



sanofi aventis

Because health matters

April 11, 2005

Via fax and UPS

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

Re: Docket No. 2005D-0022

ICH; Draft Guidance on S8 Immunotoxicity Studies for Human Pharmaceuticals

Dear Sir/Madam:

Sanofi-Synthelabo Inc. and Aventis Pharmaceuticals, members of the sanofi-aventis Group, appreciates the opportunity to comment on the above-referenced Draft Guidance entitled "*S8 Immunotoxicity Studies for Human Pharmaceuticals*".

This draft guidance describes a weight-of-evidence approach to determining whether additional immunotoxicity testing for nonbiological pharmaceuticals is appropriate when the findings from standard toxicity studies indicate signs of immunotoxicity.

We have evaluated the content of the draft guidance and offer the following comments and/or clarifications for your consideration.

GENERAL COMMENTS

We are concerned that the document only deals with an evaluation of immunosuppression and fails to consider adequately that environmental chemicals and some drugs have been observed to enhance or stimulate the immune response that may also have as important consequences as immunosuppression. Beyond the introduction, nothing is discussed about evaluating for immune enhancement. Since similar methods proposed for detecting immunosuppression can be used to detect immune stimulation this should also be considered in the document and this should not be confused with drug allergy/hypersensitivity that is not discussed.

It is also not clear why this document does not propose a more rigorous approach to the potential of new chemical entities (NCEs) to alter the immune system. Unfortunately, this document significantly dilutes the approach proposed in the previous published US FDA and EMEA immunotoxicology guidelines for pharmaceuticals. Although the US and European approaches were somewhat different they went much further to protect public health than this current very diluted ICH approach. It appears that there are sufficient caveats provided so that one might never test a compound for a direct effect in an immune function test.

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Also, the document fails to adequately address the increased vulnerability of the developing immune system in children.

An additional concern is that the document, through failure to reference the extensive literature published over the past 25 years detailing the suppressive effect of some environmental chemicals and drugs on the immune system of animals, inappropriately creates the impression that the only drugs found to be immunosuppressive have been anticancer agents.

It appears that this attempt to harmonize the US and European guidelines has in fact produced an approach to assessing the potential immunotoxicity of NCEs that is less stringent and may potentially allow the potential adverse effects of NCEs on the immune system to go undetected.

SPECIFIC COMMENTS:

1. Introduction

Lines 63-64: *“These include suppression or enhancement of the immune response.”*

We suggest adding hypersensitivity (drug allergy) to this sentence so that it is consistent with Lines 68 and 71: *“These include suppression or enhancement of the immune response as well as drug hypersensitivity (drug allergy).”*

1.1 Objectives of the Guideline (Line 73)

1.3 Scope of the Guideline (Line 101)

These sections only focus on immune suppression and do not deal with enhancement. Likewise, there is some redundancy between the content of these two sections and it is suggested to combine this into a single section.

Lines 102-103: *“This guideline is focused on providing recommendations on nonclinical testing for immunosuppression induced by low molecular weight drugs (non-biologicals).”*

Additional clarification is requested as to why this refers to “low molecular weight drugs (non-biological)” rather than “new chemical entities (NCEs)”.

Lines 109-111: *“The term immunotoxicity in this guideline will primarily refer to immunosuppression, i.e. a state of increased susceptibility to infections or the development of tumors.”*

This implies that increased tumor development is as an indicator of immunotoxicity which is an over simplification. Although it is recognized that immune surveillance plays a role in development for some tumor types, increased tumor development in the absence of genotoxicity alone does not necessarily indicate immunosuppression and should not mandate functional immunotoxicity testing.

Secondly, tumors are rarely observed in chronic toxicology studies other than in carcinogenicity studies that are done late in development so this end point would only trigger an immunotoxicology study after significant patient exposure.

2.1.1 Standard Toxicology Studies

Lines 148-150: *“(1) Hematological changes - Evidence of myelosuppression, usually seen in peripheral blood changes (e.g. pancytopenia, leukopenia, lymphopenia, or other blood dyscrasias);”*

We suggest deleting "pancytopenia and other blood dyscrasias" so that it is consistent with Section 1 in Appendix 1.

Line 158: *“(5) Evidence of carcinogenicity, especially in the absence of genotoxicity.”*

Same concern as above regarding positive carcinogenicity test results in the absence of genotoxicity as evidence of immunosuppression. There can be many other explanations in the absence of genotoxicity mandating functional immunotoxicity testing.

Lines 160-175: *“If the findings from the STS indicate that there are signs of immunotoxicity, the decision to conduct additional immunotoxicity testing should be considered in a weight-of-evidence review of the data. Similar to the assessment of risk with toxicities in other organ systems, the assessment of immunotoxicity should include the following: ...*

- *study duration, ...*

We suggest changing "study duration" to "treatment duration".

2.1.2. Other Causes for Concern in the Weight-of-Evidence Review (Line 177)

We suggest deleting "Other" in the title and moving the title to Line 159 since everything from Lines 160 to 206 relates to the weight of evidence review.

Lines 189-191: *“The decision to conduct additional immunotoxicity studies should be based on a weight of evidence approach.”*

We suggest deleting this sentence as it does not give any further information.

Lines 193-195: *“(2) The targeted patient population should also be considered. For instance, additional immunotoxicity testing might be needed if the majority of the targeted patient population is immunocompromised.”*

We suggest adding a “pediatric population” in addition to the immunocompromised population.

Lines 200-202: *“(4) If the compound and/or its metabolites are known to be retained at high concentrations in cells of the immune system, additional immunotoxicity testing should be considered.”*

We request clarification on the definition for high concentrations and method of assessment.

2.2.2 Study Design

Lines 227-228: *“It is a generally accepted study design to assess drug-induced immunosuppression in studies with 28 consecutive daily oral doses in mice or rats.”*

This sentence is not clear. We suggest revising the sentence to read: *“A 28-day study, in mice or rats, with consecutive daily oral doses is generally accepted as an appropriate design to assess drug-induced immunosuppression.”*

Lines 231-232: *“The high dose should be above the no observed adverse effect level (NOAEL) but below a level inducing changes secondary to stress.”*

We suggest revising the sentence to read: *The high dose should be above the no observed adverse effect level (NOAEL), a multiple of the proposed therapeutic dose, but below a level inducing changes secondary to significant stress.*

We recommend inserting “significant” in front of “stress” as this stress effect on immune suppression is over played and not well documented in the literature; most experienced toxicologists have observed numerous toxicology studies where stress was observed without evidence of immune suppression.

Lines 234-236: *“Adaptations of immune function assays developed in rodents have been described using non-rodent species. Under most circumstances, immunological test methods can be appropriately modified for these other species.”*

We request further clarification of these two sentences and to add some literature references. Additionally, we suggest changing “most” to “some” circumstances.

Appendix 1

1.2 Gross Pathology and Organ Weights

Lines 294-296: *“Spleen and thymus weights should be recorded. To minimize variability of spleen weights in dogs and monkeys, bleeding the animals thoroughly at necropsy is recommended.”*

Canine spleen weight is highly variable depending upon completeness of exsanguination. This is recognized in the text in Line 296. Practical experience suggests that complete exsanguination is difficult to achieve in a reproducible fashion. The value of spleen weights for dogs in toxicology testing is questionable and therefore should not be mandated.

1.3 Histopathological Examination

Lines 311-313: *“It is recommended that a “semi-quantitative” description of changes in compartments of lymphoid tissues should be used in recording changes and reporting treatment-related changes in lymphoid tissues.”*

We suggest revising the sentence to read as follows since the “semi-quantitative” compartment approach is not universally accepted and not clear: *“It is recommended that a detailed description of changes in lymphoid tissues should be made for any treatment related change.”*

In addition, why was an enhanced histopathology evaluation using specific lymphoid subpopulations histochemical stains not recommended? With the current lymphoid cell histochemical biomarkers available to evaluate lymphoid tissues compartments, lack of emphasis on histopathological studies in most species would seem a gross oversight. Furthermore, reference is not made to using histochemical staining.

1.4 Interpretation of Stress Related Changes

Lines 317-322: *“These effects on the immune system are most likely mediated by increased corticosterone or cortisol release. Commonly observed stress-related immune changes include increases in circulating neutrophils, decreases in circulating lymphocytes, decreases in thymus weight, decreases in thymic cortical cellularity and associated histopathologic changes (“starry sky” appearance), and changes in spleen and lymph node cellularity.”*

We recommend that references should be included for these stress related changes and the amount of stress required to produce these changes should be described. Additionally, we suggest deleting “starry sky” appearance because it is only one of the many changes that can be observed.

2.2 T-cell Dependent Antibody Response (TDAR)

Lines 355-357: *“With outbred rats, there can be significant variability among rats within the same group. Inbred rat strains should not be used unless sufficient exposure data are provided.”*

Additional clarification is requested since justification for using outbred versus inbred rats is not supplied and outbred animals are most frequently used in drug safety evaluation.

The TDAR can also be used to measure immune stimulation and this should be mentioned in this section.

2.3 Immunophenotyping (Line 373)

It should be recognized that there is not good agreement among clinical immunologists concerning the sensitivity or predictive value of immunophenotyping for detecting subtle immune function effects. Immunohistochemical staining should also be mentioned in the histopathology section as previously discussed.

2.4 Natural Killer Cell Activity Assays (Line 398)

We recommend that the effect of drugs on Natural Killer Cell activity and the implication of this finding should be documented before this method is recommended.

On behalf of the sanofi-aventis Group, we appreciate the opportunity to comment on the *Draft Guidance on S8 Immunotoxicity Studies for Human Pharmaceuticals* and are much obliged for your consideration.

Sincerely,



Steve Caffé, M.D.

Vice President, Head US Regulatory Affairs