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Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Dr., Room 1-23
Rockville, MD 20857

Dear Sir or Madam:

This letter contains comments and suggestions from Lilly Research Laboratories, a Division of Eli Lilly and Company, regarding the draft Guidance for Industry, Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals. Please forward to the appropriate parties.

1. Lines 56, 57, 74-77. Random assignment of animals to different treatment groups is very important, and is discussed in the document (Lines 74-77). Since carciongenicity studies usually last for 2 years, the relative locations of the animals, within the cage racks and within the room, may confound the treatment effects. We ask the agency to consider including some of the discussion in the draft guidance because proper randomization is crucial to the validity of the study. Possible approaches to minimizing the location bias include rotating the cages/racks around the room during the study and randomly assigning columns on a rack to treatment groups and ensure that all groups are represented on each rack. If methods of avoiding location bias are suggested, they should avoid complexity that might lead to logistical problems and increase chance for errors in animal dosing and handling.

2. Lines 119-121. Clarify the statement: "However, early termination of a study for mortality, even if unavoidable, may render a study uninformative, leaving too few animals living long enough to represent adequate exposure to the chemical." This is confusing because if a study is terminated early, no animals are left alive. Suggested wording could be: "However, early termination of a study for mortality, even if unavoidable, may render a study uninformative, if a sufficient number of animals had not survived for a sufficient duration to provide adequate exposure to the test compound."

3. Lines 185-209. The draft guidance correctly states that most neoplasms are occult and not discovered until necropsy. The onset time for neoplasms that cannot be detected by palpation or visual inspection cannot be determined accurately by pathologists.

Pathologists and statisticians have different definitions of the term Fatal. Pathologists classify a neoplasm as Fatal when the neoplasm contributes to the death of the animal or to bringing the animal to necropsy prior to scheduled sacrifice, regardless of the time of onset of the neoplasm. The death rate method within the Peto test models all Fatal neoplasms as instantly fatal, and uses the time of death of animals with Fatal neoplasms as a surrogate for the time of onset of each Fatal neoplasm. In most cases, Fatal neoplasms (i.e. those that the pathologist believe caused the death of the animal) are not instantly or rapidly fatal, but may have been present in the animal for weeks or months prior to necropsy. It is not appropriate for the Peto test to model the time of tumor onset for all Fatal neoplasms as the time of death. We agree that, in the context of determining tumor onset, "the difficulty and subjectivity in the determination of cause of death and lethality of a tumor" renders this information "too inaccurate and unobjective to allow valid analysis." As stated in lines 191-193, "The analyses will become biased if the assumption or information on tumor lethality and cause of death is not valid or accurate." Our scientists believe that classification of neoplasms as Fatal or Incidental should not be performed if Fatal neoplasms are modeled as instantly or rapidly fatal.

We recommend that neoplasms not be classified as Fatal or Incidental for purposes of determining/analyzing tumor incidence and/or onset. The FDA should accept Peto or poly-k analyses using the prevalence method for all neoplasms that are not Mortality Independent. The time of onset of superficial, mortality-independent neoplasms of the skin, subcutis, and limbs, and other neoplasms that can be reliably detected when small should be analyzed by the onset rate method using the time of first observation as the time of onset. Deep visceral neoplasms should not be considered mortality-independent, even if palpated in life, since these masses cannot be reliably detected when small and time of onset cannot be estimated accurately.

(Note: Identifying the cause(s) of death in individual animals adds significant value to interpretation of carcinogenicity studies. Pathologists should identify 'cause of death' for animals dying or killed before scheduled sacrifice as a means to interpret causes of differential mortality among groups, however, this classification can not be construed to imply time of onset or rate of progression of lesions and can not be used to model onset of neoplastic or non-neoplastic lesions unless the study is specifically designed to monitor onset.)

4. Lines 59-72. Dose selection is thoroughly covered in the International Conference on Harmonization guidance S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals. These lines offer no guidance and should be deleted.

5. Lines 79-92. This paragraph discusses pros and cons of blind evaluation of microscopic slides, but offers no conclusions or guidance. This paragraph should be deleted.

6. Lines 96-97. The guidance should clearly state that a minimum 50 animals per sex should be assigned to each treatment group. The current statement that 50-60 animals of each sex should be assigned to each group is unnecessarily vague.

7. Lines 600-603. Since the normality based approximation results for positive trend in tumor incidence may not be stable or reliable and tend to underestimate the exact p-values, the exact permutation trend test should be used when the total numbers of tumor occurrence across treatment groups are small. The agency should specify a guidance for performing the exact trend tests (i.e. applied when incidence less than or equal to 10 occurrences, as was stated previously in the draft guidance).

8. Lines 1021 and 1066. "CD mice" should read "CD-1 mice."

9. Lines 1045-1046, and Lines 40. Performing both trend test and pairwise comparisons on a routine basis is overly conservative, especially after considerable effort is made in controlling the false positive rate. Clearly, the trend in tumor incidence is of primary interest as indicated by the selection of a series of increasing doses in the design of a carcinogenicity study. The selection of the dose levels is based on the results of a series of shorter-term studies. For some situations (Lines 40-41), pairwise comparisons may be more indicative of drug effects than trend tests. In those cases, there is no reason to perform trend tests at all and pairwise comparisons should be specified in the study protocols and performed accordingly. A single statistical method should be recommended for routine use. The test for trend is more powerful and seems to be the most appropriate method for routine use. Pairwise comparison tests should be performed only if one or more criteria listed in lines 1038-1043 are fulfilled.

10. Lines 1112-1114. Husbandry and housing conditions are often very similar between laboratories and, if similar, will contribute little variation to historical control data. The source (vendor) of the animal model and specific husbandry practices such as diet optimization or *ad libitum* feeding may influence the appropriateness of historical control data to a greater extent than the laboratory conducting the studies. Furthermore, there may not be sufficient historical control data within a single laboratory to make appropriate assessments. In interpreting carcinogenicity studies, it may be necessary and appropriate to pool historical control data from multiple laboratories. We recommend that the guidance state: "It is therefore extremely important that the historical control data chosen be from studies comparable to the current study, generally recent studies using the same strain of rodent." Additionally, historical control data are said to be based on "recent studies'. Please be more specific by defining recent studies as "studies completed in the last 5 years or another time interval as may be justified" .

11. Lines 1212-1214. It is stated "In the sponsor's report, in addition to the volumes containing study data of individual animals, a statistical analysis section should be included containing summary statistics of the study data, results of statistical analyses of the data, results and findings, and main conclusions of the study...". Based on the

discussion on food consumption in this document, we concluded that information of drug effects on food consumption is not expected in the reports of oncogenicity studies except for dietary studies. Therefore, we recommend specifying the data that are expected in the reports as "In the sponsor's report, in addition to the volumes containing study data of individual animals, a statistical analysis section should be included containing summary statistics of survival, tumors, body weight, and food consumption (only for dietary studies), results of statistical analyses of the data, and main conclusions of the study…"

12. Lines 1386-1415. For historical control data, please specify whether the denominators the numbers of tissues examined or the numbers of animals at the beginning of the study?

13. Typographical comments

Line 220. Bieler should be Bailer

Line 311. Please pick one of the two but not both: "not directly" and "indirectly".

Line 312. change "autopsy" to "necropsy".

Line 363. change "autopsies" to "necropsies".

Line 435. change "autopsy" to "necropsy".

Line 437. change "autopsied" to "necropsied".

Line 438. the summation sign is printed at a "." for Oik.

Line 482. Table 5. Time intervals for weeks 81-106 is missing from the first column.

Line 572. onset rate methods is the "time to" the occurrence of such a tumor.

Line 639. Drop the extra "(" in (P(Y>=y).

Line 642. change "k-th observed table" to "k-th observed table corresponding to the k-th time interval" to be consistent with the use of subscript k=1, 2,…, K in S_k

Line 646. subscript "i" should be "1" in $Y_1=y_i$ as $Y_1=y_1$.

Line 649. subscript "i" should be "1" in y_i as y_1.

Line 671. change "The observed subtables formed from the last two time intervals are given in Table 9." to "The observed subtables corresponding to the last two time intervals, 3rd and 4th, are given in Table 9."

Lines 673-716. Change all the subscripts from 1 to 3 and from 2 to 4. Change the subtable numbers referenced from 1 to 3 and 2 to 4 accordingly.

Line 693. drop "…" in the probability display.

Line 715. The subscripts of 1 in Table 11 should be either "2" if by the original document or "4 " by our suggestion for consistency.

Line 762. The second "{" should be "(".

Lines 813-4. "The class of.., do not.., and call for.." should be "The class of.., does not.., and calls for.. "

Line 904. add a "," after Category A".

Line 906. "on the test animals" should be "of the test animals".

Line 908. change "be subject to…" to "be subjected to...".

Line 913.change "identifying the extent.." to "evaluating the extent"

Line 948. change "either control…" to "including either control…".

Line 971. change "take into account…" to "takes into account…"

Line 977. change "Control Over False Positive Error" to "Control Overall False Positive Error".
Line 1097. change "Control Over False Negative Error" to "Control Overall False Negative Error".
Line 1140. The sentence is not complete.
Line 1255. Change "have been" to "has been".
Line 1389. Change "1995 to 2000" to "1992 to 1996" for this example.
Line 1411. Change "3,2%" to "3.2%".

Thank you for the opportunity to comment.

Sincerely,

Lilly Research Laboratories

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Senior Research Scientist

GGL:dlc