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

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

ABBVIE BIOTECHNOLOGY, LTD.,

Appellant,

v.

COHERUS BIOSCIENCES INC.,

Appellee.

ABBVIE BIOTECHNOLOGY, LTD.,

Appellant,

v.

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

Appellees.

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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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: May 4, 2018

/s/ Thomas G. Saunders

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INTRODUCTION

Petitioners Boehringer and Coherus strive to transform this appeal into a series of individual factual disputes, but the Court should not let their arguments distract from the legal errors at the heart of the Board's decisions. Petitioners' 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. Petitioners do 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.* Petitioners' entire case thus depends on the proposition that a person of ordinary skill seeking a long-term treatment for a chronic, progressive disease like rheumatoid arthritis would have not only followed this abandoned path over the more promising alternatives available 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 Petitioners' 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. Petitioners try to downplay the issue by noting that drug labels sometimes mention the possibility of up-dosing, but there is a fundamental difference between occasional up-dosing of specific patients and the pervasive up-dosing of patients receiving a 0.5 mg/kg dose every other week reported in the prior art. 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.

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. Petitioners' briefs invite this Court to repeat this error. Petitioners string together citations to make individual arguments about what the prior art disclosed. But they repeatedly rely on statements made in the context of doses that were higher or administered more frequently—along with 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. PETITIONERS' DISCUSSION OF UP-DOSING HIGHLIGHTS THE BOARD'S LEGAL ERRORS

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 imputation of uncertainty against AbbVie. Petitioners' attempts to rehabilitate the Board's analysis only make the problem worse.

All of Petitioners' asserted grounds 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.

Moreover, numerous statements connected the up-dosing 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., doses *higher than* 0.5 mg/kg—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. 21-25. Yet the Board did not hold them 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 to show otherwise, 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.").

Petitioners' responses are unavailing. *First*, Coherus (at 41) and Boehringer (at 31) argue that the Board *elsewhere* recited their burden to prove unpatentability. But boilerplate is no substitute for correctly applying the burden of proof in practice, particularly on such a critical point as up-dosing. *See, e.g.*, *Robinson v. United States*, 305 F.3d 1330, 1332 (Fed. Cir. 2002). The Board's decisions do not provide adequate assurance that it applied the correct rule when it mattered and, at minimum, the Court should remand for an explanation that clearly applies the correct burden.

Second, Boehringer argues (at 32 n.24) that the burden of proof does not matter in an IPR "absent a showing that the evidence was in equipoise." But this case perfectly illustrates why Boehringer is wrong. Up-dosing was a critical issue, and Petitioners' own experts struggled to explain why it had occurred. *See* Appx6187-6189 (Coherus expert admitting she did not know the criteria for up-dosing); Appx31323-31324 (Boehringer expert stating he had "no idea" why up-dosing occurred). Had the Board not shifted the burden to AbbVie to prove that "*all* patients receiving a 0.5 mg/kg dose" were up-dosed due to lack of efficacy, 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 is more than just a tiebreaker when the evidence is in equipoise, but rather can powerfully shape the way individual pieces of evidence are viewed, as it did here.

Third, this Court should reject Coherus's (at 32 and 44) and Boehringer's (at 22, 47 n.32) suggestion that up-dosing does not matter because the 0.5 mg/kg dose in the DE003 study arguably showed some efficacy in some patients before its discontinuance. Coherus stresses (at 33) that the Board's claim construction does not require a significant reduction in the signs and symptoms of RA. Although claims construed to require greater efficacy would present a stronger case of

nonobviousness, Petitioners' arguments are flawed even under the Board's construction.[1]

RA is a chronic, progressive condition. A skilled artisan would not have been looking for a treatment that provided most patients with, at most, limited benefit for only a short period. 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.

Coherus incorrectly contends (at 40) that *Yamanouchi* and *Rembrandt* "are inapposite, because neither included prior art teaching the benefits of the claimed method, while in both cases the fact-finder had found there were drawbacks to the claimed method." Both cases did identify a possible benefit: baseline drug

[1] Boehringer's argument (at 19 n.18) that "these proceedings did not turn on issues of claim construction" is incorrect. Although AbbVie has not challenged the Board's claim construction on appeal, that does not mean the Board's claim construction was irrelevant to its opinion. The Board stressed that "the claims do not require a particular level of efficacy" (Appx144) and therefore it did not speak to the patentability of claims that do so.

activity (*Yamanouchi*, 231 F.3d at 1345) and device communication (*Rembrandt*, 853 F.3d at 1379). And here, 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, 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).

Petitioners also miss the mark when they tout that 42% of patients on the 0.5 mg/kg dose in the DE003 study achieved ACR20. That statement 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

[2] Boehringer attempts (at 48) 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.

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 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, Boehringer argues (at 51) that even if an option is not the "best," there is sufficient motivation to pursue any "suitable" option. 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.

Fifth, Boehringer's suggestion (at 22) that up-dosing of Remicade® would have eliminated concerns about up-dosing D2E7 is unsupported. *See also* Boehringer Br. 51-52. The Remicade® label states that, "[f]or patients who have

an incomplete response, *consideration may be given* to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks." Appx30268 (emphasis added); *see also* Appx167. This statement merely reflects that every patient is different and that there can be exceptions to a generally applicable dosing regimen. That is a far cry from the extensive up-dosing in the prior art, where no patient receiving a 0.5 mg/kg dose in the DE003 study made it past 12 weeks. Boehringer's reliance (at 52) on the ad hoc "additional benefit" of switching to weekly doses that AbbVie's own label describes for "[s]ome patients" not taking methotrexate (Appx28641) fails for the same reason—not to mention that AbbVie's label was neither prior art nor relied on by the Board.

Finally, unable to defend the prior-art combinations that were the subject of their petitions and the Board's institution decisions, Coherus (at 39-40, 53) and Boehringer (at 9-10, 48-49, 50 n.34) cite the Weisman reference. But Weisman was not relied upon by the Board in the Coherus IPRs and therefore cannot provide a basis for affirmance. *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.").

As for the Boehringer IPRs, Boehringer argues (at 49 n.33) that Weisman "was not used to reject the claims, but rather to rebut AbbVie's teaching away

arguments." But if that is correct, then Boehringer cannot rely on Weisman to fill the holes in its prima facie case, as it now attempts.

Regardless, Weisman does not help Boehringer or Coherus. Petitioners do not dispute that Weismann 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 relying on Weisman, the Board never addressed this critical fact. AbbVie Br. 42-43; Appx166; Appx45182-45183. Boehringer extrapolates (at 50 n.34) from the Board's discussion of Rau to argue that the Board implicitly responded to the up-dosing in Weisman as well. But the Board never even acknowledged the up-dosing in Weisman and, indeed, relied 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 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.

Boehringer attempts (at 50 n.34) to explain away this problem by referring to Weisman's recognition of the DE001/DE003 trial generally, some results of which were reported in Rau 1998. But 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. The Court should also reject Boehringer's brazen attempt (*id.*) to dismiss AbbVie's point as an "argument raised for the first time on appeal." 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). More

importantly, the error under discussion appeared for the first time in the Board's final written decision.

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. Here, in contrast, AbbVie lacked notice that the Board would use Weisman in the unusual manner that it did. This Court should correct, not indulge, that error.

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.

Coherus (at 36-37) and Boehringer (at 29-30) contend 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.").

Coherus's and Boehringer's briefs reveal the same hindsight. Coherus ventures (at 40) that "[t]here were few real options given the overwhelming and well-known benefits of fixed doses over weight-based doses, subcutaneous doses over intravenous doses, and biweekly doses over weekly doses." That is a remarkable statement considering that, 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. 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.

Boehringer similarly engages in hindsight reasoning when (at 43) it attempts to leverage "the common-sense motivation to pursue a low effective dose." This high-level abstraction blows past all the uncertainty that surrounded what the lowest effective dose actually was, how a unified set of aggressive dosing parameters would affect safety and efficacy, and the counterincentives that must be weighed with regard to 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—Boehringer's generalization would eliminate the requirement to show motivation to pursue *any* "low" dose. *See infra* pp. 23-24.

Petitioners fare no better with their more specific arguments. *First*, Coherus (at 46-48) and Boehringer (at 52-56) downplay the importance of the expected reduction in C_{min} from switching to every-other-week dosing. Their own experts,

however, conceded the importance of C_{min}. Coherus's expert admitted 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 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.

Second, although Coherus (at 52) and Boehringer (at 59) attempt to equate the bioavailability of a subcutaneous 40 mg dose with an intravenous 0.5 mg/kg dose, they do 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, they rely—as did the Board—on references involving *higher average doses* administered *more frequently* than those at issue here. Moreover, those references did not even include an intravenous arm, so Petitioners' own witnesses could not say what was being compared. *See* AbbVie. Br. 51; Appx6134.

Third, Boehringer (at 46) and Coherus (at 28) attempt to equate weight-based dosing with fixed dosing. But they 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.

Fourth, Coherus is mistaken when it contends (at 15) that AbbVie did not preserve its arguments based on the 24-week limitation. Unlike in the case Coherus cites, *In re NuVasive, Inc.*, 842 F.3d 1376, 1380 (Fed. Cir. 2016), where a party waived arguments as to the public accessibility or scope of prior art, AbbVie did not concede that the 24-week limitation was disclosed in the instituted art. Moreover, AbbVie made numerous arguments in the Coherus IPRs based on the importance of long-term treatment, which were more than sufficient to preserve the issue. *See*, *e.g.*, Appx43226 (evaluating differences in ACR response and other efficacy criteria across three months of treatment versus six months of treatment); Appx43222 (noting that DE004 study lasted for only three months); Appx43234 (emphasizing that "[RA] is a chronic disease requiring long-term, usually life-long, treatment"); Appx43248 (arguing that van de Putte's six-month and one-year data show inferiority of lower dose); Appx43261 (arguing against motivation to combine based on the fact that one reference highlighted that only larger doses "resulted in long-lasting reduction of disease activity"); Appx43083 (pointing out 24-week data in AbbVie's specification); Appx43223 (discussing up-dosing). That is particularly true given the unfair surprise engendered by the Board's rejection of Coherus's half-life theory (on which review had been instituted) and alternative

reliance on the theory of transforming a 0.5 mg/kg intravenous biweekly dose into a 40 mg subcutaneous biweekly dose (which the Board had explicitly not adopted on institution). *See* AbbVie Br. 42 n.5.

Finally, Coherus cannot salvage the Board's determination with its objection (at 35) that "AbbVie … acknowledge[s] that 'the Board did not come out and say that it was relying on hindsight.'" 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).

Coherus (at 42-43, 45) and Boehringer (at 31-32) contend 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. 3-12. 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.

The Board shifted the burden when it dismissed concerns about low C_{min}. The Board arrived at an aggressive combination of treatment parameters that would have resulted in a lower C_{min} at steady state than the 20 mg weekly dose in van de Putte. AbbVie Br. 44-46; *see also supra* p. 14; 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.

Coherus (at 38, 46-47) and Boehringer (at 53-54) embrace the same fallacy of imputing uncertainty against AbbVie. 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. Boehringer nonetheless argues (at 53) that a lower C_{min} would have been inconsequential, noting that AbbVie's expert could not identify the minimum C_{min} required for efficacy. But the more salient point is that Petitioners, as the parties with the burden of proof, could not identify that minimum level either.[3]

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. Petitioners' briefs are rife with this same sort of reverse reasoning, which leverages non-specific statements out of context to fit any given treatment parameter. *See, e.g.*, Coherus Br. 29 ("Kempeni did not

[3] Boehringer attempts to backfill (at 54) by citing the biweekly 0.25 mg/kg dose in Weisman, but Boehringer's experts did not offer an opinion on the C_{min} in Weisman.

qualify these statements or limit them to doses higher than 0.5 mg/kg."); Coherus Br. 31 ("Kempeni concluded by explaining that the studies it reported suggest that D2E7 'is safe and effective,' without ever limiting that statement to a subset of the doses reported."); Coherus Br. 33-34 (Rau 2000's penultimate sentence "did not qualify [its] statements in any way or suggest that they did not apply to the 0.5 mg/kg intravenous dose."); Boehringer Br. 13, 39 n.27 (Rau 2000's penultimate sentence "is made without limitation or caveat, including with respect to dose," but acknowledging in a later footnote that Rau 2000 did not report 20 mg data).

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).[4]

[4] 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). Coherus's argument (at 49) that the presumption is rebutted merely by presenting contrary

III. ALTERNATIVELY, THE BOARD'S OBVIOUSNESS DETERMINATIONS ARE UNSUPPORTED BY SUBSTANTIAL EVIDENCE

AbbVie additionally argued that substantial evidence did not support the Board's erroneous findings of motivation to combine and reasonable expectation for the reasons presented elsewhere in AbbVie's brief, which highlighted up-dosing and other unknowns or cumulative uncertainties in the art. AbbVie Br. 53-54. Boehringer's waiver argument (at 35-36)—which is not joined by Coherus—can be quickly dispatched. AbbVie did not "ask [the] Court to wade through the roughly 9,500-page underlying record … without guidance." Boehringer Br. 36. AbbVie explained the deficiencies in the Board's reasoning throughout its argument section. AbbVie Br. 30-53. Moreover, to the extent Boehringer suggests additional evidence was relevant, it was the Board's duty to consider and recite that evidence. *DSS Tech. Mgmt.*, 885 F.3d at 1377 n.4 (declining "invitation to consider evidence that the Board did not cite in its decision.").

IV. 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

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evidence conflicts with this Court's guidance that the patent challenger has the "burden of disproving" nexus, citing the principle that, "[t]o overturn a patent, the challenger must clearly prove those facts which support patent invalidity." *Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 1378 (Fed. Cir. 2000) (emphasis added; quotation marks omitted).

the standard for instituting an IPR ("reasonable likelihood of prevailing at trial") in the final written decision. Boehringer argues (at 58) that this Court should overlook the mistake as a mere "typographical error or misstatement." 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 adequately sustained." *Chenery*, 318 U.S. at 94. 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.

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

In *Oil States Energy Services LLC v. Greene's Energy Group, LLC*, 584 U.S. __, 2018 WL 1914662 (Apr. 24, 2018), the Supreme Court rejected a facial challenge to *inter partes* review under Article III and the Seventh Amendment. But the Court went out of its way to "emphasize the narrowness of [its] holding," which "address[ed] only the precise constitutional challenges that Oil States raised." *Id*. at *11. In particular, the Court stressed that "Oil States d[id] not challenge the retroactive application of inter partes review" and did not "raise[] a

due process challenge." *Id*. The Court thus left the door open to challenge the retroactive application of inter partes review.

As the Supreme Court recognized, the retroactive application of IPR to patents filed before the America Invents Act raises distinct constitutional problems. 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. The terms of the bargain were clear from the outset, including the possibility that the patent could be cancelled in contested proceedings that go beyond continued examination, in which an administrative agency exercises powers previously exercised by Article III courts.

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 discloses its invention. The public cannot subsequently change the terms of the bargain, at least not when it comes to something as fundamental as eliminating the traditional role of an Article III court or eroding the safeguards provided by the presumption of validity.

AbbVie fulfilled its side of the bargain when it disclosed its invention in an application filed on June 5, 2002, which published in December 2003. Appx231.

The ’135 patent issued directly from that original application. *Id.* Moreover, although the ’135 patent did not technically issue until after the AIA, this was in no small part due to delay in the PTO, as reflected in the 944 days of patent term adjustment that the ’135 patent received.[5]

“Elementary considerations of fairness dictate that individuals should have an opportunity to know what the law is and to conform their conduct accordingly; settled expectations should not be lightly disrupted.” *Landgraf v. USI Film Prods.*, 511 U.S. 244, 265 (1994). This is particularly true with respect to patents where “[f]undamental alterations … risk destroying the legitimate expectations of inventors in their property.” *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002); *cf. Kimble v. Marvel Entm’t, LLC*, 135 S. Ct. 2401, 2410 (2015) (concerns for preserving stability in the law are “‘at their acme’” in cases involving patent and contract rights).

This Court’s decision in *Patlex Corp. v. Mossinghoff*, 758 F.2d 594 (Fed. Cir. 1985), is not to the contrary. Although this Court ruled that the retroactive application of ex parte reexamination did not violate due process or Article III, ex parte reexaminations are different from IPRs in critical respects, including the limited third-party involvement, the use of examination procedures rather than trial

[5] The ’680 and ’987 patents also claim priority to the application that matured into the ’135 patent. Although each resulted from a continuation filed after the AIA, the underlying disclosure was made well before the AIA.

procedures, and the ease of amending claims. *Oil States* did not consider these differences sufficient to doom IPRs in all circumstances, but where a patent is retroactively subject to IPR, the balance shifts and both Article III and due process prohibit such a fundamental change.

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 4th day of May, 2018, I filed the foregoing 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 6,974 words.

2. The brief has been prepared in proportionally spaced typeface using Microsoft Word 2010 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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