

# Clinical safety data requirements for a new drug application

Drugs are approved based on a balance of the benefits and risks of a treatment (i.e., its efficacy and safety). The requirements for proving the efficacy of a product are somewhat dependent on the product itself and its indication. Over the years, both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have endeavoured to publish documents to assist companies with guidance on appropriate efficacy endpoints to be used in pivotal clinical studies, but it is almost impossible to establish guidelines for all indications. The agencies suggest that companies meet with them to discuss the planned studies and endpoints to be used. The FDA suggests this meeting should happen prior to the initiation of phase III trials, usually at an end-of-phase-II meeting.

This document discusses the general safety requirements required to be collected during a clinical drug development program.

The E1 guideline of the International Conference on Harmonisation (ICH [[www.ich.org](http://www.ich.org)]) discusses the extent of population exposure required to assess the clinical safety for drugs that are intended for long-term treatment of non-life-threatening conditions.<sup>1</sup> The guideline is aimed at providing direction to sponsors to develop a sufficient safety database for drugs that are given for more than six months for non-life-threatening diseases.

Most adverse events occur within the first few months of drug treatment; therefore, the collection of data from patients treated for six months should sufficiently characterize the pattern of adverse events over time.

According to the guideline, the safety evaluation of rare adverse events (those occurring in less than 1 in 1,000 patients) is not expected to be characterized during clinical drug development.

The design of clinical studies can significantly influence the collection of safety data. For instance, a clinical study that uses a placebo control permits the collection of a background rate of adverse events in the given patient population. However, a clinical study that uses an active comparator only permits the comparison of adverse events occurring with the drug under study and the comparison drug. It provides no background rate. A study that has no control group makes it difficult to assess any causal relationship between adverse events and the investigational drug.

The guideline suggests the following in regards to drug exposure:

- Treatment of 300 to 600 patients for six months should be adequate to determine adverse events in the range of 0.5% to 5%.
- Treatment of 100 patients for one year in a prospectively designed study with no serious adverse event having been observed should be adequate to conclude that the true cumulative one-year incidence is no greater than 3%.
- The total number of individuals exposed to the drug, including short-term exposure, should be about 1,500.

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<sup>1</sup> International Conference on Harmonisation. (1994, October 27). *The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* [Efficacy guideline E1]. Retrieved March 4, 2010, from <http://www.ich.org/cache/compo/475-272-1.html#E1>

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## Exhibit 1: Patient exposure requirements for drugs for long-term treatment of non-life-threatening conditions

	Number of patients
Length of exposure—six months:	300 to 600
Length of exposure—one year:	100
Total number of patients exposed to drug:	1,500

Source: International Conference on Harmonisation. *The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* [Efficacy guideline E1], <http://www.ich.org/cache/compo/475-272-1.html#E1>

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### Exceptions

There will always be exceptions to these guidelines when late-developing adverse events, or adverse events that increase in severity or frequency over time, require a larger or longer-term safety database. The concern could arise from any of the following:

- data from animal studies
- clinical information from other agents with a related chemical structure or from a related pharmacokinetic class
- pharmacokinetic or pharmacodynamic properties known to be associated with such adverse events
- situations in which there is the need to quantitate the occurrence rate of an expected low-frequency adverse event
- larger safety databases may be needed to make risk/benefit decisions when the therapeutic benefit is expected to be small or will be experienced by only a fraction of the patients treated, or is of uncertain magnitude
- situations where a drug may add to an already significant background of mortality or morbidity
- in some cases, small safety databases may be acceptable where the intended treatment population is small<sup>2</sup>

Therefore, the ICH guidelines for patient exposure are just guidelines, and there may be specific instances or characteristics of a certain drug or indication that warrant greater exposure prior to marketing authorization.

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<sup>2</sup> International Conference on Harmonisation. (1994, October 27). *The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* [Efficacy guideline E1]. Retrieved March 4, 2010, from <http://www.ich.org/cache/compo/475-272-1.html#E1>