

Lilly ICOS LLC

c/o

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**Lilly Research Laboratories**

A Division of Eli Lilly and Company

Lilly Corporate Center  
Indianapolis, Indiana 46285

July 14, 2000

Food and Drug Administration  
Dockets Management Branch, HFA-305  
Room 1061  
5630 Fishers Lane  
Rockville, Maryland 20852

**COMMENTS ON DRAFT GUIDANCE**

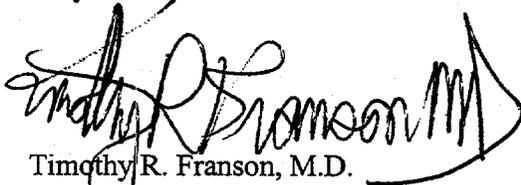
Re: Docket No. 00D-1278  
Guidance for Industry: DRAFT GUIDANCE

Please find attached comments and suggestions regarding the draft guidance entitled  
"Female Sexual Dysfunction: Clinical Development of Drug Products for Treatment."

Please call Ms. Susan Sullivan at (425) 415-5649, Gary Higdon at (317) 276-9136 or me  
at (317) 277-3799 with any questions or comments. You may also send a FAX message  
to my attention at (317) 433-2255. Thank you for your assistance.

Sincerely,

Lilly Research Laboratories on behalf of Lilly ICOS LLC



Timothy R. Franson, M.D.  
Vice President  
Clinical Research and Regulatory Affairs - U.S.

00D-1278

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**ATTACHMENT**

## **Comments on Draft Guidance for Industry – Female Sexual Dysfunction: Clinical Development of Drug Products for Treatment (Docket 00D-1278)**

The FDA is to be commended for undertaking the difficult task of developing guidelines for the clinical development of drug products for the treatment of female sexual dysfunction (FSD). We appreciate the challenge of developing these guidelines given the current underdeveloped status of theory and research related to FSD. In addition, we welcome the revised classification of FSD as reported by the Consensus Conference in March 2000 (Basson et al. 2000). A major emphasis in this classification is that of personal distress as a diagnostic factor in every identified segment of FSD. This is most important as it clearly defines the presenting problems as those of the patient and not of her partner.

In response to the request for feedback regarding the Guidance for Industry on Female Sexual Dysfunction document issued in May 2000, we offer our comments on the following points:

- Clinical trial endpoints;
- Duration of clinical trials; and
- Collection of subject diary data.

### **1. CLINICAL TRIAL ENDPOINTS**

#### **Current Draft Guidance for Industry**

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

- Satisfactory sexual intercourse;
- Sexual intercourse resulting in orgasm;
- Oral sex resulting in orgasm; and
- Partner-initiated or self masturbation resulting in orgasm.

#### **Comment**

Given the present understanding of FSD, it is recognized that a major challenge is to objectively measure a clinically meaningful sexual event, in particular as it relates to a specific component of FSD. In the above listing of events or encounters, three of the four examples describe sexual events leading to orgasm. The emphasis on orgasm, as given in these examples, gives the perception that the endpoints for drug treatments for FSD should end in orgasm. It is also not clear whether these are merely examples or actual standards for endpoints. Using

orgasm as the ultimate endpoint for all components of FSD does not appear to be congruent with clinical experience. It also conflicts with current thinking about female sexual response. Rosemary Basson, an expert in sexual medicine and a leader in female sexual response, suggests that not all women begin their sexual encounter with sexual desire, or indeed with orgasm as a goal, but rather make a decision based on non-sexual reasons to engage in sexual stimulation (Basson 2000). It is after the woman becomes engaged in the encounter, that she experiences sexual arousal and then desires to continue. This concept challenges the idea that desire precedes arousal, which then leads to orgasm. In other words, women may experience arousal and desire at the same time. In addition, for many reasons, she may have sexual arousal that is pleasurable and satisfying, but which does not result in an orgasm.

Consequently, drugs to treat female sexual desire disorder should be measured on a clinically significant *change or improvement* in sexual thoughts, desire, fantasies, and receptivity to sex. Drugs to treat female sexual arousal disorder should be measured on a clinically significant *change or improvement* in the intensity and ease in which arousal is achieved and maintained. Moreover, drugs to treat female orgasmic disorder would measure improvement in the difficulty and delay in getting an orgasm. This would be consistent with the diagnostic Consensus Conference classifications for FSD.

For endpoints based on the number of satisfactory sexual encounters, we request that FDA clearly indicate the need to have the quantity measure linked to a quality (ie, satisfactory) outcome which could also be expressed as a percentage. Measuring only the number of sexual events or encounters would not provide sufficient information on the *improvement* of the specific disorder. For example, the number of sexual events may sometimes be an inadequate measurement tool, since with some FSD components increased numbers of events may not be as significant to the woman as the quality of the sexual encounters. Consequently, to avoid the outcome of therapy deemed ineffective by number of events alone in which a subject with, for example, a baseline of three sexual events per month that she judges unsatisfactory, has three sexual events on treatment the next month that she judges clinically improved (rated satisfactory), inclusion of a quality or satisfaction dimension would clearly indicate effectiveness for that individual.

Finally, we recommend removing the term "successful" from the phrase "number of successful and satisfactory sexual events" because "success" suggests that attaining a goal such as orgasm is necessary for a woman's sexual encounter to be satisfying. This is not consistent with current clinical experience.

### **Suggested Rewording of Guidance for Industry**

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

- Sexual encounters with satisfactory desire;
- Sexual encounters with satisfactory arousal;
- Sexual encounters with satisfactory orgasm; or
- Sexual encounters without pain.

Sexual encounters may include:

- Sexual intercourse;
- Oral sex; and
- Partner-initiated or self masturbation.

## **2. DURATION OF CLINICAL TRIALS**

### **Current Draft Guidance for Industry**

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

### **Comment**

It should not be presupposed that all drugs take a certain length of time to show effectiveness. Rather, this is drug specific and should be determined on a case-by-case basis. Therefore, with this in mind we suggest more flexibility in the duration of FSD clinical trials and note that the duration of the trial should be sufficient to assess quality of response for specified endpoints.

### **Suggested Rewording of Guidance for Industry**

Drug development should include appropriate dose-finding studies and determination of the lowest effective dose for the indication sought. Generally, two adequate and well-controlled Phase 3 trials are recommended for approval of drug products for FSD indications. The duration of trials should be sufficient to assess quality of response for specified endpoints.

### 3. COLLECTION OF SUBJECT DIARY DATA

#### **Current Draft Guidance for Industry**

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

#### **Comment**

We agree with the need to minimize recall bias and recommend that subject diaries be completed as soon after the sexual event or encounter as possible. However, the method prescribed in the draft guidance to minimize recall bias (eg, collecting subject diaries every 1 or 2 weeks) is too specific. There may be other equally or more effective means.

#### **Suggested Rewording of Guidance for Industry**

Objective data based on sexual events or encounters can be collected by having each enrolled subject record the number and quality of events she experiences during a pretreatment baseline period and throughout each month of trial participation. The pretreatment period should be 4 to 8 weeks in duration. Sexual event data should be recorded by the study subject as soon as possible after the sexual event, using diaries or other credible means. Measures should be instituted to minimize recall bias.

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#### **References:**

Basson R, Berman J, Burnett A, et al. 2000. Report of the international consensus development conference on female sexual dysfunction: Definitions and classifications. J Urol 163(3):888-893.

Basson R. 2000. The female sexual response: A different model. J Sex Marital Ther 26:51-65.

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