United States Court of Appeals for the Federal Circuit

MERCK SHARP & DOHME CORP.,
Plaintiff-Appellant

v.

HOSPIRA, INC.,
Defendant-Appellee

2017-1115

Appeal from the United States District Court for the District of Delaware in Nos. 1:14-cv-00915-RGA, 1:14-cv-00916-RGA, Judge Richard G. Andrews.

Decided: October 26, 2017

JESSICA LYNN ELLSWORTH, Hogan Lovells US LLP, Washington, DC, argued for plaintiff-appellant. Also represented by CATHERINE EMILY STETSON; JOSEPH D. ENG, TONY VALENTINE PEZZANO, MICHAEL P. DOUGHERTY, NITYA ANAND, New York, NY; GERARD M. DEVLIN, JR., ALYSIA A. FINNEGAN, RAYNARD YURO, Merck & Co., Inc., Rahway, NJ.

THOMAS J. MELORO, Willkie Farr & Gallagher LLP, New York, NY, argued for defendant-appellee. Also represented by MICHAEL JOHNSON.

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

Opinion for the court filed by *Circuit Judge* LOURIE.

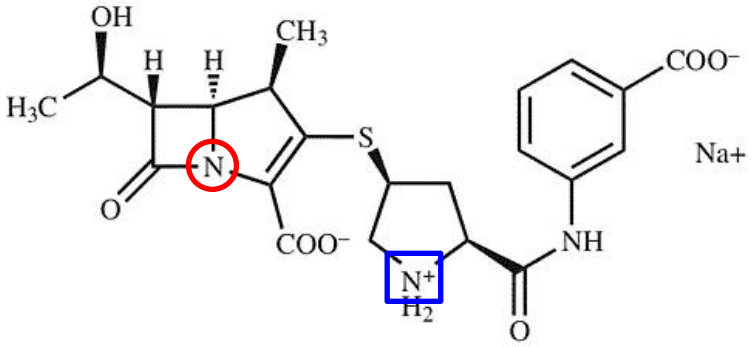
Dissenting opinion filed by *Circuit Judge* NEWMAN.

LOURIE, *Circuit Judge*.

Merck Sharp & Dohme Corp. ("Merck") appeals from the decision of the United States District Court for the District of Delaware concluding, after a bench trial, that claims 21–34 ("the asserted claims") of U.S. Patent 6,486,150 ("the '150 patent") are invalid under 35 U.S.C. § 103 (2006). *See Merck Sharp & Dohme Corp. v. Hospira Inc.*, No. CV 14-915-RGA, 2016 WL 5872620, at *21 (D. Del. July 10, 2016) (*Decision*). Because the district court did not err in its conclusion of obviousness, we affirm.

BACKGROUND

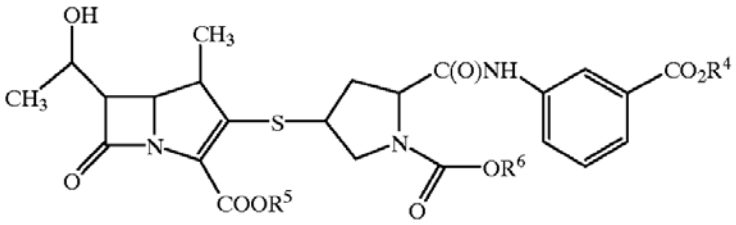
Merck owns the '150 patent, which is directed to a process for preparing a stable formulation of ertapenem, an antibiotic compound, shown below:



Ertapenem is known to be unstable because of two degradation reactions—hydrolysis of the lactam nitrogen (highlighted by a red circle) and dimerization via the pyrrolidine nitrogen (highlighted by a blue square).

The prior art taught that ertapenem can be stabilized from *dimerization* by reacting the pyrrolidine nitrogen with carbon dioxide to form a "carbon dioxide adduct."

The method of the '150 patent claims a manufacturing process for a final formulation of the antibiotic that purportedly minimizes *both* dimerization and hydrolysis degradation pathways. *See* Appellant's Br. 12–14. Claim 21 is representative and reads as follows:

> 21. A process for preparing a final formulation product of a compound of formula Ia,
>
> Ia
>
> 
>
>
> or its pharmaceutically acceptable salt, or hydrates wherein, R^4, R^5, and R^6 are independently:
>
> (a) hydrogen
>
> (b) (C_1–C_6)-alkyl, or
>
> (c) alkali-metal or alkali earth-metal wherein the alkali-metal or alkali earth-metal is sodium, potassium, lithium, cesium, rubidium, barium, calcium or magnesium;
>
> comprising the steps of:
>
> (1) charging a solution of carbon dioxide source having a pH range of about 6.0 to about 12.0 into a reaction vessel;
>
> (2) adding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel containing the solution of carbon dioxide source to maintain pH at about 6.0 to about 9.0 and a tem-

> perature range of about –3° C. to about 15° C.; [and]
>
> (3) lyophilizing the solution of Step (2) to yield the final formulation product of a compound of formula Ia with less than about 10% of moisture content.

'150 patent col. 18 ll. 11–43.

On May 29, 2014, Hospira, Inc. ("Hospira") notified Merck that it had filed an abbreviated new drug application ("ANDA"), seeking approval to engage in the commercial manufacture, use, or sale of generic versions of Merck's Invanz® product, the principal component of which is the carbon dioxide adduct of ertapenem. In response, Merck sued Hospira for infringement of two patents—the '150 patent and U.S. Patent 5,952,323 ("the '323 patent"). The district court concluded that the asserted claims of the '323 patent were not invalid and were infringed and that the asserted claims of the '150 patent would also be infringed, but were invalid as obvious over the '323 patent and PCT publication WO 98/18800 ("Almarsson"). *See Decision*, 2016 WL 5872620, at *11, *16, *21.

The district court found that, while none of the three steps of claim 21 of the '150 patent was individually taught by the prior art, the "recipe" for the final formulation was disclosed and the three steps leading to that formulation were nothing more than conventional manufacturing steps that would have been obvious from the disclosures and thus were the product of routine experimentation. *Id.* at *17–20. The court found that both references expressly taught that the formation of the carbon dioxide adduct is pH-dependent and requires a pH range of about 6.0 to about 9.0; sodium hydroxide could be used to adjust the pH; and the carbon dioxide adduct could be produced using "standard lyophilization techniques." *Id.* at *16–17. The court also found that, while

the claimed temperature range was not explicitly taught in the prior art, it was understood that degradation is minimized at low temperatures, so one of ordinary skill would have wanted to keep the temperature as low as possible without freezing. *Id.* at *18.

Regarding the dependent claims, the district court noted that Merck "focused entirely on the validity of claim 21" and thus provided no evidence rebutting Hospira's expert's testimony that each of the dependent claims' narrower limitations was either expressly disclosed by the references or would have been obvious from routine experimentation. *Id.* at *21.

The district court reviewed Merck's objective evidence and concluded that commercial success and copying by others were shown, but that the objective evidence could not overcome the "strong prima facie case of obviousness" established by Hospira. *Id.* The court found that, while there was commercial success tied to the asserted claims, the evidence was "weak[ened]" by the "blocking effect" of U.S. Patent 5,478,820 ("the '820 patent")—directed to ertapenem itself—of which Merck was the exclusive licensee. The court explained that no other entity aside from Zeneca, the original patentee, and Merck would have had any incentive to develop a formulation of ertapenem for fear of infringing the '820 patent. *Id.* at *9.

The district court also found copying by others because Hospira tried five alternative formulations in an attempt to avoid copying the '150 patent, but ultimately it had to rely on the accused process, which the court found would infringe the '150 patent. *Id.* at *10. However, while the court found that Hospira's "decision to copy [Merck's] formulation and process 'is an indicium of nonobviousness,'" it concluded that the evidence could not overcome the strong showing of obviousness presented by Hospira based on the prior art. *Id.* at *10, *21 (first citing *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 679

(Fed. Cir. 1988); then citing *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)).

Merck timely appealed to this court. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

On appeal from a bench trial, we review a district court's conclusions of law *de novo* and its findings of fact for clear error. *Golden Blount, Inc. v. Robert H. Peterson Co.*, 365 F.3d 1054, 1058 (Fed. Cir. 2004). A factual finding is only clearly erroneous if, despite some supporting evidence, we are left with the definite and firm conviction that a mistake has been made. *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948); *see also Polaroid Corp. v. Eastman Kodak Co.*, 789 F.2d 1556, 1559 (Fed. Cir. 1986) ("The burden of overcoming the district court's factual findings is, as it should be, a heavy one."). Obviousness is a question of law, based on underlying factual findings, including what a reference teaches, whether a person of ordinary skill in the art would have been motivated to combine references, and any relevant objective indicia of nonobviousness. *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1047–48, 1051 (Fed. Cir. 2016) (en banc).

I

On appeal, Merck argues that the district court erred in finding that the claims would have been obvious over either the '323 patent or Almarsson because it is undisputed that none of the claimed steps is disclosed in the prior art. Merck contends that the court erred in relying solely on the "knowledge, creativity, and common sense" of a skilled artisan because "common sense" is properly invoked to provide a motivation to combine, not to supply a missing claim limitation. Furthermore, Merck continues, the prior art focused solely on degradation by dimerization, not hydrolysis. In that way, Merck argues, the

prior art taught away from the claimed invention because pH values favorable for reducing dimerization result in increased hydrolysis, and vice versa. Merck also argues that the narrow ranges recited in the dependent claims are the result of the inventors' extensive research efforts, belying the court's finding that routine experimentation would have led to their discovery.

Hospira responds that the district court properly evaluated the claims as a whole and determined that they recite nothing more than an obvious implementation of the disclosures of the '323 patent and Almarsson. Hospira contends that claim 21 recites three broad, general processing steps that constitute nothing more than the routine way a skilled artisan would have implemented the teachings of the '323 patent.

First, Hospira argues, the pH range recited in claim 21 was expressly disclosed in both prior art references as the preferred pH range for forming the carbon dioxide adduct of ertapenem. Thus, Hospira maintains, a skilled chemist would want to first adjust a solution to the preferred pH, thereby minimizing the amount of time ertapenem spends in solution at unstable pH levels. Second, Hospira argues, one of ordinary skill would have understood that the ertapenem salt is slightly acidic (as was disclosed in the prior art), and so would have *simultaneously* added base and ertapenem to the carbon dioxide solution, in order to maintain the preferred pH range disclosed in the prior art. Furthermore, Hospira continues, it was widely known that lower temperatures tend to slow degradation, so one of ordinary skill would have sought to achieve the lowest temperature possible without freezing. Finally, Hospira maintains that the prior art taught that the carbon dioxide adduct could be obtained by "standard lyophilization techniques," and claim 21 does not require any specific lyophilization conditions.

We agree with Hospira that the district court did not err in finding that the claimed process would have been obvious at the time the invention was made. The court found that both references expressly taught minimizing dimerization by forming the carbon dioxide adduct of ertapenem at pH 6.0–9.0, that sodium hydroxide could be used to adjust the pH, and that the final adduct was to be obtained using "standard lyophilization techniques." *See Decision*, 2016 WL 5872620, at *16–17. The court also found that, while the claimed temperature range was not explicitly taught in the prior art, it was understood that degradation is minimized at low temperatures, so one of ordinary skill would have wanted to keep the temperature as low as possible without freezing. *Id.* at *18. Those findings are supported by substantial record evidence.

Merck argues that the specific order and detail of the claimed steps constitute a novel solution to minimizing degradation by *hydrolysis*—a problem not addressed by the prior art—while operating in the pH range of 6.0–9.0, as disclosed in the prior art for minimizing *dimerization*. While that may be so, Merck's problem is that the purported "solution" for minimizing both degradation pathways constitutes nothing more than conventional manufacturing steps that implement principles disclosed in the prior art.

Merck does not dispute that the '323 patent and Almarsson taught exposing ertapenem to a carbon dioxide solution, while maintaining a pH range of 6.0–9.0, followed by lyophilization. Merck also does not dispute that hydrolysis was a known degradation pathway that one of ordinary skill would have sought to minimize. *See* Oral Arg. at 3:45–3:55, http://oralarguments.cafc.uscourts.gov-/default.aspx?fl=2017-1115.mp3 (Merck's counsel stating that "open ring degradation was something that was known in the prior art to affect all beta-lactams").

Merck's purported solution for minimizing both hydrolysis and dimerization was to create the carbon dioxide solution *first*, at the pH range disclosed in the prior art; then *simultaneously* add the ertapenem and a base to the solution, in order to maintain the pH range taught by the prior art; maintain a *low temperature* during the process; and lyophilize the final product to contain *less than 10% moisture content*. The only elements of that process that were not expressly disclosed in the prior art are emphasized in italics above—namely, the order of the steps, the simultaneous addition of base, the specific temperature range, and a final moisture content of less than 10%. But, as the court found, those are all experimental details that one of ordinary skill would have utilized via routine experimentation, armed with the principles disclosed in the prior art.

Thus, it was reasonable for the district court to deduce from the evidence that the order and detail of the steps, if not already known, would have been discovered by routine experimentation while implementing known principles. The court's analysis thus involved no legal error.

II

We next address the district court's treatment of Merck's objective evidence. Merck maintains that the court improperly discounted Merck's objective evidence, which it found to be persuasive, when weighing the obviousness factors.

Hospira responds that the district court correctly found that Merck's evidence of secondary considerations could not overcome Hospira's strong showing of obviousness based on the teachings of the prior art. According to Hospira, that finding warrants deference on appeal and Merck has pointed to no clear error in the district court's findings.

Considering all the evidence, we conclude that the court did not err in finding the invention to have been obvious at the time the invention was made.

The district court found that there was commercial success of Merck's Invanz® product, and that it was sufficiently linked to the asserted claims of the '150 patent. *Decision*, 2016 WL 5872620, at *8–9, *21. However, the court found that this evidence was "weak[ened]" by the "blocking effect" of the '820 patent, which is directed to ertapenem itself, the point being that commercial success was not due to the qualities of ertapenem, but rather to the fact that Merck had control of another patent that precluded competition from others. *Id.* at *9.

Merck's evidence of commercial success should not have been discounted simply because of the existence of another patent of which Merck was the exclusive licensee. We have previously held that where "market entry was precluded" by another patent and by exclusive statutory rights stemming from FDA marketing approvals, "the inference of nonobviousness . . . from evidence of commercial success[] is weak." *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005).

But developers of new compounds often obtain a package of patents protecting the product, including compound, formulation, use, and process patents. Often such patents result from Patent Office restriction requirements relating to the technicalities of patent classifications and rulings that various aspects of claiming an invention cannot be claimed in the same patent. Or they may result from continuing improvements in a product or process. Thus, multiple patents do not necessarily detract from evidence of commercial success of a product or process, which speaks to the *merits of the invention*, not to how many patents are owned by a patentee. Commercial success is thus a fact-specific inquiry that may be relevant

to an inference of nonobviousness, even given the existence of other relevant patents.

Nonetheless, we do not discern clear error in the district court's determination that Merck's evidence of commercial success could not overcome the weight of the evidence that the claimed process was substantially described in the prior art and required only improvement by the use of established variations.

Thus, even giving the evidence of commercial success its full and proper weight, the court did not err in concluding that the claims would have been obvious at the time the invention was made in light of the merely ordinary experimentation required to arrive at the '150 patent, starting from either the '323 patent or Almarsson, for the reasons discussed above.

Second, the district court found that there was evidence of copying by others because Hospira tried five alternative formulations in an attempt to avoid copying the '150 patent, but ultimately had to rely on the accused process, which the court found would infringe the '150 patent. *Decision*, 2016 WL 5872620, at *10. Hospira argues that "evidence of copying is not compelling in the context of ANDA cases because the [Hatch-Waxman Act] requires generic drug manufacturers to copy the approved drug." Appellee Br. 55–56.

We do not agree with Hospira's argument, nor did the district court. The Act does not, as the court noted, require the generic manufacturer to copy the NDA holder's process of *manufacturing* the drug. In any event, as with the evidence of commercial success, the district court found that the evidence of copying could not overcome the weight of the competing evidence of obviousness of the claimed process. We agree with the district court. The claimed process differs from the disclosure of the '323 patent only in routine details, the implementation of which would have been well within the capabilities of one

of ordinary skill in the art. Thus, we conclude that the district court did not err in its conclusion of obviousness.

CONCLUSION

We have considered the parties' remaining arguments but find them to be unpersuasive. For the foregoing reasons, we affirm the decision of the district court.

AFFIRMED

United States Court of Appeals for the Federal Circuit

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Appeal from the United States District Court for the District of Delaware in Nos. 1:14-cv-00915-RGA, 1:14-cv-00916-RGA, Judge Richard G. Andrews.

Newman, *Circuit Judge*, dissenting.

It is time to remedy our inconsistent treatment of the procedures and burdens in applying the evidentiary factors of obviousness, despite the clarifying precedent in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). The Court in *Graham* resolved prior inconsistencies and established what was seen as a wiser standard of obviousness. The Court established the factual premises and fixed the placement of the burdens. It is time to restore this salutary rigor.

In *Graham*, the Court discussed the four factual premises of obviousness[1] and explored the interaction among these factors, explaining that each may affect the weight of the others. The Court also clarified its own precedent, which had separated the objective considerations from the other factual criteria. *See Great Atl. & Pac. Tea Co. v. Supermarket Equip. Corp.*, 340 U.S. 147, 153 (1950) ("[C]ommercial success without invention will not make patentability."); *Jungersen v. Ostby & Barton Co.*, 335 U.S. 560, 567 (1949) (patent invalid despite "considerable commercial success"); *Cuno Eng'g Corp. v. Automatic Devices Corp.*, 314 U.S. 84, 91 (1941) (replacing "flash of creative genius" standard with the *Graham* factors).

The *Graham* Court recognized that the objective indicia are "more susceptible of judicial treatment than are the highly technical facts often present in patent litigation" and such indicia "may lend a helping hand to the judiciary." 383 U.S. at 35–36. Contemporaneous scholarship explained that "[t]he expressed relevance of the 'secondary considerations' in the determination of nonobviousness and the impact of their application in *Adams* was in striking contrast to the Court's prior standards for the determination of 'invention.'" Herbert Mintz & Charles L. O'Rourke, *After* Black Rock*: New Tests of Patentability—The Old Tests of Invention*, 39 Geo. Wash. L. Rev. 123, 142 (1970).

Many Federal Circuit cases have recognized and correctly applied the *Graham* factors; *e.g.*, *Apple Inc. v.*

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[1] The four *Graham* factors are: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the field of the invention; and (4) objective ("secondary") considerations such as commercial success, failure of others, and long-felt need.

Samsung Electronics Co., 839 F.3d 1034, 1048 (Fed. Cir. 2016) (en banc) ("A determination of whether a patent claim is invalid as obvious under § 103 requires consideration of all four *Graham* factors, and it is error to reach a conclusion of obviousness until all those factors are considered."); *In re Cyclobenzaprine Hydrochloride*, 676 F.3d 1063, 1077 (Fed. Cir. 2012) ("[A] fact finder must consider *all* evidence of obviousness and nonobviousness before reaching a determination."); and *Leo Pharmaceutical Products, Ltd. v. Rea*, 726 F.3d 1346, 1357–58 (Fed. Cir. 2013) ("Whether before the Board or a court, this court has emphasized that consideration of the objective indicia is *part of* the whole obviousness analysis, not just an afterthought.").

The Court's analysis was reconfirmed in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 399 (2007) (listing the four *Graham* factors and stating "[w]hile the sequence of these questions might be reordered in any particular case, the factors define the controlling inquiry").

However, some Federal Circuit decisions appear to have sought a shortcut, and converted three of the four *Graham* factors into a self-standing "prima facie" case, whereby the objective considerations must achieve rebuttal weight. This path of analysis was followed by the district court herein, finding that Hospira "made a *prima facie* showing" based solely on the prior art. *Merck Sharp & Dohme Corp. v. Hospira Inc.*, No. CV 14-915-RGA, 2016 WL 5872620, at *19–21 (D. Del. July 10, 2016). The district court stated that "[w]hile the copying and commercial evidence supports the argument for nonobviousness, 'secondary considerations of nonobviousness . . . simply cannot overcome a strong prima facie case of obviousness.'" *Id.* at *21 (citing *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)). Thus, the district court weighed that evidence against the conclusion that the order and detail of the steps would have been discovered by routine experimentation, and placed the obliga-

tion of achieving rebuttal weight on the fourth *Graham* factor.

However, as the Court established, it is incorrect to consign the objective evidence to rebuttal against the other three *Graham* factors. Merck is correct that the question is not whether the evidence of copying and commercial success "could not overcome the weight of the competing evidence of obviousness of the claimed process." Maj. Op. at 11. The question is whether the entirety of the evidence relating to the Merck process, including the evidence of copying and commercial success, establish obviousness. The analysis whereby less than the full factual record is consulted for the "prima facie case," with one of the four *Graham* factors shifted to rebuttal, distorts the placement and the burden of proof.

Merck correctly points out that "the district court either accorded insufficient weight or failed to acknowledge" the objective indicia of nonobviousness. Merck Reply Br. at 17. The objective indicia of nonobviousness play a critical role in the obviousness analysis. They are "not just a cumulative or confirmatory part of the obviousness calculus but constitutes independent evidence of nonobviousness." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). Indeed, objective indicia "may often be the most probative and cogent evidence in the record" and are "to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983).

The Federal Circuit has strayed, leading the district courts into error. Illustration is seen in the case now at bench; and also, for example, in *Cubist Pharmaceuticals, Inc. v. Hospira, Inc.*, 805 F.3d 1112, 1130 (Fed. Cir. 2015) ("We sustain the district court's determination that the secondary consideration evidence did not overcome the

showing of obviousness based on the prior art."); *Novo Nordisk A/S v. Caraco Pharmaceutical Laboratories, Ltd.*, 719 F.3d 1346, 1353 (Fed. Cir. 2013) ("In this case, the court found that Caraco's prima facie evidence, if unrebutted, would be sufficient to establish that the repaglinide/metformin combination was obvious to try . . . . Having so found, it was entirely appropriate for the court to next consider whether Novo's countervailing secondary consideration evidence of unexpected synergy (i.e., its 'attempt to prove unexpected results') was sufficient to 'overcome' Caraco's prima facie case."); *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364 (Fed. Cir. 2012) ("[T]he district court properly discounted the evidence of commercial success as a secondary consideration rebutting Cadbury's showing that the claimed invention would have been obvious.").

Also, *Otsuka Pharmaceutical Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("Because we agree with the district court that the Defendants failed to prove that claim 12 of the '528 patent would have been *prima facie* obvious over the asserted prior art compounds, we need not address the court's findings regarding objective evidence of nonobviousness."); *Tokai Corp. v. Easton Enterprises, Inc.*, 632 F.3d 1358, 1370 (Fed. Cir. 2011) ("[E]ven assuming the existence of a nexus, we see no error in the district court's determination that Tokai failed to establish 'that any of these secondary factors are significant' . . . in light of the strong showing of prima facie obviousness."); *Wyers*, 616 F.3d at 1246 (Fed. Cir. 2010) ("[S]econdary considerations of nonobviousness—considered here by the district court—simply cannot overcome a strong 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."); *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007) ("Aventis has thus failed to show unexpected results that would tend to rebut a prima facie case of 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.").

It is time to restore conformity to precedent, in the interest of stability of practice and procedure, and predictability and fairness of result. I would reestablish the proper analytic criteria under the four *Graham* factors, and would remand to the district court to apply the correct law.