United States Court of Appeals for the Federal Circuit

LEO PHARMACEUTICAL PRODUCTS, LTD.
Appellant,

v.

Teresa Stanek Rea, ACTING DIRECTOR, UNITED STATES PATENT AND TRADEMARK OFFICE,
Appellee.

2012-1520

Appeal from the United States Patent and Trademark Office, Board of Patent Appeals and Interferences in No. 95/000,153.

Decided: August 12, 2013

WILLIAM E. SOLANDER, Fitzpatrick, Cella, Harper & Scinto, of New York, New York, argued for appellant. On the brief were ANDREW D. MEIKLE , LEONARD R. SVENSSON and EUGENE T. PEREZ, Birch, Stewart, Kolasch & Birch, LLP, of Falls Church, Virginia.

AMY J. NELSON, Associate Solicitor, United States Patent & Trademark Office, of Alexandria, Virginia, argued for appellee. With her on the brief was FRANCES M.

LYNCH, Associate Solicitor. Of counsel was NATHAN K. KELLEY, Deputy Solicitor.

Before RADER, *Chief Judge,* O'MALLEY, and REYNA, *Circuit Judges.*

RADER, *Chief Judge*.

This appeal arises from an *inter partes* reexamination of U.S. Patent No. 6,753,013 (the '013 patent). The '013 patent is owned by Leo Pharmaceutical Products, Ltd. (Leo Pharmaceuticals) and challenged by third party requester Galderma R&D. While the "substantial evidence" standard of review for fact findings made by the Board of Patent Appeals and Interferences (Board)[1] makes Leo Pharmaceutical's burden on appeal a challenging one, after careful review, this court finds that Leo Pharmaceuticals has met that burden. Because the Board incorrectly construed the claim term "storage stable," this court reverses the Board's claim construction. *See Ex parte Leo Pharm. Prods., Ltd.*, No. 2012-003165 (B.P.A.I. Apr. 30, 2012). Furthermore, because the Board incorrectly found the claimed invention would have been obvious in view of the prior art and incorrectly weighed the objective indicia of nonobviousness, this court reverses the Board's obviousness determination.

I.

This case concerns pharmaceutical compositions for the topical treatment of certain skin conditions, *e.g.*,

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[1] Under the Leahy-Smith America Invents Act, Pub. L. No. 112-29 § 7(a)(1), 125 Stat. 284, 313 (2011), the Board changed its name from the Board of Patent Appeals and Interferences to the Patent Trial and Appeal Board. This court uses the prior designation for consistency with the decision below.

psoriasis. *See* '013 patent col. 1, ll. 8–10, 19–25. Psoriasis can be a painful and socially debilitating disease. The prior art discloses that psoriasis is commonly treated through a combination treatment of: (1) a vitamin D analog and (2) a corticosteroid. '013 patent col. 1, ll. 23–26.

The '013 patent teaches that simultaneous treatment with vitamin D and corticosteroids can heal psoriasis faster and more effectively. '013 patent col. 9, ll. 1–11. However, according to the '013 patent, a storage stable combination of vitamin D and corticosteroids in a single formulation did not exist in the prior art. '013 patent col. 1, ll. 29–31. The '013 patent teaches that previous combination formulations were not storage stable because vitamin D and corticosteroids have divergent pH requirements for optimum stability. '013 patent col. 1, ll. 31–36. Specifically, vitamin D analogs require basic environments with a higher pH value (above 8) for optimal stability, but corticosteroids are most stable in acidic environments with a lower pH value (in the range of 4–6). '013 patent col. 1, ll. 48–53. Because of the storage stability problem, physicians had to prescribe a two-drug regimen that required patients to apply one drug in the morning and another at night. '013 patent col. 1, ll. 61–67. This two-drug regimen generated patient compliance issues.

After recognizing the storage stability problem, Leo Pharmaceuticals began testing formulations that combined vitamin D analogs and corticosteroids. In testing formulations from the prior art, Leo Pharmaceuticals found that several ingredients—including almond oil, propylene glycol, and water—did not solve the problem. *See* J.A. 566–68 (aqueous alcohol-based solvents); J.A. 561–63, 570 (propylene glycol and almond oil). Leo Pharmaceuticals then discovered that a new set of solvents, including polyoxypropylene 15 stearyl ether (POP-15-SE), solved the storage stability problem by allowing

the vitamin D analog and the corticosteroid to coexist in a single pharmaceutical product.

The '013 patent claims a pharmaceutical composition comprising three components: a category A component (vitamin D analog); a category B component (corticosteroid); and a category C solvent. '013 patent col. 12, ll. 23–53. As amended during reexamination, independent claim 1 is representative:

> 1. A pharmaceutical composition for dermal use, said composition comprising:
>
> a first pharmacologically active *component A consisting of at least one vitamin D analogue* selected from the group consisting of seocalcitol, calcipotriol, calcitriol, tacalcitol, maxacalcitol, paricalcitol, falecalcitriol, 1α,24S-dihydroxy-vitamin D2, 1(S),3(R)-dihydroxy-20(R)-[((3-(2-hydroxy-2-propyl)-phenyl)-methoxy)-methyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene and mixtures thereof; and
>
> a second pharmacologically active *component B consisting of at least one corticosteroid*, wherein the difference between the maximum stability pH of said first component A and the maximum stability pH of said second component B is at least 1; and
>
> at least one *solvent component C* selected from the group consisting of:
>
> (i) compounds of the general formula $R^3(OCH_2C(R^1)H)_xOR^2$ (I) wherein x is in the range of 2-60, R^1 in each of the x units is CH_3, R^2 is straight chain or branched C_{1-20} alkyl or benzoyl, and R^3 is H or phenylcarbonyloxy;
>
> (ii) straight or branched C_{2-4}-alkyl esters of straight or branched C_{10-18}-alkanoic or -alkenoic acids;

> (iii) propyleneglycol diesters with C_{8-14}-alkanoic acids; and
>
> (iv) branched primary C_{18-24} alkanols,
>
> wherein said pharmaceutical composition is *storage stable and non-aqueous*.

J.A. 3867 (emphases added).

Among other changes, Leo Pharmaceuticals amended claim 1 during reexamination to include the phrase "wherein said pharmaceutical composition is storage stable and non-aqueous." J.A. 3867. Leo Pharmaceuticals also added new claims 24–148, and amended and canceled other claims. Leo Pharmaceuticals contends that the commercial embodiment of the '013 patent, as amended, is the Taclonex® ointment.

The Board construed the term "storage stable" and "non-aqueous." J.A. 6. Then the Board—relying on the examiner's findings—rejected the claims of the '013 patent as obvious over three prior art references: U.S. Patent No. 4,083,974 (Turi); U.S. Patent No. 4,610,978 (Dikstein); and WO 94/13353 (Serup). J.A. 9.

Turi was filed in 1977 and is titled "Topical Steroidal Anti-Inflammatory Preparations Containing Polyoxypropyene 15 Stearyl Ether." Turi discloses pharmaceutical compositions comprising a steroid contained within a solvent, POP-15-SE, but it does not teach the use of vitamin D. Turi col. 1, ll. 58–63. Turi specifically discloses that the claimed invention *does not* contain water, gels, or alcohols. Turi col. 1, ll. 24–38. Instead, Turi discloses the use of POP-15-SE as "well known to those skilled in the art of formulating and compounding topical ointment like compositions and preparations." Turi col. 4, ll. 5–9. Turi teaches that POP-15-SE is antifungal, antibacterial, nonirritating, and lubricating. Turi col. 2, ll. 12–16. Turi further teaches that while these properties are not sufficient to provide therapeutic value, they are useful because they render additional preservatives unnecessary. Turi

col. 2, ll. 18–30. Turi's claimed invention thereby reduces exposure of tissue to chemical compounds and reduces manufacturing costs. Turi col. 2, ll. 18–30. Turi addresses neither stability concerns from combining vitamin D analogs and corticosteroids, nor the use of POP-15-SE or corticosteroids for the treatment of psoriasis.

The second prior art reference, Dikstein, was filed in 1984 and is titled "Compositions Containing 1α-Hydroxycholecalciferol for Topical Treatment of Skin Disorders and Methods Employing Same." Dikstein discloses dermatological compositions, including creams, ointments, and lotions, comprising a vitamin D analog and a corticosteroid. Dikstein col. 3, ll. 4–48. Dikstein teaches that vitamin D can treat psoriasis and that corticosteroids have side effects, but it does not teach using vitamin D to treat the side effects of corticosteroids. Dikstein col. 1, ll. 26–36; col. 2, ll. 55–60. Every example composition in Dikstein contains almond oil or propylene glycol and several also contain water. Dikstein col. 9, l. 40–col. 11, l. 60. Yet, Dikstein does not disclose or recognize the storage stability problems associated with using water, almond oil, or propylene glycol in the combination formulations. Nor does Dikstein disclose the use of POP-15-SE or any other solvent that could solve the storage stability concerns.

The third prior art reference, Serup, was filed in 1993 and is titled "Hydroxy Vitamin D3 Compounds for Treating Skin Atrophy." Serup describes a composition containing a vitamin D analog and a steroid. Serup col. 1, ll. 7–13. Serup further teaches the use of vitamin D analogs to treat skin atrophy, a well-known side effect of steroid treatment. Serup col. 1, ll. 14–15; col. 2, ll. 8–10. Atrophy is associated with reduced skin thickness—vitamin D can prevent atrophy and normalize skin thickness. Serup col. 3, ll. 3–6. Although Serup describes the benefits of using vitamin D to treat steroid-induced atrophy, Serup does not address any storage stability concerns associated with this combination. While Serup teaches that preparations

may include "creams, ointments, pastes, or gels," every example composition disclosed in Serup is aqueous, containing either purified or hot water. Serup col. 19, l. 34–col. 23, l. 15. Every example also contains almond oil, propylene glycol, or alcohol. Serup col. 19, l. 34–col. 23, l. 15. Thus, Serup does not recognize the stability problems associated with using water, almond oil, or propylene glycol in the combination formulations. Nor does Serup disclose the use of POP-15-SE or any other solvent that could solve the storage stability concerns.

Based on these three prior art references, the Board rejected claims 1, 2, 4–8, 14, 16–19, 21, 23, 39–91, and 143–146 of the '013 patent as obvious under 35 U.S.C. § 103(a). J.A. 19. The Board relied on Turi as the primary reference because Turi disclosed a category B corticosteroid and a category C solvent. J.A. 4. The Board then used Serup or Dikstein with Turi to reject various dependent claims concerning different vitamin D analogs. J.A. 9–14, 19–22.

Regarding the combination of Turi with Serup, the Board found that the reason for combining them was "for the [Turi] solvent's advantages and 'to obtain a more effective preparation without the potential of causing skin atrophy.'" J.A. 10 (quoting the examiner's reasoning). According to the Board, because both Serup and Turi describe compositions with corticosteroids, an artisan would have found the two references reasonably pertinent for the "same type of compositions with the same therapeutic purpose." J.A. 10. The Board concluded that adding vitamin D to Turi "would have been obvious to address the well-known side effects of topical steroid treatment." J.A. 10–11. The Board also found that because Serup discloses selecting ingredients that are "compatible" and "not deleterious," an artisan would have been familiar with selecting components by routinely "picking and choosing" from a list to achieve a compatible and non-deleterious preparation. J.A. 12.

Regarding the combination of Turi with Dikstein, the Board found that Dikstein "teaches the benefit of combining a vitamin D analog with a corticosteroid to achieve more complete skin healing," which was a reason to add a vitamin D analog to Turi's corticosteroid treatment. J.A. 22. The Board further concluded that the analysis for Serup also applied to Dikstein. J.A. 19–21.

The Board acknowledged that Leo Pharmaceuticals provided "extensive experimental evidence" that water, alcohol, and propylene glycol cause unacceptable degradation of vitamin D and steroid compositions. J.A. 14. However, the Board found that Turi provided explicit guidance to exclude these ingredients. J.A. 13. Specifically, the Board found that Turi excluded water, alcohol, and propylene glycol; taught that propylene glycol is "irritating to the skin" and "a nonlubricant;" and taught that POP-15-SE solved the problems associated with propylene glycol. J.A. 13 (quoting Turi col. 1, ll. 55–58). The Board also concluded that because Serup uses almond oil, but does not teach that almond oil is necessary, an artisan, at the time of the claimed invention, would have considered both compositions excluding or including almond oil to be obvious. J.A. 13–14, 23.

Addressing the objective indicia of nonobviousness, the Board found that the objective indicia did not overcome a prima facie case of obviousness. J.A. 15–17. The Board acknowledged that the claimed compositions were "adequately shown to be more storage stable than compositions formulated with certain ingredients that had been used in the prior art, such as water," "propylene glycol," and "alcohol." J.A. 15. However, the Board concluded that the "unexpected results" claimed by Leo Pharmaceuticals were not unexpected because Turi "provided explicit reason to use POP-15-SE as a solvent." J.A. 18–19. Therefore, the Board found that Leo Pharmaceuticals "did not establish that the improvement observed was unexpected to one of ordinary skill in the art in view of the strong reason to have utilized POP-15-SE." J.A. 19. Even

though the Board found that Turi did not teach POP-15-SE as a solvent to allow "vitamin D and corticosteroid to coexist," the Board nonetheless concluded that "the reason for utilizing the solvent does not have to be the same reason [the solvent] was employed by the inventors." J.A. 17 (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419–20 (2007)).

II.

This court reviews claim construction without deference. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1455–56 (Fed. Cir. 1998) (en banc). "During reexamination, as with original examination, the PTO must give claims their broadest reasonable construction consistent with the specification." *In re Suitco Surface, Inc.*, 603 F.3d 1255, 1259 (Fed. Cir. 2010).

For claim construction, the portion of the representative claim at issue reads:

> 1. A pharmaceutical composition for dermal use, said composition comprising . . . [components A, B, & C] . . . wherein said *pharmaceutical composition is storage stable and nonaqueous*.

J.A. 3867 (emphasis added) (claim 1 of the '013 patent as amended during reexamination).

Although the claim term, "storage stable" is not defined in the '013 patent, the specification teaches a combination composition of a vitamin D analog, a corticosteroid, and a component C solvent, coexisting "without degradation." '013 patent col. 8, ll. 1–6. The Board construed "ability to resist degradation"—even though "ability to resist degradation" is not a claim term—to denote "that the composition is stable, i.e., not changing or fluctuating because it doesn't significantly degrade." J.A. 6 (citing http://www.merriam-webster.com/stable).

The Board then adopted a disclosure in the specification to define "storage stable." J.A. 6–7. Example two

discloses an accelerated chemical stability test "after storage for one month at 40ºC and three months at 25ºC and 40ºC, respectively." '013 patent col. 10, ll. 54–56. This test "describes a specific stability test to determine the chemical stability of a composition comprising all three components stored for a period of time." J.A. 6; *see also* '013 patent col. 10, l. 50–col. 11, l. 56. The Board adopted this test because one of ordinary skill "would have reasonably looked to the described stability test as defining what was meant by 'storage stable.'" J.A. 6–7.

At the outset, the Board's construction of "storage stable" is impermissibly narrow because example two is just one disclosure of an accelerated stability test. Under its accepted and customary meaning, "storage stable" would include a composition that maintains its stability during its shelf life for its intended use as an approved pharmaceutical product for sale and home use by ordinary customers. *See* Appellant's Br. 30.

The Board erred by narrowing the definition of "storage stable" to something far short of its broadest reasonable meaning. The plain meaning of "storage stable" is broader than the disclosure in example two.

Accordingly, this court vacates the Board's construction. Because it is unnecessary for this court to adopt a specific alternative construction to resolve this appeal, this court declines to do so, leaving that question to a later forum where the issue is determinative.

III.

> Obviousness is a question of law based on underlying findings of fact. An analysis of obviousness must be based on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any.

In re Kubin, 561 F.3d 1351, 1355 (Fed. Cir. 2009); *see also Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). This court reviews the Board's fact findings for substantial evidence. *In re Mouttet*, 686 F.3d 1322, 1330 (Fed. Cir. 2012). Based on the underlying fact findings, whether a claimed invention would have been obvious under 35 U.S.C. § 103(a) is a question of law reviewed de novo. *Id.*

As the Board acknowledges, this record does not present unresolved issues of fact. J.A. 9. Thus, at bottom, this court confronts a question of law: whether, in light of the prior art references and objective indicia of nonobviousness, the claimed invention would have been obvious to a person of ordinary skill in the art at a time just before the time of invention.

A.

Relying on Turi, Dikstein, and Serup, the Board concluded that "a skilled worker familiar with a wide range of possible ingredients to incorporate into a composition comprising a steroid and vitamin D analog" would have arrived at the '013 patent's claimed invention. J.A. 14.

The '013 patent, however, is not simply a combination of elements found in the prior art. The inventors of the '013 patent recognized and solved a problem with the storage stability of certain formulations—a problem that the prior art did not recognize and a problem that was not solved for over a decade.

As an initial matter, an invention can often be the recognition of a problem itself. *See Cardiac Pacemakers, Inc. v. St. Jude Med., Inc.*, 381 F.3d 1371, 1377 (Fed. Cir. 2004) ("There can of course arise situations wherein identification of the problem is itself the invention."). Here, the prior art either discouraged combining vitamin D analogs and corticosteroids in a single formulation, or attempted the combination without recognizing or solving the storage stability problems associated with the combination.

During reexamination, Leo Pharmaceuticals presented several medical research articles published as early as 1995 discouraging the combination of a vitamin D analog with a corticosteroid because of the stability problems of vitamin D analogs at lower pHs. *See* J.A. 612 (Knud Kragballe, *Vitamin D3 Analogues*, 13 DERMATOLOGICAL CLINICS 835, 838 (1995)); J.A. 6237 (Mark G. Lebwohl, *The Evolution of Vitamin D Analogs for the Treatment of Psoriasis*, ARCHIVES OF DERMATOLOGY, 285 (Nov. 1995)). These articles taught away from mixing topical vitamin D formulations with other drugs. *See, e.g.,* J.A. 612. Even though studies in the prior art compared the effectiveness of treating psoriasis with vitamin D versus corticosteroid, those studies did not describe combining the two into one formulation. *See id.* Researchers noted that it was "only natural" for clinicians to attempt to try combinations of vitamin D with other ingredients, but warned that vitamin D should not be combined with other drugs requiring a low pH (*e.g.*, corticosteroids). *See* J.A. 6237. These researchers recognized possible advantages from combining a vitamin D treatment with topical corticosteroids, but nevertheless they recommended a two-drug regimen where patients applied the drugs at different times of a day or on alternating days. *See id.*

Although Dikstein and Serup attempt the combination of a vitamin D analog with a corticosteroid, neither discloses or addresses the stability problems of combining vitamin D analogs and corticosteroids into one pharmaceutical formulation. As evidenced by the experiments Leo Pharmaceuticals conducted, the prior art does not teach any composition that exhibits storage stable properties. Every example disclosed in Dikstein contains either almond oil or propylene glycol. Similarly, the examples disclosed in Serup contain not only water, but also almond oil, alcohol, or propylene glycol.

Leo Pharmaceuticals presented experimental evidence to the Board that each of these ingredients harmed the storage stability of the vitamin D analog and cortico-

steroid combination. *See* J.A. 562–64, 570 (Hoy Decls. discussing propylene glycol and almond oil); J.A. 566–68 (Didriksen Decl. discussing aqueous alcohol-based solvents). For example, the use of propylene glycol as a solvent resulted in 100% degradation of the vitamin D analog. J.A. 562–564, 692–702. Similarly, the use of aqueous solvents resulted in almost complete degradation of the vitamin D analog after three months of storage—98.3% degradation in one formulation and 100% degradation in another. J.A. 710–16, 1025–26. And, when almond oil was used as a solvent, vitamin D analogs degraded 13–29% after three months of storage. J.A. 570, 723–24. The vitamin D analogs were not the only components at risk for degradation. When commercial ointments with vitamin D analogs or corticosteroids were combined, one corticosteroid degraded by 10% after four weeks and another degraded by almost 50% within 24 hours. J.A. 563; *see also* J.A. 723–24 (range of 5–12% corticosteroid degradation after 6 months of storage in combination with a vitamin D analog).

Moreover, because neither Dikstein nor Serup recognized or disclosed the stability problem, the record shows no reason for one of ordinary skill in the art to attempt to improve upon either Dikstein or Serup using Turi. The ordinary artisan would first have needed to recognize the problem, i.e., that the formulations disclosed in Dikstein and Serup were not storage stable. To discover this problem, the ordinary artisan would have needed to spend several months running storage stability tests. *See* '013 patent col. 10, l. 50–col. 11, l. 56; *see also* J.A. 545, 563–68. Only after recognizing the existence of the problem would an artisan *then* turn to the prior art and attempt to develop a new formulation for storage stability. If these discoveries and advances were routine and relatively easy, the record would undoubtedly have shown that some ordinary artisan would have achieved this invention within months of Dikstein or Serup. Instead this invention does not appear for more than a decade.

Although the Board acknowledges "compositions within the scope of the ['013 patent claims] were adequately shown to be more storage stable than compositions formulated with certain ingredients that had been used in the prior art," the Board went on to find this evidence insufficient "to overcome the strong case of obviousness." J.A. 15. By brushing aside the storage stability issue, the Board erred by collapsing the obviousness analysis into a hindsight-guided combination of elements. This record, however, discloses several reasons that a person of ordinary skill in the art would not have been motivated to try, let alone make, the claimed invention of the '013 patent.

First, the Board found motivation to combine Dikstein or Serup with Turi because one of ordinary skill would have used vitamin D to solve the well-known side effects of steroid treatment. However, combining Turi and vitamin D to address the side effects of a steroid treatment is only straightforward in hindsight. Turi was publicly available in the prior art for twenty-two years before the '013 patent was filed, yet there is no evidence that anyone sought to improve Turi with vitamin D. According to the record, even when Serup published the well-known side effects of steroid-induced atrophy in 1994, no one—including Serup—sought to improve Turi by adding vitamin D to Turi's corticosteroid composition. Serup even targeted the precise side effects that the Board believed would have motivated the addition of a vitamin D analog to Turi's corticosteroid composition, yet Serup did not seek to improve Turi by adding vitamin D.

Moreover, focusing on the "non-aqueous" claim element, the Board found "there was a strong reason to have made a non-aqueous composition with POP-15-SE." J.A. 15. The Board believed an artisan would have "add[ed] the Vitamin D analog of Serup [or Dikstein] to Turi's POP-15-SE containing steroid composition for the solvent's advantages and to obtain a more effective steroid preparation." J.A. 10 (internal quotations marks omitted). However, substantial evidence does not support the

Board's finding that an ordinary artisan would have deviated from the aqueous composition of Serup or the composition of Dikstein—plucking the vitamin D analog from those two references and incorporating the analog into Turi. The Board found that statements in Turi exclude the solvents used by Serup and Dikstein. J.A. 13 ("Turi provides explicit guidance to exclude water, alcohol, and propylene glycol . . . ."). Thus, Turi's guidance actually teaches *away* from the Board's posited combination or, at a minimum, provides no evidence of motivation to combine Turi with those prior solvents.

For example, Turi distinguishes its compositions from aqueous compositions: "The pharmaceutical compositions of the present invention contain no water." Turi col. 1, ll. 26–27. Indeed, all of Turi's examples are non-aqueous. Turi col. 8, l. 40–col. 10, l. 54. Yet, Serup's list of preparations are all aqueous, Serup col. 19, ll. 5–9, and Serup's examples are all aqueous, Serup col. 19, l. 34–col. 24, l. 17. Similarly, Dikstein discloses that dermatological creams are preferably formulated with, among other ingredients, water. Dikstein col. 3, ll. 14–26. And, five of Dikstein's examples include water. Dikstein col. 9, l. 40–col. 11, l. 21.

Moreover, Turi specifically disclaims the use of propylene glycol because of its "very undesirable qualities from a pharmacological point of view." Turi col. 1, ll. 24–61. Despite Turi's teaching away from that solvent, four of Dikstein's examples, Dikstein Exs. 7, 8, 15, 16, and five of Serup's examples, Serup Exs. 4–8, involve propylene glycol. Further, Dikstein discloses that propylene glycol is a convenient solvent in the preparation of dermatological lotions. Dikstein col. 3, ll. 14–26.

Even with the differing solvents taught by the prior art, the Board explained that, because Turi provided a reason to exclude water and propylene glycol, POP-15-SE would have been a logical non-aqueous choice to use for improving upon Serup and Dikstein. However, Serup "surprisingly observed that certain vitamin D analogues

can prevent and/or treat skin atrophy induced by topical steroid treatment." Serup col. 2, ll. 8–10. Similarly, when Dikstein combined a corticosteroid and vitamin D analog, it noted that "[s]urprisingly" the combination "led to more complete healing." Dikstein col. 6, ll. 48–54. With surprisingly successful results, an ordinary artisan would not have been motivated to change the solvents Serup or Dikstein relied upon and use the different solvent disclosed in Turi.

Thus, in the face of such divergent compositions with express disclaimers of the other's contents, the record showing that Turi, Serup, and Dikstein describe compositions for the same therapeutic purpose does not rise to the level of a motivation to combine. Without more, and especially in the face of such strong objective indicia of nonobviousness discussed *infra*, the Board erred by using hindsight to determine that the addition of Serup's or Dikstein's vitamin D analog to Turi's formulation would have been obvious.

In addition, the Board found that a person of ordinary skill in the art would have been capable of selecting the correct formulation from available alternatives. J.A. 12. Specifically, the Board found more than eight different classes of additives (*e.g.*, diluents, buffers, thickeners, lubricants). J.A. 12; Serup col. 19, ll. 10–15. The Board also found more than ten different categories of composition forms (*e.g.*, liniments, lotions, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments, pastes, or gels). J.A. 12; Serup col. 19, ll. 5–9. "Based on these broad and general disclosures," the Board reasoned that an artisan would have been able to "mak[e] choices about what ingredients to include, and which to exclude" in formulating a composition with a vitamin D analog and steroid. J.A. 12. To the contrary, the breadth of these choices and the numerous combinations indicate that these disclosures would not have rendered the claimed invention obvious to try. *See Rolls-Royce PLC v. United Techs. Corp.*, 603 F.3d 1325, 1339 (Fed. Cir. 2010)

(claimed invention was not obvious to try because the prior art disclosed a "broad selection of choices for further investigation").

The '013 patent's claimed combination would not have been obvious to try. "[W]here the prior art, at best gives only general guidance as to the particular form of the claimed invention or how to achieve it, relying on an obvious-to-try theory to support an obviousness finding is impermissible." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1073 (Fed. Cir. 2012) (internal citations and quotation marks omitted). Further, "KSR did not create a presumption that all experimentation in fields where there is already a background of useful knowledge is 'obvious to try,' without considering the nature of the science or technology." *Abbot Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2008).

Here, the "background of useful knowledge"—including the prior art relied on by the Board—was published decades before the '013 patent: Turi issued in 1978, Dikstein issued in 1986, and Serup was published in 1994. The elapsed time between the prior art and the '013 patent's filing date evinces that the '013 patent's claimed invention was not obvious to try. Indeed this considerable time lapse suggests instead that the Board only traverses the obstacles to this inventive enterprise with a resort to hindsight. It took over a decade—after Dikstein's disclosure of the benefits of combining vitamin D and corticosteroid treatments into one formulation—for Dikstein's formulations to be tested for storage stability. And, until the advancement made by the inventors of the '013 patent, no one had proposed a new formulation that would be storage stable. The problem was not known, the possible approaches to solving the problem were not known or finite, and the solution was not predictable. Therefore, the claimed invention would not have been obvious to try to one of ordinary skill in the art.

Indeed ordinary artisans would not have thought to try at all because they would not have recognized the problem.

And, even if it was obvious to experiment with these options, "there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective." *See Cyclobenzaprine*, 676 F.3d at 1070. There is no indication in the prior art which of these possible formulations would be the most promising to try. And, according to the '013 patent, the storage stability of these formulations cannot be determined based on a few days of work—testing would likely take one to three months per formulation. *See* '013 patent col. 10, l. 50–col. 11, l. 55. Without a reasonable expectation of success or clues pointing to the most promising combinations, an artisan could have spent years experimenting without success.

This court and obviousness law in general recognizes an important distinction between combining known options into "a finite number of identified, predictable solutions," *KSR*, 550 U.S. at 421, and "'merely throwing metaphorical darts at a board' in hopes of arriving at a successful result," *Cyclobenzaprine*, 676 F.3d at 1071 (quoting *In re Kubin*, 561 F.3d at 1359). While the record shows that, as early as 1995, the prior art indicated that both vitamin D analogs and corticosteroids were effective treatments for psoriasis, *see* J.A. 610, 6237, that same prior art gave no direction as to which of the many possible combination choices were likely to be successful. Instead, the prior art consistently taught away from combining vitamin D analogs and corticosteroids.

This court recognizes that the record need only supply "substantial evidence" to support the Board's finding. *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000). In this case, however, with no material factual disputes, this court cannot share the Board's analysis and application of the law to those facts. In light of the lack of expectation of a successful result, the failure of the prior art to provide direction, and the substantial number of intervening

years between the publication of the prior art and the '013 patent's filing date, this invention is not simply a case of "'picking and choosing' from a list in order to achieve a compatible and non-deleterious preparation" as the Board suggests. J.A. 12. Because the problem was not known, the possible approaches to solving the problem were not known or finite, and the solution was not predictable, it would not have been obvious for a person of ordinary skill to make the claimed invention.

B.

The court now turns to the Board's analysis of the objective indicia of nonobviousness. The Board reasoned that "the strong case of obviousness outweighs the experimental evidence and testimony about the advantages of the claimed composition." J.A. 17. Contrary to the Board's conclusion, this court finds the objective indicia, in concert with the entire obviousness analysis, present a compelling case of nonobviousness. In fact, the objective indicia of nonobviousness highlight that the Board's analysis regarding the combination of Serup or Dikstein with Turi was colored by hindsight.

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. *See Cyclobenzaprine*, 676 F.3d at 1075–76 (A fact finder "may not defer examination of the objective considerations until after the fact finder makes an obviousness finding." (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983))). When an applicant appeals an examiner's objection to the patentability of an *application's* claims for obviousness, the PTO necessarily has the burden to establish a prima facie case of obviousness which the applicant then rebuts. *In re Mouttet*, 686 F.3d at 1330. However, during *inter partes* reexamination, the Board is reviewing evidence of obviousness—including objective indicia—submitted by two adversarial parties for the claims of an issued *patent*. Thus, the Board should give the objective indicia its

proper weight and place in the obviousness analysis, and not treat objective indicia of nonobviousness as an afterthought.

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 constitute[] independent evidence of nonobviousness." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). This case illustrates a good reason for considering objective indicia as a critical piece of the obviousness analysis: Objective indicia "can be the most probative evidence of nonobviousness in the record, and enables the court to avert the trap of hindsight." *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010) (internal quotation marks omitted). Here, the objective indicia of nonobviousness are crucial in avoiding the trap of hindsight when reviewing, what otherwise seems like, a combination of known elements.

Unexpected results are useful to show the "improved properties provided by the claimed compositions are much greater than would have been predicted." *See In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995) (internal quotation marks omitted). This record shows "extensive experimental evidence" of unexpected results that contradict the Board's obviousness finding. J.A. 14. The Board concluded that the "unexpected results" claimed by Leo Pharmaceuticals were not surprising or unexpected. J.A. 19. However, substantial evidence does not support the Board's conclusion.

During reexamination, the inventors of the '013 patent submitted test results that analyzed the Dikstein and Serup formulations. The inventors found that the formulations disclosed by Dikstein and Serup result in significant degradation of the vitamin D analog and corticosteroid. *See* J.A. 1041–46 (testing formulations in Serup); J.A. 1625–27, 2152–2154 (testing formulations in Dikstein). The inventors also tested an improvement of Serup using Turi, by replacing Serup's solvent with POP-

15-SE, and still found significant degradation of the corticosteroid component. *See* J.A. 1045–46. These test results are a strong indication that the '013 patent's combination of known elements yields more than just predictable results.

In addition to evidence of unexpected results, Leo Pharmaceuticals provided other objective indicia of nonobviousness. For example, the commercial success of Leo Pharmaceutical's Taclonex® ointment is a testament to the improved properties of the '013 patent's claimed invention. Taclonex® is the first FDA-approved drug to combine vitamin D and corticosteroids into a single formulation for topical application. While FDA approval is not determinative of nonobviousness, it can be relevant in evaluating the objective indicia of nonobviousness. *See Knoll Pharm. Co., Inc. v. Teva. Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004). Here, FDA approval highlights that Leo Pharmaceutical's formulation is truly storage stable, something that the prior art formulations did not achieve.

The record also shows evidence of *long* felt but unsolved need, *i.e.*, the need for a single formulation to treat psoriasis. The length of the intervening time between the publication dates of the prior art and the claimed invention can also qualify as an objective indicator of nonobviousness. *See Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1376–77 (Fed. Cir. 2000). Here, the researchers were aware of the benefits of using both vitamin D and corticosteroids in the treatment of psoriasis as early as 1986. *See, e.g.,* Dikstein col. 1, ll. 9–16. And Turi, upon which the Board relied to make its case, issued in 1978. Yet, it was not until the '013 patent's filing in 2000—*twenty-two years* after Turi and *fourteen years* after Dikstein—that the solution to the long felt but unsolved need for a combined treatment of vitamin D and corticosteroid was created. The intervening time between the prior art's teaching of the components and the eventual

preparation of a successful composition speaks volumes to the nonobviousness of the '013 patent.

Here, the objective indicia—taken in sum—are the most "probative evidence of nonobviousness . . . enabl[ing] the court to avert the trap of hindsight." *Crocs, Inc.*, 598 F.3d at 1310. Viewed through the lens of the objective indicia, as opposed to the hindsight lens used by the Board, the '013 patent would not have been not obvious over Turi in combination with Dikstein or Serup. Therefore, this court reverses the Board's obviousness determination.

IV.

For the foregoing reasons, this court reverses the Board's claim construction of the term "storage stable" and its obviousness determination.

REVERSED