Stephen Ostroff
Acting Commissioner
Food and Drug Administration

July 13, 2015

Dear Dr. Ostroff,

The undersigned health experts, sex researchers and clinicians write to request that the FDA reject the NDA for flibanserin submitted by Sprout Pharmaceuticals for the treatment of HSDD in premenopausal women.

We believe that the 0-18-6 advisory committee vote on June 4 occurred because of a confusing scientific picture and the interference of "Even the Score," a carefully orchestrated public relations campaign initiated by the makers of flibanserin and other companies with sexual pharmaceuticals in the pipeline. Approval would set a dangerous precedent and send the wrong message to the public that a drug for chronic use with a poor risk-benefit profile can be successfully promoted by unethical tactics.

The discussion after the vote revealed the extraordinary ambivalence on the part of the B (approval with reservations) voters. For example,
K. Curtis: "I voted B, but a somewhat conflicted and still uncomfortable B"
V. Lewis: "I voted B, a difficult B"
T. Gerhard: "I also voted B; a very difficult B, definitely; between a B and C"
J. Perrone: "I voted B, but I applaud the people who voted C"
T. Stürmer: "I voted B. I was on the fence here, I have to admit."
E. Bell-Perkins: "I voted B; it was difficult."
W. Gellad: "I have serious, serious, serious safety concerns."

We will leave the topic of flibanserin's safety to others, except for mentioning the truly absurd situation of approving a daily drug to boost the sex lives of women in their 30s and 40s that must not be taken with alcohol. As sexologists we can say with confidence that this advice is both preposterous and doomed.

I.
As sex reseachers and clinicians we recommend that flibanserin be rejected because **clinical definitions of women's sexual problems are changing** in important ways that flibanserin studies have ignored. The classification changes between DSM-IV to DSM-5 represent a substantial and **beneficial** shift in our understanding of sexual desire.

The FDA Scientific Workshop on Female Sexual Interest/Arousal Disorder held October 28, 2014 was supposed to illuminate these issues, and the comprehensive list of questions posed by the FDA to the Scientific Workshop Panel[i] should have produced a thoughtful examination. However, as discussed in a recent *Journal of Sex Research* commentary, "Missed Opportunities in the Patient-Focused Drug Development Public Meeting…,"[ii] the makeup of the Panel Roster and the contentious atmosphere engendered by the lobbying of the "Even the Score" campaign prevented this from happening. The discussion was largely based on opinion and anecdote and the meaning and implications of the HSDD-FSIAD shift were never explored.

The scientific discussion should have included DSM-5 experts to explain why the changes between HSDD to FSIAD reflected an **evidence-based paradigm shift from viewing women's sexual desire as a straightforward matter of internal and spontaneous drive ("lust") to a more complex incentive motivation model of sexual response that emphasizes the interaction of desire with psychological, stimulus and relational context**. This shift in professsional nomenclature was rejected by some of the October 28 panel members who argued, without evidence, that the language was confusing and might have utility in clinical practice but not in clinical trials. However, many of those panel members either were not sexologists or were involved with Sprout Pharmaceuticals, making their judgments suspect. This incentive model has been developed for over a decade, culminating in the DSM-5 nomenclature.[iii]

An important consequence of the diagnostic change is likely to be its impact on desire assessent and clinical trial endpoints. In the most recent trial of flibanserin Sprout substituted a new co-primary endpoint (the desire component of the Female Sexual Function Index - FSFI) in place of the diary co-primary endpoint used in previous (failed) studies, a switch discussed at some length in the DBRUP Division's Report. Careful examination of the items and scoring of the two desire questions supports the Division's concerns about the weaknesses of the FSFI for assessing desire. Problems with content validity and recall reflect variety in women's experience of sexual desire, a main reason for the new nomenclature.

The DSM-IV definition of HSDD cited in the Sprout briefing document (P. 11) and used in its Appropriate Use Checklist (Appendix Q, P. 290) denotes desire problems as a loss of spontaneous desire ("A persistent or recurrent deficiency or absence of sexual fantasies and desire for sexual activity", briefing P. 11), not the capacity for sexual desire, arousal, satisfaction or pleasure which is the current standard. **Lack of spontaneous sexual desire is not a sexual disorder or even uncommon**. Clinical sexologists do not diagnose on the basis of questionnaires. Women's ratings of their "level of desire" fluctuate markedly in conjunction with life events.

On June 4, the only sexologists on the Advisory Committees (N=24) were Dr. Julia Heiman, who played no role in the DSM, and Dr. Marianne Brandon, a private practice sex therapist. This gave undue weight to the anecdotes of physicians and patients at the Open Public Hearing, most of whom were connected to Sprout or the "Even The Score" campaign.

II.

In addition to the definitional issues, we are very concerned that Sprout's marketing plans are likely to ignore **the importance of sex education and the quality of sexual relations.** The sex research literature is replete with studies showing the effectiveness of women's discussion groups, sex therapy, cognitive behavior therapy and couples counseling in ameliorating sexual complaints, including loss of desire.[iv] Yet Sprout's "Comprehensive Risk Management Program" **omits any mention whatsoever of counseling or education**. There is no mention of assessing the patient's or couple's **sexual expectations, attitudes or knowledge** in the Appropriate Use of Flibanserin text

(Appendix Q), despite the extensive literature on the central importance of those factors. Nor does the "decreased desire screener" (Appendix P) or Package Insert and Medication Guide (Appendix O) refer to any sexual knowledge or skills. Sexual desire is presented without psychological or relationship context - exactly the opposite of the approach most clinical sexologists recommend.

At the flibanserin hearing on June 4, several physicians in the OPH emphasized that they have "nothing, nothing" to offer their patients. In a memorable bit of theater, one North Carolina doctor paused for many long seconds to dramatize that she had only "silence" to offer her patients. As sexologists we find this statement dismaying and unbelievable. How can we be having such success with educational materials, group discussions and therapy of various kinds, and yet these resources be unknown to sexual medicine physicians? The answer to this situation is not a drug with marginal effectiveness and a long list of safety issues. The answer is to increase the knowledge and skills of those experts in the field of sexual medicine who feel that in 2015 they have "nothing" to offer their patients.

III.
We request that the FDA follow the advice of its scientific staff and reject this drug for the third time. Research on sexual psychotherapy, neuroscience, hormones, genetics, attitudes, etiologies and expectations continues apace. Better trial outcome measures and definitions will emerge. The political pressure levied on the FDA by "Even the Score" is distasteful and must be resisted. The public health will be ill-served by flibanserin and it should not be approved.

Sincerely,
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[i] http://www.fda.gov/downloads/Drugs/NewsEvents/UCM420311.pdf, p. 2-4
[ii] http://dx.doi.org/10.1080/00224499.2014.1003362
[iii] See an especially lucid analysis in the *NYT Magazine* in 2009 titled "Women who Want to Want." http://www.nytimes.com/2009/11/29/magazine/29sex-t.html
[iv] Frühauf, S. Gerger, H. Schmidt, H. M. Munder, T. Barth, J. (2013). Efficacy of psychological interventions for sexual dysfunction: a systematic review and meta-analysis. *Archives of Sexual Behavior*, 42(6), 915-33.

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