



Regulatory Affairs and Compliance

July 14, 2000

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Re: Docket No. 00D-1278
Comments on Draft Guidance for Industry

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Dear Sir or Madam:

Reference is made to the draft Guidance for Industry, entitled "Female Sexual Dysfunction: Clinical Development of Drug Products for Treatment," that was published in the U.S. Federal Register (Volume 65, No. 98, Docket No. 00D-1278) on Friday, May 19, 2000. Ligand Pharmaceuticals Inc. appreciates this opportunity to submit comments for the Agency's consideration as it proceeds towards finalization of the Guidance document. Ligand's comments include some general points related to the Agency's philosophy, as we have interpreted it from the Guidance, as well as several specific comments and suggested changes that are organized by section number.

GENERAL POINTS OF CONSIDERATION

Ligand acknowledges the complexity of the condition described as female sexual dysfunction (FSD) and the corresponding difficulty in establishing consistent parameters that can be used for assessing potential therapies. We believe, however, that the draft guidance would be improved if it more clearly defined female sexual *function*.

The current draft Guidance defines FSD as consisting of four distinct components, namely decreased sexual desire and arousal, dyspareunia, and anorgasmia. Although it is stated in the Guidance that in order to establish a diagnosis of FSD, the components must be associated with personal distress as determined by the affected woman, we remain concerned that the definition, itself, neglects to indicate the important impact of the components of FSD on quality of life.

In particular, it appears from the draft guidance that the Agency perceives female sexual function to be only expressed quantitatively as frequency of intercourse, oral sex or masturbation when used as primary endpoints for clinical studies. We contend that sexual function for women involves additional, important qualitative components especially those associated with libido such as desire to be intimate, sensuousness and passion. These parameters can best be measured by quality of life instruments and should be considered as an additional appropriate primary end point in the guidance.

Experts with whom we've consulted have attested to the fact that measuring the effect of improved libido and overall quality of life (QOL) is profoundly important in the assessment of new therapies for FSD. Therefore, the focus of the guidance on

evaluating response based exclusively on the number of defined sexual events is too limiting.

To measure improvement in libido, the Guidance should allow for more emphasis to be placed on assessing parameters such as sexual interest, initiation, receptivity, pleasure, and satisfaction. We therefore propose that the Guidance be revised to allow the use of validated instruments which assess these parameters as primary endpoints in clinical trials. Furthermore, QOL instruments must be weighted appropriately in the assessment of new compounds intended to treat FSD.

SECTION II

It is clear that a clinical development program can be based on only one (or more) of the recognized components, but it is not clear from the definition of FSD (as presented in this Section) if all four recognized components are required to make the diagnosis of FSD. Please clarify if the diagnosis can be made when at least one component is met and causing distress to the patient.

SECTION III

1. It is stated that "clinical trials intended to demonstrate efficacy for the treatment of FSD should enroll women who are sexually active and who have a valid and reliable diagnosis of FSD." We have the following comments:
 - Instead of "women who are sexually active," we suggest that it read "women who are sexually active or desire to be sexually active" in order to allow enrollment of women whose FSD is advanced to the point that they are not currently sexually active.
 - Please clarify what assessments are required for the diagnosis and how the reliability of the diagnosis should be assessed.
2. In the list of subgroups, we suggest that the category described as "surgically menopausal women" be further defined as follows: surgically menopausal or other hypoandrogenic women. In addition, we suggest the addition of a subgroup: women with premature ovarian failure or iatrogenic ovarian failure (postchemo- or radiotherapy).
3. In the paragraph regarding inclusion and exclusion criteria, the statement is made that such criteria should be chosen to "protect volunteer safety." We suggest that the word "volunteer" be changed to "patient" because subjects with FSD would not be normal volunteers.
4. We contend that the list of subjects deemed potentially appropriate for excluding from clinical trials is problematic because major target populations would be excluded for the following reasons:
 - Women with relationship difficulties should not be excluded because loss of libido may be a cause of the relationship difficulty. Moreover, women do not

require a partner (receptive or otherwise) in order to have improved sexual function or libido. Indeed, the Guidance specifies masturbation as one of the parameters for evaluation.

- It is not uncommon for women with low libido to be depressed. In some cases low libido may be an underlying cause of depression. Unless undergoing treatment with psychotropic drugs for clinical depression, such women should not be excluded because they may, in fact, represent a very appropriate and responsive subset.
- Sexual dysfunction of a woman's partner should be irrelevant to a woman's treatment for FSD. Women do not require a partner (receptive or otherwise) in order to have improved sexual function or libido.

SECTION IV

1. It is stated that "personal distress should be measured to ensure appropriate patient selection" for clinical studies. The term "distress" should be more clearly defined in the Guidance. Distress could be projected very differently by different women – it may manifest as depression or pain, or be discussed in consultation with a physician. What guidance can be given with regard to measuring distress and do the instruments used need to be validated?
2. In lieu of the pretreatment baseline period described in the Guidance, a placebo run-in phase prior to randomization may be useful to lower the "placebo-response" rate and to enrich the sensitivity of the trial for measuring effectiveness.
3. It is stated that the "lowest effective dose for the indication sought" should be determined. We believe that when seeking a broad indication for FSD (i.e., encompassing more than one component of the disease), it should be sufficient to determine the lowest effective dose for only one component.

SECTION V

In the absence of any demonstrated effective therapy for FSD, please provide additional guidance for validating an instrument with regard to "responsiveness and ability to measure minimal meaningful differences."

SECTION VI

1. In the list of events or encounters that may be included in the response assessment, there appear to be no events that might be directly linked to hypoactive sexual desire or arousal, two of the components of FSD described in Section II. As mentioned above under the heading General Points of Consideration, we believe that at least as much emphasis should be placed on assessing sexual interest, initiation, receptivity, pleasure, and satisfaction as is placed on having intercourse or other sexual events resulting in orgasm. Furthermore, the Guidance appears to indicate that successful or satisfactory sexual function can only be achieved when certain listed events result in orgasm. We contend that this is not the case, and that

a woman may consider various sexual encounters to be "successful" or "satisfactory" regardless of whether these encounters result in orgasm.

2. In the first paragraph, it is stated that the primary endpoints should be based on the number of successful and satisfactory sexual events or encounters over time. If the primary endpoint is based on number of successful events/encounters, the evaluation should not be based only on the absolute number of successful encounters because this approach may be limiting and could fail to measure substantial improvement. In many cases, the percent success rate per patient may be more reliable. For example, if a woman has to try 10 times in order to achieve two successful sexual encounters (20% success rate), she is likely to be distressed about the 80% failure rate. If that same woman now achieves success in two out of two encounters (100% success rate), the number of successes is unchanged (still two) but the success rate increased from 20% to 100%. Therefore, the primary endpoint should be based on percent success rate rather than number of successful/satisfactory encounters.
3. The Guidance is silent with respect to evaluating drugs used in combination with other therapies (e.g., hormone replacement therapy, HRT). For a study in which combination therapy is used, please clarify whether the effects of the new agent can be evaluated as improvement over a baseline of HRT.
4. A detailed statistical analysis plan prior to initiating Phase III trials is suggested in the draft Guidance. It would be useful if the Guidance outlined the essential elements to be included in such a statistical plan and addressed the following statistical issues:
 - If the desired study design for a Phase III trial includes more than one component of FSD and/or more than one sexual event/encounter, what guidance can be given regarding the issues of statistical significance related to the multiplicity in hypothesis testing. Should the p-values be adjusted across the FSD components in order to demonstrate the attainment of statistical significance of the effectiveness in each component? Should the p-values be adjusted across multiple sexual events/encounters within a component in order to demonstrate the attainment of statistical significance for that particular component?
 - It is stated that "effectiveness should be demonstrated by statistically and clinically significant improvements in [the] event-endpoints over time in the active treatment arms when compared to the placebo treatment arms." We contend that it may be desirable to quantify the clinically significant improvement in effectiveness, defined as an improvement over the baseline or as a relative improvement compared with the placebo group, using a pre-specified amount of difference or %-change in scores. Such a definition could be used to "filter out" placebo responders before randomization as well as for sample size estimation and statistical analysis of study data.

Ligand Pharmaceuticals Inc.

July 14, 2000

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We appreciate your consideration of the points outlined above. If you have any questions, please contact the undersigned at 858-550-7600 (fax 858-550-1827).

Sincerely,



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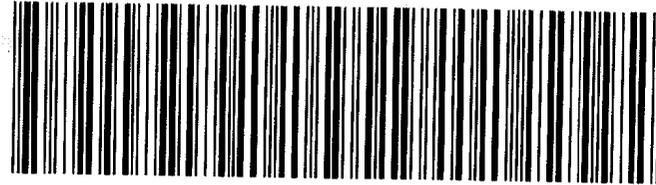
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