



Amgen  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1799  
805.447.1000

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

**Subject:** **Docket No. 2005D-0022**  
Draft Guidance on *Immunotoxicity Studies for Human Pharmaceuticals* (ICH S8)

Dear Sir/Madam:

Amgen is a global biotechnology and pharmaceuticals products company based in Thousand Oaks, CA. We are pleased to provide the following comments on the draft guidance, *Immunotoxicity Studies for Human Pharmaceuticals*.

- 1) The guidance states (lines 102 to 103) that its focus is on low molecular weight drugs (non-biologicals). We suggest that this distinction be reiterated at appropriate points in the guidance. For example, we suggest the following modification to lines 107 to 109: "In addition, the guideline might also apply to **low molecular weight** drugs in which clinical signs of immunosuppression are observed during clinical trials and following approval to market." We also recommend that the title of the flow diagram (line 268) be reworded as follows: "Flow Diagram for Recommended Immunotoxicity Evaluations **of Low Molecular Weight Drugs**."
- 2) Literature references should be provided throughout the guidance. References would be especially useful in Appendix 1 as sources of additional information on methods to evaluate immunotoxicity.
- 3) Line 158 states that evidence of carcinogenicity, especially in the absence of genotoxicity, should be taken into consideration in determining the necessity of additional immunotoxicity testing. We believe that this statement should be removed for the following reasons: (a) the occurrence of immune suppression-related carcinogenicity without prior evidence of immune suppression in other standard toxicity studies is highly unlikely and (b) numerous other mechanisms, unrelated to immune suppression, could account for the occurrence of carcinogenicity in the absence of genotoxicity.
- 4) Lines 188 to 189: We recommend removing the following sentence: "These non-GLP pharmacology studies could be used in deciding if additional immunotoxicity studies are needed." Many non-GLP pharmacology studies conducted during discovery or early development phases do not focus on safety, and thus often do not

have adequate animal numbers or valid control groups to make decisions on safety. The decision to conduct additional immunotoxicity testing should be based on the findings in early stage toxicology studies rather than pharmacology/efficacy studies.

- 5) Lines 195 and 265: We recommend changing the word "immunocompromised" to "immunosuppressed." The latter term better defines the patient population that might be at increased risk when exposed to an immunosuppressive agent.
- 6) Lines 234 to 235: References should be provided for non-human primate adaptations of immune function assays that were developed in rodents.
- 7) Lines 265 to 267: We recommend the following modification: "If the target patient population is **immunosuppressed**, immunotoxicity testing **should** be initiated at an earlier time point in the development of the drug."
- 8) Line 269 (flow diagram): The safety factor based on clinical dose is listed as a recommended consideration in reviewing the standard toxicity study data. Is the inclusion of this factor meant to indicate that the need for additional immunotoxicity evaluations may be obviated by a sufficiently broad safety factor between the clinical dose and the dose at which potentially immunosuppression-related findings occur in standard toxicity studies? This should be clarified in the guidance.
- 9) Lines 277 to 280: Citations should be provided for the referenced documents that describe methods to obtain and evaluate samples in standard toxicity tests.
- 10) Lines 300 to 313: We suggest that histopathological evaluation of bone marrow should be addressed specifically in this section. We do not routinely evaluate bone marrow in standard toxicity studies unless effects have been observed in other tissues that suggest potential immunotoxicity. We, therefore, recommend adding the following statement: "**Bone marrow samples should be routinely collected in standard toxicity studies and should be evaluated if an indication of potential immunotoxicity has been obtained (eg, from other tissues, from previous studies, or based on the mechanism of action).**"
- 11) Lines 325 to 326: We suggest the following modification: "The evidence of stress should be compelling **in order to justify not conducting additional immunotoxicity studies.**"
- 12) Lines 344 to 346: We suggest the following modification: "It is recommended that each laboratory conduct a positive control study periodically (**at least yearly**) in order to demonstrate proficiency of performance, except for studies with non-human primates."
- 13) Line 352: A literature citation should be given.

- 14) Lines 369 to 371: We suggest removing this sentence: "For the rat TDAR and immunophenotyping assays, the addition of positive controls for each study with test compound might not be needed if the method used has been demonstrated to be adequately sensitive to immunosuppressive compounds." We agree with the recommendation to conduct periodic positive control studies (as stated in lines 344 to 346), which therefore makes the inclusion of positive controls in each study unnecessary.
- 15) Lines 386 to 388: We suggest the following modification: "When immunophenotyping studies are used to characterize or identify alterations in specific leukocyte populations, the choice of the lymphoid organs to be evaluated **or the use of peripheral blood** should be based on changes observed." We believe that the use of peripheral blood should be acceptable when changes in hematologic parameters are the only indication of immunotoxicity in standard toxicity studies.
- 16) Lines 404 to 405: A literature citation should be provided for the new methods that involve non-radioactive labels.
- 17) Line 430: We recommend the addition of the following sentence: "**An in vitro assay to test direct effects on the organism is recommended.**"

If you have any questions regarding our comments, or how we may assist with further development of this guidance, please contact Jenny Peters at 805-447-8840.

Sincerely,

A handwritten signature in black ink, appearing to be 'Jenny Peters', written over a light blue horizontal line.

Jenny Peters  
Amgen Regulatory Affairs