

**United States Court of Appeals
for the Federal Circuit**

OREXO AB, OREXO US INC.,
Plaintiffs-Appellants

v.

ACTAVIS ELIZABETH LLC,
Defendant-Appellee

2017-1333

Appeal from the United States District Court for the
District of Delaware in No. 1:14-cv-00829-SLR-SRF,
Judge Sue L. Robinson.

Decided: September 10, 2018

ERROL TAYLOR, Milbank, Tweed, Hadley & McCloy,
LLP, New York, NY, argued for plaintiffs-appellants.
Also represented by ANNA BROOK, JORDAN P. MARKHAM,
FREDRICK ZULLOW.

GEORGE C. LOMBARDI, Winston & Strawn LLP, Chica-
go, IL, argued for defendant-appellee. Also represented
by TYLER JOHANNES, MICHAEL KEENAN NUTTER, IVAN
MICHAEL POULLAOS; GEOFFREY P. EATON, Washington,
DC.

Before NEWMAN, HUGHES, and STOLL, *Circuit Judges*.

NEWMAN, *Circuit Judge*.

Orexo AB and Orexo US Inc. (collectively “Orexo”) appeal the decision of the United States District Court for the District of Delaware, holding claims 1, 3–6, and 8–10 of U.S. Patent No. 8,940,330 (“the ’330 Patent”) invalid on the ground of obviousness.¹ The ’330 Patent, entitled “Abuse-Resistant Pharmaceutical Composition for the Treatment of Opioid Dependence,” claims a product having the brand name Zubsolv®, approved by the FDA for treatment of opioid dependence.

Actavis Elizabeth LLC (“Actavis”) filed an Abbreviated New Drug Application (“ANDA”) for a generic counterpart of Zubsolv, accompanied by a Paragraph IV certification, leading to this Hatch-Waxman litigation in accordance with 21 U.S.C. § 355(j) and 35 U.S.C. § 271(e)(2)(A). Two Orexo patents were challenged by Actavis, but U.S. Patent No. 8,454,996 (“the ’996 Patent”), entitled “Pharmaceutical Composition for the Treatment of Acute Disorders,” which was held valid in the district court, is not involved in this appeal.

We reverse the judgment of invalidity of the ’330 Patent, for we conclude that obviousness was not proved by clear and convincing evidence.

BACKGROUND

A

The ’330 Patent

The ’330 Patent specification explains that opioid-based pharmaceutical products intended for the relief of

¹ *Orexo AB v. Actavis Elizabeth LLC*, 217 F. Supp. 3d 756 (D. Del. 2016) (“Dist. Ct. Op.”).

pain have become a source of addiction, dependency, and abuse. Treatment for opioid addiction includes a protocol called “substitution therapy,” where partial opioid agonists² that have higher binding affinities at opioid receptors but produce lowered dependency than full agonists like heroin, can lead to cessation of addiction by relieving the opioid craving. The prior art shows use for this purpose of the partial agonist buprenorphine, administered in sublingual tablets and in oral films.

The '330 Patent explains that while buprenorphine has less narcotic effect than a full opioid, addicts were known to dissolve the buprenorphine from the substitution therapy tablet, and inject the dissolved buprenorphine intravenously to achieve an enhanced opioid effect. To counteract this abuse, it was known to combine buprenorphine with the opioid antagonist³ naloxone in substitution therapy.

It was known that formulations containing buprenorphine to naloxone at a ratio of 4:1 provide the therapeuti-

² An agonist is a chemical compound that binds to a receptor and activates the receptor to produce a biological response. Partial opioid agonists have opioid agonist effects that “are less than the maximal effects of other, ‘full’ opioid agonists, such as morphine, and are limited by a ‘ceiling’ effect. The drug thus produces a lower degree of physical dependence than other opioid agonists, such as heroin, morphine, or methadone, and is therefore particularly useful in substitution therapy.” '330 Patent, col. 9, ll. 19–29.

³ “Opioid antagonists are used to reverse the pharmacological effects of opioids. Selective opioid antagonists, such as naloxone, may therefore be used to treat drug overdose or to diagnose suspected opioid addiction.” '330 Patent, col. 1, l. 65–col. 2, l. 1.

cally optimal balance for sublingual treatment. Naloxone has poor transmucosal bioavailability so that if the mixture is taken in tablet form as directed, the buprenorphine will act as intended to treat opioid dependence with little interference from the naloxone. However, if the tablet is dissolved and injected, the naloxone will antagonize the effects of the buprenorphine, resulting in withdrawal symptoms and thus deterring abuse of the formulation. The 4:1 ratio provides for appropriate pharmacological amounts of naloxone to deter abuse when injected, but does not interfere with buprenorphine when taken in tablet form. '330 Patent, col. 2, ll. 13–22; *id.*, col. 9, ll. 37–50. However, naloxone's "functional blockade of buprenorphine's action is also only partial and is short-lived in its nature," *id.*, col. 2, ll. 23–25, and there was a continuing need for improvement in substitution therapy formulations.

The '330 Patent is for a sublingual tablet formulation that is less subject to abuse. The formulation enhances the agonist effectiveness of buprenorphine, permitting a reduced amount of buprenorphine in the tablet and thus reducing the amount available on dissolving and injecting the product. In this formulation, microparticles of buprenorphine are adhered to the surface of carrier particles of citric acid, and the formulation also contains naloxone in the 4:1 ratio. The '330 Patent explains that the buprenorphine in the microparticles acts with little interference from the naloxone, but if the tablet is dissolved in water for injection into the bloodstream, the naloxone will also be dissolved and will antagonize buprenorphine's effects.

All parties agree that the product in the '330 Patent provides improved treatment of opioid dependence, as compared with the prior art. The '330 Patent specification includes data from clinical trials comparing the related sublingual product Suboxone®. Patent Example 2 shows a 66% improvement in bioavailability of buprenor-

phine, and Patent Examples 7 and 8 show bioequivalent results for a sublingual tablet containing 29% less buprenorphine than in Suboxone tablets.

Actavis does not dispute the improvement, or its value in treatment of addiction. Rather, Actavis argues that this formulation is obvious based on a combination of references, and that improved function and use are irrelevant if the product is obvious. This theory is flawed, for an unobvious improvement in properties or use is highly relevant to patentability of a new product.

Claims 1 and 6 were deemed representative:

1. A tablet composition suitable for sublingual administration comprising:

microparticles of a pharmacologically-effective amount of buprenorphine, or a pharmaceutically-acceptable salt thereof, presented upon the surface of carrier particles,

wherein microparticles of buprenorphine or a pharmaceutically acceptable salt thereof are in contact with particles comprising citric acid,

wherein the buprenorphine or pharmaceutically acceptable salt thereof and the citric acid are not in the same particle;

a pharmacologically-effective amount of naloxone, or a pharmaceutically-acceptable salt thereof;

and a disintegrant selected from the group consisting of croscarmellose sodium, sodium starch glycolate, crosslinked polyvinylpyrrolidone and mixtures thereof.

6. The composition as claimed in claim 1, wherein the particles of citric acid are presented and act as carrier particles.

The district court found that all the ingredients in the claims were generally known, and held that although the

specific formulation was not shown or suggested in any reference, the new combination would have been obvious to a person of ordinary skill. However, the prior art does not show or suggest the claimed combination, and does not show or suggest that this combination would achieve enhanced therapeutic effect while being less subject to abuse.

B

The Prior Art

1. Suboxone® and Subutex®

The buprenorphine and naloxone combination in the 4:1 ratio has been used for substitution therapy at least since 2002. The prior art Suboxone sublingual tablets are a homogeneous combination made by mixing the ingredients of buprenorphine, naloxone, citric acid, sodium citrate, and sublingual excipients. Dist. Ct. Op. at 769 n.17 (citing Physicians' Desk Reference, 58th ed. 2004). Subutex® is the same formulation as Suboxone, but without the naloxone. WO2008/152347 ("Cairns"), cited by the examiner during prosecution, describes the tablet formulation as a wet granulation process where buprenorphine, citric acid, and sodium citrate are dissolved together and then mixed with excipients. *See* Orexo Br. at 14 & n.2 ("Cairns provides the manufacturing process for Subutex® tablets, a product with essentially the same formulation as Suboxone® tablets, but without naloxone.").

Orexo attributes the improvements achieved by the Zubsolv product to the microparticles of buprenorphine adhered to the surface of citric acid carrier particles. Orexo states that the 66% higher bioavailability is not suggested or reasonably predictable from the prior art. We have been directed to no reference to show or suggest otherwise. Orexo stresses the Examiner's statement in

allowing the '330 Patent, that the improvement is due to the ingredients and the structure:

[T]he mere presence of citric acid in the sublingual tablets formulated according to the prior art (e.g. Cairns) is insufficient to achieve the superior pharmacokinetic profile exhibited by the instant invention. Applicant has persuasively demonstrated that the instant tablet exhibits unexpectedly superior sublingual buprenorphine bioavailability due to the ingredients as well as the structural characteristics recited in the instant claims.

Notice of Allowability at 5 (emphasis original), Application No. 14/127,470 (issued as the '330 Patent) (Nov. 4, 2014); *see also* Orexo Br. at 29 (quoting Notice of Allowability at 5).

2. Suboxone® Film

U.S. Patent No. 8,475,832 (“the '832 Patent”) describes an orally dissolvable film that cannot be easily removed once placed inside the mouth. The film contains the buprenorphine/naloxone combination in the 4:1 ratio, and is described as bioequivalent to Suboxone sublingual tablets. The '832 Patent teaches that optimum bioavailability of buprenorphine and naloxone from the film is achieved at pH 3–3.5, with citric acid included in the film to lower the pH. The district court relied on this presence of citric acid to render obvious the citric acid carrier particles in the Zubsolv formulation.

However, the '832 Patent does not reduce the amount of buprenorphine needed to provide an effective substitution therapy dose. And the use of film in substitution therapy presents recognized problems, as stated in the '330 Patent, for the film does not dissolve quickly and a maximum of only two films may be administered simultaneously, producing inadequate dosage as well as prob-

lems of compliance and administration. '330 Patent, col. 2, ll. 43–50.

3. The Orexo Application

Orexo's U.S. Patent Application No. 2010/0129443 ("the '443 Application"), titled "Non-Abusable Pharmaceutical Composition Comprising Opioids," was filed on December 3, 2007, published on May 27, 2010, and issued as U.S. Patent No. 8,470,361 on June 25, 2013. It is prior art as of its filing date.

The '443 Application describes sublingual tablets where smaller particles of opioid agonists are carried on larger particles that include an opioid antagonist. The '443 Application lists many opioid agonists including buprenorphine, and many antagonists including naloxone. However, citric acid is not mentioned or suggested as the carrier particle.

4. European Patent Application No. EP 0324725

European Patent Application No. EP 0324725 ("the EP '725 Application") lists a large number of water-soluble carrier particles, to which smaller particles of a pharmaceutically active substance may be adhered. The EP '725 Application does not mention sublingual tablets, does not mention opioids as the active substance, and does not mention citric acid as a carrier.

C

The District Court Decision

The district court held the asserted '330 Patent claims invalid, ruling that a skilled artisan would obviously have selected these components from the prior art and reformulated them as in the '330 Patent. The district court stated that the '443 Application taught that "a person of ordinary skill in the art would have been motivated to reformulate Suboxone tablets as an interactive mixture to

improve bioavailability,” Dist. Ct. Op. at 773; that the ’832 Patent for an oral film “expressly taught a person of ordinary skill that the addition of citric acid facilitated an increased level of absorption of buprenorphine despite a lower pH,” *id.* at 772–73; and that the EP ’725 Application “described how to make such a mixture using dry mixing,” *id.* at 773.

In response to Orexo’s argument that no reference showed the new formulation in the ’330 Patent, stressing the unexpectedly enhanced bioavailability and its benefits, the district court reasoned that a skilled artisan “would not have excluded citric acid” as a carrier and “would have known how to form an interactive mixture using citric acid.” *Id.* The district court found that the ’832 Patent taught “the use of citric acid with an interactive mixture would also improve [buprenorphine] bioavailability,” *id.*, and concluded that it would have been obvious to use citric acid as carrier particles.

Orexo argued that a person of ordinary skill would have been dissuaded from using citric acid in this interactive mixture because Examples 6–8 of the ’832 Patent taught that as the pH is lowered through use of citric acid, the buprenorphine bioavailability increase is accompanied by a compromised naloxone availability such that the 4:1 ratio is lost. The district court described this argument as irrelevant because the 4:1 ratio is an “unclaimed feature” of the ’330 Patent, the court stating “any problems with maintaining the ratio forecast by the ’832 patent goes to the reasonable expectation of success requirement, not to motivation to combine; i.e., this argument is irrelevant in this context.” *Id.* at 773 n.23.

Orexo stresses that no reference teaches or suggests using citric acid particles as a carrier for micronized buprenorphine, and that the benefits of this formulation were unexpected. Rejecting this argument, the district court cited the testimony of Actavis’ expert that citric acid

“fits the definition of a carrier particle” and “therefore it would act as a carrier particle, because it is in the Suboxone tablet.” Dist. Ct. Op. at 771 (quoting testimony of Dr. Dyar). However, no reference suggests citric acid carrier particles.

The district court also discussed the objective indicia of unobviousness, responding to Orexo’s arguments of unexpectedly increased bioavailability, long-felt need for improved treatment of opioid dependence, copying by Actavis, and hindsight. The court stated that “the unexpected result of increased bioavailability provides some support for nonobviousness,” Dist. Ct. Op. at 776, but found that interactive mixtures were generally known to improve bioavailability and that the increase here was a “‘difference in degree,’ not a difference in ‘kind.’” *Id.* at 774. The district court stated that Orexo’s arguments of teaching away, long-felt need, and copying were “not persuasive evidence.” *Id.* at 773 n.27, 776. The court concluded that “Actavis has met its burden to prove, by clear and convincing evidence, that claims 1, 3–6, and 8–10 are obvious.” *Id.* at 776.

DISCUSSION

Standard of Review

Following a bench trial, we review the district court’s factual findings for clear error. Conclusions of law receive de novo determination. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012) (“While we afford deference to a district court’s factual findings, however, we retain plenary review to determine whether, as a legal matter, the evidence satisfies the clear-and-convincing standard of proof.”).

Obviousness is a question of law, based on the facts of (1) the scope and content of the prior art, (2) the level of ordinary skill in the field, (3) the differences between the

claimed invention and the prior art, and (4) any objective indicia of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). To invalidate a patent on the ground of obviousness, the challenger has the burden of proving that the subject matter as a whole would have been obvious to a person of ordinary skill in the field of the invention. 35 U.S.C. § 103(a). A party seeking to invalidate a patent on obviousness grounds must demonstrate by clear and convincing evidence that a person of ordinary skill would have selected and combined and modified the subject matter of the references in the manner of the claimed invention, with a reasonable expectation of success. *E.g.*, *InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1347 (Fed. Cir. 2014).

Judicial hindsight must be avoided. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) (“A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning.”). It is inappropriate to use the template provided by the inventor, to render the inventor’s contribution obvious. *See Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985) (“The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time. The invention must be evaluated not through the eyes of the inventor, who may have been of exceptional skill, but as by one of ‘ordinary skill.’”).

Obviousness

In holding the ’330 Patent’s claims invalid for obviousness, the district court cited the ’832 Patent to show that “the use of citric acid with an interactive mixture would also improve bioavailability.” Dist. Ct. Op. at 773. The ’832 Patent is for a film that includes citric acid to lower the pH of the film. Example 7 of the ’832 Patent shows that a lowering of pH to 5.5 increases buprenorphine bioavailability, but also compromises the desired

4:1 ratio of buprenorphine to naloxone. '832 Patent, col. 21, ll. 17–26. Example 8 of the '832 Patent shows that a further decrease in pH to 3.5 using citric acid maintained the 4:1 ratio but did not increase buprenorphine bioavailability. *Id.*, col. 23, ll. 1–11. The '832 Patent is directed to replacing sublingual tablets with oral film, for possible advantage in administration. There is no suggestion of the different structure of the Zubsolv tablet and its advantage in deterring abuse. The Zubsolv structure is achieved solely upon the hindsight knowledge of the structure and benefits described in the '330 Patent.

The district court cited the Orexo '443 Application for its disclosure of particles of buprenorphine adhered to carrier particles. However, the '443 Application does not mention citric acid in its extensive list of carriers, and does not suggest that citric acid carrier particles may provide benefits compared with the prior art. These benefits were not predicted or suggested in any reference.

The district court cited the EP '725 Application for its general description of interactive mixtures as pharmaceutical formulations. This reference does not mention opioids, does not mention sublingual tablets, does not mention citric acid in its extensive list of carrier particles, and does not suggest the formulation in the '330 Patent or its unexpected benefits.

The product herein is admittedly new. The district court acknowledged the undisputed testimony of Orexo's co-founder, Mr. Thomas Lundqvist, and Orexo's global chief medical officer, Dr. Michael Sumner. The district court wrote:

Lundqvist testified that the first clinical results showed that Zubsolv had a 66% improvement in bioavailability. (D.I. 202 at 58:9–15; D.I. 211 at 36) According to a bioequivalence study, Zubsolv increases the bioavailability of buprenorphine, such that patients require a 29% lower dose using

Zubsolv as compared to Suboxone. (JTX 153; D.I. 202 at 63:11–17 [Testimony of Mr. Lundqvist]; D.I. 205 at 770:22–771:3 [Testimony of Dr. Sumner]; D.I. 196 at 12) Orexo’s pharmaceutical development report stated that “[d]ue to the anticipated improved dissolution of buprenorphine the selected dose of 6 mg buprenorphine is expected to give approximately the same systemic buprenorphine exposure in humans as a Suboxone® tablet with 8 mg buprenorphine.” (JTX 123 at 4; JTX 128 at 32; D.I. 203 at 352:11–22)

Dist. Ct. Op. at 760 (citations in original, bracketed information added).

The district court nonetheless concluded that the Zubsolv formulation was obvious. The court cited Actavis’s expert Dr. Dyar as showing that “citric acid is pharmaceutically acceptable, water soluble, and of the right size, so therefore it would act as a carrier particle, because it is in the Suboxone tablet.” Dist. Ct. Op. at 771 (quoting J.A. 6685, June 8, 2016 Trial Tr. at 433:12–15, ECF No. 204 (Testimony of Dr. Dyar)). Orexo points out that Dr. Dyar cited no reference, and describes this reasoning as “hindsight bias,” for it recreates the prior art from the teaching in the ’330 Patent. Orexo points out that citric acid is nowhere used or listed or suggested as a carrier particle, and it is not so used in the Suboxone tablet.

At the oral argument of this appeal, Actavis conceded that no reference teaches using citric acid as a carrier particle, or that citric acid should be used as a carrier particle:

Actavis Counsel: Your Honor, I will confirm what counsel said before and what we’ve said in our briefs. There is no piece of prior art that was presented that says citric acid is a carrier particle or should be used as a carrier particle.

Oral. Arg. at 21:19–21:36, <http://oralarguments.cafc.uscourts.gov/default.aspx?fl=2017-1333.mp3>.

Court: If both of those things are really well known, then one would think that if citric acid were routinely or it was obvious to use it as a carrier particle, you could have found some reference that used it. . . . Your expert didn't even testify that he was familiar with this industry and that citric acid was routinely used as a carrier particle in interactive mixtures. He just said it was the right size and it could be used.

Actavis Counsel: Well. You're right Your Honor in terms of your characterization of the record. There was not citric acid used as a carrier particle that was in the record.

Id. at 26:12–26:50.

Dr. Dyar did not testify that a skilled artisan would obviously select citric acid as a carrier for buprenorphine; he stated that if it were selected, the artisan would expect it to work. The district court's finding that "a person of ordinary skill in the art would not have excluded citric acid," Dist. Ct. Op. at 773, is not a teaching or suggestion to use citric acid. *See In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984) ("The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification."). The record does not contain clear and convincing evidence of a teaching or suggestion to use citric acid particles as a carrier for this opioid product in substitution therapy, or that the actual beneficial results would be obtained.

Orexo also argued that the specific formulation in the '330 Patent preserves the 4:1 ratio of buprenorphine to naloxone during use of the product, unlike the prior art products. The district court stated that this benefit is

irrelevant because it “goes to the reasonable expectation of success requirement, not to motivation to combine.” Dist. Ct. Op. at 773 n.23. The district court found that “there is nothing in the prior art which would have discouraged a person of ordinary skill from following the path set out in the various references.” *Id.* at 773. However, no reference or combination of references proposes the path of the ’330 Patent.

The question is not whether the various references separately taught components of the ’330 Patent formulation, but whether the prior art suggested the selection and combination achieved by the ’330 inventors. Although the reference ’832 Patent showed that buprenorphine bioavailability in the film formulation is affected by pH, this is not a suggestion of the sublingual tablet interactive formulation in the ’330 Patent or a teaching of its benefit in deterring abuse.

The references show that the field of opioid biopharmacology has received extensive scientific study. The ’330 Patent provides a significant improvement. Despite the extensive study, this improvement over the then-available treatments for addiction is not proposed or suggested in the references. There is no suggestion that the specified elements should be selected and combined, and that the designated sublingual formulation would be less subject to abuse than prior formulations for substitution therapy. Although the need to reduce this abuse was known, recognizing a need does not render the solution obvious.

Here, the objective indicia guide the analysis of obviousness. *See, e.g., Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357–58 (Fed. Cir. 2013) (“[T]his court has emphasized that consideration of the objective indicia is *part of* the whole obviousness analysis, not just an afterthought.”). The district court stated, “the unexpected result of increased bioavailability provides some support for nonobviousness,” although the court also stated that

Orexo's long-felt need and copying arguments "are not persuasive evidence of such." Dist. Ct. Op. at 776. The court reasoned that the prior art sought to improve bioavailability, that interactive mixtures were known to improve bioavailability, and therefore that the improved result of the '330 Patent's formulation was inadequate to serve as probative evidence of unexpected results. *See id.* at 774.

Orexo states that the district court erred, for the prior art does not teach or suggest the '330 Patent's formulation as a way to improve bioavailability. Actavis responds that the prior art is silent "about whether it would be expected or difficult 'to increase buprenorphine absorption without simultaneously increasing naloxone absorption to unacceptable levels.'" Actavis Br. at 62. Orexo counters that silence is not a teaching or suggestion; and that the beneficial results could not be predicted, and were indeed unexpected.⁴

The district court erred in discounting the enhanced bioavailability in the '330 Patent's formulation as "a 'difference in degree,' not a difference in 'kind,'" Dist. Ct. Op. at 774, for the clinical studies reported in the '330 Patent show 66% improved bioavailability. Particularly

⁴ Actavis states that Orexo did not argue to the district court that maintenance of the 4:1 ratio was an unexpected result, and thus that this argument was waived. Actavis Br. at 61–62. Contrary to Actavis' statement, the record shows Orexo's arguments that "the '330 invention's novel structure and arrangement unexpectedly improves bioavailability over the closest prior art (Cairns / Suboxone), while maintaining the 4:1 buprenorphine to naloxone ratio." Orexo's Resp. Dist. Ct. Br. at 53, ECF No. 200; *id.* at 54 ("The 4:1 ratio is unexpected and relevant.").

in the context of this invention, this is more than a trivial “degree.”

The district court also discounted Orexo’s evidence that Zubsolv is less susceptible to abuse than Suboxone, stating that “Orexo’s ‘real world evidence’ set forth above is not compelling or unrebutted,” and that “[t]he only objective evidence for this factor is that which was presented to, and rejected by, the FDA.” *Id.* at 776. Orexo stated that evidence of Zubsolv’s effectiveness in reducing abuse accumulated after FDA approval, and was presented to the district court. Although the weight of this evidence was disputed, the FDA deemed the product worthy of approval for the efficacy that was established in the clinical trials. It was established that this novel formulation enables reduced dosage and enhanced efficacy in substitution therapy products, deterring abuse.

On the entirety of the record, Actavis did not establish obviousness by clear and convincing evidence. The judgment of invalidity is reversed. We remand for appropriate further proceedings.

REVERSED AND REMANDED