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August 6, 2001

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

Re: Docket No. 01D-0177; Draft Guidance on Immunotoxicology Evaluation of Investigational New Drugs, *Reference to 65 Federal Register 175 (April 10, 2001)*

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, nutritionals, and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurologic disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventative agents, with a focus on 10 therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 2000, pharmaceutical research and development spending totaled $1.8 billion.

For these reasons, we are very interested in and well qualified to comment on this FDA Draft Guidance on Immunotoxicology Evaluation of Investigation New Drugs that was published in the Federal Register on 10 April, 2001. We begin with general comments followed by more specific concerns with the proposal.

General Comments

With this guidance, the FDA is proposing that all investigational new drugs be evaluated for effects on the immune system with further provisions where additional nonclinical testing may be necessary. We agree that the evaluation criteria presently included in standard repeat-dose toxicology studies are generally sufficient to assess potential effects on the immune system. The design of these studies can often accommodate inclusion of additional specific immunologic tests on a case-by-case basis driven by scientific need or risk/benefit for the class of drug. However, on occasion more specific studies may sometimes be needed to evaluate potential functional effects or mechanism(s) of immunotoxicity.

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Nevertheless, we are concerned that the proposed guidance does not factor in 1) the inability of the assays to be able to distinguish a biologically significant effect and 2) the lack of validation of the assays with respect to human prediction. Overall, we are concerned that the development of important pharmaceuticals may be curtailed on the basis of immunologic changes observed in nonclinical testing that either can not be interpreted in the species tested or have no relevance to humans.

We give as an example Videx ®(didanosine), which has been shown to clearly improve the immunologic function and survivability of patients infected with HIV. Immunologic testing in normal mice showed a 90% reduction in the ability of the animals to respond to a T-cell dependent antigen, which the authors interpreted as a profound effect (Phillips et al., 1997). Nevertheless, this effect did not prove relevant to the intended human population. In fact, it was not even predictive of any significant adverse effect in the species tested. In a 2-year carcinogenicity study in rats, female animals given the same dose that produced the "profound" effect actually had a significant increase in their lifespan (SBA Videx, 1991).

Of additional concern is the present state of our knowledge with respect to hypersensitivity and autoimmune disease. Nonclinical testing in animals to support clinical trials and retrospective testing completed following observation of these events in humans have not provided any meaningful predictive models. Thus, while we support the agency's efforts to provide guidance in this area, we strongly believe that the guidance should be scientifically driven and should recommend only valid predictive animal models.

Specific Comments

We strongly agree with the FDA that changes in immune parameters need to be biologically significant and not just statistically significant to trigger follow-up studies, and that a dose response relationship is important (lines 50-60). However, with our present state of knowledge, it is often not possible to discern the degree of change that would be biologically significant. As you are aware, the immune system has great reserve and redundancy and can often compensate when only one component is affected. Thus, a very large change in a parameter may be required to affect host resistance. We therefore recommend that the uncertainty of what may be considered biologically significant be emphasized in the guidance.

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 (lines 70-76). However, it is inherent to the purpose of toxicology studies to produce significant toxicity, which itself can be a source of stress to the animal, and it is often difficult or impossible to distinguish a direct immunologic effect of the drug at doses that might induce stress-related immunologic changes. Thus, we believe the agency should discuss the importance of studying the potential for immunotoxic effects at doses that do not produce overt toxicity.

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 GLP-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 143-150).

Although immune cell phenotyping can be readily incorporated into repeat-dose toxicity studies in rodents and non-human primates, it is not as easily incorporated into dog studies due to limited availability of reagents (lines 168-170). If peripheral blood phenotyping is incorporated, it should not be necessary to include splenic phenotyping as well. Since peripheral blood phenotyping would be used to monitor for adverse events in the clinic, it makes sense to use it when practical.

We do not agree that the assessment of antibody titer by ELISA is not a true test of immune function (lines 202-204), and we recommend that this definition be modified. The ELISA measures a different endpoint of the same 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. We do agree that either assay should be acceptable (lines 199-202). In fact, the ELISA method adds a number of advantages since time course can be followed and recovery assessed within the same animals by using a different antigen.

It is unclear whether a study of the F1 offspring should be considered every time a drug could be used in pregnant women, or if it should be considered specifically for drugs that would be prescribed for a condition linked to the pregnancy (lines 217-222 and 491-494). It is also not clear at what age the F1 generation should be evaluated. We recommend that these sections be clarified. Furthermore, although this paragraph is under the section of "Immune Function Studies," the parameters the agency recommends to be evaluated are not immune function parameters. We suggest moving this under a different heading to avoid confusion.

We agree that in some situations, such as for drugs intended for use in an immunocompromised population, more thorough testing of immune function should be needed (lines 224-228). However, it is important that data generated from immune function studies do not trigger termination of the drug's development, but rather serve as guidance for parameters/biomarkers that could be monitored in human trials. Wording to this effect should be added.

This guidance states, "Under certain circumstances, attempts should be made to determine the potential antigenicity of large molecular weight drugs" (line 257). Should that read "small" rather than "large"? In our experience, large molecular weight drugs are usually antigenic. Thus, large molecular weight drugs should be routinely monitored for antigenicity. This section is unclear and should be clarified.

This guidance states, "Assays to identify anti-drug immune responses should be considered part of nonclinical assessment, because peptides, polymer, and protein drugs and classes are known to be potentially haptenic" (lines 265-267). This sentence is confusing and needs to be reworded. The potential of a drug to be haptenic does not on its own warrant the need for the

evaluation of anti-drug antibody responses in standard toxicology assays (lines 257-259 and 488-490). There are a number of drugs on the market that are known to produce reactive intermediates that bind to macromolecules but are associated only with a very low incidence of clinical hypersensitivity reactions. The decision to evaluate an anti-drug antibody response should be based on findings observed in the study or earlier studies suggesting that an antibody response to drug may have occurred. In contrast to lines 257-259 and 488-490, lines 407-412 indicate that anti-drug antibody responses should be conducted if the test compound belongs 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 antibody 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 antibody response may be attributed to the amount of reactive intermediate generated, how quickly it is inactivated, and the immunogenicity of the hapten-protein conjugate. Additionally, it is important to emphasize that a positive response in an anti-drug antibody assay is likely to be a true positive, but that a negative response may be a false negative due to the lack of the appropriate antigen (e.g., in an ELISA, the coating antigen is drug conjugated to an irrelevant protein which may not mimic the antigen *in vivo*) and that the presence of the drug may interfere with the assay. These assays are also resource intensive to develop and require the generation of a positive control for validation. For these reasons, we believe that evaluating anti-drug antibody responses in routine toxicity studies will not be helpful, and recommend that the guidance specify that anti-drug antibody responses be conducted only when warranted by specific findings suggesting an anti-drug antibody response might have occurred. Studies that 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 antigenicity (lines 409-412) should not be recommended at this time.

The lymphocyte blastogenesis assays have been shown to be poorly informative, even in allergic patients, and therefore are generally not used by physicians for drug allergy diagnosis (lines 265-269). Thus, we suggest deletion of lymphocyte blastogenesis from the sentence.

VI. Hypersensitivity

Small molecular weight compounds can 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 pathologic reaction. We suggest changing "allergenic" to "antigenic" in line 282.

We suggest that you add that the type of hypersensitivity reaction can also depend on genetic background (lines 283-287).

We agree that the active systemic anaphylaxis and passive cutaneous anaphylaxis assays add little predictive or mechanistic value and should not be conducted on a routine basis (lines 293-300).

We agree that all dermal drugs should be routinely tested for the potential for dermal sensitization, since validated and predictive assays are available (367-398 and 481-484). We do not believe that sufficient data are available to justify using contact sensitization assays to screen for respiratory sensitization potential of inhaled drugs (lines 311-326 and 478-484). These data should be referenced, if available. The mouse IgE test has not been adequately validated for the detection of respiratory sensitizers and should not be recommended at this time. It is recommended that the guinea pig method of Karol (1995), which involves dermal or inhalation induction followed by inhalation challenge, be used for inhalation drugs (lines 321-326). Since the model of Karol 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 chemicals described by Sarlo and Clark (1992) should be considered, although they should be validated for pharmaceutics prior to more routine use.

BMS appreciates the opportunity to provide comments and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

Peter L Sibley

Peter L. Sibley, Ph.D.
Vice President, Drug Safety Evaluation
and Veterinary Sciences

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Summary Basis of Approval for Videx (didanosine) NDA, October 9, 1991.

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