Trials@uspto.gov
Tel: 571-272-7822

Paper 35
Entered: February 10, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEPTUNE GENERICS, LLC,
Petitioner,

v.

CORCEPT THERAPEUTICS, INC.,
Patent Owner.

IPR2018-01494
Patent 8,921,348 B2

Before TINA E. HULSE, ROBERT A. POLLOCK, and DAVID COTTA, *Administrative Patent Judges*.

COTTA, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining No Challenged Claims Unpatentable
35 U.S.C. § 318(a)

I. INTRODUCTION

Neptune Generics, LLC ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–7 of U.S. Patent No. 8,921,348 B2 (Ex. 1001, "the '348 patent").[1] Paper 1 ("Pet."). Corcept Therapeutics, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 9 (Prelim. Resp.).[2]

Following our Institution Decision, Patent Owner filed a Response to the Petition (Paper 24, "PO Resp."), Petitioner filed a Reply to Patent Owner's Response (Paper 29, "Reply"), and Patent Owner filed a Sur-Reply (Paper 30, "Sur-Reply"). On November 19, 2019, the parties presented arguments at an oral hearing. The transcript of the hearing has been entered into the record. Paper 34 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. We issue this Final Written Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Based on the record before us, we conclude that Petitioner has not demonstrated by a preponderance of the evidence that claims 1–7 of the '348 patent are unpatentable.

---

[1] Petitioner identifies Neptune Generics, LLC; Niagara Funding Co, LLC; GKC Partners II, LP; GKC General Partner II, LP; Burford Capital Ireland DAC; GKC PII Holdings, LLC; Burford Capital Investment Management LLC; Burford Capital Holdings (UK) Limited; and Burford Capital Limited as the real parties in interest (collectively, "RPI"). Paper 6, 2–3. Petitioner further represents that GKC Partners II, LP is now known as BCIM Partners II, LP, GKC General Partner II, LP is now known as BCIM General Partner II, LP, and GKC PII Holdings, LLC is now known as BCIM PII Holdings, LLC. Paper 28, 3.

[2] Patent Owner identifies Corcept Therapeutics, Inc. as the real party in interest. Paper 4, 1.

A. Related Proceedings

Petitioner represents that it is unaware of any other matters related to the '348 patent. Pet. 1. Patent Owner identifies *Corcept Therapeutics, Inc. v. Teva Pharmaceuticals USA, Inc.*, No. 18-cv-03632-SDW (D.N.J. Mar. 15, 2018), and *Corcept Therapeutics, Inc. v. Sun Pharma Global FZE et al.*, No. 19-cv-15678-SDW-CLW (D.N.J. July 22, 2019) as relating to the '348 patent. Paper 4, 1; Paper 27, 1.

B. The '348 Patent (Ex. 1001)

The '348 patent issued December 30, 2014, identifying Joseph K. Belanoff as the inventor. Ex. 1001. The patent discloses "a method for optimizing levels of mifepristone in a patient suffering from a mental disorder amenable to treatment by mifepristone." *Id.* at Abstract.

The '348 patent teaches that "[i]t has been surprisingly discovered that administration of the same dose of mifepristone can produce widely varying blood serum levels in different patients," which can result in "some patients not receiving an efficacious dose of mifepristone." *Id.* at 1:28–32. "[T]he blood serum levels can differ by as much as 800% from one patient to another. Thus, a method for ensuring that blood serum levels of mifepristone remain in an efficacious and safe range is needed." *Id.* at 1:33–36.

According to the '348 patent, the disclosed invention provides a method for optimizing mifepristone levels by treating the patient with seven or more doses for a period of seven or more days and then "testing the serum levels of the patient to determine whether the blood levels of mifepristone are greater than 1300 ng/ml [] and adjusting the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL." *Id.* at 1:40–49.

C. Challenged Claims

Petitioner challenges claims 1–7 of the '348 patent. Claim 1 is representative and is reproduced below:

> 1. A method for optimizing levels of mifepristone in a patient suffering from a disorder amenable to treatment by mifepristone, the method comprising:
>
> treating the patient with seven or more daily doses of mifepristone over a period of seven or more days;
>
> testing the serum levels of the patient to determine whether the blood levels of mifepristone are greater than 1300 ng/mL; and
>
> adjusting the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.

Ex. 1001, 16:26–35.

D. The Prosecution History

We provide a discussion of the prosecution history of the '348 patent for context given that one of the prior art references asserted in this proceeding (Belanoff '953[3]) was cited by the Examiner during prosecution.

The application that issued as the '348 patent (Application No. 14/065,792), was filed on October 29, 2013 with 8 original claims. Ex. 1002, 142. During prosecution, the Examiner entered an obviousness-type double patenting rejection over claims 1–7 of US Patent 8,598,149 ("the '149 patent"). *Id.* at 45–48. Patent Owner overcame this rejection by filing a terminal disclaimer. *Id.* at 20–32. No other rejections were entered.

The application that issued as the '348 patent was a continuation of Application No. 12/199,144 ("the '144 application"), which issued as the '149 patent. The claims at issue in the '144 application are very similar to

[3] Belanoff, US Patent No. 6,964,953, issued Nov. 15, 2005 (Ex. 1010, "Belanoff '953").

those in the issued '348 patent.[4] Accordingly, the '144 application is informative as to the reasons why the Examiner allowed the '348 patent.

In an Office Action mailed August 3, 2011, the Examiner rejected the pending claims of the '144 application as obvious under 35 U.S.C. § 103(a) over the combination of the Medical Encyclopedia of Medline,[5] Sarkar,[6] and Belanoff '953. The Examiner found that the Medical Encyclopedia of Medline taught that "[t]herapeutic drug levels are usually performed to look for the presence and the amount of specific drug in the blood" and that "[w]ith most medications, a certain level of drug is needed in the blood stream to obtain the desired therapeutic effect." Ex. 1003, 163. The Examiner found that Belanoff '953 disclosed that mifepristone was useful for treating acute stress disorder and taught dosages of 1 to 10 mg/kg, which

---

[4] Claim 1 of the '144 application, as originally filed, reads as follows:

> 1. A method for optimizing levels of mifepristone in a patient suffering from a mental disorder amenable to treatment by mifepristone, the method comprising:
>
> treating the patient with seven or more daily doses of mifepristone over a period of seven or more days;
>
> testing the serum levels of the patient to determine whether the blood levels of mifepristone are greater than 1300 ng/mL; and
>
> adjusting the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.

Ex. 1003, 233 (emphasis added to reflect differences as compared to claim 1 of the '348 patent).

[5] U.S. National Library of Medicine, Medical Encyclopedia: Therapeutic Drug Levels, http://www.nlm.nih.gov/medlineplus/ency/article/003430.htm, ("Medical Encyclopedia of Medline").

[6] Sarkar, *Mifepristone: Bioavailability, Pharmacokinetics, and Use-Effectiveness,* 101(2) European Journal of Obstetrics and Gynecology and Reproductive Biology, 113-120 (2002) ("Sarkar").

translates to 75–750 mg for an average adult weighing 75 kg. *Id.* The Examiner found that Sarkar taught that serum concentrations for a 100–200 mg dose of mifepristone ranged from 1933.2–2276.88 ng/ml. *Id.*

Based on the combination of the Medical Encyclopedia, Sarkar, and Belanoff '953, the Examiner concluded that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to optimize the serum level of mefipristone [sic] in patients suffering from Acute Stress Disorder." *Id.* The Examiner explained:

> One of ordinary skill in the art would have been motivated to optimize the serum level of mefipristone [sic] in patients suffering from Acute Stress Disorder. Adjusting the therapeutic serum levels to obtain a therapeutic effect is well-known in the art. Since both the serum concentration and the dosage of mifepristone useful in treating the Acute Stress Disorder are both well-known. Adjusting the serum level of mifepristone would be seen as equivalent to adjusting the dosage of mifepristone to effectively treat Acute Stress Disorder [and] would be reasonably expected to be successful.

Id. at 163–164.

In response to the August 3, 2011 Office Action, Patent Owner argued that the claimed method was non-obvious because mifepristone exhibits nonlinear serum pharmacokinetics in humans and thus it was "unpredictable what mifepristone serum concentration would provide an effective treatment for mental disorders." *Id.* at 146; *see also generally id.* at 145–148. In an April 4, 2012, Office Action, the Examiner rejected these arguments explaining that it was "well-known that mifepristone [dose] and the serum level are positively correlated, i.e., increasing the dose will increase the serum level." *Id.* at 135–136.

In response to the April 4, 2012, Office Action, Patent Owner argued that the data the Examiner relied upon to correlate mifepristone dosage with

serum levels was unreliable because it "was obtained using a radioimmunoassay, which is unable to distinguish between mifepristone and mifepristone's metabolites." *Id.* at 64. According to Patent Owner, this contrasts with what was disclosed in the '144 application, which was to measure mifepristone serum levels using "High Pressure Liquid Chromatography (HPLC) methods capable of separating mifepristone from its metabolites and accurately measuring mifepristone serum levels." *Id.* at 65 (emphasis omitted). Patent Owner thus argued that

> [i]n view of the inability of [radioimmunoassay] and [radio receptor assay] detection methods to distinguish mifepristone from its metabolites . . . there is no reasonable expectation of success for identifying 1300 ng/ml as the serum level of *mifepristone* only necessary to treat a patient suffering from a mental disorder amenable to treatment by mifepristone.

Id. at 68.

In a May 24, 2013 Office Action, the Examiner indicated that Patent Owner's arguments were persuasive. The Examiner stated:

> The method of using the mifepristone level for adjusting the treatment of mental disorder is not taught or fairly suggested by the prior art. Although the effective dosages of mifepristone for treating mental disorders are known, the correlation of the level of mifepristone to the therapeutic effectiveness of mifepristone is not known.

Id. at 52; *see also id.* at 34 (Notice of Allowability).

D. The Asserted Ground of Unpatentability

Petitioner challenges the patentability of claims 1–7 of the '348 patent on the following grounds:

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1, 2, 4, 6, 7	§ 103(a)[7]	Belanoff '848[8]
1, 2, 4, 6, 7	§ 103(a)	Belanoff 2002, Sitruk-Ware,[9] Chu and Belanoff[10]
3	§ 103(a)	Belanoff 2002, Sitruk-Ware, Chu and Belanoff, Belanoff '953
5	§ 103(a)	Belanoff 2002, Sitruk-Ware, Chu and Belanoff, Murphy[11]
3	§ 103(a)	Belanoff '848, Belanoff '953
5	§ 103(a)	Belanoff '848, Murphy

Petitioner submits the Declaration of Dr. Mikko A. Oskari Heikinheimo (Ex. 1004) in support of the Petition. Patent Owner submits the Declarations of Dr. Hartmut Derendorf (Ex. 2014) and Dr. Ned. H. Kalin (Ex. 2016) in support of its Response to the Petition.

[7] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287 (2011), amended 35 U.S.C. § 103. Because the application from which the '348 patent issued has an effective filing date before March 16, 2013, the effective date of the relevant amendment, the pre-AIA version of § 103 applies.

[8] Belanoff, US Patent Publication No. 2004/0029848 A1, published Feb. 12, 2004 (Ex. 1024, "Belanoff '848").

[9] Sitruk-Ware et al., *Pharmacological Properties of Mifepristone: Toxicology and Safety in Animal and Human Studies,* 68 Contraception 409–420 (2003) (Ex. 1008, "Sitruk-Ware").

[10] Chu et al., *Successful Long-Term Treatment of Refractory Cushing's Disease with High-Dose Mifepristone (RU 486),* 86(8) Journal of Clinical Endocrinology & Metabolism 3568–3573 (2001) (Ex. 1023, "Chu and Belanoff").

[11] Murphy et al., *Possible Use of Glucocorticoid Receptor Agonists in the Treatment of Major Depression: Preliminary Results Using RU 486,* 18(5) J. Psychiatr. Neurosci. 209–213 (1993) (Ex. 1006, "Murphy").

II. ANALYSIS

A. Person of Ordinary Skill in the Art

Factual indicators of the level of ordinary skill in the art include "the various prior art approaches employed, the types of problems encountered in the art, the rapidity with which innovations are made, the sophistication of the technology involved, and the educational background of those actively working in the field." *Jacobson Bros., Inc. v. U.S.*, 512 F.2d 1065, 1071 (Ct. Cl. 1975); *see also Orthopedic Equip. Co., v. U.S.*, 702 F.2d 1005, 1011 (Fed. Cir. 1983) (quoting with approval *Jacobson Bros.*).

Petitioner contends that the person of ordinary skill in the art ("POSA") would have:

> either a Pharm. D. or a Ph.D. in organic chemistry, pharmacy, pharmacology, or a related discipline; or a Bachelor's or Master's degree in organic chemistry or a related field with at least four years of experience relating to the study of pharmacokinetics or dosing of drugs, their detection and quantification, or their metabolism.

Pet. 12. Patent Owner does not challenge Petitioner's definition. Accordingly, we accept Petitioner's definition, which is consistent with the level of skill reflected in the asserted prior art references. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art itself can reflect the appropriate level of ordinary skill in the art).

B. Claim Construction

We interpret claims of an unexpired patent using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R. § 42.100(b) (2018); *see also Cuozzo Speed*

Techs., LLC v. Lee, 136 S. Ct. 2131, 2144–46 (2016).[12] Under the broadest reasonable construction standard, claim terms are generally given their ordinary and customary meaning as would be understood by one of ordinary skill in the art at the time of the invention. *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).

Although the parties propose constructions for several claim terms (Pet. 12–15; PO Resp. 17–18), we determine that no explicit construction of any claim term is necessary to resolve this case. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))); *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy'").

[12] The broadest reasonable interpretation ("BRI") construction standard applies to *inter partes* reviews filed before November 13, 2018. 77 Fed. Reg. 48,727 (Aug. 14, 2012) (codified at 37 C.F.R. § 42.100(b)), as amended at 81 Fed. Reg. 18766 (Apr. 1, 2016); *see also* 83 Fed. Reg. 51,340 (Oct. 11, 2018) (changing the standard for interpreting claims in *inter partes* reviews filed on or after November 13, 2018). Because the Petition was filed prior to this date, on August 2, 2018, the BRI construction standard applies.

C. Principles of Law

To prevail in this *inter partes* review of the challenged claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e) (2012); 37 C.F.R. § 42.1(d).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter 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. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

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

D. Ground 1: Obviousness of Claims 1, 2, 4, 6, and 7 over Belanoff '848

Petitioner asserts that claims 1, 2, 4, 6, and 7 would have been obvious over Belanoff '848. *See* Pet. 25–32. We have considered the question of patentability in view of all the evidence and arguments presented in this proceeding. Based on the record developed during this proceeding, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1, 2, 4, 6, and 7 would have been obvious over Belanoff '848.

i. Disclosures of the Asserted Prior Art

Belanoff '848

Belanoff '848 discloses administering mifepristone in dosages of 600–1200 mg daily for one week to treat delirium. Ex. 1024, ¶¶ 94–96. Dosages may be "adjusted if necessary." *Id.* ¶ 96. "The dosage regimen . . . takes into consideration pharmacokinetics parameters well known in the art, i.e., the GR [glucocorticoid receptor] antagonists' rate of absorption, bioavailability, metabolism, clearance, and the like." *Id.* ¶ 88. According to Belanoff '848, it was known in the art to "determine the dosage regimen for each individual patient, GR antagonist and disease or condition treated." *Id.* Belanoff '848 discloses that "it may be necessary to measure blood and urine levels of GR antagonist" and that "[m]eans for such monitoring are well described in the scientific and patent literature." *Id.* ¶ 41. But Belanoff '848 also teaches that "[t]o delineate and assess the effectiveness of mifepristone in ameliorating the symptoms of delirium, formal psychiatric assessment and a battery of neuro-psychological tests and assessments are administered to all patients." *Id.* ¶ 99. Belanoff '848 teaches that "[t]hese tests and diagnostic assessments take place at baseline (patient's entry into treatment) and periodically throughout treatment." *Id.*

ii. Analysis

Claim 1, the only independent claim in the '348 patent, requires "testing the serum levels of the patient to determine whether the blood levels of mifepristone are greater than 1300 ng/mL" and "adjusting the daily dose of the patient to achieve mifepristone levels greater than 1300 ng/mL." Ex. 1001, 16:31–35. With respect to the "greater than 1300 ng/mL" threshold

recited in claim 1, the position set forth in the Petition, in its entirety, reads as follows:

> The only missing claim element from *Belanoff '848* is the desired serum level (1300 ng/mL) of mifepristone. However, it is well-settled that optimization of a range or other variable within a claim that flows from the "normal desire of scientists or artisans to improve upon what is already generally known" is *prima facie* obvious. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368-69 (Fed. Cir. 2007) (citing, *inter alia*, *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003); *In re Aller*, 42 C.C.P.A. 824, 220 F.2d 454, 456 (1955); *In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980); *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997); *In re Kulling*, 897 F.2d 1147, 1149 (Fed. Cir. 1990)).
>
> *Belanoff '848* certainly gives a range of mifepristone oral dosage levels. (*See* Ex. 1024 at [0096] (600-1200 mg/day)) These dosage levels inherently translate directly into mifepristone serum levels. *See*, *e.g.*, *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) ("The initial blood serum concentration resulting from administering a PPI dosage is an inherent property of the formulation."). In fact, the mifepristone dosage level ranges taught by *Belanoff '848* are exactly the same as the mifepristone dosage level ranges that are taught by the '348 Patent. The clinical studies described in the '348 Patent show mifepristone dosage levels of 300, 600, and 1200 mg/day. (Ex. 1001 at. 13:50 through 15:54)[.] Those dosages resulted in serum levels over 1357 ng/mL in 269 of 443 patients, and serum levels over 1661 ng/mL in 166 of 443 patients (*id*. at Figs. 1-3). [E]ven higher patient percentages above those serum levels at the 1200 mg/day mifepristone dosage level (*id.* at Figs. 4-6).
>
> Accordingly, administration of mifepristone at the dosage levels taught by *Belanoff '848* would necessarily and inevitably result in a range of blood serum concentrations that achieve mifepristone blood levels greater than 1300 ng/mL as claimed. (Ex. 1004 at ¶20)[.] It would have been readily obvious to one

> of ordinary skill in the art with a very high expectation of success that the daily dosing of the patient could be adjusted to optimize mifepristone blood level, whatever level that might be. (*Id.*)[.]

Id. at 29–30.

"In an inter partes review . . . , the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence." 35 U.S.C. § 316(e); *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375 (Fed. Cir. 2016). Petitioner has not met this burden here because the Petition does not clearly articulate why an optimization rationale would have led the skilled artisan to "adjust[] the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL."

We analyze the positions set forth in the Petition with respect to this limitation in the order set forth in the Petition. Petitioner begins by asserting that "optimization of a range or other variable within a claim that flows from the 'normal desire of scientists or artisans to improve upon what is already generally known' is *prima facie* obvious." Pet. 29 (citing case law). This argument is not persuasive because Petitioner does not establish that Belanoff '848 discloses a range of blood serum levels.

Recognizing this deficiency, Petitioner next asserts that Belanoff '848 provides a range of oral dosages and that these dosages "inherently translate directly into mifepristone serum levels." *Id.* We acknowledge that Belanoff '848 discloses a range of oral doses. The record, however, does not support that administration of mifepristone at the levels disclosed in Belanoff '848 would inherently translate into a range of blood serum concentrations that achieve mifepristone blood levels greater than 1300 ng/mL as claimed. To the contrary, the record supports that blood serum levels were known *not* to

correlate with dosage. Ex. 1004, Heikinheimo Decl. ¶ 25 ("It is in no way surprising that administration of the same dose of mifepristone can produce widely varying blood serum levels in different patients."); Pet. 48 ("administration of the same dose of mifepristone can produce widely varying blood serum levels in different patients."); Ex. 1001, 1:33–34 ("For the same dose of mifepristone, the blood serum levels can differ by as much as 800% from one patient to another."). Accordingly, administration of the dosages taught in Belanoff may, or may not, result in blood serum levels greater than 1300 ng/ml as claimed. To establish that a prior art reference inherently teaches a claim limitation, however, Petitioner must show that "the limitation at issue necessarily must be present, or [is] the natural result of the combination of elements explicitly disclosed by the prior art." *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014). Petitioner has failed to make that showing.

Finally, Petitioner asserts that it would have been obvious that "the daily dosing of the patient could be adjusted to optimize mifepristone blood level, whatever level that might be." Pet. 30. This argument is not persuasive for several reasons. First, Petitioner must do more than show that the ordinary artisan could have done what was claimed. *Belden Inc. v. Berk–Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) ("[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.").

Second, the testimony of Petitioner's own expert calls into question whether a POSA could indeed have optimized serum levels by adjusting dosing (and whether a POSA would have seen value in doing so). Ex. 2009,

48:15–49:19 (Dr. Heikenhimo testimony that, absent a clinical trial, a POSA would have no reason to expect that they could adjust the dose of mifepristone to increase serum level); *id.* at 135:15–21 (Dr. Heikenhimo deposition testimony on redirect examination that he has not "seen any scientific evidence" that adjusting the daily dose of mifepristone to levels greater than 1,300 nanograms per milliliter "would be of clinical value or that it could be done"); Ex. 1013, 24–25 (article coauthored by Dr. Heikenhimo stating that "due to saturation of the serum binding capacity for [mifepristone], the quantitation of [mifepristone] in serum following intake of doses exceeding 50 mg may not be very informative."); *see also* Ex. 1012 (article coauthored by Dr. Heikenhimo reporting that prior studies have shown that doses above 400 mg are needed to promote antiglucocorticoid effects and stating "[i]n view of the fact that plasma concentrations of [mifepristone] are not elevated by increasing the oral dose of [mifepristone] from 100 to 800 mg, . . . it still remains an enigma why systemic antiglucocorticoidal effects are virtually never seen at [mifepristone] doses below 400 mg").

Third, even Belanoff '848 relied upon psychological testing rather than blood serum levels to assess the effectiveness of mifepristone and adjust the dose. Ex. 1024, ¶¶ 95–99; Ex. 2014, ¶¶ 145–149; Ex. 2016 ¶¶ 36–38. Specifically, Belanoff '848 teaches that mifepristone is administered in dosages of 600–1200 mg daily for one week and then the patients are evaluated through "a battery of neuro-psychological tests and assessments." Ex. 1024 ¶ 99. Belanoff '848 further teaches that "[d]osages will be adjusted if necessary and further evaluations will be performed periodically throughout treatment" as a result of the assessments. *Id.* ¶ 96.

Finally, Petitioner provides no explanation of how or why the ability to optimize blood serum levels would have led the ordinary artisan to adjust the daily dose of mifepristone administered to achieve the claimed serum levels. *See* Pet. 29–30. Rather, Petitioner and Dr. Heikinheimo conclusorily state that "[i]t would have been readily obvious to one of ordinary skill in the art with a very high expectation of success that the daily dosing of the patient could be adjusted to optimize mifepristone blood level, whatever level that might be." *Id.* at 30; Ex. 1004 ¶ 20.

We recognize that Belanoff '848 teaches that it "may be necessary" to measure serum levels and discloses that the dosing regimen takes pharmacokinetic parameters into consideration. Ex. 1024 ¶¶ 41, 88. But, Petitioner's own expert, Dr. Heikinheimo concedes that the disclosure in Belanof '848 of measuring plasma concentrations (Ex. 1024 ¶ 41) teaches only that "a very vague laboratory test may be used, may by useful." Ex. 2009, 131:9–10. Dr. Heikinheimo further testified that the sentence in Belanoff '848 disclosing measurement of plasma concentrations was a "very general sentence" and that "[i]t dosen't really say anything very specific." *Id.* at 131:5, 10–11. Even assuming that Belanoff '848 supports a motivation to measure blood serum levels, it is not clear how this motivation would lead the POSA to adjust the dose to achieve the specific claimed blood serum levels. Petitioner must do more than establish a motivation to measure blood serum levels in order to render obvious the limitation requiring "adjusting the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL." Petitioner must explain why the motivation to test blood serum levels would cause the ordinary artisan to adjust mifepristone dosing to achieve a particular serum level.

Considering all of the arguments and evidence provided in the Petition with respect to this limitation together, Petitioner does little more than assert – without explanation – that the ordinary artisan would have arrived at this limitation through routine optimization. Our decision thus turns on whether Petitioner can carry its burden to establish that it would have been obvious to adjust the dose of mifepristone to attain the claimed serum levels simply by invoking the desire of the ordinary artisan to optimize. Our reviewing court has instructed that more is required. *In re Stepan Co.,* 868 F.3d 1342, 1346 (Fed. Cir. 2017) (explaining that there must be "some rational underpinning explaining why a person of ordinary skill in the art would have arrived at the claimed invention through routine optimization"); *see also KSR*, 550 U.S. at 418 (explaining that "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). Here, we find that Petitioner's invocation of a desire to optimize is not sufficient to render the "adjusting the dose" limitation obvious, particularly given that: 1) Petitioner has not established that Belanoff '848 discloses a range of blood serum concentrations, 2) blood serum levels were known not to correlate with dosage, 3) Petitioner's own expert questioned the ability of the POSA to adjust serum levels and the value in making such adjustments, and 4) Belanoff '848 relied upon psychological testing rather than blood serum levels to adjust dose.

In sum, for the reasons given above, Petitioner has not established, by a preponderance of the evidence, that Belanoff '848 would have rendered the challenged claims obvious.

E. Ground 2: Obviousness of Claims 1, 2, 4, 6, and 7 over Belanoff 2002, Chu and Belanoff, and Sitruk-Ware

Petitioner asserts that claims 1, 2, 4, 6, and 7 are rendered obvious by the combination of Belanoff 2002, Chu and Belanoff, and Sitruk-Ware. Pet. 32–42. We have considered the question of patentability in view of all the evidence and arguments presented in this proceeding. Based on the record developed during this proceeding, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1, 2, 4, 6, and 7 would have been obvious over the combination of Belanoff 2002, Chu and Belanoff, and Sitruk-Ware.

i. Disclosures of the Asserted Prior Art

Belanoff 2002

Belanoff 2002 discloses an open label trial of mifepristone in which thirty patients with psychotic major depression ("PMD") received 50 mg, 600 mg or 1200 mg of mifepristone administered once daily for 7 days. Ex. 1007, 386, 388. Belanoff 2002 reports that "nearly two thirds of the subjects showed significant reductions in their psychosis in a week or less." *Id.* at 389–390.

Chu and Belanoff

Chu and Belanoff disclose the treatment of a patient with Cushing's syndrome ("CS") with high-dose long-term mifepristone therapy. Ex. 1023, 3568. Chu and Belanoff teach that the dosage of the patient was adjusted over the course of treatment. *Id.* at 3570. Thus, the patient "was initiated on mifepristone at 400 mg/d (~6 mg/kg•d)." *Id.* "During the initial 8 months of mifepristone treatment, the dose was gradually increased to a maximum of 2000 mg/d (~25 mg/kg•d) in response to continued signs of

hypercortisolism." *Id.* "[C]linical findings attributable to CS slowly improved, and the mifepristone dosage was titrated downward over the following 10 months." *Id.*

Sitruk-Ware

> Sitruk-Ware discloses:
>
> Following single-dose administration of mifepristone (600 mg), to healthy female volunteers, mean maximum plasma concentrations were about 2.0 mg/L at 1.35 h (t_{max}). After oral ingestion, mifepristone is rapidly absorbed, and the time to peak serum concentration (t_{max}) is approximately 1–2 h (Table 1). When analyzed by specific RIA [radioimmunoassay] or HPLC [high-performance liquid chromatography], t_{max} is similar within the dose range of 200–600 mg. Peak drug plasma concentration (C_{max}) rises according to the dose of mifepristone within the dose range of 2–25 mg.

Ex. 1008, 414.

ii. Analysis

Claim 1, the only independent claim of the '348 patent, requires "testing the serum levels of the patient to determine whether the blood levels of mifepristone are greater than 1300 ng/mL" and "adjusting the daily dose of the patient to achieve mifepristone levels greater than 1300 ng/mL." Ex. 1001, 16:31–35. With respect to the "greater than 1300 ng/mL" threshold recited in claim 1, Petitioner contends that Belanoff 2002 teaches that a daily dose of 600 mg/day is efficacious and that Sitruk-Ware teaches that a single dose of 600 mg rapidly results in serum levels of 2000 ng/mL. Pet. 36. Petitioner asserts that in view of this knowledge, it would have been obvious "to test the serum levels of a patient to determine if blood levels of mifepristone were greater than 1300 ng/mL since it was known that such dosages were efficacious in the treatment of stress disorders." *Id.* at 36–37 (citing Ex. 1004 ¶ 19).

The parties agree that the claims require that the testing of the patient's serum levels occur after treatment of the patient over a period of seven days. PO Resp. 48 ("The '348 Patent specifically requires that the 1300 ng/mL level be obtained after 'treating the patient with seven or more daily doses of mifepristone over a period of seven or more days.'"); Reply 3 ("[T]here is no part of the claim or the specification the indicates when, after seven daily doses, serum levels are to be measured"); Tr. 9 (Petitioner's counsel agreeing that the claims require blood serum level to be measured after seven days of treatment).

Patent Owner argues that Sitruk-Ware, upon which Petitioner relies to establish a blood serum level that correlates with efficacy, "only conducts and reports data from single-dose studies – that is, acute administration, which is quite unlike the longer-term administration (at least seven days) required by the claimed methods." PO Resp. 47. According to Patent Owner, "the PK parameters after a single-dose, such as that reported in Sitruk-Ware, and those after multiple-dose studies are vastly different." *Id.* We agree with Patent Owner that the record supports that PK parameters for single-dose and multiple-doses of mifepristone may differ. For the reasons discussed below, we find that given this potential difference, Petitioner has not established that the claimed serum levels would be efficacious for mifepristone administered over the course of seven days.

Patent Owner directs us to evidence that the PK parameters for single-dose administration differ from those for multiple-dose administration. In particular, Patent Owner's expert Dr. Derendorf testifies:

> [T]he PK profiles after a single dose and after multiple doses are usually different. When multiple doses are administered, drug concentration in the blood can accumulate. For drugs with

> a linear PK profile, multiple-dose administration shows a higher and predictable mean concentration in the blood (as well as a higher C_{max} and C_{min}), because of the continued addition of drug. For drugs with a non-linear PK profile, multiple doses could result in a higher than predicted concentration in the blood, or could result in the same or lower than predicted blood concentrations. This is because dose does not proportionally correlate with concentration. Furthermore, pharmacokinetic parameters may not be constant with time. For example, enzymatic auto-induction leads to increased clearance with time and to lower blood levels at later time points. Some of the mifepristone literature reported that the blood concentration after four daily doses was lower than that reported after three daily doses. Ex. 1013 (Heikinheimo 1989) at 2; *see also* Ex. 2009 (Heikinheimo Deposition) at 102-106.
>
> For these reasons, drug development studies frequently conduct PK studies based on single-dose and multiple-dose administration. Both of these are separately done because they provide separate and distinct information that guides the understanding of the drug's PK profile and influences the determination of pharmacodynamics, as discussed in further detail below.

Ex. 2014 ¶ 44–45. Dr. Derendorf further testifies:

> [T]he body shows a different PK profile, with different concentrations in the blood when given a single dose versus multiple, continuous doses. This is because drug concentration peaks and declines after a single dose, whereas drug concentration accumulates in a different manner upon multiple doses (with a different C_{max} and C_{min} after each dose, and eventually steady state).

Id. ¶ 172. Given the potential differences in serum concentration following multi-dose as compared to single-dose treatment, Dr. Derendorf concludes that "the single-dose serum levels (in Sitruk-Ware) do not inform the serum levels that would be present after seven or more doses." *Id.*

Dr. Derendorf's testimony is consistent with the prior art. *See* Ex. 1013, 22 (Table 1 showing that C_{min} serum concentrations for five different doses administered over periods of four or seven days peak at some point during treatment and then declined as treatment continued). Moreover, Petitioner does not direct us to persuasive evidence or argument contradicting or otherwise calling into question Dr. Derendorf's testimony. Absent a basis to question Dr. Derendorf's testimony, we find it credible.

Petitioner relies solely on Sitruk-Ware as teaching that an oral mifepristone dose of 600 mg, which Belanoff teaches is efficacious, correlates with serum levels of 2000 ng/mL. Pet. 36. Petitioner thus argues:

> As *Belanoff 2002* uses an effective amount of 600 mg daily it would have been obvious to one of ordinary skill in the art that 600 mg daily would have had a reasonable expectation of success in attaining the target level of 1300 ng/mL in view of the dosing studies of *Sitruk-Ware* that indicates a single dose of 600 mg results in serum levels of about 2.0 mg/L (2000 ng/mL) very rapidly.

Id. (citing Ex. 1004 ¶¶ 17–18 (Heikenhimo Decl.)). Sitruk-Ware, however, discloses serum levels after a single 600 mg dose of mifepristone. Ex. 1008, 413. Petitioner does not direct us to persuasive evidence that the serum level after Sitruk-Ware's single dose is representative of an efficacious serum level after seven days of treatment. *See* Pet. 35–36 (discussing serum level limitation without addressing multi-dose treatment).

Petitioner asserts that "one of ordinary skill in the art would have no expectation that the effective dosing of 600 mg daily of mifepristone as taught by *Belanoff 2002* would have resulted in a ***lowered*** level of serum mifepristone, below that indicated by *Sitruk-Ware*." *Id.* But Patent Owner provides evidence that "enzymatic auto-induction" following multi-dose

treatment may "lead[] to increased clearance with time and to lower blood levels at later time points" and that for this reason, it is common to conduct separate studies on pK parameters for single and multi-dose treatments. Ex. 2014 ¶ 44–45. In contrast, the evidence Petitioner cites as support for its argument that the POSA would not expect "a *lowered* level of serum mifepristone" does not speak to multi-dose treatment. Pet. 36 (citing Ex. 1004 ¶¶ 17–18). Rather, Petitioner's supporting evidence is testimony from Dr. Heikinheimo: 1) that in view of the single dose serum level taught in Sitruk-Ware, the POSA "would have had a reasonable expectation of success in attaining the target level of approximately 1300 ng/mL," and 2) that the Mifeprix label reports a peak plasma concentration following administration of "a single dose of 600 mg" consistent with that reported in Sitruk-Ware. Ex. 1004, ¶¶ 17–18. Accordingly, the record does not provide persuasive evidentiary support for Petitioner's position that the POSA "would have no expectation that the effective dosing of 600 mg daily of mifepristone as taught by *Belanoff 2002* would have resulted in a *lowered* level of serum mifepristone, below that indicated by *Sitruk-Ware*." Pet. 35–36.

We recognize that the Declaration of Dr. Heikinheimo includes a paragraph opining on what the serum levels would be after a patient took seven or more sequential doses of 600 mg of oral mifepristone. Ex. 1004 ¶ 30. This testimony, however, is not identified in the Petition itself.[13] *See generally* Pet.; *see* Pet. 35–36 (discussing Sitruk-Ware without explaining why its single dose serum level is representative of serum level after seven

[13] Nor was it cited in Petitioner's Reply or in response to repeated questioning on multi-dose treatment at oral argument.

days of treatment). A petition seeking *inter partes* review must identify "[t]he exhibit number of the supporting evidence relied upon to support the challenge and the relevance of the evidence to the challenge raised, including identifying specific portions of the evidence that support the challenge." 37 C.F.R. § 42.104(b)(5). "The Board may exclude or give no weight to the evidence where a party has failed to state its relevance or to identify specific portions of the evidence that support the challenge." *Id.*; *see also* 37 C.F.R. § 42.22(a)(2) (a petition must include a "full statement of the reasons for the relief requested, including a detailed explanation of the significance of the evidence"); *Cisco Sys., Inc., v. C-Cation Techs., LLC*, IPR2014–00454, Paper 12 at 9–10 (PTAB Aug. 29, 2014) (informative) (explaining that arguments not made in the Petition will not be considered); *Liberty Mutual Ins. Co. v. Progressive Casualty Ins. Co.*, CBM2012–00003, Paper 8 at 10, 14 (PTAB Oct. 25, 2012) (stating that the Board "will address only the basis, rationale, and reasoning *put forth by the Petitioner in the petition*") (emphasis added); *see also DeSilva v. DiLeonardi*, 181 F.3d 865, 866-67 (7th Cir. 1999) (Incorporation by reference "is a pointless imposition on the court's time. A brief must make all arguments accessible to the judges, rather than ask them to play archeologist with the record."). Accordingly, we do not consider this testimony.

Even if we were to consider this testimony, we would not find it persuasive when weighed against Dr. Derendorf's testimony because it is not clear that Dr. Heikinheimo took into consideration how multi-dose treatment may affect serum levels. Dr. Heikinheimo states that his opinion is based on "data from the *Shi* 1993 publication" as well as "the nonlinear pharmacokinetics of mifepristone." Ex. 1004 ¶ 30. The focus of the Shi

reference was on the time required to clear a single dose of mifepristone rather than serum levels following multi-dose administration. Ex. 1016, Abstract (Shi publication reporting serum levels following doses of mifepristone taken by women "once per menstrual cycle."). Given that Dr. Heikinheimo's testimony is based on Shi, and given that Shi is limited to single dose treatments, we are not persuaded that Dr. Heikinheimo's opinion on serum levels following multi-day treatment sufficiently accounts for how multi-dose treatment would affect serum levels.

In summary, it is Petitioner's burden to prove obviousness by a preponderance of the evidence. Based on the obviousness rationale articulated in Ground 2, this requires proving that administration of 600 mg of mifepristone over a course of seven days, would have resulted in a blood serum level above 1,300 ng/ml. *See* Tr. 60 (Petitioner's counsel acknowledging, "we needed to show, for ground 2, that a level above 1,300 was achieved with generally an effective dose as shown in Belanoff 2002 reference"). The Petition relies solely on Sitruk-Ware to make this showing. Pet. 35–36. For the reasons discussed above, Petitioner has not carried the burden to show that the blood serum level for a single dose of mifepristone administered in Sitruk-Ware is representative of the serum level that would be obtained upon administration for seven days, as required by the claim.

Accordingly, for the reasons given above, Petitioner has not established, by a preponderance of the evidence, that the combination of Belanoff 2002, Chu and Belanoff, and Sitruk-Ware would have rendered the challenged claims obvious.

F. Ground 3: Obviousness of Claim 3 over Belanoff 2002, Chu and Belanoff, Sitruk-Ware and Belanoff '953

Petitioner asserts that claim 3 would have been obvious over the combination of Belanoff 2002, Chu and Belanoff, Sitruk-Ware, and Belanoff '953. Pet. 42–43. In its analysis of this ground, Petitioner relies on Belanoff '953 to address limitations found in dependent claim 3 and does not address the issues discussed above. Accordingly, for the reasons given above, Petitioner has not established, by a preponderance of the evidence, that the combination of Belanoff 2002, Chu and Belanoff, Sitruk-Ware, and Belanoff '953 would have rendered claim 3 obvious.

G. Ground 4: Obviousness of Claim 5 over Belanoff 2002, Chu and Belanoff, Sitruk-Ware and Murphy

Petitioner asserts that claim 5 would have been obvious over the combination of Belanoff 2002, Chu and Belanoff, Sitruk-Ware, and Murphy. Pet. 43–45. In its analysis of this ground, Petitioner relies on Murphy to address limitations found in dependent claim 5 and does not address the issues discussed above. Accordingly, for the reasons given above, Petitioner has not established, by a preponderance of the evidence, that the combination of Belanoff 2002, Chu and Belanoff, Sitruk-Ware, and Murphy would have rendered claim 5 obvious.

H. Ground 5: Obviousness of Claim 3 over Belanoff '848 and Belanoff '953

Petitioner asserts that claim 3 would have been obvious over the combination of Belanoff '848 and Belanoff '953. Pet. 45–46. In its analysis of this ground, Petitioner relies on Belanoff '953 to address limitations found in dependent claim 3 and does not address the issues discussed above. Accordingly, for the reasons given above, Petitioner has not established, by

a preponderance of the evidence, that the combination of Belanoff '848 and Belanoff '953 would have rendered claim 3 obvious.

I. Ground 6: Obviousness of Claim 3 over Belanoff '848 and Murphy

Petitioner asserts that claim 5 would have been obvious over the combination of Belanoff '848 and Murphy. Pet. 46–47. In its analysis of this ground, Petitioner relies on Murphy to address limitations found in dependent claim 5 and does not address the issues discussed above. Accordingly, for the reasons given above, Petitioner has not established, by a preponderance of the evidence, that the combination of Belanoff '848 and Murphy would have rendered claim 5 obvious.

III. CONCLUSION

Upon consideration of the Petition, Response, Reply, Sur-Reply, and the evidence before us, we determine that Petitioner has not proven by a preponderance of the evidence that claims 1–7 would have been obvious over the prior art cited in the Petition.

In Summary:

Claims	**35 U.S.C. §**	**Reference(s)/Basis**	**Claims Shown Unpatentable**	**Claims Not Shown Unpatentable**
1,2,4,6, 7	§ 103(a)	Belanoff '848		1, 2, 4, 6, 7
1,2,4,6, 7	§ 103(a)	Belanoff 2002, Sitruk-Ware, Chu and Belanoff		1, 2, 4, 6, 7
3	§ 103(a)	Belanoff 2002, Sitruk-Ware, Chu and Belanoff, Belanoff '953		3
5	§ 103(a)	Belanoff 2002, Sitruk-Ware, Chu		5

		and Belanoff, Murphy		
3	§ 103(a)	Belanoff ’848, Belanoff ’953		3
5	§ 103(a)	Belanoff ’848, Murphy		5
Overall Outcome				1, 2, 3, 4, 5, 6, 7

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner has not proven by a preponderance of the evidence that claims 1–7 are unpatentable; and

FURTHER ORDERED that, because this is a Final Written Decision, 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.

PETITIONER:

Kenneth Goldman
Christopher L. May
Leonard A. Gail
MASSEY & GAIL LLP
kgoldman@masseygail.com
cmay@masseygail.com
lgail@masseygail.com

PATENT OWNER:

Robert Steinberg
David P. Frazier
Michelle L. Ernst
LATHAM & WATKINS LLP
bob.steinberg@lw.com
david.frazier@lw.com
michelle.ernst@lw.com