Final Concept Paper
S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
Dated and endorsed by the Steering Committee on 26 October 1994

This concept paper proposes that ICH develops a point to consider document safety testing of biotechnology products. The position statement is expected to be presented and discussed at ICH 3 Yokohama in November 1995. The position statement is not intended to be a guideline for harmonisation in ICH.

Problem Statement

1. Biotechnology product categories include hormones, cytokines and similar factors, blood products, monoclonal antibodies and vaccines. Each of these product categories have evolved and expanded recently as a result of world-wide scientific advances. Many advances have been directed towards decreasing immunogenicity through pegylation, encapsulation, and humanisation. While many biotechnology products were initially approved for either replacement therapy or acute therapy in life-threatening diseases, an increasing number are now being proposed for chronic therapy.
2. Because of the rapid growth in biotechnology science, the amount of safety data for certain products, such as pharmaceuticals produced in transgenic animals, cellular and gene therapies, and/or tissue engineering, is uncertain. Specific unresolved issues in safety assessment of biotechnology products include the use of animal models of disease, when genotoxicity assays and carcinogenicity studies should be performed, and the impact of antibody formation on duration of toxicology studies. Additional issues for consideration include the necessity for the routine use of two species, definition of a relevant species (for example the determination of relative receptor affinity and cell sensitivities between the test species and humans), use of homologous proteins in short term repeated dose toxicity studies and in specialised studies, such as reproductive toxicology studies, and longer term studies. The requirement for additional toxicology studies in the presence of certain manufacturing process changes also requires discussion.

Proposals for Resolving the Problem

In planning for ICH 1 in Brussels in 1991, members of the Safety Expert Working Group concluded that development of ICH guidelines for safety testing of biotechnology products, corresponding to guidelines for safety testing of traditional pharmaceuticals, was premature. These members believed, however, that the topic of safety testing of biotechnology products merited discussion, and one hour was allotted in the ICH 1 program for this purpose. Based on this discussion, attendees agreed that regulatory requirements were generally comparable in the three ICH regions and, further, that a flexible, case-by-case approach should be utilised to determine safety studies of biotechnology products. Despite support for a case-by-case approach, discussants at ICH 1 also noted that this approach might lead to different expectations for application requirements between regulatory and industrial scientists. To avoid this possibility, members of the Safety Expert Working Group at ICH 1 agreed that guiding principles for safety testing of biotechnology products should be revisited on a continuing basis. This concept paper, proposing that the ICH Steering Committee endorse the preparation of a position statement on this topic for discussion at ICH 3, reflects this agreement.

Impact

Given that no guideline is expected from the effort and no changes in regulatory laws and/or regulations will be required, the regulatory impact of the position statement on application requirements is expected to be modest. Benefit will accrue from a public discussion of the rapidly evolving science of safety testing of biotechnology products and a review of current regulatory data and practices for this testing.

Regulatory Changes Needed

No changes in laws, regulations, or current guidelines in Japan, European Union, or the United States are expected to arise from the position statement on biotechnology safety proposed in this concept paper.

Time frame

1. A full meeting of an Safety Expert Working Group is proposed to occur in March 1995 in Washington DC. This group will develop the initial draft of a point to consider document for presentation and discussion at ICH 3 in Yokohama in November 1995

2. Depending on the progress made in March 1995, the Safety Expert Working Group may request an additional meeting to occur between March 1995 and prior to ICH 3 in November 1995.

3. The points to consider document is expected to provide information to both industry and regulatory agencies in the preclinical safety assessment of biotechnology products.

Expert Group

Certain members of this group participated in ICH 1 discussion of biotechnology safety, and the efforts of these contributors should be continued. Other current members of the Safety Expert Working Group will be encouraged to participate. Additional experts may be required, and if this is determined to be the case, requests will be made of the six parties to ICH subject to approval of the ICH Steering Committee.

ADDENDUM: The group discussed and agreed to a proposed informal meeting of the regulators on this proposed topic possibly in Europe in January before the meeting in March.

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