DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97D–0113]

International Conference on Harmonisation; Draft Guideline for the Preclinical Testing of Biotechnology-Derived Pharmaceuticals; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft guideline entitled ''Guideline for the Preclinical Testing of Biotechnology-Derived Pharmaceuticals.'' The draft guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft guideline is intended to provide general principles for the design of internationally acceptable preclinical safety evaluation programs for biopharmaceuticals.

DATES: Written comments by June 3, 1997.

ADDRESSES: Submit written comments on the draft guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Copies of the draft guideline 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 guideline may be obtained by mail from the Office of Communication, Training and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research, 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 guideline: 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.

At a meeting held on November 7, 1996, the ICH Steering Committee agreed that a draft guideline entitled ''Guideline for the Preclinical Testing of Biotechnology-Derived Pharmaceuticals'' should be made available for public comment. The draft guideline is the product of the Safety Expert Working Group of the ICH. Comments on this draft will be considered by FDA and the Safety Expert Working Group.

The draft guideline recommends a basic framework for the preclinical safety testing of biotechnology-derived pharmaceutical products. Adherence to the preclinical safety testing principles presented in the guideline will allow for continual improvement in the quality and consistency of data supporting the development of biopharmaceuticals.

Although not required, FDA has in the past provided a 75- or 90-day comment period for draft ICH guidelines. However, the comment period for this guideline has been shortened to 60 days so that comments may be received by FDA in time to be reviewed and then discussed at a July 1997 ICH meeting involving this guideline.

This guideline represents the agency's current thinking on preclinical testing 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.

Interested persons may, on or before June 3, 1997, submit to the Dockets Management Branch (address above) written comments on the draft guideline. 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 draft guideline 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 guideline is available via Internet by using the World Wide Web (WWW). To connect to the CDER home page, type http://www.fda.gov/cder and go to the ''Regulatory Guidance'' section. To connect to CBER's WWW site, type http://www.fda.gov/cber/cberftp.html.

The text of the draft guideline follows:

Preclinical Testing of Biotechnology-Derived Pharmaceuticals

1. Introduction

1.1 Objectives

Regulatory standards for biotechnology-derived pharmaceutical products/biopharmaceuticals have generally been comparable among the United States, Europe, and Japan. All regions appear to have a flexible, case-by-case, science-based approach to preclinical safety evaluation needed to support clinical development and marketing authorization. For a case-by-case philosophy to succeed in a harmonized way, there is a need for a common understanding among the regions.

Biotechnology-derived pharmaceutical products were initially developed in the early 1980's. The first marketing authorizations were granted later in the decade, followed soon after by the adoption of the first pharmacopeial monographs. Since this time considerable experience has been gathered. Critical review of this experience has been the basis for development of this guidance which is intended to help provide the general principles for design of internationally acceptable preclinical safety

evaluation programs for biopharmaceuticals. The principles in this guidance should be implemented in a flexible way.

The primary goals of preclinical safety evaluation are: (1) To identify an initial safe starting dose and subsequent dose escalation scheme in humans; (2) to identify potential target organs for toxicity and possible reversibility; and (3) to identify parameters for clinical monitoring. Adherence to the principles presented in this document will allow for continual improvement in the quality and consistency of the data supporting the development of biopharmaceuticals.

1.2 Background

Several guidelines and points-to-consider documents are available from the various regulatory agencies regarding the assessment of biotechnology-derived pharmaceutical products. Review of such documents may provide useful background data in developing new products.

1.3 Scope

This guideline recommends a basic framework for the preclinical safety testing of biotechnology-derived pharmaceutical products. 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 DNA technology. Examples include but are not limited to: Cytokines, plasminogen activators, recombinant blood plasma factors, growth factors, hormones, and monoclonal antibodies.

Some of the following guidance may also be applicable to recombinant DNA protein vaccines, chemically synthesized peptides, blood plasma extracted factors, 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, and cellular and gene therapies.

2. Safety and specification of the test material

Biotechnology-derived pharmaceutical products may have potential risks associated with host cell contaminants from bacteria, yeast, insect, plant, and mammalian cell sources. 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 and include potential integration into the host genome. For products derived from insect, plant, or mammalian cells or transgenic animals, there may be the additional risk of viral infections. These issues are not covered in this document but they are addressed elsewhere (Note 1). 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 studies.

In general, the product used in the definitive pharmacology, toxicology, absorption, distribution, metabolism, and excretion (ADME) 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.

In order to allow the timely use of the product made by a new or modified manufacturing process in an ongoing development program, the comparability of the test material should be demonstrated throughout development on the basis of biochemical and biological characterization (i.e., identity, purity, stability, and potency). In some cases additional studies may be needed to assure product comparability (e.g., pharmacokinetics). The scientific rationale for the approach taken should be provided.

3. Preclinical testing

3.1 General principles

The objectives of the preclinical 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 structurally and pharmacologically comparable to a product for which there is wide experience in clinical practice may, under certain conditions, need less extensive toxicity testing, especially if a similar kinetic profile has been demonstrated.

Preclinical models should consider: (1) Selection of the animal species and physiological state and (2) the manner of delivery, including dose, route of administration, and treatment regimen.

Pivotal toxicology studies are expected to be performed in compliance with Good Laboratory Practices (GLP's). However, it is recognized that some specialized test systems often needed for biopharmaceuticals may not be able to comply fully. Areas of noncompliance should be identified and their significance evaluated relative to the overall safety assessment. In some cases, a lack of overall 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 which 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 effects of the product which are 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 pharmaceutical products, it is important to select an appropriate animal species for toxicity testing. In vitro cell lines from mammalian cells can be used to predict specific aspects of in vivo activity. 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 will 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 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. Testing to include such cross-reactivity should be carried out by appropriate immunohistochemical procedures using a range of human tissues.

3.3 Animal species/model selection

The pharmacological activity together with species and/or tissue specificity of many biotechnology-derived pharmaceutical products often preclude standard toxicology testing designs in commonly used species (e.g., rats and dogs). Safety evaluation programs will normally include two relevant species. In certain situations one relevant species may suffice. In these cases the rationale should be provided.

Toxicology studies in pharmacologically nonrelevant species are not needed and are discouraged. However, if in vitro preclinical studies have not identified a relevant animal species, due to the unique species restriction to human cells, 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) including the evaluation of important functional endpoints (e.g., cardiovascular, respiratory).

Alternative approaches, when no relevant species exist, may include the use of transgenic animals expressing the human receptor or the use of homologous proteins. The information gained from use of a transgenic species expressing the human receptor is optimized when the interaction of the product and the humanized receptor has physiological consequences similar 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.

In recent years, there has been much progress in the development of animal models that are thought to be similar to the

disease to be treated in humans. These animal models include spontaneous disease models or spontaneous models of disease. 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 in animal models of disease may be used as an acceptable alternative to toxicology studies in normal animals. The scientific justification for the use of these animal models of disease to support safety should be provided (Note 2).

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 a failure to observe toxic events due to observed frequency alone regardless of severity. The limitations 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 the proposed clinical use and should also take into account the pharmacokinetics and bioavailability of the product in the species being used, and the volume which can safely and humanely be 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 test animal exposure relative to the clinical exposure should be presented. Considerations should be given to the effects of volume of the administered dose, size of the animal species, and muscle mass, on the absorption of products into the systemic circulation. 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 size/physiology of the animal species.

Ideally, dose levels should be selected to provide information on a dose-response relationship, 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 strong 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 or potency in the cells of the target species than in human cells, testing of higher doses may be important. The multiples of the human dose necessary to determine adequate safety margins may vary with each class of biotechnology-derived pharmaceutical product and its clinical indication(s).

3.6 Immunogenicity

It is likely that many biotechnology-derived pharmaceutical products will be 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., 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 characteristics, incidence and/or severity of adverse effects, or the emergence of new toxic effects, should be considered when interpreting the data.

The detection of antibodies should not be the sole criterion for the early termination of a preclinical study or modification in the duration of the study design unless the immune response neutralizes the pharmacological and/or toxicological effect in a large proportion of the animals. In most cases, the immune response to recombinant proteins is variable, like that observed in humans. Specific attention should be paid to the evaluation of possible pathological changes related to immune complex formation and deposition. 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 significance of antibody formation in animals to the potential for antibody formation in humans is often questionable. Humans develop serum antibodies even 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 humans. Therefore, such studies are considered of little value for 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 this activity in the toxicity studies and/or clinical studies. Safety pharmacology studies provide functional indices of toxicity. These functional indices may be investigated in separate studies or incorporated into the design of the toxicology studies. The aim of the safety pharmacology studies should be to establish the functional effects on the major physiological systems. Investigations may include use of isolated organs or other test systems not involving intact animals. The evaluation of function of specific organ systems (e.g., cardiovascular, respiratory, CNS, and autonomic nervous systems, and the renal system) depends on the pharmacological properties of the product. Such studies should 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 Toxicokinetics and pharmacokinetics (Absorption, Distribution, Metabolism, Excretion—ADME)

Toxicokinetics and pharmacokinetics should follow relevant ICH guidelines (Note 1). It is difficult to establish uniform guidelines for ADME studies for biotechnology-derived pharmaceutical products. Single dose pharmacokinetics and tissue distribution studies are often useful; however, routine studies that attempt to assess mass balance, accumulation, and excretion are not useful. Differences in ADME among animal species may have significant impact on the predictiveness of animal studies or on the assessment of dose-response relationships in toxicology studies. Alterations in the pharmacokinetic profile due to immune-mediated clearance mechanisms may affect the ADME profiles and the interpretation of the toxicity data. ADME studies should, whenever possible, utilize test material that is representative of that intended for clinical use using a route of administration relevant to the anticipated clinical studies.

4.2.1 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 assay 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. It is important to show that the radiolabeled test material administered maintains equivalent activity and biological properties to the unlabeled compound. Ideally the assay methods should be the same for animals and humans. The possible influence of plasma binding proteins and/or antibodies on the assay performance should be determined.

4.2.2 Animal species selection

Relevant animal species should be selected to retain comparability of the data with data obtained from pharmacology and toxicology studies.

4.2.3 Absorption

Absorption and/or bioavailability should be characterized in relation to the proposed route of clinical administration. Absorption studies may be performed in conjunction with toxicology studies. Patterns of absorption may be influenced by formulation and/or volume. Some information on disposition in relevant animal models should be available prior to clinical studies in order to project expected margins of safety based upon exposure and dose.

4.2.4 Distribution

Studies of extravascular distribution and mechanisms of clearance may be useful in understanding pharmacological and toxicological properties. Tissue levels of

radioactivity and/or autoradiography data from iodinated proteins may be difficult to interpret with rapid in vivo metabolism and ensuing deiodination. Care should be taken in the interpretation of studies using radioactive tracers incorporated into specific amino acids because of recycling of radiolabeled amino acids into non-drug related proteins/peptides.

4.2.5 Metabolism

Metabolic pathways for biotechnology-derived pharmaceutical products are less complex than for conventional pharmaceuticals and therefore major species differences in metabolic profiles are not an issue.

Metabolite/disposition patterns can be discerned by a range of detection techniques (e.g., immunochemical detection, chromatographic separation, SDS–PAGE).

4.2.6 Excretion

Several organ systems and mechanisms may contribute to the elimination of biotechnology-derived pharmaceutical products. When feasible, these studies should characterize the rate and contribution of the various organs to the overall elimination process.

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 toxicology studies. Data on dose-response relationships may be gathered as a component of pharmacology or animal model efficacy studies or through the conduct of a single dose toxicology study.

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 reversal, potential worsening of pharmacological/toxicological effects, and/or potential delayed toxic effects.

The duration of repeated dose studies should be based on the intended duration of clinical exposure and disease indication. This duration has generally been 1–3 months for most biotechnology-derived products. For products intended for short-term use (e.g., ≤ to 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 products 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.

4.5 Immunotoxicity

One aspect of immunotoxicological evaluation includes assessment of potential immunogenicity and hypersensitivity (see section 3.6). In addition, many biotechnology-derived pharmaceutical products are intended to stimulate or suppress the immune system. Inflammatory reactions at the injection site may be indicative of a stimulatory response. In addition, the expression of surface antigens on target cells may be altered with implications for their autoimmune potential. Immunotoxicological testing strategies should be applied to clarify any such issues; however, routine tiered testing approaches or standard testing batteries are not recommended.

4.6 Reproductive performance and developmental toxicity

The need for reproductive/developmental toxicity studies is dependent upon the product, clinical indication, and intended patient population. Reproductive and developmental toxicity studies should follow the relevant ICH guidelines (Note 1). The specific study design and dosing schedule may be modified based on issues related to species specificity and/or antigenicity (Note 3).

4.7 Genotoxicity studies

The range and type of genotoxicity studies routinely conducted for conventional pharmaceuticals are not applicable to the active components of biotechnology-derived pharmaceutical products. The administration of large quantities of peptides/ proteins may yield uninterpretable results; moreover, it is not expected that these substances would interact directly with DNA or other chromosomal material (Note 4).

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 (because of the presence of an organic linker molecule in a conjugated protein product).

4.8 Carcinogenicity studies

Product-specific assessment of carcinogenic potential may be needed, depending upon duration of clinical dosing and patient population (Note 1). However, where rodents are not the relevant species for assessing toxicity and/or the product is immunogenic, conventional carcinogenicity bioassays are not appropriate. When there is a concern about carcinogenic potential (e.g., growth factors) a variety of approaches should be considered.

Products that may have the potential to support or induce proliferation of transformed cells and clonal expansion leading to tumor formation should be evaluated for 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 the malignant cells expressing the receptor or to initiate malignant cell growth in normal cells expressing the receptor should be determined. When in vitro data for tumor promotion give cause for concern, further studies in relevant animal models may be needed.

In those cases where the product is biologically active and nonimmunogenic in rodents, then an assessment of carcinogenic potential in a single species should be considered. Careful consideration should be given to the selection of doses. The use of pharmacokinetic or pharmacodynamic endpoints with consideration of receptor characteristics and intended exposures in humans represents the most scientifically valid 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. Ideally, the formulation intended for marketing should be tested. However, in certain cases, the testing of representative formulations may be acceptable. In some cases, the potential local effects of the product can be evaluated in single or repeated dose toxicity studies thus obviating the need for separate local tolerance studies.

Note 1

''Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human and Animal Origin'' (Q5A).

''Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products'' (Q5D).

''Specifications for New Drug Substances and Products: Biotechnolgical Products'' (Q6B).

''Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals'' (S1A).

''Carcinogenicity: Testing for Carcinogenicity of Pharmaceuticals'' (S1B).

''Toxicokinetics: Guidance on the Assessment of Systemic Exposure in Toxicity Studies'' (S3A).

''Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies'' (S3B).

''Detection of Toxicity to Reproduction for Medicinal Products'' (S5A).

''Reproductive Toxicology: Toxicity to Male Fertility'' (S5B).

Note 2

Animal models of disease may be useful in defining toxicity endpoints, selection of clinical indications, and determination of appropriate formulations. 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 3

In cases where extensive public information is available regarding potential reproductive and/or developmental effects of a particular class of compounds (e.g., interferons) and the only relevant species is the nonhuman primate, 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 4

With some types of products there is a potential concern of accumulation of spontaneously mutated cells (e.g., via facilitating a selective advantage of proliferation). This could lead to concerns

regarding the potential carcinogenicity of such compounds. The standard battery of genotoxicity tests is not designed to test for these circumstances. Alternative responsive in vitro or in vivo models for such conditions may have to be developed and evaluated.

Dated: March 29, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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