United States Court of Appeals for the Federal Circuit

06-1019

ALZA CORPORATION,

Plaintiff-Appellant,

v.

MYLAN LABORATORIES, INC.
and MYLAN PHARMACEUTICALS, INC.,

Defendants-Appellees.

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Appealed from: United States District Court for the Northern District of West Virginia

Chief Judge Irene M. Keeley

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DECIDED: September 6, 2006

Before GAJARSA, Circuit Judge, CLEVENGER, Senior Circuit Judge, and PROST, Circuit Judge.

GAJARSA, Circuit Judge.

Alza Corp. ("Alza") appeals from the district court's judgment, after a bench trial, of noninfringement and invalidity of claims 1-3, 11, 13 and 14 of U.S. Patent No. 6,124,355[1] ("the '355 patent") in favor of Mylan Laboratories, Inc. and Mylan Pharmaceuticals, Inc. (collectively, "Mylan"). Alza Corp. v. Mylan Labs., Inc., 388 F. Supp. 2d 717 (N.D.W. Va. 2005) ("Alza II"). The infringement arose from Mylan's filing of two Abbreviated New Drug Applications ("ANDAs") for a generic version of the once-a-day extended release formulation of the anti-incontinence drug oxybutynin, id. at 720, which Alza has been marketing as Ditropan XL®. Id. at 738. This court has jurisdiction

[1] The '355 patent issued to Guittard et al. and was assigned to Alza.

pursuant to 28 U.S.C. § 1295(a)(1). For the reasons stated below, we affirm the district court's judgment of noninfringement and invalidity.

I. BACKGROUND

This litigation arose from Mylan's and Impax's filings of ANDAs for once-daily, controlled-release oxybutynin formulations. Oxybutynin is a drug used to treat urinary incontinence. Once-a-day dosing provides the usual benefits of convenience, steady-dosing, and in addition, possibly reduced absorption of a metabolite that leads to side-effects. Claim 2 of the '355 patent is representative.

> 2. A sustained-release oxybutynin formulation for oral administration to a patient in need of treatment for urge incontinence comprising a therapeutic dose of an oxybutynin selected from the group consisting of oxybutynin and its pharmaceutically acceptable salt that delivers from 0 to 1 mg in 0 to 4 hours, from 1 mg to 2.5 mg in 0 to 8 hours, from 2.75 to 4.25 mg in 0 to 14 hours, and 3.75 mg to 5 mg in 0 to 24 hours for treating urge incontinence in the patient.

col. 17, ll. 31-38 (emphasis added).

The district court construed the '355 patent claims in its Markman Order, reported at Alza Corp. v. Mylan Labs., Inc., 349 F. Supp. 2d 1002 (N.D.W. Va. 2004) ("Alza I"). The court construed the word "deliver" to refer to the rate of in vivo release in the gastrointestinal ("GI") tract. See id. at 1019.

Alza did not present direct evidence that Mylan's ANDA formulation released drug in the GI tract at the rates claimed by the '355 patent. However, it did offer two other types of evidence: 1) the rate at which the generic product released oxybutynin in an in vitro dissolution apparatus, and 2) the rate at which the ANDA product resulted in the accumulation of oxybutynin in the bloodstream.

The district court found that Alza had failed to meet its burden of proof on infringement. The district court also found the asserted claims of the '355 patent to be invalid as both anticipated and obvious in light of the prior art. For the reasons stated below, we affirm the invalidity holding on obviousness grounds, and consequently, we do not need to reach Alza's arguments regarding anticipation. We also affirm the holding of noninfringement.

II. DISCUSSION

A. Standard of review

Infringement is a question of fact that, after a bench trial, we review for clear error. See, e.g., Ferguson Beauregard/Logic Controls, Div. of Dover Res., Inc. v. Mega Sys., LLC, 350 F.3d 1327, 1338 (Fed. Cir. 2003). Under the clear error standard, a reversal is permitted only when this court is left with a definite and firm conviction that the district court was in error. Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1164 (Fed. Cir. 2006).

As for obviousness, a claimed invention is unpatentable if the differences between it 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." 35 U.S.C. § 103(a) (2000); In re Kahn, 441 F.3d 977, 985 (Fed. Cir. 2006) (citing Graham v. John Deere Co., 383 U.S. 1, 13-14, (1966)). Obviousness is a question of law, reviewed de novo, based upon underlying factual questions which are reviewed for clear error following a bench trial. Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1275 (Fed. Cir. 2004). These "underlying factual inquiries includ[e]: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the

claimed invention and the prior art; and (4) objective evidence of nonobviousness." In re Dembiczak, 175 F.3d 994, 998 (Fed. Cir. 1999). Similarly, "[t]he presence or absence of a motivation to combine references in an obviousness determination is a pure question of fact," In re Gartside, 203 F.3d 1305, 1316 (Fed. Cir. 2000); accord Winner Int'l Royalty Corp. v. Wang, 202 F.3d 1340, 1348 (Fed. Cir. 2000), as is the presence or absence of a "reasonable expectation of success" from making such a combination, Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006). Because "a patent retains its statutory presumption of validity, see 35 U.S.C. § 282, . . . the movant retains the burden to show the invalidity of the claims by clear and convincing evidence as to underlying facts." McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1349 (Fed. Cir. 2001) (internal quotations omitted).

In Graham, the Court held that that the obviousness analysis begins with several basic factual inquiries: "[(1)] the scope and content of the prior art are to be determined; [(2)] differences between the prior art and the claims at issue are to be ascertained; and [(3)] the level of ordinary skill in the pertinent art resolved." 383 U.S. at 17. After ascertaining these facts, the Court held that the obviousness vel non of the invention is then determined "against th[e] background" of the Graham factors. Id. at 17-18 (emphasis added). Clearly, the Court recognized the importance of guarding against hindsight, as is evident in its discussion of the role of secondary considerations as "serv[ing] to guard against slipping into use of hindsight and to resist the temptation to read into the prior art the teachings of the invention in issue." Id. at 36.

The Court of Appeals for the Federal Circuit's and its predecessor's "motivation to combine" requirement likewise prevents statutorily proscribed hindsight reasoning

when determining the obviousness of an invention. Kahn, 441 F.3d at 986 ("[T]he 'motivation-suggesting-teaching' requirement protects against the entry of hindsight into the obviousness analysis."); In re Fridolph, 30 CCPA 939, 942 (1943) ("[I]n considering more than one reference, the question always is: does such art suggest doing the thing the [inventor] did."). According to the "motivation-suggesting-teaching" test, a court must ask "whether a person of ordinary skill in the art, possessed with the understandings and knowledge reflected in the prior art, and motivated by the general problem facing the inventor, would have been led to make the combination recited in the claims." Kahn, 441 F.3d at 988 (citing Cross Med. Prods., Inc., v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1321-24 (Fed. Cir. 2005)).

This requirement has been developed consistent with the Supreme Court's obviousness jurisprudence as expressed in Graham and the text of the obviousness statute that directs us to conduct the obviousness inquiry "at the time the invention was made" 35 U.S.C. § 103. As we explained in Kahn,

> The motivation-suggestion-teaching test picks up where the analogous art test leaves off and informs the Graham analysis. To reach a non-hindsight driven conclusion as to whether a person having ordinary skill in the art at the time of the invention would have viewed the subject matter as a whole to have been obvious in view of multiple references, the Board must provide some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct. The requirement of such an explanation is consistent with governing obviousness law . . . .

441 F.3d at 987. We further explained that the "motivation to combine" requirement "[e]ntails consideration of both the 'scope and content of the prior art' and 'level of ordinary skill in the pertinent art' aspects of the Graham test." Id. at 986.

At its core, our anti-hindsight jurisprudence is a test that rests on the unremarkable premise that legal determinations of obviousness, as with such

determinations generally, should be based on evidence rather than on mere speculation or conjecture. Our court's analysis in Kahn bears repeating:

> A suggestion, teaching, or motivation to combine the relevant prior art teachings does not have to be found explicitly in the prior art, as "the teaching, motivation, or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references. . . . The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." However, rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. This requirement is as much rooted in the Administrative Procedure Act [for our review of Board determinations], which ensures due process and non-arbitrary decisionmaking, as it is in § 103.

441 F.3d at 987-88 (quoting In re Kotzab, 217 F.3d 1365, 1370 (Fed. Cir. 2000)) (citations omitted) (emphases added)). There is flexibility in our obviousness jurisprudence because a motivation may be found implicitly in the prior art. We do not have a rigid test that requires an actual teaching to combine before concluding that one of ordinary skill in the art would know to combine references. This approach, moreover, does not exist merely in theory but in practice, as well. Our recent decisions in Kahn and in Cross Medical Products amply illustrate the current state of this court's views. See Kahn, 441 F.3d at 988 (affirming the PTO's obviousness finding, explaining that a motivation to combine may be found in implicit factors, such as the "knowledge of one of ordinary skill in the art, and [what] the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art"); Cross Med. Prods., 424 F.3d at 1322 (reversing a district court ruling of nonobviousness and explaining that "the motivation to combine need not be found in prior art references, but equally can be

found in the knowledge generally available to one of ordinary skill in the art" such as knowledge of a problem to be solved).

In conclusion, our approach has permitted us to continue to address an issue of law not readily amenable to bright-line rules, as we recall and are guided by the wisdom of the Supreme Court in striving for a "practical test of patentability." Graham, 383 U.S. at 17.

B. Description of the technology

The patent at issue is directed generally to an extended release form of oxybutynin. Because the subject matter of the patent falls roughly under the rubric of pharmacology, we give a brief orientation to the field, based upon the record. In general, when a drug is swallowed, it is (1) dissolved in the gastrointestinal ("GI") tract; (2) absorbed from the GI tract into the bloodstream; (3) distributed from the blood into body tissues; and (4) metabolized and eliminated from the bloodstream. The GI tract includes the stomach, small intestine and the colon, and orally administered drugs pass through these portions of the GI tract in turn. Drugs may be administered in different dosage forms,[2] which may include not only the drug itself but also ingredients intended to modulate the rate of release of the drug from the dosage form.

Dosage forms may be described as immediate-release, e.g., such as where the drug is quickly released in the stomach, or as sustained/extended-release, where the drug is slowly released as the formulation traverses the GI tract. The rate of absorption of a drug from the GI tract into the bloodstream may change as it passes through the GI

[2] Here we are discussing oral dosage forms, specifically.

tract. The rate of absorption for a dissolved drug in a given portion of the GI tract also varies from drug to drug.

After roughly 8-12 hours a typical dosage form will reach the colon. If, hypothetically, a particular drug is simply not absorbed from the colon into the bloodstream, then it may make little sense to develop an extended-release dosage form that is capable of "withholding" the release of some fraction of that drug until it reaches the colon. In other words, under these hypothetical conditions, there may be little motivation to design an oral dosage form capable of releasing drug more slowly than over an approximately 8-12 hour time course, because such drug would be released in the colon, where it is (hypothetically) not absorbed.

The '355 patent claims an extended release oxybutynin formulation. Alza argues that one of ordinary skill in the art would not have believed that oxybutynin could be absorbed in the colon. Absent such absorption, Alza contends that one of ordinary skill in the art lacked the motivation to make the claimed extended release formulation, and that the district court therefore erred in holding that the asserted claims are invalid as obvious over the prior art. For the reasons set forth below, Alza's arguments fail.

C. Invalidity

The district court based its invalidity holding both on anticipation and obviousness grounds. Because we affirm its holding based on obviousness, we do not need to address the parties' anticipation arguments.

In finding the asserted claims of the '355 patent to be obvious, the district court considered, inter alia, the following prior art: U.S Patent Nos. 5,399,359 ("the Baichwal patent"); 5,082,688 ("the Wong patent"); and 5,330,766 ("the Morella patent").

The Morella patent discloses a "sustained-release pharmaceutical composition including an active ingredient of high solubility in water . . . ." According to the specification, highly soluble drugs had posed special challenges for the development of sustained release forms, which the inventors had set out to solve. "Sustained-release" is defined as release of the active ingredient at a rate that maintains therapeutic, non-toxic blood levels "over an extended period of time e.g. 10 to 24 hours or greater." Highly water soluble drugs were considered to be those having an aqueous solubility of at least roughly 1 part in 30. The commercially available hydrochloride salt of oxybutynin is freely soluble at neutral pH. The patent uses morphine as an example of an active ingredient that can be used in its compositions. Figure 5 demonstrates that one such composition is capable of dispensing morphine at what appears to be an approximately steady rate over the course of 24 hours. Claim 2 of the patent claims "genitourinary smooth muscle relaxants" as one of several types of active ingredients to use in the dosage form identified in claim 1. The specification also identifies oxybutynin as a highly water soluble genitourinary smooth muscle relaxant. Morella also teaches that "the dissolution rate of the soluble drug at various pH's can be modified at will."

The Baichwal patent teaches a 24 hour extended release oxybutynin formulation. These formulations use an enteric-coated polymer matrix similar to Mylan's accused product. It also teaches methods of modifying the dosage forms to slow the release rates. During prosecution of the '355 patent, the inventor overcame an anticipation rejection by arguing that his invention had a release rate slower than those of the

dissolution data presented in Baichwal.[3] The examiner agreed and withdrew his rejection.

The Wong patent teaches a bilayer osmotic pump dosage form ("the OROS system") used in the preferred embodiment of the '355 patent. Wong teaches that this system can be used to deliver any drug over a 24 hour period, and Figure 11 of the patent discloses release rates falling within the claimed release rates of the '355 patent. The Wong patent does not specifically teach using oxybutynin with the claimed release technology, but it does teach using several categories of drugs of which oxybutynin is a member, such as anti-cholinergics, analgesis, muscle relaxants and urinary tract drugs.

In analyzing the obviousness issue, the district court first identified the level of ordinary skill in the art, finding the person of ordinary skill to have either an advanced degree in pharmacy, biology, chemistry or chemical engineering and at least two years of experience with controlled-release technology; or a bachelor's degree in one (or more) of those fields plus five years of experience with such technology. Second, the court examined whether there was a motivation "in the prior art or elsewhere that would have led one of the ordinary skill in the art to combine references," Alza II, 388 F. Supp. 2d at 737 (citing Ruiz, 234 F.3d at 664 (internal quotations omitted)), and with a "reasonable expectation of success," id. (citing In re O'Farrell, 853 F.2d 894, 904 (Fed. Cir. 1988)). Third, the district court examined secondary considerations of nonobviousness. After making these factual determinations, it concluded that Mylan had established a strong prima facie case of obviousness, which Alza had failed to rebut through secondary considerations. The court concluded that Mylan had

[3] Tables 15 and 18 of Baichwal, for example, disclose in vitro dissolution rates in which roughly half of the drug is dissolved by four hours.

demonstrated Alza's patent to be invalid for obviousness by clear and convincing evidence.[4] We agree.

While we have carefully considered all of the parties' arguments, we discuss principally the dispute over satisfaction of one predicate to a finding of obviousness: that a person of ordinary skill in the art would have had a "motivation to combine" the prior art to achieve the claimed invention and that she would have had a "reasonable expectation of success" in doing so. As an initial matter, we agree with the district court that "on a purely mechanical level, a person of ordinary skill in the art would have a reasonable expectation of success of manufacturing a 24 hour controlled-release oxybutynin formulation . . . . once motivated to use oxybutynin." Id. at 739. For example, Wong teaches a rate adjustable extended release dosing technology and release rates falling within the claimed parameters. Baichwal and Wong likewise teach ways of achieving slow rates of release, with Baichwal actually teaching extended-release oxybutynin, although arguably not as slowly as is claimed in the '355 patent.[5]

Indeed, Alza's principal argument is that no one of ordinary skill in the art would have been motivated to adapt the Morella, Baichwal and Wong technology to oxybutynin in the first place, because a person of ordinary skill in the art would have had no reason to expect that such an extended release oxybutynin formulation would have therapeutic value. The issues, as explained above, reduce essentially to whether one of ordinary skill in the art in 1995 would have had a reasonable expectation that

[4] Having reviewed Alza's sundry contentions that the district court made findings inconsistent with the appropriate burdens of proof for infringement and invalidity, we find them to be without merit.

[5] The patent examiner initially rejected the '355 patent as anticipated by Baichwal, but subsequently allowed its issuance.

oxybutynin would be colonically absorbed and therefore would have been motivated to produce the claimed extended release formulation.

The district court concluded that "the weight of the evidence clearly and convincingly establishes that a person of ordinary skill in the art in 1995 would reasonably expect oxybutynin to absorb in the colon . . . [and] have a reasonable expectation of success of producing a 24 hour oxybuytnin formulation meeting the claims of the '355 patent."[6] Alza II, 388 F. Supp. 2d at 740. Alza argues, however, that the district court erred because "[t]here was no prior art evidence supporting this finding." According to Alza, "[t]here was no contemporaneous documentation supporting the view that any one factor—lipophilicity or anything else—existed to identify successful candidates for once-a-day delivery." It also argues that two prior art references "decisively undercut" the opinion of Mylan's expert, Dr. Amidon, which the district court cited in support of its conclusion. See Alza II, 388 F. Supp. 2d at 739-740.

As an initial matter, it is essential to recognize that, as we have explained above, under our non-rigid "motivation-suggesting-teaching" test, a suggestion to combine need not be found in the prior art. See Cross Med. Prods., 424 F.3d at 1322 ("[T]he motivation to combine need not be found in prior art references, but equally can be found in the knowledge generally available to one of ordinary skill in the art . . . .").

[6] The '355 patent issued on September 26, 2000 and claimed priority as far back as 1995. See '355 patent, col. 1, ll. 5-12. The district court treated 1995 as the relevant date for the obviousness inquiry, see Alza II, 388 F. Supp. 2d at 740, as do both parties in their obviousness arguments before this court. See, e.g., Alza Reply Br. at 13 (stating that "[t]he dispositive obviousness issue was whether colonic absorption of oxybutynin was reasonably expected in 1995") (emphasis added); Mylan Br. at 6 & n.2 (referring to evidence establishing "the clear expectation of one skilled in the art in 1995" and noting in a footnote that 1995 is "[t]he earliest possible date to which Alza asserts priority.") (emphasis added).

Accordingly, where the testimony of an expert witness is relevant to determining the knowledge that a person of ordinary skill in the art would have possessed at a given time, this is one kind of evidence that is pertinent to our evaluation of a prima facie case of obviousness. We now turn to consider whether the relevant evidence, including the expert testimony and the prior art, when viewed as a whole supports the findings of the district court. We conclude that the findings of the district court were not clearly erroneous.

Mylan's expert, Dr. Amidon, testified that based on its lipophilicity, he would "expect oxybutynin to be a highly permeable" compound that is "rapidly absorbed" along the length of the GI tract, including the colon. Later, when challenged about the predictive value of lipophilicity, Dr. Amidon explained, "I would say there were some unknowns, but again lipophilic drugs would be well absorbed. That would be—that was the general understanding at the time."

Although Alza argues that two prior art references "decisively undercut Dr. Amidon's hindsight opinion," these references are in fact not inconsistent with the general principle that the extent of a drug's colonic absorption correlates with its lipophilicity. Indeed, the first reference, a 1990 publication in the Journal of Pharmaceutical Sciences, states that "[i]n general, the more lipophilic drugs were transported rapidly." P. Artursson, Epithelial Transport of Drugs in Cell Culture. I: A Model for Studying the Passive Diffusion of Drugs over Intestinal Absorptive (Caco-2) Cells. 79 J. Pharm. Sci. 476, 481 (1990). Alza, however, cites this reference narrowly for its observation that a highly lipophilic analog of a particular drug did not follow the general rule that lipophilic drugs were transported more quickly. Id. Granted, the

authors admit that "[t]he reason for this [deviation] is currently unknown," and they postulate that it may be related to a physicochemical factor other than lipophilicity, namely steric hindrance.[7] Id. But the mere fact that the colonic absorption rate of a drug may be predicted most precisely by using "many factors," rather than "lipophilicity" alone, does not negate the general predictive utility of lipophilicity in estimating the extent of colonic absorption.

The second prior art reference cited by Alza, Absorption of Polar Drugs Following Caecal Instillation in Healthy Volunteers, is similarly unavailing to it. Riley, et al., 6 Aliment. Pharmacol. Ther. 701, 705 (1992). Again, this reference teaches that while the correlation is not perfect, lipophilicity tended to suggest colonic absorption, stating that "[t]he relationship between the physical characteristics of a drug and its colonic absorption is not yet clear but studies in the rat suggest that lipophilic drugs are well absorbed along the length of the gastrointestinal tract, whereas hydrophobic polar drugs are absorbed much less from the colon than from the small intestine." Id. (emphasis added).

Far from teaching away or detracting from the weight of Dr. Amidon's testimony, these prior art references, taken as a whole, are entirely consistent with the finding that in 1995 a person of ordinary skill in the art would have expected a general, albeit imperfect, correlation between a drug's lipophilicity and its colonic absorptivity. Accordingly, we cannot perceive clear error in the district court's factual findings that while colonic absorption was not guaranteed, the evidence, viewed as a whole, is clear

[7] Dr. Chancellor, Alza's expert, likewise characterized colonic absorption as having been understood as being dependent on several physicochemical and physiological variables, of which lipophilicity was one.

and convincing that a person of ordinary skill in the art would nonetheless have perceived a reasonable likelihood of success and that she would have been motivated to combine prior art references to make the claimed invention.

Likewise, we find no error in the district court's consideration of secondary indicia of obviousness. We therefore affirm its legal conclusion of obviousness, finding the district court to have correctly held that Mylan met its burden of overcoming the presumption of validity that attaches to an issued patent.

D. Infringement

The '355 patent specifically describes the rate of oxybutynin release from its "extended release" formulations, requiring that the time-course of in vivo oxybutynin release falls within certain boundaries. That is, at certain times, the cumulative amount of dissolved (released) drug must fall within certain ranges. To prove infringement, Alza bore the burden of proving, inter alia, that Mylan's accused generic formulation exhibited an in vivo release profile falling within the claimed ranges at the relevant times.

At trial, Alza presented no direct evidence of how quickly the accused product dissolved in vivo. Alza II, at 722. However, it did offer two kinds of indirect evidence as measures of the rate of in vivo release. Id. First, it presented evidence of the blood plasma concentration versus time profiles for both the accused ANDA formulation and Ditropan, an embodiment of the '355 patent. Second, it presented evidence of the rate of release not in the GI tract but in pieces of laboratory apparatus under certain experimental conditions, so-called in vitro dissolution. The critical deficiency in the evidence presented by Alza was not that it was "indirect" rather than "direct," but rather

that it failed to credibly link these pieces of evidence with the relevant pharmacokinetic parameter—the rate of in vivo dissolution in the GI tract.

Thus, the district court explained that Alza had failed to demonstrate how evidence of the rate of dissolution of drug in the GI tract could be extracted from plots of plasma concentration versus time. The district court accepted Alza's simplifying assumption about oxybutynin rapidly being absorbed following dissolution such that the rates of in vivo dissolution parallel the rate of drug uptake into the blood. However, it found that only one expert, Dr. Amidon, had "endorsed Alza's subjective comparison of blood plasma levels with in vivo release rates." As for that one expert, moreover, he "rejected the very conclusion that Alza attributed to him."

Alza criticizes the district court for "fail[ing] to come to grips with the significance of the testimony" that Dr. Amidon "recanted . . . immediately after he made it." Specifically, Alza urges that notwithstanding the expert's recantation, we should nonetheless draw our independent conclusions from the "point of his testimony" that release rates in blood and the appearance in the GI tract are essentially the same. We have considered Alza's arguments and find them to lack legal and factual coherency. Even if we were to presume to be experts and to apply the simplifying assumption that the drug is rapidly taken up into the bloodstream upon dissolution, it is not clear to us how to abstract from each plasma concentration versus time curve the rate of uptake into the bloodstream. This would require factoring out of the curve the effects, inter alia, of the elimination of drug from the bloodstream over the relevant 24 hour period. But this is not our province. Such evidence, if it exists, must have been presented at trial, or in its stead other evidence sufficient to persuade the trial court.

From what can be discerned, Dr. Amidon's immediately recanted statement appears to have been based on his comparison of the relative areas under the curves of plasma concentration versus time plots of both the accused ANDA formulation and Ditropan XL. Indeed, Alza reproduces in its appellate brief Dr. Amidon's testimony that the accused product has only 92 to 93 percent of the area under the curve of Ditropan XL. This appears to have resulted in the drawing of a line (referred to by the parties as "line A") on a plot of in vitro dissolution of both Ditropan XL and the accused ANDA formulation, wherein the rate of in vitro dissolution of Mylan's ANDA formulation has been adjusted according to that percentage. The basis for, and significance of, line A is simply not apparent from the record, and Alza fails to provide us with any persuasive line of argument as to how we should imbue line A with any relevant meaning. In short, we agree with Mylan that the plasma concentration versus time data fail to establish in vivo release rates for either Ditropan XL or the accused ANDA product.

The district court similarly found unpersuasive Alza's evidence that Ditropan XL and the accused ANDA product sometimes exhibited in vitro dissolution rates falling within the claims. The court cited testimony by Dr. Amidon explaining that these in vitro procedures are "not designed to reflect the in vivo dissolution process." This accords with the common sense notion that one cannot simply proclaim without proof that he has constructed an apparatus capable of mimicking pertinent environmental variables of the GI tract (along the length of the tract, nonetheless). Indeed, the obtained in vitro dissolution rates vary widely with the choice of experimental parameters. We agree with the district court that Alza's evidence of in vitro dissolution rates is irrelevant absent

evidence demonstrating that the in vitro system is a good model of actual in vivo behavior. On that point, Alza's evidence is severely lacking.

We therefore affirm the district court's finding of noninfringement. In so doing we explicitly reject Alza's suggestion that the district court erred in failing to specifically state that not only did it find Alza's plasma concentration data and its "in vitro" data to be inadequate in isolation, but that it had also found the data to be inadequate in combination. Even if we were to entertain the suggestion that the district court was in fact unfamiliar with the basic precept that it is the totality of the evidence that it must consider in making factual determinations, we would merely conclude that where as here, if each of two pieces of evidence, assessed separately, is severely inadequate to support a proposition, when their probative values are tallied, they still fall short. While it is possible to envision cases in which two pieces of evidence may create great probative value synergistically, this is not one of those cases.

* * *

In conclusion, we affirm the judgment of the district court that the asserted claims of the '355 patent were invalid, and that notwithstanding, the patent was not infringed.

AFFIRMED.

Costs to Mylan.