Guidance for Industry

Female Sexual Dysfunction: Clinical Development of Drug Products for Treatment

DRAFT GUIDANCE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)
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Draft – Not for Implementation

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I. INTRODUCTION

This guidance is intended to provide recommendations for sponsors on the design of clinical trials in support of new drug applications (NDAs) for the treatment of female sexual dysfunction (FSD).

II. DEFINITION OF FEMALE SEXUAL DYSFUNCTION

Although the definition of FSD continues to evolve, it currently consists of four recognized components:

- decreased sexual desire;
- decreased sexual arousal;
- dyspareunia; and
- persistent difficulty in achieving or inability to achieve orgasm.

To establish a diagnosis of FSD, these components must be associated with personal distress, as determined by the affected woman.

Appropriate definition of the patient population to be studied is an important component of drug development for the treatment of FSD. If the indication for which drug approval is sought is based on a comprehensive definition of FSD that incorporates all four recognized components and any associated subtypes of the disorder, sufficient numbers of women having each component and associated subtype should be enrolled in clinical trials. A sponsor can choose one or any combination of the four components to study. In order to obtain approval for the desired indication (i.e., one or more components), safety and effectiveness should be demonstrated in each component group chosen.

III. APPROPRIATE STUDY POPULATIONS FOR CLINICAL TRIALS INTENDED TO DEMONSTRATE EFFICACY

[1] This guidance has been prepared by the Division of Reproductive and Urologic Drug Products (DRUDP) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the development of drug products to treat female sexual dysfunction. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statues, regulations, or both.

Clinical trials intended to demonstrate efficacy for the treatment of FSD should enroll women who are sexually active and who have a valid and reliable diagnosis of FSD. Study populations for such trials may focus on or be limited to one of the following subgroups if it is anticipated that response to therapy may differ across these subgroups:

- premenopausal women
- naturally menopausal women
- surgically menopausal women
- women taking hormone-containing products for hormone replacement therapy (e.g., estrogen and/or estrogen-progestin containing products)
- women taking hormone-containing products for contraception

Inclusion and exclusion criteria for clinical trials of drug products to treat FSD should be based on the specific research question being posed for the trial and should be chosen to protect volunteer safety. To increase the likelihood of demonstrating a treatment effect in clinical trials of FSD, it may be appropriate in some trials to exclude subjects with the following:

- relationship difficulties with a sexual partner
- use of concomitant medications that could affect sexual function (e.g., certain antidepressant medications)
- the presence of medical conditions that could affect sexual function (e.g., depression, anxiety, the first few weeks of the postpartum period)
- sexual dysfunction on the part of the woman's partner

IV. OTHER STUDY CONSIDERATIONS

Appropriate patient selection should include identification and enrollment of women for whom sexual dysfunction causes personal distress. *Personal distress* should be measured to ensure appropriate patient selection for trial participation but should not serve as the primary endpoint for establishing effectiveness.

Study populations can be stratified by or limited to one or more of the subgroups listed in section III of this guidance.

Objective data based on sexual events or encounters can be collected by having each enrolled subject record the number of events she experiences during a pretreatment baseline period and throughout each month of trial participation. The pretreatment baseline period should be a minimum of 4 weeks, and preferably 8 weeks, in duration. To minimize recall bias, this data should be recorded daily by the study subjects, using diaries. This data should be collected from the study subjects every 1 or 2 weeks.

Drug development should include appropriate dose-finding studies and determination of the lowest effective dose for the indication sought. Generally, two adequate and well-controlled, phase 3 trials are recommended for approval of drug products for FSD indications. The trials should typically be 6 months in duration, excluding the baseline period.

V. USE OF SCALES, QUESTIONNAIRES AND OTHER INSTRUMENTS DURING DRUG DEVELOPMENT

New scales, questionnaires, and other instruments to diagnose FSD and/or particular components or to measure response to treatment over time should be developed, tested, and validated in women with FSD. The validation process for the scale should demonstrate its reliability, validity, responsiveness, and ability to measure minimal meaningful differences.

Diagnostic scales and questionnaires should be able to distinguish patients with FSD from those without the disorder. If a scale is meant to detect a specific component of FSD, such as decreased sexual desire or decreased sexual arousal, the scale should also attempt to differentiate between women who have the component for which approval is sought and women having a different component of the disorder.

To minimize the risk that an instrument or scale may prove inadequate in post-trial analysis for identifying women with FSD or for detecting response to treatment, instrument validation should precede initiation of phase 3 efficacy studies.

VI. CLINICAL TRIAL ENDPOINTS

Primary endpoints for trials of drug products to treat FSD should be clinically meaningful and specifically related to the component or components of FSD being studied in the trials. These endpoints should be based on the number of successful and satisfactory sexual events or encounters over time. The determination of *successful* and *satisfactory* should be made by the woman participating in the trial, as opposed to her partner. Such *events* or *encounters* include:

- satisfactory sexual intercourse;
- sexual intercourse resulting in orgasm;
- oral sex resulting in orgasm; and
- partner-initiated or self masturbation resulting in orgasm.

In addition to the daily records kept by study participants, partners can also complete diaries, but the information obtained from those diaries should not constitute primary endpoints in phase 3 studies.

If physical genital changes (such as increased vaginal blood flow, increased clitoral blood flow, clitoral

engorgement, or vaginal lubrication) are measured, they should be linked to clinically significant changes in the number of successful and satisfying sexual events experienced by the woman during the trial.

Effectiveness should be demonstrated by statistically and clinically significant improvements in these event-endpoints over time in the active treatment arms when compared to the placebo treatment arms. These demonstrations should be based on between-group differences in the change in the number of successful and satisfactory events from baseline to end of treatment.

The primary efficacy endpoints and statistical analysis plans for phase 3 trials should be specified in detail prior to initiating the studies. Selection of efficacy endpoints after completion of any trial should be considered exploratory. Results from these exploratory post-trial analyses should not be considered to establish effectiveness.

Many of the diagnostic and treatment response instruments being developed for FSD are based on health-related quality of life (HRQL) claims. Although these instruments can be useful in providing supportive information, they most likely should not serve as primary endpoints for phase 3 trials. Endpoints based on HRQL claims should be linked to clinically meaningful objective endpoints as described above.