737 F.3d 731 (2013)

GALDERMA LABORATORIES, L.P., Galderma S.A., and Galderma Research and Development, S.N.C., Plaintiffs-Appellees,

v.

TOLMAR, INC., Defendant-Appellant.

No. 2013-1034.

United States Court of Appeals, Federal Circuit.

December 11, 2013.

734 *734 Charles E. Lipsey, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, of Reston, VA, 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, IL.

Before NEWMAN, BRYSON, and PROST, Circuit Judges.

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

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 *735 ("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.17col. 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 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. *736 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 acne. See Verschoore 1997; Allec 1997; Czernielewski et al.

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, 86 S.Ct. 684, 15 L.Ed.2d 545 (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, 86 S.Ct. 684. 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, 127 S.Ct. 1727, 167 L.Ed.2d 705 (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, ___ U.S. ___, 131 S.Ct. 2238, 2242, 180 L.Ed.2d 131 (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,
737 and, therefore, non-inventive." Galderma Labs., L.P. v. Tolmar, Inc., 891 F.Supp.2d *737 588, 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

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, 127 S.Ct. 1727 ("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
738 0.3% adapalene composition in the disclosed *738 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 Nordi*sk* 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.

DePu*y* Spine, Inc. v. Medtroni*c* Sofamo*r* Danek, Inc., 567 F.3d 1314, 1327 (Fed.Cir. 2009). With respect to the 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.

739 These articles show increased side effects associated with 0.1% adapalene as *739 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 Czernielewski 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 nonobviousness.

Unexpected results that are probative of nonobviousness 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, 50 C.C.P.A. 1491, 319 F.2d 242, 246 (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, 42 C.C.P.A. 824, 220 F.2d 454, 456-57 (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.

740 *740 ## 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")

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