AstraZeneca

1233 '03 MAR 18 A9:13

Date: MAR 17 2003

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number 02D-0492
Response to FDA Call for Comments
Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers.

Dear Sir or Madam:

Reference is made to the January 16, 2003 Federal Register notice announcing the request for comments on Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers.

AstraZeneca has reviewed this guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to James Sullivan, Regulatory Project Manager, at (302) 885-1423.

Sincerely,

James Sullivan for:

Barry Sickels
Executive Director, Regulatory Affairs
Telephone: (302) 886-5895
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BS/JSS

Enclosure 02D-0492 C 9

US Regulatory Affairs
AstraZeneca LP
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Comments from AstraZeneca on the FDA Draft Guidance for Industry Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers

Comments are summarized below:

General Comments

- Comment 1

  The draft guidance focuses on scaling, using dose rather than pharmacokinetic parameters. When data are available, scaling using body surface, along with the PK allometric scaling should be performed. As safety is the first priority in choosing the starting dose for the entry-into-man, the different methods should be compared, and a "conservative" safe approach be used.

- Comment 2

  Consider extrapolating using allometry combined with measurement of hepatic clearance *in vitro* using primary human hepatocytes.

- Comment 3

  Estimating a MRSD (maximal recommended starting dose) may be too flexible.

- Comment 4

  Consider that non-absorbable agents with an intended action in the GI tract may require a different basis for estimating the starting doses. Possibilities might include bile acid sequestrants, non-absorbable inhibitors of cholesterol absorption and perhaps some anti-obesity agents.

Specific Comments

Section	Line Number	Comment or proposed replacement text
II.	36-37	The guidance could be considerably strengthened if it addressed dose escalation and maximum dose strategies, specifically for "first in man" trials.
IV.	147	The NOAEL must be determined *case-by-case* for each substance.
IV.	149-151	Statistically significant effects are not necessarily adverse.
IV.	176-186	Consider expanding the guidance to include the magnitude of effects that would routinely be considered adverse by the reviewers, e.g., liver enzyme increase, or clinical signs, etc.
V. A.	214	Propose revising line 214 to read as follows: "Deviations from the surface area approach should be justified *when describing the conversion of animal doses to HED".*
V. A	233	Table 1: This table compares 6 orders (out of 20 or so) of mammals (primates, rodents, lagomorphs (rabbit), carnivore (dog) and Artiodactyla (Micro and Mini Pigs). Humans, although primates, would best be listed in their own class for the purposes of this table. Note that the closest km (first column) to humans is that of the "Mini-pig". In addition, this swine type has the conversion factor closest to 1 (2^{nd} and 3^{rd} column). Therefore, very little variation should result among doses between the 2. The animal km closest to a human child was that of the Micro-pig (another swine type), not as perfectly close to 1 as the Mini-Pig / human adult comparison but certainly closest than the rest. Please note the scaling proximity between swine and humans is much more notable than between humans and the other primates as listed in the table.

Specific Comments (continued)

Section	Line Number	Comment or proposed replacement text
Appendix B	595-601	Table 3: Please clarify that similarities are merely a function of the surface area as noted (4th column - BSA). Or is there a potential evolutionary/ontogenic connection between humans and the Artiodactyla order that might explain this finding? Please note that the Artiodactyla order includes sub-orders that have ruminating stomachs (3-4 chambered) as well as single-chambered non-ruminating ones (swine). Humans would fit in between since they have a single non-ruminating stomach and yet have the ability to "ruminate" (a condition seen in some young children).