DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 94D–0017]

International Conference on Harmonisation; Guidance on Dose Selection for Carcinogenicity Studies of Pharmaceuticals: Addendum on a Limit Dose and Related Notes; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a guidance entitled ''S1C(R) Addendum to 'Dose Selection for Carcinogenicity Studies of Pharmaceuticals': Addition of a Limit Dose and Related Notes.'' The guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guidance is intended to define the conditions under which it would be considered acceptable to use a ''limit dose'' for the high dose selection of nongenotoxic pharmaceuticals in long-term carcinogenicity studies, and is an addendum to an earlier ICH guidance on criteria for establishing uniformity among international regulatory agencies for dose selection for carcinogenicity studies of human pharmaceuticals.

DATES: Effective December 4, 1997. Submit written comments at any time.

ADDRESSES: Submit written comments on the guidance to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Copies of the guidance are available from the Drug Information Branch (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–4573.

FOR FURTHER INFORMATION CONTACT:

Regarding the guidance: Joseph J. DeGeorge, Center for Drug Evaluation and Research (HFD–24), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–6758.

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 is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA, and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

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

In the **Federal Register** of April 2, 1997 (62 FR 15715), FDA published a draft tripartite guideline entitled ''Dose Selection for Carcinogenicity Studies of Pharmaceuticals: Addendum on the Limit Dose'' (S1C(R)). The notice gave interested persons an opportunity to submit comments by June 2, 1997.

After consideration of the comments received and revisions to the guidance, a final draft of the guidance was submitted to the ICH Steering Committee and endorsed by the three participating regulatory agencies on July 17, 1997.

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

The guidance is an addendum to an ICH final guidance published in the **Federal Register** of March 1, 1995 (60 FR 11278), entitled ''Dose Selection for Carcinogenicity Studies of Pharmaceuticals.'' The guidance is intended to define the conditions under which it would be considered acceptable to use a ''limit dose'' for the high dose selection of nongenotoxic pharmaceuticals in long-term carcinogenicity studies.

This guidance represents the agency's current thinking on dose selection for carcinogenicity studies of 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.

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

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

The text of the guidance follows:

''S1C(R) Addendum to 'Dose Selection for Carcinogenicity Studies of Pharmaceuticals': Addition of a Limit Dose and Related Notes''[1]

Limit Dose

In determining the high dose for carcinogenicity studies using the approaches outlined in this guidance, it may not be necessary to exceed a dose of 1500 milligrams (mg)/kilograms (kg)/day (Note 1). This limit dose applies only in cases where there is no evidence of genotoxicity and where the maximum recommended human dose does not exceed 500 mg/day (Note 2).

Data should be provided comparing exposure of rodents and humans to drug and

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metabolites primarily to support dose selection for and interpretation of the carcinogenicity study. Based on such information, there may be cases where the limit of 1500 mg/kg/day is not acceptable because it cannot be assured that animal exposure after 1500 mg/kg/day is sufficiently high compared to the exposure achieved in humans. The rodent systemic exposure at 1500 mg/kg/day should be greater by at least an order of magnitude than human exposure measured at the intended human therapeutic dose. [If this is not the case, efforts should be made to increase the rodent exposure or to reconsider the animal model in a case-by-case approach.] If the human dose exceeds 500 mg/day, the high dose may be increased up to the maximum feasible dose.

Note 1

Review of the FDA carcinogenicity database of nearly 900 carcinogenicity tests indicated that about 20 tests had been conducted that used doses of 1000 mg/kg or greater as the highest dose tested. About 10 of these tests were considered as having demonstrated a carcinogenic response. Seven of these were positive only at or above 1000 mg/kg, including two that were positive in two species (in neither case were doses above 1000 mg/kg necessary to detect the carcinogenic response in both species, but rather in only one of the two species was a dose greater than 1000 mg/kg necessary).

Some of the one species positives were also only positive at doses greater than 1000 mg/kg. In one case where the drug was considered as demonstrating a significant tumor response only above 1000 mg/kg, it was positive in several nonstandard genotoxicity assays but not in standard genotoxicity studies. Regulatory action has resulted from some of these cases. Based on these results, the limit dose for carcinogenicity testing should be 1500 mg/kg rather than 1000 mg/kg to eliminate the risk that a genotoxic carcinogen will not be able to be identified as a result of adoption of a limit dose of 1000 mg/kg.

Note 2

It has been agreed that if a nongenotoxic drug is only positive in rodents at doses above those producing a 25-fold exposure over humans, such finding would not be considered likely to pose a relevant risk to humans.

It has been shown that systemic exposure comparisons between rodents and humans are better estimated by dose using mg/square meters (m^2) than using mg/kg (Note 4 of the S1C document ''Dose Selection for Carcinogenicity Studies of Pharmaceuticals''). Therefore, the human dose should be at least 25-fold lower on a mg/m^2 basis than the high dose in the carcinogenicity study. The factor, 6–7 (6.5), is used to convert rat doses from mg/kg to mg/m^2 and 40 is used to convert human doses from mg/kg to mg/m^2 . Thus, the estimated systemic exposure ratio of 25-fold rodent to human is equal to about a 25-fold mg/m^2 ratio or a 150-fold mg/kg ratio (150 ≈ 25 x 40/6.5). Therefore, a human dose below 10 mg/kg/day (about 500 mg/day or less) could be tested in rats at 1500 mg/kg as the high dose.

Dated: November 24, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 97–31780 Filed 12–4–97; 8:45 am]

BILLING CODE 4160–01–F