DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 96D–0235]

International Conference on Harmonisation; Draft Guideline on Testing for Carcinogenicity of Pharmaceuticals

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft guideline entitled ''Testing for Carcinogenicity of Pharmaceuticals.'' 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 outlines experimental approaches to evaluating the carcinogenic potential of pharmaceuticals to humans that may obviate the necessity for the routine conduct of two long-term rodent carcinogenicity studies.

DATES: Written comments by October 21, 1996.

ADDRESSES: Submit written comments on the draft guideline entitled ''Testing for Carcinogenicity of Pharmaceuticals'' 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, 7500 Standish Pl., Rockville, MD 20855, 301–594–1012; written requests for single copies of the ICH documents can be submitted to the Manufacturers Assistance and Communication Staff (HFM–42), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448. Send one self-addressed adhesive label to assist that office in processing your requests. The document may also be obtained by mail or FAX by calling the Center for Biologics Evaluation and Research Voice Information System at 1–800–835–4709.

Persons with access to the INTERNET may obtain the document in several ways.

Users of ''Web Browser'' software, such as Mosaic, Netscape, or Microsoft Internet Explorer may obtain this document via the World Wide Web by using the following Uniform Resource Locators (URL's):

http://www.fda.gov/cber/cberftp.html
ftp://ftp.fda.gov/CBER/

The document may also be obtained via File Transfer Protocol (FTP). Requesters should connect to the FDA FTP Server, FTP.FDA.GOV (192.73.61.21). The Center for Biologics Evaluation and Research's (CBER's) documents are maintained in a subdirectory called ''CBER'' on the server. Logins with the user name of anonymous are permitted, and the user's e-mail address should be sent as the password.

The ''READ.ME'' file in that subdirectory describes the available documents which may be available as an ASCII text file (*.TXT), or a WordPerfect 5.1 or 6.x document (*.w51,wp6), or both.

The document can be obtained by ''bounce-back e-mail.'' A message should be sent to: ICH_CARCIN@a1.cber.fda.gov.

Finally, an electronic version of this guideline is available via the U.S. Government Printing Office's ''GPO Access.'' Internet users can access the database through the World Wide Web; the Superintendent of Documents home page address is http://www.access.gpo.gov/su_docs/

FOR FURTHER INFORMATION CONTACT:

Regarding the guideline: Joseph Contrera, Center for Drug Evaluation and Research (HFD–900), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4750.

Regarding 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 it 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 April 30, 1996, the ICH Steering Committee agreed that a draft guideline entitled ''Testing for Carcinogenicity of Pharmaceuticals'' should be made available for public comment. The draft guideline is the product of the Safety Expert Working Group of ICH. Comments are requested on this draft and will be considered by FDA and the Safety Expert Working Group. Ultimately, FDA intends to adopt the ICH Steering Committee's guideline.

Long-term rodent carcinogenicity studies for assessing the carcinogenic potential of pharmaceuticals to humans are currently receiving critical examination. Many investigations have shown that it is possible to provoke a carcinogenic response in rodents by a diversity of experimental procedures, some of which are now considered to have little or no relevance for human risk assessment. It is in keeping with the mission of ICH to examine whether the need for carcinogenicity studies in two species could be reduced without compromising human safety. This draft guideline outlines experimental approaches to the evaluation of carcinogenic potential that may obviate the necessity for the routine conduct of two long-term rodent carcinogenicity studies for those pharmaceuticals that need such evaluation.

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 for or on any person and does not operate to bind FDA, it does represent the agency's current thinking on methods for evaluating the carcinogenic activity of pharmaceuticals.

Although not required, FDA would normally provide at least a 75-day comment period and preferably a 90-day comment period to provide interested persons with ample time to review and comment upon this type of action. However, the comment period for this draft guideline has been shortened to 60 days so that comments and scientific data can be received by FDA in time to be discussed at an upcoming ICH meeting involving this guideline.

Interested persons may, on or before October 21, 1996, submit written comments on the draft 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 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:

Testing for Carcinogenicity of Pharmaceuticals

1. Objective

This document provides guidance on methods for evaluating the carcinogenic activity of pharmaceuticals.

2. Background

The current regulatory requirements for the assessment of the carcinogenic potential of pharmaceuticals in the three regions (E.U., Japan, U.S.) provide for the conduct of long-term carcinogenicity studies in two rodent species, usually the rat and the mouse. Given the cost of bioassays and their extensive use of animals, it is in keeping with the mission of ICH to examine whether the need for carcinogenicity studies in two species could be reduced without compromising human safety.

This guideline should be read in conjunction with other guidelines, especially:

S1.A: Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals.

S1.C: Dose Selection for Carcinogenicity Studies of Pharmaceuticals.

Long-term rodent carcinogenicity studies for assessing the carcinogenic potential of chemicals (including pharmaceuticals) to humans are currently receiving critical examination. Since the early 1970's, many investigations have shown that it is possible to provoke a carcinogenic response in rodents by a diversity of experimental procedures, some of which are now considered to have little or no relevance for human risk assessment. This guideline outlines experimental approaches to the evaluation of carcinogenic potential that may obviate the necessity for the routine conduct of two long-term rodent carcinogenicity studies for those pharmaceuticals that need such evaluation. The question of whether the use of rats or mice alone would result in the loss of information on carcinogenicity relevant to human risk assessment has been addressed by a survey of six pharmaceutical data bases. The data bases were those of the International Agency for Research on Cancer (IARC), the U.S. Food and Drug Administration (FDA), the U.S. Physicians' Desk Reference (PDR), the Japanese Pharmaceutical Manufacturers' Association (JPMA), the EU European Medicines Evaluation Agency (Committee for Proprietary Medicinal Products) (CPMP), and the UK Centre for Medicines Research (CMR). The dimensions of these data bases and the principal conclusions of the analyses can be found in the Proceedings of the Third International Conference (1995) on Harmonization.

Positive results in long-term carcinogenicity studies that are not relevant to the therapeutic use of a pharmaceutical present a dilemma to all parties—regulatory reviewers and companies developing drugs. The conduct of only one long-term carcinogenicity study (rather than two) would, in part, allow resources to be diverted towards other currently evolving experimental approaches. The totality of the data derived from one long-term study and other appropriate experimental investigations contribute to a ''weight of evidence'' approach that should improve the assessment of carcinogenic risk to humans.

3. Scope of the Guideline

The guideline embraces all pharmaceutical agents, including biotechnology-derived pharmaceuticals, that need carcinogenic testing as indicated by Guidelines S1A and S6.

4. The Guideline

4.1 Preamble.

The decision to conduct a long-term carcinogenicity study of a pharmaceutical is made only after the acquisition of certain key units of information, including the results of genetic toxicology (Guidelines S2A and S2B), intended patient population, clinical dosage regimen (Guideline S1A), pharmacodynamics, in animals and in humans (selectivity, dose-response) (Guideline S1C), and repeated-dose toxicology in two species. Repeated-dose toxicology studies in any species (including nonrodents) may indicate that the test compound possesses immunosuppressant properties or hormonal activity known to be a risk factor for humans, and this information should be considered in the design of any further studies for the assessment of carcinogenic potential (see also Note 1).

4.2 Experimental approaches to testing for carcinogenic activity.

Flexibility and judgment should be exercised in the choice of approach. It should be influenced by the information cited in the above preamble. Given the complexity of the process of carcinogenesis, no single experimental approach can be expected to predict accurately the carcinogenic potential of a chemical in humans.

The basic principle:

The basic scheme comprises one long-term rodent carcinogenicity study, plus one other study of the type mentioned in section 4.2.2 (see Note 2).

4.2.1 Choice of species for a long-term carcinogenicity study.

The species selected should be the most appropriate one, based on considerations that may include the following comparative studies in two or more rodent species:

(a) Pharmacology.

(b) Repeated-dose toxicology studies.

(c) Metabolism (see also Guidelines S1C and S3A).

(d) Toxicokinetics (see also Guidelines S1C, S3A, and S3B).

(e) Route of administration (e.g., less common routes such as dermal and inhalation).

In the absence of clear evidence favoring one species, it is recommended that the rat be selected. This view is based on the factors discussed in section 6.

4.2.2 Additional tests for carcinogenic activity in vivo.

(a) Short or medium-term rodent test systems.

Possibilities include the use of models providing insight into carcinogenic endpoints in vivo. These may include models of initiation-promotion in rodents, or transgenic rodents, or new-born rodents (Note 3).

(b) A long-term carcinogenicity study in a second rodent species.

It is still acceptable to conduct a long-term carcinogenicity study in a second rodent species.

5. Mechanistic Studies

Mechanistic studies are often useful for the interpretation of tumor findings in a carcinogenicity study, and to provide a perspective on their relevance to human risk assessment. The choice of investigative study will be dictated by the particular properties of the drug and/or the specific results from carcinogenicity testing. Suggestions include:

5.1. Cellular changes.

Relevant tissues may be examined for changes at the cellular level using morphological, histochemical, or functional criteria. As appropriate, attention may be directed to such changes as the dose-relationships for apoptosis, cell proliferation, liver foci, or changes in intercellular communication.

5.2. Biochemical measurements.

Depending on the putative mode of action, investigations could involve measurements of and dose-dependency of such areas as circulating prolactin, thyroid stimulating hormone, luteinizing hormone, 17β-estradiol, gastrin, cholecystokinin, binding to α2μ-globulin, and growth factors.

In some situations, it may be possible to test a hypothesis of, for example, a hormone imbalance with another study in which the

imbalance has been, at least in part, compensated.

5.3. Considerations for additional genotoxicity testing (see Guidelines S2A and S2B).

Additional genotoxicity testing in appropriate models may be invoked for compounds that were negative in the standard 3-test battery but which have shown effects in a carcinogenicity test with no clear evidence for an epigenetic mechanism. Additional testing can include modified conditions for metabolic activation in in vitro tests or can include in vivo tests measuring genotoxic damage in target organs of tumor induction (e.g., liver UDS test, 32P-postlabeling, mutation induction in transgenes).

5.4. Modified protocols.

Sponsors are encouraged to develop modified protocols that may clarify the mode of action of the test substance. Such protocols might include groups of animals to explore, for example, the consequence of interrupted dosage regimens, or the reversibility of cellular changes after cessation of dosing.

6. General Considerations in the Choice of the Most Appropriate Species

There are several general considerations which, in the absence of other clear indications, suggest that the rat will normally be the species of choice for a bioassay.

6.1. Information from pharmaceutical data bases.

In the analysis of the six data bases, attention was given to data on genetic toxicology, tumor incidence, strain of animal, route and dosage regimen, pharmacological or therapeutic activity, development and/or regulatory status, and, if relevant, reason for termination of development. Inevitably, there was considerable overlap between the data bases, but that is not necessarily an impediment to drawing valid conclusions.

The main overall conclusions from the analysis were:

a. Although very few instances have been identified of mouse tumors being the sole reason for regulatory action concerning a pharmaceutical, data from this species may have contributed to a weight-of-evidence decision and in identifying agents that caused tumors in two rodent species.

b. Of the compounds displaying carcinogenic activity in only one species, the number of ''rat-only'' compounds was about double the number of ''mouse-only'' compounds, implying in a simplistic sense that the rat is more ''sensitive'' than the mouse.

c. As with other data bases accessible in the literature, the pharmaceutical data bases were dominated by the high incidence of rodent liver tumors. The high susceptibility of rodent liver to nongenotoxic chemicals has been the subject of many symposia and workshops. These have concluded that these tumors may not always have relevance to carcinogenic risk in humans and frequently make the use of the rodent for this purpose misleading.

6.2. Potential to study mechanisms.

The carcinogenic activity of nongenotoxic chemicals in rodents is characterized by a high degree of species, strain, and target organ specificity and by the existence of thresholds in the dose-response relationship. Mechanistic studies in recent years have permitted the distinction between effects that are specific to the rodent model and those that are likely to have relevance for humans. Progress has often been associated with increased understanding of species and tissue specificity of receptors and receptor sub-types. Receptor-mediated carcinogenesis is of growing importance. Nearly all of these advances are being made in the rat, and only rarely in the mouse.

6.3. Metabolic disposition.

Neither rats nor mice would seem, on metabolic grounds, to be a priori generally more suitable for the conduct of bioassays. However, much attention is now being given to pharmacokinetic-pharmacodynamic relationships and rapid progress is occurring in knowledge of the P–450 isozymes that mediate the biotransformation of drugs. Nearly all of this research activity is confined to rats and humans. Therefore, in the near future at least, it appears that mice would be less likely to provide metabolic information useful in mechanistic studies.

6.4. Practicality.

Pertinent to the above two topics is the question of feasibility of investigative studies. Size considerations alone put the mouse at a severe disadvantage when it comes to the taking of serial blood samples, microsurgery/catheterization, and the weighing of organs. Blood sampling often requires the sacrifice of the animals, with the result that many extra animals may be required when mice are subject to such investigations.

6.5. Exceptions.

Despite the above considerations, there may be circumstances when the mouse or another rodent species could be justified on mechanistic, metabolic, or other grounds as being a more appropriate species than the rat for human risk assessment.

Notes

Note 1. Data from cell transformation assays can be useful at the compound selection stage. Data exist in the literature for over 200 agents including rodent carcinogens and noncarcinogens that have been tested in both cell transformation assays and in long-term rodent carcinogenicity tests.

Note 2. If the findings of a long-term carcinogenicity study and of genotoxicity tests and other data indicate that a pharmaceutical poses a carcinogenic hazard to humans, a second carcinogenicity study would not be necessary.

Note 3. Several experimental methods are currently under investigation but, thus far, relatively few pharmaceutical agents have been evaluated. During the ICH Step 2 to Step 3 process, i.e., during the open comment period, interested parties are invited to submit information on in vivo models for which there is currently sufficient experience available for human risk assessment. The evaluation will include consideration of animal numbers and welfare. The following list of approaches may be revised in the light of further information.

(a) One rat initiator-promoter model for the detection of hepatocarcinogens (and modifiers of hepatocarcinogenicity) employs an initiator, followed by several weeks' exposure to the test substance. Another multi-organ model employs up to five initiators followed by several months' exposure to the test substance.

(b) Several transgenic mouse assays are currently under evaluation. These include the p53 deficient model, the TG.AC model, the ras H2 model, the Eμ-pim-1 model, the TGF-α model, the XPA deficient model, etc.

(c) Neonatal rodents have been studied since the 1960's. The chemicals tested are mostly genotoxic. A number of nongenotoxic pharmaceutical agents are currently being evaluated.

Other ICH Guidelines Cited

Guideline S2A: Notes for Guidance on Specific Aspects of Regulatory Genotoxicity Tests.

Guideline S2B: A Standard Battery of Genotoxicity Testing of Pharmaceuticals.

Guideline S3A: Notes for Guidance on Toxicokinetics. The Assessment of Systemic Exposure in Toxicity Studies.

Guideline S3B: Guidance on Repeat-Dose Tissue Distribution Studies.

Guideline S6: Preclinical Testing of Biotechnology-derived Pharmaceuticals.

Dated: August 13, 1996.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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