Assessment of Male-Mediated Developmental Risk for Pharmaceuticals

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2015
Pharmacology and Toxicology

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Assessment of Male-Mediated Developmental Risk for Pharmaceuticals Guidance for Industry[1]

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I. INTRODUCTION

This guidance provides recommendations to sponsors for assessing risks to embryo/fetal development resulting from administration of an investigational active pharmaceutical ingredient (API)[2] to males, either through an effect on the male germ cell or from seminal transfer of an API that has been shown to be genotoxic or a potent developmental toxicant[3] when administered to pregnant animals or humans.

The guidance presents an overview of FDA's current approach to assessing the following potential risks associated with pharmaceutical use in male patients:

- Male-mediated developmental risk involving effects of the API on the germ cell
- Developmental toxicity in the conceptus associated with transfer of the API in seminal fluid to pregnant partners

The guidance also applies to a new molecular entity for which the risk has not yet been assessed.

Specifically, the guidance discusses recommendations for examining the potential for API exposure in males to adversely affect offspring development based on the following considerations:

[1] This guidance has been prepared by the Pharmacology and Toxicology staff in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] API refers to the active component in drug and biologic products.

[3] A *potent developmental toxicant* is defined as one associated with adverse fetal outcomes at or near clinical exposures or for which a no observed adverse effect level has not been defined.

- Evaluation of mechanism of action, genotoxicity, reproductive toxicity,[4] and developmental toxicity studies

- Known effects of API or pharmaceutical class in animals or humans

- Assessment of potential embryo/fetal exposure through transfer and vaginal uptake of reproductive or developmental toxicants[5] secreted into seminal fluid

The guidance also covers overall considerations in assessing male-mediated developmental risk, including factors that investigators should consider when testing a new API in males, and recommendations on risk mitigation (e.g., measures to prevent pregnancy or seminal transfer to a pregnant sexual partner when risk is anticipated).

This guidance does not address the potential risks to partners exposed to seminal fluid transfer of an API from men taking pharmaceutical products, nor does it discuss potential effects on embryo/fetal development resulting from exposure to pregnant women via any route other than seminal transfer. It also does not specifically address potential effects on the ability of the treated population or their partners to conceive.

General guidance on assessing genotoxicity and reproductive and developmental risk is available in appropriate nonclinical guidances.[6]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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[4] Male reproductive toxicity refers to an adverse effect on the reproductive competence of sexually mature males, and includes genetic and nongenetic damage to the male germ cell.

[5] For the purposes of this guidance, a *developmental toxicant* is defined as any pharmaceutical that adversely affects survival, structure, growth, and/or function of the developing organism following exposure before conception or in utero.

[6] For genotoxicity, see the ICH guidance for industry *S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use*. For reproductive and developmental risk, see the guidance for industry *Reproductive and Developmental Toxicities — Integrating Study Results to Assess Concerns* and the ICH guidances for industry *S5A Detection of Toxicity to Reproduction for Medicinal Products* and *S5B Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility*. (In November 2005, ICH combined the S5A and S5B guidances and titled the combined document *S5(R2) Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility.* The contents of the guidances were not revised.) We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

II. BACKGROUND

Current regulatory guidance exists regarding the need to assess the genotoxic and embryo/fetal developmental toxicity potential of pharmaceuticals before their administration to pregnant women and females of reproductive potential.[7] However, there is a lack of consistency in clinical trial protocol designs (e.g., recommendations for contraception use and inclusion/exclusion criteria) regarding pregnancy risk for sexual partners of men being administered an API. The conceptus of a female sexual partner may be subject to developmental risk associated with pre- or postconception exposure of a male to an API. Such male-mediated developmental toxicity may result from an effect of the API on the male germ cell before conception or occur as a result of direct exposure of the conceptus to the pharmaceutical following seminal transfer and vaginal uptake in a pregnant partner (Davis, Friedler, et al. 1992; Trasler and Doerksen 1999; Hales and Robaire 2012).

At the time of the design of a clinical trial with an investigational drug, it is likely that the only information regarding potential risks to male reproduction or the development of offspring will be from nonclinical studies. When a trial involves exposure to a potential reproductive or developmental toxicant, issues of risk characterization, informed consent, and contraceptive options are important considerations. Investigators designing clinical studies involving male subjects need to consider the potential for adverse effects on the conceptus of a sexual partner who is or may become pregnant. Given a lack of clinical information, nonclinical data will be used to assess this risk and to inform decisions regarding the need for appropriate precautions during clinical trials.

III. CONSIDERATIONS AND RECOMMENDATIONS FOR ASSESSING MALE-MEDIATED DEVELOPMENTAL RISK

Evaluation of male-mediated developmental risk to inform risk mitigation strategies depends on the availability of pertinent nonclinical and clinical information. Important factors to consider when evaluating the potential for developmental toxicity include what is known about:

- The reproductive and developmental toxicity of the pharmaceutical or related compounds
- The cytotoxic or genotoxic properties of the drug
- Pharmacologic properties that suggest risk (e.g., whether the compound targets or indirectly affects developmental signaling pathways, rapidly dividing cells, or endocrine function)
- The absorption, distribution, metabolism, and excretion (ADME) properties of the drug (e.g., distribution to and/or accumulation in male reproductive tissues or partitioning into semen)

[7] See the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.

It is the intent of FDA to consider the totality of the evidence provided by a sponsor to support recommendations regarding the need for male contraception at the time of trial design or to support labeling recommendations at the time of drug approval.

Unless existing data demonstrate that only germ cells are affected, FDA recommendations for contraceptive use apply to both reproductively competent men as well as vasectomized men because risks associated with transfer of a drug or biologic via seminal fluid also apply to men who have had a vasectomy.

The following recommendations are based on consideration of this information.

A. Unknown Genotoxic, Reproductive, and/or Developmental Risk Potential

Until the genotoxicity and reproductive and/or developmental risk potential of an API have been adequately characterized in nonclinical studies, male subjects in clinical trials should take precautions to prevent pregnancy of a partner and/or exposure of a conceptus during and after the period of pharmaceutical exposure.

B. Known Genotoxic, Reproductive, and/or Developmental Effects in Nonclinical Studies

1. Genotoxic Agents

Putative mechanisms of male-mediated developmental toxicity include those based on the induction of genetic damage or mutations in the male germ cell before conception (Olshan and Faustman 1993; Harrouk, Codrington, et al. 2000; Robaire and Hales 2003). Genotoxic agents present in the seminal fluid may also have direct effects on the conceptus. Various adverse developmental outcomes, including embryo/fetal mortality, structural defects, growth impairment, and behavioral abnormalities, have been reported in animals after paternal exposure to known genotoxins; and epidemiological studies have reported associations between paternal genotoxin exposure and increases in adverse pregnancy outcomes in humans (Brinkworth 2000; Anderson, Schmid, et al. 2014). In addition to genotoxic mechanisms, other forms of heritable sperm damage (e.g., epigenetic modifications) may be involved in paternally mediated developmental toxicity (Doerksen, Benoits, et al. 2000; Barton, Robaire, et al. 2005).

FDA recommends appropriate contraception for males who are administered any API identified as genotoxic, based on an integrated assessment of nonclinical data.

2. Reproductive Toxicants

Studies of male reproductive toxicity can identify a range of effects relevant to the assessment of potential male-mediated developmental toxicity, including effects on sperm quality, implantation, and the early embryo (Safarinejad 2008; Lewis and Aitken 2005). In the event that an API has been identified as having the potential to affect male reproduction based on either the mechanism of action or through demonstrated animal toxicity (e.g., in a repeat-dose toxicity

study or study evaluating fertility), appropriate contraception should be considered until the possible implications for developmental risk have been assessed.

3. Developmental Toxicants

Seminal transfer of a developmentally toxic pharmaceutical may result in direct adverse effects on the conceptus. A number of developmental toxicants present in seminal fluid have been reported to affect pregnancy outcomes adversely in animals by this mechanism (Robaire and Hales 1994). For example, the presence of thalidomide in semen was associated with evidence of developmental toxicity, including fetal malformations, in the progeny of treated male rabbits (Lutwak-Mann, Schmid, et al. 1967), and increased preimplantation loss after mating cyclophosphamide-treated male rats with untreated females was attributed to the presence of the drug in seminal fluid (Hales, Smith, et al. 1986). Thalidomide has been measured in human semen after oral dosing, with an apparent correlation between semen and plasma levels (Teo, Harden, et al. 2001).

Therefore, when a significant developmental risk has been identified in nonclinical studies in which the pregnant female is dosed, precautions to prevent pregnancy or exposure of a conceptus in partners of a treated male should be considered until the potential for male-mediated effects has been fully assessed (e.g., determination of API levels in human seminal fluid ejaculate).

IV. NONCLINICAL STUDIES RELEVANT TO ASSESSING DRUG-INDUCED MALE-MEDIATED DEVELOPMENTAL EFFECTS IN ANIMALS

A. In Vitro Studies

Nonclinical in vitro studies relevant to the assessment of potential male-mediated developmental toxicity include the standard genotoxicity assays (ICH S2(R1)) and any miscellaneous studies of pharmaceutical effects on the sperm (e.g., spermicidal assays and various tests of sperm genetic integrity (Sawyer, Hillman, et al. 1998; Liu, Hales, et al. 2014) or conceptus (e.g., whole embryo culture). Based on the strength of an in vitro signal, precautionary measures or follow-up in vivo studies may be warranted using reproductive outcome as a more definitive measure of paternally mediated effects.

B. In Vivo Studies

The in vivo nonclinical studies of interest for assessment of potential male-mediated developmental toxicity include general toxicity studies with appropriate histopathology and/or semen analysis in adult males and the standard battery of reproductive and developmental toxicity studies (Chaterjee, Haines, et al. 2000; Doerksen, Benoit, et al. 2000). When maternally mediated developmental toxicity has been identified in the nonclinical studies, a risk assessment should be performed to assess the potential for exposure to fetuses through seminal transfer and vaginal uptake, particularly for potent developmental toxicants.

For most pharmaceuticals, the only standard in vivo study that evaluates potential paternally mediated developmental effects is the fertility and early embryonic development study, with a direct effect assessed when only males are treated. If effects are observed in these studies (e.g., peri-implantation lethality or early signs of structural abnormalities), sponsors should conduct appropriate studies with only one treated sex per mating, to determine the role of treated males and/or females separately. Because standard fertility and early embryonic development studies may be inadequate to identify the full range of potential male-mediated developmental effects, additional studies in which pregnancies are followed to term should be considered if there is a signal for developmental toxicity following mating of treated males to untreated females.

C. ADME Information

For potent developmental toxicants in animals or humans, consideration should be given to ascertaining the API levels in ejaculated material in an attempt to quantify the potential levels that may reach the conceptus. This assessment should involve clinical determination of the amount of drug or biologic secreted into semen or by pharmacokinetic (PK) modeling (Picini, Zuccaro, et al. 1994). Fetal exposures can be modeled using the following assumptions (Banholzer, Buergin, et al. 2012):

- For small molecules
  - Ejaculation volume = 5 milliliter (mL)
    - Seminal fluid concentration = plasma C_{max}
  - 100 percent vaginal uptake
  - Female blood volume = 5,000 mL
    - 100 percent placental transfer

Example: Compound 421 is a potent teratogen in rats and rabbits. Delayed development was observed at maternal C_{max} concentrations of 7 micrograms (µg)/mL and complete resorptions at 50 µg/mL. The developmental no observed adverse effect level (NOAEL) was determined to be 0.5 µg/mL.

Plasma C_{max} in men = 10 µg/mL

Calculations: 10 µg/mL x 5 mL = 50 µg ÷ 5,000 mL = 0.01 µg/mL in circulation

An option with slightly more detail:

Mass of compound 421 in male semen = 10 µg/mL X 5 mL = 50 µg

After transfer to female, blood concentration = 50 µg ÷ 5,000 mL = 0.01 µg/mL

Based on this model, there is a 50-fold exposure multiple between the NOAEL and a 700-fold exposure multiple between the lowest observed adverse effect level (LOAEL). Semen PK studies would not be needed for compound 421.

- For monoclonal antibodies and Fc-conjugated pharmaceuticals

  - Ejaculation volume = 5 mL
    - Seminal fluid concentration = 1 percent of plasma C_{max}
  - 10 percent vaginal uptake
  - Female blood volume = 5,000 mL
    - 10 percent placental transfer (first trimester)
    - 100 percent placental transfer (at term)

  Example: Compound M is an IgG4 monoclonal antibody. It is a potent teratogen in monkeys targeting an important developmental pathway. In rabbits, malformations were observed at maternal C_{max} concentrations of 450 µg/mL. The developmental NOAEL was determined to be 10 µg/mL.

  Plasma C_{max} in men = 500 µg/mL

  Calculations: 500 µg/mL x 5 = 2,500 µg ÷ 5,000 mL = 0.5 µg/mL in circulation

  Based on this model, there is a 20-fold exposure multiple between the NOAEL and a 900-fold exposure multiple between the LOAEL. Semen PK studies would not be recommended for compound M.

  Using this model, when potential fetal exposures to the API are greater than 10-fold lower than the NOAEL determined in the animal reproductive and developmental studies, no further evaluations are recommended. However, if, based on the above calculations, there is a potential risk to the fetus, risk mitigation strategies should be considered until the risk can be further defined by determining the actual level secreted into human seminal fluid.

V. CONCLUSION

Although the mechanisms are not fully understood, male-mediated developmental toxicity may result from an effect of a pharmaceutical on the male germ cell before conception or from seminal transfer of a developmental toxicant to a pregnant partner. A variety of in vitro and in vivo nonclinical data can inform the assessment of male-mediated developmental toxicity risk and any decisions or recommendations regarding the need for contraception in men exposed to a pharmaceutical. These include the results of standard genotoxicity, repeat dose toxicity, reproductive toxicity, and developmental toxicity studies as well as pharmacology and ADME information. Appropriate precautions to avoid exposure or pregnancy should be considered when integration of all relevant nonclinical information indicates a possible risk to humans.

If the risk is uncertain or if a risk of male-mediated developmental toxicity has been determined to exist, the male subject or patient should be advised on the type (i.e., condom and/or reliable contraceptive use by female partner) and duration of precautions needed to prevent pregnancy or

exposure of a conceptus in sexual partners.[8] It is important to convey to the subjects or patients that the study API may have detrimental effects on a partner's pregnancy outcome for a period of time after drug administration has ceased. It is also important to convey whether these recommendations apply to vasectomized men, because these individuals may believe contraception recommendations aren't relevant.

For most small molecules, use of male contraception for a period of time equal to 5 half-lives plus 90 days (the duration of one spermatogenic cycle in men and residence time for unejaculated sperm) after pharmaceutical exposure should be sufficient to avoid risk to the conceptus of a female sexual partner. However, other considerations, including pharmacodynamic activity and pharmacokinetics, may influence the recommended duration of contraceptive use following cessation of therapy, especially for biologics (Peou, Moinard, et al. 2009).

[8] Per the ICH guidance for industry *E8 General Considerations for Clinical Trials*, "For male subjects, potential hazards of drug exposure in the trial to their sexual partners or resulting progeny should be considered. When indicated (e.g., trials involving drugs that are potentially mutagenic, or toxic to the reproductive system), an appropriate contaception provision should be included in the trial."

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