

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 95D-0217]

International Conference on Harmonisation; Final Guideline on the Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a final guideline entitled "Guideline on the Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals." The guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The 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: Effective March 1, 1996. Submit written comments at any time.

ADDRESSES: Submit written comments on the guideline to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. Copies of the guideline are available from the Division of Communications Management (HFD-210), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1012. An electronic version of this guideline is also available via Internet by connecting to the CDER file transfer protocol (FTP) server (CDVS2.CDER.FDA.GOV).

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 ICH: Janet Showalter, Office of Health Affairs (HFY-1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1382.

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 August 21, 1995 (60 FR 43498), FDA published a draft tripartite guideline entitled "Conditions Which Require Carcinogenicity Studies for Pharmaceuticals." The notice gave interested persons an opportunity to submit comments by October 5, 1995.

After consideration of the comments received and revisions to the guideline, a final draft of the guideline was submitted to the ICH Steering Committee and endorsed by the three participating regulatory agencies at the ICH meeting held on November 29, 1995.

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

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). Although this guideline does not create or confer any rights on or for any person and does not operate to bind FDA in any way, it does represent the agency's current thinking on long-term rodent carcinogenicity studies of pharmaceuticals.

As with all of FDA's guidelines, the public is encouraged to submit written comments with new data or other new information pertinent to this guideline. The comments in the docket will be periodically reviewed, and, where appropriate, the guideline 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 final guideline 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 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 guideline follows:

Guideline on the Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals

1. Introduction

The objectives of carcinogenicity studies are to identify a tumorigenic potential in

animals and to assess the relevant 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 be performed only when human exposure warrants the need for information from life-time studies in animals in order to assess carcinogenic potential.

2. Historical Background

In Japan, according to the 1990 "Guidelines for Toxicity Studies of Drugs Manual," carcinogenicity studies were needed if the clinical use was expected to be continuously for 6 months or longer. If there was cause for concern, pharmaceuticals generally used continuously for less than 6 months may have needed carcinogenicity studies. In the United States, most pharmaceuticals were tested in animals for their carcinogenic potential before widespread use in humans. According to the U.S. Food and Drug Administration, pharmaceuticals generally used for 3 months or more necessitated carcinogenicity studies. In Europe, the Rules Governing Medicinal Products in the European Community defined the circumstances when carcinogenicity studies were required. These circumstances included 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 was similar.

3. Objective of the Guideline

The objective of this guideline is to define the conditions under which carcinogenicity studies should be conducted 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 the maximum duration of patient treatment and any perceived cause for concern arising from other investigations. Other factors may also be considered such as the intended patient population, prior assessment of carcinogenic potential, the extent of systemic exposure, the

(dis)similarity to endogenous substances, the appropriate study design, or the timing of study performance relative to clinical development.

4. Factors to Consider for Carcinogenicity Testing

4.1 Duration and Exposure

Carcinogenicity studies should be performed for any pharmaceutical whose expected clinical use is continuous for at least 6 months (see Note 1).

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 a clinically relevant treatment period 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. 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 duration of exposure (e.g., anesthetics and radiolabeled imaging agents) do not need carcinogenicity studies unless there is cause for concern.

4.2 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) Previous demonstration of carcinogenic potential in the product class that is considered relevant to humans; (2) structure-activity relationship suggesting carcinogenic risk; (3) evidence of preneoplastic lesions in repeated dose toxicity studies; and (4) long-term tissue retention of parent compound or metabolite(s) resulting in local tissue reactions or other pathophysiological responses.

4.3 Genotoxicity

Unequivocally genotoxic compounds, in the absence of other data, are presumed to be transspecies carcinogens, implying a hazard to humans. Such compounds need not be subjected to long-term carcinogenicity studies. However, if such a drug is intended to be administered chronically to humans, a chronic toxicity study (up to 1 year) may be necessary to detect early tumorigenic effects.

Assessment of the genotoxic potential of a compound should 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 single positive result in any

assay for genotoxicity does not necessarily mean that the test compound poses a genotoxic hazard to humans (see the ICH Guideline on Specific Aspects of Regulatory Genotoxicity Tests).

4.4 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 serious diseases, carcinogenicity testing need not be conducted before market approval although these studies should be conducted post-approval. This speeds the availability of pharmaceuticals for life-threatening or severely debilitating diseases, especially where no satisfactory alternative therapy exists.

In instances where the life-expectancy in the indicated population is short (i.e., less than 2 to 3 years), no long-term carcinogenicity studies may be required. 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.

4.5 Route of Exposure

The route of exposure in animals should be the same as the intended clinical route when feasible (see the ICH Guideline on Dose Selection for Carcinogenicity Studies of Pharmaceuticals). If similar metabolism and systemic exposure can be demonstrated by differing routes of administration, carcinogenicity studies should only be conducted by a single route, recognizing that it is important that relevant organs for the clinical route (e.g., lung for inhalational agents) be adequately exposed to the test material. Evidence of adequate exposure may be derived from pharmacokinetic data (see the ICH Guideline on Repeated Dose Tissue Distribution Studies).

4.6 Extent of Systemic Exposure

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

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, additional bridging studies may be used 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.

4.7 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 (e.g., animal insulins,

pituitary-derived growth hormone, and calcitonin).

Although not usually necessary, long-term carcinogenicity studies in rodent species should be considered for the other biotechnology products noted above if indicated by the treatment duration, clinical indication, or patient population (provided neutralizing antibodies are not elicited to such an extent in repeated dose studies as to invalidate the results). Conduct of carcinogenicity studies may be important 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).

5. 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. Mechanistic studies are useful to evaluate the relevance of tumor findings in animals for human safety.

Supplementary Note

Note 1: It is expected that most pharmaceuticals indicated for 3-months treatment would also likely be used for 6 months. In an inquiry to a number of pharmaceutical research and regulatory groups, no cases were identified in which a pharmaceutical would be used only for 3 months.

Dated: February 23, 1996

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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