DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 94D–0029]

International Conference on Harmonisation; Guideline on the Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a final guideline entitled ''The Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-life-threatening Conditions.'' This guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guideline is intended to present an accepted set of principles for the safety evaluation of drugs intended for the long-term treatment (chronic or repeated intermittent use for longer than 6 months) of non-life-threatening diseases.

DATES: Effective on March 1, 1995. Submit written comments at any time.

ADDRESSES: Submit written comments on the guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Copies of the guideline are available from CDER Executive Secretariat Staff (HFD–8), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

FOR FURTHER INFORMATION CONTACT:

Regarding the guideline: Leah Ripper, Center for Drug Evaluation and Research (HFD–500), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–2544.

Regarding ICH: Janet J. Showalter, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–1382.

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 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 Industry 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 Association (IFPMA).

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

Harmonization of the safety evaluation of drugs intended for the long-term treatment of non-life-threatening diseases was selected as a priority topic during the early stages of the ICH initiative. In the **Federal Register** of March 1, 1994 (59 FR 9746), FDA published a draft tripartite guideline entitled ''Draft Guideline on the Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions.'' The notice gave interested persons an opportunity to submit comments by May 16, 1994.

After consideration of the comments received and revisions to the guideline, a final draft of the guideline was submitted to the ICH Steering Committee and endorsed by the three participating regulatory agencies at the ICH meeting held in October 1994.

The guideline presents an accepted set of principles for the safety evaluation of drugs intended for the long-term treatment of non-life-threatening diseases. The guideline distinguishes between clinical data on adverse drug events (ADE's) derived from studies of shorter duration of exposure and data from studies of longer duration, which frequently include nonconcurrently controlled studies. The principles discussed in the guideline are summarized as follows: (1) Regulatory standards are valuable for the extent and duration of treatment needed to provide the safety data base for drugs intended for long-term treatment of non-life-threatening conditions; however, there are a number of circumstances where harmonized regulatory standards for the clinical safety evaluation may not be applicable; (2) further investigation is needed about the occurrence of ADE's in relation to duration of treatment for different drug classes; (3) because most ADE's first occur within the first 3 to 6 months of drug treatment, many patients should be treated and observed for 6 months at dosage levels intended for clinical use; and (4) because some serious ADE's may occur only after drug treatment for more than 6 months, some patients should be treated with the drug for 12 months.

In the past, guidelines have generally been issued under § 10.90(b) (21 CFR 10.90(b)), which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but are acceptable to FDA. The agency is now in the process of revising § 10.90(b). Therefore, this guideline is not being issued under the authority of § 10.90(b), and it does not create or confer any rights, privileges, or benefits for or on any person, nor does it operate to bind FDA in any way.

As with all of FDA's guidelines, the public is encouraged to submit written comments with new data or other new information pertinent to this guideline. The comments in the docket will be periodically reviewed, and, where appropriate, the guideline will be amended. The public will be notified of any such amendments through a notice in the **Federal Register**.

Interested persons may, at any time, submit written comments on the guideline to the Dockets Management Branch (address above). 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 guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the guideline follows:

The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions

The objective of this guideline is to present an accepted set of principles for the safety evaluation of drugs intended for the long-term treatment (chronic or repeated intermittent use for longer than 6 months) of non-life-threatening diseases. The safety evaluation during clinical drug development is expected to characterize and quantify the safety profile of a drug over a reasonable duration of time consistent with the intended long-term use of the drug. Thus, duration of drug exposure and its relationship to both time and magnitude of occurrence of adverse events are important considerations in determining the size of the data base necessary to achieve such goals.

For the purpose of this guideline, it is useful to distinguish between clinical data on adverse drug events (ADE's) derived from studies of shorter duration of exposure and data from studies of longer duration, which frequently are nonconcurrently controlled studies. It is expected that short-term event rates (cumulative 3-month incidence of about 1 percent) will be well characterized. Events where the rate of occurrence changes over a longer period of time may need to be characterized depending on their severity and importance to the risk-benefit assessment of the drug. The safety evaluation during clinical drug development is not expected to characterize rare adverse events, for example, those occurring in less than 1 in 1,000 patients.

The design of the clinical studies can significantly influence the ability to make causality judgments about the relationships between the drug and adverse events. A placebo-controlled trial allows the adverse event rate in the drug-treated group to be compared directly with the background event rate in the patient population being studied. Although a study with a positive or active control will allow a comparison of adverse event rates to be made between the test drug and the control drug, no direct assessment of the background event rate in the population studied can be made. A study that has no concurrent control group makes it more difficult to assess the causality relationship between adverse events observed and the test drug.

There was general agreement on the following:

1. A harmonized regulatory standard is of value for the extent and duration of treatment needed to provide the safety data base for drugs intended for long-term treatment of non-life-threatening conditions. Although this standard covers many indications and drug classes, there are exceptions.

2. Regulatory standards for the safety evaluation of drugs should be based on previous experience with the occurrence and detection of ADE's, statistical considerations of the probability of detecting specified frequencies of ADE's, and practical considerations.

3. Information about the occurrence of ADE's in relation to duration of treatment for different drug classes is incomplete, and further investigations to obtain this information would be useful.

4. Available information suggests that most ADE's first occur, and are most frequent, within the first few months of drug treatment. The number of patients treated for 6 months at dosage levels intended for clinical use, should be adequate to characterize the pattern of ADE's over time.

To achieve this objective, the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5 percent to 5 percent). Usually 300 to 600 patients should be adequate.

5. There is concern that, although they are likely to be uncommon, some ADE's may increase in frequency or severity with time or that some serious ADE's may occur only after drug treatment for more than 6 months. Therefore, some patients should be treated with the drug for 12 months. In the absence of more information about the relationship of ADE's to treatment duration, selection of a specific number of patients to be followed for 1 year is to a large extent a judgment based on the probability of detecting a given ADE frequency level and practical considerations.

One hundred patients exposed for a minimum of 1 year are considered to be acceptable to include as part of the safety data base. The data should come from prospective studies appropriately designed to provide at least 1-year exposure at dosage levels intended for clinical use. When no serious ADE is observed in a 1-year exposure period, this number of patients can provide reasonable assurance that the true cumulative 1-year incidence is no greater than 3 percent.

6. It is anticipated that the total number of individuals treated with the investigational drug, including short-term exposure, will be about 1,500. Japan currently accepts 500 to 1,500 patients; the potential for a smaller number of patients is due to the postmarketing surveillance requirement, the actual number for a specific drug being determined by the information available on the drug and drug class.

7. There are a number of circumstances where the harmonized general standards for the clinical safety evaluation may not be applicable. Reasons for, and examples of, these exceptions are listed below. It is expected that additional examples may arise. It should also be recognized that the clinical data base required for efficacy testing may be occasionally larger or may require longer patient observation than that suggested by this guideline.

Exceptions:

a. Instances where there is concern that the drug will cause late developing ADE's, or cause ADE's that increase in severity or frequency over time, would require a larger and/or longer-term safety data base. The concern could arise from:

(1) Data from animal studies;

(2) Clinical information from other agents with related chemical structures or from a related pharmacologic class;

(3) Pharmacokinetic or pharmacodynamic properties known to be associated with such ADE's.

b. Situations in which there is a need to quantitate the occurrence rate of an expected specific low frequency ADE will require a greater long-term data base. Examples would include situations where a specific serious ADE has been identified in similar drugs or where a serious event that could represent an alert event is observed in early clinical trials.

c. Larger safety data bases may be needed to make risk/benefit decisions in situations where the benefit from the drug is either: (1) small (e.g., symptomatic improvement in less serious medical conditions), (2) will be experienced by only a fraction of the treated patients (e.g., certain preventive therapies administered to healthy populations), or (3) is of uncertain magnitude (e.g., efficacy determination on a surrogate endpoint).

d. In situations where there is concern that a drug may add to an already significant background rate of morbidity or mortality, clinical trials may need to be designed with a sufficient number of patients to provide adequate statistical power to detect prespecified increases over the baseline morbidity or mortality.

e. In some cases, a smaller number of patients may be acceptable, for example, where the intended treatment population is small.

8. Filing for approval will usually be possible based on the data from patients treated through 6 months. Data on patients treated through 12 months should be submitted as soon as available and prior to approval in the United States and Japan but may be submitted after approval in the European Union. In the United States, the initial submission for those drugs designated as priority drugs should include the 12-month patient data.

Dated: February 23, 1995.

William B. Schultz,

Deputy Commissioner for Policy.

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