



Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852.
<http://www.fda.gov/dockets/ecomments>
Docket No. 2003D-0466

Dear FDA Representatives:

The Society of Toxicologic Pathology (STP) is a non-profit association of pathologists and other scientists whose principal aim is the advancement of pathology as it pertains to changes elicited by pharmacological, chemical and environmental agents, and factors that modify these responses. The Society of Toxicologic Pathology appreciates an opportunity to comment on the Draft Guidance for Industry: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (Chronic) Toxicity Testing, VICH GL-37.

The STP has published a list of tissues that the STP believes meets the requirements for most toxicology and carcinogenicity studies supporting the registration of new pharmaceutical and chemical products (1). This list provides for a comprehensive tissue evaluation encompassing a diverse array of epithelial, connective/muscular/vascular, and neural tissues. Most of the tissues recommended in the draft VICH Guidance were considered by the STP, and reasons for their exclusion from the STP tissue list are provided in the publication. It is important to note that the STP tissue list was intended to be expanded on a case-by-case basis if there are known or suspected class effects of a test compound, if warranted by the route of administration of the test agent (e.g., inhalation, IM, IV, etc.) or previous experience with the test agent or similar test agents, or if clinical, organ weight, macroscopic or other findings are present in organs not routinely examined microscopically.

The proposal in the VICH draft guidance to add tissues for routine microscopic examination will add significantly to the cost of a chronic study and affect the cost of product development. It is important that the added tissues mentioned in this guidance add value to the human risk assessment process. The STP acknowledges that scientific justification exists for examination of sternum, bone (femur) with joint, and optic nerve, and these tissues already are examined routinely by many companies. These tissues have human counterparts and are broadly relevant to the risk assessment process. The STP does not support the addition of lacrimal gland, larynx, pharynx, clitoral/preputial glands (rodents) and Zymbal's glands (rodents) to the list of tissues to be routinely examined in all chronic studies. Microscopic examination of gross lesions should be performed in all species, as presented in the original STP recommendations.

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STP Executive Office~ 1821 Michael Faraday Drive, Suite 300 ~ Reston, VA
Phone: (703) 438- 7508 ~ Fax: (703) 438-3113
Web Site: www.toxpath.org Email: stp@toxpath.org

The Harderian gland is an accessory ocular gland and should meet the requirement for examination of a lacrimal gland in rodents. However, it should be noted that none of the over 200 compounds evaluated by the NCI/NTP in carcinogenicity studies in F344 rats caused Harderian or lacrimal gland neoplasms (3). The Harderian gland should be examined only in rodents, as this specific gland does not exist in the dog or monkey. Lacrimal glands in non-rodent studies infrequently have findings that cannot be detected by gross examination or by clinical evidence of inadequate tear production. The STP believes that routine examination of lacrimal tissues in nonrodents should not be mandatory, but that lacrimal tissues should be examined on a case-by-case basis using sound scientific judgment. If tear-producing glands are included for non-rodents in the final regulatory guidance, it is recommended that the term 'accessory ocular gland' replace 'lacrimal gland' so that the gland of the third eyelid can be examined as a representative tear-producing gland for these species.

Several of the tissues listed in the proposed draft guidance have no human counterpart, and their relevance to human toxicity can be questioned. As stated in section 2.1.2 of the draft guidance, "Species selection should take into account relevance to human metabolism, pharmacokinetics and pharmacodynamics." The STP believes that tissue selection for histopathological examination should be based on human relevance. Clitoral, preputial, and Zymbal's glands are modified sebaceous glands; effects on sebaceous glands are monitored effectively during microscopic examination of the skin. Chemicals that cause neoplasms in modified sebaceous glands historically have been mutagenic in Salmonella assays (2). Hormonally responsive lesions of clitoral and preputial glands usually are accompanied by lesions in other hormonally responsive organs (2). Thus, STP recommends that histopathological examination clitoral/preputial glands (rodents only) and Zymbal's glands (rodents only) should not be required routinely in chronic studies. These glands should be examined microscopically on a case-by-case basis only if there is macroscopic or other evidence of treatment effects.

The STP believes that the nasal cavity, pharynx, and larynx should be examined in inhalation studies because these are important areas of direct drug contact (or exposure) on mucosal surfaces when test compounds are delivered by the inhalation route. Chemically-induced lesions of the upper respiratory tract are most common in inhalation studies. The STP also supports examination of these tissues in non-inhalation studies if warranted by class effects, previous experience with related compounds, clinical findings, gross lesions, etc. However, the STP does not support the routine examination of pharynx and larynx in non-inhalation studies. Respiratory tissues of the trachea and lungs are examined in all studies, and provide sufficient routine surveillance of the respiratory tract for orally and parenterally administered chemicals. For irritating test compounds delivered via gavage, pharynx and larynx could be considered an extension of the application site, and added to the tissue list on a case-by-case basis.

The collection, processing, and microscopic examination of nasal tissues add significantly to the cost and effort required for a chronic study. We doubt that routine microscopic examination of nasal tissues is an effective screening method for human hazard identification. It appears to the STP that a case-by-case decision to evaluate nasal

tissues based on all available information would be appropriate. If nasal tissues are included in the regulatory guidance, the STP recommends that only nasal tissues in rodents be examined routinely. Nasal tissues in nonrodents should be examined only if there is evidence to justify this examination. Industry would benefit by understanding the FDA's rationale for routine examination of nasal tissues prior to inclusion of nasal cavity in the recommended tissue list. The STP suggests that a panel of experts address this issue and report their findings before the nasal cavity is added to a list of routinely examined tissues in regulatory guidance.

Sincerely,



Glenn S. Elliott, D.V.M., Ph.D., Diplomate ACVP
Chair, Scientific and Regulatory Policy Committee
Society of Toxicologic Pathology

References:

1. Bregman CL, et al. (2003). Recommended Tissue List for Histopathologic Examination in Repeat-Dose Toxicity and Carcinogenicity Studies: A Proposal of the Society of Toxicologic Pathology (STP). *Toxicol Pathol* 31:252-253.
2. Copeland-Haines, D and Eustis, SL. 1990. Specialized sebaceous glands, in Pathology of the Fischer Rat, GA Boorman, SL Eustis, MR Elwell, CA Montgomery and WF MacKenzie, eds, Academic Press, Inc San Diego, CA, pp 279-293.
3. Yoshitomi, K; Boorman, GA. 1990. Eye and associated glands, in Pathology of the Fischer Rat, GA Boorman, SL Eustis, MR Elwell, CA Montgomery and WF MacKenzie, eds, Academic Press, Inc San Diego, CA, pp 239-259.