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DRAFT GUIDANCE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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Pharmacology and Toxicology

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

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10 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current
11 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to
12 bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements
13 of the applicable statutes and regulations.

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17 **I.   INTRODUCTION**

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

23

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

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31 **II.   SCOPE**

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

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[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.

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

47

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

56

57   The remainder of this document will focus on the recommended algorithmic process for starting
58   dose extrapolation from animals to humans based on administered doses, since this method will
59   likely be useful for the majority of new INDs seeking to investigate new drugs in healthy
60   volunteers. Some classes of drugs (e.g., many cytotoxic or biological agents) are commonly
61   introduced into initial clinical trials in patient volunteers rather than healthy volunteers.
62   Typically, this occurs when a drug is suspected or known to be unavoidably toxic. Although this
63   document does not specifically address starting doses in patients, many principles and some
64   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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