dispensed into multiple containers, and stored under defined conditions. The MCB is used to derive all working cell banks. The testing performed on a new MCB (from a previous initial cell clone, MCB or WCB) should be the same as for the MCB, unless justified.

Pilot Plant Scale

The production of a recombinant protein by a procedure fully representative of and simulating that to be applied on a full commercial manufacturing scale. The methods of cell expansion, harvest, and product purification should be identical except for the scale of production.

Relevant Genotypic and Phenotypic Markers

Those markers permitting the identification of the strain or the cell line which should include the expression of the recombinant protein or presence of the expression construct.

Working Cell Bank (WCB)

The Working Cell Bank is prepared from aliquots of a homogeneous suspension of cells obtained from culturing the MCB under defined culture conditions.

Dated: August 14, 1995.

William K. Hubbard,

Acting Deputy Commissioner for Policy.

[FR Doc. 95–20611 Filed 8–18–95; 8:45 am]

BILLING CODE 4160–01–F

[Docket No. 95D–0217]

International Conference on Harmonisation; Draft Guideline on Conditions Which Require Carcinogenicity Studies for Pharmaceuticals; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft guideline entitled ''Conditions Which Require Carcinogenicity Studies for Pharmaceuticals.'' This 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 define the conditions for which carcinogenicity studies should be conducted, to provide guidance to avoid the unnecessary use of animals in testing, and to provide consistency in worldwide regulatory assessments of applications.

DATES: Written comments by October 5, 1995.

ADDRESSES: Submit written comments on the draft guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Copies of the draft guideline are available from the CDER Executive Secretariat Staff (HFD–8), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

FOR FURTHER INFORMATION CONTACT:

Regarding the guideline: Joy A. Cavagnaro, Center for Biologics Evaluation and Research (HFM–500), 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 March 29, 1995, the ICH Steering Committee agreed that a draft guideline entitled ''Conditions Which Require Carcinogenicity Studies for Pharmaceuticals'' should be made available for public comment. The draft guideline is the product of the Safety Expert Working Group of the ICH. Comments about this draft will be considered by FDA and the Expert Working Group. Ultimately, FDA intends to adopt the ICH Steering Committee's final guideline.

The draft guideline is intended to define the conditions which require carcinogenicity studies, to provide guidance in order to avoid the unnecessary use of animals in testing, and to provide consistency in worldwide regulatory assessments of applications. The objectives of carcinogenicity studies are to identify a tumorigenic potential in animals and to understand the potential for such risk in humans. Any cause for concern derived from laboratory investigations, animal toxicity studies, and data in humans may lead to a need for carcinogenicity studies. The fundamental considerations in assessing the need for carcinogenicity studies are any perceived cause for concern arising from other investigations and the maximum duration of patient treatment. Other factors may also be considered such as the appropriate study design, the timing of study performance relative to clinical development, the intended patient population, prior assessment of carcinogenic potential, the extent of systemic exposure, or the (dis)similarity to endogenous substances.

In the past, guidelines have generally been issued under § 10.90(b) (21 CFR 10.90(b)), which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but are acceptable to FDA. The agency is now in the process of revising § 10.90(b). Therefore, this guideline is not being issued under the authority of § 10.90(b), and it does not create or confer any rights, privileges, or benefits for or on any person, nor does it operate to bind FDA in any way.

Interested persons may, on or before October 5, 1995, 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.

The text of the draft guideline follows:

Conditions Which Require Carcinogenicity Studies for Pharmaceuticals

Purpose

The objectives of carcinogenicity studies are to identify a tumorigenic potential in animals and to understand the potential for such risk in humans. Any cause for concern derived from laboratory investigations, animal toxicology studies, and data in humans may lead to a need for carcinogenicity studies. The practice of requiring carcinogenicity studies in rodents was instituted for pharmaceuticals that were expected to be administered regularly over a substantial part of a patient's lifetime. The design and interpretation of the results from these studies preceded much of the available current technology to test for genotoxic potential and the more recent advances in technologies to assess systemic exposure. These studies also preceded our current understanding of tumorigenesis with nongenotoxic agents. Results from genotoxicity studies, toxicokinetics, and mechanistic studies can now be routinely applied in preclinical safety assessment. These additional data are important not only in considering whether to perform carcinogenicity studies but for interpreting study outcomes with respect to relevance for human safety. Since carcinogenicity studies are time consuming and resource intensive they should only be performed when human exposure warrants the need for information from life-time studies in animals in order to assess carcinogenic potential.

Historical Background

In Japan, according to the 1990 ''Guidelines for Toxicity Studies of Drugs Manual,'' carcinogenicity studies are needed if the clinical use is expected to be continuously for 6 months or longer. If there is cause for concern, pharmaceuticals generally used continuously for less than 6 months may need carcinogenicity studies. In the United States, most pharmaceuticals are tested in animals for their carcinogenic potential before widespread use in humans. According to the U.S. Food and Drug Administration, pharmaceuticals generally used 3 months or more require carcinogenicity studies. In Europe, the Rules Governing Medicinal Products in the European Community define the circumstances when carcinogenicity studies are required. These circumstances include administration over a substantial period of life, i.e., continuously during a minimum period of 6 months or frequently in an intermittent manner so that the total exposure is similar.

Introduction

The objective of this guideline is to define the conditions that require carcinogenicity studies, to provide the appropriate guidance to avoid the unnecessary use of animals in testing, and to provide consistency in worldwide regulatory assessments of applications. It is expected that these studies will be performed in a manner that reflects currently accepted scientific standards.

The fundamental considerations in assessing the need for carcinogenicity studies are any perceived cause for concern arising from other investigations and the maximum duration of patient treatment. Other factors may also be considered such as the appropriate study design, the timing of study performance relative to clinical development, the intended patient population, prior assessment of carcinogenic potential, the extent of systemic exposure, or the (dis)similarity to endogenous substances.

For novel compounds, for which the pharmacologic profile or spectrum of biological effects is poorly understood, mechanistic studies may be particularly appropriate. Important research initiatives over the next decade will include optimization of study designs, modifications in diet, and development of new animal models, such as the newborn mouse, partially hepatectomized rats, and transgenic animals.

Cause for Concern

Carcinogenicity studies may be recommended for some pharmaceuticals if there is concern about their carcinogenic potential. Criteria for defining these cases should be very carefully considered because this is the most important reason to conduct carcinogenicity studies for most categories of pharmaceuticals. Several factors which could be considered may include: (1) Findings in genotoxicity studies (Note 1); (2) previous demonstration of carcinogenic potential in the product class that is considered relevant to humans; (3) structure-activity relationship suggesting genotoxic or carcinogenic risk; (4) evidence of preneoplastic toxicity in repeated dose toxicity studies; and (5) long-term tissue retention of parent compound or metabolite(s) resulting in local tissue reactions or other pathophysiological responses.

Duration and Exposure

Carcinogenicity studies should be performed for any pharmaceutical whose expected clinical use is continuous for at least 6 months. It is expected that most pharmaceuticals indicated for 3-months treatment would also likely be used for 6 months.

Certain classes of compounds may not be used continuously over a minimum of 6 months but may be expected to be used repeatedly in an intermittent manner. It is difficult to determine and to justify scientifically what time represents clinically relevant treatment periods for frequent use with regard to carcinogenic potential, especially for discontinuous treatment periods. For pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions, carcinogenicity studies are generally needed. Some examples of such conditions include allergic rhinitis, depression, and anxiety. Carcinogenicity studies may also need to be considered for certain delivery systems which may result in prolonged exposures. Pharmaceuticals administered infrequently or for short durations of exposure (e.g., anesthetics and radiolabeled imaging agents) do not need carcinogenicity studies unless there is cause for concern.

Indication and Patient Population

When carcinogenicity studies are required they usually need to be completed before application for marketing approval. However, completed rodent carcinogenicity studies are not needed in advance of the conduct of large scale clinical trials, unless there is special concern for the patient population.

For pharmaceuticals developed to treat certain diseases it is not considered appropriate to require carcinogenicity testing before market approval. For example, oncolytic agents intended for treatment of advanced systemic disease do not generally need carcinogenicity studies. In cases where the therapeutic agent for cancer is generally successful and life is significantly prolonged there may be later concerns regarding secondary cancers. When such pharmaceuticals are intended for adjuvant therapy in tumor free patients or for prolonged use in noncancer indications, carcinogenicity studies are usually needed. In other cases to speed the availability of pharmaceuticals for life-threatening or severely debilitating diseases, especially where no satisfactory alternative therapy exists, carcinogenicity studies may be completed postapproval.

Route of Exposure

The route of exposure in animals should be the same as the intended clinical route when feasible (reference ICH Safety Topic S1C). If similar metabolism and systemic exposure can be demonstrated by differing routes of administration, then it is only necessary to conduct carcinogenicity studies by a single route. It is important that relevant organs for the clinical effect be adequately exposed to the test material. Evidence of adequate exposure may be derived from pharmacokinetic data (reference ICH Safety Topic S3B).

Extent of Systemic Exposure

Pharmaceuticals applied topically (e.g., dermal and ocular routes of administration) may need carcinogenicity studies. Where there is cause for concern for photocarcinogenic potential or if chronic irritation occurs, carcinogenicity studies by dermal application (generally in mice) may be needed. Pharmaceuticals showing poor systemic exposure from topical routes may not need studies by the oral route to assess the carcinogenic potential to internal organs.

For different salts, acids, or bases of the same therapeutic moiety, where prior carcinogenicity studies are available, evidence should be provided that there are no significant changes in pharmacokinetics, pharmacodynamics, or toxicity. When changes in exposure and consequent toxicity are noted, then the results of additional bridging studies may be necessary to determine whether additional carcinogenicity studies are needed. For esters and complex derivatives, similar data would be valuable in assessing the need for an additional carcinogenicity study, but this should be considered on a case-by-case basis.

Endogenous Peptides and Protein Substances or Their Analogs

Endogenous peptides or proteins and their analogs, produced by chemical synthesis, by extraction/purification from an animal/human source or by biotechnological methods such as recombinant DNA technology may require special considerations.

Carcinogenicity studies are not generally needed for endogenous substances given essentially as replacement therapy (i.e., physiological levels), particularly where there is previous clinical experience with similar products (for example, animal insulins, pituitary-derived growth hormone, and calcitonin).

The need for carcinogenicity studies in rodent species should be considered if indicated by the treatment duration, clinical indication, or patient population (providing neutralizing antibodies are not elicited to such an extent in repeated dose studies as to invalidate the results). Carcinogenicity studies may be needed in the following circumstances: (1) For products where there are significant differences in biological effects to the natural counterpart(s); (2) for products where modifications lead to significant changes in structure compared to the natural counterpart; and (3) for products resulting in humans in a significant increase over the existing local or systemic concentration (i.e., pharmacological levels).

Need for Additional Testing

The relevance of the results obtained from animal carcinogenicity studies for assessment of human safety are often cause for debate. Further research may be needed, investigating the mode of action, which may result in confirming the presence or the lack of carcinogenic potential for humans. When it is considered important to evaluate the relevance of tumor findings in animals for human safety, mechanistic studies are essential.

Supplementary Notes

Note 1: Assessment of the genotoxic potential of a compound must take into account the totality of the findings and acknowledge the intrinsic value and limitations of both in vitro and in vivo tests. The test battery approach of in vitro and in vivo tests is designed to reduce the risk of false negative results for compounds with genotoxic potential. A positive result in any assay for genotoxicity does not necessarily mean that the test compound poses a genotoxic hazard to humans (reference ICH Safety Topic S2A).

Dated: August 14, 1995.

William K. Hubbard,

Acting Deputy Commissioner for Policy.

[FR Doc. 95–20610 Filed 8–18–95; 8:45 am]

BILLING CODE 4160–01–F

[Docket No. 93D–0140]

International Conference on Harmonisation; Draft Guideline on Detection of Toxicity to Reproduction: Addendum on Toxicity to Male Fertility; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing portions of a revised draft guideline entitled ''Detection of Toxicity to Reproduction: Addendum on Toxicity to Male Fertility.'' This 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 reflect sound scientific principles for reproductive toxicity testing concerning male fertility, and is an addendum to an earlier ICH guideline on the detection of toxicity to reproduction for medicinal products.

DATES: Written comments by October 5, 1995.

ADDRESSES: Submit written comments on the draft guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Copies of the draft guideline are available from the CDER Executive Secretariat Staff (HFD–8), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

FOR FURTHER INFORMATION CONTACT:

Regarding the guideline: Joy A. Cavagnaro, Center for Biologics Evaluation and Research (HFM–2), 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 March 29, 1995, the ICH Steering Committee agreed that a draft guideline entitled ''Detection of Toxicity to Reproduction: Addendum on Toxicity to Male Fertility'' should be made available for public comment. The draft guideline is the product of the Safety Expert Working Group of the ICH. Comments about this draft will be considered by FDA and the Expert Working Group. Ultimately, FDA intends to adopt the ICH Steering Committee's final guideline.

This draft guideline is an addendum to an ICH final guideline published in the **Federal Register** of September 22, 1994 (59 FR 48746) entitled ''Guideline on Detection of Toxicity to Reproduction for Medicinal Products.'' This draft guideline is intended to reflect sound scientific principles for reproductive toxicity testing concerning male fertility.

In the past, guidelines have generally been issued under § 10.90(b) (21 CFR 10.90(b)), which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but are acceptable to FDA. The agency is now in the process of revising § 10.90(b). Therefore, this guideline is not being issued under the authority of § 10.90(b),