Implementation of Bridging Strategy in Taiwan

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Introduction

Recently, with the advance of human genome decoding and pharmacogenomics, issues on ethnic and population differences have taken the center stage in the new drug approval process. Since most of the new medicines were developed in western countries, the efficacy and safety of a drug was generally established based on Caucasian majority. Whether the foreign clinical data could be naively extrapolated to the population of a new region would be a major concern, especially in Asia. In March 1997, a consensus has been reached for ICH-E5 (1). The guidelines address both the intrinsic and the extrinsic factors that are associated with drug characteristics, culture and environment; and provide a framework for evaluating the impact of ethnic factors upon the medicines’ effect. The principal objective of E5 is to expedite the global development and availability of new medicines to patients without sacrificing the quality, safety and efficacy. While minimizing duplication of clinical studies, the guidelines also facilitate the use of bridging studies to allow extrapolation of foreign clinical data to a new region. Since the introduction of ICH-E5 and the bridging concepts, awareness has increased among nations about the need for local clinical trials. Many Asian countries including Japan, Korea, and Taiwan, have formally announced the implementation of the bridging study requirement. Other Asian countries are also showing great interest in setting up a well-designed bridging study system.

In order to create a united Asian market under the harmonized regulatory system, Taiwan is leading and promoting the “APEC (Asian Pacific Economic Cooperation) Network of Pharmaceutical Regulatory Science - APEC Joint Research Project on Bridging Study”. Two regional workshops were held in Taipei in 2000, and 2001. Scientific data related to ethnic factors were reviewed systematically in the meetings. With the help from CDE (Center for Drug Evaluation), the Department of Health has successfully developed a sponsor self-evaluation check-list, a decision-making tree, and consultation
procedures (see CDE Website at <www.cde.org.tw>). As well, the Department has planned educational workshops and set up a statistical working group. Requirement of a possible bridging study was formally announced on Dec. 12, 2000, giving a 2-year transition period (until Dec. 12, 2002) to phase out the current local registration trial requirement.

**Evaluating the necessity of a bridging study**

In general, Taiwan accepts all Asian data. A study by Lin et al. in 2001 (2) found that the so-called “Taiwanese”, accounting for 91% of the total population in Taiwan, is comprised of Minnan and Hakka people who are closely related to the southern Han, and are clustered with other southern Asian populations in terms of HLA typing. Those who are the descendants of northern Han are separated from the southern Asian cluster, and form a cluster with the other northern Asian populations. As the Taiwanese regulatory authority acknowledges the trial data conducted in Taiwan regardless of the ethnic origin of the subjects, it will acknowledge all Asian data as well.

From the regulatory point of view, ethnic factor should not be defined completely by “Citizenship” or “Race”. In the evaluation of ethnic differences, “Drug Characteristics” and “Indication” are the two fundamental elements to be considered. For example, some medicines are metabolized by enzymes with genetic polymorphism. If there is a higher percentage of poor metabolizers in Taiwanese patient population for a particular drug, adjustment of the claimed marketing dose may become necessary. Usually, hepato-toxicity is a major safety concern in bridging assessment. Due to the high prevalence rate (18%-20%) of HBsAg carriers in Taiwan, the need for more experiences with the usage of liver toxic agents in hepatitis B or C carriers may lead to the necessity of an additional bridging study. Difference in disease epidemiology and disease manifestations is another important issue. As illustrated in the case with female postmenopausal syndrome, Caucasian women usually present more vasomotor symptoms in contrast to Taiwanese women in whom vasomotor symptoms are not predominant (3). Therefore, new agents whose efficacy was demonstrated by improved Kupperman Index score (which is weighted on vasomotor symptom domain) may not be accepted outright. Further investigations on Taiwanese postmenopausal women, using an index scale more suitable for this
population (i.e., Greene Climacteric Scale) may be needed. Furthermore, medical practice between regions usually reflects one of the greatest variation and is the most difficult to harmonize. Differences in diagnostic criteria for some diseases, potential of drug abuse and possible drug-drug interactions are all essential considerations in evaluation for bridging studies.

In the past, little Asian clinical data were provided with the clinical data package used for new drug registration in Taiwan. Statisticians usually made no contribution in the bridging assessment since no information could be obtained from such limited data points. In some situations, PK profile obtained from a small number of Asian subjects might be presented. For such cases, the point estimate, 95% confidence interval and the corresponding descriptive plot for each PK parameter might be compared among ethnic groups by scientific judgement rather than a formal statistical procedure. Recently, in compliance with the ICH E5 and the regional needs for Asian data, as well as a good clinical research infrastructure being set up in the Asian regions, more and more industry sponsors have agreed to involve Asian populations in global R & D trials, i.e., early phase IIIa trials. For a concurrently performed multinational, multicenter phase III trial including Asian clinical sites as study centers, the “consistency trial” approach by Shih (4) may be applied to the evaluation of the bridging evidence. In some particular cases, an early phase III trial is performed completely on Asian population, using an identical protocol as the concurrently ongoing Caucasian trial. For such cases, conventional meta-analysis by pooling the data from two or more trials may be utilized to detect the heterogeneity between and/or among patient populations.

Designing a bridging study

The acceptance of foreign clinical data will depend completely on its ability to be extrapolated to Taiwanese population. When this is in doubt, supplemental bridging data may be requested by the regulatory authority. In general, bridging study could be widely applicable to trials of any phase, including pharmacokinetic and pharmacodynamic studies, and phase III controlled clinical trials. However, a phase III controlled clinical trial is preferred because it is the most favorable study when there are uncertainties about dose, when there is limited experience with the drug class, or when there are safety concerns.
Ideally, a bridging phase III trial should have a study design identical to the foreign pivotal study. However, a full phase III clinical trial may not be practical considering small individual market in the local region. To remedy this and to accelerate the approval of a good medicine to be marketed in Taiwan, several compromising strategies are proposed. For example, we may allow the widely accepted surrogate endpoints to serve as primary efficacy endpoints, i.e., bone density in place of bone fracture in osteoporosis trials and objective tumor response rate in place of patient survival in cancer trials. Under some circumstances, the study period may be shortened if clinically justifiable. Though a sample size computed to powerfully address similar efficacy and safety to those of pivotal studies is scientifically more sound, it is to our knowledge that the calculated sample size is often too large to be practical. Alternatively, a positive drug effect ($d_N$) in Asian population is thought to be sufficient in sample size justification given that the effect of the original pivotal studies ($d_O$) has been shown positive, and, $d_N$ is within an acceptable range of $d_O$ (5). In terms of significance level and power used in computing required sample size, we consider protecting only the type I error. The one-sided alpha level could be relaxed with an upper bound of 10%. As for the power, we deem it the sponsor’s responsibility.

**Conclusions**

The new requirements for bridging study have ushered a new paradigm for regulatory approvals in Taiwan. Previous administrative formality such as the requirement of small-scale local registration trial for all drugs and free sale certificates will be gradually phased out. However, to draw a statistical inference with regard to bridging evidence by comparing two extremely unbalanced samples (i.e., size 20:1) of two patient populations from a single trial, or two separate studies is non-trivial. The statistical work on this field is still in a preliminary stage. We encourage all ICSA members to join us in settling these interesting and challenging issues.

Perhaps what is more important than the specifics of our statistical approach is that all pharmaceutical parties worldwide should work collaboratively in the process of new drug development. We would emphasize that “bridging study” is only a transitional strategy. We believe that with accumulated empirical experiences over time, bi-directional
extrapolation (Asian data being extrapolated to European population and vice versa) for several classes of drugs will become a reality and, therefore, additional local clinical trials will not be needed.

With the implementation of ICH E5 accompanied by practice of good regulatory sciences, great opportunities exist for Taiwan to participate in the global R & D and to establish sound IND consultation process. These efforts will ultimately benefit the health of Taiwan populations.

References