

In a number of cases there were findings observed by 12 months, but not by 6 months. It was concluded that these would, or could, have been detected in a study of 9 months duration. Varying degrees of concern for the differences in findings detected between the studies of different durations were expressed. An agreement on the clinical relevance of these findings could not be reached.

Studies of 12 months duration are usually not necessary and studies of shorter than 9 months duration may be sufficient.

In the European Union, studies of 6 months duration in nonrodents are acceptable according to Council Directive 75/318/EEC, as amended. To avoid duplication, where studies with a longer duration have been conducted, it would not be necessary to conduct a study of 6 months.

Guidance on duration of chronic toxicity testing for tripartite development plan:

Arising from the extensive analysis and review of the above mentioned data in nonrodents and based upon the achievements of ICH 1 for testing in rodents, and so as to avoid duplication and to follow a single development plan for chronic toxicity testing of new medicinal products, the following studies are considered acceptable for submission in the three regions:

- (1) *Rodents*: a study of 6 months duration;
- (2) *Nonrodents*: a study of 9 months duration.

Dated: November 12, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 97-30273 Filed 11-17-97; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97D-0113]

International Conference on Harmonisation; Guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a guidance entitled "S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals." The guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guidance is intended to provide general principles for designing scientifically acceptable preclinical

safety evaluation programs for biopharmaceuticals.

DATES: Effective November 18, 1997. Submit written comments at any time.

ADDRESSES: Submit written comments on the guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. Copies of the guidance are available from the Drug Information Branch (HFD-210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4573. Single copies of the draft guidance may be obtained by mail from the Office of Communication, Training and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research (CBER), or by calling the CBER Voice Information System at 1-800-835-4709 or 301-827-1800. Copies may be obtained from CBER's Fax Information System at 1-888-CBER-FAX or 301-827-3844.

FOR FURTHER INFORMATION CONTACT:

Regarding the guidance: Joy A. Cavagnaro, Center for Biologics Evaluation and Research (HFM-5), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301-827-0379.

Regarding the ICH: Janet J. Showalter, Office of Health Affairs (HFY-20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-0864.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industries Associations,

the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA, and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

In the **Federal Register** of April 4, 1997 (62 FR 16438), FDA published a draft tripartite guideline entitled "Preclinical Testing of Biotechnology-Derived Pharmaceuticals" (S6). The notice gave interested persons an opportunity to submit comments by June 3, 1997.

After consideration of the comments received and revisions to the guidance, a final draft of the guidance was submitted to the ICH Steering Committee and endorsed by the three participating regulatory agencies on July 16, 1997.

In accordance with FDA's Good Guidance Practices (62 FR 8961, February 27, 1997), this document has been designated a guidance, rather than a guideline.

The guidance recommends a basic framework for the preclinical safety evaluation of biotechnology-derived pharmaceuticals. Adherence to the principles presented in the guidance will allow for improvement in the quality and consistency of preclinical safety data supporting the development of biopharmaceuticals.

This guidance represents the agency's current thinking on preclinical safety evaluation of biotechnology-derived pharmaceuticals. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

As with all of FDA's guidances, the public is encouraged to submit written comments with new data or other new information pertinent to this guidance. The comments in the docket will be periodically reviewed, and, where appropriate, the guidance will be amended. The public will be notified of any such amendments through a notice in the **Federal Register**.

Interested persons may, at any time, submit written comments on the guidance to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The guidance and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. An electronic version of this guidance is available on the Internet at "<http://www.fda.gov/cder/guidance.htm>" or at CBER's World Wide Web site at "<http://www.fda.gov/cber/publications.htm>".

The text of the guidance follows:

S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals¹

1. Introduction

1.1. Background

Biotechnology-derived pharmaceuticals (biopharmaceuticals) were initially developed in the early 1980's. The first marketing authorizations were granted later in the decade. Several guidelines and points-to-consider documents have been issued by various regulatory agencies regarding safety assessment of these products. Review of such documents, which are available from regulatory authorities, may provide useful background in developing new biopharmaceuticals.

Considerable experience has now been gathered with submission of applications for biopharmaceuticals. Critical review of this experience has been the basis for development of this guidance, which is intended to provide general principles for designing scientifically acceptable preclinical safety evaluation programs.

1.2 Objectives

Regulatory standards for biotechnology-derived pharmaceuticals have generally been comparable among the European Union, Japan, and the United States. All three regions have adopted a flexible, case-by-case, science-based approach to preclinical safety evaluation needed to support clinical development and marketing authorization. In this rapidly evolving scientific area, there is a need for common understanding and continuing dialogue among the regions.

The primary goals of preclinical safety evaluation are: (1) To identify an initial safe dose and subsequent dose escalation schemes in humans; (2) to identify potential target organs for toxicity and for the study of whether such toxicity is reversible; and (3) to identify safety parameters for clinical monitoring. Adherence to the principles

¹ This guidance represents the agency's current thinking on preclinical safety evaluation of biotechnology-derived pharmaceuticals. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used of such approach satisfies the requirements of the applicable statute, regulations, or both.

presented in this document should improve the quality and consistency of the preclinical safety data supporting the development of biopharmaceuticals.

1.3 Scope

This guidance is intended primarily to recommend a basic framework for the preclinical safety evaluation of biotechnology-derived pharmaceuticals. It applies to products derived from characterized cells through the use of a variety of expression systems including bacteria, yeast, insect, plant, and mammalian cells. The intended indications may include in vivo diagnostic, therapeutic, or prophylactic uses. The active substances include proteins and peptides, their derivatives, and products of which they are components; they could be derived from cell cultures or produced using recombinant deoxyribonucleic acid (DNA) technology, including production by transgenic plants and animals. Examples include but are not limited to: Cytokines, plasminogen activators, recombinant plasma factors, growth factors, fusion proteins, enzymes, receptors, hormones, and monoclonal antibodies.

The principles outlined in this guidance may also be applicable to recombinant DNA protein vaccines, chemically synthesized peptides, plasma derived products, endogenous proteins extracted from human tissue, and oligonucleotide drugs.

This document does not cover antibiotics, allergenic extracts, heparin, vitamins, cellular blood components, conventional bacterial or viral vaccines, DNA vaccines, or cellular and gene therapies.

2. Specification of the Test Material

Safety concerns may arise from the presence of impurities or contaminants. It is preferable to rely on purification processes to remove impurities and contaminants rather than to establish a preclinical testing program for their qualification. In all cases, the product should be sufficiently characterized to allow an appropriate design of preclinical safety studies.

There are potential risks associated with host cell contaminants derived from bacteria, yeast, insect, plants, and mammalian cells. The presence of cellular host contaminants can result in allergic reactions and other immunopathological effects. The adverse effects associated with nucleic acid contaminants are theoretical but include potential integration into the host genome. For products derived from insect, plant, and mammalian cells, or transgenic plants and animals, there may be an additional risk of viral infections.

In general, the product that is used in the definitive pharmacology and toxicology studies should be comparable to the product proposed for the initial clinical studies. However, it is appreciated that during the course of development programs, changes normally occur in the manufacturing process in order to improve product quality and yields. The potential impact of such changes for extrapolation of the animal findings to humans should be considered.

The comparability of the test material during a development program should be

demonstrated when a new or modified manufacturing process is developed or other significant changes in the product or formulation are made in an ongoing development program. Comparability can be evaluated on the basis of biochemical and biological characterization (i.e., identity, purity, stability, and potency). In some cases, additional studies may be needed (i.e., pharmacokinetics, pharmacodynamics and/or safety). The scientific rationale for the approach taken should be provided.

3. Preclinical Safety Testing

3.1 General Principles

The objectives of the preclinical safety studies are to define pharmacological and toxicological effects not only prior to initiation of human studies but throughout clinical development. Both in vitro and in vivo studies can contribute to this characterization. Biopharmaceuticals that are structurally and pharmacologically comparable to a product for which there is wide experience in clinical practice may need less extensive toxicity testing.

Preclinical safety testing should consider:

- (1) Selection of the relevant animal species;
- (2) age;
- (3) physiological state;
- (4) the manner of delivery, including dose, route of administration, and treatment regimen; and
- (5) stability of the test material under the conditions of use.

Toxicity studies are expected to be performed in compliance with Good Laboratory Practice (GLP); however, it is recognized that some studies employing specialized test systems, which are often needed for biopharmaceuticals, may not be able to comply fully with GLP. Areas of noncompliance should be identified and their significance evaluated relative to the overall safety assessment. In some cases, lack of full GLP compliance does not necessarily mean that the data from these studies cannot be used to support clinical trials and marketing authorizations.

Conventional approaches to toxicity testing of pharmaceuticals may not be appropriate for biopharmaceuticals due to the unique and diverse structural and biological properties of the latter that may include species specificity, immunogenicity, and unpredicted pleiotropic activities.

3.2 Biological Activity/Pharmacodynamics

Biological activity may be evaluated using in vitro assays to determine which effects of the product may be related to clinical activity. The use of cell lines and/or primary cell cultures can be useful to examine the direct effects on cellular phenotype and proliferation. Due to the species specificity of many biotechnology-derived pharmaceuticals, it is important to select relevant animal species for toxicity testing. In vitro cell lines derived from mammalian cells can be used to predict specific aspects of in vivo activity and to assess quantitatively the relative sensitivity of various species (including human) to the biopharmaceutical. Such studies may be designed to determine, for example, receptor occupancy, receptor affinity, and/or pharmacological effects, and to assist in the selection of an appropriate animal species for further in vivo

pharmacology and toxicology studies. The combined results from *in vitro* and *in vivo* studies assist in the extrapolation of the findings to humans. *In vivo* studies to assess pharmacological activity, including defining mechanism(s) of action, are often used to support the rationale of the proposed use of the product in clinical studies.

For monoclonal antibodies, the immunological properties of the antibody should be described in detail, including its antigenic specificity, complement binding, and any unintentional reactivity and/or cytotoxicity towards human tissues distinct from the intended target. Such cross-reactivity studies should be carried out by appropriate immunohistochemical procedures using a range of human tissues.

3.3 Animal Species/Model Selection

The biological activity together with species and/or tissue specificity of many biotechnology-derived pharmaceuticals often preclude standard toxicity testing designs in commonly used species (e.g., rats and dogs). Safety evaluation programs should include the use of relevant species. A relevant species is one in which the test material is pharmacologically active due to the expression of the receptor or an epitope (in the case of monoclonal antibodies). A variety of techniques (e.g., immunochemical or functional tests) can be used to identify a relevant species. Knowledge of receptor/epitope distribution can provide greater understanding of potential *in vivo* toxicity.

Relevant animal species for testing of monoclonal antibodies are those that express the desired epitope and demonstrate a similar tissue cross-reactivity profile as for human tissues. This would optimize the ability to evaluate toxicity arising from the binding to the epitope and any unintentional tissue cross-reactivity. An animal species that does not express the desired epitope may still be of some relevance for assessing toxicity if comparable unintentional tissue cross-reactivity to humans is demonstrated.

Safety evaluation programs should normally include two relevant species. However, in certain justified cases one relevant species may suffice (e.g., when only one relevant species can be identified or where the biological activity of the biopharmaceutical is well understood). In addition, even where two species may be necessary to characterize toxicity in short term studies, it may be possible to justify the use of only one species for subsequent long-term toxicity studies (e.g., if the toxicity profile in the two species is comparable in the short term).

Toxicity studies in nonrelevant species may be misleading and are discouraged. When no relevant species exists, the use of relevant transgenic animals expressing the human receptor or the use of homologous proteins should be considered. The information gained from use of a transgenic animal model expressing the human receptor is optimized when the interaction of the product and the humanized receptor has similar physiological consequences to those expected in humans. While useful information may also be gained from the use of homologous proteins, it should be noted

that the production process, range of impurities/contaminants, pharmacokinetics, and exact pharmacological mechanism(s) may differ between the homologous form and the product intended for clinical use. Where it is not possible to use transgenic animal models or homologous proteins, it may still be prudent to assess some aspects of potential toxicity in a limited toxicity evaluation in a single species, e.g., a repeated dose toxicity study of < 14 days duration that includes an evaluation of important functional endpoints (e.g., cardiovascular and respiratory).

In recent years, there has been much progress in the development of animal models that are thought to be similar to the human disease. These animal models include induced and spontaneous models of disease, gene knockout(s), and transgenic animals. These models may provide further insight, not only in determining the pharmacological action of the product, pharmacokinetics, and dosimetry, but may also be useful in the determination of safety (e.g., evaluation of undesirable promotion of disease progression). In certain cases, studies performed in animal models of disease may be used as an acceptable alternative to toxicity studies in normal animals (Note 1). The scientific justification for the use of these animal models of disease to support safety should be provided.

3.4 Number/Gender of Animals

The number of animals used per dose has a direct bearing on the ability to detect toxicity. A small sample size may lead to failure to observe toxic events due to observed frequency alone regardless of severity. The limitations that are imposed by sample size, as often is the case for nonhuman primate studies, may be in part compensated by increasing the frequency and duration of monitoring. Both genders should generally be used or justification given for specific omissions.

3.5 Administration/Dose Selection

The route and frequency of administration should be as close as possible to that proposed for clinical use. Consideration should be given to pharmacokinetics and bioavailability of the product in the species being used and to the volume which can be safely and humanely administered to the test animals. For example, the frequency of administration in laboratory animals may be increased compared to the proposed schedule for the human clinical studies in order to compensate for faster clearance rates or low solubility of the active ingredient. In these cases, the level of exposure of the test animal relative to the clinical exposure should be defined. Consideration should also be given to the effects of volume, concentration, formulation, and site of administration. The use of routes of administration other than those used clinically may be acceptable if the route must be modified due to limited bioavailability, limitations due to the route of administration, or to size/physiology of the animal species.

Dosage levels should be selected to provide information on a dose-response relationship,

including a toxic dose and a no observed adverse effect level (NOAEL). For some classes of products with little to no toxicity, it may not be possible to define a specific maximum dose. In these cases, a scientific justification of the rationale for the dose selection and projected multiples of human exposure should be provided. To justify high dose selection, consideration should be given to the expected pharmacological/physiological effects, availability of suitable test material, and the intended clinical use. Where a product has a lower affinity to or potency in the cells of the selected species than in human cells, testing of higher doses may be important. The multiples of the human dose that are needed to determine adequate safety margins may vary with each class of biotechnology-derived pharmaceutical and its clinical indication(s).

3.6 Immunogenicity

Many biotechnology-derived pharmaceuticals intended for humans are immunogenic in animals. Therefore, measurement of antibodies associated with administration of these types of products should be performed when conducting repeated dose toxicity studies in order to aid in the interpretation of these studies. Antibody responses should be characterized (e.g., titer, number of responding animals, neutralizing or non-neutralizing) and their appearance should be correlated with any pharmacological and/or toxicological changes. Specifically, the effects of antibody formation on pharmacokinetic/pharmacodynamic parameters, incidence and/or severity of adverse effects, complement activation, or the emergence of new toxic effects should be considered when interpreting the data. Attention should also be paid to the evaluation of possible pathological changes related to immune complex formation and deposition.

The detection of antibodies should not be the sole criterion for the early termination of a preclinical safety study or modification in the duration of the study design unless the immune response neutralizes the pharmacological and/or toxicological effects of the biopharmaceutical in a large proportion of the animals. In most cases, the immune response to biopharmaceuticals is variable, like that observed in humans. If the interpretation of the data from the safety study is not compromised by these issues, then no special significance should be ascribed to the antibody response.

The induction of antibody formation in animals is not predictive of a potential for antibody formation in humans. Humans may develop serum antibodies against humanized proteins, and frequently the therapeutic response persists in their presence. The occurrence of severe anaphylactic responses to recombinant proteins is rare in humans. In this regard, the results of guinea pig anaphylaxis tests, which are generally positive for protein products, are not predictive for reactions in humans; therefore, such studies are considered of little value for the routine evaluation of these types of products.

4. Specific Considerations

4.1 Safety Pharmacology

It is important to investigate the potential for undesirable pharmacological activity in appropriate animal models and, where necessary, to incorporate particular monitoring for these activities in the toxicity studies and/or clinical studies. Safety pharmacology studies measure functional indices of potential toxicity. These functional indices may be investigated in separate studies or incorporated in the design of toxicity studies. The aim of the safety pharmacology studies should be to reveal any functional effects on the major physiological systems (e.g., cardiovascular, respiratory, renal, and central nervous systems). Investigations may also include the use of isolated organs or other test systems not involving intact animals. All of these studies may allow for a mechanistically-based explanation of specific organ toxicities, which should be considered carefully with respect to human use and indication(s).

4.2 Exposure assessment

4.2.1 Pharmacokinetics and Toxicokinetics

It is difficult to establish uniform guidances for pharmacokinetic studies for biotechnology-derived pharmaceuticals. Single and multiple dose pharmacokinetics, toxicokinetics, and tissue distribution studies in relevant species are useful; however, routine studies that attempt to assess mass balance are not useful. Differences in pharmacokinetics among animal species may have a significant impact on the predictiveness of animal studies or on the assessment of dose-response relationships in toxicity studies. Alterations in the pharmacokinetic profile due to immune-mediated clearance mechanisms may affect the kinetic profiles and the interpretation of the toxicity data. For some products, there may also be inherent, significant delays in the expression of pharmacodynamic effects relative to the pharmacokinetic profile (e.g., cytokines) or there may be prolonged expression of pharmacodynamic effects relative to plasma levels.

Pharmacokinetic studies should, whenever possible, utilize preparations that are representative of those intended for toxicity testing and clinical use and employ a route of administration that is relevant to the anticipated clinical studies. Patterns of absorption may be influenced by formulation, concentration, site, and/or volume. Whenever possible, systemic exposure should be monitored during the toxicity studies.

When using radiolabeled proteins, it is important to show that the radiolabeled test material maintains activity and biological properties equivalent to that of the unlabeled material. Tissue concentrations of radioactivity and/or autoradiography data using radiolabeled proteins may be difficult to interpret due to rapid in vivo metabolism or unstable radiolabeled linkage. Care should be taken in the interpretation of studies using radioactive tracers incorporated into specific amino acids because of recycling of amino acids into nondrug related proteins/peptides.

Some information on absorption, disposition, and clearance in relevant animal

models should be available prior to clinical studies in order to predict margins of safety based upon exposure and dose.

4.2.2 Assays

The use of one or more assay methods should be addressed on a case-by-case basis and the scientific rationale should be provided. One validated method is usually considered sufficient. For example, quantitation of TCA-precipitable radioactivity following administration of a radiolabeled protein may provide adequate information, but a specific assay for the analyte is preferred. Ideally, the assay methods should be the same for animals and humans. The possible influence of plasma binding proteins and/or antibodies in plasma/serum on the assay performance should be determined.

4.2.3 Metabolism

The expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids. Therefore, the metabolic pathways are generally understood. Classical biotransformation studies as performed for pharmaceuticals are not needed.

Understanding the behavior of the biopharmaceutical in the biologic matrix (e.g., plasma, serum, cerebral spinal fluid) and the possible influence of binding proteins is important for understanding the pharmacodynamic effect.

4.3 Single Dose Toxicity Studies

Single dose studies may generate useful data to describe the relationship of dose to systemic and/or local toxicity. These data can be used to select doses for repeated dose toxicity studies. Information on dose-response relationships may be gathered through the conduct of a single dose toxicity study or as a component of pharmacology or animal model efficacy studies. The incorporation of safety pharmacology parameters in the design of these studies should be considered.

4.4 Repeated Dose Toxicity Studies

For consideration of the selection of animal species for repeated dose studies, see section 3.3. The route and dosing regimen (e.g., daily versus intermittent dosing) should reflect the intended clinical use or exposure. When feasible, these studies should include toxicokinetics.

A recovery period should generally be included in study designs to determine the reversal or potential worsening of pharmacological/toxicological effects, and/or potential delayed toxic effects. For biopharmaceuticals that induce prolonged pharmacological/toxicological effects, recovery group animals should be monitored until reversibility is demonstrated. The duration of repeated dose studies should be based on the intended duration of clinical exposure and disease indication. This duration of animal dosing has generally been 1-3 months for most biotechnology-derived pharmaceuticals. For biopharmaceuticals intended for short-term use (e.g., < 7 days) and for acute life-threatening diseases, repeated dose studies up to 2 weeks duration have been considered adequate to support

clinical studies as well as marketing authorization. For those biopharmaceuticals intended for chronic indications, studies of 6 months duration have generally been appropriate, although in some cases shorter or longer durations have supported marketing authorizations. For biopharmaceuticals intended for chronic use, the duration of long-term toxicity studies should be scientifically justified.

4.5 Immunotoxicity Studies

One aspect of immunotoxicological evaluation includes assessment of potential immunogenicity (see section 3.6). Many biotechnology-derived pharmaceuticals are intended to stimulate or suppress the immune system and, therefore, may affect not only humoral but also cell-mediated immunity. Inflammatory reactions at the injection site may be indicative of a stimulatory response. It is important, however, to recognize that simple injection trauma and/or specific toxic effects caused by the formulation vehicle may also result in toxic changes at the injection site. In addition, the expression of surface antigens on target cells may be altered, which has implications for autoimmune potential. Immunotoxicological testing strategies may require screening studies followed by mechanistic studies to clarify such issues. Routine tiered testing approaches or standard testing batteries, however, are not recommended for biotechnology-derived pharmaceuticals.

4.6 Reproductive Performance and Developmental Toxicity Studies

The need for reproductive/developmental toxicity studies is dependent upon the product, clinical indication and intended patient population (Note 2). The specific study design and dosing schedule may be modified based on issues related to species specificity, immunogenicity, biological activity, and/or a long elimination half-life. For example, concerns regarding potential developmental immunotoxicity, which may apply particularly to certain monoclonal antibodies with prolonged immunological effects, could be addressed in a study design modified to assess immune function of the neonate.

4.7 Genotoxicity Studies

The range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed. Moreover, the administration of large quantities of peptides/proteins may yield uninterpretable results. It is not expected that these substances would interact directly with DNA or other chromosomal material (Note 3).

Studies in available and relevant systems, including newly developed systems, should be performed in those cases where there is cause for concern about the product (e.g., because of the presence of an organic linker molecule in a conjugated protein product). The use of standard genotoxicity studies for assessing the genotoxic potential of process contaminants is not considered appropriate. If performed for this purpose, however, the rationale should be provided.

4.8 Carcinogenicity Studies

Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals. However, product-specific assessment of carcinogenic potential may still be needed depending upon duration of clinical dosing, patient population, and/or biological activity of the product (e.g., growth factors, immunosuppressive agents, etc.). When there is a concern about carcinogenic potential, a variety of approaches may be considered to evaluate risk.

Products that may have the potential to support or induce proliferation of transformed cells and clonal expansion possibly leading to neoplasia should be evaluated with respect to receptor expression in various malignant and normal human cells that are potentially relevant to the patient population under study. The ability of the product to stimulate growth of normal or malignant cells expressing the receptor should be determined. When *in vitro* data give cause for concern about carcinogenic potential, further studies in relevant animal models may be needed. Incorporation of sensitive indices of cellular proliferation in long-term repeated dose toxicity studies may provide useful information.

In those cases where the product is biologically active and nonimmunogenic in rodents and other studies have not provided sufficient information to allow an assessment of carcinogenic potential, then the utility of a single rodent species should be considered. Careful consideration should be given to the selection of doses. The use of a combination of pharmacokinetic and pharmacodynamic endpoints with consideration of comparative receptor characteristics and intended human exposures represents the most scientifically based approach for defining the appropriate doses. The rationale for the selection of doses should be provided.

4.9 Local Tolerance Studies

Local tolerance should be evaluated. The formulation intended for marketing should be tested; however, in certain justified cases, the testing of representative formulations may be acceptable. In some cases, the potential adverse effects of the product can be evaluated in single or repeated dose toxicity studies, thus obviating the need for separate local tolerance studies.

Notes

Note 1

Animal models of disease may be useful in defining toxicity endpoints, selection of clinical indications, and determination of appropriate formulations, route of administration, and treatment regimen. It should be noted that with these models of disease there is often a paucity of historical data for use as a reference when evaluating study results. Therefore, the collection of concurrent control and baseline data is critical to optimize study design.

Note 2

There may be extensive public information available regarding potential reproductive and/or developmental effects of a particular class of compounds (e.g., interferons) where the only relevant species is the nonhuman

primate. In such cases, mechanistic studies indicating that similar effects are likely to be caused by a new but related molecule may obviate the need for formal reproductive/developmental toxicity studies. In each case, the scientific basis for assessing the potential for possible effects on reproduction/development should be provided.

Note 3

With some biopharmaceuticals, there is a potential concern about accumulation of spontaneously mutated cells (e.g., via facilitating a selective advantage of proliferation) leading to carcinogenicity. The standard battery of genotoxicity tests is not designed to detect these conditions. Alternative *in vitro* or *in vivo* models to address such concerns may have to be developed and evaluated.

Dated: November 12, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 97-30274 Filed 11-17-97; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Arthritis and Musculoskeletal and Skin Diseases; Notice of Closed Meeting

Pursuant to Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of the following National Institute of Arthritis and Musculoskeletal and Skin Diseases Special Emphasis Panel (SEP) meeting:

Name of SEP: Mechano Transduction in Bone.

Date: December 18, 1997.

Time: 8:00 a.m.-5:00 p.m.

Place: Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland 20814.

Contact Person: Tommy L. Broadwater, Ph.D., Scientific Review Administrator, Natcher Building, 45 Center Drive, Rm 5AS25U, Bethesda, Maryland 20892-6500, Telephone: 301-594-4952.

Purpose/Agenda: To evaluate and review a research grant application.

This meeting will be closed in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C. The discussion of this application could reveal confidential trade secrets or commercial property such as patentable material and personal information concerning individual associated with the application, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

(Catalog of Federal Domestic Assistance Program Nos. [93.846, Project Grants in Arthritis, Musculoskeletal and Skin Disease Research], National Institutes of Health, HHS)

Dated: November 10, 1997.

LaVerne Y. Stringfield,

Committee Management Officer, NIH.

[FR Doc. 97-30204 Filed 11-17-97; 8:45 am]

BILLING CODE 4140-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Prospective Grant of Exclusive License: Immunodampening Technology

AGENCY: National Institutes of Health, Public Health Service, DHHS.

ACTION: Notice.

SUMMARY: This is notice in accordance with 35 U.S.C. 209(c)(1) and 37 CFR 404.7(a)(1)(i) that the National Institutes of Health (NIH), Department of Health and Human Services, is contemplating the grant of an exclusive world-wide license to practice the invention embodied in U.S. Patent Number 5,585,250 and pending U.S. Patent Application Serial No. 08/764,575 both entitled "Dampening of an Immunodominant Epitope of an Antigen for Use in Plant, Animal and Human Compositions and Immunotherapies" and related foreign patent applications to Biological Memetics, Inc., of Frederick, Maryland. The patent rights in this invention have been assigned to the United States of America.

It is anticipated that this license will be limited to the field of vaccines for the treatment and prevention of infectious diseases in animals and humans.

DATES: Only written comments and/or applications for a license which are received by NIH on or before February 17, 1998 will be considered.

ADDRESSES: Requests for a copy of the patent and/or patent application, inquires, comments and other materials relating to the contemplated license should be directed to: Robert Benson, Patent Advisor, Office of Technology Transfer, National Institutes of Health, 6011 Executive Blvd., Suite 325, Rockville, MD 20852-3804; Telephone: (301) 496-7056, x267; Facsimile: (301) 402-0220.

SUPPLEMENTARY INFORMATION: The patent and pending patent application describe a broadly applicable method of redirecting the immune response to an antigen from an immunodominant epitope to another epitope by altering the immunogenicity of the immunodominant epitope. The method is most useful for those pathogens with a highly variable immunodominant epitope, such as HIV, HCV or gonorrhea.