DEPARTMENT OF HEALTH AND HUMAN SERVICES

[Docket No. 93D–0140]

International Conference on Harmonisation; Guideline on Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration is publishing a guideline entitled ''Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility.'' 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 reflect sound scientific principles for reproductive toxicity testing concerning male fertility, and is an addendum to an earlier ICH guideline on the detection of toxicity to reproduction for medicinal products.

DATES: Effective April 5, 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, rm. 1–23, 12420 Parklawn Dr., 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 43500), FDA published a draft tripartite guideline entitled ''Detection of Toxicity to Reproduction: Addendum on Toxicity to Male Fertility.'' 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 an addendum to an ICH guideline published in the Federal Register of September 22, 1994 (59 FR 48746), entitled ''Guideline on Detection of Toxicity to Reproduction for Medicinal Products.'' The guideline is intended to reflect sound scientific principles for reproductive toxicity testing concerning male fertility.

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 that 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 the detection of toxicity to reproduction for medicinal products.

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 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:

Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility

1. Introduction

This text is an addendum to the ICH Tripartite Guideline on Detection of Toxicity to Reproduction for Medicinal Products and provides amendments to the published text.

At the time of adoption, it was accepted that the male fertility investigation, as included in the currently harmonized guideline, would need scientific and regulatory improvement and optimization of test designs.

The amendments are intended to provide a better description of the testing concept and recommendations, especially those addressing:

- Flexibility
- Premating treatment duration
- Observations

The general principles and background were contained in two papers published in the *Journal of American College of Toxicology*. These papers contain the necessary experimental data (prospective and retrospective) for reaching consensus and have been commented on. The individual data from the Japanese collaborative study were also published in the *Journal of Toxicological Science*.

2. Amendments

Introduction (Last Paragraph)

To employ this concept successfully, flexibility is needed (Note 1). No guideline can provide sufficient information to cover all possible cases. All persons involved should be willing to discuss and consider variations in test strategy according to the state-of-the-art and ethical standards in human and animal experimentation.

4.1.1. Study of Fertility and Early Embryonic Development to Implantation

Administration period

The design assumes that, especially for effects on spermatogenesis, use will be made of available data from toxicity studies (e.g., histopathology, weight of reproductive organs, in some cases hormone assays and genotoxicity data). Provided no effects have been found in repeated dose toxicity studies of at least 4 weeks duration that preclude this, a premating treatment interval of 2 weeks for females and 4 weeks for males can be used (Note 12). Selection of the length of the premating administration period should be stated and justified. Treatment should continue throughout mating to termination for males and at least through implantation for females. This will permit evaluation of functional effects on male fertility that cannot be detected by histopathologic examination in repeated dose toxicity studies and effects on mating behavior in both sexes. If data from other studies show there are effects on weight or histology of reproductive organs in males or females, or if the quality of examinations is dubious, or if there are no data from other studies, the need for a more comprehensive study should be considered (Note 12).

Observations

At terminal examination, the following should be done:

- Perform necropsy (macroscopic examination) of all adults;
- Preserve organs with macroscopic findings for possible histopathological evaluation; keep corresponding organs of sufficient controls for comparison;
- Preserve testes, epididymides, ovaries, and uteri from all animals for possible histopathological examination and evaluation on a case by case basis;
- Count corpora lutea, implantation sites (Note 16);
- Count live and dead conceptuses; and
- Sperm analysis can be used as an optional procedure for confirmation or better characterization of the effects observed (Note 12).

Note 12 (4.1.1) Premating Treatment

The design of the fertility study, especially the reduction in the premating period for males, is based on evidence accumulated and on re-appraisal of the basic research on the process of spermatogenesis. Compounds inducing selective effects on male reproduction are rare; compounds affecting spermatogenesis almost invariably affect postmeiotic states and weight of testis; mating with females is an insensitive means of detecting effects on spermatogenesis. Histopathology of the testis has been shown to be the most sensitive method for the detection of effects of spermatogenesis. Good pathological and histopathological examination (e.g., by employing Bouin's fixation, paraffin embedding, transverse section of 2–4 microns for testes, longitudinal section for epididymides, PAS and hematoxylin staining) of the male reproductive organs provides a direct means of detection. Sperm analysis (sperm counts, sperm motility, sperm morphology) can be used as an optional method to confirm findings by other methods and to further characterize effects. Sperm analysis data are considered more relevant for fertility assessment when samples from vas deferens or from cauda epididymis are used. Information on potential effects on spermatogenesis (and female reproductive organs) can be derived from repeated dose toxicity studies or reproductive toxicity studies.

For detection of effects not detectable by histopathology of male reproductive organs and sperm analysis, mating with females after a premating treatment of 4 weeks has been shown to be at least as efficient as mating after a longer duration of treatment (2 weeks may be acceptable in some cases). However, when 2 weeks treatment period is selected, more convincing justification should be provided. When the available evidence suggests that the scope of investigations in the fertility study should be increased, appropriate studies should be designed to characterize the effects further.

Dated: March 29, 1996.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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