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.

[FR Doc. 97–20246 Filed 7–30–97; 8:45 am]

BILLING CODE 4160–01–F

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

Consultants Staff (address above), 301–443–5455, or FAX 301–443–0699.

SUPPLEMENTARY INFORMATION:

I. Background

Under the Federal Food, Drug, and Cosmetic Act (the act), FDA has responsibility for ensuring that prescription drug and biological products are accompanied by labeling (prescribing information) that summarizes essential scientific information needed for their safe and effective use. Unless a drug is not absorbed systemically and is not known to have a potential for indirect harm to a fetus, its labeling must include a ''Pregnancy subsection'' containing narrative information on the drug's teratogenic effects and other effects on reproduction and pregnancy, and, when relevant, effects on later growth, development, and functional maturation of the child (21 CFR 201.57(f)(6)). The regulation also requires that each product be classified under one of five pregnancy categories (A, B, C, D, or X) on the basis of risk of reproductive and developmental adverse effects or, for certain categories, on the basis of such risk weighed against potential benefit. A drug's pregnancy category is identified at the beginning of its pregnancy labeling subsection.

Clinicians who treat pregnant women and women of childbearing potential, academic and specialty medical organizations, women's health organizations and others have expressed to FDA concern that the information contained in the typical pregnancy labeling subsection, and the manner in which such information is presented, are not sufficient to adequately inform decisions about drug therapy in pregnant women and women of childbearing potential, or decisions about how to respond to inadvertent fetal drug exposure.

In response to these concerns and FDA's growing awareness of the limitations of the pregnancy subsection of the labeling, FDA is currently engaged in a comprehensive evaluation of the way the agency assesses reproductive and developmental toxicities associated with human drugs and biologics, and the way the agency communicates this information to clinicians and patients. This evaluation is focused on assessing the adequacy of animal and human exposure data currently developed or maintained, developing consistency in interpretation of reproductive and developmental risk from animal and human exposure data, and identifying means to optimize communication of this risk information.

FDA has created a multidisciplinary task force to explore these issues. This group intends to develop, for use by FDA reviewers and industry, a guidance document on interpretation of reproductive and developmental toxicity data from animals and a guidance document on interpretation of human exposure data. The task force will also consider other possible actions that may be necessary to make pregnancy labeling content more consistent, informative, and accessible including: (1) Changing, or creating alternatives to, the pregnancy labeling categories; (2) clearly distinguishing in labeling between information that addresses whether to prescribe a therapeutic option during pregnancy, whether to prescribe a therapeutic option in a woman of childbearing potential, and the potential consequences of inadvertent fetal exposure; and (3) attempting to better delineate the different types of reproductive and developmental risks associated with a product. This hearing is intended to gather information to inform future task force recommendations.

II. The Pregnancy Categories

FDA's information gathering and evaluation to date have identified the pregnancy categories as a source of concern for those who use or are affected by pregnancy labeling. The categories have been criticized for being confusing and misleading because they convey the impression that there is a gradation of reproductive risk from drug exposure across categories (i.e., that risk increases from A to B to C to D to X) and that there is similar risk within any given category, but the criteria for designating drugs in particular categories are not consistent with these impressions.

The confusion concerning gradation of risk across categories is believed to be due, in part, to the fact that the criteria for inclusion in categories A, B, and to a certain extent C, are based primarily on risk with risk increasing from A to C, while criteria for inclusion in categories D, X, and to a certain extent C, are based on risk weighed against potential benefit. Thus, while it is intended that there be gradation of risk for categories A through C, drugs designated D, X, and in some cases C, may pose a very similar risk, but be categorized differently on the basis of potential benefit.

The impression that there is similar risk for drugs within the same category is undercut by inclusion criteria that permit a broad range of risk within certain categories. For example, category C (the largest category) is intended to include both drugs with demonstrated adverse reproductive effects in animals and drugs for which there are no animal studies at all, situations that may be quite different in terms of risk. For the category C drugs that were tested in animals, moreover, there is a wide range of severity of adverse effects and often no distinction between teratogenic and other toxic effects.

The confusion inherent in the current category designations may be exacerbated by inconsistent application of category classifications in certain instances, such that drugs with similar risk, or with similar risk-benefit assessments, may be found in different categories.

Some who expressed concern to the agency about pregnancy labeling argue that failure of the category designations to accurately reflect reproductive and developmental risk, either across categories or within a category, presents potentially serious public health consequences. They maintain that many clinicians assume the categories reflect gradation of risk from category A through X, that any given category is homogenous in terms of risk, and based on those assumptions make decisions based largely or entirely on category designation rather than on careful evaluation of the available data. They also argue that, in addition to the potential for category designations to be misleading, the mere presence of category designations affords an overly simplistic evaluation of a complex problem that can deter the clinician from seeking additional information that could lead to a better informed decision. They maintain that clinicians making decisions based on category designation alone are more likely to overestimate risk, with potentially profound consequences. For example, decisions based on an overestimation of teratogenic risk may result in unnecessary withholding of beneficial therapy or in termination of wanted pregnancies.

III. Scope of the Hearing

Because of the breadth and complexity of issues involved in assessing, interpreting, and communicating information that bears on therapeutic use and exposure to drugs in pregnancy and in women of childbearing potential, this part 15 (21 CFR part 15) hearing will focus on the pregnancy categories. To guide its future decision making, the agency is seeking public comment and data on the practical utility and effects of the pregnancy categories, problems associated with the categories, and the

means to address problems associated with the categories, including possible alternatives to the categories for communicating information on reproductive and developmental toxicity. The agency is specifically seeking comment and data on the following:

(1) The extent to which the category designations are relied upon in making decisions about drug therapy in pregnant women and women of childbearing potential and decisions about inadvertent fetal exposure, the extent to which such reliance may be misplaced, and the extent to which such reliance may have untoward public health consequences;

(2) The extent to which current pregnancy labeling (category designation and accompanying narrative text) is effective in communicating risk of reproductive and developmental toxicity;

(3) The extent to which current pregnancy labeling may not adequately address the range of issues that may bear on decisions about drug therapy in pregnant women and women of childbearing potential and decisions about inadvertent fetal exposure (e.g., indication-specific concerns, pregnancy status, magnitude of exposure, incidental exposure, chronic exposure, timing of exposure);

(4) Additional information (data or interpretation of data) that could be included in pregnancy labeling to better address the range of issues that bear on decisions about drug therapy in pregnant women and women of childbearing potential and decisions about inadvertent fetal exposure; and

(5) Options to improve communication of reproductive and developmental risk in labeling, which could include alternatives to the categories (both content and format options) or efforts to make the current category scheme and accompanying narrative text more consistent and informative.

The agency encourages individuals, industry, consumer groups, health care professionals, and researchers with particular expertise in this area, as well as other interested persons, to respond to this notice. The agency strongly encourages persons who cannot attend the hearing to send information relevant to the topics and questions listed above to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm 1–23, Rockville, MD 20857. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with Docket No. 97N–0289. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

IV. Notice Of Hearing Under Part 15

The Commissioner of Food and Drugs (the Commissioner) is announcing that the public hearing will be held in accordance with part 15. The presiding officer will be the Commissioner or his designee. The presiding officer will be accompanied by a panel of Public Health Service employees with relevant expertise.

Persons who wish to participate in the part 15 hearing must file a written or facsimile notice of participation with the Advisors and Consultants Staff by August 28, 1997. To ensure timely handling, the outer envelope or facsimile cover sheet should be clearly marked with Docket No. 97N–0289 and the statement ''Pregnancy Labeling Hearing.'' Groups should submit two copies. The notice of participation should contain the speaker's name, address, telephone number, FAX number, title, business affiliation, if any, a brief summary of the presentation, and approximate amount of time requested for the presentation.

The agency requests that persons or groups having similar interests consolidate their presentations and present them through a single representative. FDA will allocate the time available for the hearing among the persons who properly file notices of participation. If time permits, FDA may allow participation at the conclusion of the hearing from interested persons attending the hearing who did not submit a written notice of participation.

After reviewing the notices of participation and accompanying information, FDA will schedule each appearance and notify each participant by mail, telephone, or FAX, of the time allotted to the person and the approximate time the person's presentation is scheduled to begin. The hearing schedule will be available at the hearing. After the hearing the schedule will be placed on file in the Dockets Management Branch (address above) under Docket Number 97N–0289.

Under § 15.30(f), the hearing is informal and the rules of evidence do not apply. The presiding officer and any panel members may question any person during or at the conclusion of their presentation. No other person attending the hearing may question a person making a presentation or interrupt the presentation of a participant.

Public hearings under part 15 are subject to FDA's guideline (part 10, subpart C (21 CFR part 10, subpart C)) concerning the policy and procedures for electronic media coverage of FDA's public administrative proceedings. Under § 10.205, representatives of the electronic media may be permitted, subject, to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including presentations by participants. Representatives of the electronic media are urged to provide advance notice of their planned attendance, to the identified contact person for the hearing, so that their needs for space and technical assistance can be anticipated and accommodated. The hearing will be transcribed as required in § 15.30(b). Orders for copies of the transcript can be placed through the Dockets Management Branch (address above).

Any disabled persons requiring special accommodations in order to attend the hearing should direct those needs to the contact person listed above.

To the extent that the conditions for the hearing, as described in this notice, conflict with any provisions set out in part 15, this notice acts as a waiver of those provisions as specified in § 15.30(h).

To permit time for all interested persons to submit data, information, or views on this subject, the administrative record will remain open following the hearing until November 12, 1997.

Dated: July 23, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 97–20247 Filed 7-30-97; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Care Financing Administration

[Form #HCFA–R–200]

Emergency Clearance: Public Information Collection Requirements Submitted to the Office of Management and Budget (OMB)

In compliance with the requirement of section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995, the Health Care Financing Administration (HCFA), Department of Health and Human Services (DHHS), has submitted to the Office of Management and Budget (OMB) the following request for Emergency review. We are requesting an emergency review because the collection of this information is needed prior to the expiration of the normal time limits under OMB's regulations at