Guidance for Industry

Single Dose Acute Toxicity Testing for Pharmaceuticals

Center for Drug Evaluation and Research (CDER)

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Teva – Fresenius

GUIDANCE FOR INDUSTRY [1]

SINGLE DOSE ACUTE TOXICITY TESTING FOR PHARMACEUTICALS

I. INTRODUCTION

Acute toxicity studies in animals are usually necessary for any pharmaceutical intended for human use. The information obtained from these studies is useful in choosing doses for repeat-dose studies, providing preliminary identification of target organs of toxicity, and, occasionally, revealing delayed toxicity. Acute toxicity studies may also aid in the selection of starting doses for Phase 1 human studies, and provide information relevant to acute overdosing in humans.

II. DEFINITION

Acute toxicity is the toxicity produced by a pharmaceutical when it is administered in one or more doses during a period not exceeding 24 hours.

III. TESTING PROCEDURES

The test compound should be administered to animals to identify doses causing no adverse effect and doses causing major (life-threatening) toxicity. The use of vehicle control groups should be considered. For compounds with low toxicity, the maximum feasible dose should be administered.

Acute toxicity studies in animals should ordinarily be conducted using two routes of drug administration: (1) The route intended for human administration, and (2) intravenous administration, if feasible. When intravenous dosing is proposed in humans, use of this route alone in animal testing is sufficient.

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[1]This guidance was originally published as a part of a proposed implementation document entitled "U.S. FDA's Proposed Implementation of International Conference on Harmonisation (ICH) Safety Working Group Consensus Regarding new Drug Applications." The Agency has revised this guidance based on comments it received on the proposed implementation. This approach, designed to facilitate the early stages of pharmaceutical development, is not and ICH consensus position although it is considered to be in general agreement with the ICH position on acute toxicity testing. This guidance was published in the *Federal Register* on August 26, 1996 (61 *FR* 43934). Although this guidance does not create or confer any rights for or on any person and does not operate to bind FDA or the industry, it does represent the Agency's current thinking on single dose acute toxicity testing for pharmaceuticals. For additional copies of this guideline, contact the Drug Information Branch, HFD-210, CDER, FDA, 5600 Fishers Lane, Rockville, MD 20857 (Phone: 301-827-4573) or the Manufacturers Assistance and Communication Staff (HFM-42), CBER, FDA, 1401 Rockville Pike, Rockville, MD 20852-1448. Send one self-addressed adhesive label to assist the offices in processing your request. An electronic version of this guidance is also available via Internet using the World Wide Web (WWW) (connect to the CDER Home Page at http://www.fda.gov/cder and go to the "Regulatory Guidance" section).

Studies should be conducted in at least two mammalian species, including a nonrodent species when reasonable. The objectives of acute studies can usually be achieved in rodents using small groups of animals (for instance, three to five rodents per sex per dose). Where nonrodent species are appropriate for investigation, use of fewer animals may be considered. Any data providing information on acute effects in nonrodent species, including preliminary dose-range finding data for repeat-dose toxicity studies, may be acceptable.

IV. OBSERVATION

Animals should be observed for 14 days after pharmaceutical administration. All mortalities, clinical signs, time of onset, duration, and reversibility of toxicity should be recorded. Gross necropsies should be performed on all animals, including those sacrificed moribund, found dead, or terminated at 14 days.

In addition, if acute toxicity studies in animals are to provide the primary safety data supporting single dose safety/kinetic studies in humans (e.g., a study screening multiple analogs to aid in the selection of a lead compound for clinical development), the toxicity studies should be designed to assess dose-response relationships and pharmacokinetics. Clinical pathology and histopathology should be monitored at an early time and at termination (i.e., ideally, for maximum effect and recovery).

V. NOTE: ANIMAL PROTECTION

Studies should be designed so that the maximum amount of information is obtained from the smallest number of animals. Calculating lethality parameters (e.g., LD<INF>50) using large numbers of animals, as was done previously, is not recommended (see the *Federal Register* of October 11, 1988, 53 FR 39650).

To avoid causing excessive pain or tissue damage in the animals, pharmaceuticals with irritant or corrosive characteristics should not be administered in concentrations that produce severe toxicity solely from local effects.