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Paper No. 11
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD.,
Patent Owner.

Case IPR2018-00156
Patent 9,187,559 B2

Before SUSAN L. C. MITCHELL, TINA E. HULSE, and MICHELLE N. ANKENBRAND, *Administrative Patent Judges*.

ANKENBRAND, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314(a)
Dismissing as Moot Petitioner's Motions for *Pro Hac Vice* Admission
37 C.F.R. § 42.10

I. INTRODUCTION

Sandoz Inc. ("Petitioner") requests an *inter partes* review of claims 1–30 of U.S. Patent No. 9,187,559 B2 ("the '559 patent," Ex. 1001). Paper 1 ("Pet."). AbbVie Biotechnology Ltd. ("Patent Owner") filed a Preliminary Response. Paper 10 ("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, and upon consideration of the information presented in the Petition and the Preliminary Response, we deny the Petition and do not institute an *inter partes* review.[1]

II. BACKGROUND

A. Related Matters

The parties do not identify any litigation, interference proceedings, or reexamination proceedings involving the '559 patent. *See* Pet. 5–7; Paper 5, 1. Petitioner identifies litigation involving two patents that Petitioner contends are related to the '559 patent because all three patents claim priority to the same application. Pet. 5 (identifying *AbbVie Inc. v. Amgen Inc.*, No. 1:16-cv-00666-MSG (D. Del. Aug. 4, 2016)).

Petitioner further identifies several *inter partes* review proceedings in which the Board previously found claims of certain of Patent Owner's

[1] Because we deny the Petition, we dismiss as moot Petitioner's pending motions for Daniel L. Reisner and Abigail Langsam to appear *pro hac vice* in this proceeding (Papers 3 and 7, respectively).

patents unpatentable, but acknowledges that those patents and the '559 patent do not claim priority to any of the same applications. Pet. 5–7. Petitioner explains that it previously filed additional petitions requesting an *inter partes* review of certain other patents assigned to Patent Owner: IPR2017-01823 (challenging U.S. Patent No. 8,802,100), IPR2017-01824 (challenging U.S. Patent No. 9,512,216), IPR2017-01987 (challenging U.S. Patent No. 8,911,737), IPR2017-01988 (challenging U.S. Patent No. 8,974,790), IPR2017-02105 (challenging U.S. Patent No. 9,090,689), IPR2017-02106 (challenging U.S. Patent No. 9,067,992), and IPR2018-00002 (challenging U.S. Patent No. 9,512,216). *Id.* at 7. According to Petitioner some of those patents and the '559 patent claim priority to the same applications. *Id.*

Finally, Patent Owner identifies a number of United States patent applications and patents that claim the benefit of priority to the '559 patent, or to which the '559 patent claims the benefit of priority. Paper 4, 1–2.

B. The '559 Patent

The '559 patent, titled "Multiple-Variable Dose Regimen for Treating Idiopathic Inflammatory Bowel Disease," issued on November 17, 2015. Ex. 1001, [45], [54]. The '559 patent relates to methods for treating tumor necrosis factor α ("TNFα") related disorders, including Crohn's disease, comprising administering a TNFα inhibitor in an induction or loading phase, followed by administering the inhibitor in a maintenance or treatment phase, wherein a higher dose is administered in the induction phase. Ex. 1001, Abstract, 28:64–66. In one embodiment, the TNFα inhibitor D2E7, or adalimumab, is administered as a multiple-variable dose regimen comprising an induction phase to induce remission of Crohn's disease and a treatment

phase. *Id.* at 4:47–53. According to the '559 patent, an "induction dose" or "loading dose" is the "first dose of TNFα inhibitor, which is larger in comparison to the maintenance or treatment dose." *Id.* at 11:62–65. The induction dose can be administered as a single dose or a set of doses, "is often used to bring the drug in the body to a steady state amount[,] and may be used to . . . achieve maintenance drug levels quickly." *Id.* at 11:65–12:1. The "treatment dose" or "maintenance dose," as described in the '559 patent, is "the amount of TNFα inhibitor taken . . . to maintain or continue a desired therapeutic effect." *Id.* at 12:16–18. Like the induction dose, the maintenance or treatment dose can be administered as a single dose or a set of doses. *Id.* at 12:19–20. Treatment doses, however, "are smaller than the induction dose." *Id.* at 12:23.

The '559 patent describes several efficacy studies involving the multiple-variable dose regimen, including studies in which patients with Crohn's disease received multiple-variable doses of adalimumab. *Id.* at 73:40–76:20. In a first study in patients with Crohn's disease, "multiple, variable doses of [adalimumab] significantly increased the frequency of remission of disease in Crohn's disease subjects." *Id.* at 75:9–11. In a second study involving patients with Crohn's disease "who had previously received and responded to infliximab [Remicade], but who no longer had a sustained response to or could not tolerate infliximab[,]" the multiple-variable dose treatment "was well tolerated and was clinically beneficial." *Id.* at 76:16–20.

C. Illustrative Claim

Of the challenged claims, claims 1 and 4 are independent. Claim 1 is illustrative of the claimed subject matter and recites:

> 1. A multiple-variable dose method for treating idiopathic inflammatory bowel disease in a human subject in need thereof, comprising subcutaneously administering to the human subject:
>
> a first dose of 160 mg of adalimumab administered to the human subject within a day; and
>
> a second dose of 80 mg of adalimumab administered to the human subject within a day, wherein the second does is administered two weeks following administration of the first dose.

Ex. 1001, 93:56–65.

D. The Asserted Ground of Unpatentability

Petitioner asserts claims 1–30 of the '559 patent are unpatentable under 35 U.S.C. § 103(a) over the combination of 2003 Humira Package Insert[2] and WO '330,[3] in view of Goodman & Gilman,[4] 2002 Remicade Package Insert,[5] and Hanauer.[6] Petitioner supports its assertions with the testimony of Ingvar Bjarnason, M.D. (Ex. 1002) and John Posner, Ph.D. (Ex. 1025).

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[2] Humira (adalimumab) Label (Abbott Laboratories) (Ex. 1026).
[3] WO 02/100330 A2, published December 19, 2002 (Ex. 1020).
[4] GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 25–27 (Joel G. Hardman et al. eds., 10th ed. 2001) (Ex. 1030).
[5] PHYSICIANS' DESK REFERENCE, Remicade entry 1178–1182 (57th ed. 2003) (Ex. 1068).
[6] Stephen B. Hanauer & Themistocles Dassopoulos, *Evolving Treatment Strategies for Inflammatory Bowel Disease*, 52 ANNUAL REVIEW MED. 299–318 (2001) (Ex. 1027).

III. ANALYSIS

We organize our analysis into four sections. First, we address the level of ordinary skill in the art. Second, we turn to claim construction. Third, we provide an overview of the asserted references. Fourth, taking account of the information presented, we consider whether Petitioner's asserted ground meets the threshold showing for instituting an *inter partes* review based on obviousness.

A. Level of Ordinary Skill in the Art

We consider the asserted ground of unpatentability in view of the understanding of a person of ordinary skill in the art. Petitioner and its experts contend that, as of April 9, 2004 (and one year prior), a person of ordinary skill in the art would have the skill sets of a team comprising a pharmacologist having experience with TNFα inhibitors and a physician treating patients for Inflammatory Bowel Disease (IBD), including Crohn's disease and ulcerative colitis. Pet. 13; Ex. 1002 ¶¶ 38–39; Ex. 1025 ¶¶ 34–35. Dr. Bjarnason testifies that the physician on the team "would have an M.D. and at least three years' post-residency experience treating patients having IBD." Ex. 1002 ¶ 40. Dr. Posner testifies that the pharmacologist on the team "would have a Ph.D. in pharmacology, pharmacokinetics, or a related field and at least three years of experience working on the pharmacokinetics/pharmacodynamics of biologic drugs." Ex. 1025 ¶ 36.

At this stage of the proceeding, Patent Owner does not dispute Petitioner's proposed level of ordinary skill, which we adopt for purposes of this decision. *See generally* Prelim. Resp. We also find, for purposes of this decision, that the prior art itself is sufficient to demonstrate the level of ordinary skill in the art at the time of the invention. *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 art). Further, based on Dr. Bjarnason's and Dr. Posner's statements of qualifications and curriculum vitae, for the purposes of this decision, we find that they are qualified to opine from the perspective of a person of ordinary skill in the art at the time of the invention. *See* Ex. 1002 ¶¶ 3–8 (Dr. Bjarnason's qualifications), App'x A (Dr. Bjarnason's curriculum vitae); Ex. 1025 ¶¶ 3–14 (Dr. Posner's qualifications), App'x A (Dr. Posner's curriculum vitae).

B. Claim Construction

The Board interprets claims in an unexpired patent using the "broadest reasonable construction in light of the specification of the patent." 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016).

Petitioner "does not assert that any special meanings apply to claim terms in the '559 patent," but does contend that the preambles to independent claims 1 and 4 are non-limiting statements of intended use. Pet. 18. Petitioner argues, alternatively, that if we conclude the preambles should be construed, "the term 'treating' in claims 1 and 4 should be given its broadest reasonable interpretation of 'reducing the signs and/or symptoms of idiopathic inflammatory bowel disease," without requiring any specific level of therapeutic effect. *Id.* Patent Owner disagrees (Prelim. Resp. 25–26), but asserts that we need not determine whether the preambles are

limiting to resolve the parties' dispute at this stage of the proceeding. Prelim. Resp. 24–25.

We agree with Patent Owner that the parties' dispute at this stage of the proceeding does not turn on whether the preambles are limiting or, if assumed limiting, the proper construction of the preambles. Thus, we determine that no claim term requires construction for purposes of this decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999) ("only those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy").

C. *Asserted References*

Before turning to Petitioner's asserted ground, we provide a brief summary of the asserted references. First, however, we address a threshold argument Patent Owner raises with respect to whether Petitioner shows sufficiently that 2003 Humira Package Insert is a prior art printed publication.

1. *2003 Humira Package Insert (Ex. 1026) as "Printed Publication" Prior Art Under 35 U.S.C. § 102(b)*

Under 35 U.S.C. § 311(b), a petitioner in an *inter partes* review may only challenge the claims of a patent based on "prior art consisting of patents or printed publications." Petitioner has the initial burden of production to establish that there is prior art that renders the challenged claims unpatentable. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1379 (Fed. Cir. 2015) (citing *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008)). For institution purposes, Petitioner has the burden to establish a reasonable likelihood that it will prevail on the merits, which includes, *inter alia*, making a sufficient showing in the Petition that 2003 Humira Package Insert qualifies as a "printed

publication" within the meaning of 35 U.S.C. §§ 102 and 311(b). 35 U.S.C. § 314(a); *see* 37 C.F.R. § 42.108(c); *see also, e.g.*, *Symantec Corp. v. Trs. of Columbia Univ.*, Case IPR2015-00371, slip op. at 5, 9 (PTAB June 17, 2015) (Paper 13) (denying institution where the Petition failed to include discussion or cite to evidence sufficient to show that the asserted reference was a prior art printed publication). Petitioner is not required at this stage of the proceeding to establish by a preponderance of the evidence that 2003 Humira Package Insert was publicly accessible before the effective filing date of the '559 patent[7] and, therefore, qualifies as a printed publication. To meet the initial burden of production under *Dynamic Drinkware*, however, the Petition must include argument and direct us to evidence sufficient to show that Petitioner would establish such public accessibility by a preponderance of the evidence during the course of the trial.

Whether a reference qualifies as a "printed publication" involves a case-by-case inquiry into the facts and circumstances surrounding the reference's disclosure to members of the public. *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004). The key inquiry is whether the reference was made "sufficiently accessible to the public interested in the art" before the effective filing date. *In re Lister*, 583 F.3d 1307, 1311 (Fed. Cir. 2009) (quoting *In re Cronyn*, 890 F.2d 1158, 1160 (Fed. Cir. 1989)). A reference is considered "publicly accessible" upon a satisfactory showing that the document has been "disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence[] can locate it." *Kyocera Wireless Corp. v.*

[7] For purposes of the Petition, Petitioner asserts that the effective filing date of the challenged claims is April 9, 2004. *See* Pet. 8.

ITC, 545 F.3d 1340, 1350 (Fed. Cir. 2008) (citation and internal quotation marks omitted). A party seeking to introduce a reference, therefore, "should produce sufficient proof of its dissemination or that it has otherwise been available and accessible to persons concerned with the art to which the document relates and thus most likely to avail themselves of its contents." *In re Wyer*, 655 F.2d 221, 227 (CCPA 1981) (quoting *Philips Elec. & Pharm. Indus. Corp. v. Thermal & Elecs. Indus., Inc.*, 450 F.2d 1164, 1171 (3d Cir. 1971)).

Petitioner identifies 2003 Humira Package Insert as prior art under § 102(b). Pet. 10 (Table). Petitioner asserts that 2003 Humira Package Insert was publicly available on the Food and Drug Administration's ("FDA") website "no later than March 31, 2003[,] as demonstrated by the Internet Archive and the Wayback Machine service which it provides." *Id.* As support, Petitioner provides a screenshot of the webpage https://www.fda.gov/ohrms/dockets/ac/03/briefing/3930B1_02_B-Abbott-Humira Prescribing Info.pdf, as shown on the Internet Archive for March 31, 2003 (Ex. 1031) and the September 27, 2017, Affidavit of Christopher Butler, Office Manager of the Internet Archive ("Butler Affidavit," Ex. 1032), which includes as Exhibit A "true and accurate copies of printouts of the Internet Archive's records of the HTML files for the URLs and the dates specified in the footer of the printout." *Id.* ¶ 6, Ex. A. Petitioner also directs us to Dr. Bjarnason's testimony regarding the accessibility of drug product inserts (or labels) on the FDA website. Pet. 11 (citing Ex. 1002 ¶¶ 10, 77).

Patent Owner responds that Petitioner fails to make a threshold showing that 2003 Humira Package Insert was available as a printed

publication before the priority date of the '559 patent, because Petitioner provides insufficient evidence that the insert was publicly accessible in March 2003. Prelim. Resp. 53–56. Patent Owner acknowledges that the screenshot of 2003 Humira Package Insert from the Wayback Machine and the Butler Affidavit "establish the existence of the Humira[] Label on an FDA website on March 31, 2003." Prelim. Resp. 53–54. Patent Owner argues, however, that "[e]xistence on an FDA website . . . is insufficient to establish *public* accessibility." *Id.* at 54 (citing *Celltrion, LLC v. Biogen, Inc.*, Case IPR2017-01230, slip op. at 11–14 (PTAB Oct. 12, 2017) (Paper 10)). Patent Owner further argues that Petitioner fails to establish whether the FDA website indexed drug information in 2003 and how such information would have been categorized, whether the FDA website had a search capability in 2003, what search would have identified 2003 Humira Package Insert, and whether the FDA website had "any 'tools for customary and meaningful research' in 2003." *Id.* at 55 (quoting *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194–97 (Fed. Cir. 2008)).

Although we agree with Patent Owner that evidence of indexing is probative of public accessibility, such evidence is not necessarily required in all cases. *See Voter Verified, Inc. v. Premier Election Sols., Inc.*, 698 F.3d 1374, 1381 (Fed. Cir. 2012); *Klopfenstein*, 380 F.3d at 1350 ("distribution and indexing are not the only factors to be considered in a § 102(b) 'printed publication' inquiry"). Rather, absent evidence of indexing, testimony indicating that the particular online publication or website on which the reference was published was well-known to the community interested in the subject matter of the reference, and that, upon accessing the website, those interested would have found the reference using the website's own search

functions can support the ultimate determination that a given reference was publicly accessible. *Id.* at 1380–81. If such evidence is sufficient to establish public accessibility, then the same evidence necessarily is sufficient to satisfy the threshold showing of public accessibility for purposes of institution. Indeed, when determining whether a petitioner's arguments and evidence are sufficient for purposes of institution we are cognizant that:

> [t]he reasonable likelihood standard for instituting *inter partes* review is . . . not a *lower* standard of proof than a preponderance of the evidence, but instead asks whether the same preponderance standard is reasonably likely to be met *at a later time*. We must assess the persuasiveness of the petitioner's evidence while "recognizing that [we are] doing so without all evidence that may come out at trial." As such, we have required only a "threshold showing" of public availability in order to institute trial. When petitioners have not come forward with any credible evidence establishing a key aspect of public availability, we have denied institution.

ServiceNow, Inc. v. Hewlett-Packard Co., Case IPR2015-00707, slip op. at 2 (PTAB Aug. 26, 2015) (Paper 12) (Crumbley, APJ, dissenting).

Here, Petitioner directs us to not only the Wayback Machine screenshot and Butler Affidavit, which evidence that 2003 Humira Package Insert was available on the FDA website as of March 31, 2003, but also to Dr. Bjarnason's testimony regarding how persons interested and ordinarily skilled in the art exercising reasonable diligence could have located 2003 Humira Package Insert on the FDA website. In particular, Dr. Bjarnason testifies that: (1) 2003 Humira Package Insert is a label for a commercially marketed prescription drug (Ex. 1002 ¶ 10); (2) physicians would have known in 2003 that labels for drugs they prescribe were available for review from a number of sources including the FDA website (*id.*); (3) physicians

could and did access such labels from the FDA website, as he "ha[s] done personally many times" (*id.*); and (4) a person interested in the art "would have accessed the FDA's website and easily found the 2003 Humira[] Package Insert using that website's own search capabilities, as physicians regularly did" (*id.* ¶ 77). At this stage of the proceeding, we credit Dr. Bjarnason's testimony, which is unrebutted and based on his personal experience with accessing labels from the FDA website.[8] Thus, we find that Petitioner provides adequate evidence to make a threshold showing that 2003 Humira Package Insert was accessible to the extent required to establish it as a "printed publication" for purposes of institution.

[8] Patent Owner contends that Dr. Bjarnason's testimony is entitled to no weight because Dr. Bjarnason fails to cite objective evidence to support his opinions, establish personal knowledge of 2003 Humira Package Insert's public availability on the FDA website, or cite any evidence establishing that 2003 Humira Package insert was actually disseminated to the interested public. Prelim. Resp. 54. Initially, we note that actual dissemination is not required to show that a reference was publicly accessible. *Kyocera*, 545 F.3d at 1350 (A reference is considered "publicly accessible" upon a satisfactory showing that the document has been "disseminated *or otherwise made available* to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence[] can locate it." (emphasis added) (citation and internal quotation marks omitted)). Further, although not based on personal experience with 2003 Humira Package Insert, we find that Dr. Bjarnason's testimony is evidence of the methods those interested in the art generally would have used to search and locate labels such as 2003 Humira Package insert on the FDA website—a well-known government website that was open and accessible to the public in March 2003.

2. 2003 Humira Package Insert (Ex. 1026)[9]

2003 Humira Package Insert provides that the recommended dose of Humira for adult patients with rheumatoid arthritis ("RA") is "40 mg administered every other week as a subcutaneous injection." Ex. 1026, 9.[10] 2003 Humira Package Insert also discloses that although the maximum tolerated dose of Humira "has not been established in humans[,] [m]ultiple doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities." *Id.*

3. WO '330 (Ex. 1020)

WO '330 discloses "[m]ethods of treating disorders in which TNFα activity is detrimental via biweekly, subcutaneous administration of human antibodies, preferably recombinant human antibodies." Ex. 1020, Abstract. WO '330 describes D2E7 (adalimumab) as "[t]he most preferred recombinant antibody of the invention." *Id.* at 4:27. WO '330 identifies a number of disorders in which TNFα is detrimental, including RA and IBD (including Crohn's disease and ulcerative colitis), and states that the antibodies of the invention can be used to treat the identified disorders. *See id.* at 28:35–38, 29:21–25, 29:33–35, 31:19–26. According to WO '330, "[a]n exemplary, non-limiting range for a therapeutically or prophylactically effective amount of an antibody . . . of the invention is 10-100 mg, more preferably 20-80 mg and most preferably about 40 mg." *Id.* at 26:37–39.

[9] Unless otherwise noted, we cite to the original page numbers of each exhibit, not the page numbers that Petitioner added to the particular exhibit.
[10] Because 2003 Humira Package Insert does not include page numbers, we cite to the page numbers that Petitioner added to the exhibit.

4. Goodman & Gilman (Ex. 1030)

Goodman & Gilman describes the concepts of loading or induction doses and maintenance or treatment doses. Maintenance dosing involves, *inter alia*, a series of repetitive doses given "to maintain a steady-state concentration of drug associated with the therapeutic window." Ex. 1030, 26. A loading dose "is one or a series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly." *Id.* at 27.

Goodman & Gilman provides an equation for calculating the appropriate magnitude of the loading dose:

Loading dose = target C_p x (V_{ss}/F)

Id. In the equation, target C_p refers to the target plasma concentration, V_{ss} refers to the distribution volume at steady-state, and F refers to the bioavailability of the drug. *Id.* at 22–24, 27. Goodman & Gilman further discloses that a "loading dose may be desirable if the time required to attain steady state by the administration of a drug at a constant rate is long relative to the temporal demands of the condition being treated." *Id.* at 27. The use of a loading dose, however, "also has significant disadvantages" with respect to toxicity and it is "usually advisable to divide the loading dose into a number of smaller fractional doses that are administered over a period of time." *Id.*

5. 2002 Remicade Package Insert (Ex. 1068)

2002 Remicade Package Insert discloses the chimeric antibody infliximab for "inducing and maintaining clinical remission in patients with moderately active to severe Crohn's disease." Ex. 1068, 1179. The recommended dose is "5 mg/kg given as an induction regimen at 0, 2 and 6

weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter." *Id.* at 1181.

6. Hanauer (Ex. 1027)

Hanauer describes "approaches to the medical therapy of ulcerative colitis and Crohn's disease" (collectively, IBD). Ex. 1027, 299 (Abstract). Hanauer explains that treatment for IBD "consists of inducing remission of active disease and then maintaining remission to prevent relapse." *Id.* at 300. According to Hanauer, many conventional approaches to treating IBD required certain drugs for inducing remission and different drugs for maintaining remission. *See, e.g.*, *id.* at 300–301 (Tables 1 and 2 showing different therapies for inducing and maintaining remission of IBD), 303 (describing corticosteroids as "the current mainstay of inductive therapy" for IBD, but "ineffective as maintenance therapies"), 304 (explaining that 6-mercaptopurine and azathioprine "are effective maintenance therapies" for IBD).

"A series of pivotal clinical trials[,]" however, "have begun to define a role for infliximab as both an inductive and maintenance agent for [Crohn's disease]." *Id.* at 306. In one study, 108 patients received a single intravenous infusion of placebo or infliximab at doses of 5, 10, or 20 mg/kg. *Id.* Hanauer reports that 33% of the infliximab-treated patients achieved clinical remission versus 4% of the placebo-treated patients at 4 weeks. *Id.* "The trial confirmed the efficacy of infliximab in the treatment of moderate to severe [Crohn's disease], with the 5 mg/kg dose showing the best results." *Id.* at 307.

D. Asserted Obviousness over 2003 Humira Package Insert and WO '330, in view of Goodman & Gilman, 2002 Remicade Package Insert, and Hanauer

Petitioner asserts that claims 1–30 of the '559 patent are unpatentable under 35 U.S.C. § 103(a) because the subject matter of those claims would have been obvious over the combination of 2003 Humira Package Insert and WO '330, in view of Goodman & Gilman, 2002 Remicade Package Insert, and Hanauer. Pet. 20–24, 35–50, 55–59 (claim charts). Petitioner argues that the asserted references expressly disclose all elements of independent claims 1 and 4, except "the precise 160 mg/80 mg induction dosing regimen required by the claims." Pet. 20. In particular, Petitioner contends that 2003 Humira Package insert discloses that the FDA-approved method for maintaining remission of RA symptoms was the subcutaneous injection of 40 mg adalimumab every other week, which WO '330 also described as the preferred dosing regimen for treating IBD. *Id.* at 21, 25. Thus, Petitioner argues that a person of ordinary skill in the art would have reasonably expected a 40 mg subcutaneous injection of adalimumab every other week to maintain remission of IBD symptoms. *Id.* at 21, 24 (citing Ex. 1002 ¶ 80; Ex. 1026, 3, 9), 26 (citing Ex. 1002 ¶ 90).

Petitioner further contends that Hanauer and 2002 Remicade Package Insert teach treating IBD by first inducing remission of symptoms, and then administering therapy to maintain remission. *Id.* at 21, 27–29 (citing Ex. 1002 ¶¶ 62, 66; Ex. 1027, 300–301; Ex. 1068, 1179). In that regard, Petitioner directs us to 2002 Remicade Package Insert's approved dosing regimen of administering 5 mg/kg infliximab at weeks 0, 2, and 6 for inducing Crohn's disease remission, followed by 5 mg/kg every 8 weeks for maintaining remission. *Id.* at 29 (citing Ex. 1068, 1181). Petitioner also

points to knowledge in the art that higher induction doses could be used for other disorders. *Id.* at 30–32. According to Petitioner, such prior art disclosures would have led a person of ordinary skill in the art to design an appropriate IBD induction dosing regimen and would have provided a reasonable expectation that "an adalimumab dosing regimen greater than the 40 mg [every other week] maintenance dose would induce IBD remission." *Id.* at 21, 36–37.

To arrive at an adalimumab induction dosing regimen, Petitioner first points to WO '330's disclosure of using higher doses of adalimumab to treat TNFα disorders, including 80 mg every other week. *Id.* at 22, 37 (citing Ex. 1020, 3:34–4:2, 26:37–39, 33:14–34:26). Petitioner asserts that an ordinarily skilled artisan would have reasonably expected an 80 mg every other week dosing regimen to provide some efficacy in inducing IBD remission, i.e., the 80 mg every other week would have served as a good basis for selecting an IBD induction or loading dose. *Id.* at 22 (citing Ex. 1002 ¶ 95), 37, 39. Petitioner further asserts that the skilled artisan would have been led to modify an 80 mg every other week induction dose into "the claimed 160 mg/80 mg dosing regimen" based on a number of teachings in the prior art, including: (1) the knowledge that IBD is a debilitating and potentially life-threatening disease; (2) administering infliximab using an induction regimen achieved remission of Crohn's disease in 4 weeks; (3) using an 80 mg every other week induction regimen would require 10 weeks to reach steady state blood levels and treating the severe symptoms of IBD required more rapid relief; (4) well-known dosing rules and equations and the known pharmacokinetics of adalimumab dictated that a 160 mg dose would achieve the desired blood levels more rapidly than

an 80 mg every other week dose; and (5) an 80 mg dose administered 2 weeks after the 160 mg dose would maintain heightened blood levels for 4 weeks, at which time the 40 mg every other week maintenance dosing would begin. *Id.* at 22–23 (citing *id.* §§ VI.B.4–VI.B.5, VI.C.1; Ex. 1025 ¶¶ 49, 62, 82–83; Ex. 1026, 2; Ex. 1027, 306), 32–33, 38–42. More specifically, Petitioner contends that the skilled artisan would have used 80 mg every other week "as the basis for an IBD induction therapy" based on the prior art disclosures, and would have doubled that basis dose in accordance with the known general rule for determining an appropriate induction dose and Gilman & Goodman's equation. *Id.* at 39–40 (citing Ex. 1003, 352–353; Ex. 1029, 285; Ex. 1025 ¶ 50).

Having considered the arguments and evidence, we are not persuaded that Petitioner shows a reasonable likelihood of prevailing in its assertion that the 160 mg/80 mg dosing regimen that the claims of '559 patent require would have been obvious over the cited prior art. Although we agree with Petitioner that it was known in the art to use a loading or induction dose for drugs with a long half-life, we determine that Petitioner does not show sufficiently on this record that an ordinarily skilled artisan—without the benefit of hindsight—would have had a reason to use 160 mg as an induction dose, or would have had a reason to select an intermediate dose to serve as a "basis" or "baseline" for calculating an induction dose.

As Petitioner acknowledges, the prior art discloses that, as a general rule, the loading dose of a drug is twice the size of the maintenance dose, if the maintenance dosing interval corresponds to the biological half-life of the drug. Pet. 34–35, 40 (applying the loading dose general rule set forth in the prior art); Ex 1003, 353 (Table 28-1) ("If the dosing interval . . . is equal to

or somewhat shorter than the elimination half-life . . ., then the dose ratio [of loading dose to maintenance dose] should be 2:1"); Ex. 1025 ¶ 50 (Dr. Posner's testimony regarding the general rule); Ex. 1029, 285. According to Petitioner, such a loading dose allows a patient to achieve blood levels that are close to steady-state from the induction dose alone. Pet. 35 (citing Ex. 1025 ¶¶ 50, 72; Ex. 1029, 285 (Fig. 19.8)).

Petitioner consistently identifies 40 mg every other week as the maintenance dosing regimen for adalimumab. *See*, *e.g.*, Pet. 3, 20–21, 24–25, 36–37. Likewise, Dr. Bjarnason testifies that a person of ordinary skill in the art "would have understood that [2003 Humira Package Insert's] recommended dosing regimen of 40 mg adalimumab [every other week] was an acceptable, long-term maintenance therapy" based on the clinical study data in 2003 Humira Package Insert and, therefore, would have selected a higher dose to use for induction therapy. Ex. 1002 ¶¶ 80, 94; *see id.* ¶ 86 ("[T]he 'most preferabl[e]' 40 mg [every other week] regimen disclosed in WO '330 is a maintenance dosing regimen, for maintaining remission of IBD and controlling flare ups, rather than an induction dosing regimen."). Petitioner and Dr. Posner also point out that the half-life of adalimumab is approximately 2 weeks. *See* Pet. 38 (citing Ex. 1026, 2); Ex. 1025 ¶ 41 ("adalimumab ha[s] an approximately 2 week half-life"). Thus, the present record demonstrates that the adalimumab every other week maintenance dosing interval corresponds to adalimumab's half-life. Applying the general rule for determining an appropriate loading dose, therefore, results in an adalimumab loading dose of 80 mg (i.e., a doubling of the 40 mg dose that Petitioner identifies as the maintenance dose), not a dose of 160 mg as recited in the claims. Accordingly, we are not persuaded on this record that

the general rule for determining an appropriate loading dose would have led the ordinarily skilled artisan to a dose of 160 mg of adalimumab (*see* Pet. 40)—a dose that is quadruple the dose that Petitioner identifies as the maintenance dose.

Petitioner further argues, however, that the person of ordinary skill in the art would have arrived at a 160 mg adalimumab dose by first selecting an 80 mg adalimumab dose as the "basis" for an induction regimen, then doubling that dose in accordance with the general rule set forth in the prior art for determining a loading dose. Pet. 40–42. But the record at this stage of the proceeding does not support Petitioner's argument. For example, the references Petitioner cites do not disclose or suggest using a basis or baseline dose to calculate an appropriate induction dose for a drug with a dosing regimen that corresponds to its half-life. Rather, as explained above, those references disclose the maintenance dose—not some other basis or baseline dose—as the appropriate dose for determining the induction dose. And neither Dr. Bjarnason nor Dr. Posner identifies sufficient factual support for arriving at a loading dose by first selecting a basis or baseline intermediate dose. *See* Ex. 1002 ¶ 95; Ex. 1025 ¶ 62 (Dr. Posner adopting Dr. Bjarnason's bare conclusion that 80 mg adalimumab every other week "would be an appropriate choice as the basis for an induction regimen to induce remission of IBD"). Thus, we determine that Petitioner does not show sufficiently on this record that a skilled artisan would have been prompted to combine and modify the disclosures of the prior art to achieve the claimed multiple-variable dose method of treatment that all of the challenged claims require. *See Grain Processing Corp. v. Am. Maize Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988) ("Care must be taken to avoid

hindsight reconstruction by using 'the patent in suit as a guide through a maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.'" (quotation omitted)).

Given the foregoing, we are not persuaded the record before us establishes a reasonable likelihood that Petitioner will prevail in showing that the subject matter of claims 1–30 would have been obvious over the combination of 2003 Humira Package Insert and WO '330, in view of Goodman & Gilman, 2002 Remicade Package Insert, and Hanauer.

IV. CONCLUSION

Taking account of the information presented in the Petition and the Preliminary Response, and the evidence of record, we determine that Petitioner fails to demonstrate a reasonable likelihood of prevailing at trial as to any challenged claim. Accordingly, the Petition is *denied*, and no trial is instituted.

V. ORDER

It is hereby

ORDERED that the Petition is *denied* as to all challenged claims of the '559 patent, and no trial is instituted;

FURTHER ORDERED that Petitioner's *Pro Hac Vice* Motion to Admit Daniel L. Reisner Pursuant to 37 C.F.R. § 42.10(c) (Paper 3) is *dismissed as moot*; and

FURTHER ORDERED that Petitioner's *Pro Hac Vice* Motion to Admit Abigail Langsam Pursuant to 37 C.F.R. § 42.10(c) (Paper 7) is *dismissed as moot*.

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