DATES: Written comments on the petitioner's environmental assessment by September 2, 1997.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Vir D. Anand, Center for Food Safety and Applied Nutrition (HFS-216), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-418-3081.

SUPPLEMENTARY INFORMATION: Under the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5) (21 U.S.C. 348(b)(5))), notice is given that a food additive petition (FAP 7B4550) has been filed by Goldschmidt Chemical Corp., c/o Keller and Heckman, 1001 G St., NW., suite 500 West, Washington, DC 20001. The petition proposes to amend the food additive regulations in § 178.3725 *Pigment dispersants* (21 CFR 178.3725) to provide for the expanded safe use of siloxanes and silicones; cetylmethyl, dimethyl, methyl 11-methoxy-11-oxoundecyl as a pigment dispersant in all pigmented polymers intended for use in contact with food.

The potential environmental impact of this action is being reviewed. To encourage public participation consistent with regulations promulgated under the National Environmental Policy Act (40 CFR 1501.4(b)), the agency is placing the environmental assessment submitted with the petition that is the subject of this notice on public display at the Dockets Management Branch (address above) for public review and comment. Interested persons may, on or before September 2, 1997, submit to the Dockets Management Branch (address above) written comments. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. FDA will also place on public display any amendments to, or comments on, the petitioner's environmental assessment without further announcement in the **Federal Register**. If, based on its review, the agency finds that an environmental impact statement is not required and this petition results in a regulation, the notice of availability of the agency's finding of no significant impact and the evidence supporting that finding will be published with the regulation in the **Federal Register** in accordance with 21 CFR 25.40(c).

Dated: July 11, 1997.

Laura M. Tarantino,

Acting Director, Office of Premarket Approval, Center for Food Safety and Applied Nutrition.

[FR Doc. 97–20079 Filed 7-30-97; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97D–0299]

International Conference on Harmonisation; Draft Guideline on Ethnic Factors in the Acceptability of Foreign Clinical Data; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft guideline entitled ''Ethnic Factors in the Acceptability of Foreign Clinical Data.'' The draft guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft guideline provides guidance on regulatory and development strategies to permit clinical data collected in one region to be used for the support of drug and biologic registrations in another region while allowing for the influence of ethnic factors.

DATES: Written comments by October 29, 1997.

ADDRESSES: Submit written comments on the draft guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Copies of the draft guideline are available from the Drug Information Branch (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–4573. Single copies of the guideline may be obtained by mail from the Office of Communication, Training and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research (CBER), 1401 Rockville Pike, Rockville, MD 20852–1448, or by calling the CBER Voice Information System at 1–800–835–4709 or 301–827–1800. Copies may be obtained from CBER's FAX Information System at 1–888–CBER–FAX or 301–827–3844.

FOR FURTHER INFORMATION CONTACT:

Regarding the guideline: Barbara G. Matthews, Center for Biologics Evaluation and Research (HFM–570), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301–827–5094.

Regarding the ICH: Janet J. Showalter, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–0864.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA, and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

In March 1997, the ICH Steering Committee agreed that a draft guideline entitled ''Ethnic Factors in the Acceptability of Foreign Clinical Data'' should be made available for public comment. The draft guideline is the product of the Efficacy Expert Working Group of the ICH. Comments about this

draft will be considered by FDA and the Efficacy Expert Working Group.

The draft guideline is intended to facilitate the registration of drugs and biologics among the 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. The draft guideline provides guidance on regulatory and development strategies that will permit adequate evaluation of the influence of ethnic factors while minimizing duplication of clinical studies, and expediting the drug approval process.

This draft guideline represents the agency's current thinking on ethnic factors in the acceptability of foreign clinical data for approval of both drugs and biologics. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Interested persons may, on or before Ocotber 29, 1997, submit to the Dockets Management Branch (address above) written comments on the draft guideline. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. An electronic version of this guideline is available via Internet using the World Wide Web (WWW) at ''http://www.fda.gov/cder/guidance.htm''. To connect to CBER's WWW site, type ''http://www.fda.gov/cber/cberftp.html''.

The text of the draft guideline follows:

Ethnic Factors in the Acceptability of Foreign Clinical Data

1.0 Introduction
1.1 Objectives
1.2 Background
1.3 Scope
2.0 Assessment of the Clinical Data Package Including Foreign Clinical Data for Its Fulfillment of Regulatory Requirements in the New Region
2.1 Additional Studies to Meet the New Region's Regulatory Requirements
3.0 Assessment of the Foreign Clinical Data Package for Extrapolation to the New Region
3.1 Characterization of the Drug's Sensitivity to Ethnic Factors
3.2 Bridging Data Package
3.2.1 Definition of Bridging Study and Bridging Data Package
3.2.2 Nature and Extent of the Bridging Study
3.2.3 Bridging Studies for Efficacy
3.2.4 Bridging Studies for Safety
4.0 Developmental Strategies for Global Development
5.0 Summary

Glossary

Appendix A: Classification of Intrinsic and Extrinsic Ethnic Factors

Appendix B: Assessment of the Clinical Data Package (CDP) for Acceptability

Appendix C: Pharmacokinetic, Pharmacodynamic, and Dose-Response Considerations

Appendix D: A Drug's Sensitivity to Ethnic Factors

(Italicized words and terms in the text of the guideline are defined or explained in the glossary.)

1.0 Introduction

The purpose of this guidance is to facilitate the registration of medicines 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*. 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. 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 drug registration 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, therefore, 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 drug's safety, efficacy, dosage, or dose regimen, many drugs 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 valuable 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 in the new region; it does seek 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 its study design and conduct, and the available data should be *complete* to the satisfaction of 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 is complete in its fulfillment of 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 drug 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:

(1) 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).

2.0 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. A data package that meets all of these regional regulatory requirements would be considered complete 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 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).
- Characterization of pharmacokinetics, and where possible, pharmacodynamics and dose response for pharmacodynamic endpoints in a population relevant to the new region of interest. This characterization need not be performed in the new region but could be performed in the foreign region in a population representative of the new region.
- 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 good clinical practice (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.

Several ICH guidelines address aspects with respect to: 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 guideline on the clinical study design question of choice of control group (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 new region's regulatory requirements, the regulatory authority may require additional clinical trials, such as:

- Clinical trials in different subsets of the population,
- Clinical trials using different comparators at the new region's approved dosage and dose regimen,
- Drug-drug interaction studies,
- Pharmacokinetic studies in a population representative of the new region.

3.0 Assessment of the Foreign Clinical Data Package for Extrapolation to the New Region

3.1 Characterization of the Drug's Sensitivity to Ethnic Factors

To assess a drug'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 drug (chemical class, metabolic pathway, pharmacologic class) make it more or less likely to be affected by ethnic factors (Appendix D). Characterization of a drug as ''ethnically insensitive,'' i.e., unlikely to behave differently in different populations, usually would make it easier to extrapolate data from one region to another and need less bridging data.

Factors that make a drug 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 drug's sensitivity to ethnic factors. It may be easier to conclude that the pharmacodynamic and clinical behavior of a drug 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 foreign region.

3.2 Bridging Data Package

3.2.1 Definition of Bridging Study and Bridging Data Package

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 package to the population in the new region. Such studies could include further pharmacokinetic information.

A *bridging data package* consists of: (1) Information from the foreign 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, (2) a bridging study to extrapolate the foreign efficacy data and/or safety data to the new region.

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 data from the 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, a single clinical endpoint, fixed dose, dose-response study may be the only one needed to bridge the foreign data, but a short-term pharmacologic endpoint study might help choose the doses for the large 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, 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 foreign 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 drugs characterized as insensitive to ethnic factors, the type of bridging study needed (if needed) will depend upon the likelihood that extrinsic ethnic factors (including design and conduct of clinical trials) could affect the drug's safety, efficacy, and dose response and upon experience with the drug class. For drugs that are ethnically sensitive, a bridging study may often be needed if the patient 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:

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

(2) If the drug 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 drug 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 foreign 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 drug'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 package demonstrates 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 percent 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:

—A known index case of a serious adverse event in a foreign clinical data package,

—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.

4.0 Developmental Strategies for Global Development

Definition of not only pharmacokinetics but also of 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 drug 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. For global development, studies should include populations representative of the regions where the drug 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 a *pharmacokinetic screen* conducted either in a population relevant to the new region or in the new region.

5.0 Summary

This guidance describes how a sponsor developing a drug for a new region can deal with the possibility that ethnic factors could influence the effects (safety and efficacy) of drugs 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 a foreign clinical data package may be achieved by generating ''bridging'' data to link the safety and effectiveness data in the foreign region(s) to the population in the new region.

Glossary

Bridging data package: Information from the foreign 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 in the new region that will allow extrapolation of the safety and efficacy data in the foreign clinical data package 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 package to the new region. Such studies could include further 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.

Compound insensitive to ethnic factors: A compound whose characteristics suggest minimal potential for clinically significant impact by ethnic factors on safety, efficacy, or dose response.

Compound 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 groups of people classed 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.

- *Extrinsic ethnic factors*: Extrinsic ethnic factors are factors associated with the environment and culture in which the patient 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 in a new region, practices in clinical trial design and conduct.
- *Intrinsic ethnic factors*: Intrinsic ethnic factors are characteristics associated with the drug recipient. These 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 ability to apply the safety, efficacy, and dose-response data from the foreign clinical data package to the population of the new region.

Foreign clinical data: Foreign clinical data is defined as clinical data generated outside the new region (i.e., in the foreign region).

ICH regions: The European Union, Japan, the United States of America.

New region: The region where product registration is sought.

Pharmacokinetic screen: A pharmacokinetic screen is 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. In order for these data to be useful in the evaluation of the relationships between pharmacokinetics and intrinsic ethnic and other factors, it is important that there be a prospective protocol for the collection of samples for drug concentration measurements and that the timing of samples relative to dosing be known precisely. While these analyses may be less precise than those from formal pharmacokinetic studies, the numbers of patients studied is greater and a much greater variety of factors that could influence pharmacokinetics, including unexpected influences, can be evaluated. Moreover, small variations which might be missed in the clinical setting are likely unimportant. Large differences detected by the screen may be definitive or may suggest the need for further evaluation for safety and efficacy in the new population.

Pharmacokinetic study: A study of how a drug is handled by the body, usually involving measurement of blood concentrations (sometimes concentrations in urine or tissues) over time of the drug and its metabolism. 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 an effect of the drug on individuals. The effect measured can be any pharmacologic or clinical effect of the drug and it is usual to seek 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 (electrocardiogram) intervals, inhibition of ACE (angiotensin converting enzyme) 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).

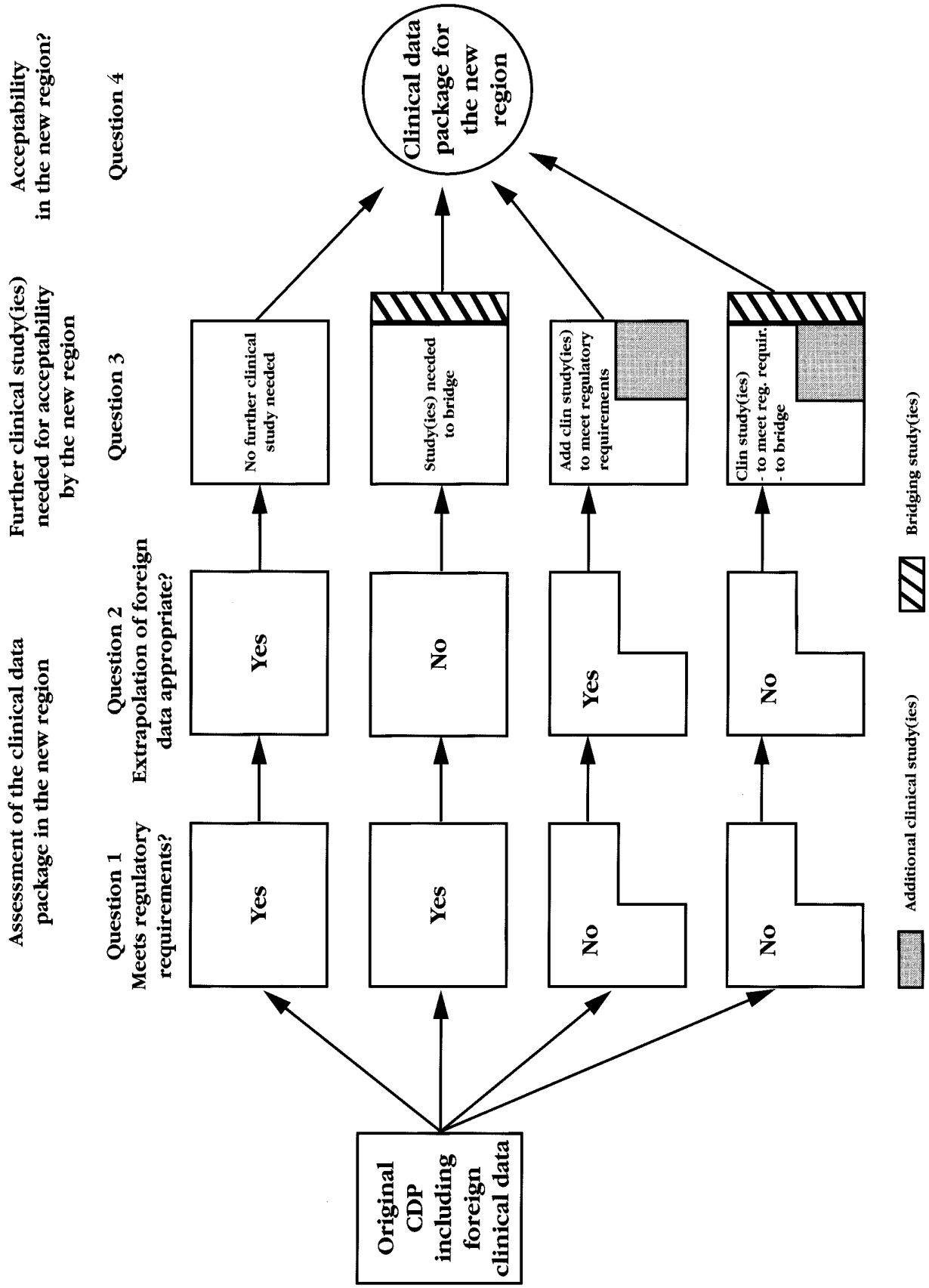
Therapeutic dose range: The difference between the lowest useful dose and the highest dose that gives further benefit.

BILLING CODE 4160–01–F

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		
	Liver Kidney Cardiovascular functions	Culture Socioeconomic factors Educational status Language
ADME Receptor sensitivity		
Race		Medical practice Disease definition/Diagnostic Therapeutic approach Drug compliance
Genetic polymorphism of the drug metabolism		
	Smoking Alcohol	
	Food habits Stress	
Genetic diseases	Diseases	
		Regulatory practice/GCP Methodology/Endpoints

Appendix B: Assessment of the Clinical Data Package (CDP) for Acceptability



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Appendix C: Pharmacokinetic, Pharmacodynamic, and Dose-Response Considerations

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

A sound pharmacokinetic comparison in the foreign and new regions allows rational consideration of what kinds of further pharmacodynamic and clinical studies (bridging studies) are needed in the new region. In contrast to a medicine's pharmacokinetics, where differences between populations may be attributed primarily to intrinsic ethnic factors and are readily identified, a medicine's 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 guideline 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 Drug's Sensitivity to Ethnic Factors

Characterization of a drug 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 drug'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 drug 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 drug 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 abuse.

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 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 intersubject variation in bioavailability.
- Low bioavailability, thus more susceptible to dietary absorption effects.
- High likelihood of use in a setting of multiple co-medications.
- High potential for abuse.

Dated: July 25, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97N–0289]

Content and Format of Labeling for Human Prescription Drugs; Pregnancy Labeling; Public Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public hearing; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is announcing a public hearing regarding requirements for the content and format of the pregnancy subsection of labeling for human prescription drugs. The public hearing will focus on the requirement that each drug product be classified in one of five pregnancy categories intended to aid clinicians and patients with decisions about drug therapy. Public comments and FDA's preliminary review of the pregnancy category designations for marketed drugs suggest that the categories may be misleading and confusing, may not accurately reflect reproductive and developmental risk, and may be used inappropriately by clinicians in making decisions about drug therapy in pregnant women and women of childbearing potential and also in making decisions about how to respond to inadvertent fetal exposure. The hearing is intended to elicit comments on the practical utility, effects, and limitations of the current pregnancy labeling categories in order to help the agency identify the range of problems associated with the categories and to identify and evaluate options that might address identified problems, and to hear the views of groups most affected.

DATES: The public hearing will be held on Friday, September 12, 1997, from 9 a.m. to 5 p.m. Submit written notices of participation and comments for consideration at the hearing by August 28, 1997. Written comments will be accepted after the hearing until November 12, 1997.

ADDRESSES: The hearing will be held at the Holiday Inn Bethesda, 8120 Wisconsin Ave.,Versailles I and II, Bethesda, MD 20814. Submit written notices of participation and comments to the Advisors and Consultants Staff, Center for Drug Evaluation and Research (HFD–21), ATTN: Pregnancy Labeling Hearing—Robin M. Spencer or Kimberly L. Topper, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, FAX 301–443–0699. Federal Express deliveries need to use the following street address: 1901 Chapman Ave., rm. 200, Rockville, MD 20852.

Transcripts of the hearing will be available from the Freedom of Information Office (HFI–35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, FAX 301–443–1726, approximately 15 business days after the hearing at a cost of 10 cents per page. Requests can also be made for microfiche or computer disk copies in place of paper copies.

FOR FURTHER INFORMATION CONTACT: Rose E. Cunningham, Center for Drug Evaluation and Research (HFD–6), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–6779, or FAX 301–594–5493; or Kimberly L. Topper, Advisors and