ICH E5

- ICH E5(R1) Ethnic Factors in the Acceptability of Foreign Clinical Data
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ICH E5(R1) Ethnic Factors in the Acceptability of Foreign Clinical Data

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1. INTRODUCTION

The purpose of this guidance is to facilitate the registration of medicines among ICH regions* (see Glossary) by recommending a framework for evaluating the impact of ethnic factors* upon a medicine's effect, i.e., its efficacy and safety at a particular dosage* and dose regimen*. It provides guidance with respect to regulatory and development strategies that will permit adequate evaluation of the influence of ethnic factors while minimizing duplication of clinical studies and supplying medicines expeditiously to patients for their benefit. This guidance should be implemented in context with the ICH guidances. For the purposes of this document, ethnic factors are defined as those factors relating to the genetic and physiologic (intrinsic*) and the cultural and environmental (extrinsic*) characteristics of a population (Appendix A).

1.1 Objectives

- To describe the characteristics of foreign clinical data that will facilitate their extrapolation to different populations and support their acceptance as a basis for registration of a medicine in a new region*.
- To describe regulatory strategies that minimize duplication of clinical data and facilitate acceptance of foreign clinical data in the new region.
- To describe the use of bridging studies*, when necessary, to allow extrapolation of foreign clinical data to a new region.
- To describe development strategies capable of characterizing ethnic factor influences on safety, efficacy, dosage and dose regimen.

1.2 Background

All regions acknowledge the desirability of utilizing foreign clinical data that meet the regulatory standards and clinical trial practices acceptable to the region considering the application for registration.

However, concern that ethnic differences may affect the medication's safety, efficacy, dosage and dose regimen in the new region has limited the willingness to rely on foreign clinical data. Historically, this has been one of the reasons, therefore, the regulatory authority in the new region has often requested that all, or much of, the foreign clinical data in support of registration be duplicated in the new region. Although ethnic differences among populations may cause differences in a medicine's safety, efficacy, dosage or dose regimen, many medicines have comparable characteristics and effects across regions. Requirements for extensive duplication of clinical evaluation for every compound can delay the availability of new therapies and unnecessarily waste drug development resources.

1.3 Scope

This guidance is based on the premise that it is not necessary to repeat the entire clinical drug development program in the new region and is intended to recommend strategies for accepting foreign clinical data as full or partial support for approval of an application in a new region. It is critical to appreciate that this guidance is not intended to alter the data requirements for registration in the new region; it seeks to recommend when these data requirements may be satisfied with foreign clinical data. All data in the clinical data package, including foreign data, should meet the standards of the new region with respect to study design and conduct and the available data should satisfy the regulatory requirements in the new region. Additional studies conducted in any region may be required by the new region to complete the clinical data package.

Once a clinical data package fulfils the regulatory requirements of the new region, the only remaining issue with respect to the acceptance of the foreign clinical data is its ability to be extrapolated to the population of the new region. When the regulatory authority or the sponsor is concerned that differences in ethnic factors could alter the efficacy or safety of the medicine in the population in the new region, the sponsor may need to generate a limited amount of clinical data in the new region in order to extrapolate or "bridge" the clinical data between the two regions.

If a sponsor needs to obtain additional clinical data to fulfil the regulatory requirements of the new region, it is possible that these clinical trials can be designed to also serve as the bridging studies.

Thus, the sponsor and the regional regulatory authority of the new region would assess an application for registration for:

its completeness with respect to the regulatory requirements of the new region; and

the ability to extrapolate to the new region those parts of the application (which could be most or all of the application) based on studies from the foreign region (Appendix B).

2. ASSESSMENT OF THE CLINICAL DATA PACKAGE INCLUDING FOREIGN CLINICAL DATA FOR ITS FULFILMENT OF REGULATORY REQUIREMENTS IN THE NEW

REGION

The regional regulatory authority would assess the clinical data package, including the foreign data, as to whether or not it meets all of the regulatory standards regarding the nature and quality of the data, irrespective of its geographic origin, i.e., data generated either totally in a foreign region (or regions) or data from studies conducted both in a foreign and the new region to which the application is being made. A clinical data package that meets all of these regional regulatory requirements is defined as a “Complete” Clinical Data Package* for submission and potential approval. The acceptability of the foreign clinical data component of the complete data package depends then upon whether it can be extrapolated to the population of the new region.

Before extrapolation can be considered, the Complete Clinical Data Package, including foreign clinical data, submitted to the new region should contain:

- Adequate characterization of pharmacokinetics*, pharmacodynamics*, dose-response, efficacy and safety in the population of the foreign region(s).
- Clinical trials establishing dose response, efficacy and safety. These trials should:
    - Be designed and conducted according to regulatory standards in the new region, e.g., choice of controls, and should be conducted according to GCP
    - Be adequate and well-controlled*
    - Utilize endpoints that are considered appropriate for assessment of treatment
    - Evaluate clinical disorders using medical and diagnostic definitions that are acceptable to the new region.

- Characterization in a population relevant to the new region of the pharmacokinetics, and where possible, pharmacodynamics and dose response for pharmacodynamic endpoints. This characterization could be performed in the foreign region in a population representative of the new region* or in the new region*.

Several ICH guidelines that address aspects of design, conduct, analysis and reporting of clinical trials will help implement the concepts of the Complete Clinical Data Package. These guidances include GCP’s (E6), evaluation of dose response (E4), adequacy of safety data (E1 and E2), conduct of studies in the elderly (E7), reporting of study results (E3), general considerations for clinical trials (E8), and statistical considerations (E9). A guidance on the choice of control group in clinical trials (E10) is under development.

2.1 Additional Studies to Meet the New Region’s Regulatory Requirements

When the foreign clinical data do not meet the regional regulatory requirements, the regulatory authority may require additional clinical trials such as:

- clinical trials in different subsets of the population such as patients with renal insufficiency, patients with hepatic dysfunction, etc.
- clinical trials using different comparators at the new region’s approved dosage and dose regimen

- drug-drug interaction studies

3. ASSESSMENT OF THE FOREIGN CLINICAL DATA FOR EXTRAPOLATION TO THE NEW REGION

3.1 Characterization of the Medicine’s Sensitivity to Ethnic Factors

knowledge of its pharmacokinetic and pharmacodynamic properties and the translation of those properties to clinical effectiveness and safety. A reasonable evaluation is described in Appendix C. Some properties of a medicine (chemical class, metabolic pathway, pharmacologic class) make it more or less likely to be affected by ethnic factors (Appendix D). Characterization of a medicine as “ethnically insensitive”, i.e., unlikely to behave differently in different populations, would usually make it easier to extrapolate data from one region to another and need less bridging data.

Factors that make a medicine ethnically sensitive or insensitive will become better understood and documented as effects in different regions are compared. It is clear at present, however, that such characteristics as clearance by an enzyme showing genetic polymorphism and a steep dose-response curve will make ethnic differences more likely. Conversely, a lack of metabolism or active excretion, a wide therapeutic dose range*, and a flat dose response curve will make ethnic differences less likely. The clinical experience with other members of the drug class in the new region will also contribute to the assessment of the medicine’s sensitivity to ethnic factors. It may be easier to conclude that the pharmacodynamic and clinical behaviour of a medicine will be similar in the foreign and new regions if other members of the pharmacologic class have been studied and approved in the new region with dosing regimens similar to those used in the original region.

3.2 Bridging Data Package

3.2.1 Definition of Bridging Data Package and Bridging Study

A bridging data package consists of: 1) selected information from the Complete Clinical Data Package that is relevant to the population of the new region, including pharmacokinetic data, and any preliminary pharmacodynamic and dose-response data, and 2) if needed, a bridging study to extrapolate the foreign efficacy data and/or safety data to the new region.

A bridging study is defined as a study performed in the new region to provide pharmacodynamic 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. A bridging study for efficacy could provide additional pharmacokinetic information in the population of the new region. When no bridging study is needed to provide clinical data for efficacy, a pharmacokinetic study in the new region may be considered as a bridging study.

3.2.2 Nature and Extent of the Bridging Study

This guidance proposes that when the regulatory authority of the new region is presented with a clinical data package that fulfils its regulatory requirements, the authority should request only those additional data necessary to assess the ability to extrapolate foreign data from the Complete Clinical Data Package to the new region. The sensitivity of the medicine to ethnic factors will help determine the amount of such data. In most cases, a single trial that successfully provides these data in the new region and confirms the ability to extrapolate data from the original region should suffice and should not need further replication. Note that even though a single study should be sufficient to "bridge" efficacy data, a sponsor may find it practical to obtain the necessary data by conducting more than one study. For example, where it is intended that a fixed dose, dose-response study using a clinical endpoint is needed as the bridging study, a short-term pharmacologic endpoint study may be used to choose the dose(s) for the larger (clinical endpoint) study.

When the regulatory authority requests, or the sponsor decides to conduct, a bridging study, discussion between the regional regulatory authority and sponsor is encouraged, when possible, to determine what kind of bridging study will be needed. The relative ethnic sensitivity will help determine the need for and the nature of the bridging study. For regions with little experience with registration based on foreign clinical data, the regulatory authorities may still request a bridging study for approval even for compounds insensitive to ethnic factors. As experience with interregional acceptance increases, there will be a better understanding of situations in which bridging studies are needed. It is hoped that with experience, the need for bridging data will lessen.

The following is general guidance about the ability to extrapolate data generated from a bridging study:

- If the bridging study shows that dose response, safety and efficacy in the new region are similar, then the study is readily interpreted as capable of "bridging" the foreign data.
- If a bridging study, properly executed, indicates that a different dose in the new region results in a safety and efficacy profile that is not substantially different from that derived in the original region, it will often be possible to extrapolate the foreign data to the new region, with appropriate dose adjustment, if this can be adequately justified (e.g., by pharmacokinetic and/or pharmacodynamic data).
- If the bridging study designed to extrapolate the foreign data is not of sufficient size to confirm adequately the extrapolation of the adverse event profile to the new population, additional safety data may be necessary (section 3.2.4).
- If the bridging study fails to verify safety and efficacy, additional clinical data (e.g., confirmatory clinical trials) would be necessary.

3.2.3 Bridging Studies for Efficacy

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. For medicines that are ethnically sensitive, a bridging study may often be needed if the populations in the two regions are different. The following examples illustrate types of bridging studies for consideration in different situations:

No Bridging Study

In some situations, extrapolation of clinical data may be feasible without a bridging study:

If the medicine is ethnically insensitive and extrinsic factors such as medical practice and conduct of clinical trials in the two regions are generally similar.

If the medicine is ethnically sensitive but the two regions are ethnically similar and there is sufficient clinical experience with pharmacologically related compounds to provide reassurance that the class behaves similarly in patients in the two regions with respect to efficacy, safety, dosage and dose regimen. This might be the case for well-established classes of drugs known to be administered similarly but not necessarily identically in the two regions.

Bridging Studies using pharmacologic endpoints

If the regions are ethnically dissimilar and the medicine is ethnically sensitive but extrinsic factors are generally similar (e.g., medical practice, design and conduct of clinical trials) and the drug class is a familiar one in the new region, a controlled pharmacodynamic study in the new region, using a pharmacologic endpoint that is thought to reflect relevant drug activity (which could be a well-established surrogate endpoint) could provide assurance that the efficacy, safety, dose and dose regimen data developed in the first region are applicable to the new region. Simultaneous pharmacokinetic (i.e., blood concentration) measurements may make such studies more interpretable.

Controlled Clinical Trials

It will usually be necessary to carry out a controlled clinical trial, often a randomized, fixed dose, dose-response study, in the new region when:

1. there are doubts about the choice of dose,

2. there is little or no experience with acceptance of controlled clinical trials carried out in the foreign region,

3. medical practice, e.g., use of concomitant medications and design and/or conduct of clinical trials are different, or

4. the drug class is not a familiar one in the new region.

Depending on the situation, the trial could replicate the foreign study or could utilize a standard clinical endpoint in a study of shorter duration than the foreign studies or utilize a validated surrogate endpoint, e.g., blood pressure or cholesterol (longer studies and other endpoints may have been used in the foreign phase III clinical trials).

If pharmacodynamic data suggest that there are interregional differences in response, it will generally be necessary to carry out a controlled trial with clinical endpoints in the new region. Pharmacokinetic differences may not always create that necessity, as dosage adjustments in some cases might be made without new trials. However, any substantial difference in metabolic pattern may often indicate a need for a controlled clinical trial.

When the practice of medicine differs significantly in the use of concomitant medications, or adjunct therapy could alter the medicine’s efficacy or safety, the bridging study should be a controlled clinical trial.

3.2.4 Bridging Studies for Safety

Even though the foreign clinical data demonstrate efficacy and safety in the foreign region, there may occasionally remain a safety concern in the new region. Safety concerns could include the accurate determination of the rates of relatively common adverse events in the new region and the detection of serious adverse events (in the 1% range and generally needing about 300 patients to assess). Depending upon the nature of the safety concern, safety data could be obtained in the following situations:

- A bridging study to assess efficacy, such as a dose-response study, could be powered to address the rates of common adverse events and could also allow identification of serious adverse events that occur more commonly in the new region. Close monitoring of such a trial would allow recognition of such serious events before an unnecessarily large number of patients in the new region is exposed. Alternatively, a small safety study could precede the bridging study to provide assurance that serious adverse effects were not occurring at a high rate.
    - If there is no efficacy bridging study needed or if the efficacy bridging study is too small or of insufficient duration to provide adequate safety information, a separate safety study may be needed. This could occur where there is:
    - an index case of a serious adverse event in the foreign clinical data
    - a concern about differences in reporting adverse events in the foreign region
    - only limited safety data in the new region arising from an efficacy bridging study, inadequate to extrapolate important aspects of the safety profile, such as rates of common adverse events or of more serious adverse events

4. DEVELOPMENTAL STRATEGIES FOR GLOBAL DEVELOPMENT

Definition of not only pharmacokinetics but also pharmacodynamics and dose response early in the development program may facilitate the determination of the need for, and nature of, any requisite bridging data. Any candidate medicine for global development should be characterized as ethnically sensitive or insensitive (Appendix D). Ideally, this characterization should be conducted during the early clinical phases of drug development, i.e., human pharmacology and therapeutic exploratory studies. In some cases, it may be useful to discuss bridging study designs with regulatory agencies prior to completion of the clinical data package. However, analysis of the data within the Complete Clinical Data Package will determine the need for, and type of bridging study. For global development, studies should include populations representative of the regions where the medicine is to be registered and should be conducted according to ICH guidelines.

A sponsor may wish to leave the assessment of pharmacokinetics, pharmacodynamics, dosage and dose regimens in populations relevant to the new region until later in the drug development

program. Pharmacokinetic assessment could be accomplished by formal pharmacokinetic studies or by applying population pharmacokinetic methods to clinical trials conducted either in a population relevant to the new region, or in the new region.

5. SUMMARY

This guidance describes how a sponsor developing a medicine for a new region can deal with the possibility that ethnic factors could influence the effects (safety and efficacy) of medicines and the risk/benefit assessment in different populations. Results from the foreign clinical trials could comprise most, or in some cases, all of the clinical data package for approval in the new region, so long as they are carried out according to the requirements of the new region. Acceptance in the new region of such foreign clinical data may be achieved by generating “bridging” data in order to extrapolate the safety and efficacy data from the population in the foreign region(s) to the population in the new region.

GLOSSARY

Term	Content
Adequate and Well-controlled Trial	An adequate and well controlled trial has the following characteristics: • a design that permits a valid comparison with a control to provide a quantitative assessment of treatment effect; • the use of methods to minimize bias in the allocation of patients to treatment groups and in the measurement and assessment of response to treatment; and • an analysis of the study results appropriate to the design to assess the effects of the treatment.
Bridging Data Package	Selected information from the Complete Clinical Data Package that is relevant to the population of the new region, including pharmacokinetic data, and any preliminary pharmacodynamic and dose-response data and, if needed, supplemental data obtained from a bridging study in the new region that will allow extrapolation of the foreign safety and efficacy data to the population of the new region.
Bridging Study	A bridging study is defined as a supplemental study performed in the new region to provide pharmacodynamic 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 new region. Such studies could include additional pharmacokinetic information.

Complete Clinical Data Package	A clinical data package intended for registration containing clinical data that fulfil the regulatory requirements of the new region and containing pharmacokinetic data relevant to the population in the new region.
Compounds Insensitive to Ethnic Factors	A compound whose characteristics suggest minimal potential for clinically significant impact by ethnic factors on safety, efficacy, or dose response.
Compounds Sensitive to Ethnic Factors	A compound whose pharmacokinetic, pharmacodynamic, or other characteristics suggest the potential for clinically significant impact by intrinsic and/or extrinsic ethnic factors on safety, efficacy, or dose response.
Dosage	The quantity of a medicine given per administration, or per day.
Dose Regimen	The route, frequency and duration of administration of the dose of a medicine over a period of time.
Ethnic Factors	The word ethnicity is derived from the Greek word “ethnos”, meaning nation or people. Ethnic factors are factors relating to races or large populations grouped according to common traits and customs. Note that this definition gives ethnicity, by virtue of its cultural as well as genetic implications, a broader meaning than racial. Ethnic factors may be classified as either intrinsic or extrinsic. (Appendix A) • Extrinsic Ethnic Factors: Extrinsic ethnic factors are factors associated with the environment and culture in which a person resides. Extrinsic factors tend to be less genetically and more culturally and behaviourally determined. Examples of extrinsic factors include the social and cultural aspects of a region such as medical practice, diet, use of tobacco, use of alcohol, exposure to pollution and sunshine, socio-economic status, compliance with prescribed medications, and, particularly important to the reliance on studies from a different region, practices in clinical trial design and conduct. • Intrinsic Ethnic Factors: Intrinsic ethnic factors are factors that help to define and identify a sub-population and may influence the ability to extrapolate clinical data between regions. Examples of intrinsic factors include genetic polymorphism, age, gender, height, weight, lean body mass, body composition, and organ dysfunction.
Extrapolation of Foreign Clinical Data	The generalization and application of the safety, efficacy and dose response data generated in a population of a foreign region to the population of the new region.
Foreign Clinical Data	Foreign clinical data is defined as clinical data generated outside of the new region (i.e., in the foreign region).

ICH Regions	European Union, Japan, The United States of America.
New Region	The region where product registration is sought.
Population Representative of the New Region	A population that includes the major racial groups within the new region.
Pharmacokinetic Study	A study of how a medicine is handled by the body, usually involving measurement of blood concentrations of drug and its metabolite(s) (sometimes concentrations in urine or tissues) as a function of time. Pharmacokinetic studies are used to characterize absorption, distribution, metabolism and excretion of a drug, either in blood or in other pertinent locations. When combined with pharmacodynamic measures (a PK/PD study) it can characterize the relation of blood concentrations to the extent and timing of pharmacodynamic effects.
Pharmacodynamic Study	A study of a pharmacological or clinical effect of the medicine in individuals to describe the relation of the effect to dose or drug concentration. A pharmacodynamic effect can be a potentially adverse effect (anticholinergic effect with a tricyclic), a measure of activity thought related to clinical benefit (various measures of beta-blockade, effect on ECG intervals, inhibition of ACE or of angiotensin I or II response), a short term desired effect, often a surrogate endpoint (blood pressure, cholesterol), or the ultimate intended clinical benefit (effects on pain, depression, sudden death).
Population Pharmacokinetic Methods	Population pharmacokinetic methods are a population-based evaluation of measurements of systemic drug concentrations, usually two or more per patient under steady state conditions, from all, or a defined subset of, patients who participate in clinical trials.
Therapeutic Dose Range	The difference between the lowest effective dose and the highest dose that gives further benefit.

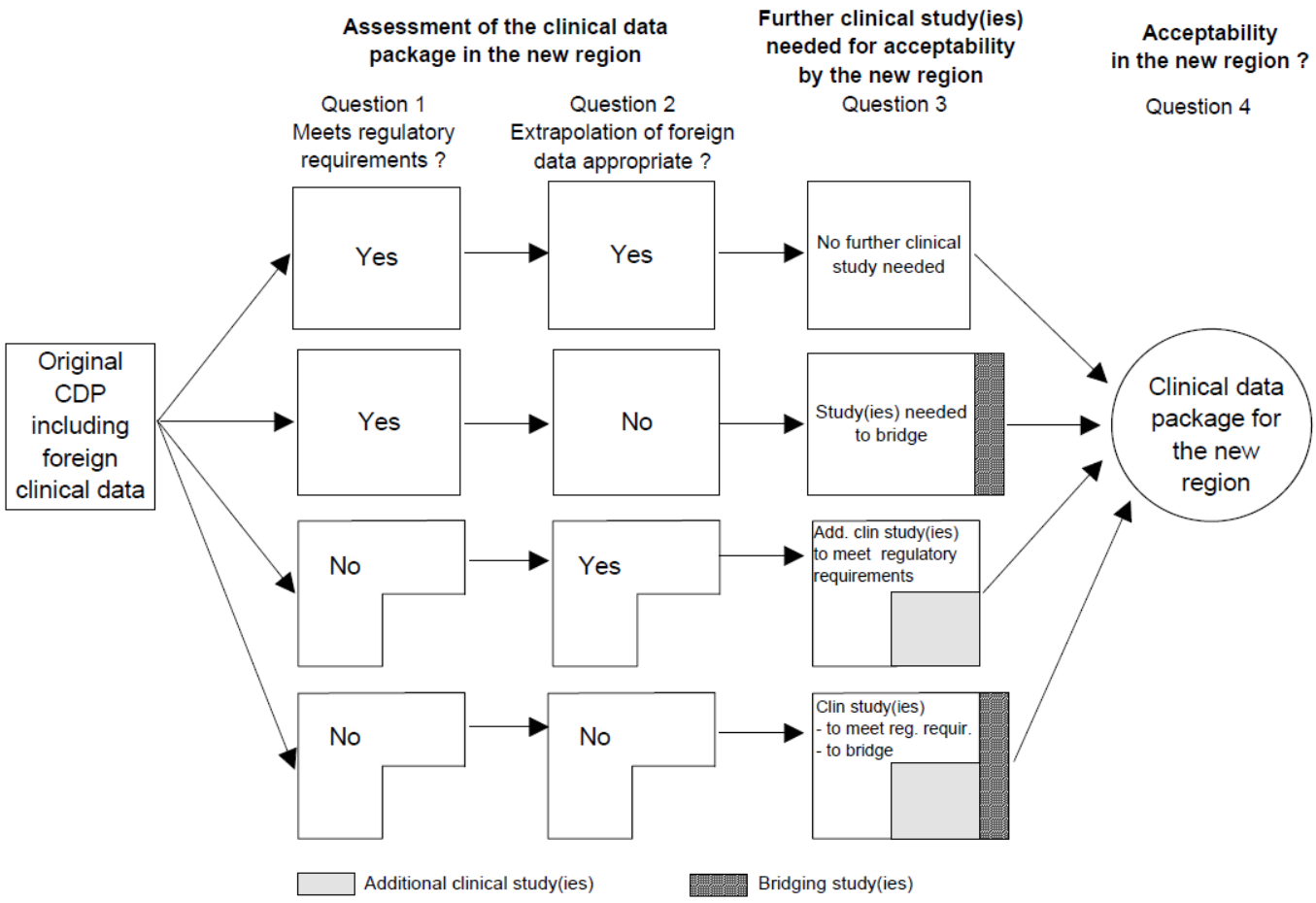
APPENDIX A

Classification of intrinsic and extrinsic ethnic factors

INTRINSIC		EXTRINSIC
Genetic	Physiological and pathological conditions	Environmental
Gender	Age (children-elderly)	Climate
		Sunlight
Height		Pollution
Bodyweight		
	Liver	**Culture**
	Kidney	Socioeconomic factors
	Cardiovascular functions	Educational status
ADME		Language
Receptor sensitivity		
Race		Medical practice
		Disease definition/Diagnostic
Genetic polymorphism of the drug metabolism		Therapeutic approach
		Drug compliance
		Smoking
		Alcohol
		Food habits
Genetic diseases	Diseases	Stress
		Regulatory practice/GCP
		Methodology/Endpoints

APPENDIX B

Assessment of the clinical data package (CDP) for acceptability



APPENDIX C

Pharmacokinetic, Pharmacodynamic, and Dose Response Considerations

Evaluation of the pharmacokinetics and pharmacodynamics, and their comparability, in the three major racial groups most relevant to the ICH regions (Asian, Black, and Caucasian) is critical to the registration of medicines in the ICH regions. Basic pharmacokinetic evaluation should characterize absorption, distribution, metabolism, excretion (ADME), and where appropriate, food-drug and drug-drug interactions.

Adequate pharmacokinetic comparison between populations of the two regions allows rational consideration of what kinds of further pharmacodynamic and clinical studies (bridging studies) are needed in the new region. In contrast to the pharmacokinetics of a medication, where differences between populations may be attributed primarily to intrinsic ethnic factors and are readily identified, the pharmacodynamic response (clinical effectiveness, safety, and dose-response) may be influenced by both intrinsic and extrinsic ethnic factors and this may be difficult to identify except by conducting clinical studies in the new region.

The ICH-E4 document describes various approaches to dose-response evaluation. In general, dose-response (or concentration response) should be evaluated for both pharmacologic effect (where one is considered pertinent) and clinical endpoints in the foreign region. The pharmacologic effect,

including dose-response, may also be evaluated in the foreign region in a population representative of the new region. Depending on the situation, data on clinical efficacy and dose-response in the new region may or may not be needed, e.g., if the drug class is familiar and the pharmacologic effect is closely linked to clinical effectiveness and dose-response, these foreign pharmacodynamic data may be a sufficient basis for approval and clinical endpoint and dose-response data may not be needed in the new region. The pharmacodynamic evaluation, and possible clinical evaluation (including dose-response) is important because of the possibility that the response curve may be shifted in a new population. Examples of this are well-documented, e.g., the decreased response in blood pressure of blacks to angiotensin-converting enzyme inhibitors.

APPENDIX D

A Medicine's Sensitivity to Ethnic Factors

Characterization of a medicine according to the potential impact of ethnic factors upon its pharmacokinetics, pharmacodynamics and therapeutic effects may be useful in determining what sort of bridging study is needed in the new region. The impact of ethnic factors upon a medicine's effect will vary depending upon the drug's pharmacologic class and indication and the age and gender of the patient. No one property of the medicine is predictive of the compound's relative sensitivity to ethnic factors. The type of bridging study needed is ultimately a matter of judgement but assessment of sensitivity to ethnic factors may help in that judgement.

The following properties of a compound make it less likely to be sensitive to ethnic factors:

- Linear pharmacokinetics (pK)
- A flat pharmacodynamic (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)
- A wide therapeutic dose range* (again, possibly an indicator of good tolerability)
- Minimal metabolism or metabolism distributed among multiple pathways
- High bioavailability, thus less susceptibility to dietary absorption effects
- Low potential for protein binding
- Little potential for drug-drug, drug-diet and drug-disease interactions
- Non-systemic mode of action
- Little potential for inappropriate use

The following properties of a compound make it more likely to be sensitive to ethnic factors:

- Non-linear pharmacokinetics
- A steep pharmacodynamic curve for both efficacy and safety (a small change in dose results in a large change in effect) in the range of the recommended dosage and dose regimen
- A narrow therapeutic dose range
- Highly metabolized, especially through a single pathway, thereby increasing the potential for drug-drug interaction

- Metabolism by enzymes known to show genetic polymorphism
- Administration as a prodrug, with the potential for ethnically variable enzymatic conversion
- High inter-subject variation in bioavailability
- Low bioavailability, thus more susceptible to dietary absorption effects
- High likelihood of use in a setting of multiple co-medications
- High likelihood for inappropriate use , e.g., analgesics and tranquilizers.

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English Version

ICH E5(R1) Ethnic Factors in the Acceptability of Foreign Clinical Data

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如果申办者需要获得额外的临床数据，以满足新地区的监管要求，则可以将这些临床试验设计成桥接研究（bridging study）。

因此，申办者和新地区的监管机构对于该项注册申请需要评估的内容包括：

（1）完全符合新地区监管要求；

（2）将国外临床研究中的部分（大部分或全部）数据应用到新地区的可能性。（附录 B）

2. ??????????????????????????????

新地区的监管机构将评估包括国外临床数据的临床数据集，以确定该数据的性质和质量是否符合该地区所有的监管标准，而不考虑该数据全部来源于国外、部分来源于国外、还是部分来源于即将申请注册的地区。可通过审批的完整临床数据集的定义为，符合所有地区监管要求的临床数据集。完整临床数据集中的国外临床数据是否被接受，取决于它能否外推到新地区人群中。

在考虑外推之前，递交给新地区的包括国外临床数据的完整临床数据集应当包括以下内容：

- 国外人群的药动学、药效学、量-效关系、安全性和有效性特点；
- 确立药物量-效关系、有效性和安全性的临床研究。这些研究包括：
  - 根据新地区监管标准进行设计和实施，例如对照药的选择，且遵照临床试验管理规范（GCP）实施；
  - 研究充分，且具有良好的对照；
  - 采用合适的治疗终点进行评价；
  - 疾病评估时所采用的治疗和诊断的定义能够被新地区所接受。

- 描述新地区人群的药动学特征，以及（在可能的情况下）药效学特征和以药效学为终点指标的量-效关系特征。应在能够代表新地区人群的国外人群，或在新地区人群中开展研究。

针对临床试验的设计、实施、分析和报告各方面的一系列 ICH 指南，将有助于实现完整临床数据集的概念。这些指南包括 GCP（E6）、量-效关系评估（E4）、充分的安全性数据（E1 和 E2）、老年用药研究（E7）、研究结果的报告（E3）、一般临床试验的总体考虑（E8）及统计学考虑（E9）。临床试验对照组的选择指导原则（E10）尚待完善。

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当国外临床资料不符合新地区的监管要求时，新地区的监管机构可能会要求增加临床试验，例如：

- 增加在特殊人群中的临床试验：如肾功能不全及肝功能不全的病人等；
- 按照新地区批准的剂量和给药方法，以不同的对照药进行临床试验；
- 药物相互作用研究。

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即使国外临床数据已表明药物在国外应用的有效性和安全性，有时在新地区仍可能出现需要关注的安全性问题，这包括对新地区常见不良事件发生率的精确估计，以及严重事件的发现（1%的发生率通常需要评估约300例患者）。依据安全性问题的性质，在下述情况下需要获得安全性资料：

- 评估有效性的桥接研究（例如量-效关系研究），因能估计常见的不良反应发生率，也可识别新地区更常见的严重不良事件，从而更具有说服力。在新地区对这样的试验进行密切监测，将有助于识别这类严重事件，避免药物暴露到新地区的大量患者当中。或者，可以在桥接研究之前进行一项小规模的安全性研究，以确保严重不良反应不会高频率发生。
    - 如果不需要有效性桥接研究，或有效性桥接研究规模过小，或研究时间过短不足以提供充分的安全性信息，则可能需要进行单独的安全性研究，可见于以下情况：
    - 国外临床数据中有严重不良反应的病例；
    - 新地区与国外报道的不良反应存在差异的；
    - 新地区只有有限的来源于药效桥接研究的安全性数据，不足以外推到安全性的重要方面，例如，常见不良反应发生率或更严重的不良反应。

4. ??????

在研发早期，药动学、药效学和量-效关系的确定，可能有助于确定进行何种桥接研究及其必要性。全球研发的候选药物可能具有种族敏感或种族不敏感的特征（附录D）。理想情况下，这些研究应在药物研发的早期阶段，例如临床药理学和药效探索研究期间进行。某些情况下，在完成临床资料收集之前，与监管机构讨论桥接研究的设计非常有益。但是，对完整临床数据集中的数据进行分析，将确定进行何种桥接研究及其必要性。为了全球研发，研究应包含即将注册地区的代表性人群，并按照ICH规范实施。申办者可能希望在药物研发的后期评估新地区相关人群的药动学、药效学、剂量和给药方案。药动学评估可采用正式的药动学研究，或在新地区采用群体药动学方法，或在新地区的相关人群中进行临床试验。

5. ??

本指南阐述申办者在新地区进行药品注册时，如何处理不同人群中，种族因素可能对药物作用（有效性和安全性）及风险/效益评估的问题。只要国外临床试验数据是按新地区的监管要求获得的，那么其结果可构成大部分，有时甚至是全部的临床药物临床数据集，从而用于药物在新地区的注册。在新地区中接受这样的国外临床数据，可通过桥接研究来实现，以便将国外人群中获得的安全性和有效性数据外推到新地区。

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术语	含义

充分良好的对照试验	一个充分和良好的对照试验具备以下特征： ● 设计正确的对照作为比较，以提供对治疗效应量化的评估； ● 治疗组的患者分配，以及检测和评估治疗效应时，尽量减少偏倚； ● 按照试验设计，对研究结果进行恰当的分析，以评估治疗效果。
桥接数据集	从完整临床数据集中选出的与新地区人群相关的信息，包括药动学数据和任何原始的药效学数据、以及量-效关系数据。如有必要，从新地区桥接研究中获得的额外数据，可促进国外的有效性和安全性数据外推到新地区人群。
桥接研究	桥接研究的定义是，在新地区进行的补充研究，提供新地区的安全性、有效性、剂量和给药方案的药效学或临床数据。促使国外临床数据外推到新地区。这些研究可能包括补充的药动学数据。
完整的临床数据集	用于注册的、含有符合新地区监管要求的临床数据，包含与新地区人群相关的药动学数据。
对种族因素不敏感的药物	种族因素对其安全性、有效性或量-效关系特征影响很小，无显著临床意义的药物。
对种族因素敏感的药物	药动学、药效学或其他特征表明，其内在和/或外在的种族因素对安全性、有效性或量-效关系可能有显著的、具有临床意义的影响的药物。
剂量	每次或每天的用药数量。
给药方法	在一段时间内，给药剂量、给药途径、频率和给药间隔。
种族因素	“种族”一词，来源于希腊语（ethnos），意思是民族或人民。种族因素是与种族相关，或根据共同特征和习惯聚集的大规模人群。种族的定义包含有民族文化和遗传学的意义，比racial更广义。种族因素又可分为内在因素和外在因素（附录A）。 ● 外在的种族因素 外在的种族因素，是与人群居住地环境和文化相关的因素。外在的因素大多由文化和行为所决定，而较少由遗传因素决定。举例来说，外在的因素包括该地区社会与文化的各方面，例如医疗实践、饮食、吸烟、饮酒、大气污染和阳光照射、社会经济状况、服药依从性，尤其重要的是，对其他地区研究数据、临床试验设计和实施情况的接受程度。 ● 内在的种族因素 内在的种族因素，有助于判断和鉴别亚群的因素，并可能影响临床数据在地区间外推的可能性，例如，基因多态性，年龄，性别，身高，体重，肌肉含量，身体构成和器官功能不全。
国外临床数据的外推	由国外人群中获得的安全性、有效性和量-效关系数据推广应用到新地区人群中。
国外临床数据	在新地区以外（如国外地区）产生的临床数据。
ICH 地区	欧盟，日本，美国、加拿大、瑞士、巴西、中国、新加坡、韩国。

新地区	药物即将申请注册的地区。
新地区的人群代表	在新地区中，包括主要种族群体的人群。
药动学研究	研究药物在体内的处置过程，包括检测血液中药物及其代谢物浓度（有时检测尿和组织中的浓度）随时间的变化情况。药动学是研究药物在血液或其他相关部位的吸收、分布、代谢和排泄特征。当与药效学检测（ PK/PD 研究）结合时，能够反映药物浓度与药效学作用的程度与时间的关系。
药效学研究	研究药物在个体中的药理效应或临床疗效，从而描述药物浓度或剂量与药物效应的关系。药物效应有可能是潜在的不良反应（如三环类的抗胆碱作用），对其活性的测定可能与临床获益 （如对 β 受体阻滞剂的测定，对 ECG 间期的影响， ACE 或血管紧张素 I/II 的抑制作用）、预期的短期疗效，通常是替代终点（血压、胆固醇），或最终预期的临床获益有关（如对疼痛、抑郁、猝死的影响）。
群体药动学研究	群体的药动学研究，是基于对群体的系统药物浓度测定的评估。通常，从参加临床试验的所有或某个亚群中，每个患者选择两个或以上的稳态样本进行研究。
治疗剂量范围	最低有效剂量与可获得的最大效应的剂量之间的范围。

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<table>
<tr><th colspan="2">内因</th><th>外因</th></tr>
<tr><th>遗传学</th><th>生理和病理状况</th><th>环境的</th></tr>
<tr><td>性别</td><td>年龄（儿童-老年人）</td><td>气候
日照
污染</td></tr>
<tr><td>身高
体重</td><td></td><td></td></tr>
<tr><td></td><td>肝脏
肾脏
心血管功能</td><td>文化
社会经济因素
教育状况</td></tr>
<tr><td></td><td></td><td>语言</td></tr>
<tr><td>ADME
受体敏感性</td><td></td><td>医疗措施</td></tr>
<tr><td>种族</td><td></td><td>疾病定义/诊断
治疗方法</td></tr>
<tr><td>药物代谢的
基因多态性</td><td>吸烟
饮酒
饮食习惯
应激</td><td></td></tr>
<tr><td>遗传性疾病</td><td>疾病</td><td>管理规范/GCP 方法学/终点</td></tr>
</table>

ADME（吸收、分布、代谢、排泄）

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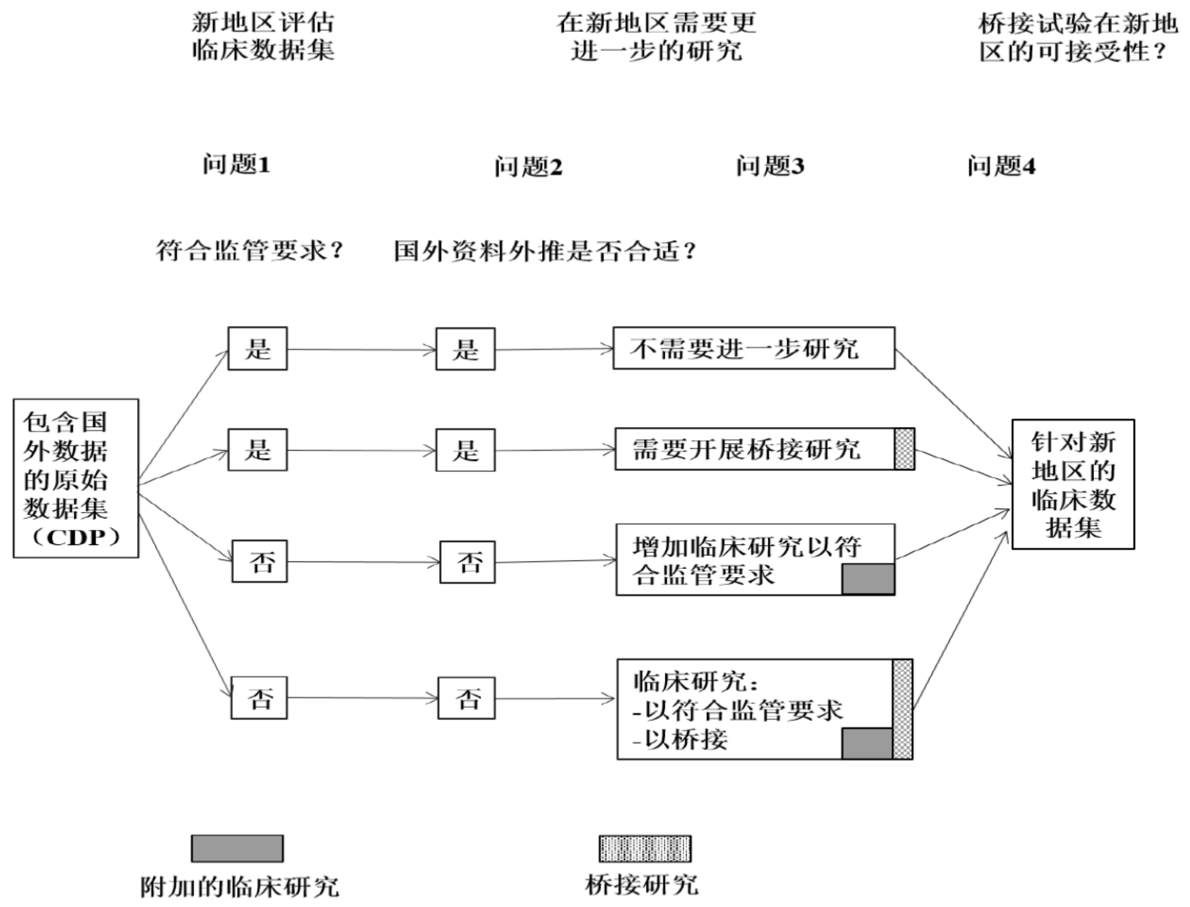

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评估 ICH 区域最相关的三个主要种族群体（亚洲人、黑种人和白种人）的药动学、药效学以及它们的可比性，对于 ICH 地区的药品注册至关重要。基本的药动学评估需阐明药物的吸收、分布、代谢、排泄（ADME）特征，以及合适的药物-食物、药物-药物相互作用。

两个地区之间充分的药动学比较，将有助于在新地区合理选择进一步的药动学研究和临床研究（桥接研究）的种类。人种间药动学的差异可能与内在的种族因素有关，且这种差异易于鉴别。与之不同的是，药效学反应（临床疗效、安全性和量-效关系）可能受到内在、外在种族因素的影响，且很难鉴别，除非在新地区进行临床试验。

ICH-E4 指南阐述了多种剂量-效应关系评估的方法。通常，国外研究应通过药理效应（被认为是相关的）和临床终点来评估剂量-效应（或浓度-效应）关系。也可以在国外能代表新地区的研究中评估药理效应，包括量-效关系。根据不同情况，新地区不一定需要临床疗效和量-效关系相关的数据。例如，当新地区对某类药物较熟悉，且药理效应与临床疗效、量-效关系密切相关时，这些国外药效学数据就足以用于申请注册，那么新地区可能不需要临床终点研究和量-效关系研究的数据。由于新地区的人群中量-效关系曲线可能会迁移，药效学评价和可能的临床终点评价（包括量-效关系）就显得非常重要。这方面已有确切的案例报道，例如黑人的血压对血管紧张素转换酶抑制剂的反应低

下。

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根据种族因素对药物的药动学、药效学以及治疗作用的潜在影响而得出的药物特征，有助于决定在新地区选择何种桥接研究。种族因素对药物的影响取决于该药的药理学分类、适应证和患者的年龄与性别。药物的任何特性都不能预测其对种族因素的相对敏感性。桥接研究种类的选择是一个最终决策，而对药物种族敏感性的分析有助于作出决策。

以下所述的特性，提示药物可能对种族因素不敏感：

- 线性药动学（PK）；
- 在推荐剂量和给药方案范围内，有效性和安全性均呈平缓的药效学（PD）曲线（浓度-效应）（这意味着药物有较好的耐受性）；
- 治疗窗宽（可能也是一个耐受性较好的指标）；
- 较少代谢，或通过多种途径代谢；
- 生物利用度高，不受饮食吸收作用的影响；
- 蛋白结合率低；
- 药物-药物，药物-食物，药物-疾病的相互作用小；
- 局部起效；
- 被不恰当使用的几率小。

以下所述的特性，提示药物对种族因素敏感：

- 非线性药动学；
- 在推荐剂量和给药方案范围内，有效性和安全性均呈陡峭的药效学曲线（很少的剂量变化引起极大的效应改变）；
- 治疗窗窄；
- 代谢率高，特别是通过单一途径代谢，增加了药物-药物相互作用的可能性；
- 药物代谢酶具有遗传多态性；
- 前体药物，其转化酶具有潜在的种族差异；
- 生物利用度的个体间差异大；
- 生物利用度低，易受饮食吸收作用的影响；
- 在多种药物联合时，使用率较高；
- 易被不恰当使用，如镇痛及镇定药。

ICH E5(R1) Implementation Working Group Questions & Answers

中文版
ICH E5(R1) 接受国外临床试验数据的种族因素问答

Date of Approval	Questions	Answers

1	Nov. 2003	I am planning to develop my new drug globally. Does E5 provide guidance for this approach?	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 data base 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 data base 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,

2	Nov. 2003	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?	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.

3	Nov. 2003	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?	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.

4	Nov. 2003	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?	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.

5	Nov. 2003	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?	There are two distinct issues that need to be considered: 1) the adequacy of the data base 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.

6	Nov. 2003	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?	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.
7	Nov. 2003	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?	No. As described, the data base 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.

8	Nov. 2003	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?	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.
9	Nov. 2003	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?	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.

10	Nov. 2003	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?	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.

11	June 2006	There seems to be an impression that the E5 bridging study would always be conducted after data in the original region is complete. Is this correct? It may be desirable in certain situations to achieve the goal of bridging by conducting a multi-regional trial under a common protocol that includes sufficient numbers of patients from each of multiple regions to reach a conclusion about the effect of the drug in all regions. Please provide points to consider in designing, analyzing and evaluating such a multi-regional trial.	Bridging data should allow for extrapolation of data from one region to another. Although E5 speaks generally to extrapolation of data to a new region, E5 was not intended to suggest that the bridging study should necessarily follow development in another region. In the answer to Q1, it is made clear that it is also possible to include earlier studies conducted in several regions in a global drug development program so that bridging data might become available sooner. This can expedite completion of a global clinical development program and facilitate registration in all regions. A bridging study therefore can be done at the beginning, during or at the end of a global development program. For a multi-regional trial to serve as a bridging study for a particular region, it would need to have persuasive results in that region, because it is these regional results that can convince the regulators in that region that the drug is effective, and can "bridge" the results of trials in other regions in the registration application. A multi-regional trial for the purpose of bridging could be conducted in the context of a global development program designed for near simultaneous world-wide registration. The objectives of such a study would be: 1) to show that the drug is effective in the region and 2) to compare the results of the study between the regions with the intent of establishing that the drug is not sensitive to ethnic factors. The primary endpoint(s) of the study should be defined and acceptable to the individual regions and data on all

ICH E5(R1) ??????????????????

English Version
ICH E5(R1) Implementation Working Group Questions & Answers

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1	2003年 11月	我计划在全球范围内研发一种新药。E5 能提供指导意见吗?	E5 正是为这种情况提供一些指导意见。E5 主要解决在一两个地区进行的研发项目如何在另一个地区获批的问题。E5 指出，通常情况下，如果在一个地区获得的临床数据符合新地区的证据要求，但需考虑到两个地区间可能存在的内在或外在种族差异性时，可以通过增加一个桥接研究使现有临床数据能够外推至新地区人群。桥接研究可以是药效学研究或完整的临床试验，也可能是剂量 -效应关系研究。 桥接研究可允许将合适的临床数据集外推至新地区人群。它作为全球研发计划的一部分，即同时而不是依次在多个地区进行，能合理且有效地评估潜在的区域差异性。例如，如果在多个地区的临床研究中有足够数量的受试人群来自于新地区，则有可能通过分析这些研究中种族差异性的影响，来确定整个临床数据集是否与新地区一致。 在全球研究设计中需要考虑到的能影响新地区对于数据的接受程度的基本问题包括：a）对病情和患者的确定与诊断；b）对照组的选择；c）区域性的治疗目标或疗效指标的选择；d）安全性评估方法；e）医疗实践；f）临床研究持续时间；g）地区性合并用药；h）纳入受试者的严重程度分布；以及 i）剂量和给药方案的相似性。 为了确定您所提出的全球试验方案是否能符合特定地区的监管要求，建议与该地区的监管机构尽早协商与讨论。

2	2003年 11月	我已在一个地区进行了药物的临床研究，涵盖了安全性、有效性、给药方案等方面以及在特殊人群如肝/肾功能不全患者、老年人、儿童以及妊娠期和哺乳期妇女中的使用。如果我能成功证明该药物在一般人群中的安全性、有效性和给药方案信息能外推至新地区人群（如通过桥接研究），是否还需进一步解决特殊人群数据外推的问题?	通常，如果特殊人群研究在试验设计上足以满足新地区的监管要求（如包括适当范围的不同损伤程度的受试人群），但是试验是在新地区以外的地区进行的，如果有证据支持一般人群研究数据可以外推至新地区，那么可能不需要重新研究新地区的特殊人群问题。但需注意，对于特殊人群中的新适应症（如儿童抑郁症），新地区可能会要求进行单独的桥接研究。
3	2003年 11月	我认为我的药物对种族因素敏感，且在不同地区其应用的医疗环境也有所差异。这是否意味着在某一地区进行的有效性研究将无法支持在另一地区进行药品申报?	不是。假设发现新地区认为其研究结果与原地区具有相关性，则新地区的监管机构可能会要求在本地区进行对照临床研究，以确定药物的有效性（和/或解决其它问题）。但是，E5指出，如果国外地区临床数据的其它方面均能符合新地区的所有要求，新地区可能会考虑仅进行一个单独的上述研究。如果新研究得出的结论与原地区相同，则原地区的临床数据被认为适用于新地区人群，因此无需进一步证实。在这种情况下，新地区的临床研究不一定需要用相同的剂量和治疗效应来证实之前在原地区的研究结果。在某些情况下，新地区可能会考虑要求额外的安全性数据。例如，如果新地区认为有必要使用更高的剂量或更高的给药频率，以及如果上述研究不是为了获得更多药代动力学结果，则申办者可能需要提供额外的安全性数据。
4	2003年 11月	我相信我的药物对种族因素不敏感，且在各地区间包括医疗实践等相关外在因素的差异没有意义。该药物的药代动力学对内在和外在因素也不敏感。在各地区间适应症的诊断和治疗也无显著性差异。但是，新地区管理局仍要求提供额外的安全性和有效性桥接研究。该要求是否与E5相矛盾?	不是，但您也可以与新地区监管机构就此问题进行商讨。E5明确指出，对桥接研究的要求始终只是一个判断性问题，并不能阻止新地区要求您进行桥接研究。E5特别指出，对其它地区的熟悉程度可能是决定新地区是否要求进行桥接研究的重要因素。E5期望新地区监管机构仅要求补充其它必需数据，以评估国外临床数据是否能外推到新地区人群，但是要求额外数据的数量则由监管机构自行议定。

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7	2003年 11月	我相信我的药物对种族因素不敏感。但是，在目标治疗领域，医疗实践和对某些药物的使用与主观需求方面存在明显差异。E5 是否有指出新地区应接受现有数据作为有效性的证据?	不是。如上所述，除了对种族差异的担忧之外，现有的数据不能适用于新地区对相关疾病的考虑，因此新地区可能不会接受现有的数据。
8	2003年 11月	我的药物已经被证实能有效预防某些临床事件的发生。但是，即使病理学结果相同，这些事件的发生率在新地区有明显不同。E5 是否有指出新地区应接受现有数据作为有效性的关键证据?	不是。可以肯定的是，在大多数情况下，在一个地区获得确定结果的研究，在另一地区则可能无需再重复。但也有例外。例如，如果某一事件的发生率在新地区确实较低，且两个地区的风险降低程度相同，那么新地区的受益患者实际人数将会有所减少，且不良反应会表现得更加重要，进而影响到药物的获益/风险比。某些情况下，新地区需要进行临床研究以评估药物的价值。
9	2003年 11月	我的药物已在一个地区被批准用于治疗多种适应症，并且在一项主要适应症的桥接研究中被证实能外推至新地区人群。这是否意味着在不提供额外临床数据的情况下，新地区会批准所有适应症的治疗。	不是。新地区是否要求提供额外的临床数据取决于具体情况，依赖于“桥接”适应症是否满足所有潜在种族差异性相关问题。例如，附加的适应症或许是主要适应症范围延伸（可能不要求补充进行桥接研究）或全新的使用范围（可能需要进行桥接研究）。建议早期与新地区监管者进行协商和讨论。
10	2003年 11月	E5 曾表述过这样的原则，即随着对地区间接受国外临床数据经验的增加，对于哪些情况下需要进行桥接研究有了更好的理解，因此可以期望随着这些经验的增加，地区间对桥接研究的需求也会逐渐减少。该原则是否仍有效?	是，这是我们所期望的。随着每个地区执行 E5 指导原则积累经验的增加，将会继续增加新地区对是否有必要进行桥接研究的理解。随着上述经验的增加，可以期望地区间对桥接研究的需求也会逐渐减少。

11	2006年 11月	印象中 E5 桥接研究通常是在原地区临床数据完成后实施。这是否正确？ 在某些情况下想要达到桥接研究的目的，可以通过在相同研究方案下进行多地区临床研究，需要保证每一个地区均涵涵足够数量的患者，从而得出药物在所有地区的有效性结论。请对多地区临床研究的设计、分析和评价方面的考虑提供指导性意见。	通过桥接研究，可以允许将研究数据从一个地区外推至另一个地区。尽管 E5 指出研究数据可以外推至新地区，但这并不表示另一个地区的桥接研究必须在整体研发之后进行。 Q1 答复中明确指出，为了尽早获得桥接数据，全球药物研发计划可以在多个地区同时进行早期研究。这样可以加速完成全球临床研发计划，并有助于药品在所有地区的注册申报。因此，桥接研究可以在全球研发计划开始时、进行中或结束时开展。以多地区临床试验来作为特定地区的桥接研究，需要获得该地区有说服力的研究结果。这是因为该地区研究结果可以使该地区监管者确认药物的有效性，且可以“桥接”注册申报中其他地区的研究结果。 出于桥接目的的多地区临床研究，可以在计划全球同步注册的研发方案中实施。该研究目的是：1）证实药物在该地区的有效性和 2）比较不同地区的研究结果以确定药物对种族因素不敏感。应确定主要终点并被各地区所认可，在相同研究方案的条件下收集所有地区的所有主要终点数据。如果不同地区所采用的主要终点有差异，则应收集所有地区的用于比较所有主要终点的数据。 对于一个预期可以作为桥接研究的试验，应考虑以下几点： 计划 多地区试验需满足申报地区在研究设计和分析方面的监管要求（见 Q1 答复）。通常，多地区研究应包括足够数量的受试者以便具有足够的把握度来合理地证明药物在每个申报地区的有效性。研究设计上的细微差异（如年龄入选标准、合并用药等）是可以接受的，鼓励与监管机构在前期讨论这些问题。对于安全性评价，尽可能就不同地区间安全性信息的收集和评价方法达成一致是十分重要的。 分析 对于以桥接为目的的多地区研究，提供各个地区有效性和安全性结果是至关重要的，并应关注常规分析结果（如人口统计学和基线指标、患者分