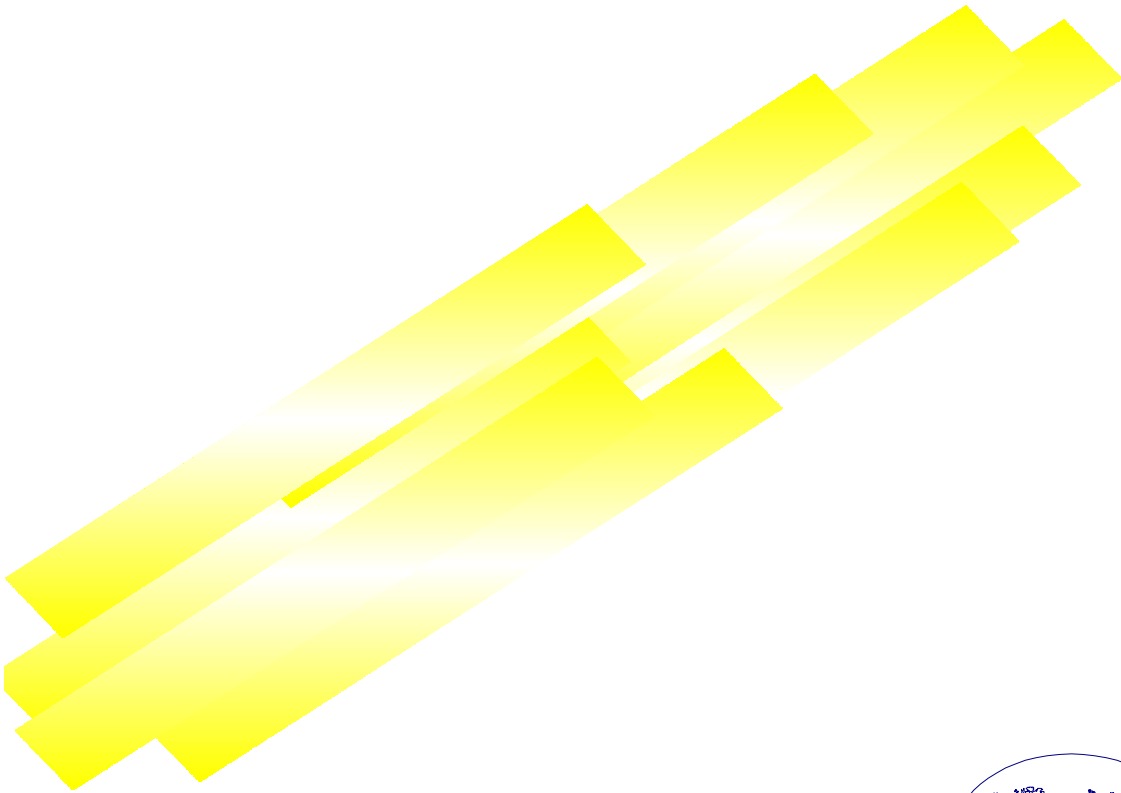


Guideline for Industry

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



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GUIDELINE FOR INDUSTRY¹

DETECTION OF TOXICITY TO REPRODUCTION FOR MEDICINAL PRODUCTS: ADDENDUM ON TOXICITY TO MALE FERTILITY

I. INTRODUCTION (1)

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*.

¹This guideline was developed within the Expert Working Group (Safety) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 29, 1995. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and the USA. This guideline was published in the *Federal Register* on April 5, 1996 (61 FR 15360) and is applicable to drug and biological products. Although this guideline does not create or confer any rights for or on any person and does not operate to bind FDA or the industry, it does represent the agency's current thinking on the detection of toxicity to reproduction for medicinal products. For additional copies of this guideline, contact the Drug Information Branch, HFD-210, CDER, FDA, 5600 Fishers Lane, Rockville, MD 20857 (Phone: 301-827-4573) or the Manufacturers Assistance and Communication Staff (HFM-42), CBER, FDA, 1401 Rockville Pike, Rockville, MD 20852-1448. Send one self-addressed adhesive label to assist the offices in processing your request. An electronic version of this guidance is also available via Internet using the World Wide Web (WWW) (connect to the CDER Home Page at <http://www.fda.gov/cder> and go to the "Regulatory Guidance" section).

II. AMENDMENTS (2)

A. Introduction (Last Paragraph) (I.A)

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.

B. Study of Fertility and Early Embryonic Development to Implantation (4.1.1)

1. Administration period (IV.A.1.e. (4.1.1))

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 pre-mating treatment interval of 2 weeks for females and 4 weeks for males can be used (Note 12). Selection of the length of the pre-mating 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).

2. Observations (IV.A.1.h (4.1.1))

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).

C. Note 12 (IV.A.1 (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 2094 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.