Establishing Effectiveness and Safety for Hormonal Drug Products Intended to Prevent Pregnancy

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Jennifer Mercier at 301-796-0957.

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

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Clinical/Medical

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TABLE OF CONTENTS

Establishing Effectiveness and Safety for Hormonal Drug Products Intended to Prevent Pregnancy[1]

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I. INTRODUCTION

This guidance provides recommendations for clinical trials designed to establish clinical effectiveness and safety for hormonal drug products intended to prevent pregnancy[2]. Drug product development in hormonal contraception has evolved over the years, especially with the development of lower-dose hormonal drug products and longer-acting reversible contraceptives. Changes in patient demographics, pregnancy testing, determinations of conception date, and dosing directions have also occurred. This guidance reflects these developments and is generally consistent with advice we have been providing to individual sponsors developing hormonal drug products.

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. CLINICAL TRIAL DESIGN FEATURES—KEY CONSIDERATIONS

A. Recommended Enrollment Criteria

Nonpregnant, premenopausal women who meet the following criteria are eligible for enrollment:

[1] This guidance has been prepared by the Division of Bone, Reproductive, and Urologic Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] This guidance does not provide development information on nonhormonal contraception or emergency contraception.

- Have normal, regular menstrual cycles that are between 21 and 35 days in duration

- Engage in regular heterosexual vaginal intercourse (at least once per month) with a partner who is not known to be subfertile or infertile

- Have no evidence of dysplasia or invasive cervical cancer on screening per current guidelines

- Have adequate washout of other contraceptives (e.g., resumption of regular menses after long-acting contraceptives and contraceptives that alter the menstrual cycle)

- Are agreeable to not using other contraceptives or other methodology to prevent pregnancy during the trial

- Have no history of infertility

The effectiveness of some contraceptives may be reduced with increasing body weight. Sponsors should not place restrictions on body mass index (BMI) for trial enrollment. The trial population should include obese women (i.e., defined as BMI of at least 30 kg/m^2), and the analysis plan should include a prespecified subgroup efficacy analysis in this population. Insufficient data in the obese population may result in a limitation of use for this population in labeling. During the trial design phase, sponsors should discuss with the division the adequacy of the number of cycles of drug exposure that will be derived from obese subjects.

Enrollment of subjects older than 35 years old is recommended for safety determinations. The number of subjects older than 35 years old who should be enrolled in the trial or trials will depend on the existing experience with the drug product ingredients and should be discussed with the division.

Trials should include subjects from all premenopausal age groups who are likely to use the drug product, including postmenarchal adolescents.

B. Study Elements

Randomizing subjects to placebo is not feasible because subjects in a contraceptive trial do not desire pregnancy. Approximately 80% to 90% of women of reproductive potential who use no contraception and engage in regular intercourse are expected to become pregnant within 1 year (Guttmacher 1956; Zinaman et al. 1996; Wang et al. 2003; Gnoth et al. 2003; Slama et al. 2012), and contraceptives typically have sizeable treatment effects. Therefore, single-arm, open-label, historically controlled trials are generally sufficient to establish efficacy. Sponsors should discuss with the division how they intend to ensure an accurate assessment of contraceptive effectiveness, such as minimizing missing data and minimizing premature subject discontinuation.

In some instances, it may be possible to conduct a single phase 3 trial (e.g., for combined estrogen and progestin products). In other instances, two phase 3 trials may be recommended (e.g., a novel contraceptive drug product). Sponsors should discuss with the division the number of trials appropriate for the drug product.

Data from single-arm, open-label trials of at least 1 year's duration are generally sufficient to establish efficacy and safety, provided that the trials are well-conducted. Trials of longer duration (covering the maximum duration of use proposed in labeling) are recommended for long-acting reversible contraceptives, such as intrauterine systems. Trials of shorter duration may be sufficient for products containing drug substances that already have well-characterized safety profiles. Sponsors should discuss the adequacy of the trial duration with the division.

For a new molecular entity (NME), the division recommends that total drug product exposure include at least 20,000 menstrual cycles, with at least 400 subjects who complete the trial or trials. For a non-NME for which one or more clinical trials are needed, the division recommends that total drug product exposure should include at least 10,000 menstrual cycles, with at least 200 subjects who complete the trial or trials.

Subjects should complete a daily diary that adequately captures whether vaginal intercourse occurred, the use of backup and emergency contraceptive methods, and bleeding and/or spotting patterns. We encourage the use of an electronic diary (ediary).

Urine pregnancy tests should be performed regularly at clinic visits, including at the end of the study or with premature subject discontinuation. Sponsors should provide subjects with home pregnancy test kits for use in case of signs and symptoms of pregnancy or multiple missed contraceptive doses. A positive urine pregnancy test (whether conducted at home or in the clinic) should be confirmed by serum testing and, if positive, an ultrasonography should be performed for dating. Sponsors should discuss the number and timing of clinic visits with the division.

Other important considerations during development of drug products intended to prevent pregnancy include the following:

- Pregnancy outcomes should be collected and reported.
- Early discussion with the division is particularly encouraged for products with novel delivery systems or device components.
- Sponsors are encouraged to conduct lactation studies for new drug products or dosing regimens, as women often want to restart contraception during the postpartum period.

C. Efficacy Considerations

On-treatment pregnancy should be defined as any pregnancy that occurs during use of the product or within a specific timeframe after last use of the product. Some examples are provided below. Sponsors should discuss with the division the appropriate timeframe after last use for other scenarios.

For contraceptives that require daily administration (e.g., oral combined hormonal contraceptives), last use includes the use of the product from the placebo (or drug-free days) or estrogen-only phase of the regimen. A positive pregnancy test within 7 days of this last use would be considered on-treatment (a detected pregnancy in this timeframe reflects conception that occurred when pregnancy should still have been prevented). For example, if a woman's estimated date of conception is 7 days after she completed Day 28 of a 21/7 (active/placebo) regimen, a positive pregnancy test would be considered on-treatment.

For long-acting injectable contraceptives (e.g., medroxyprogesterone acetate), a positive pregnancy test after the last dosing and prior to the next scheduled dose would be considered on-treatment.

For an intrauterine system (IUS), a positive pregnancy test within 7 days after IUS removal would be considered on-treatment (a detected pregnancy in this timeframe reflects conception that occurred while the IUS was still in place).

The primary efficacy endpoint should be the pregnancy rate described by the Pearl Index (PI) during the first year of use of the product. The PI is defined as the number of pregnancies per 100 woman-years and is calculated as follows:

$$PI = \frac{Number\ of\ pregnancies \times 13\ cycles}{Number\ of\ 28\text{-}day\ cycles\ as\ defined\ below} \times 100$$

Calculation of the PI for the primary efficacy evaluation should include only cycles during which (a) vaginal intercourse occurred and (b) no backup or emergency contraception was used based on diary data.

Life table analysis should also be used as a supportive analysis to provide monthly and cumulative failure rates for any specific length of exposure and will be included in labeling for long-acting contraceptive products that are evaluated in trials of more than 1 year's duration.

The assessment of efficacy is based on the point estimate and the upper bound of the corresponding 95% confidence interval for the PI. Combined hormonal contraceptives are very effective at preventing pregnancy, typically having an upper bound of this 95% confidence interval below 5 in adequately designed and conducted trials. For hormonal contraceptives with fewer risks, such as oral progestin-only contraceptives, a slightly higher upper bound of this 95% confidence interval may be acceptable.

The primary efficacy results should be calculated using the trial population of women younger than or equal to 35 years old at study enrollment because the likelihood of pregnancy decreases with advancing age. Include additional efficacy analyses for the overall trial population and a subgroup analysis for those older than 35 years old.

For the overall trial population, as well as for those younger than or equal to 35 years old at study enrollment and those older than 35 years old, sponsors should perform subgroup analyses based on BMI at study enrollment and geographic region (United States and Canada versus rest of the world).

Efficacy results can differ considerably between countries and may be related to factors that impact the single-arm, open-label trial results (e.g., treatment adherence, body weight, and smoking). When there are apparent differences in efficacy results across geographic regions, the labeled efficacy results will be solely based on data from cycles derived from study sites in the United States and Canada to provide efficacy data that is pertinent to the overall United States population.

D. Safety Considerations

The safety evaluation should include data from all enrolled subjects (from all participating countries), including those older than and younger than 35 years old.

Hormonal contraceptives have well-known risks, some of which are infrequent, such as venous thromboembolism. The division may require postmarketing evaluation of risks such as venous thromboembolism if the benefits of a new drug product outweigh its risks, but additional characterization of the risk is required postapproval.

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