AstraZeneca

Dockets Managements Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

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Dear Sir or Madam:

Re: Docket No. 01D-0177: AstraZeneca Comments on FDA's Draft Guidance entitled: "Guidance for Industry: Immunotoxicology Evaluation of Investigational New Drugs"

AstraZeneca Pharmaceuticals LP (AstraZeneca) respectfully submits the following comments on the above-referenced draft guidance document published in the May 11, 2001 Federal Register:

General Comments:

AstraZeneca believes the draft guidance is a useful document that has the potential to assist sponsors in navigating the rapidly expanding sub-discipline of immunotoxicology when potential signals are detected in general toxicology studies. However, validated assays to detect immunotoxicity are few, beyond those that are now routinely employed, such as blood cell counts and bone marrow histopathology. Accordingly, this guidance may be premature and any changes to the studies required for approval of an NDA should not be implemented until the scientific community validates the assay.

The timing of the testing requirements relative to the stage of IND development is unclear. Will these studies need to be conducted in a particular stage of development (Phase 1, 2 or 3), or are they only required to be completed prior to NDA submission? Similarly, clarification is requested with respect to studies that are required and studies that are only recommended or suggested.

Specific Comments:

Section IV: IMMUNOSUPPRESSION

Page 3, Line 109 and page 4, Line 134: Serum immunoglobulin

Serum immunoglobulin is not normally included in the standard battery during a routine toxicology study. Since such a test is regarded as insensitive, why should it be added to the standard battery of tests? Conversely, if a routine toxicology test indicated that there might be an immunotoxic effect of the test compound, the serum immunoglobulins should be included in a general follow-up assessment on the effects of the compound on the immune system.

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Page 4, Line 149: "This mechanism of immunosuppression, however, is rarely observed in standard nonclinical toxicology studies."

AstraZeneca is not clear as to what one should conclude from this statement. We suggest that this statement be clarified to indicate that this is more of a follow-up or mechanistic type of study that is not required in routine testing.

Page 4, Line 152: "The timing of the onset of any dyscrasia should be carefully evaluated."

AstraZeneca recommends revising the line to read, "The timing of the onset of any blood dyscrasia should be carefully evaluated."

Page 4, Line 160: "B. Immune Cell Phenotyping"

AstraZeneca recommends revising the Section B title to read, "Follow-up Studies to Determine Potential Mechanisms of Immunosuppression."

Page 4, Line 164: "... modifications to trial entry criteria or guide the management of adverse symptoms."

AstraZeneca recommends revising the line to read, "... modifications to trial entry criteria or guide the detection and management of adverse symptoms."

Page 5, Line 167 – 168: "... cell surface phenotype determinations should be made on splenocytes obtained at necropsy ..."

This appears to be a departure from the current standard using blood. The use of spleen cells will also require dedicated groups of animals. Methods using peripheral blood should therefore be encouraged when appropriate.

Page 5, Line 194 - 195: "For example, if decreases in total lymphocytes or specific T-cells (e.g., CD4 cells) ..."

While changes in total lymphocytes or increased infections may have been observed in routine toxicology studies, it is unlikely that changes in specific T-cells (e.g., CD4 cells) would have been monitored, therefore, AstraZeneca recommends deleting this example from the statement.

Page 5, Line 199 – 201: "However, there is aversion in which the assay is integrated into standard nonclinical toxicology studies. Animals in the study are immunized with an antigen (e.g., SRBC, tetanus toxoid) …"

Unless there was a very compelling reason, the conduct of a standard toxicology study should not be compromised by immunizing the animals with such an antigen. AstraZeneca believes that this type of test (i.e., immunization with antigen) should be reserved for follow-up or mechanistic studies.

Page 6, Line 222: "… in the F_1 generation offspring…"

Literally, the F_1 generation offspring would be the F_2 generation. Was this line intended to read "… in the F_0 generation offspring…"

Section V: ANTIGENICITY

Page 6, Line 238: "… immunogen (e.g., high dose tolerance) can …"

Please clarify "high dose tolerance" in the text, since the guidance is meant to be a stand-alone document.

Page 7, Line 264:

AstraZeneca recommends adding a subheading entitled "Detection of Antigenicity" to the last paragraph before Section VI.

Page 7, Line 265: "Assays to identify anti-drug immune responses…"

AstraZeneca recommends revising the line to read, "Assays to identify specific anti-drug immune responses…"

Page 7, Line 266: "… should be considered part of nonclinical safety assessment, because peptide, …"

AstraZeneca recommends revising to read, "… should be considered part of nonclincial safety assessment, for peptide, …"

Page 7, Line 269: "Immunoassays for specific cell-mediated immunity should also be considered."

AstraZeneca recommends removing this sentence, because the lymphocyte blastogenesis assay mentioned on Page 7, Line 265 is designed to detect such specific cell-mediated immunity.

Section VI: HYPERSENSITIVITY (DRUG ALLERGY)

Page 7, Line 282: "Small molecular weight drugs are allergenic…"

AstraZeneca recommends revising this line to read, "Small molecular weight drugs might be allergenic…"

Page 7, Lines 283 – 287:

AstraZeneca recommends that the discussion about what allergy type is induced be divided as follows:

1. The potential of a drug to induce allergy: e.g., a single dose is more unlikely to produce a hypersensitivity reaction than repeated dosing and

2. Allergy type induced: The degree of antigenicity or the dosing regimen has nothing to do with e.g., a type I or type IV reaction being induced, however, the route of administration affects this parameter.

Page 7, Line 289: "A. Type I"

AstraZeneca recommends revising the line to read, "A. Prediction of Type I Hypersensitivity".

Page 8, Lines 325 – 326:

Lines 325 – 326 indicate that, "Drugs intended for inhalation should be tested for their sensitizing potential". However, Line 293 states: "Two tests for anaphylactic reactions are commonly used: passive cutaneous anaphylaxis (PCA) and active systemic anaphylaxis (ASA)". Neither the PCA nor ASA is generally considered an essential test for safety assessment of drugs. They are also not useful for exploring the mechanisms of hypersensitivity. Perhaps this section could be reorganized to put the most important points up front and the less significant ones last.

Page 8, Line 328: "B. Type II & III"

AstraZeneca recommends revising the line to read, "B. Prediction of Type II & III Hypersensitivity".

Page 8, Line 329:

A sentence recommending when to perform these tests or not should be included. A suggestion is to move Lines 341 – 352 (Page 9) to this location.

Page 9, Lines 337 – 339: "Type II and III immunopathies appear to be only rarely modeled in animals and signs of these immunopathies are most commonly indicative of direct, nonimmune-mediated drug toxicity."

AstraZeneca requests clarification of this statement and examples.

Page 9, Line 365: "C. Type IV"

AstraZeneca recommends revising the line to read, "C. Prediction of Type IV Hypersensitivity".

Page 10, Line 418 – 419: "This reaction is likely to be dose-related."

The mechanism of action of these reactions is that they are threshold phenomena and thus are likely to be all-or-none type reactions (not dose response). Further, in AstraZeneca's experience, these reactions often demonstrate tachyphylaxis. As tachyphylaxis can make the study of these reactions problematic, it should be mentioned here.

Page 11, Line 437: "… complement activation, or stimulation of target function".

Please clarify the expression "stimulation of target function".

Page 11, Line 441:

AstraZeneca recommends including the header, "Prediction of Autoimmunity". It should be stressed that FDA does not require predictive studies for assessment of autoimmunity.

Page 11, Line 461:

AstraZeneca recommends including the header, "Prediction of Adverse Immunostimulation." It should be stressed that FDA does not require predictive studies for assessment of adverse immunostimulation.

Page 13, Lines 504 – 505: "… the final consideration is whether the drug is intended for the treatment of HIV infection or a related immune disease."

In addition to HIV drugs, any drug designed as an immunomodulator, either stimulatory or suppressive, should be tested for immune functions and extended phenotyping. This should also be emphasized in the flow chart Attachment 1.

Page 13, Line 532: "the final indication of whether to undertake additional immunotoxicity testing is tumorigenicity."

Currently, in the presence of a positive two-year bioassay, initiator or promotor transgenic assays are done. Is FDA recommending that tumor host resistance models be added?

Page 14, Line 567 and Page 21, Attachment 1: "...(2) use during pregnancy..."

Excepting drugs restricted to men, postmenopausal women and possibly children, virtually all drugs are likely to be used in women of childbearing age (possibly pregnant). Thus, this trigger is virtually automatic, meaning that one must "consider lymphoid system assessments in F1 offspring" for virtually all drugs. Although no specific recommendations is made, it can be assumed that such assessments be made in young animals. Such requirement would be difficult to carry out, as these studies would have to be done in small animals with limited amounts of available tissue.

Page 21, Attachment 1:

Asthma is a disease that involves an allergic response in the acute phase, hence making the treatment of asthma an immunomodulatory attempt. Some treatments are known immunosuppressants. Using the flow chart (Page 21), it is unclear how these types of compounds fit in. Do we still have to consider its sensitization potential? Other asthma drugs modify cytokines; where would they fall in the flow chart? Should there be exceptions in the flow chart?

We hope these comments are helpful in assisting FDA in finalizing the draft guidance. If you have any questions regarding this correspondence, please contact Mr. Barry Sickels at (302) 886-5895 or Ms. Tara Chapman at (610) 695-1616.

Sincerely,

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AFR/BDS/djr
Enclosures