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Paper 15
Date: February 20, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GILEAD SCIENCES, INC.,
Petitioner,

v.

THE UNITED STATES OF AMERICA,
REPRESENTED BY THE SECRETARY OF THE DEPARTMENT OF HEALTH & HUMAN SERVICES,
Patent Owner.

IPR2019-01454
Patent 9,579,333 B2

Before ZHENYU YANG, CHRISTOPHER M. KAISER, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

INTRODUCTION

Gilead Sciences, Inc. ("Petitioner") filed a Petition (Paper 1 ("Pet.")), seeking an *inter partes* review of claims 1–17 of U.S. Patent No. 9,579,333 B2 (Ex. 1003, "the '333 patent"). The United States of America ("Patent Owner") filed a Preliminary Response. Paper 9 ("Prelim. Resp."). With our authorization, Petitioner filed a Reply (Paper 12) and Patent Owner filed a Sur-reply (Paper 13).

We have authority under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a).

For the reasons provided below, we determine that Petitioner has not demonstrated a reasonable likelihood that it would prevail with respect to at least one of the claims challenged in the Petition. Accordingly, we deny institution of an *inter partes* review.

Related Matters

According to Patent Owner, the '333 patent is the subject of *United States v. Gilead Sciences, Inc. & Gilead Sciences Ireland UC*, No. 1:19-02103 (D. Del.). Paper 8, 1.

Petitioner concurrently filed other petitions for *inter partes* review of three related patents in the same family as the '333 patent. Pet. 1.

Background of Technology and the '333 Patent

The '333 patent discloses a process "for protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus." Ex. 1003, Abstract.

According to the ’333 patent, at the time of its invention, then-current treatments of HIV did not prevent new infections, and HIV continued to spread globally. *Id.* at 1:30–39. The ’333 patent explains that “[a]n attractive method of controlling the spread of HIV would be to provide an individual exposed to a potential source of HIV with a pre-exposure prophylactic treatment.” *Id.* at 1:40–42. Because “[p]revious attempts at pre-exposure prophylaxis ha[d] met with limited success,” it reasons, “there exist[ed] a need for a chemoprophylactic composition and dosing regimen effective in blocking early stage infection by retrovirus in a host founder cell population.” *Id.* at 1:50–2:6.

According to the ’333 patent, its process protects a primate host from a self-replicating infection by an immunodeficiency retrovirus by “administering to the primate host a combination of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor [(NRTI)] and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor [(NtRTI)] prior to exposure to the immunodeficiency retrovirus.” *Id.* at 2:12–19. The ’333 patent identifies emtricitabine (an NRTI) and tenofovir (an NtRTI), as well as prodrugs of tenofovir, as preferred compounds for use in its prophylactic combination therapy. *See id.* at 7:45–60 (Example 1, describing oral administration of emtricitabine (“FTC”) and tenofovir disoproxil fumarate (“TDF”), a prodrug of tenofovir).

The ’333 patent describes, in examples, testing that compares the protection against a retroviral challenge provided by the disclosed combination therapy, monotherapies, and no therapeutic treatment. *See, e.g.*, Ex. 1003, 9:14–10:21 (Examples 7 and 8), Figs. 1–2. Specifically, the

'333 patent describes a comparison of groups of primates (i.e., macaques) receiving a combination of agents (Groups 2 and 3), macaques receiving therapy with a single agent (Group 1, FTC only (subcutaneous), n=6), and a control arm of subjects (n=18) receiving no treatment. *Id.* at 9:14–31. The Group 2 macaques (n=6) received oral administration of FTC and TDF, and the Group 3 macaques (n=6) received subcutaneous administration of FTC and tenofovir. *Id.* at 9:25–29, Fig. 1. The macaques in the experimental and control groups are exposed to weekly viral challenges (for up to 14 weeks), and the viral challenges for any particular macaque were terminated once that subject became infected. *Id.* at 9:14–20, Fig. 1.

Results of this testing are described in the '333 patent and illustrated in, for example, Figure 2, which is reproduced below.

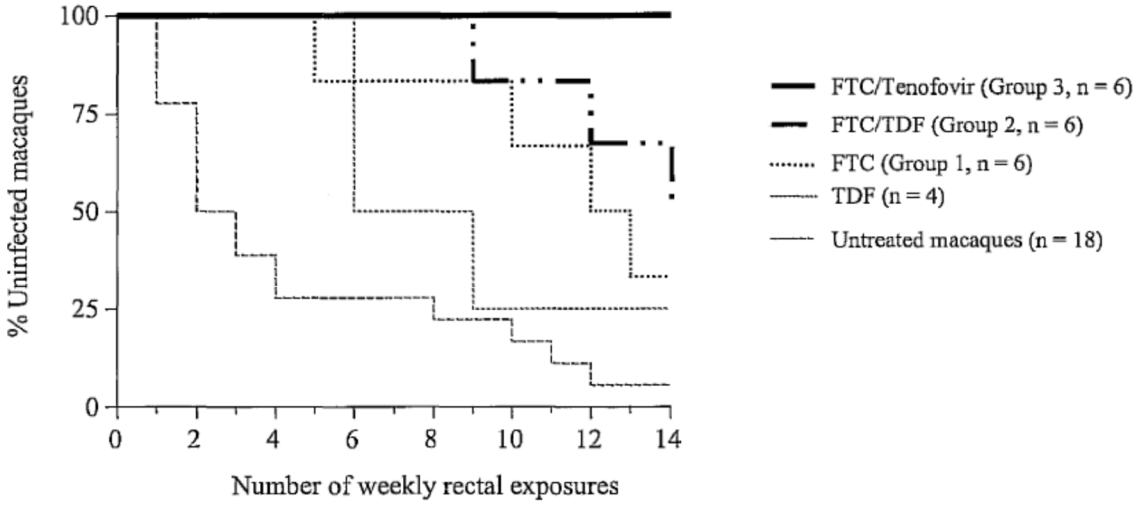

FIG. 2

Figure 2 shows survival curves for the groups of primates tested according to Example 7 of the '333 patent, plotted as a percent of uninfected subjects relative to the number of weekly viral exposures. *Id.* at 9:47–10:21. Data for

monotherapy with TDF (n=4) is also shown. *Id.* at 9:48–49. As the patent explains, "[u]ntreated macaques are infected after a median of two rectal exposures . . . [and] the majority of the [control] animals (13/18 or 72%) are infected during the first 4 challenges." *Id.* at 9:49–52. Only one (6%) of the control subjects "remained uninfected after 14 exposures." *Id.* at 9:53–54. In contrast, "[a]ll 6 macaques in Group 3 [FTC plus tenofovir] . . . remained uninfected demonstrating that full protection against repeated challenges is possible." *Id.* at 9:60–63. And, "[o]f the 6 macaques in Group 2 [FTC plus TDF], 4 were protected and only 2 . . . became infected at exposures 9 and 12," demonstrating that "[c]ompared to controls, infection in this group is reduced by 7.8 fold." *Id.* at 9:63–67, *see also id.* at 10:1–2 ("[i]nfection in both [Group 2] animals is significantly delayed compared to untreated controls," with infection at weeks 10 and 12).[1]

Illustrative Claims

Petitioner challenges the patentability of claims 1–17 of the '333 patent. Patent Owner disclaimed claims 12 and 14–17. Ex. 2028. Among the remaining claims, claim 1 is independent and is reproduced below:

> 1. A process of protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus comprising:
>
> (a) selecting a primate host not infected with the immunodeficiency retrovirus, and

[1] For Group 1 (FTC only), 2 of the 6 macaques remained uninfected at week 14, which the patent indicates is a 3.8-fold reduction in infection compared to the control. Ex. 1003, 9:63–10:4. Figure 2 indicates that 1 of the 4 macaques receiving TDF monotherapy remained uninfected at week 14. *See id.* at 10:8–12, 11:66–12:6 (citing Ex. 1050).

(b) administering directly to an uninfected primate host a combination comprising:

i. a pharmaceutically effective amount of emtricitabine, wherein the pharmaceutically effective amount of the emtricitabine is administered orally, subcutaneously or vaginally; and

ii. a pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate, wherein the pharmaceutically effective amount of the tenofovir or tenofovir disoproxil fumarate is administered orally, subcutaneously or vaginally, and

wherein the combination is administered prior to the exposure of the primate host to the immunodeficiency retrovirus, thereby protecting the primate host from infection with the immunodeficiency retrovirus.

Independent claim 12, although disclaimed, serves as the basis for dependent claim 13, which remains at issue. Claims 12 and 13 are reproduced below:

12. A process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human, comprising:

(a) selecting an uninfected human that does not have the self-replicating infection; and

(b) administering to the uninfected human a combination comprising:

i. a pharmaceutically effective amount of emtricitabine wherein the pharmaceutically effective amount of the emtricitabine is administered orally, subcutaneously or vaginally; and

ii. a pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate wherein the pharmaceutically effective amount of the tenofovir or tenofovir disoproxil fumarate is administered orally, subcutaneously or vaginally;

thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human.

13. The process of claim 12, wherein the combination is administered prior to a potential exposure of the human to the human immunodeficiency retrovirus.

Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claims Challenged	35 U.S.C. §	Reference(s)
1–17	102(b)	Szekeres[2]
12–17	102(b)	Smith[3]
1–17	103(a)	Smith, Szekeres

In support of its patentability challenge, Petitioner relies on the Declaration of Michael Youle, MB ChB. Ex. 1009 ("Youle Decl.").

ANALYSIS

§ 325(d)

Patent Owner contends that we should deny institution under 35 U.S.C. § 325(d) because the examiner fully considered Szekeres and

[2] Szekeres et al., *Anticipating the Efficacy of HIV Pre-Exposure Prophylaxis (PrEP) and the Needs of At-Risk Californians* (Nov. 2004) (Ex. 1011, "Szekeres"). The Petition refers to this reference as "Cal-PrEP." We, however, refer to it as Szekeres because this nomenclature (using the lead author's last name) is more consistent with Office practice and the prosecution history.

[3] Smith et al., Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States, 54 RR-2 MORBIDITY AND MORTALITY WEEKLY REPORT 1–19, CE1–CE4 (2005) (Ex. 1012, "Smith"). The Petition refers to this reference as "CDC-PEP," but we refer to it as "Smith" for the same reasons noted above.

Smith "when recognizing patentability of very similar claims" during the prosecution of a related patent. Prelim. Resp. 19–28.

Neither Szekeres nor Smith was cited during examination of the '333 patent. Pet. 87. Instead, they "were considered during examination of a subsequently filed application." *Id.* at 88; *see also* Prelim. Resp. 20 (Patent Owner concedes that "the Examiner considered Petitioner's asserted references in the '191 patent after the '333 patent issued").

Under such circumstances, and because, as explained below, we deny institution based on substantive analysis of the Petition, we decline to decide whether institution should be denied on a discretionary basis under § 325(d).

Claim Construction

In an *inter partes* review, we construe a claim term "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b)." 37 C.F.R. § 42.100(b). Under that standard, the words of a claim "are generally given their ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips v. AWH Corp*., 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

"protecting a primate host from a self-replicating infection" (claims 1) / "inhibiting establishment of a . . . self-replicating infection" (claim 13, through dependency from claim 12)[4]

The preamble of claim 1 recites "[a] process of protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus." Later in the body, claim 1 recites "thereby protecting the primate host from infection with the immunodeficiency retrovirus."

Petitioner argues that this preamble and related language in the body of claim 1 are not limiting. Pet. 21. According to Petitioner, this language is not necessary to give meaning to the claim, and merely conveys an intended and inherent result of practicing the "operative steps" of claim 1. *Id.* at 21–23. Petitioner reaches the same conclusion, based on substantially the same argument, with respect to claim 13's language reciting "inhibiting establishment of a . . . self-replicating infection." *Id.* at 23. So, Petitioner concludes that "100% inhibition or prevention in any particular individual" is not required by the claims. *Id.* at 24.

Patent Owner counters that claims 1 and 13 "positively recite efficacy limitations" that should be given patentable weight. Prelim. Resp. 28–32. Patent Owner points out that the Specification expressly defines

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[4] Both parties treat the "inhibiting establishment" language of claim 13 as essentially equivalent to claim 1's "protecting" from infection language. *See, e.g.*, Ex. 1009 ¶ 191 (Dr. Youle testifying that "these phrases are referring to the same thing"); Prelim. Resp. 30 ("For the limited purposes of this Response . . . Patent Owner adopts Petitioner's assumption that the efficacy limitations of Claims 1 and 13 should be treated equivalently for the purpose of evaluating the Petition."). For purposes of this Decision, we do the same.

"protection," to which the claims are directed. *Id.* at 28–29. Further, Patent Owner notes that the efficacy language appears not only in the preamble, but in the body of the claims. *Id.* at 30–31. According to Patent Owner, the efficacy language in the body of the claims was "introduced to overcome prior art rejections and explicitly reflect the claimed method's unexpected results of preventing HIV infection in the face of uncertainty and skepticism in the art." *Id.* at 31.

Patent Owner also asserts that efficacy is not inherent in administering a combination of FTC and DTF to an uninfected person. *Id.* at 31–32. As support, Patent Owner points to Petitioner's product label, which indicates that administering Truvada (FTC and DTF) is "not always effective in preventing acquisition of HIV-1." *Id.* at 31 (quoting Ex. 2002, 6). Thus, Patent Owner argues that the claims demand efficacy "by requiring the particular primate host, which received the claimed combination . . . prior to exposure, be HIV negative after exposure." *Id.* We find Patent Owner's argument persuasive.

A preamble is limiting when it is "necessary to give life, meaning, and vitality to the claim." *MBO Labs., Inc. v. Becton Dickinson & Co.*, 474 F.3d 1323, 1330 (Fed. Cir. 2007) (quoting *Pitney Bowes, Inc. v. Hewlett–Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999)). "When limitations in the body of the claim rely upon and derive antecedent basis from the preamble, then the preamble may act as a necessary component of the claimed invention." *Eaton Corp. v. Rockwell Int'l Corp*., 323 F.3d 1332, 1339 (Fed. Cir. 2003).

There is no general rule that efficacy language in a claim is non-limiting. Whether such language should be given patentable weight turns on

facts unique to each patent. *See, e.g.*, *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1373–76 (Fed. Cir. 2019) (affirming construction that result or efficacy language appearing in a wherein clause was limiting in light of the intrinsic evidence as a whole). Indeed, determining whether allegedly non-limiting language in a preamble or otherwise "involves examination of the entire patent record to determine what invention the patentee intended to define and protect." *Rowe v. Dror*, 112 F.3d 473, 478–80 (Fed. Cir. 1997); *Allergan*, 935 F.3d at 1374 (holding the court "must read the claims in view of the *entire* specification" and prosecution history) (internal quotation marks and citations omitted). Based on the entire intrinsic record, we find "protection" is at the heart of the '333 patent's invention.

In the body of claim 1, step (a) recites "selecting a primate host not **infected** with **the** immunodeficiency retrovirus." Ex. 1003, 12:51–52 (emphases added). The "immunodeficiency retrovirus" in step (a), therefore, requires the preamble language for antecedent basis. Also, the preamble provides meaning about the nature of the infection recited in the body of the claim: "a self-replicating infection by an immunodeficiency retrovirus."[5] *Id.* at 12:48–49.

Furthermore, the body of claims 1 and 13 requires administering "a pharmaceutically effective amount" of each agent. The preamble and other allegedly non-limiting portions of the claims provide necessary context for the "effective amount" language. That is, these are amounts that can bring

[5] Reliance on the preamble also appears in claim 13. There, step (a) recites "selecting an *uninfected* human that does not have *the self-replicating infection*." Ex. 1003, 14:1–2 (emphases added).

on the recited efficacy—in claim 1, "protecting" the host from infection.

Petitioner relies on *Bristol-Myers* to support its argument. Pet. 21 (citing *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368 (Fed. Cir. 2001)). The facts in this case are distinguishable from those in *Bristol-Myers*. There, the independent claims expressly included, for example, specific dosage information as material claim elements, and the "effective amount" language suggested no additional meaning nor implied any particular efficacy. *Bristol-Myers*, 246 F.3d at 1375. Not so here. Instead, the "protecting . . . from infection" and "inhibiting . . . infection" language provides necessary meaning to the claimed invention, including the "effective amount" language for the combination therapy appearing in the body of the claim.

The Specification also supports our conclusion. A specification "replete with references" to preamble language may show the inventor regarded the language as "an important characteristic of the claimed invention," and thus, limiting the claims. *Poly-Am., LP v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1310 (Fed. Cir. 2004). Here, the Specification expressly defines "protection" to mean that "the host primate being serologically negative and negative in response to a polymerase chain reaction (PCR) testing for the viral genome." Ex. 1003, 4:8–12. And the Specification discusses "protection" (or "protect," "protecting") throughout.

For example, the Summary of the Invention describes a process "for *protecting* a primate host from . . . infection," wherein "*[p]rotection* is achieved," and a regime "is also effective in providing *protection*." Ex. 1003, 2:12–24 (emphases added). It also describes a kit with a

combination dose "sufficient to *protect* a primate host from developing a self-replicating retroviral infection." *Id.* at 2:34–39 (emphasis added). Elsewhere, the Specification describes that through the administration of the combination therapy "prior to a retrovirus exposure[,] *protection* is provided against . . . retroviral infection." *Id.* at 3:24–28.

The working examples also describe the nature and extent of the prevention provided by the invention, to detail the invention and contrast the prevention it provides versus monotherapies and no treatment. *See, e.g.*, *id.* at 9:47–10:24; *Allergan*, 935 F.3d at 1375 ("[T]he specification demonstrates that [patent owner] believed the increased efficacy and safety of the claimed methods to be material to patentability.").

"Protection" is also key in the patent's prosecution. As Patent Owner highlights, the efficacy limitations were added to the body of the claims (in the parent application) to overcome the examiner's obviousness rejections. Ex. 1002, 103–20, 74–84. And the examiner specifically relied on the protection (i.e., the "superior effect") provided by the invention in allowing the claims. *See, e.g., id.* at 78, 81–82 ("As amended, the claims are drawn to the employment of particular combination of tenofovir and emtricitabine for protecting a primate."). Indeed, the examiner remarked that monotherapy with tenofovir prodrugs "has been shown as being *failed to protect*[] animal from viral infection," yet "the claimed combination has clinically significant results [i.e., degree of protection], which would have not been expected in view [of] the prior art." *Id.* at 82 (emphasis added). "The prosecution history thus demonstrates that the formulation's efficacy and safety . . . were

expressly relied on to define the claimed methods and distinguish them from the prior art." *Allergan*, 935 F.3d at 1376–77.

Petitioner suggests "protection" would "inherently result[]" from administering any combination of NRTI and NtRTI. Pet. 21. We disagree. Indeed, the Specification indicates the opposite. For example, of the six animals in "Group 2" that were treated with a combination of FTC and DTF according to Example 7, four were protected, but two became infected. Ex. 1003, 9:63–65. Moreover, as Patent Owner points out, Petitioner's own product label for Truvada (oral, fixed dose combinations of emtricitabine (200 mg) and tenofovir disoproxil fumarate (300 mg)) explains that TRUVADA "is not always effective in preventing acquisition of HIV-1." Prelim. Resp. 31 (quoting Ex. 2002 (2018 Truvada Label)); *see also* Ex. 2002, 6 (citing clinical studies and recommending "TRUVADA for HIV-1 PrEP only as part of a comprehensive prevention strategy that includes other prevention measures"). In other words, "it is possible for a patient to take Truvada prior to exposure to HIV and still become HIV positive." Prelim. Resp. 31–32.

In sum, we conclude that the efficacy language of claims 1 and 13, including "protecting a primate host from a self-replicating infection" and "inhibiting establishment of a . . . self-replicating infection," should be given patentable weight. As a result, the claims require the particular primate host receiving the claimed combination prior to exposure "be HIV negative after exposure." *Id.* at 31.

"self-replicating infection"

According to Petitioner, "self-replicating infection" relates to "a point in time after an HIV exposure when the body's immune system alone cannot prevent progression of the HIV infection." Pet. 24 (citing 1009 ¶¶ 187–188). Petitioner asserts that this corresponds to a time about 72 hours after exposure "when infected CD4+ cells are being produced faster than the immune system can destroy them." *Id.* at 24–25; Ex. 1003, 1:43–47 (describing retroviral particles being transferred to an individual and "self-replicating" "within a few days"). Petitioner, thus, asserts that "self-replicating infection" means "an HIV infection that can no longer be suppressed solely by the host's immune system." Pet. 25 (italics omitted).

Petitioner provides sufficient support for its interpretation on this record and, as it is unopposed at present by Patent Owner, we adopt Petitioner's proposed construction of this phrase for purposes of this Decision.

"prior to the exposure" (claim 1) / "prior to a potential exposure" (claim 13, through dependency from claim 12)

Petitioner contends that the claims use phrases, such as "prior to the exposure," to "specify when" the combined therapy is to be administered relative to the retroviral exposure. Pet. 25. According to Petitioner, "the exposure" need not be the *first* exposure, provided that, consistent with the requirement of the claims that the subject selected for the treatment be "not infected" or "uninfected," any "earlier exposure did not result in an HIV infection." *Id.* at 27 (citing Ex. 1003, 1:67–2:3; 3:34–37). For claim 13, Petitioner contends that the phrase "a potential exposure" does not require

"an HIV exposure to actually occur after administration of the antiretroviral agents." *Id.* at 27–28.

Petitioner asserts that each of claims 1 and 13 encompasses a process where the combination is "administered after an HIV exposure of the individual that did not result in an infection." *Id.* at 28. And, Petitioner asserts, claim 1, but not claim 13, "requires an administration to precede an actual HIV exposure." *Id.*[6]

Petitioner provides sufficient support for its assertions. Patent Owner does not contest Petitioner's assertions on the meaning of these phrases or offer its own interpretation. We conclude, for purposes of this Decision, that claim 1 requires an actual exposure to the immunodeficiency retrovirus, but note that it need not be the first such exposure with the proviso that the host is "not infected" for purposes of selection in accordance with claim 1's step (a). Ex. 1003, 12:51–52 ("(a) selecting a primate host not infected with the immunodeficiency retrovirus"). Claim 1 also requires, as asserted by Petitioner, the administration in step (b) occurs "before a future [actual] exposure." Pet. 27. Claim 13 similarly requires "selecting an uninfected human that does not have the self-replicating infection" in its step (a) and, therefore, does not preclude selecting a human that may have been exposed to the immunodeficiency retrovirus at some earlier time so long as the earlier exposure did not result in infection. Ex. 1003, 14:1–2. And, the

[6] As Petitioner notes, dependent claim 10 requires administering the combination both before and after exposure to the immunodeficiency retrovirus. Pet. 28.

"administering" in claim 13 may precede an actual or a possible HIV exposure in the uninfected human. *See* Pet. 27–28.

Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). On this record and for purposes of this Decision, we see no need to expressly construe any other claim terms.

Anticipation by Szekeres

Petitioner asserts that claims 1–18 are anticipated by Szekeres. Pet. 33–52. Because Patent Owner has disclaimed claims 12 and 14–17 (Ex. 2028), we only analyze Petitioner's challenge of claims 1–11 and 13. Based on this record, we determine Petitioner has not established a reasonable likelihood that it would prevail in this assertion.

Szekeres

Szekeres is a monograph on potential strategies for combatting HIV infection, including in particular, pre-exposure prophylaxis ("PrEP") and whether PrEP might be effectively implemented for at-risk individuals in California. Ex. 1011, 1–3.

Szekeres discloses that "[p]re-exposure prophylaxis (PrEP) is a novel approach to HIV prevention in which antiretroviral drugs (ARVs) are used by an individual prior to potential HIV exposure to reduce the likelihood of infection." *Id.* at 1. PrEP, Szekeres explains, "should be distinguished from postexposure prophylaxis (PEP), in which an individual takes ARVs soon after a potential HIV exposure with the goal of reducing the likelihood of infection." *Id.*

According to Szekeres, it had been hypothesized that "PrEP could be a viable prevention strategy for certain people at high risk of HIV infection, such as commercial sex workers." *Id.* at 3. It was, however, "not yet known whether PrEP is a safe or effective approach to HIV prevention . . . as studies for its evaluation in several populations [were] just preparing to begin." *Id.* ("These planned studies and future, yet-to-be-planned clinical trials will determine whether and to what degree PrEP is safe and effective."); *see also id.* at 6 ("Whether or not HIV PrEP will come to play as significant a role in HIV prevention as the use of ARVs for prevention of perinatal transmission . . . will largely depend on the outcome of current and future studies evaluating the safety and effectiveness of PrEP as an HIV prevention strategy.").

Szekeres describes ongoing and planned PrEP research to investigate its safety and/or efficacy in at-risk individuals. *See, e.g.*, *id.* at 6–10. For example, Szekeres describes an ongoing study among men and women in certain countries in Africa, indicating that "[e]nrollment began in summer 2004," that the study was "to last approximately 2 years," and that the study's aims included evaluating the safety and efficacy of TDF for PrEP. *Id.* at 7–8.

In addition, Szekeres identifies a planned U.S.-based study of men who have sex with men ("MSM"), evaluating "TDF for PrEP," and indicating that a 9-month recruitment of participants was "scheduled to begin in fall 2004," with the study expected to last 2 years. *Id.* at 7, 9 ("The CDC has plans to begin a randomized, double-blinded, placebo-controlled study of PrEP using TDF in high-risk, HIV-negative MSM in two cities in

the United States in the fall of 2004."); *see also id.* at 9 ("This Phase II extended safety study will examine biological safety (clinical safety and tolerability) and behavioral safety (affect [sic] on risk behaviors), and as such will not include an evaluation of efficacy.").

Szekeres further discloses that "[p]lanned studies of PrEP will screen for HIV infection prior to enrollment." *Id.* at 13. According to Szekeres, "[g]iven that these studies are still in the planning stages or have just recently begun . . . final data will likely not be available until mid-2006, at the earliest." *Id.* at 9–10; *see also id.* at 12 ("How it would be determined whether PrEP use should be episodic or continuous, or for how long use of PrEP should continue for a given population or individual, are questions that are currently unanswerable and may or may not be clarified by currently planned studies.").

With respect to the studies, Szekeres discloses that they "are providing participants with 300 mg TDF tablets (or placebo) to be taken once daily during the study period." *Id.* at 12; *see also id.* at 8 ("These studies all make use of tenofovir disoproxil fumarate (TDF) as the investigational PrEP agent."). According to Szekeres, "[t]enofovir disoproxil fumarate (TDF) is the NRTI that is currently most suitable for use as PrEP." *Id.* at 11. Szekeres discloses that "[i]t is important to note, however, that data on TDF safety to date have been from HIV-infected patients, and that unanticipated toxicities could result from chronic use of TDF in uninfected patients, as was the case with nevirapine use for PEP." *Id.*; *see also id.* at 12 ("[I]t is hoped that the results of these studies will begin to shed light on the safety of using TDF for PrEP.").

Szekeres identifies a number of known antiretroviral drugs and formulations. According to Szekeres, "[t]here are currently 20 antiretroviral drugs approved for treating HIV infection in the United States," and "there are four fixed-dose formulations available that combine more than one drug into a single pill." *Id.* at 10. According to Szekeres, "[w]hile all of the available drugs could potentially provide some efficacy as PrEP, not all of them are ideal candidates." *Id.* at 10–11. Szekeres identifies several of these drugs, by category (e.g., "[p]rotease inhibitors," "[f]usion inhibitors," "NRTIs," etc.) and by name (e.g., "CCR5 antagonist UK 427,857," "nevirapine," "[l]amivudine (3TC)," "emtricitabine (FTC)," and "[t]enofovir disoproxil fumarate (TDF)"). *Id.* at 11. With respect to TDF, as noted above, Szekeres discloses that it "is the NRTI that is currently most suitable for use as PrEP" and "the investigational agent in the major PrEP studies." *Id.* Finally, Szekeres mentions Truvada, describing it, in full, as follows: "a once-daily, fixed-dose combination tablet of TDF and emtricitabine (Truvada™) was approved in August 2004 (both Gilead Sciences, Inc., Foster City, CA)." *Id.*

Analysis

We focus our analysis on claim 1. Petitioner argues Szekeres discloses step (a), step (b), and the two wherein clauses. Pet. 37–42. Regarding the preamble and the thereby clause, Petitioner contends that, although they are "not limiting," Szekeres describes a process that "necessarily satisfies" the efficacy language. *Id.* at 36, 42–43. Patent Owner counters that Szekeres does not anticipate claim 1 because it discloses neither step (b) nor the

claimed efficacy. Prelim. Resp. 32–39. We find Patent Owner's argument more persuasive.

Step (b)

For step (b), Petitioner contends Szekeres discloses administering antiretroviral agents to uninfected individuals prior to viral exposure. Pet. 38. According to Petitioner, Szekeres identifies properties (e.g., daily dosing, favorable toxicity) of agents that may make them ideal PrEP agents. *Id.* Petitioner contends that FTC has such properties, as does TDF. *Id.* at 39 (citing Ex. 1011, 11).

Szekeres teaches that FTC is susceptible to a mutation that "confers resistance, especially when taken alone." Ex. 1011, 11. Petitioner argues this teaching "would have been understood by the skilled person as indicating FTC should be co-administered with another antiretroviral," such as TDF. Pet. 39. Petitioner further asserts that Szekeres "identifies Truvada as one of two TDF-based drug products that can be used in PrEP." *Id.* at 40 (citing Ex. 1011, 11).

Citing Truvada's 2004 label, Petitioner contends that Truvada combines 200 mg of FTC and 300 mg TDF. *Id.* at 40–41 (citing Ex. 1025, 21). According to Petitioner, because Truvada "will suppress HIV viral replication and exhibit potent antiviral activity" in a human, it "not only effectively treats an HIV infection but prevents establishment of an HIV infection." *Id.* at 41 (citing Ex. 1009 ¶¶ 92, 95, 237, 242). Thus, Petitioner asserts that the FDA-approved doses of FTC and TDF in Truvada are the "pharmaceutically effective amount[s]," as recited in step (b). *Id.* at 41.

Because Szekeres teaches "administering Truvada to an uninfected individual before an HIV exposure, which results in that individual being given pharmaceutically effective amounts of TDF and FTC," Petitioner concludes that Szekeres discloses step (b). *Id.* at 42.

Patent Owner contends that Szekeres discloses TDF as a monotherapy for PrEP, and that a single, tangential reference to Truvada does not rise to an anticipatory description of what is claimed. Prelim. Resp. 33–36. On this record, we agree with Patent Owner.

Szekeres describes PrEP monotherapy using TDF as the agent. In fact, it is the only agent Szekeres describes being used in the numerous ongoing PrEP studies/trials or even projected for use in PrEP studies planned for the future. Ex. 1011, 6–11 ("These studies all make use of tenofovir disoproxil fumarate (TDF) as the investigational PrEP agent."). And, even with respect to those studies, Szekeres expresses reservations as to whether TDF monotherapy, much less a combination therapy like claimed, would be safe or effective. *See id.* at 1 ("*If* PrEP proves to be safe and effective, numerous clinical questions will need to be resolved."), 3 ("It is *not yet known whether PrEP is a safe or effective approach* to HIV prevention."), 12 (describing questions about PrEP's use as "currently *unanswerable* and *may or may not be clarified* by currently planned studies") (all emphases added). These repeated reservations are not, as Petitioner characterizes, merely "epidemiological questions." *See* Pet. 35–36. Instead, they cast doubt over whether PrEP would be safe or effective.

Moreover, the brief, high-level mention in Szekeres of Truvada's FDA-approval does not sufficiently describe Truvada's use in a PrEP

treatment that satisfies step (b) of the claims. When anticipation is the issue, close is not enough. *Jamesbury Corp. v. Litton Indus. Prods., Inc.*, 756 F.2d 1556, 1560 (Fed. Cir. 1985) (holding "anticipation is not shown by a prior art disclosure which is only 'substantially the same' as the claimed invention"), *overruled on other grounds*, *A.C. Aukerman Co. v. R.L. Chaides Constr. Co.*, 960 F.2d 1020 (Fed. Cir. 1992) (en banc). Indeed, "[a] prior art disclosure that 'almost'" discloses all the elements arranged exactly as in the claim, "may render the claim invalid under § 103, [but] it does not 'anticipate.'" *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983); *see also Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008) ("[D]ifferences between the prior art reference and a claimed invention, however slight, invoke the question of obviousness, not anticipation.").

Here, Petitioner's theory pieces together a host of disclosures, such as a potential for resistance with certain agents, and then filters and combines those disclosures based on what an ordinarily skilled person allegedly would have "understood" to ultimately conclude that Szekeres unambiguously describes PrEP combination therapy with Truvada. Pet. 38–42. For example, Petitioner argues that Szekeres's teaching of a potential for mutation and resistance with FTC monotherapy "would have been understood by the skilled person as indicating FTC should be co-administered with another antiretroviral." *Id.* at 39. From that, Petitioner contends Szekeres suggests FTC should be combined with TDF (the known agent actually being investigated in the PrEP studies described in Szekeres), with Truvada hence representing the combination of those therapeutic agents. *Id.* at 39–40. But

Szekeres simply does not describe in any adequate detail actual or prophetic use of Truvada in a PrEP regimen. In sum, Szekeres does not disclose step (b).

Efficacy Requirement

On efficacy, Patent Owner contends that Petitioner's challenge is flawed for (i) interpreting the claims to delete any efficacy requirement, and (ii) failing to show that the claimed efficacy is expressly or inherently described in Szekeres. Prelim. Resp. 36–39. We agree.

As explained above in the claim-construction section, we determine that the preamble "protecting . . . from infection" and the efficacy language in the thereby clause are entitled to patentable weight. Also as explained above regarding step (b), Szekeres does not describe administering the claimed combination of agents (e.g., Truvada) as PrEP. Unsurprisingly, Szekeres provides no information about the efficacy of such a combination for PrEP, and thus, does not expressly disclose the limitation of efficacy.

Nor does Szekeres disclose the limitation of efficacy inherently. *See* Prelim. Resp. 31–32, 36–38. Inherency "may not be established by probabilities or possibilities." *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011) ("The mere fact that a certain thing may result from a given set of circumstances is not sufficient" to show inherency). Here, evidence of record, including Petitioner's own product label for Truvada, shows that the combination therapy of FTC and DTF "is not always effective in preventing acquisition of HIV-1." Ex. 2002, 6. Szekeres confirms this. Ex. 1011, 14 ("If PrEP is not 100% effective when used properly . . . then it is possible people may still seroconvert while

taking PrEP."), 19 (PrEP "is unlikely to be 100% effective").[7] We are, thus, unpersuaded that Petitioner has demonstrated that Szekeres discloses, expressly or inherently, the claimed efficacy.

For the reasons above, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing that claim 1 is anticipated by Szekeres. The analysis of claim 13 is the same. *See* Prelim. Resp. 39–40. And each of claims 2–11 depends from, and thus, cannot be broader than, claim 1. *See Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012). As a result, Petitioner has not established a reasonable likelihood that it would prevail in showing that claims 2–11 are anticipated by Szekeres either.

Anticipation by Smith

Petitioner asserts that claims 12–17 are anticipated by Smith. Pet. 52–64. Because Patent Owner has disclaimed claims 12 and 14–17 (Ex. 2028), we only analyze Petitioner's challenge of claim 13. Based on this record, we determine Petitioner has not established a reasonable likelihood that it would prevail in this assertion.

[7] Even if these disclosures of potential PrEP efficacy in Szekeres pertain to a "community" as Petitioner appears to suggest (Pet. 35–36), it would still not guarantee that PrEP would be effective in preventing infection in any particular individual. Such an individual may be part of a subgroup for which treatment is not efficacious and preventative against infection.

Smith

Smith is a publication related to recommendations from the U.S. Department of Health and Human Services on nonoccupational post-exposure prophylaxis (i.e., "nPEP") for HIV infection. Ex. 1012, 1–2.

Smith discloses:

> For persons seeking care ≤ 72 hours after nonoccupational exposure to blood, genital secretions, or other potentially infectious body fluids of a person known to be HIV infected, when that exposure represents a substantial risk for transmission, a 28-day course of highly active antiretroviral therapy (HAART) is recommended. Antiretroviral medications should be initiated as soon as possible after exposure.

Id. at 1, *see also id.* at 8, Fig. 1.

Pointing to data available from animal transmission models, Smith discloses that "[t]hese data indicate that nPEP might sometimes reduce the risk of HIV infection after nonoccupational exposures." *Id.* at 2. But, Smith states that animal studies "demonstrated mixed results." *Id.* For example, "[t]wo macaque studies of combination antiretroviral therapy . . . initiated 4 hours after" viral challenge and continued for 28 days "did not protect against infection but did result in reduced viral load among the animals infected." *Id.* According to Smith, "[a]lthough nPEP might reduce the risk for HIV infection, it is not believed to be 100% effective." *Id.* at 13.

Smith observes that "[n]o evidence indicates that any specific antiretroviral medication or combination of medications is optimal for use as nPEP." *Id.* at 8 ("[E]vidence is insufficient to recommend a specific antiretroviral medication as most effective for nPEP."). Nevertheless, Smith teaches that, "on the basis of the degree of experience with individual agents

in the treatment of HIV-infected persons, certain agents and combinations are preferred." *Id.* Smith teaches that "[p]referred regimens include efavirenz and lamivudine or emtricitabine with zidovudine or tenofovir (as a nonnucleoside-based regimen) and lopinavir/ritonavir . . . and zidovudine with either lamivudine or emtricitabine." *Id.* Moreover, Smith teaches that "[d]ifferent alternative regimens are possible (Table 2)." *Id.*

Smith's Table 2 identifies the combination of "Efavirenz[] plus (lamivudine or emtricitabine) plus (zidovudine or tenofovir)" as one of its "[p]referred regimens." *Id.* at 9 (Table 2). Smith's Table 3 identifies several additional HAART medications, including "Emtricitabine/tenofovir (Truvada®)," and notes the adult dosage as "1 tablet once daily," which includes "200 mg emtricitabine/300 mg tenofovir." *Id.* at 10 (Table 3); *see also id.* at 8 ("One of the HAART combinations recommended for the treatment of persons with established HIV infection should be selected on the basis of adherence, toxicity, and cost considerations (Tables 2 and 3).").

Analysis

Claim 13 depends from claim 12, and further recites that "wherein the combination is administered prior to a potential exposure of the human to the human immunodeficiency retrovirus."

Petitioner argues Smith discloses step (a), step (b), and the wherein clause of claim 12. Pet. 56–60. Regarding the preamble and the thereby clause, Petitioner contends that, although they are "not limiting," Smith describes a process that meets the efficacy language. *Id.* at 55–56, 60–61.

Regarding the wherein clause of claim 13, Petitioner argues that Smith teaches "PEP is to be followed for at least a 28-day period." *Id.* at 61.

According to Petitioner, high-risk individuals, "are likely to nonetheless engage in activities that may expose them to HIV during the 28-day PEP period" despite being counseled against doing so. *Id.* at 62. Petitioner argues that "[s]uch individuals who have remained HIV-negative after a prior exposure will be administered TDF+FTC prior to the next (i.e., 'a') potential exposure as Claim 13 specifies." *Id.*

Patent Owner counters that Szekeres does not anticipate claim 13 because it discloses neither pre-exposure prophylaxis nor the claimed efficacy. Prelim. Resp. 40–42. We find Patent Owner's argument more persuasive.

Pre-exposure prophylaxis

Smith expressly teaches post-exposure prophylaxis PEP, not pre-exposure prophylaxis PrEP. *See, e.g.*, Ex. 1012, 1 ("The provision of antiretroviral drugs to prevent HIV infection after unanticipated sexual or injection-drug-use exposure might be beneficial."). In fact, Petitioner concedes so. Pet. 61 (arguing that Smith "repeatedly states that PEP regimens are effective in preventing HIV infection if commenced early enough *after* an exposure") (emphasis added).

Petitioner's theory that high-risk individuals "are *likely* to nonetheless engage in activities that may expose them to HIV during the 28-day PEP period" (Pet. 62 (emphasis added)), even if true, would not amount to an inherent disclosure either. *Bettcher Indus.*, 661 F.3d at 639 (explaining that inherency "may not be established by probabilities or possibilities").

Efficacy Requirement

As explained above in the claim-construction section, we determine that the preamble "inhibiting establishment of a . . . infection" and the efficacy language in the thereby clause are entitled to patentable weight. Because Smith does not describe administering the claimed combination of agents as PrEP, it does not provide any information about the efficacy of such a combination for PrEP. Thus, Smith does not expressly disclose the limitation of efficacy.

Petitioner argues that Smith discloses the limitation of efficacy inherently. Pet. 60–61 (contending because Smith "teaches administering a daily oral dose of the same, FDA-approved and pharmaceutically effective amounts of TDF+FTC as the claims, it must yield the same result specified in the claims"). But as Patent Owner points out, "Smith itself discloses 'nPEP is not 100% effective.'" Prelim. Resp. 41 (citing Ex. 1012, 3, 5, 6, 13). And as explained above, Petitioner's own product label for Truvada shows that the combination therapy of FTC and DTF "is not always effective in preventing acquisition of HIV-1." Ex. 2002, 6. We are, thus, unpersuaded that Petitioner has demonstrated that Smith discloses, expressly or inherently, the claimed efficacy.

For the reasons above, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing that claim 13 is anticipated by Smith.

Obviousness over Smith and Szekeres

Petitioner asserts that claims 1–18 would have been obvious over Smith in combination with Szekeres. Pet. 64–86. Because Patent Owner has

disclaimed claims 12 and 14–18 (Ex. 2028), we only analyze Petitioner's challenge of claims 1–11 and 13. Based on this record, we determine Petitioner has not established a reasonable likelihood that it would prevail in this assertion.

Petitioner argues that an ordinary artisan would have been motivated to use Truvada in the PEP regimen based on its favorable side-effects profile compared to other antiretrovirals and to minimize resistance that can arise from monotherapies. Pet. 65–70. Acknowledging Szekeres's observation that clinical trials to test its effectiveness were underway but not completed, Petitioner contends that Szekeres would have provided a motivation "to modify the PEP regimen described in [Smith] by administering Truvada (TDF+FTC) to high-risk individuals before (rather than after) an actual HIV exposure." *Id.* at 64. According to Petitioner, an ordinary artisan would have had a reasonable expectation of success in modifying Smith and Szekeres in this way to arrive at the claimed subject matter. *Id.* at 72–84. Petitioner further argues that there is no objective indicia of non-obviousness. *Id.* at 84–86.

Patent Owner contends that Petitioner's obviousness challenge fails because (1) the combined teachings do not disclose all claim limitations; (2) there is no motivation to combine the teachings of Smith and Szkeres; and (3) there is no reasonable expectation of success. Prelim. Resp. 47–64. Patent Owner also argues that we should reject Petitioner's obviousness challenge because Petitioner fails to address known objective evidence of non-obviousness, including unexpected results evidence that persuaded the examiner to allow the challenged claims. *Id.* at 42–46. Patent Owner also

points to additional objective evidence as evidence to show that the challenged claims are nonobvious. *Id.* at 64–68. We find Patent Owner's argument more persuasive.

Efficacy Requirement

As explained above in the claim-construction section, we determine that the efficacy language in the preamble and the thereby clause are entitled to patentable weight. Also, as explained above, neither Szekeres nor Smith discloses the limitation of efficacy, either expressly or inherently. Indeed, evidence of record—including Petitioner's own product label for Truvada (Ex. 2002, 6), as well as both asserted prior art (*see, e.g.*, Ex. 1011, 14; Ex. 1012, 3, 5, 6, 13)—suggests it is possible for particular individuals taking the combination of FTC+DTF to become infected with HIV even when taking the combination.

Secondary Considerations

Objective indicia of non-obviousness, also known as secondary considerations, plays a key role in the obviousness inquiry and, among other things, guards against proscribed hindsight reasoning. *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966). Such evidence "may often be the most probative and cogent evidence in the record" and, accordingly, "must always when present be considered en route to a determination of obviousness." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983); *see also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075–80 (Fed. Cir. 2012) (holding that it is error to make an obviousness determination without considering objective indicia of nonobviousness in evidence).

In this case, as Patent Owner correctly points out, Petitioner has failed to grapple persuasively with well-developed evidence of unexpected results presented during the prosecution of the '333 patent and the parent U.S. Patent No. 9,044,509 B2 (Ex. 1003, (65)). Such evidence was key to the allowance of the claims despite the examiner's determination that the claimed subject matter was otherwise taught or suggested in the prior art.

Prosecution History

Indeed, during the prosecution of the '509 patent, the examiner rejected the then-pending claims, which later issued after minor amendments,[8] as obvious over the combined teachings of certain prior art. Ex. 1002, 204–10. In response, the applicant argued and presented, among others, evidence of objective indicia of nonobviousness, in particular, evidence of unexpected results with the claimed combination therapy. *Id.* at 118–20. Specifically, citing a post-filing publication, the applicant argued that the data in Example 7 of the '509 patent "showed that an exemplary claimed combination comprising FTC and TDF reduced the risk of rectal infection by 7.8-fold in an SIV macaque model."[9] *Id.* at 119 (citing Ex. 1155), *see also id.* (the applicant arguing, comparing with another reference, that data "showed that the study group which received FTC and TDF on various dosing schedules showed a reduced risk of infection by

[8] The claims of the '509 patent are similar to those of the '333 patent. *Compare*, e.g., Ex. 1001, claim 1, *with* Ex. 1003, claim 1.
[9] The '509 patent and the '333 patent share the same, or substantially the same, Specification. *Compare*, e.g., Ex. 1001, 9:1–10:10 (Examples 7 and 8), *with* Ex. 1003, 9:10–10:21 (Examples 7 and 8).

16.7-fold relative to untreated controls," a "superior result" that "could not have been predicted from the cited prior art").

The applicant also relied on Grant-2010 (Ex. 2004) to demonstrate the unexpected superior effect of an exemplary claimed combination. *Id.* at 119. According to the applicant, Grant-2010 showed "test subjects who had detectable blood levels of a study test drug combination (FTC and TDF) decreased their odds of an HIV infection by 92-95%." *Id.* at 119–120. Accordingly, applicant argued that "the references cited . . . as well as the specification of the present application" demonstrate "that the claims provide an unexpected superior result." *Id.* at 120.

Thereafter, the applicant and the examiner participated in two interviews. In the first one, the applicant discussed "the unpredictability of HIV art, particularly in the aspect of prevention, or prophylactic treatment," and the examiner noted "several post filing publications . . . supporting the alleged unexpected benefit residing in [the] claimed invention." *Id.* at 99. In the follow-up interview, the examiner stated that prior art teaches "the combination of tenofovir and emtricitabine for treating HIV" as well as suggesting applications for prophylaxis. *Id.* at 78. The examiner noted, however, that the "claims are allowable in view of the high unpredictability of chemoprophylaxis against HIV infection and the supe[r]ior and unexpected results shown in the application and exhibits. Particularly, [the] Grant reference." *Id.*

Later, in the "statement of reasons for allowance," the examiner commented that "the application shows that the [claimed] combination has superior effect as compared to tenofovir alone in animal model and

evidences on the record has shown the claimed combination has clinically significant results, which would have not been expected in view of the prior art as a whole." *Id.* at 81–82 (citing Ex. 2004).

A few months after indicating that the claims of the '509 patent were allowable, during the prosecution of the '333 patent, the Examiner rejected similar pending claims over similar prior art. *See, e.g.*, Ex. 1004, 77–84, 168–74. The applicant responded by: (1) amending the claims to specify that the combination therapy is administered orally, subcutaneously, or vaginally; (2) reiterating the argument and evidence related to unexpected results raised during prosecution of the '509 patent (citing, for example, data in Grant-2010 and the Specification's examples); and (3) submitting a declaration from two of the inventors detailing further testing of the claimed combination therapy. *Id.* at 34–36, 44–45, 49–52. The declaration provided survival curves (similar to Fig. 2 of the '333 patent, above) for different routes of administration of the combination therapy. *Id.* at 50 (showing data for oral administration), 51 (showing data for subcutaneous and vaginal administrations).

Shortly thereafter, the Examiner stated that the claims were allowable. *Id.* at 15–20. The Examiner explained that the applicant had provided evidence of "unexpected superior results residing in the claimed invention," and that evidence, together with the amendments and remarks were "fully considered and found persuasive." *Id.* at 17–18.

Unexpected Results

Petitioner argues there are no unexpected results because there is no nexus to the invention, and the results of using TDF+FTC in a PrEP regimen

are attributable to the prior art, not the '333 patent. Pet. 84–85 ("[A]t best, the '333 Patent provided simply a confirmation of what scientists knew and expected from the prior art."). In any event, Petitioner urges that "any evidence of secondary indicia advanced by Patent Owner in its response should be addressed after institution." *Id.* at 86.

The Board sometimes puts off until trial exploration into, and conclusions on, alleged objective indicia of nonobviousness, especially when the objective indicia are raised for the first time in a patent owner's preliminary response, and a petitioner has no reasonable *a priori* notice of such evidence or argument. That might be an appropriate approach to deal with, for example, Patent Owner's assertions of industry praise or copying at the institution stage. *See* Prelim. Resp. 65–68. But the same cannot be said for the specific evidence of unexpected results, which was presented time and again during prosecution of both the '509 and the '333 patents, and which resulted in the allowance of the challenged claims.

Petitioner's conclusory assertions about the results being attributable to the prior art and a lack of a nexus are insufficient to rebut the specific evidence on unexpected results here. As recounted above, the Examiner considered such evidence decisive in overcoming the obviousness rejections of the claims in the '509 and '333 patents. *See, e.g.* Ex. 1002, 78 (noting the "unexpected results shown in the application and exhibits. Particularly, [the] Grant reference"); *id.* at 81–82 (finding the "application shows that the combination has superior effect . . . and evidences on the record has shown the claimed combination has clinically significant results, which would have not been expected."); *see also* Ex. 1004, 18 ("Particularly, applicants

provide sufficient evidence for establishing a prima facie case of unexpected superior results residing in claimed invention."). On this record, Petitioner should have addressed those results—at minimum, the actual results exhibited with the claimed combination as shown in the '333 patent's examples or Grant-2010—in the Petition, particularly in view of the pivotal role they played in securing allowance of the claims. This, Petitioner has not done.

Patent Owner also persuades us that Petitioner knew of, indeed relied upon, those results in the past. Prelim. Resp. 43–44; Ex. 2025 (2012 Truvada label), 32–33 ("The iPrEx study and Partners PrEP study support the use of TRUVADA to help reduce the risk of acquiring HIV-1"). Under these circumstances, we find that Petitioner's failure to persuasively address the results in its Petition means Petitioner falls short of its burden to establish a reasonable likelihood of success in prevailing on its challenge.

For the reasons explained above, we determine the Petition has not established a reasonable likelihood that Petitioner would prevail in showing that the challenged claims are unpatentable as obvious over Smith and Szekeres.

CONCLUSION

In view of the foregoing, Petitioner has not demonstrated a reasonable likelihood of prevailing on any grounds set forth in the Petition. Thus, we do not institute an *inter partes* review.

ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is denied, and we do not institute *inter partes* review of any claim of the '333 patent based on the grounds asserted in the Petition.

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