United States Court of Appeals for the Federal Circuit

ELI LILLY AND COMPANY,
Plaintiff-Cross Appellant,

v.

TEVA PHARMACEUTICALS USA, INC.,
Defendant-Appellant.

2010-1005, -1033

Appeals from the United States District Court for the Southern District of Indiana in case no. 06-CV-1017, Judge Sarah Evans Barker.

Decided: September 1, 2010

CHARLES E. LIPSEY, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, of Reston, Virginia, argued for plaintiff-cross appellant. With him on the brief were L. SCOTT BURWELL; DAVID S. FORMAN, HOWARD W. LEVINE, LAURA P. MASUROVSKY, MARK J. FELDSTEIN, and J. DEREK MCCORQUINDALE, of Washington, DC. Of counsel on the brief was GILBERT T. VOY, Eli Lilly and Company, of Indianapolis, Indiana.

EDWARD H. RICE, Loeb & Loeb LLP, of Chicago, Illinois, argued for defendant-appellant. With him on the

brief were MARINA N. SAITO, STEVEN M. LUBEZNY and JULIE P. SAMUELS.

Before RADER, *Chief Judge*, LINN and PROST, *Circuit Judges*.

RADER, *Chief Judge*.

Following an 11-day bench trial, defendant Teva Pharmaceuticals USA, Inc. ("Teva") appeals the district court'3s permanent injunction preventing any manufacture or distribution of a generic version of the drug Evista® until the expiration of U.S. Patent Nos. 6,906,086 (the "'086 patent"); RE39,049 (the "'049 patent"); RE38,968 (the "'968 patent) (collectively the "Bone Loss Patents"); and RE39,050 (the "'050 patent" or the "Low Dose Patent"). *See Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 657 F. Supp. 2d 967 (S.D. Ind. 2009). Plaintiff Eli Lilly & Co. ("Lilly") cross appeals the district court's ruling that certain claims of its U.S. Patent Nos. 6,458,811 (the "'811 patent") and 6,894,064 (the "'064 patent") are invalid for lack of written description. Detecting no reversible error, this court affirms.

I

A

Osteoporosis is a major debilitating disease that causes loss of bone mass (decreased density and enlargement of bone spaces) without a reduction in bone volume. Thus, osteoporosis makes bones porous and fragile.

Healthy human bones go through a number of changes over time, in part due to remodeling. Bone remodeling is the process by which a portion of the bone called the trabecular portion is removed and then replaced. The first stage of remodeling is bone absorption,

whereby certain cells essentially dig out part of the bone and remove it. The second stage of the remodeling process is bone formation, or resorption, during which different cells replace the bone that was lost via absorption.

In healthy adults, the skeletal mass remains constant throughout the remodeling process because the amount of bone that is lost is replaced in similar amounts. With the onset of osteoporosis, the remodeling process does not completely replace the lost bone mass. Thus, more bone is removed than is replaced. Accordingly, remodeling leaves a thinner, weaker bone.

Osteoporosis is largely a consequence of a lack of sufficient estrogen in the system. Before menopause, estrogen naturally slows the process of remodeling in women, essentially acting as a "brake" on the process. Following menopause, when women's bodies lose significant levels of systemic estrogen, the remodeling process becomes more vigorous. Osteoporosis is a relatively common condition: approximately one in two women beyond the age of fifty suffers an osteoporotic fracture at some point during the remainder of their lives.

Because osteoporosis results mainly from a lack of estrogen in the system following menopause, the principal treatment, historically, for postmenopausal osteoporosis has been estrogen replacement therapy ("ERT"). ERT successfully prevents bone loss as well as fractures. ERT, however, presents other problems, including increased risk of both breast and uterine cancer. Therefore, researchers sought a therapeutic remedy to treat and prevent postmenopausal osteoporosis that would act like estrogen in preventing bone loss but would not cause damaging side effects in other tissues.

B

Evista® treats postmenopausal osteoporosis. The active ingredient in Evista® is raloxifene hydrochloride. Raloxifene is part of a class of compounds known as antiestrogens, which were originally developed for the treatment of estrogen-dependent breast cancer. A large number of breast cancers are estrogen dependent, which means that estrogen stimulates their growth. Antiestrogens work to inhibit the growth of a cancer by binding to estrogen receptors in breast cancer cells, thereby blocking the action of the estrogen.

Antiestrogens, however, often carry side effects similar to the side effects of estrogen itself. Researchers discovered that when certain antiestrogens were not competing with estrogen for receptors (i.e., when there was little estrogen already in the system, such as in postmenopausal women), the antiestrogens were found to have a stimulatory estrogenic effect in the uterus. This effect was ultimately associated with an increased risk of endometrial cancer.

Various antiestrogens mimic the effect of estrogen in varying degrees, and the degree to which a particular antiestrogen mimics estrogen is referred to as its intrinsic estrogenicity. One of the first clinically successful antiestrogens used in the treatment of breast cancer, tamoxifen, has significant intrinsic estrogenicity.

C

Researchers at Lilly first synthesized and tested the molecule now known as raloxifene in the late 1970s in an effort to find a purer antiestrogen that would have positive effects in breast tissue but less damaging effects in the uterus. Dr. C. David Jones and Mr. Larry Black, the

ultimate inventor of the Bone Loss patents, first identified that molecule as "LY156758."

Mr. Black published his findings in an abstract entitled "LY156758: A Unique Antiestrogen Displaying High Affinity for Estrogen Receptors, Negligible Estrogenic Activity and Near-Total Estrogen Antagonism *In Vivo*." In that abstract, published in 1982, Mr. Black reported that raloxifene produced a very minimal increase in uterine weight in rats (one measure of a compound's intrinsic estrogenicity), while tamoxifen caused marked uterine growth.

Lilly completed pharmacokinetic tests of raloxifene, also referred to as "Phase I" tests, in September and October of 1982. A Phase I test is a safety test used generally in the drug development process before clinical trials in patients can begin. The results of Lilly's Phase I tests on raloxifene, as reported in Lilly's internal documents, revealed that the bioavailability of raloxifene was low. In other words, very little of the ingested raloxifene was detected in the human bloodstream.

The results of Lilly's Phase I tests were similar to the results of others published by Dr. Terry Lindstrom, another Lilly scientist, in 1983 and 1984. Dr. Lindstrom conducted various animal studies using raloxifene in which he found that the bioavailability of raloxifene was approximately 39% in rats, 17% in dogs, and 5% in monkeys. Dr. Lindstrom's study did not test whether, despite the bioavailability problem, raloxifene had any effect on the animals.

Although attempts at measuring the parent raloxifene in Lilly's Phase I tests had been unsuccessful, the human volunteers showed a considerable amount of raloxifene conjugated to glucuronide in their serum. A conjugate

forms when a molecule in the body attaches to the administered (i.e., "parent") compound.

Unlike tamoxifen, the chemical structure of raloxifene includes two free hydroxyl groups, which enable the liver to rapidly metabolize the raloxifene. In the vast majority of compounds, the process of glucuronidation serves to deactivate the drug. At least one compound, however, was known to be active in conjugated form (morphine-6), and certain enzymes were known to be able to reverse the effects of conjugation.

A number of researchers outside Lilly also published articles that discussed raloxifene's rapid metabolic conversion. For example, in a 1983 article A.E. Wakeling addressed the decreased potency of several compounds, including raloxifene, when administered orally versus when administered subcutaneously. Dr. Craig Jordan also stated in a 1983 publication that an analog to raloxifene with a similar chemical structure "should be classified as an ultra short-acting estrogen antagonist" when compared to tamoxifen. J.A. 9929. And in 1984, Dr. Jordan published a review article in which he discussed the hydroxylation of compounds such as raloxifene and stated that "[c]learly this will facilitate a rapid metabolism and excretion of those compounds." J.A. 9929.

Following the Phase I tests, Lilly concluded that "it [was] not appropriate to go directly into breast cancer as first line therapy with a compound so extensively conjugated and possibly poorly bioavailable since other forms of therapy are available." J.A. 9842. A clinical trial for raloxifene was then initiated in 1985 under the direction of Dr. Aman Buzdar for female breast cancer patients whose cancer had not responded to tamoxifen. Dr. Buzdar published the results of his study in a 1988 article titled "Phase II Evaluation of Ly156758 in Metastatic

Breast Cancer." In that article, Dr. Buzdar reported that, with the exception of one minor response, raloxifene produced no complete or partial responses. From these results, Dr. Buzdar concluded that raloxifene "did not show any antitumor activity . . . and no further evaluation of this drug is recommended." J.A. 6867. Although Dr. Buzdar's reports do not attribute raloxifene's lack of efficacy to a bioavailability problem, Lilly's Dr. Lindstrom testified at trial that he believed the breast cancer trials had failed for that reason. J.A. 3091 at 366:9-367:4.

D

Shortly after completing its Phase I tests on raloxifene, Lilly undertook an effort to determine whether raloxifene could still have efficacy notwithstanding its rapid conjugation. Mr. Black conducted studies on the raloxifene conjugate that led him to two conclusions. First, Mr. Black concluded that the lack of detectable parent compound did not necessarily preclude efficacy. Second, he concluded that, under physiological conditions, the conjugate could possibly be converted back to the parent compound. The results of these experiments, which Mr. Black obtained before Dr. Buzdar conducted his breast cancer trials, were not published.

After Mr. Black conducted those conjugate studies, he conducted experiments to study the effects of raloxifene on bone in various ovariectomized rat models. The results of those experiments showed that raloxifene prevented bone loss in that model. Lilly's Project Team Approval Committee (PTAC) then approved a human clinical trial of raloxifene in postmenopausal women for the treatment of postmenopausal osteoporosis in November of 1991. The PTAC meeting, however, featured significant concerns regarding bioavailability. Many of the members expressed reluctance to go forward with a compound that

exhibited known bioavailability issues. According to Dr. Thomas Bumol, a member of PTAC at the time, the committee gave its approval for the clinical test despite these concerns, at least in part because Lilly already had an open Investigative New Drug (IND) approval on raloxifene from the Food and Drug Administration (FDA). This IND approval would permit Lilly to conduct clinical tests within six months, rather than the usual twelve to twenty-four months.

E

Before the results of the PTAC-approved clinical study had been collected, Lilly filed its patent application for what became the Bone Loss Patents. (All citations to the three Bone Loss Patents, which share the same specification, are to the '086 patent.) Because the study results were still pending at that time, the Bone Loss Patents contain no clinical human data. Example 5 in the Patents, however, set forth the blueprint for the PTAC-approved clinical study. This example specifies doses of 200 mg and 600 mg of raloxifene per day. Example 1 of the Bone Loss Patents explains Mr. Black's study on ovariectomized rats. The patent specification also disclosed publicly for the first time Mr. Black's studies of the glucoronide conjugate and explained that the rapid conjugation of raloxifene would not necessarily undermine its efficacy in humans.

The U.S. Patent Office (PTO) rejected the original parent application to the Bone Loss Patents, based on an article published by Dr. Jordan, et al., in 1987 entitled "Effects of anti-estrogens on bone in castrated and intact female rats" (the "Jordan Reference"). Following these rejections, Lilly scientist Dr. Henry Bryant submitted a declaration in which he attacked the methodology behind and the credibility of the conclusions in the Jordan Refer-

ence. The PTO subsequently allowed the parent application to the Bone Loss Patents.

Claim 1 of the '086 patent is representative and provides:

> A method of inhibiting post-menopausal bone loss in a post-menopausal woman in need of treatment to prevent or treat post-menopausal osteoporosis comprising administering a single daily oral dose to said woman of an effective amount of [raloxifene] hydrochloride.

F

In May 1992, enrollment began for Lilly's Phase II, proof-of-concept study, referred to as the "GGGB" study, to test raloxifene's efficacy in humans as described in Example 5 of the '086 patent. Dr. Michael Draper conducted that study. The results of that study unequivocally demonstrated activity in humans at both the 200 mg and the 600 mg doses of raloxifene.

After the results of the GGGB study showed activity in humans, Dr. Draper designed and conducted a "GGGC" study to further characterize the dose response curve of raloxifene. The GGGC study was the first of a number of dose-ranging studies conducted by Lilly in order to determine the minimal effective dose of raloxifene. Dr. Draper chose 10, 50, and 200 mg/day doses for the GGGC study.

Based on the results of the GGGC study, Lilly filed its application for what became the Low Dose Patent on May 2, 1994, naming Dr. Draper and Mr. Black as the inventors. Claim 14 of the Low Dose Patent is representative and reads as follows (emphasis added):

> A method of preventing post-menopausal osteoporosis in a post-menopausal woman in need of treatment to prevent post-menopausal osteoporosis comprising administering to said woman a hydrochloride salt of . . . [raloxifene] *in an amount of 60 mg/day*.

G

The core concept of Lilly's '811 and '064 patents (collectively the "Particle Size Patents") is to process raloxifene particles until their size falls "within a specified narrow range." '811 patent, col.3 ll.15-18. (All references to the two Particle Size Patents, which share the same specification, are to the '811 patent.) The Particle Size Patents disclose that, within the claimed particle size range, the raloxifene particles provide "surprisingly consistent in vivo absorption/bioavailability characteristics." *Id.* at col.29 ll.17-20. The patents also teach that restricting raloxifene's particle size to the claimed limits results in manufacturing benefits. Representative claim 1 of the '811 patent recites (emphasis added):

> A compound of formula I . . . [raloxifene] and pharmaceutically acceptable salts and solvates thereof, characterized in that the compound is *in particulate form*, said particles having a mean particle size of less than about 25 microns, at least about 90% of said particles have a size of less than about 50 microns.

II

Teva filed Abbreviated New Drug Application ("ANDA") No. 78-193 with the FDA for raloxifene hydrochloride 60 mg tablets for the prevention of osteoporosis in postmenopausal women. Under 21 U.S.C. §

355(j)(2)(A)(vii)(IV), Teva's ANDA included a "Paragraph IV Certification" to Lilly's patents for Evista®, certifying that each of those patents is invalid, unenforceable, or would not be infringed by Teva's manufacture, use, or sale of its generic raloxifene product. After receiving notice of the Paragraph IV Certification, Lilly brought this patent infringement suit on the Bone Loss Patents, the Low Dose Patent, and the Particle Size Patents.

Following trial, the district court ruled that Teva did not show that the Bone Loss Patents or the Low Dose Patent would have been obvious to one of skill in the art or that those patents were invalid for lack of enablement. The district court concluded that the Particle Size Patents, however, did not comply with the written description requirement of § 112. This court has jurisdiction under 28 U.S.C. § 1295(a)(1).

III

Under 35 U.S.C. § 103, a patent claim is invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." An accused infringer must prove invalidity by clear and convincing evidence. *Robotic Vision Sys., Inc. v. View Eng'g, Inc.*, 189 F.3d 1370, 1377 (Fed. Cir. 1999). "On appeal from a bench trial, the ultimate determination of whether an invention would have been obvious under 35 U.S.C. § 103 is a legal conclusion that we review *de novo*." *Id.* at 1376. An obviousness determination, however, is based on underlying factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. *Id.*; *see KSR Int'l Co. v.*

Teleflex Inc., 550 U.S. 398, 405 (2007). This court reviews those underlying factual determinations for clear error. *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 663 (Fed. Cir. 2000).

A

The district court concluded that the widely reported bioavailability concerns would have precluded a person of ordinary skill in the art from reasonably expecting to successfully treat postmenopausal osteoporosis with raloxifene. On appeal, Teva primarily relies on three prior art references to argue that the Bone Loss Patents would have been obvious notwithstanding the published concerns regarding raloxifene's bioavailability: (1) U.S. Patent No. 5,075,321 (the "Schreiber Patent"); (2) the Jordan Reference, and (3) U.S. Patent No. 4,418,068 (the "Jones Patent"). Teva also argues that Lilly's own actions demonstrate that the district court's bioavailability findings were clearly erroneous. To the contrary, Teva points to no evidence from before the time of invention that would teach, suggest, or motivate or supply any common sense reason for a person of ordinary skill in the art to reject the bioavailability concerns and routinely, simply, or easily arrive at the inventive result.

1

In 1988, Dr. Alan Schrieber from the University of Pennsylvania filed an application for a patent claiming the use of raloxifene to treat human autoimmune disorders. As a result of that application, the Schrieber Patent issued on December 24, 1991. The Schrieber Patent is a continuation-in-part of an application that Dr. Schrieber filed in March of 1987. The Schreiber Patent suggests clinical uses for raloxifene, namely, the treatment of autoimmune diseases. The Schreiber Patent relies solely on animal studies.

The year before he filed his application for the Schrieber Patent, Dr. Schrieber visited Lilly to propose developing raloxifene for the treatment of autoimmune diseases. A group of Lilly scientists who had been associated with the Phase I clinical trial convened to discuss Dr. Schrieber's proposal. On October 5, 1987, shortly before Dr. Buzdar published his Phase II Study results with respect to breast cancer, Lilly informed Dr. Schrieber that it had decided to reject his proposal, stating, "Not insignificant in our consideration of [raloxifene] are [sic] the disappointing bioavailability results observed during our Phase I clinical trial." J.A. 10022.

At trial, Dr. Schreiber, testified that Lilly disclosed the adverse bioavailability findings of the Phase I clinical trial to him during his visit. In a subsequently published article, Dr. Schreiber referenced that disclosure and acknowledged that raloxifene "appears to have a short serum half-life, which may be a result of rapid biotransformation." J.A. 6880. Nonetheless, the publication stated that antiestrogens such as raloxifene "may represent an alternative therapeutic approach" for autoimmune disorders. *Id.*

In 2003, Lilly filed reissue patent applications for two of the Bone Loss Patents in light of the Schrieber Patent. Lilly sought to clarify that the claims of its patents were directed strictly to the treatment of postmenopausal bone loss and did not also encompass the treatment of autoimmune disorders. The PTO reissued the two Bone Loss Patents in 2006.

As noted, the district court concluded that one of skill in the art would have been dissuaded from using raloxifene to treat postmenopausal osteoporosis in light of published bioavailability data. Teva argues that this conclusion was clearly erroneous because the Schrieber

Patent's disclosure that raloxifene could be used for autoimmune disorders would have suggested to one of skill in the art that raloxifene's low bioavailability in humans could be ignored when looking for a treatment for postmenopausal osteoporosis.

The record, however, does not leave this court with a "definite and firm conviction" that the district court made a mistake. *Ruiz*, 234 F.3d at 663 (internal quotation marks omitted). The record simply does not contain sufficient evidence that would allow this court to conclude that Dr. Schrieber's decision to continue to suggest raloxifene as a treatment for autoimmune disorders in the face of bioavailability concerns would influence a person of ordinary skill to pursue a treatment for postmenopausal osteoporosis.

As an initial matter, the record does not indicate that autoimmune disorders can cause osteoporosis. Although some evidence suggests that a person of ordinary skill might appreciate a connection between osteoporosis and autoimmune disorders—such as Lilly's decision to seek to reissue its patents due to the Schrieber Patent—Teva itself appears less certain. *See* Teva Post-trial Brief (Dist. Ct. Dkt # 645) at 13 (noting that autoimmune diseases only "arguably include some forms of osteoporosis").

The record shows that Teva was not able to show a credible connection between the type of osteoporosis at issue in this case—postmenopausal osteoporosis—and autoimmune diseases. Contrary to Teva's assumption, the record indicates that raloxifene combats the two diseases differently. Dr. Schrieber's article explains that raloxifene treats autoimmune disorders by disrupting the effect that estrogen has on immunoglobulin G-coated erythrocytes (IgC-coated cells). On the other hand, raloxifene treats postmenopausal osteoporosis by dupli-

cating the effect that estrogen has on the bone-remodeling process. Without a closer relationship, Teva cannot show that an ordinarily skilled artisan would have expected Dr. Schrieber's article to have relevance for the treatment of postmenopausal osteoporosis.

Instead, Teva suggests that "the bioavailability issue has nothing to do with bone loss specifically; it simply addresses whether raloxifene is biologically active in humans at all." Appellant's Reply Br. at 4; *see id.* ("If people in the art at the time reasonably believed that raloxifene might be active in humans, then raloxifene's ability to treat human bone loss would have been obvious."). And Teva separately highlights that Dr. Schrieber—and Lilly when it rejected Dr. Schrieber's proposal—cited the same bioavailability concerns that were thought to preclude raloxifene's efficacy as a treatment for breast cancer.

These arguments and proposed inferences cannot overcome the dual problems with the Schreiber Patent. In the first place, as discussed, a person of ordinary skill would not have drawn a connection between Dr. Schreiber's proposed treatment of autoimmune diseases in humans and a treatment for a very different condition. This new use of raloxifene would not have been readily apparent as a likely successful application for a compound that might fight autoimmune diseases. Beyond that, Dr. Schrieber's bare proposal to use raloxifene in humans to treat autoimmune diseases, based only on animal studies, is insufficient to require a finding that an ordinary skilled artisan would have expected that a compound with known bioavailability issues—and known clinical failures—would successfully treat any human condition.

2

The same year that Lilly rejected Dr. Schrieber's proposal, Dr. Jordan conducted a study on intact and ovariectomized 9-month-old retired breeder rats to determine the effects of tamoxifen and raloxifene (then called "keoxifene") on bone density. The research community sought additional insight to address the concern that long-term tamoxifen treatment in breast cancer patients could lead to premature bone loss. In October 1987, the results of that study were published in the Jordan Reference.

The Jordan Reference reported that both tamoxifen and raloxifene inhibited bone loss in overiectomized rats. The study went on to report that raloxifene had a minimal estrogenic response in the uterus. Dr. Jordan concluded that these results "may have important implications for the clinical [human] applications of antiestrogens." J.A. 6852. He further stated that "[i]t is possible . . . that in the future, *tamoxifen* could be considered to be used as a substitute for estrogen [for the prevention of osteoporosis in postmenopausal women]." *Id.* (emphasis added). Dr. Jordan called for clinical work on tamoxifen to extend the rat studies to humans:

> These contrasting pharmacological actions of antiestrogens suggest that patients receiving long-term adjuvant tamoxifen therapy for breast cancer should be evaluated to determine whether tamoxifen can retard the development of osteoporosis.

J.A. 6849. The Jordan Reference did not propose further development of raloxifene to treat or prevent postmenopausal osteoporosis. At the time, the FDA had only approved tamoxifen for clinical use in humans.

According to the district court, the Jordan Reference exemplified the bioavailability concerns because, after reporting successful tests with both tamoxifen and raloxifene, it "suggested that *tamoxifen* could possibly be considered for the prevention of osteoporosis in postmenopausal women, but included no specific suggestion that *raloxifene* could have such clinical use." *Eli Lilly*, 657 F. Supp. 2d at 1005. The Jordan Reference's preference for tamoxifen, coupled with "the extensive evidence adduced at trial regarding bioavailability concerns associated with raloxifene in humans and the fact that Dr. Jordan himself had published at the time regarding the rapid metabolism of compounds with free hydroxyl groups, such as raloxifene, suggesting its unsuitability for this purpose," led the district court to conclude that a person of skill "would not have had a reasonable expectation of success in using raloxifene to treat human postmenopausal osteoporosis." *Id.* at 1005-06. This court detects no error in these findings or conclusions.

On appeal, Teva relies on the results of the study described in the Jordan Reference, which showed that raloxifene, as well as tamoxifen, inhibited bone loss. Teva also relies on Dr. Jordan's conclusion that those results "may have important implications for the clinical [i.e., human] applications of antiestrogens." Teva argues that a person of ordinary skill in the art would have relied on Dr. Jordan's results and conclusion to consider raloxifene as a treatment for postmenopausal osteoporosis. To bolster its argument, Teva points to an internal Lilly communication from 1989 in which the Chairman of Lilly's Bone Biology Group acknowledged that "Craig Jordan has already published a paper relating to [raloxifene's] potential in bone related disorders." J.A. 7046. Teva also points to a statement, made by Dr. Russell Turner in 1997 during an FDA advisory meeting

for raloxifene, that Dr. Jordan's study was "very, very good at predicting the actions of pharmacological agents on the skeleton at least regarding estrogen deficiency induced bone loss." J.A. 7209-10. Teva also highlights that when the PTO rejected the Bone Loss Patents in light of the Jordan Reference, Lilly attacked the methodology underlying Dr. Jordan's experiments rather than relying on bioavailability concerns.

The district court did not clearly err in relying on the Jordan Reference to support its conclusion that the Bone Loss Patents would not have been obvious. The reference itself clearly supports the district court's conclusion that Dr. Jordan preferred tamoxifen over raloxifene. Teva's reliance on the statement by Lilly's Bone Biology Group Chairman is unavailing because he had more knowledge than one of ordinary skill in the art, namely, the results of Black's unpublished conjugate studies, which demonstrated that raloxifene was effective notwithstanding its rapid conjugation. Thus, he would have likely viewed the Jordan Reference differently. Similarly, Teva mischaracterizes Dr. Turner's 1997 statement, which stands for nothing more than the unremarkable conclusion that Dr. Jordan's rat models turned out to accurately predict what happened in humans. Dr. Turner's statement does not suggest that five years earlier one of ordinary skill in the art would have understood the Jordan Reference to have overcome the bioavailability concerns associated with raloxifene. Finally, that a patentee used one argument to successfully overcome an office action rejection in light of a piece of prior art does not, by itself, diminish the strength of other arguments that otherwise effectively reduce the significance of that prior art. This court, therefore, perceives that this record does not show that the prosecution history of the Bone Loss Patents creates a difficulty for the trial court's finding of nonobviousness.

3

Dr. Jones applied for the Jones Patent in 1981, shortly after Lilly first synthesized raloxifene. The Jones Patent, which issued in 1983, covers a class of compounds that includes raloxifene. The Jones Patent teaches that the claimed compounds have less inherent estrogenicity and that "use in human subjects is preferred." Col.34 l.26. Teva argues that the Jones Patent discloses using raloxifene for the treatment of breast cancer, which indicates that raloxifene's proclivity for conjugation was not a deterrence.

The Jones Patent does not help Teva overcome concerns about bioavailability that would have prompted one of ordinary skill in the art to look elsewhere for a postmenopausal osteoporosis treatment. The Jones Patent was filed before Lilly had published its failures in testing raloxifene as a treatment for breast cancer and before publications by Dr. Jordan, Dr. Lindstrom, and others that highlighted the bioavailability problems associated with raloxifene. The record does not contain any reason that a person of ordinary skill would have ignored those later publications.

4

Teva also argues that Lilly's pursuit of raloxifene as a treatment for both breast cancer and postmenopausal osteoporosis indicates that a person of ordinary skill would have had a reasonable expectation that raloxifene would be useful in humans despite its chemical structure. Teva argues that at the time it performed the Buzdar study, "Lilly scientists . . . had to have a basis for reasonably believing raloxifene would work in humans." Appellant's Br. at 29.

The record belies this argument for two reasons. First, the record will not allow this court to conflate Lilly scientists with those of ordinary skill in the art. *See KSR*, 550 U.S. at 420 ("The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person of ordinary skill in the art."). The district court found, and the parties do not dispute, that the level of ordinary skill in the art for the Bone Loss Patents was a bachelor's degree in a scientific discipline with basic knowledge about (1) animal studies and their usefulness in osteoporosis research and (2) how bioavailability characteristics relate to the success of a drug. The Lilly researchers had both knowledge and credentials superior to the ordinary artisan. Second, and perhaps more importantly, the record shows that the Buzdar study failed. In light of Dr. Buzdar's published report describing that failure, the district court correctly found that a person of ordinary skill would have been discouraged from using raloxifene.

Teva argues that the Buzdar study failed for reasons unrelated to the rapid conjugation of raloxifene. Teva relies on three pieces of evidence to support this conclusion. First, Dr. Buzdar did not mention bioavailability issues in his published report on his study. To the contrary, Teva argues, the Buzdar publication says that "[t]he toxicity of [raloxifene] was comparable to tamoxifen" J.A. 6867, which, Teva argues, suggests that raloxifene is active in humans. Second, Dr. Draper, the co-inventor of the Low Dose Patent, testified at trial that "[t]he raloxifene in breast cancer effort was discontinued for a variety of reasons, but it was not because the definitive study had shown the drug either to be inactive . . . and bioavailability had not been commented on in [the Buzdar] trial." J.A. 3188 at 749:22-750:12. Third, Teva points to Dr. Draper's statements to the FDA in 1991

discussing the Buzdar study, which do not mention bioavailability as a reason for its failure.

The record again leads to a different conclusion completely. The record indeed shows that the Buzdar study did not expressly attribute its failure to bioavailability concerns. The record nonetheless shows that a person of ordinary skill would have seen the bioavailability issue as a likely reason underlying the failure. For instance, Lilly's Dr. Lindstrom testified that the result of the Buzdar study "was consistent with the Phase I studies . . . in the human volunteers that there was no bioavailability." J.A. 3091 at 366:18-21. That testimony supports the district court's conclusion that the results of the Buzdar study would have suggested to a person of ordinary skill that low bioavailability would likely interfere with raloxifene's efficacy.

5

The record thus amply supports the District Court's conclusion that the ordinary artisan would not have considered it obvious to use raloxifene to treat postmenopausal osteoporosis. This court detects no clear error in the trial court's findings on the underlying facts of obviousness and detects no error in its conclusion that the record does not contain a clear and convincing showing that the Bone Loss Patents would have been obvious at the time of invention.

IV

Teva also challenges the validity of the Low Dose Patent in two respects, both of which fail.

First, Teva argues that the Low Dose Patent is invalid as obvious under § 103. But its obviousness argument hinges on the success of its attack of the Bone Loss Patents. Specifically, Teva argues that "*If* the district court

erred in concluding that bioavailability questions rendered the Bone Loss Patents unobvious, . . . it also err[ed] in finding that the Low Dose Patent was unobvious[.]" Appellant Br. at 2 (emphasis added). Because this court affirms the district court's conclusion that the Bone Loss Patents would not have been obvious, it affirms its conclusion as to the Low Dose Patent as well.

Second, Teva contends that if the Bone Loss Patents are valid, then the Low Dose Patent claims are invalid for nonstatutory double patenting. Nonstatutory double patenting was borne out of 35 U.S.C. § 101, not § 103. Specifically, § 101 precludes more than one patent on the same invention. This court's predecessor, concerned that applicants could evade that § 101 requirement by drafting claims that "vary slightly from the earlier patent," fashioned the doctrine of nonstatutory double patenting "to prevent issuance of a patent on claims that are nearly identical to claims in an earlier patent." *Geneva Pharm., Inc. v. Glaxosmithkline PLC*, 349 F.3d 1373, 1377-78 (Fed. Cir. 2003). The primary inquiry in double patenting cases is therefore whether the claims in the latter patent are more than a "slight variant" from the claims in the earlier patent. *Id.* (citing *In re Lonardo*, 119 F.3d 960, 965 (Fed. Cir. 1997)). Nonetheless, nonstatutory double patenting is sometimes referred to as "obviousness-type" double patenting, *id.* at 967, and "prevents the extension of the term of the original patent via the patenting of an obvious variation." *Georgia-Pacific Corp. v. U.S. Gypsum Co.*, 195 F.3d 1322, 1326 (Fed. Cir. 1999).

The district court found that conducting clinical trials to test for an optimal dose for a drug "is generally a routine process and that Dr. Draper's [GGGC] tests did not incorporate any concepts or ideas that would have been beyond the reach of a person having ordinary skill in the art at that time." *Eli Lilly & Co.*, 657 F. Supp. 2d at

1014 (quotation marks omitted). Teva relies on that uncontested finding to argue on appeal that the Low Dose Patent is merely an obvious variant of what Lilly already patented.

Teva acknowledges, however, that it did not raise its double patenting argument before the district court. Yet Teva contends that this court should address the issue anyway. Teva provides a number of reasons why this court should address the double patenting issue in the first instance, all of which boil down to the argument that the proper resolution of the issue is beyond any doubt. *See, e.g.*, Appellants Br. at 49 ("Allowing Lilly to extend its raloxifene monopoly for two years as a reward for routine dose testing . . . would harm the general public by depriving post-menopausal women of a cost-effective, generic alternative to Lilly's Evista® for nearly two years after Lilly's monopoly rights should have expired.").

This court concludes that the record is insufficiently clear for it to conclude that the proper resolution is beyond any doubt. For example, the district court made findings adverse to Teva, including that a person of ordinary skill in the art would not have had a reasonable likelihood of success in using such a low dose of raloxifene to treat postmenopausal osteoporosis. Further, the PTO, in allowing the Low Dose Patent, represented that the Bone Loss Patents taught away from the dosages claimed in the Low Dose Patent. Thus, the record creates at least some doubt that the dosage claimed in the Low Dose Patent is merely a slight variant from the claims of the Bone Loss Patents. Thus, this court declines to excuse Teva for failing to raise the nonstatutory double patenting issue at trial.

V

Teva also alleges that the Bone Loss Patents and Low Dose Patent do not meet the enablement requirement of 35 U.S.C. § 112, first paragraph. Section 112, first paragraph, requires a patent specification to enable a person of skill in the art to make and use the claimed invention. The enablement requirement "incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose as a matter of fact a practical utility for the invention." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005) (internal quotation marks omitted). "In the context of determining whether sufficient utility as a drug, medicant, and the like in human therapy has been alleged, it is proper for the examiner to ask for substantiating evidence unless one with ordinary skill in the art would accept the allegations as obviously correct." *Id.* (internal quotation marks omitted).

Teva argues that if the Jordan Reference did not render the Bone Loss Patents obvious due to concerns about raloxifene's bioavailability, then the disclosure in the Bone Loss Patents and the Low Dose Patent could not have been enabling because of the prevailing view that raloxifene would not work in humans. This contention fails on this record because the Bone Loss Patents disclose two sets of information not found in the prior art.

First, the Bone Loss Patents describe the results of Mr. Black's conjugate studies and explains that the conjugation of raloxifene would not be detrimental to its efficacy in treating human bone loss. Teva argues that the results of Mr. Black's conjugate studies do not provide a person of skill in the art with a reasonable expectation of success. According to Teva, scientists at Lilly knew of those results before Dr. Buzdar concluded his failed

breast cancer study, yet those same scientists argued at trial that the Buzdar study was thought to have failed due to bioavailability concerns.

The problem with Teva's argument is that it once again treats all bioavailability issues the same. As the party with the burden both in the district court and in this court, Teva must do more. The Bone Loss Patents describe Black's conjugation studies as specifically relevant to bone loss, not breast cancer. *See* col.3 ll.52-60 ("ß-Glucuronidase is fairly ubiquitous and is thought to be active in the resorption process of bone remodeling . . . . Therefore, conjugation of the benzothiophenes of formula I is not considered to be necessarily detrimental to their bioavailability as an inhibitor of bone loss."). The record simply does not show that the failed breast cancer tests make the results of Black's conjugate studies less reliable.

Second, the Bone Loss Patents describe the details of a human clinical study, which was ongoing at the time the application was filed. As the district court acknowledged, the Manual of Patent Examining Procedure (MPEP) explains that the initiation of a clinical trial has a significant impact on the PTO's utility inquiry:

> Before a drug can enter human clinical trials, the sponsor, often the applicant, must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. Such a rational would provide a basis for the sponsor's expectation that the investigation may be successful. In order to determine a protocol for phase I testing, the first phase of the clinical investigation, some credible rationale of how the drug might be effective or could be effective would be necessary. *Thus, as a general rule, if an applicant has initi-*

> *ated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.*

MPEP (2008) § 2107.03 at IV (emphasis added).

Teva does not challenge this presumption of utility, but instead argues that it simply helps its obviousness argument because neither Lilly nor the FDA relied on anything more than what was in the prior art before approving Lilly's GGGB "proof of concept" trial. Specifically, Teva contends that the record contains no evidence that Lilly or the FDA relied on Black's conjugate studies—the only other piece of evidence that Teva acknowledges was not in the prior art—to approve the human clinical trials.

For the reasons discussed in Section III.4, *supra*, this court rejects Teva's argument that the Bone Loss Patents would have been obvious based on Lilly's own actions. To the extent that Teva revisits this argument in the enablement context, it appears to contend that Lilly's actions provide circumstantial evidence that an ordinarily skilled artisan would not have found helpful the facts on which the district court relied to hold that the patents are enabled. This court rejects that argument as well, and for essentially the same reason: it conflates the expertise of Lilly scientists with the knowledge of one of ordinary skill in the art. Just because Lilly or the FDA might not have actually relied on the results of Black's conjugate studies to approve the proof of concept trial does not create clear and convincing evidence that a person of ordinary skill would not rely on the disclosure of the human trials to conclude that the claimed invention was useful. Indeed, Lilly appears to have had many advantages that a person

of ordinary skill would not have had, not the least of which was the FDA's prior approval of Lilly's IND application. Lilly's reliance on those advantages rather than its knowledge of Black's conjugate studies to proceed with human trials does not create clear and convincing evidence that a person of ordinary skill would fail to find comfort in the latter.

This court therefore affirms the district court's ruling on enablement.

VI

At trial, the parties contested whether Teva infringed the Particle Size Patents. As noted, the asserted claims of the Particle Size Patents required that the raloxifene particles have a mean particle size of "less than about 25 microns" and that at least about 90% of the particles have a size of "less than about 50 microns." Following the district court's initial claim construction order, in which it construed claim terms that are not relevant here, Teva notified Lilly that it had altered its proposed drug product by changing the particle size manufacturing specification of its bulk raloxifene.

Lilly's expert then conducted tests on samples of Teva's altered bulk raloxifene as well as samples of tablets that contained the altered bulk raloxifene. The results of those tests revealed that the particle size of Teva's altered bulk raloxifene, measured before formulation (i.e., before it was blended with standard material used to optimize solubility and tableted), fell outside of the range claimed in the Particle Size Patents. Nevertheless, Lilly contended that Teva's raloxifene product infringed the Particle Size Patents because the raloxifene particles contained within the tablet (i.e., measured after formulation) fell within the claimed size range.

According to Lilly, Teva modified its production process in order to produce larger, more fragile raloxifene particles in their bulk form to create the illusion of non-infringement. Lilly alleges, however, that upon processing, the artificially large particles fracture into smaller particles that fall within the size range claimed in the Particle Size Patents.

Thus, the district court determined that the question of infringement turned on an issue of claim construction, namely, "whether the particle size patents claim only size measurements made on bulk raloxifene *before* it is formulated or, by contrast, whether the patents also claim the particle size of raloxifene *within* a formulated tablet, as measured after extraction from the tablet." *Eli Lilly*, 657 F. Supp. 2d at 1021. The district court concluded that the limitation "in particulate form" as used in the Particle Size Patents should be construed broadly to include raloxifene particles both before and after formulation.

Even though Lilly won on claim construction, the district court ruled that the breadth of the limitation rendered the Particle Size Patents invalid for failure to comply with the written description requirement of 35 U.S.C. § 112, first paragraph. The district court noted that the Particle Size Patents did not disclose the idea of measuring the particle size of raloxifene extracted from a tablet, nor did the inventors perform any tests to determine how the granulation or tableting process could affect particle size. Moreover, the district court concluded,

> after reading the patent, a person of ordinary skill in the art would not understand how to extract raloxifene particles from a formulation in order to determine whether they fall within the claimed particle size range and, in fact, would have no indication that size measurements on anything

> other than unformulated raloxifene would bear any relevance to the invention.

Id. at 1027. On appeal, Lilly attacks this conclusion on two grounds.

First, Lilly argues that the district court should have excluded Teva's written description argument as untimely. Lilly argues that it was prejudiced because Teva failed to include its written description argument in its final invalidity contentions before trial. The district court, however, held that Lilly had sufficient notice of that argument based on the testimony at trial. *Id.* at 1024 n.54. Lilly has failed to establish that the district court's decision was an abuse of discretion.

Second, Lilly argues that the district court applied an improper test in determining whether the Particle Size Patents comply with the written description requirement of § 112, first paragraph. As this court recently confirmed, the test for written description is "whether the disclosure of the application . . . reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). The district court's decision, which was issued before this court's en banc decision in *Ariad*, appears in some places to have been premised on a misunderstanding of that test. Certain statements indicate that the district court may have been focused on whether "a person of ordinary skill in the art would . . . understand how to extract raloxifene particles from formulation in order to determine whether they fall within the claimed particle size range." *Eli Lilly*, 657 F. Supp. 2d at 1027. The test for written description, however, has never been whether the patent includes a description of the steps that may be used to prove infringement.

Nonetheless, the written description requirement is a question of fact, *Ariad*, 598 F.3d at 1351, which this court reviews for clear error, *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). The district court here concluded that "a person of skill in the art would not understand the inventors of the particle size patents to have invented anything other than 'a control strategy for . . . the particle size distribution . . . *of the bulk drug substance*,' as expressly provided in the specification." *Eli Lilly*, 657 F. Supp. 2d at 1027 (quoting the '811 patent, col.25 ll.60-61).

This court cannot characterize that finding as clearly erroneous. The patent specification only discloses measurements of bulk raloxifene. The record then features conflicting evidence about the reading a person of ordinary skill in the art would give to the passages to determine that the inventor possessed the invention of formulated raloxifene falling within the claimed size range. Lilly's own expert conceded that "[o]ne reading the [Particle Size Patent] in 1996 would not know whether the particle size was being increased or decreased [or remain the same] in the formulation." J.A. 3362 at 1434:1-10. With that concession, Lilly cannot establish that the district court made a clearly erroneous factual finding. Thus, this court affirms the district court's judgment invalidating the asserted claims of the Particle Size Patents.

VII

For the foregoing reasons, the district court's judgment is affirmed.

AFFIRMED