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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BOEHRINGER INGELHEIM INTERNATIONAL GMBH and
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.,

Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD.,

Patent Owner.

Case No. IPR2016-00408
U.S. Patent No. 8,889,135

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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I. Introduction

It is undisputed that van de Putte 2000 and Rau 2000 disclose each element of the claims at issue. van de Putte 2000 teaches every claim element except every-other-week (*i.e.,* biweekly) administration, and Rau 2000, reviewing the prior art, expressly teaches just that. The cross-examination testimony of Patent Owner AbbVie's five experts only further confirms that, at the time of the alleged invention, a person of skill in the art ("POSA") would have been motivated to combine the teachings of van de Putte 2000 and Rau 2000 to arrive at the claimed dosing regimen with a reasonable expectation of success. At a minimum, the claimed dosing regimen was one of a discrete number of promising approaches that would have been obvious to try.

In its response, AbbVie largely does not dispute van de Putte 2000's efficacy-related teachings, and only half-heartedly contests Rau 2000's teaching to pursue subcutaneous biweekly dosing. Shifting from its prior public touting of 20mg weekly and 0.5mg/kg biweekly doses, AbbVie now attempts to misdirect the Board from the instituted ground through speculative, *post hoc* teaching away arguments. But these arguments fall well short of the mark. *First*, AbbVie's "up-dosing" argument (1) is rebutted by numerous prior art disclosures, including the state-of-the-art disclosures set forth in Petitioner's obviousness ground, and (2) overlooks that neither obviousness nor the claims

require the single most effective dose. *Second*, AbbVie's newly created, hypothetical pharmacokinetic ("PK") modeling does not support efficacy- or anti-drug antibody ("ADA")-related concerns pointing away from what the art actually taught. Because none of AbbVie's arguments shows that the prior art criticizes, discredits, or otherwise discourages investigation of the claimed dosing regimen, it cannot prove teaching away.[1]

Nor can AbbVie's three alleged secondary considerations — none of which are applicable to or commensurate with the scope of the claims — rebut Petitioner's strong obviousness showing. Accordingly, Petitioner respectfully submits that the Board should find the '135 patent claims obvious.

[1] Petitioner raised in IPR2016-00408, also involving the '135 patent, another invalidity ground. Although that ground presents an independent basis for invalidity, AbbVie's responses are nearly identical to those it provides here. Accordingly, Petitioner's reply arguments are similar to those it presents in IPR2016-00408. Further, while AbbVie asserts that Petitioner's arguments "should be rejected for the same reasons" outlined in its response to Coherus (Response, 2), the record of this Petition includes additional prior art, expert testimony, and arguments, and thus should be considered independently, as the Board has recognized. (Decision, 8.)

II. AbbVie Failed to Rebut the Petition's Key Arguments and Evidence

The starting point of Petitioner's obviousness ground is van de Putte 2000's disclosure of the results of a large-scale Phase II efficacy and safety trial that built on earlier Phase I safety studies. (Ex. 1009, 2; Ex. 1037, 152:19-153:7.) AbbVie does not dispute that van de Putte 2000 expressly teaches each limitation of claims 1-5 (long-term, subcutaneous administration of fixed doses of D2E7) except for biweekly administration. (Response, 17-50.) AbbVie also admits that van de Putte 2000 discloses that each dose — including 20mg weekly — was statistically superior to placebo and "was not powered to provide statistically meaningful comparisons between doses." (Response, 12; Ex. 1037, 155:11-159:8.)[2]

[2] At the same time, AbbVie ignores that, after these 20/40/80mg doses were continued through 6 and then 12 months, the prior art still reported that "all doses of D2E7 were statistically significantly superior to placebo." (Ex. 1009, 2; Ex. 1010, 5; Ex. 1037, 155:6-160:11.) Moreover, although AbbVie seeks to minimize van de Putte 2000 as an abstract (Response, 6), its rheumatoid arthritis ("RA") expert confirmed that it would have been peer-reviewed by four to twelve reviewers (Ex. 1037, 112:9-13).

Rau 2000 summarizes numerous Phase I and II studies concerning D2E7 and expressly teaches biweekly dosing, concluding that "D2E7, with a half-life of 12 days, can be administered every two weeks as an intravenous injection over 3-5 minutes or subcutaneously." (Ex. 1012, 8.) AbbVie contends that Rau 2000 teaches only (a) biweekly intravenous administration or (b) subcutaneous administration generally "[g]iven that there were no trials . . . involving the subcutaneous administration of D2E7 every two weeks." (Response, 11.) But, in addition to misreading the above-quoted language, study DE010 discussed in Rau 2000 involved precisely that dosing interval and route of administration. (Ex. 1038, 79:20:80:2; Ex. 1030, 3 (cited in Rau 2000 n.4).) Indeed, AbbVie's PK expert admitted that in June 2000, D2E7's then-developer[3] was "able to show efficacy through clinical trials with both a once-weekly and an ***every-other-week*** dosing regimen" with "intravenous and ***subcutaneous*** dosing." (Ex. 1038, 115:12-116:1 (emphasis added); Ex. 1052, 2.)[4]

[3] Various entities, including Knoll/BASF Pharma and Cambridge Antibody Technology plc ("CAT"), worked on the development of D2E7 before AbbVie purchased it.

[4] Unless otherwise noted, all internal citations and modifications are omitted.

Given the advantages of less frequent subcutaneous dosing, which AbbVie's experts conceded were known in the prior art, a POSA would have been motivated to modify van de Putte 2000's safe and effective 20mg weekly dose to biweekly, as expressly taught by Rau 2000, with a reasonable expectation of success. (Ex. 1037, 67:1-68:8; Decision, 15 n.7.) AbbVie's arguments, including its attempt to change the ground adopted by the Board, should be rejected.

III. The Prior Art Does Not Teach Away

A. AbbVie's Arguments Do Not Meet the Standard for Teaching Away

AbbVie's primary contention is that the claims at issue would have been nonobvious because certain prior art allegedly teaches away. (*See, e.g.*, Response, 19.) To teach away, however, a reference must "criticize, discredit, or otherwise discourage investigation into the invention claimed." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013). "A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005). Finally, "the totality of a reference's teachings must be considered" in view of the art as a whole in assessing any alleged teaching away. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). None of AbbVie's arguments meet this standard.

B. The Clinical Data Do Not Teach Away

Contrary to AbbVie's *post hoc* re-characterizations, the prior art, including van de Putte 2000 and Rau 2000, reported that D2E7 was safe and efficacious, including 0.5mg/kg biweekly and 20mg weekly doses. As explained below, AbbVie fails to show that the clinical data teach away from claims that do not require the single most effective dose.

1. Rau 2000's Clinical Data Do Not Teach Away

To argue that the clinical data in Rau 2000 teach away, AbbVie speculates that the 0.5mg/kg biweekly dose from the early DE001/003 Phase I study discussed in Rau 2000 "did not work" because of the option for up-dosing and because no data for 0.5mg/kg is reported after week 12 (at which time the dose, as explained below, ***was in fact effective***). (Response, 19-25.) That argument does not withstand scrutiny, and AbbVie's experts were unwilling to take that position on cross-examination. (Ex. 1037, 197:21-198:6; Ex. 1038, 171:9-174:17.)

Rau 2000 does not show that 0.5mg/kg biweekly doses were ineffective. As a preliminary matter, Rau 2000 does not criticize or disparage the effectiveness of 0.5mg/kg biweekly doses. (Ex. 1012.) Rather, it concludes that D2E7 "can be administered every two weeks" without disclosing a minimum

effective dose. (Ex. 1012, 8; Ex. 1037, 170:8-19.)[5] This is consistent with the data in Rau 2000, which show that 0.5mg/kg was effective at treating RA through 12 weeks with substantial reductions in both DAS and ESR values. (Ex. 1012, 6-7, Figs. 4-5; Ex. 2070, 61:20-64:17; Ex. 1037, 61:9-15, 122:18-125:7; Ex. 1032; Response, 22.) Moreover, these conclusions are supported by the prior art as a whole, which likewise do not state that 0.5mg/kg biweekly was ineffective. (Ex. 1006, 5; Ex. 1007, 5; Ex. 1011, 4; Ex. 1029, 3-4; Ex. 1056, 3.) In fact, a D2E7 co-developer identified this dose in the prior art as the "minimum ***effective dose***" after "chronic treatment of up to six months." (Ex. 1054; Ex. 1038, 179:3-180:21.) And a later prior art study expressly confirmed

[5] AbbVie relies on Rau 2000's statement that doses greater than 1mg/kg provided long-term efficacy (Response, 23), but ignores that this refers to 1½-year data (Ex. 1012, 4). The statement is therefore a positive report of efficacy at that time point, but is not expressly or impliedly reporting inefficacy for 0.5mg/kg, whose efficacy data was reported through 12 weeks.

that 0.5mg/kg biweekly — and, indeed, ***even half that dose*** — was effective. (Ex. 1014, 5.)[6]

In the face of Rau 2000's clear data, AbbVie speculates that the 0.5mg/kg arm included up-dosed patients. (Response, 19-25.) Yet AbbVie does not cite any evidence to support this conclusion, and unsupported speculation cannot constitute teaching away. *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1364 (Fed. Cir. 2006) ("We will not read into a reference a teaching away . . . where no such language exists."). Such a conclusion is in any event contradicted by the teachings of Rau 2000, which are confirmed by the prior art disclosures summarized above.

Nor would up-dosing, even assuming it occurred, support the conclusion that 0.5mg/kg was ineffective. *First*, the prior art showed that even the FDA-approved dosing regimen for the then-most successful RA biologic, Remicade, was up-dosed for certain patients. (Ex. 1055, 29; Ex. 1038, 197:1-204:14.) Thus, a POSA would have been aware that more than one dosing regimen may be used to treat RA, and that the option of up-dosing does not itself imply that

[6] AbbVie discussed this study in its Preliminary Response (at 13), yet its Response — accompanied by a new round of expert declarations — conspicuously ignored it.

the original dose has no efficacy. (Ex. 1037, 94:19-95:5; Ex. 1038, 203:18-204:9.) *Second*, the reference does not state that all patients were up-dosed. (Exs.1012; Ex. 2070, 84:17-21, 86:10-18.) *Third*, AbbVie contends that 1.0mg/kg was also up-dosed (Preliminary Response at 11), yet that dose was reported to be effective after 1½ years of administration. (Ex. 1012, 4-8 & Figs. 4-5.) *Fourth*, such a conclusion is also contradicted by the DE001/003 protocol, which indicates that up-dosing occurred only if a patient failed to exhibit a "good" response, although such patients may have exhibited a "moderate" response demonstrating efficacy. (Ex. 1011, 4; Ex. 1012, 4; Ex. 1002, 813; Ex. 1003, ¶¶20, 24, 26; Ex. 1056, 3.) Moreover, as discussed above (*supra*, 7-8) and below (*infra*, 15 n.11), 0.5 mg/kg and even lower doses continued to be used and were shown to have efficacy after this early study. Thus, at a minimum, a POSA would not have concluded, as AbbVie asserts (at 19-25), that up-dosing or any termination of the 0.5mg/kg dose means ***lack of efficacy*** such that the prior art teaches away.

AbbVie's entire teaching away argument with respect to Rau 2000 is based on an incorrect understanding of the Petition as well as the Board's Institution Decision. The Petition relied on Rau 2000's teaching of ***biweekly dosing***, not its disclosure of a particular intravenous weight-based dose (0.5mg/kg biweekly) from early, smaller Phase I safety studies (Ex. 1038,

132:13-133:13), in asserting that a POSA would have been motivated to modify the van de Putte 20mg weekly subcutaneous dose. (Petition, 20-33.)

In sum, the absence of post-12-week data from an earlier Phase I study cannot constitute a teaching away with respect to an obviousness ground stemming from the Phase II successes disclosed in van de Putte 2000 in view of Rau 2000's express teaching of biweekly dosing.

2. Van de Putte 2000's Clinical Data Do Not Teach Away

In arguing that van de Putte 2000 discloses that a 20mg weekly dose was "sub-optimal," AbbVie merely rehashes erroneous arguments that have already been considered and rejected. (Response, 25-27; Preliminary Response, 22-26, Decision, 14 n.6.) As noted in Section II above, van de Putte 2000 expressly teaches that "all doses of D2E7 [20, 40, and 80mg] were statistically significantly superior to placebo . . . [and] were statistically equally efficacious," and AbbVie's RA expert conceded this, as he had to. (Ex. 1009, 2; Ex. 1037, 157:4-160:5; Petition, 12.)[7]

[7] Indeed, even AbbVie cited non-prior art publication stated that study DE007 "was neither designed nor powered to show statistical differences between the adalimumab groups" and that "all adalimumab groups had consistently better ACR responses and improvements in ACR core criteria from baseline." (Ex. 2041, 9.) This is consistent with a ***prior art*** publication by named inventor Joachim Kempeni

And even if 20mg weekly had marginally lower efficacy data, that still does not meet the legal standard for "teaching away." *See Galderma*, 737 F.3d at 739 ("A teaching that a composition may be optimal or standard does not criticize, discredit, or otherwise discourage investigation into other compositions."). This is particularly true given that the claims do not require the single most effective dose, and that there would be therapeutically desirable reasons to treat RA patients with lower effective doses. (Decision, 6-7; Ex. 1037, 44:16-45:4, 93:20-94:17, 95:11-96:7.) Indeed, it was known that even efficacious, FDA-approved dosage regimens for RA may involve up-dosing. (*Supra*, 8.) And finally, obviousness does not require the single most desirable combination, especially where, as here, there is a strong motivation toward the ***lower*** effective dose. *See In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) ("Our case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention.").

— ignored by AbbVie — stating that "all three doses of D2E7 [20, 40 and 80mg] were efficacious." (Ex. 1029, 4; Ex. 1037, 165:19-166:4.)

C. Pharmacokinetic Data Do Not Teach Away

AbbVie's teaching away argument based upon its newly created PK modeling fares no better. In arguing that theoretically lower C_{min} values associated with biweekly dosing teach away from the claimed dosing regimen, AbbVie uses incorrect assumptions, overstates the significance of that parameter, and most importantly presents an analysis that its PK expert confirmed lacks relevant context. AbbVie also relies on speculative ADA concerns that are inapplicable to even its own PK modeling and admittedly absent from the prior art. At the same time, AbbVie ignores other relevant PK data (*e.g.*, D2E7's half-life, linear pharmacokinetics, and a mean dosing interval of 2.5 weeks) that were ***actually correlated*** with prior art efficacy data.

1. AbbVie's PK Modeling of Hypothetical C_{min} Values and "Fluctuations" with Biweekly Dosing Is Irrelevant

Contrary to AbbVie's assertions (which are not even supported by the declaration paragraphs it cites, Ex. 1038, 117:6-119:21), the PK data do not suggest "that a 40 mg every-other-week dose would have delivered too low a dose of D2E7 to be safe and effective." (Response, 27-28.) AbbVie's argument is based on the unremarkable assertion that biweekly 40mg doses may have somewhat lower steady-state C_{min} values than its corresponding 20mg weekly

dose.[8] (Response, 29-34.) As its PK expert admitted, however, he never "identif[ied] a specific threshold C_{min} for which efficacy in treating RA is necessary." (Ex. 1038, 127:11-16; *see also* Ex. 1002, 1220 n.2 (AbbVie prosecution declarant explaining that the minimum effective dose for assessing potential overdosing and underdosing "was undefined in June 2001").) This is consistent with AbbVie's Response. (Response, 33 ("This ***could be*** the difference between a drug working and a drug not working") (emphasis added).) Thus, AbbVie's PK modeling exercise can be dismissed as lacking context.

AbbVie also focuses on alleged "greater fluctuations" in concentration levels. (Response, 32.) But the literature relied upon for this argument makes clear that this concern applies to "drug[s] that ha[ve] a narrow therapeutic range." (Ex. 2075, ¶ 149.) AbbVie's PK expert admitted he never suggests that D2E7 has such a narrow range. (Ex. 1038, 128:22-129:7.) Nor could he based

[8] AbbVie's PK modeling is suspect because the figures it chose to exemplify its analysis were based on parameters that correlate to a roughly 7.8-day half-life, which would have been known to be incorrect for D2E7 based on prior art PK data. (Ex. 1038, 155:10-16.) Moreover, Dr. Jusko's testimony that the magnitude of C_{min} differences focused on by AbbVie would be considered "inconsequential" stands unrebutted. (Ex. 1004, ¶ 23.)

on the efficacy shown for various doses in the prior art. (Exs. 1006-1007, 1011-1014.) Accordingly, a POSA would not have concluded that AbbVie's PK modeling taught away.[9]

2. Hypothetical Concerns about Potential ADAs Do Not Teach Away

Equally unavailing is AbbVie's assertion that the C_{min} values associated with biweekly dosing ***could*** lead to ADAs, which would in turn allegedly dissuade a POSA from pursuing the claimed dosing regimen. (Response, 34-38.) As an initial matter, AbbVie's discussion of ADAs is not directed to D2E7, but instead relies on equivocal reports of ADAs associated with ***other*** proteins that are ***not*** fully human. (*See* Response, 34-37; Ex. 1037, 48:16-52:7; Ex. 1036, 18:6-20:6, 59:11-61:6; Ex. 2024 (discussing, *e.g.*, Remicade, Enbrel, and lenercept).) Because D2E7, unlike these other treatments, is a "fully human antibody against TNFα" with "no non-human or artificial sequences," a POSA

[9] AbbVie asserts that the Petition and accompanying declarations "fail[] to address steady-state concentrations." (Response, 29.) But even a cursory review of these papers reveals that this argument lacks merit. (Ex. 1004, 13 (referring to "steady state" data); Ex 1003, 30 (referring to D2E7 concentrations "over time").) AbbVie later acknowledges this when referring to Dr. Jusko's "steady-state C_{min}" analysis. (Response, 31.)

would have expected it to be "less immunogenic" and less likely to cause ADAs. (Ex. 1012, 5; Ex. 1029, 3; Ex. 1011, 3 & Tbl.1; Ex. 1036, 33:7-22; Ex. 1037, 166:20-167:7; Ex. 1002, 1309.) Indeed, AbbVie's experts[10] admitted that ***no*** prior art reported the development of D2E7 ADAs or any lack of efficacy or side effects resulting therefrom, irrespective of dosing regimen. (Response, 36; Ex. 1036, 36:14-37:9, 43:16-44:7, 53:9-14; Ex. 1037, 114:18-115:1.) Rather, the prior art positively reported the safety and efficacy of D2E7. (Ex. 1012, 8; Ex. 1009, 2.[11])

[10] AbbVie's PK expert, Dr. Vinks, spent much of his 99-page declaration discussing ADAs, but acknowledged that he has never participated in an ADA study, has no publications focused on ADAs, has never consulted regarding ADAs, and is not an ADA expert. (Ex. 1038, 24:13- 25:15.) Similarly, Dr. Vinks opines on RA clinical data, yet conceded that he is not an expert in treating RA and never interpreted ACR_{20} or RA-related up-dosing data before these proceedings. (*Id.* at 14:6-9, 29:5-8, 126:10-14, 160:17-20.)

[11] AbbVie asserts that ADA risk increases "as serum concentrations of the biologic decrease" and that drugs "administered subcutaneously often display greater immunogenicity" (Response, 35-36), yet AbbVie's ADA expert confirmed that no prior art publications applied these points to D2E7 (Ex. 1036, 72:9-13, 76:10-14).

AbbVie's citation of Rau 2000's statement that "ideotypical epitopes ***can*** represent ***a theoretical potential*** for allergic reactions" is also misguided because (1) the allergic response occurred in only a small number of patients and "did not recur" and (2) Rau 2000 concludes that D2E7 "has not lost its efficacy in the course of long-term treatment" and "is well tolerated and must be called a therapeutic step forward." (Ex. 1012, 8 (emphasis added).) In any event, AbbVie's ADA expert explained that the possibility of ADAs developing at the "low" C_{min} values discussed by AbbVie refers to situations where the plasma concentration drops to "unmeasurable or close to measurable" levels between doses (Ex. 1036, 53:15-54:17, 61:7-11), which its PK expert confirmed does ***not*** occur even in AbbVie's PK model (Ex. 1038, 141:22-142:15; Ex. 2075, ¶140, Fig.7).

In fact, 0.25 mg/kg IV biweekly D2E7 (*i.e.*, roughly ***half*** the claimed dosing regimen) was known to be "well tolerated, safe and efficacious." (Ex. 1014 at 5.) That C_{min} values would have been generally expected to be comparatively higher, and "concentration fluctuations" lower, for subcutaneous versus intravenous dosing only further undermines AbbVie's argument. (Ex. 1038, 71:3-75:11; Ex. 1051, 69; Ex. 2069, 120:24-122:11; Ex. 1033.)

Finally and most importantly, even if ADAs were a theoretical possibility, that would not have dissuaded a POSA from biweekly versions of the van de Putte 2000 dosing regimens. (Ex. 1036, 40:9-14, 41:17-42:9, 43:11-15.) As AbbVie's experts acknowledged, no drug is completely safe in every patient, and clinicians focused on the safety and efficacy of treatment regardless of the development of ADAs (particularly given that they do not necessarily abolish efficacy or cause adverse events). (Ex. 1036, 37:15-38:4, 80:14-17; 85:18-86:7; Ex. 1037, 100:16-102:6.) Indeed, ADAs were associated with Remicade and Enbrel, yet both drugs were approved and went onto great success, as AbbVie acknowledges. (Ex. 1002, 1284; Response, 35-37; Ex. 2071, ¶¶ 32-33; Ex. 1036, 46:8-20, 49:5-51:14; Ex. 1037, 97:2-13.)[12] Accordingly, the asserted theoretical potential for ADAs is not a teaching away. *Galderma*, 737 F.3d at 738-39 (no teaching away even where prior art reported "increased side effects" with higher dose, yet "failed to discourage" its use).

[12] Given the reported concerns about infections associated with higher doses of anti-TNFα treatments and patient compliance associated with IV administration, this further supports a motivation toward a lower effective subcutaneous dose. (*See* Ex. 1037, 88:6-13; Ex. 1002, 805.)

3. D2E7's Half-Life and Linear Pharmacokinetics Further Support Biweekly Dosing

AbbVie makes the straw-man argument that "[h]alf-life does not provide sufficient information to design a dosing regimen." (Response, 38-42.) As an initial matter, even AbbVie and its experts have acknowledged that half-life is a "meaningful parameter" in developing a dosing regimen. (Ex. 1002, 1324; Ex. 1038, 88:6-90:17.) More importantly, the prior art did not simply disclose D2E7's half-life divorced from all other information, but correlated that PK parameter with ***clinical data*** supporting the safety and efficacy of biweekly dosing. (Ex. 1011, 4; Ex. 1012, 8.) For example, Kempeni 1999 reports D2E7's half-life as 11.6 to 13.7 days, and explains that patients began to lose response after 2.5 weeks.[13] (Ex. 1011, 4.) In fact, in reporting that D2E7 may be administered every two weeks, Rau 2000 expressly touts its half-life. (Ex. 1012, 8; Ex. 1052, 1-2 (explaining that "the half-life [of D2E7] could be extended, which may mean it is possible to administer the drug on a less frequent basis," and that this hypothesis was confirmed through clinical studies).)

[13] AbbVie's reliance (at 43) on an April 9, 2010 study report involving 80mg administered every four weeks — which discusses a "noncomplian[t]" investigator whose data was excluded (Ex. 2015, 4) — is misplaced given the prior art teachings regarding this mean dosing interval.

That other PK parameters can also be considered (Response, 27-38) is therefore irrelevant to whether a POSA would have pursued the claimed dosing regimen based on prior art expressing a clear relationship between D2E7's half-life and dosing frequency. Likewise, irrespective of whether ***other, different*** "antibodies were dosed both more and less frequently than their half-lives" (Response, 41), or certain other drugs were assuredly ineffective when dose and interval are doubled (Response, 43-44), a POSA would not be taught away from the D2E7-specific teachings supporting a reasonable expectation of success with regard to the claimed D2E7 dosing regimen. (Ex. 1038, 144:15-146:9; Ex. 1011, 4; Ex. 1012, 8.)[14]

IV. AbbVie Admitted That 40mg Biweekly Is Equivalent to 20mg Weekly

AbbVie's *post hoc* explanations of its prior statements confirming the equivalence of 20mg weekly and 40mg biweekly doses are unpersuasive. In addressing its concession that, "[o]ver time, patients treated . . . with [a] 40 mg flat dose, subcutaneously biweekly, receive the same amount of D2E7 as those

[14] None of the cases AbbVie cites (at 39-40) supports a general rule requiring "complete PK/PD data," especially where, as here, the prior art disclosed multiple, clinically effective doses and associated that efficacy with pertinent PK parameters. Nor do the claims at issue include specific PK/PD limitations.

treated . . . with [a] 20 mg flat dose weekly" (Ex. 1023, 45), AbbVie cites its own statements that the PK profiles of these dosing schedules would have been different. (Response, 44-45.) As explained above, a POSA would not have found such differences meaningful for safety and efficacy.

Likewise, while AbbVie tries to limit its statement to the FDA that every other week doses are assumed to be similar to one-half the same dose given weekly to a "post-hoc" comparison of "infection rates," no such qualification is found in the cited documents. (Ex. 1016, 2; Ex. 1017, 109; Response, 44-45.) This is not surprising, for AbbVie cannot credibly contend that the stated equivalence is relevant for certain clinical considerations, but not others. Tellingly, AbbVie's Response does not even address the statement of the European Medicines Agency, the FDA's European counterpart, in the context of dose-response studies that "40 mg every other week" is "equivalent to 20 mg weekly." (Ex. 1018, 14; Petition, 29-30.) Accordingly, consistent with the teachings of the prior art, these statements and admissions confirm the therapeutic equivalence of 20mg weekly and 40mg biweekly doses.

V. AbbVie Fails to Overcome Arguments That the Claims Would Have Been Obvious to Try and the Result of Routine Optimization

In addition to repeating its teaching away arguments that are flawed for the reasons discussed above, AbbVie asserts that a POSA would have faced "a

large range of different dosing regimens." (Response, 46-48.) The Board, however, has already considered and rejected that argument. (Decision, 14 n.5.) Moreover, in seeking to inflate the number of dosing options, AbbVie disregards the prior art's (1) progression from Phase I, weight-based-dosing safety studies to a large-scale, efficacy-based Phase II dose-finding study demonstrating a preference for a finite number of subcutaneous fixed doses and (2) disclosure that the early clinical trials supported one of two dosing intervals. (Ex. 1052.) Thus, AbbVie's assertions that drug development generally may involve many choices, if anything, only emphasize that in this case a POSA would have been motivated by the prior art's specific teachings.

Further, even if more than one dosing regimen is theoretically available, that does not mean that a dosing regimen suggested by the prior art is nonobvious. *See Hoffmann-La Roche, Inc. v. Apotex Inc*., 748 F.3d 1326 (Fed. Cir. 2014) (affirming invalidity of a claimed dosing regimen of 150mg monthly over a prior art dose of 5mg daily).[15] This is particularly true given that the '135

[15] *See also Warner Chilcott Co. v. Teva Pharms. USA*, 594 F. App'x 630 (Fed. Cir. 2014) (non-precedential); *In re Copaxone*, Civ. No. 14-1171-GMS, Dkt. No. 294 (D. Del. Jan. 30, 2017); *Mylan Pharms. Inc. v. Yeda Research & Dev. Co.*, IPR2015-00643, Paper 85 (Aug. 24, 2016).

patent is not purporting to claim the single most effective dosing regimen. (Decision, 6-7.)

Finally, the fact that drugs under development may not gain FDA approval under strict regulatory standards does not mean that the claimed dosing regimen is not the result of routine optimization. (Response, 7, 56.) In the same way that regulatory approval is not a requirement of patentability, an obvious combination need not carry absolute certainty of regulatory approval. *Compare Merck & Co. v. Biocraft Labs., Inc.*, 874 F. 2d 804, 809 (Fed. Cir. 1989) ("But, absolute predictability of success is not the criterion; for obviousness under § 103, all that is required is a reasonable expectation of success."), *with* Ex. 1035, 35:2-7, 38:15-40:11 (applying wrong standard). Moreover, while AbbVie asserts that "[p]oor dose selection was ***the leading reason*** for delay and denial of FDA approval for new drug products" (Response, 49 (citing Ex. 2080)), only 4.9% of NDAs (15 of 302) were rejected for that reason, and by "the time drugs enter the later stages of development extensive clinical and nonclinical information is already available and sponsors are often confident about the safety and potential efficacy of investigational drugs." (Ex. 2080, 4, 6; Ex. 1035, 44:9-18, 49:1-52:20.) That is the case here. The claimed subject matter would have at a minimum been obvious to try and resulted from routine optimization.

VI. Alleged Secondary Considerations Do Not Overcome Petitioner's Showing of Obviousness

Evidence of secondary considerations cannot overcome a strong *prima facie* showing of obviousness, like that made here. (Petition, 44; *Agrizap, Inc. v. Woodstream Corp.*, 520 F.3d 1337, 1344 (Fed. Cir. 2008).) Moreover, none of the purported secondary considerations identified by AbbVie supports nonobviousness.

A. There Was No Long-Felt, But Unmet Need for "New RA Therapies"

By AbbVie's own admission, as of 2001, there were already multiple "breakthrough" anti-TNFα agents for treating RA, along with other more-established methods. (Response, 51.) Moreover, while AbbVie asserts that there was a need "for additional biologics with more advantageous dosing regimens," the prior art already had also disclosed biweekly and subcutaneous D2E7 dosing regimens satisfying any purported need. (Response, 51 (criticizing intravenous and twice weekly dosing regimens)[16]; Ex. 1009, 2.) Not

[16] The putative disadvantages of Enbrel and Remicade identified by AbbVie (multiple doses per week; intravenous administration at a doctor's office) provide additional evidence that a POSA would have been motivated to pursue subcutaneous, fixed-dose administration of D2E7 on a less-frequent basis.

surprisingly, then, neither AbbVie nor its declarants attempted to connect the allegedly unmet need to the allegedly inventive aspects of the claims. (*See* Response, 50-52; Ex. 2071, ¶¶95-96.) And, at his deposition, Dr. Gibofsky conceded that his discussion of "failure of others and long-felt need" referred to "***other antibodies*** than . . . D2E7" and that D2E7's beneficial properties were disclosed in the prior art, including U.S. Patent No. 6,090,382 ("the '382 patent"). (Ex. 1037, 63:11-64:16; Ex. 1048.[17])

AbbVie's evidence fails to show a long-felt, unmet need over the prior art. *Merck v. Gnosis, S.P.A.*, 808 F.3d 829, 838 (Fed. Cir. 2015) (long-felt need "not sufficiently connected with the novel elements of the asserted claims").

B. The Claimed Dosing Regimen Was Not "Unexpectedly Effective"

AbbVie's "unexpectedly effective" argument should be rejected as a mere repackaging of its alleged teaching away. *Hoffmann-La Roche,* 748 F.3d at 1330-1334.

Contrary to its current position, AbbVie consistently touted the safety and efficacy of each element of the claimed invention in prior art publications. (Ex. 1009, 2; Ex. 1012, 8.) Moreover, "unexpected results . . . must be shown to be

[17] Dr. Gibofsky did not even review the '382 patent before his declaration and AbbVie did not supply it to him. (Ex. 1037, 54:8-55:21.)

unexpected compared with the closest prior art." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006). AbbVie does not show that the claimed dosing regimen has unexpectedly better properties than the 20 or 40mg weekly doses disclosed in van de Putte 1999, and indeed the Humira label itself allows for 40 mg weekly dosing if the claimed biweekly dosing regimen does not provide sufficient efficacy. (Ex.1024, 1; Response, 52-53; Ex. 1037, 65:4-9.) Finally, AbbVie does not and cannot demonstrate any unexpected difference "in kind" against the closest prior art. *Galderma*, 737 F.3d at 739.

C. Commercial Success Is Within the Exclusivity of AbbVie's Blocking Patent and Not Due to the Claimed Subject Matter

In arguing that the sales of Humira support a finding of nonobviousness, AbbVie largely rehashes arguments that the Board has already considered and rejected. (Preliminary Response, 50-52; Decision, 18-19; Response, 53-55.) AbbVie again fails to show that Humira's sales are due to the claimed 40mg biweekly dosing, as opposed to prior art features (including the attributes of the fully humanized D2E7 antibody itself). *Galderma*, 737 F.3d at 740 ("[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent."). Indeed, AbbVie expressly relies on a number of features — including active ingredient (D2E7), method of administration (subcutaneous), and dosing interval (biweekly) — that were disclosed in the

prior art. (Response, 54.) And AbbVie's commercial success expert conceded that he did not consider the properties of the active ingredient itself or other uses of Humira in his analysis. (Response, 53-55; Decision, 18-19; Ex. 1034, 14:3-6; 16:24-18:2; 49:23-50:10.)

The probative value of Humira's sales is especially minimal here. AbbVie and its expert do not dispute that the prior art '382 patent covering D2E7 itself (issued July 18, 2000) blocked competitors from commercializing any D2E7 product for years (expiring in 2016). (Ex. 1034, 21:9-22:4, 23:5-26:14; Ex. 2188, 7.) "Where market entry by others was precluded due to blocking patents, the inference of non-obviousness of the asserted claims, from evidence of commercial success, is weak." *Galderma*, 737 F.3d at 740; *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376-77 (Fed. Cir. 2005) (same);[18] *In re Copaxone*, Dkt. No. 294, at 45. That is the case here, and the alleged commercial success of Humira does not support a finding of nonobviousness.

[18] Contrary to AbbVie's assertions (Response, 54-55), *Merck* is not limited to situations where "the claimed invention was a modification of an already-marketed dosage," but was expressly based on the existence of blocking patents (and regulatory exclusivity). 395 F.3d at 1377.

VII. Claim Construction

AbbVie concedes that "the proper interpretation of the claims and the level of efficacy they require is irrelevant to resolving the IPR," and does not cite any new intrinsic evidence supporting its proposed construction. (Response, 55.) There is thus no need or basis for the Board to reconsider its claim construction. And because van de Putte 2000 and Rau 2000 disclose meaningful therapeutic efficacy, AbbVie's argument is largely academic, as those references would have rendered the claims obvious even under AbbVie's construction. (Ex. 1037, 109:18-110:17 (ACR_{20} used to assess efficacy).)[19]

[19] In fact, the '135 patent cites efficacy data from van de Putte 1999 as putative support for the claimed subject matter. (Ex. 1037, 74:1-75:9; *see also id.*, 69:15-71:7 (disclosing efficacy over a broad dosage range).)

VIII. Conclusion

For at least the reasons set forth in the Petition and above, the Board should enter judgment against AbbVie and find claims 1-5 of the '135 patent unpatentable as obvious.

Dated: February 16, 2017

Respectfully Submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petitioner's Reply to Patent Owner's Response contains, as measured by the word-processing system used to prepare this paper, 5,591 words. This word count does not include the items excluded by 37 C.F.R. § 42.24.

Respectfully submitted,

Dated: February 16, 2017

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that I caused to be served on the counsel for Patent Owner a true and correct copy of the foregoing Petitioner's Reply to Patent Owner's Response by electronic means on February 16, 2017 at the following addresses of record:

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