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DATE July 30, 2001

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 01D-0194; Draft Guidance for Industry on the Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals; Availability *Federal Resister, Vol. 66, No. 89,23266 (May 8, 2001)*

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified global health and personal care company with principal businesses in pharmaceuticals, consumer medicines, nutritionals and medical devices. We are a leader in the research and development of innovative therapies for cardiovascular, metabolic, infectious diseases, neurological disorders and oncology. In 2000 alone, Bristol-Myers Squibb dedicated more than $1.8 billion for pharmaceutical research and development activities. The company's more than 4,300 scientists are committed to discover and develop best in class, therapeutic and preventive agents that extend and enhance human life. Our current pipeline comprises more than 50 compounds under active development.

For these reasons, we are very interested in and well qualified to comment on this U.S. Food and Drug Administration ("FDA") guidance.

We commend the FDA for a well-written and helpful document. However, we would like to take this opportunity to offer the following comments:

General:

Since sponsors also submit studies to CBER, we assume that CBER is either writing a similar guidance or will accept submissions that follow the CDER guidance. Nevertheless, we recommend that FDA clarify how submissions to CBER should be treated.

Specific:

Lines 74 - 77: We recommend that the guidance allow sponsors to randomize animals to groups to achieve similar initial weights (e.g., block on initial body weight).

Lines 79-92: It is strongly recommended that this section be deleted from the guideline because discussion of methods used to conduct the histopathologic evaluation of tissues is not within the scope of a statistical guideline.

Line 111: CDER recommends that drug sponsors conduct mouse studies for 24 months unless there is excessive mortality. It would be helpful to those conducting studies for the Guidance to

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be clear that the normal life span of the experimental animals, not the number of months of duration of the study per se, is the important criterion.

Lines 122-123: We agree with the reasoning that 50% survival from weeks 80-90 is adequate. The age of 80 - 90 is long enough to evaluate carcinogenicity.

Line 161: Misprint "Petro" should be "Peto" and "McKight" should be "McKnight".

Line 167: Misprint "McKight" should be "McKnight".

Line 203: Misprint "McKight" should be "McKnight".

Lines 211-235: We recommend that the guidance state that the agency would consider an analysis using the poly-k or ratio trend test, if Peto grades were not used in the study.

Lines 237 - 290: The two examples show that the survival adjusted p-value corrects the effects due to higher mortality in the treated group early in the study. It would be useful to add an example to show the effect of a lower mortality rate in the treated groups. This example could show a case where the overall p-value is significant but the survival adjusted p-value is not significant for a positive trend.

Lines 505-513: We recommend that sponsors should be allowed to use the normal approximation since the normal approximation p-values will be less than the exact p-value for equally spaced scoring of the dose levels.

Line 567-590: We recommend that the onset rate method be used at the discretion of the sponsor and not routinely for carcinogenicity studies. One important reason not to use the onset rate method is that palpable masses in aging rodents often turn out to be cysts or abscesses, not neoplasms. In addition, when palpable masses are recorded in the clinical history often times these "masses" disappear over time.

Lines 599-603: It is true (especially when the scores are equally spaced) that the approximation p-value is smaller than the exact test p-value. The exact tests tend to reject less often than the nominal level due to sample size and the discrete nature of the test. Although the approximation provides smaller p-values than the exact test, it is closer to the nominal testing level. If a sponsor uses the approximation, they may find more significant results than an exact test. If a sponsor is willing to take the risk of finding additional "significant" results by using the approximation, they should be allowed to use the approximation.

Lines 722-892: Section D provides a lengthy discussion for the analysis of data without information about cause of death and without multiple sacrifices. We assume that these types of analyses would be acceptable to CDER. We believe, however, that it would be helpful if the FDA clarified this section to address this issue.

Lines 882-884: We assume that the ratio trend test would be acceptable to CDER when cause of death information is not provided. We believe, however, that it would be helpful if the FDA clarified this section to address this issue.

Lines 923-931: For Category A control groups, an acceptable approach should be to compare the vehicle control and untreated control and if there is no difference, they should be combined for the analysis of trend. Three separate analyses should not be required.

Lines 933-951: For Category B control groups, we agree that if there are no differences in the treatment and handling of the two groups, they should be pooled. The arbitrary assignment of the animals to the two control groups may be useful from a biological perspective. However, from a statistical perspective, the best estimate of the proportion of tumors in the control group is the combined control group proportion. If the two control groups are different from one another, the first approach given in the guidance is less likely to obtain a significant result while the second approach tends to find too many false positives, which may not be appropriate.

Lines 972-975: We recommend replacing "preneoplastic lesions at the target organs/tissues" with "drug-related non-neoplastic lesions at the target organs/tissues or known pharmacodynamic effects of the drug on the target tissue/organ".

Lines 991, 1021, and 1066: Instead of "CD rats and CD mice", this should read "Sprague Dawley rats and CD-1 mice".

Line 1045: When all tissues of all animals are evaluated and the study is not compromised by excessive toxicity at higher doses, a trend test should be sufficient. Tumor response is expected to be progressive with increasing dose. Therefore, a trend test (taking into account differences in mortality) would provide the most rigorous analysis of the data. The need for additional pairwise comparisons should be considered when scientifically justified.

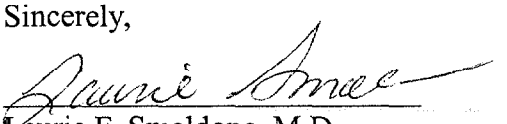
Lines 1107-1179: This section should be deleted from the guideline because it is not appropriate to conduct statistical analysis or trend tests on historical control data.

Lines 1241-1246: We object to electronic submission of the Group B data sets, as this information does not add anything to the conduct of the statistical analysis.

Lines 1386-1416: We recommend that this table be generated only for tumors with significant trends in the submitted study. Also, rats should be changed to mice in the Table title.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,



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