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DRAFT GUIDANCE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

**October 2016
Clinical/Medical**

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Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002*

*Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
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1 **Low Sexual Interest, Desire, and/or Arousal in Women:**
2 **Developing Drugs for Treatment**
3 **Guidance for Industry¹**
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6

7
8 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
9 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
10 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
11 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
12 for this guidance as listed on the title page.
13

14
15
16
17 **I. INTRODUCTION**
18

19 The purpose of this guidance is to assist sponsors in developing drugs for the treatment of low
20 sexual interest, desire, and/or arousal in women.² Specifically, this guidance addresses the Food
21 and Drug Administration's (FDA's) current thinking regarding the overall clinical development
22 program, with a focus on phase 3 trial designs, to support an indication for the treatment of these
23 conditions. This draft guidance is intended to serve as a focus for continued discussions among
24 the Division of Bone, Reproductive, and Urologic Products, pharmaceutical companies, the
25 academic community, and the public.³
26

27 This guidance focuses on conditions of low sexual interest, desire, and/or arousal that cause
28 marked distress or interpersonal difficulty in women, including female sexual interest/arousal
29 disorder (FSIAD), hypoactive sexual desire disorder (HSDD), and female sexual arousal disorder
30 (FSAD).⁴ The symptoms of these conditions are NOT considered to be caused by:
31

- 32 • A coexisting medical or psychiatric condition
33 • Problems within the relationship
34 • 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.

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35
36 The diagnostic criteria for disorders of low sexual interest, desire, and/or arousal in women were
37 recently revised in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders
38 (DSM). These revisions have not been universally accepted by the scientific community. The
39 recommendations proposed in this guidance can be applied to the diagnostic framework outlined
40 in both the fourth and fifth editions of the DSM.

41
42 This guidance does not address the development of drugs to treat other forms of female sexual
43 dysfunction such as orgasmic disorder, genito-pelvic pain/penetration disorder, or
44 substance/medication-induced sexual dysfunction in women. In addition, this guidance does not
45 address the treatment of dyspareunia, which is often, but not always, related to vulvovaginal
46 atrophy (VVA) associated with menopause. VVA symptoms are addressed in a separate
47 guidance.⁵

48
49 Although this guidance discusses the selection of endpoints for clinical trials, it does not address
50 detailed design considerations for patient-reported outcome (PRO) instruments. Those issues are
51 addressed in the guidance for industry *Patient-Reported Outcome Measures: Use in Medical*
52 *Product Development to Support Labeling Claims* (PRO guidance).⁶ In addition, this guidance
53 does not contain discussion of the general issues of statistical analysis or clinical trial design.
54 Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for*
55 *Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*,
56 respectively.

57
58 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
59 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
60 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
61 the word *should* in Agency guidances means that something is suggested or recommended, but
62 not required.

63
64

65 **II. BACKGROUND**

66
67 The term *female sexual dysfunction* encompasses a heterogeneous group of sexual disorders,
68 such as dyspareunia and problems related to sexual arousal, desire, interest, or orgasm. The
69 sexual response has a physiological basis but can be affected by interpersonal context, such as
70 emotional and relationship dynamics. Significant changes in any of these components can affect
71 a woman’s sexual desire, response, and satisfaction. A variety of factors can cause or contribute
72 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>.

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73 menopause), psychiatric conditions (such as depression and anxiety), use of medications (such as
74 selective serotonin-reuptake inhibitors), and stressors (such as fatigue or relationship
75 difficulties). Sexual dysfunction can adversely affect various aspects of life for a woman,
76 including her relationship with her partner. There is a medical need for development of drugs
77 with a favorable benefit-risk profile to treat women with sexual dysfunction.
78

79
80 **III. DEVELOPMENT PROGRAM**

81
82 **A. General Considerations**

83
84 As with any drug development program, early clinical development should include appropriate
85 dose-finding in the target population to ensure that the most appropriate dosing regimen(s) are
86 selected for further study. The FDA recommends evaluating more than one dose in phase 3
87 trials. See the following for additional information regarding dose response:
88

- 89 • The Fit-for-Purpose Initiative dose-finding tool MCP-MOD (Multiple Comparison
90 Procedure-modeling), a statistical methodology for dose response⁷
- 91
- 92 • The guidance for industry *Exposure-Response Relationships — Study Design, Data*
93 *Analysis, and Regulatory Applications*
- 94
- 95 • The guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug*
96 *and Biological Products*
- 97
- 98 • The ICH guidance for industry *E4 Dose-Response Information to Support Drug*
99 *Registration*

100
101 If the investigational drug contains two or more drug components, the sponsor should address the
102 combination drug rule by demonstrating that: (1) each component makes a contribution to the
103 claimed effects; and (2) the dosage of each component (amount, frequency, duration) is such that
104 the combination is safe and effective for the intended patient population.⁸
105

106 Exploration of new PRO instruments or novel diagnostic measures in early development may
107 allow correlation of results obtained from these modalities with dose-response findings. We
108 encourage early and regular discussions with the FDA regarding trial design to help ensure the
109 use of adequate and interpretable assessments of treatment benefit.
110

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>.

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152 in different geographical regions. These differences may affect the generalizability of efficacy
153 data from patients outside the United States to the U.S. population. If the development program
154 includes trials conducted in other geographical regions, these data can be used to support safety.
155

156 To support efficacy, the trial population should be representative of U.S. women in whom the
157 drug will be intended for use and should reflect the demographic characteristics of the target
158 population with the disorder. Trial subjects should be North American patients who are sexually
159 active and are at least 18 years of age. They should have a documented history of personal
160 distress related to low sexual interest, desire, and/or arousal. Although women who are not in a
161 stable relationship may also experience sexual dysfunction, the FDA recommends that the
162 clinical trials limit enrollment to women who are in a stable relationship. This approach reduces
163 the likelihood of having changes in relationship status during the trials, which could confound
164 the results. Patients should be excluded if the symptoms and associated distress are related to a
165 comorbidity, problems within the relationship, or the effects of a drug or other drug substance.
166

167 Female sexual dysfunction occurs in adult women. Sponsors can request a full waiver for
168 pediatric studies on the grounds that necessary studies would be impossible because the
169 condition does not exist in the pediatric age group.
170

171 2. *Eligibility*

172
173 The exclusion criteria (e.g., coexisting medical conditions, concomitant medications, restrictions
174 based on body mass index, history of substance use) should be limited to ensure that the trial
175 population is representative of North American women anticipated to use the drug, if approved.
176 We also encourage sponsors to include patients with a broad range of severity of sexual
177 dysfunction at baseline, provided that the dysfunction causes marked distress (see section
178 III.D.3., Instruments for Measuring Patient-Reported Outcomes, for an assessment of distress).
179 Furthermore, because the eligibility criteria do not need to be identical in all phase 3 trials
180 comprising the clinical program, subsequent trial(s) can have less restrictive entry criteria than
181 the first trial.
182

183 3. *Menopausal Status*

184
185 Because conditions of low sexual interest, desire, and/or arousal occur in both pre- and
186 postmenopausal women, both groups represent appropriate target populations. Development
187 programs targeting only one of these subgroups should be justified by safety concerns or other
188 clinical grounds.
189

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

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198
199 The FDA recommends subgroup analyses based on the cause of menopause (natural versus
200 surgical) if both naturally and surgically menopausal women are enrolled in the same trial. The
201 FDA also recommends subgroup analyses according to baseline hormonal contraceptive use (for
202 premenopausal women) and according to baseline hormone therapy use (for postmenopausal
203 women, if these drugs are allowed during the trials).

204
205 The FDA also requires additional subgroup analyses based on age and race.¹¹

206
207 **D. Clinical Outcome Assessment Instruments**

208
209 Because decreased sexual interest, desire, and/or arousal are symptomatic conditions, a PRO is
210 the most appropriate clinical outcome assessment for evaluating symptoms. It is essential that
211 sponsors use well-defined and reliable PRO instruments.¹² For any PRO instrument proposed as
212 a key study endpoint to support labeling claims, the sponsor should provide supportive
213 information for FDA review (e.g., a copy of the assessment, the instrument’s conceptual
214 framework and scoring, evidence of the instrument’s content validity¹³ and other measurement
215 properties including reliability, construct validity, and ability to detect change). See the PRO
216 guidance for additional information.

217
218 *1. Recall Period*

219
220 Key signs and symptoms should be recorded frequently by subjects to minimize inaccurate
221 responses resulting from problems with subject recall. We recognize that shorter recall periods
222 may be more burdensome to subjects over the course of a lengthy trial and could lead to *diary*
223 *fatigue*, which could adversely affect compliance with diary entry over time. However, longer
224 recall periods (e.g., monthly) may adversely affect the ability to accurately reflect on symptoms.
225 For example, the longer recall period may increase noise in the assessment making it more
226 difficult to detect or interpret change during a trial. With a longer recall, it is also possible that
227 subject recollection could be more heavily influenced by other experiences or by more recent
228 experiences.

229
230 Because of the problems with long-term recall, we recommend using a short recall period
231 (sponsors using a short recall period who are concerned about subject burden can propose
232 approaches to minimizing burden). Sponsors who wish to use a longer recall period should
233 evaluate the accuracy of the longer recall period compared to shorter recall.

234

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.

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

246
247 For drugs that are administered continuously, we also recommend shorter (e.g., daily or weekly)
248 recall periods with a 1-day lockout period for evaluation of primary endpoints such as desire or
249 arousal.

250

251 *2. Format of Data Capture*

252

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

261

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

268

269 *3. Instruments for Measuring Patient-Reported Outcomes*

270

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

277

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

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

286

287 a. Female Sexual Function Index¹⁴

288

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

298

299 The assessment of desire in the FSFI includes introductory instructions that define desire as
300 being “a feeling that includes wanting to have a sexual experience, feeling receptive to a
301 partner’s sexual initiation, and thinking or fantasizing about having sex.” Question 1 asks “How
302 often did you feel sexual desire or interest?” with response options ranging from 5 (Almost
303 always or always) to 1 (Almost never or never). Question 2 asks “How would you rate your
304 level (degree) of sexual desire or interest?” with response options ranging from 5 (Very high) to
305 1 (Very low or none at all). These two questions ask the subject to reflect on her symptoms over
306 the preceding 4 weeks. The two response scores are summed, and raw scores are multiplied by a
307 factor of 0.6, providing a sexual desire domain score that ranges from 1.2 to 6.0.

308

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

312

- 313 • The FDA’s content validity concerns for the sexual desire domain arise from the
314 multibarreled instructions that make it unclear what is driving any change identified on
315 the assessment (e.g., receptivity, sexual fantasies, or initiating sexual activity). For
316 example, if only one component (e.g., sexual fantasies) is increased with the drug, but
317 other components (e.g., wanting, initiating, or feeling receptive to sexual activity) have
318 not improved, a score change suggesting improvement could be shown; however, it is
319 unclear whether this represents a meaningful benefit to patients.
- 320 • The FDA’s concerns with the response scale relate to the response option of “Almost
321 always or always” feeling sexual desire or interest (question 1) and a response indicating
322 a “Very high” level of sexual desire or interest (question 2). For example, it is unclear
323

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.

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

326

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

329

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

334

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

339

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

343

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

347

348 b. Female Sexual Distress Scale-Revised, Item 13¹⁵

349

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

354

355 c. Other scoring proposals

356

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

360

361 **E. Trial Endpoints**

362

363 Primary efficacy assessments for adequate and well-controlled trials should be well-defined and
364 reliable to provide a basis for determining whether there is “substantial evidence” to support the
365 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

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

369
370 The following outcome measures can be used as primary endpoints:

- 371
- 372 • The change from baseline in the number of satisfying sexual events (SSEs)
 - 373 • The change from baseline in the level of sexual interest or desire
 - 374 • The change from baseline in the level of sexual arousal
 - 375 • The change from baseline in the level of distress
- 376

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

379
380 Baseline has been defined as a 4-week no-treatment phase or a 4-week placebo run-in period.
381 Changes from baseline typically refer to the treatment responses obtained during the last 4 weeks
382 of the double-blinded treatment period relative to the baseline. With this approach, the time
383 period used for assessing baseline status (e.g., 4 weeks) should be the same as the time period
384 used for assessing treatment responses (e.g., 4 weeks at the end of the treatment period).
385 However, one limitation is that this approach uses only a small portion of the efficacy data
386 collected during the treatment period. The FDA recommends alternative approaches that use a
387 greater portion of the efficacy data obtained during the course of the treatment period.

388
389 *1. Primary and Key Secondary Endpoints*

390
391 The primary efficacy analysis should demonstrate a clinically meaningful treatment benefit that
392 is statistically significant. Sponsors should describe in detail what constitutes a clinically
393 meaningful change for each of the scales used in the trials and provide justification of the
394 selected clinically meaningful threshold to define treatment success. In clinical programs for
395 drugs intended to treat decreased sexual interest or desire, one approach is to assess the change
396 from baseline in SSEs and the change from baseline in sexual interest or desire scores as
397 coprimary endpoints,¹⁷ and associated distress as a key secondary endpoint. Similarly, in clinical
398 programs for drugs intended to treat decreased sexual arousal, one approach is to assess the
399 change from baseline in SSEs and the change from baseline in sexual arousal as coprimary
400 endpoints, and associated distress as a key secondary endpoint.

401
402 However, it is important to note that the definitions for disorders of low sexual interest or desire
403 and low sexual arousal include associated distress and do not include a reduction in SSEs. For
404 this reason, comments received from two October 2014 public meetings have stated that
405 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.

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

408

409 **2. *Other Secondary Endpoints***

410

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

415

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

422

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

428

429 **F. *Other Considerations***

430

431 **1. *Safety Considerations***

432

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

440

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

445

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>.

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446 The FDA may request additional studies based on specific characteristics of the drug, such as its
447 pharmacology, signals that emerge during drug development, or the intended route of
448 administration. Sponsors should discuss these specifics with the FDA during drug development.
449

450 Development programs for all new molecular entities, including treatments for low sexual
451 interest, desire, and/or arousal, should include an assessment of cardiac repolarization potential.¹⁹
452 Development programs for drugs with a potential psychotropic mechanism of action should also
453 include prospective assessment of treatment-emergent suicidal ideation and behavior.²⁰
454

455 2. *Pharmacokinetic/Pharmacodynamic Considerations*
456

457 We recommend conducting an adequately designed dose-finding study with measurements of
458 systemic exposure to assess the dose and exposure-response relationship. If feasible, blood
459 samples collected during the phase 3 trials would also be helpful in correlating efficacy or safety
460 findings with systemic exposure.
461

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.