NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

SUN PHARMACEUTICAL INDUSTRIES, INC., F/D/B/A CONCERT PHARMACEUTICALS, INC.
Appellant

v.

INCYTE CORPORATION,
Appellee

KATHERINE K. VIDAL, UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND DIRECTOR OFTHE UNITED STATES PATENT AND TRADEMARK OFFICE,
Intervenor

2019-2011

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2017-01256.

Decided: August 22, 2023

WILLIAM M. JAY, Goodwin Procter LLP, Washington, DC, argued for appellant. Also represented by GERARD JUSTIN CEDRONE, EMILY L. RAPALINO, DARYL L. WIESEN,

DAVID ZIMMER, Boston, MA.

MARK J. FELDSTEIN, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, Washington, DC, argued for appellee. Also represented by DREW CHRISTIE, C. COLLETTE CORSER, JASON LEE ROMRELL; J. DEREK MCCORQUINDALE, Reston, VA; TRENTON A. WARD, Atlanta, GA.

ROBERT MCBRIDE, Office of the Solicitor, United States Patent and Trademark Office, Alexandria, VA, for intervenor. Also represented by THOMAS W. KRAUSE, FARHEENA YASMEEN RASHEED; SCOTT R. MCINTOSH, MELISSA N. PATTERSON, Civil Division, Appellate Staff, United Department of Justice, Washington, DC.

JOHN C. KAPPOS, O'Melveny & Myers LLP, Dallas, TX, for amicus curiae Bald Girls Do Lunch. Also represented by CAITLIN P. HOGAN, New York, NY.

Before HUGHES, LINN, and STARK, *Circuit Judges*.

STARK, *Circuit Judge*.

Sun Pharmaceutical Industries, Inc. ("Sun")[1] appeals the Final Written Decision of the Patent and Trial Appeal Board ("Board") in an *inter partes* review ("IPR") in which Petitioner, Incyte Corporation ("Incyte"), challenged all claims of Sun's U.S. Patent No. 9,249,149 ("'149 patent"). The Board concluded that the claims were invalid as obvious. Sun sought review by the Director of the Patent and Trademark Office, which was denied, and then timely filed an appeal to this court. We have jurisdiction pursuant to

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[1] The original appellant was Concert Pharmaceuticals, Inc. ("Concert"), which merged with Sun on March 31, 2023. We granted Sun's motion to replace Concert as the appellant on April 26, 2023.

28 U.S.C. § 1295(a)(4) and 35 U.S.C. §§ 141(c) and 319. We affirm.

I

A

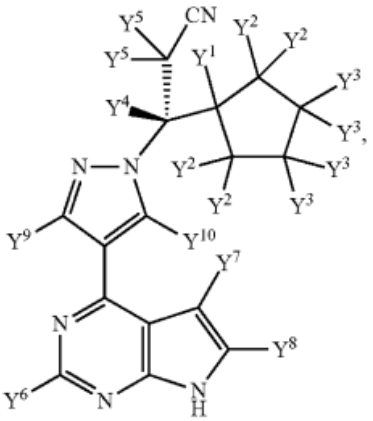
The '149 patent, entitled "Deuterated Derivatives of Ruxolitinib," "relates to novel heteroaryl-substituted pyrrolo[2,3-d]pyrimidines, and pharmaceutically acceptable salts thereof," including the compounds and their use "in methods of treating diseases and conditions that are beneficially treated by administering an inhibitor of Janus-associated kinase with selectivity for subtypes 1 and 2 (JAK1/JAK2)." '149 patent 3:25-32. Ruxolitinib is a known JAK1/JAK2 inhibitor and is "currently approved for the treatment of patients with intermediate or high-risk myelofibrosis." *Id.* at 2:53-67. Common adverse reactions associated with ruxolitinib include thrombocytopenia, anemia, bruising, dizziness, and headache. *Id.* at 3:15-18.

Deuteration involves replacing one or more hydrogen atoms of a drug with deuterium, an isotope of hydrogen, "to slow" the "CYP-mediated metabolism" (i.e., cytochrome P450 enzyme) "of a drug or to reduce the formation of undesirable metabolites." *Id.* at 2:7-10. The bonds formed between deuterium and carbon are stronger than carbon-hydrogen bonds; this stronger bond "can positively impact the ADME [absorption, distribution, metabolism, and/or excretion] properties of a drug, creating the potential for improved drug efficacy, safety, and/or tolerability" without "affect[ing] the biochemical potency and selectivity of the drug as compared to the original chemical entity that contains only hydrogen." *Id.* at 2:12-20. These measures of how a human body processes a drug, ADME, are also referred to as the drug's pharmacokinetic properties. J.A. 8225-46.

The '149 patent has two independent claims, 1 and 9. Claim 1 claims deuterated variations of Formula A and is reproduced below:

1. A compound of Formula A:

Formula A



or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is hydrogen;

each Y^2 is selected from hydrogen and deuterium, and each Y^2 is the same;

each Y^3 is selected from hydrogen and deuterium, and each Y^3 is the same;

Y^4 is selected from hydrogen and deuterium;

each Y^5 is the same and is selected from hydrogen and deuterium; and

Y^6, Y^7, Y^8, Y^9, and Y^{10} are each independently selected from hydrogen and deuterium; provided that:

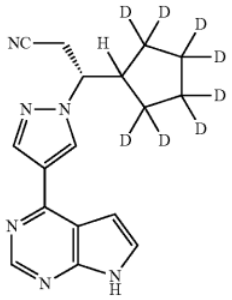
each Y^2 is deuterium; or

each Y^3 is deuterium; or

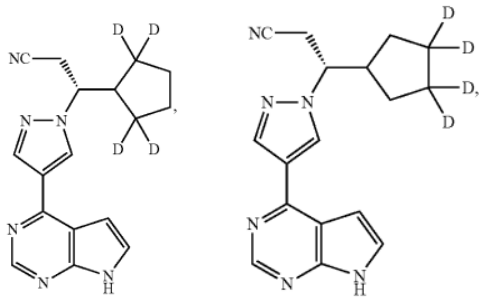
each Y^2 and each Y^3 is deuterium.

Id. at 36:17-53.

The IPR focused primarily on three compounds, pictured below, all of which are within the scope of claim 7, which depends from claim 1: an "octo-deuterated" ruxolitinib analog, in which every Y^2 and Y^3 hydrogen is deuterated,



and two "tetra-deuterated" ruxolitinib analogs,



in which either Y^2 hydrogens or Y^3 hydrogens are deuterated. *Id.* at 36:66-40.

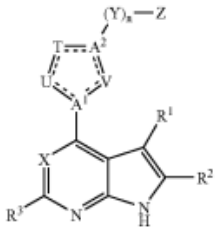
Sun named the octo-deuterated analog with a high isotopic purity CTP-543. Sun contends that CTP-543 has the potential to be a desirable treatment for alopecia areata. The FDA has given "Fast Track" and "Breakthrough Therapy" designations to CTP-543, which means the FDA will

expedite its review of CTP-543 as a new drug. *See, e.g.*, J.A. 10102.

B

In its IPR petition, Incyte presented two obviousness grounds, but the Board only considered one: the combination of Rodgers, Shilling, and the Concert Backgrounder.[2] We summarize these prior art references below.

Rodgers is a U.S. patent directed to "heteroaryl substituted pyrrolo[2,3,-b]pyridines and heteroaryl substituted pyrrolo[2,3-b]pyrmidines that modulate the activity of Janus kinases." J.A. 1747. Rodgers' claimed compounds all depend on "Formula I," reproduced below, and include ruxolitinib. J.A. 1749, 1933.



Shilling discloses a study of the "metabolism, excretion, and pharmacokinetics" of ruxolitinib and teaches that ruxolitinib is a "potent, selective inhibitor" of JAK1/JAK2. J.A. 1729. It adds that ruxolitinib was the "first

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[2] U.S. Patent No. 7,598,257 ("Rodgers") (J.A. 1744-933); Adam D. Shilling et al., *Metabolism, Excretion, and Pharmacokinetics of [^{14}C]INCB018424, a Selective Janus Tyrosine Kinase 1/2 Inhibitor, in Humans*, 38 Drug Metabolism & Disposition 2023 (2010) ("Shilling") (J.A. 1729-37); Concert Pharmaceuticals, Inc., Precision Deuterium Chemistry Backgrounder (2007) ("Concert Backgrounder") (J.A. 1738-43).

investigational drug of its class in phase III studies for the treatment of myelofibrosis." *Id.* Importantly, Shilling also identifies ruxolitinib's metabolic "hotspots," which are the sites on a compound where oxidative metabolism occurs during *in vivo* metabolism. J.A. 154, 1734. The study identifies that the majority of ruxolitinib's metabolism occurs on its cyclopentyl ring at its four methylene carbons (the Y^2 and Y^3 positions in Formulas A and I of the '149 patent and the positions that are deuterated in octo-deuterated and tetra-deuterated ruxolitinib). *See* J.A. 1736.

The Concert Backgrounder is a marketing publication issued by the original owner of the '149 patent, Concert. It teaches that deuteration of compounds provides the potential for improved safety, better tolerability, and enhanced efficacy. J.A. 1739 ("[S]ince deuterium is heavier than hydrogen, it forms significantly stronger bonds with carbon resulting in differentiated ADME (Adsorption, Distribution, Metabolism and Excretion). . . . [Hence,] [d]euterium substitution has the potential to create NCEs [new chemical entities] with improved safety, tolerability and efficacy."). The Concert Backgrounder observes that "the magnitude and nature of the deuterium benefit cannot be predicted *a priori*," so it is necessary to first "test multiple compounds in a range of assays to identify those that are differentiated." J.A. 1740. It further emphasizes, however, that "[d]euteration provides novel agents with the potential for . . . [i]mproved safety[,] . . . [b]etter tolerability[,] . . . [and] [e]nhanced efficacy," adding that Concert "is deploying its product technology platform to rapidly assemble a pipeline of valuable new deuterated drugs." J.A. 1740, 1743 (emphasis omitted).

II

"Obviousness under 35 U.S.C. § 103 is a mixed question of law and fact. We review the Board's ultimate obviousness determination de novo and underlying fact-

findings for substantial evidence." *Hologic, Inc. v. Smith & Nephew, Inc.*, 884 F.3d 1357, 1361 (Fed. Cir. 2018). "A claimed invention is unpatentable if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious to one of ordinary skill in the relevant art." *Intercontinental Great Brands LLC v. Kellogg N. Am. Co.*, 869 F.3d 1336, 1343 (Fed. Cir. 2017) (internal quotation marks omitted). The presence or absence of a motivation to combine prior art references, and a reasonable expectation of success in doing so, are questions of fact. *See Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1366 (Fed. Cir. 2016).

In an IPR, it is the petitioner's burden to prove, by a preponderance of the evidence, that a person of ordinary skill in the art would have been motivated to combine the prior art references the petitioner is relying on in its obviousness grounds. *See* 35 U.S.C. § 316(e) ("In an inter partes review instituted under this chapter, the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence.").[3] Motivation

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[3] The parties disagree as to whether our case law limits the reasonable expectation of success inquiry to only those properties that are actually claimed in the patent being challenged. *Compare*, *e.g.*, Appellee Resp. Br. at 51 ("Although an unclaimed property may be relevant to the motivation-to-combine inquiry where it is the reason proffered for the motivation, unclaimed properties are 'of no moment' to the separate 'reasonable expectation of success' inquiry directed to 'success in meeting the claims.'") (internal emphasis omitted; quoting *Intelligent BioSystems*, 821 F.3d at 1367-68), *with* Appellant Reply Br. at 18-19 (responding "that has never been this Court's approach to compound patents" and citing *Takeda Chem. Indus., Ltd.*

to combine "need not be [based on] an explicit teaching that the claimed compound will have a particular utility; it is sufficient to show that the claimed and prior art compounds possess a sufficiently close relationship to create an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old." *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) (internal quotation marks and alterations omitted). "[T]he greater the structural similarity between the compounds, the greater the motivation to combine and reasonable expectation of success." *Anacor Pharms. Inc. v. Iancu*, 889 F.3d 1372, 1385 (Fed. Cir. 2018).

In evaluating an obviousness claim, we also consider, where present, the objective indicia of nonobviousness. *See Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016). These can include "commercial success enjoyed by devices practicing the patented invention, industry praise for the patented invention, copying by others, and the existence of a long-felt but unsatisfied need for the invention." *Id.* at 1052. A patentee's evidence of objective indicia can rebut a petitioner's *prima facie* showing of obviousness. *See WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999).

A

For new chemical compounds, we apply a two-step test for determining obviousness. "First, the court determines

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v. Alphapharm Pty., Ltd., 492 F.3d 1350 (Fed. Cir. 2007)). This case does not call on us to resolve this dispute. Instead, we conclude that the Board had substantial evidence to support its conclusion of obviousness even assuming (without deciding) that a skilled artisan would have needed to have reasonably expected success in obtaining the beneficial (though possibly unclaimed) properties Sun posits for it claimed compounds.

whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012). "The second inquiry in the analysis is whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Id.* at 1292.

The parties do not dispute that a person of ordinary skill would have selected ruxolitinib as the lead compound. Rather, Sun argues that the Board erred, in three respects, in connection with the second portion of this test. Specifically, Sun contends the Board failed to (1) ask whether a person of ordinary skill would have been motivated to deuterate ruxolitinib to alter its pharmacokinetic properties, (2) determine whether the skilled artisan would have been motivated to make the specific molecular modifications claimed in the '149 patent, and (3) consider whether the person of ordinary skill would have reasonably expected success in modifying ruxolitinib. We review each of these arguments in turn.

1

Sun asks us to reject the Board's finding of obviousness because the Board purportedly failed to consider whether a person of ordinary skill would have been motivated to deuterate ruxolitinib to modify its pharmacokinetic properties, including its ADME. We conclude that the Board had substantial evidence, including the testimony of Incyte's expert, Dr. Guengerich, to find that the combined teachings of Shilling, Rodgers, and the Concert Backgrounder would have provided a skilled artisan with motivation to deuterate ruxolitinib, at its metabolic hotspots, in order "to achieve the potential benefits that the Concert Backgrounder disclosed, e.g., improved safety, tolerability,

and efficacy." J.A. 23-24; *see also* J.A. 1472-87 (Dr. Guengerich testifying to deuteration's effect on compound's ADME, including improved safety, tolerability, and efficacy), J.A. 1491-92 (Dr. Guengerich stating that Concert Backgrounder teaches deuteration has "substantially reduced R&D risk, time and expense"). The close structural similarity between prior art ruxolitinib and the deuterated ruxolitinib analogs of the '149 patent is undisputed and was reasonably found by the Board to have motivated a skilled artisan to modify ruxolitinib to retain its potency and selectivity, but improve the pharmacokinetic properties identified in the Backgrounder. This conclusion is further supported by Sun's own expert, Dr. Harbeson, J.A. 6016, and Concert's chief executive officer, who added "we've never seen any biologically relevant differences in target selectivity or potency of a drug when we deuterate it," J.A. 2406; *see also* J.A. 2919 ("The attraction of specific deuterium substitution as a parameter in drug design is based on the facts that not only is the replacement of one or a few hydrogens in a drug molecule by deuterium the smallest structural change that can be made but also such a change will have negligible steric consequences or influence on physicochemical properties . . . .").

2

Sun argues that the Board erred in failing to ask whether a person of ordinary skill would have pursued the specific modifications claimed in the '149 patent, particularly those that would have resulted in the tetra- and octodeuterated analogs of ruxolitinib. But the combination of the Concert Backgrounder, Shilling, and Dr. Guengerich's declaration provides substantial evidence for the Board's finding that a person of ordinary skill would have been motivated to modify ruxolitinib at its metabolic hotspots on its cyclopentyl ring. J.A. 23-24; *see also* J.A. 1736 (Shilling identifying ruxolitinib's metabolic hotspots as four methylene carbons on its cyclopentyl ring); J.A. 1739-42

(Concert Backgrounder teaching that "[m]etabolic 'hotspots'" are deuterated to improve compound's efficacy, safety, and tolerability). Dr. Guengerich testified that a skilled artisan "would have deuterated at the site corresponding to Y^2 and/or Y^3 in Formula A or Formula I . . . at every Y^2 and/or every Y^3," meaning that the "most reasonable deuterated analogs" would be the tetra- and octo-deuterated analogs of dependent claim 7. J.A. 1500-02 (emphasis omitted). Hence, there is substantial evidence that an ordinarily skilled artisan would have been motivated to make the specific modifications necessary to modify ruxolitinib to its deuterated analogs.

3

Sun argues that, in finding Incyte had proven a reasonable expectation of success, the Board erred by ignoring the unpredictable effects of deuterating ruxolitinib and by not considering how that unpredictability would have deterred a skilled artisan. "The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention. . . . [O]ne must have . . . a reasonable expectation of achieving what is claimed in the patent-at-issue." *Intelligent Bio-Sys.*, 821 F.3d at 1367.

The Board had substantial evidence to conclude that a person of ordinary skill would have had a reasonable expectation that she could succeed in modifying ruxolitinib to arrive at its tetra- and octo-deuterated analogs, which she would expect to display "superior ADME properties." J.A. 32; *see also* J.A. 1491-92, 1495-96 (Dr. Guengerich Decl.). Dr. Guengerich opined that a person of ordinary skill would have viewed the deuteration strategy as predictable, would have been able to synthesize the claimed compounds of the '149 patent, and would also have expected the resulting compounds to demonstrate metabolic stability. J.A. 1503-22. The Board acknowledged that the Concert

Backgrounder discloses that the "magnitude and nature of the deuterium benefit cannot be predicted *a priori*," J.A. 14, 31, 1740, but found, nonetheless, that an ordinarily skilled artisan would have reasonably expected – based on the overall teachings of the Backgrounder and the opinions of Dr. Guengerich – that deuterium modification could "result[] in differentiated ADME," including potential "[r]educed C_{max}-driven side effects" and "[i]mproved efficacy, convenience and compliance," J.A. 1739; *see also* J.A. 1491-92 (Dr. Guengerich explaining that deuteration "substantially reduce[s] R&D risk, time, and expense," notwithstanding lack of *a priori* predictability). "[O]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007).

Thus, the Board had substantial evidence to support its findings that a person of ordinary skill in the art would have been motivated to modify ruxolitinib to create the '149 patent's deuterated analogs to alter its pharmacokinetic properties and would have reasonably expected that such modifications would lead to the beneficial changes suggested by the Concert Backgrounder.

B

Sun further argues the Board erred in its evaluation of two objective indicia of nonobviousness: unexpected results and long-felt need. We disagree. Nothing about Sun's objective indicia evidence rebuts Incyte's *prima facie* showing of obviousness.[4]

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[4] Incyte argues that none of Sun's objective indicia evidence is probative of nonobviousness because it all relates solely to CTP-543, which is a single embodiment and

Sun argues that CTP-543, the highly pure octo-deuterated embodiment of claim 7 of its '149 patent, displays two unexpected results: (1) a flatter pharmacokinetic curve, which increases the time of the drug in the therapeutic window, and (2) a greater relative increase in half-life for patients who metabolized ruxolitinib most quickly. The record contains substantial evidence to support the Board's contrary finding that CTP-543's results were "an increase in the same clinical activity observed with ruxolitinib, and therefore represent merely a difference in degree and not in kind." J.A. 35; *see Bristol-Myers Squibb Co. v. Teva Pharms. USA Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) ("While a 'marked superiority' in an expected property may be enough in some circumstances to render a compound patentable, a 'mere difference in degree' is insufficient."). That is, the Board reasonably concluded that CTP-543's increased time in the therapeutic window and increased clinical response at a given dose were differences in degree that did not indicate a marked superiority in these properties. *See* J.A. 6636-37, 6745-55 (Incyte's experts testifying that therapeutic differences between CTP-543 and ruxolitinib were not "clinically meaningful" or "clinically impactful").

"The existence of a long-felt but unsolved need that is met by the claimed invention is further objective evidence of non-obviousness." *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1369 (Fed. Cir. 2017). "Evidence of a long-felt need is particularly probative of obviousness when it demonstrates both that a demand existed for the

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not commensurate with the scope of any claim of the '149 patent. It is sufficient for our purposes, as it was for the Board, *see* J.A. 35, to assume without deciding that Sun has met its burden to show that CTP-543 is representative of all embodiments within the scope of a challenged claim, as Sun's evidence lacks significant probative value for other reasons that we explain.

patented invention, and that others tried but failed to satisfy that demand." *Id.* (internal quotation marks omitted). Assuming, without deciding, that the need for an effective and safe alopecia areata treatment existed, the Board had substantial evidence for its finding that CTP-543 had not actually satisfied this long-felt need, but only had the "potential" and "likelihood" to do so. J.A. 36-37; *see also* J.A. 9385-86 (Dr. Mackay-Wiggin Decl.). While we agree with Sun (and amicus Bald Girls Do Lunch) that FDA approval is not a prerequisite to showing that a long-felt need has been met, and FDA's designation of CTP-543 for "Breakthrough Therapy" and "Fast-Track" approval are probative of nonobviousness, here Sun expressly framed its objective indicia argument as "CTP-543 satisfies the long-felt need for an *FDA-approved*, evidence-based alopecia areata treatment," J.A. 465 (emphasis added), and the Board reasonably found that CTP-543 had not met this need because it lacked FDA approval, *see* J.A. 1366.[5] Thus, substantial evidence supports the Board's conclusion that Sun did not prove that CTP-543 has satisfied this long-felt need.

III

We have considered Sun's remaining arguments and find them unpersuasive. For the foregoing reasons, we affirm.

AFFIRMED

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[5] Evidence provided by the amicus, Bald Girls Do Lunch, but not otherwise in the record cannot be considered on appeal. *See In re Watts*, 354 F.3d 1362, 1367 (Fed. Cir. 2004).