BIOTECHNOLOGY
INDUSTRY
ORGANIZATION

**1225 Eye Street NW, Ste. 400**
**Washington, DC 20005**

April 26th, 2005

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 2005D-0004, Federal Register: January 26th, 2005 (Volume 70, Pages 3714-3715)

Dear Sir/Madam:

The following comments are provided by the Biotechnology Industry Organization (BIO). BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 U.S. states and 33 other nations. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products. BIO appreciates the opportunity to comment on the Food and Drug Administration's (FDA's, the Agency's) Draft Guidance on Nonclinical Safety Evaluation of Drug Combinations. The following comments were developed by members of BIO's Preclinical Safety Expert Working Group (BioSafe).

Comment: As written, the FDA Draft Guidance for Industry: Nonclinical Safety Evaluation of Drug Combinations, is largely not applicable to biological products (monoclonal antibodies, cytokines, fusion proteins, etc) in combination with other large molecules or in combination(s) with small molecules. The majority of issues raised in the Draft Guidance are specific for small molecules, for example genotoxicity, metabolism, and drug-drug interactions. In addition, several of the suggested study designs would often not be appropriate for biological products. First, biological products are not metabolized in the same manner as small molecules, and secondly they require testing in species that may not be relevant. Preclinical studies for biological products in animal models of disease, in toxicology evaluations, and in developmental toxicity evaluations all require relevant species, and these species are typically not the same as those used in preclinical studies of small molecules (i.e. rat, rabbit and dog vs. non-human primate). In instances where relevant species are similar, potential interaction studies would be handled on a case-by-case basis as defined in the ICH S6 guidance rather than by defaulting to a decision tree format. For instance, the length of studies may be compromised by an immunological Ab (anti-human) response and appropriate studies would need to be defined based on very specific criteria for each biological product in a combination. Combinations of biological products or combinations of biological products with small molecules may be subject to potential interactions, such as molecules interacting with the same molecular target or those with overlapping biological activity. Because of the complexity of the dynamics of each molecule, individualized preclinical evaluations would still be required rather than a decision tree approach.

Comment: Since oncology drugs will be the subject of a separate document, combinations of these with biological products were not considered in this response.

Recommendation: BIO recommends that the Final Guidance refer to ICH S6 as a reference for biological products. In addition, we request that the Final Guidance contain detailed language and instructions that differentiate biological products from small molecules, and stress a case-by-case approach. If ICH S6 is considered to be incomplete in offering guidance, then a specific addendum may be considered.

In conclusion, BIO appreciates this opportunity to comment on FDA's Draft Guidance on Nonclinical Safety Evaluation of Drug Combinations. We look forward to seeing the Final Guidance, and would be glad to provide the Agency with further input or clarification of our comments.

Sincerely,

Sara Radcliffe

Sara Radcliffe
Managing Director
Science and Regulatory Affairs