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Paper 39
Entered: August 2, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LUPIN LIMITED,
Petitioner,

v.

VERTEX PHARMACEUTICALS INCORPORATED,
Patent Owner.

Case IPR2016-00558
Patent 6,436,989 B1

Before LORA M. GREEN, SHERIDAN K. SNEDDEN, and ROBERT A. POLLOCK, *Administrative Patent Judges*.

SNEDDEN, Administrative Patent Judge.

FINAL WRITTEN DECISION
Determining Claims 2, 3, and 10–12 Not Shown to be Unpatentable
35 U.S.C. § 318(a); 37 C.F.R. § 42.73

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 2, 3, and 10–12 (collectively, "the challenged claims") of U.S. Patent No. 6,436,989 B1 (Ex. 1001; "the '989 Patent"). We have jurisdiction under 35 U.S.C. § 6. For the reasons that follow, we determine that Petitioner failed to demonstrate, by a preponderance of evidence, that claims 2, 3, and 10–12 are unpatentable.

A. Procedural History

Lupin Limited ("Petitioner") filed a Petition (Paper 1; "Pet.") to institute an *inter partes* review of claims 2, 3, and 10–12 of the '989 Patent. Vertex Pharmaceuticals Incorporated ("Patent Owner") filed a Patent Owner Preliminary Response. Paper 8 ("Prelim. Resp."). Based on these submissions, we instituted trial on the following grounds of unpatentability asserted by Petitioners:

Reference[s]	Basis	Claims challenged
Roy[1] and Grobelny[2]	§ 103(a)	2
Roy, Grobelny, and Bighley[3]	§ 103(a)	3, 10–12

Decision to Institute (Paper 9, "Dec.").

[1] Ex. 1021, U.S. Patent No. 6,730,679 B1, issued May 4, 2004 to Roy et al. (hereinafter "Roy" or "the '679 Patent").

[2] Ex. 1022, International Patent Application Publication Number WO 95/07269, published March 16, 1995, and naming Damian Grobelny as the sole inventor (hereinafter "Grobelny" or "the '269 Publication").

[3] Ex. 1027, Bighley, et al., *Salt Forms of Drugs and Absorption*, *in* 13 ENCYCLOPEDIA OF PHARMACEUTICAL TECHNOLOGY 453–499 (James Swarbrick & James C. Boylan eds. 1996) (hereinafter "Bighley").

After institution of trial, Patent Owner filed a Patent Owner Response (Paper 13, "PO Resp."), to which Petitioners filed a Reply (Paper 24, "Reply").

Petitioners rely on the Declarations of Jed Fisher (Ex. 1002 and Ex. 1096) in support of the proposed grounds of unpatentability.

Patent Owner relies on the Declaration of Richard Ogden, Ph.D. (Ex. 2017).

Patent Owner filed a motion to exclude certain of Petitioners' evidence. Paper 27. Petitioners filed an opposition (Paper 29), and Patent Owner filed a reply (Paper 30).

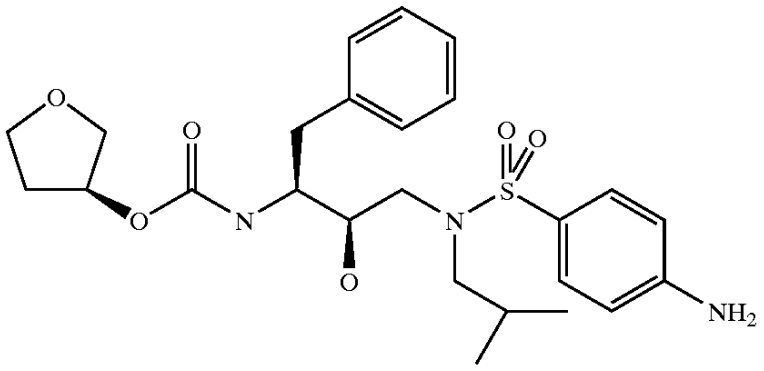
Oral argument was conducted on April 5, 2017. A transcript is entered as Paper 38 ("Tr.").

B. The '989 Patent (Ex. 1001)

The '989 patent is directed to prodrugs of HIV aspartyl protease inhibitors, pharmaceutical compositions thereof, and methods of treating mammals therewith. Ex. 1001, 1:5–17. Prodrugs generally are inactive compounds that convert to an active form in the body. *Id.* at 2:7–16, 33:25–34. Usually, a prodrug has some improved pharmacological property over the active drug, such as improved stability or solubility. *Id.* The prodrugs of the '989 patent are said to have favorable aqueous solubility, to have high oral bioavailability and facile in vivo generation of the active ingredient, and to be particularly well suited for decreasing pill burden and increasing patient compliance. *Id.* at 1:6–15.

The relevant compound of the '989 patent is a prodrug of the known HIV aspartyl protease inhibitor, VX-478 (4-amino-N-((2-syn, 3S)-2-hydroxy-4-phenyl-2((S)-tetrahydrofuran-3-yl-oxycarbonylamino)butyl-N-

isobutyl-benzenesulfonamide), also known as amprenavir. *Id.* at 1:30–42, 30:29–34:67; Prelim. Resp. 18; Ex. 1002, ¶ 20, n.1. Amprenavir has the following structure:



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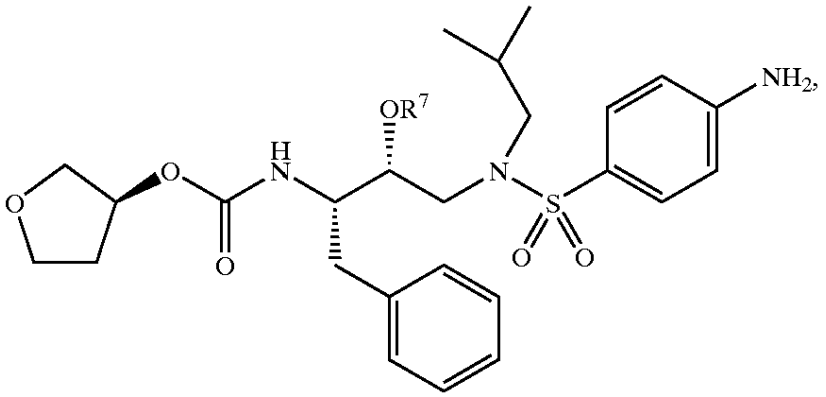
Ex. 1001, 30:32–31:5.

Examples 27 to 30 detail the process for forming phosphate ester derived prodrugs of amprenavir. *Id.* at 57:1–60:14. Example 30, in particular, describes a disodium phosphate ester salt prodrug of amprenavir. *Id.* at 59:9–20, 60:1–21.

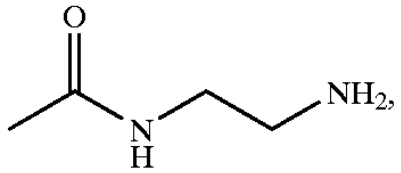
C. Challenged Claims

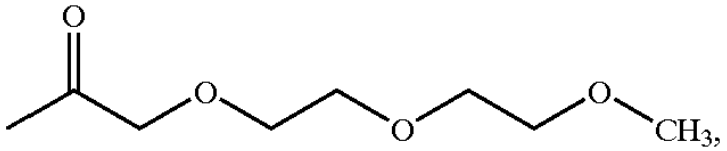
The challenged "claims cover the drug Lexiva® (fosamprenavir calcium), which is marketed for the treatment of human immunodeficiency virus-1 ('HIV')." PO Resp. 1; *see* Pet. 4–5. Challenged claims 2 and 3 depend from claim 1 of the '989 patent. Challenged claims 10–12 depend from claim 4 of the '989 patent. Claims 1–4 and 10–12 of the '989 patent are reproduced below:

1. A compound of the formula:

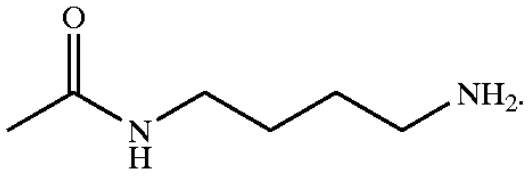


wherein: R^7 is selected from $-PO_3^{2-}Na_2^+$, $-PO_3^{2-}K_2^+$, $-PO_3^{2-}Mg^{2+}$, $-PO_3^{2-}Ca^{2+}$,





or



2. The compound according to claim 1, wherein:

R^7 is selected from —$PO_3^{2-}Na_2^+$, —$PO_3^{2-}K_2^+$, or —$PO_3^{2-}Ca^{2+}$.

3. The compound according to claim 2, wherein R^7 is — $PO_3^{2-}Ca^{2+}$.

4. A pharmaceutical composition, comprising a compound according to any one of claims 1 to 3 in an amount effective to treat infection by a virus that is characterized by a virally-encoded aspartyl protease; and a pharmaceutically acceptable carrier, adjuvant or vehicle.

> 10. A method for treating HIV infection in a mammal comprising the step of administering to said mammal a pharmaceutical composition according to claim 4.
>
> 11. The method according to claim 10, wherein said mammal is additionally administered one or more additional agents independently selected from an anti-viral agent, an HIV protease inhibitor, or an immunostimulator, either as a part of a single dosage form with said pharmaceutical composition or as a separate dosage form.
>
> 12. The method according to claim 11, wherein said one or more additional agents are selected from zidovudine (AZT), zalcitabine (dideoxycytidine, ddC), didanosine (ddI), stavudine (d4T), lamivudine (3TC), abacavir (1592U89), saquinavir (Ro 31-8959), indinavir (L-735,524), ritonavir (ABT 538, A84538), nelfinavir (AG 1343), XM 450, CGP 53,437, polysulfated polysaccharides, ganciclovir, ribavirin, acyclovir, TIBO, nevirapine, IL-2, GM-CSF, interferon alpha, or erythropoietin (EPO).

Ex. 1001, 74:24–76:17.

II. DISCUSSION

Petitioner bears the burden of proving unpatentability of the challenged claims, and the burden of persuasion never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). To prevail, Petitioner must establish the facts supporting its challenge by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). Below, we explain why Petitioner has failed to meet its burden with respect to the challenged claims.

A. Claim Interpretation

We interpret claims using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R.

§ 42.100(b); *see Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, claim terms generally are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). "Absent claim language carrying a narrow meaning, the PTO should only limit the claim based on the specification . . . when [it] expressly disclaim[s] the broader definition." *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004) (citation omitted). "Although an inventor is indeed free to define the specific terms used to describe his or her invention, this must be done with reasonable clarity, deliberateness, and precision." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Neither party provides any express claim constructions for terms in the challenged claims. Pet. 17; PO Resp. 24. Except as discussed below, we determine that no claim term requires express construction. *See, e.g.*, *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.").

We acknowledge and agree, however, with Patent Owner's general contention that claims 10–12, "as understood by a person of ordinary skill in the art at the time of the invention, would require bioavailability of the parent compound upon administration of the prodrug." PO Resp. 24. Claims 10–12 are directed to a method of treating HIV infection, which requires the compound to enter the blood in an amount effective to treat HIV. Ex. 2017 ¶ 7; Ex. 2003, 203:14–205:14, 206:3–18. In this regard, the terms of the challenged claims are given their plain and ordinary meaning as

set forth above.

B. Obviousness Analysis

1. Principles of Law

A claim is unpatentable under 35 U.S.C. § 103(a) if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness, i.e., secondary considerations. *Id.* (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)).

Secondary considerations include commercial success, long-felt but unsolved needs, failure of others, and unexpected results. *KSR*, 550 U.S. at 406; *In re Soni*, 54 F.3d 746 (Fed. Cir. 1995). Secondary considerations are "not just a cumulative or confirmatory part of the obviousness calculus but constitute[] independent evidence of nonobviousness . . . and enable[] the court to avert the trap of hindsight." *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (internal quotation marks and citations omitted). "This objective evidence must be 'considered as part of all the evidence, not just when the decision maker remains in doubt after reviewing the art.'" *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (citations omitted).

The obviousness analysis requires that "the factfinder should further consider whether a person of ordinary skill in the art would [have been] motivated to combine those references, and whether in making that combination, a person of ordinary skill would have [had] a reasonable expectation of success," even "[i]f all elements of the claims are found in a combination of prior art references." *Merck & Cie v. Gnosis S.p.A.*, 808 F.3d 829, 833 (Fed. Cir. 2015). The "motivation to combine" and "reasonable expectation of success" factors are subsidiary requirements for obviousness subsumed within the *Graham* factors. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007).

The degree of unpredictability in the art and guidance in the art must also be considered in determining whether a person of ordinary skill in the art would have had a reasonable expectation of success. *Pfizer*, 480 at 1364; *In re O'Farrell*, 853 F.2d 894, 903 (Fed.Cir.1988) (The prior art must provide more than "general guidance as to the particular form of the claimed invention or how to achieve it."). "To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on [ ] 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) (quoting KSR, 550 U.S. at 402). Indeed,

> [c]ases following *KSR* have considered whether a given molecular modification would have been carried out as part of routine testing. *See, e.g., [Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1360 (Fed. Cir. 2007)] (discussing the district court's finding that a modification was not known to be beneficial and was not considered "routine"). When a person of ordinary skill is faced with "a finite number of identified, predictable solutions" to a problem and pursues "the known options within his or her technical grasp," the resulting

> discovery "is likely the product not of innovation but of ordinary skill and common sense." *KSR*, 127 S.Ct. at 1742. So too, "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress." *Id*. at 1741. In other cases, though, researchers can only "vary all parameters or try each of numerous possible choices until one possibly arrive[s] at a successful result, where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F.2d 894, 903 (Fed.Cir.1988). In such cases, "courts should not succumb to hindsight claims of obviousness." *In re Kubin*, 561 F.3d 1351 (Fed.Cir.2009). Similarly, patents are not barred just because it was obvious "to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell*, 853 F.2d at 903.

Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 996–997 (Fed. Cir. 2009).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

2. Scope and Content of the Prior Art

a. Summary of Roy

Roy discloses an oral pharmaceutical composition of amprenavir that results in effective treatment of the HIV virus upon administration. Ex. 1021, 1:38–2:16, 2:43–57.

Roy discloses that amprenavir is difficult to formulate due to its limited solubility. In particular, Roy states that "the aqueous solubility of [amprenavir] is only 0.095 mg/mL at room temperature and does not significantly vary with pH. In addition, [amprenavir] is poorly wetted. Therefore, formulating the compound using standard formulary techniques is

difficult and leads in any event to a formulation with low bioavailability." *Id.* at 2:32–38 (citing Roy, Fig. 1).

Roy discloses a solution formulation of amprenavir having improved solubility and oral bioavailability. *Id.* at 2:45–47, 53–58.

b. Summary of Grobelny

Grobelny discloses retroviral protease inhibitors, such as HIV protease inhibitors, comprising a solubilizing group. Ex. 1022, Abstract. Grobelny describes the problem of HIV protease inhibitors having poor solubility and, thus, low oral absorption as follows:

> HIV proteases which have hitherto been described . . . typically exhibit low to very low water solubility. Inhibitors of HIV proteases which have hitherto been described, and many other pharmaceutically or veterinarily active substances also typically exhibit low to very low water solubility. This property tends to cause the bioavailability of such substances to be relatively low. There is thus a need for a HIV protease inhibitor having enhanced water solubility.

Id. at 74:7–10.

Grobelny describes the inclusion of a "solubilising group Px" to enhance water solubility of HIV protease inhibitors. *Id.* at 74:11–75:11; *see also id.* at 37:19–22 ("Typically, the solubilising group is a sodium or potassium salt of a phosphate or phosphite residue."). Grobelny discloses that "substances in accordance with the invention which include a solubilising group Px exhibit superior bioavailability, including superior is oral bioavailability, compared to compounds in accordance with the invention which do not include a solubilising group Px." *Id.* at 74:11–16.

Example 5 of Grobelny describes introducing a disodium phosphate ester to the hydroxyl group of a known HIV protease inhibitor. *Id.* at

87:1–87:19. Example 8 of Grobelny describes blood and animal experiments performed using the product of Example 5. *Id.* at 89:20–90:29; Ex. 1002 ¶¶ 65–66. The results are summarized in the follow excerpt from Grobelny:

> When prodrug was administered to a dog orally at a dose of 20mg/kg, the blood plasma concentration of drug was found to be 0.044, 0.141, 0.189, 0.172, 0.164, 0.132, 0.089 and 0.060 μM, respectively, after 5, 15, 30, 47, 63, 93, 124 and 155 minutes. When prodrug was administered to a second dog orally at a dose of 10mg/kg, the blood plasma concentration of drug was found to be 0.137, 0.371, 0.297, 0.242, 0.176, 0.11, 0.071, and 0.050 μM, respectively, after 5, 15, 30, 45, 60, 94, 123 and 154 minutes.

Ex. 1022, 90:24–29.

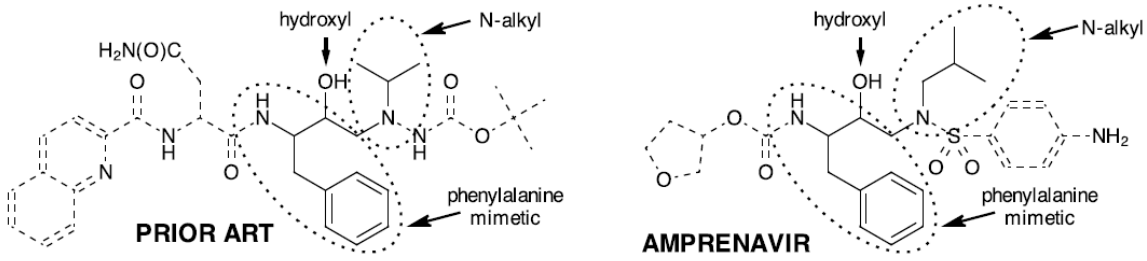
3. Petitioner's Ground 1: Obviousness of Claim 2 over the Combination of Roy and Grobelny

Petitioner contends that claim 2 of the '989 patent would have been obvious over the combination of Roy and Grobelny. Pet. 25–36. Claim 2 includes a disodium phosphate ester of amprenavir.

Petitioner contends that Roy discloses amprenavir as an "especially effective" protease inhibitor of HIV virus. *Id.* at 26 (Ex. 1021, 1:15–67). Due to amprenavir's solubility-related problems, however, it was known that amprenavir required relatively large amounts of excipients in each capsule to improve oral absorption. Ex. 1002 ¶ 59. The result is that each capsule contains a relatively small amount of amprenavir and, as such, a large number of capsules is required to achieve therapeutic dosages. *Id.* at 60. Such a large number of capsules each day to obtain therapeutic dosages would have negatively affected patient compliance, which would have been disfavored because "patient compliance with the dosing regimen was

considered essential to prevent HIV from developing drug-resistant mutations." Pet. 27, 60 (citing Ex. 1002 ¶ 60). Accordingly, Petitioner contends that a person of ordinary skill in the art would have sought to modify amprenavir to address the known solubility-related problems. *Id.* at 25–31.

Petitioner contends that a person of ordinary skill would have been motivated to modify amprenavir using the methods disclosed in Grobelny to improve its solubility. *Id.* Grobelny discloses introducing phosphate esters salts to the hydroxyl group of HIV protease inhibitors for improving the solubility of HIV protease inhibitors.[4] *Id.* at 27–28 (citing Ex. 1022, 74:17–75:12, 37:19–20, 90:10–29; Ex. 1002 ¶¶ 87–90, 95). Specifically, Grobelny disclose derivatizing a free hydroxyl positioned similarly to that of the free hydroxyl of amprenavir, and that this modification improved the solubility of the compound. Pet. 29–32; Ex. 1022, 86:8–15, 76:4–7; Ex. 1002 ¶¶ 65, 87–90, 96. Petitioner further describes the similarities in structure between amprenavir and the exemplary compound of Grobelny, namely the presence of a free hydroxyl group between a phenylalanine mimetic and an N-alkyl group, as exemplified in the comparative structures from the Petition reproduced below. Pet. 32–33; Ex. 1002 ¶¶ 93–95.



[4] Grobelny does not disclose amprenavir.

Id.

The figure above is purported to be a comparison of the structures disclosed in Grobelny (labeled as "Prior Art") with that of amprenavir. Pet. 32–33; Ex. 1002 ¶ 94. According to Petitioner, the figure highlights structural similarities between the two compounds and, in particular, a hydroxyl group positioned between the circled "phenylalanine mimetic" and "N-alkyl" moieties, with the remaining portions of the structures drawn in phantom lines. *Id.* Given the structural similarities between amprenavir and the HIV protease inhibitor of Grobelny, along with Grobelny's disclosure of a precise method for modifying that compound, Petitioner argues that there was a reasonable likelihood that one of ordinary skill in the art would have been successful in preparing a derivative of amprenavir having the claimed structure with similar improvement in solubility and bioavailability (*i.e.*, fosamprenavir), using the teachings of Grobelny. Pet. 32–35.

4. Petitioner's Ground 2: Obviousness of Claims 3 and 10–12 over the Combination of Roy, Grobelny and Bighley

Petitioner contends that claims 3 and 10–12 of the '989 patent would have been obvious over the combination of Roy, Grobelny, and Bighley. Pet. 36–49.

a. Claim 3

Claim 3 recites a "compound according to claim 2, wherein R^7 is — $PO_3^{2-}Ca^{2+}$," which Petitioner identifies as the calcium phosphate ester of amprenavir (i.e., fosamprenavir calcium). Pet. 5, 38.

Petitioner contends that the claimed compound would have been obvious to one of ordinary skill in the art in light of Gorbelny's "teach[ing] that pharmaceutically acceptable salts for acidic HIV protease inhibitors

include cation-addition salts of sodium, potassium, calcium, and magnesium." *Id.* 36 (citing Ex. 1022, 35:9–11). Petitioner further contends that the "decision tree" and disclosure of the "four most common salts" of Bighley evinces that calcium salts were known alternative salts to the sodium, potassium, and magnesium salts disclosed by Grobelny. *Id.* at 36–37 (citing Ex. 1027, 456; Ex. 1002 ¶¶ 76–80, 100–103). Accordingly, Petitioner argues that the teachings of Grobelny would have prompted a person of ordinary skill in the art to prepare the calcium phosphate ester of amprenavir as set forth in claim 3.

b. Claims 10–12

Claims 10–12 are drawn to methods for treating HIV infection comprising administering the pharmaceutical compositions of claim 4. Ex. 1001, 75:17–76:15.

Petitioner contends that Roy and Grobelny disclose pharmaceutical compositions and methods of treating HIV infection meeting the elements of claims 10–12. Pet. 39–49; Ex. 1021, 6:13–15, 6:59–61, 6:66–7:24; Ex. 1022, 76:26–28, 78:22–27. Petitioner's position is that claims 10–12 recite elements that naturally would follow using an HIV protease as indicated by the teachings of Roy and Grobelny. Specifically, Petitioner contends that: (1) "HIV is inherently characterized by a virally-encoded aspartyl protease" (Pet. 39 (citing Ex. 1007,[5] 96–97)) and administering the phosphate ester salt of [amprenavir] would inherently inhibit aspartyl protease activity; (2)

[5] Stuart Noble & Diana Faulds, *Saquinavir: A Review of its Pharmacology and Clinical Potential in the Management of HIV Infection*, 52 DRUGS 93–112 (July 1996).

"[t]he phosphate ester salt of amprenavir would have been expected to reconvert to amprenavir in the body to provide a potent HIV protease inhibitor" (*id.* (citing Fisher Decl. ¶ 95)); (3) and "[o]nly routine optimization was needed to identify suitable dosages for treating HIV using the phosphate ester salt of amprenavir based on its known dosages [for amprenavir]" (*id.* (citing Fisher Decl. ¶ 105–6)). Thus, according to Petitioner, a person of ordinary skill would have used the prodrug of amprenavir in a similar way to other HIV protease inhibitors, and in particular, similar to amprenavir. *Id.*

5. Analysis

The issue of whether a person of ordinary skill in the art would have combined the teachings of Roy and Grobelny to achieve the compound of claims 2 and 3 is dispositive to each of Petitioner's ground, and is addressed below.

a. No Reasonable Expectation of Success that Fosamprenavir Would Be a Successful Drug

To decide whether fosamprenavir was obvious in light of the prior art, we must determine whether, at the time of invention, a person having ordinary skill in the art would have had a reasonable expectation of success in making fosamprenavir, a bioavailable prodrug to amprenavir, based on guidance in the prior art. *Procter & Gamble Co*., 566 F.3d at 997; *In re O'Farrell*, 853 F.2d at 903.

As discussed above, Grobelny teaches that the inclusion of a solubilizing group to a protease inhibitor compound having low water solubility for the purposes of improving water solubility and bioavailability of those compounds. Ex. 1022, 74:11–16. In this regard, Grobelny provides

general guidance for using a solubilizing agent phosphate ester salt to solve the solubility problem of amprenavir. However, the success of discovering fosamprenavir was not discovering a compound with improved solubility. Rather, the success was finding a compound that had the requisite bioavailability to treat HIV and minimize the development of drug-resistance mutations in patients.[6] The evidence of record does not support a finding that a person of ordinary skill in the art would have had a reasonable expectation of success in developing fosamprenavir, a protease inhibitor prodrug having the same or improved bioavailability as its parent drug.

First, we note that the evidence of record fails to demonstrate that Grobelny's compound was anything more than a "physiological failure". Ex. 2003, 303:19–304:10. The data presented in Grobelny—along with the data contained in Tyssen[7,8]—shows that the prodrug of Grobelny did not deliver the parent compound consistently in animal models. Ex. 1022, 89:22–90:29; Ex. 1056. Specifically, the data shows variable delivery of the parent compound in rats ranging from "0% to greater than 35%", suggesting that certain rats received 0% of the active ingredient in their system. Ex.

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[6] We are persuaded by Patent Owner's argument and evidence that variability of the bioavailability of the drug is just as problematic as noncompliance by the patient as both can lead to poor treatment and development of drug resistance. PO Resp. 31–32; Ex. 2016, 276:11–277:9.

[7] Ex. 1056, Tyssen, D. et al., "*Nonclinical Pharmacokinetics of an HIV Protease Inhibitor*," Australasian Society for HIV Med., 8th Annual Conference, 8:14 (1996) (hereinafter "Tyssen").

[8] Petitioner argues that Tyseen confirms Grobelny's success, however, we are not persuaded that the results disclosed in Tyseen are different from those disclosed in Grobelny.

2061 ¶¶ 76, 82–83; Ex. 2017 ¶¶ 115, 120.

Example 8 of Grobelny discloses the results of an experiment in which a prodrug was administered orally to two individual dogs. Ex. 1022, 90:24–29. Patent Owner provides a table, reproduced below, summarizing the data presented in Example 8.

Time[6] / Dose	5	15	30	45/47	60/63	94/93	123/124	154/155
10mg/kg	0.137	0.371	0.291	0.242	0.176	0.11	0.071	0.050
20mg/kg	0.044	0.141	0.189	0.172	0.164	0.132	0.089	0.060

PO Resp. 30. The data shows that some conversion of the prodrug to the parent occurred, but that conversion was highly variable. Ex. 2061 ¶¶ 65–72. Indeed, as noted by Patent Owner, "[t]hese data show that the second dog, which received a *lower* dose of 10mg/kg of the prodrug, achieved a *higher* concentration of the parent in its bloodstream than the first dog, which received a higher 20mg/kg dose." PO Resp. 29.

Hoy[9] discloses a study of Grobelny's prodrug, DG17, in healthy human volunteers. Ex. 2040. Hoy concludes that the prodrug "was well tolerated, and single dose pharmacokinetics in healthy volunteers reveal good oral bioavailability." *Id.* Although we agree with Petitioner that such a statement may provide encouragement to a person of ordinary skill in the art for the "good oral bioavailability" of Grobelny's prodrug (see Reply, 16–18), we credit the testimony from Drs. Ogden and Sinko that the raw data presented in Hoy continues to show variability in the bioavailability of the

[9] Ex. 2040, Hoy, et al., "*Pharmacokinetics of DG17, a Protease Inhibitor, in Healthy Volunteers*," Australasian Society for HIV Med., 8th Annual Conference, 8:184 (1996) (hereinafter "Hoy").

Grobelny's prodrug. Ex. 2061 ¶¶ 77–82; Ex. 2017 ¶¶ 118–121.

Even if we could conclude that the bioavailability data for Grobelny's compound was sufficient to show that Grobelny's compound would work within a reasonable expectation of success, the evidence of record does not establish that the same prodrug approach disclosed in Grobelny would work for all protease inhibitors. Rather, we note that the preponderance of evidence shows that the development of HIV protease inhibitors prodrugs was not at all predictable, but produced compounds with varying degree of effectiveness. PO Resp. 43–44, 59; Ex. 2061 ¶¶ 106–109; Ex. 1040, 128 ("the success of the [prodrug] strategy has been limited"); Ex. 2004[10], 2965 (discussing the importance of structural features in the vicinity of the phosphate ester on the rate at which prodrug reverted to back to parent drug).

The varying degree of effectiveness of prodrugs is partly explained by the complexity of *in vivo* conversion, which rendered prodrugs unpredictable for achieving adequate conversion at the time of the invention. PO Resp. 11–14; Ex. 2061 ¶¶ 118–122; Ex. 2017 ¶¶ 128–130, 133–136. Patent Owner summarizes its position, which we adopt, in the following excerpt:

> Researchers often investigate creating a prodrug in order to address characteristics of an active compound that may limit its effectiveness, but in doing so, new problems may arise. Ex. 2061, Sinko ¶ 91; Ex. 1002 Fisher ¶ 50. For instance, an oral prodrug designed to increase aqueous solubility often results in a decreased ability to cross through the intestinal membrane for delivery to the site of infection. Ex. 1019 at 361. Thus, it is

[10] Ex. 2004, DeGoey, et al., *Water-Soluble Prodrugs of the Human Immunodeficiency Virus Protease Inhibitors Lopinavir and Ritonavir*, J. Med. Chem., 52:2964–70 (2009).

> critical that reconversion from such a prodrug to the parent compound take place at the site of absorption, and that the kinetics and mechanism of the conversion are such that the parent drug will be absorbed into the bloodstream. Ex. 1019 at 361; Ex. 1002 Fisher ¶ 55 (explaining the desired site for conversion of a phosphate ester prodrug). Therefore, identification of an oral prodrug that can address the limitations of the parent compound is a complex task.
>
> In large part, the complexity exists because of the numerous variables associated with the GI tract . . . . If the prodrug converts to the parent drug too soon, then the parent drug's insoluble nature will cause it to precipitate within the GI tract, rendering it unable to cross into the bloodstream. Ex. 2061, Sinko ¶ 98; Ex. 2003, 150:16-21, 152:9-153:5. On the other hand, if the prodrug fails to reconvert to the active parent drug at the brush border, then its polarity will diminish its ability to cross the GI membrane into the bloodstream. Ex. 2061, Sinko ¶ 98; Ex. 2003, 185:11-186:7.

PO Resp. 11–13.

Furthermore, developing a phosphate ester prodrug would have been particularly challenging in the treatment of HIV. Prodrugs using phosphate ester promoieties were made to target reconversion by alkaline phosphatase in the intestine. Ex. 2052[11], 934, 939. ("The increased permeability for the phosphate prodrug is the result of alkaline phosphatase activity [in the upper small intestine].") However, it was known at the time of the invention that HIV-infected patients showed decreased alkaline phosphatase activity as compared to healthy patients. Ex. 2061 ¶¶ 43–45; Ex. 1055,[12] 117 ("gut

[11] Ex. 2052, Fleisher, D. et al., *Oral Absorption of 21-Corticosteroid Esters: A Function of Aqueous Stability and Intestinal Enzyme Activity and Distribution*, J. Pharm Scis., 75(10): 934–939 (Oct. 1986).

[12] Ex. 1055, Wood R., et al., *Six-week randomized control trial to compare*

levels of alkaline phosphatase may be lower than those found in healthy subjects"); Ex. 2059,[13] 1487 (Figure 3), 1488; Ex. 2060,[14] 208.

A review of the prior art suggests that the complexity of *in vivo* conversion was indeed a hurdle to the development of HIV protease inhibitor prodrugs. The record shows that, by December 1997 there were four FDA approved HIV protease inhibitors (saquinavir, indinavir, ritonavir, and nelfinavir) and at least another 30 HIV protease inhibitors, including amprenavir, in clinical or pre-clinical investigation. Ex. 2017 ¶ 103; Ex. 1010, 160–161. In addition to the compound disclosed in Grobelny, attempts were made to put the phosphate ester progroup onto the central hydroxyl of lopinavir and ritonavir, but these attempts failed to produce a viable prodrug. Ex. 2004, 2965 (Table 1), 2967 (disclosing that phosphate esters attached directly to the central hydroxyl groups of lopinavir and ritonavir were not cleaved by phosphatase *in vitro* and were ineffective for delivery of parent drugs *in vivo*, in contrast to fosamprenavir). As of 1997, there were no HIV protease inhibiters prodrugs and history shows that fosamprenavir was the first prodrug to show adequate bioavailability and is

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the tolerabilities, pharmacokinetics, and antiviral activities of GW433908 and amprenavir in human immunodeficiency virus type 1-infected patients, Antimicrobial Agents and Chemotherapy, Jan. 48 (1):116–123 (2004) (hereinafter "Wood").

[13] Ex. 2059, Ullrich, R. et al., *Effects of Zidovudine Treatment on the Small Intestinal Mucosa in Patients Infected With the Human Immunodeficiency Virus*, Gastroenterology, 102:1483–1492 (1992).

[14] Ex. 2060, Asmuth, D.M, et al., *Physiological effects of HIV infection on human intestinal epithelial cells: an in vitro model for HIV enteropathy*, AIDS, 8:205–211 (1994).

still the only HIV protease inhibitor prodrug on the market. Ex. 2017 ¶¶ 157–158, 122; Ex. 2061 ¶¶ 71–72.

In view of the above, we find that the evidence of record supports a finding that there was no reasonable expectation that modifying amprenavir with a phosphate ester progroup would result in a successful compound. In particular, the complexity of *in vivo* conversion renders the treatment with HIV protease inhibitor prodrugs unpredictable such that there was not a reasonable expectation of success that a phosphate ester salt derivative of amprenavir would have been successful as a bioavailable alternative.

b. Unexpected Results

We further conclude that Patent Owner has demonstrated evidence of unexpected results regarding fosamprenavir's improved resistance profile, pharmacokinetics, and side effect profile, which weighs in favor of patentability.

(1) Fosamprenavir's Different Resistance Profile

The prior art describes amprenavir's "signature" mutation to be the I50V mutation. PO Resp. 49 (citing Ex. 2017 ¶¶ 144–147; Ex. 1059). Additional mutations of amprenavir include the I54L/M, I84V, and V32I+I47V mutations. *Id.*

Patent Owner has demonstrated sufficient evidence showing that fosamprenavir has a different and improved resistance profile as compared to amprenavir. Specifically, the absence of a selection for the I50V mutation, which is unexpected "because fosamprenavir delivers amprenavir as the active compound." *Id.* at 50; Ex. 2017 ¶¶ 146–47; Ex. 2057,[15] 2103;

[15] Ex. 2057, Chapman, T.M., et al., *Review of its Use in the Management of Antiretroviral Therapy-Naive Patients with HIV Infection Fosamprenavir*,

Ex. 2056,[16] 337 (Table 1). For example, using data from the NEAT trial,[17] Ross discloses that fosamprenavir does not select for I50V. Ex. 2056, 337 (Table 1). Petitioner's expert, Dr. Fisher, agreed that the NEAT trial, discussed in Ross, shows patients receiving fosamprenavir alone (i.e., "unboosted" fosamprenavir, not supplemented with ritonavir) for three to five years did not develop the I50V and I84V mutations. PO Resp. 50, 54–55; Ex. 2016, 148:13–15, 149:23–150:7–20, 166:5–168:14, 182:5–7.

In view of the above, we conclude that the preponderance of evidence shows that, when unboosted fosamprenavir is compared with amprenavir, a different resistance profile is seen with fosamprenavir, which would not have been expected because as its prodrug, fosamprenavir, delivers amprenavir.

(2) Fosamprenavir's Superior Pharmacokinetics and Side Effect Profile

Patent Owner contends that fosamprenavir has improved pharmacokinetics, as compared with amprenavir, in the form of statistically significantly higher C_{min} and lower C_{max} with equal extent of absorption. PO Resp. 46–49 (citing Ex. 1055, 116, 120–122; Ex. 2017 ¶¶ 141–142, 147). Specifically, with regard to the pharmacokinetics of the fosamprenavir,

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Drugs 64(18): 2101–2124 (2004) (hereinafter Chapman).

[16] Ex. 2056, Ross, L., et al., *Fosamprenavir Clinical Study Meta-Analysis in ART-Naïve Subjects: Rare Occurrence of Virologic Failure and Selection of Protease-Associated Mutations*, HIV Clin. Trials, 7(6):334–338 (2006) (hereinafter "Ross").

[17] We understand that the NEAT trial investigated unboosted fosamprenavir, whereas the SOLO trial investigated fosamprenavir boosted with another HIV protease inhibitor, ritonavir. Ex. 1056.

Patent Owner directs our attention to the following disclosure in Wood:

> The $C_{min,ss}$ for [amprenavir] 1,200 mg was greater than the previously reported [amprenavir] concentration required to inhibit 50% of viral replication that was determined from clinical isolates of HIV (0.26 μg/ml versus 0.146 μg/ml after adjustment for protein binding) (11). The higher inhibitory quotient of [fosamprenavir] might translate into more favorable antiviral activity and durability. As the C_{max} obtained after administering both doses of [fosamprenavir] was significantly lower than that for [amprenavir] 1,200 mg, this could lead to further increases in tolerability, because a lowered C_{max} may decrease the incidence of gastrointestinal adverse drug effects, as was suggested but not conclusively demonstrated by this study.

Ex. 2005, 121–122.

Patent Owner further directs our attention to data presented in the '989 patent showing that fosamprenavir has low variability in bioavailability. Ex. 2061 ¶ 50; Ex. 1001, 73 (Tables IV, V) (when administered with water, the C_{max} for fosamprenavir achieved was 7.1 +/- 1.7 μM).

In view of the data summarized above, and testimony from Drs. Ogden and Sinko, we conclude that the preponderance of evidence supports a finding that fosamprenavir's substantial superiority to amprenavir was unexpected. In particular, we credit the following testimony from Dr. Ogden, which provides an instructive analysis of the data disclosed in Wood:

> Clinical comparisons of amprenavir and fosamprenavir show surprising and unexpected results because fosamprenavir achieved better pharmacokinetic results than had been observed in patients taking amprenavir. Ex. 1055 (Wood). The clinical comparison shows that administration of fosamprenavir led to attainment in patients of an equivalent plasma concentration to

> that following administration of amprenavir (i.e., $AUC_{0-\infty}$), but that the peak plasma concentration following administration of fosamprenavir was 30% to 40% lower. Ex. 1055 (Wood) at 116-117, 118, 122. The lower peak plasma concentration is beneficial in reducing side effects and may be the reason that patients who received fosamprenavir had fewer gastrointestinal problems. *Id.* at 120-121. Upon administration of fosamprenavir, the C_{min} or trough concentration was about 28% higher compared to patients dosed with amprenavir. Id. at 118, 121. This is beneficial as a higher C_{min} or trough concentration will lower the likelihood that a patient will experience sub-optimal dosing levels that may, in turn, lead to the generation of mutant strains of the virus that are resistant to antiviral medication. Ex. 2035 (Moyle 2001); Ex. 2036 (Moyle 2002); Ex. 2020 at 258-261 (Ogden et al., eds.); Ex. 1055 at 121-122 (Wood) ("The higher inhibitory quotient of [amprenavir] might translate into more favorable antiviral activity and durability.")) Durability with respect to antiviral medications refers to their ability to avoid generating viral resistance.

Ex. 2017 ¶141.

The evidence supports a finding that fosamprenavir's improved resistance profile is related to the prodrug's improved pharmacokinetic profile. Further, the improved pharmacokinetics of fosamprenavir are accompanied with lower number of gastrointestinal side effects. Ex. 2051,[18] 636–637 ("The lower peak concentration might explain the lower number of gastrointestinal symptoms."); Ex. 2048,[19] 558 ("Preliminary safety data show [fosamprenavir] to have better gastrointestinal tolerability."). Taken

[18] Ex. 2051, Arvieux, et al., *Amprenavir or Fosamprenavir plus Ritonavir in HIV Infection Pharmacology*, Efficacy and Tolerability Profile, Drugs, 65, 633–659 (2005).

[19] Ex. 2048, Nadler, *New Anti-HIV Protease Inhibitors Provide More Treatment Options*, AIDS Patient Care and STDs 17(11):551–564 (2003).

together, we conclude that the preponderance of evidence shows fosamprenavir's substantial superiority as compared to its parent drug amprenavir, which would have been unexpected because fosamprenavir delivers amprenavir.

6. Conclusion as to Obviousness

Having considered the parties' arguments and evidence, we evaluate all of the evidence together to make a final determination of obviousness. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075 (Fed. Cir. 2012) (stating that a fact finder must consider all evidence relating to obviousness before finding patent claims invalid). In so doing, we conclude that Petitioner has failed to satisfy its burden of demonstrating, by a preponderance of the evidence, that the subject matter of claims 2, 3, 10, 11, and 12 of the '989 patent would have been obvious over any ground relying on the combination of Roy and Grobelny.

III. PATENT OWNER'S MOTION TO EXCLUDE

Patent Owner seeks to exclude Ex. 1093. Paper 27, 1–6. Because we do not rely on Ex. 1093 to reach the final decision, we dismiss the Patent Owner's motion to exclude as moot.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 2, 3, and 10–12 of the '989 patent are not shown to be unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude Evidence is dismissed as moot; and

FURTHER ORDERED that this is a Final Written Decision;

therefore, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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