United States Court of Appeals for the Federal Circuit

AMGEN INC.,
Plaintiff-Cross-Appellant

v.

SANDOZ INC., ZYDUS PHARMACEUTICALS (USA) INC.,
Defendants-Appellants

MANKIND PHARMA LTD., TORRENT PHARMACEUTICALS LTD., GLENMARK PHARMACEUTICALS LIMITED, MACLEODS PHARMACEUTICALS LTD., MSN LABORATORIES PRIVATE LTD., ACTAVIS LLC, PRINSTON PHARMACEUTICAL INC., EMCURE PHARMACEUTICALS LTD., HERITAGE PHARMACEUTICALS INC., AUROBINDO PHARMA LTD., AUROBINDO PHARMA USA, INC., ANNORA PHARMA PRIVATE LIMITED, HETERO USA, INC., CIPLA LIMITED, ALKEM LABORATORIES LTD., DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., AMNEAL PHARMACEUTICALS LLC, PHARMASCIENCE INC.,
Defendants

2022-1147, 2022-1149, 2022-1150, 2022-1151

Appeals from the United States District Court for the District of New Jersey in Nos. 3:18-cv-11026-MAS-DEA,

3:18-cv-11267-MAS-DEA, 3:18-cv-11269-MAS-DEA, 3:19-cv-18806- MAS-DEA, Judge Michael A. Shipp.

Decided: April 19, 2023

STEVEN J. HOROWITZ, Sidley Austin LLP, Chicago, IL, argued for plaintiff-cross-appellant. Also represented by PAUL J. ROGERSON, JULIA G. TABAT; JOSHUA JOHN FOUGERE, Washington, DC; SUE WANG, San Francisco, CA; ERIC MICHAEL AGOVINO, GREGORY DAVID BONIFIELD, CHRISTINA NICHOLE GIFFORD, DENNIS J. SMITH, STUART WATT, WENDY A. WHITEFORD, Amgen Inc., Thousand Oaks, CA; JEFFREY B. ELIKAN, MICHAEL N. KENNEDY, GEORGE FRANK PAPPAS, Covington & Burling LLP, Washington, DC; ALEXA HANSEN, San Francisco, CA.

MAUREEN L. RURKA, Winston & Strawn LLP, Chicago, IL, argued for all defendants-appellants. Defendant-appellant Sandoz Inc. also represented by SAMANTHA MAXFIELD LERNER; EIMERIC REIG-PLESSIS, San Francisco, CA.

MICHAEL GAERTNER, Locke Lord LLP, Chicago, IL, for defendant-appellant Zydus Pharmaceuticals (USA) Inc. Also represented by DAVID BRIAN ABRAMOWITZ, HUGH S. BALSAM, CAROLYN ANNE BLESSING, AUGUST MELCHER, EMILY SAVAS.

Before LOURIE, CUNNINGHAM, and STARK, *Circuit Judges*.

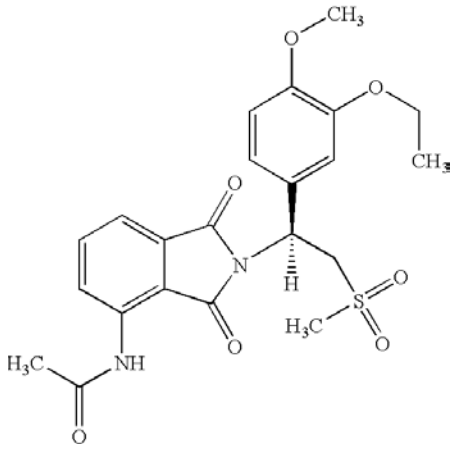
LOURIE, *Circuit Judge*.

Sandoz Inc. ("Sandoz") appeals from a decision of the United States District Court for the District of New Jersey holding that claims 3 and 6 of Amgen Inc.'s ("Amgen") U.S. Patent 7,427,638 (the "'638 patent") and claims 1 and 15 of Amgen's U.S. Patent 7,893,101 (the "'101 patent") had not

been shown to be invalid as obvious. Amgen cross-appeals from the district court's decision holding that claims 2, 19, and 21 of its U.S. Patent 10,092,541 (the "'541 patent") were shown to be invalid as obvious. *See Amgen Inc. v. Sandoz Inc.*, No. 18-11026, 2021 WL 5366800 (D.N.J. Sept. 20, 2021) ("*Decision*"). For the reasons provided below, we affirm.

BACKGROUND

Amgen produces apremilast, which is stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, with the following structure:



Amgen markets apremilast, a phosphodiesterase-4 ("PDE4") inhibitor, which is used for treating psoriasis and related conditions, under the brand name Otezla®. The '638, '101, and '541 patents, covering Otezla, were initially owned by Celgene Corporation ("Celgene") and later assigned to Amgen.

Sandoz submitted an Abbreviated New Drug Application ("ANDA") seeking approval from the United States Food and Drug Administration ("FDA") to market a generic version of apremilast. Celgene, the original plaintiff, then

brought this Hatch-Waxman suit, asserting that Sandoz's generic product would infringe the '638 and '101 patents. After the '541 patent issued, Celgene asserted infringement of that patent as well. In February 2020, Amgen was substituted as plaintiff.

I. The '638 Patent

The '638 patent is directed to pharmaceutical compositions comprising stereomerically pure apremilast, including oral formulations, as well as dosing forms.

Asserted claims 3 and 6 are dependent claims. For ease of understanding, we incorporate the parent claims into the claims that are asserted.

Asserted claim 3 of the '638 patent reads as follows:

> 3. The pharmaceutical composition of claim 2 [*A pharmaceutical composition comprising stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or a pharmaceutically acceptable salt, solvate or hydrate, thereof; and a pharmaceutically acceptable carrier, excipient or diluent, wherein said pharmaceutical composition is suitable for parenteral, transdermal, mucosal, nasal, buccal, sublingual, or oral administration to a patient*], wherein said pharmaceutical composition is suitable for oral administration to a patient.

'638 patent at col. 31 ll. 27–39.

Asserted claim 6 of the '638 patent reads as follows:

> 6. The pharmaceutical composition of claim 5 [*A pharmaceutical composition comprising stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-*

> *methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or a pharmaceutically acceptable salt, solvate or hydrate, thereof; and a pharmaceutically acceptable carrier, excipient or diluent, wherein said pharmaceutical composition is suitable for parenteral, transdermal, mucosal, nasal, buccal, sublingual, or oral administration to a patient, wherein the amount of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is from 1 mg to 1000 mg, wherein the amount of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is from 5 mg to 500 mg*], wherein the amount of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is from 10 mg to 200 mg.

'638 patent at col. 31 ll. 27–36, col. 32 ll. 1–12.

At the district court, Amgen asserted infringement of claims 3 and 6. In response, Sandoz alleged that those claims were invalid as obvious over U.S. Patent 6,020,358 (the "'358 patent") and PCT application WO 01/034606 (the "'606 application"). The '358 patent is the first U.S. patent describing a racemic mixture containing apremilast, and it claims a genus of phosphodiesterase inhibitors, including a racemic mixture containing apremilast. The '358 patent discloses seventeen example compounds that fall within the scope of the claimed genus. Example 12 of the '358 patent is a racemic mixture comprised of 50% of the (+) enantiomer of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione and 50% of the (-) enantiomer. The (+) enantiomer is

apremilast. The '358 patent more generally discloses that racemates can be separated into individual enantiomers. The '606 application is directed to a group of phosphodiesterase inhibitors and teaches that the individual enantiomers of racemic mixtures can be separated. Sandoz asserted the '606 application as reinforcing the teachings disclosed in the '358 patent.

The district court held that Sandoz had failed to show by clear and convincing evidence that claims 3 and 6 would have been obvious over the '358 patent and the '606 application. In particular, the court found that Sandoz failed to meet the burden of establishing that the '358 patent and the '606 application gave a skilled artisan reason or motivation to resolve the Example 12 racemic mixture into its enantiomers, further finding that there was not sufficient evidence to conclude that a skilled artisan would have had reason to believe that the desirable properties of Example 12 derived in whole or in part from the apremilast enantiomer (*i.e.*, the (+) enantiomer). The court also concluded that Sandoz had not demonstrated that a skilled artisan would have had a reasonable expectation of success in resolving Example 12 into its individual enantiomeric components.

The district court also looked to objective indicia of nonobviousness, also known as secondary considerations. In particular, the court noted that apremilast unexpectedly provided substantial improvement over previously known phosphodiesterase inhibitors in terms of both efficacy and tolerability and that there was a nexus between the unexpected potency and side-effect profile of apremilast and the compounds of asserted claims 3 and 6 of the '638 patent. The court also looked to long-felt, unmet need, noting that before apremilast, there was a long-felt need for a psoriasis treatment that was suitable for oral administration to a patient, without the risks and barriers to adherence that were common with other psoriasis treatments. The court also

found a nexus between the compounds of the asserted claims and this long-felt, unmet need.

The district court further found that others in the field had attempted to develop other PDE4 inhibitors, but that several had been discontinued due to disappointing efficacy or failure to progress in the drug-development pipeline and that there had been a degree of skepticism about the safety of apremilast because of its structural similarity to thalidomide, which was found to have teratogenic effects in fetuses leading to severe and debilitating birth defects. Finally, the court noted the commercial success of Otezla since it achieved FDA approval, noting approximately 1.7 million prescriptions for the drug between its 2014 launch and April 2020. In view of these findings, the court found that the objective indicia of nonobviousness weighed strongly in favor of a finding that claims 3 and 6 of the '638 patent would not have been obvious over the relevant art.

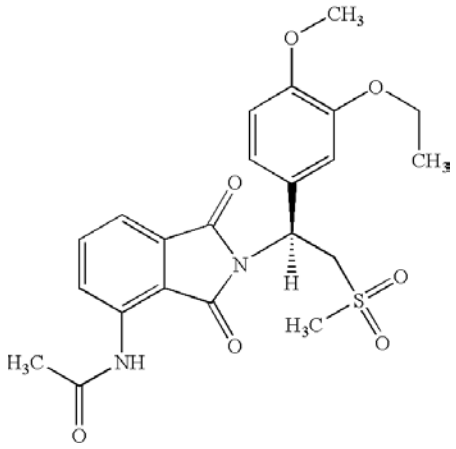
In view of its objective indicia analysis, as well as its finding that there was not sufficient motivation or reasonable expectation of success in isolating apremilast from the racemic mixture disclosed in Example 12 of the '358 patent, the district court held that claims 3 and 6 of the '638 patent were not invalid as obvious.

II. The '101 Patent

The '101 patent is directed to solid forms (*e.g.*, crystalline polymorphic forms) of apremilast and claims priority from several earlier-filed applications, including U.S. Provisional Application 60/366,515 (the "'515 provisional application"), which was filed on March 20, 2002.

Asserted claim 1 of the '101 patent reads as follows:

> 1. A Form B crystal form of the compound of Formula (I):



> which is enantiomerically pure, and which has an X-ray powder diffraction pattern comprising peaks at about 10.1, 13.5, 20.7, and 26.9 degrees 2θ.

'101 patent at col. 59 ll. 2–24.

Asserted claim 15 of the '101 patent reads as follows:

> 15. A solid pharmaceutical composition comprising the crystal form of any one of claims 1 and 2 to 13.

'101 patent at col. 60 ll. 28–29.

At the district court, the parties disputed the priority date to which the '101 patent was entitled, and therefore, which date should be used for purposes of an obviousness analysis. Amgen argued that claims 1 and 15 were entitled to a priority date of March 20, 2002, the filing date of the '515 provisional application. Amgen asserted that Example 2 of the '515 provisional application provided written description and enablement support for the asserted claims, arguing that crystalline Form B of apremilast was inherently disclosed in the '515 provisional application.

Sandoz responded, arguing that the claims of the '101 patent were only entitled to a priority date of March 27,

2008, the filing date of the application resulting in the '101 patent since, according to Sandoz, the crystalline Form B of apremilast was neither explicitly nor inherently disclosed in the '515 provisional application. Sandoz also argued that Celgene represented to the European Patent Office that following Example 2 could result in crystalline Form C of apremilast as well as Form B.

The district court held that claims 1 and 15 of the '101 patent were entitled to the March 2002 priority date, noting that the parties did not dispute that Example 2 of the '515 provisional application disclosed a synthetic chemical procedure for preparing apremilast. Although the court noted that Example 2 did not explicitly describe the final resulting form of apremilast as a crystalline polymorphic structure, but rather as a solid, the court credited Amgen's expert, who testified that Example 2 inherently produces crystalline Form B and that thirteen third-party experiments that replicated the procedures in Example 2 resulted in the crystalline Form B of apremilast. The court also noted that Amgen's expert's uncontradicted trial testimony stated that, although Celgene once claimed that it made crystalline Form C of apremilast by following the procedures in Example 2 of the '515 provisional application, Form C involves a toluene solvent, which becomes a part of the crystalline structure, and toluene is not mentioned in Example 2. Therefore, the court credited Amgen's expert's testimony that Celgene made a mistake in representing that Example 2 could produce crystalline Form C of apremilast.

The district court concluded that Amgen met its burden of showing that the '101 patent is entitled to the '515 provisional application's March 20, 2002 filing date as its priority date. The court further concluded that Sandoz failed to argue that art prior to March 2002 rendered the claims of the '101 patent invalid for obviousness and that Sandoz's arguments merely reduced to a question whether claims 1

and 15 were entitled to claim priority from March 20, 2002 through the '515 provisional application.

III. The '541 Patent

The '541 patent is directed to methods for the treatment of diseases ameliorated by inhibition of phosphodiesterases using dose titration of apremilast. Asserted claim 2 of the '541 patent claims a dose-titration schedule and reads as follows:

> 2. A method for treating a patient with stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, wherein the patient is suffering from psoriasis, the method consisting of:
>
> (a) administering to the patient stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione in an initial titration dosing schedule consisting of
>
> (i) 10 mg in the morning on the first day of administration;
>
> (ii) 10 mg in the morning and 10 mg after noon on the second day of administration;
>
> (iii) 10 mg in the morning and 20 mg after noon on the third day of administration;
>
> (iv) 20 mg in the morning and 20 mg after noon on the fourth day of administration;

> (v) 20 mg in the morning and 30 mg after noon on the fifth day of administration; and
>
> (b) on the sixth and every subsequent day, administering to the patient 30 mg in the morning and 30 mg after noon of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.

'541 patent at col. 31 ll. 3–26.

Asserted claim 19 of the '541 patent reads as follows:

> 19. A method as in any one of claims 1–14, wherein the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione comprises greater than about 98% by weight of the (+) isomer of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione based on the total weight percent of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.

'541 patent at col. 36 ll. 22–29.

Asserted claim 21 of the '541 patent reads as follows:

> 21. A method as in any one of claims 1–14, wherein the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is administered in tablet form.

'541 patent at col. 36 ll. 38–41.

At the district court, Amgen asserted infringement of claims 2, 19, and 21. In response, Sandoz alleged that the claims would have been obvious over Papp,[1] Schett,[2] and Pathan.[3]

Papp reports the results of a Phase IIb clinical trial investigating the clinical efficacy and safety of different doses of apremilast in the treatment of patients with moderate to severe plaque psoriasis. The district court found that Papp teaches the following five-day dose titration of apremilast while initiating treatment to mitigate potential dose-dependent adverse events:

- Day 1: 10 mg first dose; 10 mg second dose
- Day 2: 10 mg first dose; 10 mg second dose
- Day 3: 20 mg first dose; 20 mg second dose
- Day 4: 20 mg first dose; 20 mg second dose
- Day 5: 30 mg first dose; 30 mg second dose.

Decision at *31; *see also* J.A. 18583; Papp at 739.

Schett reports the results of a Phase II clinical trial on apremilast in which patients were given a 40 mg daily dose, either as a single 40 mg dose or as two 20 mg doses. Although Schett did not evaluate treatment of plaque psoriasis, it discloses a dose-escalation protocol during the first seven days of treatment for psoriatic arthritis with the aim

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[1] Kim Papp et al., *Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial*, 380 LANCET 738 (2012).

[2] Georg Schett et al., *Oral apremilast in the treatment of active psoriatic arthritis: results of a multicenter, randomized, double-blind, placebo-controlled study*, 64 ARTHRITIS & RHEUMATOLOGY 3156 (2012).

[3] Ejaz Pathan et al., *Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in ankylosing spondylitis*, 72 ANNALS OF RHEUMATIC DISEASES 1475 (2012).

of decreasing the likelihood of adverse events related to treatment initiation. Schett at 3157–58. Pathan also teaches initiation of apremilast using a dose-escalation protocol, starting patients suffering from ankylosing spondylitis with 10 mg apremilast twice daily, titrating the dose by 20 mg every two days until a maximum dose of 30 mg twice daily was achieved on day 5. Pathan at 1476, 1479.

The district court found that it would have been within the ability of a skilled artisan to titrate apremilast for a patient presenting with psoriasis and that doing so would have been a routine aspect of treating psoriasis with a drug like apremilast that was known in the art to require dose titration to ameliorate side effects. Thus, the court held that claims 2, 19, and 21 of the '541 patent were invalid as obvious.

In summary, the district court concluded that claims 3 and 6 of the '638 patent and claims 1 and 15 of the '101 patent were not invalid as obvious and that claims 2, 19, and 21 of the '541 patent were invalid as obvious. Sandoz appealed, and Amgen cross-appealed. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

Sandoz raises two issues on appeal. First, with regard to the '639 patent, Sandoz contends that the district court erred in failing to find a motivation to isolate apremilast from a known racemic mixture and also for failing to find a reasonable expectation of success in separating the mixture. Second, with regard to the '101 patent, Sandoz argues that the court erred in holding that the '515 provisional application inherently disclosed the crystalline Form B of apremilast, and thus provided the necessary written description support to entitle claims 1 and 15 of the '101 patent to a March 2002 priority date. Amgen raises one issue on cross-appeal, asserting that the court erred in holding that the dose-titration schedule in claims 2, 19, and

21 of the '541 patent would have been obvious. We address each argument in turn.

"Obviousness is a question of law, reviewed *de novo*, based upon underlying factual questions which are reviewed for clear error following a bench trial." *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1300 (Fed. Cir. 2007) (quoting *Alza Corp. v. Mylan Lab'ys, Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006)). The presence or absence of a motivation to arrive at the claimed invention, and of a reasonable expectation of success in doing so, are questions of fact. *Alza Corp.*, 464 F.3d at 1289.

I. The '638 Patent

We first consider Sandoz's challenge to the district court's determination that it failed to prove that claims 3 and 6 of the '638 patent would have been obvious over the '358 patent and the '606 application. Sandoz argues that the court erred in failing to find a motivation to isolate apremilast from a known racemic mixture. Sandoz asserts that, where the methods of isolation are known, as it argues they are here, there is a motivation to separate racemic mixtures. Sandoz also asserts that its expert established that the '606 application taught that compounds, including the apremilast-containing racemic mixture in Example 12, were preferably administered as substantially stereomerically pure and that, by the late 1980s, there was pressure from regulatory agencies, including the FDA, to synthesize new drugs as single enantiomers. Sandoz argues that apremilast being a thalidomide analogue taught toward, rather than away from, separating the enantiomers in the racemic mixture.

Sandoz further argues that the district court erred in holding that a skilled artisan would not have had a reasonable expectation of success in isolating apremilast from a known racemic mixture. Sandoz asserts that the '358 patent discloses a racemic mixture containing apremilast in Example 12 and states that apremilast can be isolated from

the racemic mixture using chiral chromatography, a technique described as well-known in the art. Sandoz also asserts that the court further erred in holding that the '358 patent would not have enabled a skilled artisan to isolate apremilast without undue experimentation. Sandoz contends that a finding of obviousness does not require that every detail for isolation of a compound be described. Sandoz further argues that the court inappropriately relied on Amgen's expert's comments about difficulties he had experienced in isolating enantiomers unrelated to apremilast in concluding that isolation of apremilast from the racemic mixture would have required undue experimentation. Lastly, Sandoz also argues that the district court failed to hold Amgen to the statement in the specification that methods for isolating apremilast (referred to as Compound A in the patent) from the racemate were known in the prior art. '638 patent at col. 9 ll. 9–24.

Sandoz also contends that the district court erred in excluding Celgene's alleged admission that the European counterpart to the '358 patent discloses stereomerically pure apremilast. According to Sandoz, where a representation to a foreign patent office is relevant and not unique to issues of foreign law, it must be considered. Sandoz argues that the court misapplied Federal Rule of Evidence Rule 703, which allows experts to rely on otherwise inadmissible statements if they meet certain criteria, including that an expert would reasonably rely on them, in excluding those statements.

Sandoz further contends that the district court erred in its consideration of objective indicia of nonobviousness. In analyzing long-felt but unmet need, failure of others, and skepticism, Sandoz argues that the court impermissibly credited evidence that lacked a nexus to the allegedly novel aspects of the '638 patent claims, namely stereomerically pure apremilast. Sandoz concedes that the court did not err in considering evidence related to novel features of the claim in the unexpected results analysis, but that the court

did err in basing its analysis on a difference of degree (*i.e.*, that apremilast was 20-fold more potent than the racemic mixture), rather than a difference in kind, which would have, Sandoz asserts, resulted in a finding of obviousness.

Amgen responds that the district court did not err in finding a lack of a motivation to resolve the racemate to achieve the claimed composition of apremilast. Amgen asserts that the prior art taught away from thalidomide analogues due to safety concerns, and that no known desirable property of apremilast would have motivated a skilled artisan to defy that teaching to select any of the multitude of compounds disclosed in the '358 patent as a starting point, much less the known racemic mixture of Example 12. Amgen asserts that, without any biological data, a skilled artisan would not have been motivated to pursue a compound that was likely to be suitable for patient administration, and that a skilled artisan would not have been able to predict properties of the individual enantiomers in the racemic mixture.

Amgen further contends that the district court did not err in finding the absence of a reasonable expectation of success in resolving the racemic mixture in Example 12. Amgen contends that resolving a racemic mixture is a time-consuming, trial-and-error process filled with unpredictability, and that the '358 patent does not provide any specific procedure beyond general techniques like chiral chromatography. Even assuming a reasonable expectation of success in isolating apremilast, Amgen contends that Sandoz would have needed to prove a reasonable expectation of success in obtaining a compound as claimed, here, apremilast for use in a pharmaceutical composition that is suitable for oral administration to a patient. Amgen asserts that there was no reason to believe which enantiomer of the Example 12 racemic mixture would have therapeutic utility or be useful in a pharmaceutical composition. Amgen also contends that Sandoz is incorrect to suggest that the court required the '358 patent to be fully enabled,

and instead asserts that Sandoz's contentions amount to a disagreement with the court's finding that there would have been no reasonable expectation of success in isolating apremilast.

Amgen further asserts that the court's exclusion under Federal Rule of Evidence Rule 703 of statements made during European prosecution was not an abuse of discretion. Amgen asserts that chemists would not routinely rely on the statements of patent lawyers, and so Rule 703 subsequently would not apply.[4]

Amgen also asserts that the court did not err in finding strong objective indicia of nonobviousness. In particular, Amgen notes that apremilast was unexpectedly potent, showing a 20-fold increase in potency relative to the racemic mixture, and that apremilast was met with widespread skepticism among industry participants because of its structural similarity to thalidomide. Amgen also asserts that apremilast met a long-felt need for better psoriasis treatments, and it succeeded where many other psoriasis drugs have failed.

We agree with Amgen that the district court did not err in finding that claims 3 and 6 of the '638 patent were not shown to have been obvious by a standard of clear and convincing evidence over the '358 patent and the '606 application. We find no clear error in the court's holding that Sandoz did not meet its burden of establishing that the prior art gave a skilled artisan reason or motivation to resolve the Example 12 racemic mixture into its enantiomers, to conclude that a skilled artisan would have had reason to believe that the desirable properties of the

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[4] Given our conclusions, particularly as to the strength of the objective evidence of nonobviousness, any error in this evidentiary determination—even assuming there was error—was harmless.

Example 12 racemic mixture derived in whole or in part from the apremilast isomer, or that a skilled artisan would have had a reasonable expectation of success in resolving the mixture of Example 12. In making these findings, the court appropriately credited the statements of both Amgen's and Sandoz's experts, finding the statements of Amgen's expert more persuasive. Included in that testimony was information establishing that resolving a racemic mixture is a difficult process based on trial-and-error experimentation and that using chiral chromatography to resolve the Example 12 racemic mixture into its enantiomers would require a skilled artisan to find an appropriate solvent system for the chiral column, of which there were many possible options at the time the invention was made. *Decision* at *14–15.

The district court did not err in not holding Amgen to the statements set forth in the specification regarding isolating apremilast. *See* Appellant's Br. 30–32 (citing *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007)). In *PharmaStem*, we held that it was not unfair to hold the inventors to the consequences of their admissions because their characterization of the prior art references was not unreasonable, and the prior art references themselves strongly supported the interpretation. 491 F.3d at 1362. In contrast, here, the district court found that Sandoz's own expert conceded that the formation of chiral salts was not a viable method for separating the Example 12 enantiomers contrary to the statement in the specification. *Decision* at *14 ("[B]oth Amgen's and Defendants' experts appear to agree that the formation of chiral salts was not a viable method for separating the enantiomers of Example 12, notwithstanding the '358 Patent's representation to the contrary."). Considering the unpredictable nature of resolving racemic mixtures and the district court's acceptance of Amgen's expert testimony as credible, *PharmaStem* is distinguishable from this case.

We also agree with Amgen that the district court did not err in its finding of strong objective indicia of nonobviousness. A court's evaluation of the objective indicia of nonobviousness "is not just a cumulative or confirmatory part of the obviousness calculus but [rather] constitutes independent evidence of nonobviousness." *Ortho-McNeil Pharm., Inc. v. Mylan Lab'ys, Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). The obviousness inquiry is one that is "expansive and flexible." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415 (2007). Thus, there are a variety of objective indicia of nonobviousness that may inform the circumstances surrounding the origin of the subject matter sought to be patented including, but not limited to, "commercial success, long-felt but unresolved need, failure of others, copying, and unexpected results." *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 660 (Fed. Cir. 2000).

"[A] court need not find that all factors are present to determine that the objective considerations support a finding of nonobviousness." *Mitsubishi Tanabe Pharma Corp. v. Sandoz, Inc.*, 533 F. Supp. 3d 170, 204 (D.N.J. 2021) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)). We focus our analysis of the objective indicia of nonobviousness on the alleged unexpected potency of apremilast discovered relative to the apremilast-containing racemic mixture during testing and experimentation. The district court found that the trial record established the presence of unexpected results, crediting testimony from Dr. Peter H. Schafer, a Celgene researcher listed as an inventor on the '638 patent. The court credited the testimony as establishing that apremilast was much more effective than the apremilast-containing racemic mixture at reducing production of tumor necrosis factor alpha ("TNFα"), a promoter of the inflammatory response linked to clinical problems associated with psoriasis, in murine models. *Decision* at *17. Dr. Schafer noted a 20-fold difference in potency between apremilast alone and the apremilast-containing racemic mixture and stated that the inventors

"didn't expect a 20-fold difference in potency . . . . Normally, if a racemate is a 50/50 mixture of two enantiomers, you might expect a two-fold difference in potency, all things being equal." *Id.* Dr. Schafer's credited testimony, in addition to a 20-fold difference in potency between apremilast and the racemic mixture, is sufficient to establish the presence of unexpected results, and thus to support a finding of nonobviousness. The district court did not err in so finding.

There is no specific fold-difference that defines what may, or may not, support a finding of nonobviousness. Nor do we draw a line between a difference in degree insufficient to rebut a showing of obviousness and a difference in kind that may be sufficient to do so; each inquiry need be fact-specific. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) ("'[D]ifferences in degree' of a known and expected property are not as persuasive in rebutting obviousness as differences in 'kind'—*i.e.*, a new property dissimilar to the known property."). Instead, we hold that the 20-fold difference, when an otherwise two-fold difference would have been expected by the skilled artisan, as shown in this case, suffices to support a finding of an unexpected result and thus to affirm the district court's finding that claims 3 and 6 of the '638 patent would not have been obvious.

We further agree with Amgen, and subsequently affirm the district court's finding, that there is no clear error in the district court's finding of a nexus between the unexpected potency of apremilast and claims 3 and 6 of the '638 patent. "To accord substantial weight to . . . evidence [of objective indicia of nonobviousness], it 'must have a "nexus" to the claims, *i.e.*, there must be "a legally and factually sufficient connection" between the evidence and the patented invention.'" *Quanergy Sys., Inc. v. Velodyne Lidar USA, Inc.*, 24 F.4th 1406, 1417 (Fed. Cir. 2022) (quoting *Teva Pharms. Int'l GmbH v. Eli Lilly & Co.*, 8 F.4th 1349, 1360 (Fed. Cir. 2021)). The court credited evidence establishing that apremilast's potency over the Example 12

racemic mixture derives from the separation of apremilast from the other enantiomer. Further, the unexpected properties of a compound necessarily have a nexus to that compound. Thus, we find no clear error in the court's holding.

Although we do not find error in the district court's finding of unexpected potency of apremilast relative to the racemic mixture, and we also find it to be dispositive, we also affirm the district court's findings pertaining to the other objective indicia of nonobviousness.

First, the district court did not err in determining that, before apremilast, there was a long-felt need for a psoriasis treatment that was suitable for oral administration to a patient without the risks and barriers to adherence that were common with other psoriasis treatments. In making this finding, the court credited expert testimony establishing that topical treatments, including creams and ointments, had several drawbacks for patients suffering from moderate to severe psoriasis, including messiness, difficulty of application to large areas of affected skin, inability to treat associated psoriatic arthritis, and the tendency for topicals to lose efficacy over time. The credited expert testimony also established that older oral systemic treatments had their own compliance barriers, including treatments that required lab monitoring before, during, and sometimes after treatment, and for being contraindicated in immunosuppressed patients. *Decision* at *18.

We also find no clear error with respect to the district court's findings that others in the field had tried and failed to develop other PDE4 inhibitors, including expert testimony establishing that many PDE4 inhibitors failed to progress in experimentation and trials or were not sufficiently effective at tolerable doses. We also find no clear error in the court's finding that there was industry and regulatory skepticism about the safety of apremilast because of its structural similarity to thalidomide, evidenced by credited expert testimony, *id.* at *20–21, or that Otezla has achieved

commercial success since receiving FDA approval, based on credited expert testimony from Amgen's economic expert, *id.* at *21–22.

In summary, the district court did not err in finding that the objective indicia of nonobviousness strongly weigh in favor of a finding that claims 3 and 6 of the '638 patent would not have been obvious over the '358 patent or the '606 application. Accordingly, we affirm the court's holding that Sandoz did not meet its burden to show by clear and convincing evidence that claims 3 and 6 of the '638 patent would have been obvious over the '358 patent and the '606 application.

II. The '101 Patent

We next consider Sandoz's challenge to the district court's determination that it failed to prove that claims 1 and 15 of the '101 patent would have been obvious. In essence, Sandoz challenges the priority date to which claims 1 and 15 of the '101 patent are entitled.

Sandoz argues that the district court erred in finding that the '515 provisional application inherently disclosed crystalline Form B of apremilast, and thus provided the necessary support for claims 1 and 15 of the '101 patent to be entitled to a March 2002 priority date. Sandoz asserts that Amgen was required to show that the '515 provisional application met the written description requirements of 35 U.S.C. § 112 and that it failed to do so. Sandoz contends that the '515 provisional application does not explicitly disclose crystalline Form B of apremilast, and that Amgen is barred from relying on inherency because crystalline Form B and the claimed X-ray powder diffraction peaks of claims 1 and 15 were material to the patentability of the claims, but an allegedly inherent limitation cannot be material to the patentability of the invention. As proof of the materiality to the patentability of the invention, Sandoz notes that Celgene relied on crystalline Form B of apremilast and

the peaks recited in the asserted claims to overcome prior art rejections during prosecution. J.A. 11383–84.

Sandoz further notes that, even assuming that crystalline Form B of apremilast and the associated X-ray powder diffraction peaks were immaterial to patentability, the district court erred in determining that the '515 provisional application inherently disclosed crystalline Form B of apremilast. Sandoz contends that Amgen was required to establish that Example 2 of the '515 provisional application necessarily disclosed crystalline Form B of apremilast, but at most, it presented thirteen third-party experiments that varied parameters of Example 2, and each experiment produced crystalline Form B. That, Sandoz contends, is not sufficient to establish inherency.

Sandoz also argues that the district court erred in disregarding Celgene's affirmative admissions made during prosecution that Example 2 of the '515 provisional application could produce crystalline Form C of apremilast, not only Form B, using procedures that fall within the confines of Example 2 of the '515 provisional application.

Amgen responds that the '515 provisional application provides written description support for the '101 patent claims. Amgen asserts that it presented thirteen experiments replicating Example 2 of the '515 provisional application under a variety of conditions and that Sandoz did not produce any studies or findings showing that Example 2 of the '515 provisional application failed to produce crystalline Form B of apremilast.

Amgen further contends that the prosecution statements were made in error because Form C requires toluene, which is not within the scope of Example 2. Amgen thus asserts that the procedure in Example 2 of the '515 provisional application necessarily discloses the claimed invention and inherently discloses crystalline Form B of apremilast. Thus, Amgen's argument concludes that

claims 1 and 15 are entitled to the priority date of the '515 provisional application.

We agree with Amgen that the district court did not clearly err in finding that claims 1 and 15 of the '101 patent were entitled to the March 2002 priority date (*i.e.*, the filing date of the '515 provisional application). As a starting point, the parties did not dispute that the '515 provisional application, filed on March 20, 2002, discloses a synthetic procedure for preparing apremilast in Example 2. Amgen provided the results of over a dozen experiments following the procedure in Example 2 of the '515 provisional application, all of which resulted in crystalline Form B of apremilast. In response, Sandoz did not produce the results of any experiments showing that Example 2 of the '515 provisional application did not produce crystalline Form B of apremilast. Thus, although Sandoz alleges that Example 2 may have been capable of producing a crystalline Form other than Form B, it provided no evidence to establish that contention.

We also note that the district court based its holding on the finding that the '515 provisional application inherently disclosed crystalline Form B of apremilast. In doing so, the district court relied on *Yeda Research & Development Co. v. Abbott GmbH & Co. KG*, 837 F.3d 1341 (Fed. Cir. 2016), a case cited to us by both Sandoz and Amgen on appeal. Appellant's Br. 55; Cross-Appellant's Br. 74–75. Demonstrating inherent disclosure requires meeting a stringent standard. *See, e.g.*, *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011) ("Inherency can be established when 'prior art necessarily functions in accordance with, or includes, the claimed limitations,'" but "'may not be established by probabilities or possibilities.'" (first quoting *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002); and then quoting *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981))). But in *Yeda*, 837 F.3d at 1345–46, we held that an earlier-filed application contained adequate written description of a claimed protein

even though the application did not explicitly disclose the complete N-terminus sequence of that protein. Here we need not reach the issue of inherent disclosure because the trial evidence credited by the district court, including the experiment-related evidence introduced by Amgen (and the lack of contrary evidence from Sandoz) as well as testimony of Amgen's expert, *see Decision* at *36, establishes that crystalline Form B of apremilast is actually disclosed in the '515 provisional application. A finding of inherency is not required, and therefore, the district court did not clearly err in holding that claims 1 and 15 of the '101 patent were entitled to the March 2002 priority date.

The district court adequately considered Amgen's uncontradicted trial testimony that crystalline Form C of apremilast requires the use of a toluene solvent, which becomes a part of the crystal structure that comprises crystalline Form C of apremilast. As the court noted, and as Amgen's expert stated, toluene is not mentioned in Example 2 of the '515 provisional application, and thus the court did not clearly err in finding that Celgene had made a mistake in asserting to the European Patent Office that Example 2 of the '515 provisional application could produce forms of apremilast other than crystalline Form B.

We further note, as the district court found, that Sandoz fails to argue that any prior art from before March 2002 renders the '101 patent claims invalid for obviousness, and thus its arguments reduce to a question whether claims 1 and 15 of the '101 patent are entitled to the March 2002 priority date. We therefore affirm the court's holding that Sandoz failed to prove that claims 1 and 15 of the '101 patent were not entitled to the March 2002 priority date or that they are otherwise not invalid as obvious.

III. The '541 Patent

We finally consider Amgen's cross-appeal challenge to the district court's determination that claims 2, 19, and 21

of the '541 patent would have been obvious over Papp, Schett, and Pathan.

Amgen argues that the district court relied on generalized characterizations of a dose-titration schedule and inappropriately analyzed the "gist" of the invention rather than the invention as claimed. Amgen argues that this error resulted in a failure to make express findings that a skilled artisan would have been motivated to achieve the claimed dosage schedule. Amgen also asserts that the court's motivation-to-combine findings did not address why a skilled artisan would have had good reason to pursue certain features of the claimed schedule, including a dosing schedule with asymmetric dosing versus symmetric dosing, a dosing schedule that mixes once-a-day and twice-a-day dosing, or using a six-day dosing schedule, all of which were absent in the prior art. Amgen further asserts that the court's obvious-to-try statements do not remedy the alleged errors in the court's motivation-to-combine analysis. Amgen contends that evidence proffered in support of an obvious-to-try theory must show that the possible options skilled artisans would have encountered were finite, small, or easily traversed. Cross-Appellant's Br. 86 (citing *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1072 (Fed. Cir. 2012)). Amgen notes that its expert alleged that there were over 70,000 possible six-day dose-titration schedules. To determine whether any were efficacious and tolerable, Amgen contends, a skilled artisan would have had to administer each schedule to patients in a controlled setting.

Sandoz responds that the district court did not err in determining that claims 2, 19, and 21 of the '541 patent would have been obvious over the prior art or in crediting expert testimony stating that dose-titration modification would have been routine to a skilled artisan. Sandoz asserts that a skilled artisan would have been motivated to modify the dosing schedule in Papp, which begins with two days of two 10 mg doses of apremilast, followed by two days

of two 20 mg doses of apremilast, and followed by a fifth day of two doses of 30 mg of apremilast, *Decision* at *31; *see also* J.A. 18583; Papp at 739, to further reduce known side effects and would have had a reasonable expectation of success in doing so. Sandoz further contends that the court did not reduce the claims to a "gist" in its motivation-to-combine analysis, and even if it did, the process of the claims would have been obvious to try. Amgen further asserts that there was evidence that a skilled artisan would have been motivated to ease the dose-escalation burden on patients to reduce the risk of known side effects by moving to a one-step-at-a-time regimen starting at 10 mg apremilast per day and increasing by 10 mg per day. Sandoz asserts that that logic naturally leads to the claimed dose-titration regimen.

Sandoz further argues that the court appropriately rejected as inflated the estimate that there were over 70,000 possible dose-titration schedules. Sandoz asserts that the faulty estimate was based on two incorrect assumptions: (1) that there were six available dose strengths of apremilast instead of three and (2) that a skilled artisan would not have preferred an evenly titrated dose, each of which is incorrect. Sandoz concludes that correction of these assumptions reduces the possible estimate to eighteen possible dose-titration schedules.

We agree with Sandoz that the district court did not err in holding that claims 2, 19, and 21 of the '541 patent would have been obvious over the prior art, principally Papp and Schett. The court credited expert testimony establishing that it was well within a skilled artisan's ability to titrate an apremilast dose for a patient presenting with psoriasis and that doing so would have been a routine aspect of treating psoriasis. *Decision* at *31. The court did not err in finding that the twice-daily fixed apremilast dosing schedule, initiating treatment at 10 mg and increasing toward a 30 mg twice-daily target dose in 10 mg increments, was rendered obvious by the prior art. Further, the court

appropriately noted that, when prescribing apremilast or other drugs with known dose-dependent adverse events in the early weeks of treatment, a skilled artisan would have been motivated to use the Papp schedule as a starting point and extend it to titrate the dosing up in smaller amounts.

We have previously held that varying a dose in response to the occurrence of side effects is a well-known, standard medical practice that may well lead to a finding of obviousness. *Genentech, Inc. v. Sandoz Inc.*, 55 F.4th 1368, 1376–77 (Fed. Cir. 2022) ("[I]t is worth noting our initial perception that, as the district court noted, varying doses in response to the occurrence of side effects would seem to be a well-established, hence obvious, practice. Thus, claiming it as an invention would appear to be at best a long shot."). We note here, as in *Genentech*, that varying a dose in response to the occurrence of side effects is well-known and obvious to the skilled artisan. Accordingly, we find no error in the district court's findings that claims 2, 19, and 21 would have been obvious over Papp, Schett, and Pathan.

CONCLUSION

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

AFFIRMED

COSTS

No costs.