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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 (*insert date of publication in the Federal Register*). 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

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.

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 satisfies the requirements of the applicable statute, regulations, or both.

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.

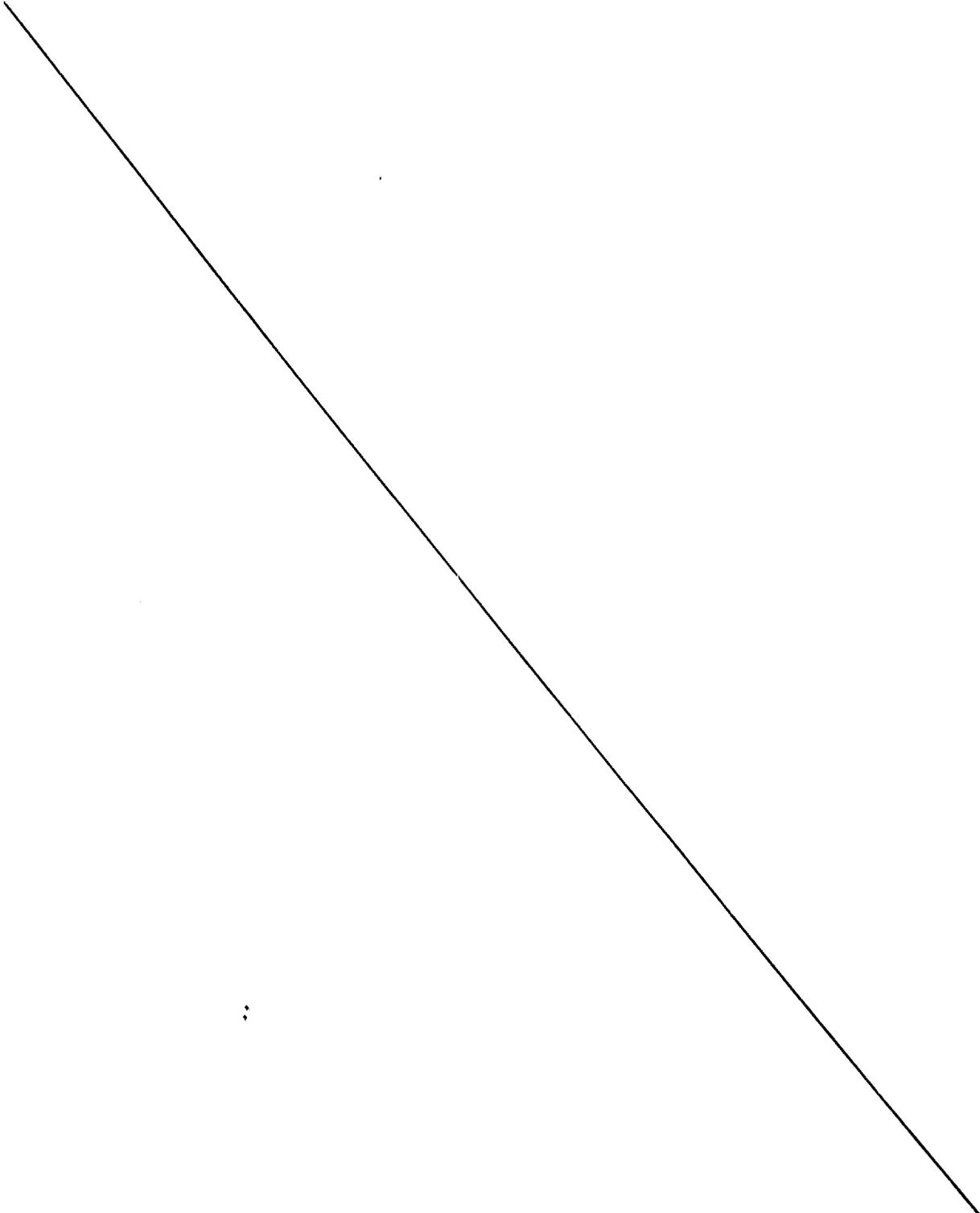
Studies of 12 months' duration are usually not necessary, and studies of shorter than 9 months' duration may be sufficient.

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:

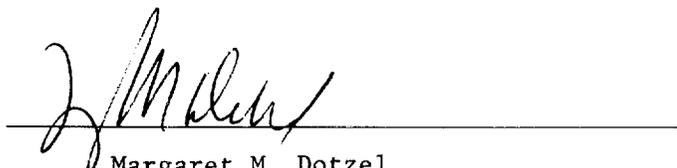


(1) *Rodents*: A study of 6 months' duration;

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

Dated: 6/17/99

June 17, 1999



Margaret M. Dotzel
Acting Associate Commissioner for
Policy Coordination

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