An Overview of Bridging Study Evaluation in Taiwan

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In 2001, the Bridging Study Evaluation (BSE) review process based on the ICH E5 guideline was introduced in Taiwan. The purpose of BSE is to assess the impact of ethnic factors on a drug's safety and efficacy and to determine whether pharmaceutical sponsors should conduct regional bridging studies in Taiwan. In this report, we provide the background and experience of BSE implementation in Taiwan and its influence on the global drug development process. Our BSE review process, allowing bridging studies to be waived, has successfully prevented conducting clinical trials with meaningless results. The trend of Investigational New Drug Application submission after New Drug Application (post-NDA) in other countries has also been shifted to the pre-NDA stage. The implementation of BSE in new regions has encouraged the pharmaceutical industry to consider the impact of ethnic factors in the early phase of clinical studies.

INTRODUCTION

In order to harmonize the regulatory requirements of the drug development process based on good regulatory science, Japan, the United States, and members of the European Union have worked together to establish the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) since 1990. The ICH announced a guideline (ICH E5) that recommends a number of criteria for evaluating the impact of ethnic factors that may affect a drug's safety and efficacy in order to extrapolate clinical data between different regions in 1998. The ethnic factors, including intrinsic and extrinsic factors, should be taken into consideration during drug development as well as the approval process (1). In Taiwan, a local registration trial with a minimum of 40 subjects was requested for New Drug Application (NDA) when the "July 7 Announcement" was issued in 1993. In compliance with the principles of the ICH E5 guideline and in order to prevent conducting clinical trials with meaningless results, the Department of Health (DoH) revoked the July 7 Announcement and issued the "Double Twelve Announcement" on December 12, 2000. The Double Twelve Announcement introduced the concept of bridging study evaluation (BSE). The purpose of BSE is to assess whether the target population using the drug in Taiwan would be affected by ethnic factors and whether the bridging studies could be waived. When bridging studies cannot be waived, the study design should aim to resolve the ethnic concern for pharmacokinetics (PK), pharmacodynamics (PD), and clinical safety and efficacy. This information can then be used to extrapolate the foreign clinical data to the new region with appropriate labeling (2).

On January 1, 2004, the Double Twelve Announcement replaced the July 7 Announcement and has been enforced fully ever since. Currently pharmaceutical sponsors are recommended to submit an application for BSE evaluation before or at the same time as NDA. When regional clinical trials are not waived, the sponsor is encouraged to submit more relevant data or design clinical protocols according to the recommendations for BSE.

REVIEW PRINCIPLES

The waiver of bridging studies depends on the following two considerations: First, whether the bridging data package meets the regional regulatory requirements and, second, whether the foreign clinical data can be extrapolated to the new region. In Taiwan, a complete bridging data package includes a summary of relevant PK, PD, and clinical data on efficacy and safety with special emphasis on the Asian population if avail-

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able. Dose-response studies and safety and efficacy studies should be adequate and well controlled with appropriate study endpoints. These studies should also fulfill good clinical practice (GCP). The BSE review process is to evaluate whether the intrinsic and extrinsic ethnic factors would modulate the foreign clinical profile and whether the foreign clinical data can be extrapolated to the regional population.

The intrinsic factors include, but are not limited to, age, gender, or organ dysfunction that are used to identify a subpopulation. A medicine's sensitivity to intrinsic factors is evaluated by its properties including PK linearity, PD curve profile, therapeutic ranges, metabolic pathway, genetic polymorphism, enzymatic conversion of pro-drugs, and variation in bioavailability. The environment and culture in which a person resides can also affect the clinical profile of a medicine. They are the so-called extrinsic factors that include, but are not limited to, regional medical practice, diet, the likelihood of use in a setting of multiple comedications, inappropriate use, and difference in indication (as shown in the checklist).

In Taiwan, we also consider the regional knowledge of the epidemiology of the target population such as incidence, demography, etiology, natural history, prognosis, response to similar drugs on the market, and so on in addition to those factors mentioned in ICH E5. An example at hand is antimicrobial drugs. The major concern of ethnic sensitivity is the potential differences in minimum inhibitory concentrations (MIC) among different regions. We recommend that the sponsor provide data to demonstrate that the foreign MIC values are comparable to those of Taiwan. In summary, when a factor is considered ethnically sensitive and clinically significant in BSE, bridging studies cannot be waived in Taiwan.

WORKING DEFINITION OF ETHNIC GROUP FOR BSE

For BSE, the working definition of "ethnic group" should not be defined as race, citizenship, or geographical district, all of which, however, are useful and convenient to administer. To extrapolate clinical data from one region to another new region, we are comparing if the clinical data of the target population taking a specific drug, that is, the ethnic group of one region, can be extrapolated to another target population taking the same specific drug, that is, the ethnic group of another region. The level of ethnic sensitivity is related to (a) the characteristics of the drug, (b) the epidemiology of the target population, and (c) the clinical impact considering all ethnic factors in totality. Race, such as Caucasian, Asian, or black, can be regarded as a relevant reference in evaluating genetic distance. However, we should not overemphasize race up to the country level, such as Chinese, Korean, or Japanese, unless there is relevant evidence to indicate that. A study of genetic distance among multiple ethnic groups using highly polymorphic HLA genotyping by M. Lin (3) has shown that Asians can be classified roughly into two clusters of northern and southern Asians. Historically, the genetic pool of Taiwanese was composed of both northern and southern Asians. Hence, we decided that all Asian data wold be considered a relevant reference for our BSE without administrative requirements for Taiwanese data in general.

PERCENTAGE OF WAIVED BRIDGING STUDIES AFTER BSE

After the Double Twelve Announcement, a total of 338 BSE applications were submitted up to the end of 2008. These applications include submissions from the domestic as well as the overseas pharmaceutical sponsors (Table 1). There were a higher number of applications (29 cases) from the domestic industry in 2006 in comparison to other years (0 to 8 cases). This is possibly due to the announcement that there would be an application fee increase in the following year. The number of submitted BSEs from the overseas industry continues to increase, possibly due to the increase of NDA submissions from abroad.

The percentage of bridging study waivers reached as high as 86% in 2002; however, the average percentage has stayed at approximately 58% (Table 1). The possible explanation for the

Checklist for Bridging Study Evaluation				Data Yes	Data No	Vol. No. (Page No.)
I. Worldwide regulatory status				☐	☐	
II. NDA expert report or investigator's brochure (Please provide information for comparison between different ethnic groups if available)				☐	☐	
III. Clinical data on pharmacokinetic, safety, and efficacy from Asian population (Such as PK data of Japanese, clinical data from Taiwanese, sample size and percentage of Asian subjects)				☐	☐	
IV. Clinical data on PK, safety, and efficacy in Asians and its comparison with other ethnic groups				☐	☐	
V. Self-evaluation (Please provide data or literature underlying the evaluation)	Y	N	U[3]	☐	☐	
1. Nonlinear pharmacokinetics?	☐	☐	☐	☐	☐	
2. A steep pharmacodynamic (effect-concentration) curve for both efficacy and safety in the range of the recommended dosage and dose regimen (this may mean that the drug is well tolerated)	☐	☐	☐	☐	☐	
3. A narrow therapeutic dose range	☐	☐	☐	☐	☐	
4. Highly metabolized, especially through a single pathway, thereby increasing the potential for drug-drug interaction	☐	☐	☐	☐	☐	
5. Metabolism by enzymes known to show genetic polymorphism	☐	☐	☐	☐	☐	
6. Administration as a prodrug, with the potential for ethnically variable enzymatic conversion	☐	☐	☐	☐	☐	
7. High intersubject variation in bioavailability	☐	☐	☐	☐	☐	
8. Low bioavailability, thus more susceptible to dietary absorption effects	☐	☐	☐	☐	☐	
9. High likelihood of use in a setting of multiple comedications	☐	☐	☐	☐	☐	
10. High likelihood for inappropriate use, eg, analgesics and tranquilizers	☐	☐	☐	☐	☐	
11. Different indications and/or epidemiology (including natural history of diseases, disease mechanism, disease prevalence, and efficacy/ safety of similar drugs)	☐	☐	☐	☐	☐	
12. Other important factors of ethnic sensitivity (eg, medical practice)	☐	☐	☐	☐	☐	
VI. Postmarketing safety surveillance				☐	☐	
Conclusion of Self-Evaluation Based upon the above considerations, please evaluate whether the drug under assessment is of any clinical or risk/benefit impact, such as whether indications are for serious disorders, whether there are alternative therapies, and whether the ethnic differences are tolerable.				☐	☐	

Notes:
1. For efficient review, please clearly indicate the volumes and page numbers of the submitted documents. When necessary, please highlight the paragraphs or section containing the important information. For example, the section of comparative data between different ethnic groups in NDA expert report. If data are not available or not provided, such statement needs to be present in the documents.
2. Please provide descriptive summary or brief description of enclosed information in order according to the checklist.
3. Y=Yes, N=No, U=Unknown.

TABLE 1

Number of BSE Submissions by Sponsors and the Percentage of Bridging Study Waived Cases in Taiwan

	Sponsor			
Year	Domestic	Overseas	Total Cases Per Year	Percentage of Waived Cases Per Year
2001	1	17	18	61
2002	0	28	28	86
2003	6	26	32	61
2004	8	36	44	61
2005	4	37	41	44
2006	29	42	71	63
2007	5	41	46	44
2008	3	55	58	47
Sum	56	282	338	—
Average	7	35	42	58

waived percentage reaching as low as 44% and 47% in recent years may be because more NDAs were submitted to other global regions that include Taiwan around the same time. Such a trend may result in a lack of clinical data for the Asian population in a BSE submission.

Among the total BSE submissions, pharmaceutical sponsors are requested to provide additional bridging study reports in 10% of the evaluated applications. After the BSE data are updated, 46% of the bridging study–supplemented data packages are granted a waiver, indicating the importance of a complete clinical data package. Because the commitment of bridging studies may lead to the delay of NDA approval and hence defer access to the new drug to the general public, we encourage the pharmaceutical industry to include the Asian population in the early phase of clinical trials.

REASONS FOR NOT GRANTING A WAIVER

There are a number of reasons why a bridging study waiver is not granted, including insufficient clinical data package, efficacy and safety concerns, and concerns over ethnic sensitivity (Table 2). A clinical data package is considered insufficient due to the following reasons. An insufficient clinical data package usually lacks adequate data in PK, PD, safety, and efficacy; clinical data on the Asian population; or epidemiology data in Taiwan. The following situations are considered insufficient: when safety data in clinical trials cannot support long-term clinical use of the drug, when efficacy cannot be demonstrated in clinical trials, and when clinical trials are not qualified because of inappropriate clinical or surrogate endpoints. When there is deficiency in clinical trials, the safety and efficacy of drugs cannot be established. Some BSE applications only provide safety and efficacy data from studies in the original country, which is not sufficient to be granted a waiver in Taiwan. Lack of clinical data on the Asian population often poses difficulty in the extrapolation of the foreign data to Taiwan, especially for drugs of new mechanisms. The other reason for not granting a waiver is the determination of optimal dosage regimen in drugs with narrow therapeutic range to the population in Taiwan. Therefore, the lack of clinical data in the Asian population is the main reason for not granting a waiver (50%). The subsequent bridging study designs should aim to resolve the issues.

Reasons for Not Granting a Waiver (103 Cases) in the BSE Review Process

TABLE 2

Reason	Number (%)
Insufficient clinical data package	
Lack of clinical data for the Asian population	52 (50)
Lack of pharmacokinetic profiles	27 (26)
Lack all of PK/PD, safety, and efficacy data	12 (12)
Lack of epidemiology in Taiwan	6 (6)
Efficacy and safety concerns	
Inadequate dose or dosage regiment	28 (27)
Potential for ethnic differences	24 (23)
Safety concerns	16 (16)
Efficacy concerns	15 (15)
Other	
Unqualified clinical trials	3 (3)
Quoted insufficient data	3 (3)

THE IMPACT OF THE BSE REVIEW PROCESS

The introduction of BSE in 2001 has influenced the timeline of IND submissions in Taiwan. The number of IND submissions from 1994 to 2008 is shown in Figure 1. The timeline of IND can be broadly divided into pre-NDA and post-NDA based on whether the test drug has been approved anywhere in the world. The IND submissions pre-NDA are usually submitted by pharmaceutical sponsors during the global drug development process. The IND submissions post-NDA may have resulted from the implementation of the July 7 Announcement for country-specific requirements or marketing purposes. Before 2001, the number of IND submissions post-NDA is close to that pre-NDA. Following the introduction of BSE, the number of IND post-NDA is reduced from 66 cases in 2001 to less than 12 onward. The number of IND pre-NDA increased from 64 in 2001 to 138 cases in

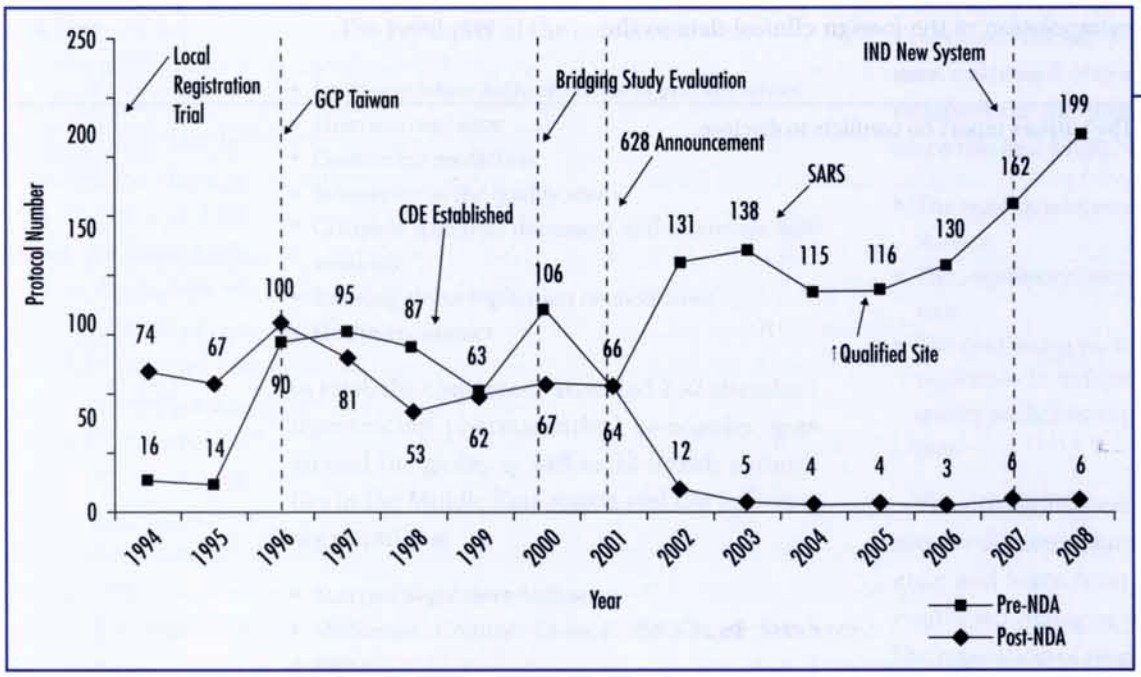

FIGURE 1

The number of protocol applications in Taiwan (1994–2008).

2003. This was followed by a slight drop due to the severe acute respiratory syndrome (SARS) outbreak. The implementation of BSE has shifted the timeline of IND submission in Taiwan from the post-NDA to the pre-NDA stage. It is clear that the pharmaceutical industry has started to consider ethnic factors in the drug development process.

CONCLUSION

In accordance with the July 7 Announcement, a local registration trial with a minimum of 40 subjects was requested for NDA in Taiwan. The minimal sample size of 40 subjects has been criticized as lacking statistical validity. When the Double Twelve Announcement replaced the July 7 Announcement, the BSE review process was enforced fully in Taiwan. In the review process, foreign clinical data are evaluated to decide whether bridging studies should be conducted or could be waived instead of the compulsory local registration trial.

In certain countries, a bridging data package must include clinical data of subjects of the country where the drug is to be marketed. However, bridging data are acceptable in Taiwan; that is, data from Asian populations such as Japanese, Koreans, and Thais are considered as relevant references in the BSE review process. When the sponsor submits Asian data that allow extrapolation of the foreign clinical data to the population in Taiwan during the BSE review process, bridging studies are usually waived even without Taiwanese data.

The implementation of BSE has also influenced the timeline of IND submission in Taiwan. The trend of IND submissions in the post-NDA stage has also been shifted to the pre-NDA stage. This observation may indicate that pharmaceutical sponsors have taken ethnic factors into consideration in the drug development process and begin to collect clinical data of the Asian population in early phase studies. When such a strategy is adopted by the industry, clinical data of the Asian population would be available for BSE and hence expedite NDA approval in Taiwan.

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