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

Ref: Docket No. 01D-0194 – Draft Guidance for Industry on the Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceutics; Availability

Abbott Laboratories is pleased to have the opportunity to provide comments on the Draft Guidance for Industry on the "Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceutics", published in the Federal Register on May 8, 2001.

We thank the Agency for your consideration of our comments. Should you have any question, please contact Ivone Takenaka, PhD. (Corporate Regulatory Affairs – Policy & Information Coordinator) at 847-935-9011 or by FAX at 847-938-3106.

Sincerely,

D. L. Sporn

Douglas L. Sporn

cc. Dr. C Thomas Lin, PPRD
Dr. Patrick Cusick, PPRD

August 2, 2001

ABBOTT's COMMENTS ON DRAFT GUIDANCE FOR INDUSTRY ON THE STATISTICAL ASPECTS OF THE DESIGN, ANALYSIS AND INTERPRETATION OF CHRONIC RODENT CARCINOGENICITY STUDIES OF PHARMACEUTICS

General Comments

The bulk of the guidance is on the aspect of statistical analysis of tumor incidence data in a two-sex two-species rodent carcinogenicity bioassay. It presents statistical methods that are appropriate in two situations: when the cause of animal deaths can be determined (Peto methods) and when the cause of deaths is not available or is unreliable (Poly-k methods). Detailed description of these methods and examples are given to allow readers (possibly limited to statisticians only) a good understanding of these methodologies.

However, Abbott believes the non-statistically oriented scientists may find it technically too challenging to comprehend. That is unfortunate because the ultimate responsibility of interpretation of the carcinogenicity test results lies on the expertise of pathologists and toxicologists conducting the experiment. The guidance should place more emphasis on the rationale behind each statistical method, how and why it works.

There are other situations quite frequently encountered in carcinogenicity studies that were not addressed in the guidance. For example, the issue of body weight adjustment in the analysis of tumor data was not mentioned or referenced. Without proper accounting of differential body weight and mortality, the results of statistical analysis of carcinogenicity studies are likely to be biased. Also, the analysis and interpretation of diet restricted experiments needs to be discussed.

Specific Comments

III. VALIDITY OF THE DESIGN

The section on early termination of a study for mortality (lines 119-147) needs clarification. The guidance mentions that a study could be terminated early if the survival of the control group goes below 50% or 20-30 surviving animals after weeks 80 to 90. Does this mean that if the number of surviving control animals after week 90 (~ 21 months) is below 20 then the study could be terminated? If so, will the study still be considered valid in terms of the duration of exposure? It seems that unless the control animals are dying off rather rapidly after week 90 it would be better to allow the experiment to continue until the number of surviving animals dwindled down to perhaps 15. A flexible decision rule based on particular situations and consultation with CDER regarding early termination of a study or a group should be emphasized.

If a group (groups) is terminated early because of mortality, the guidance needs to discuss how the data from this group (groups) should be handled in the statistical analysis.

Should the early sacrificed animal data be grouped with the rest of the groups that are terminated at the scheduled terminal necropsy, or be treated as a separate interim sacrifice?

VI. PRESENTATION OF RESULTS AND DATA SUBMISSION

On the format of Table 15 (p. 35), the usefulness of providing the context of tumor observations in a summary table should be explained, as this information is available in the individual animal tumor data files that are routinely provided to the Agency. Also, the purpose of conducting pairwise comparisons involving the low and mid dose groups should be explained. The decision rules as described in Table 13 (p. 30) concern only the trend test and the high dose to control comparison.

TYPOGRAPHICAL ERRORS AND EDITS ARE GIVEN BELOW

1. page 4 (line 156). "effect" should be "affect"
2. page 4 (line 161). "Petro" should be "Peto"
3. pages 4,5 (lines 161,167, 203). "McKight" should be "McKnight"
4. page 10 (line 411). $E_i = \sum_k V_{ijk}$ should be $E_i = \sum_k E_{ik}$
5. page 12.(line 438) Table 3, last footnote on $O_{.k}$ should read $\sum_i O_{ik}$
6. page 14 (Table 5 under column titled "Time Intervals") "81-106" should be entered into the empty cell
7. page 18 (line 637). $Y=\sum Y_k$ should be $Y=\sum_k Y_k$
8. page 18 (line 639). (P(Y>=y) should be P(Y>=y)
9. page 18 (line 646). $P(Y_1=y_i)$ should be $P(Y_1=y_1)$
10. page 18 (line 649). $y_i+y_2+\ldots$ should be $y_1+y_2+\ldots$
11. page 20 (line 686). $o_{.1}$ should be $O_{.1}$
12. page 20 (line 693). On the formula for $P(Y_1=1)$, delete the 3 dots "..."
13. page 20 (line 699). $y_1=(0x0)+(2x2)=4$ should be corrected to $y_1=(0x0)+(0x1)+(2x2)=4$
14. page 20 (line 701). $y_2=(0x0)+(1x1)+(0x0)$ should be $y_2=(0x0)+(1x1)+(0x2)$
15. page 26 (line 948). Delete "either control and pooled control"
16. page 31 (lines 1141 and 1142). Change "...the historical control rates. The range does not ..." to "...the historical control rates, the range does not ..."
17. page 37 (line 1411). Table 16: 3,2% should be 3.2%

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