Trials@uspto.gov
571-272-7822

Paper No. 14
Entered: June 25, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,
Petitioner,

v.

MERCK SHARP & DOHME CORP.,
Patent Owner.

Case IPR2015-00419
Patent 5,691,336

Before LORA M. GREEN, ZHENYU YANG, and ROBERT A. POLLOCK, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

INTRODUCTION

Apotex Inc. ("Petitioner") filed a Petition for an *inter partes* review of claims 1, 3–8, and 10–25 of U.S. Patent No. 5,691,336 ("the '336 patent," Ex. 1001). Paper 1 ("Pet."). Merck Sharp & Dohme Corp. ("Patent Owner") timely filed a Preliminary Response. Paper 13 ("Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 314.

For the reasons provided below, we determine Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim. *See* 35 U.S.C. § 314(a). Therefore, we deny the Petition for an *inter partes* review.

Related Proceedings

According to the parties, Patent Owner previously asserted the '336 patent against several entities, but not Petitioner, in district court proceedings. Pet. 1, 2; Paper 9, 1–2.

The '336 Patent

The '336 patent is directed to a genus of tachykinin receptor antagonists useful in treating inflammatory diseases, pain or migraine, asthma, and emesis. Ex. 1001, 5:15–39. The compounds are prodrugs of their parent compounds. *Id.* at 12:26–27.

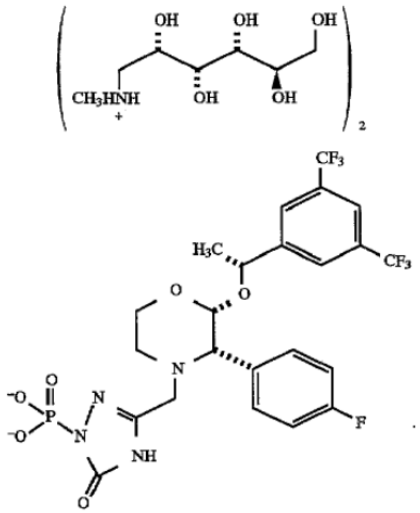
According to the '336 patent,

> Prodrugs are entities structurally related to a[] biologically active substance (the "parent drug")[,] which, after administration, release the parent drug in vivo as the result of some metabolic process, such as enzymatic or chemical

> hydrolysis of a carboxylic, phosphoric or sulfate ester or reduction or oxidation of a susceptible functionality.

Id. at 12:38–43. "[T]he activity exhibited upon administration of the prodrug is principally due to the presence of the parent compound that results from cleavage of the prodrug." *Id.* at 12:31–34. Compared with their parent compounds, the prodrugs of the '336 patent have enhanced solubility. *Id.* at 12:27–29, 13:9–12.

The '336 patent discloses 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-triazolo)methylmorpholine as "a particularly preferred compound" within the scope of its invention. *Id.* at 43:19–23. Today this compound is referred to as fosaprepitant. Pet. 5. The '336 patent also discloses 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)pheny l-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-triazolo)methylmorpholine, bis(N-methyl-D-glucamine) as "a specific particularly preferred compound" within the scope of its invention. *Id.* at 43:23–27. It has the structure:



Id. at 159:23–45. Today this compound is referred to as fosaprepitant dimeglumine, which is the active ingredient in Patent Owner's FDA-approved product, Emend® for Injection. Prelim. Resp. 1.

Among the challenged claims, claims 15, 16, 18, and 19 are directed to the compound fosaprepitant dimeglumine; and claim 23 is directed to a pharmaceutical composition comprising fosaprepitant dimeglumine. The other claims are broader in scope, but each encompasses fosaprepitant dimeglumine, the composition thereof, or the use thereof.

Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claims	Basis	References
1, 3–8, and 10–25	§ 103	Dorn '699[1] and Murdock '082[2]
1, 3–8, and 10–25	§ 103	Dorn '699, Murdock '082, Atanassova,[3] and Van Den Bos[4]
12, 15, 16, 18, 19, and 23	§ 103	Dorn '699, Murdock '082, Atanassova, Van Den Bos, Sommer,[5] Veronesi,[6] and Chromy[7]

[1] Dorn et al., U.S. Patent No. 5,637,699, issued June 10, 1997 (Ex. 1003, "Dorn '699").
[2] Murdock et al., U.S. Patent No. 5,070,082, issued December 3, 1991 (Ex. 1004, "Murdock '082").
[3] Atanassova, T. et al., *Synthesis of N-substituted derivatives of 2-imidazolidinone*, 46 PHARMAZIE 670–71 (1991) (Ex. 1007, "Atanassova").
[4] Van Den Bos et al., U.S. Patent No. 3,661,926, issued May 9, 1972 (Ex. 1006, "Van Den Bos").
[5] Sommer, F.G., et al., *Pain Accompanying Leg Venography: A Comparison of Sodium and Methylglucamine Diatrizoates*, 133 RADIOLOGY 790–91 (1979) (Ex. 1017, "Sommer").

According to Petitioner, Dorn '699 is prior art under 35 U.S.C. § 102(e) because it has an effective filing date of at least December 17, 1993, before the priority date of the challenged claims.[8] Pet. 32. Petitioner asserts that the other references are prior art under 35 U.S.C. § 102(b). *Id.* at 33, 48, 53.

In support of its patentability challenge, Petitioner relies on the Declaration of Dr. Longqin Hu. Ex. 1002.

ANALYSIS

Claim Construction

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 778 F.3d 1271, 1278–81 (Fed. Cir. 2015). Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the

---

[6] Veronesi, U.S. Patent No. 4,748,174, issued May 31, 1988 (Ex. 1022, "Veronesi").
[7] Chromy, V., et al., *D(–)-N-Methylglucamine Buffer for pH 8.5 to 10.5*, 24 CLIN. CHEM. 379–81 (1978) (Ex. 1018, "Chromy").
[8] The earliest possible priority date of the '336 patent is March 4, 1994. Ex. 1001, 1:9–10. For purposes of its Preliminary Response, Patent Owner asserts February 28, 1995 as the priority date. Prelim. Resp. 9–10 & n.2.

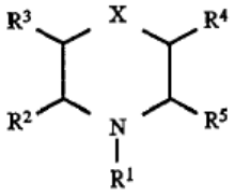
entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

We agree with the parties that for purposes of this Decision, none of the terms requires express construction. *See* Pet. 8; Prelim. Resp. 10.

Patentability Analysis

Prior Art Disclosures

Dorn '699 teaches a genus of tachykinin receptor antagonists with the structure:



wherein R^1, R^2, R^3, R^4, R^5, and X are defined therein. Ex. 1003, 4:66–11:67. It specifies preferred substituents. *Id.* at 12:51–13:55. It also lists 601 specific compounds as within the scope of its invention. *Id.* at 17:66–41:12. Dorn '699 teaches that the compounds of its invention are useful in treating inflammatory diseases, pain or migraine, asthma, and emesis. *Id.* at 1:28–30.

Murdock '082 teaches N-phosphorylation of basic nitrogenous drug compounds to produce prodrugs. Ex. 1004, Abstract. Atanassova teaches the synthesis of N-substituted derivatives of 2-imidazolidinone, including N-phosphorylated imidazolidinone. Ex. 1007, 670. Van Den Bos teaches oxadiazoline or thiadiazoline derivatives of phosphoric or thiophosphoric acid. Ex. 1006, 1:16–17. Sommer reports lower incidence of pain at the

injection site in patients receiving meglumine diatrizoate as compared to those receiving sodium diatrizoate. Ex. 1017, 790–91. Veronesi teaches that the acid addition salts of meglumine are "admirably water soluble." Ex. 1022, 1:24–26. Chromy teaches that meglumine has a pKa of 9.6. Ex. 1018, 380.

Obviousness over Dorn '699 and Murdock '082

Petitioner asserts that claims 1, 3–8, and 10–25 would have been obvious over Dorn '699 and Murdock '082. Pet. 14–48. According to Petitioner, it would have been obvious for one of ordinary skill in the art to select the parent compound of fosaprepitant, disclosed in Dorn '699, to prepare a prodrug for intravenous administration. *Id.* at 33. In addition, a skilled artisan would have looked to Murdock '082, which teaches using phosphoramidate prodrugs to improve the aqueous solubility of a parent nitrogenous compound, to modify the parent compound of fosaprepitant to arrive at the claimed invention. *Id.* at 44. Based on the current record, we determine that Petitioner has not established a reasonable likelihood it would prevail in this assertion.

We generally follow a two-part inquiry to determine whether a new chemical compound would have been obvious over particular prior art compounds. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291–93 (Fed. Cir. 2012). First, we determine "whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *Id.* at 1291. Second, we

analyze whether there was a reason to modify a lead compound to make the claimed compound with a reasonable expectation of success. *Id.* at 1292.

Even "post-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound." *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). Petitioner asserts that a skilled artisan seeking a tachykinin receptor antagonist prodrug would have selected the parent compound of fosaprepitant,[9] disclosed in Dorn '699 as compound 96, to develop a prodrug. Pet. 33–35. Petitioner argues that Dorn '699 "specifies a narrowed range of preferred substituents, which encompass [compound 96]." *Id.* at 33–34. Dorn '699 also specifically identifies compound 96 by its chemical name 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methyl-morpholine, and states it is a "specific compound[] within the scope of the [Dorn '699] invention." *Id.* at 35 (citing Ex. 1003, 17:66, 21:32–34). Petitioner further refers to claim 2 of Dorn '699 for reciting a process for producing compound 96. *Id.* at 35.

Patent Owner counters that given the content and scope of the prior art at the time of the invention, one of ordinary skill in the art would not have looked to Dorn '699 to develop tachykinin receptor antagonists. Prelim. Resp. 16–18. And even if starting from Dorn '699, a skilled artisan would

[9] The generic name of the parent compound of fosaprepitant is aprepitant. Pet. 14–15. Petitioner uses the term aprepitant throughout the Petition. *See id.*, *in passim*. Patent Owner asserts that the generic name did not exist until 2000, years after the issuance of the '336 patent. *See* Prelim. Resp. 20–21 n.6 (citing Ex. 2009, 83).

not have picked compound 96 from the hundreds of compounds listed therein. *Id.* at 18–23. We agree with Patent Owner.

Citing several research articles and patent literature, Patent Owner contends that, by the time of the '336 patent invention, a body of well-studied, potent tachykinin receptor antagonists had been extensively explored and discussed in the literature. Prelim. Resp. 16–18 (citing Exs. 2001–05, 2007, 2008). In contrast, there was no biological or pharmacokinetic data reported for compound 96 of Dorn '699. *Id.* at 16. As a result, Patent Owner argues, a skilled artisan would have pursued those more promising lead compounds, not compound 96, and thus, would not have arrived at fosaprepitant dimeglumine, the prodrug of compound 96. *Id.* at 18. We find Patent Owner's argument persuasive.

A lead compound is "a compound in the prior art that would be most promising to modify in order to improve upon its . . . activity and obtain a compound with better activity." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). "In determining whether a chemist would have selected a prior art compound as a lead, the analysis is guided by evidence of the compound's pertinent properties." *Otsuka Pharm.*, 678 F.3d at 1292. Here, absent any reported activity data, compound 96 could not have served as "a natural choice for further development efforts." *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009).

Even within Dorn '699, Petitioner does not explain sufficiently why a skilled artisan would have picked compound 96 over hundreds of other compounds. We disagree with Petitioner for characterizing the preferred

substituents in Dorn '699 as "a narrowed range." *See* Pet. 33. For example, according to Petitioner, Dorn '699 specifies R^2 and R^3 as independently hydrogen. *Id.* at 34. In fact, Dorn '699 states:

> [The preferred] R^2 and R^3 are independently selected from the group consisting of:
> (1) hydrogen,
> (2) C_{1-6} alkyl,
> (3) C_{2-6} alkenyl, and
> (4) phenyl.

Ex. 1003, 13:26–31. According to Dorn '699,

> [T]he term "alkyl" includes those alkyl groups of a designated number of carbon atoms of either a straight, branched, or cyclic configuration. Examples of "alkyl" include methyl, ethyl, propyl, isopropyl, butyl, iso-[,] sec-[,] and tert-butyl, pentyl, hexyl, heptyl, 3-ethylbutyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and the like. . . . "Alkenyl" is intended to include hydrocarbon chains of a specified number of carbon atoms of either a straight- or branched- configuration and at least one unsaturation, which may occur at any point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, dimethylpentyl, and the like, and includes E and Z forms, where applicable.

Id. at 12:11–26. In other words, the scope of R^2 and R^3 each includes possibly hundreds of preferred substituents—hardly the "narrowed range" suggested by Petitioner. Petitioner also does not explain why one skilled in the art would have chosen hydrogen independently for each position, let alone simultaneously for both R^2 and R^3 to arrive at compound 96. Similarly, Petitioner does not adequately explain why a skilled artisan would have chosen any of the preferred substituents for each of R^1, R^4 (which further includes R^6, R^7, R^8, and Z), and R^5 according to compound 96, not to

mention all of them at the same time. Thus, we reject Petitioner's contention that the substituents for compound 96 "were preferred." *See* Pet. 35.

Petitioner is correct that Dorn '699 identifies compound 96 as a specific compound within the scope of its invention. Pet. 35 (citing Ex. 1003, 17:66, 21:32–34). Petitioner, however, neglects to mention that Dorn '699 also discloses a laundry list of 600 other specific compounds by their chemical names as specific compounds within the scope of its invention. Ex. 1003, 17:66–41:12. Petitioner does not explain, and we do not find any reason, why a skilled artisan, having no reported activity data on any of the 601 enumerated compounds, would have picked compound 96 for further development. *See Otsuka Pharm.*, 678 F.3d at 1295 (affirming the rejection of a proposed lead compound, when the prior art lists the compound as one among hundreds of examples that may be useful).

Petitioner is also correct that claim 2 of Dorn '699 is directed to a process for producing compound 96. Pet. 35. But, as filed, the parent application, to which Dorn '699 claims priority in order to qualify as prior art under 35 U.S.C. 102(e), did not include any claim directed specifically to compound 96. Ex. 1025, 240–360. Instead, it included claim 14, which recites 601 compounds listed in the specification. *Id.* at 263–316. As Patent Owner points out, a claim specifically directed to compound 96 was added by amendment dated May 19, 1995, several months *after* the February 28, 1995 priority date of the '336 patent. Prelim. Resp. 23 (citing Ex. 1029, 529). As a result, at the time of the '336 patent invention, one of ordinary skill in the art would not have had the benefit of claim 2 of Dorn '699 to focus on compound 96.

In sum, Petitioner has failed to sufficiently explain why, at the time of the '336 patent invention, a skilled artisan would have chosen compound 96 of Dorn '699 to further develop its prodrug, which is the subject matter of the challenged claims. Therefore, we conclude that Petitioner has not established a reasonable likelihood it would prevail in showing any of the challenged claims would have been obvious over Dorn '699 and Murdock '082.

The Other Obviousness Grounds

Petitioner also argues that claims 1, 3–8, and 10–25 would have been obvious over Dorn '699, Murdock '082, Atanassova, and Van Den Bos. Pet. 48–53. Petitioner further contends that claims 12, 15, 16, 18, 19, and 23 would have been obvious over Dorn '699, Murdock '082, Atanassova, and Van Den Bos, and further in view of Sommer, Veronesi, and Chromy. *Id.* at 53–56. In both these grounds, Petitioner solely relies on Dorn '699 for selecting compound 96 as the lead compound. *Id.* at 48, 54. As explained above, we are not persuaded by Petitioner's argument on this issue. Thus, we conclude that Petitioner has not established a reasonable likelihood it would prevail in showing any of the challenged claims would have been obvious on either of these grounds.

CONCLUSION

For the foregoing reasons, the information presented in the Petition and accompanying evidence does not establish a reasonable likelihood that

Petitioner would prevail in showing the unpatentability of claims 1, 3–8, and 10–25 of the ’336 patent.

ORDER

Accordingly, it is

ORDERED that Petitioner’s request for an *inter partes* review of claims 1, 3–8, and 10–25 of the ’336 patent is *denied*.

PETITIONER:

Kenneth J. Burchfiel
Grant S. Shackelford
SUGHRUE MION, PLLC
kburchfiel@sughrue.com
gshackelford@sughrue.com

PATENT OWNER:

Bruce M. Wexler
Gregory A. Morris
Preston K. Ratliff II
Naveen Modi
PAUL HASTINGS LLP
brucewexler@paulhastings.com
gregorymorris@paulhastings.com
prestonratliff@paulhastings.com
naveenmodi@paulhastings.com

Gerard M. Devlin
Richard C. Billups
MERCK SHARP & DOHME CORP.
gerard_devlin@merck.com
richard_billups@merck.com