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:

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP: John Williamson

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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: December 13, 2017

/s/ Thomas G. Saunders

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STATEMENT OF RELATED CASES

No appeal from the same proceedings was previously before this Court or any other appellate court. Counsel are aware of no other cases that will directly affect or be directly affected by this Court's decision in the pending appeal.

JURISDICTIONAL STATEMENT

The Patent Trial and Appeal Board asserted jurisdiction under 35 U.S.C. §§ 311-319. Although currently foreclosed by this Court's precedent, AbbVie preserves its challenge to the Board's jurisdiction based on the arguments presented in *Oil States Energy Services LLC v. Greene's Energy Group, LLC*, No. 16-712 (U.S.). *See infra* § III. This Court has jurisdiction over AbbVie's consolidated appeals from the Board's final written decisions pursuant to 28 U.S.C. § 1295(a)(4)(A) and 35 U.S.C. §§ 141(c) & 319. AbbVie filed timely notices of appeal on July 14, 2017 in IPR2016-00172, -00188, and -00189 (Appx43494-43497; Appx44039-44042; Appx44563-44566), and on July 31, 2017 in IPR2016-00408 and -409 (Appx45205-45208; Appx45871-45874).

INTRODUCTION

The patents at issue in this appeal claim the first-approved treatment regimen for AbbVie's blockbuster drug HUMIRA®. Before AbbVie's breakthrough, the FDA had never approved *any* monoclonal antibody for subcutaneous administration to treat *any* condition. Nor had it ever approved *any* treatment

using a fully human antibody. AbbVie achieved those historic firsts through ingenuity and investment in the face of great uncertainty. For years after the discovery of the antibody in HUMIRA® (D2E7), scientists worked to figure out the best regimen for using it to treat patients with rheumatoid arthritis (RA). Those efforts ultimately yielded a novel course of treatment involving every-other-week, subcutaneous administration of 40 mg fixed doses of the antibody D2E7 for a period sufficient to treat RA. That regimen has helped hundreds of thousands of patients and made HUMIRA® the most successful drug in the world. Nonetheless, through a series of legal errors and improper hindsight, the Patent Trial and Appeal Board deemed AbbVie's invention obvious. This Court should reverse those errors and restore the claims on AbbVie's pioneering inventions.

The Board's obviousness ruling mixed and matched preliminary data from early trials of D2E7 using the roadmap provided by AbbVie's claims. The first set of trials that the Board relied on involved *intravenous* administration of *patient-specific, weight-based doses* ranging from 0.5 mg/kg to 10 mg/kg of D2E7 with a minimum interval of *every other week*. A later trial involved *subcutaneous* administration of *fixed doses* of 20 mg, 40 mg, and 80 mg *weekly*. These early trials showed promise but left numerous questions unanswered.

In particular, it was unclear that low and less frequent subcutaneous doses would be safe and effective. The longest interval between subcutaneous doses of

D2E7 discussed in the instituted prior art combinations was one week. It was understood that less frequent doses would have led to larger swings in plasma concentration and lower trough concentrations (C_{min}) between doses than administration of the same total dose over a shorter interval. Thus, the average C_{min} of a 40 mg dose administered subcutaneously every other week would have been expected to be *lower* than the average steady-state C_{min} of the *lowest subcutaneous dose* tested in the prior art. Further, the prior art disclosed that *every patient* who received an every-other-week intravenous dose of 0.5 mg/kg (which the Board equated to 40 mg for an 80 kg patient) had been *switched to a higher dose (i.e., up-dosed)* or withdrawn from the study by the end of 12 weeks. That up-dosing occurred, moreover, even in the absence of the decreased bioavailability caused by subcutaneous dosing and the additional variability caused by administering a fixed dose across an entire patient population.

Despite these uncertainties and risks, AbbVie took a plunge into the unknown and developed a dosing regimen with a unique combination of features. The inventors unexpectedly discovered that an every-other-week, subcutaneous fixed dose of 40 mg of D2E7, alone or in combination with methotrexate, was safe and effective to treat RA. The inventors further claimed the administration of this regimen for at least 24 weeks.

The Board's obviousness determination, made sixteen years after AbbVie achieved these breakthroughs and ushered in a new era in RA treatment, is rife with error. Particularly pernicious were two fundamental errors of law that pervaded the Board's analysis.

First, the Board consistently treated points of uncertainty in the prior art as counting against AbbVie, even though Petitioners had the burden of proof. This caused the Board to discount the up-dosing in the prior art, the concerns about low trough concentrations, and other factors that would have impacted a skilled artisan's motivation to combine and reasonable expectation of success. Had the Board properly placed the burden of overcoming these uncertainties on Petitioners, it could not have reached the determination that it did.

Second, the Board exacerbated these errors by engaging in a compartmentalized analysis that considered the elements of each claim in isolation rather than the claim as a whole. This caused the Board to ignore the cumulative impact of the uncertainties that underscored the nonobviousness of AbbVie's discovery, including the loss of bioavailability that comes with using a low dose less frequently and administering it subcutaneously, and the loss of margin for error that comes with a single fixed dose that must work across a diverse patient population. Moreover, the Board failed to meaningfully analyze the additional 24-week treatment limitation in two of the dependent claims—a striking failure given

that all the patients at the lowest dose in one study had been up-dosed or withdrawn after only 12 weeks.

The Board applied a flawed legal framework and, as a consequence, found unpatentable claims covering the original treatment regimen for the most successful drug in the world. To the extent the Board had constitutional authority to issue its decision, this Court should correct the Board's legal errors and reverse on the merits.

STATEMENT OF ISSUES ON APPEAL

With regard to all claims:

1. Whether the Board committed legal error by basing its obviousness decisions on hindsight mixing and matching of prior art elements.

2. Whether the Board committed legal error in relieving Petitioners of their burden of proof by counting uncertainties against AbbVie rather than treating them as a failure of proof on motivation to combine and/or reasonable expectation of success.

3. Whether the Board committed legal error by considering the elements of each claim in isolation rather than the claim as a whole, including disregarding the "at least 24 weeks" limitation in claims 3 and 4 of U.S. Patent No. 8,889,135.

4. Whether the Board's decisions are unconstitutional under Article III and the Seventh Amendment for at least the reasons raised in *Oil States Energy Services LLC v. Greene's Energy Group, LLC*, No. 16-712 (U.S.).

With regard to IPR2016-00409 (claims 1-5 of the '135 patent):

5. Whether the Board erred by evaluating the combination of Rau 1998, Schattenkirchner, and van de Putte 1999 under 35 U.S.C. § 314(a)'s institution-stage requirement to show a "reasonable likelihood [of] … prevail[ing]" instead of 35 U.S.C. § 316(e)'s trial-stage requirement to "prov[e] a proposition of unpatentability by a preponderance of the evidence."

STATEMENT OF THE CASE

A. Rheumatoid Arthritis

RA is a chronic, progressive inflammatory disease of the joints and surrounding tissue. Appx5500-5501. There is no cure for RA, and if it is left untreated or undertreated, it can cause irreversible damage. Appx5501. Tumor necrosis factor α (TNFα) is a cytokine believed to play a harmful role in RA. Appx244(1:12-35); Appx48.

In 1995, AbbVie's predecessor created D2E7, the anti-TNFα antibody in HUMIRA®. It took another seven years for AbbVie to develop a product and secure approval from the FDA. Appx6756-6760. One of the major struggles during that period was to develop a dosing regimen for patients with RA.

The use of monoclonal antibodies as therapeutic agents was still in its infancy at the time. As of AbbVie's June 2001 priority date, only eleven such antibodies had been approved, most for acute rather than chronic conditions. Appx5551-5552. No antibody had ever been approved for subcutaneous injection. Appx5551.

B. Prior Art Combinations

The Board instituted five IPR proceedings to determine the patentability of three AbbVie patents: (1) U.S. Patent No. 8,889,135; (2) U.S. Patent No. 9,017,680; and (3) U.S. Patent No. 9,073,987. At issue were three obviousness combinations involving references discussing five preliminary clinical studies of D2E7. Appx5510; Appx31638.

IPR Proceeding	Patent Claims Found Unpatentable	Prior Art Combination(s)	Studies Reported
IPR2016-00172	'135 patent (claims 1-5)	Kempeni	DE001/DE003; DE004; DE010
		van de Putte 1999	DE007
IPR2016-00188	'680 patent (claims 1-4)	Kempeni	DE001/DE003; DE004; DE010
		van de Putte 1999	DE007
IPR2016-00189	'987 patent (claims 1-2)	Kempeni	DE001/DE003; DE004; DE010
		van de Putte 1999	DE007
IPR2016-00408	'135 patent (claims 1-5)	van de Putte 2000	DE007
		Rau 2000	DE001/DE003, DE004, DE010, DE007

IPR Proceeding	Patent Claims Found Unpatentable	Prior Art Combination(s)	Studies Reported
IPR2016-00409	'135 patent (claims 1-5)	Kempeni[1]	DE001/DE003; DE004; DE010
		van de Putte 1999	DE007
		Rau 1998	DE003
		Schattenkirchner	DE004
		van de Putte 1999	DE007

At their core, the Board decisions relied on combining the DE007 study (which involved *subcutaneous* administration of *fixed* doses of *20 mg, 40 mg, and 80 mg once-weekly*) with the DE003 study (which involved *intravenous* administration of *weight-based* doses ranging from *0.5 mg/kg to 10 mg/kg* roughly *every-other-week*, with *all patients receiving 0.5 mg/kg either up-dosed or withdrawn from the study by 12 weeks*). The Board focused in particular on (1) the 20 mg and 40 mg *weekly subcutaneous* doses reported in the DE007 study, and (2) the *weight-based 0.5 mg/kg dose* (which the Board treated as approximately 40 mg for an 80 kg patient) administered *intravenously* with a minimum interval of *every other week*, in the DE003 study.

1. van de Putte 1999 and 2000 (DE007)

The van de Putte 1999 (Appx28063-28069) and van de Putte 2000 (Appx28070-28076) abstracts reported on the DE007 trial, in which patients

[1] The final written decision in the -409 IPR mistakenly refers at one point to the combination of "van de Putte 2000 and Rau 2000." Appx186. The actual combination that was analyzed as the first ground in that IPR was van de Putte 1999 and Kempeni. Appx182; Appx192-196.

received weekly fixed doses of placebo or D2E7 at 20, 40, or 80 mg by subcutaneous self-injection. van de Putte 1999 reported three-month results, while van de Putte 2000 reported both three-month and six-month results. Both van de Putte 1999 and 2000 concluded that, "[f]or all efficacy parameters studied, all doses of D2E7 were statistically significantly superior to placebo." The abstracts also reported that, compared to placebo, "20, 40 and 80 mg/week were nearly" (Appx28069), or "statistically" (Appx28076), "equally efficacious when given s.c. in patients with active RA." But the DE007 trial was not powered to compare the experimental arms to each other statistically. Appx5659-5660; Appx31789-31790.

Neither abstract disclosed any dosing interval longer than one week. Further, van de Putte 1999 did not disclose administering D2E7 for a period of at least 24 weeks. Appx15; Appx 197.

2. Kempeni and Rau 2000 (DE001, DE003, DE004, DE007, DE010)

Kempeni was a review article published in 1999 that briefly described four clinical trials. Appx2703-2705. Later references labelled the trials discussed as DE001, DE003, DE004, and DE010. *Compare* Appx2703-2705 *with* Appx28086-28089. Rau 2000 was an article published in German that described five clinical trials. Appx28082-28092 (English translation). Four were the same as discussed in Kempeni: DE001, DE003, DE004, and DE010. The fifth was the trial discussed in van de Putte 1999 and 2000: DE007.

DE001. Patients in DE001 received a single intravenous injection with a weight-based dose of D2E7 in amounts ranging from 0.5 to 10 mg/kg or placebo. Appx28086. Patients were evaluated for at least four weeks to determine D2E7's pharmacokinetics, safety, and efficacy. Appx28086; Appx11.

Kempeni did not report any results from the lowest dose of 0.5 mg/kg. In contrast, Kempeni highlighted the results in "the three *highest* dose groups"—*i.e.*, 3, 5, and 10 mg/kg. Appx2704 (emphasis added). Kempeni estimated that the mean terminal half-life of D2E7 was "11.6 to 13.7 days." Appx2704.

Rau 2000 reported that 80% of patients administered 3-10 mg/kg and 65% of patients administered 1 mg/kg achieved an ACR 20 response.[2] It noted that, in contrast to the higher doses, "after the lower doses (0.5 or 1 mg per kg of body weight) the number of swollen joints gradually increased again," and that "[i]n the 0.5 mg group there was a worsening again [in the erythrocyte sedimentation rate] already after one week." Appx28087.

DE003. DE003 was an open-label extension of DE001. Appx2704; Appx28086. Patients were given a second blinded dose of D2E7 identical to the first after a minimum period of four weeks. Appx2704; Appx28086. Subsequent

[2] ACR 20 (named for the American College of Rheumatology) is achieved if the number of joints painful to pressure and the number of swollen joints each improve by 20% and at least three of five additional criteria also improve by 20%. Appx28087.

doses were administered with a minimum interval of two weeks until patients achieved a "good" Disease Activity Score (DAS). Appx2704; Appx28086.[3]

Kempeni reported that "patients who did not respond well after 0.5 mg/kg or 1 mg/kg received higher doses of up to a maximum of 3 mg/kg." Appx2704. Doses were "kept constant" without any up-dosing for patients receiving the higher doses of 3, 5, or 10 mg/kg. Appx2704.

Rau 2000 confirmed this up-dosing of patients on the lower doses and showed that *all patients receiving an intravenous dose of 0.5 mg/kg* (i.e., 40 mg for an 80 kg patient) had been either *up-dosed or withdrawn from the study* by week 12:

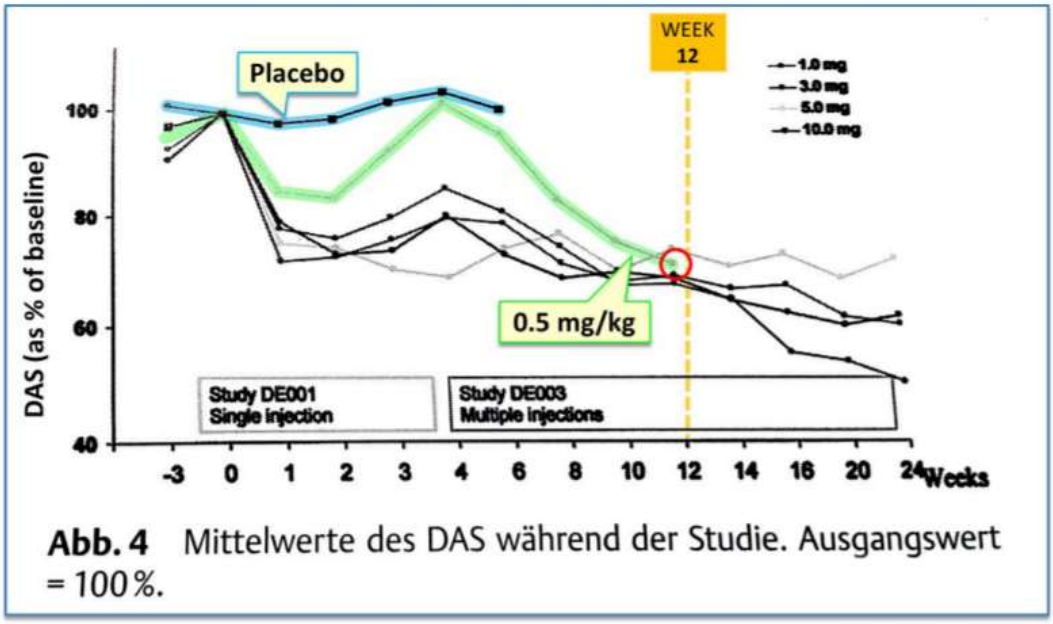


Abb. 4 Mittelwerte des DAS während der Studie. Ausgangswert = 100 %.

Fig. 4 (Rau 2000)

[3] DAS is a "composite index, calculated from the number of joints painful to pressure, the number of swollen joints, the ESR [erythrocyte sedimentation rate], and the general condition of health." Appx28087.

Appx31655 (annotated version of Appx33396, Fig. 4); *see also* Appx31655 (annotated version of Appx33397 Fig. 5 showing the same up-dosing or withdrawal of all patients receiving 0.5 mg/kg by week 12); Appx31821-31822.

Rau also reported that, over 1.5 years, D2E7 "resulted in an impressive statistically significant and long-lasting reduction of disease activity … with all doses >1 (3) mg/kg body weight." Appx28085. This positive assessment notably did not encompass the low-end dose of 0.5 mg/kg. Rau 2000 also said 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." Appx28089. Again, there was no indication that this assessment applied to the low-end dose of 0.5 mg/kg.

DE004. DE004 tested weekly subcutaneous administration of D2E7 in weight-based doses of 0.5-1 mg/kg. Appx28088; Appx2704-2705. The study lasted 12 weeks and included 24 patients. Appx28088. Kempeni noted that, "[b]ased on preliminary data, plasma concentrations of D2E7 after multiple subcutaneous doses were comparable to those achieved with intravenous administration." Appx2705. It is unclear what doses were being compared because DE004 did not include an intravenous arm. Appx31787; Appx6134. Kempeni also reported that, even with weekly subcutaneous administration, some patients receiving 0.5 mg/kg still had to be up-dosed. Appx2705. Rau 2000 reported that 78% of patients receiving 0.5-1 mg/kg *weekly* achieved a "'moderate

response'" in their Disease Activity Score and concluded that D2E7 is "also effective subcutaneously," in the context of discussing those dosages. Appx28088.

DE010. DE010 tested D2E7 in combination with methotrexate. Appx28089. Patients were randomly assigned to receive a stable dose of methotrexate in combination with 1 mg/kg subcutaneously, 1 mg/kg intravenously, or placebo. Appx28089. After the second injection, patients were treated openly with 1 mg/kg subcutaneously. Appx28089. Kempeni and Rau 2000 reported only preliminary results after a single injection. Appx2705; Appx28089. Rau 2000 noted that "[i]ntravenous administration gives advantages" compared to subcutaneous administration across multiple criteria. Appx28089.

DE007. DE007 was the phase II study discussed in the van de Putte abstracts, in which patients received weekly subcutaneous injections of 20 mg, 40 mg, 80 mg, or placebo. It was not mentioned in Kempeni and received only a single paragraph in Rau 2000. Appx28088-28089. Rau 2000 did not even report any results from patients receiving the lowest dose of 20 mg weekly.

3. Rau 1998 and Schattenkirchner (DE003, DE004)

The final combination considered by the Board involved van de Putte 1999, Rau 1998, and Schattenkirchner. Rau 1998 and Schattenkirchner did not add any material information to the disclosures of Kempeni and Rau 2000.

Rau 1998 was an abstract reporting results from DE003. Appx36289-36293. It reinforced that up-dosing had occurred, noting that "dose escalation was offered to patients treated with 0.5 and 1 mg D2E7/kg body weight." Appx36293. Looking at 12-month results (*i.e.*, *after* up-dosing of patients receiving 0.5 or 1 mg/kg), it reported that 80% of patients on all remaining doses "achieved and sustained responder status." Appx36293.

Schattenkirchner was an abstract reporting six-month results from DE004, in which 24 patients were given weekly subcutaneous injections of 0.5 mg/kg D2E7 or placebo. Appx36284-36288; Appx227. Like Kempeni, Schattenkirchner reported that, "[b]ased on preliminary data, plasma concentrations of D2E7 after multiple s.c. injections are comparable with those after i.v. injections of D2E7" and that "s.c. administration of D2E7 has been shown to be safe and efficacious." Appx36288. But, again like Kempeni, it was unclear what doses were being compared, and Schattenkirchner reported that patients who did not respond or lost their responder status to 0.5 mg/kg *weekly* subcutaneous injection, had to be up-dosed to 1 mg/kg. Appx36288.

4. Summary of the Prior Art

The five trials discussed in the prior art can be summarized as follows:

Study	**Dose**	**Route**	**Frequency**	**Reported in**
DE001	Weight-based (0.5-10 mg/kg)	IV	Single dose, second dose no sooner than	Kempeni Rau 2000

Study	Dose	Route	Frequency	Reported in
DE003	Weight-based (0.5-10 mg/kg), with up-dosing	IV	4 weeks later, biweekly dose until "good" then minimum 2-week interval.	Kempeni Rau 2000 Rau 1998
DE004	Weight-based (0.5 mg/kg), with up-dosing	SC	Weekly dose.	Kempeni Rau 2000 Schattenkirchner
DE010	Weight-based (1 mg/kg), with methotrexate	SC & IV	Single dose, second dose, open label extension. Frequency not reported in Kempeni or Rau 2000.	Kempeni Rau 2000
DE007	Fixed (20, 40, 80 mg)	SC	Weekly dose.	van de Putte 1999 van de Putte 2000 Rau 2000

Even artificially restricting the variables to those reported in the references asserted by Petitioners would have yielded 96 different possible combinations of route of administration (intravenous or subcutaneous), dose (0.5 mg/kg, 1 mg/kg, 3 mg/kg, 5 mg/kg, 10 mg/kg, 20 mg, 40 mg, 80 mg), interval (weekly, every-other-week, when response status is lost), and co-administration (with or without methotrexate). Appx5517-5518. The number of options increased significantly with the addition of more variables, including doses and intervals other than those used in the asserted references, doses and intervals other than those previously

reported in the prior art, use of a loading dose, co-administration with agents other than methotrexate, and measures to individualize treatment. Appx5518.

C. Multi-Dose Pharmacokinetics

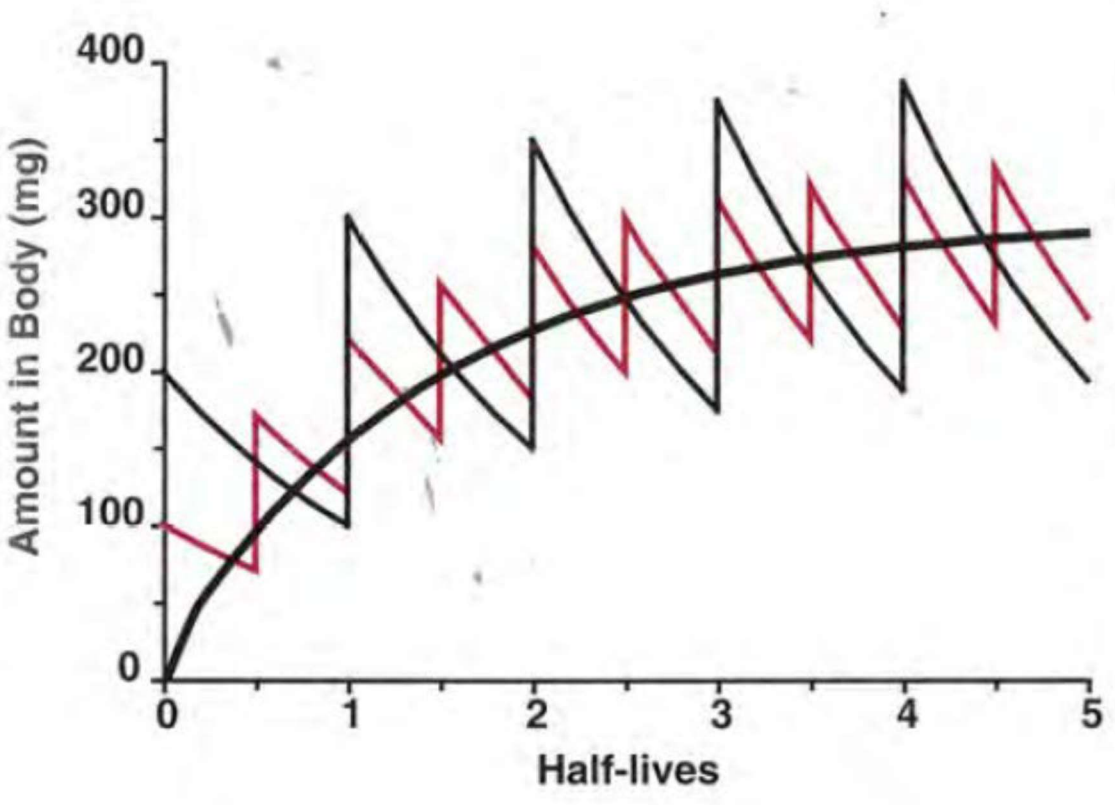
The difficulty of designing a treatment regimen was further complicated by basic principles of pharmacokinetics (PK) and pharmacodynamics (PD), including the fact that delivering more of a drug less frequently is not necessarily equivalent to delivering a proportionately smaller dose more frequently. Appx31769-31772.

Chronic diseases like RA are treated with multiple-dose regimens, which have a more complex PK profile than single-dose administration. Appx31767-31768. Over multiple administrations, a drug typically accumulates in the body until it reaches "steady state," when the amount of drug eliminated from the body is equal to the amount absorbed into the body following the previous dose. Appx31767-31768. C_{max} is the highest concentration of the drug reached at the site of measurement. C_{min}, also called trough level, reflects the lowest concentration experienced between doses. Appx31768.

The size of the dose and the interval between doses can affect the magnitude of fluctuations between C_{max} and C_{min} at steady state. Appx31769-31770. For example, giving a higher dose less frequently will produce greater fluctuations at steady state, with higher peaks and lower trough concentrations. Appx31770-31771. Thus, even when higher doses and a longer gap between doses result in

administration of the same total amount of drug over time as a regimen with lower doses administered more frequently, the higher dose/less frequent regimen would be expected to produce lower average C_{min} values at steady state. Appx31770-31771.

The diagram below illustrates this principle by contrasting the PK profile of a drug given as 200 mg once every half-life (black line) with the profile of a drug given as 100 mg twice every half-life (red line). As can be seen, "[a]dministration at double the dose and double the dosing interval results in higher peak (C_{max}) and lower trough (C_{min}) concentrations." Appx31770-31771.



Appx31771; Appx32148. Similarly, a well-known textbook in the prior art stated that the "'C_{max} and C_{min} fluctuation' for a 250 mg dose given every 3 hours would be half that of a 500 mg dose given every 6 hours." Appx31771.

The method of administration can also affect a drug's PK profile. Subcutaneous administration delivers a drug under the skin and typically causes loss and/or delay as the drug is absorbed into the bloodstream. Appx31763. "The bioavailability of a [subcutaneously] administered drug is almost always lower than for the same drug administered intravenously." Appx31765.

Researchers must also account for variation within a patient population. Age, weight, severity of disease, renal and liver function, genetics, concurrent drugs, and environmental factors can all impact a drug's PK/PD profile. Appx31773; Appx32052; Appx30819. A "fixed dosing regimen" that is "therapeutic in some patients" may prove "ineffective" or "toxic" in others. Appx31773; Appx32052.

D. The Challenged AbbVie Patents

The inventors of the '135, '680, and '987 patents overcame all these challenges and uncertainties in designing a novel and nonobvious method of treatment for RA. Despite the positive results achieved with higher doses/more frequent administration and the concerns generated by lower doses/less frequent administration, the inventors counterintuitively designed a treatment regimen in

which 40 mg of D2E7 is administered subcutaneously, every other week, with or without methotrexate, for a time period sufficient to treat RA.

In 2002, that protocol became the original FDA-approved regimen for D2E7, which AbbVie released as HUMIRA® in 2003. Appx3304; Appx5570. HUMIRA® was the first-ever FDA-approved fully human monoclonal antibody treatment and the first monoclonal antibody of any kind labeled for subcutaneous administration. Appx5551; Appx5507. Since its historic introduction, HUMIRA® has become the most successful drug in the world. Appx5572.

'135 Patent. U.S. Patent No. 8,889,135, which has a June 8, 2001 priority date, contains five claims. Independent claim 1 recites:

> A method for treating rheumatoid arthritis in a human subject, comprising administering *subcutaneously* to a human subject having rheumatoid arthritis a *total body dose of 40 mg* of a human anti-TNFα antibody once *every 13-15 days* for a *time period sufficient to treat the rheumatoid arthritis*, wherein the anti-TNFα antibody comprises an IgG1 heavy chain constant region; a variable light ("V_L") chain region comprising [three CDRs with specified sequences]; and a variable heavy ("V_H") chain region comprising [three CDRs with specified sequences].

Appx266 (emphases added). Dependent claim 2 specifies particular sequences for the V_L and V_H chains. Appx266. Dependent claim 3 specifies that the antibody in claim 2 "is administered for a period of *at least 24 weeks*," and dependent claim 4 specifies that the antibody in claim 1 "is administered for a period of *at least 24 weeks*." Appx266 (emphases added). Independent claim 5 resembles claim 1, but

it replaces "comprising" with "consisting of" and further recites that the antibody is "administered in the form of a pharmaceutically acceptable composition." Appx266.

'680 and '987 Patents. U.S. Patent No. 9,017,680 and U.S. Patent No. 9,073,987, which also have a June 8, 2001 priority date, contain claims directed to reducing signs and symptoms in a patient with moderately to severely active RA by administering an anti-TNFα antibody having the six CDRs and heavy chain constant region of D2E7. Appx305; Appx48-49. Each of the claims requires administering a total body dose of 40 mg subcutaneously once every 13-15 days (*i.e.*, every other week). Appx305; Appx48-49. This administration occurs in combination with methotrexate in the claims of the '680 patent.

E. The Board Proceedings

1. IPR2016-00172, -00188, and -00189 (Coherus IPRs)

In the -172, -188, and -189 IPR proceedings brought by Coherus BioSciences, Inc. (Coherus), the Board held that the claims of the '135 patent, the '680 patent, and the '987 patent, respectively, would have been obvious over the combination of Kempeni and van de Putte 1999.

The Board began its analysis by construing the claims of the challenged patents. Noting that the claims "do not recite any particular level of efficacy," it held that they do not require significant reduction in the signs and symptoms of

RA. Appx8. On that assumption, the Board concluded that "van de Putte and Kempeni collectively disclose each limitation" of the challenged claims. Appx15. The Board then turned to whether a skilled artisan would have been motivated to combine the references with a reasonable expectation of success.

The Board first analyzed the abstract question of whether a skilled artisan would have had "reason to select … and a reasonable expectation of success in achieving *a* subcutaneous fixed dose." Appx17 (emphasis added). The Board then singled out the 40 mg weekly subcutaneous dose discussed in van de Putte 1999—without explaining why it was selected over a higher dose—and asked whether "a skilled artisan would have had a reason to modify the van de Putte dosing regimen to administer 40 mg doses on a biweekly schedule and expect success in treating RA with that regimen." Appx18.

Notably, the Board rejected Coherus's theory, which had formed the basis for its institution decision, that D2E7's terminal half-life and the 20 mg weekly dose reported in van de Putte 1999 would have supported every-other-week administration of 40 mg of D2E7. Appx18-24. The Board explained that Coherus's expert, who had opined that the amount of D2E7 circulating two weeks after a 40 mg dose would have been equivalent to or greater than the 20 mg dose in van de Putte 1999, "takes an overly simplistic approach to modeling a dosing

regimen." Appx23. It also noted that "several prior art therapeutic antibodies … were not dosed … at a frequency equal to a single half-life." Appx22.

The Board, however, adopted the alternative theory that Kempeni's discussion of an every-other-week 0.5 mg/kg intravenous dose would have led a skilled artisan to convert van de Putte 1999's 40 mg weekly dose into an every-other-week 40 mg dose. Appx22. The Board stated that "a 0.5 mg/kg dose is equivalent to a 40 mg fixed dose for an 80 kg (i.e., average) patient." Appx25. It then quoted Kempeni's statement that long-term treatment in the dose range from 0.5 to 10 mg/kg "was well tolerated" (Appx25), without acknowledging that "well tolerated" does not speak to or suggest efficacy (Appx2726; Appx6577).[4]

After this single paragraph of analysis, the Board framed the rest of its discussion as a rejection of the proposition that the prior art taught away. Appx26-37; Appx71-83; Appx114-127. The Board agreed that "a drug administered subcutaneously can be less bioavailable than a drug administered intravenously," but it dismissed this concern based on Kempeni's statement that subcutaneous administration produced "comparable" plasma concentrations. Appx27-28. The Board did not acknowledge that Kempeni was referring to a study in which

[4] In IPR2016-00188, the Board also relied on Kempeni to teach co-administration with methotrexate. Appx61.

patients received *weekly* weight-based doses of 0.5 mg/kg, with up-dosing for non-responders. Appx2704-2705.

The Board also dismissed the prior art reports of up-dosing and other problems with the low-end dose of 0.5 mg/kg administered intravenously every-other-week. Citing attorney argument in Coherus's reply brief that was unsupported by any expert testimony, the Board concluded that up-dosing did not show an inadequate response because it *may* have occurred even when patients achieved a "moderate response." Appx28-29. The Board did not discuss the fact that, after 12 weeks, no patients in the DE003 study were receiving the 0.5 mg/kg dose (Appx43392; Appx43459), even though the Board relied on the DE003 study in Kempeni to supply the "at least 24 weeks" limitation in claims 3 and 4 of the '135 patent, which it acknowledged *was not disclosed in van de Putte 1999* (Appx15).

The Board also concluded that PK principles predicting low C_{min} values from less frequent dosing would not have discouraged a skilled artisan. Improperly relying on the path followed by the inventors, the Board observed that the "Patent Owner developed the D2E7 dosing regimen through clinical trials," not modeling. Appx33; Appx78; Appx121. The Board also discounted concerns about low C_{min} values based on the lack of information in the prior art, saying that "the publicly available PK information in June 2001 would not have permitted a

PK/PD correlation for modeling purposes," and that "the minimum effective dose of D2E7 'was undefined in June 2001.'" Appx33.

Finally, the Board rejected AbbVie's evidence of HUMIRA®'s commercial success, long-felt need, and unexpected efficacy of the dosing regimen as objective indicia of nonobviousness. Appx38-43; Appx83-89; Appx126-132.

2. IPR2016-00408 and -409 (Boehringer IPRs)

The -408 and -409 IPR proceedings brought by Boehringer Ingelheim International GmbH and Boehringer Ingelheim Pharmaceuticals, Inc. (together, Boehringer) challenged only the '135 patent. In the -408 proceeding, the Board held that the '135 patent is unpatentable as obvious over the combination of van de Putte 2000 and Rau 2000. Appx178. In the -409 proceeding, the Board held that the '135 patent is unpatentable as obvious over the combination of van de Putte 1999 and Kempeni. Appx226. The Board further concluded that Boehringer had "establishe[d] a reasonable likelihood of prevailing at trial on claims 1-5 of the '135 patent" with respect to Boehringer's third obviousness combination: Rau 1998, Schattenkirchner, and van de Putte 1999. Appx228.

The Board's analysis largely mirrored its decisions in the three Coherus IPRs. The Board again construed the claims not to require any particular level of efficacy, and on that basis found that the prior art disclosed every element in the challenged claims. Appx141-145; Appx149-152; Appx187-191; Appx197-199.

The Board then repeated its separate analyses of the selection of a subcutaneous fixed dose and the selection of a dose amount and interval. Once again, the largest portion of its analysis focused on whether the Board thought there was sufficient evidence of teaching away. Appx160-172; Appx207-220.

The primary difference from the Coherus IPRs is that, in the -408 IPR, the Board was combining the discussion of the DE007 study in van de Putte 2000 (rather than van de Putte 1999) with the discussion of the DE003 study in Rau 2000 (rather than Kempeni). Appx147-148. The Board also relied on a third reference (Weisman) that had not been part of the instituted ground. Appx166. Finally, the Board once again agreed that half-life alone does not provide sufficient information to design a dosing regimen, but relied on D2E7's reported half-life coupled with the clinical data in the prior art. Appx172.

The Board's -409 decision largely repeated the same discussion, but with the combination of van de Putte 1999 and Kempeni that was addressed in the Coherus IPRs. The decision also included a three-page section at the end devoted to the alternative combination of Rau 1998, Schattenkirchner, and van de Putte 1999. Appx226-228. In that section, the Board applied the standard for instituting an IPR ("reasonable likelihood of prevailing at trial") rather than the standard applicable to a final written decision. Appx228.

SUMMARY OF THE ARGUMENT

1. The Board improperly relied on hindsight to piece together the elements of AbbVie's invention. The prior art presented a wide range of possible approaches to treating RA with D2E7. The choices included whether to administer a fixed dose or patient-specific weight-based dose, the size of the dose, the treatment interval, the method of administration, and other variables. But the Board focused only on doses at the lowest end of what the prior art disclosed. It then pushed beyond the boundaries of anything discussed in the prior art by selecting: (1) an every-other-week dosing interval that would have been expected to result in a lower C_{min} compared to the weekly doses in the van de Putte abstracts; (2) a subcutaneous method of administration that would have been expected to diminish bioavailability compared to the intravenous doses in Kempeni and Rau 2000; (3) a fixed-dosing paradigm that increased the risk of underdosing; and (4) a 24-week treatment interval that went beyond the point at which every patient receiving 0.5 mg/kg intravenously in the DE003 trial had been up-dosed. The Board improperly relied on hindsight to steer its way through these choices, ignoring more promising alternatives and improperly examining the motivation to achieve the specific combination that AbbVie made rather than a contemporaneous motivation to produce an improved treatment regimen.

2. The Board compounded this hindsight-driven approach with other legal errors. First, the Board repeatedly treated uncertainties in the prior art as a failure *by AbbVie* to prove teaching away rather than a failure *by Petitioners* to prove motivation to combine and a reasonable expectation of success. The most glaring example came in the Board's discussion of up-dosing. Every patient receiving the 0.5 mg/kg every-other-week intravenous dose on which the Board's analysis hinged had been up-dosed or withdrawn from the study by week 12. The Board disregarded this fact based on its speculation—supported nowhere in the prior art—that *some* of the up-dosed patients were achieving a moderate response when they were up-dosed. But it was not AbbVie's burden to overcome this speculation and prove that all patients were up-dosed due to ineffectiveness. Rather, it was Petitioners' burden to overcome the uncertainty in the prior art and prove that a skilled artisan would have been guided by the 0.5 mg/kg intravenous dose despite the up-dosing.

The Board continued this improper pattern of burden shifting when it disregarded concerns about low C_{min} based on a lack of information regarding the minimum effective dose and PK/PD of D2E7. Those unknowns should have weighed against finding obviousness. The Board also improperly shifted the burden in analyzing a statement from Rau 2000, which did not apply to the claimed dose or, at most, left uncertainty on that point. Finally, the Board's burden shifting

extended to objective indicia of nonobviousness, where the Board's finding that it was "not clear" whether the claimed dosing regimen drove sales of HUMIRA® was insufficient to carry Petitioners' burden of overcoming the presumption of nexus.

3. The cumulative effect of all the uncertainties in the prior art multiplied their individual impact. But the Board failed to consider this cumulative effect because it failed to consider the claims as an integrated whole. It devoted separate sections of its opinion to the issue of selecting a fixed subcutaneous dose and the issue of selecting a dose and dosing interval, without returning to consider all the elements as an ordered combination. Under this siloed analysis, the Board never considered how up-dosing, and the uncertainties that came with delivering a relatively low dose over a longer interval, would have impacted the selection of a fixed dose expected to increase the risk of underdosing some patients. Similarly, the Board's effort to equate subcutaneous and intravenous administration in the abstract never addressed whether a study involving weekly weight-based doses and up-dosing would apply where a lower average dose was administered less frequently as a fixed dose across an entire patient population.

The Board's clearest failure to consider the claims as a whole involved the "at least 24 weeks" limitation in claims 3 and 4 of the '135 patent. Regardless of the reason for up-dosing, the fact that every single patient receiving a 0.5 mg/kg intravenous dose had been up-dosed or withdrawn by week 12 left a complete

absence of information regarding the performance of that dose beyond 12 weeks. The Board never addressed this gaping hole in the prior art in part because it viewed the 24-week limitation in isolation rather in combination with all the other elements of the claimed invention.

4. The Board's discussion in the -409 IPR of the combination of Rau 1998, Schattenkirchner, and van de Putte 1999 incorporated all its other errors and added a new one: Rather than concluding that Boehringer had proved unpatentability, the Board erroneously applied the institution-stage standard and concluded only that Petitioner had established "a reasonable likelihood of prevailing at trial."

5. The Board's decisions violated Article III and the Seventh Amendment because the IPR process authorizes an executive-branch agency, rather than an Article III court with a jury, to extinguish a previously issued private-property right without the consent of the owner. Although the panel cannot reverse on this ground under Federal Circuit precedent, AbbVie preserves the argument in light of the Supreme Court's impending decision in *Oil States Energy Services LLC v. Greene's Energy Group, LLC*, No. 16-712 (U.S.).

STANDARD OF REVIEW

Whether a tribunal applied the proper legal test is a question of law reviewed de novo. *See Alcon Research Ltd. v. Barr Labs., Inc*., 745 F.3d 1180, 1190-1192

(Fed. Cir. 2014). "[T]he Board's ultimate determination of obviousness" is reviewed "de novo and its underlying factual determinations" are reviewed "for substantial evidence." *Personal Web Techs., LLC v. Apple, Inc*., 848 F.3d 987, 991 (Fed. Cir. 2017). On the factual side of the inquiry, the question is "whether a reasonable fact finder could have arrived at the agency's decision, which requires examination of the record as a whole, taking into account evidence that both justifies and detracts from an agency's decision." *Id.* (quotation marks omitted).

ARGUMENT

I. THE BOARD'S OBVIOUSNESS DETERMINATIONS WERE BASED ON LEGAL ERROR

A. The Board Relied On Hindsight To Thread Its Way Through The Prior Art

The treatment regimen that AbbVie developed was a leap into the unknown that shunned more promising alternatives in favor of pushing the boundaries of what was possible. AbbVie took a relatively low dose of D2E7 and combined it with subcutaneous administration, the use of a fixed dose, and a longer interval between treatments to produce a groundbreaking method of treatment for RA. AbbVie also discovered that this method could be used for long-term treatment of 24 weeks or more. Each aspect of that novel combination layered uncertainty on top of uncertainty in a manner that would have left a skilled artisan unmotivated to pursue the combination at all, let alone with a reasonable expectation of success.

The Board nonetheless pieced together the various aspects of AbbVie's patented methods based on a hindsight analysis. The prior art presented a wide range of possible approaches to treating RA with D2E7. The choices confronting a skilled artisan included whether to administer a patient-specific weight-based dose or a fixed dose, the size of the dose, the treatment interval, the route of administration, and other variables. Appx5518. The prior art that the Board relied on to guide these decisions consisted of only abstracts and preliminary reports of early, on-going investigations from which key safety and efficacy information were missing. Appx5520; Appx5527. Even improperly restricting the variables to the values for four key parameters discussed in those references, there were 96 different combinations of route of administration, dose, interval, and co-administration. Appx5518. Additional variables, such as other doses or dosing frequencies, increased the options significantly. Appx5518; Appx5552.

The Board threaded its way through these possibilities in an effort to reach the invention that AbbVie had disclosed. At each step of its analysis, the Board focused on doses at the *lowest* end of what was disclosed, to the exclusion of other possibilities. It looked to the 20 mg weekly subcutaneous dose in the van de Putte abstracts and the 0.5 mg/kg every-other-week intravenous dose in Kempeni and Rau 2000. These were not obvious choices comfortably within a range shown to be safe and effective, but rather the lower limits tested in the references being

combined. *See Merck Sharp & Dohme B.V. v. Warner Chilcott Co., LLC*, 2017 U.S. App. LEXIS 20441, at *8 (Fed. Cir. Oct. 19, 2017) (reversing judgment of obviousness where district court selected values at end of ranges disclosed in prior art). Indeed, every single patient receiving the 0.5 mg/kg intravenous dose on which the Board relied had been up-dosed due to insufficient treatment or withdrawn from the study by 12 weeks. *See supra* pp. 11-12.

The Board then made choices that pushed beyond the boundaries of anything the prior art disclosed. It selected a dosing interval (every-other-week) that would have been expected to result in a lower average C_{min} than the weekly dosing discussed in the van de Putte abstracts. *See supra* pp. 16-18; *infra* pp. 44-46; Appx31770-31771; Appx32148; Appx31822-31823. It selected a method of administration (subcutaneous) that would have been expected to slow delivery and diminish bioavailability compared to the intravenous doses discussed in Kempeni and Rau 2000. *See infra* pp. 35, 51; Appx31763-31765; Appx31780-31781; Appx31805-31806; *see also* Appx27. It selected a dosing paradigm (fixed doses) that would have produced more variability and risk of underdosing than the more personalized, weight-based dosing in the DE003 trial. *See* Appx31773; Appx31806; Appx31822-31823; Appx32052. And it selected a treatment interval—"at least 24 weeks" for claims 3 and 4 of the '135 patent—that went far beyond the point at which every patient receiving a 0.5 mg/kg intravenous dose in

the DE003 trial had been up-dosed. *See supra* pp. 11-12; Appx15; Appx19; Appx28088; Appx31655; Appx31821-31822.

Each choice would have added to a skilled artisan's uncertainty. But, having the benefit of knowing that AbbVie had succeeded, the Board did not let the evidence of up-dosing, the lower anticipated C_{min} of the claimed regimen, and various pieces of missing information give it pause in reaching its goal.

Throughout this determined march, the Board ignored the more reliable alternatives disclosed in the prior art, including options involving a higher dose, a shorter dosing interval, and no reported up-dosing. The Board did not ask which of the many possibilities a skilled artisan would have been motivated to pursue with a reasonable expectation of success. Instead, it asked whether there was "a reason to modify the van de Putte dosing regimen to administer a 40 mg dose on a biweekly schedule." Appx18; Appx157-158. In other words, the Board examined the motivation to achieve *the claimed invention*, taking into account its eventual success, rather than the motivation to produce an improved treatment regimen, taking into account all the options available. This approach of "[d]efining the problem in terms of its solution reveals improper hindsight." *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

The Board's primary justification for focusing exclusively on low doses and other changes that would have further reduced the level of treatment was that the

claims at issue did not require any particular level of efficacy. Appx163-164; Appx211; Appx31; Appx76; Appx119. But while it is true that the Board's analysis would not apply to claims requiring a higher level of efficacy, that fact does not justify the Board's narrow focus. The prospect of achieving mediocrity, and doing so with a higher risk of failure, would not have motivated a skilled artisan or justified the enormous investments required to conduct the necessary clinical research. *See 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 protocol that was at best equivalent and perhaps inferior); *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 to find a compound with "baseline" activity).

This is particularly true given that "RA is a chronic inflammatory disease" that causes "irreversible outcomes such as work disability, joint destruction and consequent surgery, and premature mortality." Appx4945. Treating physicians would not have been motivated to start at a lower, potentially inadequate dose and risk faster, permanent progression of RA. Appx5524. It was only with knowledge of AbbVie's invention that the Board gravitated toward the low-end disclosures in the prior art over the numerous other, less-criticized options.

To be sure, the Board did not come out and say that it was relying on hindsight. But it is precisely because hindsight can have such a subtle but pernicious impact that this Court should not hesitate to act when hindsight has infected a decision. *See Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013) (noting need to "avoid[] … even a hint of hindsight"). Before plunging into the details of the references, this Court should take a step back and consider the overall thrust of the Board's decision. The sheer number of more promising options available (Appx5518; Appx5552), the need to go beyond the lower boundaries of what had been disclosed (*supra* pp. 32-33), the up-dosing of every patient who received the lowest dose in the DE003 trial (Appx2704; Appx31644-31655; Appx31821-31822), and all the other uncertainties that came from combining a low dose with a longer dosing interval involving fixed subcutaneous administration (Appx31770-31771; Appx31763-31765; Appx31777; Appx31822-31823) show that, instead of following the prior art to the invention, the Board was allowing the disclosure of the invention to guide it through the prior art. This was legal error and violated the fundamental principle that "[c]are must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.'" *Grain Processing Corp. v. American Maize-Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988).

B. The Board Improperly Relieved Petitioners Of Their Burden Of Proof By Treating Uncertainties In The Prior Art Exclusively As A Failure By AbbVie To Prove Teaching Away

The Board coupled its hindsight-driven approach with more specific legal errors that skewed its analysis. For example, although the Board correctly recited Petitioners' burden of proof, it failed to hold Petitioners to that burden. Instead, the Board repeatedly treated uncertainties in the prior art as a failure *by AbbVie* to prove teaching away rather than a failure *by Petitioners* to prove motivation to combine and a reasonable expectation of success. This effective burden shifting was legal error. *See In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375 (Fed. Cir. 2016) ("In an *inter partes* review, the burden of persuasion is on the petitioner" and "never shifts to the patentee." (quotation marks omitted)).

1. The structure of the Board's decisions set up a pattern of improper burden shifting

The Board set itself up to commit legal error by structuring its analysis as an extended discussion of teaching away prefaced by only a brief discussion of motivation to combine and reasonable expectation of success. This structure caused the Board to view the most relevant disclosures in the prior art exclusively through the lens of whether they "criticize[d], discredit[ed], or would have discouraged a person of ordinary skill in the art." Appx26; Appx76; Appx114-115; Appx164; Appx211-212.

The Board's focus on teaching away ignored this Court's admonition that, even where prior art statements fall short of a formal teaching away, they can still inform whether a skilled artisan would have been motivated to combine references with a reasonable expectation of success. *Rembrandt*, 853 F.3d at 1378-1380; *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1052 (Fed. Cir. 2016) (en banc). The Board instead slipped into a pattern of treating uncertainty surrounding certain prior art statements exclusively as a purported failure to prove teaching away, without considering the impact of such uncertainty on motivation and reasonable expectation of success. Appx26-37; Appx71-83; Appx114-126; Appx160-172; Appx207-220.

This treatment of uncertainty was "reverse reasoning." *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, whereas that which is predictable is more likely to be obvious." *Id.* "[R]easoning that one would no more have expected failure than success is not a valid ground for holding an invention to have been obvious," as "the standard is not whether the patent owner can persuasively show that one of ordinary skill would have expected failure. Rather, the burden is on the [challenger] to show that one of ordinary skill would have had a motivation to combine the references with a reasonable expectation of success." *Id.* at 1355-1356. Here, Petitioners' failure to

dispel the uncertainty in the prior art meant that they failed to carry their burden of proving motivation to combine with a reasonable expectation of success.

2. The Board improperly analyzed the evidence of up-dosing

The most glaring example of the Board's backwards approach to uncertainty in the prior art came in its discussion of up-dosing. The Board's final written decisions all rested on the proposition that a skilled artisan would have combined the weekly subcutaneous administration of the fixed 40 mg dose disclosed in the van de Putte abstracts with the every-other-week, intravenous administration of an allegedly equivalent weight-based dose of 0.5 mg/kg disclosed in Kempeni or Rau 2000. Appx18; Appx63; Appx107; Appx165; Appx212-213. The reports of up-dosing with an every-other-week 0.5 mg/kg dose belie this theory.

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. It contrasted this result with patients at higher doses, who did not need to be up-dosed. Appx2704. Rau 1998 similarly reported that "dose escalation was offered to patients treated with 0.5 and 1 mg D2E7/kg body weight." Appx36293.

Rau 2000 showed that *none* of the 24 patients receiving 0.5 mg/kg continued that treatment beyond 12 weeks. Graphs reporting results from the DE003 trial showed no result trend line for the 0.5 mg/kg dose beyond week 12, whereas results for the other doses continue past this period. Appx33396-33397. These

graphs reflect that all patients dosed at 0.5 mg/kg were either up-dosed or withdrawn from the study by week 12, as illustrated in the annotations below:

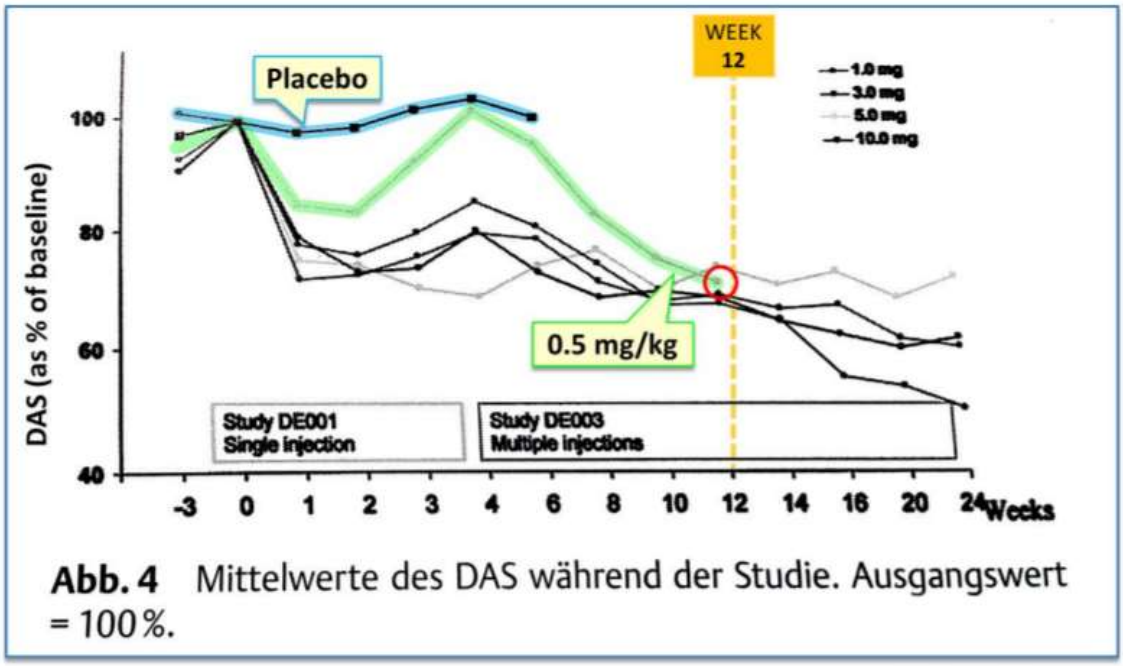


Abb. 4 Mittelwerte des DAS während der Studie. Ausgangswert = 100 %.

Fig. 4 (Rau 2000)

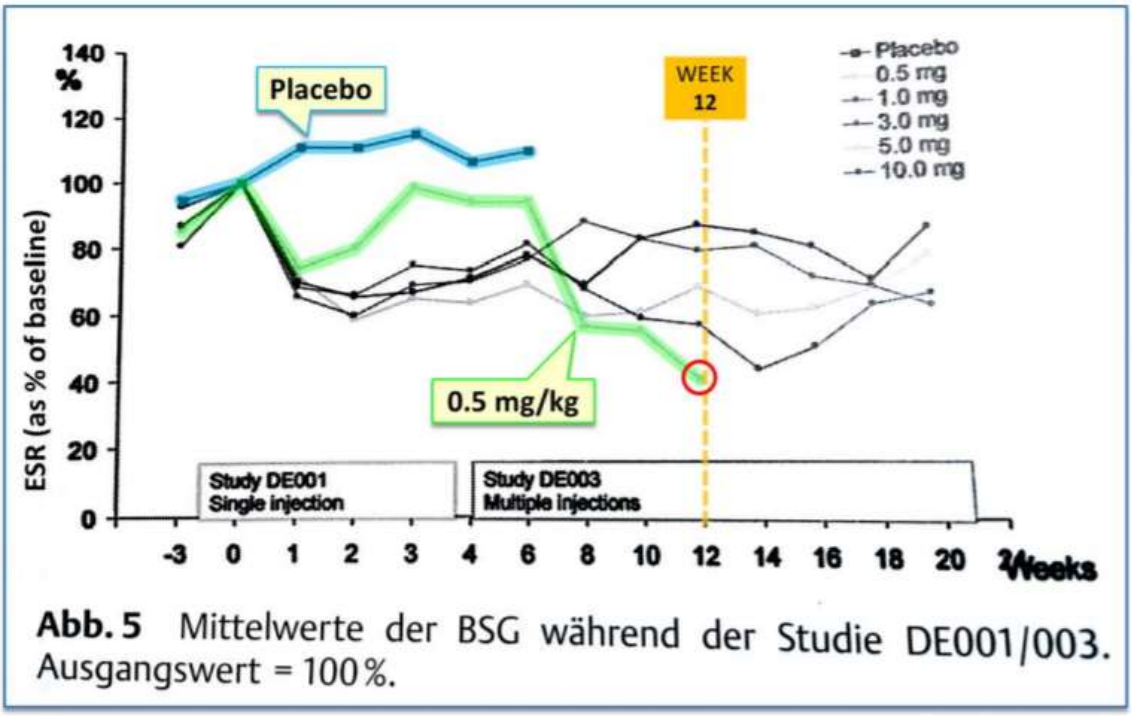


Abb. 5 Mittelwerte der BSG während der Studie DE001/003. Ausgangswert = 100 %.

Fig. 5 (Rau 2000)

Appx31655; *see also* Appx31654; Appx31821-31822. Boehringer's clinical expert conceded that the 0.5 mg/kg "dose was dropped" because termination of the lines "indicates there's no longer a dosing group at [0.5 mg/kg] in week 12." Appx31323-31324; *see also* Appx31323-31326 (admitting, among other things, that the graphs "indicate[] that nobody received the .5 mg/kg dose after week 12").

This change in dosing would have, at best, left a skilled artisan with serious doubts that a 0.5 mg/kg every-other-week dose was a reliable guide to developing a new treatment regimen for RA. Appx31627; Appx31639-31640; Appx31653-31657; Appx31661-31662. In fact, "there can be little better evidence negating an expectation of success than actual reports of failure." *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003).

The Board, however, entirely discounted the evidence of up-dosing based on residual uncertainty regarding the reason for up-dosing some patients. Relying on Kempeni, the Board concluded that up-dosing was provided to patients whose response was not rated as "good." Appx167. The Board thus 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). It also flipped the inquiry by 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." Appx167 (second emphasis added).

This treatment of the striking fact that every single patient receiving 0.5 mg/kg was up-dosed or withdrawn exemplifies the Board's legally flawed approach. The Board had no idea how many, if any, up-dosed patients were exhibiting a moderate response at the time they were up-dosed or withdrawn. Appx31656; Appx29440-29444; *see also* Appx2949 (FDA guidance for developing RA drugs noting that "[f]requently, dropouts occur for reasons related to" "adverse effects or lack of efficacy"). Rau notably omitted 0.5 mg/kg when it said that there was "an impressive statistically significant and long-lasting reduction of disease activity (*moderate* DAS response in 80%, decrease in the number of swollen and tender joints and the ESR > 50%) *with all doses > 1 (3) mg/kg*." Appx28085 (emphases added). Moreover, the absence of a statement that *all* patients were up-dosed due to ineffectiveness did not remove the uncertainty engendered by the fact that all patients receiving 0.5 mg/kg were in fact up-dosed or withdrawn from the study.

The Board never looked past its conclusion that there was no definitive teaching away to consider the effect that the same uncertainty would have had on a skilled artisan's motivation to combine and reasonable expectation of success. For researchers considering a fixed dose to treat a large population of patients suffering

from a chronic disease that requires long-term treatment, arguments that *some* of those patients *may* have been up-dosed for exhibiting a moderate response less favorable than the response with higher doses would have provided little comfort. And the notion that, merely because there was some uncertainty as to the precise reason for the up-dosing, such an artisan would have plunged ahead and reasonably expected success exemplifies the type of "reverse reasoning" this Court condemned in *Honeywell*.

The Board only compounded the error in the Boehringer IPRs when it argued that Weisman's testing of a 0.5 mg/kg biweekly intravenous dose showed that the up-dosing in the DE003 trial did not deter further experimentation. Appx166; Appx214. As an initial matter, it was error for the Board to reach beyond the grounds on which it instituted review to rely so prominently on Weisman, a reference unaddressed at the petition stage. *See EmeraChem Holdings, LLC v. Volkswagen Grp. of Am., Inc.*, 859 F.3d 1341, 1348-1351 (Fed. Cir. 2017).[5] In any event, that reliance was misplaced. The Board failed to

[5] The Board did not rely on Weisman in the Coherus IPRs. But that does not mean those proceedings were free from surprise. The institution decisions in the Coherus IPRs relied on a half-life theory and specifically noted that Petitioner's argument was "not based primarily on transforming a 0.5 mg/kg intravenous biweekly dose into a 40 mg subcutaneous biweekly dose." Appx43134; Appx43683-43684; Appx44224-44225. The Board's final written decisions, however, rejected Coherus's half-life theory on which review had been instituted and instead adopted the theory that the Board had pointedly avoided adopting in its institution decisions. *See supra* pp. 21-24.

acknowledge that approximately half of the patents receiving the 0.5 mg/kg dose with methotrexate were up-dosed or withdrawn from the study in Weisman, which only reinforced concerns about the 0.5 mg/kg dose. *See* Appx28107 ("Treatment group change or dropout status was determined by clinical response."); *see also* Appx29678-29679; Appx30328; Appx30359-30360. Furthermore, Weisman co-administered D2E7 with methotrexate, an independent treatment for RA. Weisman thus does not speak to AbbVie's monotherapy claim. *See* Appx266.[6]

The Board also missed the mark when it relied on Kempeni's statement that "long term intravenous treatment with D2E7 in the dose range from 0.5 to 10 mg/kg was well tolerated." Appx167; Appx2704. The Board overlooked that "well tolerated" says nothing about efficacy. *See* Appx2726; Appx6577. Moreover, Kempeni's statement has to be read in conjunction with Rau 2000's emphasis that every-other-week doses *greater than 1 mg/kg*—but notably not 0.5 mg/kg—resulted in "statistically significant and long-lasting reduction of disease activity." Appx28085. The Board treated the uncertainty created by these

[6] In addition, the Board's premise for relying on Weisman was misguided. The Board reasoned that Rau 2000 would not have steered a skilled artisan away from a 0.5 mg/kg dose because Weisman had been undeterred from testing relatively low doses in combination with methotrexate. Appx166; Appx214. But Weisman published six-month results only three months after Rau 2000. *Compare* Appx28103 *with* Appx28082. The Board never explained how a study already in progress at the time Rau 2000 was published could have said anything about how a person of ordinary skill would have reacted to Rau 2000.

conflicting signals as a failure to prove teaching away, when in reality that same uncertainty would have also left a skilled artisan unsure about relying on the every-other-week 0.5 mg/kg dose to inform the design of a new treatment regimen.

The Board, in other words, failed to appreciate that, even if a reference does not affirmatively teach away by actively discrediting a particular path, it can still create doubt, which the party challenging a patent has the burden of overcoming. As it happens, the evidence of up-dosing did powerfully teach away. But to the extent uncertainty about the precise reasons for up-dosing prevented such a conclusion, it was legal error for the Board to count that uncertainty against AbbVie rather than the parties with the burden of proof.

3. The Board improperly shifted the burden on other issues

The Board's burden shifting on up-dosing was not an isolated incident. As discussed in the examples below, the Board repeatedly and improperly counted uncertainty against AbbVie, rather than holding Petitioners to their burden.

First, the Board shifted the burden when it dismissed concerns about low C_{min}. Basic pharmacokinetic principles predicted that the claimed combination would yield a lower average C_{min} at steady state than any regimen discussed in the prior art on which the Board instituted. *See supra* pp. 16-18; Appx31159. This would have raised efficacy and safety concerns. Coherus's PK expert admitted that "many in the industry believed" that C_{min} was "the best parameter" for

determining the threshold efficacy of a dosing regimen. Appx2739. Boehringer's PK expert similarly wrote an article explaining 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. And Coherus's PK expert further conceded 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).[7]

The Board's stated reasons for disregarding these concerns about low C_{min} improperly shifted the burden of overcoming uncertainty onto AbbVie. The Board said 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; Appx170. But the absence of that information was precisely the point. The prior art disclosed several higher doses that showed promise without reported safety concerns. A skilled artisan searching for a less frequent subcutaneous dosing regimen would have been drawn to those options and reluctant to push beyond the

[7] *See also* Appx31294-31295; Appx31480-31481 (Boehringer's clinical expert acknowledging C_{min} is considered in developing dosage regimens); Appx5605-5606; Appx4939-4941; Appx7645-7647; Appx7629; Appx6914; Appx31780-31781; Appx7580.

lower boundary of what had been tried—lest the researcher cross that "undefined" lower threshold.

The Board similarly missed the mark when it dismissed C_{min} concerns on the ground that "the publicly available PK information in June 2001 would not have permitted a PK/PD correlation for modeling purposes." Appx33. This Court has recognized that "lack of a known PK/PD relationship" is an important signal of the *nonobviousness* of drug claims with "limitation[s] requiring therapeutic effectiveness." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069-1070 (Fed. Cir. 2012). In *Cyclobenzaprine*, the district court found that claims directed to a modified-release dosage form and methods of treatment using that formulation were obvious in light of immediate-release formulations. *Id*. at 1069. This Court reversed, holding that without a known PK/PD relationship, "skilled artisans could not predict whether any particular PK profile, including a bioequivalent one, would produce a therapeutically effective formulation." *Id*. at 1070. The uncertainty regarding fundamental aspects of D2E7's PK/PD relationship likewise should have counted against Petitioners, not AbbVie.[8]

[8] The Board only enhanced the problem when it tried to draw a sharp distinction between "clinical" and "theoretical model" approaches "to designing a dosing regimen." Appx33. The Board's lead reason for favoring the former over the latter was that "Patent Owner developed the D2E7 dosing regimen through clinical trials." Appx33. But reliance on the inventor's own path to justify a

Second, the Board improperly shifted the burden when it placed heavy weight on the penultimate sentence in Rau 2000, 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." Appx159; Appx165; *see also* Appx25; Appx71; Appx114; Appx213. That statement had an obvious omission: It did not specify any dose. Appx31652-31653. But the Board treated this omission as an invitation to apply the statement broadly on the ground that it did not "exclude any dosage level." Appx165.

Counting that silence against AbbVie was improper. Statements in the prior art must be "read in context." *Shire LLC v. Amneal Pharms., LLC*, 802 F.3d 1301, 1308 (Fed. Cir. 2015); *see also Sud-Chemie, Inc. v. Multisorb Techs., Inc.*, 554 F.3d 1001, 1005-1006 (Fed. Cir. 2009). Given Rau 2000's reports of up-dosing and praise only for long-term treatment with doses higher than 0.5 mg/kg, a skilled artisan would not have understood Rau 2000 to be recommending every-other-week treatment at the low dose used in AbbVie's claimed inventions. Appx31652-31653. That is particularly true because the only possible subcutaneous, every-

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finding of obviousness is clearly prohibited. *E.g.*, *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight."); *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000) ("[T]he path that leads an inventor to the invention is expressly made irrelevant to patentability by statute."); 35 U.S.C. § 103(a) (2011) ("Patentability shall not be negatived by the manner in which the invention was made.").

other-week dose Rau 2000 could have been referring to is the 1 mg/kg dose in the DE010 study (a study which Rau 2000 mentions only in passing in a single instance). *See* Appx28089. Therefore, the burden should have remained on Petitioners to prove that Rau 2000's statement applied to such a low dose as the one AbbVie claimed, not on AbbVie to show that such a dose was excluded.

Third, the Board's pattern of improper burden shifting extended to its analysis of objective indicia of nonobviousness. HUMIRA® is the most successful pharmaceutical product in the world. Appx5572. It embodies the claimed features of the challenged patents, which cover the treatment regimen for which HUMIRA® was first approved. Appx5573. AbbVie was therefore entitled to a presumption of a nexus between the commercial success of HUMIRA® and the patented invention. *See* Appx5573-5593; Appx39 (Board determining only whether "any presumption of nexus has been rebutted"); Appx85; Appx128; Appx174; Appx222.

The Board, however, failed to hold Petitioners to its "burden of disproving" the nexus. *Ecolochem, Inc. v. Southern Cal. Edison Co.*, 227 F.3d 1361, 1378 (Fed. Cir. 2000). Instead, the Board found that the Petitioners had rebutted the presumption merely by injecting uncertainty, stating that, "[o]n this record, it is *not clear whether* the sales of HUMIRA® are due to the dosing regimen recited in the '135 patent." Appx41 (emphasis added); *see also* Appx86; Appx129-130; Appx175; Appx223. To the extent there was uncertainty, it should have counted

against Petitioners, not AbbVie, because uncertainty meant that Petitioners had not carried their burden of proving that AbbVie's commercial success was attributable to factors other than the claimed combination of biological agent, method of administration, dose, and dosing interval.

Moreover, the Board's cursory reliance on "blocking patent" cases was misplaced. After the Board's decision, this Court explained that "developers of new compounds often obtain a package of patents protecting the product, including compound, formulation, use, and process patents" that "may result from continuing improvements in a product or process." *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 731 (Fed. Cir. 2017). These "multiple patents do not necessarily detract from evidence of commercial success of a product or process, which speaks to the *merits of the invention*, not to how many patents are owned by a patentee." *Id*. Commercial success may therefore "be relevant to an inference of nonobviousness, even given the existence of other relevant patents." *Id*.

Here, the "merits of the invention" are clear. AbbVie did not have a commercial product until the right method of administration, dose, and dosing interval for D2E7 were brought together in an integrated treatment for RA. Moreover, AbbVie's main patent on D2E7 did not even issue until July 18, 2000 (Appx2780), meaning that there was no blocking patent in place at the time of the prior art references on which the Board relied. Had AbbVie's invention been as

obvious as the Board now claims with the benefit of hindsight, there was ample incentive to try to get there before the named inventors.

C. The Board Failed To View The Claims As An Integrated Whole

1. The Board ignored the cumulative effect of the uncertainties in the prior art

The cumulative effect of the uncertainties faced by a skilled artisan multiplied the individual impact of those uncertainties. The Board was combining references that differed not just in one parameter, but across many parameters: dose amount; weekly vs. every-other-week dosing; subcutaneous vs. intravenous administration; fixed doses vs. patient-specific weight-based doses; and the length of treatment. The Board's reductive approach, however, largely addressed each difference in isolation, causing the Board to ignore their cumulative impact. This violated the fundamental precept that "[t]he determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim." *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008).

The Board devoted a section of its decisions to the benefits of selecting "*a* subcutaneous fixed dose" in the abstract. Appx17 (emphasis added). It then separately asked whether a skilled artisan would have transformed the 40 mg weekly dose in the van de Putte abstracts into an every-other-week dose. Appx18-37. But the Board never put all the elements together. For example, despite the evidence of up-dosing and questions regarding the safety and efficacy of

administering a relatively low dose over a longer interval, the Board never returned to the question of fixed dosing to ask whether a skilled artisan still would have been motivated and reasonably expected success from using that regimen across a broad population, where some patients on a subcutaneous fixed dose of 40 mg would be expected to receive *less than* the intravenous weight-based dose of 0.5 mg/kg that had already proved problematic.

Similarly, the Board's analysis of the alleged equivalence between subcutaneous and intravenous administration never considered that choice in connection with the dose, dosing interval, and use of a fixed dose. Instead, despite acknowledging that "a drug administered subcutaneously can be less bioavailable than a drug administered intravenously," the Board relied in the Coherus IPRs on prior art involving *weekly weight-based* doses of 0.5 mg/kg *with up-dosing of some patients to 1 mg/kg* to assume as a general matter that subcutaneous and intravenous administration would produce comparable plasma levels of D2E7. *See* Appx27-28; Appx2704-2705. But that begged the question whether this assumption remained true at a *lower average dose* administered *less frequently* as a *fixed dose* in which some patients would receive proportionately less drug. *See, e.g.*, Appx31805-31806; Appx31822-31823.[9]

[9] AbbVie's expert testified that a "subcutaneous 40-milligram dose would be less than a 40-milligram intravenous dose in terms of exposure in the body." Appx29646. And the statements of AbbVie's counsel regarding the "best case"

As these errors demonstrate, the Board's "[f]ocus[] on the obviousness of substitutions and differences, instead of on the invention as a whole, [was] a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 724 (Fed. Cir. 1990).

2. The Board failed to meaningfully address the "at least 24 weeks" limitation

The Board's clearest failure to consider the claims as a whole involved the "at least 24 weeks" limitation in claims 3 and 4 of the '135 patent. In the -172 and -409 IPRs, the Board began its obviousness combination with van de Putte 1999, which the Board conceded did not disclose "administering the antibody for a period of at least 24 weeks." Appx15. The Board therefore relied on Kempeni for "the dosing period of at least 24 weeks." Appx15. The problem with this approach was that, at the 0.5 mg/kg dose the Board was relying on, every single patient in the DE003 trial had been up-dosed by the end of 12 weeks. *See supra* pp. 11-12. Thus, regardless of the reason for up-dosing, there was a *complete absence of information* regarding the performance of the relevant dose beyond 12 weeks.

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equivalence between 40 mg and 0.5 mg/kg for an 80 kg patient made clear that, in reality, "the bioavailability is going to be lower and, therefore, the amount of drug that actually gets in by subcutaneous administration is not as high as it would have been by IV." Appx43456; *see also* Appx45174.

This absence was not filled by Kempeni's statement that "long term intravenous treatment with D2E7 in the dose range from 0.5 to 10 mg/kg was well tolerated" because "86% of patients continued to receive treatment" after six months. Appx2704. A skilled artisan would have known from Kempeni's discussion of up-dosing and Rau 2000 that no patient had continued receiving 0.5 mg/kg beyond 12 weeks. *See supra* pp. 11-12.

The disclosure of six-month results in van de Putte 2000, which was part of the instituted ground in the -408 IPR, likewise failed to fill the gap. van de Putte 2000 disclosed results only for *weekly* subcutaneous injections and therefore left the same hole in the reported data regarding every-other-week doses of less than 1 mg/kg. The Board, however, never analyzed the claims as an integrated whole. It therefore never grappled with the absence of evidence indicating that the claimed combination—as opposed to more frequent doses or higher doses—could be used to treat RA for 24 weeks or more.

D. In The Alternative, The Board's Decisions Were Not Supported By Substantial Evidence

The Board's legal errors should be reviewed de novo. But even viewing the Board's decisions through the lens of substantial evidence review, reversal is still warranted. The arguments above regarding the Board's use of hindsight, the unknowns in the prior art, and the layering of uncertainty on top of uncertainty all illustrate that, "taking into account evidence that both justifies and detracts from an

agency's decision," a "reasonable fact finder" could not "have arrived at the agency's decision" regarding motivation and a reasonable expectation of success. *Personal Web Techs*., 848 F.3d at 991.

II. THE BOARD APPLIED THE WRONG STANDARD IN EVALUATING THE RAU, SCHATTENKIRCHNER, AND VAN DE PUTTE COMBINATION

The Board's consideration of the alternative combination of Rau 1998, Schattenkirchner, and van de Putte 1999 in IPR2016-00409 cross-referenced the Board's discussion of Kempeni and van de Putte 1999, and thereby incorporated all the errors discussed above. Appx228. In addition, the Board committed a basic procedural error: Rather than concluding that Boehringer had proved unpatentability, the Board applied the institution-stage standard and concluded only that "Petitioner establishes a reasonable likelihood of prevailing at trial." Appx228. This application of the wrong legal standard precludes affirmance on this ground.

III. THE BOARD'S FINAL DECISIONS SHOULD BE REVERSED AS UNCONSTITUTIONAL

Each of the Board's decisions should be reversed as unconstitutional under Article III of the Constitution and the Seventh Amendment because the *inter partes* review process authorizes an executive branch agency, rather than an Article III court with a jury, to extinguish the private property right in a previously issued patent without the consent of the patent owner. Although this argument is

currently foreclosed by circuit precedent, *see MCM Portfolio LLC v. Hewlett-Packard Co.*, 812 F.3d 1284 (Fed. Cir. 2015), AbbVie preserves this argument in light of the Supreme Court's impending decision in *Oil States Energy Services LLC v. Greene's Energy Group, LLC*, No. 16-712 (U.S).

CONCLUSION

The Board's decisions should be reversed or, at the very least, vacated and remanded for further proceedings.

Respectfully submitted,

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