Final Concept Paper
S8: Immunotoxicology Studies for Human Pharmaceuticals
Dated and endorsed by the Steering Committee on 11 November 2003

Type of Harmonisation Action Proposed

A harmonised guideline on nonclinical assessment for unintended immunosuppression is to be published. The scope of this guideline is restricted to conventional pharmaceuticals and will exclude biological/biotechnological products.

Statement of the Perceived Problems

The evaluation methods of immunotoxicological assessment have been independently discussed in Europe, the USA and Japan, and different guidelines have been issued.

According to the European (CPMP) guidance, all new chemical entities applied for marketing authorization should be screened for immunotoxic potential by distribution of lymphocyte subsets and NK-cell activity or the primary antibody response to a T-cell dependent antigen in addition to the standard toxicological parameters. The CDER/FDA guidance states that when warranted by observations in nonclinical general toxicology studies, additional studies to determine potential drug effects on immune function should be considered. The Japanese MHLW draft guidance indicates that when an abnormal finding is observed in repeated dose toxicity study, the antibody response should be examined before phase 1 studies.

There are significant differences between the guidelines of each region. Even when no toxicological findings suggestive of immunotoxicity are observed in the repeated dose toxicity study, distribution of lymphocyte subsets and NK cell activity, or the primary response to a T cell dependent antigen should be examined according to CPMP guidelines. In contrast, the CDER/FDA and draft MHLW guidances recommend immune function testing only in certain situations. This inconsistency between guidelines complicates mutual acceptance of immunotoxicological data among the regions and countries contrary to the goal of ICH.

Issues to be Resolved

1) Necessity of immune function testing on a routine-basis versus a cause for concern basis
2) Defining cause for concern
3) Appropriate conduct of immune function assays
4) Timing of conduct of the immune function assays with respect to clinical studies

Background to the Proposal

The CPMP first published a revised note for guidance on repeated-dose toxicity which included a guidance on immunotoxicity in July, 2000. Meanwhile, the CDER/FDA published their guidance in October 2002. Finally, MHLW published a draft guideline in March 2003.

An ICH informal expert working group meeting was held in Brussels on February 7, 2002,

which concluded that the guidelines should be harmonised after collecting and analyzing additional immunotoxicity data. As a result, the "ICH Survey on Immunotoxicity Data for Development of the Harmonised Guideline of Immunotoxicity Study of Pharmaceuticals" was conducted to collect immunotoxicity data from pharmaceutical companies in the three regions. The aim of the survey is to clarify the additional value of immune function assays in nonclinical studies and their clinical relevance. The first analysis group meeting was held in London on October 8 and 9, 2003. The information provided by the survey was considered to be useful to scientifically support the process of harmonisation. The Informal Expert Working Group identified areas where further information is needed.

Type of Expert Working Group

We recommend the establishment of an Expert Working Group (EWG) which includes representatives/experts of the six ICH parties and observers on request.

Parties Making the Proposal

All parties of the informal EWG propose immunotoxicity (unintended immunosuppression) as a new topic for harmonisation.

Business plan

- **Added value of harmonised guideline**
  The most stringent published guideline requires a routine testing approach. Results of the current survey indicate a basis for harmonisation on a cause for concern approach. A cause for concern approach will reduce the number of animals used during drug development.
- **Timetable**
  - Formation of the EWG: Nov. 2003
  - Start to write guideline: Nov. 2003
  - Completion of a sufficient data set: June 2004
  - Step 2 document: Nov. 2004
  - Step 4 document: Nov. 2005
- **Working process**

To facilitate an efficient exchange of information, e-mail and teleconference will be used to minimize the need for face-to-face meetings.