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Guideline for Industry

The Extent of Population Exposure to Assess Clinical Safety:

For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions

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GUIDELINE FOR INDUSTRY[1]

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 (ADEs) derived from studies of shorter duration of exposure and data from studies of longer duration, which frequently are nonconcurrently controlled

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[1]This guideline was developed within the Expert Working Group (Efficacy) of the International Conference on Harmonisation of the Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, October 27, 1994. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and the USA. This guidance was published in the Federal Register on March 1, 1995 (60 FR 11270) and is applicable to drug and biological products. 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 that 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. For additional copies of this guideline, contact the Consumer Affairs Branch (formerly the Executive Secretariat Staff), HFD-210, Center for Drug Evaluation and Research, 7500 Standish Place, Rockville, MD 20855, 301-594-1012. An electronic version of this guideline is also available via Internet by connecting to the CDER file transfer protocol (FTP) server (CDVS2.CDER.FDA.GOV).

studies. It is expected that short-term event rates (cumulative 3-month incidence of about 1%) 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 1000 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 adverse drug events (ADEs), statistical considerations of the probability of detecting specified frequencies of ADEs, and practical considerations.

3.Information about the occurrence of ADEs 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 ADEs 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 ADEs 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%-5%). Usually 300 to 600 patients should be adequate.

5.There is concern that, although they are likely to be uncommon, some ADEs may

increase in frequency or severity with time or that some serious ADEs 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 ADEs to treatment duration, selection of a specific number of patients to be followed for 1 year is to a large extent a judgement based on the probability of detecting a given ADE frequency level and practical considerations.

100 patients exposed for a minimum of one-year is 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 one year exposure at dosage levels intended for clinical use. When no serious ADE is observed in a one-year exposure period this number of patients can provide reasonable assurance that the true cumulative one year incidence is no greater than 3%.

6.It is anticipated that the total number of individuals treated with the investigational drug, including short-term exposure, will be about 1500. Japan currently accepts 500 to 1500 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 required by this guideline.

Exceptions:

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

I.Data from animal studies;

ii.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 ADEs.

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) or (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 must include the 12 months patient data.