3M Pharmaceuticals

3M Center, Building 270-3A-08
St. Paul, MN 55144-1000

3M

August 3, 2001

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, Maryland 20852

Re: **Docket Number 01D-0177**

Subject: **3M Pharmaceuticals' Comments to *Draft Guidance for Industry* – Immunotoxicological Evaluation of Investigational New Drugs**

Dear Sir/Madam,

Enclosed please find 3M Pharmaceuticals' comments on FDA's *Draft Guidance for Industry* – Immunotoxicological Evaluation of Investigational New Drugs. These comments are provided with reference to Docket Number 01D-0177.

Should you have any questions regarding the comments, please don't hesitate to call me (651 736-5015).

Respectfully,

D. M. Markoe Jr.

David M. Markoe, Jr.
Senior Regulatory Specialist
3M Pharmaceuticals

01D-0177

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Guidance for Industry
"Immunotoxicological Evaluation of Investigational New Drugs"
US FDA (5/10/01)

Comments prepared by:
Pathology/Toxicology
3M Pharmaceuticals
3M Center, Bldg 270-3S-05
Saint Paul, MN 55144-1000
July 31, 2001

GENERAL COMMENTS

This document provides an overview on the state of immunotoxicology testing for pharmaceuticals.

The guidance explains that evidence of immunotoxicity (immunosuppression) can usually be observed in standard non-clinical toxicology studies and that follow up studies may be necessary to define potential mechanisms.
The guidance also evaluates the concerns and complexities around drug hypersensitivity or autoimmune reactions.

We provide the C.D.E.R. with some specific comments we have regarding the description of the strategy that should be used in order to evaluate the immunotoxic potential of new drug candidates (immunosuppression and hypersensitivity/autoimmunity).

SPECIFIC COMMENTS

Lines 54-56: We would recommend removing reference to specific percent changes in lymphocytes and neutrophils because mentioning a threshold could become dogma while there is no clear definition of a biologically significant change.

Lines 70-76: We agree that environmental factors may cause stress-induced immunologic effects, and that in carefully designed studies these effects should be reflected in non-drug-treated control animals. However, we propose to discuss in the guidance the importance of studying the potential for immunotoxic effects at doses that do not produce overt toxicity in order to avoid confusion between a direct and a stress-related effect.

Line 86-87: "For example, if distribution studies indicate that the drug concentrates in reticuloendothelial tissues (usually macrophages) and no signs ..." should be replaced by "For example, if distribution studies indicate that the drug concentrates in lymphoreticular tissues and no signs ...".

Line 107: "Increased incidence of tumors" is cited as an indicator of immunosuppression. It is known from studying immuno-compromized patients that the increased incidence of tumors is essentially if not always related to virus related tumors (skin/lips cancer and HSV; non-Hodgkin lymphoma and EBV, Kaposi sarcoma and CMV, uterus cervix cancer and HPV). To associate any kind of increased tumor incidence with immunotoxicity, and then recommend (p.22, Attachment 2) to use tumor host resistance assays when there is evidence of carcinogenicity might not be appropriate. A link between carcinogenicity and immunosuppression should not be made in the absence of other evident signs of immunosuppression (bone marrow toxicity, ...). A rodent tumor response is almost never associated with immunosuppression.

Lines 111-116: A comment on permanent versus transitory changes due for instance to trafficking of leukocytes could be added. This comment could also be added in lines 152-158 (p.4).

Line 134-136: A precise measurement of serum immunoglobulins is not currently done. It could require the use of methods such as ELISA or electrophoresis. It is probably not that easy to incorporate in a standard battery of clinical pathology tests. In addition, it has been described as a poor indicator of immunosuppression in short term tox studies.

Line 167-168: "cell surface phenotype determinations should be made on splenocytes obtained at necropsy and, when practical, on circulating white blood cells" could be replaced by : "cell surface phenotype determinations should be made on splenocytes obtained at necropsy or, when practical, on circulating white blood cells"

Line 174: about the use of NK cell markers. There are not, to our knowledge, compounds that specifically affect NK cell numbers, without affecting B and/or T cells numbers. Markers for B and T lymphocytes only seems more appropriate.

Lines 191-192: Guidance should be given about dose selection for follow-up studies. Should selection be based on multiples of the efficacious dose or of the no observable effect level? Doses that result in overt toxicity should not be evaluated.

Lines 202-204: We disagree that measuring the serum antibody response to a specific antigen challenge by ELISA procedures 'is not a true test of immune function'. The plaque assay measures the number of antibody-forming cells in the spleen; the ELISA quantitates the amount of antibody produced from all immune organs, not just the spleen. Either assay should be acceptable. In fact, the ELISA method adds a number of advantages since time course can be followed and recovery assessed within the same animals. We recommend that allowance be made for the use of immunoassays and the assessment of specific antibody responses to T cell dependent antigens other than SRBCs.

Line 217-222: It is unclear whether a study of the F1 offspring generation should be considered every time a drug could be used in pregnant women, or where effects on maternal immune function have already been demonstrated, or if it should be considered specifically for drugs that would be prescribed for a condition linked to the pregnancy.

Line 265: In order to run an ELISA for anti-drug antibodies, a capturing antigen consisting in a drug-protein conjugate would be necessary. It is suggested that no assay to identify antidrug immune response would be run unless there is evidence that such a covalent binding exists *in vivo*. The lymphocyte blastogenesis assays have been shown to be poorly informative, even in allergic patients, and are therefore barely used by physicians for drug allergy diagnosis. It is suggested to not include such an assay as part of the routine nonclinical safety assessment of drug candidates.

Lines 282-283: Small molecular weight compounds may be antigenic -- not allergenic -- if they bind directly to proteins, either as the parent or via metabolites (lines 282-283). They are allergenic if they produce an exaggerated or pathological reaction. We suggest changing "allergenic" to "antigenic."

Line 311-319: It could be added that these assays/approaches have been used with a very limited number of compounds and have not been validated in interlaboratory studies.

Line 326: There is very limited data available to support the idea that non-protein inhaled drugs could successfully be assessed by these assays that focus on identification of cell-mediated hypersensitivity reactions. As mentioned later about Attachment 1, we think that none of these assays have been demonstrated to be appropriate for inhaled drugs.

Lines 367-398: We agree that all dermal drugs should be routinely tested for the potential for dermal sensitization, since validated and predictive assays are available. We recommend including a reference to the ICCVAM proceedings (NIH publication No. 99-4494) which supports using the LLNA as an alternative for contact sensitivity testing.

Line 400-405: This paragraph does not reflect what is described in the CDER Guidance for Industry for Photosafety Testing which states that "Short-term photosensitivity testing in animals, perhaps followed by studies in humans, should be considered for all drug products that absorb UVB, UVA, or visible radiation...". An agreement between the guidances should be reached.

Lines 439-440: It is stated that "Immune stimulation due to specific immune reactions (stimulatory hypersensitivity) may be considered a type of autoimmunity." It is not clear what type of specific immune reaction will result in immune stimulation and why this is considered a type of autoimmunity. To clarify this section, examples of stimulatory hypersensitivity should be provided.

Lines 442-446: We agree that given the lack of "extensive evaluation", the PLNA should not be used to determine if a drug has the potential to produce autoimmune reaction.

Lines 457-460. We are concerned that the definition of adverse immunostimulation as "any antigen-nonspecific, inappropriate, or unintended activation of some component of the immune system" is too broad. Perhaps a better definition would be "uncontrolled immune stimulation".

Lines 469-473. "A relatively common manifestation of immunostimulation is leukocyte infiltration of tissues", could be replaced by "A relatively common manifestation of immunostimulation is leukocyte infiltration of tissues *above the naturally existing level*". We also do not understand the link made between adverse immunostimulation and the diffuse capillary leakage observed in with IL-2 (lines 472-473).

Line 478-484: The MIGET should not be mentioned as if it was as validated or accepted as the guinea pig assays and the LLNA. There is not a comparable scientific rationale for assessing drugs intended to be used through the inhalational and topical routes with the guinea pig assays and the LLNA. Xenobiotic-induced pulmonary hypersensitivity following inhalation and contact allergic dermatitis involve quite different mechanisms. The tier approach described by Sarlo and Clark [Fundam. Appl. Toxicol. (1994), 18, 107-114] could be considered if it was demonstrated to be valid for pharmaceutical compounds, in addition to what observed with phthalic anhydride, black b dye, and toluene diisocyanate.

Line 489: Is any compound with a molecular weight above 1,000 considered as a large molecular weight drug? This should be specified.

Line 500-501: Reticuloendothelial tissues should be replaced by lymphoreticular tissues.

Line 532-536: see comment for line 107. To associate any kind of increased tumor incidence with immunotoxicity, and then recommend (p.22, Attachment 2) to use tumor host resistance assays when there is evidence of carcinogenicity might not be appropriate. A link between carcinogenicity and immunosuppression should not be made in the absence of other evident signs of immunosuppression (bone marrow toxicity, ...). A rodent tumor response is almost never associated with immunosuppression.

Line 562: There is not a comparable scientific rationale for assessing drugs intended to be used through the inhalational and topical routes with the guinea pig assays and the LLNA. Allergic contact dermatitis assays should be required only for topically applied compounds.

Flow Charts

In flowchart 1, the validated GPMT, BA, LLNA should be linked to cutaneous hypersensitivity and the inhalation guinea pig assays (without MIGET) should refer to the inhalation route. Therefore remove these assays from the first decision box. The PLNA in flowchart 2 should be deleted or clearly marked as a scientifically meaningful but not validated method.

ABBREVIATIONS

BA - Buehler assay
EBV - Epstein Barr virus
ELISA - enzyme linked immunosorbent assay
GPMT - guinea pig maximization test
HSV - herpes simplex virus
HPV - human papilloma virus
ICCVAM - The Interagency Coordinating Committee on the Validation of Alternative Methods
LLNA - local lymph node assay
MIGET - mouse immunoglobulin E test
PLNA - popliteal lymph node assay
SRBC - sheep red blood cells
WBC - white blood cells

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