United States Court of Appeals for the Federal Circuit

MILLENNIUM PHARMACEUTICALS, INC.,
Plaintiff-Appellant

v.

SANDOZ INC., ACCORD HEALTHCARE, INC., ACTAVIS LLC, MYLAN LABORATORIES LIMITED, AGILA SPECIALTIES INC., DR. REDDY'S LABORATORIES, LTD., DR. REDDY'S LABORATORIES, INC., SUN PHARMACEUTICAL INDUSTRIES LIMITED, SUN PHARMA GLOBAL FZE, APOTEX CORP., APOTEX INC., TEVA PHARMACEUTICALS USA, INC., GLENMARK PHARMACEUTICALS LTD., GLENMARK GENERICS LTD., GLENMARK GENERICS INC., USA, HOSPIRA, INC., WOCKHARDT BIO AG, WOCKHARDT USA LLC,
Defendants-Appellees

2015-2066, 2016-1008, 2016-1009, 2016-1010, 2016-1109, 2016-1110, 2016-1283, 2016-1762

Appeals from the United States District Court for the District of Delaware in Nos. 1:12-cv-01011-GMS, 1:12-cv-01490-GMS, 1:12-cv-01750-GMS, 1:13-cv-01874-GMS, 1:14-cv-01156-GMS, 1:15-cv-00040-GMS, 1:15-cv-00539-GMS, 1:15-cv-00540-GMS, 1:15-cv-00804-GMS, 1:16-cv-00034-GMS, Judge Gregory M. Sleet.

Decided: July 17, 2017

WILLIAM F. LEE, Wilmer Cutler Pickering Hale and Dorr LLP, Boston, MA, argued for plaintiff-appellant. Also represented by MARK CHRISTOPHER FLEMING, LISA JON PIROZZOLO, JASON H. LISS, ANNA E. LUMELSKY, TASHA JOY BAHAL, EMILY R. WHELAN; ROBERT M. GALVIN, Palo Alto, CA.

THOMAS J. MELORO, Willkie Farr & Gallagher LLP, New York, NY, argued for all defendants-appellees. Defendant-appellee Hospira, Inc. also represented by MICHAEL JOHNSON.

GEORGE C. LOMBARDI, Winston & Strawn LLP, Chicago, IL, for defendant-appellee Sandoz Inc. Also represented by KATHLEEN BRIDGET BARRY, MAUREEN L. RURKA.

PAUL BRAIER, Greenblum & Bernstein, P.L.C., Reston, VA, for defendant-appellee Accord Healthcare, Inc. Also represented by PETER BRANKO PEJIC.

GARY EDWARD HOOD, Polsinelli PC, Chicago, IL, for defendant-appellee Actavis LLC. Also represented by MARK THOMAS DEMING, KHURRAM NAIK; ROBYN ASTGMOSER, St. Louis, MO.

TUNG ON KONG, Rhodes Attorneys at Law P.C., San Francisco, CA, for defendants-appellees Mylan Laboratories Limited, Agila Specialties Inc. Also represented by ELHAM FIROUZI STEINER, Wilson, Sonsini, Goodrich & Rosati, PC, San Diego, CA.

LOUIS HARRY WEINSTEIN, Budd Larner, P.C., Short Hills, NJ, for defendants-appellees Dr. Reddy's Laboratories, Ltd., Dr. Reddy's Laboratories, Inc. Also represented by ELLEN TCHORNI LOWENTHAL, STUART D. SENDER.

RACHEL C. HUGHEY, Merchant & Gould P.C., Minneapolis, MN, for defendants-appellees Sun Pharmaceutical Industries Limited, Sun Pharma Global FZE. Also represented by AARON M. JOHNSON, CHRISTOPHER J. SORENSON.

WILLIAM A. RAKOCZY, Rakoczy Molino Mazzochi Siwik LLP, Chicago, IL, for defendants-appellees Apotex Corp., Apotex Inc. Also represented by PETER JAMES CURTIN, THOMAS EHRICH, LUKE TIMOTHY SHANNON.

MARK DAVID SCHUMAN, Carlson, Caspers, Vandenburgh, Lindquist & Schuman, P.A., Minneapolis, MN, for defendant-appellee Teva Pharmaceuticals USA, Inc. Also represented by JENNELL CHRISTINE BILEK, SAMUEL T. LOCKNER, ALEXANDRA JANE OLSON, TODD S. WERNER.

JAY PHILIP LESSLER, Blank Rome LLP, New York, NY, for defendants-appellees Glenmark Pharmaceuticals Ltd., Glenmark Generics Ltd., Glenmark Generics Inc., USA. Also represented by CHRISTOPHER K. HU, PAUL M. ZAGAR; DAVID ANTHONY DOREY, Wilmington, DE.

KEVIN MICHAEL NELSON, Duane Morris LLP, Chicago, IL, for defendants-appellees Wockhardt Bio AG, Wockhardt USA LLC. Also represented by PATRICK GALLAGHER.

Before NEWMAN, MAYER, and O'MALLEY, *Circuit Judges.*

NEWMAN, *Circuit Judge.*

Millennium Pharmaceuticals, Inc. is the exclusive licensee of U.S. Patent No. 6,713,446 ("the '446 Patent"), issued March 30, 2004 and assigned to the United States. Millennium developed the patented product for treatment of oncology disease, particularly multiple myeloma and mantle cell lymphoma. The product has the brand name

Velcade®. Appellees in Appeal Nos. 15-2066, 16-1008, 16-1009, 16-1010, 16-1110, 16-1283, and 16-1762 (collectively, "Sandoz") all filed abbreviated new drug applications ("ANDAs"), admitting infringement and seeking to invalidate various claims of the '446 Patent. Based on the litigation that ensued, the district court held that claims 20, 31, 49, and 53 of the '446 Patent were invalid,[1] leading to this appeal.

Millennium filed a notice of appeal in Appeal No. 16-1109 after the district court entered final judgment against Millennium in separate cases arising from ANDAs filed by Apotex and Teva, based on collateral estoppel arising from the district court's judgment of invalidity of claims 20, 31, 49, and 53 of the '446 Patent in the Sandoz-Millennium action. We consolidated the appeals in the Sandoz, Apotex, and Teva actions.

On review of the record and the applicable law, we conclude that the district court erred in the Sandoz litigation and that invalidity was not established. We reverse and enter judgment in favor of Millennium in the Sandoz litigation. We also vacate the district court's judgment in the action between Millennium, Teva, and Apotex based on our decision in the Sandoz litigation and remand that action for further proceedings.

I. BACKGROUND

A. The '446 Patent

The '446 Patent describes the chemical compound D-mannitol N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronate. The compound is described as a boro-

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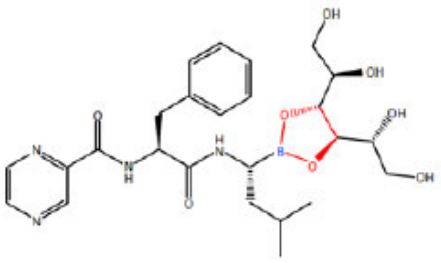
[1] *Millennium Pharm., Inc. v. Sandoz Inc.*, No. 12-1011, 2015 WL 4966438 (D. Del. Aug. 20, 2015) ("Dist. Ct. Op.").

nate ester of bortezomib (a boronic acid) and D-mannitol (a hydroxy compound) and has the following chemical structure, with Millennium's highlight of the bonds between the bortezomib moiety and the D-mannitol moiety:



Millennium Br. 13. The lyophilized compound is claimed in Claim 20:

> 20. The lyophilized compound D-mannitol N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronate.

Other asserted claims include the new compound as a lyophilized cake, the method of preparation of the new compound, and its reconstitution with a pharmaceutically acceptable carrier. Dist. Ct. Op. *2.

Bortezomib and its properties as a proteasome inhibitor were previously known and are described in United States Patent No. 5,780,454 ("the Adams Patent"). However, despite its known efficacy against various cancers, bortezomib never achieved FDA approval and market status because of its instability, its rapid degradation in liquid formulations, and its insolubility. The record states that these problems remained unsolved despite extensive research effort by the inventor Dr. Adams and others at Millennium and its predecessor company. Dr. Adams' team attempted to develop a stable liquid formulation of bortezomib, but after evaluating approximately 20 different formulations, the team failed to develop a formulation that was stable enough for transportation, storage, and

administration to patients under conditions of clinical use and distribution.

The inventor of the '446 Patent was associated with the National Cancer Institute and the University of Kansas, and was consulted by Dr. Adams after years of unsuccessful attempts to solve formulation and stability problems with bortezomib. Despite preparing approximately twenty-five different liquid formulations, these efforts encountered the same stability and solubility problems as had other researchers attempting to solve this problem.

After failing to develop a viable liquid formulation, researchers began work on a lyophilized formulation for injection. The process of lyophilization (freeze-drying) is not intended to change the chemical structure of the active pharmaceutical ingredient. After experimenting with multiple variables that affect the lyophilization process, including solvents and bulking agents, researchers produced a promising lyophilized formulation using mannitol, a known bulking agent. It was discovered that the reason for the dramatic improvement in dissolution and stability for this formulation was the formation of a new chemical compound during lyophilization: the claimed ester of bortezomib and mannitol. The mannitol ester of bortezomib acts as a "prodrug," a compound that converts to or releases the active pharmaceutical ingredient upon administration to a patient. This discovery is described and claimed in the '446 Patent.

The ensuing drug product (Velcade®) became "a cancer treatment that changed the decades-old standard of care for multiple myeloma and has saved thousands of lives. The FDA approved Velcade® in record time, despite its novel structure and mechanism of action." Millennium Br. 1.

B. Proceedings in Sandoz Litigation

After the Sandoz defendants each filed an ANDA seeking FDA approval for the commercial manufacture, use, and sale of generic counterparts of Velcade®, Millennium filed patent infringement suits alleging that the products infringe at least claims 20, 31, 49, and 53 of the '446 Patent. The defendants stipulated to infringement of all asserted claims, and raised the defense of patent invalidity based on obviousness.

The district court held that the claims were obvious because they were the inherent result of an allegedly obvious process, *viz*., lyophilizing bortezomib in the presence of the bulking agent mannitol. Millennium argued that a person of ordinary skill would avoid lyophilization in developing a formulation involving bortezomib because "bortezomib was known to be unstable even in the dry state as a freestanding solid compound." Dist. Ct. Op. *6. The court was not persuaded by this argument and instead relied on the testimony of Sandoz's witness, Dr. Repta, to find that, as of the '446 Patent's priority date, lyophilization "was well-known in the field of formulation" and that it was considered an obvious alternative "when a liquid formulation provided limited success." *Id.*

The district court did not find that the prior art taught or suggested that the claimed new compound would be formed, or taught or suggested making the claimed new compound by any method, or taught or suggested that this new compound would have the properties of stability, solubility, and dissociability that it exhibited. No reference taught or suggested reacting bortezomib with mannitol, and no reference hinted that such an esterification reaction might occur during lyophilization. No reference taught or suggested that the product of such lyophilization would be a new chemical compound that would solve the problems that had inhibited development of bortezomib in oncology. However, the

district court concluded that lyophilizing bortezomib with mannitol was an obvious option "from which the prior art did not teach away." *Id.* at *7. The district court found that the Adams Patent "pointed directly to mannitol" despite the Adams Patent's failure to mention mannitol. *Id.*

The district court received testimony from the inventor and others that the formation of this new compound was not expected or intended when they conducted the lyophilization. There was no contrary evidence. Nonetheless, the district court held the claims invalid on the ground of obviousness, agreeing with Sandoz that "Millennium conceded as a matter of law that the ester is the 'natural result' of freeze-drying bortezomib with mannitol." *Id.* at *8. The court reasoned that the "natural result" of a chemical procedure is inherent in the procedure, and thus the product thereof "would have been obvious to a person of ordinary skill," in the words of § 103.

On the evidence of objective indicia of obviousness, the district court found that Millennium did not establish unexpected results because it did not compare the claimed invention to a glycerol ester of bortezomib. *Id.* at *9. The court also rejected long-felt need as objective evidence of non-obviousness, stating that "the lyophilized mannitol ester of bortezomib did not solve any problem having persisted over a long period of time without resolution by the prior art." *Id.* at *10 (quoting *Hitachi Koki Co. v. Doll*, 620 F. Supp. 2d 4, 30 (D.D.C. 2009)).

C. Proceedings in Apotex and Teva Litigations

Millennium also filed suit against Appellees Apotex and Teva after each filed an ANDA seeking approval for the commercial manufacture, use, and sale of a generic

version of Velcade®.[2] After the district court invalidated claims 20, 31, 49, and 53 of the '446 Patent in the Sandoz litigation, Apotex moved to dismiss Millennium's infringement claims, arguing that the district court's opinion created collateral estoppel barring Millennium from re-litigating the validity of the asserted claims. Eventually the parties stipulated that collateral estoppel warranted entry of judgment and dismissal in favor of Apotex and Teva.

II. DISCUSSION

A. Sandoz Litigation

In this Hatch-Waxman litigation, the district court invalidated the '446 patent on the ground of obviousness. The determination of obviousness under 35 U.S.C. § 103 is a legal conclusion based on underlying facts. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966). After a bench trial, appellate review of the district court's factual findings is for clear error, and conclusions of law receive de novo review. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1290 (Fed. Cir. 2013) (citation omitted). Invalidity of an issued patent must be shown by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011). "While we afford deference to a district court's factual findings, however, we retain plenary review to determine whether, as a legal matter, the evidence satisfies the clear-and-convincing standard of proof." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012) (citing *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 993-94 (Fed. Cir. 2009)).

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[2] The district court consolidated Millennium's litigation against Teva and Apotex.

1.

Recognizing our obligation to give deference to a district court's greater familiarity with the record and authority to reach factual conclusions therefrom, we conclude that the district court erred in its evaluation of obviousness. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419-20 (2007) (the question of law is whether the prior art rendered the invention obvious). In the case at bar, the question is whether a person of ordinary skill, seeking to remedy the known instability and insolubility and to produce an efficacious formulation of bortezomib, would obviously produce the D-mannitol ester of bortezomib, a previously unknown compound.

The prior art contains no teaching or suggestion of this new compound, or that it would form during lyophilization. Sandoz identifies no reference or combination of references that shows or suggests a reason to make the claimed compound. No reference teaches or suggests that such a new compound would have the long-sought properties of stability and solubility, and sufficiently dissociate to release bortezomib at an effective rate in the bloodstream, all critical to effective use for treating multiple myeloma.

The D-mannitol ester of bortezomib is a new compound with distinct chemical properties. We consider 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." *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.,* 678 F.3d 1280, 1292 (Fed. Cir. 2012); *see also Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.,* 752 F.3d 967, 973 (Fed. Cir. 2014) ("To establish obviousness in cases involving new chemical compounds, the accused infringer must identify some reason that would have led a chemist to modify a known compound."); *In re Rosuvastatin Calcium Patent Litig.,* 703 F.3d 511,

518 (Fed. Cir. 2012) (affirming district court conclusion that "the Defendants did not demonstrate the required motivation for selecting Sandoz Compound 1b as a lead compound"). The parties agree that bortezomib is the proper lead compound for this analysis. It is not disputed that the Velcade® compound provided unexpected properties, solving the problems that accompanied bortezomib.

The district court clearly erred in its obviousness analysis. There is no teaching or suggestion in the references to produce the claimed mannitol ester. No reference shows or suggests ester formation at freeze-drying conditions, or that any such ester might solve the problems of instability and insolubility of the free acid while dissociating rapidly in the bloodstream. No reference provides a reason to make the mannitol ester of bortezomib.

Sandoz argues that lyophilization was generally known in formulating pharmaceutical products. It states that bulking agents were known for use in lyophilization, and that mannitol was a known bulking agent. All true. However, the prior art does not teach or suggest that lyophilization of bortezomib in the presence of mannitol would produce a chemical reaction and form a new chemical compound, or provide a reason to make this specific new chemical compound, or that this new compound would solve the previously intractable problems of bortezomib formulation. Although mannitol was a known bulking agent, and lyophilization was a known method of drug formulation, nothing on the record teaches or suggests that a person of ordinary skill should have used mannitol as part of a synthetic reaction to make an ester through lyophilization. A result is obvious when it is "the natural result flowing from the operation as taught," or a "property that is necessarily present" when applying a process disclosed in the prior art. *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014) (emphasis omitted) (first quoting *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981); then quoting *Alcon Research, Ltd. v.*

Apotex Inc., 687 F.3d 1362, 1369 (Fed. Cir. 2012), and *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009)). Sandoz failed to show that it was obvious to use mannitol to make an ester during lyophilization, or that the ester would solve the problems experienced with bortezomib.

Sandoz defends the district court's ruling by citing three groups of references that purportedly provide the required teaching or suggestion. The first group shows that lyophilization is a known technique to prepare pharmaceutical formulations, although no reference shows lyophilization of bortezomib. The second group shows that mannitol is a known inert bulking agent, although no reference shows mannitol as a bulking agent for bortezomib. The third group starts from the Adams Patent that states that boronic acids can form esters, although mannitol is not included in the ester-forming alcohols mentioned in the Adams Patent. None of these references, alone or in combination, suggests or teaches that the solution to the problems of creating an efficacious formulation of bortezomib lay in freeze-drying bortezomib with mannitol to form an ester having the necessary properties for stability, storage, and treatment.

Nor does the Adams Patent provide the requisite teaching. As noted, bortezomib is described in the Adams Patent. That reference states that bortezomib is a boronic acid and that esters may be made, and it lists ten alcohols for this purpose. Adams Patent, col. 10, ll. 15–18. Mannitol is not mentioned. Nor does the Adams Patent teach or suggest that the esters provide a solution to the problems of instability and insolubility of bortezomib.

None of the experts presented by the many defendants stated that they were aware of prior art to fill any of the gaps in teaching or suggestion of the Velcade® product—although they variously opined that this long-sought discovery was obvious. Sandoz's expert Dr. Repta, who offered an opinion of obviousness, conceded that he had

"never worked with any boronic acid compound and has not performed or supervised any lyophilization experiments since 1983." Repta Dep. Tr. at 190, l. 10–192, l. 8. Dr. Repta cited seventeen references, none of which teaches or suggests the claimed new compound, or proposes lyophilization in the presence of mannitol to produce a new compound, or suggests that such new compound should be prepared in order to obtain the necessary stability, solubility, and dissociability for treatment of multiple myeloma.

Sandoz argues in this appeal that a Brown reference[3] and the Adams Patent teach that esters are more stable to oxidation than boronic acids. Sandoz Br. 33 (citing Adams, scheme 1, col. 29–30; Brown at 4526). However, Sandoz's witness Dr. Repta testified that (1) he could not identify any portion of the Brown reference making this point, Repta Dep. Tr. at 291, l. 18-292, l. 16, and (2) the Adams Patent says nothing about the stability of any ester, *id.* at 214, ll. 5–12. In *Pfizer, Inc. v. Apotex, Inc.,* 480 F.3d 1348, 1361 (Fed. Cir. 2007), the court held that, in determining obviousness, the challenger bears the burden of establishing that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." Here, neither the requisite motivation nor expectation of success is found in the prior art.

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[3] Herbert C. Brown and J.V.N. Vara Prasad, *Chiral Synthesis via Organoboranes. 9. Crystalline "Chelates" from Borinic and Boronic Esters. A Simple Procedure for Upgrading Borinates and Boronates to Materials Approaching 100% Optical Purity*, 51 J. ORGANIC CHEMISTRY 4526 (1986).

No reference supports the district court's conclusion that "skilled formulators would be motivated to create a mannitol ester to improve bortezomib's stability and solubility." Dist. Ct. Op. *8. No reference suggests producing this ester for this purpose. The undisputed facts are of failed attempts to achieve a stable formulation with the necessary properties of solubility and dissolution in the bloodstream.

We take note of Sandoz's reliance on selected portions of Dr. McCubbin's testimony in another case, for Sandoz does not mention that he also testified that Millennium could not have predicted that bortezomib would be stabilized by forming the mannitol ester. *See* McCubbin Dep. Tr. at 333, l. 24–334, l.4 ("But for any specific compound, you don't know what that stability is or whether it truly stabilizes it. There's examples where you can't form that ester or you form the ester, but it's not particularly stable. There – It's very mixed. It's a very compound-specific analysis that one has to do to really justify its stability difference.").

The sole reason Sandoz provides for choosing mannitol to make a new ester of bortezomib is because mannitol is one of a relatively small number of bulking agents used in lyophilization. Sandoz provides no reason why a person of ordinary skill who is seeking to make esters of bortezomib would look to lyophilization bulking agents. Dr. Anderson explained that mannitol is used as a bulking agent in lyophilization, and he also explained that persons experienced with bortezomib would know of crystallization-and boroxine-related concerns, but would not expect the bulking agent to react with the bortezomib to form a new compound.

2.

The district court also clearly erred in its determination that lyophilizing bortezomib with mannitol to form an ester was a "suitable option from which the prior art

did not teach away." Dist. Ct. Op. *7 (citing *Par Pharm.*, 773 F.3d at 1198). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Urbanski*, 809 F.3d 1237, 1244 (Fed. Cir. 2016) (quoting *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)). Millennium offered persuasive evidence that the chemical modification of bortezomib would have been unattractive to a person of ordinary skill for fear of disturbing the chemical properties whereby bortezomib functions effectively as an anti-cancer agent; in particular, a person of ordinary skill would have noted that the ester blocks a portion of the bortezomib molecule. Without the knowledge that the D-mannitol bortezomib ester dissociates in the bloodstream at a rate of pharmaceutical efficacy, a person of ordinary skill would not have been led to create the ester. Dr. Repta's testimony that dissociation of boronic esters would be "virtually instantaneous" was contradicted on cross-examination, and is not supported by the Adams Patent, which does not discuss the dissociation or stability of the esters.

We agree with Millennium that a person of ordinary skill would have avoided creating an ester with mannitol because several different esters, each with different chemical and possibly biological properties, could have formed. Dr. Adams testified that he was surprised when he learned that such a multiplicity of mannitol esters did not form with bortezomib.

3.

The district court also clearly erred in its consideration of inherency. "A party must . . . meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis." *Par Pharm.,* 773 F.3d at 1195–96. "The mere

fact that a certain thing may result from a given set of circumstances is not sufficient" to render the result inherent. *In re Oelrich,* 666 F.2d at 581 (quoting *Hansgirg v. Kemmer,* 102 F.2d 212, 214 (CCPA 1939)).

The district court stated that Millennium "conceded as a matter of law that the ester is the 'natural result' of freeze-drying bortezomib with mannitol." Dist. Ct. Op. *8. However, "[t]he inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art." *Otsuka*, 678 F.3d at 1296. This oft-cited principle is explained in, for example, *In re Kratz*, 592 F.2d 1169, 1175 (CCPA 1979):

> However, making weight of the method appellant used in finding the invention is beside the point. The last sentence of 35 U.S.C. § 103, with great clarity, excludes such methodology in stating that "(p)atentability shall not be negatived by the manner in which the invention was made."

See also, e.g., Life Techs., Inc. v. Clontech Labs., Inc., 224 F.3d 1320, 1325 (Fed. Cir. 2000) ("[T]he path that leads an inventor to the invention is expressly made irrelevant to patentability by statute.").

Sandoz argues that although lyophilization in the presence of mannitol produced an unexpected result, the result was "inevitable" and thus "inherent," and thus not "inventive." Sandoz Br. at 1, 12-17. However, invention is not a matter of what the inventor intended when the experiment was performed; obviousness is measured objectively in light of the prior art, as viewed by a person of ordinary skill in the field of the invention. "Those charged with determining compliance with 35 U.S.C. § 103 are required to place themselves in the minds of those of ordinary skill in the relevant art at the time the invention was made, to determine whether that which is

now plainly at hand would have been obvious at such earlier time." *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985). No expert testified that they foresaw, or expected, or would have intended, the reaction between bortezomib and mannitol, or that the resulting ester would have the long-sought properties and advantages.

4.

We conclude finally that the district court clearly erred in its examination of the objective indicia of unexpected results and long-felt need. All of the *Graham* factors must be considered, including the objective indicia when present, before any conclusion regarding obviousness is reached. *In re Cyclobenzaprine*, 676 F.3d at 1075–76 (citation omitted); *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1579 (Fed. Cir. 1997); *see Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (stating that objective indicia are "not just a cumulative or confirmatory part of the obviousness calculus but constitute[] independent evidence of nonobviousness").

Evidence of objective indicia "can be the most probative evidence of nonobviousness in the record," and objective indicia enable "the court to avert the trap of hindsight." *Leo Pharm. Prods., Ltd. v. Rea,* 726 F.3d 1346, 1358 (Fed. Cir. 2013) (quoting *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010)). These indicia cannot be set aside in the analysis of obviousness.

i.

"Unexpected results are useful to show the improved properties provided by the claimed compositions are much greater than would have been predicted." *Leo Pharm.*, 726 F.3d at 1358 (quoting *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995) (internal quotation marks omitted)).

Nonobviousness may be established when an invention "yield[ed] more than predictable results." *Crocs, Inc.*, 598 F.3d at 1309; *see also In re Soni,* 54 F.3d at 750–51; *In re Chupp*, 816 F.2d 643, 646–47 (Fed. Cir. 1987) (considering improved properties as selective herbicide); *In re May,* 574 F.2d 1082, 1093 (CCPA 1978) (considering non-addictive property of analgesic compound). "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006) (quotation and citation omitted); *Pfizer*, 480 F.3d at 1370–71 (quoting same).

Millennium presented expert testimony that the lyophilized mannitol ester of bortezomib yielded unexpected results as compared to bortezomib, *viz.*, greatly improved stability, solubility, and dissolution. However, the district court ruled that bortezomib itself was not the closest prior art, and declined to consider the advantages and benefits of the Velcade® product. The district court's error stems from its determination that Millennium should have compared the glycerol bortezomib ester, for the Adams Patent included glycerol as one of ten "[p]referred . . . dihydroxy compounds"[4] for "boronate esters." Adams Patent, col. 10, ll. 11-18.

The bortezomib glycerol ester was not specifically disclosed, prepared, or tested in the Adams Patent. Although Sandoz now argues that the bortezomib glycerol ester is "generically" encompassed by the Adams Patent, Sandoz has not argued that any glycerol ester is specifically disclosed or actually identified in the Adams Patent (or in any other reference).

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[4] Glycerol is a trihydroxy compound.

Nor does the Adams Patent disclose the stability or solubility of any ester compound. Unexpected results are shown in comparison to what was known, not what was unknown. *See Pfizer*, 480 F.3d at 1370–71; *see also Kao*, 441 F.3d at 970. Millennium was not required to create the glycerol ester, when the product had not been created in the prior art. *See In re Geiger*, 815 F.2d 686, 690 (Fed. Cir. 1987) (Newman, J., concurring) ("The applicant is not required to create prior art, nor to prove that his invention would have been obvious if the prior art were different than it actually was.").

We conclude that the district court should have treated bortezomib as the closest prior art compound, and acknowledged the unrebutted evidence that the D-mannitol ester of bortezomib exhibited unexpected results compared with bortezomib, including unexpectedly superior stability, solubility, and dissolution.

ii.

The existence of a long-felt but unsolved need that is met by the claimed invention is further objective evidence of non-obviousness. *See In re Cyclobenzaprine*, 676 F.3d at 1081–83 ("[W]here . . . the obviousness determination turns on whether . . . a particular formulation of [a drug] would be [a] successful . . . [or] effective treatment[,] objective indicia of . . . longfelt need [is] particularly telling."). Evidence of long-felt need is "particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand." *Id.* at 1082–83 (citing *In re Piasecki*, 745 F.2d 1468, 1475 (Fed. Cir. 1984); *Alco Standard Corp. v. Tenn. Valley Auth.*, 808 F.2d 1490, 1500 (Fed. Cir. 1986) (finding nonobviousness where the relevant industry had searched for a

solution, and major manufacturers tried but failed to develop a reliable solution)).[5]

The district court's conclusion that the lyophilized mannitol ester of bortezomib did not meet a long-felt need was both perfunctory and clearly erroneous. There is no dispute that there was a long-felt need for a product to treat multiple myeloma, for treatments prior to Velcade® gave poor remission and low survival rates. Although it is agreed that bortezomib is the effective product in the body, bortezomib alone is not an available product. Sandoz offered no evidence of successful solution of the problems that had barred bortezomib from clinical approval.

The district court clearly erred in attributing Velcade®'s commercial success to bortezomib alone, as bortezomib is not a viable commercial product and had been denied FDA approval because of its instability. The D-mannitol ester was responsible for Velcade®'s successful results, for the D-mannitol ester is necessary to provide the required solubility and stability.

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[5] Sandoz argues that there was no "failure of others" because the Adams Patent blocked others from bringing a bortezomib formulation to market until patent expiration in 2017. This question is not before us. We have noted that, although long-felt need is closely related to failure of others, these considerations are distinct and we treat each separately. *See, e.g.*, *In re Cyclobenzaprine*, 676 F.3d at 1081–83; *Graham*, 383 U.S. at 17-18. Although "[e]vidence is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand," a patent owner may establish a long-felt need without presenting evidence of failure of others. *In re Cyclobenzaprine*, 676 F.3d at 1082.

On the entirety of the record, we conclude that the district court clearly erred in finding that a person of ordinary skill would obviously make the D-mannitol ester in order to solve the problem of providing an effective form of bortezomib. The unexpected properties of an unexpectedly produced new compound, and the ensuing pharmaceutical efficacy and benefit, negate the district court's ruling of obviousness. We therefore reverse the district court's invalidity determination.

B. Apotex and Teva Litigation

Apotex, Teva, and Millennium agree that, if the judgment in the Sandoz case is reversed, the dismissal of the litigation between Millennium and Apotex and Teva should be vacated and remanded, so that Apotex and Teva have the opportunity to present their case. Apotex Br. 18; Millennium Reply Br. 31. Because we reverse the judgment in the Sandoz litigation, we vacate and remand the Apotex and Teva litigation to the district court for appropriate further proceedings.

III. CONCLUSION

We conclude that the Sandoz group of defendants did not establish the obviousness of the asserted claims of the '446 Patent by clear and convincing evidence. The district court's judgment of invalidity is reversed, and judgment is entered in favor of Millennium as to the Sandoz defendants. We remand for any appropriate further proceedings in that action.

The judgment between Millennium and Apotex and Teva is vacated, and remanded for further proceedings in those actions.

REVERSED-IN-PART AND REMANDED-IN-PART; VACATED-IN-PART AND REMANDED-IN-PART

COSTS

Costs to Millennium in Case Nos. 15-2066, 16-1008, 16-1009, 16-1010, 16-1110, 16-1283, and 16-1762.

No costs in Case No. 16-1109.