Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations

Guidance for Industry

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

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Pharmacology/Toxicology

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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in evaluating reproductive toxicity (mainly for effects on embryo-fetal development (EFD)) for oncology pharmaceuticals and to provide recommendations for product labeling on duration of contraception following cessation of therapy to minimize potential risk to a developing embryo or fetus. This guidance is intended to facilitate the development of oncology pharmaceuticals while avoiding unnecessary use of animals, in accordance with the 3R (reduce, refine, replace) principles. The following concepts are discussed in this guidance:

- Evaluation of EFD toxicity for various types of pharmaceuticals
- Evaluation of EFD toxicity for pharmaceuticals intended for specific populations
- Use of available information, such as the results of genotoxicity and general toxicity studies, knowledge of target biology, and available data on genetically modified animals in assessing the need for a dedicated EFD study
- Labeling recommendations for duration of contraception in male and female patients to minimize risk to a developing embryo or fetus (Females and Males of Reproductive Potential subsection of labeling)[2]

[1] This guidance has been prepared by the Division of Hematology Oncology Toxicology in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] See 21 CFR 201.57(c)(9)(i) and (iii) and the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2014). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

This guidance provides information for development of pharmaceuticals that are intended to treat patients with cancer. The patient population is the same as that described in the scope of the International Council for Harmonisation (ICH) guidance for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (ICH S9) (March 2010) [3] and further clarified in ICH *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals—Questions and Answers* (ICH S9 Questions and Answers) (June 2018). [4] Although an assessment of EFD toxicity is needed to support marketing applications for the treatment of patients with advanced malignancies, fertility and pre- and postnatal development (PPND) studies are generally not warranted.[5] For pharmaceuticals used in certain adjuvant (e.g., breast cancer) or neoadjuvant indications, however, an assessment of fertility and PPND may be needed on a case-by-case basis and results could be submitted after approval.[6] Therefore, this guidance also discusses fertility and PPND studies. For additional information on the timing of study result submission to the Agency, consult ICH S9 and ICH S9 Questions and Answers.

This guidance does not address risks of reproductive toxicity from radiopharmaceuticals, cellular and gene therapy products, cancer vaccines, biosimilar or interchangeable products, or generic drugs. This guidance does not address margins of safety by systemic exposure or dose. For many oncology pharmaceuticals—especially small molecules—a safety margin is not identified (i.e., embryo-fetal toxicities are observed in animals at exposures or doses that are comparable to or below those in patients (National Toxicology Program 2013)). This guidance does not address the potential risks to a developing embryo or fetus during clinical trials because pregnancy testing and use of highly effective methods of birth control are usually adequate to minimize the risk of unintentional exposure of the embryo or fetus when including women of reproductive potential in clinical trials.

This guidance complements ICH S9 and ICH S9 Questions and Answers. Specific study designs for evaluating reproductive toxicity are addressed in the ICH guidances for industry *S5(R3) Detection of Toxicity to Reproduction for Human Pharmaceuticals* (November 2017) and *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (S6(R1)) (May 2012). In general, when the weight of evidence (WOE) indicates clear adverse reproductive effects, additional reproductive toxicology studies may not be warranted. This guidance provides examples of WOE approaches (see section II. A., General Recommendations) not described in ICH S9. Because of the potential risk of developmental toxicity from oncology pharmaceuticals, a consistent approach is needed in the duration of contraception to minimize exposure of a developing embryo or fetus to these pharmaceuticals.

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[3] See ICH S9, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM085389.pdf.

[4] See ICH S9 Questions and Answers, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM520942.pdf.

[5] See ICH S9.

[6] See ICH S9 Questions and Answers, questions 5 through 7.

For this guidance, the term *pharmaceuticals* refers to small molecules, biotechnology-derived products, and related compounds, such as conjugated products. The term *teratogenicity* in this guidance refers to events leading to a disruption of normal EFD that may lead to malformations. For certain classes of pharmaceuticals (e.g., immune oncology), embryo-fetal lethality may arise by mechanisms other than direct action on the fetus, such as immune rejection with no overt teratogenicity. For this guidance, the phrase *embryo-fetal lethality* indicates mortality of the embryo or fetus, irrespective of its cause.

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.

II. ASSESSMENT OF EMBRYO-FETAL DEVELOPMENTAL TOXICITY

A. General Recommendations

In general, EFD toxicity testing should follow the recommendations outlined in ICH S9 and ICH S9 Questions and Answers. A WOE approach showing potential for reproductive toxicity may eliminate the need to conduct a dedicated EFD study and could be applied to pharmaceuticals discussed in section II.B-F. For small molecules, EFD studies, when needed, are typically conducted in two species; and when the study is positive for teratogenicity or embryo-fetal lethality in one species, generally a study in the second species is not warranted. For biotechnology-derived pharmaceuticals, when an EFD study is needed, generally a study in one pharmacologically relevant species should be sufficient. In general, a definitive study is not warranted if a dose-range finding study (including non-good laboratory practice) shows clear evidence of embryo-fetal lethality or teratogenicity.

A WOE approach may include the following information:

- Reproductive findings in humans, such as when a drug is in a class of pharmaceuticals with extensive publicly available information on potential reproductive effects

- Reproductive findings from genetically-modified animals or models employing pharmacologic inhibition, as appropriate

- Information from a surrogate molecule, when a surrogate is available and the target biology in the animal species is relevant to humans

- Literature-based assessment of target biology in humans or animal species, which can describe the following:

  – Expression and the role of the molecular target during embryo-fetal development

  - Any other relevant information, such as the role of the target in placental development, placental transfer, maternal tolerance, etc.

- Use of alternative assays, such as fit-for-purpose in vitro or ex vivo, or nonmammalian in vivo assays

The Agency supports the principles of the 3Rs to reduce, refine, and replace animal use in testing when feasible. Sponsors can consult with the Agency if they wish to use other testing methods or strategies not described above. The Agency will consider whether such an alternative method or strategy could be used instead of an animal study.

B. Genotoxic Pharmaceuticals

Pharmaceuticals that target rapidly dividing cells (e.g., crypt cells, bone marrow) in general toxicology studies and are genotoxic (e.g., positive in the bacterial mutation (Ames) assay or negative in Ames, but positive in two mammalian genotoxicity assays) are presumed to be teratogenic and/or lethal to an embryo or fetus. In this case, FDA does not consider EFD studies to be essential.

C. Biotechnology-Derived Pharmaceuticals

For biotechnology-derived pharmaceuticals, when the WOE is insufficient for EFD hazard identification, in general, an EFD study in one pharmacologically relevant species should be sufficient. When no pharmacologically relevant species is available to test the pharmaceutical and a relevant surrogate pharmaceutical is not available, in general, an EFD study is not warranted.

D. Conjugated Pharmaceuticals

For conjugated pharmaceuticals containing both a biological and a small-molecule moiety, the design of the EFD study depends on several factors, such as binding of the biological moiety to the target, the potential for release of the small molecule, the nature of the small molecule (e.g., mechanism of action), and knowledge about the source of the toxicities (biological versus the small-molecule moiety). For example, for antibody-drug conjugates (ADCs), when the small molecule is a cytotoxic pharmaceutical (genotoxic and targeting rapidly dividing cells), no EFD study is warranted (see section II. B., Genotoxic Pharmaceuticals). If an EFD study with an ADC is considered necessary (e.g., insufficient WOE), the sponsor could conduct the study with the small molecule alone (or the small-molecule linker) when toxicities of the conjugated pharmaceutical are related to the small molecule and the antibody does not bind to the target in the animal species.

E. Combination Products

A combination product should be used in EFD studies when the pharmaceuticals in the combination will not be used as monotherapy and the toxicity profile is expected to be different in the combination product compared with each pharmaceutical alone (e.g., when the

combination product may generate a new metabolite or result in a substantially increased level of a previously identified metabolite). In this case, the EFD study of each pharmaceutical alone may provide an incomplete EFD assessment. If the EFD data or WOE assessment is available with one (or more) of the pharmaceuticals in the combination product, indicating teratogenicity and/or embryo-fetal lethality, in general, an additional EFD of the combination product is not warranted. When pharmaceuticals in a combination will be also used as monotherapy, then an EFD assessment or study of each pharmaceutical alone should be conducted.

F. Liposomal Products

In general, liposomal formulations are produced to change the pharmacokinetic parameters of the active pharmaceutical ingredient (API) (e.g., to increase the exposure or change the distribution of the API). No EFD study is warranted when the liposomal product contains a genotoxic pharmaceutical targeting rapidly dividing cells (see section II. B., Genotoxic Pharmaceuticals) or when the WOE indicates teratogenicity or embryo-fetal lethality. In addition, if an EFD study was previously evaluated with the unencapsulated pharmaceutical and showed teratogenicity and/or embryo-fetal lethality, in general, separate EFD studies with the liposomal product are not warranted. However, the sponsor should conduct EFD studies with the liposomal pharmaceutical if WOE is insufficient and the API has not previously been shown to cause teratogenicity or embryo-fetal lethality, because changes in pharmacokinetic parameters and novel components used in a liposome could affect EFD.

III. ASSESSMENT OF FERTILITY

A study of fertility and early embryonic development is not warranted for pharmaceuticals intended for the treatment of patients with advanced cancer. The sponsor should use information available from general toxicology studies on the pharmaceutical's effect on reproductive organs as the basis of the assessment on impairment of fertility.[7] A general toxicology study in sexually mature NHPs is not warranted to assess fertility.

When the indication is not for an advanced cancer, stand-alone fertility studies may be warranted on a case-by-case basis.[8] When the NHP is the only relevant species, the sponsor can assess fertility effects in repeat-dose toxicology studies, and a separate fertility study is not warranted. A stand-alone fertility study is not warranted if, based on the totality of data (e.g., knowledge of the target biology and/or results of general toxicology studies), potential fertility risk is identified or if, based on the patient population, a fertility study is not warranted. For example, if a pharmaceutical intended to treat early-stage prostate cancer depletes male hormones, a male fertility study is not warranted (because the pharmaceutical is assumed to reduce fertility) and a female fertility study also is not warranted (because the pharmaceutical is male specific).

[7] See ICH S9.

[8] See ICH S9 Questions and Answers, questions 5 through 7.

IV. ASSESSMENT OF PRE- AND POSTNATAL DEVELOPMENTAL EFFECTS

In general, a PPND study is not warranted for pharmaceuticals intended to treat patients with advanced cancer. A PPND study may be warranted on a case-by-case basis when the cancer is not advanced.[9] The following examples describe when a PPND study is not needed when treating patients with nonadvanced cancer, because the study outcome is expected or the study will not provide useful information:

- A PPND usually is not warranted for a teratogenic pharmaceutical. The pharmaceutical is expected to adversely affect the growth and development of the offspring.

- When a pharmaceutical causes embryo-fetal death, the sponsor should consider whether a sufficient number of offspring may be available to assess developmental effects. For a pharmaceutical causing high embryo-fetal mortality, in general, a PPND study is not warranted.

V. ASSESSMENT OF RISK FOR SPECIFIC POPULATIONS

A. Pharmaceuticals for Use in Males Only

EFD studies are not warranted for pharmaceuticals indicated for use in males only (e.g., for prostate cancer). Any concern regarding risk to a developing embryo or fetus resulting from seminal transfer could be addressed through duration of contraception (see section VI., Recommendations on Contraception). The information on contraception should be communicated in the Females and Males of Reproductive Potential subsection of labeling. A PPND study is not warranted for pharmaceuticals intended to treat this patient population. The sponsor should consider a male fertility study in animals when the pharmaceutical's indication is not for an advanced cancer (e.g., early-stage prostate cancer) and adequate assessment of fertility is not available based on results of general toxicology studies or target biology (see section III, Assessment of Fertility).

B. Pharmaceuticals for Use in Postmenopausal Women Only

Reproductive toxicity studies are not warranted for oncology pharmaceuticals indicated in postmenopausal women only. In general, menopause is defined as the permanent cessation of menses of greater than 12 months with no alternative medical cause or may be defined based on additional factors, such as serum follicle-stimulating hormone levels and surgical bilateral oophorectomy. The sponsor should discuss with the appropriate FDA clinical review division the criteria used to define menopausal status.

C. Pharmaceuticals for Use in Pediatric Populations

For pharmaceuticals used for advanced cancer, the sponsor should provide an EFD study or assessment (as appropriate) when the indication includes patients who have reached puberty; this

[9] See ICH S9 Questions and Answers, questions 5 through 7.

generally includes females and males of reproductive potential, including adolescents (12 to 17 years of age). For additional information on EFD studies, see section II, Assessment of Embryo-Fetal Developmental Toxicity. If the treatment is curative or substantially increases survival, the sponsor should consider the entire battery of reproductive toxicology studies (i.e., fertility, EFD, and PPND),[10] unless the treatment falls under the categories described in sections II. through V. A. of this guidance, in which case the studies may not be warranted.

VI. RECOMMENDATIONS ON CONTRACEPTION

After determining that a risk of pharmaceutical-mediated developmental toxicity exists, the applicant's proposed labeling should include recommendations on the duration of contraception after completion of therapy. When a recommendation is necessary (see Tables 1 and 2), the Females and Males of Reproductive Potential subsection of labeling should include the duration of contraception, to minimize EFD risk in female patients receiving the oncology pharmaceutical and to female sexual partners of male patients receiving the oncology pharmaceutical.

The scientific underpinning for the following labeling recommendations is based on several factors, including the knowledge of gametogenesis and sex-specific differences in this process. The rationale is provided in sections VI. A., Genotoxic Pharmaceuticals, and VI. B., Nongenotoxic Pharmaceuticals. The labeling recommendations are based on prevention of developmental toxicity, such as malformations and embryo-fetal lethality, not restoration of fertility. Although the following labeling recommendations are for reducing EFD risk associated with the parent pharmaceutical, the same approach could be used for metabolites of concern as appropriate (e.g., for a genotoxic metabolite).

For conjugated pharmaceuticals containing both a biological and a small-molecule component, the applicant should consider both moieties for a labeling recommendation. For instance, for an ADC with a genotoxic payload, teratogenicity or embryo-fetal lethality is expected, and the applicant should use the labeling recommendations in Table 1. If a pharmaceutical consists of two biological moieties conjugated to each other and the pharmaceutical is not expected to cause malformations or embryo-fetal lethality, the applicant should use the labeling recommendations in Table 2. The applicant should scientifically justify any proposed labeling recommendation.

A. Genotoxic Pharmaceuticals

1. Males

Genotoxic pharmaceuticals may cause DNA damage in the sperm, potentially resulting in adverse effects in the embryo or fetus of a female sexual partner. Although there are no reports of increased malformation in offspring of men treated with oncology pharmaceuticals (Trasler and Doersken 1999; Mulvihill 2012), no report has adequately examined effects on children born within the first year after cessation of therapy. In addition, adverse embryo-fetal effects have been observed in animals when males treated with genotoxic pharmaceuticals were mated with untreated females. Use of contraception for a period of 3 months after cessation of therapy (see

[10] See ICH S9 Questions and Answers, questions 6 and 7.

Table 1) will minimize the risk of adverse embryo-fetal effects from genotoxic pharmaceuticals. The 3 months cover the period of spermatogenesis and the epididymal maturation.

2. Females

Genotoxic pharmaceuticals may directly affect the embryo or fetus or may cause DNA damage in the oocytes. The duration of folliculogenesis is described as 6 to 12 months (Meirow et al. 2001; Meirow and Schiff 2005). Exposure to a genotoxic pharmaceutical in the initial step of folliculogenesis results mainly in follicular loss (Kalich-Philosoph et al. 2013). Although a damaged follicle may be further eliminated through the natural process of atresia, adverse embryo-fetal effects, including malformations, have been observed in offspring of mice treated with the genotoxic pharmaceutical cyclophosphamide at various stages of follicular growth (Meirow et al. 2001; Meirow and Schiff 2005). The 6-month contraception labeling recommendation for genotoxic pharmaceuticals after cessation of therapy (see Table 1) covers the growth and maturation phase of folliculogenesis and is expected to allow elimination of most damaged follicles and oocytes. Deviations from this labeling recommendation are acceptable when justified. For instance, for a pharmaceutical that is only aneugenic, a contraception period of 1 month (with an additional 5 half-lives) is generally acceptable because only dividing oocytes are affected by aneugenicity.

Table 1. Genotoxic Pharmaceuticals: Recommendation on the Duration of Contraception After Cessation of Therapy

Sex	Recommended Duration of Contraception
Male	5 x $T_{1/2}$* + 3 months
Female	5 x $T_{1/2}$* + 6 months

* $T_{1/2}$ = half-life.

B. Nongenotoxic Pharmaceuticals

1. Males

A hypothetical risk of teratogenicity or embryo-fetal lethality exists because of the transfer of a pharmaceutical (or its metabolites) through the seminal fluid to a woman. Although reports indicate that there is no increased malformation rate in the offspring of males exposed to oncology pharmaceuticals (Trasler and Doersken 1999; Mulvihill 2012), no report has adequately examined effects on children born within the first year after cessation of therapy.

Scientific articles indicate that pharmaceuticals administered intravaginally, including thalidomide, at clinically relevant concentrations did not cause malformation in the fetus (Hui et al. 2014; Breslin et al. 2014; Moffat et al. 2014). However, an earlier study showed adverse embryo-fetal effects when male rabbits were administered thalidomide (Lutwak-Mann 1964).

Although thalidomide does not accumulate in the semen, many small-molecule pharmaceuticals do (Klemmt and Scialli 2005). Given the data gaps for small-molecule teratogenic pharmaceuticals, FDA recommends a contraception period of 5 half-lives. For teratogenic biological products, however, no duration of contraception is necessary because these products have not been seen to accumulate in the semen, have limited absorption, and may undergo proteolytic degradation caused by the presence of vaginal and cervical enzymes (Scialli et al. 2015). See Table 2 for recommendations on the contraception period.

2. Females

For nongenotoxic pharmaceuticals causing teratogenicity or embryo-fetal lethality, FDA recommends a contraception period of 5 half-lives after completion of therapy. For pharmaceuticals that do not cause teratogenicity or embryo-fetal lethality, no duration of contraception is necessary (see Table 2).

Table 2. Nongenotoxic Pharmaceuticals: Recommendation on the Duration of Contraception After Cessation of Therapy[*]

Sex	Teratogenicity or Embryo-Fetal Lethality	No Teratogenicity and No Embryo-Fetal Lethality
Male	Small molecules: 5 x $T_{1/2}$[**] Biologics: Not necessary	Not necessary
Female	5 x $T_{1/2}$[**]	Not necessary

[*] This table can also be used for pharmaceuticals that are only aneugenic in the battery of genotoxicity studies and when aneugenicity occurs only at high multiples of clinical exposures.

[**] $T_{1/2}$ = half-life. For pharmaceuticals with short half-lives (5 x $T_{1/2}$ of less than 1 week), FDA recommends a minimum contraception period of 1 week.

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