Low Sexual Interest, Desire, and/or Arousal in Women: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE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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Low Sexual Interest, Desire, and/or Arousal in Women: Developing Drugs for Treatment Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 developing drugs for the treatment of low sexual interest, desire, and/or arousal in women.[2] Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall clinical development program, with a focus on phase 3 trial designs, to support an indication for the treatment of these conditions. This draft guidance is intended to serve as a focus for continued discussions among the Division of Bone, Reproductive, and Urologic Products, pharmaceutical companies, the academic community, and the public.[3]

This guidance focuses on conditions of low sexual interest, desire, and/or arousal that cause marked distress or interpersonal difficulty in women, including female sexual interest/arousal disorder (FSIAD), hypoactive sexual desire disorder (HSDD), and female sexual arousal disorder (FSAD).[4] The symptoms of these conditions are NOT considered to be caused by:

- A coexisting medical or psychiatric condition
- Problems within the relationship
- The effects of a medication or other drug substance

[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] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during drug development.

[4] FSIAD is a clinical entity described in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) that was published in 2013, whereas HSDD and FSAD are conditions described in the fourth edition of the DSM.

The diagnostic criteria for disorders of low sexual interest, desire, and/or arousal in women were recently revised in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM). These revisions have not been universally accepted by the scientific community. The recommendations proposed in this guidance can be applied to the diagnostic framework outlined in both the fourth and fifth editions of the DSM.

This guidance does not address the development of drugs to treat other forms of female sexual dysfunction such as orgasmic disorder, genito-pelvic pain/penetration disorder, or substance/medication-induced sexual dysfunction in women. In addition, this guidance does not address the treatment of dyspareunia, which is often, but not always, related to vulvovaginal atrophy (VVA) associated with menopause. VVA symptoms are addressed in a separate guidance.[5]

Although this guidance discusses the selection of endpoints for clinical trials, it does not address detailed design considerations for patient-reported outcome (PRO) instruments. Those issues are addressed in the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (PRO guidance).[6] In addition, this guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.

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. BACKGROUND

The term *female sexual dysfunction* encompasses a heterogeneous group of sexual disorders, such as dyspareunia and problems related to sexual arousal, desire, interest, or orgasm. The sexual response has a physiological basis but can be affected by interpersonal context, such as emotional and relationship dynamics. Significant changes in any of these components can affect a woman's sexual desire, response, and satisfaction. A variety of factors can cause or contribute to sexual dysfunction, including medical conditions (such as symptoms of VVA related to

[5] See the draft guidance for industry *Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation.* 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 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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

menopause), psychiatric conditions (such as depression and anxiety), use of medications (such as selective serotonin-reuptake inhibitors), and stressors (such as fatigue or relationship difficulties). Sexual dysfunction can adversely affect various aspects of life for a woman, including her relationship with her partner. There is a medical need for development of drugs with a favorable benefit-risk profile to treat women with sexual dysfunction.

III. DEVELOPMENT PROGRAM

A. General Considerations

As with any drug development program, early clinical development should include appropriate dose-finding in the target population to ensure that the most appropriate dosing regimen(s) are selected for further study. The FDA recommends evaluating more than one dose in phase 3 trials. See the following for additional information regarding dose response:

- The Fit-for-Purpose Initiative dose-finding tool MCP-MOD (Multiple Comparison Procedure-modeling), a statistical methodology for dose response[7]
- The guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*
- The guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*
- The ICH guidance for industry *E4 Dose-Response Information to Support Drug Registration*

If the investigational drug contains two or more drug components, the sponsor should address the combination drug rule by demonstrating that: (1) each component makes a contribution to the claimed effects; and (2) the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for the intended patient population.[8]

Exploration of new PRO instruments or novel diagnostic measures in early development may allow correlation of results obtained from these modalities with dose-response findings. We encourage early and regular discussions with the FDA regarding trial design to help ensure the use of adequate and interpretable assessments of treatment benefit.

[7] See the Drug Development Tools: Fit-for-Purpose Initiative Web page at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm505485.htm. See also Bretz F, Pinheiro JC, and Branson M, 2005, Combining Multiple Comparisons and Modeling Techniques in Dose-Response Studies, Biometrics, 61(3), 738-748.

[8] 21 CFR 300.50(a)

B. Specific Efficacy Trial Considerations

In general, support from two adequate and well-controlled trials is required to establish efficacy.[9] These trials should be randomized and placebo-controlled, but do not need to be identical in design. Each trial should include at least 24 weeks of blinded treatment to allow demonstration of effect onset and persistence while on treatment. A placebo run-in period is recommended for assessing whether subjects will likely adhere to the proposed dosing regimen through the trial and for obtaining baseline data for the key efficacy measures.

For a drug intended for use *as needed*, we recommend that the sponsor determine the time period following each dose of the investigational drug when the drug is likely to exert its effect, taking into account pharmacokinetic/pharmacodynamic relationships. This information should inform key aspects of the phase 3 trial design, such as the time interval following drug administration for assessing efficacy and the appropriate recall periods for PRO instruments.

If, in addition to the investigational drug, the proposed treatment involves a novel companion diagnostic procedure or device, contemporaneous development of the drug and the diagnostic is preferable such that the clinical performance and the clinical significance of the diagnostic can be established using data from the drug development program.[10] The FDA encourages sponsors to seek advice on the diagnostic as early in development as possible. The FDA's review of the investigational drug and the diagnostic procedure or device will be carried out collaboratively among relevant review staff.

C. Trial Populations

1. Appropriate Target Population

The FDA encourages sponsors to conduct trials in a well-defined patient population. This is particularly relevant for sponsors who propose to study women with FSIAD, because patients could meet the DSM-5 criteria for this condition if they predominantly have symptoms of low sexual desire, if they predominantly have symptoms of low sexual arousal, or if they have symptoms of both low sexual desire and low sexual arousal. Including women with these various combinations of symptoms in clinical trials is only recommended if the investigational drug is expected to have beneficial effects on both sexual desire and sexual arousal (e.g., based on the drug's mechanism of action). For those investigational drugs that are expected to have beneficial effects on either sexual desire or sexual arousal — but not both — the FDA recommends that the enrolled population include patients with the symptoms most likely to respond to the investigational drug. Otherwise, the sponsor risks a failed study.

The phase 3 trials should be conducted in North America (i.e., United States and Canada) because of differences in the diagnosis, practice of medicine, and expectation of treatment effects

[9] 21 U.S.C. 355(d)

[10] See the guidance for industry and Food and Drug Administration staff *In Vitro Companion Diagnostic Devices* available on the Guidance Documents (Medical Devices and Radiation-Emitting Products) Web page at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm.

in different geographical regions. These differences may affect the generalizability of efficacy data from patients outside the United States to the U.S. population. If the development program includes trials conducted in other geographical regions, these data can be used to support safety.

To support efficacy, the trial population should be representative of U.S. women in whom the drug will be intended for use and should reflect the demographic characteristics of the target population with the disorder. Trial subjects should be North American patients who are sexually active and are at least 18 years of age. They should have a documented history of personal distress related to low sexual interest, desire, and/or arousal. Although women who are not in a stable relationship may also experience sexual dysfunction, the FDA recommends that the clinical trials limit enrollment to women who are in a stable relationship. This approach reduces the likelihood of having changes in relationship status during the trials, which could confound the results. Patients should be excluded if the symptoms and associated distress are related to a comorbidity, problems within the relationship, or the effects of a drug or other drug substance.

Female sexual dysfunction occurs in adult women. Sponsors can request a full waiver for pediatric studies on the grounds that necessary studies would be impossible because the condition does not exist in the pediatric age group.

2. Eligibility

The exclusion criteria (e.g., coexisting medical conditions, concomitant medications, restrictions based on body mass index, history of substance use) should be limited to ensure that the trial population is representative of North American women anticipated to use the drug, if approved. We also encourage sponsors to include patients with a broad range of severity of sexual dysfunction at baseline, provided that the dysfunction causes marked distress (see section III.D.3., Instruments for Measuring Patient-Reported Outcomes, for an assessment of distress). Furthermore, because the eligibility criteria do not need to be identical in all phase 3 trials comprising the clinical program, subsequent trial(s) can have less restrictive entry criteria than the first trial.

3. Menopausal Status

Because conditions of low sexual interest, desire, and/or arousal occur in both pre- and postmenopausal women, both groups represent appropriate target populations. Development programs targeting only one of these subgroups should be justified by safety concerns or other clinical grounds.

Sponsors can choose to study pre- and postmenopausal women in separate trials or study these populations within the same trial. If studied in the same trial, randomization of subjects should be stratified by menopausal status. Regardless of the approach chosen, dose-finding, safety, and efficacy should be established independently for each of these populations, because the benefit-risk profile may differ and there may be differences in etiologies and treatment responses. Therefore, if both pre- and postmenopausal women are included in the same clinical trial, the trial should be powered adequately to demonstrate statistical and clinical significance for each of these subgroups.

The FDA recommends subgroup analyses based on the cause of menopause (natural versus surgical) if both naturally and surgically menopausal women are enrolled in the same trial. The FDA also recommends subgroup analyses according to baseline hormonal contraceptive use (for premenopausal women) and according to baseline hormone therapy use (for postmenopausal women, if these drugs are allowed during the trials).

The FDA also requires additional subgroup analyses based on age and race.[11]

D. Clinical Outcome Assessment Instruments

Because decreased sexual interest, desire, and/or arousal are symptomatic conditions, a PRO is the most appropriate clinical outcome assessment for evaluating symptoms. It is essential that sponsors use well-defined and reliable PRO instruments.[12] For any PRO instrument proposed as a key study endpoint to support labeling claims, the sponsor should provide supportive information for FDA review (e.g., a copy of the assessment, the instrument's conceptual framework and scoring, evidence of the instrument's content validity[13] and other measurement properties including reliability, construct validity, and ability to detect change). See the PRO guidance for additional information.

1. Recall Period

Key signs and symptoms should be recorded frequently by subjects to minimize inaccurate responses resulting from problems with subject recall. We recognize that shorter recall periods may be more burdensome to subjects over the course of a lengthy trial and could lead to *diary fatigue*, which could adversely affect compliance with diary entry over time. However, longer recall periods (e.g., monthly) may adversely affect the ability to accurately reflect on symptoms. For example, the longer recall period may increase noise in the assessment making it more difficult to detect or interpret change during a trial. With a longer recall, it is also possible that subject recollection could be more heavily influenced by other experiences or by more recent experiences.

Because of the problems with long-term recall, we recommend using a short recall period (sponsors using a short recall period who are concerned about subject burden can propose approaches to minimizing burden). Sponsors who wish to use a longer recall period should evaluate the accuracy of the longer recall period compared to shorter recall.

[11] 21 CFR 314.50(d)(5)(v)

[12] 21 CFR 314.126(a)(6)

[13] *Content validity* is defined as the "Evidence from qualitative research demonstrating that the instrument measures the concept of interest including evidence that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use. Testing other measurement properties will not replace or rectify problems with content validity." See section III.D., Content Validity, of the PRO guidance.

For drugs intended to be administered on an as-needed basis, the FDA recommends that symptoms be assessed following each dose of the placebo and investigational drug. The length of time after each dose when symptoms should be assessed should be based on the investigational drug's expected duration of action, taking into account pharmacokinetic/pharmacodynamic relationships. Including efficacy data from days when the investigational drug is not used may increase the difficulty in detecting and attributing a treatment difference to the drug, and is not recommended. For similar reasons, the FDA does not recommend recall periods longer than 24 hours for an as-needed drug. A longer recall period may make it more difficult for subjects to accurately reflect on symptoms because their recall may be affected by symptoms that occurred on the days when the placebo and investigational drug were not used.

For drugs that are administered continuously, we also recommend shorter (e.g., daily or weekly) recall periods with a 1-day lockout period for evaluation of primary endpoints such as desire or arousal.

2. Format of Data Capture

Sponsors should specify the format used by subjects to record daily signs and symptoms, such as an interactive voice response system (IVRS), electronic tablet, smartphone, personal digital assistant, or paper diary. We prefer use of an electronic format with reminders or alarms, when appropriate and feasible, to ensure real-time data capture and limit missing data, as well as to accurately capture the timing of the assessment. Sponsors should address lockout of delayed entry (see section III.D.1., Recall Period) and frequency of downloads. In addition, sponsors should be able to generate, upon request, accurate and completed copies of electronic records in a form suitable for FDA review and inspection.

Such a diary should capture, at a minimum, whether a sexual encounter occurred, whether the investigational drug was taken, and any other information pertinent to the key efficacy endpoints. Sponsors should account for the occurrence of multiple sexual encounters on the same day or within a 24-hour period. Dosing times for drugs administered on an as-needed basis also should be captured. The FDA recommends that the diary be submitted for review (e.g., screenshots, script for IVRS) in advance of its use.

3. Instruments for Measuring Patient-Reported Outcomes

Phase 2 studies represent an important opportunity to evaluate measurement properties of PRO instruments. Therefore, piloting the instrument and obtaining results from such exploratory studies can inform instrument design and the adequacy for use in the phase 3 trials. Before use in phase 2 studies, it is important to establish that the questionnaire instructions and items are interpreted by subjects as intended and that the items adequately cover the relevant symptoms and are worded such that they do not overlap in their measurement concept.

We strongly recommend that sponsors discuss the selection and implementation of proposed PRO instruments with the FDA as early as possible during drug development. Two instruments are discussed below. The FDA is open to considering other instruments to measure sexual desire

and distress. We encourage the research and drug development community to collaborate with the FDA in development of a publicly available fit-for-purpose PRO instrument that can be used across multiple drug development programs over time. A framework for such collaboration is available within the FDA Development Tool Qualification program. See the guidance for industry and FDA Staff *Qualification Process for Drug Development Tools*.

a. Female Sexual Function Index[14]

The Female Sexual Function Index (FSFI) is a 19-item instrument that has been used in clinical trials to measure overall sexual function, although the FDA is unaware of data that adequately establish the validity of the instrument as a whole for regulatory purposes. Individual domain questions from the FSFI have been used to measure specific components of sexual function such as sexual desire (questions 1 and 2) and sexual arousal (questions 3 through 6). Below we focus on the FSFI sexual desire domain. To date, the FDA's experience with the FSFI sexual arousal domain is limited. Sponsors who wish to use that domain or other portions of the FSFI to establish efficacy for other aspects of sexual function should provide supporting data consistent with the recommendations in the PRO guidance.

The assessment of desire in the FSFI includes introductory instructions that define desire as being "a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex." Question 1 asks "How often did you feel sexual desire or interest?" with response options ranging from 5 (Almost always or always) to 1 (Almost never or never). Question 2 asks "How would you rate your level (degree) of sexual desire or interest?" with response options ranging from 5 (Very high) to 1 (Very low or none at all). These two questions ask the subject to reflect on her symptoms over the preceding 4 weeks. The two response scores are summed, and raw scores are multiplied by a factor of 0.6, providing a sexual desire domain score that ranges from 1.2 to 6.0.

The FDA has the following concerns with the content validity and response scale of the FSFI desire domain, in addition to the long recall period (28 days) as discussed in section III.D.1., Recall Period.

- The FDA's content validity concerns for the sexual desire domain arise from the multibarreled instructions that make it unclear what is driving any change identified on the assessment (e.g., receptivity, sexual fantasies, or initiating sexual activity). For example, if only one component (e.g., sexual fantasies) is increased with the drug, but other components (e.g., wanting, initiating, or feeling receptive to sexual activity) have not improved, a score change suggesting improvement could be shown; however, it is unclear whether this represents a meaningful benefit to patients.

- The FDA's concerns with the response scale relate to the response option of "Almost always or always" feeling sexual desire or interest (question 1) and a response indicating a "Very high" level of sexual desire or interest (question 2). For example, it is unclear

[14] Rosen R, Brown C, et al., 2000, The Female Sexual Function Index (FSFI): A Multidimensional Self-Report Instrument for the Assessment of Female Sexual Function, J Sex Marital Ther, 26(2):191-208.

whether women experiencing sexual desire all or most of the time would identify this as a benefit, or whether this could represent a different concern to women.

If a sponsor elects to use the FSFI, or a modified FSFI, some potential approaches for doing so are delineated below:

(1) A sponsor could develop a new modified FSFI desire domain that includes individual assessment of the components of desire captured on a daily basis with subsequent validation (evaluation of measurement properties). This approach is preferred because it addresses each of the concerns delineated above.

(2) A sponsor could use the FSFI desire domain and 28-day recall as currently designed and show that this recall period does not affect conclusions by comparing these results with a subset of subjects who use a shorter recall period (e.g., daily assessment) for the individual desire items.

(3) A sponsor could use the FSFI desire domain but remove the multibarreled instructions in the current instrument, and consider including secondary endpoints assessing other components of desire.

(4) A sponsor could use the FSFI desire domain and 28-day recall as currently designed without any modifications. This approach carries more risk because the aforementioned issues could make it more difficult to detect or interpret changes in a trial.

b. Female Sexual Distress Scale-Revised, Item 13[15]

Question 13 of the Female Sexual Distress Scale-Revised (FSDS-R) instrument is considered acceptable for measuring *bother* (a component of distress) related to decreased sexual desire. This question asks "How often did you feel: Bothered by low sexual desire?" Subjects assess their sexual distress over a 7-day recall period and respond on a scale of 0 (never) to 4 (always).

c. Other scoring proposals

Total scores of the FSFI and FSDS-R are not specific to the outcome measures of interest for the conditions addressed in this guidance. Therefore, the total scores will not be considered acceptable for any labeling claim.

E. Trial Endpoints

Primary efficacy assessments for adequate and well-controlled trials should be well-defined and reliable to provide a basis for determining whether there is "substantial evidence" to support the claims of effectiveness for a new drug.[16] Endpoint decisions should reflect the primary

[15] DeRogatis L, Clayton A, et al., 2008, Validation of the Female Sexual Distress Scale-Revised for Assessing Distress in Women With Hypoactive Sexual Desire Disorder, J Sex Med, 5:357-364.

[16] 21 CFR 314.126

symptoms targeted by the drug (e.g., low sexual interest, desire, and/or arousal) and should be supported by the proposed mechanism(s) of action of the drug, if known. Sponsors are encouraged to discuss endpoint selection with the FDA early in drug development.

The following outcome measures can be used as primary endpoints:

- The change from baseline in the number of satisfying sexual events (SSEs)
- The change from baseline in the level of sexual interest or desire
- The change from baseline in the level of sexual arousal
- The change from baseline in the level of distress

If a trial will use an endpoint of SSEs, the protocol and PRO instruments should define the term *satisfying* and what activities will be classified as a sexual encounter.

Baseline has been defined as a 4-week no-treatment phase or a 4-week placebo run-in period. Changes from baseline typically refer to the treatment responses obtained during the last 4 weeks of the double-blinded treatment period relative to the baseline. With this approach, the time period used for assessing baseline status (e.g., 4 weeks) should be the same as the time period used for assessing treatment responses (e.g., 4 weeks at the end of the treatment period). However, one limitation is that this approach uses only a small portion of the efficacy data collected during the treatment period. The FDA recommends alternative approaches that use a greater portion of the efficacy data obtained during the course of the treatment period.

1. Primary and Key Secondary Endpoints

The primary efficacy analysis should demonstrate a clinically meaningful treatment benefit that is statistically significant. Sponsors should describe in detail what constitutes a clinically meaningful change for each of the scales used in the trials and provide justification of the selected clinically meaningful threshold to define treatment success. In clinical programs for drugs intended to treat decreased sexual interest or desire, one approach is to assess the change from baseline in SSEs and the change from baseline in sexual interest or desire scores as coprimary endpoints,[17] and associated distress as a key secondary endpoint. Similarly, in clinical programs for drugs intended to treat decreased sexual arousal, one approach is to assess the change from baseline in SSEs and the change from baseline in sexual arousal as coprimary endpoints, and associated distress as a key secondary endpoint.

However, it is important to note that the definitions for disorders of low sexual interest or desire and low sexual arousal include associated distress and do not include a reduction in SSEs. For this reason, comments received from two October 2014 public meetings have stated that associated distress should replace SSEs as a coprimary efficacy endpoint for trials of drugs

[17] Multiple primary endpoints become coprimary endpoints when it is necessary to demonstrate an effect on each of the endpoints to conclude that a drug is effective.

intended to treat low sexual interest, desire, and/or arousal disorders, with SSEs relegated to a secondary endpoint.[18] The FDA also considers this approach acceptable.

2. Other Secondary Endpoints

Definitions of a responder demonstrating improvement in SSEs, interest, desire, arousal, or distress also can be assessed as secondary endpoints. Responder definitions should be prospectively described before starting the trial and should be based on actual data that establish that the change is clinically important.

Responder definitions should be derived using anchor-based methods. At a minimum, a static current-state patient global impression of severity (PGI-S) should be used as the anchor to evaluate the responder definition. The PGI-S is not subject to recall error like the patient global impression of change (PGI-C) anchor. A PGI-C can be used in addition to the PGI-S to provide additional evidence in interpreting a clinically meaningful change. See the PRO guidance for additional information. The FDA is open to considering other anchor-based methods as well.

If the investigational drug is expected to have an effect on both sexual desire and sexual arousal, the sponsor should designate, a priori, whether all these components will be evaluated as coprimary endpoints or whether some of these components will be tested as secondary endpoints. The sponsor should include justification for the proposed approach in the protocol, including the plan for controlling type I error for endpoints the sponsor hopes will lead to labeling claims.

F. Other Considerations

1. Safety Considerations

Drugs treating conditions of low sexual interest, desire, and/or arousal are likely to be taken long-term (defined as continuous or intermittent use for at least 6 months during the course of a lifetime). Therefore, the safety database should meet the patient exposures outlined in the ICH guidance for industry *E1 The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions*. Note that these are minimum patient exposures and that larger exposures may be needed for specific drugs depending on safety concerns identified during drug development.

Drugs intended for as-needed use may also cumulatively lead to use of at least 6 months during the course of a lifetime, and, in this case, should meet the patient exposures outlined in ICH E1, unless the sponsor provides adequate justification for why cumulative use would not exceed 6 months.

[18] See the Patient-Focused Drug Development Public Meeting and Scientific Workshop on Female Sexual Dysfunction Web page at http://www.fda.gov/Drugs/NewsEvents/ucm401167.htm. See also the public meeting minutes The Voice of the Patient, A series of reports from the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative: Female Sexual Dysfunction, accessed at http://www.fda.gov/downloads/Drugs/NewsEvents/UCM453718.pdf.

The FDA may request additional studies based on specific characteristics of the drug, such as its pharmacology, signals that emerge during drug development, or the intended route of administration. Sponsors should discuss these specifics with the FDA during drug development.

Development programs for all new molecular entities, including treatments for low sexual interest, desire, and/or arousal, should include an assessment of cardiac repolarization potential.[19] Development programs for drugs with a potential psychotropic mechanism of action should also include prospective assessment of treatment-emergent suicidal ideation and behavior.[20]

2. Pharmacokinetic/Pharmacodynamic Considerations

We recommend conducting an adequately designed dose-finding study with measurements of systemic exposure to assess the dose and exposure-response relationship. If feasible, blood samples collected during the phase 3 trials would also be helpful in correlating efficacy or safety findings with systemic exposure.

[19] See the guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*.

[20] See the revised draft guidance for industry *Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials*. When final, this guidance will represent the FDA's current thinking on this topic.