Implications of ICH-E5: Assessment of drug’s sensitivity to ethnic factors and necessity of a bridging study for global drug development

The ICH-E5 guideline provides a general framework for evaluating the potential impact of ethnic factors on the acceptability of foreign clinical data, with the underlying objective of minimizing duplication of clinical data, and it also describes the requirement of bridging studies for extrapolation of foreign clinical data to a new region. The ICH-E5 guideline brought great change in concept and strategy of global drug development for pharmaceutical companies. The procedures described in the ICH-E5 guideline have proved useful in the assessment of the ethnic sensitivity of a medicinal product that is to be introduced to a foreign region for registration purpose. Many companies are now developing various products based on ICH-E5 strategies and many successful cases will continuously appear within coming years.

**Key words:** Bridging study, ethnic factors, global drug development, ICH-E5

**INTRODUCTION**

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) had issued E5 document entitled “Ethnic Factors in the Acceptability of Foreign Clinical Data” in 1998. Before the process of assessing the acceptability of the of foreign clinical data for registration purposes was implemented, regulatory authorities frequently requested duplicate data due to concerns that ethnic differences might affect a medication’s efficacy and safety in the new region. Hence, the main aims of this guideline were to prevent unnecessary and redundant repetition of clinical trials.\[1-6\]

The ICH-E5 guideline provides a general framework for evaluating the potential impact of ethnic factors on the acceptability of foreign clinical data, with the underlying objective of minimizing duplication of clinical data, and it also describes the requirement of bridging studies for extrapolation of foreign clinical data to a new region. The ICH-E5 guideline basically suggests a three-step process for judging the acceptability of foreign clinical data. The first step is assessment of completeness of clinical data package of the medicine and if clinical data package is found to be complete, then second step is to assess the product’s sensitivity to ethnic factors and third and final step is to judge the requirement of bridging study (if needed) based on medicine’s sensitivity to ethnic factors and on likelihood that extrinsic ethnic factors could affect the medicine’s safety, efficacy, and dose-response.\[1,2,6-8\]

**REGULATORY REQUIREMENTS AS PER ICH-E5**

As per ICH-E5, the pharmaceutical industry should first submit the clinical data package. Clinical data generated in foreign regions can be either complete or incomplete, with the acceptability of the data depending on whether it can be accurately extrapolated to the new region. Extrapolation is
the key concept behind accepting foreign clinical data and is highly contingent on the completeness of the package.\[1\]

The clinical data package would be assessed by the regional regulatory authority regarding the nature and quality of the data, irrespective of its geographic origin. A clinical data package would be defined as a “complete” clinical data package for submission and potential approval if it meets all of the regional regulatory requirements.\[1\]

For extrapolation to be considered, the complete clinical data package, including foreign clinical data, submitted to the new region should contain adequate characterization of pharmacokinetics (PK), pharmacodynamics (PD), dose-response, efficacy, and safety in the population of the foreign region(s). Clinical trials data establishing dose-response, efficacy, and safety are required. These trials should be designed and conducted according to regulatory standards in the new region. These trials should be adequate and well-controlled and utilize endpoints that are considered appropriate for assessment of treatment. Also, clinical disorders should be evaluated using medical and diagnostic definitions that are acceptable to the new region.\[1\]

If foreign data do not meet these stringent standards, the regulatory authority may require additional clinical trials. These clinical trials may focus on different subsets of the population (for example, including patients with renal or hepatic impairment), distinct comparator groups at clearly specified dosages or dose regimens, or drug–drug interactions.\[1\]

### ETHNIC CONSIDERATION AS PER ICH-E5

According to the ICH-E5 guideline, the next step would be to assess the product’s sensitivity to ethnic factors by assessing the PK, PD, or other characteristics that have the potential to be influenced by ethnic factors.\[1\]

A medicine’s sensitivity to ethnic factors can be judged by PK, PD, or other characteristics which suggest the potential for clinically significant or minimal impact by intrinsic and/or extrinsic ethnic factors on safety, efficacy, or dose-response.\[1\]

ICH-E5 defines ethnic factors as arising from two sources, extrinsic and intrinsic.\[1\]

Extrinsic Ethnic Factors - Factors associated with environment and culture in which a person resides. These factors tend to be less genetically, more culturally, and behaviorally determined.\[1\]

Intrinsic Ethnic Factors - Factors that help to define and identify a subpopulation and may influence the ability to extrapolate.\[1\]

The critical properties of a medicine for assessment of sensitivity to ethnic factors have been enumerated in appendix D of the ICH-E5 guideline [Table 1].\[1,6\]

The critical properties of a medicine that make it less likely to be sensitive to ethnic factors include nonsystemic mode of action, linear PK, a flat PD (effect-concentration) curve for both efficacy and safety in the range of the recommended dosage and dose regimen (this may mean that the medicine is well-tolerated), wide therapeutic range (again, possibly an indicator of good tolerability), minimal metabolism, high bioavailability thus less susceptibility to dietary absorption effects, low potential for protein binding, little potential for interactions, and little potential for inappropriate use.\[1\]

The critical properties of a medicine that make it more likely to be sensitive to ethnic factors include nonlinear PK, steep PD curve, narrow therapeutic range, high metabolism, genetic polymorphism, administration as a prodrug with the potential for ethnically variable enzymatic conversion, high intersubject variability, low bioavailability, high likelihood of use in a setting of multiple comediations, and high potential for inappropriate use.\[1\]

### REQUIREMENT FOR BRIDGING STUDIES AS PER ICH-E5

As mentioned above, the third and final step as per ICH-E5 is to judge the requirement of bridging study (if needed) based on medicine’s sensitivity to ethnic factors.

| Table 1: The critical properties of a medicine that help in assessing its ethnic sensitivity\[1,6\] |
|---------------------------------------------------------------|
| Linear or nonlinear pharmacokinetics                          |
| Steep or flat concentration-effect curve for efficacy and safety |
| Narrow or wide therapeutic dose range                         |
| Whether the product is minimally or highly metabolized        |
| Whether the product is metabolized by enzymes demonstrating genetic polymorphism |
| Whether the product is administered as a prodrug with potential for ethnically variable enzymatic conversion |
| High or low bioavailability                                   |
| Potential for protein binding                                 |
| Potential for interactions                                   |
| Likelihood of use in a setting of multiple comediations        |
| Likelihood of inappropriate use                               |
and on likelihood that extrinsic ethnic factors could affect the medicine’s safety, efficacy, and dose-response.

A “bridging” study, as its name implies, is designed to allow one to bridge from the original region’s (foreign) data in the original population to the new region. ICH-E5 define bridging study as a study performed in the new region to provide PD 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 population in the new region.[1,4,6-8]

Generally, for medicines characterized as insensitive to ethnic factors, the type of bridging study needed (if needed) will depend upon experience with the drug class and upon the likelihood that extrinsic ethnic factors (including design and conduct of clinical trials) could affect the medicine’s safety, efficacy, and dose-response.[1]

A bridging study may not be needed in two conditions, first, if medicine is ethnically insensitive and extrinsic factors such as medical practice and conduct of trials are similar in each region, or medicine is ethnically sensitive but the two regions are ethnically similar and there is sufficient experience with pharmacologically related compounds in the two regions [Table 2].[1]

Bridging study with pharmacologic endpoints may be needed if drug is ethnically sensitive and region is ethnically dissimilar, but extrinsic factors are similar. In this condition, a controlled PD study in new region using a pharmacologic endpoint or established surrogate endpoint could bridge foreign data [Table 2].[1]

When there are doubts about the choice of dose or there is insufficient clinical experience about the drug or drug class is unfamiliar or medical practice is different between the two regions, then bridging study with controlled clinical trial may be required [Table 2].[1]

For a drug which may induce high incidence of serious adverse drug reactions, a premarketing clinical trial to clarify the local safety concern is required. Moreover, in some cases, the incidence of a serious adverse reaction is rare and the large sample size is needed to detect the reaction.[1]

**CONCLUSION**

The procedures described in the ICH-E5 guideline have proved useful in the assessment of the ethnic sensitivity of a medicinal product that is to be introduced to a foreign region for registration purpose. The PK/PD and clinical tools are properties mentioned in this guideline are good screening tools to assess ethnic sensitivity.[1,3,6] The ICH-E5 guideline brought great change in concept and strategy of global drug development for pharmaceutical companies. Viagra was the first product that obtained NDA (New Drug Application) approval in Japan with ICH-E5-based strategy. Many companies are now developing various products based on ICH-E5 strategies and many successful cases will continuously appear within coming years.[3]

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**Table 2: Types of bridging studies**

| Medicine                     | Ethnicity of region | Medical practice | Drug class | Clinical experience | Bridging studies |
|------------------------------|---------------------|------------------|------------|--------------------|------------------|
| Ethnically insensitive       | -                   | Similar          | -          | -                  | No               |
| Ethnically sensitive         | Similar             | -                | Sufficient | No                 | No               |
| Ethnically sensitive         | Dissimilar          | Similar          | Familiar   | PD                 | CCT              |
| Doubts about choice of dose  | -                   | Different        | Unfamiliar | Insufficient       |                  |

PD, pharmacodynamics; CCT, controlled clinical trials