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Dockets Management Branch (HFA-305)
Food and Drug Administration
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MERCK
Research Laboratories

RE: Docket No. 01D-0194
Draft Guidance: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals

Merck & Co., Inc., is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than $2 billion annually on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. MRL tests many compounds as potential drug candidates through comprehensive, state-of-the-art R & D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment.

In the course of bringing Merck product candidates through developmental testing and clinical trials, Merck scientists regularly address issues affected by this proposed Guidance. We have extensive experience in conducting chronic animal carcinogenicity studies for new molecular entities intended for human use and therefore, are very interested in, and well qualified to comment on, this draft Guidance.

Merck commends the FDA for guiding sponsors on the design of animal carcinogenicity studies, methods of statistical analysis, interpretation of study results, presentation of data in reports, and the submission of tumor data to FDA statistical reviewers. This draft Guidance is scientifically correct in encouraging alternative statistical approaches that satisfy the applicable statutes and regulations. Statistical analyses serve as a powerful aid in assessing carcinogenicity studies. However, by promoting the use of many more statistical tests than are currently performed by most sponsors, this Guidance may exacerbate the problem of false positives. For example, proposing three sets of analyses for studies with two control groups or recommending both pair-wise comparisons of each treated group with a control group in addition to a trend test, amplifies the serious statistical problem of multiplicity of tests. Biologically significant changes in rodents remain our most valuable tool to assess the carcinogenic potential of a pharmaceutical product in humans. Our specific comments follow. We present our statistical comments followed by other comments, and lastly editorial comments. Each comment is referenced by line number.

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Recommendation: The draft Guidance should be revised to suggest that sponsors avoid multiple analyses or the addition of pair-wise comparisons following the performance of a trend test.

Section IV, Lines 1061-1065

Comment: The Guidance states with respect to short-term *in vivo* carcinogenicity assays, "in general these studies do not produce false positive results because tumor background rates are very low." To say that short-term genetically engineered mouse bioassays have a desirable low false positive rate should be qualified. The small number of animals (typically 15 per sex/group) and their short duration of exposure to the test substance (6 months) potentially lowers the statistical power of these assays to detect very many common non-genotoxic rodent carcinogens. In addition, these short term assays do not come close to the rodents' life-span (much greater than 6 months) or allow all of the complex mechanisms of carcinogenesis to become operative. While lowering the false positive rate in these bioassays is desirable, the short term assays as presently performed will not offset the high false positive rate of many of the two-year bioassays conducted at maximum tolerated doses to achieve maximum lifetime exposure.

Recommendation: Since we cannot say that every tumor is treatment-related with certainty, it may be better to state that there is no inflated risk of false positive results.

Section IV, Lines 1154-1159

Comment: Since the assumption that historical control tumor rates are normally distributed may not be true, it may be best to use the historical control data for biological assessment rather than including them in the statistical analyses of a specific study.

Recommendation: While historical data provide important biological insights into the tumor incidence trends over time, the incidence of rare tumors, and biological variability, their utility is most helpful in the overall biological evaluation of these studies rather than in repeated statistical analyses that may produce confounding results or Type 1 or 2 errors.

II. OTHER COMMENTS

Section III, Lines 80-92

Comment: The unconditional use of blinded histopathological evaluation should be discouraged. The loss of knowledge about the degenerative and proliferative lesions and tumors that occur in concurrent control animals predisposes the pathologist to an over-interpretation of spontaneous changes and may hinder the detection of subtle treatment-related effects since many of the hyperplastic lesions and tumors also occur spontaneously in control animals. Thus, grading the relative severity of the degenerative and proliferative lesions becomes important and the criteria for grading such lesions in treated animals must take into account the spectrum of changes observed in controls. It is important that the pathologist have access to all the information available for each animal, including the dose and duration of xenobiotic treatment. It may be appropriate after the initial evaluation to conduct a blinded reading of the slides to determine no-treatment-effect-levels in a particular target tissue in disputed cases, as well as during the peer review process.

Recommendation: We endorse the current standard practice of open or non-blinded, microscopic evaluation of animal tissues in carcinogenicity studies.

Section III, Lines 122-123
Comment: The Guidance states that a 50% survival rate to 80-90 weeks is considered adequate. However, it neglects to address whether the treatment groups should be followed until the end of the study.

Recommendation: The Guidance should explicitly state if the groups should or should not be continued to the end of the study and evaluated by the pathologist. We suggest the following statement be added,

"If treatment-related mortality of a group exceeds 50% by 80-90 weeks, the maximum tolerated dose has been exceeded and that dose group should be discontinued without further evaluation. If nontreatment-related mortality exceeds 50% in controls or other groups by 80-90 weeks, the sponsor and Agency should consult to agree on the early termination and evaluation of the entire study for optimal statistical analysis and pathological evaluation."

Section III, Line 131-133
Comment: The Guidance suggests that no controls are to be sampled if the high dose group is terminated due to high mortality or dosing is discontinued prior to the terminal necropsy. This is problematic in that an unbiased statistical evaluation of data from the high dose group requires a concurrent sacrifice of at least a partial sample of the controls.

Recommendation: Recommendation: The Guidance should clearly state any requirement for statistical evaluation of a treatment group terminated early due to mortality should permit concurrent sacrifice of a sample of controls.

Section IV, lines 1190-1194
Comment: The draft Guidance states that a 50% survival or 20 to 30 animals alive between weeks 80 to 90 in the two-year study would be considered sufficient for a valid study.

Recommendation: This paragraph should clarify whether the survival includes single groups of treated or control animals or only one treated group. It is also advisable to restate the recommendation that the Agency should be contacted and concur before a study is terminated early as a result of mortality, or if groups with low mortality are to be continued until the scheduled study termination.

In addition, it should be stated that since sponsors must determine the cause of death in animals exhibiting early mortality, it is necessary to classify tumors as incidental or fatal. However, the time of death of an animal with a lethal tumor should not be used as a surrogate for the time of tumor onset. The draft Guidance should state that the Agency will use these cause of death data to conduct the trend test designed by Peto for analysis of the databases on the sponsor's carcinogenicity studies. Since these data are commonly provided by the sponsor, it would be expected that a trend Peto analyses rather than multiple pair-wise comparisons would be conducted by the Agency.

III. EDITORIAL COMMENTS

Section III, Line 97
Comment: The Guidance states that each group should contain at least 50-60 animals.

Recommendation: Since the sentence is defining a minimum, it would be more appropriately stated as, "at least 50 animals of each sex," rather than as a range of 50-60.

Section III, Lines 141-142
Comment: A decision to terminate a group or study due to excessive mortality results in considerable complexities for the statistical and biological evaluation of these pivotal studies. Therefore, timely and well documented discussions between CDER and the sponsor are critical.

Recommendation: The Guidance should acknowledge that the Center and the reviewing division will provide the sponsor with timely (and preferably written) approval of early termination of a study or group.

Section IV, Lines 311-315
Comment: The Guidance appears inconsistent in that it states that, "Tumors that are not directly or are indirectly responsible for an animal's death," are classified as "incidental." However, in the next sentence, the Guidance states that tumors that kill the animal indirectly are classified as "fatal."

Recommendation: Only neoplasms that were not observed prior to necropsy and did not contribute to the death of the animal or the submission of the animal to an unscheduled necropsy should be classified as "incidental."

Section IV, Lines 333-335
Comment: The Guidance cites a statement by Haseman (1999) regarding classifying tumors as incidental, fatal, or mortality independent.

Recommendation: The Guidance would be strengthened by citing a recently published paper, *Draft Recommendations-On The Classification of Rodent Neoplasms for Peto analyses. Toxicologic Pathology, 29(2):265-268, 2001.* This published reference summarizes the background issues and recommendations of a Society of Toxicologic Pathologists working group of industrial and government pathologists and statisticians on the problems of classifying tumors for purposes of analyses.

Section IV, Line 917
Recommendation: We suggest that "contemporary historical data" would be better stated as "contemporary control data."

CONCLUSION

Although biologically significant changes in rodents remain our most valuable tool to assess the carcinogenic potential of a pharmaceutical product in humans, statistical analyses serve as a powerful aid in assessing carcinogenicity studies. This draft Guidance is scientifically correct in encouraging alternative statistical approaches to satisfy applicable statutes and regulations. However, it promotes the use of many more statistical tests than are currently performed by most sponsors, thereby potentially exacerbating the problem of false positives. Therefore, the Guidance should be revised as noted above. Attention to these points will guide sponsors in the design of animal carcinogenicity studies and methods of statistical analysis of tumor data thereby enabling sponsors to present meaningful data and results in reports submitted to the Agency.

We welcome the opportunity to meet with you to discuss these issues.

Sincerely,

Bonnie J. Goldmann, M.D.
Vice President, Regulatory Affairs-Domestic