Guidance for Industry and Reviewers

Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance outlines a process (algorithm) and vocabulary for deriving the maximum recommended starting dose (MRSD) for "first in human" clinical trials of new molecular entities in adult healthy volunteers and recommends a standardized process by which the MRSD can be selected. The purpose of this process is to ensure the safety of the human volunteers.

The goals of this guidance are to (1) establish a consistent terminology for discussing the starting dose, (2) provide common conversion factors for deriving a human equivalent dose, and (3) delineate a strategy for selecting the MRSD for adult healthy volunteers, regardless of the projected clinical use. This process is diagrammed with a flow chart that presents the decisions and calculations used to generate the MRSD from animal data.

II. SCOPE

The process identified in this document pertains to determining the MRSD for adult healthy subjects when beginning a clinical investigation of any new drug or biological therapeutic that has been studied in animals. This document is not pertinent to prophylactic vaccines or endogenous proteins (i.e., recombinant clotting factors) used at physiologic concentrations. The process outlined in this document does not address dose escalation or maximum allowable doses in clinical trials.

[1] This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

Although the process outlined in this document uses observed toxicities, administered doses, and an algorithmic approach to calculate the MRSD, an alternative approach could be proposed that places primary emphasis on animal pharmacokinetics and modeling rather than dose. In a limited number of cases, animal pharmacokinetic data may be useful in determining initial clinical doses.[2] However, in the majority of new INDs, animal data are not available in sufficient detail to construct a scientifically valid, pharmacokinetic model whose aim is to accurately project an MRSD.

Toxicity should be avoided at the initial dose. However, doses should be chosen that allow reasonably rapid attainment of the phase 1 trial objectives (e.g., assessment of the therapeutic's tolerability, pharmacodynamic or pharmacokinetic profile). All of the relevant preclinical data, including information on the pharmacologically active dose, the full toxicologic profile of the compound, and the pharmacokinetics (absorption, distribution, metabolism, and excretion) of the therapeutic, should be considered when determining the MRSD. Starting with doses lower than the MRSD is always a possible option and may be particularly appropriate to meet some clinical trial objectives.

The remainder of this document will focus on the recommended algorithmic process for starting dose extrapolation from animals to humans based on administered doses, since this method will likely be useful for the majority of new INDs seeking to investigate new drugs in healthy volunteers. Some classes of drugs (e.g., many cytotoxic or biological agents) are commonly introduced into initial clinical trials in patient volunteers rather than healthy volunteers. Typically, this occurs when a drug is suspected or known to be unavoidably toxic. Although this document does not specifically address starting doses in patients, many principles and some approaches recommended here may be applicable to designing such trials.

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[2] If the parent drug is measured in the plasma at multiple times and fits the range of toxic dose for two or more animal species, it may be possible to develop a pharmacokinetic model predicting human doses and concentrations and draw inferences about human safe plasma levels in the absence of prior human data. While quantitative modeling for this purpose may be straightforward, the following points suggest this approach may present a number of difficulties when evaluating estimates of a safe starting dose. Generally, at the time of IND initiation, there are a number of unknowns regarding animal toxicity and comparability of human and animal pharmacokinetics and metabolism: (1) human bioavailability and metabolism may differ significantly from that of animals; (2) mechanisms of toxicity may not be known (i.e., toxic accumulation in a peripheral compartment; and/or (3) toxicity may be due to an unidentified metabolite, not parent drug. Thus, to rely on pharmacokinetic models (based on parent drug in plasma) to gauge starting doses would require multiple untested assumptions. Modeling may be used with greatest validity to estimate human starting doses in special cases where few underlying assumptions would be necessary. Such cases are exemplified by large molecular weight proteins (like humanized monoclonal antibodies), which are intravenously administered, are removed from circulation by endocytosis rather than metabolizism, have immediate and detectable effects on blood cells, and have a volume of distribution limited to the plasma volume. Here, allometric, pharmacokinetic, and pharmacodynamic models have been useful in identifying the human mg/kg dose that would be predicted to correlate with safe drug plasma levels in nonhuman primates. Even in these cases, uncertainties (such as differences between human and chimpanzee receptor sensitivity or density) have been shown to affect human pharmacologic or toxicologic outcomes, and the use of safety factors as described in this document is still warranted.

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