DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97D–0444]

International Conference on Harmonisation; Guidance on the Duration of Chronic Toxicity Testing in Animals (Rodent and Nonrodent Toxicity Testing); Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a guidance entitled ''S4A Duration of Chronic Toxicity Testing in Animals (Rodent and Nonrodent Toxicity Testing).'' The guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and is intended to provide guidance on the duration of chronic toxicity testing in rodents and nonrodents as part of the safety evaluation of a drug product. FDA is also noting circumstances in which it may accept durations of chronic toxicity testing in nonrodents that differ from the duration generally recommended by ICH.

DATES: Effective June 25, 1999. Submit written comments at any time.

ADDRESSES: Submit written comments on the guidance to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. 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. Single copies of the guidance may be obtained by mail from the Office of Communication, Training and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research (CBER), 1401 Rockville Pike, Rockville, MD 20852–1448, 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 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 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.

In the **Federal Register** of November 18, 1997 (62 FR 61513), FDA published a draft tripartite guidance entitled ''S4A Duration of Chronic Toxicity Testing in Animals (Rodent and Nonrodent Toxicity Testing).'' The notice gave interested persons an opportunity to submit comments by January 20, 1998.

There were no comments received and no 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 September 2, 1998.

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 document provides guidance on the duration of chronic toxicity testing in rodents and nonrodents as part of the safety evaluation of a drug product. The guidance is intended to help eliminate or reduce the need for pharmaceutical companies to duplicate testing in animals during the development of new drug products. The guidance is based on information currently available to the agency, and this information is available to the public in Docket No. 97D–0444.

This guidance represents the agency's current thinking on the duration of chronic toxicity testing in animals (rodent and nonrodent toxicity testing). 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.

For guidance on biotechnology-derived pharmaceuticals, interested parties are advised to consult the ICH guidance ''S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals'' (62 FR 61515, November 18, 1997).

FDA note on duration of chronic toxicity testing in nonrodents: The ICH guidance recommends 9-month chronic toxicity studies in nonrodents. FDA considers 9-month studies in nonrodents acceptable for most drug development programs, shorter studies may be equally acceptable in some circumstances and longer studies may be more appropriate in others, as follows:

- Six-month studies may be acceptable for indications of chronic conditions associated with short-term, intermittent drug exposure, such as bacterial infections, migraine, erectile dysfunction, and herpes.
- Six-month studies may be acceptable for drugs intended for indications for life-threatening diseases for which substantial long-term human clinical data are available, such as cancer chemotherapy in advanced disease or in adjuvant use.
- Twelve-month studies may be more appropriate for chronically used drugs to be approved on the basis of short-term clinical trials employing efficacy surrogate markers where safety data from humans are limited to short-term exposure, such as some acquired immunodeficiency syndrome (AIDS) therapies.

• Twelve-month studies may be more appropriate for new molecular entities acting at new molecular targets where postmarketing experience is not available for the pharmacological class. Thus, the therapeutic is the first in a pharmacological class for which there is limited human or animal experience on its long-term toxic potential.

As with all of FDA's guidances, 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 at ''http://www.fda.gov/cder/guidance/index.htm'' or at CBER's World Wide Web site at ''http://www.fda.gov/cber/publications.htm''.

The text of the guidance follows:

S4A Duration of Chronic Toxicity Testing in Animals (Rodent and Nonrodent Toxicity Testing)[1]

1. Objective

The objective of this guidance is to set out the considerations that apply to chronic toxicity testing in rodents and nonrodents as part of the safety evaluation of a medicinal product. Since guidance is not legally binding, an applicant may submit justification for an alternative approach.

2. Scope

This guidance has been prepared for the development of medicinal products with the exception of those already covered by the ICH guidance ''S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals'' (62 FR 61515, November 18, 1997), e.g., monoclonal antibodies, recombinant DNA proteins.

3. Background

During the first International Conference on Harmonisation in 1991, the practices for the testing of chronic toxicity in the three regions (the European Union, Japan, and the United States) were reviewed. Arising from this, it emerged that there was a scientific consensus on the approach for chronic testing in rodents, supporting the harmonized duration of testing of 6 months. However, for chronic toxicity testing in nonrodents, there were different approaches to the duration of testing.

The lack of harmonized duration led to the need for pharmaceutical companies to perform partially duplicative studies for both 6 and 12 months' duration when developing new medicinal products. As the objective of ICH is to reduce or eliminate the need to duplicate testing during development of medicinal products and to ensure a more economical use of material, animal, and human resources, while at the same time maintaining safeguards to protect public health, further scientific evaluation was undertaken.

Each of the regulatory authorities in the European Union, Japan, and the United States undertook a review to determine whether a single duration for chronic toxicity testing in nonrodents could be identified. From this analysis, it emerged that in 16 cases a more detailed evaluation of 6 versus 12 months' data should be undertaken.

This evaluation was conducted as a joint exercise by the competent authorities in the three regions.

In some of the cases analyzed at the tripartite meetings, there were no additional findings at 12 months. For some other cases, there was not complete agreement among the regulators with respect to the comparability in study design and conduct to allow assessment of whether there were differences in the findings at 6 and 12 months due to duration of treatment alone.

In a number of cases there were findings observed by 12 months, but not by 6 months. It was concluded that these would, or could, have been detected in a study of 9 months' duration. Varying degrees of concern for the differences in findings detected between the studies of different durations were expressed. An agreement on the clinical relevance of these findings could not be reached.

Studies of 12 months' duration are usually not necessary, and studies of shorter than 9 months' duration may be sufficient.

In the European Union, studies of 6 months' duration in nonrodents are acceptable according to Council Directive 75/318/EEC, as amended. To avoid duplication, where studies with a longer duration have been conducted, it would not be necessary to conduct a study of 6 months.

4. Guidance on Duration of Chronic Toxicity Testing for Tripartite Development Plan

Arising from the extensive analysis and review of the above mentioned data in nonrodents and based upon the achievements of ICH 1 for testing in rodents, and so as to avoid duplication and follow a single development plan for chronic toxicity testing of new medicinal products, the following studies are considered acceptable for submission in the three regions:

(1) *Rodents*:A study of 6 months' duration;

(2) *Nonrodents*: A study of 9 months' duration.

[1] This guidance represents the agency's current thinking on the duration of chronic toxicity testing in animals (rodent and nonrodent toxicity testing). 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 satisifes the requirements of the applicable statute, regulations, or both.

Dated: June 17, 1999.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy Coordination.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Blood Donor Suitability Workshop: Donor History of Hepatitis

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

The Food and Drug Administration (FDA) is announcing the following public workshop entitled ''Blood Donor Suitability Workshop: Donor History of Hepatitis.'' The purpose of the workshop is to discuss whether prospective blood donors with a history of viral hepatitis should be deferred from donating blood.

Date and Time: The workshop will be held on Wednesday, July 21, 1999, 8:30 a.m. to 5 p.m.

Location: The workshop will be held at Natcher Auditorium, Bldg. 45, 45 Center Dr., National Institutes of Health, 8800 Rockville Pike, Bethesda, MD.

Contact: Joseph Wilczek, Center for Biologics Evaluation and Research (HFM–350), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–6129, FAX 301–827–2843.

Registration: Early registration is recommended. Mail or fax registration information (including name, title, firm name, address, telephone, and fax number), to the contact person on or before Friday, July 2, 1999.

Registration at the site will be done on a space available basis on the day of the workshop beginning at 7:30 a.m. There is no registration fee for the workshop.

If you need special accommodations due to disability, please contact Joseph Wilczek at least 7 days in advance.

Agenda: The public workshop is intended to discuss a variety of issues concerning blood donor deferrals based on a history of viral hepatitis. These issues include, but are not limited to, the following: (1) Definitions and clarification of terms such as ''history of hepatitis'' and ''history of jaundice'' in the context of blood donation; (2) whether a prospective blood donor with a history of hepatitis A, who is anti-HAV IgG positive, is an unacceptable donor; (3) whether deferrals are appropriate for individuals with a