



**ICH Topic E 5 (R1)
Ethnic Factors in the Acceptability of Foreign Clinical Data**

Step 5

**NOTE FOR GUIDANCE ON ETHNIC FACTORS IN THE ACCEPTABILITY OF
FOREIGN CLINICAL DATA
(CPMP/ICH/289/95)**

TRANSMISSION TO CPMP	March 1997
RELEASE FOR CONSULTATION	March 1997
DEADLINE FOR COMMENTS	June 1997
FINAL APPROVAL BY CPMP	March 1998
DATE FOR COMING INTO OPERATION	September 1998

ETHNIC FACTORS IN THE ACCEPTABILITY OF FOREIGN CLINICAL DATA

ICH Harmonised Tripartite Guideline

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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 minimising 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 minimise 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 characterising ethnic factor influences on safety, efficacy, dosage and dose regimen.

1.2 Background

All regions acknowledge the desirability of utilising 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 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 fulfills 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 fulfill 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:

1. its completeness with respect to the regulatory requirements of the new region, and
2. 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 FULFILLMENT 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 characterisation 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*
 - Utilise endpoints that are considered appropriate for assessment of treatment
 - Evaluate clinical disorders using medical and diagnostic definitions that are acceptable to the new region.
- Characterisation in a population relevant to the new region of the pharmacokinetics, and where possible, pharmacodynamics and dose response for pharmacodynamic

endpoints. This characterisation 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 Characterisation of the Medicine's Sensitivity to Ethnic Factors

To assess a medicine's sensitivity to ethnic factors it is important that there be 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). Characterisation 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 behavior 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 fulfills 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 characterised 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 randomised, 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 utilise a standard clinical endpoint in a study of shorter duration than the foreign studies or utilise 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 characterised as ethnically sensitive or insensitive (Appendix D). Ideally, this characterisation 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

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 minimise 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 fulfill 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 behaviorally 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, socioeconomic

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 subpopulation 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 generalisation 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 characterise 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 characterise 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).

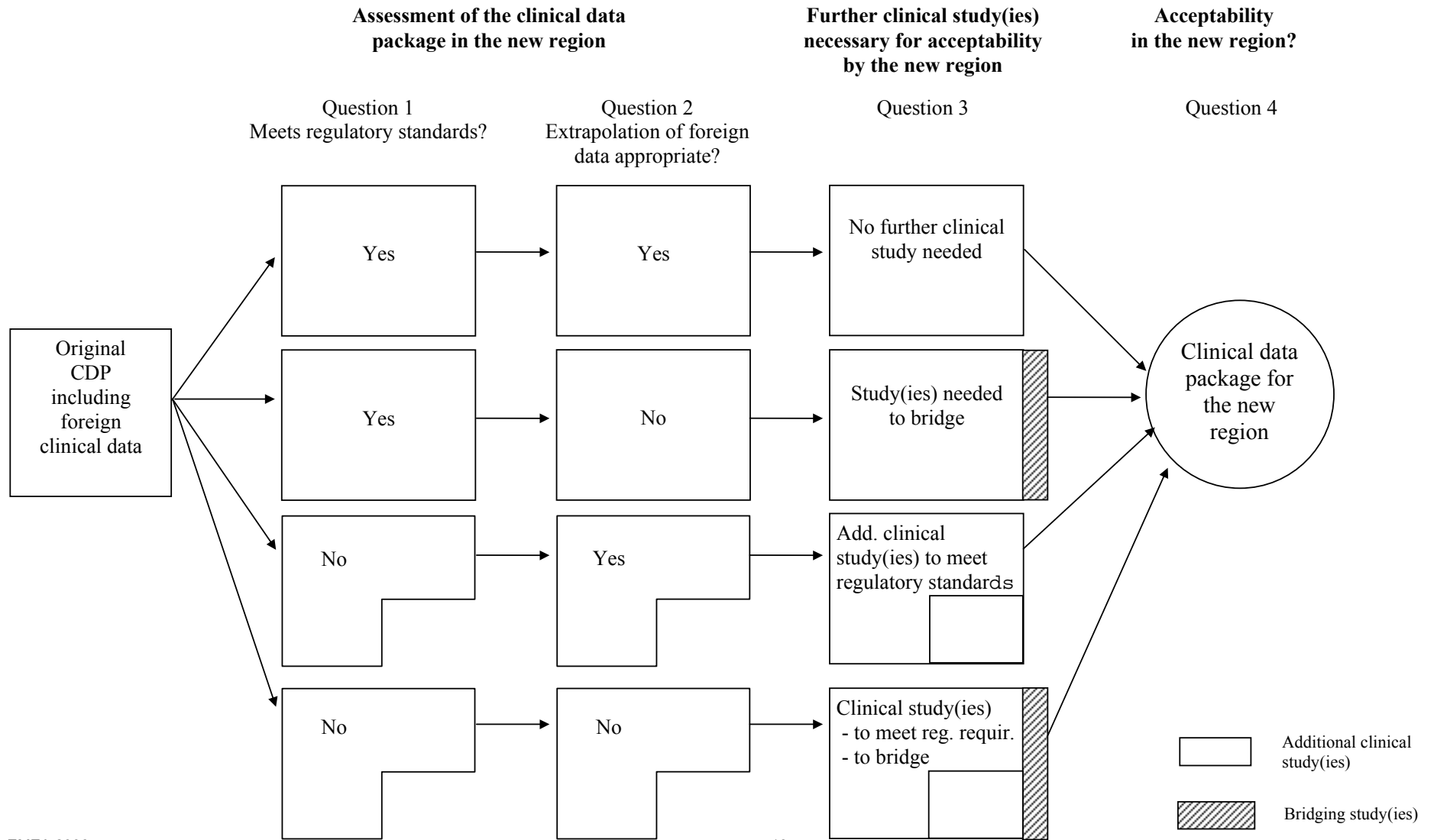
Population Pharmacokinetic Methods: Population pharmacokinetic methods are a population-based evaluation of measurements of systemic drug concentrations, usually two or more per patient under steady state conditions, from all, or a defined subset of, patients who participate in clinical trials.

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 Pollution
	Height Bodyweight	Culture Socio-economic factors Educational status Language
	Liver Kidney Cardiovascular functions	Medical practice Disease definition/Diagnostic Therapeutic approach Drug compliance
	ADME Receptor sensitivity	
Race		Smoking Alcohol
Genetic polymorphism of the drug metabolism		Food habits Stress
Genetic disease	Diseases	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 characterise 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

Characterisation 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 judgment but assessment of sensitivity to ethnic factors may help in that judgment.

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
- Nonsystemic mode of action
- Little potential for inappropriate use

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

- Nonlinear 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 metabolised, 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.