Triangle Pharmaceuticals

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1 August 2001

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

re: Immunotoxicology Evaluation
of Investigational New Drugs
(J:\GUIDANC\3010DFT2.DOC)

Dear Madams and Sirs:

I write to submit comments on the draft guidance entitled ***Immunotoxicology Evaluation of Investigational New Drugs***. My comments are presented in the attached table by line number of the document in .pdf format.

With appreciation for the opportunity to comment upon the document and trusting you will find my suggestions of some use, I am

Sincerely yours,

John E. Dillberger

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Line No(s).	Issue/Concern/Rationale for Proposed Change	Proposed Revision
27-37	List of adverse events could be better organized and the events better defined. The 5 categories in the list could be reduced to 3 categories of potentially adverse effects on immune system function. In particular, the distinction between what is called 'antigenicity' and 'hypersensitivity' is fuzzy and distinguishing the two doesn't help readers or the FDA decide upon immunotoxicity evaluation schemes or interpret the results of such schemes. The proposed revision makes the types of potentially adverse reactions clearer and defines them as functional rather than structural changes.	This guidance discusses three categories of adverse effects on the immune system: 1. Immunosuppression, defined as a functional impairment of the immune system that is adverse in the context of the drug's intended use. 2. Immunostimulation, defined as a functional enhancement of the immune system that is adverse in the context of the drug's intended use. 3. Inappropriately directed immune response, defined as an immune reaction against an inappropriate target, which is adverse in the context of the drug's intended use. This category includes induction of • an immune response to the drug or its metabolites or • an autoimmune response.
42-44 50-51 190-228	"Evidence of immunotoxicity can usually be observed in standard nonclinical toxicology studies..." "Signs of immunotoxicity in nonclinical studies should be evaluated to determine whether more specific studies would be useful." These sentences imply that additional specific immunotoxicity studies will be the exception rather than the rule, but don't spell out what the exceptions are. Section III does so, but in a general way. Clear, precise, specific language is needed.	The guidance ought to spell out clearly in which circumstances a sponsor should consider or conduct immunotoxicity studies even when standard nonclinical toxicity studies reveal no evidence of immunotoxicity. For example: "Regardless of the presence or absence of evidence of immunotoxicity in nonclinical toxicity studies, additional immunotoxicity studies should be conducted if: • The drug is administered topically or by inhalation, or • The drug concentrates in immune system cells or tissues or • Patients with HIV or a related immune disease will use the drug." If neither of these situations exists, then additional immunotoxicity studies should be considered only if there is evidence of immunotoxicity in nonclinical toxicity studies. Deciding whether to conduct additional studies and which studies to conduct will be influenced by several considerations." The guidance then could go on to discuss immunotoxicity 'markers' as it does now.

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62-64	"Potential immunotoxic effects should be evaluated in terms of both dose and, when data are available, systemic exposure. Where possible, dose comparisons to clinical use should be based on relative body surface areas." First sentence suggests systemic exposure comparison is better than dose comparison, making the second sentence ambiguous. The proposed revision clarifies that in the absence of systemic exposure comparison, dose comparison based on body surface area is preferred to dose comparison based on body mass.	"Potential immunotoxic effects should be extrapolated to humans by comparing systemic exposure or, if data are unavailable, by comparing dose expressed on a body surface area basis."
76	"...effects of the drug that are stress inducing." Typographical error.	"...effects of the drug that are stress-induced."
99-100	Several clinical conditions listed as evidence of myelosuppression in this bullet point don't belong here, and others that belong here are omitted. Specifically, anemia and thrombocytopenia suggest not immunosuppression but instead an inappropriately directed immune response (immune-mediated RBC or platelet destruction).	• "Hematologic evidence of myelosuppression, such as such as leukopenia (alone or as a component of pancytopenia), neutropenia, lymphopenia, or monocytopenia.
102-103	This bullet point could be better worded.	• "Evidence of structural changes in immune system organs or tissues, such as reduced spleen or thymus weight or histopathologic alterations in lymph nodes, thymus, spleen, bone marrow, or epithelia-associated lymphoid tissues (GALT, BALT, etc.)."
109 134-136	This bullet point lists a parameter not routinely measured in nonclinical toxicity studies. Thus, it probably should be omitted here. "Although decreases in serum immunoglobulin might be considered a relatively insensitive indicator of immunosuppression, this measurement is useful because it can be readily incorporated into the standard battery of clinical pathology tests." Is FDA suggesting that this parameter (serum immunoglobulin concentration), acknowledged as of doubtful usefulness, should be incorporated routinely into the clinical pathology tests run as part of general toxicity studies? If so, then I would suggest rethinking this idea.	Unless you are intending to tell sponsors to include serum immunoglobulin concentration routinely in the clinical pathology tests run as part of general toxicity studies, then omit the bullet point in line 109 and the sentence in lines 134-136.

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111-116	This paragraph is unnecessary. Any sponsor developing a drug will understand from the outset whether or not immunosuppression is a desirable effect or an undesirable one within the context of the drug's intended clinical use.	Omit this paragraph.
138-150	This paragraph describes anemias and blood dyscrasias, and seems to try to link reductions in blood cell counts (e.g. anemia) to immunosuppression. Then in the last sentence, it talks about an "autoimmune or antidrug antibody component." Either I or the authors are confused here. To my knowledge, immunosuppression is not associated with blood dyscrasias, except in two situations: • lymphopenia when the immunosuppression is a consequence of lymphocyte death or • granulocytopenia when the immunosuppression is a consequence of impaired granulocytopoiesis or increased granulocyte death.	Omit this paragraph that seems to link anemias and blood dyscrasias to immunosuppression. If want to mention something about lymphopenia and granulocytopenia as correlated with immunosuppression, then fine—but present paragraph is misleading if not outright wrong.
162-163	"...studies to determine potential mechanisms are encouraged." Ambiguous language—either the situation requires that mechanistic studies be done, or it doesn't. FDA needs to provide clear guidance to sponsors here.	Decide if the situation calls for additional mechanistic studies or if it doesn't, and say so.
206-207	"...when...infections are observed in nonclinical toxicology studies, the cause of infections should be determined." This is not routinely done now, so the advice constitutes a 'new' practice. Is FDA suggesting that any infection be 'cultured' and the responsible microorganism identified? That seems the only interpretation of this sentence.	Suggesting a 'new' practice in general toxicology studies in the midst of a guidance document on immunotoxicity probably isn't the best way to make sponsors aware. If FDA does indeed wish this 'new' practice adopted, then flag it up in a text box or "Summary of Suggested New Practices" section at the end of the document.
217-222	This paragraph says that a sponsor should consider adding unspecified immunotoxicity assessments to the Stage C-F reprotoxicity study (pre- and post-natal developmental toxicity study) if a drug likely will be used by pregnant women. This is too vague to constitute guidance. FDA needs to bite the bullet here and suggest a particular assessment.	Choose a specific parameter/assessment/endpoint and state unequivocally that sponsors should measure it in Stage C-F reprotoxicity study, if that is the agency's intent. If not, then omit this paragraph.

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226-228	"Because of the presumed increased susceptibility to drug-associated immunotoxicity of patients with impaired immune function [in patients infected with HIV or a 'related immune disease'], extra nonclinical effort to detect immunotoxic effects is warranted." Actually, I would reason just oppositely. Patients known to have an 'immunosuppressive' disease already are being monitored intensively for potential immunosuppression. This is the one drug-related risk that can't sneak up on them. I don't see the rationale for singling out drugs to be used in such patients for increased scrutiny—on the contrary, I would instead single out for greater scrutiny drugs to be used in patients whose immune systems are presumed normal. These patients are most likely to be caught off-guard and harmed by an unexpected immunosuppressive effect.	I would suggest that drugs intended for use in immunocompromised patients not be treated differently from drugs to be used in other sorts of patients.
257	"Under certain circumstances,..." The circumstances aren't detailed and they should be. This is too vague to provide guidance to sponsors.	Detail the circumstances you have in mind.
231, 272, and 429	As mentioned already, sections V (Antigenicity), VI (Hypersensitivity), and VII (Autoimmunity) each discuss an immune response that is inappropriately targeted—either to the drug itself, to a metabolite, to a hapten created by interaction of drug/metabolite with a host molecule, or to a host molecule. The distinctions between the labels hypersensitivity, antigenicity, and autoimmunity are fuzzy and of no nonclinical relevance. The essential point is that we have no good nonclinical tests to predict this sort of inappropriately targeted immune response in people. Tests do exist for evaluating potential contact sensitization/hypersensitivity, but even these aren't considered very predictive. While the discussion encompassed in these three sections is fine, the document needs somewhere to clearly spell out what findings, if any, in general toxicity studies would suggest a potential for an inappropriately targeted immune response and what specific additional studies, if any, would a sponsor should consider or conduct to follow up.	Re-think and re-write the material in sections V, VI, and VII, paying particular attention to clearly defining terms/labels and also to clearly spelling out when sponsors should consider conducting additional studies and what specific assessments they should make in such studies. Give consideration to downplaying distinctions among the three sections and instead emphasizing that all three are facets of an underlying problem—specifically, that drug administration leads to an inappropriately targeted immune response with adverse consequences.

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491-492	"If a drug is expected to be used in pregnant women, incorporation of immunotoxicology in the ICH Stage C-F reproductive toxicology study should be considered."	
190-228 491-492	Section IV.C. reads "When warranted by observation in nonclinical toxicology studies, additional studies to determine potential drug effects on immune function should be considered....The importance of follow-up immune function studies for overall safety assessment depends on the intended use of the drug. If a drug is likely to be used in pregnant women...immunotoxicology determinations in the ICH Stage C-F reproductive toxicology study should be considered." This seems to say that if a drug shows evidence of immunotoxicity in general toxicity studies and is likely to be used in pregnant women, then immunotoxicity assessment should be included in the Stage C-F reprotoxicity study. However, Section IX seems to contradict this by saying that "If a drug is expected to be used in pregnant women, incorporation of immunotoxicology in the ICH Stage C-F reproductive toxicology study should be considered." This seems to say that a drug that will be used in pregnant women should have an immunotoxicity assessment in Stage C-F studies regardless of whether or not there are indications of general toxicity. Appendix I implies the same thing.	No suggested text, but need to clarify the apparent contradiction.

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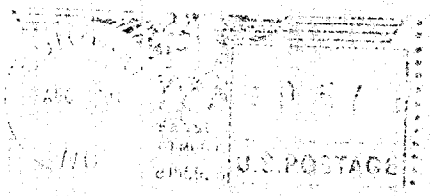

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