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Dockets Management Branch (HFA-305)
Food and Drug Administration
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MERCK
Research Laboratories

RE: Docket No. 01D-0177
Draft Guidance: Immunotoxicology Evaluation of Investigational New Drugs

Merck & Co., Inc., is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than $2 billion annually on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. MRL tests many compounds as potential drug candidates through comprehensive, state-of-the-art R & D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment.

In the course of bringing Merck product candidates through developmental testing and clinical trials, Merck scientists regularly address issues affected by this proposed Guidance. We have extensive experience in assessing parameters of immune function, and in conducting additional immunotoxicity studies to evaluate the significance of an effect of a new molecular entity on the immune system.

Merck commends the FDA for examining the immunotoxicity evaluation of new drugs and supports the recommendation that parameters examined in standard nonclinical repeat-dose toxicity studies should be used to screen for immunotoxicity with no need for specific functional tests. However, we are concerned that this draft Guidance requires that sponsors routinely conduct specific additional tests, on the basis of drug distribution, drug class, and intended use, instead of considering such studies only when signs of toxicity have been observed. Our specific comments follow. We present each comment, referenced by line number, followed by our recommendation.

Section III, Lines 86-90; and Section IX, Lines 499-503

Comment: The draft Guidance refers to the concentration of drug in reticuloendothelial tissue as it relates to potential adverse effects on macrophage function. There is little evidence that the concentration of a drug in macrophages induces functional adverse effects. Therefore, the rationale for assessing macrophage functions on the basis of drug accumulation in this cell type is not supported. In addition, tissue distribution studies do not readily distinguish cells of the reticuloendothelial system (RES) from other cell types

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in a given tissue. Thus, data on the concentration of a drug in the RES are not routinely available.

Recommendation: The assessment of drug distribution in the RES and any further exploration of macrophage functions should be considered only if justified by relevant signs of toxicity in the repeated-dose studies or during the clinical phase of drug development.

Section III, Line 86; and Section IX, Line 500
For purposes of clarity, *reticuloendothelial tissues* should be replaced by *reticuloendothelial system*.

Section IV A, Line 109 and Lines 134-136
Comment: The draft Guidance states that 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.

Recommendation: Merck agrees that decreases in serum immunoglobulin levels are considered a relatively insensitive indicator of immunosuppression. Changes in hematological parameters, and gross and histopathologic changes of hematopoietic and lymphoid tissues are more sensitive indicators of immunosuppression than the measurement of serum immunoglobulin levels. Therefore, the measurement of serum immunoglobulin levels should not be recommended. Line 134 should be modified to read,

"~~Although~~ Decreases in serum immunoglobulin **are** ~~might be~~ considered a relatively insensitive indicator of immunosuppression **and are not recommended**~~, this measurement is useful because it can be readily incorporated into the standard battery of clinical pathology tests~~."

Section IV B, Immune Cell Phenotyping
Comment: This draft Guidance states that immune cell phenotype changes (as determined by flow cytometry) have been demonstrated by the National Toxicology Program to be one of the best single correlations with host resistance against pathogens and tumors. However, since the NTP studies examined murine spleen cells, it is not known whether the same correlation exists for circulating white blood cells.

Recommendation: Immune phenotyping on circulating white blood cells should be validated before it is recommended. Therefore, *when practical* should be replaced by *when appropriate* in Line 168.

Section IV C, Lines 202-204
Comment: The draft Guidance states that the ELISA demonstrates a high correlation with the plaque assay.

Recommendation: In order to be consistent with the recommendation made in Section X, Lines 571-573, the text should be modified to clearly state that the assessment of T

cell-dependent antibody response by ELISA is a validated alternative to the plaque assay. The text should be modified to read,

"~~Although~~ The ELISA variation ~~is not a true test of immune function, it~~ has demonstrated a high correlation with the plaque assay (Holsapple 1995; Temple et al., 1993, 1995) **and therefore, is recommended as an alternative to the plaque assay**."

Section IV C, Lines 217-222; Section IX, Lines 491-494; and Section X, Line 567
Comment: The draft Guidance states that immunotoxicity determinations in the ICH Stage C-F reproductive toxicology study should be considered for a drug that is likely to be used in pregnant women. However, reproductive immunotoxicology is an extremely young discipline for which standard practices, historical data, and the appreciation for variability among controls have yet to be determined.

Recommendation: The Guidance should acknowledge the limitations of reproductive immunotoxicology studies. It would be helpful if the Guidance addressed the age at which the F1 offspring should be examined post weaning to assess the effect of maternal drug exposure on lymphoid system histopathology.

The Guidance should clearly state that the inclusion of immunotoxicology determinations in reproductive toxicology studies should be considered, "If a drug is intended to be used in pregnant women," according to the example given in Line 219 (prevention of perinatal transmission of an infectious disease such as HIV).

Section IV C, Lines 224-228; and Section IX, Lines 503-510
Comment: Investigational new drugs are assessed for unintended immunosuppression in standard toxicology studies through chemistry, hematology, and gross and histopathology. In the absence of signs of immunotoxicity, there is little justification for considering extra immune function studies in animals when developing drugs for persons with normal immune function; the same holds for drugs intended to be used in patients with impaired immune function. Based on our experience, further animal studies do not help predict adverse effects that are unique to persons with impaired immunity.

Recommendation: Absent signs of immunotoxicity in animals, no further nonclinical studies assessing the effects of drugs on immune function are needed.

Section V, Lines 257-258
Comment: The Guidance states that under certain circumstances attempts should be made to determine the antigenic potential of large molecular weight drugs.

Recommendation: The Guidance should be explicit regarding the circumstances when attempts should be made to determine the antigenic potential of large molecular weight drugs and should clearly define a "large molecular weight drug" (Line 257).

Section V, Lines 265-26; and Section IX, Lines 486-490

Comment: The Guidance states that "Studies have demonstrated that haptenic compounds known to produce hypersensitivity reactions in humans, such as penicillin and sulfamethoxazole, do not produce an anti-drug response when administered to rats in clinically relevant conditions[1,2]."

Recommendation: The evaluation of anti-drug responses in routine toxicity studies does not appear helpful and should not be recommended. Assays for identifying anti-drug immune responses should be considered optional in follow-up studies to help interpret toxicity findings in animals.

Section VI A, Lines 312-326

Comment: Assays for detecting respiratory sensitizers have been tested with a limited number of compounds, mostly highly reactive chemicals. To date, the value of such assays in predicting the risk of hypersensitivity reactions of inhaled drugs has not been demonstrated.

Recommendation: Since no appropriate validated tests are available for the assessment of the sensitizing potential of drugs intended for inhalation, the statement (Line 326), "Drugs intended for inhalation should be tested for their sensitizing potential," should be removed.

Section IX, Lines 478-484

Comment: Line 484 lists the mouse IgE test (MIGET) among appropriate tests for detecting the sensitizing potential of a drug. However, this is inconsistent with Annotation 2 in Attachment 1, which states "(there is only a relatively small database available for assessing the usefulness of the MIGET for drug regulatory purposes)."

The guinea pig sensitization test (GPMT), the Buehler assay (BA), and the local lymph node assay (LLNA) are accepted as validated methods for detecting the sensitizing potential of topical compounds. However, their usefulness for detecting the sensitizing potential of inhaled drugs has not been demonstrated.

Recommendation: Line 484 and Attachment 1 (Annotation 2) should be consistent. Since no appropriate validated tests are available, the assessment of the sensitizing potential of drugs intended for inhalation cannot be expected. Therefore, Line 480 should read,

"additional immunotoxicology studies to complement the standard repeat-dose toxicology studies are expected when the drug is administered by ~~inhalation or~~ **the** topical routes."

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[1] Gill, H.J., Hough, S.J., Naisbitt, D.J., Maggs, J.L., Kitteringham, N.R., Pirmohamed, M., Park, B.K. *Journal of Pharmacology and Experimental Therapeutics*, 282, 795-801, 1997.

[2] Kitteringham, N.R., Christie, G., Coleman, J.W., Yeung, J.H.K., Park, B.K. *Biochemical Pharmacology*, 36, 601-608, 1987.

Section X, Line 564
Comment: Tests for detecting contact sensitization have not demonstrated their usefulness for detecting the sensitizing potential of inhaled drugs.

Recommendation: Lines 562-564 should read,

"For the safety assessment of investigational new drugs, specific immunotoxicity testing should be conducted (in addition to the standard toxicology studies in two species) when drugs are to be administered by the ~~inhalation or~~ topical routes."

Conclusion
In summary, we support the recommendation that the parameters examined in standard nonclinical repeat-dose toxicity studies should be used as the screen for immunotoxicity of investigational new drugs with no need for specific functional tests. The parameters currently examined in standard repeat-dose studies appear adequate for this purpose.

We appreciate the fact that biologically significant changes rather than statistically significant changes should be considered when performing follow-up studies in cases where signs of immunotoxicity have been observed.

The requirement for specific additional studies on the basis of drug distribution, drug class, and intended use (with the exception of topical drugs) is inappropriate. The recommended studies should not be required in the standard battery of tests. Instead, the studies should only be considered when relevant signs of toxicity have been detected.

Therefore, we recommend the Guidance be revised to address the points outlined above. We welcome the opportunity to meet with you to discuss these issues.

Sincerely,

Bonnie J. Goldmann, M.D.
Vice President, Regulatory Affairs-Domestic