

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

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Introduction

On October 27, 2014, FDA held a public meeting to hear perspectives from women with female sexual dysfunction (FSD) on their condition and on currently available therapies. FDA focused the meeting on the sexual interest and arousal symptoms associated with FSD because disorders of sexual interest and arousal are reported to be the most common forms of FSD and there are no FDA-approved therapies for treating these symptoms. FDA conducted the meeting as part of the agency's Patient-Focused Drug Development initiative, an FDA commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) to more systematically gather patients' perspectives on their condition and available therapies to treat their condition. As part of this commitment, FDA is holding at least 20 public meetings between Fiscal Years 2013 - 2017, each focused on a specific disease area. More information on this initiative can be found at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>.

The October 27 patient-focused meeting was part of a two-day FDA workshop to explore important issues with respect to the development of safe and effective drug therapies for FSD. On October 28, 2014, FDA held a scientific meeting with experts to discuss several scientific challenges associated with drug development, including diagnostic criteria, endpoints, and patient-reported outcome instruments. This report focuses on the October 27 patient-focused meeting. The archived webcast and transcript for the October 28 meeting are available on the [meeting webpage](#).

Overview of female sexual dysfunction

Female sexual dysfunction (FSD) is a complex and multi-faceted disorder that has a wide spectrum of symptoms and severity. The term FSD covers a heterogeneous collection of conditions that have previously been classified into four different disorders: hypoactive sexual desire disorder (HSDD) characterized by a reduced or absent interest in sexual activity, female sexual arousal disorder (FSAD) characterized by an inability to attain or maintain sexual excitement, female orgasmic disorder characterized by the difficulty to attain orgasm despite sufficient arousal, and sexual pain disorder characterized by pain during sexual intercourse.

In May 2013, HSDD and FSAD were combined into a single diagnosis of female sexual interest/arousal disorder (FSIAD) in the Fifth Edition of the Diagnostic and Statistical Manual (DSM-5).¹ For a woman to be diagnosed with FSIAD, her symptoms of reduced sexual interest/arousal must have been present for at least six months, and must be severe enough to be a source of personal distress. FSIAD can be lifelong or acquired, range from mild to severe, and may be generalized or situational. There is currently no precise measure of the prevalence of FSIAD. However, one survey of U.S. women found that 12% of women reported experiencing personally distressing sexual problems.²

Pharmaceutical treatments for FSD are limited. There are FDA-approved products for treating moderate to severe pain during sexual intercourse related to vulvar and vaginal atrophy associated with menopause; however there are no drugs approved by FDA to specifically treat FSIAD, HSDD, or FSAD. Other prescription products are used off-label by patients, including sildenafil, testosterone or estrogen

¹ American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC

² Shifren et al. Sexual problems and distress in United States women – prevalence and correlates. *Obstet Gynecol.* 2008;112:970-8

hormonal therapies, and antidepressants. However, these products have either not demonstrated effectiveness for FSD or have potential safety issues if taken long-term. Non-drug therapies include lubricants, devices, behavioral or couples therapy, and lifestyle modifications.

Drug development for FSIAD is complicated due to many factors, such as the limited understanding of the underlying medical condition that may be responsible for the dysfunction, challenges in diagnosing the condition, difficulty in identifying outcomes that are both meaningful to patients and are measurable, and the complexity associated with designing trials that can reliably assess the drug's efficacy and safety.

Meeting overview

This meeting gave FDA the opportunity to hear directly from patients and patient representatives (including partners, healthcare providers, and patient advocates) about their experiences with female sexual dysfunction and its treatments. Discussion focused on two key topics: (1) the effects of female sexual dysfunction that matter most to patients and (2) patients' perspectives on treatments for female sexual dysfunction. The discussion questions (Appendix 1) were published in a [Federal Register notice](#) that announced the meeting.

For each topic, a panel of patients with FSD (Appendix 2) shared comments to begin the dialogue. Panel comments were followed by a facilitated discussion inviting comments from other patients and patient representatives in the audience. An FDA facilitator led the discussion, and a panel of FDA staff (Appendix 2) asked follow-up questions. Participants who joined the meeting via live webcast (referred to in this report as web participants) were also able to contribute comments. In addition, in-person and web participants were periodically invited to respond to polling questions (Appendix 3), which provided a sense of the demographic makeup of participants and how many participants shared a particular perspective on a given topic.³

Approximately 50 patients with FSD or patient representatives attended the meeting in-person, and approximately 30 patients or patient representatives provided input through the live webcast. According to their responses to the polling questions, in-person participants represented an even distribution of age (from below 30 to above 70), whereas the majority of web participants were less than 50 years of age. About one-half of in-person participants and most web participants indicated that they have had symptoms for 10 years or less. Most in-person participants reported that they were diagnosed with a form of FSD by a healthcare provider, while most web participants reported that they were not formally diagnosed. Based on the meeting discussion, it appears that in-person participants in general have received more specific care (e.g., from a specialist on sexual health) than is expected in the patient population and they were more familiar with FSD treatments and other aspects of drug development. Some participants voluntarily disclosed that their travel to the meeting was funded. Although meeting participants may not fully represent the population living with FSD, their input reflected a range of experiences with its symptoms and treatments.

³ The polling questions were intended as a discussion aid only, and not for scientific purposes. Polling results should not be interpreted as being representative of the overall FSD patient population.

To supplement the input gathered at the meeting, patients and others were encouraged to submit comments on FSD to a [public docket](#),⁴ which was open until December 29, 2014. A total of 110 comments were submitted to the public docket by patients and other stakeholders, including academicians, healthcare professionals, consumer groups, and women’s health advocates.

More information, including the archived webcast and meeting transcript, is available on the meeting website: <http://www.fda.gov/Drugs/NewsEvents/ucm401167.htm>

Report overview and key themes

This report summarizes the input provided by patients and patient representatives at the meeting or through the webcast. It also includes a summary of comments submitted to the public docket. The report is intended to reflect the content of this meeting and the docket comment submissions as they relate to patient perspectives on FSD symptoms, impacts, and current treatments.⁵ To the extent possible, the terms used in this summary to describe symptoms, impacts, and treatment experiences reflect the words used by in-person participants, web participants, and docket commenters. The report is not purported to be representative in any way of the views and experiences of the entire FSD patient population or of any specific group of individuals or entities. There may be symptoms, impacts, treatments, or other perspectives on the condition that are not included in the report.

The input from the meeting and docket comments underscores the significant impact that symptoms of FSD can have on women’s lives, and the challenges they face in finding safe, effective, and tolerable therapies to manage their condition. It also highlights the range of perspectives on the need for drug therapies for FSIAD. Several key themes emerged from this meeting:

- The women who participated in this meeting conceptualize and experience sexual *interest* (or *desire*, as the term most participants used) distinct from sexual *arousal*. They varied in their experience of reduced or absent interest, reduced or absent arousal, or both. Some, but not all, also experience other aspects of FSD, including pain, dryness, or inability to orgasm, which they believe contributes to their lack of desire. Participants appeared to believe that their most significant symptoms of their condition are multi-faceted and broader than the six specific sexual symptoms of FSIAD outlined in the DSM-5.
- Many participants and docket commenters described a distinct transition from a prior fulfilling sex life to a total loss of interest or arousal. Regardless of their varying beliefs about the causes or triggers of their interest or arousal symptoms, participants stressed the significant distress it causes daily. They described never initiating sexual contact, the measures they take to avoid intimacy, and persistent anxiety. They further described the profound impact their FSD has on their relationships, their self-identity, and their emotional well-being.

⁴ A *docket* is a repository through which the public can submit electronic and written comments on specific topics to U.S. federal agencies such as FDA. More information can be found at www.regulations.gov.

⁵ The public was also able to provide input at the October 27 meeting on other issues related to drug development, through an open public comment session. These comments are available through the meeting transcript and archived webcast, but may not be summarized in this report.

- Participants shared multifaceted views on the concept of a *satisfying sexual event* (a measure used to assess treatment efficacy, described further in the report), largely focusing on their interaction with their partner. Many indicated that although orgasm is important, it is not a necessary component of a satisfying sexual event. Several stressed the importance of feeling desire regardless of whether it is accompanied by a satisfying sexual event.
- Participants and docket commenters shared their complex journeys to find effective and tolerable therapies to address their interest and arousal symptoms. They described their experiences with hormonal therapies and other prescription drugs used off label, investigational therapies studied in a clinical trial, over-the-counter products, non-drug therapies, and couples or behavioral therapy, all varying in their degree of effectiveness.
- Participants had varying perspectives on the best way to adequately manage their condition, particularly with respect to the use of pharmaceutical therapies. Some participants believe that given the significant cultural component of sex and sexuality, interest and arousal effects can and should be primarily addressed through counselling and other behavioral therapies. However, many participants indicated that they see a need to determine and address underlying physiological causes or contributors to their interest and arousal symptoms.

The sections that follow provide greater detail on the experiences and views shared by meeting participants and docket commenters. The patient input generated through this Patient-Focused Drug Development meeting and public docket comments strengthens FDA’s understanding of the burden of FSD on patients and the therapies currently used to treat FSD and its symptoms. FDA staff will carefully consider this input as it fulfills its role in the drug development process, including when advising sponsors on their drug development programs and when assessing products under review for marketing approval. For example, Appendix 4 shows how this input may directly support our benefit-risk assessments for products under review. This input may also be of value to the drug development process more broadly. For example, the report may be useful to drug developers as they explore new outcome measures, outcome assessments, and clinical trial designs.

Topic 1: The Effects of Female Sexual Dysfunction that Matter Most to Patients

The first discussion topic focused on patients’ experiences with their female sexual dysfunction symptoms and the resulting effects on their daily lives. FDA was particularly interested in hearing about participants’ symptoms relating to sexual interest and arousal, how these symptoms affect their sexual experiences, and how their symptoms have changed over time.

Four women with FSD (Appendix 2) provided comments to start the dialogue. Two panelists described beginning to experience interest and/or arousal symptoms within the past five years, and the other two spoke of their experiences dealing with these symptoms for many years. The panelists described the challenges they face living with FSD, and the impact that their condition has on their ability to lead a fulfilling sexual life and maintain relationships. They also described the significant frustration, anxiety, and loss that they have experienced because of their condition.

In the large-group facilitated discussion that followed the panel discussion, most patients with FSD in the audience indicated, by a show of hands, that their experiences were reflected in at least one of the panelists' comments. A summary of the Topic 1 discussion is provided below.

Perspectives on most significant symptoms

The facilitated discussion provided a look into how symptoms manifest and how they have changed over time. The range of symptoms discussed by in-person and web participants is described in more detail below. Note that while FDA focused discussion on sexual interest and arousal symptoms to narrow the meeting scope, this report includes the wider range of symptoms and impacts described at the meeting. Generally speaking, participants appeared to believe that their most significant symptoms are multi-faceted and broader than the six specific sexual symptoms outlined in the DSM-5.

Sexual Interest or Desire

FDA began the large group discussion by asking participants how they conceptualize the terms *interest* and *arousal*. One participant described desire as “if you are interested in having sex or receptive to your partner approaching you” and arousal as “when you are getting wet... tingly, when you are having the bodily changes.” Several other participants shared similar conceptualizations. However, one participant stressed the challenge in finding consistent, overarching terms given the significant diversity in personal experiences.

Reduction or loss of sexual interest was the most frequently discussed symptom by in-person and web participants. Participants used the terms *desire* (most frequently used), *interest*, *libido*, and *sexual appetite* when describing this aspect of their condition. Their comments focused on thinking about sex, the desire to have sex, and their response to (or avoidance of) their partner's initiation, as illustrated below:

- “I don't even think about sex.”
- “I knew I wanted to have sex but I had no desire. I refrained.”
- “In a beautiful place with the man I love, my body was like a shell with nothing inside.”
- “I am able to grit through [sex], but I do it for [my partner], not for me.”

According to the results of a polling question (Appendix 3, Question 6) few in-person and web participants considered “no or reduced sexual/erotic thoughts or fantasies” (one of the diagnostic criteria in the DSM-5) to have a significant impact on daily life.

Several participants commented on the loss of their ability to become aroused. Participants used the terms *arousal*, *response*, *stimulated*, *sexual excitement*, and *becoming lubricated* when describing this aspect of their condition, as illustrated below:

- “The ability to be stimulated by being touched slowly disappeared. Sexual arousal and response time kept taking longer and longer until it became nonexistent.”
- “It is not a matter of how much foreplay we do or not. I'll be approached and we can spend forever trying to make something happen.”
- “[E]ven if I'm willing when my husband initiates to have sex, I can't stay in the moment necessarily, and then your body stops responding.”

The facilitator and FDA panel asked a number of follow-up questions throughout the discussion for a better understanding of patients' experiences with sexual interest and arousal. The topics raised are summarized below.

Onset of interest and arousal symptoms, and changes over time

When asked by show of hands, a few participants indicated that they have been living with their conditions for their entire lives. However, most participants indicated that they had acquired their symptoms, framing their experience as a transition from a fulfilling sex life to a total loss of interest and arousal. Some participants noted a gradual change over the course of several months or years, while for others the change happened "like a switch that went off."

Several participants attributed the onset of their condition (either sudden or gradual) to specific life events, including childbirth, hysterectomy or mastectomy, intrauterine device complications, early-onset menopause, discontinuing hormone therapy, and adverse reactions to medications. Some commented that their lack of interest was related to, or even caused by, other FSD effects. Other participants, however, indicated that they could not pinpoint a possible cause of their symptoms.

Beyond the onset of symptoms, several participants identified other factors that they believe exacerbate or contribute to their symptoms of FSD. Many in-person participants commented on the waxing and waning in symptoms associated with their testosterone treatments (discussed more in Topic 2). A few participants described the impact that stress has on their symptoms. For example, one participant described "the loss of a good job, the illnesses and deaths of my parents, et cetera, added to that ebb and flow in my sex life." A few participants focused their comments on menopause and "the challenge of aging," which "presents an additional issue [to] sexual functioning."

Some participants expressed their belief that there is a natural variation in sexual desire from one person to the next or over the course of time and discussed learning to temper expectations associated with cultural pressures and unrealistic expectations. As one participant explained, "[my husband and I] exposed a war between us sexually that had to do with the stereotypical ideas about men and women that we had personalized to each other." Other participants, however, emphasized that their symptoms do not stem from relationship or communication issues, and are purely physiological. One participant shared, "we don't have any other stressors in our relationship; there are no issues in our life."

Other symptoms and their effect on interest and arousal

Although the focus of the meeting was on interest and arousal, discussion on other FSD symptoms was raised as well, including their relationship to interest and arousal.

- *Reduced or loss of orgasm:* Some participants commented on their inability to achieve orgasm most or all of the time, as well as the subsequent role that orgasm plays in their sexual experience. As one participant explained, "I stopped having desire for sex ... [and] although I was alarmed, it wasn't until about four years later when I lost my orgasm that my attention was captured." Some participants commented that although they experience a lack of desire, they do not experience trouble with orgasm. Participants discussed in detail the role that orgasm plays or does not play in a satisfying sexual experience, covered in Topic 2.
- *Pain:* A few participants discussed pain symptoms that manifest whenever they engage in sexual intimacy or intercourse. These participants described the impact that pain can have on their

interest and arousal. For example, one participant commented that “as my arousal builds often times I experience just an unbelievable migraine...so some of my low libido might just be [due to] the fact that there is pain waiting at the end.” Another participant described the effects of how vaginal dryness and pain affects her interest, stating that “Having sex was not at all appealing. The pain during intercourse was excruciating. Both my desire and interest were overshadowed by my fear of pain.” One participant, however, commented that her FSD first manifested as a lack of desire and then progressed to include vaginal dryness.

- *Anxiety*: Several participants commented on the anxiety they feel when facing a sexual encounter. Some described the loop of negative thoughts that constantly runs through their head as they are engaged with their partners, for example wondering “am I going to be able to orgasm during this and is that going to impact how he feels about our relationship,” or “I know that I’m not going to be able to respond back.” Participants reported these feelings to be a significant deterrent from having sex. In addition, when asked by FDA, about one-half of meeting participants indicated by show of hand that they would place anxiety among the top symptoms of FSD that have the most significant impact on daily life.
- *Other symptoms*, such as hot flashes, sleep disturbances, and mood swings were also mentioned.

Initiation of Sex

Although not asked through polling, most in-person participants referenced having a long-term relationship with a partner. In response to a question asked by FDA, nearly all participants indicated that their partner is the one who typically initiates sexual activity. Participants described engaging in “duty sex” and having sex “out of obligation.” As one participant explained, “I might not even want to have sex but if he wants sex then and I give it to him then, yes, I was a good wife today.” A web participant commented that “I have to pretend to enjoy for my husband otherwise he won't even approach me to have sex. He has to know that he has pleased me and satisfied me.”

Participants also described their reluctance to engage in sexual activity and the measures they take to avoid intimacy “at all costs.” One comment resonated with many in-person and web participants: “I found myself avoiding any situations where a sexual experience may occur... going to bed after my husband fell asleep or jumping out of bed in the morning before he got up just so he wouldn't try to initiate sex. I even found myself avoiding simple hugs and kisses.”

Overall impact of female sexual dysfunction on daily life

Participants throughout the meeting described the larger impact sexual interest and arousal symptoms have on their lives and the lives of their partners and families, summarized below.

- *Impact on relationships*: Most participants discussed the strain that their FSD placed on their partners and their relationships. A few participants described their partners’ reluctance to initiate contact, because of their perceived failure to stimulate sexual response, their fear of rejection, or their fear of causing their partner physical or emotional pain. As one participant’s partner commented during the meeting, “It does have a huge impact when your lover, your soul mate, is no longer interested in having sex with you.” Another participant shared that her partner “has said to me that he feels stupid at times when he keeps getting shut down. I know he feels rejected.” Other

participants commented on relationships that have failed because of their FSD. One participant explained, “I lost a major relationship to this issue, and I never want to go back there.” A few participants stressed that the negative impact of their condition affects not just relationship with partners, but their relationships with family and friends.

- *Impact on self-esteem and identity:* Participants said that their loss of sexual functioning left them with feelings of low self-esteem and inadequacy. Many noticed a drop in their levels of confidence as it related to their sexuality, attractiveness, and femininity. One participant shared, “I had difficulty coping with my new reality and coming to terms with the discrepancy between who I was and who I became.” Another participant commented that her condition “affects things like my self-confidence and how I approach the world and how I feel about myself and what I project to other people.”
- *Emotional impacts:* Several participants described the devastation they felt after they failed to regain sexual function and were unable to perform in intimate situations with partners. One participant shared, “I became so frustrated that any attempt to have sexual intercourse would end up in me crying.” Other participants discussed the guilt their difficulties caused them to feel when they said, “I can’t be the woman he married” and “I feel like I pulled a bait and switch with my poor husband, who is undoubtedly wondering where the old me has run off to.” Participants also linked the shame and stigma associated with their condition to the isolation they felt. They described being embarrassed and reluctant to talk about their issues.

Topic 2: Patient Perspectives on Treatments for Female Sexual Dysfunction

The second discussion topic focused on patients’ experiences with therapies used to treat FSD, with particular focus on therapies to address interest and arousal. Four patient panelists provided comments to begin the dialogue. Panelists included a woman living with FSD for almost 20 years and who has found hormonal therapies to be effective; a woman in her 30s with a more recent onset of symptoms who has yet to find an effective therapy; a woman living with FSD for twenty-five years and who did not have success with hormonal therapies but who did find benefit by participating in a clinical trial for an investigational drug therapy; and a woman whose management of her condition focuses entirely on her relationships and her consciousness of sex and sexuality.

In the large-group facilitated discussion that followed, nearly all patients in the audience indicated by a show of hands that their experiences were reflected in the panelists’ comments. According to the results of a polling question (Appendix 3, Question 8), the majority of in-person participants reported taking prescription medication to treat their symptoms, followed closely by over-the-counter products. Dietary and lifestyle changes were also identified by participants as an important component of therapy. Fewer web participants reported taking prescription medications, although many did report using over-the-counter products and undergoing lifestyle changes. A number of in-person and web participants reported they were not currently doing or taking anything to treat their symptoms.

Throughout the dialogue, participants described in detail the benefits and downsides they have experienced from various therapies and modifications used to manage their condition. Participant experiences and perspectives shared at the meeting are summarized below. This section ends with participants’ perspectives on ideal treatments and broader considerations regarding FSD treatment.

Experimental or off-label prescription therapies

Hormonal therapy

Hormonal therapy, particularly testosterone, was discussed at length by several participants at the meeting.⁶ Products mentioned included testosterone topical creams or gels, injections, or implanted pellets (these products are not FDA-approved to treat female sexual dysfunction and thus their uses are considered to be off-label). These participants described being prescribed hormonal therapies after blood tests revealed low levels of testosterone for their age range.

Participants described a range of effectiveness for testosterone products. Several described noticeable alleviation of symptoms, including an increase in desire, arousal, and ability to orgasm and described their excitement at discovering that they were interested in initiating sexual contact on their own. Some participants noted variability in effectiveness, or waxing and waning effect, over the course of treatment. A few participants, however, commented that they did not notice benefit or that they briefly experienced benefits but then suddenly ceased responding to treatment.

Participants who used testosterone therapies described experiencing side effects such as acne, unwanted hair growth, and nausea. In addition, participants discussed the downsides to using gels and creams that are odorous and sticky, pellets that require costly surgical procedures, and injections that can cause bruising and bleeding. They discussed their general preference for one type of product over another based on a number of factors such as duration of results, consistency in effect, and convenience. Several participants stated that they did not mind the side effects they experienced when they weighed the benefits against them, while others reported discontinuing use after experiencing downsides with minimal or no improvement of symptoms. A few participants expressed concern about what the long-term effects of testosterone may be, especially if hormone levels were frequently fluctuating. Some participants said that the costs of these treatments not covered by insurance prevented them from continuing treatment even though they had helped to improve their symptoms.

Some participants commented on their success with using estrogen and progestin therapies to treat FSD symptoms, particularly those symptoms associated with menopause or hysterectomy complications. Throughout their treatment regimens they underwent blood testing and updated their dosages periodically under the guidance of their healthcare professionals. These participants noted improvement in both their daily function and sexual responsiveness.

Antidepressants

Several participants described being prescribed antidepressants to address their interest and arousal symptoms. Most of these participants stated that these medications did not relieve their sexual dysfunction symptoms, and only made it more difficult to orgasm. As one participant explained “I had also been prescribed Wellbutrin (bupropion) at the beginning to see if that would maybe help me at least enjoy life. And, it probably made me kinder to my children, but it still didn’t give me any better desire.” A few women expressed frustration about being prescribed antidepressants to treat their distress associated with FSD, without being treated for their underlying sexual dysfunction symptoms.

⁶ It should be noted that in-person meeting participants appeared to have more extensive experience with testosterone products than would be expected in the general population of women with FSD.

Other drug therapies

Two participants commented on their experiences with the investigational therapy flibanserin. One participant stated that she took the therapy as part of an open-label (not blinded) clinical trial extension, and one participant noted being part of a clinical trial for flibanserin. These participants described an improvement in sexual desire within a few weeks of use, and described the benefits as having sexual feelings, initiating sex, and enjoying intimacy once again.

Other drug therapies mentioned included muscle relaxants, pain killers, nerve injections, and Viagra (sildenafil). Participants did not report any positive impacts of these therapies on their symptoms.

Non-prescription or non-drug therapies

Participants discussed using or trying a number of non-prescription or non-drug approaches in an attempt to treat their sexual dysfunction, to rule out potential root causes of their symptoms, or to supplement their therapeutic regimens. A summary of these therapies is listed below:

- *Couples therapy*: Participants discussed their experiences with couples therapy, in which they worked on their relationship with their partner in hopes of improving sexual difficulties. Some stressed the benefits they have seen in such therapy, believing that the root of their problems stemmed either from their relationship or from their partner's approach to sex. As one participant explained, "accepting our sexual differences has been part of the whole change." Some said that they did not have any success in resolving their symptoms with couples therapy.
- *Behavioral therapies*: Several participants described practicing behavioral techniques in varying ways during their sexual encounters. One participant described practicing mindfulness, making sure she stays in the moment during intimacy, and refocusing back if she is having difficulty responding. A few participants commented on changing their conceptualization of sexuality and incorporating positive sexuality and sensuality techniques to enhance their sexual experiences. A few participants commented on the benefit of visual or physical stimulation aids (e.g., erotica, devices) for some women. A webcast participant, however, commented on the challenge associated with some partners' perceptions of failure if devices are used.
- *Over-the-counter products* cited by participants included lubricants, use of supplements such as DHEA (dehydroepiandrosterone), Provestra, and male enhancement supplements. Participants generally commented that they did not notice any improvement of desire or arousal symptoms with the use of these products.
- *Physical therapy*: A few participants described trying manual pelvic floor physical therapy, massage, or acupuncture, without success.

Perspectives on an ideal treatment for female sexual dysfunction

Throughout the meeting, participants provided their perspectives on what they would look for in a treatment that addresses their interest and arousal symptoms. Many participants stressed their desire to return to the quality of life they had before they began to experience FSD. For example, participants commented that they want "that part of my life back," "the old me," and "to be the woman my husband married not too long ago." A few participants emphasized the importance of having intimacy in which

both parties know, as one participant explained, that “it’s not duty sex but that I actually want him.” Participants commented on their desire to regain spontaneity in their sex lives, to respond to advances without issue, and to have more satisfying sexual experiences. As one participant concluded, “I want to think about sex. I want to initiate sex. I want to have more of it.”

FDA asked participants their perspectives on consistent treatments that would be taken every day versus intermittent treatments that would be taken on specific days. Most participants responded that they would prefer to have a medication that consistently increases their interest and arousal. One participant explained, “I want to always desire my husband and I don’t want it to be situational.” Another participant, however, stated that constant desire may be too lofty a goal, and that “perfection when it comes to sex” cannot be easily attained. Several participants also commented on wanting to address their sexuality and self-identity more globally. For example, one participant commented that she wants to regain her identity as a woman, which extends beyond thinking about the next sexual event.

Some participants cautioned that the ideal treatment requires understanding of the natural variation among women, the cultural aspects of sex, and their impacts on women’s sexual experiences. For example, one participant commented that an ideal treatment would move away from “a broader definition of normal sexuality for both sexes.” Another person commented that an ideal treatment would “account for the human waxing and waning of physical and sexual desire and arousal.”

Other considerations on drug development for female sexual dysfunction

Given the complex factors underlying drug development for FSD, and in particular treatments targeting interest and arousal, FDA was interested in listening to patient input on some particular issues, summarized below.

Satisfying Sexual Events (SSE) as a clinical endpoint

Evaluating the efficacy of a potential pharmaceutical treatment for sexual interest or arousal symptoms often relies on a measure that assesses changes in the frequency of a woman’s *satisfying sexual events* over time. FDA was interested in hearing how participants conceptualize a satisfying sexual event and its importance to their overall sexual experience, with respect to their FSD. Participants largely appeared to believe that having satisfying sexual events was important to them; however they expressed varying perspectives on what they consider the term to mean in the context of their symptoms. Some participants stressed that desire and arousal are important components of a satisfying sexual event, so that they were not simply performing for their partner’s benefit.

Participants also had differing views on whether or not orgasms are a necessary component of satisfying sexual events. In a show of hands, many participants indicated that an orgasm is not a necessary part of sexual excitement. As one healthcare provider explained, “sexual excitement is often akin to the building of an orgasm but not necessarily the actual orgasm.” Another participant responded, “... for me sex is not just about orgasm... a successful or satisfying event for me is more about feeling connected to [my husband] and being close and feeling arousal.” Other participants, however, stated that orgasm is a very important aspect of sexual experience, particularly for women who never experience orgasm. As one participant explained, “for some people who know that orgasm is... an option that they can have relatively easily, then it is not as crucial of a factor. But when it is never a factor then it is a very crucial one.”

Tracking symptoms over time

FDA was also interested in hearing participants' experiences and perspectives on tracking symptoms over time and how best to record symptoms. Participants had mixed responses. Some said that they do currently track symptoms because it helps them to better understand the patterns of their dysfunction, guide discussions with their physicians, and track how well their treatments are working (e.g., if they need to get another dose of testosterone). Most participants, however, especially those who were not on a testosterone treatment, indicated they do not systematically track symptoms. As one participant explained, there is "no need to write it down because [my symptoms] are the same every single day." Another commented that she did not see the value of daily tracking in her experience with a clinical trial, viewing the management of her condition as a long-term process of weeks and months rather than daily. Another added that she is opposed to daily recordings because her symptoms are too "depressing and distressing to think about on a daily basis." One participant commented that the considerations on monitoring depend on the nature of the therapy; in the framework of sex therapy "obsessional self-focus [can become the] magnifying problem rather than a useful intervention."

Other issues raised by participants

Throughout the meeting, participants shared experiences and perspectives on several other issues related to FSD, including difficulty in receiving a diagnosis, lack of understanding among healthcare providers, difficulty in accessing treatments, financial burden of treatments, the complexities of sexuality and sexual health, and beliefs that the healthcare system is more cognizant of male sexual dysfunction than female sexual dysfunction.

Summary of Comments Submitted to the Public Docket

FDA received 110 comment submissions to the public docket that supplemented the October 27 -28, 2014 public meeting. About one-quarter of submitted comments were contributed by individual patients with FSD or the partners of patients with FSD. Other comments were submitted by academicians, healthcare professionals, consumer groups, women's health advocates, and pharmaceutical industry representatives. Generally speaking, the comments from patients, partners, healthcare providers, and advocates largely reflected the range of input generated at the meeting, and provided greater depth of explanation in areas such as comorbid conditions, contributing factors, and onset of symptoms. The following is a brief summary of the comments on the topics addressed at the October 27 patient-focused meeting,⁷ highlighting areas of similarity and difference as compared to the meeting input.

⁷ Because this report centers on patient perspectives of FSD symptoms, impacts, and treatment, this report focuses on comments pertaining to these subject matters. The comments to the docket covered a wide range of other important topics related to drug development for FSD, such as perspectives on the need for drug therapies, clinical endpoints, the medicalization of women's sexual health, conflicts of interest between healthcare professionals and pharmaceutical companies, marketing influences on the consumer, and the state of female sexual education in the U.S. Comments on these topics were also reviewed and considered by FDA but are not summarized in this report.

Submitted comments on symptoms of female sexual dysfunction

Submissions from the docket reinforced the conceptualizations of FSD symptoms that participants described at the October 27 meeting. Commenters emphasized the distress felt from being unable to respond to sexual advances by partners, and reiterated that, as one commenter stated, “sex is more out of obligation than pleasure.” For example, one commenter explained that “it is horrible to have someone you love want you, make love to you, and wish that they would stop.” Commenters also described employing a variety of tactics to constantly avoid their partners and intimate situations. Below are further highlights of a selection of frequently mentioned symptoms.

- *Onset of reduced or absent sexual interest:* Sexual interest or desire was the most frequently commented upon aspect of FSD in the docket. Most commenters echoed meeting participants’ experiences describing a significant change from a former “healthy interest in sex.” While a few commented that their libido rises and falls, the majority described a reduction of interest over time until stabilizing at low or absent levels of desire. For some, the loss of interest and arousal was a more abrupt transformation, one that caused their active sex lives to “end overnight.” Comments from a few women in their 20s and 30s expressed concerns with suddenly losing interest in sex at such an early stage in their lives. In contrast to the majority of commenters and meeting participants, one woman described living with a lifelong lack of sexual interest, explaining that “although I went through puberty, I did not develop any sexual interest in people. The idea of sex with another person actually disgusted me. I had virtually no libido.”
- *Reduced or absent arousal and orgasm:* A few commenters specified that they did not have any issues with desire, but were more distressed by their inability to become aroused and have an orgasm. Commenters described a “lack of physical sensation in former erogenous zones,” to the point where “the clitoris does not respond to stimulation.” One individual described strong feelings of desire that occur without any downstream physical effects, noting, “I want to have sex with my husband and do so on a regular basis... I just want my 'tingle' back.”
- *Contributing factors:* Similar to what was heard at the meeting, almost all commenters were able to pinpoint a specific time when they began to experience symptoms (either gradually or all at once). For some, interest and/or arousal “bottomed out completely” after menopause, hysterectomies, or oophorectomies, and a few mentioned additional symptoms that occurred with menopause, including vaginal dryness, pain, and odor. A few commenters stressed the importance of addressing the effects of menopause and aging on sexual interest and desire. A few commenters described the significance of interest and arousal symptoms as side effects of their antidepressant medication.

In contrast, several commenters stressed that their FSD symptoms occur independently of other factors, including relationship or emotional problems. As one commenter stated, “I have not noticed any relation to my emotions or anything else in my life. I am just simply not even interested in intercourse in any way much of the time.” Another explained, “even when on vacation when stressors are not present, sexual desire does not return, even temporarily.”

Submitted comments on the overall impact of female sexual dysfunction on daily life

The submitted comments strongly reiterated the significant impacts that lack of sexual interest and arousal has on many patients' lives more broadly.

- *Impact on relationships:* A common theme in the submitted comments was the toll that FSD symptoms take on partner relationships. Several described the contribution of FSD to divorce, separation, or dissolution of a relationship. Commenters, including the partners of women with FSD, overwhelmingly reiterated the significance of the partner's perceptions of inadequacy, rejection, and frustration. A few commenters described feeling depressed and worried that their partner would leave them for "another woman who can satisfy him."
- *Emotional Impacts:* Commenters reiterated the isolation, guilt, and emotional distress they experience because of their FSD and its impact on relationship and other aspects of life. A healthcare professional said that the constant, unchanging nature of FSD symptoms is what "in part contributes to [the woman's] belief that the symptoms will never get better, there is nothing that will help restore her desire, and leads to isolation and hopelessness." As another commenter explained, "I'm being deprived of having a fulfilling life and marriage because of something I don't seem to have any control over."

Submitted comments on current treatments for female sexual dysfunction

Similar to the meeting input, the submitted comments covered a range of experiences on a multitude of treatments that patients use or have tried in an effort to address their symptoms.

- *Hormonal therapy:* A few commenters described complex treatment regimens consisting of hormone therapies, which often did not help or had benefits that lessened in effect over time. A commenter who used testosterone and estrogen creams said she has some success with "pulsing" her medication (discontinuing and restarting treatment). One commenter described being offered a low dose testosterone therapy by her doctor but said she was "reluctant to take it because of all the warnings that the long term health benefits to women were unknown."
- *Antidepressants:* Comments on the effects of antidepressants largely reflected what was heard at the meeting. Commenters who have had depression described an inability to feel desire or achieve an orgasm while on antidepressants. One commenter stated, "For many years, I blamed the depression for all my problems with sex... In the end, however, what helped me more than anything else was simply getting off the antidepressants, and realizing the effects they'd had on my sexuality for years."
- *Other drug therapies* mentioned included sildenafil and leuprolide, both of which were reported to be unsuccessful in long-term improvement of symptoms for those individuals.
- *Couples therapy and behavioral therapies:* A few commenters shared their experiences and perspectives on counseling to address FSD, with varying perspectives on its effectiveness. One commenter noted that being informed about female sexuality and common misconceptions has helped her to better understand her body and learn to work within her limits.

- *Other products:* A few commenters shared that the dietary supplement and herbal products they have tried did not alleviate symptoms. For example, one individual said, “I was so desperate that I started trying home-remedies and other unsafe herbal products. Although they didn’t help my sexual desire, they definitely had adverse effects.” One commenter described using marijuana and reported improvements in her sexual experiences.
- *Non-drug therapies:* One commenter discussed the benefits of non-drug lifestyle changes such as stopping smoking, regular exercise, and weight loss.

Submitted comments on ideal treatments for female sexual dysfunction

The submitted comments reflected the varying perspectives shared at the meeting with respect to the best approach for the treatment of FSD, particularly sexual interest and arousal components. Many patients and partners stressed their desire for pharmaceutical treatment options, and a few patients commented that they felt confident in weighing the personal risks and benefits of therapies in order to choose a regimen that works best for them. Several other commenters, however, stressed the need for caution in the push for pharmaceutical treatments and that more focus should be placed on acknowledging the complexity and addressing the psychosocial and cultural aspects of sex and sexuality.

Conclusion

Drug development for female sexual dysfunction is a complex and challenging process, and there are still many scientific issues that need to be resolved in this field. The input received through the October 27 Patient-Focused Drug Development meeting and subsequent October 28 Scientific Workshop enabled FDA and other stakeholders the chance to explore important aspects of drug development for FSD. Importantly, the October 27 patient-focused meeting and accompanying public docket provided FDA an opportunity to listen directly to patients about what aspects of their condition matter most to them, and how their condition affects their sexual experience and their daily life. FDA recognizes that patients have a unique ability to contribute to the understanding of the broader context of this condition, which is important to our role, and that of others, in the drug development process. Of particular value is patient perspective on what they would value in treatment for FSD, which can guide efforts to identify endpoints and develop tools to effectively measure and evaluate the benefit of potential therapies.

FDA is appreciative of the patients and patient representatives who thoughtfully shared their experiences and perspectives on this sensitive topic, including the helplessness and frustration they experience as their conditions affect their relationships, their emotional well-being, and their overall quality of life. The variability in the nature of symptoms and in the current approaches to treatment is considerable. Many participants expressed a strong desire for improvements to their existing treatments and for new treatments that better target the underlying cause of FSD. FDA is committed to supporting the development of safe and effective drug therapies for FSD.



Appendix 1: Meeting Agenda and Discussion Questions

Female Sexual Dysfunction Patient-Focused Drug Development Meeting



October 27, 2014

11:00 – 12:00 pm	Registration
12:00 – 12:05 pm	Welcome
12:05 – 12:10 pm	Opening Remarks Audrey Gassman, M.D. <i>Deputy Director, Division of Bone, Reproductive and Urologic Products (DBRUP) Office of Drug Evaluation 3 (ODE3), Office of New Drugs (OND), CDER, FDA</i>
12:10 – 12:20 pm	Overview of FDA’s Patient-Focused Drug Development Initiative Theresa Mullin, PhD <i>Director, Office of Strategic Programs (OSP), CDER, FDA</i>
12:20 – 12:35 pm	Background on Disease Area and Treatment Christina Chang, M.D., M.P.H. <i>Clinical Team Leader, DBRUP, ODE3, OND, CDER, FDA</i>
12:35 – 12:45 pm	Overview of Discussion Format Sara Eggers, Ph.D. <i>OSP, CDER, FDA</i>
12:45 – 1:15 pm	Panel #1 Comments: <u>Topic 1</u> Disease symptoms and daily impacts that matter most to patients. A panel of patients and patient representatives will provide comments to start the discussion.
1:15 – 2:15 pm	Large-Group Facilitated Discussion: <u>Topic 1</u> Patients and patient representatives in the audience are invited to add to the dialogue.
2:15 – 2:30 pm	Break
2:30 – 3:00 pm	Panel #2 Comments: <u>Topic 2</u> Patient perspectives on current approaches to treating female sexual interest/arousal disorder. A panel of patients and patient representatives will provide comments to start the discussion.
3:00 – 3:50 pm	Large-Group Facilitated Discussion: <u>Topic 2</u> Patients and patient representatives in the audience are invited to add to the dialogue.
3:50 – 4:20 pm	Open Public Comment
4:20 – 4:30 pm	Closing Remarks RADM (retired) Sandra Kweder, M.D. <i>Deputy Director, OND, CDER, FDA</i>

Discussion Questions

Topic 1: Disease symptoms and daily impacts that matter most to patients

- 1) Have you ever received a diagnosis from a healthcare provider of sexual interest/arousal disorder, hypoactive sexual desire disorder, or sexual arousal disorder?
 - a) How was the diagnosis made? For example, what type of healthcare provider made the diagnosis? Were any tests or questionnaires used to help make the diagnosis?
- 2) Of all the symptoms that you experience because of your condition, which **1-3 symptoms** have the most significant impact on your life? Please describe each symptom in detail, including how this symptom specifically affects your sexual experiences.
- 3) Do your symptoms wax and wane over time? For example, do you have better days and worse days? If your symptoms wax and wane, please answer the following questions:
 - a) Which symptoms vary the most, and in what ways?
 - b) How do your symptoms and their negative impacts on your sexual experiences compare between your “best days” and your “worst days”?
 - c) Do the changes in your symptoms typically happen over a period of minutes, hours, days, weeks, or months?
- 4) If you were asked today to accurately rate how good or how bad your symptoms have been over time, would you be able to accurately remember how your symptoms felt one day ago? Over the past 3 days? Over the past week? Over the past 2 weeks? Over the past 3 weeks? Over the past month? Is there anything else that you believe makes your symptoms better? Is there anything that you believe makes your symptoms worse? For example, menstruation, stress, etc.
- 5) Overall, have you experienced your condition and its symptoms getting progressively worse, improving, or remaining stable over the past few years?
- 6) What worries you most about your condition?

Topic 2: Patient perspectives on current approaches to treat FSIAD

- 1) What are you currently doing to help treat your condition or its symptoms? (Examples may include prescription medicines, over-the-counter products, physical or other therapies, support groups, and lifestyle changes.)
- 2) How well do your current treatments specifically treat the most significant symptoms of your condition?
- 3) How well have your treatments improved your sexual experience?
- 4) How has your treatment regimen changed over time, and why?
- 5) Are there any downsides to the treatments you have used? (Examples of downsides may include bothersome side effects, difficulty identifying appropriate healthcare providers, etc.)
- 6) What specific things would you look for in an ideal treatment for your condition? For example, which symptom would you most like a treatment to target and what would you consider to be a meaningful improvement in this symptom?

Appendix 2: FDA and Patient Panel Participants

Patient Panel, Topic 1

- Carol – Patient
- Beverly – Patient
- Karen – Patient
- Victoria – Patient

Patient Panel, Topic 2

- Barbara – Patient
- Judith – Patient
- Susan – Patient
- Katherine – Patient

FDA Panel

- Sandra Kweder (Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER))
- Julie Beitz (Office of Drug Evaluation (ODE) III, OND, CDER)
- Hylton Joffe (Division of Bone, Reproductive and Urologic Products (DBRUP), ODE III, CDER)
- Audrey Gassman (DBRUP, ODE III, OND, CDER)
- Christina Chang (DBRUP, ODE III, OND, CDER)
- Marcea Whittaker (DBRUP, ODE III, OND, CDER)
- Theresa Mullin (Office of Strategic Programs, CDER)
- Ashley Slagle (OND, CDER)

Appendix 3: Meeting Polling Questions

The following questions were posed to in-person and web meeting participants at various points throughout the October 27, 2014, Female Sexual Dysfunction Patient-Focused Drug Development meeting. Participation in the polling questions was voluntary. The results were used as a discussion aid only and should not be considered scientific data.

Demographic Questions

1. Where do you live?
 - a. Within the Washington, D.C. metropolitan area (including the Virginia and Maryland suburbs)
 - b. Outside of the Washington, D.C. metropolitan area
2. Are you participating today because you, personally, are significantly bothered by:
 - a. Absent or reduced desire for/interest in sexual activity or sexual fantasies
 - b. Absent or reduced sexual excitement, sexual pleasure or sexual arousal during sexual activity
 - c. Both
 - d. Neither. I have other symptoms associated with FSD
3. What is your age?
 - a. Younger than 30
 - b. 31 – 40
 - c. 41 – 50
 - d. 51 – 60
 - e. 61 – 70
 - f. 71 or greater
4. Have you received a diagnosis of female sexual interest/arousal disorder (FSIAD), hypoactive sexual desire disorder (HSDD), or female sexual arousal disorder (FSAD) from a healthcare provider?
 - a. Yes
 - b. No
 - c. I'm not sure
5. How long have you had symptoms of FSIAD (or HSDD, FSAD)?
 - a. Less than 5 years
 - b. 5 – 10 years
 - c. 10 – 20 years
 - d. More than 20 years
 - e. I'm not sure

Questions for Topic 1

6. For those of you who experience **absent or reduced sexual interest**, which of the following effects do you consider to have the most significant impact on your daily life? Please choose up to 2 effects.
- No or reduced interest in sexual activity
 - No or reduced sexual/erotic thoughts or fantasies
 - No or reduced initiation of sexual activity
 - Not being responsive to my partner's attempt to initiate sexual activity
 - Other
7. For those of you who experience **absent or reduced sexual arousal**, which effects do you consider to have the most significant impact on your daily life? Please choose up to 2 effects.
- No or reduced sexual excitement/pleasure during sexual activity
 - No or reduced sexual arousal in response to written, verbal, or visual cues
 - No or reduced genital or non-genital sensation during sexual activity
 - Other

Questions for Topic 2

8. What are you currently doing to treat your condition or its symptoms? Check all that apply.
- Prescription medicines
 - Over-the-counter products (for example, a lubricant)
 - Physical therapy, massage, or acupuncture
 - Dietary supplements or diet changes
 - Lifestyle changes, such as exercise or avoiding stressful situations
 - Behavioral therapies or couples sex therapy
 - Support group
 - Other
 - I am not doing or taking any therapies

Appendix 4: Incorporating Patient Input into a Benefit-Risk Assessment Framework for Female Sexual Interest/Arousal Disorder (FSIAD)

Introduction

Over the past several years, FDA has developed an enhanced structured approach to benefit-risk assessment in regulatory decision-making for human drugs and biologics.⁸ The Benefit-Risk Assessment Framework involves assessing five key decision factors: *Analysis of Condition*, *Current Treatment Options*, *Benefit*, *Risk*, and *Risk Management*. When completed for a particular product, the Framework provides a succinct summary of each decision factor and explains FDA's rationale for its regulatory decision.

In the Framework, the *Analysis of Condition* and *Current Treatment Options* rows summarize and assess the severity of the condition and therapies available to treat the condition. The assessment provides an important context for drug regulatory decision-making, including valuable information for weighing the specific benefits and risks of a particular medical product under review.

The input provided by patients and patient representatives through the FSD Patient-Focused Drug Development meeting and docket comments will inform our understanding of the *Analysis of Condition* and *Current Treatment Options* for this disease. The information in the top two rows of the sample framework for FSIAD (next page) draws from various sources, including the input summarized in this report. This sample framework contains the kind of information that we anticipate could be included in a framework completed for a drug under review for FSIAD. This information is likely to be added to or changed over time based on a further understanding of the condition or changes in the treatment armamentarium.

⁸ Commitments in the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) include further development and implementation of the Framework into FDA's review process. Section 905 of the FDA Safety and Innovation Act also requires FDA to implement a structured benefit-risk framework in the new drug approval process. For more information on FDA's benefit-risk efforts, refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> – Female sexual interest/arousal disorder (FSIAD) is characterized, in the Fifth Edition of the Diagnostic and Statistical Manual (DSM-5), by absent or significantly reduced sexual interest and/or arousal for at least 6 months and severe enough to be a source of personal distress. – FSIAD can be lifelong or acquired, range from mild to severe, and may be generalized or situational. Some women may experience a gradual change in their sexual experiences, while others may notice a sudden and immediate difference. – Women with FSIAD rarely initiate sexual contact, often avoid intimate situations, and feel significant distress or anxiety when they are unable to feel desire or arousal before or during intimacy or in response to sexual advances. For many women, FSIAD has a profound impact on their relationships, their self-identity, and their self-esteem. – There is currently no precise measure of the prevalence of FSIAD. However, one survey of U.S. women found that 12% of individuals reported experiencing personally distressing sexual problems.⁹ 	<p>FSIAD is a complex and multi-faceted disorder that has a spectrum of symptoms and severity. FSIAD can have a significant impact on patients' quality of life.</p>
Current Treatment Options	<ul style="list-style-type: none"> – There are currently no drugs approved by FDA to treat interest or arousal symptoms associated with FSIAD. – Other prescription products are sometimes used off-label by patients, including sildenafil, testosterone or estrogen hormonal therapies, and antidepressants. However, the effectiveness and safety of these products for FSIAD have not been established. – Non-drug therapies used include lubricants, devices, behavioral or couples therapy, and lifestyle modifications, with varying success. 	<p>There is an unmet need for effective and safe treatments for FSIAD.</p>

⁹ Shifren et al. Sexual problems and distress in United States women – prevalence and correlates. *Obstet Gynecol.* 2008;112:970-8