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Not Reported in F.Supp.2d
Not Reported in F.Supp.2d, 2004 WL 1724632 (S.D.Ind.)
**(Cite as: 2004 WL 1724632 (S.D.Ind.))**



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Only the Westlaw citation is currently available.

United States District Court,
S.D. Indiana, Indianapolis Division.
ELI LILLY AND COMPANY, Plaintiff,
MASSACHUSETTS INSTITUTE OF TECHNOLOGY, and Interneuron Pharmaceuticals, Inc.,
Involuntary Plaintiffs,
v.
TEVA PHARMACEUTICALS USA, INC.,
Defendant.
**No. IP 02-0512-C-B/S.**

July 29, 2004.

Dominick A Conde, Fitzpatrick Cella Harper & Scinto, New York, NY, for Plaintiff.

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Timothy J Vezeau, Katten Muchin Zavis Rosenman, Chicago, IL, for Plaintiff.

*FINDINGS OF FACT AND CONCLUSIONS OF LAW*

BARKER, J.

***1** This case comes before the court, after a bench trial held November 12- 24, 2003, for decision on the issue of patent invalidity under 35 U.S.C. § § 102 and 103. Plaintiff, Eli Lilly and Company ("Lilly"), filed suit against Defendant, Teva Pharmaceuticals USA, Inc. ("Teva"), for infringement of U.S. Patent No. 4,971,998 ("the '998 patent"). Teva conceded, based on the court's July 21, 2003 Claim Construction ruling, that its generic drug indication infringed Claim 2 of the '998 patent Therefore, the only decision currently before the court is whether the '998 patent is invalid, either as anticipated under 35 U.S.C. § 102 or obvious under 35 U.S.C. § 103. For the reasons explicated below, we conclude that the '998 patent was neither anticipated nor obvious, and is, therefore, valid and enforceable.

*Findings of Fact*

I. *Background* [FN1]

FN1. Unless otherwise indicated, these background facts are taken from the parties' joint submission of Facts That Are Admitted and Will Require No Proof at Trial. (Dkt.# 167.)

Plaintiff Eli Lilly and Company ("Lilly") is a corporation organized and existing under the laws of the State of Indiana, having its principal place of business in Indianapolis, Indiana. Lilly is engaged in the business of research, development, and commercialization of pharmaceutical drugs. (*See* Tollefson Tr. p. 883). Involuntary plaintiff Massachusetts Institute of Technology ("MIT") is a university located in Cambridge, Massachusetts. Involuntary plaintiff Interneuron Pharmaceuticals, Inc. ("Interneuron") is a Delaware corporation having its principal place of business in Lexington, Massachusetts. Intemeuron is now known as Indevus Pharmaceuticals, Inc. Defendant Teva Pharmaceuticals USA, Inc. ("Teva") is a corporation organized and existing under the laws of the State of Delaware, having its administrative offices in North Wales, Pennsylvania, and a principal place of business in Selleville, Pennsylvania. Teva is engaged in the generic manufacture of pharmaceutical drugs.

This patent infringement action arises under 35 U.S.C. § § 271(e) and 281-283. Subject matter jurisdiction is proper under 28 U.S.C. § § 1331 and 1338(a). Venue is proper under 28 U.S.C. § § 1391(c) and 1400(b).

II. *Trial Witnesses*

A. Lilly's trial witnesses:

- *Dr. Richard Wurtman,* a co-inventor of the '998 patent, is the Cecil H. Green Distinguished Professor in the Department of Brain and Cognitive Science at MIT. (R. Wurtman Tr. pp. 6-7, 11). He holds an M.D. from Harvard University and also trained at the National Institutes of Health. (R. Wurtman Tr. p. 7). Dr. Wurtman has published about 1000 articles relating to his research, which

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Illinois at Chicago ("UIC"). Her responsibilities include designing and implementing clinical and teaching programs related to women's mental health. (DTX VN, ZE; Miller Tr. p. 204.) Dr. Miller has never, however, been involved with a clinical trial relating to PMS. (Miller Tr. p. 373.) Dr. Miller graduated from Harvard Medical School in 1982 and completed her psychiatry residency at the University of Chicago from 1983-86. (DTX VN, ZE.) Though, as of October 1987, Dr. Miller was not board certified (DTX ZE) and had not prescribed any agents to women suffering from LLPDD (Miller 375:12-19), she has since become a board-certified psychiatrist and developed particular expertise in the treatment of women's reproductive-related mental illness, including premenstrual mood disturbances. (DTX VN, ZE; Miller Tr. pp. 204-5.) The use of fenfluramine, which is not a psychotropic drug, to treat eating disorders is outside her area of expertise. (Miller Tr. pp. 502-03). She has authored or co-authored numerous articles, given talks or discussions at university or professional forums and taught graduate level and continuing medical education classes related to psychiatric conditions in women, including those related to the menstrual cycle. (DTX ZE.) She published her first article on PMS in 2000. (Miller Tr. pp. 372-73). In addition, Dr. Miller was asked by both the American Psychiatric Association and Continuing Medical Education Incorporated to write their review articles on premenstrual mood disorders. (DTX ZE.)

• *Dr. Andrea Rapkin* is a Professor in the Department of Obstetrics and Gynecology ("OB/GYN") of the UCLA Medical Center. (DTX VO; Rapkin Tr. p. 541-42.) Dr. Rapkin graduated from medical school in 1979, and finished her OB/GYN residency in 1983. (*Id.*) Dr. Rapkin has been a principal investigator on approximately thirty clinical studies and has published over thirty research papers. She is a reviewer for the major OB/GYN journals. (Rapkin Tr. pp. 542-43.) Dr. Rapkin is also the lead author of the prior art reference entitled "Whole Blood Serotonin in Premenstrual Syndrome," which was published in the journal "Obstetrics and Gynecology." (DTX FF; Rapkin Tr. p. 544.)

***4** • *Dr. Walter Brown* is a Clinical Professor of Psychiatry at the Brown University School of Medicine and at the Tufts University School of Medicine. Dr. Brown has been on the faculty at Brown University since 1974. Prior to joining the faculty of Brown University, he held academic appointments at the Mount Sinai School of Medicine in New York and at the Yale University School of Medicine in Connecticut. (DTX VL, ZG; Brown Tr. p. 651.) Dr. Brown received an M.D. from Duke University in 1967, and completed his residency at the Yale University Department of Psychiatry from July 1968 through June 1969, and from July 1971 through June 1972. He held fellowship positions at the National Institute of Child Health and Human Development/National Institutes of Health in Bethesda, Maryland, from July 1969 through June 1971, and at Yale University from July 1972 through June 1974. (DTX VL, ZG.) Dr. Brown has been a practicing psychiatrist and has conducted clinical research in the area of psychiatry for about thirty years. (Brown Tr. p. 651.) Dr. Brown has been a principal investigator in over 100 clinical trials, including trials relating to the drug fluoxetine. (DTX VL, ZG; Brown Tr. pp. 651, 653.) Dr. Brown has co-authored several articles relating to the use of fluoxetine in the treatment of PMS, the first in 1990. (DTX VL, ZG, GJ; Brown Tr. p. 651; 653-54.)

• *Dr. Sanford Bolton* is an expert in biostatistics. (DTX VK, ZF; Bolton Tr. p. 833.) He received his Ph.D. in Pharmacy from the University of Wisconsin in 1958, and his Masters in Biostatistics from Columbia University in 1966. (*Id.*) Over his forty-year career in biostatistics, he has published numerous articles in the field and is the author of the treatise entitled "Statistics in Clinical Studies and Pharmaceutical Processes." (*Id.*)

• *Mr. George Gould* is an expert in pharmaceutical licensing. (DTX VM, XR; Gould Tr. p. 1001.) He received a B.A. in Organic Chemistry in 1958 from Johns Hopkins University, a J.D. in 1963 from Columbia University School of Law, and a LL.M. in 1973 from New York University Law School. (DTX VM, XR.) Mr. Gould has over thirty years of licensing experience in the pharmaceutical industry. Among other things, Mr. Gould was vice-president of licensing and corporate development and chief patent counsel at an international pharmaceutical company, Hoffmann-La Roche Inc. (DTX VM, XR; Gould Tr. p. 1002-3.) Over the course of his career, Mr. Gould has negotiated several hundred licenses in the pharmaceutical field for large pharmaceutical as well as start-up biotech companies. (*Id.*)

• *Dr. David Schmittlein* is a marketing expert. He is currently the Ira A. Lipman Professor, Professor of Marketing and the Deputy Dean and Chief Academic Officer of the Wharton School of the University of Pennsylvania. His twenty-three years at the Wharton School have been spent teaching, consulting and conducting research in the field of

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reference or the Cohn reference during the prosecution of the applications that led to the issuance of the '998 patent. (DTX K, M, N.) However, the Stark and Cohn references lend further support to the claims of the '895 and '213 patents. They neither teach away from the patented inventions nor extend the serotonin hypothesis to PMS.

In addition to clinical trials like those conducted by Stark and Cohn, Lilly conducted large-scale clinical trials of fluoxetine in order to gain FDA approval to market the drug ("Fluoxetine Trials"). (Dk. # 167, ¶ 19; *see also* Bolton Tr. p. 836.) The records of these clinical trials were confidential, and as such, were not known to anyone outside of Lilly, including the Wurtmans or the examiner of the '998 patent. Lilly and the clinical investigators conducting the trials were required to maintain the confidentiality of these records. (DTX MW at P 104 3236)

A number of the pre-October 1986 Fluoxetine Trials had an "open label" arm where both the patient and the physician knew whether the patient was being treated with fluoxetine. (DTX AV at 26, MP, Brown Tr. p. 653.) During these open-label trials, fluoxetine was administered to, among others, at least 112 women between the ages of 18 and 45 who were diagnosed with major depressive disorder. This diagnosis did not include PMS specifically as these trials were not intended to test the efficacy of fluoxetine as a PMS therapy. PMS requires a careful diagnosis, which must be charted over several menstrual cycles in order to avoid the retrospective misallocation of mood changes to the menstrual cycle. (*See* Rapkin Tr. pp. 593, 596-97; Brown Tr. pp. 783-84, 787; Bolton Tr. 864-65; Endicott Tr. pp. 1063, 1066; PTX 206 at 1539; PTX 205 at 46; DTX FR p. 390). These 112 women with major depressive disorder were administered fluoxetine in daily dosages between 5 mg to 120 mg over a period of at least thirty days. (D-DEM O; DTX XC; Bolton Tr. p. 843.)

*7 As part of Teva's anticipation claim, Teva engaged Dr. Bolton, a statistical expert, to calculate the probability that one or more of these 112 women with major depressive disorder also had disturbances of mood, disturbance of appetite, or both associated with PMS. Dr. Bolton used the binomial equation to calculate the probability of a specific event occurring where there are two possible outcomes, *i.e.*, the woman has a disturbance of mood and/or appetite associated with PMS or does not have such a disturbance. (Bolton Tr. pp. 845-46; D-DEM P.) In performing his calculations, Dr. Bolton assumed the prevalence rate of premenstrual depression among these women to be 65 percent, a rate taken from the expert report of Dr. Miller. [FN3] (Bolton Tr. p. 851; 865-66.) With this prevalence rate, Dr. Bolton calculated the probability that one or more of the 112 women with major depressive disorder also had disturbances of mood, disturbance of appetite, or both associated with PMS to be greater than 99.99999 percent. (Bolton 852:7-852:16; D-DEM W). Lilly challenges the 65 percent prevalence rate used by Dr. Bolton because it measures a lifetime, not a concurrent, possibility that the two disorders will co-occur. (DTX FR at 390.) Dr. Bolton, however, responded that even if the prevalence rate of premenstrual depression among women who suffer from depressive disorders was as low as 10 percent, the probability that at least one of the 112 women had PMS would be 99.99925 percent. (Bolton Tr. pp. 853- 54; D-DEM Y.)

FN3. Dr. Miller testified that the prevalence rate of premenstrual depression among women who suffer from depressive disorders has been estimated in several studies to be approximately 65 percent. (*See, e.g.*, DTX FR (June 1987) at 390; Miller Tr. pp. 232-33 .)

Dr. Bolton, of course, speaks in probabilities. He could not identify any one patient record and say with certainty that a female subject actually had PMS. (Bolton Tr. p. 871). Moreover, as stated above, none of the clinical trial participants, which included both men and women, were actually diagnosed with PMS. They were not diagnosed with PMS because in that context it was irrelevant; the purpose of the Prozac clinical trials was to determine the effectiveness of fluoxetine in treating depression, not PMS. (Brown Tr. pp. 783-84; Bolton Tr. pp. 864-65, 868-69; Endicott Tr. pp. 1063-65). To address this criticism of Dr. Bolton's analysis, Teva asked another of its experts, Dr. Brown, to examine the patient record for one of the 112 women in Dr. Bolton's sample. A patient record is a document used by clinical researchers to record all of the information gathered on a single research subject during a clinical trial. (Brown Tr. p. 686). The patient record was of a 37-year old woman with major depressive disorder ("the patient") who participated in a fluoxetine clinical trial in 1982. (DTX LD; Brown Tr. pp. 688-89.) At the beginning of the trial, the patient was asked from what other illnesses or conditions did she suffer. She indicated that she had hay fever, but did not mention PMS. (Endicott Tr. pp. 1064-65; DTX LD at P 58 730). In the normal course, however, Dr. Endicott

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Because this individual patient was on fluoxetine in the open-label portion and had substantially improved during the double-blind phase, we conclude that she was on fluoxetine during the double-blind portion. (*See* Brown Tr. pp. 722-23.) This reasoning is supported by her Hamilton Depression Ratings, which substantially improved over four weeks, a result consistent with the patient taking fluoxetine. (*See* Brown Tr. p. 703.) In addition, the patient lost weight, which was also consistent with fluoxetine effects. (Brown Tr. pp. 689, 705-06, 707-08, 711; Miller Tr. p. 263). However, one inconsistency: if the patient was being treated with fluoxetine at the time of her comment, then one would expect (based on what we now know) that given the rapid action of fluoxetine in relieving PMS symptoms, she would not have any PMS symptoms in Week 5 because she would have been administered fluoxetine for at least one week prior to her comments. (Endicott Tr. pp. 1068-69, 1146- 47). Therefore, we conclude that the patient, while likely given fluoxetine to treat her major depression, did not have PMS.

The patent examiner did not consider the Fluoxetine Trials during prosecution of the applications that led to the issuance of the '998 patent. (DTX M, N.) In an August 4, 1988 office action during prosecution of U.S. Patent Application Ser. No. 111,771, the first application in the series from which the '998 patent issued, the patent examiner rejected the pending claims, which included methods of treatment using the drug d-fenfluramine. One of the bases of the patent examiner's rejection was that the prior use of d-fenfluramine in clinical work would have inherently anticipated the pending claims:

> ***10** [A]ll of the clinical work with [d-fenfluramine] has clearly involved treating a large number of women of menstruating age with this compound. Given the common occurrence of PMS among such women the claimed method would have to inherently haven't [sic] been practiced in one or more of the patients used in the study. In addition, if this drug is now a commonly prescribed drug this would provide further evidence that it would have inherently (if unintentionally) been used in carrying out claimed process.

(DTX M at 137, Office Action, U.S.App. Ser. 07/111,771, dated Aug. 4, 1988 at 5.) In the same office action, the patent examiner requested more information from the Wurtmans and MIT: "In evaluating the merits of the above prior art rejection it would be helpful to know approximately what percentage of menstruating women regularly experience PMS. If applicants have knowledge on this question they are requested to make it of record with their response to this office action." (DTX M at 138, Office Action, U.S.App. Ser. 07/111,771, dated Aug. 4, 1988 at 6.)

First, we disagree with the patent examiner that the Fluoxetine Trials would have been relevant. Not only did they not demonstrate an intent to treat PMS, but as shown above, without a specific diagnosis of PMS, it would have been impossible to tell whether the claimed method had been inherently practiced. In addition, although some studies indicate that the prevalence rate of PMS among women with major depression is approximately 65 percent, as shown above, that number reflects a lifetime, not concurrent, prevalence rate. Most importantly, assuming *arguendo* that these records would have been relevant, the Wurtmans would not have had access to these Fluoxetine Trial records at the time of the filing of the '998 patent. The clinical records were the confidential property of Lilly. (DTX MW p. P 104 3236).

On September 6, 1983, Lilly filed a New Drug Application ("NDA"), No. 18- 936, with the FDA, seeking approval to market fluoxetine for major depressive disorder. The FDA approved Lilly's NDA on December 29, 1987. Lilly was the exclusive marketer of fluoxetine in the U.S. from January 1988, when Prozac came on the market, through August 2001, when the Federal Circuit declared invalid the last of Lilly's fluoxetine-related patents. (Dkt. # 167, *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955 (Fed.Cir.2001).) Prozac was one of the best-selling drugs in the world, having achieved over a billion dollars in sales. (*See* Smith Tr. p. 984.)

IV. *The '998 patent*

In the mid-to-late 1970's, the Wurtmans, inventors of the '998 patent, developed a theory that the food individuals consume affects brain serotonin. (R. Wurtman Tr. pp. 17-18). To test this theory scientifically, they conducted animal studies to determine if the administration of drugs known to increase serotonin, in particular fenfluramine and fluoxetine, would cause a reduction in carbohydrate consumption. (*Id.* pp. 18-19.). From these studies, they concluded that fenfluramine and fluoxetine caused the animals to eat less carbohydrate in proportion to protein, and also to consume fewer calories. (R. Wurtman Tr. pp. 19-20; J. Wurtman Tr. pp. 159-60). In about 1977, they published this research. (DTX HA at 1179; PTX 133 at 902).

***11** The Wurtmans then applied their theory to

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Next, the Wurtmans prepared a clinical trial protocol proposing: (1) to measure the amount and type of food that women with PMS consumed during the luteal phase and compare it with the amount and type of food consumed during the follicular phase, and (2) if there was a difference, to determine the effect of the serotoninergic agent fenfluramine on the mood changes and increased carbohydrate consumption of women suffering from PMS. (PTX 126 at WURT-000949). On February 11, 1986, the protocol was submitted to the MIT institutional review board, the committee responsible for authorizing such studies. (R. Wurtman Tr. pp. 28-29; J. Wurtman p. 169; PTX 126 p. WURT-000947). This protocol, however, did not include the serotoninergic agent fluoxetine.

The protocol was approved on April 1, 1986, and the clinical trial commenced shortly thereafter. (R. Wurtman Tr. p. 32; J. Wurtman Tr. p. 170; PTX 158). Potential patients were examined by a gynecologist and psychiatrist, who used well-established rating scales to confirm a diagnosis of PMS or severe PMS. (R. Wurtman Tr. pp. 32-34; J. Wurtman Tr. pp. 170-71; PTX 126 p. WURT-000955-60). The results of the food intake portion of the study demonstrated that non-PMS women did not alter their caloric intake and did not show a preference for any particular type of food. In contrast, women with PMS had a higher caloric intake and a higher intake of carbohydrates during the luteal phase of their menstrual cycle as compared to control subjects. (R. Wurtman 34:19-35:21, 36:17-37:7; J. Wurtman 167:17-168:21; PTX 89 at WURT-000577). Contrary to what was generally believed prior to their study, PMS patients craved all types of carbohydrates, sweet and salty. (R. Wurtman Tr. pp. 35-36; PTX 89 p. WURT-000577).

***13** Once the intake portion of the study was completed, in the summer of 1986, those patients suffering from PMS participated in the second part of the protocol, the administration of fenfluramine to treat PMS. (R. Wurtman Tr. p. 37). At that time, there were no known effective agents for the treatment of PMS. No one had ever used fenfluramine to treat PMS before, and the Wurtmans did not know what to expect. (R. Wurtman Tr. p. 38; J. Wurtman Tr. p. 171; PTX 1, col. 1, l. 62-col. 2, l. 2). The results from the use of fenfluramine to treat PMS were very positive. (R. Wurtman Tr. pp. 38-40; J. Wurtman 171:23-172:25; PTX 131 at HAM 04592). The patients showed major improvement, not only in carbohydrate cravings, but also in their mood. For the first time "they had something that really made them feel better when they had PMS." (R. Wurtman Tr. p. 38).

In early 1987, having obtained excellent results using fenfluramine, the Wurtmans discussed the possibility of administering another agent that might generate responses similar to those of fenfluramine to some of the PMS subjects who had participated in the fenfluramine study. [FN5] Dr. Richard Wurtman came up with the idea of fluoxetine, a known serotonin-enhancing agent, having become familiar with the drug from his research and from his work as a consultant to Dr. Ray Fuller at Lilly, the inventor of fluoxetine. (R. Wurtman Tr. pp. 40-41; J. Wurtman Tr. pp. 173-74). At this time, several clinical researchers had access to fluoxetine and had published clinical trial results on its use in other disorders, which showed that fluoxetine was safe. (R. Wurtman pp. 42-43; 43-44; *see* DTX AC, GB). Dr. Wurtman testified that he requested a quantity of fluoxetine directly from Dr. Fuller, his friend of twenty years, as he had done previously approximately ten or fifteen times over the years. (*Id.* p. 94)

> FN5. Teva challenges Dr. Richard Wurtman's memory on this point at his deposition, but we find his trial testimony, which was corroborated by Dr. Judith Wurtman, credible. (J. Wurtman Tr. p. 174). The Wurtmans' testimony required them to remember various events that happened approximately fifteen to seventeen years ago, events which resemble in large part other clinical trials in which they have participated over the years. Such a time lapse would allow for some slippage in their memories as they piece back together again the events at issue in this trial.

Dr. Richard Wurtman did not, however, have enough fluoxetine for a full-blown clinical trial. Therefore, in about May 1987, he conducted a case study of the treatment of PMS using fluoxetine. (R. Wurtman Tr. p. 41). At trial, Dr. Wurtman testified that the fluoxetine came directly from Dr. Fuller and that he never asked Dr. Fuller for large amounts of the drug; Dr. Wurtman's deposition revealed that at the time of the case study, Dr. Wurtman's graduate student was also doing research with fluoxetine, but it was expressly limited to use on animals. (*Id.* p. 92-93). Because Dr. Wurtman and his graduate student had made a formal request of Lilly for the fluoxetine used in the rat study, had complied with all of the conditions placed on that request, and through that

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MIT authorized the filing of a patent application covering the Wurtmans' work. (R. Wurtman Tr. pp. 45, 47). On October 22, 1987, MIT filed U.S. Patent Application Ser. No. 111,771, naming Richard J. Wurtman and Judith J. Wurtman (collectively, "the Wurtmans") as inventors. On September 15, 1988, MIT filed U.S. Patent Application Ser. No. 244,944 as a continuation-in-part of Ser. No. 111,771. Although the patent at issue in this case, U.S. Patent No. 4,971,998 ("the '998 patent"), issued from Ser. No. 244,944, the effective filing date of the '998 patent is October 22, 1987. During prosecution of the '998 patent, the patent examiner reviewed, among other things, patents and publications disclosing the use of fluoxetine to treat depressive and anxiety disorders and the use of fenfluramine to treat SAD and CCO, and publications discussing blood serotonin levels in PMS patients. The '998 patent, entitled "Methods For Treating the Premenstrual or Late Luteal Phase Syndrome," issued on November 20, 1990, to MIT as the assignee of the Wurtmans.

V. *The State of the Art in 1987*

A. *The Nature of PMS*

***15** The '998 patent is directed to the use of fenfluramine and fluoxetine to treat PMS. Claim 2, the only claim at issue, states:

> A method for treating disturbances of mood, disturbances of appetite, or both, associated with pre-menstrual syndrome, comprising administering to a woman prior to the onset of her menstrual period, a composition consisting essentially of approximately 5 mg to approximately 120 mg of fluoxetine.

('998 patent (PTX 1), col. 7, ll. 7-12.).

The Court has construed the claim terms "pre-menstrual syndrome," "disturbances of mood," "disturbances of appetite," and "prior to the onset of her menstrual period" as follows:

> 1) the term "pre-menstrual syndrome" as used in Claim 2 of the '998 patent includes LLPDD/PMDD; 2) the term "disturbances of mood" we construe to mean negative changes in a person's normal mood associated with PMS; 3) the term "disturbances of appetite" we construe to mean negative changes to a person's normal appetite associated with PMS; and 4) "prior to the onset of her menstrual period" we construe to include not only late-luteal phase dosing regimens, but also all dosing regimens that begin prior to the onset of a woman's menstrual period, including those that go on continuously thereafter.

(PTX 192 at 10, Dk # 119). [FN8] "PMDD" and "LLPDD" are terms that can be used interchangeably and refer to a severe type of PMS. (Rapkin Tr. pp. 601- 02; Brown Tr. pp. 731-32).

> FN8. A guide to the phases of a woman's menstrual cycle:
> Women of child-bearing age experience monthly menstrual cycles, which prepare the body for a potential pregnancy. A woman's menstrual cycle begins on the first day of her period. Towards the beginning of the cycle, a hormone called follicle stimulating hormone ("FSH") is released from the brain. FSH stimulates the growth of 15 to 20 of the hundreds of thousands of immature eggs contained in a woman's ovaries. Each of the growing eggs is surrounded by a sac known as a follicle. As the follicles mature, they begin producing a hormone called estrogen, which stimulates the lining of the uterus, or endometrium, to thicken. One of the growing eggs will mature more quickly than the others and suppress the growth of the other eggs. (Miller Tr. pp. 210-11.)
> At about midpoint in the cycle, a hormone called luteinizing hormone causes the dominant follicle to release its egg in a process called ovulation. After the egg is released, it enters the fallopian tube and journeys toward the uterus. If the egg is not fertilized, the endometrium begins to break down. The dead endometrial cells, along with blood and mucus, are discharged as menstrual flow. (Miller Tr. pp. 211-13.)
> The menstrual cycle takes an average of 28 days. The follicular phase of the cycle begins with menstruation and ends with ovulation. Assuming a 28- day cycle, the follicular phase stretches from approximately day 1 to day 14. The luteal phase of the cycle begins with ovulation and ends with menstruation. Again, assuming a 28-day cycle, the luteal phase stretches from approximately day 14 to day 28 of the cycle. (Miller Tr. pp. 213- 14.)

Under the Court's definition, PMS includes PMDD and is a condition that begins during the luteal phase and remits during the follicular phase. (Endicott Tr. p. 1055; *see also* Smirz Tr. p. 1299). Teva's expert, Dr. Rapkin, confirmed at trial what she had written in 1987, that PMS was defined as "a cyclical disorder manifested by diverse physical and psychological symptoms in the luteal phase with relief soon after

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studies suggest that a special relationship exists between premenstrual syndromes and major psychiatric disorders, particularly affective illness." *Premenstrual Mood Disorder and Psychiatric Illness,* 142 Am. J. Psychiatry 1359 (1985). (DTX BC p. 1359). [FN10]

> FN10. In a study published in June 1987, Parry was motivated to test the effect of sleep deprivation, a known therapy for major depressive disorder, on PMS because "[p]remenstrual syndrome and affective disorders may be related illnesses." (DTX DV p. 808). Although the Parry reference was not published more than a year before the effective date of the '998 patent and cannot be considered in our obviousness analysis, it is relevant in deciding the level of ordinary skill in the art.

***17** While PMS and affective disorders such as anxiety and depression share some common symptoms, they also have significant differences. For example, PMS is dependant on the menstrual cycle; thus, it, as a cyclic disorder, is characterized by symptom-free days. Depression, by contrast, involves an ongoing persistence of symptoms. (Rapkin Tr. pp. 588, 591-92; Blier Tr. pp. 1393-94, 1395). In 1987, it had not been proven that people suffering from PMS had the same biological characteristics as people suffering from depression. For example, PMS affects only women. (Rapkin Tr. pp. 604- 05). PMS sufferers have some symptoms that patients with depression do not have (irritability and certain physical symptoms such as breast tenderness and bloating). Likewise, patients with depression have some symptoms that PMS sufferers do not have (depressed patients may experience early morning awakenings and evidence a lack interest in the world around them, and not all PMS patients are depressed). (Brown Tr. pp. 745-49). Because of these differences, a treatment designed for depression or anxiety would not necessarily be an effective PMS therapy.

Also in the early 1980s, clinical researchers attempted to measure the serotonin functioning in women with PMS to determine if a serotonin deficiency caused PMS. In a 1984 article, *Serotonin Levels and Platelet Uptake during Premenstrual Tension,* 12 Neuropyschobiology 16-18 (1984), Dorothy L. Taylor, *et al.,* studied the correlation between the severity of a woman's PMS and the decrease in that woman's peripheral serotonin levels. (DTX GP p. 16). She compared a woman's premenstrual platelet serotonin levels with her postmenstrual platelet serotonin levels, and the degree of change was correlated with the degrees of distress experienced by the patient pre-and postmenstrually. Building on Taylor's findings, in a study published in October 1987, [FN11] Andrea J. Rapkin, *et al.,* compared women with PMS to asymptomatic women and found changes in serotonergic function in patients with PMS. *Whole-Blood Serotonin in Premenstrual Syndrome,* 70 Obstetrics & Gynecology 533 (1987). (DTX FF pp. 536-37). Contrary to what is usually attributed to her, Rapkin did not find that PMS patients' serotonin levels decreased premenstrually. Rather, Rapkin showed that women with PMS had lower serotonin levels throughout the menstrual cycle, as compared with women who did not have PMS. (Blier Tr. pp. 1367-69; DTX FF at Fig. 1).

> FN11. Although Rapkin's article does not qualify as 102(b) prior art because it was not published more than one year before the filing of the '998 patent, this article was before the patent examiner.

Dr. Blier, a serotonin expert testifying for Lilly, discounts Taylor's work because of "a major methodological flaw." Taylor only measured serotonin changes in women with PMS, and made no comparison of PMS patients with a control group of women who did not have PMS. (Blier Tr. pp. 1365-66; Endicott Tr. p. 1097). In addition, Dr. Blier challenges Rapkin's findings by showing that she did not control for diet, which was known in 1987 to affect serotonin. (Blier Tr. pp. 1369-70). Dr. Blier also argues that although blood platelets model serotonin neurons in the brain, changes in serotonin levels in the blood do not indicate the same type of activity in the brain, a fact Rapkin also noted in her article. (Blier Tr. pp. 1360-63; DTX FF p. 537; *see also* R. Wurtman Tr. pp. 59-61).

***18** Although we credit Dr. Blier's testimony as to the mechanics of serotonin functioning and note his criticisms of the Taylor and Rapkin articles, we conclude that there is substantial evidence that those of ordinary skill in the art relied, at least in part, on Taylor and/or Rapkin, including the authors of the DSM-IV. (Miller Tr. pp. 319-20; *see, e.g.,* DTX GG p. 242; WR p. 616; QQ p. SA 1520 1707; Endicott Tr. pp. 1189-94). These references, however, suggest only the involvement of serotonin with PMS, nothing more. (*See* Brown Tr. pp. 736-37; Endicott Tr. p. 1189). Neither doctor conducted a clinical trial of any drug, including fluoxetine. Furthermore, Rapkin specifically states that as of 1987 further studies were

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unaware of any OB/GYN who used fenfluramine to treat PMS prior to the Wurtmans. (*Id.* pp. 503-04.) In addition, Dr. Blier testified that the prior art teaches away from the use of fluoxetine to treat PMS. According to Rapkin's 1987 data, serotonin levels in whole blood were lower for women with PMS as compared to control subjects. Thus, one skilled in the art would want to increase whole blood serotonin levels. Fluoxetine, however, does the opposite; it decreases, not increases, whole blood serotonin. (Blier Tr. pp. 1381-82; PTX 52 at 14). Therefore, one skilled in the art who was relying on Rapkin's data would not have been motivated to use fluoxetine to treat PMS. (Blier Tr. pp. 1380-81, 1423- 24).

As of October 1987, what was known about fluoxetine was that it was an effective treatment of depression and anxiety. Fluoxetine had been used in clinical trials since 1976, and studies confirming its efficacy in the treatment of major depressive disorder were published in 1985. (DTX AV, GB; Miller Tr. pp. 405-06). None of these prior art references, however, suggested the use of fluoxetine to treat PMS. Given the treatment options described above, fluoxetine, with its high level of effectiveness and improved side effect profile, was a "therapeutic triumph." (Brown Tr. p. 774).

Although the Wurtmans were the first to propose fluoxetine as a PMS therapy in October 1987, Teva asserts that several other people arrived at the same conclusion at about the same time. On February 5, 1988, Wilma Harrison, et. al. ("the Harrison group"), proposed the *Treatment of Premenstrual Exacerbation of Chronic Mild Depression with Fluoxetine: A Pilot Study.* (DTX OW). About five months later, on July 12, 1988, Andrea B. Stone and Dr. Brown, Teva's expert in this case ("the Stone group"), proposed an *Assessment of Fluoxetine in the Treatment of Premenstrual Syndrome* . (DTX NX; published as *Fluoxetine in the Treatment of Premenstrual Syndrome,* 26 Psychopharmacol. Bull. 331-35 (1990), DTX GJ). [FN13] As both of these studies were proposed after January 1, 1988, however, they likely reflect the subtle shift in the state of the art that occurred on that date when the FDA approved fluoxetine (Prozac) for the treatment of depression.

> FN13. In July 1990, Karl Rickels, et al., published *Fluoxetine in the Treatment of Premenstrual Syndrome,* 48 Current Therapeutic Res. 161-66 (1990) ("Rickels"). (DTX FN.) As Rickels did not express interest in using fluoxetine to treat patients suffering from PMS until June 30, 1989, almost two years after the filing of the '998 patent, and did not publish his findings until July 13, 1990, we conclude that his contribution is too far removed to be considered probative of simultaneous invention. (*See also* D-Dem-H, listing physicians proposing the use of fluoxetine after 1989). By mid-1989, the Wurtmans and the Stone group were already speaking publically about and publishing their findings. (*See* J. Wurtman 185-87; DTX HM, XQ).
>
> Teva also offers four letters to the editor offering anecdotal evidence of the use of fluoxetine to treat PMS prior to the issuance of the '998 patent. However, as stated at trial, these exhibits, DTX BQ, CO, DE and DY, are hearsay "plain and simple," and thus, not be considered evidence of simultaneous invention. *See* Tr. pp. 1181-82.

***20** Teva asserts that before FDA approval of fluoxetine, Lilly allowed its use only for research in furtherance of its commercial goals, which did not include an indication for PMS. Teva, however, does not support this allegation with evidence. In all of the voluminous exhibits that the parties have provided us, we see no letter dated before the filing of the '998 patent from a clinician to Lilly asking Lilly for fluoxetine with which to study the treatment of PMS or any letter from Lilly to any clinician denying him or her the same. In fact, when Drs. Stone and Brown proposed their study to Lilly in 1988, Lilly agreed to fund it even though Lilly indicated that it would not be seeking an indication for fluoxetine in the treatment of PMS. (*See* DTX XN, XO, XP, YB). [FN14]

> FN14. In 1992, after Lilly become aware of the '998 patent, when Drs. Brown and Stone applied to Lilly for permission to do a follow-up study of fluoxetine in the treatment of PMS, Lilly referred them to Intemeuron, then the exclusive licensee from MIT of the technology. (DTX OC, OD, OE).

Although the subjects in the Harrison protocol had premenstrual exacerbation not PMS, the two study proposals offer, generally speaking, the same motivation to use fluoxetine to treat PMS: (1) patients with premenstrual depression have symptoms associated with affective disorders; (2) "pathophysiologic links between PMS and mood disorder" suggested that an agent like fluoxetine,

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Having licensed the '998 patent, on December 21, 1998, Lilly filed a Supplemental New Drug Application ("sNDA") with the U.S. Food and Drug Administration ("FDA") seeking approval to manufacture and market the use of fluoxetine to treat Premenstrual Dysphoric Disorder ("PMDD"). On July 6, 2000, Lilly received approval from the FDA to manufacture and market fluoxetine under the tradename Sarafem for treatment of Premenstrual Dysphoric Disorder ("PMDD"), a severe form of Premenstrual Syndrome ("PMS"). In August 2000, Lilly began marketing fluoxetine under the tradename Sarafem. (Dkt.167).

From August 2000 through December 2002, sales of Sarafem in the United States totaled more than $176 million (Tate Tr. pp. 1216, 1222-23; PTX 156), and Sarafem was the market share leader for the treatment of PMDD. (Smith Tr. p. 951; PTX 120 at SA 1508 806). [FN16] However, Dr. Schmittlein, Teva's marketing expert, testified that Sarafem was not a commercially successful product "by Lilly's standards" because sales figures did not meet expectations. (Schmittlein Tr. pp. 1251-52, 1257; DTX RP p. SA 5 35). Dr. Schmittlein determined "Lilly's standards" from a speech made in 2002 by Jonathan Northrup, the Director of Strategic Asset Management for Lilly, in which he said that one of his primary responsibilities "over the past three years is really trying to exit the market from the $300 million type of product." (DTX SO at 24.)

> FN16. The parties use data from August 2000 to December 2002, presumably the most recent figures available. Neither party introduced any evidence tending to show that this data is no longer representative of the market for Sarafem®.

***22** Lilly is an international pharmaceutical company; its business strategies are not representative of what the broader pharmaceutical market would deem a commercial success. In fact, we find persuasive the patent certification letter that Teva sent to Lilly on February 19, 2002, which declared Sarafem to be a "commercially successful product" due in large part to the fact that "[p]hysicians felt comfortable prescribing Sarafem for PMS because of their familiarity with prescribing Prozac for depression." (PTX 98 at p. 9 or p. TEV-SA 06815; Schmittlein Tr. pp. 1285-86). Dr. Schmittlein also attempted to compare the sales of Sarafem to those of Prozac and Lipitor®. (Schmittlein Tr. pp. 1254-57). Lipitor, the top-selling drug for 2002, lowers cholesterol; as Lipitor has nothing to do with PMS, we find its sales figures unhelpful. Dr. Schmittlein testified that Sarafem did not perform as well in its market (PMDD) as Prozac performed in its market (depression). However, because Prozac did extraordinarily well in its market, we don't find that to be a fair standard by which to evaluate Sarafem either.

Sarafem's prescription data supports a finding of commercial success. (PTX 120). Total prescriptions of Sarafem remained fairly constant, with only a slight decline, from 2001 to 2002. Repeat prescriptions of Sarafem, which Lilly's marketing expert Dr. Smith testified are highly indicative of the success of the inherent properties of the product, grew in 2002 compared to 2001 and remained stable through 2002, even though a competitor, Zoloft®, was approved to treat PMDD in May 2002. (Smith Tr. p. 955-56; PTX 182 at SA 3542-44; PTX 120 at SA 1508 804). New prescriptions, which Dr. Schmittlein opined are the most important indicators of future product success, remained relatively stable from April 2001 (the first month after Lilly ended its direct-to-consumer marketing campaign) to April 2002 (the month before Zoloft was introduced). (Schmittlein Tr. pp. 1265-66). After the introduction of Zoloft to the market, the number of new Sarafem prescriptions declined slightly for the rest of 2002; however, Sarafem remained the market leader. (PTX 120 p. SA 1508 806).

Dr. Schmittlein opined that whatever success Sarafem did enjoy was attributable to Lilly's marketing efforts, and that in the absence of any marketing and advertising, the sales of Sarafem would drop to near zero by 2005. (DTX RV at SA 1508 809; Smith Tr. pp. 989-90; Schmittlein Tr. pp. 1267-69). Dr. Schmittlein offers many figures to describe how much money Lilly spent marketing Sarafem. (Schmittlein Tr. pp. 1259-63). For example, he asserts that approximately 80 percent of the $75.4 million Lilly spent developing Sarafem consisted of marketing expenditures. Again, however, Dr. Schmittlein does not identify a drug comparable to Sarafem so that we may understand these numbers in context. Considering that much of Sarafem's product development would have been coincident with the development of Prozac, spending 80 percent of development costs on marketing may not have been out of line. We also question the basis for the near zero sales figure (*i.e.*, what were the author's assumptions) and what would happen to the sales of a comparable drug in the absence of advertising.

***23** In any case, as stated above, prescriptions of

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(Fed.Cir.1991)). "[T]he dispositive question regarding anticipation is whether one skilled in the art would reasonably understand or infer from the prior art reference's teaching that every claim [limitation] was disclosed in that single reference." *Dayco Prods. ., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1368 (Fed.Cir.2003) (internal quotation marks and alterations omitted).

Teva contends that Claim 2 of the '998 patent was inherently anticipated by one or all of the following prior art references: the '895 patent (DTX A), the '213 patent (DTX WY), the Stark article (DTX GB), and the Cohn article (DTX AV). In addition, Teva asserts that Lilly's Fluoxetine Trials are an inherently anticipating public use of the technology claimed by the '998 patent. "Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent." *Bristol-Myers Squibb Co. v. Ben Venue Lab., Inc.*, 246 F.3d 1368, 1377-78 (Fed.Cir.2001).

Lilly, however, argues that Teva's cited prior art references and alleged public use do not anticipate Claim 2 of the '998 patent because they do not disclose the use of fluoxetine for "the same purpose." Rather, the prior art references and alleged public use direct the use of fluoxetine to treat affective disorders, a purpose different from the treatment of PMS. Because PMS is linked to the menstrual cycle, PMS is distinguishable from affective disorders, including depression and anxiety. For example, only women suffer from PMS, and their symptoms are on-again, off-again in nature, depending upon the menstrual cycle. As a result of these differences, a symptom common to both PMS and depression, such as depressed mood, may require different treatment depending on the context in which it appears.

***25** Specifically, Lilly contends that to anticipate a claim reciting the use of an agent to treat a particular disorder, the prior art must disclose the use of that agent with the *intent* or *purpose* of treating the claimed disorder, here PMS. *Rapoport v.. Dement*, 254 F.3d 1053 (Fed.Cir.2001); *Jansen v. Rexall Sundown*, 342 F.3d 1329 (Fed.Cir.2003). Teva, to the contrary, asserts that the authority relied upon by Lilly is factually distinguishable from this case.

The claim at issue in *Jansen* reads in pertinent part as follows:

> 1. A method of *treating or preventing macrocytic-megaloblastic anemia* in humans which anemia is caused by ... which comprises administering a daily oral dosage of a vitamin preparation *to a human in need thereof* comprising ...

342 F.3d at 1330. The *Jansen* court held that, as in *Rapoport*, "the claim preamble sets forth the objective of the method, and the body of the claim directs that the method be performed on someone 'in need.' In both cases, the claims' recitation of a patient or a human 'in need' gives life and meaning to the preambles' statement of purpose.... The preamble is therefore not merely a statement of effect that may or may not be desired or appreciated. Rather, it is a statement of intentional purpose for which the method must be performed." 342 F.3d at 1333.

To compare, Claim 2 states:

> A method for *treating* disturbances of mood, disturbances of appetite, or both, *associated with pre-menstrual syndrome,* comprising administering *to a woman* prior to the onset of her menstrual period a composition consisting essentially of approximately 5 mg to 120 mg of fluoxetine."

Teva argues that because Claim 2 "does not expressly limit treatment to individuals 'in need thereof,' the claim language 'a method for treating' should be construed as a 'statement of effect that may or may not be desired or appreciated." ' Teva Corrected Post-Trial Br. pp. 16-17.

Teva's argument, however, is incomplete. The *Jansen* court expressly declined to reach the situation we face here, one in which the "to a human in need thereof" phrase was not a part of the disputed claim. *Jansen* held only that the "to a human in need thereof" phrase *together with* the "treating or preventing" phrase required an intent to treat the specified condition. 342 F.3d at 1333. Therefore, we must decide whether the "method for treating" phrase in the context of Claim 2 is sufficient to compel an intent to treat PMS.

Teva uses the prosecution history of U.S. Patent No. 5,223,540 ("the '540 patent"), which issued from a later-filed application in the same chain as the '998 patent, to demonstrate the significance of the "human in need thereof" language. Teva contends that during prosecution, the patent examiner rejected a claim identical in form to Claim 2 of the '998 patent because the claim as written covered administration to "any woman." (DTX O p. 62). To address the examiner's concerns, the claim in the '540 application was amended to add the phrase "in need of such treatment." (DTX O pp. 75, 79). [FN17]

> FN17. The claim was amended as stated; however, we note that the examiner rejected the '540 amendment on obviousness

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reference to provide missing disclosure of the claimed invention, the proper ground is not anticipation, but obviousness.") Rather, his calculations rely both on an examination of case report data and on 65 percent prevalence rate taken from the report of Teva's expert, Dr. Miller. (Bolton Tr. pp. 843, 851). Lilly challenges the accuracy of the prevalence rate chosen by Dr. Miller because it reflects the rate at which patients with major depressive disorder also had PMS at some point in their lifetime, not simultaneously with the disorder. *See* Lilly's Reply Br. p. 12. Teva responds that the calculations would remain relatively unchanged even if Dr. Bolton used a hypothetical prevalence rate of ten percent.

To the extent that Teva maintains that the prevalence rate is irrelevant, we agree, but for a different reason. Dr. Bolton bases his testimony on probabilities-concededly, very strong probabilities, but probabilities nonetheless. A claim limitation is inherent in the prior art if it is necessarily present in the prior art, *not merely probably or possibly present.* *Rosco v. Mirror Lite*, 304 F.3d 1373, 1380 (Fed.Cir.2002) (emphasis added). "Inherency ... may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function," the prior art has anticipated the claim at issue. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed.Cir.1991).

***28** Dr. Bolton's result is not a "necessary" or "natural" one. He could not identify any one patient record and say with certainty that any one female subject actually had PMS. *Contrast* *Proctor & Gamble Co. v. Nabisco Brands, Inc.*, 711 F.Supp. 759, 11 U.S.P.Q.2d 1241, 1252-53 (D.Del.1989) (noting that defendant produced evidence that an employee of plaintiff produced the desired result following the claimed method on her first try). We find credible the experts' collective testimony that PMS requires a careful diagnosis, which to be confirmed must be charted over several menstrual cycles.

To supplement Dr. Bolton's statistical analysis, Teva offers the testimony of Dr. Brown to show that a patient record from Lilly's pre-October 1986 Fluoxetine Trials anticipated Claim 2. Dr. Brown testified that: (1) the subject woman suffered from disturbances of mood associated with PMS, and (2) both she and her physician appreciated that the fluoxetine she received in the clinical trial ameliorated those disturbances. This characterization misstates the facts, however.

In week 5 of the double-blind trial, the patient complained of "premenstrual tension," which abated as of week 6. Such an anecdotal comment is insufficient to diagnose PMS, however. Even Dr. Brown acknowledged that the patient was not given a thorough evaluation (*i.e.*, no documentation of the start of menses exists) and that frequently women erroneously attribute symptoms to PMS. Based on the structure of the clinical trial, we were able to determine that the patient was taking fluoxetine during the blinded portion of the trial. Depending on the length of the placebo lead-in period, by her fifth visit, she would have been taking fluoxetine for at least a week. Fluoxetine relieves symptoms of PMS within a day, but takes two to three weeks to relieve symptoms of depression. Therefore, we conclude that the patient did not suffer from disturbances of mood or disturbances of appetite associated with PMS.

The evidence as presented does not convincingly demonstrate a use of the method claimed in the '998 patent-the treatment of PMS. Nevertheless, Teva maintains that Lilly's Fluoxetine Trials constitute a "public use" under § 102. The statutory phrase "public use" does not mean open and visible in the ordinary sense. Rather, it includes any use of the claimed invention by a person other than the inventor who is under no limitation, restriction, or obligation of secrecy to the inventor. *New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1297 (Fed.Cir.2002) (citations omitted). Because the inventors named on the '998 patent are Richard and Judith Wurtman, who were affiliated with MIT, and Lilly did not sublicense the '998 patent until 1997, almost a decade after the clinical trials at issue were completed, Teva contends that Lilly should therefore be considered a person other than the inventor who used the claimed invention.

We see at least two problems with Teva's contention. First, because Lilly's Fluoxetine Trials did not practice the claimed method, the use of fluoxetine to treat PMS, they do not constitute a "use" of the claimed invention, public or private. *Contrast* *SmithKline Beecham Corp. v. Apotex Corp.*, 365 F.3d 1306, 1318 (Fed.Cir.2004) (concluding that where the claim covered the compound regardless of its use as an antidepressant, the clinical tests, which measured the efficacy and safety of the compound as an antidepressant, did not constitute an experimental

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documents are not enough. *Hahn v. Wong*, 892 F.2d 1028, 1032 (Fed.Cir.1989).

In this case, the filing date of the '998 patent is October 22, 1987. The only evidence Lilly offers to support an earlier date of invention is the testimony of the inventor, Dr. Richard Wurtman. Lilly does not produce any document or witness testimony to corroborate his testimony. Dr. Judith Wurtman, a co-inventor, was not involved with the fluoxetine study; she did not see the results except as they were presented in the '998 patent. Therefore, in the absence of sufficient proof of an earlier conception and actual reduction to practice, we must conclude that the date of invention is the filing date of the '998 patent, October 22, 1987. Accordingly, the relevant prior art consists of those references dated one year or more before the date of invention. In this case, that date is October 22, 1986. *See Scripps Clinic & Research Foundation*, 927 F.2d at 1576-77.

Next, we must determine what the prior art had taught about fluoxetine as of the filing of the '998 patent. Although fluoxetine was not on the market in the United States, it was available in Europe as of November 1986. Clinical trials involving fluoxetine and the nature of the drug itself had also been described in the scientific literature.

In its obviousness argument, Teva again relies on the prior art discussed in our anticipation analysis, among other references. The '895 patent, which was filed in September 1975 and issued in April 1977, teaches that fluoxetine is an effective treatment of depression in humans. Similarly, the '213 patent, which was filed in 1983 and issued in 1986, establishes that fluoxetine is an effective treatment of anxiety in humans. In separate articles in March 1985, Cohn and Stark tested the efficacy of fluoxetine and found that fluoxetine relieved the symptoms of depression significantly better than placebo and that it caused fewer and less severe side effects than another antidepressant, impramine. [FN18] These prior art references teach all but one, key element of the '998 patent-that fluoxetine is an effective treatment of symptoms *associated with PMS*.

> FN18. Other publications of the same era support these findings. For example, in December 1 1986, Benfield *et al* published a drug evaluation, which stated that fluoxetine was known to be a SSRI, and therefore, to be effective in treating conditions caused by serotonergic deficiencies, including depression. (Miller Tr. pp. 250-51; DTX AC pp. 482-83). Benfield also discussed fluoxetine's side effect profile, which improved upon that of tricyclic antidepressants. *Id.* p. 484. This reference was published after October 1986, but it was before the patent examiner during the prosecution of the '998 patent.

In order to determine whether one of ordinary skill in the art would have thought it obvious to use fluoxetine to treat PMS, we must first establish what was known about PMS as of October 22, 1987. The answer is not much. There were many theories as to the cause of PMS, but none had been definitively proven. In 1985, after having surveyed the many theories as to the etiology of PMS, Janowsky stated that "no existing hypothesis of PMT [premenstrual tension syndrome] is even close to being proved at this time." (DTX CQ p. 7). While a leading theory in 1987 was one related to sex hormone changes (*i.e.*, progesterone) linked to a woman's menstrual period, many other theories were being tested. Another theory, which will be discussed below, was serotonin deficiency.

***31** In considering whether one of ordinary skill in the art would have been motivated to use fluoxetine, an effective treatment of depression, to treat PMS, we note as of October 1987, the nature of the relationship between PMS and affective disorders was still being explored. PMS is not a subset of depression, which is itself a stand alone affective disorder. Depression in the sense of depressed mood, however, may be a symptom of PMS. There are significant differences between PMS and affective disorders such as depression or anxiety. PMS is dependant on the menstrual cycle; thus, it, as a cyclic disorder, is characterized by symptom-free days. Depression, by contrast, involves an ongoing persistence of symptoms. PMS affects only women whereas both men and women suffer from depression. PMS sufferers have some symptoms that patients with depression do not have (irritability and certain physical symptoms such as breast tenderness and bloating). Likewise, patients with depression have some symptoms that PMS sufferers do not have (depressed patients may awake early in the morning and lack interest in the world around them, and not all PMS patients are depressed). Because of these differences, a treatment designed for depression or anxiety would not necessarily be an effective PMS therapy.

As of October 1987, those skilled in the art were just

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November 1985 article, "[a]dequate trials of [MAO] inhibitors [and] of tricyclic antidepressant in premenstrual syndrome have not yet been reported.... While psychoactive drugs may relieve a selected premenstrual symptom such as depression or anxiety, none would appear to be broad enough in its effect to provide satisfactory relief for women with severe and multiple symptoms." (DTX CU pp. 483-84). Furthermore, the relief available from the antidepressants available at the time, tricyclic antidepressants and MAO Inhbitiors, had to be weighed against the unpleasant side effects. For example, such risks and side effects include risk of suicide with tricyclics (PTX 10 at 2627), drug interactions with MAOIs (PTX 10 at 2563), and lithium toxicity with lithium. ACOG did not recommend treatment of PMS with antidepressants until 1995.

*33 Another treatment which was known to relieve, at least in part, the mood symptoms of PMS was alprazolam, which is an anti-anxiety agent. However, alprazolam has harmful side effects such as palpitations, tremors and seizures. Additionally, physicians were not particularly comfortable using alprazolam to treat PMS in part because it was addictive.

Proponents of the serotonin hypothesis recommended testing agents that influence the serotoninergic pathway, namely tryptophan, chlorimipramine, and trazodone hydrochloride. As of October 1987, however, tryptophan had been shown, by Dr. Endicott, to be ineffective agent for the treatment of PMS. Noticeably, no one suggested the use of fluoxetine or fenfluramine, two known serotoninergic enhancing agents, to treat PMS before the Wurtmans. Given the available treatment options, fluoxetine, with its high level of effectiveness and improved side effect profile, understandably was a "therapeutic triumph." (Brown Tr. p. 774).

B. *Level of ordinary skill in the prior art*

The parties dispute the appropriate level of ordinary skill in the art. Lilly argues that the one of ordinary skill in the art is a community-based OB/GYN or family practitioner. Teva, by contrast, contends that "the person of ordinary skill in the art must be an individual who, in the October 1987 time frame, would have been seeking to find a medication that would be effective in treating the specific PMS symptoms listed in claim 2 of the '998 patent-disturbances of mood and/or appetite." Teva Corrected Post-Trial Br. p. 24. The Federal Circuit teaches that factors pertinent to ascertaining the theoretical ordinary level of skill in the art are: (i) the inventor's educational background; (ii) the kinds of problems confronted in the art; (iii) solutions found previously; (iv) the speed of innovation in the art; (v) the level of sophistication of the technology; and (vi) the educational level of active workers in the field. *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 696 (Fed.Cir.1983).

In this case, the Wurtmans, who were the inventors of the '998 patent, were clinical researchers interested in using serotoninergic drugs to alleviate a constellation of symptoms associated with PMS. Dr. Richard Wurtman has an M.D. and Dr. Judith Wurtman has a Ph.D. in cell biology. As explicated above, in October 1987, although many theories existed as to the cause and treatment of PMS, none was generally accepted. During the prosecution of the '998 patent, the art, including the theory of serotonin deficiency, was continuously evolving. The "educational level of active workers in the field" varied. Those active in the development of new drug therapies, such as clinical researchers like the Wurtmans, read academic literature and conducted experimental clinical trials. However, community-based physicians, whether OB/GYNs, family practice physicians or psychiatrists, ordinarily did not.

In this context, we conclude that a community-based physician would not be one of ordinary skill in the art because, as Dr. Endicott acknowledged, community-based physicians, on average, not only do not conduct independent research or seek patents, but they also do not read academic literature. If a person is not generally aware of the relevant prior art, he or she cannot be considered someone of ordinary skill in that art. Yet, to limit "one of ordinary skill in the art" to clinical researchers would be too restrictive. Therefore, in our view, one of ordinary skill in the art is a hypothetical medical doctor (an OB/GYN, a family practice physician, or a psychiatrist) who: (1) regularly sees and treats patients suffering from PMS, and (2) is familiar with the relevant prior art. *See Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc.*, 777 F.Supp. 330, 352 (D.Del.1991) (finding that where the patent was directed to the development of beta-blockers for the treatment of hypertension, "the person of ordinary skill in the art would be an individual with a PhD degree in organic chemistry, with an emphasis in medicinal chemistry ..., who would have some experience with the development of beta-blockers, and would be thoroughly familiar with the prior art which discusses the structure-activity relationships of the existing beta-blockers and have

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disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." *Gillette Co. v. S.C. Johnson,* 919 F.2d 720, 725 (Fed.Cir.1990) (internal citations omitted). However, "obvious to try" is not the standard in a § 103 obviousness inquiry. *Ecolochem,* 227 F.3d at 1374. Teva must point to "the specific sources of the motivation to combine prior art references" in order to prevail on this theory. *Id.*

Our considered judgment is that Teva has not provided clear and convincing evidence of a motivation to combine references. History has shown that not even those with extraordinary skill in the art and unfettered access to fluoxetine, clinical researchers at Lilly, for example, were motivated to treat PMS with fluoxetine prior to the Wurtmans.

One of ordinary skill in the art must also have a reasonable expectation of success, which we find also lacking here. In 1987, scant information was known about the etiology of PMS. Any new method of treatment that proved to be effective would have been unexpected, and like fluoxetine, a "therapeutic triumph." In sum, we conclude that Teva has failed to produce clear and convincing evidence that "a skilled artisan confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the matter claimed." *In re Rouffet,* 149 F.3d 1350, 1357 (Fed.Cir.1998).

D. *Objective indicia of nonobviousness*

Our primary finding of nonobviousness is buttressed by secondary indicia of nonobviousness. Objective evidence such as commercial success, failure of others, long-felt need, and unexpected results must be considered before a conclusion on obviousness is reached. *Minnesota Min. and Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc. .,* 976 F.2d 1559, 1573 (Fed.Cir.1992). "[E]vidence of secondary considerations may often be the most probative and cogent evidence in the record." *Stratoflex, Inc. v. Aeroquip Corp.,* 713 F.2d 1530, 1538 (Fed.Cir.1983). Lilly offers many alleged objective indicia of nonobviousness for our consideration.

1. *Commercial success*

***36** With regard to commercial success, Lilly, the patentee, bears the burden of proving a "nexus," or a legally and factually sufficient connection between the proven commercial success and the patented invention. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.,* 851 F.2d 1387, 1392 (Fed.Cir.1988). The Federal Circuit has held that "a presumption arises that the patented invention is commercially successful 'when a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent." ' *Ecolochem,* 227 F.3d at 1377. Once Lilly makes the requisite showing of nexus between commercial success and the patented invention, the burden shifts to Teva to prove that the commercial success was instead due to other factors extraneous to the patented invention. *Id.*

Lilly has satisfied its burden by offering evidence that Sarafem, its product covered by Claim 2 of the '998 patent, had sales of $176 .2 million from August 2000 to December 2002 and was the most prescribed product for the treatment of severe PMS during that time. *See Tec Air, Inc. v. Denso Mfg. Mich., Inc.,* 192 F.3d 1353, 1361 (Fed.Cir.1999) (providing that sales figures coupled with market data provide stronger evidence of commercial success than sales figures alone). As evidence of its market share, Lilly also produced Sarafem's prescription data.

Even though a competitor, Zoloft, entered the PMDD market in May 2002, total prescriptions of Sarafem declined only slightly from 2001 to 2002. Repeat prescriptions, which Lilly's expert Dr. Smith testified are highly indicative of the success of the inherent properties of the product, grew in 2002 as compared to 2001 and remained stable with a slight decline through 2002. Teva's expert, Dr. Schmittlein, opined that new prescriptions, not repeat prescriptions, are the most important indicators of future product success because they demonstrate whether physicians view the product as continuing to play an important role in their treatment practice. However, new prescriptions, too, remained stable from April 2001 (the first month after Lilly ended its direct-to-consumer marketing campaign) to April 2002 (the month before Zoloft was introduced). Although Zoloft's appearance on the scene no doubt diverted some new prescriptions from Sarafem, Sarafem remained the market leader.

Teva disputes even the presumption that Sarafem achieved "significant sales in a relevant market." Teva argues that Sarafem was not a successful

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patent, Lilly could list it in the Orange Book with respect to Sarafem. Lilly then would have standing to bring suit for infringement against a generic drug manufacturer and keep the generic manufacturer off the market for up to 30 months. The estimated sales value to Lilly of being the exclusive marketer of Sarafem was about $580,000,000. (Gould Tr. pp. 1018-23). Thus, while the 1997 license had considerable value to Lilly, it is not necessarily evidence of nonobviousness.

Ultimately, we find that Sarafem was a commercial success and as such, this factor weighs in favor of nonobviousness.

2. *Long-Felt Need / Failure of Others / Simultaneous Invention* [FN21]

> FN21. Lilly encourages us to consider Teva's "copying" of Sarafem as secondary evidence of nonobviousness. However, because the very nature of a generic drug indicates that it is equivalent to the branded drug in certain significant respects, Teva's demonstration of equivalency of Sarafem to the extent required by the FDA is not an indication of the non-obviousness of the claimed invention.

Lilly asserts that, as of October 1987, there was a widespread failure of others to develop a safe and effective treatment for patients suffering from PMS. As established above, many hypotheses existed as to the etiology of PMS, but no known treatments had been devised or developed that provided relief to both the physical and emotional symptoms of PMS. Fluoxetine was the first drug to provide relief for both kinds of symptoms, and the '998 patent was the first indication that fluoxetine was effective for PMS. Teva, by contrast, contends that the long-felt need that existed was simply for a serotoninergic drug with fewer side effects, and that the discovery of the fluoxetine molecule itself, in the form of Prozac, satisfied this need. Teva's contention, however, fails to account for the specific need to treat PMS. The identification of fluoxetine as an effective treatment of PMS did not occur until the '998 patent.

Next, Teva argues that others of ordinary skill in the art not only did not fail to develop the patented technology, but they also discovered it simultaneously with the Wurtmans. [FN22] Teva offers two clinical study protocols, Harrison, et al.'s *Treatment of Premenstrual Exacerbation of Chronic Mild Depression with Fluoxetine: A Pilot Study* dated February 5, 1988, and Stone, et al .'s *Assessment of Fluoxetine in the Treatment of Premenstrual Syndrome* dated July 12, 1988, to establish simultaneous invention. [FN23]

> FN22. Teva stresses the unlikelihood of Dr. Richard Wurtman's story of invention. We, however, find him credible. While we agree with Teva that Dr. Wurtman's version of events cannot establish an earlier date of invention than the filing of the '998 patent, Teva noticeably fails to identify any effect of the alleged surreptitiousness of Dr. Wurtman's actions on the validity of the '998 patent. The patent examiner was as aware of Dr. Wurtman's work as we are. *See also, infra,* note 7.

> FN23. As explained, *infra,* note 11, Teva's other evidence of simultaneous invention is either irrelevant because it is hearsay or is dated after the Wurtmans and the Stone group had publicized their findings of fluoxetine's efficacy in treating PMS. Therefore, we do not consider it.

With respect to simultaneous invention, "[e]vidence of independent development of a patented device is indicative of obviousness if the circumstances of the development are shown to be similar to the state of the art when the patent was filed." *Pratt & Whitney Canada, Inc. v. U.S.*, 17 Cl.Ct. 777, 787 (Cl.Ct.1989) (citing *Stewart-Warner Corp. v. Pontiac*, 767 F.2d 1563, 1570 (Fed.Cir.1985)). Before we discuss the specifics of Teva's prior art references, we note the subtle change in the state of the art that occurred after the filing of the '998 patent in October 1987 and before the conception of any of these references stemming from the fact that, in January 1988, the FDA approved fluoxetine (Prozac) for the treatment of depression.

***39** Although Teva asserts that before the FDA approved fluoxetine Lilly allowed its use only for research in furtherance of its commercial goals, which did not include an indication for PMS, Teva does not support this allegation with any corroborative evidence. In all of the voluminous exhibits which the parties have introduced into evidence, we find no request dated before the filing of the '998 patent from a clinician to Lilly asking Lilly for fluoxetine to permit the study of the treatment of PMS, or any letter from Lilly to any clinician denying him or her the same. In fact, when Dr. Brown proposed his study to Lilly in 1988, Lilly

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nonobviousness (commercial success, failure of others, long-felt need and unexpected results). It would not outweigh our primary finding that, in 1987, the technology claimed in the '998 patent would not have been obvious to one of ordinary skill in the art.

*Conclusion*

For the reasons explained above, we hold that Teva has failed to prove by clear and convincing evidence that the '998 patent was invalid as anticipated under 35 U.S.C. § 102 or as obvious under 35 U.S.C. § 103. Accordingly, the '998 patent is valid and enforceable. [FN25]

> FN25. The only remaining issue still before the court is Lilly's claim of willful infringement.

It is so ORDERED.

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