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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CSL BEHRING LLC, CSL BEHRING GMBH, and
CSL BEHRING RECOMBINANT FACILITY AG,
Petitioners,

v.

BIOVERATIV THERAPEUTICS INC.,
Patent Owner.

IPR2018-01313
Patent 9,623,091 B2

Before GEORGIANNA W. BRADEN, WESLEY B. DERRICK, and MICHELLE N. ANKENBRAND, *Administrative Patent Judges*.

DERRICK, *Administrative Patent Judge*.

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

I. INTRODUCTION

CSL Behring LLC, CSL Behring GmbH, and CSL Behring Recombinant Facility AG (collectively, "Petitioners")[1] request an *inter partes* review of claims 1–28 of U.S. Patent 9,623,091 B2 (Ex. 1001, "the '091 patent"). Paper 1 ("Pet."). Bioverativ Therapeutics Inc. ("Patent Owner") filed a Preliminary Response. Paper 9 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b); 37 C.F.R. § 42.4(a). We may not institute an *inter partes* review "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). Applying that standard, for the reasons set forth below, we decline to institute an *inter partes* review because Petitioners have not shown a reasonable likelihood that they would prevail in establishing the unpatentability of any challenged claim.

II. BACKGROUND

A. Related Proceedings

Petitioners have filed a second petition for *inter partes* review of the '091 patent, IPR2018-01345. The parties identify additional proceedings involving the '091 patent—*In the matter of Certain Recombinant Factor IX Prods.*, Inv. No. 337-TA-1066 (terminated) ("ITC investigation") and *Bioverativ Inc. v. CSL Behring LLC*, CA No. 17-914-GMS (D. Del.)

[1] Petitioners have updated the identified real-parties-in-interest in providing notice that "the real-parties in interest in this proceeding are: CSL Behring LLC, CSL Behring GmbH, CSL Behring Lengnau AG (successor in interest to CSL Behring Recombinant Facility AG), CSL Limited, and CSL Behring Beteilgungs- und Verwaltungs GmbH & Co. KG." Paper 5, 2.

(pending) ("district court litigation"). Pet. 6; Paper 7 (Patent Owner's Mandatory Notices).

B. The '091 Patent (Ex. 1001)

The '091 patent is directed to methods of administering Factor IX using chimeric polypeptides comprising Factor IX and an FcRn binding partner in order to treat hemophilia B in a human subject.[2] Ex. 1001, 2:34–35, 79:25–35, Abstract. The '091 patent issued from application No. 15/043,455, filed February 12, 2016, a continuation application of application No. 13/809,276, which is the U.S. National Stage of International Application PCT/US2011/043569, filed July 11, 2011, which claims the benefit of priority of earlier-filed provisional applications: 61/363,064, filed July 9, 2010 (Ex. 1008); 61/424,555, filed December 17, 2010 (Ex. 1012); 61/430,819, filed January 7, 2011 (Ex. 1011); 61/438,572, filed February 1, 2011 (Ex. 1010); 61/442,079, filed on February 11, 2011 (Ex. 1009); and 61/470,951, filed April 1, 2011 (Ex. 1013). Ex. 1001 [21], [60], [63], 1:7–20.

C. Illustrative Claim

Claim 1, the sole independent claim, is reproduced below:

> 1. A method of treating hemophilia B in a human subject in need thereof comprising intravenously administering to the subject multiple doses of about 50 IU/kg to about 100 IU/kg of a chimeric factor IX ("FIX") polypeptide comprising FIX and an FcRn binding partner ("FcRn BP") at a dosing interval of about 10 days to about 14 days between two doses, wherein the FcRn BP comprises Fc or albumin, wherein the administration maintains the plasma FIX activity of the subject above 1 IU/dL

[2] Factor IX is a serine protease required for normal *in vivo* blood coagulation, Ex. 1001, 1:52–54, and FcRn is the neonatal Fc receptor, Ex. 1042, 2057.

between the dosing interval, and wherein the administration treats the human subject by reducing the frequency of spontaneous bleeding.

Ex. 1001, 79:25–35.

D. The Asserted Grounds of Unpatentability

Petitioners contend that the challenged claims are unpatentable under 35 U.S.C. § 103 as follows:

Ground	Claims	References[3]
I	1–17, 20, 22, 24, 28	Peters 2010[4] in view of Shapiro[5]
II	1–16, 18, 19, 21, 23–27	Metzner[6] and/or the '755 Publication,[7] in view of Shapiro and Carlsson[8]

Petitioners support the Petition with the testimony of Claude Negrier, M.D., Ph.D. (Ex. 1002).

[3] Petitioners also explicitly relies on the knowledge of a person of skill in the art for each ground.
[4] Peters et al., *Prolonged activity of factor IX as a monomeric Fc fusion protein*, BLOOD 115(10):2057–2064 (Mar. 11, 2010) (Ex. 1042).
[5] Shapiro et al., *The safety and efficacy of recombinant human blood coagulation factor IX in previously untreated patients with severe or moderately severe hemophilia B*, BLOOD 105(2):518–25 (Jan. 15, 2005) (Ex. 1049).
[6] Metzner et al., *Genetic fusion to albumin improves the pharmacokinetic properties of factor IX*, THROMBOSIS & HAEMOSTASIS 102(4):634–44 (Oct. 2009) (Ex. 1036).
[7] Metzner et al., US 2008/0260755 A1, published October 23, 2008 (Ex. 1007).
[8] Carlsson et al., *Multidose pharmacokinetics of factor IX: implications for dosing in prophylaxis*, HAEMOPHILIA 4(2):83–88 (Mar. 1998) (Ex. 1025).

The parties also discuss the Peters Declaration[9] (Ex. 1016) submitted during the prosecution leading to the issuance of the '091 patent. Pet. 18–22; Prelim. Resp. 12–14.

III. ANALYSIS

A. Level of Skill in the Art

Petitioners, relying on the hypothetical person of ordinary skill in the art being a team of individuals, contend that the team would include

> an M.D. with experience treating hemophilia patients and/or researching hemophilia treatments; an M.D., Pharm.D., and/or Ph.D. in pharmacology or a related field with experience in pharmacokinetics and pharmacodynamics; and a Ph.D. in molecular biology or a related field with knowledge of fusion protein therapeutics and/or protein therapeutics for treating hemophilia.

Pet. 26 (citing Ex. 1002 ¶ 96).

Patent Owner agrees that the skilled artisan would be part of such a team. Prelim. Resp. 14.

On this record, we adopt Petitioners' uncontested definition of the level of ordinary skill. We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that "specific findings on the level of skill in the art . . . [are not required] 'where the prior art itself reflects an appropriate level and a need for testimony is not shown'" (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985))).

[9] Declaration under 37 C.F.R. § 1.132 of Robert T. Peters, dated January 30, 2017.

B. Claim Construction

For petitions requesting an *inter partes* review filed before November 13, 2018, the Board interprets claim terms in an unexpired patent according to their broadest reasonable construction in light of the specification of the patent in which they occur. 37 C.F.R. § 42.100(b) (2016).[10] Under that standard, we interpret claim terms using "the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). Only those terms that are in controversy need to be construed and only to the extent necessary to resolve the controversy. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017); *see also U.S. Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997) (holding claim construction is not necessary when it is not "directed to, or has been shown reasonably to affect, the determination of obviousness").

Petitioners note that "Petitioners and Patent Owner agreed to a set of constructions" in the ITC investigation, but that "none . . . [are] critical here." Pet. 27; Ex. 1029.

Patent Owner contends that Petitioners' arguments in this proceeding do not turn on any disputed claim construction issue, but notes that the

[10] 77 Fed. Reg. 48,727 (Aug. 14, 2012) (codified at 37 C.F.R. § 42.100(b)), as amended at 81 Fed. Reg. 18,766 (Apr. 1, 2016); *see also* 83 Fed. Reg. 51,340 (Oct. 11, 2018) (to be codified at 37 C.F.R. pt. 42) (changing the standard for interpreting claims in petitions requesting an *inter partes* review filed on or after November 13, 2018).

parties do "dispute whether 'comprising/comprises' requires construction" in the district court litigation. Prelim. Resp. 14–15 n.2 (citing Ex. 2033).

We determine that no claim term requires express construction for the purpose of determining whether to institute review.

C. Overview of Asserted Prior Art

1. Peters 2010 (Ex. 1042)

Peters 2010 is titled "Prolonged activity of factor IX as a monomeric Fc fusion protein" and discloses a recombinant fusion protein (rFIXFc) containing a single, functional factor IX (FIX) molecule attached to the Fc region of immunoglobulin G. Ex. 1042, 2057. Peters 2010 teaches that recombinant FIX (rFIX) used in prophylactic treatment of patients with hemophilia B typically requires 2 to 3 injections per week due to the relatively short half-lives of these products and that the rFIXFc fusion protein "was developed to address the unmet medical need for a long-acting FIX product." *Id.* Peters 2010 explains that "[t]he presence of the Fc domain enables the fusion protein to bind to the neonatal Fc receptor (FcRn) . . . [which] protect[s] the Fc-containing molecules from catabolism." *Id.* Peters 2010 discloses comparative testing of rFIXFc and rFIX in a number of different animals. *Id.* at 2058–62.

The prior art status of Peters 2010, as discussed below, is disputed.

2. Shapiro (Ex. 1049)

Shapiro is titled "The safety and efficacy of recombinant human blood coagulation factor IX in previously untreated patients with severe or moderately severe hemophilia B" and discloses the results of a clinical study testing the efficacy and safety of rFIX in treating hemophilia B. Ex. 1049, 518–519. The testing study included patients who received rFIX for

prophylaxis, some receiving routine infusions two or more times per week, and others receiving an infusion once a week. *Id.* at 521.

3. Metzner (Ex. 1036)

Metzner is titled "Genetic fusion to albumin improves the pharmacokinetic properties of factor IX" and discloses various fusions of FIX with albumin via cleavable linkers expressed by encoding genes in mammalian cells. Ex. 1036, 634. Pharmacokinetic properties of FIX albumin fusion proteins (rIX-FPs) were tested in rats, rabbits, and mice, and compared to the plasma-derived FIX and rFIX controls. *Id.* at 634, 636–43. The results are reported as "suggest[ing] that rIX-FPs with a cleavable linker between FIX and albumin are a promising concept that may support the use of the albumin fusion technology to extend the half-life of FIX." *Id.* at 634.

4. The '755 Publication (Ex. 1007)

The '755 Publication is titled "Proteolytically Cleavable Fusion Proteins with High Molar Specific Activity" and discloses the technique of preparing "therapeutic fusion proteins in which a coagulation factor is fused to a half-life enhancing polypeptide, . . . in which both are connected by a linker peptide that is proteolytically cleavable." Ex. 1007, Abstract. Human FIX and albumin are, respectively, disclosed as a suitable coagulation factor and half-life enhancing polypeptide. *Id.* ¶¶ 42–43, 48–58. The '755 Publication discloses testing of various FIX and albumin fusions, including determining relative clotting activity in an assay and *in vivo* half-lives in rats and rabbits. *Id.* ¶¶ 114–119, Tables 5 & 6; *see also id.* ¶¶ 110–111.

5. Carlsson (Ex. 1025)

Carlsson is titled "Multidose pharmacokinetics of factor IX: implications for dosing in prophylaxis" and discloses use of single-dose

pharmacokinetic data for FIX to predict multidose pharmacokinetics with a particular purpose to obtain dosages and dosing intervals to maintain FIX activity at or above 1 U/dL (1% of normal activity). Ex. 1025, 83, 86; *see also id.* at 87–88. Carlsson discloses that "[t]he 1% level [1 IU/dL] is . . . adequate to prevent development of haemophilic arthropathy in most cases." *Id.* at 87. Carlsson also discloses dosing patients every two or three days to be suitable to maintain this threshold level, but that once weekly dosing, i.e., with patient 8, would not be suitable. *Id.*, Table 3.

D. Alleged Unpatentability over Peters 2010 in view of Shapiro

Petitioners assert that claims 1–17, 20, 22, 24, and 28 are unpatentable because the subject matter of those claims would have been obvious over Peters 2010 and Shapiro. Pet. 27–44. Patent Owner disagrees, arguing, *inter alia*, that Petitioners fail to establish Peters 2010 as prior art. Prelim. Resp. 15–28.

Petitioners contend that Peters 2010 is prior art. First, Petitioners maintain that it is the work of another and, as such, cannot be removed as 35 U.S.C. § 102(a) prior art by a § 1.132 declaration as was done during the prosecution leading to the issuance of the '091 patent. Pet. 18–22. Second, Petitioners maintain that the '091 patent is not entitled to the benefit of priority of any provisional application filed less than one year after the publication of Peters 2010 and, as such, Peters 2010 is 35 U.S.C. § 102(b) prior art. *Id.* at 22–26.

Under 35 U.S.C. § 311(b), in an *inter partes* review, a petitioner may only challenge the claims of a patent based on "prior art consisting of patents or printed publications," and the petitioner has the initial burden of producing evidence to support a conclusion of unpatentability under § 102 or

§ 103, including that an asserted reference is prior art to the challenged claims under a relevant subsection of § 102. Conclusory statements or reasoning lacking corroboration or evidentiary support are not sufficient. *Cf. In re Magnum Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016) (explaining that the ultimate legal conclusion of obviousness must be supported by more than mere conclusory statements).

1. Sufficiency of the Peters Declaration

During prosecution, Patent Owner overcame prior art rejections over Peters 2010 in combination with other references by establishing that Peters 2010 was not the work of another and thus was not § 103(a) prior art. Pet. 18–19 (citing Ex. 1015, 5; Ex. 1016 ¶ 3; Ex. 1017, 3). In particular, Patent Owner relied on the Peters Declaration (Ex. 1016), which, as Petitioners set forth, "avers that '[Peters' coauthors] made no inventive contribution to the conception of the claims,' 'carried out experiments under [Peters'] direction and control, and were properly not named as inventors of the present application.'" *Id.* (quoting Ex. 1016 ¶ 3).

Petitioners, nonetheless, contend that "[t]he Examiner's reliance on the Peters Declaration to allow the claims was erroneous." *Id.* at 19. First, Petitioners contend that the relevant inquiry is not whether the co-authors made an inventive contribution and were properly not named as inventors, but rather "whether the Peters 2010 disclosure was attributable only to inventors of the '091 patent." *Id.* at 19–20 (citing *In re Katz*, 687 F.2d 450, 455 (CCPA 1982)). Second, Petitioners contend that the averments that coauthors were carrying out experiments under Peters' direction and control are insufficient, particularly in light of the authorship section of Peters 2010, which indicates that other coauthors designed research, and "paragraphs 4-5

of Peters's declaration[, which] suggest that he took credit for directing and controlling all the work . . . because he was 'project leader.'" *Id.* at 20–21 (citing Ex. 1016 ¶¶ 4–5; Ex. 1042, 2063). Petitioners further contend that "[t]he Peters declaration constitutes nothing more than a bare assertion" and, thus, is insufficient because it lacks corroboration and fails to "explain the inconsistency between the Declaration and the authorship section in the article." *Id.* at 21–22.

As to what inquiry is relevant, in *Katz*, the Federal Circuit determined that a reference by an inventor co-authored with non-inventors was not § 102(a) prior art on the basis that the co-authors contribution fails to rise to joint inventorship, and not on the basis that they made no contribution. *Katz*, 687 F.2d at 455–56 ("the board . . . should have accepted that [the co-authors] were acting in the capacity indicated, that is, students working under the direction and supervision of appellant").

Petitioners' reliance on *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 968–69 (Fed. Cir. 2014), likewise is unavailing on this record. In *Allergan*, there was *no evidence* produced showing that the named inventor of the patent "was responsible for directing the production of either article's content, which includes the design, trial, and analysis of results." *Allergan*, 754 F.3d at 969. There was, accordingly, "no supported explanation demonstrating that the . . . references were in fact printed publications authored by [the named inventor] for the purposes of § 102(a)." *Id.* Here, in contrast, the record supports Patent Owner's position that Peters was responsible for the content of Peters 2010. *See* Ex. 1016 ¶ 3 (coauthors "carried out experiments under my direction and control"), ¶ 4 ("I designed and lead [sic] the FIX project, and the experiments performed by the co-

authors listed above were carried out under my direction"), ¶ 5 (explaining experiments were performed elsewhere, "but were performed under my direction"). Further, Petitioners provide neither persuasive argument nor evidence that the level of direction and control for co-authors indicated as designing research is insufficient for the work not to be considered the work of another in the same manner as for the students in *Katz*. *See generally* Pet.

Petitioners contend that the Peters Declaration is no more than a bare assertion because it fails to "explain the inconsistency between the Declaration and the authorship section in the article." Pet. 21–22 (citing *EmeraChem Holdings, LLC v. Volkswagen Grp. of Am. Inc.*, 859 F.3d 1341, 1345 (Fed. Cir. 2017)). Petitioners have failed, however, to establish that there is an inconsistency, as discussed above, and to sufficiently explain how the more informative averments in the Peters Declaration are similarly deficient as the naked assertion found lacking in *EmeraChem Holdings*.

Having considered the arguments and evidence, we are not persuaded that Petitioners have shown sufficiently for purposes of institution that Peters 2010 is, in fact, the work of another and not properly removed as prior art by the Peters Declaration submitted during prosecution leading to the issuance of the '091 Patent.

2. Priority Benefit of Provisional Applications

Petitioners contend that the '091 Patent is not entitled to benefit of priority of the provisional applications, including the first-filed provisional application no. 61/363,064 ("the '064 provisional" (Ex. 1008)).[11] Pet. 22,

[11] Petitioners address the provisional applications as a group, citing only the '064 provisional in particular (Pet. 24), and Petitioners' expert similarly relies on the '064 provisional in addressing what is disclosed in the provisional applications (Ex. 1002 ¶ 64).

24. Absent the benefit of priority of the provisional applications filed within a year of its publication, Peters 2010 would qualify as a § 102(b) prior art reference. Pet. 4 n.4; Prelim. Resp. 16 n.3. Petitioners contend that the '091 Patent is not entitled to the priority benefit of the provisional applications because they "do not satisfy the written description and enablement requirements for the '091 patent claims." Pet. 22 (citing Ex. 1002 ¶¶ 63–67).

As to written description, Petitioners contend that the recited genus of "'chimeric factor IX ("FIX") polypeptide comprising FIX and an FcRn binding partner ("FcRn BP") . . . wherein the FcRn BP comprises Fc or albumin' . . . includes an incalculable number of proteins with a wide range of possible structural variations." *Id.* at 23 (quoting Ex. 1001, claim 1). Petitioners highlight that "each of the FIX and Fc or albumin polypeptides can be human or animal, including any functional variants or fragments" (*id.* (citing Ex. 1001, 7:39–12:4; Ex. 1002 ¶¶ 55, 65)), that "each chimeric FX polypeptide can contain any number of domains" (*id.* (citing Ex. 1001, 7:39–63; Ex. 1002 ¶¶ 55, 65)), and that "the domains may be joined together in any order, without a linker, or with a linker of any length and sequence" (*id.* (citing Ex. 1001, 7:45–50, 9:61–66; Ex. 1002 ¶¶ 55, 65)).

Petitioners contend that the provisional applications do not provide sufficient written description because they "specifically describe and provide data for only ***one*** molecule: rFIXFc." *Id.* at 24 (citing Ex. 1001, 23:19–40; Ex. 1008 ¶¶ 100–102; Ex. 1002 ¶ 64). Petitioners further contend that a person of skill in the art "would know that *in vivo* data from one molecule could not be extrapolated across the broad recited genus to determine which proteins could be administered to treat hemophilia B" and that, thus, the

provisional applications "fail to provide a representative number of species falling within the recited genus, or describe common structural features such that one of skill in the art could visualize or recognize the members of the genus." *Id.* (citing Ex. 1002 ¶¶ 65–67); *see also id.* at 23–24 (citing *Ariad Pharms. Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010 (en banc))).

As to enablement, Petitioners contend that the claims are not enabled, highlighting that the provisional applications "provide data and working examples for only ***one*** protein." Pet. 24–25. Petitioners maintain that reliance on one protein is "inconsistent with Patent Owner's arguments during prosecution that the nature of the alleged invention—dosing regimen design—is 'unpredictable' and requires 'more than simply conducting "routine experimentation."'" *Id.* at 25 (quoting Ex. 1015, 10–11). Petitioners rely on Dr. Negrier's testimony that "*in vivo* data cannot be extrapolated from *one molecule* across a broad and diverse protein genus" (emphasis added) and the differences in pharmacokinetic parameters and activity that Dr. Negrier identifies between different molecules falling within the recited genus. *Id.* at 25 (citing Ex. 1002 ¶¶ 65–66). Specifically, Dr. Negrier notes differences between rFIXFc heterodimer and rFIXFc homodimer and between FIX albumin fusion proteins with a cleavable linker and those with a non-cleavable linker. Ex. 1002 ¶ 65 (citing Ex. 1003, 56:5–22, Figs. 9–10; Ex. 1036, 635–637, 639–640, 642, Table 1).

Patent Owner responds that "the Petition's priority claim analysis rests on the facially erroneous assertion that there is only a single example of a chimeric FIX polypeptide described in the specifications." Prelim. Resp. 18–19 (citing Pet. 24). Patent Owner argues that "the Petition fails to

demonstrate that the ’091 Patent is not entitled to claim priority to the Provisional Applications” because it is “based on an incomplete reading of the Priority Applications” and, thus, ignores disclosure relevant to the adequacy of the written description. *Id.* at 20–21. Patent Owner contends that the provisional applications “provide dozens of functional variants of human FIX sequences by citing to specific sections of PCT application[s] . . . expressly incorporated by reference into the specification,” and cites to paragraph 46 of the ’064 provisional, in particular, as incorporating relevant disclosure from the enumerated PCT applications. *Id.* at 19 (citing Ex. 2009; Ex. 2010; Ex. 2015; Ex. 2016; Ex. 2018; Ex. 2107; Ex. 2019). Patent Owner further contends that the ’064 provisional “also provides dozens of functional variant human Fc sequences, both directly within the disclosure and by citing PCT application[s]” incorporated by reference. *Id.* at 20 (citing Ex. 1008 ¶¶ 50, 54; Ex. 2011, Ex. 2012). As for variant human albumin sequences that can be incorporated into chimeric FIX proteins, Patent Owner similarly relies on the relevant disclosure incorporated from “U.S. Patent Nos. 7,592, 010 (Ex. 2006) and 6,686,179 (Ex. 2005), as well as Schulte (Ex. 1048).” *Id.* (citing Ex. 1008 ¶ 51).

In addressing Petitioners’ argument as to enablement, Patent Owner also addresses the cited differences between rFIXFc heterodimer and rFIXFc homodimer and between FIX albumin fusion proteins with a cleavable linker and those with a non-cleavable linker that Dr. Negrier identifies. *Id.* at 21–22. In addressing those differences, Patent Owner relies, in particular, on the disclosure of the ’064 provisional, including that incorporated by reference. *Id.* (citing Ex. 1008 ¶¶ 50, 51, 56; Ex. 1048; Ex. 2011; Ex. 2012).

As Patent Owner explains, the material incorporated by reference constitutes part of the disclosure just as if it were explicitly contained therein. *Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1329 (Fed. Cir. 2001). Thus, by failing to consider material incorporated by reference in the '064 provisional (and other provisional applications), Petitioners and Dr. Negrier have failed to consider the full scope of the disclosure for purposes of written description and enablement. We, therefore, give Dr. Negrier's opinion regarding priority little weight. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) ("Lack of factual support for expert opinion going to factual determinations" is sufficient to "render the testimony of little probative value in a validity determination.").

Having considered the arguments and evidence, we determine that, under the circumstances of this case and without reaching whether the disclosure of the '064 provisional (and other provisional applications) satisfy § 112 ¶ 1, we are not persuaded that Petitioners have shown sufficiently that the challenged claims are not entitled to the benefit of the filing date of the '064 provisional (and other provisional applications). As a result, we are not persuaded that Petitioners have shown sufficiently that Peters is § 102(b) prior art.

3. Alleged Unpatentability of Claims

Petitioners contend that claims 1–17, 20, 22, 24, and 28 are unpatentable as obvious over the combination of Peters 2010 and Shapiro, identified as prior art by Petitioners. Pet. 27–44. The unavailability of Peters 2010 undermines Petitioners' obviousness ground, which relies on Peters 2010 alone as teaching or suggesting the "chimeric factor IX ('FIX')

polypeptide comprising FIX and an FcRn binding partner ('FcRn BP') . . . wherein the FcRn BP comprises Fc or albumin." *Id.*

Petitioners, thus, fail to bear the burden required to support institution of *inter partes* review on the ground of Peters 2010 in view of Shapiro. Particularly, Petitioners fail to make a sufficient showing that Peters 2010 is prior art. Accordingly, we are not persuaded that Petitioners establish a reasonable likelihood of prevailing in showing that the subject matter of any of claims 1–17, 20, 22, 24, and 28 is unpatentable over Peters 2010 and Shapiro.

E. Alleged Unpatentability over Metzner and/or the '755 Publication in view of Shapiro and Carlsson

Petitioners assert that claims 1–16, 18, 19, 21, and 23–27 are unpatentable because the subject matter of those claims would have been obvious over Metzner, the '755 publication, Shapiro, and Carlsson. Pet. 44–63. Petitioners rely on Metzner and the '755 publication as disclosing chimeric FIX polypeptides (rIX-FP) that are disclosed as having activity and extended half-lives in animal testing. *Id.* at 44 (citing Ex. 1002 ¶¶ 87–91, 94–95; Ex. 1007 ¶ 119; Ex. 1036, 641). Petitioners rely on Shapiro and Carlsson for their teachings as to FIX prophylaxis regimens. *Id.* at 44–45 (citing Ex. 1002 ¶¶ 68–74; Ex. 1025, 83, 87; Ex. 1049, 521).

Petitioners maintain that a person of ordinary skill in the art would have been motivated to combine the teachings of extended half-life rIX-FP from the '755 publication and Metzner with the teachings about established FIX prophylaxis regimens from Shapiro and Carlsson to obtain the claimed dosing regimens. *Id.* at 53 (citing Ex. 1002 ¶¶ 187–194); *see also id.* at 54–55 (discussing how all of the references relate to prophylactic treatment

of hemophilia B and how both Metzner and the ’755 publication indicate the desirability of increasing the half-life of the Factor IX product to increase dosing intervals).

Petitioners contend that a person of ordinary skill in the art “would have been motivated to administer rIXFP at doses similar to rFIX but at longer intervals of about 10-14 days” by “the animal data disclosed in Metzner and the ’755 publication showing rIX-FP with a 2- to 4-fold half-life extension compared to rFIX,” and that they would have had a reasonable expectation of success in reducing the frequency of spontaneous bleeding by doing so. *Id.* at 45 (citing Ex. 1002 ¶¶ 187–230); *see also id.* at 55 (citing Ex. 1002 ¶¶ 193–194).

More specifically, Petitioners contend that the prior art teaches or suggests all elements of claim 1, and set forth the basis for this contention as follows.

“Method of treating hemophilia B in a human subject in need thereof”

Petitioners maintain that Carlsson, Shapiro, Metzner, and the ’755 publication each teach methods of treating hemophilia B patients. *Id.* at 45–46 (citing Ex. 1002 ¶¶ 163–165; Ex. 1007 ¶ 43; Ex. 1025, 83, 84, 87; Ex. 1036, 643; Ex. 1049, 518, 519, 521, 522). Petitioners further contend that the ’755 publication and Metzner teach treating hemophilia B with rIX-FP. *Id.* at 46–47 (citing Ex. 1002 ¶¶ 163–164; Ex. 1007 ¶¶ 114–122, claims 26–28; Ex. 1036, 643). The cited paragraphs of the ’755 Publication disclose testing of various FIX and albumin fusions, including determining relative clotting activity in an assay and *in vivo* half-lives in rats and rabbits, and claims 26–28 are directed to administering an effective amount of a fusion protein comprising a coagulation factor, a half-life enhancing

polypeptide, and a peptide linker to a patient "in need thereof" (claim 26), wherein "the patient suffers from a blood coagulation disorder" (claim 27), and wherein "the blood coagulation disorder is hemophilia B" (claim 28).

"intraveneously administering to the subject multiple doses of about 50 IU/kg to about 100 IU/kg"

Petitioners maintain that "Shapiro, the '755 publication, Metzner, and Carlsson disclose intravenous administration of FIX replacement therapy." *Id.* at 47 (citing Ex. 1002 ¶ 166; Ex. 1007 ¶¶ 47, 118; Ex. 1025, 87; Ex. 1036, 634, 637, 638; Ex. 1049, 519). Petitioners rely on Shapiro as "disclos[ing] effective prophylaxis with rFIX injections of 72.5±37.1 (35.4-109.6) IU/kg two times a week or more, and once weekly injections of 75.9±17.9 (58-93.8) IU/kg," and also as "disclos[ing] a [broader] range of prophylaxis doses between 9.7 and 230.4 IU/kg." *Id.* (citing Ex. 1049, 518, 519, 521, 523, Table 2). Petitioners contend that "Shapiro's once weekly dose of 75.9±17.9 IU/kg is very similar to the claimed range of about 50-100 IU/kg, [and] render[s] the claimed range obvious." *Id.* at 48. Petitioners further contend that "[i]t would have been obvious for a [person of ordinary skill in the art] to administer rIX-FP, which had established good *in vivo* clotting activity, at the same doses demonstrated to be effective by Shapiro," particularly absent any indication in the '091 patent of "criticality to the recited dosage range, or that it yields unexpected results." *Id.* at 48 (citing Ex. 1002 ¶¶ 169, 208; Ex. 1014, 6). Petitioners further rely on Metzner as "support[ing] this conclusion, [in] stating that '[a]pplying equal doses of FIX clotting activity it was demonstrated that within the inherent variability of this method rFIX and rIX-FP/cll(HEK) equally well reduced the bleeding time in a dose-dependent manner.'" *Id.* (citing Ex. 1036, 643).

Petitioners further contend that a person of ordinary skill in the art would "start with an established FIX dose in IU/kg and identify the specific dose for an individual patient through routine optimization" and then conclude that "it would have been obvious based on the '755 publication and/or Metzner and Shapiro for a [person of ordinary skill in the art] to treat hemophilia B using about 50-100 IU/kg doses of rIX-FP as claimed." *Id.* at 48–49 (citing Ex. 1002 ¶ 169; Ex. 1049, 523).

"a chimeric factor IX ('FIX') polypeptide comprising FIX and an FcRN binding partner ('FcRn BP') . . . wherein the FcRn BP comprises Fc or albumin"

Petitioners maintain that "[t]he '755 publication teaches a . . . rIX-FP containing human FIX joined to human albumin via a proteolytically cleavable linker, such that FIX is released from albumin when it is activated during the coagulation cascade." *Id.* at 49 (citing Ex. 1002 ¶¶ 170–171; Ex. 1007 ¶¶ 3, 7–10, 29, 30, 84, 85, 112–113, 116, 117). Petitioners further rely on the '755 publication as "disclos[ing] specific FIX, albumin, and linker sequences, and processes to make rIX-FP." *Id.* (citing Ex. 1002 ¶ 171; Ex. 1007, SEQ ID NOs:1–114, ¶¶ 95–109, Tables 3a, 3b, 4, 5).

Petitioners maintain that "Metzner likewise teaches the preparation of rIX-FP fusion proteins with human FIX fused to human albumin via a cleavable linker derived from the FIX activation sequence." *Id.* (citing Ex. 1002 ¶ 170; Ex. 1036, 634–636, 638, 642, Figure 1, Table 1).

Petitioners maintain that both the '755 publication and Metzner "disclose animal studies establishing the clotting activity and extend half-life *in vivo* of rIX-FP." *Id.* at 49–50 (citing Ex. 1002 ¶¶ 170–171; Ex. 1007 ¶¶ 114–122, Tables 5–7; Ex. 1036, 640–641, Table 2, Figure 5). The cited portions of the '755 publication report *in vivo* half-life data from

experiments in rats and rabbits. Ex. 1007 ¶¶ 114–122, Tables 6–7. The cited portions of Metzner report *in vivo* half-life data from FIX-deficient mice, as well as from rats and rabbits. Ex. 1036, 640–641, Table 2, Figure 5.

"*at a dosing interval of about 10 days to about 14 days between two doses*"

Petitioners contend that "[t]he '755 publication and/or Metzner in light of Shapiro and the knowledge of a [person of ordinary skill in the art] suggest administering rIX-FP at a dosing interval of about 10–14 days." *Id.* at 50. Petitioners rely on Shapiro as teaching effective prophylaxis with once weekly doses of 75.9±17.9 IU/kg rFIX and on Metzner and the '755 publication as "disclos[ing] animal data showing that rIX-FP is efficacious and has a half-life up to 4-5 times longer than rFIX in animals." *Id.* (citing Ex. 1002 ¶¶ 172–174; Ex. 1007 ¶¶ 114–119, Table 5, Table 6; Ex. 1036, 634, 637, 640, 641, Table 2, Figure 5; Ex. 1049, 521). As Dr. Negrier testifies, as to *in vivo* half-life, "there was 'a statistically significant 3.4- to 4.7-fold increase in rats and a significant 3.2- to 4.0-fold increase in rabbits for rIX-FP/cl1 . . . compared to rFIX,' as well as a 1.2-fold increase in FIX-deficient mice." Ex. 1002 ¶ 173 (citing Ex. 1036, 637, 640–642, Table 2).

Petitioners also rely on Metzner and the '755 publication further "indicat[ing] that rIX-FP 'should facilitate a relevant reduction of dosing frequency in haemophilia B patients.'" Pet. 50 (citing Ex. 1002 ¶¶ 173–175; Ex. 1007 ¶¶ 4, 43; Ex. 1036, 643).

Petitioners also rely on Dr. Negrier's explanation that "a FIX therapeutic exhibiting longer half-life in animal models would be expected to do so in humans as well" and on starting with an established FIX dose and identifying the most appropriate dosing interval for an individual through

routine optimization based on the individual's response. *Id.* at 51 (citing Ex. 1002 ¶ 176; Ex. 1049, 523).

Petitioners contend, therefore, that it would have been obvious for a person of ordinary skill in the art "to treat hemophilia B by administering rIX-FP at similar doses but a longer interval than rFIX, *i.e.*, once every 10-14 days as claimed." *Id.* (citing Ex. 1002 ¶ 178).

Petitioners also cite *Biomarin Pharm., Inc. v. Genzyme Therapeutic Prods., LP*, Case IPR2013-00537, Paper 79 at 13–21 (PTAB Feb. 23, 2015). *Id.* Although not explaining its particular relevance for this ground, Petitioners rely on *Biomarin* in the asserted ground over Peters 2010 in view of Shapiro as supporting the argument that selecting a dose and dosing schedule would have been nothing more than routine optimization. Pet. 39–40.

"wherein the administration maintains the plasma FIX activity of the subject above 1 IU/dL between the dosing interval"

Petitioners rely on Carlsson's disclosure that "[p]rophylactic treatment . . . aims to prevent bleeding and maintain normal joint status" and that a "strategy to achieve this is to 'keep the plasma level of factor . . . IX procoagulant activity . . . at or above 1 U dL^{-1} at all times,'" and that this was "'adequate to prevent development of haemophilic arthropathy in most cases.'" *Id.* at 51–52 (citing Ex. 1002 ¶ 179; Ex. 1025 83, 84, 86, 87).

Petitioners then maintain that "effectively managing spontaneous bleeding generally entails maintaining FIX activity levels above 1IU/dL between doses" and that a person of ordinary skill in the art "would therefore understand that Shapiro's once weekly regimen of 75.9±17.9 IU/kg rFIX successfully maintained FIX activity levels above 1IU/dL." *Id.* at 52 (citing Ex. 1002 ¶¶ 179–180).

Petitioners contend that "it would have been obvious that patients such as those successfully treated on Shapiro's once weekly regimen would successfully maintain FIX activity levels above 1 IU/dL when administered about 50-100 IU/kg of rIX-FP about every 10–14 days." *Id.* (citing Ex. 1002 ¶ 181).

"wherein the administration treats the human subject by reducing the frequency of spontaneous bleeding"

Petitioners rely on Carlsson for teaching that the aim of prophylactic treatment is "to prevent bleedings" (citing Ex. 1002 ¶ 183; Ex. 1025, 83, 87) and on Shapiro as "disclos[ing] that prophylaxis doses between 50-100 IU/kg rFIX once weekly reduced spontaneous bleeding" (citing Ex. 1002 182; Ex. 1049, 518, 519, 521, 522–524), and on both the '755 publication and Metzner as "indicat[ing] that rIX-FP is effective and can be administered at a longer dosing interval than rFIX" (citing Ex. 1002 ¶¶ 173–176; Ex. 1007 ¶¶ 114–119, Table 5, Table 6; Ex. 1036, 634, 637, 640–641, 643, Figure 5, Table 2). *Id.* at 52–53.

Petitioners contend that "it would have been obvious that patients such as those successfully treated on Shapiro's once weekly regimen of 75.9±17.9 IU/kg rFIX would experience decreased frequency of spontaneous bleeding when administered about 50-100 IU/kg rIX-FP every 10-14 days." *Id.* at 53 (citing Ex. 1002 ¶¶ 184–186).

Petitioners contend that a person of ordinary skill in the art "would have had a reasonable expectation of success in maintaining plasma FIX activity above 1 IU/dL between doses and reducing the frequency of spontaneous bleeding, thus treating hemophilia B, by administering 50-100 IU/kg rIX-FP every 10-14 days." *Id.* at 55 (Ex. 1002 ¶¶ 195–202). Petitioners ground their contention on a person of ordinary skill in the art

knowing, from Shapiro, that "once weekly doses between 50-100 IU/kg rFIX reduced the frequency of spontaneous bleeding" (citing Ex. 1002, ¶¶ 197–199; Ex. 1049, 521) and knowing, from Carlsson, that "effective prophylactic treatment generally maintains FIX activity above 1 U/dL to reduce the frequency of spontaneous bleeding" (citing Ex. 1002 ¶ 196; Ex. 1025, 83, 87). Pet. 55–56. Petitioners, in effect, maintain that a person of ordinary skill in the art also would have recognized from these teachings that the level of FIX activity was maintained at or above 1 IU/dL with once weekly doses between 50–100 IU/kg.

Petitioners then rely on rFIX-FP being comparably effective and having a longer half-life than rFIX as supporting a reasonable expectation of success. *Id.* at 56 (citing Ex. 1002 ¶¶ 200–202; Ex. 1007, ¶¶ 114–119, Tables 5–6; Ex. 1036, 639–641, Table 2).

Petitioners also maintain that arriving at a 10–14 day interval would have required no more than routine optimization. *Id.* (citing Ex. 1002 ¶¶ 36, 109, 113, 169, 176; Ex. 1014, 6). Petitioners cite *In re Applied Materials, Inc.*, 692 F.3d 1289, 1297–1298 (Fed. Cir. 2012). *Id.*

In response, Patent Owner contends that the asserted ground fails because it is grounded "on the false premise that Shapiro discloses effective weekly dosing of recombinant FIX to maintain a patient's plasma FIX activity levels above 1 IU/dL" and because of the unreliability in the animal model data, particularly inconsistencies in Metzner and the '755 publication. Prelim. Resp. 39–49. As explained below, Petitioners have failed to establish a reasonable likelihood of prevailing on its assertion that any of the claims are unpatentable over the asserted prior art.

On this record, Petitioners fail to establish that once weekly doses in Shapiro maintained FIX activity above 1 IU/dL. First, although Carlsson teaches maintaining a level of FIX activity above 1 IU/dL as a strategy for prophylactic treatment, that only establishes that such a level suffices, not that it is necessary for prophylaxis. Ex. 1025, 83. Thus, even if Shapiro did maintain a prophylactic effect with once weekly dosing, it does not reasonably support that the levels of FIX activity were maintained above 1 IU/dL. Second, as Patent Owner highlights, the art, including Petitioners' work published after Shapiro, "demonstrate[es] that Shapiro did not overturn the prevailing consensus that 2-3 FIX infusions per week are required to maintain 1 IU/dL of FIX activity in a patient's plasma." Prelim. Resp. 39 (citing Ex. 2001 ¶ 42; Ex. 1034, 1; Ex. 1036, 634; Ex. 1048, S6); *see also id.* at 31 (citing Ex. 2001 ¶ 95; Ex. 1036, 634; Ex. 1042, 2057; Ex. 1048, S6). Dr. Negrier does not squarely address these contrary teachings of the art, including that of Petitioners, in reaching its opinion as to Shapiro maintaining FIX activity above 1 IU/dL with once weekly doses. *See* Ex. 1002 ¶¶ 179–185. Accordingly, we give Dr. Negrier's opinion that a person of ordinary skill in the art would have recognized Shapiro as maintaining a level of FIX activity above 1 IU/dL little weight. *See Ashland Oil*, 776 F.2d at 294.

Petitioners similarly fail to squarely address inconsistencies in Metzner and the '755 publication as to half-life data in animal models, and the application of that half-life data to dosing and dosing intervals in human patients. As Patent Owner highlights, the FIX-albumin polypeptides were tested in only mice, rats, and rabbits, and there was no half-life extension observed in mice. Prelim. Resp. 41 (citing Ex. 2001 ¶ 110; Ex. 1036, 641).

Patent Owner further explains that "of the three animal models tested, only the mouse was FIX deficient and represented a true hemophilia B animal model–the rats and rabbits used in these experiments had normal endogenous FIX levels." *Id.* at 41–42 (citing Ex. 2001 ¶ 110; Ex. 1036, 641). Patent Owner's expert, Dr. Pasi, testifies that an ordinarily skilled artisan would have viewed the absence of any half-life extension in FIX deficient mice "as a black mark against the FIX-albumin product." Ex. 2001 ¶ 110; Prelim. Resp. 42. Patent Owner further highlights inconsistent half-life extension results in rats obtained for the same HEK- and CHO-expressed FIX-albumin fusion proteins in different studies.[12] *Id.* (citing Ex. 2001 ¶ 111; Ex. 1036, Table 2; Ex. 1048, S8).

Petitioners' treatment of the FIX-deficient mouse data is limited. Dr. Negrier references the half-life ratio of 1.2 for rIX-FP compared to rFIX in FIX-deficient mice as a 1.2-fold increase, but, in contrast to that for rats and rabbits, does not explain why or how the result in mice is significant. Ex. 1002 ¶ 90. In discussing these results, Dr. Negrier notes that "FIX-deficient animals provide disease state-specific models used to test hemophilia B drugs . . . [and that] [w]hen a drug is able to correct FIX deficiency in animals, it is highly likely to have the same effect in humans." *Id.* ¶ 89 n.16. Nonetheless, Petitioners do not sufficiently explain why one skilled in the art would not have found the half-life data for FIX-deficient mice to undercut an expectation of half-life extension in human patients suffering from hemophilia B.

[12] HEK (human embryonic kidney) and CHO (Chinese hamster ovary) cells are particular cell lines commonly used to express recombinant proteins.

Moreover, on this record, Petitioners fail to establish that the inconsistencies between animal models are not similarly reflective of inconsistencies between the animal models relied on and human patients suffering from hemophilia B, particularly with respect to half-life. Petitioners rely, in particular, on Dr. Negrier's testimony that "skilled artisans would have understood that efficacy and half-life extension in animal models were reasonably predictive of efficacy and half-life extension in humans." Pet. 14 (citing Ex. 1002 ¶¶ 81 n.12, 85 nn.14–15, 89 n.16, 90 n.17, 113, 176). The cited portions of Dr. Negrier's declaration, however, fail to squarely address discrepancies in half-life between animal models, as highlighted above, and are directed in the main to efficacy, not half-life. We, therefore, give Dr. Negrier's opinion regarding the animal models being understood to be reasonably predictive of half-life in humans little weight. *See Ashland Oil*, 776 F.2d at 294.

With these deficiencies in mind, Petitioners' contention that "it would have been obvious . . . to treat hemophilia B by administering rIX-FP at similar doses but a longer interval than rFIX, *i.e.*, once every 10-14 days as claimed" falls short where the cited portion of Dr. Negrier's declaration relies both on "the successful once weekly dosing of rFIX (BeneFIX®) described in Shapiro and . . . the extended half-life . . . of rIX-FP as established by Metzner and/or the '755 publication." Pet. 51 (citing Ex. 1002 ¶ 178).

As to the citation to *Biomarin*, Paper 79 at 13–21, Petitioners fail to sufficiently set forth how the case relates to the particular facts of this ground. *Id.* Moreover, we find the Petition fails to set forth clearly the basis of the challenge where it explicitly relies on the level of activity in Shapiro

with once weekly doses and on the half-life of rIX-FP being increased to meet the claim limitations in citing paragraph 178 of the Negrier declaration, and does not set forth an alternative theory grounded on *Biomarin*. *Id.*

Petitioners' further reliance on Dr. Negrier's testimony that arriving at a 10–14 day interval would have required no more than routine optimization is similarly insufficient on this record. Pet. 56 (citing Ex. 1002 ¶¶ 36, 109, 113, 169, 176; Ex. 1014, 6). Cited paragraphs 109 and 169 relate to dosing, not intervals. Cited paragraph 113 relates to rFIXFc, not rIX-FP. Although Dr. Negrier testifies in paragraphs 36 and 176 that clinicians commonly tailor dose and/or the dosing interval based on patient response and the risk of bleeding, paragraph 176 concludes that "[i]t would have been obvious to a person of ordinary skill in the art that rIX-FP, . . . display[ing] a longer half-life than rFIX . . . would have a similar therapeutic effect . . . but over longer dosing intervals, due to its longer half-life." As such, Petitioners fail to provide sufficient, separate reasoning on this record that is not based on the animal models, found lacking above. Petitioners' citations to Exhibit 1014 and *Applied Materials*, 692 F.3d at 1297–1298, do not salvage Petitioners' conclusory, undeveloped argument, particularly where Petitioners do not identify the purpose for which either is cited.[13] Pet. 56.

As to the dependent claims challenged, we discern nothing that remedies the deficiencies as to the challenge to claim 1, discussed above.

[13] Exhibit 1014 is the November 29, 2016, Final Office Action in which all combinations over which the claims were rejected included Peters 2010 (Ex. 1042), and which was overcome by the Peters declaration (Ex. 1016), which removed Peters 2010 as prior art. Pet. 18–19 n.11. As set forth above, Petitioners fail to establish a reasonable likelihood that Peters 2010 is § 102 prior art.

For example, Petitioners' additional argument for the more specific dosing intervals that claims 6–11 require similarly relies on Shapiro and animal testing data, and further relies on adjusting the dosing interval within the range of 10–14 days, the range contended to have been obvious on the basis of Petitioners' challenge to claim 1. *Id.* at 58–59; Ex. 1002 ¶¶ 210–215.

Accordingly, we are not persuaded that Petitioners establish a reasonable likelihood of prevailing in showing that the subject matter of any of claims 1–16, 18, 19, 21, and 23–27 is unpatentable over Metzner and/or the '755 publication in view of Shapiro and Carlsson.

IV. CONCLUSION

Petitioners have not established a reasonable likelihood of prevailing on its assertion that claims 1–28 are unpatentable.

V. ORDER

For the reasons given, it is:

ORDERED that the Petition is *denied* as to all challenged claims of the '091 patent and no trial is instituted.

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