



# JAPAN PHARMACEUTICAL MANUFACTURERS ASSOCIATION

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To: Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, rm. 1061  
Rockville, MD 20852  
U.S.A.

## Docket No. 01D-0177

We have some comments upon the Guidance for Industry 'Immunotoxicology Evaluation of Investigational New Drugs' dated April 10, 2001.

Line 53-56: We think these criteria are very important and useful to evaluate immunotoxicity, but we cannot locate them in the literature cited. Are these references appropriate for these criteria?

Similar criteria for immune cell phenotypes are also considered to be useful to judge whether the changes are biologically significant or not. As the draft guidance mentions, changes in some parameters might not be cause for concern when the changes are small but statistically significant. Is it possible to add the criteria for immune cell phenotypes?

Line 96-97 and 107: The lines say "Indicators of immunosuppression can be observed in standard nonclinical toxicology studies and include increased incidence of tumors." This description is misleading, because the readers might think that they should always undertake the follow-up immunotoxicology studies when increased incidence of tumors is observed in the carcinogenicity study.

Line 131-132: In lymph nodes, the cortex and medulla are B-cell areas, and the paracortex is a T-cell area. On the other hand, there are not cortex or medulla in splenic white pulp. The sentence on these lines makes no sense.

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Line 160-204: The draft guidance suggests that immune cell phenotypes should be the first option of immunotoxicological parameter aside from those in the standard toxicology studies, and T-cell dependent antibody response the second. When decreases in lymphocytes in the T-cell and/or B-cell areas of spleens are noted by histopathological observation, T-cell dependent antibody response assay is thought to be more useful than immune cell phenotype determinations. Even in such cases, should the pharmaceutical company conduct immune cell phenotype determinations? How much do you weigh immune cell phenotype determinations against histopathology?

Line 194-196: We think that decrease in B-cells diminishes T-cell dependent antibody response more effectively than decrease in specific T-cells. We would suggest that the Guidance should draw attention to decrease in B-cells as well as that in T-cells.

Line 217-222: Pharmaceutical companies conduct the ICH Stage C-F reproductive toxicology studies because the drug is likely to be used in pregnant women. However, the draft guidance shows a special example in the brackets for which immunotoxicology determinations in those studies should be considered. It is confusing. Does the draft guidance intend to recommend evaluating immunotoxicity of all drugs or to indicate some special categories of drugs for immunotoxicology evaluation in the F1 generation if they are likely to be used in pregnant women?

These are all the comments we would like to make. Your attention and consideration would be appreciated. If you have any questions, please contact Kazuichi Nakamura (e-mail: kazuichi.nakamura@shionogi.co.jp). Thank you very much.

Yours faithfully,

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Kazuichi Nakamura, Fumio Sagami and Toshiaki  
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