Assessment of Ovarian Toxicity in Premenopausal Adults During Drug Development for Oncologic Products

Guidance for Industry

DRAFT GUIDANCE

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Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

This guidance provides recommendations to sponsors regarding measurement of ovarian toxicity using clinical measures and biomarkers of ovarian function in relevant cancer clinical trials that enroll premenopausal adults. Specifically, this guidance applies in the cancer setting where life expectancy based on tumor type is of a sufficient time where ovarian toxicities may be relevant. Ovarian toxicity should be considered as a safety endpoint in trials including premenopausal adults and should be considered an integral part of a drug[2] development program when the intended therapy will be used in premenopausal adults.

Recommendations regarding ovarian function in pediatric patients with cancer and nonclinical recommendations are outside the scope of this guidance and are not addressed. For recommendations regarding the nonclinical assessment of reproductive toxicities of anticancer pharmaceuticals, refer to the following guidances for industry: ICH *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (2010), ICH *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Questions and Answers* (2018), and FDA guidance *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations* (2019). For cancer prevention trials in otherwise healthy individuals, refer to nonclinical recommendations in the guidance *ICH M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (2010). For nonclinical recommendations for cell and gene therapy products, refer to the final guidance for industry *Preclinical Assessment of Investigational Cellular and Gene Therapy Products* (2013).

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

[1] This guidance has been prepared by the Oncology Center of Excellence (OCE), Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, references to drugs include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Loss of ovarian function is a potentially irreversible toxicity associated with systemic anti-cancer agents. Ovarian dysfunction may result in infertility and long-term morbidities related to early-onset menopause and estrogen deficiency, including vasomotor symptoms, sexual dysfunction, osteoporosis, and earlier onset of cardiovascular disease. Routine collection of ovarian toxicity data in cancer clinical trials of investigational agents is currently lacking. For example, from 2008 to 2019 only 9% of phase 3 (neo)adjuvant breast cancer trials prespecified ovarian function as an endpoint, and only 20% collected pre- and post-intervention ovarian function data, mostly just menstrual status[3]. Assessment of ovarian toxicity in cancer trials is essential to ensure that patients and clinicians have information about the possible long-term impacts of cancer treatments on ovarian function and thus facilitate informed decision-making regarding anti-cancer agents.

III. RECOMMENDATIONS

FDA encourages sponsors to discuss their drug development plan early in development with the relevant review teams in CDER or CBER, as applicable, when enrolling premenopausal adults in trials that are likely to enroll premenopausal patients with high survival rates (e.g., adjuvant therapy). FDA recommends the following:

- Sponsors should assess ovarian toxicity in relevant clinical trials of anti-cancer agents that enroll premenopausal adults with ovaries.
- Sponsors should evaluate ovarian function with the following clinical measures and laboratory biomarkers:
    - Gynecologic history: clinical gynecologic data including menstrual history (e.g., date of last menstrual period, cycle length and duration of menstrual bleeding, and prior history and cause of irregular cycles, if applicable), prior pregnancies, and live births.
    - Laboratory biomarkers: serum anti-Mullerian hormone (AMH), serum follicle stimulating hormone (FSH), and serum estradiol (E2) levels, preferably on days 3-5 of the follicular phase of the menstrual cycle.
        - The concomitant measurement of serum AMH, serum FSH, and serum E2 in the early follicular phase provides the most comprehensive information regarding the ovarian effects of exposure to anti-cancer therapies, and potential reversibility of impaired ovarian function.

i) Sponsors should specify during trial design the type of assay used to measure AMH, FSH, and E2 and a standardized laboratory methodology across sites is preferable.

[3] Cui W, Francis PA, Loi S, Hickey M, Stern C, Na L, et al. Assessment of Ovarian Function in Phase 3 (Neo)adjuvant Breast Cancer Clinical Trials: A Systematic Evaluation. J Natl Cancer Inst. 2021;113(12):1770-1778.

  - Data collection of possible confounders: history of hysterectomy, prior attempts at pregnancy, use of any hormonal contraceptives within the previous 90 days, Gonadotropin-Releasing Hormone (GnRH) analogs, ovulatory stimulation, and Assisted Reproductive Technology (ART) procedure, or any other hormonal therapies for conditions that may also impact fertility and/or ovarian function.
  - Additional monitoring considerations: menstrual diaries (documented directly by patients), menstrual data collection (investigator-assessed collection), collection of adverse events related to the reproductive system including abnormal vaginal and menstrual bleeding.
- At a minimum, sponsors should collect ovarian function measures (clinical, biomarkers, and confounders) at baseline, every 6-12 months while on treatment, at the end of treatment, and at 12-24 months after completion of treatment, and consider additional time points during the study based on the agent and duration of treatment.
  - For agents with limited existing data on ovarian toxicity, where the mechanism of ovarian toxicity (if any), the extent of ovarian toxicity, and the time to recovery from ovarian toxicity are not known, sponsors should collect these data at additional timepoints (e.g., within 30 days of the end of treatment and beyond 12-24 months).
- If there is an identified risk of ovarian toxicity associated with an anti-cancer agent, for example based on nonclinical data or previous clinical data that is suggestive of ovarian toxicity, the sponsor should assess ovarian toxicity in at least a subset of premenopausal study participants (e.g., N=40) during pre-market trials intended to support a marketing application.
- If the sponsor justifies why it is not able to assess ovarian toxicity during pre-market trials, the sponsor should discuss a plan with FDA to evaluate ovarian function in the post-marketing setting.
  - When a post-marketing study to assess ovarian toxicity is appropriate, the sponsor should incorporate the following recommendations:
    - A minimum of 40 premenopausal adults should be enrolled and have follow-up data collected.
    - Ensure characterization of the incidence and severity of ovarian toxicity after a minimum of 12 months post-treatment.
    - Follow-up assessments including reproductive hormone measurements (Serum AMH, FSH, and E2) should be obtained at regularly scheduled 6-month intervals and at 12 months post-treatment.