report**			**FDA review report for the same product**
	a) Endpoint	b) Metric	c) Coefficient of CI	
Trastuzumab Biosimilar 1	Pathological CR rate (binary)	RD	Two-sided 95%	RR and the two-sided 90% were used for the FDA submission.
Trastuzumab Biosimilar 2	Pathological CR rate (binary)	RD	Two-sided 95%	Not available at this time.
Trastuzumab Biosimilar 3	Objective Response Rate (binary)	RR	Two-sided 95%	RR and the two-sided 95%*[2] were used for the FDA submission
Infliximab Biosimilar 1	ACR20 (binary)	RD	Two-sided 95%	RR and the two-sided 95%*[3] were used for the FDA submission
Infliximab Biosimilar 2	Change from BL of DAS28-ESR (continuous)	Mean difference	Two-sided 95%	Not available at this time.
Infliximab Biosimilar 3	ACR20 (binary)	RD	Two-sided 95%	RD and the two-sided 90% were used for the FDA submission.
Etanercept Biosimilar 1	Change from BL of DAS28-ESR (continuous)	Mean difference	Two-sided 95%	Not available at this time.
Etanercept Biosimilar 2	ACR20 (binary)	RD	Two-sided 95%	Not available at this time.

Abbreviation: ACR20 = American College of Rheumatology 20% improvement response criteria; BL = Baseline, CI = Confidential Interval; CR = Complete Response; DAS28-ESR = Disease Activity Score 28-erythrocyte sedimentation rate; RD = Response Difference; RR = Response Ratio

*1: Biosimilar products that two or more Biosimilar products for a reference biological product were approved in Japan (as of June, 2019).

*2: FDA Comment: In general, biosimilar comparative clinical studies use a two-sided 90% CI in the primary analysis so that alpha is controlled ≤0.05. This study was designed to use a two-sided 95% CI in the primary analysis, which is more conservative.

*3: FDA Comment: FDA generally expects the type I error rate of a test of similarity to be controlled at 5%.

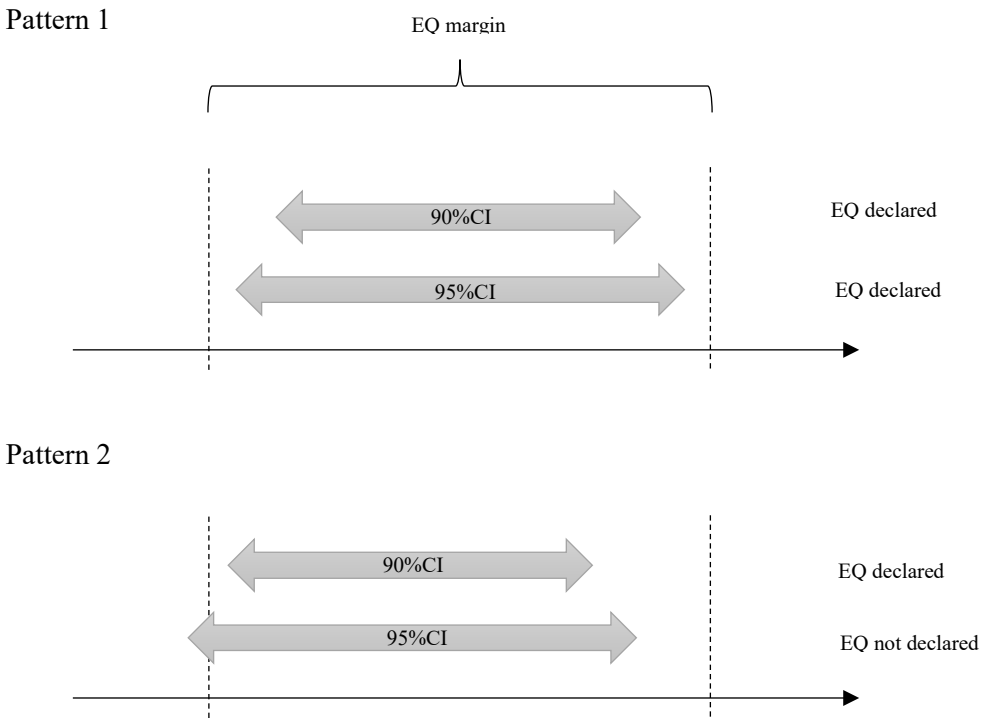
2.2.2 Guidelines related to statistical analyses for Biosimilar in Japan

The Ministry of Health, Labor and Welfare (MHLW) released a Biosimilar guideline in 2009 and three versions of Biosimilar Q&A in 2009, 2010 and 2015[10]. The third version of Biosimilar Q&A (2015) states that clinical PK studies can use two-sided 90% CIs, however clinical efficacy studies need to use two-sided 95% CIs for EQ designs, according to the Questions and Answers (1998) (hereafter, Statistical Q&A) which is an original document by MHLW attached to Statistical Principles for Clinical Trials (i.e., the MHLW version of ICH E9)[10, 11]. There are no specific descriptions about type I error rates in the MHLW Biosimilar guideline and Biosimilar Q&A.

The Statistical Q&A states that two-sided 95% CIs need to be used for estimation of treatment effects in confirmatory studies in general, no matter whether a one-sided test or a two-sided test is used. On the other hand, the cover page of the MHLW version of ICH E9 (in Japanese only available) states regarding the significance level (type I error) for testing a confirmatory study, in principle 2.5% should be used to test the one-sided hypothesis, and 5% for the two-sided hypothesis from a regulatory standpoint. As for EQ evaluation of Biosimilar products, although the wording "two-sided hypothesis" in Japanese may be vague, controlling type I error rate at 5% for two-sided hypothesis seems to contradict using a 95% CI required by the Statistical Q&A if "the significance level (type I error)" in the cover page means a study-wise type I error rate.

2.3 Proposals: Two one-sided tests (TOST) for EQ designs

Figure 2-1 explains an EQ design between a RBP and a Biosimilar product. The two dotted lines explains the EQ margin for the example. If the double arrows are the 90% or 95% CIs of the response rate between the RBP and the Biosimilar product, Pattern 1 can declare EQ for both of 90% and 95% CIs, however Pattern 2 can declare EQ only for 90% CI and not for 95% CI because the lower limit of the 95% CI exceeds the lower limit of the EQ margin.



Abbreviations: CI, confidence interval; EQ, equivalence.

Figure 2-1. Equivalence (EQ) design and the margin

Let Δ present the true difference between the test and reference groups, and $\Delta_L\ (\leq 0)$ and $\Delta_U\ (\geq 0)$ present pre-specified EQ margins, the hypothesis to evaluate EQ is

$$H_0: \Delta \leq \Delta_L \ or\ \Delta \geq\ \Delta_U\ vs. H_A: \Delta_L <\ \Delta <\ \Delta_U \quad \text{--- (2-1)}$$

L: Lower limit, U: Upper limit

In another expression, the above hypothesis can be tested using two one-sided tests (TOST)

$$H_{0L}: \Delta \leq \Delta_L\ \ vs. H_{AL}: \Delta >\ \Delta_L$$

and

$$H_{0U}: \Delta \geq \Delta_U\ \ vs. H_{AU}: \Delta <\ \Delta_U$$

--- (2-2)

L: Lower limit, U: Upper limit

A TOST at significance level α for (2-2) is identical to comparing the two-sided 100(1-2α)% CI to the pre-specified EQ margin for (2-1), to preserve a study-wise type I error rate at α[12, 13, 14]. For example, if a TOST is conducted at significance level 0.05 (α = 0.05), it is operationally identical to comparing the two-sided 90% CI to the pre-specified margin at a study-wise type I error rate 0.05. In other words, the two-sided 90% CI can be used if a clinical efficacy EQ study needs to preserve a study-level type I error rate at 0.05 like other types of clinical efficacy studies such as superiority study. Table 2-2 shows significance level for TOST, study-wise type I error rate and coefficient of CI.

Table 2-2. Significance level for TOST, study-wise type I error rate and coefficient of CI

Significance level for TOST	Study-wise type I error rate	Coefficient of CI
0.025 (2.5%)	0.025 (2.5%)	Two-sided 95%
0.05 (5.0%)	0.05 (5.0%)	Two-sided 90%

Abbreviations: TOST, two one-sided tests; CI, confidence interval.

2.4 Results and discussion

As shown in Table 2-1, even though the same study is used, the coefficients of CI were different between the submissions for PMDA and FDA to evaluate EQ of efficacy in some products. The MHLW Biosimilar guideline and the Q&A do not mention type I error rates, and PMDA requires to use 95% CIs based on the Statistical Q&A which was released before the MHLW Biosimilar guideline and did not foresee clinical efficacy studies of Biosimilar. On the other hand, FDA requires to preserve a study-wise type I error rate at 0.05. As explained, if a TOST is conducted at significant level 0.05, the study-wise type I error rate is preserved at 0.05 because the TOST is identical to comparing the 90% CI with the margin. We expect an active discussion based on not coefficients of CI but study-wise type I error rates regarding clinical efficacy studies of Biosimilar in Japan.

In some cases, non-inferiority (NI) designs would be used for Biosimilar products. The synthesis method[6] with an appropriately chosen value for the preservation rate is more efficient than a fixed-margin approach that achieves the same control of the type 1 error rate[4]. The method is usually used for NI designs, and could be used for EQ designs. The MHLW Biosimilar guideline requires to pre-specify margins, but the margin is not pre-specified for the synthesis method because it synthesizes data from the historical studies and the NI/EQ study to be conducted. To resolve this, back-calculation margins can be obtained at the design stage for a NI/EQ study to be conducted[15].

We explained TOST and the type I error rate for equivalence design of clinical efficacy studies in Biosimilar, for which there has been little discussion in Japan. And we summarized some PMDA's and FDA's review reports of Biosimilar products in terms of elements of the primary

endpoints such as the coefficients of CI and the metrics. In addition, we perused the Biosimilar Q&A in Japan, and the MHLW version of ICH E9 which includes some Japan specific descriptions in the cover page and the attachment of the Statistical Q&A. There has been confusion and/or unclear points regarding TOST, a study-wise type I error rate and the coefficients of CI across some guidelines in Japan. There were several discussions about the coefficients of CI between the PMDA and the Japanese pharmaceutical industry, during which it was explained that the requirement of using the 95% coefficients of CI was based rigidly on the attachment of the Statistical Q&A of the MHLW version of ICH E9 [16]. We expect an active discussion about study-wise type I error rates for clinical efficacy studies of Biosimilar, and future research in utilizing other advanced statistical methods for Biosimilar in order to accelerate Biosimilar development globally and in Japan.

3. JAPAN-SPECIFIC ANALYSIS PLAN FOR NON-INFERIORITY

3. JAPAN-SPECIFIC ANALYSIS PLAN FOR NON-INFERIORITY

3.1 Background

3.1.1 Overview

In the FDA non-inferiority (NI) guidance[6], two margins are called M1 and M2. The synthesis method can be used for M2. If the synthesis method is used for M2, the fraction preservation of the control effect (that effect to be preserved in evaluating NI) is specified in advance, but the quantity of M2 is not specified because it synthesizes data from the historical studies and the NI study to be conducted, reflecting variability in both data sources depending on the outcome of the NI study. The synthesis method with an appropriately chosen value for the preservation rate is more efficient than a fixed-margin approach that achieves the same control of the type 1 error rate[4]. However, considering the above feature, another argument is that a fixed-margin method is more intuitive and easier to understand than the synthesis method, because the quantity of the margin for a fixed-margin method is specified in advance and can be visualized. Particularly in Japan, even if the synthesis method is used, the NI margin would be required to be present according to some Japanese guidelines[17, 18].

3.1.2 FDA non-inferiority guidance and the synthesis method

Non Inferiority Clinical Trials to Establish Effectiveness; Guidance for Industry (hereafter, FDA NI guidance) explains both of a fixed-margin method and the synthesis method. A fixed margin method, also called the 95% - 95% method uses 95% confidence intervals for both margin determination and in the NI study in order to demonstrate non-inferiority. The synthesis method is outlined below.

The objective of an NI study is to confirm that the effect of the test drug (T) is not inferior to the effect of the active control (C) by a specified amount, i.e., the NI margin. The null and alternative hypotheses are as follows[1]:

H_0: C – T ≥ NI margin

H_A: C – T < NI margin

For example, when applying the synthesis method for a time-to-event endpoint using HR (HR_{TC} <1 favors T), the NI test statistics that T preserves at least $100\delta_0$% of the effect of C ($0 \leq \delta_0 \leq 1$) is given as

$$Z = \frac{\log(HR_{TC}) - (1-\delta_0)\log(HR_{PC})}{\sqrt{\sigma_{TC}^2 + (1-\delta_0)^2\sigma_{PC}^2}} \quad \text{--- (3-1)}$$

HR_{TC} : Hazard ratio of T compared with C

HR_{PC} : Hazard ratio of Placebo (P) compared with C

σ_{TC} : Standard error for $\log(HR_{TC})$

σ_{PC} : Standard error for $\log(HR_{PC})$

δ_0 : T preserves at least $100\delta_0$% of the effect of C

NI will be claimed if Z is < -1.96 at a significance level of 0.05.

The synthesis method would be acceptable with a careful justification of the constancy assumption for determining whether a loss of effect greater than M2 has been ruled out.[12]

3.1.3 Comparison between synthesis and fixed-margin methods

Table 3-1 shows comparisons between the fixed-margin and synthesis methods. Both the fixed-margin and synthesis methods require pre-specification of the quantity of the fraction of the control effect (e.g., 50%), but the synthesis method is not able to pre-specify the quantity of M2. An example description for the synthesis method in a statistical analysis plan would be "The testing of NI of T to C will be based on the synthesis method designed to demonstrate that T preserves at least 50% of the treatment effect of C" with no specific NI margin. Figure 3-1 shows a conceptual illustration for M1 by a fixed-margin method and M2 by the synthesis method.

Table 3-1. Comparison between the fixed-margin and synthesis methods

Method / **Features**	**Fixed-margin method**	**Synthesis method**
Fraction Preservation of the control effect	Fraction Preservation of the control effect (e.g., 50%) needs to be pre-specified.	
Quantity of M2	Needs to be pre-specified (e.g., HR=1.20) in the planning phase of an NI study.	Unable to be pre-specified in the planning phase of an NI study.
Statistically successful claim of **NI**	The lower (or upper) limit of the 95% CI around the difference between the new treatment and the active control lies above (or below) that margin, under the condition that the margin M2 has been established.	NI test statistics (Z) is < -1.96 at a significance level of 0.05.

Note: NI = non-inferiority; M1 = entire effect of the active control assumed to be present in the NI study;

M2 = representing clinical judgement about the amount of the new formula effect that must be retained

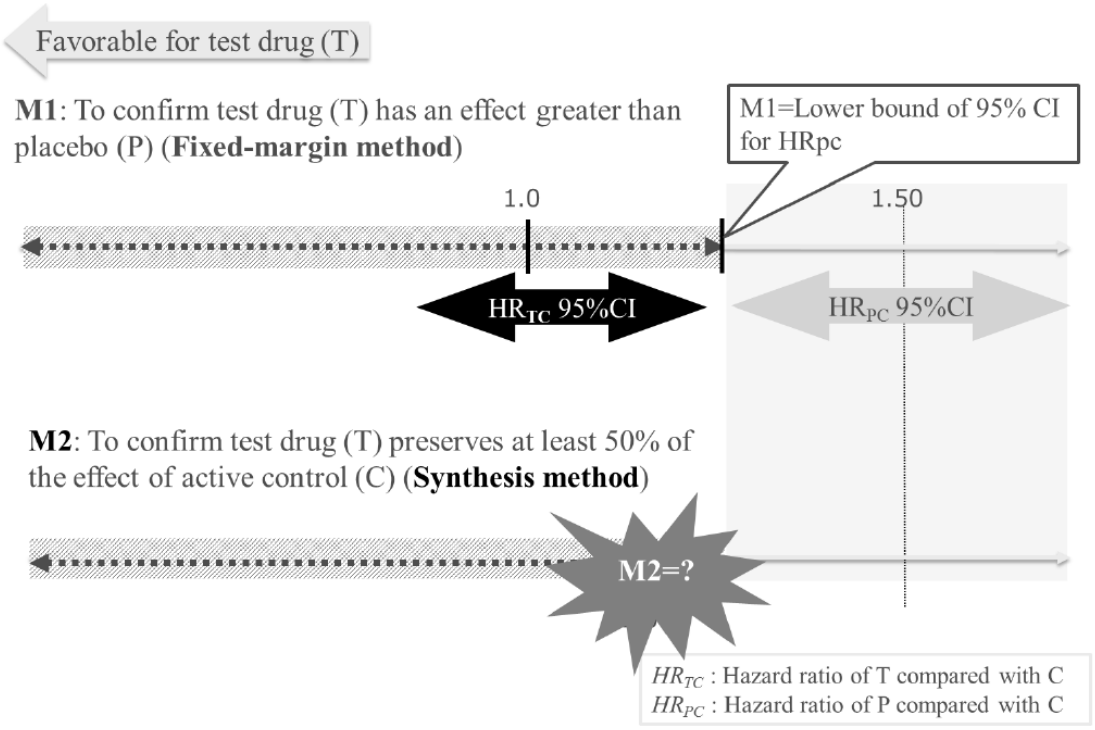


Figure 3-1. Conceptual illustration for M1 by a fixed-margin method and M2 by the synthesis method

3.1.4 Guidelines regarding NI in Japan

There is no regulatory guidance specifically focus on NI in Japan. There are two documents in Japan that include NI-related guidelines, as below.

A) Points to Consider for Reviewers Related to Review Practices for New Drug Approval[17]
B) Guideline for Product Information Brochures of Ethical Drugs[18]

PMDA reviewers require that an appropriate quantity of a NI margin be predefined for an NI study in NDAs according to Guideline A. Furthermore, a sponsor should show the NI margin(s) in a product information brochure, regardless of the statistical method used based on guideline B for a product information brochure.

3.2 Proposals: How to back-calculate the NI margin for the synthesis method

As a preparation, a hazard ratio for a clinical trial is calculated as below using an example of osteoporosis.

- Collect data of randomized date and date when a patient experiences a fracture at a clinical trial

If a patient does not experience a fracture, s/he will be treated as “Censored” at analyses

- Calculate “Time to fracture or concerned date” per patient
- Calculate Hazard = number of factures/total exposure time per treatment group
- Calculate the ratio of hazard rate between the treatment groups

By rearranging (3-1), the left side of (3-2) is equal to the upper bound of the 95% CI in natural log scale.

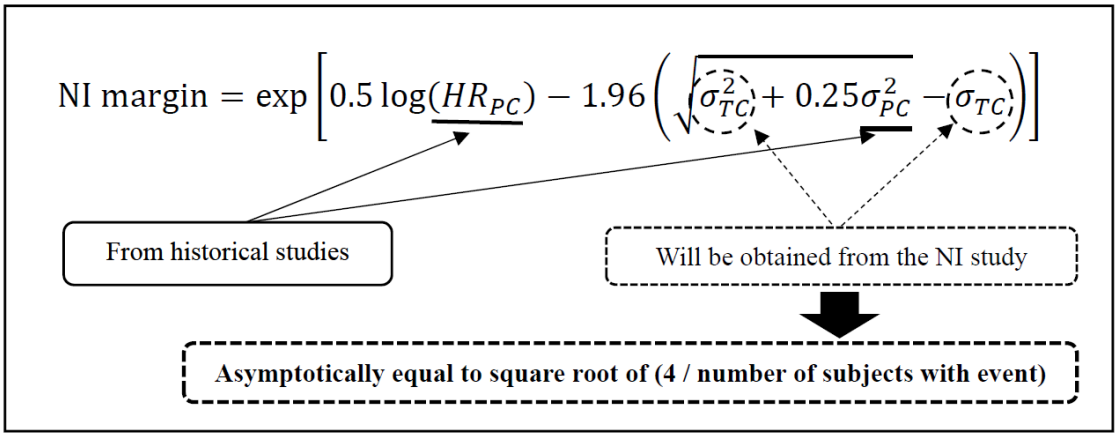
$$\log(HR_{TC}) - (1-\delta_0)\log(HR_{PC}) < -1.96\sqrt{\sigma_{TC}^2 + (1-\delta_0)^2\sigma_{PC}^2}$$

$$\log(HR_{TC}) + 1.96\sigma_{TC} < (1-\delta_0)\log(HR_{PC}) - 1.96\left(\sqrt{\sigma_{TC}^2 + (1-\delta_0)^2\sigma_{PC}^2} - \sigma_{TC}\right) \quad \text{---(3-2)}$$

By exponentiating both sides of (3-2), the NI margin is:

$$\exp\left[(1-\delta_0)\log(HR_{PC}) - 1.96\left(\sqrt{\sigma_{TC}^2 + (1-\delta_0)^2\sigma_{PC}^2} - \sigma_{TC}\right)\right] \text{ --- (3-3)}$$

(3-3) includes σ_{TC}, which will be obtained at the NI study to be conducted. This means the quantity of an NI margin is unable to be pre-specified for the synthesis method. However, σ_{TC} is asymptotically equal to the square root of $\{(r+1)^2/(E*r)\}$ when 1:r randomization is conducted and E is the total number of subjects with events. In cases of 1:1 randomization, σ_{TC} is the square root of (4/ number of subjects with events) [19, 20]. Based on the target number of subjects with event, the NI margin for the synthesis method was able to be back-calculated at the design stage for a NI study to be conducted. Figure 3-2 is an illustration of how to calculate the NI margin for the synthesis method.



*In case of an NI study to demonstrate whether test drug T preserves at least 50% of the treatment effect of C with 1:1 randomization

Figure 3-2. Method for calculating the NI margin in the synthesis method

3.3 Results and discussion

We back-calculated the NI margin for the synthesis method using a conceptual example of an NI study, as below.

- The objective was to confirm that T preserves at least 50% of the effect of C using the synthesis method (1:1 randomization)
- $HR_{PC} = 1.50$, $\sigma_{PC} = 0.075$ from historical studies
- The target number of subjects with event at an analysis point = 700

Based on (3-3), the back-calculated NI margin of the example was

$$\exp\left[0.5\log(1.5) - 1.96\left(\sqrt{\frac{4}{700} + 0.25 * 0.075^2} - \sqrt{\frac{4}{700}}\right)\right]$$

=1.204.

There are NI studies with the fixed-margin (M2) to preserve 50% or 67% fraction of the control effect in Japan[21, 22]. For time-to-event endpoint, since $\log(HR_{PT}) = \log(HR_{PC}) - \log(HR_{TC})$, a $100\delta_0$% preservation of the effect, i.e., $\log(HR_{PT}) = \delta_0 * \log(HR_{PC})$ implies a fixed-margin

$$\log(HR_{TC}) = (1 - \delta_0) * \log(HR_{PC}).$$

Therefore, the margins can be calculated as exp(log(HR_{PC})/2) or exp(log(HR_{PC})/3, respectively. In the above example, the back-calculated margin for the synthesis method (M2) is smaller than exp(log (HR_{PC})/2) (Figure 3-3).

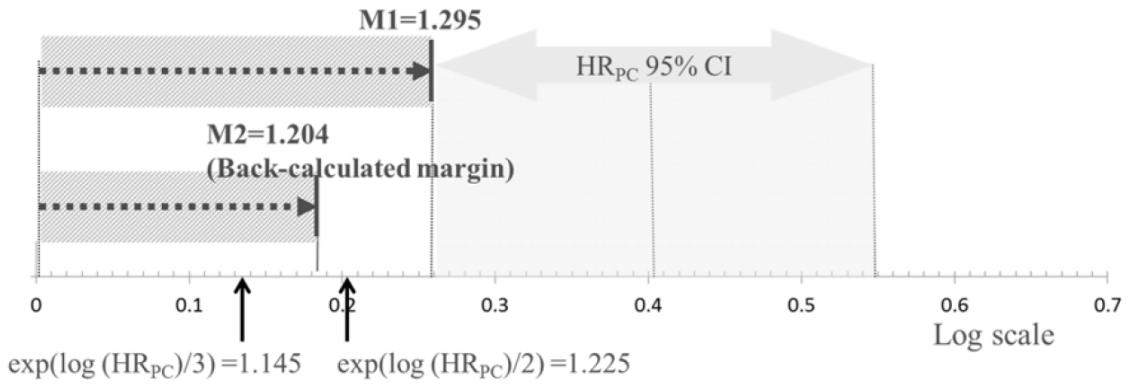


Figure 3-3. Calculated M2 compared with M1 and others

In the above example, if the number of subjects with event changes to 600–500, the back-calculated margin falls within 1.205 to 1.207. If the number of subjects with event changes to 800–1000, the back-calculated margin falls within 1.203 to 1.200.

A sponsor needs to select an appropriate statistical method for an NI study, then appropriately evaluate the results of the study regardless of the statistical method used. The feature of the synthesis method regarding the NI margin might affect NDAs for PMDA, especially when an NI

study with the synthesis method is used for global NDAs. The proposed method in this manuscript enables fulfilment of the guidelines in Japan.

Additionally, the proposed method provides stable values of the back-calculated margins, even if the actual number of subjects with event changes.

In general, it is required to use time-to-event endpoints (e.g., overall survival) for oncology, time to fracture for osteoporosis and time to heart disease event for ischemic heart disease. Therefore, clinical trials of major therapeutic area such as oncology would use HR to compare treatment effects of time-to-event endpoints. As the results, the proposed method could be applied to a broad therapeutic area of clinical trials.

The proposed method in this manuscript is able to produce the NI margin for the synthesis method in advance of conduct of an NI study and facilitates the use of the synthesis method for non-inferiority studies in Japan.

4. DEVELOPMENT OF A STATISTICAL ANALYSIS PROCEDURE FOR GLOBAL SUBMISSION AND JAPAN-SPECIFIC PREPARATIONS FOR E-DATA SUBMISSION TO THE PMDA

4. DEVELOPMENT OF A STATISTICAL ANALYSIS PROCEDURE FOR GLOBAL SUBMISSION AND JAPAN-SPECIFIC PREPARATIONS FOR E-DATA SUBMISSION TO THE PMDA

4.1 Background

4.1.1 Differences in clinical data standards and specifications

Sponsors need to conduct statistical analyses to generate clinical study reports (CSRs) on individual studies as well as perform integrated analyses used for the Common Technical Document (CTD) for regulatory authorities such as the Food and Drug Administration (FDA) and the PMDA. Standardization of analysis datasets across clinical studies is critical for the integrated analyses. The FDA has recommended that sponsors should submit electronic clinical study data using the CDISC standards since 2004, while the PMDA did not request electronic datasets (regardless of data standard) until 2016.

The FDA has mandated that sponsors must submit electronic datasets with CDISC standards for studies starting after December 17, 2016[22]. The PMDA started accepting electronic datasets for new NDAs from October 2016, with a transition period lasting until March 2020.[23] Both regulatory authorities require sponsors to use the CDISC standards, Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM); however, they accept different SDTM and ADaM versions[24, 25].

4.1.2 Decisions on clinical data package and NDA timeline

Sponsors should decide studies to be included in NDA submissions based on consultation meeting(s) with each regulatory authority. Studies conducted by partner companies and/or in other geographical regions may be included. Decisions on clinical data packages have an impact on the studies to be identified as integrated summary of safety (ISS) and/or effectiveness (ISE) and electronic datasets to be submitted. In terms of efficiency for sponsors, the PMDA, FDA and other health regulatory authorities would ideally require electronic datasets of the same studies to be submitted, but a certain authority might require electronic datasets for additional studies according to its local regulations and/or scientific reasons.

Differences in clinical data packages, integrated analyses and/or electronic datasets to be submitted, and additional analyses such as Japan-specific analyses may impact the timeline for each NDA submission.

4.1.3 Other differences and communication

Due to the regional and time zone differences between the US and Japan, it is necessary to consider the time spent on translation in addition to the time spent on strategy discussions and analyses. These considerations become critical when conducting additional analyses is required based on the queries from regulatory agencies and the clinical study team members are located in the US and Japan. Communication may become more complicated since the pathway involves various functions within each participating entity.

4.2 Proposals

4.2.1 Japan-specific TLFs to PMDA

We identified the Japan-specific analyses required by PMDA in advance. While FDA has developed guidelines for the submission of electronic investigational new drug application (IND) in the CTD format, it does not require specific analyses across clinical trials like PMDA. Some specific analyses may be required by the FDA depending on specific protocols, products, or indications after consultation with them. The three guidance documents listed below explain the tables, listings, and figures (TLFs) required for submissions to the PMDA.

A) Organization of Application Dossier Appended to New Drug Application (NDA) for Approval [26]

B) Format for Preparing the Common Technical Document for Submission of NDAs to Reduce Total Review Time [27]

C) Procedures for Implementation of Document-based Assessment and GCP On-site Inspection for Drug Application [28]

Certain TLFs are required for PMDA submission based on the guidance A, B, and C (Table 4-1). In addition, sponsors are expected to conduct several sub-group analyses using the Japanese population in a global trial[1]. Apart from the guidance documents, each agency might require different statistical analyses for the primary analysis or other important analyses, such as methods or metrics for multiplicity adjustments, non-inferiority or equivalence designs, even for an identical global trial[29,30].

Table 4-1. Tables, listings, and figures (TLFs) specifically required for PMDA submission (as of November 2021)

#	TLF	Remarks
1-1	Subject listings (For major studies that became the basis for dose-setting and major confirmatory studies on efficacy)	There is no clear guidance regarding which variables should be presented in the listings, but they would include demographics, major efficacy/safety endpoints and analysis population flags. The listing(s) can be omitted if electronic datasets are submitted[23].
1-2	Subject listings of adverse events (AEs) related to the investigational product(s)	See #2-1
1-3	Subject listings of serious AEs	
1-4	Subject listings of abnormal changes in laboratory tests	
1-5	Figures that appropriately display changes in laboratory values	Spaghetti plots or scatter plots can be created. The figure(s) can be omitted if electronic datasets are submitted[23].
2-1	Subject listings of AEs	All AE terms (MedDRA terms) in listings/tables should preferably be written in Japanese.
2-2	Summary tables of AEs by causality	The specific shell described in the guidance should be used. Tables should be presented in CTD section 2.7.4.
2-3	Summary tables of AEs by grade (For oncology projects)	The specific shell described in the guidance should be used. Tables should be presented in CTD section 2.7.4.
2-4	Summaries of AEs by time period (For long-term studies of non-life-threatening diseases)	Tables should be included in CTD section 2.7.4.

#	TLF	Remarks
3-1	Subject listings for discontinued subjects, protocol deviations, subjects excluded from efficacy analyses, demographics, AEs, other safety endpoints, abnormal values of laboratory tests, concomitant medications	The listings will be used for PMDA document-based assessment and GCP on-site inspection. If included in CSR section 16.2, these listings can be reused for the inspection.

Note: This table is based on Guidance A (#1-X), B (#2-X) and C (#3-X). Other TLFs may be required for a PMDA submission according to PMDA consultation meeting(s)

4.2.2 Development of a statistical analysis procedure for global submission and Japan-specific preparations for e-Data submission to the PMDA

We developed a three-step statistical analysis procedure for global NDA submission as described in Table 4-2. The steps include: A) developing a global NDA submission plan for a clinical data package, planning for consulting meetings with various regulatory agencies, and creating timelines for CTD preparation for each regulatory authority; B) specifying clinical studies to be included in the ISS/ISE and submitted as electronic data for each regulatory authority; and C) planning and implementing statistical analyses including (1) setting up the expectations and responsibilities for the statisticians, programmers, and team members of Japan and US sponsors, (2) creating the supplemental Statistical Analysis Plans (SAPs) for regional filing (such as Japan) based on the global SAP and country-specific requirements, (3) preparing statistical specifications for data derivation and TLFs, (4) creating CDISC datasets (SDTM/ADaM), and (5) generating TLFs with Figure 4-1 serving as an example of TLF shells required by the PMDA guidance documents.

Table 4-2. Statistical analysis procedure for global NDA submission

Step	Action
A. Global NDA submission plan	- Make decisions on clinical data package(s) - Develop timelines for consultation meetings with each regulatory agency - Develop timelines for CTD preparation and NDAs to each regulatory agency
B. Specification of clinical studies	- Specify clinical studies to be included in ISS/ISE - Specify clinical studies and analyses to be submitted as electronic data (SDTM, ADaM) to each regulatory agency
C. Statistical analyses 1. Project management planning	- Clarify RACI (Responsible, Accountable, Consulted, Informed) for Japan and US sponsors' statisticians, programmers and project team members - Establish communication plan - Set milestones and timeline
2. Creating Statistical Analysis Plan (SAP)	- Document SAP(s) considering the results of gap analyses regarding regulations or practices regarding statistical analysis between Japan PMDA and FDA - Finalize SAP(s) * If multiple SAPs are created (e.g., Global SAP and supplemental SAP for each regulatory agency), each CSR/CTD needs to clarify which SAP(s) and version(s) are used.
3. Preparing other statistical specifications	- Create specifications for SDTM/ADaM datasets - Create TLF shells with related information such as analysis variables and fragments of statistical programs * TLF shells for several Japan-specific analyses should be compliant with definitions or specifications described in the Japan guidance documents (example shown in Fig.1)
4. Creating SDTM/ADaM datasets	- Run programs to create SDTM/ADaM datasets * If SDTM/ADaM datasets are submitted to Japan PMDA, validation program with PMDA's validation rules should be run.
5. Generating TLFs	- Run programs to create TLFs

Table X.X. Adverse events by system organ class and preferred term ("All Grade" and "Grade 3 or higher" for treatment-emergent adverse events occurring with ≥ X% frequency in either arm)

(Safety Analysis Set)

System Organ Class Preferred Term	Treatment Group X N=xx		Treatment Group Y N=xx	
	All Grade n (%)	Grade 3 or higher n (%)	All Grade n (%)	Grade 3 or higher n (%)
Number of subjects reporting at least one adverse event	x (x.d)	x (x.d)	x (x.d)	x (x.d)
SOC 1 (in Japanese)	x (x.d)	x (x.d)	x (x.d)	x (x.d)
PT1-1 (in Japanese)	x (x.d)	x (x.d)	x (x.d)	x (x.d)
PT1-2 (in Japanese)	x (x.d)	x (x.d)	x (x.d)	x (x.d)
<...>	x (x.d)	x (x.d)	x (x.d)	x (x.d)
<...>				

Figure 4-1. An example of TLF shells required by the PMDA guidance documents

CDISC datasets should be validated by both PMDA and FDA guidelines if both submissions are planned. For a PMDA submission, if any validation issue categorized as "Error" has not been resolved, the sponsor must explain it in a briefing document with a specific format called "Attachment 8"[31], and receive agreement on them from the PMDA prior to an NDA submission.

4.2.3 Development of a regulatory response process to PMDA

In addition, we developed a response process for the queries from PMDA in the case where the clinical database is located within a US company, considering efficient use of the time difference between Japan and the US. Figure 4-2 shows the regulatory response process including the assignment of roles and responsibilities in handling and triage of queries based on the necessities of additional analyses.

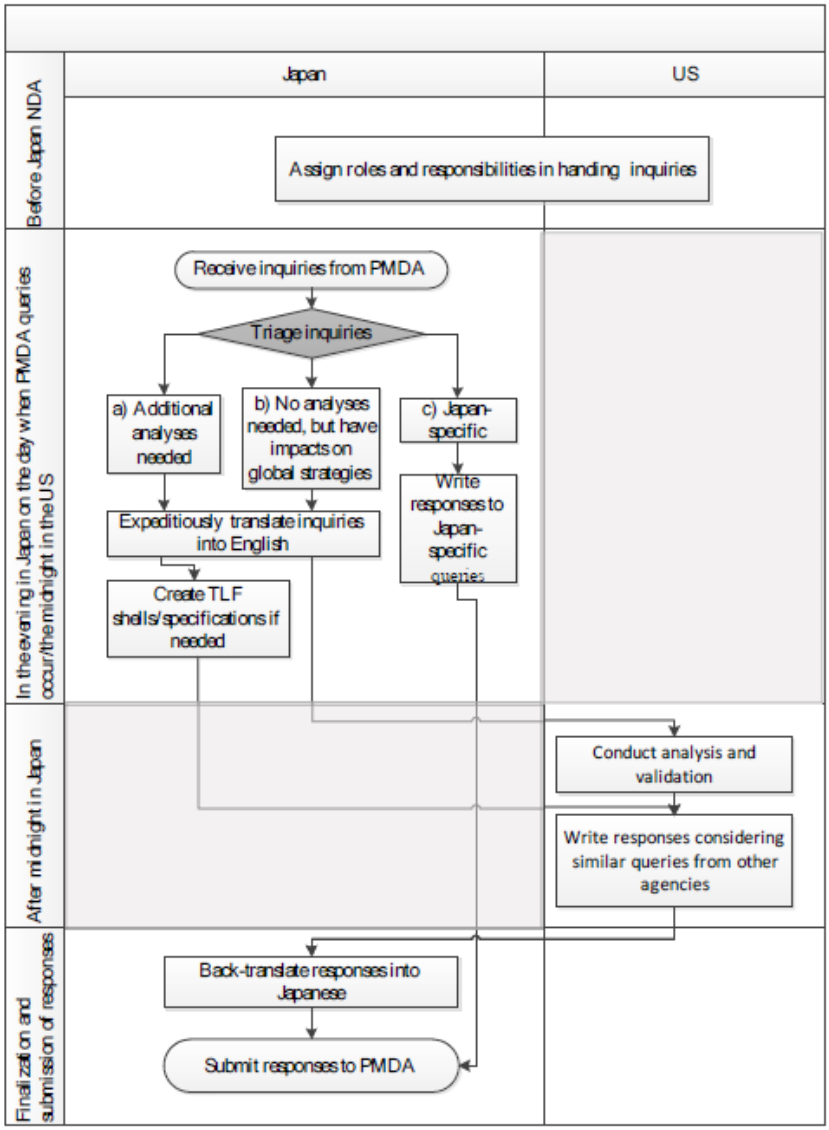


Figure 4-2. Regulatory response process for queries from the PMDA for global drug development

4.3 Results and discussion

We applied the process for implementing statistical analyses and regulatory responses, as described above, to four global drug development projects in the therapeutics of oncology and bone. Each project included more than two global trials including Japan, and 1-2 Japan local studies. Although each project was slightly different in terms of number of clinical studies, the following benefits were gained for all submissions:

- We were able to plan and prepare all TLFs required by the PMDA
- We were able to use resources efficiently between Japanese and US project members
- We were able to use datasets and analyses for both PMDA and FDA submissions, thus minimizing the need for PMDA-specific additional analyses
- Statistical analysis and related tasks were prepared early as planned and did not become a road-block on the NDA timeline
- We were able to prepare TLFs and responses in a timely manner for queries from the PMDA

The full-time equivalent (FTE) for statisticians in Japan was reduced by approximately 50% in the four submissions based on actual time and human resource needed using the proposed process compared to other global projects not using it. It is difficult to compare these accurately to other NDAs since some conditions, such as the number of clinical trials included in an NDA package, were different; however, the average FTEs were 12 while using the proposed process compared to 24 while using the standard process in terms of statistical works including creating SAPs, TFL shells and other related specifications.

As described above, the PMDA requires Japan-specific TLFs (Table 4-1) that would necessitate additional resources and impact an NDA timeline. Lack of awareness about the Japan-specific TLFs and documentation required by the PMDA may be one of the reasons for the sponsors not filing the Japan NDA included in global simultaneous NDA filings[32]. In addition, the two types of PMDA consultation meetings should be held and briefing document "Attachment 8 Form A" should be finalized accordingly prior to NDA submission, which may cause a delay in the NDA submission of global drug development projects. We believe that the submitted electronic CDISC SDTM and/or ADaM datasets can be used to substitute several PMDA-required TLFs listed in Table 4-1 such as various listings of Adverse Events (AEs) (#1-2, #1-3, and #2-1), subject listings of abnormal changes in laboratory tests (#1-5), and other subject listings (#3-1). These listings are redundant with the SDTM and/or ADaM datasets since the datasets contain all the information present in these listings and the reviewers can find the information in the datasets directly. We encourage an active discussion between the industry and PMDA to consider the CDISC datasets as sufficient for submission, without requiring Japan-specific TLFs. We expect that Japan-specific listings will no longer be required in the future.

Any delay in responses to queries during review period would cause delay in marketing approval by the regulatory agencies. If we prepare responses with additional analyses in a global drug development project, additional analyses might require more time than that for a local Japan project because of the differences in geographic locations and languages. Thus, we have proposed the regulatory response process (Figure 4-2) to reduce the negative impacts and utilize the differences, which has accelerated the regulatory responses of global drug development.

To further improve efficiency based on the proposed statistical procedure, we have proceeded with automation of statistical analyses for global development. First, we developed automated translation tool of adverse event TLFs according to PMDA regulation. Additionally, we produced a semi-automated macro to create Analysis Results Metadata required by PMDA. Furthermore, we plan to develop a automated macro to generate Japan-specific TLFs.

5. OVERALL DISCUSSION

5. OVERALL DISCUSSION

5.1 Significance of this research

Table 5-1 summarizes the significance of this research from both of practical and academical perspectives. The proposed solution for the difference 1 enables to use the same CI between US and Japan from a practical perspective. In addition, it can reduce the sample size of the patients considering the type I error rate based on TOST from a statistical perspective. The solution for the difference 2 enables to use the synthesis method for PMDA submissions which are used for FDA submissions from a practical perspective and enable to calculate the non-inferiority margin based on the statistical approximation. Regarding the solution for the difference 3,4 and 5, it enables to use resources efficiently between Japanese and US project members, and datasets and analyses for both PMDA and FDA submissions, thereby minimizing the need for PMDA-specific additional analyses from a practical perspective. In addition, it can be enhanced for another process of global drug development in terms of project management framework.

Table 5-1. Significance of this research from practical and academical perspectives

	1. Statistical analysis plan		2. Analysis datasets		3. Analysis results
Diff. of regulations between Japan and US/EU	Diff-1. Equivalence Study design for Biosimilars	Diff-2. Non-inferiority Study design	Diff-3. Format of datasets	Diff-4. Data validation document	Diff-5. Additional tables and listings only for Japan
Practical significance from this research	-Can use the same CI between US and Japan	-Can use the synthesis method for PMDA	- Can use resources efficiently between Japanese and US project members - Can datasets and analyses for both PMDA and FDA submissions, thus minimizing the need for PMDA-specific additional analyses		
Academic significance from this research	-Can reduce sample size of patients considering Type I error from TOST	- Can calculate the non-inferiority margin based on the statistical approximation	- Can be enhanced another process of global drug development in terms of project management framework		

Abbreviation: Diff, difference.

5.2 Impact by the proposed methods on the PMDA review process

"Drug lag" is one of major issues in the Japanese pharmaceutical industry and PMDA. This would accelerate the Japanese participants in global clinical trials and global drug development. In general, "Drug lag" is defined as the sum of the following (Table 5-2)[33].

Table 5-2. Two elements of "Drug lag"

Element	Definition	In Japanese
1. Development lag	Median difference from the time of application in US for new drugs applied for new approval in Japan	"Kaihatsu" lag
2. Review lag	Median difference for total examination period (median) of newly approved new drugs between Japan and US	"Shinsa" lag

The proposed solutions would reduce mainly the duration of 1. Development lag ("Kaihatsu" lag) which would be spent in an applicant (pharmaceutical company) for a PMDA submission. Thus, we consider there would be no negative impact on the quality of PMDA review process.

5.3 Clinical studies to which the proposed methods can apply

The percentage of global clinical trials was 50.9% (389/764) per all the clinical trials which were registered to PMDA in the fiscal year of 2018[34]. In the situation, “Development lag" from 2017 to 2019 were 0.2, 0.7 and 0.5 years, respectively. “Development lag" still exists by approximately half a year[35]. Many global clinical studies targeting submission to PMDA could be beneficial by applying the proposed methods.

Additionally, there are two perspectives for “Drug lag” in global drug development (Table 5-3)[36].

Table 5-3. Two perspectives of “Drug lag”

Perspective	Situation
A) Not approved in Japan	The marketing authorizations were granted for a drug in foreign countries but not in Japan.
B) Late approved in Japan	It took longer time in Japan compared with in foreign countries until the marketing authorization was granted for a drug.

Regarding B) Late approved in Japan, the delay in approval in Japan could shorten the period until the expiration of the patent period, and as a result, the amount of money that pharmaceutical companies can "recover" might be reduced. Therefore, we concern that Japan might be lower prioritized in the global development strategy (i.e., drug development and NDA in Japan might not be done)[37, 38]. The solutions from this research could reduce not only the loss in the above-mentioned pharmaceutical companies but also the loss that patients in Japan do not have access to optimal medical care.

The solution for the difference 1 can be referred to almost all the Biosimilar in Japan which evaluate efficacy. The solution for the difference 2 can be used for non-inferiority and equivalence designs. The solution for the difference 3-5 can be used for all the global drug development which will be submitted to PMDA.

5.4 PMDA's policy

PMDA has a unique three-pillar system follows[39].

1. Relief- Relief measures for health damages cause by adverse drug reactions
2. Review- Reduction in risk
3. Safety- Continues risk mitigation efforts

In Japan, there were several lawsuits concerning drug-induced suffering in the past and it might cause conservative attitude at PMDA. PMDA and JPMA have been continuously discussing e-Data/CDISC regulations since 2014, however, there are still differences between PMDA and FDA. In addition, lack of number of staff at PMDA compared to FDA's might be impactful on the regulatory differences. PMDA/MHLW had 636 staff of review departments and FDA has approximately 5400 staff of review departments as of 2014[40].

6. CONCLUSION

6. CONCLUSION

I have provided several solutions and resolved the issues caused by the five differences in the regulation of statistical analyses.

I explained and proposed to use two one-sided tests (TOST) and the type I error rate for equivalence design of clinical efficacy studies in Biosimilar, for which there has been little discussion in Japan. By using the proposed method, the number of subjects could be reduced and some existing confusion about different statistical settings between PMDA and FDA for an identical clinical trial could be avoided.

The proposed method to visualize the non-inferiority margin (NI) for the synthesis method can produce the NI margin for the synthesis method in advance of conduct of an NI study and facilitates the use of the synthesis method for NI studies in Japan.

The proposed procedure for implementing statistical analyses and regulatory responses for NDAs aims to understand the differences in regulatory authority, geographic region, and time zone between Japan and the US to conduct statistical analyses for global clinical trials in an appropriate manner. It has also enhanced the quality of global submissions by allowing the team to plan any quality management work required before PMDA submission.

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