Guidance for Industry

E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data

Questions and Answers

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2004
ICH

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I. INTRODUCTION

This question and answers (Q&As) guidance is intended to assist applicants in evaluating the impact of ethnic factors in the acceptability of foreign clinical data. This guidance provides answers to questions that have arisen since the implementation of the E5 guidance in June 1998. The questions and answers provided here reflect the consensus of the ICH parties. This guidance will be revised to include additional Q&As as new questions arise.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance was developed within the E5 Implementation Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 11, 2003. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

II. BACKGROUND

The ICH guidance *E5 Ethnic Factors in the Acceptability of Foreign Clinical Data* was endorsed by the International Conference on Harmonisation in February 1998 and issued by the FDA in June 1998. *ICH E5* is intended to facilitate the registration of drugs and biologics among ICH regions by recommending a framework for evaluating the impact of ethnic factors on a drug's effect, i.e., its efficacy and safety at a particular dosage and dose regimen.

III. QUESTIONS AND ANSWERS

Q1: I am planning to develop my new drug globally. Does E5 provide guidance for this approach?

A1: E5 does provide some guidance in this situation. E5 addresses primarily how development programs in one or two regions might support approval in another region. E5 says, in general, that if the data developed in one region satisfy the requirements for evidence in a new region, but there is a concern about possible intrinsic or extrinsic ethnic differences between the two regions, then it should be possible to extrapolate the data to the new region with a single bridging study. The bridging study could be a pharmacodynamic study or a full clinical trial, possibly a dose-response study.

The bridging study would allow extrapolation of an adequate database to the new region. It would seem possible, and efficient, to assess potential regional differences as part of a global development program, i.e., for development of data to occur simultaneously in various regions, rather than sequentially. For example, if multi-regional trials had a sufficient number of trial subjects from the new region, it might be possible to analyze the impact of ethnic differences in those studied, to determine whether the entire database is pertinent to the new region.

The basic issues to be considered in a global study design that could affect a region's willingness to rely on these data are: (a) definition and diagnoses of disease condition and patient, (b) choice of control group, (c) regional target or objective of treatment with choice of efficacy variables, (d) methods of assessment of safety, (e) medical practice, (f) duration of the trial, (g) regional concomitant medications, (h) severity distribution of eligible subjects, and (i) similarity of dose and dose regimens.

To determine whether your proposed global program will address the requirements of a specific region, it is recommended that early consultation and discussions be held with regulatory authorities in that region.

Q2: ***I have developed my drug in one region, addressing safety, efficacy, dosing, etc., as well as use in special populations such as patients with renal/hepatic impairment, the elderly, children, and pregnant and lactating women. If I can successfully demonstrate (e.g., through a bridging study) that my safety, efficacy, and dosing information in the general population are relevant to the new region, will I also need to further address the extrapolatability of the special population data?***

A2: In general, if the studies of special populations are sufficient in design (e.g. include an appropriate range of severity of impairment) to address regulatory requirements of the new region, but are conducted in a foreign region, and if evidence supports the extrapolation of the data in the general population to the new region, you will probably not need to address the issue of special populations again in the new region. Note, however, that for a new indication in a special population (e.g., pediatric depression), a region might require a separate bridging study.

Q3: ***I believe that my drug is sensitive to ethnic factors and that the medical settings in which it is used may vary among regions. Does this mean that my efficacy study in one region is of no value in support of my application in another?***

A3: No. Assuming the new region finds the studies in the first region pertinent, the regulatory authority of the new region will likely require a controlled study in its own region to establish efficacy (and/or to address other issues). E5 indicates, however, that the second region would be likely to consider a single such study adequate if the data from the foreign region otherwise meet all the requirements of the new region. If the new study supports the same conclusions as the study(ies) in the original region, no further confirmation should be needed, as the data from the original region would likely be considered to confirm the finding in the new region. In that case, the study in the new region need not necessarily have the identical dose and treatment effect size to confirm the findings from the initial region. There might also be situations in which the region would consider further safety data necessary. For example, if the new region considered a higher dose or more frequent dosing necessary and if this finding were not a pharmacokinetic effect, sponsors might need to provide additional safety data.

Q4: ***I believe that my drug is insensitive to ethnic factors and that there are no significant relevant differences in extrinsic factors, including the practice of medicine, among the regions. The pharmacokinetics of the drug are insensitive to intrinsic and extrinsic factors. The diagnosis and therapy of the conditions in the indication do not significantly vary among regions. Nonetheless, the regulatory authority of the new region is requiring an additional study of safety and efficacy for bridging. Is this requirement inconsistent with E5?***

A4: No, although you might want to discuss the issue with the regulatory authorities in the new region. E5 makes it clear that the need for a bridging study is always a matter of judgment and does not seek to discourage the new region's asking for one. E5

specifically notes that familiarity with the other region is likely to be an important determinant of whether the new region asks for a bridging study. E5 does indicate the expectation that the regulatory authorities of new regions would request only those additional data necessary to assess the ability to extrapolate foreign data to the new region, but the amount of additional data called for is a matter of judgement on the part of the regulatory authority.

Q5: My drug has been approved in two ICH regions and I am about to meet with regulatory authorities in the third region to discuss an application for marketing. I believe that the new regulatory authority should accept the present data, and that regulatory authority should require little or no additional data. What information should I submit to support my case that additional data are not needed?

A5: There are two distinct issues that need to be considered: (1) the adequacy of the database and (2) the need for a bridging study. You will need to convince the regulatory authority that the available data are both adequate to meet the new region's requirements and that the data are applicable to the population of the new region. You should therefore indicate how your data address all the regulatory requirements of the new region. Where the choice of control groups, primary endpoints, or other key clinical trial design features are not those known to be considered acceptable to the new region, you should explain how and why they should be considered to meet the regulatory requirements of the new region.

You should also indicate why the data and conclusions should be considered relevant to the new population. In doing this, you should identify the intrinsic factors (e.g., racial distribution) that differ between the regions and show that those factors do not substantially affect the drug effect (i.e., demonstrate that the drug is insensitive to any differences in ethnic factors). Data indicating that pharmacologically related compounds have similar effects in the two regions can be quite useful.

You should also identify the extrinsic factors (e.g., diagnosis or management of the patient population studied) that you believe are generally similar to those in the intended population in the new region and explain why any significant differences would not alter conclusions to be drawn about the drug effect.

Dose-response relationships should be evaluated to determine if these are sensitive to intrinsic or extrinsic factors, and whether the appropriate doses might vary markedly among individuals or ethnic groups.

Q6: I believe that my drug is insensitive to ethnic factors and that drugs in its class have similar activity in all regions. However, the endpoints I studied and/or the control group I used were considered acceptable to the regions in which the studies were conducted but not to the new region. Does E5 indicate that the new region should accept those data as evidence of efficacy?

A6: No. E5 indicates clearly that it applies only when the foreign clinical data address all the regulatory requirements of the new region, but come from a different region. E5 does not address the regulatory requirements of individual regions. If your choice of clinical endpoints or control group is not considered acceptable to the new region, and if you cannot convince regulators in that region otherwise, then E5 does not apply to this situation. Early discussion with regulators in regions where endpoints, control groups, inclusion criteria or diagnostic criteria might differ should be considered part of planning clinical studies to meet an individual region's requirements. In this situation, the regulatory authority in the new region may require you to conduct a study using agreed-upon criteria in the new region.

Q7: I believe my drug is insensitive to ethnic factors. However, there is a clear difference in medical practice and the use and perceived need for certain drugs in the targeted therapeutic area. Does E5 indicate that the new region should accept those data as evidence of efficacy?

A7: No. As described, the database might not be acceptable to the new region, apart from concerns about ethnic differences, because the data do not refer to a disease that the new region considers pertinent.

Q8: My drug has been shown to be effective in preventing certain clinical events. However, the rate of these events is clearly different in the new region, even though the pathophysiology is the same. Does E5 indicate that the new region should accept those data as pivotal evidence of efficacy?

A8: No. Certainly, in most cases where there is a definitive outcome study in another region, a region would probably not require that the study be repeated locally. There could, however, be exceptions; for example, if the event rate is indeed lower in the new region, and the risk reduction is the same in both regions, the actual number of patients benefited will be smaller and an adverse effect could become more important, affecting the benefit-to-risk relationship of the drug. A new region, in some cases, might need a clinical trial to assess the value of the drug.

Q9: My drug is approved for various indications in one region and it is shown in a bridging study in the primary indication that the data can be extrapolated. Does this mean that the new regions should accept all indications without further data?

A9: No. Whether or not the new region will require further data would be decided on a case-by-case basis, depending on whether the "bridged" indication was thought to satisfy all concerns about potential ethnic differences. For example, the additional indications might be extensions of the primary indication (perhaps not calling for an additional

bridging study) or quite new uses (perhaps calling for bridging). It is recommended that early consultation and discussions be held with the authorities in the new region.

Q10: ***E5 expresses the principle that, as experience with interregional acceptance of foreign clinical data increases, there will be a better understanding of situations in which bridging studies are needed and that it is hoped that, with these experiences, the need for bridging data will lessen. Is this principle still valid?***

A10: Yes, this is the expectation. The accumulation of experience by each region with implementation of the E5 guidance continues to add to our understanding of situations in which a bridging study would be considered necessary by a new region. The expectation continues to be that, with this experience, the need for a bridging study will lessen.