The American College of Veterinary Pathologists

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August 1, 2001

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

Dear Sir/Madam:

I am wriring this letter on behalf of the Council of the American College of Veterinary Pathologists (ACVP). The ACVP is the non-profit certifying organization for veterinary anatomic and clinical pathologists in North America and is recognized and approved by the American Veterinary Medical Association. We have over 1300 members (many of whom work for the pharmaceutical industry) and have been in existence for more than 50 years.

This letter is to strongly support the attached response from the Society of Toxicologic Pathologists (STP) to the draft Guidance for Industry, Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals.

Specifically the ACVP supports the STP in that we feel:

1. Pathologists cannot accurately predict the time of onset of neoplasia based on gross and histologic findings alone. The date of death in rodents with fatal neoplasia should not be used to estimate the time of onset of the neoplasm. The death rate component of the Peto test is not an appropriate use of pathology data. Classification of neoplasms as Fatal or Incidental may contribute to misuse of pathology data, and should not be performed.

2. Routine blinded evaluation of slides is not recommended. Blinded evaluation can be useful to reach detailed conclusions regarding specific findings but this should be left to the discretion of the pathologist.

We hope the support of the ACVP for these changes recommended by the STP will be influential in your process of finalizing the Guidance.

Sincerely,

Steven E. Weisbrode, V.M.D, Ph.D.
President

cc: R. Maronpot
D. Morton
P. Stromberg

Society of Toxicologic Pathology

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Rockville, MD 20857

Dear Sir or Madam:

This communication contains comments and suggestions from the Society of Toxicologic Pathology regarding the draft Guidance for Industry, Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals.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.

The Society of Toxicologic Pathology is a nonprofit organization dedicated to improving the discipline of toxicologic pathology through education and professional interactions. The Society's membership includes over 800 pathologists and toxicologists involved in the nonclinical assessment of toxicity and carcinogenicity of chemicals, pharmaceutical candidates, and medical devices. Many of the study pathologists who interpret rodent carcinogenicity studies are members of the Society of Toxicologic Pathology. On June 25, 2001 approximately 165 members of the Society attended a special session at our annual symposium to discuss current statistical methods of rodent carcinogenicity testing. At this meeting, an overwhelming majority believed that pathologists could not accurately and reliably estimate the time of onset of a neoplasm or the length of time a neoplasm had been present based on the gross and microscopic appearances of the neoplasm. The membership also believed that the date of death for a rodent with a neoplasm that caused death of the animal (a Fatal neoplasm) is a very poor estimate of the date of tumor onset for most Fatal neoplasms. These conclusions are very important to the analysis of rodent carcinogenicity study data, since the Peto death rate method uses the date of death as a surrogate for date of onset for all neoplasms that the pathologist classifies as Fatal.

1. Lines 185-209. The draft guidance correctly states that most neoplasms are occult and not discovered until necropsy. The date of onset cannot be determined accurately by pathologists for neoplasms that cannot be detected by palpation or visual inspection. 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 date of onset of the neoplasm. The death rate method within the Peto test models all Fatal neoplasms as instantly fatal, and uses the date of death of animals with Fatal neoplasms as a surrogate for the date of onset of each Fatal neoplasm. In most cases, Fatal

neoplasms (i.e. those that the pathologist believes 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 date of tumor onset for all Fatal neoplasms as the date of death. The Society of Toxicologic Pathology agrees with the draft Guidance 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."
The membership of the Society of Toxicologic Pathology believes strongly that neoplasms should not be classified as Fatal or Incidental if the Fatal neoplasms are modeled as instantly or rapidly fatal. The Society of Toxicologic Pathology considered dividing Fatal neoplasms into Rapidly Fatal and Not Rapidly Fatal categories, with the time of death used as a surrogate for the time of onset in the Peto analysis only for Rapidly Fatal neoplasms, however, our members are confident that this new classification could not be done reliably or accurately. Additionally, an acceptable statistical method for estimating time of onset of Not Rapidly Fatal neoplasms was not readily available (Draft recommendations on classification of rodent neoplasms for Peto analysis, Toxicologic Pathology 29(2):265-268, 2001).

The Society of Toxicologic Pathology recommends 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 cannot be detected at a small size in the living animal. The date 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 date of first observation as the date 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 date of onset cannot be estimated accurately.

(Note: Identifying the cause(s) of death in individual animals adds significant value to interpretation of carcinogenicity studies. Whenever possible, 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 date 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.)

2. 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.

3. 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.

4. Lines 96-97. The FDA guidance should clearly state that a minimum of 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.

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

6. Lines 1045-1046. 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.

7. Lines 1112-1114. The genetic background (strain or stock) is the most important factor determining the incidences of spontaneous neoplasms in rodents. 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."

Thank you for the opportunity to comment.

Sincerely,

RR Maronpot

Robert R. Maronpot, D.V.M., Diplomate ACVP, Diplomate ABT
President, Society of Toxicologic Pathology

128

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406