United States Court of Appeals for the Federal Circuit

GALDERMA LABORATORIES, L.P., GALDERMA S.A., AND GALDERMA RESEARCH AND DEVELOPMENT, S.N.C.,
Plaintiffs-Appellees,

v.

TOLMAR, INC.,
Defendant-Appellant.

2013-1034

Appeal from the United States District Court for the District of Delaware in No. 10-CV-0045, Judge Leonard P. Stark.

Decided: December 11, 2013

CHARLES E. LIPSEY, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, of Reston, Virginia, argued for plaintiffs-appellees. With him on the brief were HOWARD W. LEVINE, SANYA SUKDUANG, CORTNEY B. CASP, and VICTORIA S. LEE, of Washington, DC.

THOMAS P. STEINDLER, McDermott Will & Emery LLP, of Washington, DC, argued for defendant-appellant. With him on the brief were JEFFREY R. GARGANO and KEITH M. STOLTE, of Chicago, Illinois.

Before NEWMAN, BRYSON, and PROST, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* PROST.
Dissenting opinion filed by *Circuit Judge* NEWMAN.

PROST, *Circuit Judge.*

In this patent infringement case, Tolmar, Inc. challenges the district court's holding that the claims of U.S. Patent Nos. 7,579,377 ('377 patent); 7,737,181 ('181 patent); 7,834,060 ('060 patent); 7,838,558 ('558 patent); and 7,868,044 ('044 patent), which are owned by Galderma Laboratories, L.P., Galderma S.A., and Galderma Research and Development, S.N.C. (collectively, "Galderma") are not invalid under 35 U.S.C. § 103. We find that the district court erred in finding the claims of the asserted patents not invalid as obvious. Accordingly, we reverse.

I. BACKGROUND

This Hatch-Waxman case is based on Tolmar's filing of an Abbreviated New Drug Application ("ANDA") seeking approval to market a generic version of Differin® Gel, 0.3%, which is a topical medication containing 0.3% by weight adapalene approved for the treatment of acne. On January 21, 2010, Galderma sued Tolmar in the United States District Court for the District of Delaware, alleging that Tolmar's ANDA product infringed certain claims of the '377 patent. Galderma subsequently filed amended complaints alleging infringement of each of the asserted patents. After a bench trial, the district court ruled against Tolmar on several issues of which only invalidity under 35 U.S.C. § 103 is at issue in this appeal.

A. Patented Technology

The asserted patents include both composition claims and claims directed to methods of treating acne using

pharmaceutical compositions. At trial, Galderma alleged infringement of claims 35 and 36 of the '181 patent, claims 24 and 27 of the '060 patent, claim 5 of the '558 patent, and claims 40 and 41 of the '044 patent.[1] Each of the asserted claims requires an aqueous gel or cream that includes 0.3% by weight of adapalene. The asserted claims also recite one or more inactive excipients included in the gel or cream. Claim 5 of the '558 patent is representative:

> 5. A topically applicable pharmaceutical composition comprising 0.3% by weight of [adapalene] relative to the total weight of the composition, effective for the treatment of acne, formulated into a topically applicable, pharmaceutically acceptable medium therefor, said composition being in the form of a topically applicable, pharmaceutically acceptable aqueous gel comprising at least one carbomer gelling agent and wherein the sole anti-acne ingredient is adapalene.

B. Prior Art

Below, Tolmar based its obviousness argument primarily on three pieces of prior art: U.S. Patent No. 4,717,720 ("Shroot '720 patent"), U.S. Reissue No. 34,440 ("Shroot '440 patent"), and the Differin® 0.1% Gel Data Sheet ("Data Sheet").

The Shroot '720 patent specifically discloses and claims adapalene along with other inventive compounds. Col. 3 ll. 9-10; col. 4 ll. 29-37; col. 9 ll. 39-54; col. 19 l.17-col. 20 l. 19. Four of the seven composition examples in the Shroot '720 patent disclose adapalene as the active ingredient, in concentrations of 0.001%, 0.1%, and 1%. Col. 16 ll. 35-53; col. 17 ll. 20-52. The specification of the Shroot '720 patent states repeatedly that the inventive

---

[1] The '377 patent was not asserted at trial.

compounds are useful for the treatment of acne. *See* col. 4 ll. 53-59; *see also* col. 5 ll. 49-53. Moreover, the specification states that the inventive compounds can be used in concentrations "preferably between 0.01 and 1 weight percent, based on the total weight of the composition." Shroot '720 patent col. 5 ll. 61-64. Finally, the Shroot '720 patent indicates that the inventive compounds "are less irritating than known retinoids of analogous structure." Col. 4 ll. 48-51. The Shroot '440 patent is largely similar to the Shroot '720 patent, but also contains claim 4, which recites a preferred range of 0.01 to 1% for cosmetic compositions which include the inventive compounds, e.g., adapalene, as the active ingredient. Shroot '440 patent col. 20 ll. 15-18. Notably, prior to their expiration, the Shroot patents were listed in the FDA's Orange Book as covering Galderma's prior art Differin® 0.1% Gel as well as Differin® Gel, 0.3%.

The Data Sheet is the product insert for Galderma's earlier launched adapalene product. The Data Sheet discloses 0.1% adapalene as a treatment for acne. It also discloses all but one of the inactive ingredients listed in the asserted claims. Other than the dosage of adapalene, the only difference between the claimed formulations and the formulation taught by the Data Sheet is that the Data Sheet discloses "poloxamer 182," while certain asserted claims list "poloxamer 124."

In addition to the Shroot patents and the Data Sheet, Tolmar provided other relevant evidence. For instance, a 1989 article by Jamoulle et al. describes the use of a lotion containing 0.3% adapalene in an animal model to determine whether adapalene was suitable for the treatment of acne. The authors concluded from this test that adapalene was "particularly suitable for the treatment of acne." J.A. 13063. A series of other prior art articles demonstrate that 0.03% and 0.1% adapalene products were effective against acne and well tolerated. These articles include: Verschoore et al., *Efficacy and Safety of CD 271*

Alcoholic Gels in the Topical Treatment of Acne Vulgaris, 124 British J. of Derm. 368-71 (1991) ("Verschoore 1991"); Alirezai et al., *Comparative Study of the Effectiveness and Tolerance of 0.1 and 0.03 Percent Adapalene Gels and of a 0.025 Percent Tretinoin Gel in the Treatment of Acne*, 123 Ann. Dermatol. Venereol. 165-70 (1996) ("Alirezai 1996"); Allec et al., *Skin Distribution and Pharmaceutical Aspects of Adapalene Gel,* 35(6) J. Am. Acad. of Dermatol. S119-25 (1997) ("Allec 1997").

The prior art also teaches the use of 0.3% adapalene for other conditions without intolerable irritability. *See* Verschoore et al., *Adapalene 0.1% Gel Has Low Skin Irritation Potential,* 36(6) J. Am. Acad. of Dermatol. S104-09 (1997) ("Verschoore 1997"); Goldfarb, *Using Adapalene to Treat Photodamage,* Supp. to Skin & Aging 4-7 (Nov. 2000) ("Goldfarb Article"); Goldfarb et al., *Photographic Assessment of the Effects of Adapalene 0.1% and 0.3% Gels and Vehicle on Photodamage Skin,* 14 (Supp. 1) J. Eur. Acad. Dermatol. Venerol. 315 (2000) ("Goldfarb Abstract"); Euvrard, "How Adapalene Can Treat Actinic Keratoses," Supp. to Skin & Aging 12-15 (Nov. 2000) ("Euvrard 2002").[2] There was also an indication in the prior art that dermatologists preferred other retinoids to adapalene at least in part because they were available in multiple concentrations whereas adapalene was only available in one. Bershad et al., *Topical Retinoids in the Treatment of Acne Vulgaris*, 64 (Supp. 2) Cutaneous Med. for the Practitioner 8-19 (Aug. 1999) ("Bershad 1999"). Finally, the prior art indicated that many skilled artisans believed at the time of the invention that 0.1% was the optimal concentration of adapalene for the treatment of

---

[2] Euvrard (2002) appears to have been published in 2000, not 2002. The district court, however, referred to the article as Euvrard (2002). For the sake of consistency, we do the same.

acne. *See* Verschoore 1997; Allec 1997; Czernielewski et al., *Adapalene Biochemistry and the Evolution of a New Topical Retinoid for Treatment of Acne*, 15 (Supp. 3) J. Eur. Acad. Dermatol. Venerol. 5-12 (2001) ("Czernielewski 2001").

II. OBVIOUSNESS

The determination of invalidity for reasons of obviousness under 35 U.S.C. § 103 is a legal conclusion based on underlying facts. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Following a bench trial, we "review the district court's factual findings for clear error and its conclusions of law *de novo*." *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1344-45 (Fed. Cir. 2000).

Factual considerations that underlie the obviousness inquiry include the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any relevant secondary considerations. *See Graham*, 383 U.S. at 17-18. Relevant secondary considerations include commercial success, long-felt but unsolved needs, failure of others, and unexpected results. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007); *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). Because patents are presumed valid, Tolmar was required to prove that the asserted claims were obvious by clear and convincing evidence. *See Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2242 (2011).

Tolmar presents an obviousness case that is both straightforward and potent. At the time of the invention, adapalene was a known compound and the prior art Shroot patents disclose topical adapalene compositions for the purpose of treating acne in a preferred range of 0.01%-1%, including several exemplary formulations containing adapalene in various concentrations. The asserted claims are directed to 0.3% topical adapalene compositions for the treatment of acne, which fall within

the concentration range disclosed in the Shroot patents. Thus, the Shroot patents disclose all of the limitations of the asserted claims, except for a precise teaching of 0.3% adapalene and the specific inactive ingredients of the asserted claims. The specific inactive ingredients of the asserted claims are, however, taught by the Data Sheet.

The Data Sheet discloses each of the inactive ingredients, except for poloxamer 124. However, the district court found poloxamer 124 equivalent to poloxamer 182, which is disclosed in the Data Sheet. Moreover, the district court held that "the record evidence establishes that the inactive ingredients in the claimed formulations [were] routine and obvious, and, therefore, non-inventive." *Galderma Labs., L.P. v. Tolmar, Inc.*, 891 F. Supp. 2d 588, 645 (D. Del. 2012). Notably, on appeal, the parties do not dispute the obviousness of the inactive ingredients of the formulation. Rather, the sole dispute between the parties is whether it was obvious to use a 0.3% adapalene composition for the treatment of acne. Accordingly, Tolmar argues that the asserted claims are obvious because they claim nothing more than the use of an old compound for a known purpose in a concentration that falls within a range disclosed in the prior art as preferred for that purpose.

Tolmar buttresses its obviousness argument with other relevant evidence. This evidence includes a study that used a lotion containing 0.3% adapalene in an animal model to determine that adapalene was "particularly suitable for the treatment of acne." J.A. 13063. Additionally, the prior art showed that 0.03% and 0.1% adapalene products were suitable for the treatment of acne and that 0.3% adapalene products were suitable for the treatment of other conditions without intolerable irritability. Moreover, the prior art indicated that dermatologists desired acne treatments that came in varying concentrations. According to Tolmar, this provides further motivation to

select a 0.3% adapalene composition for the treatment of acne.

The district court rejected Tolmar's obviousness case, finding that Tolmar "failed to establish, by clear and convincing evidence, that the claimed inventions would have been obvious to a person of ordinary skill at the time of the invention." *Galderma Labs.*, 891 F. Supp. 2d at 637. In reaching this conclusion, the district court relied heavily on evidence showing that increasing the dose of adapalene was likely to increase the incidence of certain side effects and evidence showing that 0.1% was considered the optimal adapalene concentration for the treatment of acne. *Id.* at 641-42. In addition, the court found "that at least two secondary considerations, unexpected results and commercial success, additionally support the determination that the asserted claims are not invalid due to obviousness." *Id.* at 642-44.

Prior to addressing the obviousness of the asserted claims, we note an error in the district court's obviousness analysis. The district court framed the obviousness inquiry as requiring Tolmar to provide motivation in the prior art to triple the concentration of adapalene from 0.1% to 0.3%. *Id.* at 638. Tolmar carried no such burden. Rather, Tolmar, like all those who seek to prove claims obvious, was required to show that "the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103. Nothing in the statute or our case law requires Tolmar to prove obviousness by starting with a prior art commercial embodiment and then providing motivation to alter that commercial embodiment. *See KSR*, 550 U.S. at 419 ("In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is

the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103."). This is particularly true where, as here, the prior art teaches a range that encompasses both the prior art commercial embodiment and the claimed invention.

The relevant dispute in this case is thus not over whether the prior art discloses all of the claim elements or over the motivation to combine the prior art references. Rather, the dispute is whether there was motivation to select the claimed 0.3% adapalene composition in the disclosed range. In these circumstances, where there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations. *See Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1352-54 (Fed. Cir. 2013).

Accordingly, Tolmar having demonstrated that the prior art taught a range of concentrations of adapalene for the treatment of acne that encompasses the claimed 0.3% adapalene composition, we now examine the district court's findings with respect to the factors listed above to determine whether the claims are invalid as obvious. The ultimate burden of proving obviousness rests with Tolmar.

A. Teaching Away

Despite express teachings in the Shroot patents indicating that adapalene would be useful in concentrations preferably between 0.01% and 1%, the district court found that the prior art taught away from a 0.3% adapalene composition. The district court based its conclusion

primarily on two related grounds.[3] First, according to the district court, the prior art taught "away from the selection of 0.3% adapalene for the treatment of acne, because of dose-dependent increases in side effects." *Galderma Labs.*, 891 F. Supp. 2d at 641 n.8. And second, the prior art taught that 0.1% was the optimal concentration of adapalene for the treatment of acne. *Id.* at 641-42. We leave undisturbed the district court's findings that increasing the dose of adapalene would result in a concomitant increase in side effects and that 0.1% was the optimal concentration of adapalene for the treatment of acne at the time of the invention. However, to the extent the court found that these facts taught away from the claimed invention, it clearly erred.

> A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. A reference does not teach away, however, if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed.

Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314, 1327 (Fed. Cir. 2009). With respect to the

---

[3] The district court also relied on evidence that other commercially available, more irritating, topical retinoids were recently introduced in lower concentrations due to tolerability issues. The district court, however, provided no rationale as to why one of ordinary skill would do the same with adapalene, which is less irritating than other retinoids. Moreover, the higher concentration formulations of the other topical retinoids remained commercially available. J.A. 10343-44, 10519.

prior art teachings of dose-dependent side effects, the district court relied on the Verschoore 1991 and Alirezai 1996 articles, which show that the increase in adapalene concentration from 0.03% to 0.1% resulted in an increase in side effects. Neither of these articles mentions 0.3% adapalene compositions, nor do they expressly teach away from the claimed invention. The district court inferred that these references taught away from a further tripling of the adapalene concentration. We cannot agree with this inference.

These articles show increased side effects associated with 0.1% adapalene as compared to 0.03% adapalene, yet they failed to discourage even the use of 0.1% adapalene. To the contrary, as the district court found, 0.1% was the optimal concentration of adapalene at the time of the invention. *Galderma Labs.*, 891 F. Supp. 2d at 641-42. Moreover, there is nothing in either of these references to indicate that increasing the concentration to 0.3% would be unproductive, nor do these articles indicate in any way that the side effects would be serious enough to dissuade the development of a 0.3% adapalene product. Therefore, the Verschoore 1991 and Alirezai 1996 articles fail to teach away from the claimed invention.

The district court relied on the Allec 1997, Verschoore 1997, and Czernielewski 2001 articles to demonstrate that 0.1% was the standard or optimal concentration of adapalene for the treatment of acne. The court concluded that this fact teaches away from 0.3% adapalene compositions. It does not. "A reference does not teach away . . . if it . . . does not 'criticize, discredit, or otherwise discourage' investigation into the invention claimed." *Depuy Spine*, 567 F.3d at 1327 (citing *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004)). A teaching that a composition may be optimal or standard does not criticize, discredit, or otherwise discourage investigation into other compositions. Accordingly, the Allec 1997, Verschoore 1997, and Czer-

nielewski 2001 articles do not teach away from the claimed invention.

B. Unexpected Results

The district court found that the comparable tolerability of 0.1% and 0.3% adapalene was unexpected in view of the prior art, since a skilled artisan would have expected that tripling the concentration of adapalene would have resulted in a clinically significant increase in side effects. *Galderma Labs.*, 891 F. Supp. 2d at 642-44. While we agree that this result was unexpected, it does not constitute an unexpected result that is probative of non-obviousness.

Unexpected results that are probative of non-obviousness are those that are "different in kind and not merely in degree from the results of the prior art." *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004) (citation omitted). Results which differ by percentages are differences in degree rather than kind, where the modification of the percentage is within the capabilities of one skilled in the art at the time. *See In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005) (finding increased efficacy, measured by percentages, to be a difference of degree and not of kind); *In re Budde*, 319 F.2d 242, 246 (C.C.P.A. 1963) (finding no unexpected results where ranges of reaction time and temperature constituted only a difference in degree rather than in kind); *In re Aller*, 220 F.2d 454, 456-57 (C.C.P.A. 1955) (finding no unexpected results where improved yields over the prior art, measured by percentages, reflect a difference in degree, not in kind). Thus, where an unexpected increase in efficacy is measured by a small percentage, as here, and the evidence indicates that skilled artisans were capable of adjusting the percentage, the result constitutes a difference in degree, not kind. So too, where an increase by a percentage is expected but not found, that result is also likely only a difference in degree. In this case, the

expected result was an increase, by some percentage, in the prevalence of certain side effects. The failure of that percent increase to materialize, though unexpected, constitutes only a difference in degree from the prior art results. Accordingly, the comparable tolerability of 0.1% and 0.3% adapalene does not indicate that the asserted claims are non-obvious.

C. Commercial Success

"Evidence of commercial success . . . is only significant if there is a nexus between the claimed invention and the commercial success." *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006). "When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention." *J.T. Eaton & Co. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). However, "if the feature that creates the commercial success was known in the prior art, the success is not pertinent." *Ormco Corp.*, 463 F.3d at 1311-12; *see also J.T. Eaton*, 106 F.3d at 1571 ("[T]he asserted commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art").

The district court found that "[t]he commercial success of Galderma's 0.3% adapalene product also supports a finding of nonobviousness." *Galderma Labs.*, 891 F. Supp. 2d at 644. The district court gave two reasons for its finding. First, Differin® 0.3%, Galderma's commercial embodiment of the claims, "quickly gained and maintained market share—even in the face of an overall declining market and decreasing promotional expenditures, and while facing competition from generic 0.1% adapalene formulations." *Id.* Second, the court found "that Tolmar (along with another ANDA filer, Actavis) seeks to enter

the market precisely because Differin® 0.3% has been commercially successful." *Id.* We discuss these findings in reverse order.

The mere fact that generic pharmaceutical companies seek approval to market a generic version of a drug, without more, is not evidence of commercial success that speaks to the non-obviousness of patent claims. Plainly, Tolmar believes that it can make a profit selling a generic version of the claimed invention. This is likely true in all Hatch-Waxman cases, if not all patent cases generally. However, that fact tells us very little about the level of commercial success of the patented invention relative to the prior art or the extent to which the commercial success of the branded drug is "due to the merits of the claimed invention beyond what was readily available in the prior art." *J.T. Eaton*, 106 F.3d at 1571. As such, it does not support a finding of non-obviousness.

The court also relied on the fact that Differin® Gel, 0.3% quickly gained and maintained market share to find commercial success. We do not disturb this finding. However, we note that it is of limited value in determining whether or not the presently asserted claims are obvious. "Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). Where "market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence of commercial success, is weak." *Id.* at 1377. This principle applies forcefully to the present case.

The now expired Shroot patents blocked the market entry of 0.3% adapalene products until their expiration in 2010, long after Galderma invented 0.3% adapalene compositions of the asserted claims. As such, no entity

other than Galderma could have successfully brought to 0.3% to market prior to 2010. Like the commercial success described in *Merck & Co.*, the commercial success of Differin® Gel, 0.3% is of "minimal probative value." *Id.* at 1376. Accordingly, we conclude the district court erred in adjudging this factor as confirming its conclusion of non-obviousness.

III. CONCLUSION

For the foregoing reasons, we hold that claims 35 and 36 of the '181 patent, claims 24 and 27 of the '060 patent, claim 5 of the '558 patent, and claims 40 and 41 of the '044 patent are invalid as obvious. We therefore reverse the district court's finding that the claims are valid.

REVERSED

United States Court of Appeals for the Federal Circuit

GALDERMA LABORATORIES, L.P., GALDERMA S.A., AND GALDERMA RESEARCH AND DEVELOPMENT, S.N.C.,
Plaintiffs-Appellees,

v.

TOLMAR, INC.,
Defendant-Appellant.

2013-1034

Appeal from the United States District Court for the District of Delaware in No. 10-CV-0045, Judge Leonard P. Stark.

Before NEWMAN, BRYSON, and PROST, *Circuit Judges.*

NEWMAN, *Circuit Judge*, dissenting.

Without doubt, the question of obviousness here presented is a close call. However, when the question is close, when it turns on findings and interpretations of biologic and medicinal evidence, when the application of law to fact invokes the policy of the patent statute to advance the useful arts, then the findings and rulings of the trial court warrant particular attention on appellate review.

Here, the district court fully explored the evidence relating to whether it would have been obvious to increase by 300% the concentration of the active ingredient adapalene without increasing its known adverse side effects. The district judge held an eight-day bench trial, heard thirteen live witnesses including expert witnesses of stature and experience, and received evidence and argument from both sides. The court issued an opinion with over 50 pages on the issue of obviousness, finding the facts and weighing the evidence and applying the law with thoughtful explanation and reasoning.[1]

My colleagues on this panel give scant attention to the district court's analysis, instead making their own findings, and applying flawed procedural and substantive law. My colleagues do not identify clear error in the district court's findings; instead they distort the burdens of proof and production, ignore the applicable standard of proof and rely on their own factual determinations and creative theories of law, and eradicate the patent.

The district court ruled that there was not clear and convincing evidence of invalidity. By contrast, my colleagues announce their rule whereby a broad teaching that includes the patented invention removes the statutory presumption of validity, and without more establishes obviousness. *See* maj. op. at 9 ("where there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee…"). Although the majority mentions the requirement of clear and convincing evidence of invalidity, the majority presumes that the prior art establishes invalidity, and places on the patentee the burden of establishing patentability based on "secondary considera-

---

[1] *Galderma Laboratories, L.P. v. Tolmar, Inc.*, 891 F. Supp. 2d 588 (D. Del. 2012) ("DCt. Op.").

tions." The majority goes on to impose a new and unprecedented view of these considerations.

For example, although the panel majority concedes that there are unexpected results for the concentration selected by the patentee, *see* maj. op. at 12 ("we agree that this result was unexpected"), my colleagues do not require the patent challenger to show any reason in the prior art (or common sense) for selection of this embodiment with its unexpected properties. Rather, they hold that unless a skilled artisan was not "capable of adjusting the percentage," *id.*, the extent of the change in percentage (here 300%) and the unexpected results and properties are irrelevant to patentability.

In refusing to credit any of the demonstrated "secondary considerations" my colleagues foreclose patentability to a vast body of improvement patents. In the field of medicaments, the denial of patentability for improvements is a disincentive to the development of such improvements. The losers are those afflicted with disease. I respectfully dissent.

DISCUSSION

Particularly for close questions of patentability, the district court's findings and assessments of credibility and weight of evidence, and the district court's application of law to found facts, compel appellate attention. The role of the trial court in considering the evidence that each party provides through examination and cross-examination of witnesses and documents, with judicial elaboration and interaction, cannot be matched on appeal. As the Supreme Court stated in *Anderson v. Bessemer City*, "duplication of the trial judge's efforts in the court of appeals would very likely contribute only negligibly to the accuracy of fact determination at a huge cost in diversion of judicial resources." 470 U.S. 564, 574-75 (1985).

Clear and convincing evidence is required to overcome the statutory presumption of validity of a duly granted patent. *See* 35 U.S.C. §282 (a patent is presumed valid); *Cardinal Chem. Co. v. Morton Int'l*, 508 U.S. 83, 93 n.15 (1993) (invalidity must be proved by clear and convincing evidence). Here the panel majority does not provide clear and convincing evidence of invalidity. Instead, the majority discards the trial judge's findings on the premise of a presumption of invalidity that the majority applies to "selection" inventions, that is, inventions within a known class or range of technology, for which the majority discards the established procedural and substantive burdens. The majority makes its own factual findings, and writes new law.

In contrast to the panel majority's dismissive analysis, the district court's findings reflect careful examination of all of the evidence. Nonetheless, my colleagues conclude that the selection of a 300% increase in dosage was obvious, after the unexpected properties of the increase were discovered by this patentee. I summarize some of the evidence before the district court, whose findings well support the conclusion that invalidity on the ground of obviousness was not established by clear and convincing evidence:

I

THE PRIOR ART

In this Hatch-Waxman case, Tolmar, Inc. seeks to invalidate Galderma's patents on the commercially successful acne medication whose active ingredient is the retinoid adapalene in 0.3% concentration. There was extensive prior art showing retinoids including adapalene in a range of concentrations for various uses, and showing the prior selection of 0.1% adapalene for treatment of acne because higher concentrations were shown to be unduly irritative to acne-ridden skin.

The district court found that the knowledge in the field taught away from the 0.3% concentration, based on the expert testimony and documentary evidence at trial. The district court, applying the correct standard, held that Tolmar did not prove invalidity by clear and convincing evidence.

The *Shroot* Patents (1988, 1992, 1993)[2]

These are Galderma's now-expired patents on benzonaphthalene derivatives including adapalene, and their use to treat acne. The issue is the selection of the 0.3% adapalene concentration in the patents-in-suit.

The district court found that "the [Shroot] range of 0.0005% to 5% for topical compositions covers four orders of magnitude (or a 10,000-fold dosage range)" and that "even the 'preferred' range of 0.01% to 1% is a hundred-fold dosage range." DCt. Op. at 609. The district court found that "[f]rom this large genus of potential treatments, Galderma selected 0.1% adapalene as the concentration of adapalene with which to begin development of a topical treatment for acne." *Id*. at 603. Dr. Shroot testified that the 0.1% dosage was considered the optimal dose for tolerance in a rabbit irritation study. Tr. at 1841:12-17.

The district court found that "[t]he broad disclosure of the Shroot patents provides no motivation or suggestion to select 0.3% adapalene for the treatment of acne." *Id*. at 608-609. The correctness of these findings is not challenged by the panel majority.

---

[2] U.S. Patent Nos. 4,717,720; 5,098,895; Reissue Patent No. 34,440.

The *Verschoore* article (1991)[3]

Verschoore (1991) discusses a Phase II clinical trial where 0.03% and 0.1% adapalene formulations, along with 0.025% tretinoin (a retinoid previously approved for topical use) were tested on the faces of patients with acne. The test data showed that the 0.1% adapalene formulation caused increased irritation compared to the 0.03% formulation. DCt. Op. at 604. Galderma's expert testified that persons of ordinary skill in this art would view these data as suggesting that "a significant increase in tolerability measures" would result from a further tripling of the adapalene dose from 0.1% to 0.3%. Tr. at 1230:15-20.

The district court found, supported by the expert testimony, that "[t]he results of this study suggest that increasing the concentration of adapalene beyond 0.1% would result in significantly increased irritation." DCt. Op. at 604. My colleagues disagree with what they call the district court's "inference" that Verschoore (1991) and Alirezai (1996) (*see infra*) taught away from a further tripling of the dose. Thus my colleagues replace the testamentary and documentary expertise that supports the district court's findings, with the expertise of the panel majority.

---

[3] Verschoore et al., *Efficacy and Safety of CD 271 Alcoholic Gels in the Topical Treatment of Acne Vulgaris,* 124 British J. of Derm. 368–71 (1991).

The *Alirezai* article (1996)[4]

The district court found that "the trend of increased irritation between the 0.03% and 0.1% dosages disclosed in Verschoore (1991) was later confirmed in the same dosages in aqueous gels in a publication by Alirezai et al. entitled 'Comparative Study of the Effectiveness and Tolerance of 0.1 and 0.03 Percent Adapalene Gels and of 0.025 Percent Tretinoin Gel in the Treatment of Acne.'" DCt. Op. at 604. The district court found that this article disclosed that "severe burning was seen in no patients treated with the 0.03% adapalene, but was seen in 13% of patients treated with the 0.1% adapalene aqueous gel" and that "significantly higher levels of 'average' burning and itching after application were observed with the 0.1% formulation as compared to the 0.03% formulation." *Id.* at 605.

The district court found that "[t]his study, conducted on the faces of acne patients, demonstrates that the tolerability of the 0.1% dosage was different than the 0.03% dosage." *Id.* The correctness of this finding is not challenged by my colleagues. In concluding that Alirezai (1996) does not teach away from the claimed invention, my colleagues ignore the district court's finding that significantly higher levels of burning and itching were observed upon increasing the adapalene concentration of the formulation.

---

[4] Alirezai et al., *Comparative Study of the Effectiveness and Tolerance of 0.1 and 0.03 Percent Adapalene Gels and of a 0.025 Percent Tretinoin Gel in the Treatment of Acne*, 123 Ann. Dermatol. Venereol. 165–170 (1996).

The *Allec* article (1997) [5]

This article, entitled "Skin Distribution and Pharmaceutical Aspects of Adapalene Gel," is discussed by the district court as "describ[ing] the results of in vivo models used to select *the optimal concentration* of adapalene for efficacy and safety…". DCt. Op. at 605 (emphasis in original). The article concludes that "[b]ased on these in vivo results, 0.1% was considered as the optimal concentration of drug for adapalene gel. This choice was subsequently confirmed in clinical trials of safety and efficacy." *Id.* at 606, quoting Allec (1997) at S123.

The district court found that "[a] person of ordinary skill in the art would have recognized these statements as a conclusion of the company that developed adapalene had determined, from all the data it had on hand, that 0.1% was the optimal concentration for acne treatment, balancing efficacy and safety." *Id.* at 606. My colleagues concede, citing Allec (1997), that "the prior art indicated that many skilled artisans believed at the time of invention that 0.1% was the optimal concentration of adapalene for the treatment of acne." Maj. op. at 5-6. My colleagues do not explain the grounds for their belief contrary to that of "many skilled artisans."

The *Verschoore* article (1997) [6]

This article describes Phase I clinical trials conducted by Galderma on healthy subjects. The article states:

---

[5] Allec et al., *Skin Distribution and Pharmaceutical Aspects of Adapalene Gel,* 35(6), J. Am. Acad. of Dermatol. S119–S125 (1997).

[6] Verschoore et al., *Adapalene 0.1% Gel Has Low Skin Irritation Potential,* 36(6) J. Am. Acad. of Dermatol. S104–109 (1997).

> We carried out 13 different controlled, randomized, intraindividual comparison phase I studies in 339 healthy human volunteers to investigate the cutaneous safety of adapalene []. The irritation potential of adapalene 0.03%, 0.1%, and 0.3% gels was found to be low, whether tested under occlusive or nonocclusive conditions on a variety of sites (face, chest, back, and buttocks).

Verschoore (1997) at S104. At the trial Tolmar stressed the testing by Verschoore of the 0.3% formulation. The district court found that "[t]he Phase I irritation test described in Verschoore (1997) was a screening test done on uncompromised healthy skin on the back as a prelude—not a substitute—to clinical testing on the face or on patients with disease. . . . A skilled person would understand that data from these Phase I studies conducted on healthy skin cannot be extrapolated to how the product will work in acne patients." DCt. Op. at 610. The district court found that "Verschoore (1997) demonstrates that Galderma decided to pursue and obtain clinical approval for 0.1% adapalene. Further the mention of the 0.3% concentration in the article demonstrates to one skilled in the art that the 0.3% adapalene was tried and rejected as the dosage to pursue for further clinical testing." *Id.* at 606-607.

The district court received testimony from experts on both sides. Galderma's expert testified that a skilled person would know that patch testing on the backs of healthy volunteers is a "poor predictor" of the irritation experienced by facial skin damaged by acne. Tr. at 1244:19-1245:6. Tolmar's expert had previously written[7]

---

[7] Saqib J. Bashir & Howard I. Maibach, *Methods for Testing the Irritation and Sensitization Potential of Drugs and Enhancers*, *in* Biochemical Modulation of Skin

that this type of irritation test "had *failed* to predict adverse reactions to skin *damaged by acne* or shaving, on *sensitive areas* such as the face." DCt. Op. at 610 (emphasis in original). Although Tolmar's expert stated a different opinion at trial, the district court found that the witness did not refute the views he had previously published on the non-predictive nature of patch tests on the backs of healthy individuals. *Id.* at 622.

These district court findings are not challenged by my colleagues.

The *Czernielewski* article (2001) [8]

This article summarizes the results of adapalene studies including those reported in Alirezai (1996) and Verschoore (1997). The article explains that the "primary objective in the development of adapalene was to create a topical agent with retinoid therapeutic effects that is considerably less irritating than topical tretinoin." DCt. Op. at 640. The court states: "Adapalene 0.1% became the standard concentration for subsequent adapalene formulations." *Id.*

The district court found that "[t]he Czernielewski article suggests that 0.1% adapalene is the optimal dose for the treatment of acne," and that the article "does not disclose any information about any doses higher than 0.1% adapalene." DCt. Op. at 607. My colleagues do not challenge the district court's findings that the prior art,

---

Reactions: Transdermals, Topicals, Cosmetics 45, 50 (Agis F. Kydonieus & John J. Wille eds., 2000).

[8] Czernielewski et al., *Adapalene Biochemistry and the Evolution of a New Topical Retinoid for Treatment of Acne*, 15 (Suppl. 3) J. Eur. Acad. Dermatol. Venerol. 5–12 (2001).

including Czernielewski (2001), shows that 0.1% was believed to be the optimal adapalene dose.

The *Goldfarb* article (2000) [9]

This article describes a study of the treatment of photodamaged skin with 0.1% and 0.3% adapalene formulations. The authors describe both of these adapalene concentrations as being "tolerated well." DCt. Op. at 613.

The district court again received evidence and testimony from experts for both sides. Galderma's expert explained the differences between photodamaged skin and skin with acne, and the different patient populations. Tr. at 1290:1-1293:1. The district court found that publications by Tolmar's expert showed that "one of ordinary skill in the art would understand older skin with photodamage and actinic keratosis to be less sensitive to the retinoid reaction compared to younger skin with acne." *Id.* The expert's contrary testimony at trial did not refute his prior published statements. Credibility findings are the particular province of the trial judge.

The district court found that the results of this study "are not predictive of how the same drug would affect patients with acne. One of ordinary skill in the art would know that these results on photodamaged skin should not be extrapolated to acne." *Id.* Without either acknowledging or disputing this finding, my colleagues cite Goldfarb as teaching that 0.3% adapalene can be used for "other conditions" without intolerable irritability. Maj. op. at 5.

---

[9] Goldfarb, *Using Adapalene to Treat Photodamage,* Supp. to Skin & Aging 4–7 (Nov. 2000).

The *Euvrard* article (2002) [10]

Euvrard (2002) describes a study using 0.1% and 0.3% adapalene to treat "actinic keratosis on the hands and forearms of organ transplant patients who were presumably on immunosuppressive drugs." DCt. Op. at 614. The district court summarized the Euvrard conclusion that "[t]olerance was excellent everywhere" and "[t]aking into account the good tolerance of adapalene, these results encourage further studies on the use of adapalene at . . . higher dosage regimens." *Id.*

There was expert testimony from both sides, and the district court found, as with Goldfarb, that "[d]ifferences exist between the properties of facial skin and skin on the extremities, such as the hands and forearms studied in Euvrard. Facial skin, more traditionally afflicted with acne, is much more prone to irritation and often thinner than skin on extremities." *Id.* The district court found that "[b]ased on these differences, one of ordinary skill in the art would not conclude from Euvrard that adapalene 0.3% gel would result in the same tolerability profile in patients with acne vulgaris." *Id.*

The correctness of this finding is not disputed by my colleagues. Instead, without acknowledging or correcting the district court's findings, my colleagues cite Euvrard (2002) as teaching the use of 0.3% adapalene for "other conditions" without intolerable irritability. However, the issue here is acne vulgaris, not "other conditions."

Differin 0.1% Gel Data Sheet (1996)

Differin® is the trademark for Galderma's adapalene products. The data sheet for 0.1% Differin cautioned against "overdosage," stating that: "If the medication is

---

[10] Euvrard, *How Adapalene Can Treat Actinic Keratoses*, Supp. to Skin & Aging 12–15 (Nov. 2000).

applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur." DCt. Op. at 607. Galderma cited the overdosage warning as evidence of teaching away from higher adapalene concentrations. The district court did not appear to give weight to the data sheet, explaining that the warning was required by law. *Id.* at 642 n.11 (citing 21 C.F.R. § 201.56).

The *Bershad* article (1999)[11]

This article describes a "roundtable" meeting of dermatologists. Referencing the commercial 0.1% adapalene product, Bershad (1999) states that "[a]lthough adapalene is commonly believed to be one of the least irritating topical retinoids, the perception of many dermatologists is that this advantage is at least partially negated by a relatively lower efficacy compared with the other topical retinoids." Bershad (1999) at 11. The district court did not discuss Bershad, although it is cited by the panel majority.

Tolmar contends that this article provides motivation to increase the concentration of adapalene. Galderma responds that this article does not show any expectation or understanding that the concentration of adapalene could be increased three-fold without the predicted irritating side effects. At trial, Tolmar's expert opined that this article suggested using doses of adapalene higher than 0.1%. Tr. at 1301:14-16. Galderma's expert disagreed, stating that the authors were merely discussing the characteristics of the various available acne treatments. Tr. at 1301:21-23. This roundtable discussion does not render obvious the three-fold increase in dosage, when so

---

[11] Bershad et al., *Topical Retinoids in the Treatment of Acne Vulgaris*, 64 (Suppl. 2) Cutaneous Med. for the Practitioner 8-19 (Aug. 1999).

many publications cautioned against the increased irritability of higher dosages.

The Jamoulle article (1989)[12]

This article describes a study involving the application of a formulation containing 0.3% adapalene to hairless rats. The district court did not discuss this article. The panel majority states that Jamoulle (1989) teaches the use of 0.3% adapalene to treat acne. Maj. op. at 4. However, results in hairless rats were not shown to establish dosage and tolerance on human skin, much less skin sensitized by acne.

II

THE "SECONDARY CONSIDERATIONS"

Commercial Success

The district court found that despite late entry into a crowded market for treatment of acne, Galderma's Differin® 0.3% gel quickly gained and maintained market share, despite an overall declining market. The district court agreed with Galderma that Tolmar seeks to sell the 0.3% formulation precisely because that formulation is preferred by consumers over the 0.1% formulation. The court found that the availability of cheaper generic 0.1% adapalene after the expiration of the Shroot patents did not appear to have affected consumer demand for the Differin® 0.3% product, whose market share and revenue were not explained by promotional activity, which had actually decreased. Clear error has not been shown in these findings.

---

[12] Jamoulle et al., *Follicular Penetration, Distribution and Migration of CD271, a New Napthoic Acid Derivative for Topical Acne Treatment*, 3 Pharmacol. & the Skin 198-200 (1989).

My colleagues discount the factor of commercial success, arguing that the entry of 0.3% adapalene products, by Tolmar or others, had previously been blocked by the Shroot patents. Maj. op. at 14. However, the evidence in the district court was that the 0.3% product was successful against the 0.1% product and other acne medications. The district court did not err in including evidence of commercial success in its evaluation of the question of obviousness.

Teaching Away

The district court found, based on the prior art and the expert testimony presented by both sides, that the evidence as a whole taught away from increasing the concentration of adapalene above 0.1%. The district court found that "[t]he increased irritation observed in [Verschoore (1991) and Alirezai (1996)] when tripling the concentration of adapalene from 0.03% to 0.1% effectively taught away from again tripling the concentration from 0.1% to 0.3%, given the potential for increased side effects." DCt. Op. at 641-42.

The district court also found that Allec (1997), Verschoore (1997) and Czernielewski (2001) "would also have taught away from tripling the concentration of adapalene from 0.1% to 0.3%, which would have been a significant deviation from the then-understood optimal concentration." DCt. Op. at 642. The court found that the experience of those skilled with other topical retinoids that had been approved for human use, such as tretinoin and tazarotene, further taught away from tripling of the concentration of adapalene. The court explained that both tretinoin and tazarotene faced tolerability problems which required the manufacturers to decrease their concentration in products for the treatment of acne. Clear error has not been shown in these findings.

Unexpected Results

The district court found that it was unexpected that the tolerability profile of 0.3% adapalene was not statistically different from that of 0.1% adapalene. Tolmar had argued—and repeats on appeal—that at most the tolerability profile of 0.3% adapalene represents a difference in degree, not in kind. However, based on expert testimony from both sides, the district court found that "[w]hereas the prior art suggested a dose-dependent, clinically meaningful increase in side effects would result from increasing the concentration of adapalene from 0.03% to 0.1%, the claimed inventions achieved a difference in kind by discontinuing that trend." *Id.* at 643.

The district court explained that differences in degree occur when the invention is merely a continuation of a trend previously described in the prior art. *Id.* at n. 14 (citing *In re Huang*, 100 F.3d 135 (Fed. Cir. 1996); *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1323 (Fed. Cir. 2004)). Here, the prior art showed a trend to increased adverse side effects with increased concentration, while Galderma's products violated that trend. This was a difference in kind, not in degree.

Clear error has not been shown in these findings, all of which are discounted or ignored by the panel majority.

III

THE DECISION AT TRIAL

The district court considered all of the evidence and argument, and concluded that the claims to the 0.3% adapalene formulations had not been proved invalid by clear and convincing evidence. The court acknowledged Tolmar's argument that obviousness should be presumed: Tolmar argued that "because 0.3% adapalene falls within the 0.01%-1.0% range previously disclosed in Galderma's Shroot patents the claimed inventions are prima facie obvious," and that "'evidence of secondary considerations

simply cannot overcome the presumption' of obviousness." DCt. Op. at 637 (quoting Tolmar's trial brief). The district court, unlike the panel majority, correctly recognized that a prima facie showing is not a presumption of obviousness, and does not change the placement of the burden of proof. The district court recited:

> Recently, the Federal Circuit rejected such an approach to obviousness in the context of litigation. The Federal Circuit noted that the Supreme Court "has never spoken in terms of a legally rebuttable presumption with respect to obviousness;" nor has it provided any "indication that it believes the burden of persuasion should shift to the patentee at [any] point to prove nonobviousness."

DCt. Op. at 637-638 (quoting *In re Cyclobenzaprine Hydrochloride Litigation*, 676 F.3d 1063, 1078 (Fed. Cir. 2012)).

The district court correctly explained that "the proper analysis of obviousness under 35 U.S.C. §103 requires that 'all evidence relevant to obviousness or nonobviousness be considered, and be considered collectively,' without resort to presumptions of prima facie obviousness or burden-shifting." DCt. Op. at 638 (quoting *Cyclobenzaprine,* 676 F.3d at 1078). This is the correct standard, established in *Graham v. John Deere* and reiterated consistently and exhaustively.

The dispositive findings in this case, *viz.* the content of the prior art, whether the prior art taught away, whether the invention produced unexpected results, and whether there was commercial success, involve factual inquires that must be accepted on appeal unless clearly erroneous. *See In re Applied Materials, Inc.*, 692 F.3d 1289, 1294 (Fed. Cir. 2012) ("Obviousness is a question of law with several underlying factual inquiries, including what a reference teaches, whether a reference teaches away, and whether there is commercial success.") (citing

Graham v. John Deere Co. of Kan. City, 383 U.S. 1, 17-18 (1966)). Clear error has not been shown in the district court's findings. Instead, on highly selective snippets of the information that was before the district court, my colleagues simply make their own findings.

The burden of overcoming a district court's factual findings is heavy. *See Anderson v. Bessemer City, N.C.,* 470 U.S. 564, 574 (1985) ("Where there are two permissible views of the evidence, the factfinder's choice between them cannot not be clearly erroneous."). Based on the expert testimony, the documentary evidence, and the factual findings of teaching away, unexpected results, and commercial success, the district court concluded that Tolmar failed to prove by clear and convincing evidence that the inventions of the patents-in-suit would have been obvious to a person of ordinary skill in the field of the inventions. For the reasons discussed by the district court, the judgment requires affirmance.

Tolmar was required to provide clear and convincing evidence that the selection of 0.3% from within the broad range in the prior art was obvious in view of the entirety of the evidence. The evidence at trial was that the increase in adapalene concentration was viewed skeptically, and that the combination of efficacy and safety of the 0.3% dose was unexpected to the experts. The experts at trial agreed that the beneficial combination of properties of the 0.3% dose could not have been predicted in advance – indeed the opposite was predicted. The resultant product was commercially successful despite the cheaper prior product at lower dosage.

The panel majority mentions but does not apply the presumption of validity. My colleagues hold that for inventions "where there is a range disclosed in the prior art, and the claimed invention falls within that range," the burden falls upon the patentee to support patentability. Maj. op. at 9. This is not just a shift in the burden of

production; the majority never requires that Tolmar meet its burden of persuasion. Instead, once Tolmar had demonstrated that the invention fell within a broad range disclosed in the prior art, according to the panel majority, Tolmar met its evidentiary burden. My colleagues do not require that the prior art provide some reason for selection of the patented embodiment. Instead, the court places the burden of "rebuttal" on the patentee, and limits rebuttal to the "secondary considerations."

The panel majority also makes creative new rules, ruling that patentability is negated "where the modification of the percentage is within the capabilities of one skilled in the art at the time." Maj. op. at 12. The holding that since "skilled artisans were *capable of* adjusting the percentage," the product containing 300% more active ingredient, "although unexpected" in properties, *id.,* is unpatentable, is new and incorrect law. A skilled artisan will nearly always be "capable" of adjusting a percentage of an ingredient; this fact does not render unexpected results not probative of unobviousness.

Thus the court places new obstacles in the path of improvement patents, a change of law that is particularly pernicious in the arts where small differences may have large consequences or benefits. This rule is of further mischief now that the nation has adopted a first-to-file law with its pressures for early filing, possibly before all embodiments have been fully explored.

The district court applied the correct law to a vast body of evidence, most of which is not discussed by the panel majority. The district court properly applied statute and precedent. From my colleagues' inappropriate rulings, I respectfully dissent.