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August 7, 2001

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Dear Sir or Madam:

Attached are the comments from Pfizer, Inc. on the Draft Guidance on Immunotoxicology Evaluation of Investigational New Drugs (Docket No. 01D-0177), that was released for public comment on May 10, 2001.

Regards,

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Draft Guidance for Industry
Immunotoxicology Evaluation of Investigational New Drugs
US FDA (Published 5/10/01)

Comments from:
Pfizer Global Research & Development, Pfizer, Inc.
August 7, 2001

GENERAL COMMENTS

In general, the testing scheme proposed in the guidelines uses a logical, "flowchart" approach to immunotoxicity testing. We fully support the recommendation that standard repeat-dose toxicity studies be used as the screen for immunotoxicity rather than special tests for immunosuppression (e.g., T-dependent antibody response, lymphocyte phenotyping) for all new drugs.

We support the inclusion of recommendations for testing of other types of immunotoxicity rather than just focusing on immunosuppression. This is very important, since hypersensitivity / autoimmune reactions have been historically known to be a much greater concern in the drug development process than immunosuppression. Unfortunately, well-characterized and validated approaches to identify drugs that may elicit anti-drug immune responses (Section III) or produce hypersensitivity (Section IV.B) and autoimmune-like reactions (Section V) have not been developed and validated. Moreover, approaches to examine developmental immunotoxicity with maternal exposure (Section II.C) or carcinogenicity mediated indirectly via immunosuppression have not been developed. Thus, unless well-developed and validated assays are available, these specific approaches should not be recommended (Attachment 2 flowchart). Those methods that are recommended need to be clearly justified.

We agree that if significant immune related effects are observed in standard toxicity studies, follow-up studies should be conducted. These follow-up studies were adequately described for most sections, however there was very little discussion regarding how the data from the follow-up studies would be used in the risk assessment process. This is a very important component and needs further emphasis. The guidance provided was scattered throughout the document and was vaguely written. The following are statements taken from the document that described how the follow-up studies should be used.

- Lines 157-158: "Although follow-up studies are not generally essential to support the safety of a new drug, they may be useful in the risk/benefit analysis. A similar statement was found in lines 513-514 and needs to be clarified.
- Lines 162-164: "If signs of immunosuppression are observed in nonclinical toxicology studies, follow-up studies to determine potential mechanisms are encouraged. Findings from such studies could suggest modification to trial entry criteria or guide the management of adverse symptoms."
- Lines 552-553: "Immunotoxicologic finding could suggest addition follow-up studies to investigate the nature and mechanism of immunotoxic effects."
- Lines 556-560: "Modifications in clinical trials could be indicated by immunotoxicity findings (e.g., certain immune parameters might be monitored). Immunotoxicity finding could be included in the investigator's brochure or in the product label. Finally, although immunotoxicity findings could indicate that a drug is unsafe for some type of clinical investigations or certain indications, this appears to be rare."

We recommend that the statements listed above should be collected into one section of the guidance document. This section should clearly state how the data from these assays should be used and potential caveats. This is very important since there is significant controversy and little supporting data on how to interpret the findings from these studies in terms of clinical significance in humans.

SPECIFIC COMMENTS

The following specific comments are presented in the order presented in the guidelines.

III. Evaluating Immunotoxicity Markers

A key point in the testing process described in the guidelines is the decision to proceed with follow-up immunotoxicity studies if warranted by findings from standard non-clinical toxicity studies. We agree that this decision should be made on biologically significant changes rather than slight to moderate changes that may be statistically significant (lines 52-56).

We agree that in nonclinical toxicity studies, effects on immune system parameters may be attributed to stress and should not be considered toxicologically significant (Lines 70-76). However, approaches to determine if stress is the cause have not been developed. If the stress produced is related to drug-exposure, it is not clear how one can use the vehicle-control group as a comparison to determine if the toxicological effects are stress-related as described in lines 75-76. This recommendation needs to be clarified.

Lines78-84 suggest that when indirect immune modulation due to pharmacological effects of the drug have been observed, the patterns produced should be evaluated to determine if additional immunotoxicity studies would be useful. The meaning of "patterns produced" need to be clarified.

The guidelines recommended that if pharmacokinetics studies demonstrate that the drug concentrates in the reticuloendothelial system (RES), the effect of drug accumulation in that specific cell type (usually macrophages) should be considered. This recommendation is described in lines 86-90 and again in lines 500-501. Signs of potential drug accumulation in the RES are usually identified during histopathological evaluation of tissues. Studies to measure drug accumulation in the RES are technically very difficult and are not routinely conducted in pharmacokinetics studies. The clinical significance of changes with in vitro macrophage function assays or in vivo clearance studies with drugs known to accumulate in the RES has not been established. Thus, unless there is significant justification, these types of studies should not be recommended.

We recommend that the lack of full GLP compliance for follow-up studies should not limit the value of these data to support clinical studies or registration. Many of these studies are investigative in nature, particularly when incorporated into an ongoing study to elucidate a possible immunologic mechanism. In these situations, methods used must often be defined in a very short period of time, or validated methods may not exist, particularly in non-rodent studies. We recommend a statement that the work be done "in the spirit of GLPs".

Lines 191-192: Guidance should be given on dose selection for follow-up studies. Should the 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.

IV. Immunosuppression

Decreased serum immunoglobulin levels is listed as an indicator of immunosuppression in standard nonclinical toxicology studies (line 109). It is also indicated that total serum immunoglobulins might be considered a relatively insensitive indicator of immunosuppression, but may be useful since it can be readily incorporated into the standard battery of clinical pathology tests (lines 134-136). Since changes in hematology, organ weights and histopathology will likely be more sensitive markers of immunosuppression; the measurement of serum immunoglobulins should not be recommended.

Lines 122-123 indicates that immune system-related organ weights should be included in repeat dose-toxicity studies. It is recommended that the following be included in this section "Given the significant variability in spleen and thymus weights in toxicity studies with dogs and monkeys, these organ weights should not be taken." In addition, due to the significant animal-to-animal variability in lymph node weights and technical challenges in separating lymphoid tissue from adipose tissue, we recommend that lymph node weights should not be taken for rodent, dog or monkey toxicity studies.

B. Immune Cell Phenotyping

In the guidelines, it is encouraged that follow-up studies be conducted to determine potential mechanism if signs of immunosuppression are observed in nonclinical toxicity studies (lines 162-163). Immune cell phenotyping is recommended as a follow-up study. However, this method may only help identify target cell types and characterize histological changes in immune cell tissues (line 176) rather than determine mechanism. Thus, this section should be revised accordingly.

Phenotyping studies were recommended since immune cell phenotype changes have been demonstrated by the National Toxicology Program (Luster et al.,1993) to be one of the best single correlations with host resistance against pathogens or tumors. However, since the NTP examined the spleen cells of B6C3F1 mouse for these studies, it is not known if the correlation exists for rats, dogs and monkeys and with peripheral blood lymphocytes (PBL). With non-rodent species, the analysis of PBL will be much more practical. Moreover, since PBLs would be used to monitor adverse effects in clinical trials, it makes more sense that PBLs be used for the preclinical studies. This difference between validation in mouse spleen and practical use of rat, dog, monkey and human PBL needs to be reconciled before stating that immune cell phenotyping in preclinical studies is a validated approach.

An additional concern is the recommendation that NK cells should also be enumerated by immune cell phenotyping experiments (line 174). Natural killer cells comprise only 1-5% of the total mononuclear cell population in the rat spleen. Thus, it may be difficult to detect decreases in NK cell numbers. It should also be pointed out that validated antibodies which label NK cells in dogs are not available commercially. Thus, NK cell markers should not be included as markers for phenotype analysis.

V. Antigenicity

It is stated that anti-drug assays should be considered as part of the nonclinical safety assessment with classes of drugs known to be potentially haptenic (e.g. penicillins) (Lines 257-259; 488-490). Many marketed drugs are known to be metabolized to reactive intermediates that bind to various macromolecules and thereby are potentially haptenic. However, these drugs are associated with a very low incidence of hypersensitivity reactions in humans. Thus,

the potential of a drug to be haptenic does not warrant the needs for the evaluation of anti-drug responses in standard toxicology assays.

In contrast to lines 257-259 and 488-490, lines 407-412 indicate that anti-drug responses should be conducted if the test compound is known to belong to a class known to produce hypersensitivity reactions through covalent binding. However, studies have demonstrated that these compounds (e.g. sulfonamides, penicillins) do not produce an anti-drug response when administered via a clinically relevant route in rats (without adjuvant or immunizing with drug-protein conjugates) (Kitteringham et al., 1987: Gill et al., 1997). Reasons for the lack of an anti-drug response may be attributed to the amount of reactive intermediates generated and inactivated and the immunogenicity of the hapten-protein conjugate. Thus, evaluating anti-drug responses in routine toxicity studies will not be helpful and should not be recommended. In addition, methods to measure anti-drug responses are time-consuming to develop and require positive control serum to validate the assay.

VI. Hypersensitivity (Drug Allergy)

A. Type I

We agree that the guinea pig methods to assess the potential of drugs to produce type I reactions with oral or parenteral routes of administration are not predictive and should not be recommended (Lines 291-309). The mouse IgE test to detect respiratory sensitizers was also discussed. However, since this method has not been validated, a statement regarding its questionable use needs to be clearly stated in the guidance document. It is recommended that the guinea pig method of Karol (1995) which "involve dermal or inhalation induction followed by inhalation challenge" be used for inhalation drugs. The method described in this report involves inhalation sensitization and inhalation challenge, but does not describe a method for dermal sensitization and inhalation challenge. Since the model of Karol (1995) is very time consuming, expensive and difficult to conduct, perhaps other alternatives such as the tiered approach for evaluating respiratory sensitizers of low molecular weight chemical described by Sarlo and Clark (1992) should be considered.

B. Type II & III

It is suggested that in the case of specific tissue damage such as vasculitis, "immunohistochemical demonstration of antibody or complement in the affected tissue could suggest immunopathy." Based on the literature, antibody-mediated vasculitis that occurs with drug treatment appears to be very rare. Specific examples of antibody-mediated vasculitis need to be included. Since drug-induced vasculitis may be mediated by several other mechanisms, the deposition of immune complexes and complement may not necessarily demonstrate a direct relationship.

It was also suggested that "specialized biomarker assays can be useful for understanding mechanisms when a drug belongs to a chemical class known to be associated with specific immunopathies." (lines 354-355). Antibodies against trifluoroacetylated proteins were proposed as an example of a potential biomarker for indirectly assessing the sensitizing potential of chemicals related to halothane. Based on this discussion, it is not clear how the biomarker will be used and in which situations it would be helpful. We suggest that this section be re-written and additional specific examples of how the biomarker will be used in nonclinical studies to identify compounds which may produce Type II or III hypersensitivity reactions.

C. Type IV

We agree that the murine local lymph node assay (LLNA) can be used as an alternative to the standard guinea pig models for contact hypersensitivity testing.

It was stated that if a drug belongs to a class known to produce hypersensitivity reactions through covalent binding (e.g., beta-lactams, sulfonamides), demonstration of covalent binding to proteins could be taken as a biomarker of sensitization potential. As stated previously in regards to the Antigenicity section of these comments, studies with beta-lactam and sulfonamide administration to rats have demonstrated that it is very difficult to detect covalent binding in rat tissues even with the administration of high doses. In addition, if covalent binding is observed, it is not known how much covalent binding should be a concern. Studies which have examined the relationship between the amount of covalent binding and immunogenicity of the hapten have not been reported. Thus, covalent binding studies to determine potential immunogenicity / antigenicity should not be recommended at this time.

VII. Autoimmunity

In 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.

The popliteal lymph node assay (PLNA) is discussed in 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 reactions. Markers of T-cell activation and of Th2 cell induction in Brown Norway rats were also suggested (lines 448-449; Attachment 2). References for these methods need to be included as well as the justification for the markers.

IX. Safety Considerations

It is recommended that for drugs administered by the inhalation route, the sensitizing potential should be screened using an appropriate test such as the guinea pig maximization test (GPMT), Buehler assay (BA), local lymph lode node assay (LLNA) or mouse IgE test (MIGET) (lines 481-484 and Attachment 1). However, justification for using a method for contact sensitivity to determine the sensitizing potential of an inhalation drug needs to be included. In addition, since the MIGET has not been adequately validated, this assay should not be recommended. The recommendations in lines 481-484 are not consistent with the guinea pig assays (Karol 1995) recommended in lines 321-326. The types of assays recommended to assess the sensitizing potential of inhaled drugs needs to be clearly stated.

In lines 491-494, it is recommended that if the drug is to be used in pregnant women, reproductive toxicology studies in which the effect of maternal drug exposure on lymphoid system histopathology and hematology in the F1 generation offspring should be included in the terminal examination. Justification and examples needs to be provided to support this recommendation.

It is stated that the PLNA and specific biomarker assays might provide insight into potential autoimmune mechanisms (lines 528-530; Attachment 2). However, it is stated in lines 444-446 that the PLNA may have promise, but no extensive evaluation has been reported that would support any recommendation for drug development. In addition, the term "specific biomarker assays" needs to be explained. If this is meant to be markers of T-cell activation and effects of

a drug on markers of TH2 cell induction (line 448-449), more information and justification for these markers needs to be included. Since the PLNA and biomarkers of T-cell activation are not validated methods to assess for potential autoimmunity induction, these assays should not be recommended.

The guidelines recommend that if a compound is found to be tumorigenic in rodent bioassays and is suspected of being immunosuppressive (unintended), follow-up tumor host-resistance studies should be considered. It is stated that these host resistance studies are appropriate for determining carcinogenic immunosuppressive potential. Studies which have demonstrated the usefulness of host-resistance assays to determine if immunosuppression results in increased tumorigenesis and to provide value to the risk assessment process have not been reported. Additional support for this recommendation is needed.

References:

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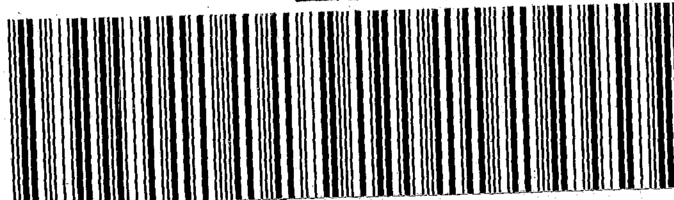

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