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July 6, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20857

RE: Docket No. 00D-1278
Comments on Draft Guidance for Industry on Female Sexual Dysfunction: Clinical
Development of Drug Products for Treatment

Dear Sir or Madam:

This provides comments to the Draft Guidance titled: "Female Sexual Dysfunction: Clinical Development of Drug products for Treatment," Docket No. 00D-1278. Procter and Gamble Pharmaceuticals acknowledges the need for the development of a guidance in this very important new therapeutic area of Female Sexual Dysfunction and commends FDA for the efforts taken to develop this guidance. We appreciate the opportunity to respond to the Agency's request for comments on the draft document. For your convenience, an electronic version of these comments is provided as a pdf file in Attachment 1.

General Comments

One overall comment applicable to the guidance is the recommendation that flexibility be provided for studies of the various categories of FSD. This general comment is based on the observation that each FSD category may have specific clinical study needs regarding appropriate endpoints and measurement methodologies.

Section II - Definitions of Female Sexual Dysfunction

Paragraph 1: For clarity of the definitions and categories of FSD, we recommend reference to the AFUD (American Federation of Urological Disease) consensus conference paper recently published in The Journal of Urology (Basson et al., Vol. 163, 888-893, March 2000)(Attachment 2-References) as this publication appears to serve as the basis of the evolving definition of FSD. In addition, it is recommended the guidance provide the definitions of the categories (as defined in the publication) as they delineate the symptoms of each FSD category along with the requirement of personal distress for a diagnosis.

For clarity, and to be in alignment with the current scientific/medical literature, which recognizes four separate FSD disease entities, it is recommended that the term "components" be changed to "categories" when referring to the recognized and defined types of FSD.

Paragraph 3: It is recommended that the Agency clarify this paragraph regarding whom to enroll in clinical trials in order to obtain approval for indications covering more than one FSD category. It is currently not clear whether a single patient could be studied for more than one clinical endpoint for the various categories of FSD in a single clinical trial. Similarly, it is not

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clear whether a patient who has been diagnosed with more than one category of FSD could be enrolled in a clinical study investigating just one category.

Section III - Appropriate Study Populations For Clinical Trails Intended To Demonstrate Efficacy

Paragraph 1: It is recommended that enrollment of women not be restricted to women who are "sexually active," since some women, as potential candidates for clinical studies and for future therapies, may not be sexually active but may want to be.

Paragraph 1: For clarification, it is recommended that an additional sentence be added to express the concept that if it is anticipated that a similar response to therapy would exist across the populations outlined, the study populations (i.e. surgical and naturally menopausal women) may be studied within a single clinical trial.

Section IV - Other Study Considerations

Paragraph 1: For clarification, it is recommended that the patient selection be based on the categorical definitions of FSD (as defined by the AFUD Consensus Conference) which include the symptoms for each category and personal distress.

Paragraph 3 - Sentence 1: It is recommended that the guidance acknowledge that the categories of FSD may require different endpoints. Therefore, beyond collection of objective data based on sexual events or encounters, it is recommended that the guidance provide for flexibility to include symptom specific data for the FSD category being studied. In both situations, appropriate prospectively developed and validated instruments must be used (Basson et al., 2000).

Paragraph 3 - Sentences 3 and 4: Because the various categories of FSD may have varying frequency of sexual parameters (activity, orgasm, satisfaction), it is recommended to provide flexibility in designating the recall period (daily or weekly) for event log/diary data. This will minimize recall bias for event logs and allow for selection of appropriate intervals of data collection for both frequent and infrequent events. A daily diary works well when the frequency of activity is high. However, evidence found in the literature indicates that a daily diary is subject to compliance issues, including high levels of study discontinuation and missing data in studies of longer duration (Reading et al., 1983; Morrison et al., 1999). Use of a weekly recall is appropriate for infrequent events which are easily remembered, such as sexual activity, orgasms related to activity and satisfaction related to sexual activity (Morrison, et. al., 1999). In this instance compliance is high and sensitivity is acceptable to measure meaningful differences in product performance.

Paragraph 4 - Sentence 3. The suggested duration of 6 months, excluding the baseline period, for clinical trials is scientifically sound for several reasons. It is an appropriate length of time for any placebo effect that may occur to have begun to wane. It is also an appropriate length of time to capture changes in events that occur with the low frequencies that are typical of sexual activity endpoints in patients with FSD. It is also an appropriate length of time for patients who experience treatment-related improvements in their FSD symptoms to re-establish stable sexual behavior patterns with their partners so that the benefits of treatment can be measured.

Section V - Use of Scales, Questionnaires, and Other Instruments During Drug Development

Paragraph 1: It is recommended that the discussion of the aspects of questionnaire development be expanded so that instruments can be developed using methodologies of

sufficient scientific rigor for the intended use of the data (endpoints, claims). Appropriately developed instruments can ensure valid, reliable, and sensitive measures of outcomes. It should be noted that questionnaires should be understandable to non-English speaking patients who may participate in clinical trials. The following concepts are recommended to be included in this section in order to have appropriate application of scientific principles for questionnaire development:

- prospectively defined research plans with specification of patient population, domains to be sampled, and instrument purpose
- items and domains generated from patient focus groups and 1:1 interviews
- cognitive interviews to establish content validity of the items and domains
- linguistic validation with international harmonization for non-English speaking populations to maintain consistent conceptual meaning of items across languages
- initial quantitative validation studies for item reduction
- confirmatory validation study of the item-reduced instrument using patients other than those used in the initial development work for content validity or the initial quantitative validation studies for item reduction

These concepts are proposed to be included for a number of reasons. Prospective development of instruments contributes to the overall validity of the instrument by ensuring relevance to the patient population and applicability to the function or disease state being investigated (Juniper, et al., 1996; Robinson, et al., 1991; Nunnally & Bernstein, 1994).

Although statistical methods can contribute to establishing content validity, the cognitive interview directly ensures that inventory content is valid (Nunnally & Bernstein, 1994; Sudman, et al., 1996). Since both structural and conceptual differences in languages can result in altered meanings of translated materials (Thomas et al., 2000) International Harmonization and Cultural Adaptation are required to ensure consistency of meaning across languages and cultures where the instruments will be used.

After item reduction, an independent confirmatory validation study (using patients who did not participate in the instrument development or item reduction studies) establishes reliability and validity (e.g. discriminant validity) of the instrument. A confirmatory validation study also addresses the potential for altered context of the instrument resulting from item reduction.

Development of a questionnaire for a specific FSD category should not be limited by an expectation that the questionnaire must differentiate between women with that category of FSD and women with other categories of FSD. Failure to discriminate between categories of FSD should not constitute invalidity of the instrument because the scientific literature reveals high correlations among categories of FSD, e.g., desire and arousal disorders (Beck et al., 1991; Graziottin 1998; Farley, Hurlber, Apt and Rabehl 1993; Schiavi & Seagraves 1995; Anderson & Cyranowski 1995).

Section VI - Clinical Trial Endpoints

Paragraph 1 - Primary Endpoints: Because manifestations of the four categories of FSD differ it is possible that not all of the categories can be optimally measured by activity-based event logs. It is therefore recommended that an additional option be provided to allow use of appropriately developed and validated questionnaires (sexual function inventories) as a basis for primary endpoints.

For women with some categories of FSD, reducing their FSD symptoms may not increase their frequency of sexual activity. Some FSD disorders, particularly Hypoactive Sexual Desire Disorder, are known not to be specifically or exclusively related to sexual activity (Beck et al., 1991; Ferroni 1994; Hurlber & Apt 1994). This is because women often engage in sexual activity due to the influence of their partner and sometimes due to the couple's long-standing habitual practices. For example, increasing a woman's libido will not necessarily increase the number of sexual events because those events often occur in response to her partner. This is particularly true for younger woman and their partners. In those cases, responsiveness to therapy and improvement of the condition might not be reflected by an activity-based endpoint. The development of an appropriate measurement tool for sexual desire or satisfying sexual activity may better address this issue. Such self-report of symptom frequency or severity is in keeping with accepted common practice in the measurement of sexual desire (Regan 1999).

A logical extension of this reasoning is to allow the possibility of category-specific endpoints for each FSD category. These category specific endpoints could include for example the number of orgasms for anorgasmia disorder, reduced pain for dyspareunia, vaginal lubrication for arousal disorder, and experience of sexual desire for hypoactive sexual desire disorder.

In some categories of FSD, it may be necessary to consider information from event logs used in conjunction with questionnaires in order to address the effectiveness of the drug. Due to the potential for utilization of a variety of measures in this evolving area, it is recommended that additional flexibility be provided in the guidance to allow all of the relevant information to be considered in approvability decisions for the drug products.

Paragraph 1 "successful" "satisfying": To accommodate the different categories of FSD, it is recommended to provide flexibility in the guidance for appropriate application of the terms "successful" and "satisfying". This is important because the term "successful" could be mistakenly interpreted as a carry-over from clinical endpoints for male erectile dysfunction. In women, "successful" for a treatment of dyspareunia may be interpreted as being able to have sexual intercourse without pain, while "successful" for a women suffering from a desire disorder may be interpreted as no longer experiencing reluctance to engage in sexual interactions.

In focus group and one-on-one interview research involving over 200 women suffering lack of desire the terminology of "successful" in relation to a sexual event was not used by the women. Women discussed "satisfying" activity which can occur either with or without orgasm. In addition, for women, the frequency of satisfying sexual activity is key. Satisfying sexual activity includes both a physical pleasure component and an emotional connection component. Our research in women leads to the conclusion that "satisfying" in terms of a sexual event is appropriate terminology for women suffering from desire disorders or other categories of FSD since it is actually used by women.

Paragraph 1- Bulleted statements concerning event or encounters: In order to capture the full spectrum of sexual activity as well as the satisfaction that a woman experiences based on sexual activity it is recommended that the currently listed 4 events or encounters be modified. When appropriate, it is recommended to allow collapsing the categories of oral sex and self or partner-initiated masturbation into a category termed "other" since some of the explicit language such as "oral sex" and "masturbation" may be considered intrusive to women of many cultures. It is recommended that when satisfying sexual activity is measured all sexual activities, rather than exclusively sexual intercourse, be included.

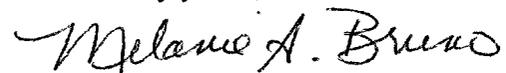
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We recommend clarifying the distinction between satisfactory and satisfying sexual activity. Whereas the term satisfactory is applicable to functional ability to perform acts like sexual intercourse, the term satisfying is applicable to the physical and emotional experience of the women. For example, in women with a diagnosis of dyspareunia or anorgasmia the measurement of both satisfactory sexual intercourse and satisfying sexual activity could be appropriate. In women with a diagnosis of desire or arousal disorders measurement of satisfying sexual activity would be more appropriate.

Since activity diaries are subject to the same social and psychological influences (such as social desirability of response, forgetting, personal and subjective definitions of what constitutes sexual activity and orgasm, acquiescent responding, etc.) as are self-report psychometric instruments, it is necessary to confirm the content and understandability of activity diaries using patient cognitive interviews as described in section V. These interviews must include confirmation of the consistent meaning of items, proper item content for the disorder of interest, and understanding of the instructions for use and proper completion of the diary.

We appreciate the opportunity to comment on this draft guidance. If you have any questions regarding these comments or recommendations, please contact me.

Sincerely yours,



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Attachment 1: pdf file of comments

Attachment 2: References