Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in reproductive toxicity assessments (mainly of embryo-fetal development (EFD)) for anticancer pharmaceuticals and to provide recommendations for product labeling on duration of contraception following cessation of therapy to minimize potential risk to a developing embryo/fetus. The following concepts are discussed in this guidance:

- Evaluation of EFD toxicity for various types of pharmaceuticals and when such studies are not needed
- Evaluation of EFD toxicity for pharmaceuticals intended for specific populations
- Use of nonclinical information such as results of genotoxicity and general toxicity studies in assessing the need for a dedicated EFD study
- Labeling recommendations concerning EFD studies and the potential risk for adverse developmental outcomes in humans (*Pregnancy* subsection of labeling) and recommendations for contraception in male and female patients to minimize risk to a developing embryo/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[2] See 21 CFR 201.57(c)(9)(i) and (iii) and the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format*. 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 Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For the purpose of this guidance, *pharmaceuticals* refers to small molecules, therapeutic proteins, antibodies, and related products such as conjugated products. This guidance does not address risks from biosimilar products, interchangeable products, radio-pharmaceuticals, cellular and gene therapy products, or cancer vaccines. The term *teratogenicity* refers to events leading to a disruption of normal embryo-fetal development that may lead to malformation or death. However, for certain classes of products (e.g., immune-oncology) embryo-fetal lethality may be due to causes other than a product directly acting on the fetus, and that result in immune rejection with no overt teratogenicity. Thus, for the purpose of this guidance, the term *embryo-fetal lethality* indicates mortality in the embryo/fetus for any cause irrespective of teratogenicity.

This guidance does not address margins of safety by exposure or dose. For many anticancer pharmaceuticals — especially the small molecules to which this guidance pertains— a margin is not identified (i.e., embryo-fetal toxicities are observed in animals at exposures that are comparable to or below the recommended human dose (National Toxicology Program 2013)). Risk to a developing embryo/fetus is the primary concern in patients and the reason for needing EFD studies so that appropriate contraceptive recommendations for patients may be included in labeling. However, this guidance does not address the potential risks to a developing embryo/fetus during clinical trials because adequate contraception is necessary during relevant drug development. Although fertility and pre- and postnatal developmental (PPND) studies typically are not needed to support marketing applications for advanced cancer indications, some aspects of these studies are included in this guidance for nonadvanced indications.

This guidance complements the ICH guidance for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals*, when applicable.[3] Specific study designs for evaluating reproductive toxicity are addressed in the ICH guidances for industry *S5 Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility* and *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*. This guidance provides examples of alternative assessments not previously described in ICH S9 and only briefly discussed in ICH S6(R1) (see section III.C., Biological Pharmaceuticals). This guidance also provides additional nonclinical recommendations related to the reproductive potential of pharmaceuticals and for contraception, which are not currently covered under ICH S9.

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.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

II. BACKGROUND

ICH S9 describes the recommended type and timing of nonclinical studies needed for an investigational new drug application and for subsequent development of anticancer pharmaceuticals. For pharmaceuticals within the scope of ICH S9, the guidance recommends that results of EFD studies be submitted with the new drug application or biologics license application.

In some cases EFD toxicity studies may not be needed. For example, if the pharmaceutical is genotoxic and targets rapidly dividing cells as demonstrated in general toxicology studies (ICH S9), then the product is presumed to be causing either teratogenicity or embryo-fetal lethality. In other cases, in lieu of an EFD study, alternative assessment of risk can be provided. Since the publication of ICH S9, FDA has gained experience in evaluating alternative approaches in reproductive toxicity assessments for anticancer pharmaceuticals conducted in lieu of animal reproductive toxicity studies.

Recommendations for contraception also are not currently covered in ICH or FDA guidances for anticancer pharmaceuticals. Because of the toxic nature of pharmaceuticals used in oncology, there is a need for a consistent approach in using contraception to minimize exposure of a developing conceptus to these products.

III. EVALUATION OF EMBRYO-FETAL DEVELOPMENTAL TOXICITY

A. General Recommendations

In general, reproductive toxicity testing should follow the recommendations outlined in ICH S9, in which risk to the developing embryo/fetus is the primary concern. EFD studies should be conducted in two species, usually the rat (or mouse) and rabbit, unless one species is positive for teratogenicity or embryo-fetal lethality, in which case the study in the second species may not be warranted. In some cases, where non-good laboratory practices (GLP) pilot studies have unequivocally demonstrated embryo-fetal lethality or teratogenicity, the definitive GLP study may not be warranted.

B. Cytotoxic Pharmaceuticals

Pharmaceuticals that are genotoxic and target rapidly dividing cells as determined in general toxicology studies are presumed to be teratogenic and/or lethal to an embryo/fetus. In this case, EFD studies are not considered essential. For the purpose of determining the need for an EFD study, positive outcomes in at least two genotoxicity assays are needed to conclude the product is genotoxic.

C. Biological Pharmaceuticals

According to ICH S9, an EFD study in one pharmacologically relevant species should be conducted. When the pharmacologically relevant species is the nonhuman primate, an enhanced

PPND as described in ICH S6(R1) could be considered; see ICH S6(R1) for study designs. When there is no pharmacologically relevant species to test the clinical candidate, use of a well-characterized and biologically relevant surrogate pharmaceutical, if available, could be considered. However, producing a surrogate pharmaceutical for the sole purpose of conducting an EFD study usually is not warranted.

When an EFD study is not warranted, an alternative assessment should be completed. The assessment should include the following information or data:

- Literature assessment. The assessment should:
  - Describe expression of target in the embryo/fetus
  - Describe the role of the molecular target in embryo-fetal development
  - If available, include data from knock-out or transgenic animals or animals with a mutated gene, as appropriate
  - Describe effects, such as loss of pregnancy or phenotypic traits in offspring based on the previous bulleted items
- In vitro studies, such as the ability of the pharmaceutical to cross the placenta (if not known) and cross reactivity to embryo-fetal tissues. The assessment should describe potential developmental effects that might arise because of target binding.

Although this section is for biological products, the concepts could be applied to small molecule pharmaceuticals as appropriate.

D. Conjugated Pharmaceuticals

For conjugated products 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 cytotoxicity), and knowledge of the source of toxicities (biological versus the small molecule moiety). For instance, for antibody-drug conjugates (ADC), when the small molecule is a cytotoxic agent (genotoxic and targeting rapidly dividing cells), no EFD study is warranted (see section III.B., Cytotoxic Pharmaceuticals). When an EFD study with an ADC is deemed necessary, the study could be conducted with the small molecule if toxicities of the conjugate are related to the small molecule and the antibody does not bind to the target in the animal species. When the biological moiety binds to the target in the animal species, the reproductive toxicology study with the conjugated product generally is recommended.

E. Combination of Pharmaceuticals

When two pharmaceuticals are only used in combination, as defined in 21 CFR 3.2(e), where both pharmaceuticals are required to achieve the intended use, indication, or effect, the

combination should be used in EFD studies. If the EFD data are already available with one of the pharmaceuticals and shows teratogenicity and/or embryo-fetal lethality, an additional EFD study of the combination may not be warranted.

F. Liposomal Products

In general, liposomal formulations are produced to change the pharmacokinetic parameters of the active pharmaceutical ingredient (API) (e.g., to increase exposure). If an EFD study was previously evaluated with the unencapsulated material and showed teratogenicity and/or embryo-fetal lethality, separate EFD studies with the liposomal product may not be warranted. However, EFD studies should be conducted with the liposomal drug if the API has not previously been shown to cause teratogenicity or embryo-fetal lethality because increased exposure and novel components used in a liposome could affect embryo-fetal development. Depending on the nature of the pharmaceutical being encapsulated, sponsors should discuss concepts in section III. For example, when the liposome contains a cytotoxic pharmaceutical, sponsors should consider section III.B., Cytotoxic Pharmaceuticals.

IV. EVALUATION OF FERTILITY

Stand-alone fertility and early embryonic studies usually are not warranted for pharmaceuticals to treat patients with advanced cancer under the scope of ICH S9. Effects on male and female reproductive organs assessed in general toxicity studies, and other relevant endpoints (e.g., changes in sex hormones), should be considered for an assessment of potential drug effects on fertility. Any fertility risk determined from these observations should be described in the *Carcinogenesis, Mutagenesis, Impairment of Fertility* subsection of labeling and summarized in the *Females and Males of Reproductive Potential* subsection of labeling.

When the indication is not for an advanced cancer, stand-alone fertility studies usually are warranted. A stand-alone fertility study is not warranted if based on the totality of data the study will not provide useful information. For example, if a pharmaceutical is intended to treat early stage prostate cancer and it depletes male hormones to a castration level, fertility studies are not warranted in male animals (because the pharmaceutical is assumed to cause infertility) or female animals (because it is a male-specific pharmaceutical). In addition, if findings in general toxicology studies indicate adverse fertility effects (e.g., reduced sperm count or follicular loss), a separate fertility study usually is not warranted.

Evaluation of testicular toxicity in clinical trials, as described in the draft guidance for industry *Testicular Toxicity: Evaluation During Drug Development*,[4] is not warranted. Because of toxicities of anticancer pharmaceuticals, the clinical study should not be conducted in healthy subjects and the study design recommended typically is not feasible in patients with cancer.

[4] When final, this guidance will represent the FDA's current thinking on this topic.

V. EVALUATION OF PRE- AND POSTNATAL DEVELOPMENTAL EFFECTS

A PPND study may not be warranted for pharmaceuticals intended to treat advanced cancer under the scope of ICH S9. However, when a study is deemed necessary (e.g., based on the indication), consideration should be made whether such study will provide information for patients or prescribers. See the following examples:

- A PPND may not be warranted for a teratogenic pharmaceutical. The pharmaceutical is expected to adversely affect the survival and general health, including growth and development, of the offspring and the risk should be communicated in the *Pregnancy* subsection of labeling.

- For a pharmaceutical causing embryo-fetal death, a consideration should be made whether a sufficient number of offspring may be available to assess developmental effects. When a pharmaceutical causes embryo-fetal lethality, a modified PPND study may be considered to increase the number of live births, such as dosing in short windows. Design modifications should not change the purpose of a PPND study (e.g., starting dose administration after birth will only provide information on postnatal growth and is not warranted).

VI. EVALUATION OF RISK FOR SPECIFIC POPULATIONS

A. Pharmaceuticals Indicated for Use in Males Only

Because the risk to be studied is to the developing embryo/fetus, EFD studies are not warranted for pharmaceuticals indicated for use in males only (e.g., for prostate cancer). As discussed in section III.A., General Recommendations, assessing risk to a developing conceptus resulting from seminal transfer is not warranted; instead, a period of contraception is recommended (see section VIII., 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 this patient population. A male fertility study in animals should be considered when the indication is not for an advanced cancer (e.g., early prostate cancer) (also see section IV., Evaluation of Fertility).

B. Pharmaceuticals Indicated for Use in Postmenopausal Women Only

Reproductive toxicity studies are not warranted for anticancer 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. However, this definition and its applicability to the intended clinical trial subjects should be discussed with the appropriate FDA clinical review division.

C. Pharmaceuticals Indicated for Pediatric Populations

For pharmaceuticals in advanced cancer under the scope of ICH S9, an EFD study or assessment (as appropriate) should be provided when the indication includes patients who have reached puberty; this generally includes females and males of reproductive potential, including adolescents (12 to 18 years of age). If the treatment is intended to be curative or substantially increases survival, the entire battery of reproductive toxicology studies (i.e., fertility, EFD, and PPND) should be considered, unless the treatment falls under the categories described above where the studies may not be warranted (see sections III. through VI.A.).

VII. PHARMACOKINETIC DATA

A. Disproportionate Metabolites

For metabolites that are human-specific or present at disproportionally higher levels in humans when compared to animal species used in toxicology studies, additional EFD studies of the metabolite may be warranted. Consideration should be given to whether there is sufficient exposure in animal species tested in EFD studies and the results obtained with the API. An EFD study of a metabolite is not warranted when studies with the API result in embryo-fetal lethality or teratogenicity.

B. Exposure Comparison

Pharmacokinetic data should be collected in EFD studies and the animal-to-human area-under-the-curve (AUC) ratios should be included in the *Pregnancy* subsection of labeling. In the event that pharmacokinetic parameters are not available from EFD studies, animal AUCs from a general toxicology study using the same species, dose, route of administration, and dosing regimen can be used when applicable (e.g., based on differences in the formulation).

VIII. RECOMMENDATIONS ON CONTRACEPTION

After a determination is made that a risk of anticancer pharmaceutical-mediated developmental toxicity exists, the following labeling recommendations on the duration of contraception following cessation of therapy should be provided to patients. The *Females and Males of Reproductive Potential* subsection of labeling should include the duration of contraception for both males and females receiving the pharmaceutical recommended to minimize EFD risk and the risk in female sexual partners of men receiving the anticancer pharmaceutical.

The scientific underpinning for the following recommendations is based on the knowledge of gametogenesis and sex-specific differences in this process and is provided in sections VIII.A., Genotoxic Pharmaceuticals, and VIII.B., Nongenotoxic Pharmaceuticals. The recommendations are based on prevention of developmental toxicity, such as malformations and lethality, not restoration of fertility.

Although the following recommendations are intended to reduce exposure to the parent pharmaceutical, they can also reduce developmental toxicity from exposure to metabolites as appropriate (e.g., for a genotoxic metabolite).

A. Genotoxic Pharmaceuticals

1. Male Subjects

Genotoxic pharmaceuticals may cause deoxyribonucleic acid (DNA) damage in the sperm, potentially resulting in adverse effects in the conceptus of a female sexual partner. Although there is no report of increased malformation in offspring of men treated with anticancer pharmaceuticals (Trasler and Doersken1999; Mulvihill 2012), such effects have been seen 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 will minimize the risk of adverse embryo-fetal effects for genotoxic pharmaceuticals with short half-lives (less than 1 week). In humans, the duration of spermatogenesis is approximately 70 days (Trasler and Doersken 1999; Amann 2008). Three months takes into account the half-life of a pharmaceutical and the residence time for unejaculated sperm. For pharmaceuticals with long half-lives (greater than or equal to 1 week), an additional contraception period of five half-lives is recommended. See Table 1.

2. Female Subjects

Genotoxic pharmaceuticals may directly affect the embryo/fetus or may cause DNA damage in the oocytes. The period of folliculogenesis is described as 6 to 12 months (Meirow, Epstein, et al. 2001; Meirow and Schiff 2005). Exposure to a genotoxic pharmaceutical in the initial step (primordial follicles) results mainly in follicular loss (Kalich-Philosoph, Roness, et al. 2013). Any remaining damaged follicle may be further eliminated through the natural process of atresia (greater than 90 percent elimination) (Gougeon 1986). The growth and maturation phase of folliculogenesis (4 to 6 months) is most susceptible to persisting DNA damage and may potentially result in embryo-fetal malformations. Hence 6-month contraception is recommended for genotoxic pharmaceuticals after cessation of therapy. For pharmaceuticals with long half-lives (greater than or equal to 1 week) an additional five half-lives is recommended. See Table 1.

Table 1. Genotoxic (Including Aneugenic) Pharmaceuticals: Recommendation on Use of Contraception After Cessation of Therapy

Male	Female
3 months[a]	6 months
3 months + 5 x $T_{1/2}$[b] for pharmaceuticals with long $T_{1/2}$[c]	6 months + 5 x $T_{1/2}$ for pharmaceuticals with long $T_{1/2}$[c]

[a] Duration of spermatogenesis and residence time for unejaculated sperm.
[b] $T_{1/2}$ = half-life
[c] Long half-life refers to $T_{1/2}$ greater than or equal to 1 week.

B. Nongenotoxic Pharmaceuticals

1. Male Subjects

There is a hypothetical risk of teratogenicity because of the presence of a pharmaceutical in the seminal fluid. Although reports indicate that there is no increased malformation rate in the offspring of males exposed to anticancer pharmaceuticals (Trasler and Doersken 1999; Mulvihill 2012), no report exclusively examines birth within the first year after cessation of therapy. Scientific articles published in 2014 indicate that pharmaceuticals administered intravaginally, including thalidomide, at clinically relevant concentrations did not cause malformation in the conceptus (Hui, Hoffman, et al. 2014; Breslin, Hilbish, et al. 2014; Moffat, Davies, 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) and investigations on embryo-fetal toxicity caused by seminal transfer have been limited. Based on data gaps, for small molecule teratogenic pharmaceuticals, a contraception period of five half-lives with an additional 3 weeks to account for the residence time of unejaculated sperm is recommended. For teratogenic biological products, however, no duration of contraception is recommended because these products do not accumulate in the semen, have limited absorption, and may undergo proteolytic degradation caused by the presence of vaginal and cervical enzymes (Scialli, Bailey, et al. 2015). See Table 2.

2. Female Subjects

Contraception post-treatment for five half-lives allows elimination of approximately 97 percent of a developmentally toxic pharmaceutical from the circulation before fertilization. For pharmaceuticals with short half-lives, a minimum of 30 days (one menstrual cycle) is recommended after cessation of therapy. See Table 2.

Table 2. Nongenotoxic Pharmaceuticals: Recommendation on Use of Contraception After Cessation of Therapy

Male		Female	
Teratogenicity or Embryo-Fetal Lethality	**No Teratogenicity and No Embryo-Fetal Lethality**	**Teratogenicity or Embryo-Fetal Lethality**	**No Teratogenicity and No Embryo-Fetal Lethality**
Small molecules: 5 x $T_{1/2}$[a] + 3 weeks Biologics: Not necessary	Not necessary	5 x $T_{1/2}$ Or one menstrual cycle (30 days), whichever is longer	Not necessary

[a] $T_{1/2}$ = half-life

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