Nos. 2017-2304, -2305, -2306, -2362, -2363

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

ABBVIE BIOTECHNOLOGY, LTD.,

Appellant,

v.

UNITED STATES, ANDREI IANCU, Director, U.S. Patent and Trademark Office,

Intervenors.

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2016-00172, IPR2016-00188, IPR2016-00189, IPR2016-00408, and IPR2016-00409

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August 20, 2019

CERTIFICATE OF INTEREST

Counsel for Appellant AbbVie Biotechnology, Ltd certifies the following:

1. The full name of every party or *amicus* represented by us is:

AbbVie Biotechnology, Ltd

2. The names of the real party in interest represented by us is:

Not applicable.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

AbbVie Bahamas Ltd.; AbbVie Limited (Cyprus); AbbVie Overseas S.à r.l.; AbbVie International S.à r.l.; AbbVie (Gibraltar) Holdings Limited Luxembourg S.C.S.; AbbVie (Gibraltar) Holdings Limited; AbbVie (Gibraltar) Limited; Pharmacyclics LLC; and AbbVie Inc.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this Court (and who have not or will not enter an appearance in this case) are:

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5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this Court's decision in the pending appeal:

None

Dated: August 20, 2019

/s/ Thomas G. Saunders

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INTRODUCTION

The government strives to transform this appeal into a series of individual factual disputes, but these arguments should not distract from the legal errors at the heart of the Board's decisions. The Board's obviousness theories all depend on selectively combining (1) the 40 mg dose administered subcutaneously on a weekly basis in the DE007 study with (2) the 0.5 mg/kg dose administered intravenously with a minimum of two weeks between doses in the DE003 study. The government does not dispute, however, that *every single patient receiving the 0.5 mg/kg dose in the DE003 study was up-dosed or withdrawn from the study by week 12*. The government's entire case thus depends on the proposition that a skilled artisan seeking a long-term treatment for a chronic, progressive disease like rheumatoid arthritis would have not only followed this abandoned path over more promising alternatives but taken a further leap into the unknown by combining it with subcutaneous administration of fixed doses.

This Court should reject the mix of hindsight and other legal errors that led the Board to accept such a tenuous theory. The Board improperly faulted AbbVie for failing to prove that *every* patient receiving a 0.5 mg/kg dose in the DE003 study was up-dosed for lack of efficacy, without acknowledging the profound problem that up-dosing posed for Petitioners' ability to carry their burden of proof. The government tries to downplay the issue, but there is a fundamental difference

between occasional up-dosing of specific patients and the pervasive up-dosing of patients receiving an every-other-week 0.5 mg/kg dose. Nor is it a response to say that some patients may have briefly benefitted before up-dosing. RA is a chronic, progressive disease, and in selecting a fixed dose to provide long-term treatment to a broad patient population, there would have been little incentive to rely on prior-art approaches that resulted in so much up-dosing. Indeed, some claims expressly require at least 24 weeks of treatment—well past the point at which the prior art contained *no information at all* regarding patients receiving the 0.5 mg/kg dose in the DE003 study.

The Board's errors on up-dosing were exacerbated by other flaws in its analysis. Working backwards from AbbVie's invention, the Board engaged in a fragmented inquiry that looked at individual aspects of AbbVie's claims without grappling with the cumulative uncertainty created by selecting low, fixed doses administered subcutaneously on a less frequent schedule. The government's brief invites this Court to repeat this error. It cites individual disclosures in the prior art, but repeatedly relies on statements made in the context of doses that were higher or administered more frequently—or question-begging statements about the incentive to select a "low" dose—while neglecting the cumulative uncertainty that would have been associated with the dosing regimen claimed.

The combination of elements that AbbVie's inventors brought together pushed beyond the boundaries of merely mixing known elements with predictable results. The risk they took yielded the original dosing regimen for the world's best-selling drug and the first treatment method involving subcutaneous administration of a monoclonal antibody ever approved by the FDA. The Board's decisions declaring this breakthrough obvious should be reversed or vacated.

ARGUMENT

I. THE GOVERNMENT'S DISCUSSION OF UP-DOSING HIGHLIGHTS THE BOARD'S LEGAL ERRORS

A. The Government Fails To Rehabilitate The Board's Flawed Up-Dosing Analysis

The Board's flawed discussion of the up-dosing in the prior art cascaded throughout its opinion and exemplified its hindsight-driven analysis and improper use of uncertainty against AbbVie. The government's attempts to rehabilitate the Board's analysis only make the problem worse.

All grounds asserted below relied on the interval between doses in the DE003 study to argue that it would have been obvious to subcutaneously administer 40 mg of D2E7 every other week. It is undisputed, however, that every patient receiving 0.5 mg/kg of D2E7 intravenously with two weeks between doses in the DE003 study was *up-dosed or withdrawn* by the twelfth week of treatment. *See* AbbVie Br. 38-40. That left no one in the DE003 study receiving an

intravenous dose lower than 1 mg/kg, which equates to an 80 mg intravenous dose for an 80 kg patient.

Numerous statements connected the up-dosing reported in the prior art to low efficacy. Kempeni reported that "patients who did not respond well after 0.5 or 1 mg/kg received higher doses of up to a maximum of 3 mg/kg." Appx2704. Rau disclosed that 58% of patients receiving 0.5 mg/kg never achieved an ACR20 response "at any point in time." Appx28087. Rau noted that the erythrocyte sedimentation rate "[i]n the 0.5 mg group" was "worsening again already after one week." *Id.* Rau also singled out "all doses > 1 (3) mg/kg body weight"—*i.e.*, *higher* doses starting at *double* the 0.5 mg/kg dose—when noting a "significant and long-lasting reduction of disease activity" that included a "*moderate*" response in 80% of patients. Appx28085 (emphasis added).

Petitioners bore the burden to overcome this powerful evidence against motivation to combine and reasonable expectation of success. *See In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375-1376 (Fed. Cir. 2016) ("the burden of persuasion is on the petitioner ... and that burden never shifts to the patentee," "especially ... where the only issues are ... whether there would have been a motivation to combine the prior art, and whether that combination would [have] render[ed] the patented claims obvious"); *see also infra* pp. 22-26. Yet the Board did not hold Petitioners to their burden. It instead speculated that "patients who

achieved a moderate response *may* have been up-dosed, which would not mean that the lower dose was ineffective." Appx167 (emphasis added). Indeed, it explicitly—and incorrectly—placed the burden on AbbVie, stating that "Patent Owner's assertion that *all* patients receiving a 0.5 mg/kg dose in Rau 2000 were up-dosed *because such a dose was ineffective* is not supported by any affirmative statement in Rau 2000 to that effect." *Id.* (second emphasis added). The Board never acknowledged that even if every single patient was not up-dosed due to ineffectiveness, the up-dosing of some or most patients due to ineffectiveness was highly relevant. Nor did the Board require Petitioners to overcome this substantial uncertainty by demonstrating that the up-dosing was unrelated to effectiveness. *See Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348, 1356 (Fed. Cir. 2017) ("Unpredictability of results equates more with nonobviousness rather than obviousness.").

The government's responses are unavailing. *First*, the government caricatures (at 30) AbbVie's position as requiring "that physicians seek to eliminate all disease activity, rather than develop a treatment regimen that balances efficacy, safety, convenience, and cost." Not so. A skilled artisan would have accounted for rheumatoid arthritis being a chronic, progressive condition. AbbVie Br. 34. In that context, a skilled artisan would not have looked for a treatment that provided most patients with, at most, limited benefit for only a short period or

marginal gains over no treatment at all. Appx6283-6285; Appx6300; Appx6308-6309; Appx6388-6389; *see also Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (motivation was to find "a compound that had high activity, few side effects, and lacked toxicity," not one with "baseline" activity); *see also Rembrandt Wireless Techs., LP v. Samsung Elecs. Co.*, 853 F.3d 1370, 1379-1380 (Fed. Cir. 2017) (no motivation to replace one computer protocol with another that was at best equivalent and perhaps inferior); *supra* pp. 1-2; AbbVie Br. 33-34, 40-44.

There were evident drawbacks to pursuing the combination of (1) a dose/dosing interval similar to the regimen that led every patient to be up-dosed or withdrawn in the DE003 study, and (2) the added uncertainty of subcutaneous, fixed doses and treatment for at least 24 weeks. The Board committed legal error when it failed to consider these drawbacks and weigh them against any potential benefit or set of benefits—such as increased efficacy without concomitant increase in risk—as *Yamanouchi*, *Rembrandt*, and other cases require. *See, e.g., Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1349 & n.8 (Fed. Cir. 2000). And although the Board's claim construction did not require a significant reduction in the signs and symptoms of RA, and claims construed to require greater efficacy would present an even stronger case of nonobviousness, the government's suggestion that a person of ordinary skill would pursue the lowest dose because it

is merely "better than placebo" (at 34-35) is flawed even under the Board's construction.[1]

The government's argument that a skilled artisan would always seek the lowest dose displaying any efficacy is misguided. The portions of Coherus's expert report the government relies upon (at 35 (citing Appx2740 ¶44, Appx2743 ¶69)) contain no support, and do not purport to describe patients suffering the effects of RA. And contrary to the government's suggestion (at 35), this Court did not enshrine the pursuit of the lowest dose as a matter of law in *Tyco Healthcare Group LP v. Mutual Pharmaceutical Co.*, 642 F.3d 1370 (Fed. Cir. 2011). The statement there was based on a case-specific concession. *Id*. at 1371. Moreover, the claimed dose that was deemed obvious in *Tyco* fell within the range disclosed by a standard reference manual. *Id*. at 1371-1372. In fact, it was *higher* than a dose used in two prior art studies and "sold abroad for more than a decade." *Id*. at 1374. *Acorda Therapeutics, Inc. v. Roxane Laboratories, Inc.*, 903 F.3d 1310 (Fed. Cir. 2018), is likewise distinguishable because there was no evidence that lower doses "would *not* be effective" and "'the art [] reduced the set of plausible doses because it suggested that higher doses [] were more likely to cause adverse

[1] Although AbbVie has not challenged the Board's claim construction on appeal, the Board's claim construction was nonetheless relevant to its opinion. The Board stressed that "the claims do not require a particular level of efficacy" (Appx144) and therefore did not speak to the patentability of claims that do.

events.'" 903 F.3d at 1330 (quoting trial court findings). Here, the art reported pervasive up-dosing, and there were no findings of significantly increased risk when the higher, more effective doses were administered. *Cf.* Appx28081 ("With the exception of mild and transient injection site reactions, adverse events occurred with the same frequency and distribution in the D2E7 and placebo groups.").

Second, the government's argument (at 42) that the "Board acknowledged that up-dosing occurred" is not a response to the fact that the Board shifted the burden to AbbVie to prove that "*all* patients receiving a 0.5 mg/kg dose," Appx167, were up-dosed due to lack of efficacy. Up-dosing was a critical issue, and Petitioners' own experts struggled to explain why it had occurred. *See* Appx31323-31324 (Boehringer expert stating he had "no idea" why up-dosing occurred); Appx6187-6189 (Coherus expert admitting she did not know the criteria for up-dosing). Had the Board not shifted the burden to AbbVie to prove that "*all* patients receiving a 0.5 mg/kg dose" were up-dosed, Petitioners' failure to prove that patients were up-dosed for reasons other than efficacy would have reinforced the cloud of uncertainty that confronted a person of ordinary skill. The burden of proof can powerfully shape the way individual pieces of evidence are viewed, as it did here.

Third, the government also misses the mark when it touts (at 31) that the 0.5 mg/kg biweekly dose in the DE003 study "was effective in treating patients."

Even the Board recognized that the 0.5 mg/kg dose was "not the most effective dose." Appx31. The Board also never found, contrary to the government's assertion (at 31), that up-dosing represented "at most, an alternative dosing schedule"—rather, the alternative referred to resuming dosing if there was a "flare up" after a "good" response had been achieved. Appx27; Appx28080; Appx31639. Rau's statement that 42% of patients on the 0.5 mg/kg dose achieved ACR20 came with the important qualifier "at any point in time," which does not indicate that the effects were sustained. Appx28087. In fact, Rau reported "worsening" in the erythrocyte sedimentation rate (a component of ACR) "already after one week." *Id.* Nor can any conclusions about sustained efficacy be inferred from Rau's Figures 4 and 5.[2] Those figures do not indicate how many patients continued to receive the 0.5 mg/kg dose at any point in time and, due to up-dosing, any apparent progress in the *average* values reported could have simply reflected the rate at which the poorest responders were being shifted off the dose. Appx31655-31657. In addition, because the patients on placebo were transitioned to treatment at week six of the DE003 study, the results shown in weeks 6-12 reflected patients receiving their first few treatments. Appx31639. And, of course, there was no data from the DE003 study on the performance of the 0.5 mg/kg dose

[2] The government attempts (at 33) to backfill with a 1998 press release, but the press release did not state how long the lowest dose was given or address the issue of up-dosing. *See* Appx29668; Appx30248-30249.

after 12 weeks. Indeed, Rau singled out *higher* doses when discussing "long-lasting reduction of disease activity." Appx28085. None of this would have motivated a person of ordinary skill looking for a long-term treatment to use a fixed dose of 40 mg administered every other week or provided a reasonable expectation of success in achieving the claimed invention.

Fourth, the government argues (at 34-35) that even if an option is not the best, there is sufficient motivation to pursue any option that is "better than placebo." But that begs the question whether modest, short-term results in some patients before an entire cohort is up-dosed would be considered suitable in treating a chronic, progressive condition. Petitioners never proved that it would be, and their experts' testimony indicated it would not. Appx6283-6285; Appx6300; Appx6308-6309; Appx6388-6389.

B. The Board's Reliance On Weisman Cannot Save Its Decision

Unable to defend the prior-art combinations that were the subject of the petitions and the Board's institution decisions, the government (at 31, 32 n.15, 39) cites the Weisman reference. The government argues (at 32 n.15) that the Board's use of Weisman was permissible because it "used Weisman to respond to AbbVie's arguments and AbbVie had a chance to" respond. But if that is correct,

then the government cannot rely on Weisman to fill the holes in its prima facie case, as it now attempts.[3]

Regardless, Weisman does not help the government. The government does not dispute that Weisman itself reported significant up-dosing of patients receiving an every-other-week intravenous dose of 0.5 mg/kg of D2E7 in combination with methotrexate. *See* AbbVie Br. 42-43; Appx28106; Appx29403-29404; Appx29678-29681; Appx30328; Appx30359-30360. But in citing Weisman, the Board never addressed this critical fact. AbbVie Br. 42-43; Appx166; Appx45182-45183. The Board never even acknowledged the up-dosing in Weisman while relying on Weisman to fill the gaps in Rau. *See* Appx166-167. This one-sided discussion of Weisman, which "failed to consider an important aspect of the problem," is itself a legal error. *Motor Vehicle Mfrs. Ass'n of the U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

Moreover, the Board made an indefensible leap of logic even within that incomplete discussion. The Board claimed that a skilled artisan would not have been deterred from pursuing the 0.5 mg/kg dose in Rau 2000 because "a later prior art study, Weisman, tested a biweekly 0.5 mg/kg dose of D2E7 (and even a 0.25

[3] Weisman cannot provide a basis for affirmance in the Coherus IPRs because the Board did not rely on it. *SEC v. Chenery Corp.*, 318 U.S. 80, 87-88 (1943); *see also, e.g., DSS Tech. Mgmt., Inc. v. Apple Inc.*, 885 F.3d 1367, 1377 n.4 (Fed. Cir. 2018) ("Under the *Chenery* doctrine, we decline Apple's invitation to consider evidence that the Board did not cite in its decision.").

mg/kg dose)" and it would have been "counterintuitive to test a dosage that previously had been determined to be ineffective." Appx166. As AbbVie explained in its opening brief, however, "Weisman published *six-month results* only *three months* after Rau 2000." AbbVie Br. 43 n.6 (emphases added); *compare* Appx28103 *and* Appx28106, *with* Appx28082 *and* Appx28085-28090. Because Weisman was already in progress before Rau 2000 was published, it sheds no light on how a skilled artisan would have reacted to the up-dosing reported in Rau 2000. Indeed, Rau 2000 was the first to report that *every* 0.5 mg/kg patient remaining in DE001/DE003 trial after 12 weeks was up-dosed or withdrawn. Weisman does not and cannot address how a skilled artisan would have responded to that crucial inflection point, and it was error for the Board to say otherwise.

This case is thus distinguishable from *Genzyme Therapeutic Products LP v. BioMarin Pharmaceutical Inc.*, 825 F.3d 1360 (Fed. Cir. 2016). There, the disputed references "merely served to describe the state of the art," *id*. at 1369, and the specific manner of their use was anticipated and addressed in advance in the patent owner's response, *id*. at 1367. Boehringer did not cite Weisman in its petition and mentioned it only once in a single sentence in its reply brief. Indeed, Weisman was not even analyzed in the declaration of Boehringer's expert, Dr. Weisman, the study's lead author. Appx44917-44918; Appx39508-39509 (citing Appx28001-28002). AbbVie lacked notice that the Board would use

Weisman in the unusual manner that it did because its error appeared for the first time in the Board's final written decision. This Court should correct, not indulge, that error.

C. The Board's Errors Were Even More Egregious In The Context Of The "At Least 24 Weeks" Limitation

The up-dosing or withdrawal by week 12 of every patient receiving a 0.5 mg/kg dose in the DE003 study is especially problematic with respect to the Board's treatment of claims 3 and 4 of the '135 patent, which require "administ[ration] for a period of *at least 24 weeks*." Appx266(45:30-46:12) (emphasis added). With no patients left after 12 weeks, a skilled artisan simply had no basis to believe that combining a low fixed dose with longer gaps between doses was sustainable for the "at least 24 weeks" claimed. A reasonable expectation of success must be grounded in sufficient scientific evidence for the expectation to be reasonable. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012). With every patient in the 0.5 mg/kg arm of the DE003 study up-dosed or withdrawn long before 24 weeks, there was no data on which such an expectation could reasonably be based. *Los Angeles Biomedical Research Inst. at Harbor-UCLA Med. Ctr. v. Eli Lilly & Co.*, 849 F.3d 1049, 1065-1066 (Fed. Cir. 2017) (prior art's observation, based on "no data," "cannot serve as an express or implicit teaching").

The government's limited attempts to defend the Board's rulings on the 24-week limitation are inadequate. The government's assertion that certain publications "disclose treatment of at least 24 weeks" (at 39) fails to acknowledge that no prior art reference in the instituted grounds described the every-other-week treatment *at the low 0.5 mg/kg dose*—which was critical to the Board's obviousness analysis—past week 12, much less continuously for at least 24 weeks.[4] The longer treatment periods cited by the Board were all for higher doses and/or shorter gaps between doses. Contrary to the government's invitation (at 17), the Board could not simply look at *other* doses or treatment schedules and check the box on the "at least 24 weeks" limitation. The question is whether there would have been a reasonable expectation that patients could successfully be treated for at least 24 weeks with the *claimed* invention. *Institut Pasteur & Universite Pierre et Marie Curie v. Focarino*, 738 F.3d 1337, 1344 (Fed. Cir. 2013). The route that the Board relied on to reach every-other-week dosing at the low fixed dose claimed did not contain data to support a reasonable expectation

[4] The government also cites Weisman, but it was not one of the references on which the Board instituted review. *See* Government Br. 4; Abbvie Br. 52-53. Further, the Board never relied on Weisman to support that "at least 24 week" limitation. Appx166; Appx214. This Court may not affirm the Board's decision on a factual ground not adopted by the Board. *See Chenery*, 318 U.S. at 88 (1943); *In re Comiskey*, 554 F.3d 967, 974 (Fed. Cir. 2009).

that successful treatment at that dose on an every-other-week schedule could be sustained.

The government's argument (at 39) that "[e]ven without 24 weeks of data, long-term treatment would be obvious" ignores the requirement to establish a reasonable expectation of success. The issue is not whether long-term treatment would be desirable in the abstract, but whether a skilled artisan would persist in maintaining a low dose when all other patients have been up-dosed, and specifically whether that artisan would have reasonably expected efficacy after 24 weeks when prior patients in the DE003 study barely made it to 12 weeks. Even if it had been "obvious to experiment" with the claimed dosing regimen—which it was not given the large number of possible combinations—"there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective. This distinction is important." *Cyclobenzaprine*, 676 F.3d at 1070 (citation omitted).

II. THE BOARD'S OTHER LEGAL ERRORS EXACERBATED ITS FLAWED ANALYSIS OF UP-DOSING

The Board's flawed analysis of up-dosing was embedded in a larger set of legal errors that relied on impermissible hindsight, failure to consider the claims as a whole, and burden shifting to disregard the cumulative uncertainty that undercut the Board's analysis.

A. The Board's Analysis Was Driven By Hindsight And Failed To Consider The Claims As A Whole

As discussed in AbbVie's opening brief, the Board layered uncertainty upon uncertainty as it pieced together the elements of AbbVie's claims, all while using AbbVie's disclosure as a guide through the prior art. AbbVie Br. 30-35. Those uncertainties should have counted against Petitioners, who bore the burden of proof. *See Magnum Oil*, 829 F.3d at 1375-1376; *Honeywell*, 865 F.3d at 1356.

The prior art presented a wide array of different doses, routes of administration, dosing intervals, and other variables. But rather than asking which of the many possibilities a person of ordinary skill would have been motivated to pursue with a reasonable expectation of success, the Board worked backwards from the claimed invention and asked whether there was a reason to modify the weekly 40 mg dose in the DE007 study (as opposed to the doses in the study that did not correspond to AbbVie's claims) by shifting to every-other-week administration of 40 mg (as opposed to other dosing intervals) without the weight-based doses or intravenous administration used in the DE003 study. This was itself error, as it is improper to use a patent's claims to motivate a particular path through the prior art. *See Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367-1368 (Fed. Cir. 2016).

The Board's picking and choosing from the references introduced cascading uncertainty with regard to the safety and efficacy of the resulting regimen. *First*, it

adopted an every-other-week dosing interval, which would have been expected to result in a lower C_{min} compared to the weekly doses in the van de Putte abstracts. *See* Appx31770-31771; *see also* AbbVie Br. 16-18, 32, 44-46. *Second*, it selected subcutaneous administration over intravenous administration, which would have been expected to diminish bioavailability. Appx31763; Appx31765; *see also* AbbVie Br. 22-23; Appx27-28. *Third*, it settled on a 40 mg fixed-dosing paradigm that increased the risk of underdosing, especially in heavier patients. *See* Appx31773; Appx32052; *see also* AbbVie Br. 32, 35. *Fourth*, it assumed the suitability of this regimen for long-term treatment (including treatment for at least 24 weeks), going beyond the point at which every patient receiving 0.5 mg/kg intravenously in the DE003 trial had been up-dosed. Appx15; Appx19; Appx28088; Appx31655; Appx31821-31822; AbbVie Br. 32-33, 52.

These aggressive choices show that the claimed combination would not have been obvious. Even where "the separate elements" of an invention can be found in the art, the "uncertainties" engendered by putting multiple elements together "counsel[] against [a claimed] combination." *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 957-958 (Fed. Cir. 1997). Here, the prior art taught the *insufficiency* of an every-other-week 0.5 mg/kg intravenous dose, and that selection became even more questionable when combined with the other claim elements.

The government contends (at 26-29) that, in making these choices, the Board sufficiently analyzed motivation to combine and reasonable expectation of success. But at no stage in the Board's analysis did it ever assess the *cumulative* impact of its aggressive choices. Although the Board identified generalized reasons for making each *individual* choice, "piecemeal analysis is precisely the kind of hindsight that the Board must not engage in." *In re NTP, Inc.*, 654 F.3d 1279, 1299 (Fed. Cir. 2011). The Board erred in failing to step back and consider the choices *in the aggregate* by weighing their effects together as a whole, both as a skilled artisan aiming to safely and effectively treat RA would have done and as the law requires. *See id.*; *see also Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) ("The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim.").

The Board's omission is compounded by its similar failure to grapple with the evidence that, with respect to each parameter, a skilled artisan had myriad more promising alternatives available. *See* AbbVie Br. 33-34. Motivation to combine concerns "what is, *on balance*, desirable," such that "benefits, both lost and gained, should be *weighed against one another*" in a holistic analysis. *Winner*, 202 F.3d at 1349 & n.8 (emphases added); *accord Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). Aside from the Board's cursory statement that a "skilled artisan designing a dosing regimen through clinical trials would have

balanced efficacy with other factors including safety and patient preference," Appx37—which is framed at a level of generality that threatens to find motivation to pursue *any* possibly effective dosing regimen—the Board did not even purport to engage in such an analysis. This failure, like the Board's failure to address cumulative uncertainty, betrays hindsight. *See In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995) ("The PTO's theory that one might have been motivated to try to do what Deuel in fact accomplished amounts to speculation and an impermissible hindsight reconstruction of the claimed invention. … [A]ny motivation that existed was a general one, to try to obtain a gene that was yet undefined and may have constituted many forms. A general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search.").

The government's brief reveals the same hindsight. The government ventures (at 6) that "physicians preferred smaller doses," "less frequent doses," "fixed doses" over "[c]ustomized doses," and "subcutaneous injections to intravenous injections." Those are remarkable statements considering, at the relevant time, no monoclonal antibody had ever been approved for subcutaneous administration and the leading anti-TNFα antibody product on the market (Remicade®) used weight-based, intravenous doses. Appx2844; Appx31776. Moreover, any abstract preference for certain features does not mean that a person

of ordinary skill would ignore the benefits of, and greater likelihood of success with, more conservative treatment regimens in combating a progressive disease. A skilled artisan would not look at the up-dosing of every patient in the DE003 study receiving 0.5 mg/kg with two weeks between doses and pursue modifications—from among the many possible combinations disclosed—that would further sacrifice efficacy for patient convenience.

Indeed, the government's high-level abstraction blows past all the uncertainty that surrounded what the lowest effective dose actually was, how combining aggressive dosing parameters would affect safety and efficacy, and the countervailing incentive to pursue more promising and conservative dosing regimens. *See ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1328 (Fed. Cir. 2012) (motivations to "build[] something better," "more efficient," "cheaper," and with "more features" too "generic" because they "fail to explain why a person of ordinary skill in the art would have combined the elements from specific references *in the way the claimed invention does*"). Indeed, if accepted as sufficient to satisfy the motivation-to-combine requirement—particularly in the context of the uncertainty and complexity of the issues here—the government's generalization would eliminate the requirement to show motivation to pursue *any* "low" dose.

The government fares no better with its more specific arguments. *First*, although the government (at 37) attempts to equate the bioavailability of a subcutaneous 40 mg dose with an intravenous 0.5 mg/kg dose, it does not dispute the general principle that "[t]he bioavailability of a [subcutaneously] administered drug is almost always lower than for the same drug administered intravenously." Appx31765. Instead, it relies—as did the Board—on references involving *higher average doses* administered *more frequently* than those at issue here to argue equivalence.[5]

Second, the government (at 37-38) downplays the importance of the expected reduction in C_{min} from switching to every-other-week dosing, while again improperly shifting the burden to AbbVie to show teaching away based on C_{min} data. Petitioners' own experts, however, conceded the nature and importance of C_{min}. Coherus's expert admitted that the "C_{min} [would be] slightly lower." Appx31159. The same expert testified that "many in the industry believed" that C_{min} was "the best parameter" for determining efficacy (Appx2739) and argued that, "to avoid underdosing," a skilled artisan with sufficient PK data would have wanted to design a dosing regimen in which the "C_{min} would be *at or above the C_{min} of other regimens* shown to be safe and effective" (Appx6123 (emphasis

[5] In addition, those references did not even include an intravenous arm, and witnesses for one of the Petitioners could not say what was being compared. See AbbVie Br. 12, 51; Appx6134.

added)). Boehringer's expert had written that "trough concentration (C_{min}) was regarded as the most important factor in dose determination because maintaining a prolonged efficacious exposure at the site of action is critical for anti-rheumatic drugs." Appx30895.

Third, the government does not even attempt to argue the equivalence of weight-based dosing and fixed dosing. The government cannot deny that fixed doses increase the risk of underdosing patients due to "patient-to-patient variability" such as differences in weight. Appx31773, Appx31803; AbbVie Br. 32.

Finally, the Board did not need to explicitly say that it was relying on hindsight to succumb to it. As this Court has warned, the "hindsight syndrome" is "insidious." *Zoltek Corp. v. United States*, 815 F.3d 1302, 1313 (Fed. Cir. 2016) (quotation marks omitted). Here, the Board's failure to grapple with the totality of the evidence before it—including on the centrally important points of cumulative uncertainty and more promising alternatives—reflects just such reliance on hindsight. *See* AbbVie Br. 30-35.

B. The Board Improperly Shifted The Burden Of Proof To AbbVie On Other Points Of Uncertainty Beyond Up-Dosing

As discussed in AbbVie's opening brief, the Board's analysis was further flawed because it relied on burden shifting. This was fueled in part by the Board's decision to structure its analysis as an extended discussion of teaching away, which

conflated the issue of motivation to combine with lack of teaching away. *See* AbbVie Br. 36-38. "Whether a reference teaches away is doctrinally distinct from whether there is no motivation to combine prior art references." *Rembrandt*, 853 F.3d at 1379; *see also Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1052 n.15 (Fed. Cir. 2016) (en banc). "[E]ven if a reference is not found to teach away, its statements regarding preferences are relevant to a finding regarding whether a skilled artisan would be motivated to combine that reference with another reference." *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1069 (Fed. Cir. 2018).

The government (at 41-42) contends that the Board made no error because AbbVie argued teaching away. But AbbVie argued both teaching away *and* lack of motivation to combine. *See, e.g.*, Appx43218 (arguing that "[a] POSA *would not have been motivated*" (emphasis added)); Appx43231 (same, also noting that "Petitioner cannot satisfy [the] requirement" to show "a reason or motivation to modify the prior art"); Appx44801 (similar). Moreover, regardless of how AbbVie framed its arguments, the Board was not entitled to disregard a bedrock element of Petitioners' prima facie case of obviousness. *Compare Polaris*, 882 F.3d at 1070 (remanding for evaluation of possible teaching away, but directing that motivation to combine be assessed to the extent "the Board determines that [the reference] does not teach away"), *with* Polaris Br., *Polaris Industries, Inc. v. Arctic Cat, Inc.*,

2016 WL 7046274, at *2, *23, *32, *39-45 (Fed. Cir. Nov. 30, 2016) (patentee arguing in terms of teaching away). Whether a patentee speaks in terms of lack of motivation to combine or teaching away, "the patentee's position is that the patent challenger failed to meet *its* burden of proving obviousness," as both sets of arguments go to the patent challenger's failure to meet its burden to show the "necessary predicate" of motivation to combine. *Magnum Oil*, 829 F.3d at 1375-1376. In other words, the patentee is not seeking to "establish a proposition" logically independent of one necessarily "relied on by the patent challenger," but rather is arguing that the patent challenger has not shown what it must. *Id.* at 1376.

The Board's burden shifting was perhaps most evident in its discussion of up-dosing. *See supra* pp. 3-5. But that was far from the only example of "reverse reasoning" in which the Board ignored that "[u]npredictability … equates more with nonobviousness rather than obviousness." *Honeywell*, 865 F.3d at 1356. For example, the Board also shifted the burden when it dismissed concerns about low C_{min}. The Board arrived at an aggressive combination of treatment parameters that, even with a two-week half-life, would have resulted in a lower C_{min} at steady state than the 20 mg weekly dose in van de Putte. AbbVie Br. 17, 44-46; *see also* Appx31152. But the Board improperly dismissed these concerns by asserting that the prediction of low C_{min} was "not entitled to much weight because … the minimum effective dose of D2E7 'was undefined in June 2001'" (Appx33;

Appx17), and "the publicly available PK information in June 2001 would not have permitted a PK/PD correlation for modeling purposes." (Appx33). The Board failed to recognize that these exact uncertainties would have made a person of ordinary skill wary of aggressively stringing together C_{min}-lowering treatment parameters.

The government (at 37) embraces the same fallacy of imputing uncertainty against AbbVie by arguing that a lower C_{min} would have been inconsequential, noting that "there was no basis to establish whether a given C_{min} was too low to be effective." That is exactly the problem. Petitioners, as the parties with the burden of proof, could not identify that minimum level either even though their own PK experts admitted that C_{min} was an important measure utilized in designing dosage regimens. Appx2739; Appx6123; Appx30895; *see also* AbbVie Br. 44-45.

The Board also improperly turned the tables against AbbVie with regard to Rau 2000's penultimate sentence, which stated 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." Appx158. The Board read the statement broadly, reasoning that it did not "exclude any dosage level." Appx165; *see also* Appx31652-31653; AbbVie Br. 47-48. This approach of assuming efficacy unless expressly told otherwise is out of step with the way that a person of ordinary skill would have read the prior art. For example, when Rau singled out *higher* doses for

praise and reported that everyone on the 0.5 mg/kg dose in the DE003 study was *up-dosed or withdrawn* from the study by 12 weeks, a skilled artisan would not have assumed that merely because Rau's broad penultimate sentence is silent on dose, it applies to the problematic 0.5 mg/kg dose. Statements in the prior art must be "read in context." *Shire LLC v. Amneal Pharms., LLC*, 802 F.3d 1301, 1308 (Fed. Cir. 2015).[6]

III. THE BOARD APPLIED THE WRONG LEGAL STANDARD TO THE RAU, SCHATTENKIRCHNER, AND VAN DE PUTTE COMBINATION

The Board's discussion of Rau 1998, Schattenkirchner, and van de Putte 1999 incorporated all the above errors, and then compounded them by relying on the standard for instituting an IPR ("reasonable likelihood of prevailing at trial") in the final written decision. The government advocates (at 42-43) overlooking the mistake as a mere "typographical" error. But if true, the Board can say so on remand. "[T]he orderly functioning of the process of review requires that the grounds upon which the administrative agency acted [are] clearly disclosed and

[6] The Board also improperly shifted the burden on commercial success when it considered the presumption of a nexus rebutted because "it is not clear whether the sales of HUMIRA® are due to the [claimed] dosing regimen recited." Appx41. A presumption is operative precisely when the weight of the evidence is unclear or in equipoise. *See, e.g.*, *Versata Dev. Grp., Inc. v. SAP Am., Inc.*, 793 F.3d 1306, 1320 (Fed. Cir. 2015); *Jensen v. Brown*, 19 F.3d 1413, 1417 (Fed. Cir. 1994). The government responds (at 41) by implying, for the first time, that AbbVie did not even trigger a presumption by proving that its product embodies the claimed invention. But it was undisputed that the claimed treatment regimen was the sole FDA-approved indication at the time AbbVie launched Humira®. Appx5570. That is clearly sufficient to trigger the presumption.

adequately sustained." *Chenery*, 318 U.S. at 94. And unlike the cases the government cites in support, the Board's error was not self-evidently harmless. *Cf. In re Depomed, Inc.*, 680 F. App'x 947, 953 (Fed. Cir. 2017) (nonprecedential) ("Even though the Board misstated" a predicate for showing long-felt need, it still "accorded some weight" to patent owner's evidence without that predicate). Further, no comfort is gained from the Board's recitation of the post-institution standard elsewhere in its decision when it said that "claims 1–5 of the '135 patent are unpatentable as obvious over the combination of van de Putte 2000 and Rau 2000 by a preponderance of the evidence." Appx186. That combination was not even an asserted ground in IPR2016-00409, and thus this statement only reinforces the Board's overall lack of care and the need for a remand.

IV. *OIL STATES* PERMITS ABBVIE'S CHALLENGE TO THE RETROACTIVE APPLICATION OF IPR

In *Oil States Energy Services LLC v. Greene's Energy Group, LLC*, 138 S. Ct. 1365 (2018), the Supreme Court rejected a facial challenge to *inter partes* review under Article III and the Seventh Amendment, but left the door open to challenge the retroactive application of *inter partes* review. Subsequent decisions by this Court appear to preclude retroactivity challenges to IPR at the panel stage. *E.g.*, *Collabo Innovations, Inc. v. Sony Corp.*, No. 18-1311, 2019 WL 3545450 (Fed. Cir. Aug. 5, 2019) (nonprecedential); *Celgene Corp. v. Peter*, No. 18-1167, __ F.3d __, 2019 WL 3418549 (Fed. Cir. July 30, 2019).

AbbVie preserves the right, however, to seek further review of its challenge to the retroactive application of IPR at the appropriate time. It is one thing for an inventor who entered the patent system by disclosing an invention after the AIA to receive a patent subject to the known possibility that it could be challenged in IPR. It is quite another thing for an inventor who entered the patent system before the AIA to have its patents subjected to a new form of invalidation. "The disclosure required by the Patent Act is 'the quid pro quo of the right to exclude.'" *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 142 (2001). An inventor pays the price for patent protection when it first discloses its invention. *Cf.* 35 U.S.C. § 100(a) (applying, *inter alia*, post-AIA § 102(a) modified sources of prior art to patents based on *filing* date). The public cannot subsequently change the terms of the bargain in the way that occurred here.

The government is wrong to contend that AbbVie waived its constitutional argument. A party is not required to raise a constitutional challenge to an agency's statutory authority before an agency lacking authority to grant the challenge. *E.g.*, *Mathews v. Diaz*, 426 U.S. 67, 76 (1976). "Adjudication of the constitutionality of congressional enactments has generally been thought beyond the jurisdiction of administrative agencies." *Johnson v. Robison*, 415 U.S. 361, 368 (1974); *see also Nebraska v. EPA*, 331 F.3d 995, 997 (D.C. Cir. 2003) ("Agencies do not ordinarily have jurisdiction to pass on the constitutionality of federal statutes."). In fact, as

the government recognizes (at 44), the Board has "decline[d] to consider [a] constitutional challenge" based on "retroactive application" of IPR. *Axis Comm'cns AB v. Avigilon Patent Holding 1 Corp.*, No. IPR2018-01268, 2019 WL 137163, at *19 (P.T.A.B. Jan. 8, 2019); *see also Ex Parte D'Agostino*, No. 2008-5833, 2009 WL 227743, at *13 (B.P.A.I. Jan. 30, 2009) (holding that constitutional arguments relating to the retroactive application of ex parte reexamination were "beyond the jurisdiction of the Board"). And unlike *In re DBC*, the Board here could not have simply "cure[d] the alleged constitutional infirmity" by providing a different panel. 545 F.3d 1373, 1379 (Fed. Cir. 2008); *see also Celgene*, 2019 WL 3418549, at *11 ("[I]t is unclear how the Board could have corrected the alleged constitutional defect as it could have in *DBC*.").

Further, unlike *VirnetX Inc. v. Apple, Inc.*, where the patent owner "never sought to provide supplemental briefing or to otherwise develop [a constitutional] argument following the Supreme Court's decision in *Oil States*," 909 F.3d 1375, 1379 (Fed. Cir. 2018), or *Trading Technologies International, Inc. v. IBG LLC*, 921 F.3d 1084, 1095 (Fed. Cir. 2019), where the patent owner said nothing in its reply brief other than the apparent concession that "*Oil States* will resolve the constitutionality of CBM Review" (Dkt. 51, at 32, No. 2017-2257), AbbVie asserted a constitutional challenge in its opening brief (AbbVie Br. 54-55) and has

preserved a retroactivity challenge following *Oil States* within the bounds permitted by this Court's precedent.

CONCLUSION

The Board's decisions should be reversed, or at least vacated and remanded.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that, on this 20th day of August, 2019, I filed the foregoing Replacement Reply Brief for Appellant AbbVie Biotechnology, Ltd with the Clerk of the United States Court of Appeals for the Federal Circuit via the CM/ECF system, which will send notice of such filing to all registered CM/ECF users.

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CERTIFICATE OF COMPLIANCE

Pursuant to Fed. R. App. P. 32(g), the undersigned hereby certifies that this brief complies with the type-volume limitation of Circuit Rule 32(a).

1. Exclusive of the exempted portions of the brief, as provided in Fed. R. App. P. 32(f), the brief contains 6,999 words.

2. The brief has been prepared in proportionally spaced typeface using Microsoft Word 2016 in 14-point Times New Roman font. As permitted by Fed. R. App. P. 32(g), the undersigned has relied upon the word count feature of this word processing system in preparing this certificate.

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