

**Letters to the FDA critical of the flibanserin application by
Boehringer-Ingelheim for a wide variety of reasons from a
wide variety of interested persons
Mostly sent by e-mail**

Ms. Kalyani Bhatt
Center for Drug Evaluation and Research (HFD-21)
Food and Drug Administration
Sunday, May 30, 2010

To the FDA Reproductive Health Advisory Committee:

I am writing to urge you not to approve Boehringer Ingelheim's drug flibanserin for 'hypoactive sexual desire disorder' in women aged 18 to 50 because of the disservice such an approval would represent for women's health and social equity. This is for two reasons: the questionable condition this drug is being considered for, and what is known publicly thus far about the drug's effects. The latter is partial and incomplete, but is likely to represent a best-case scenario.

I have expertise in two areas of relevance to this application. I work with the Therapeutics Initiative, an academic research group that carries out systematic reviews of clinical trial evidence of drug effectiveness and safety as a background to reimbursement decisions. I also carry out research on direct-to-consumer advertising and other forms of drug promotion, which are likely to have a major role to play in the case of this drug and condition.

Hypoactive sexual desire disorder

Hypoactive sexual desire disorder (HSDD) is a classic example of 'diseasemongering', a highly questionable new diagnosis shifting the boundaries of treatable illness in order to market a product. Sexual desire differs over time and between people for a range of reasons largely related to relationships, life situations, past experiences and personal and social expectations. The requirement for distress and repeated lowered libido is no guarantee that any underlying health problem exists, or that if a problem exists, it is the woman's sexuality that is at fault.

If Boehringer Ingelheim is successful in obtaining the HSDD indication for flibanserin, we can expect to see very intensive marketing aiming to convince women that lowered interest in sex is a treatable health problem with a solution – in the form of a pill – leading to a happy relationship. This type of hype has already begun in websites such as www.sexbrainbody.com sponsored by Boehringer Ingelheim.

This framing of women's sexual problems also raises gender equity concerns. In emotionally or physically abusive relationships, women are often coerced into sex that they do not desire. Will they also find themselves facing pressure from partners to ask their doctors for a flibanserin prescription?

Flibanserin was initially developed as an antidepressant and shares many characteristics of drugs in this class. One concern is that marketing to women of reproductive age will lead to accidental exposures in pregnancy. If, like SSRI antidepressants, flibanserin leads to withdrawal reactions and requires gradual discontinuation over several weeks or months, such exposures are likely to extend well into the first trimester or beyond. There is growing evidence that SSRI antidepressant exposure in pregnancy is associated with harm, including increased rates of cardiac malformations, persistent pulmonary hypertension in the newborn and a neonatal syndrome with third trimester exposures. Will flibanserin also be linked with similar harm? Additionally, if normal post-partum lower libido levels, particularly among breastfeeding women, are interpreted as hypoactive sexual desire disorder, exposure during lactation becomes a concern even if this is an off-label use.

Flibanserin's effects on sexuality: underwhelming at best

There are no published clinical trials, making it impossible to systematically appraise the clinical trial evidence that has been released in Boehringer Ingelheim press releases and in conference abstracts. This type of piecemeal release of information without any clinical trial publication is highly problematic, particularly given the intense promotional campaign focussing on flibanserin and HSDD. The public and health professionals do not have access to comprehensive information about the drug's effects, both beneficial and harmful, to judge the accuracy or completeness of the information in abstracts and press releases.

It is probably fair to assume that the partial information released thus far provides a best-case scenario of the drug's effects, as the manufacturer has largely chosen which data to release, with the greatest degree of detail available in press releases.

Boehringer Ingelheim press releases and conference abstracts focus mainly on the 100mg dose of flibanserin due to lack of evidence of efficacy at lower doses. A treatment arm in three clinical trials included this dose level: DAISY and VIOLET in North America (n=1378 combined, 100mg arms) and ORCHID (n=945) in Europe. In the two trials DAISY and VIOLET, the primary outcome of numbers of satisfying sexual events per woman is reported to have increased from a mean of 2.8 per month at baseline among women on flibanserin to a mean of 4.5 events per month at 24 weeks, in women on the 100mg dose. On placebo the increase was from 2.7 at baseline to 3.7. The mean difference versus baseline was 1.7 on drug versus 1.0 on placebo, or 0.7 per month among these two trials. (Boehringer Ingelheim press release, Nov 16, 2009)

No data on individual trial results for these two trials is public and for the third trial, the ORCHID trial, no significant difference was observed between drug and placebo, (no numerical data available). Thus the reported difference in 0.7 events per month does not include 1 of 3 clinical trials with a 100mg dose. The difference in 0.7 events per month, marginal as this seems, is an overestimate of the

true observed difference in the three clinical trials. Pooling of results of two out of the three trials is not acceptable as it reflects only a selected subset of the full clinical trial evidence.

It is also unclear whether this 0.7 event difference is an intention-to-treat or a per protocol result. If it is the latter, it likely further overestimates the degree of observed difference. Only 971 of the 1378 women (70%) completed these two 24-week trials.

(Boehringer Ingelheim Press release, May 2010)

Secondly, in trials that are testing a highly subjective outcome such as numbers of satisfying sexual events or sexual desire scores, considerable expectation bias is expected. It is therefore important to know whether allocation concealment was successful. If women can guess accurately whether or not they are on flibanserin, as could occur through symptoms of adverse effects such as somnolence, dizziness, fatigue etc. the degree of observed difference as compared with placebo is expected to reflect such partial unblinding. Adequacy of blinding can easily be tested: each subject is asked whether she thinks she is taking the experimental drug or placebo and results compared to what she is taking. If women guessed accurately no more often than would have been expected by chance, allocation concealment can be considered successful. No such testing has been publicly reported.

In the two North American trials with 100mg arms, publicly released data indicate a higher rate of withdrawals due to adverse events and a higher rate of total withdrawals among flibanserin users as compared with women on placebo.

These are partial results due to the inadequate public release of clinical trial information. The lack of fully published clinical trials, in the face of heavy promotion to the public and the press via disease awareness campaigns, has left the public in an especially vulnerable position. This experience with flibanserin highlights the need for stronger measures to ensure full public access to clinical trial data prior to a drug's approval, as well as stronger controls on disease-oriented marketing that is part of an integrated promotional campaign aiming to stimulate sales.

In conclusion, when drugs of marginal benefit are marketed for healthy people, harm from medicine use is likely to outweigh benefits. No clear criteria exist to distinguish the diagnosis of 'hypoactive sexual desire disorder' from relationship effects on desire or from social influences on the level of desire considered to be healthy or unhealthy. For these reasons I recommend strongly against flibanserin's approval for hypoactive sexual desire disorder.

Yours sincerely

Barbara Mintzes

Assistant Professor,

Department of Anesthesiology, Pharmacology & Therapeutics

University of British Columbia

Vancouver, B.C. Canada

Ms. Kalyani Bhatt
Center for Drug Evaluation and Research (HFD-21)
Food and Drug Administration
5600 Fishers Lane, Rockville, MD 20857
Friday, 28 May 2010

To the FDA Reproductive Health Advisory Committee:

I write to express my grave concern about the Boehringer-Ingelheim application for FDA approval for its serotonergic drug, Flibanserin, to be used in the treatment of so-called 'Hypoactive Sexual Desire Disorder' in women aged between 18 and 50. I understand that the application is based on Phase III trials, the detail of which have not been made public.

This seems to be an almost classic case of a drug developed for one purpose (in this case, as an antidepressant), then found to be ineffective, leading the company to trawl for a different profit-making niche. Boehringer-Ingelheim has already initiated a high-profile marketing campaign which has all the hallmarks of contemporary disease-mongering in terms of the medicalisation of normal human experience and the systematic exaggeration of both the prevalence and the severity of the putative condition.

Sexual desire and satisfaction is embedded within human relationships and are often undermined by difficulties within those relationships. Those who experience these problems are not helped by having them cast as disease conditions, a process which marginalises the necessity of both parties to contribute to resolving the difficulties. Women all too often find themselves within abusive relationships and subject to coercive sexual activity and will be yet further disempowered if they can be labelled as suffering from 'Hypoactive Sexual Desire Disorder'.

Finally, I understand that the proposal is that the drug should be marketed to women of child-bearing age after trials lasting only 24 weeks. Existing serotonergic drugs are not recommended for use in pregnancy because of fears of harm to the foetus. There seems a real possibility that any possible benefit of this drug will come at the cost of substantial harms both to individuals and to healthcare system costs.

Yours sincerely



Iona Heath
President, Royal College of General Practitioners
UK

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Friday, 28 May 2010
To the FDA Reproductive Health Advisory Committee:

I am writing to express my concern about Boehringer-Ingelheim's application for FDA approval for its drug, Flibanserin, to be used in the treatment of so-called 'Hypoactive Sexual Desire Disorder' in women. I understand that the application is based on Phase III trials, the detail of which have not been made public.

It appears the manufacturer's efforts to find a new niche for this drug, found to be ineffective for depression, is driven by profit motive, not clinical need or medication effectiveness,

Sexual desire and satisfaction is a widely varying and very personal human attribute, and pathologizing the normal spectrum of human behavior reeks of "disease mongering." Also, as occurs with potency enhancing medication such as Viagra, the potential for "recreational" use is great. That is, people expect their performances should (always) be greater or more frequent, which can lead to both risky behavior and feelings of inadequacy. Those who experience these problems are not helped by having them cast as disease conditions.

Existing serotonergic drugs are not recommended for use in pregnancy because of concerns about teratogenicity. There seems a real possibility that any possible benefit of this drug will come at the cost of substantial harms both to individuals and their offspring, and to healthcare system costs.

Sincerely,

Nicholas Rosenlicht, MD
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29 May 2010

Ms. Kalyani Bhatt

Center for Drug Evaluation and Research

Food and Drug Administration

Reproductive Health Drugs Advisory Committee Meeting, 18 June 2010

Regarding Boehringer-Ingelheim's application for approval of flibanserin, I have two main concerns I would ask the committee to consider

1. the proposed indication, Hypoactive Sexual Desire Disorder (HSDD), is controversial and subject to serious doubts regarding validity. One important challenge arises from the fact that sexual desire is highly subjective, individual, and dependent on the context of intimate relationships. The HSDD screening measure promoted by Boehringer-Ingelheim, the DSDS, simply cannot do justice to the complexity of sexual desire and is prone to indicate drug treatment inappropriately. There is a corresponding risk of treatment-related harm, if a pharmaceutical 'fix' is applied to problems that are fundamentally social and emotional.
2. the application is largely based on clinical data that have not appeared in the peer reviewed scientific literature. What data are available, in studies of highly selected participants, suggest that beneficial effects are modest. On the basis of these concerns, there are serious doubts about the flibanserin's efficacy.

While it is understandable that Boehringer-Ingelheim wishes to recoup its investment in flibanserin, the case for the drug's approval to treat 'HSDD' is unconvincing, based both on the validity of the proposed indication and the available evidence of efficacy. I encourage the Committee to recommend that this application be declined.

Sincerely

David Menkes, MD (Yale), PhD (pharmacology)

Associate Professor of Psychiatry

New Zealand National Committee, Australian and NZ College of Psychiatrists

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30 May 2010

Kalyani Bhatt

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Dear Ms Bhatt

I am writing to provide feedback to the Reproductive Health Advisory Committee for the Flibanserin hearing on June 18. I am an American citizen living overseas, but being far away from the hearings does not lessen my concern about the drug which is under consideration, and should not be given approval for use.

The whole premise upon which the development of this drug is based is flawed. Women are not suffering from a "disease" of low desire. As any woman or man would know, there are a whole range of different levels of desire from complete asexuality to sexual obsession. None of these are "diseases," despite the fact that they trouble people. Approving this drug would do irreparable harm by communicating the idea that only sick people have low sexual drive, when practically all women who have lived a bit, and have ever talked about sex with their female friends know profoundly well that we are all different. Having difficulty with sex drive is only ever relational: if our sex drive doesn't match that of our partner, or doesn't match what we have been led to believe, by media (and if this drug were to be approved, by the advertising of the pharmaceutical industry) it should be.

What's more, Boehringer-Ingelheim has incorrectly identified the prevalence of low sexual desire in women. They rely on highly contested statistics about the prevalence of the disease and on a consensus statement that was developed with no independent voices. Furthermore, the scientists developed the screening tool that they are using to "detect" the "disease" were their own consultants with inadequate independence from the company.

Approving this drug would be condoning the medicalization of women's sexuality in ways that would have long lasting impacts on ourselves, our daughters and granddaughters. It would impose new high standards of sexual desire that are artificial, and will hurt far more women than could ever conceivably benefit from such a drug.

Annemarie Jutel

Wellington New Zealand

Charlottesville, Virginia

May 28, 2010

Dear Ms. Bhatt,

I am concerned about the coming FDA review of a drug for so-called "hypoactive sexual desire disorder." As a breast cancer survivor who was thrust by dint of chemotherapy into premature menopause, I have an interest in these "replacement" therapies, but as a feminist and a skeptical person, I am wary of being told by self-interested companies what should be considered sexually "normal." Even a casual reading of For Her Own Good: Two Centuries of the Experts Advice to Women (Ehrenreich, English) is a powerful inoculation against their rhetoric.

I do not believe the "disorder" that Flibanserin is said to alleviate has been shown to exist, so I cannot credit the science that claims to show this drug alleviates it. I hope the FDA will perform as rigorously this time out as it did when it unanimously voted not to approve the equally specious offering of the testosterone patch. That performance may have been provoked by the embarrassment of the then-recent Vioxx scandal. If so, let the next one be a simple instance of intellectual integrity and concern for the health of women. We will be watching.

Yours sincerely,

Prudence Crowther
NYC

May 30, 2010

Dear Kalyani Bhatt,

I am writing to urge you to recommend against the approval of the drug Flibanserin. This drug is being promoted as an anti-dote to "low sexual desire" in woman; however the research and safety data are very weak and the actual medical impact is unknown.

Low sexual desire is not an illness, but regarding things sexual, people are quite vulnerable to the slick promises of the drug industry. This drug, in-particularly, preys on this vulnerability and is likely to make a hefty profit for its producers. Research has clearly shown that women's sexual problems are quite complex, involving cultural, social, relational, psychological and physical factors -- not just brain chemistry.

The proper assessment and treatment of desire problems necessitates an understanding of the impact of all these factors. Having been a psychotherapist and a sex therapist for more than thirty years, I know this to be true. The research agrees.

Moreover, this drug is likely to be harmful, for example, to pregnant women, breast-feeding woman and women already taking anti-depressants. Yet even more worrisome is the fact that most of our beliefs about sexual desire and function are driven by Hollywood notions, not sexual science.

Once again, I'd like to urge you to recommend against the approval of Flibanserin.

Sincerely,

Linda Alperstein

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31 May 2010

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Dear Ms. Bhatt:

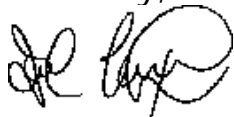
I am writing to provide feedback to the Reproductive Health Advisory Committee for the Flibanserin hearing on June 18. In my view it would be a serious mistake for the Reproductive Health Advisory Committee to recommend the approval of Flibanserin. The evidence behind the safety and effectiveness of this drug is minimal at best. The statistics quoted about the percent of women experiencing low sexual drive that are cited in favour of its use are seriously distorted and come largely from sources associated with the manufacturer Boehringer Ingelheim and do not have any independent validation. There are similar problems with other information about Flibanserin; the purported effectiveness of the drug is essentially meaningless and the screening tool to identify women who would allegedly benefit from the drug has been developed by consultants associated with Boehringer Ingelheim.

More importantly, approval of this medication would be another example of the medicalization of problems that arise in the normal course of human relationships. The evidence from research is that women's sexual problems are much more a product of their relationships than they are of their physiology. However, marketing of Flibanserin will promote the idea that the etiology of sexual problems in women arises from disturbances in neurotransmitters and minimize any social causes. Human sexuality is highly variable but the idea behind this drug is that everyone should function identically thereby creating a "standard" where none should exist.

Finally, there is no long-term safety data on Flibanserin that is especially important since its activity on serotonin could have serious consequences in pregnancy and during breast-feeding.

Recommending approval of this drug would send a strong message that normal human emotions should be controlled through chemicals, a message with profound implications for the way that women (and men) should live their lives.

Sincerely,



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30 May 2010

Re: (NDA) 22-526

Reproductive Health Drugs Advisory Committee
Food and Drug Administration, HHS
Dear Members of the Advisory Committee:

In my opinion, the new drug application (NDA) 22-526, for flibanserin 100 milligram tablets, is premature, underinvestigated, poorly documented and reported, and potentially damaging to the health of proposed users.

Little or nothing about the proposed uses have appeared in peer reviewed publications. There have been numerous selective releases to the popular press, and placements of unsubstantiated claims in industry-sponsored websites. This reveals that presumptuous marketing effort, including direct-to-consumer strategies, has advanced prior to FDA review. Everything I have seen could be misleading to uncritical observers, and some is just plain cheerleading. I have found abbreviated versions of clinical trial protocols, but I cannot access full text of the proposals for any flibanserin clinical trials. Why not? And, according to your FDA website, it sounds like essential details of the trial protocol as well as the specific results are being restricted for reasons that are not stated. This circumstance makes it difficult for objective observers to evaluate and comment on the validity of studies that have been done.

The releases ignore or undervalue the lower dose trials [25 and 50 mg] and some of those conducted in Europe. The results presented for the 100 mg trial in premenopausal women seem extraordinary in their outcomes, and raise compelling concerns:

- 1) The placebo group reported a considerably larger value than the boost above it claimed for the treatment group. This suggests that the screening process itself provided information or "permission giving" to the subjects that was more valuable than the treatment itself.
- 2) It is not clear if the "screening" interview and the assignment to control or treatment groups were truly independent. Screening, informed consent interview, and assignment to study groups should be double blind and randomized.
- 3) We are told that the statistics show clear significance, but the **magnitude** of the purported benefit is small. Among treated

women who did **not** report a benefit, is there an analysis of outcomes? Was the reporting profile for negative outcomes for the treated and untreated group similar?

4) It is not clear if the treated women could tell if they were in the treated or control cohort. Did they have evidence from the investigators or from their own side effects, physiological or emotional reactions to the drug that would allow them to believe that they were actually in the treated group? If they suspected that they were in the treatment group, it might bias their reporting in the direction of justifying their participation in the trial.

5) A substantial number of women did not complete the trial. Is there an analysis of the reasons why, and how those reasons distribute between the treatment and control groups? In fact, the number who left the trial appears to be much larger than the net number above placebo rates who "benefitted" from the treatment. Why, and is there a selective influence on the data?

6) The duration of the trial is relatively short. I presume that the manufacturers wish this treatment to be for systemic long term use. Do they have convincing data on safety and efficacy for long term use?

7) The treatment is intended to enhance and expand women's sex lives (which is an admirable ambition). However, women who were likely to become pregnant or who were not using some approved method of birth control were excluded from the trial. Are there any data on possible effects of this treatment on women or early embryos in cases where fertilization does take place?

8) Since the drug is intended for long term use, perhaps well beyond the duration of any trial, and considering parallels with known addictive drugs, what is the addictive potential of this treatment? Have there been follow-up studies on women who have completed a trial? Do any changes in their behavior persist? Or do possible changes in their behavior deteriorate? Do they seek alternate gratification?

9) The parameters studied in clinical trials have been limited. What evidence is available regarding safety for brain functions and other organ systems following long term use?

10) Have appropriate disclosures regarding possible conflicts of interests been forthcoming from parties who have been promoting use of this treatment?

In addition, women in the age range of the expected users are often using multiple prescription and nonprescription remedies. Adverse

effects from drug combinations and interactions should be anticipated.

Before such a therapy is considered, deeper, more critical, and objective analysis should be completed. Full information should be published well in advance for critical scientific review. In the absence of such information, the approval and marketing of specific products is not justified.

Sincerely,

A handwritten signature in cursive script that reads "Barry Bean". The letters are fluid and connected, with a prominent loop at the end of the word "Bean".

Barry Bean, Ph.D.
Professor of Biological Sciences

Email: bb00@Lehigh.edu
Phone: 610-758-3678

B. Bean

p2

Ms. Kalyani Bhatt
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Food and Drug Administration
5600 Fishers Lane ; Rockville, MD 20857
May 31, 2010

To the FDA Reproductive Health Advisory Committee
RE: Flibanserin hearing June 18, 2010

The purpose of this letter to express our strong concern about the application for FDA approval of Flibanserin for the treatment of "Hypoactive Sexual Desire Disorder" (approval requested by Boehringer-Ingelheim). Not only has this disorder been the subject of much controversy and criticism, but the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* acknowledges that there are no "normative age-or gender-related data on the frequency or degree of sexual desire. . ." (p. 539). Clearly, this lack of data renders the reliability and validity of Hypoactive Sexual Desire Disorder suspect.

There is increasing evidence that serotonergic agents have a host of adverse side effects, including increased risk of upper gastrointestinal tract bleeding, sexual dysfunction (see e.g., Dalton, et al. 2003; Montejo et al., 2001) and adverse neonatal outcomes in relation to maternal exposure. In addition, serotonergic agents are potent inhibitors of the cytochrome P450 monooxygenase enzymatic system (a system that metabolizes antineoplastic as well as other agents). Progress in the field of pharmacogenomics has led to increasing concerns about the complex relationships among serotonin, serotonergic agents, prolactin, and tamoxifen, and how these inter-relationships affect pharmacodynamics and cancer risk (Kelly 2010 et al).

Further, the details of the Phase III trials upon which Flibanserin's application are based have not been made available to the public, raising concerns about its safety and efficacy. The financial conflicts of interest (FCOI) that exist between drug companies and researchers sometimes lead to an under-representation of adverse effects and lack of accurate information on the efficacy of medications (Angell, 2004, Bekelman 2003). The under-reporting of negative results and publication bias leading to unsubstantiated efficacy data may prevent clinicians from being able to fully inform patients on their decision to take newly approved medications. Recently, Pitrou et al (2009) examined reporting and presentation of harm-related results in RCTs published in general medical journals with high-impact factors. They concluded that "the reporting of harms remains inadequate" and found that information related to severity of adverse events and withdrawal of patients because of adverse events was "lacking in 27.1% and 47.4% of the reports respectively" (p. 1759). These findings have led some to

question whether FCOI and marketing needs have triumphed over the scientific “gold standard” of RCTs (Ioannidis, 2009).

In view of the likelihood of risk underreporting, the existence of alternative treatments (including a variety of psychotherapies for the target symptom of a decrease in sexual desire), and the still unstudied but foreseeable risks of withdrawal, we believe that it is premature at best for the FDA to approve this agent for what is an under-described target symptom. If the FDA nonetheless does approve this agent, a black box warning about the unexamined but possible withdrawal risks and the presence of safer alternatives should be included.

Having studied for years the ways in which FCOI can compromise the integrity of scientific research and thus put the public at risk, we strongly believe that limiting iatrogenic harm should be a major consideration of the Committee when assessing the application for FDA approval of Flibanserin.

Sincerely,

Lisa Cosgrove, PhD, University of Massachusetts, Boston
 Abilash A. Gopal, MD, University of California, San Francisco
 Harold J. Bursztajn, MD, Beth Israel Deaconess Medical Center,
 Harvard Medical School

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June 3, 2010

Kalyani Bhatt

Center for Drug Evaluation and Research (HFD-21)

Food and Drug Administration

Dear Ms. Bhatt:

Please direct this letter to the Reproductive Health Advisory Committee which meets on June 18, 2010 to consider the drug Flibanserin.

I urge this committee to reject Boehringer Ingelheim's application for approval of Flibanserin as a so-called sexual desire enhancing drug for women. It is frightening to me that there are no long term safety data for a drug affecting brain chemistry, for a drug whose mechanism the company admits it doesn't understand. I am also offended by the blatant promotion by the drug company of a "disease" for which they have the cure.

The claim that low sexual desire, or Hypoactive Sexual Desire Disorder (HSDD), is a medical condition due to a chemical imbalance is spurious. Sexual desire is variable and personal for every individual. Every individual, man or woman, has her or his own definition of what sexual desire means to them. Everyone experiences it differently.

For example, it can be a physical sensation anywhere in the body: in the groin, breasts, armpits; or psychologically or spiritually throughout the mind and body. There is no standard for a "normal" sexual desire. Thus a measure such as hypoactive sexual desire is fiction. Please be aware that even in the proposed changes of the DSM V the "diagnosis" of HSDD has been downgraded.

Recent research has shown that women's desire for sex comes from many different motivations and is affected by many external social and cultural, as well as psychological issues. My experience as a psychotherapist working with women and couples of all ages has been that feeling emotionally connected and cherished by a partner contributes powerfully to a desire for sexual connection and a satisfying sexual experience. These emotions can only be expressed through effective communication in a safe psychological and physical environment. A pill affecting brain chemistry does not produce this.

Thank you very much for your consideration.

Sincerely,

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Department of Sociology

Kalyani Bhatt
Center for Drug Evaluation and Research
Food and Drug Administration
June 3, 2010
Re: Flibanserin

I am writing to express my concern about the proposed FDA approval of Flibanserin for the treatment of "Hypoactive Sexual Arousal Disorder". I am a professor of sociology with research expertise in the sociology of medicine, focussing on the medical management of sexual dysfunction. My concerns revolve around three key issues:

- 1) "Female Hypoactive Sexual Desire Disorder" is not an established medical condition for which there are clear diagnostic criteria.
- 2) There is no evidence that, even if a clearly diagnosable disorder could be identified, a serotonin imbalance is the root cause, calling into question the rationale for prescribing this drug.
- 3) There is a distinct lack of peer-reviewed, published data demonstrating a sufficient level of efficacy and long-term safety to warrant promotion of this drug treatment to the public. This is particularly problematic when it is a drug designed to be taken continuously by women of child-bearing age.

I urge the FDA to resist letting Boehringer-Ingelheim use their imprimatur as part of what is already an extensive marketing campaign for both the disorder and their remedy.

Sincerely,

Barbara L. Marshall
Chair, Department of Sociology
Trent University
Peterborough, ON
Canada K9J 7B8

Ms. Kalyani Bhatt
Center for Drug Evaluation and Research (HFD-21)
Food and Drug Administration
Wednesday 2 June 2010

Dear Ms Bhatt:

I write to express my concern about the Boehringer-Ingelheim application for FDA approval for its serotonergic drug, Flibanserin, for treatment of so-called 'Hypoactive Sexual Desire Disorder' in women aged between 18 and 50. The fact that there is no agreement that there is such a disorder and it is about to be removed from the latest versions of the DSM provides a number of issues for the committee to consider. There are two overarching areas of concern – scientific concerns and social concerns.

Scientific concerns.

In summary there is inadequate efficacy data available for public scrutiny. The absence of robust indicators of effect that reflect that true nature of sexuality, in particular there is no long term data on efficacy and on issues such as tolerance and the flow on effects if tolerance does develop on normal function on stopping the drug.

This leads to a further and probably more serious question. This drug acts on the serotonin system. Other drugs acting on the serotonin system have been shown to double the risk of birth defects when taken in the first trimester of pregnancy. As I understand it there is no long term safety data and no safety data at all on the potential for human teratogenicity, yet the target effect is increased sexual activity. Given that around one third of pregnancies are unplanned and it will be all but impossible to avoid exposure in the first trimester. Given also the target effect of increased sexual activity, the usual cautions of 'avoid in pregnancy' will not suffice as a safeguard - there is a key question of responsibility here.

There is a complete absence of any long term safety data. Concerns around aspects of safety that are issues with other drugs acting on the serotonergic system need exploring in particular discontinuation effects and the difficulties some patients have in being able to stop these medications at all.

The biological model proposed gives a great deal more certainty to the biological processes around desire than is warranted. Work in this area is exploratory at best and currently inadequate for promoting use in the population. We know a great deal more about the non pharmacological causes and solutions for reduced desire than we do about its neurochemistry.

Social Concerns

There are a number of important social concerns:

The likely medicalisation of normal human emotions and experience.

Likely pressure brought to bear on women to use the drug.

The potential for use as a date rape drug.

Other questions that require careful consideration are:

What are the implications for liability if the drug is prescribed to women with normal sexual function and it results in less inhibited sexual behaviour than would be the norm for that woman? Who might be liable if the woman contracts a sexually transmitted infection such as HIV or HPV leading to cervical cancer?

If the heightened sexual desire overrides the normal cautions about precautions what are the liability implications in the case of unwanted pregnancy and termination of pregnancy.

The drug is not target – specific. If the heightened sexual desire results in interest and sexual activity with other than a current long term partner what are the implications for relationships and families?

The only data available on this drug is company generated and not available for scrutiny. The material now circulating in the general and electronic media has all the hallmarks of a disease mongering campaign –

- Raising awareness among physicians of the condition as important and under treated
- Educating physicians in importance of condition and provide diagnostic tools (usually rating scales or symptoms scores)
- Positioning the company's drug as the drug of choice for this condition
- Driving patients to physicians' offices to ask for the company's drug using direct to consumer advertising and PR campaigns including press releases and pre-packaged 'news' videos.
- Market expansion techniques 'creating need' beyond currently accepted medical need.

This has little more scientific credibility than the "Motivational Desire Disorder" published as a spoof in recent years in the British Medical Journal. There is little evidence that any putative benefit will outweigh the serious potential for direct and indirect harm. Given the grave concerns about genetic engineering and stem cell use, the use of chemicals to alter one of the most fundamental of human emotions, desire, requires a great deal more public consultation and discussion about the likely social consequences

Yours sincerely

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Ms. Kalyani Bhatt
Center for Drug Evaluation and Research (HFD-21)
Food and Drug Administration
June 3, 2010
Dear Ms. Bhatt:

I am writing to express my opposition to the approval of flibanserin for hypoactive sexual desire disorder.

The reasons for this are:

1. Recommendations have been made to eliminate this disorder from the Diagnostic and Statistical Manual of Mental Disorders.
2. Boehringer-Ingelheim, the company which is marketing flibanserin, has over the past several years engaged in a campaign to establish hypoactive sexual desire disorder as a bone fide disorder in women. However, the existence of this disorder is controversial and many have suggested that a prominent motivation for advertising this as a disorder would be to create an indication to sell this drug.
3. It is furthermore asserted that damage is being done to women by the promulgation of such a disorder inasmuch as it starts to establish expectations which are unrealistic and wrong for women's sexual appetite and performance.
4. While many trials of flibanserin are listed on clinicaltrials.gov, there are no peer-reviewed publications presenting these conclusions.

Thank you.

Richard B. Krueger, M.D.

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Ms. Kalyani Bhatt
Center for Drug Evaluation and Research (HFD-21)
Food and Drug Administration
Wednesday 2 June 2010

Concerns re: Boehringer-Ingelheim application for FDA approval for flibanserin, to be used in the treatment of Hypoactive Sexual Desire Disorder in women.

It is likely that if licensed Flibanserin, just as Viagra, will be marketed to hitherto normal women offering the promise of the perfect sexual experience every time. With this background the committee needs to consider a number of questions.

In the same sense that if Eve not taken flibanerSin she might never have offered Adam the Apple, there also exists the potential for a number of possible adverse effects and unintended consequences wider than just the direct adverse effects of the drug. There is potential for I-Premature Orgasm Disorder (I-POD) if flibanserin should be prescribed for women with normal sexual function. This has implications for the quality of life of the women taking the drug but also implication for their life partners in terms of sexual satisfaction and quality of life.

There is also potential for I Performance Anxiety Disorder (I-PAD) – if women are released from the constraints of desire, with the focus then shifting away from desire and sensuality to simply successful completion of coitus, this may result in escalation of anxiety levels in her and her partner about the ability to achieve a perfect orgasm with every encounter.

It is well known that there are particular times in a woman's life when low sexual desire is more common. These include the period after childbirth, and other times as a response to accommodating increased demands in other areas of life – times of increased work load for example. Correcting any chemical imbalance during these times may have unintended opportunity costs for work productivity and family roles. There are also flow on effects for other activities traditionally used to increase sexual desire in women – this may be the death of romance as we know it – these are areas that require exploration in a full cost benefit analysis before licensing is considered.

I look forward to the FDA response to these questions.

Your humble serpent

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June 2nd 2010

**To the FDA Reproductive Health Advisory Committee:
Hearings on Flibanserin**

Dear Ms Bhatt

This submission aims at raising issues surrounding the potential of flibanserin to cause dependence and birth defects in women.

Psychotropic agents active on the serotonin system are increasingly recognized as causing dependence and equally recognized for their potential to cause birth defects. Given this there is some acceptance by bodies such as NICE in the UK that women of child-bearing years being put on these drugs should be informed both of the risk of birth defects and the potential of a dependence severe enough to make it difficult for them to get off treatment in the event that they wish to become pregnant or after finding out they are pregnant.

If flibanserin is going to be licensed to help promote sexual activity in women there would seem to be a need to have good data on its potential to cause dependence and the risk of birth defects, given that this group of women will be most likely to engage in sexual relations.

A pharmaceutical company cannot be relied upon to put the interests of either women or their children before the lure of commercial profits, as the attached report on the Marketing of Paxil to Women of Child Bearing Years may help to establish. This report arose in the course of medico-legal work undertaken in cases involving children with severe congenital defects born to women taking Paxil. The confidential elements of the report have been eliminated.

The same marketing would doubtless apply in the case of flibanserin, overpowering any natural safeguards women or doctors might have. Quite astonishingly the antidepressants are now the most commonly prescribed drugs in pregnancy – and rates of prescription are growing in the face of ever clearer evidence of the potential of these drugs to cause birth defects, miscarriage and to increase rates of abortion.

Given the risks to completely innocent parties, it would be helpful to have clear information on risks prior to the licensing of flibanserin.

Yours sincerely

Professor David Healy MD FRCPsych