United States Court of Appeals for the Federal Circuit

IN RE CYCLOBENZAPRINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULE PATENT LITIGATION

EURAND, INC. (NOW KNOWN AS APTALIS PHARMATECH, INC.), CEPHALON, INC., AND ANESTA AG,
Plaintiffs-Cross Appellants,

v.

MYLAN PHARMACEUTICALS INC. AND MYLAN INC.,
Defendants-Appellants,

and

PAR PHARMACEUTICAL, INC.,
Defendant-Appellee.

2011-1399, -1409

Appeals from the United States District Court for the District of Delaware in Case No. 09-MD-2118, Judge Sue L. Robinson.

Decided: April 16, 2012

JONATHAN E. SINGER Fish & Richardson, P.C., of Wilmington, Delaware, argued for plaintiff-cross appellant. With him on the brief were WILLIAM J. MARSDEN, JR. of Minneapolis, Minnesota, JUANITA R. BROOKS, of San Diego, California, and CHERYLYN ESOY MIZZO, of Washington, DC.

JAMES H. WALLACE, JR., Wiley Rein LLP, of Washington, DC, argued defendants-appellants. With him on the brief were MARK A. PACELLA, ROBERT J. SCHEFFEL, MATTHEW J. DOWD, KEVIN P. ANDERSON and BRIAN H. PANDYA.

Before NEWMAN, O'MALLEY, and REYNA, *Circuit Judges*.

O'MALLEY, *Circuit Judge*.

After a bench trial, the U.S. District Court for the District of Delaware found U.S. Patent Nos. 7,387,793 and 7,544,372 invalid as obvious. Case No. 2011-1409 is an appeal from that judgment. We reverse and vacate the district court's judgment of invalidity because the district court erred when it declared the patents in suit invalid as obvious. Specifically, by failing to consider the lack of a known pharmacokinetic/pharmacodynamic relationship for the claimed drug formulation, the trial court erred when it assessed the importance of the teachings of the prior art to the obviousness analysis.

As an alternative ground in support of the district court's judgment invalidating the '793 and '372 patents, the defendants argue that the district court erred when it found that the patents satisfy the best mode disclosure requirement. We affirm the district court's best mode ruling. The evidence supports a finding that the patents

in suit enable one of ordinary skill in the art to practice the inventor's preferred dew points.

After invalidating the '793 and '372 patents as obvious, the district court enjoined the defendants—the parties who prevailed at trial—from launching their generic product pending appeal to this court. That order is challenged in Case No. 2011-1399. We dismiss that appeal as premature because several outstanding issues in the district court leave uncertain whether the defendants could recover on their appeal bond.

I.

Plaintiff Aptalis Pharmatech, Inc. is the owner of the '793 and '372 patents. Plaintiff Anesta AG, a wholly owned subsidiary of plaintiff Cephalon, Inc., is the exclusive licensee of the patents. We refer to the plaintiffs collectively as Cephalon.

The '793 patent covers a modified-release dosage form of skeletal muscle relaxants. The '372 patent covers a method of relieving muscle spasms with the formulation disclosed in the '793 patent. Cephalon markets a drug covered by the patents under the brand name Amrix. The active pharmaceutical ingredient in Amrix is cyclobenzaprine hydrochloride. A single dose of Amrix releases cyclobenzaprine hydrochloride in the body during a twenty-four-hour period. Immediate-release formulations, by contrast, release the drug in a shorter amount of time and require multiple daily doses.

The '793 and '372 patents share the same specification and, as relevant to this appeal, have the same limitations in claims 1–3. Claim 1 recites a dosage form of a skeletal muscle relaxant (in the '793 patent) and a method of relieving muscle spasms (in the '372 patent), which, in relevant part, "provides [a] therapeutically

effective plasma concentration over a period of 24 hours to treat muscle spasm associated with painful musculoskeletal conditions . . . ." '793 patent col.10 ll.23, 43–46 (filed Nov. 14, 2003); '372 patent col.10 ll.21, 43–46 (filed Feb. 6, 2008). Claim 2 depends on claim 1 and specifies the claimed skeletal muscle relaxant as cyclobenzaprine hydrochloride. '793 patent col.10 ll.62–64; '372 patent col.10 ll.61–62. Claim 3 depends on claim 2 and specifies the following pharmacokinetic values:

> [A] maximum blood plasma concentration (C_{max}) within the range of about 80% to 125% of about 20 ng/mL of cyclobenzaprine HCl and an $AUC_{0–168}$ within the range of about 80% to 125% of about 740 ng·hr/mL and a T_{max} within the range of 80% to 125% of about 7 hours following oral administration . . . .

'793 patent col.10 l.65–col.11 l.5; '372 patent col.10 l.63–col.11 l.3.

Pharmacokinetics is the study of what a person's body does to a drug after administration. The pharmacokinetic ("PK") values recited in claim 3 measure various characteristics about the drug's behavior in a patient's blood plasma. C_{max}, as claim 3 alludes, represents the maximum concentration of the drug in a person's blood plasma. $AUC_{0–168}$ represents the area under the blood plasma concentration curve, or, in other words, the body's total exposure to the drug. T_{max} represents the time after administration when the maximum concentration of the drug in the blood plasma (C_{max}) occurs.

To formulate a therapeutically effective, extended-release version of cyclobenzaprine hydrochloride, the inventors had to ascertain the correct pharmacokinetic/pharmacodynamic ("PK/PD") profile. The PK side of

the relationship—what a person's body does to the drug—includes the $C_{max,}$ AUC, and T_{max}, as identified in claim 3. The PD side of the relationship describes the effect that a drug renders on a person's body. The PD of cyclobenzaprine hydrochloride is the relief of muscle spasms.

The determination of a PK profile is a quantitative exercise. The determination of PD, or therapeutic effectiveness, however, is a qualitative exercise. As one of Cephalon's experts, Dr. Stanley Davis, explained, a therapeutically effective plasma concentration is "a concentration that the formulation provides when the formulation works." The district court, likewise, construed the claim limitation "therapeutically effective plasma concentration" to mean "the amount of a drug required to produce the therapeutic result."

One of the patents' inventors, Dr. Gopi Venkatesh, testified at trial about how he and his co-inventor, Dr. James Clevenger, ascertained the correct PK/PD profile for the patented formulation. First, they estimated PK values with computer models. They started by creating PK profiles for the immediate-release formulation. The immediate-release formulation is dosed at 10 mg. Using immediate-release PK data, the inventors created models for twice-a-day dosing and three-times-a-day dosing at 10 mg per dose. Then, they drew on that data to create a model for a single, 30 mg dose. The inventors then created an in vitro dissolution profile, which modeled how much drug would be released over time if the formulation with the model PK values were placed in a solution such as water. Finally, the inventors tested a formulation with the model PK values and dissolution profile in a clinic. Clinical test results confirmed that the formulation was therapeutically effective.

II.

The defendants, Mylan Pharmaceuticals Inc. and Mylan Inc. (collectively, "Mylan"), and Par Pharmaceutical, Inc. ("Par"), filed abbreviated new drug applications ("ANDAs") for generic versions of extended-release cyclobenzaprine hydrochloride. In support of their ANDAs, Mylan and Par filed "Paragraph IV" certifications, in which they alleged that their generic products would not infringe the '793 patent, or that the patent was invalid or unenforceable. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (2006). The U.S. Food and Drug Administration ("FDA") approved both defendants' applications. Because Mylan was the first party to file a Paragraph IV certification, the FDA granted Mylan a 180-day exclusive marketing period for its generic product.

Cephalon sued Mylan and Par for patent infringement, claiming that the defendants' filing of their ANDAs infringed the '793 patent. *See* 35 U.S.C. § 271(e)(2) (2006 & Supp. IV 2010). The FDA stayed Mylan's exclusive marketing period for thirty months because of the litigation. The district court conducted a bench trial in September and October 2010. Rather than ruling from the bench, the district court took the matter under advisement to prepare a written opinion. The end of the FDA's thirty-month stay approached as the parties waited for the district court's opinion. On April 8, 2011, the district court, sua sponte, temporarily enjoined Mylan from launching its generic product pending the issuance of an opinion. The thirty-month stay expired on April 17, 2011.

The district court issued its written opinion on May 12, 2011. It ruled that Mylan's and Par's products infringed the '793 and '372 patents, but that Cephalon's asserted patent claims were invalid as obvious. The district court entered judgment of invalidity in favor of

Mylan and Par. The district court's sua sponte injunction expired by its own terms upon entry of judgment.

On May 13, 2011, the day after the district court entered judgment, Mylan launched its generic product. On May 15, 2011, Cephalon moved for an injunction to bar Mylan's launch pending appeal and to recapture product already released. Cephalon argued that it was likely to prevail on appeal because it believed the district court had made a number of errors in its obviousness analysis. In response, the district court conceded certain errors and modified some of its findings, but reaffirmed its obviousness ruling. Notwithstanding that it affirmed Mylan's victory, the district court granted Cephalon's motion for injunctive relief and issued an injunction pending appeal to this court. The district court expressed uncertainty about whether this court would affirm its invalidity ruling and found that Cephalon was "just as likely as not" to succeed on appeal. The district court then found that the potential harm to Cephalon and a lack of a corresponding threat of harm to Mylan weighed in favor of an injunction.

Mylan appealed the injunction. Cephalon appealed the district court's invalidity ruling. Mylan moved this court to stay the injunction pending resolution of the appeal, and this court did so temporarily, pending full briefing of Mylan's motion. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, No. 2011-1399 (Fed. Cir. May 25, 2011) (order granting immediate stay of preliminary injunction). After briefing from the parties, this court lifted the temporary stay, but declined to require that Mylan recall any product it had sold while the stay was in place. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, Nos. 2011-1399, 2011-1409 (Fed. Cir. July 7, 2011) (order granting temporary stay in part). We now consider both appeals on their merits.

III.

We address the district court's obviousness ruling first. A patent may not issue "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 to which said subject matter pertains." 35 U.S.C. § 103(a) (2006). Obviousness is a question of law based on underlying factual findings: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). Generally, a party seeking to invalidate a patent as obvious must "demonstrate 'by clear and convincing evidence that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.'" *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)). *See also Amgen, Inc. v. F. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art.") (citations omitted). The Supreme Court has warned, however, that, while an analysis of any teaching, suggestion, or motivation to combine known elements is useful to an obviousness analysis, the overall obviousness inquiry must be expansive and flexible. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 415, 419 (2007).

In reviewing a district court's obviousness ruling after a bench trial, we review its legal conclusion de novo, but

we review its underlying factual findings for clear error. *Proctor & Gamble*, 566 F.3d at 993–94. The clear-error standard of review applied to a district court's factual findings demands that we defer to those findings unless we are left with "a definite and firm conviction that a mistake has been committed." *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948). 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. *Proctor & Gamble*, 566 F.3d at 993–94. Indeed, the Supreme Court recently confirmed that a party asserting an obviousness claim bears that high burden of persuasion. *Microsoft Corp. v. i4i Ltd.*, 131 S. Ct. 2238, 2242 (2011).

A.

We find that the district court's legal conclusion that bioequivalence alone was sufficient to render the claims at issue obvious was in error. We also find clear error in a number of the district court's factual findings, as identified below.

The obviousness inquiry in this case is focused on bioequivalence. The concept of bioequivalence means the body is exposed to the same amount of active pharmaceutical ingredient at the same rate after administration of either an immediate-release or extended-release formulation. The district court found the asserted claims obvious because it believed the claimed extended-release PK profile is bioequivalent to the immediate-release PK profile. Mylan agrees with the district court's approach of resting its obviousness finding on bioequivalence. Cephalon, however, argues that the district court placed undue weight on bioequivalence and, as a result, misinterpreted the proffered prior art references.

We agree with Cephalon. The district court treated bioequivalence as the end of its inquiry when the court found that it would have been obvious to a person having ordinary skill in the art to target extended-release PK values "mirroring"—in other words, bioequivalent to—those of the immediate-release cyclobenzaprine formulation. The district court, however, was also required to consider the asserted claims' limitation requiring therapeutic effectiveness, and whether it would have been obvious to one of ordinary skill in the art at the time of the invention that a bioequivalent PK value would satisfy that limitation. *Graham*, 383 U.S. at 17–18 (making clear that "differences between the prior art and *the claims at issue* are to be ascertained") (emphasis added).

Mylan and Par argued, and the district court agreed, that the undisputed fact that cyclobenzaprine lacked a known PK/PD relationship at the time of invention was irrelevant. Without such a known relationship, however, skilled artisans could not predict whether any particular PK profile, including a bioequivalent one, would produce a therapeutically effective formulation. Dr. Davis, Cephalon's expert, testified that cyclobenzaprine's "mode of action was not really well known and there [was] certainly no clear relationship between a given pharmacokinetic profile and the pharmacodynamic effect, what it actually does to the body." One of the defendants' experts, Dr. Gordon Amidon, acknowledged that there was nothing in the prior art or published literature "that would help a person skilled in the art determine a therapeutically effective plasma concentration over a 24-hour period."

Mylan and Par did not dispute that cyclobenzaprine lacked a known PK/PD relationship. Rather, they attempted to avoid that fact in two ways. First, they asserted the truism that skilled artisans would need only a reasonable expectation of success and would not need to

be certain of what a particular PK profile would yield. *See* Defs.' Resp. & Reply Br. 26. Second, Mylan and Par argued to the district court that the patents in suit lack sufficient written description to support the "therapeutically effective" limitation. Lack of written description, however, is a separate defense, which the defendants do not advance on appeal. For purposes of obviousness, therefore, we must accept as true that cyclobenzaprine lacked a known PK/PD relationship at the time of invention, and that the asserted claims contain a valid "therapeutically effective" limitation.

The district court misapprehended the importance of the lack of a known PK/PD relationship. The district court stated that "[t]he lack of a PK/PD relationship is of no moment . . . given that one of ordinary skill in the art would expect the extended release formulation to have the same PD effect on the body if it has the immediate release formulation's PK profile." That statement contains an inherent contradiction. By stating that skilled artisans would assume that the immediate-release and extended-release PK profiles produce the same PD effect, the district court was assuming that a known PK/PD relationship existed for the immediate-release formulation. Because all experts and parties agree, however, that skilled artisans did *not* know the PK/PD relationship even for the immediate-release formulation, there was no way to match the dosage for the extended-release formulation to achieve a known therapeutic effect. The district court, therefore, could not find obviousness without finding that the prior art would have taught or suggested a therapeutically effective formulation to one of ordinary skill in the art. The record lacks any such evidence. While it may have been obvious to experiment with the use of the same PK profile when contemplating an extended-release formulation, there is nothing to indicate that a skilled

artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective. *See Proctor & Gamble*, 566 F.3d at 994 (requiring a reasonable expectation of success to prove obviousness).

This distinction is important. Where a skilled artisan merely pursues "known options" from "a finite number of identified, predictable solutions," the resulting invention is obvious under Section 103. *KSR*, 550 U.S. at 421. Where, however, a defendant urges an obviousness finding by "merely throw[ing] metaphorical darts at a board" in hopes of arriving at a successful result, but "the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful," courts should reject "hindsight claims of obviousness." *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

B.

The district court's failure to appreciate the lack of a known PK/PD relationship for *any* formulation of cyclobenzaprine rendered deficient its analysis of the evidence that Mylan and Par offered to prove the claimed PK values obvious and its analysis of the implications of that evidence on its legal conclusion of obviousness. We explain below why the district court's analysis was deficient.

1.

The district court found that a skilled artisan could calculate the claimed AUC and T_{max} by conducting what it called "routine experimentation": creating computer models based on data from articles by Winchell and Hucker, and PK data for Flexeril, the branded immediate-

release formulation. The district court relied on the testimony of Dr. Amidon in interpreting those prior art references.[1] Mylan and Par agree with the district court, arguing that the evidence shows that "one of ordinary skill in the art could readily convert the known pharmacokinetic data for Flexeril® administered 10 mg three times a day to an equivalent pharmacokinetic profile for a single daily 30 mg administration." Defs.' Resp. & Reply Br. 40.

Dr. Amidon's testimony, however, was insufficient to support the conclusion that a skilled artisan would reasonably expect to achieve a therapeutically effective AUC and T_{max}. Indeed, it was actually inconsistent with that conclusion. As Dr. Amidon explained, Winchell reveals that cyclobenzaprine is linear, which means that blood plasma concentration increases proportionally to dosage. The fact that a skilled artisan could have predicted a particular blood plasma concentration, however, does not mean that such knowledge would have provided a skilled artisan a reasonable expectation of success in calculating a blood plasma concentration that was therapeutically effective. As Dr. Amidon also explained, Winchell suggests that cyclobenzaprine is well absorbed in the body. That information, however, pertains to the body's physical absorption of the drug rather than the correct PK/PD relationship. As Dr. Amidon further explained, Winchell provides PK values for immediate-release cycloben-

[1] The district court also relied upon the testimony of another defense expert, Dr. Courtney Fletcher, to find that the T_{max} can be calculated when the other parameters of the model are known. Because Cephalon is correct that Dr. Fletcher was not qualified to testify to that point, any reliance on Dr. Fletcher for this proposition was clear error. Indeed, the district court seemed to concede this point when responding to the errors that Cephalon identified in the court's trial opinion.

zaprine, and Hucker provides plasma concentration time curves for the immediate-release formulation. Without a known PK/PD relationship, however, immediate-release PK values are of little use in calculating extended-release values, because there is no proof that a skilled artisan would expect the extended-release values to produce a therapeutic effect solely because they are drawn from immediate-release values.

The evidence on which the district court relied to find the claimed C_{max} obvious similarly focuses on bare PK values rather than the PD effect that the PK values could be expected to produce. The district court found that Winchell "undisputably [sic]" disclosed the claimed C_{max}. Winchell indicates that, after subjects are dosed every eight hours for seven days at 10 mg/dose, subjects have a C_{max} of 25.9 ng/ml. That value is 129.5% of 20 ng/ml. Claim 3 of the patents in suit claims a C_{max} range of about 80% to 125% of about 20 ng/ml. The district court, however, cited no evidence specifically indicating that a cyclobenzaprine PK profile with a C_{max} of 129.5% of 20 ng/ml would be expected to yield the same therapeutic effect as that with a C_{max} range of about 80% to 125% of about 20 ng/ml.

The district court, moreover, cited nothing to support a finding that the claimed C_{max} range of about 80% to 125% of about 20 ng/ml even encompasses Winchell's C_{max} of 129.5% of 20 ng/ml. Claim 3 does specify that the claimed range is *about* 80% to 125% of *about* 20 ng/ml. The district court construed the term "about" to mean "approximately," but failed to cite any evidence indicating that 129.5% of 20 ng/ml is approximately 125% of 20

ng/ml. The parties have not directed us to any such proof.[2]

The district court found persuasive Dr. Amidon's ultimate opinion that a skilled artisan could expect to achieve efficacy by relying on the Winchell and Hucker articles to estimate a PK profile for an extended-release formulation by using computer software. While we would normally afford the district court deference in crediting such an opinion, we cannot do so here because Dr. Amidon failed to discuss why, in the specific context of cyclobenzaprine, a skilled artisan would expect PK values drawn from the prior art to yield a therapeutically effective formulation. Indeed, the portion of Dr. Amidon's testimony on which the district court relied conflicts with his acknowledgement that the prior art and published literature lacked any guidance to help a skilled artisan determine a therapeutically effective, extended-release plasma concentration. Dr. Amidon's own computer modeling, moreover, failed to generate PK values within the claimed ranges.

Mylan and Par rely extensively on Dr. Amidon's testimony about the prior art in arguing that it would have been obvious to try to develop extended-release cycloben-

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[2] While it might appear to a layperson that 129.5% is "about" 125%, expert testimony is necessary to establish how a person having ordinary skill in the art would perceive those figures. We have no way of knowing the importance of even small differences in these percentages in the absence of some evidence in the record addressing that point. *See Ortho-McNeil Pharm., Inc. v. Caraco Pharm. Labs., Inc.*, 476 F.3d 1321, 1326 (Fed. Cir. 2007) ("The use of the word "about," avoids a strict numerical boundary to the specified parameter. Its range must be interpreted in its technological and stylistic context." (quoting *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217 (Fed. Cir. 1995))).

zaprine bioequivalent to the immediate-release PK profile, and that skilled artisans would have had a reasonable expectation of success in doing so. The insufficiency of that evidence demonstrates why the defendants' argument stands on a weak foundation. Evidence of obviousness, especially when that evidence is proffered in support of an "obvious-to-try" theory, is insufficient unless it indicates that the possible options skilled artisans would have encountered were "finite," "small," or "easily traversed," and that skilled artisans would have had a reason to select the route that produced the claimed invention. *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (citing *KSR*, 550 U.S. at 421). While it is true that Section 103 bars patentability unless "the improvement is more than the predictable use of prior art elements according to their established functions," *KSR*, 550 U.S. at 417, where the prior art, at best, "[gives] only general guidance as to the particular form of the claimed invention or how to achieve it," relying on an "obvious-to-try" theory to support an obviousness finding is "impermissible." *In re Kubin*, 561 F.3d at 1359 (quoting *In re O'Farrell*, 853 F.2d at 903). Nothing in Dr. Amidon's testimony sheds light on why a skilled artisan would have chosen a bioequivalent PK profile in the absence of a known PK/PD relationship for cyclobenzaprine. Thus, the absence of such testimony suggests that skilled artisans would not have encountered finite, small, or easily traversed options in developing a therapeutically effective, extended-release formulation. *See id.* And, there is nothing in the record to support the conclusion that what the co-inventors did here was no more than a "predictable use of known prior art elements." *KSR*, 550 U.S. at 417.

The Winchell and Hucker articles, the Flexeril data, and the defense experts' interpretation of those references, fail to indicate that a skilled artisan would have

reasonably expected to calculate therapeutically effective PK values based on those references. While the district court's assessment of this evidence may be understandable given its predicate mistake regarding the absence of a known PK/PD profile for the immediate-release formulation, it was, nonetheless, clear error.

2.

The district court also relied on other evidence to support its obviousness analysis. The district court's factual conclusions from this evidence again were clearly erroneous, however, and the weight given to them in the court's obviousness conclusion was undue.

The district court noted that Dr. Clevenger, co-inventor of the patents in suit, created computer models of the claimed PK values after he reviewed the Flexeril PK data. The district court cited Dr. Clevenger's approach when it concluded that the claimed AUC and T_{max} could be obtained by "routine experimentation." In relying on Dr. Clevenger's testimony, the district court merely retraced the inventor's steps. This hindsight analysis is inappropriate because obviousness must be assessed at the time the invention was made. *See Ortho-McNeil*, 520 F.3d at 1364 (noting that 35 U.S.C. § 103(a) directs an inquiry into whether the subject matter as a whole "would have been obvious at the time the invention was made"). Like the district court, Mylan and Par rely on Dr. Clevenger's testimony for the proposition that "one of ordinary skill could use the available software . . . and estimate the parameters identified by Mylan's experts." Defs.' Resp. & Reply Br. 41. Like the district court, however, Mylan and Par employ hindsight analysis.

Dr. Clevenger's testimony, moreover, does not support the proposition for which the district court cited it. The district court found significant Dr. Clevenger's testimony

that "[i]t can be assumed that the [immediate-release product] produced a therapeutic effect . . ." and that "if we get something similar to those blood levels . . . then we, too, will have a product that will produce a therapeutic effect." The district court, however, omitted the next exchange in Dr. Clevenger's examination: "[Question:] . . . So the idea is that if the blood levels were similar to Flexeril, then hopefully, the effect would be similar—the therapeutic effect would be similar to Flexeril? [Answer:] Hopefully. Depends on the relationship between blood levels and therapeutic effect." The district court later attempted to minimize the importance of Dr. Clevenger's omitted testimony, concluding that "this testimony simply shows that the inventor needed to verify his results in the lab. Obviousness calls for an expectation of success, not a guarantee." A plain reading of the testimony, however, indicates that Dr. Clevenger never expressed even an expectation of success. He merely testified that, whether blood levels similar to those produced by Flexeril would produce a therapeutic effect similar to that of Flexeril, depended on the relationship between blood levels and therapeutic effectiveness—a relationship that all concede was unknown.

The district court also relied on an FDA guidance document, which it found directed skilled artisans to pursue bioequivalence when formulating extended-release formulations. The title of the document the district court cited is "Guidance for Industry." The district court found that the document sets forth an FDA directive that an extended-release dosage form have the same AUC and C_{max} of an already-approved immediate-release formulation. The FDA document, however, states that its purpose is "to provide recommendations to sponsors and/or applicants planning to include . . . bioequivalence information" in applications. The document provides advice on

what they should do *if* they plan to pursue bioequivalence. The document provides little support for an obviousness finding here, because, in the absence of a known PK/PD relationship for cyclobenzaprine, there is no evidence that a skilled artisan would have targeted bioequivalence in the first instance.

One judge of our court has observed that the FDA's publishing of approval requirements for extended-release formulations does not necessarily render obvious a drug that meets those requirements, because "knowledge of the goal does not render its achievement obvious." *Abbott Labs., Inc. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2009). That observation is particularly salient here because Mylan and Par fail to demonstrate that skilled artisans would have even viewed bioequivalence as the goal when creating an extended-release cyclobenzaprine formulation. Indeed, while there might have been a desire for an extended-release formulation, there is no evidence that skilled artisans would have known how to achieve it. *See Cardiac Pacemakers, Inc. v. St. Jude Med., Inc.*, 381 F.3d 1371, 1377 (Fed. Cir. 2004) ("Recognition of a need does not render obvious the achievement that meets that need. . . . Recognition of an unsolved problem does not render the solution obvious.").

3.

Finally, the district court relied on two other prior art references, neither of which supports a finding that the "therapeutically effective" limitation is obvious. Those references—U.S. Patent No. 6,344,215 and European Patent Application No. 518,263A1 ("Urban")—disclose formulation technology and dissolution profiles rather than pharmacokinetics. The Urban reference discloses a micropellet that can be used for an extended-release formulation. It lists cyclobenzaprine as a suitable me-

dicament for the formulation. The '215 patent—Dr. Venkatesh is the named inventor—discloses a multiparticulate dosage form, for use with methylphenidate, that features the same dissolution profile claimed in the patents in suit. The district court believed that it would have been obvious to use the same drug delivery system because it had already been proven effective with methylphenidate. Mylan and Par, likewise, argue that "[t]he only meaningful structural difference between the asserted claims of the '793 patent and '215 patent was the active ingredient, cyclobenzaprine versus methylphenidate." Defs.' Resp. & Reply Br. 8.

Even if the '215 patent and Urban teach the claimed physical drug delivery system and dissolution profile, they reveal nothing about the critical limitation at issue here: a therapeutically effective PK profile. Cephalon has acknowledged that the structure of the drug delivery system and the dissolution profile are not novel aspects of the claimed invention. Oral Argument at 22:40, *available at* http://www.cafc.uscourts.gov/oral-argument-recordings/2011-1399/all. Urban and the '215 patent provide no support for the district court's obviousness finding with respect to pharmacokinetics.

C.

After the district court found that Mylan and Par proved the asserted claims obvious, it considered Cephalon's proof of objective considerations of nonobviousness to determine whether Cephalon's proofs were sufficient to "rebut" that obviousness determination. Specifically, the district court considered Cephalon's evidence of the failure of others to make the patented invention; longfelt but unsolved needs fulfilled by the patented invention; commercial success of the patented invention; and unexpected results produced by the patented invention. *See Graham*,

383 U.S. at 17–18; *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir. 2007). The district court found Cephalon's evidence insufficient to rebut Mylan's and Par's showing. The district court erred, however, by making its finding that the patents in suit were obvious before it considered the objective considerations and by shifting the burden of persuasion to Cephalon. In doing so, the district court contravened this court's precedent requiring that a fact finder consider all evidence relating to obviousness before finding a patent invalid on those grounds, and the court imposed a burden-shifting framework in a context in which none exists.

1.

The premature nature of the court's obviousness finding is apparent. Before it reached the objective considerations, the district court stated that the claimed PK profile "would have been obvious to one of skill in the art at the time of the invention" and that "a person of ordinary skill in the art would have been motivated to take a group of known elements to create an extended release version of cyclobenzaprine, and [would have had] a reasonable expectation of success in doing so." It was not until after the district court found the asserted claims obvious that it proceeded to analyze the objective considerations, or what it called the "secondary considerations."

2.

The district court's error is understandable because this court has inconsistently articulated the burden of proof applicable to an obviousness defense in district court litigation. It was error nonetheless.

In *Stratoflex, Inc. v. Aeroquip Corp.*, we held that a fact finder in district court litigation may not defer ex-

amination of the objective considerations until after the fact finder makes an obviousness finding:

> It is jurisprudentially inappropriate to disregard any relevant evidence on any issue in any case, patent cases included. Thus evidence rising out of the so-called "secondary considerations" must always when present be considered en route to a determination of obviousness. . . . Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.

713 F.2d 1530, 1538–39 (Fed. Cir. 1983) (citations omitted). Many subsequent cases have expressly followed *Stratoflex*'s directive that courts consider all objective evidence before reaching an obviousness conclusion. *See Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 663 (Fed. Cir. 2000) ("Our precedent clearly establishes that the district court must make *Graham* findings before invalidating a patent for obviousness."); *Cable Elec. Prods. v. Genmark, Inc.*, 770 F.2d 1015, 1026 (Fed. Cir. 1985) (quoting *Stratoflex*, 713 F.2d at 1539) ("The opinions of this court have suggested that evidence on these secondary considerations is to be taken into account *always*, 'not just when the decisionmaker remains in doubt after reviewing the art.'"); *Simmons Fastener Corp. v. Illinois Tool Works, Inc.*, 739 F.2d 1573, 1575 (Fed. Cir. 1984); ("The section 103 test of nonobviousness set forth in *Graham* is a four part inquiry comprising, not only the three familiar elements (scope and content of the prior art, differences

between the prior art and the claims at issue, and level of ordinary skill in the pertinent art), but also evidence of secondary considerations when such evidence is, of course, present"); *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997) (holding that "we must consider all of the evidence under the *Graham* factors before reaching our decision"); *Rockwell Int'l Corp. v. United States*, 147 F.3d 1358, 1366 (Fed. Cir. 1998) (following *Richardson-Vicks*); and *Kan. Jack, Inc. v. Kuhn*, 719 F.2d 1144, 1150–51 (Fed. Cir. 1983) (finding that a district court's consideration of commercial success complied with "the basic requirement that *all* evidence touching the obvious-nonobvious issue be fully considered before a conclusion is reached on that issue" (citing *In re Sernaker*, 702 F.2d 989, 996 (Fed. Cir. 1983))).

While many panels of this court have adhered to *Stratoflex*'s directive, some instead have spoken of the obviousness analysis in terms of a "prima facie" case which must then be "rebutted" by the patentee. Under that framework, a court inquires whether the party challenging validity has proven a "prima facie" case of obviousness, based only on reference to the patent and the proffered prior art, and only then considers objective evidence, asking whether such evidence is sufficient to *overcome* the prima facie case.[3]

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[3] *See, e.g.*, *Innovention Toys, L.L.C. v. MGA Entm't, Inc.*, 637 F.3d 1314, 1323 (Fed. Cir. 2011) ("[S]hould the district court conclude [on remand] that [defendant] has made out a *prima facie* case of obviousness based on the [prior art], the court must then determine whether [plaintiff's] secondary considerations overcome [defendant's] *prima facie* case"); *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc.*, 617 F.3d 1296, 1305 (Fed. Cir. 2010) ("If all of the factual disputes regarding the objective evidence resolve in favor of [plaintiff], it has presented a strong basis for rebutting the

Despite this language, however, those cases should not be interpreted as establishing a formal burden-shifting framework. This is so for a number of reasons. First, a review of those cases indicates that in none was the placement of the burden with respect to evidence of objective considerations, or the timing of the fact finder's consideration of that evidence, determinative. *See supra* n.3.

Second, even panels that have used the "prima facie" and "rebuttal" language generally have made clear that a fact finder must consider *all* evidence of obviousness and nonobviousness before reaching a determination. For example, in *Iron Grip Barbell Co. v. USA Sports, Inc.*, while the panel did hold that "there is no objective evidence to rebut the strong showing of obviousness based on

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prima facie case [of obviousness]."); *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1327 (Fed. Cir. 2008) ("Under the foregoing analysis, we conclude that [defendant] has clearly and convincingly established a prima facie case that claims 1 and 31 of the '099 patent are obvious as a matter of law. Accordingly, we turn to [plaintiff's] attempt to rebut this prima facie case with secondary considerations of nonobviousness."); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006) ("[Plaintiff] overcame any prima facie case of obviousness . . . [because it] proved extensive secondary considerations to rebut obviousness"); *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311 (Fed. Cir. 2006) ("A nonmovant may rebut a prima facie showing of obviousness with objective indicia of nonobviousness."); *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004) ("[W]e conclude that there is no objective evidence to rebut the strong showing of obviousness based on the prior art."); and *WMS Gaming Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999) ("The objective evidence of non-obviousness may be used to rebut a prima facie case of obviousness based on prior art references.").

the prior art," 392 F.3d 1317, 1325 (Fed. Cir. 2004), it also cautioned that, in "determining the question of obviousness, inquiry should always be made into whatever objective evidence of nonobviousness there may be." *Id.* at 1323 (quoting *Vandenberg v. Dairy Equip. Co.*, 740 F.2d 1560, 1567 (Fed. Cir. 1984)). In *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc.*, while the panel observed that, "[i]f all of the factual disputes regarding the objective evidence resolve in favor of [plaintiff], it has presented a strong basis for rebutting the *prima facie* case [of obviousness]," the panel stated, "[t]o be clear, a district court must *always* consider any objective evidence of nonobviousness presented in a case." 617 F.3d 1296, 1305 (Fed. Cir. 2010). And in *WMS Gaming Inc. v. International Game Technology*, while the panel stated that "[t]he objective evidence of nonobviousness may be used to rebut a prima facie case of obviousness based on prior art references," it also stated that "[t]he consideration of the objective evidence presented by the patentee is a necessary part of the obviousness determination." 184 F.3d 1339, 1359 (Fed. Cir. 1999). Thus, a reading of these cases that permits a fact finder to reach a conclusion of obviousness before considering all relevant evidence, including evidence of objective considerations, would not only conflict with *Stratoflex*'s directive that objective considerations are "to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art," 713 F.2d at 1538, but would ignore their actual holdings.

Next, the Supreme Court has never imposed nor even contemplated a formal burden-shifting framework in the patent litigation context.[4] It has, instead, required that

[4] The Court's treatment of the burden of persuasion in the obviousness context markedly differs from its treatment of the burden of persuasion in other contexts,

all evidence relevant to obviousness or nonobviousness be considered, and be considered collectively. In *Graham*, the Court stated that "[s]uch secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented," along with the scope and content of the prior art, the differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art. 383 U.S. at 17–18. Notably, the Court did

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such as employment discrimination claims under Title VII of the Civil Rights Act of 1964. In *McDonnell Douglas Corp. v. Green*, the Court established the well-known formal, three-part burden-shifting framework that a plaintiff must satisfy to prove a discrimination claim with circumstantial evidence. 411 U.S. 792 (1973). Several differences are apparent between the Court's burden-shifting framework under *McDonnell Douglas* and its treatment of the burden of proof with respect to obviousness. First, the term "prima facie," as used in the *McDonnell Douglas* context, means "the establishment of a legally mandatory, rebuttable presumption," as opposed to "the plaintiff's burden of producing enough evidence to permit the trier of fact to infer the fact at issue." *Tex. Dep't of Cmty. Affairs v. Burdine*, 450 U.S. 248, 254 n.7 (1981). As discussed above, the Court has never spoken in terms of a legally rebuttable presumption with respect to obviousness. Second, the Court's rationale for fashioning a formal burden-shifting framework in employment discrimination cases is to facilitate inquiry into an employer's intent: "the allocation of burdens and the creation of a presumption by the establishment of a prima facie case is intended progressively to sharpen the inquiry into the elusive factual question of intentional discrimination." *Burdine*, 256 F.3d at 256 n.8. While the obviousness inquiry undoubtedly demands precision, the Court has never identified a problem in its application such that "sharpening" by way of a burden-shifting scheme is necessary.

not characterize the objective factors as after-the-fact considerations or relegate them to "secondary status." The Court, rather, indicated that the objective considerations have broader applicability, noting that, "[a]s indicia of obviousness or nonobviousness, these inquiries may have relevancy." *Id.* The Court recently reaffirmed this approach to objective considerations when it described the obviousness inquiry as "expansive and flexible" and noted that *Graham* "invite[s] the courts, where appropriate, to look at any secondary considerations that would prove instructive." *KSR*, 550 U.S. at 415. And, in *i4i*, the Court reaffirmed both the scope and placement of the burden of proof in these circumstances. 131 S. Ct. at 2245, n.4.

In *i4i*, the Court was asked to articulate the standard of proof a party must satisfy to prove an invalidity defense. 131 S. Ct. at 2242. The Court held that the standard of proof is proof by clear and convincing evidence. *Id.* In explaining that holding, the Court differentiated between the concepts of burden of proof, burden of production, burden of persuasion, and standard of proof. *Id.* at 2245. As the Court explained, the commonly used term "burden of proof" encompasses the concepts of "burden of persuasion" and "burden of production." *Id.* at 2245 n.4. The burden of persuasion specifies "which party loses if the evidence is balanced," while the burden of production specifies "which party must come forward with evidence at various stages in the litigation." *Id.* at 2245 n.4. The standard of proof, the court further explained, specifies "how difficult it will be for the party bearing the burden of persuasion to convince the jury of the facts in its favor." *Id.* at 2245 n.4.

The Court resorted to common-law principles to determine that the standard of proof is proof by clear and convincing evidence because the Patent Act does not explicitly articulate the standard of proof. *Id.* at 2245–

46. By contrast, the Court noted, the Patent Act specifies that the burden of proof is placed on the party challenging validity: "The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity." *Id.* at 2245 (quoting 35 U.S.C. § 282). The Court provided no indication that it believes the burden of persuasion should shift to the patentee at some point to prove nonobviousness. [5]

Finally, not only is *Stratoflex* the law, it is sound in requiring that a fact finder consider the objective evidence before reaching an obviousness determination. The objective considerations, when considered with the balance of the obviousness evidence in the record, guard as a check against hindsight bias. *Graham*, 383 U.S. at 36 (quoting *Monroe Auto Equip. Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (6th Cir. 1964)). In *Graham*, the Court recognized the danger of hindsight bias and the ameliorative effect that the objective considerations might offer. In discussing the utility of the objective considerations, the Court cited a law review note published after the nonobviousness requirement was enacted in the 1952 Patent Act. *Id.* at 18 (citing Richard L. Rob-

[5] It is true that, in most cases, it is a patentee who chooses to offer proof of objective considerations as evidence of nonobviousness. It is also true that district courts will often impose a discovery obligation on patentees to be the first to produce evidence relating to objective considerations. And, it is true that district courts also often require patentees to present their objective evidence during their case in chief to make an efficient use of time and resources during trial, relying on their authority under Federal Rule of Evidence 611(a) to structure the presentation of evidence. Those realities do not change the fact that the party challenging validity bears the burden of persuasion throughout the litigation. *i4i*, 131 S. Ct. at 2245 & n.4.

bins, *Subtests of "Nonobviousness": A Nontechnical Approach to Patent Validity*, 112 U. Pa. L. Rev. 1169 (1964) ("Robbins")). In that note, the author argued that the instruments of decision-making applied in patent cases at the time were inadequate and allowed judges to rely on "judicial hunches," thereby deciding cases on extralegal grounds. Robbins, 112 U. Pa. L. Rev. at 1170 & n.11 (citing Joseph C. Hutcheson, Jr., *The Judgment Intuitive: The Function of the "Hunch" in Judicial Decisions*, 14 Cornell L.Q. 274, 278 (1929)). Such "judicial hunches" are encouraged by hindsight bias. As one commentator recently observed, "decision-makers unconsciously let knowledge of the invention bias their conclusion concerning whether the invention was obvious in the first instance." Gregory N. Mandel, *Patently Non-Obvious: Empirical Demonstration that the Hindsight Bias Renders Patent Decisions Irrational*, 67 Ohio St. L.J. 1391, 1393 (2006). In other words, knowing that the inventor succeeded in making the patented invention, a fact finder might develop a hunch that the claimed invention was obvious, and then construct a selective version of the facts that confirms that hunch. This is precisely why the Supreme Court explained that objective considerations might prevent a fact finder from falling into such a trap, observing that objective considerations might serve to "resist the temptation to read into the prior art the teachings of the invention in issue." 383 U.S. at 36.[6] And, it is

[6] To be sure, courts must exercise care in assessing proffered evidence of objective considerations, giving such evidence weight only where the objective indicia are "attributable to the inventive characteristics of the discovery as claimed in the patent." *See* Rochelle Cooper Dreyfuss, *The Federal Circuit: A Case Study in Specialized Courts*, 64 N.Y.U. L. Rev. 1, 10 (1989) (noting that this court has imposed such a "nexus" requirement on the objective considerations). *See also Ormco Corp. v. Align*

precisely why fact finders must withhold judgment on an obviousness challenge until it considers all relevant evidence, including that relating to the objective considerations.

In sum, opinions of this court should not be read to require a burden-shifting framework in derogation of *Stratoflex*'s directive that objective evidence be considered before making an obviousness determination and in disregard of where the burdens of proof and persuasion are properly placed in district court litigation.[7] Such a

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Tech., Inc., 463 F.3d 1299, 1311–12 (Fed. Cir. 2006) (noting that a nexus must exist between a product's commercial success and the claimed invention).

[7] It appears that the language discussing a two-part, burden-shifting inquiry may have originated in and been borrowed from the test employed in appeals from the Board of Patent Appeals and Interferences. In *Iron Grip Barbell*, for example, we stated that a "presumption of obviousness" that exists when a claimed invention falls within a range disclosed in the prior art could be "rebutted if it can be shown: (1) That the prior art taught away from the claimed invention . . . or (2) that there are new and unexpected results." 392 F.3d at 1322. For that proposition, we cited *In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997), and *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990). Both of those cases were appeals from obviousness rejections during prosecution. *In re Geisler*, 116 F.3d at 1467; *In re Woodruff*, 919 F.2d at 1575.

Unlike in district court litigation, a burden-shifting framework makes sense in the prosecution context. The prima facie case furnishes a "procedural tool of patent examination, allocating the burdens of going forward as between examiner and applicant." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). During prosecution, a patent applicant, as a practical matter, may not have the opportunity to present objective evidence unless and until an examiner reviews the application and issues an obvious-

reading disregards our own precedent and is inconsistent with Supreme Court case law, including very recent case law.

3.

The district court appears to have fallen into the understandable but improper trap of constructing a selective version of the facts relating to the objective considerations so as to confirm its hunch that the asserted claims were obvious. The district court focused on objective evidence that supported its obviousness determination, but ignored

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ness rejection. This is because "the examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a prima facie case of unpatentability. If that burden is met, the burden of coming forward with evidence or argument shifts to the applicant." *Id.* Courts should not apply the burden-shifting framework for patentability appeals to invalidity determinations appealed from a district court, however, because the prosecution and litigation contexts are distinct.

In the prosecution context, not only are the decision maker and the patent holder the only two parties involved, but that decision maker—the examiner—is required to determine patentability by a preponderance of the evidence. *Id.* Evidence of objective considerations also may not be available until years after an application is filed, and until long after the examiner first considers the prior art. Litigation differs significantly from the examination process. First, in the litigation context, validity, rather than patentability, is the issue. The challenged patent enjoys a presumption of validity, and the challenger must convince a third-party decision maker of the patent's invalidity by clear and convincing evidence. 35 U.S.C. § 282; *i4i*, 131 S. Ct. at 2242. And, in litigation, all relevant evidence is presented to the fact finder in a single proceeding. There is simply no practical need to impose a burden-shifting framework in litigation.

other evidence that cast the objective considerations in a light favorable to Cephalon. And, it is clear that the district court assumed that it was Cephalon's burden to disprove the court's initial obviousness finding.

Had the district court, instead, considered the objective evidence in its entirety before making an obviousness finding, and considered that evidence in light of the actual burden imposed upon a patentee and a patent challenger, much of that evidence would have encouraged the district court to question the claim that the mere existence of an immediate-release formulation of cyclobenzaprine made an extended-release version of that drug obvious. Specifically, we find that evidence of a longfelt need for an extended-release formulation and the failure of others to formulate one strongly support a conclusion of nonobviousness. We address each of these considerations.[8]

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[8] We find no error in the district court's conclusion that Cephalon failed to offer adequate proof of reduced sedation through its formulation and, thus, could not rely on unexpected results to support its contention that Mylan and Par failed to prove obviousness by clear and convincing evidence. While we question the trial court's interpretation of Eurand's evidence of commercial success, moreover, we cannot find clear error therein. That these objective criteria do not strongly support a finding of nonobviousness does not affect our conclusions, however. On both points, we find the evidence to be neutral; while they do not support a finding of nonobviousness, they add little to Mylan and Par's claim of obviousness. While evidence of reduced sedation may not have been strong, the patents in suit do not claim that benefit; they claim only therapeutic effectiveness. And, while Amrix's commercial success may be slow in coming, it is clear its success is increasing, as its benefits—particularly greater compliance—become known.

a.

Cephalon claims that another pharmaceutical company, ALZA, tried but failed to develop an extended-release cyclobenzaprine formulation.[9] The district court rejected this claim, because, in its view, ALZA's goals were different than Cephalon's. Mylan and Par endorse the district court's reasoning. The district court, however, ignored the fact that Cephalon and ALZA shared a common goal: to make a therapeutically effective product. This was clear error.

Evidence that others tried but failed to develop a claimed invention may carry significant weight in an obviousness inquiry. "While absolute certainty is not necessary to establish a reasonable expectation of success, there can be little better evidence negating an expectation of success than actual reports of failure." *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003). This is particularly true when the evidence indicates that others found development of the claimed invention difficult and failed to achieve any success. *Advanced Display Sys. v. Kent State Univ.*, 212 F.3d 1272, 1285 (Fed. Cir. 2000). In such circumstances, "evidence of failed attempts by others could be determinative on the issue of obviousness." *Id.*

The evidence of ALZA's failure to develop an extended-release formulation strongly supports a nonobviousness finding. In the late 1990s, ALZA performed pharmacokinetic modeling and created a PK profile for immediate-release cyclobenzaprine dosed three times a

[9] Cephalon also claims that Merck and Schering-Plough tried but failed to develop an extended-release formulation. The evidence of Merck's and Schering-Plough's alleged failures, however, is weak, and the district court did not clearly err in disregarding it.

day. This approach was similar to the manner in which Drs. Venkatesh and Clevenger modeled their PK profile. The immediate-release PK profile that ALZA modeled represented "peaks and valleys" on a graph, with blood plasma concentrations undulating as time passed. ALZA then hypothesized a PK profile for an extended-release cyclobenzaprine product based on its model for the immediate-release product. For its extended-release PK profile, ALZA chose a straight line that cut through the immediate-release profile, staying below the peaks and above the valleys. ALZA hoped that staying below the peaks would avoid side effects and that staying above the valleys would maintain therapeutic effectiveness. Clinical trials, however, revealed that ALZA's product was not therapeutically effective. ALZA lost $10 million in its unsuccessful attempt to develop an extended-release formulation.

At trial, Cephalon called a former ALZA vice president, Dr. Samuel Saks. Cephalon's counsel showed Dr. Saks Cephalon's PK profile. That profile indicated that Cephalon had departed from ALZA's attempt to cut through the immediate release PK profile's peaks and valleys. Rather, Cephalon had chosen a PK profile in which the C_{max} rose higher and the minimum blood plasma concentration (C_{min}) dipped lower than those of the immediate-release profile. After reviewing Cephalon's PK profile, Dr. Saks expressed surprise that Cephalon succeeded, because he believed a lower C_{min} would be less effective. Thus, where ALZA failed to develop a therapeutically effective product, Cephalon took a materially different approach and succeeded. Evidence that others were "'going in different ways' is strong evidence that the [inventor's] way would not have been obvious." *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1099 (Fed. Cir. 1985), *vacated and remanded on other grounds*, 475 U.S. 809 (1986).

The district court disregarded ALZA's failures. ALZA intended to make a formulation that was not only therapeutically effective, but one that also reduced side effects. Cephalon's patents do not cover a formulation that reduces side effects. The district court noted that an alleged failure must be directed to the problem that a patent purports to solve. *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578 (Fed. Cir. 1991). Because ALZA had the additional goal of reducing side effects, the district court believed that ALZA's failure was not directed to the problem that Cephalon's patents purport to solve.

The district court clearly erred because it disregarded that Cephalon and ALZA did share a central common goal: to create a therapeutically effective product. There is no dispute that AZLA sought to create a product that worked. The patents in suit, of course, cover a therapeutically effective PK profile. The district court was not required to disregard Cephalon and ALZA's common goal simply because ALZA had an *additional* goal not encompassed by the patents in suit. The purpose of evidence of failure of others is to show "indirectly the presence of a significant defect in the prior art, while serving as a simulated laboratory test of the obviousness of the solution to a skilled artisan." *Symbol Techs.*, 935 F.2d at 1578–79 (quoting Robbins, 112 U. Pa. L. Rev. at 1173). ALZA's failure accomplishes that purpose, confirming that a therapeutically effective PK profile was lacking in the prior art and that skilled artisans struggled to attain it. Such a scenario is classic evidence of nonobviousness. *See, e.g.*, *Advanced Display Sys.*, 212 F.3d at 1285 (holding that the objective evidence supported an obviousness finding where others had "tried for a long time" to develop the claimed invention but found it "very hard" and "were all not successful"). ALZA's failure to develop a therapeutically effective product, in sum, is keyed to the problem

that the patents in suit purport to solve, and it supports a finding that Cephalon's accomplishment was not obvious to those skilled in the art.

b.

Cephalon also claimed that a longfelt need existed for an extended-release cyclobenzaprine formulation and that Amrix satisfied that need. The district court rejected that argument because it believed Cephalon failed to offer any expert testimony to support it. The district court's assessment of this factor was inadequate.

Longfelt need is closely related to the failure of others. Evidence is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand. *See, e.g.*, *In re Piasecki*, 745 F.2d 1468, 1475 (Fed. Cir. 1984) (finding nonobviousness where the evidence demonstrated a failure of others to provide a feasible solution to a longstanding problem); *Alco Standard Corp. v. Tenn. Valley Auth.*, 808 F.2d 1490, 1500 (Fed. Cir. 1986) (affirming a nonobviousness finding where the evidence showed that the relevant industry had searched for more than a decade for a reliable solution and that major manufacturers in the industry had tried but failed to develop such a solution).

Cephalon's proof indicates that a longfelt need existed for a therapeutically effective, extended-release cyclobenzaprine formulation. The immediate-release formulation existed for decades, but that formulation's regimen of multiple daily doses led to poor patient compliance. As discussed above, moreover, others tried but failed to develop an extended-release version. In addition to these facts, Cephalon called Dr. David Steiner, a physician who has practiced in pain management for more than a decade. Dr. Steiner discussed his experiences treating his

patients' pain in the clinic. He testified that patient compliance with a medical regimen is important and that he began prescribing Amrix, in part, because of the prospect of more convenient dosing for his patients.

Not only was the district court wrong that Cephalon produced no expert testimony on this issue, but the district court was wrong to ignore the non-expert evidence proffered on this point. In combination with compelling evidence of the failure of others to produce an extended-release formulation, this factor further supports a nonobviousness finding.

4.

Where, as here, the obviousness determination turns on whether one of ordinary skill in the art would have expected that a particular formulation of an extended-release drug would be successful—in other words, would render a therapeutically effective treatment—objective indicia of failure of others and longfelt need are particularly telling. The district court would have encountered a different landscape had it examined the objective evidence in light of the absence of a known PK/PD relationship. ALZA's failure to develop a therapeutically effective, extended-release formulation suggests that skilled artisans would not have reasonably expected to succeed in developing the claimed formulation. The long delay between the marketing of an immediate-release formulation and Amrix, and Dr. Steiner's testimony of longfelt need, moreover, supports the inference that it was difficult for researchers to create a therapeutically effective, extended-release product. Because a desire existed for such a product, researchers, presumably, would have created one if they were able to do so.

Rather than supporting a finding of obviousness, the most relevant objective considerations, when considered

as part of the totality of the evidence, support a nonobviousness finding.

D.

The record, in sum, is insufficient to support a conclusion of obviousness by clear and convincing evidence. At its core, Mylan and Par's proof of obviousness is that the claimed PK profile is bioequivalent to the immediate-release profile. In rejecting the sufficiency of Mylan and Par's proof, we do not hold that bioequivalence can never serve as evidence of obviousness. Indeed, it is most certainly relevant to that inquiry. We only hold that, on the facts of this case—in which therapeutic effectiveness is a claimed limitation and the parties do not dispute that cyclobenzaprine lacked a known PK/PD relationship—Mylan and Par cannot rely on bioequivalence as the sole basis for an obviousness finding, particularly given the heavy burden of proof imposed on them in this context. Indeed, defense counsel acknowledged at oral argument that Mylan and Par are not requesting a categorical rule that it is always obvious to try to target bioequivalence when formulating an extended-release formulation. *See* Oral Argument at 8:54, *available at* http://www.cafc.uscourts.gov/oral-argument-recordings/2011-1399/all. If we were to affirm the district court's obviousness ruling on the basis of this record, we effectively would announce such a rule.[10]

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[10] The parties have not cited any cases in which the presence or absence of a known PK/PD relationship was determinative. Indeed, in other cases, it appears that the parties and the court assumed bioequivalence would produce a therapeutically effective result. *See Abbott Labs. v. Andrx Pharms., Inc.*, 452 F.3d 1331, 1340–43 (Fed Cir. 2006) (finding a substantial question of validity on a preliminary injunction motion where the prior art disclosed substantially bioequivalent PK values, but

The district court erred in finding that Mylan and Par proved that the asserted claims are obvious by clear and convincing evidence.

IV.

We address next Mylan and Par's best mode defense. The district court rejected Mylan and Par's claim that the patents in suit are invalid for failure to disclose the best mode. Although the district court applied the incorrect test for a best mode disclosure violation, the district court's findings support its ultimate conclusion that no best mode disclosure violation existed.

A patent's specification must "set forth the best mode contemplated by the inventor of carrying out his invention." 35 U.S.C. § 112 ¶ 1 (2006). The version of the Patent Act currently in effect provides that, although an applicant must disclose the best mode to register a patent, a party to a lawsuit may not rely on an alleged best mode disclosure violation to cancel, invalidate, or hold a patent otherwise unenforceable. *Id.*; Leahy-Smith America Invents Act, Pub. L. No. 112-29, sec. 15(a), 125 Stat. 284, 328 (2011) (to be codified at 35 U.S.C. § 282 ¶ 2(3)(A)). That provision, however, is inapplicable to this case because it is the product of amendments made to the Patent Act that became effective after this action was filed. Leahy-Smith America Invents Act, Pub. L. No. 112-29, sec. 15(c), 125 Stat. 284, 328 (2011) (providing that the best mode amendments apply only to actions commenced

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failing to address whether bioequivalent PK values would produce a therapeutically effective result); *Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 616 F.3d 1283, 1289 (Fed. Cir. 2010) (reversing a district court's grant of summary judgment because a fact finder could reasonably find infringement based on the accused ANDA product's having a C_{max} equivalent to that of a standard immediate-release product).

on or after the effective date of the amendments). The version of the Patent Act applicable to this case permits an accused infringer to assert a best mode disclosure violation as a defense. 35 U.S.C. § 282 ¶ 2(3) (2006).

A defense of failure to disclose the best mode is a question of fact. *Zygo Corp. v. Wyko Corp.*, 79 F.3d 1563, 1566–67 (Fed. Cir. 1996). We review a lower court's finding of no best mode disclosure violation for clear error. *Id.*

Mylan and Par claim that the specification fails to disclose the best mode because it omits a particular range of dew points. The claimed cyclobenzaprine formulation is made with a coated bead. During the formulation process, the bead is placed in a fluid bed machine, which sprays a layer of the drug and a layer of extended-release coating on the bead. The dew point of the air entering the fluid bed must be controlled. Mylan and Par claim that Dr. Venkatesh preferred dew points of 6–12ºC for immediate-release coating and 7–16ºC for extended-release coating, with target dew points of 8ºC and 10ºC, respectively. The specification does not disclose those dew points.

To determine whether a best mode disclosure violation exists, a fact finder applies a two-prong test. First, the fact finder determines whether, at the time the application was filed, the inventor possessed a best mode for practicing the invention. *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 963 (Fed. Cir. 2001) (citations omitted). A subjective inquiry, the first prong focuses on "the inventor's state of mind at the time he filed the patent application, and asks whether the inventor considered a particular mode of practicing the invention to be superior to all other modes at the time of filing." *Teleflex, Inc. v.*

Ficosa N. Am. Corp., 299 F.3d 1313, 1330 (Fed. Cir. 2002) (citation omitted).

The district court found that Dr. Venkatesh preferred particular dew points at the time the applications were filed. In March 2003, before the patent applications were filed, Dr. Venkatesh told the FDA that, during scale-up experiments, "the dew point of the incoming air was monitored by setting the control at a very low target of 8°C (6–12)°C" and that "[d]ecreasing the dew point of the incoming process air reduced the tackiness of the beads and reduced the tendency of the coated beads from clumping together." Dr. Venkatesh acknowledged that dew points could affect dissolution: "If you don't use the proper optimization, then you may not get good yield or you may not get the proper coating . . . [t]hen the product will not be good . . . ." While Cephalon argued to the district court that Dr. Venkatesh did not have a subjective belief in a best mode, Cephalon does not contest on appeal the district court's finding that he did have such a belief, and we do not find that finding to have been clearly erroneous in any event.

If the inventor possessed a best mode at the time of filing, as the district court found Dr. Venkatesh did, the second prong of the inquiry requires the fact finder to determine whether the specification discloses sufficient information such that one reasonably skilled in the art could practice the best mode. *Eli Lilly*, 251 F.3d at 963 (citations omitted). Because the second prong focuses on what the specification teaches to a person of ordinary skill in the art, the inquiry is objective. *Id.*

Mylan and Par mistakenly attempt to cast the second prong as an inquiry concerning whether Dr. Venkatesh "concealed" his best mode. Defs.' Resp. & Reply Br. 50. That characterization is inaccurate. Concealment impli-

cates an inventor's state of mind, which is inconsistent with an objective inquiry focused on what the specification teaches to a skilled artisan. *U.S. Gypsum Co. v. Nat'l Gypsum Co.*, 74 F.3d 1209, 1215–16 (Fed. Cir. 1996). As we explained in *U.S. Gypsum*, this court has used the term "concealment" as a shorthand way of inquiring about the adequacy of the disclosure:

> The "concealment" language of our case law originated in *In re Gay*, 309 F.2d 769 (CCPA 1962). In *Gay*, the Court of Customs and Patent Appeals (CCPA) explained that "the sole purpose of [the best mode] requirement is to restrain inventors from applying for patents while at the same time concealing from the public preferred embodiments of their inventions which they have in fact conceived." . . . Subsequently, the CCPA clarified that "only evidence of concealment (whether accidental or intentional) is to be considered. That evidence, in order to result in affirmance of a best mode rejection, must tend to show that the *quality* of an applicant's best mode disclosure is so poor as to effectively result in concealment." *In re Sherwood*, 613 F.2d 809, 816 (CCPA 1980).

Id. Thus, the proper inquiry focuses on the adequacy of the disclosure rather than motivation for any nondisclosure. *See also Bayer AG v. Schein Pharms., Inc.*, 301 F.3d 1306, 1320 (Fed. Cir. 2002) (explaining that the inquiry is objective).

The district court did not directly address whether the specification adequately disclosed the best mode. Rather,

the district court found that the dew points did not need to be disclosed because they amounted to routine details. We have recognized that routine details apparent to one of ordinary skill in the art need not be disclosed to satisfy the best mode disclosure requirement. *E.g.*, *Teleflex*, 299 F.3d at 1331–32; *Eli Lilly*, 251 F.3d at 963; and *Young Dental Mfg. Co. v. Q3 Special Prods., Inc.*, 112 F.3d 1137, 1144 (Fed. Cir. 1997).

To conclude that the optimal dew points were routine details exempt from disclosure, the district court was required to find that the dew points would be apparent to a person of ordinary skill in the art. *Teleflex*, 299 F.3d at 1331–32. The district court found the following: (1) it would be routine to control humidity during product fabrication; (2) the allegedly concealed dew points were within the normal operating range of a commonly used fluid-bed coating device; (3) Dr. Venkatesh's optimal dew point was within the normal operating range; and (4) the defendants' own technicians were able to optimize the dew point in just a few days. That evidence does not indicate that the optimal dew points would actually be apparent to one of ordinary skill in the art. If they were, the evidence, presumably, would indicate that skilled artisans would know the optimal dew points and program the fluid bed accordingly before commencing production. The district court's findings indicate, rather, that some, albeit minimal, work was required to ascertain the optimal dew points.

Rather than finding that the dew points were routine details apparent to one of ordinary skill in the art, the district court could, and should, have made a more fundamental finding: that the specification need not disclose the optimal dew points to enable skilled artisans to practice the best mode. *See U.S. Gypsum*, 74 F.3d at 1215–16 (focusing the inquiry on the adequacy of the disclosure).

As one expert, Dr. Robert Williams, explained, skilled artisans do not begin the fabrication process by attempting to attain a particular dew point in the fluid bed. Rather, they attempt to manipulate and harmonize a number of parameters, including, for example, air humidity, inlet air quantity, inlet air temperature, and spray rate. Dew point is a function of the other parameters. The totality of these parameters, when harmonized, creates the optimal condition for fabricating product. Thus, as the district court's findings suggest, skilled artisans would expect to attain the optimal dew points during the ordinary harmonization process by employing routine steps such as controlling the humidity and operating the fluid bed within the normal operating range. Because harmonization—a process known to skilled artisans—would produce the optimal dew points, the specification need not disclose them to enable skilled artisans to practice the best mode. The disclosure is adequate without them.

Mylan and Par argue that, because the dew points materially affect the claimed invention, express disclosure in the specification was required. For this proposition, they cite *Bayer*, 301 F.3d at 1312. Mylan and Par misread *Bayer*. There, we held that, to prove inadequate disclosure of the best mode, an accused infringer must prove that the undisclosed information affects the properties of the claimed invention. *Id.* at 1319. The panel also held that an accused infringer may prove a best mode disclosure violation if the undisclosed subject matter materially affects the properties of the claimed invention, even if the undisclosed subject matter is not strictly within the bounds of the patent claims. *Id.* at 1316. *Bayer* created an exception to the general rule that "the best mode disclosure requirement only refers to the invention defined by the claims." *Id.* at 1315–16. *Bayer* is

inapposite here because there is no dispute that the dew points are within the bounds of the asserted claims: The claims cover a particular dissolution profile, and dew point affects dissolution. The only issue here is whether the disclosure is adequate to enable a person of ordinary skill in the art to practice the invention incorporating the optimal dew points. Mylan and Par cannot avoid that issue merely by claiming that the dew points are material to the claimed invention.

Invalidation as a result of a best mode disclosure violation requires proof by clear and convincing evidence. *Teleflex*, 299 F.3d at 1330. Mylan and Par cannot meet that burden because the record indicates that skilled artisans could readily obtain the optimal dew points using a common fluid bed. We find, therefore, that the district court did not err in rejecting Mylan and Par's best mode defense.

V.

We address next Mylan's appeal in Case No. 2011-1399. Mylan appeals from the district court's order entering an injunction against launch of its generic version of Amrix. Mylan argues that it is virtually always improper to enjoin a prevailing party from acting in a manner authorized by a district court's own judgment; that it is particularly inappropriate to enter an injunction pending appeal against a prevailing generic in an ANDA action; and that, even if such an injunction is permissible in the abstract, the district court abused its discretion when it entered an injunction in this case. Mylan contends that it is entitled to recapture damages, capped by the amount of the bond imposed, regardless of the outcome on appeal.

Given our ruling today, Mylan is no longer a prevailing party or a prevailing generic, however. We have

reversed the judgment of invalidity upon which Mylan predicates its objections in this appeal. If our resolution of the appeal in Case No. 2011-1409 resulted in an order directing judgment in favor of Cephalon and a permanent injunction, Mylan's own appeal would certainly be moot. *See Grupo Mexicano de Desarrollo, S.A. v. Alliance Bond Fund, Inc.*, 527 U.S. 308, 314 (1998). In *Grupo Mexicano de Desarrollo*, the Supreme Court explained:

> [I]f [a plaintiff's] lawsuit turns out to be meritorious—if he is found to be entitled to the permanent injunction that he seeks—even if the preliminary injunction was wrongly issued (because at that stage of the litigation the plaintiff's prospects of winning were not sufficiently clear, or the plaintiff was not suffering irreparable injury) its issuance would in any event be harmless error. The final injunction establishes that the defendant should not have been engaging in the conduct that was enjoined.

Id. at 314–15. *See also Global NAPs, Inc. v. Verizon New England, Inc.*, 489 F.3d 13, 22 (1st Cir. 2007) ("[A] party is wrongfully enjoined when it had a right all along to do what it was enjoined from doing."); *Blumenthal v. Merrill Lynch, Pierce, Fenner & Smith, Inc.*, 910 F.2d 1049, 1054 (2d Cir. 1990) ("A party has been 'wrongfully enjoined' . . . if it is ultimately found that the enjoined party had at all times the right to do the enjoined act.") Thus, if Mylan was simply enjoined from engaging in conduct in which it had no right to engage, Mylan's complaints about that injunction become meaningless. This simple principle may or may not ultimately apply in this case, however. It is unclear at this stage what the ultimate resolution of this matter will be and whether launch of Mylan's generic

will be deemed unauthorized. *See, e.g.*, *Grupo Mexicano de Desarrollo*, 527 U.S. at 314–15 (indicating that where a permanent injunction either does not ultimately issue or is narrower in scope than a preliminary injunction, a claim against the bond could lie).

Here, it is unclear whether a final judgment against Mylan will be entered and, if so, what the scope of an injunctive remedy, if any, might be. There is much litigation that is yet to occur—both as to Cephalon's claims for relief and as to Mylan's currently stayed counterclaims. For these reasons, we find it premature to address Mylan's claim on the appeal bond or to resolve the questions Mylan poses regarding the circumstances under which, or the standards by which, an injunction pending appeal may be imposed on a prevailing party in an ANDA action. We dismiss Mylan's appeal without prejudice to reassert a claim for damages against the appeal bond if and when such a claim might be ripe and appropriate. In the interim, the appeal bond will remain in place unless the parties stipulate to its release.

VI.

On a final matter, we note that, because Mylan's patent misuse and antitrust claims remained unresolved at the time of appeal, the parties did not appeal from a final judgment, which normally precludes an appellate court from exercising jurisdiction. *See* Fed. R. Civ. P. 54. After the appeals were filed, the parties moved the district court for entry of a certificate pursuant to Rule 54(b) of the Federal Rules of Civil Procedure, which would allow the disposed issues to be immediately appealed. The district court granted the motion and entered the Rule 54(b) certificate. We have permitted parties to establish appellate jurisdiction with a nunc-pro-tunc Rule 54(b) certificate. *Storage Tech. Corp. v. Cisco Sys., Inc.*, 329

F.3d 823, 829–30 (Fed. Cir. 2003); *State Contracting & Eng'g Corp. v. Fla.*, 258 F.3d 1329, 1334–35 (Fed. Cir. 2001). While the parties should have moved for entry of a Rule 54(b) certificate before filing their appeals, the late-filed certificate is sufficient to establish appellate jurisdiction under our precedent.

VII.

We reverse and vacate the district court's invalidity judgment and affirm its best mode ruling. We dismiss as premature Mylan's appeal from the district court's entry of the injunction. To allow the district court an opportunity to assess the propriety of a preliminary injunction pending further proceedings, the injunction will remain in place for forty-five days post-mandate, or until further order of the district court, whichever occurs sooner.

AFFIRMED IN PART, REVERSED IN PART, VACATED IN PART, DISMISSED IN PART