

ABBOTT LABORATORIES

Global Pharmaceutical Regulatory Affairs

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

March 16, 2005

Re: Docket No. 05D-0022
Draft Guidance on S8 Immunotoxicity Studies for Human Pharmaceuticals

Abbott Laboratories (Abbott) is pleased to comment on the draft *ICH Guidance on S8 Immunotoxicity Studies for Human Pharmaceuticals* published in the *Federal Register* on February 8, 2005.

In general, we find the draft Guidance thorough and reasonable in its approach. We have no major objections to the principles contained within the Guidance. We offer the following comments, referenced by the line number where the text appears in the draft guidance, for your consideration when finalizing this Guidance.

Line 222 (Section 2.2.1, *Selection of Assays*): The text reads, "Immunophenotyping of leukocyte populations, a non-functional assay, can be conducted to identify the specific cell populations affected and useful clinical biomarkers." Immunophenotyping enumerates the specific cell types that are present, but does not necessarily identify functional changes that may have occurred within those cell populations. Therefore, it would be more accurate to state, "Immunophenotyping of leukocyte populations, a non-functional assay, may help to identify the specific cell populations affected . . .".

Line 228 (Section 2.2.2, *Study Design*): The first sentence states, ". . . studies with 28 consecutive daily oral doses in mice or rats." The "oral" should be deleted as compounds may be administered via alternate routes.

Line 249 (Section 3, *Follow-up Immunotoxicity Studies*): The host resistance assay gives information regarding the biological impact/relevance of the immunotoxic event, not necessarily the specific cell type affected or the mechanism of action. Therefore, it would be more accurate to state, "If changes are observed . . . further studies should be considered to help determine the cell type affected, the mechanism of action, and the biological impact of the immunotoxic event."

Lines 276-313 (Appendix 1, Section 1, *Standard Toxicity Studies*): This section refers to an “additional lymph node” and states that node selection is at the discretion of the sponsor. We support this discretion due to the ongoing controversy regarding whether or not to examine a distant lymph node. The Society of Toxicological Pathologists (STP) recently issued their recommendations against performing histology on distant lymph nodes due to the variability that is not necessarily reflective of immunotoxicity. The STP recommendation should be respected when finalizing this Guidance. The “additional lymph node” should not be required to be a non-draining node.

Line 281 (Appendix 1, Section 1, *Standard Toxicity Studies, Table*): Although the text in Section 1.3 provides examples of sites to sample based on the route of administration of the drug, the table in Section 1 under *Histology*, does not differentiate based on the route of administration. It would help if a note could be added to the table to link to the text in Section 1.3.

Line 293 (Appendix 1, Section 1.2, *Gross Pathology and Organ Weights*): The authorities recommend that all lymphoid tissues be evaluated for gross changes at necropsy. It would help to give examples of the tissues to be examined and acknowledge their importance relative to each other.

Should you have any questions, please contact Ms. Lauren Hetrick, Senior Director, Regulatory Intelligence/FDA Liaison Office at (301) 255-0080.

Sincerely,


Douglas L. Sporn