Filed: September 13, 2016

Filed on behalf of: AbbVie Biotechnology Ltd.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COHERUS BIOSCIENCES INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD.,
Patent Owner.

Case IPR2016-00189
Patent No. 9,073,987 B2

PATENT OWNER'S RESPONSE

TABLE OF CONTENTS

Page(s)

TABLE OF AUTHORITIES

Page(s)

Federal Cases

Federal Statutes

I. INTRODUCTION

The Board instituted *inter partes* review of U.S. Patent No. 9,073,987 ("the '987 patent") on the single ground that claims 1-2 would have been obvious based on a combination of van de Putte (Ex. 1004) and Kempeni (Ex. 1003). In its decision, the Board indicated that a trial was required to resolve "whether a skilled artisan would have relied upon half-life or dose-stretching based on known half-life to establish a dosing regimen for D2E7." Paper 8, 19. The evidence now before the Board definitely answers that question in Patent Owner's favor: a skilled artisan would ***not*** have relied on D2E7's reported half-life to establish the claimed dosing regimen. Indeed, serious safety and efficacy concerns would have steered a POSA away from the claimed regimen.

Among the many problems with Petitioner's argument is that, under undisputed pharmacokinetic ("PK") principles, a person of ordinary skill ("POSA") would have expected the minimum drug concentration between each dose ("C_{min}") in the claimed dosing regimen to be substantially less than the minimum drug concentration in the dosing regimens disclosed in van de Putte. Those lower troughs of drug concentration would have raised both efficacy and safety issues. The available clinical and PK data, including the half-life information on which Petitioner relies, would thus have discouraged a POSA from

stretching the 20mg weekly regimen of van de Putte to a 40mg every-other-week regimen.

A. Dr. Baughman's Half-Life Analysis Is Flawed

As the Board recognized, Petitioner's obviousness theory is primarily based on the declaration of Dr. Sharon Baughman and her claim "that a skilled artisan would have been led to biweekly dosing based on the known 11.6 to 13.7 day half-life of D2E7." Paper 8, 17-18. The centerpiece of that theory is Dr. Baughman's contention that a POSA would have expected the claimed 40mg every-other-week dose to be effective because the amount of drug in the blood two weeks after the 40mg dose would allegedly be higher than the amount of drug in the blood one week after a 20mg dose. Ex. 1006 ¶¶67-68, 71.

Dr. Baughman's analysis is based on a table in her declaration, cited by the Board in it institution decision. Paper 8, 18 (citing Ex. 1006 ¶¶66-67, 72). In the table, Dr. Baughman purports to calculate and compare the amount of D2E7 circulating in a patient's blood one week and two weeks following an initial dose of the 20, 40, or 80mg weekly doses described by van de Putte. Ex. 1006 ¶67. Based on her calculations, she concludes that the C_{min} of a 40mg every-other-week dose would be higher than the C_{min} of a 20mg weekly dose. *Id.* ¶71.

Dr. Baughman's analysis is flawed in numerous ways. But the critical flaw is that Dr. Baughman approximated the amount of drug in the blood after just a

single dose, rather than examining the steady-state drug concentrations achieved after multiple doses.[1] The claimed dosing regimen is not to a single dose; it is an every-other-week dosing regimen administered to reduce signs and symptoms in a patient with moderately to severely active rheumatoid arthritis ("RA"). Likewise, the efficacy data in van de Putte on which Dr. Baughman relies was generated after three months of weekly injections, not a single dose.

As explained in the declaration of Dr. Alexander Vinks, once the concentration of D2E7 in the body reaches a steady-state, a POSA applying fundamental PK principles would have expected that a multi-dose regimen delivering twice as much drug at twice the dosing interval would produce higher peaks and lower troughs of drug concentration in the body. A POSA thus would have expected that the C_{min} of a 40mg every-other-week dose would be substantially ***lower*** for the average patient than the C_{min} of the 20mg weekly regimen of van de Putte, not higher as Dr. Baughman suggests. While insufficient information was available in the prior art to perform a true PK/PD (pharmacodynamic) correlation for D2E7, Dr. Vinks further shows that the

[1] Steady-state concentrations are reached when the amount of drug eliminated from the body over each dosing interval is equal to the amount that was absorbed into the body after the previous dose.

existing PK information taught away from the claimed 40mg every-other-week dosing regimen because it indicated that the steady-state trough concentrations (C_{min}) for the 40mg every-other-week dosing regimen would have been substantially lower than the trough concentrations for the 20mg prior art weekly regimen.

Dr. Baughman's analysis improperly ignored these effects. At her deposition, however, Dr. Baughman conceded that, at steady-state, lower C_{min} levels would have been the expectation of a POSA based on "pharmacokinetic principles." Ex. 2072, 90:20-91:3.

B. A POSA Would Have Been Concerned About Lower Minimum Drug Concentrations

Dr. Baughman admitted that a POSA would have wanted to design a dosing regimen in which the C_{min} would be at or higher than the C_{min} of a dosing regimen previously shown to be safe and efficacious. *Id.*, 68:15-20. Dr. Baughman further acknowledged that many in industry believed that C_{min} was the best parameter for determining the threshold of efficacy for a dosing regimen. Ex. 1006 ¶62. For D2E7, a POSA would have been particularly concerned about low C_{min} values in view of prior art clinical trials involving dosing based on a patient's weight, in which amounts that would have been expected to result in greater circulating drug concentrations than the claimed dosing regimen were shown to be insufficient.

Those results indicated that the claimed dosing regimen would also have been insufficient.

Dr. Baughman also concedes that a POSA would have been concerned about under-dosing patients with D2E7 because of the fear that too little drug in the blood would increase the risk of anti-drug antibodies ("ADAs"). Ex. 1006 ¶71. In addition to safety concerns, ADAs were known to block a biologic's efficacy by increasing the speed at which the biologic is removed from the body or by interfering with the biologic's ability to bind to its target. Once an immune response to an anti-TNFα biologic is generated, any loss of efficacy is typically permanent and the patient may no longer respond to the drug at all.

Dr. Baughman primarily relies on her flawed C_{min} analysis to dismiss these concerns with respect to the claimed invention. She and Petitioner's clinical expert, Dr. O'Dell, further contend that the D2E7 prior art was silent about the existence of ADAs. They infer from this silence that a POSA would have dismissed the concern that too low a dose of D2E7 would trigger an immune response. *Id.*; Ex. 1007 ¶41. This argument is also refuted by the evidence.

As an initial matter, the factual predicate of Dr. Baughman's opinion is wrong. There ***are*** indications in the prior art of the possibility of ADAs to D2E7 as well as concerns about their effect on safety and efficacy. *See* §IV.A.5.

Further, no inference can be drawn from the absence of experimental proof showing ADAs in the D2E7 prior art. The prior art references consist of a handful of abstracts and reviews providing preliminary information on early, on-going, studies. None of the references discussed testing for ADAs. And it is not surprising that such testing was not reported. As explained in the declaration of Jeffrey Sailstad, the assays for detecting ADAs during this time period were inadequate, typically requiring a "wash-out" period, *i.e.*, a period in which D2E7 was not administered. Consequently, reliable ADA assays could not be performed during an ongoing clinical trial, such as that reported in van de Putte and the other references.

C. Half-Life Does Not Provide Sufficient Information For Designing A Dosing Regimen

More generally, the core premise of Petitioner's theory is incorrect. Half-life is inadequate for designing a dosing regimen because it does not impart any information about drug concentration, the key determinant of safety and efficacy. Indeed, in the case of subcutaneous dosing, terminal half-life (what is reported in Kempeni) does not even tell a POSA how long the drug remains in the body, let alone at the site of action. It is a measure of drug elimination ***after*** the drug has reached the blood stream, which takes days following subcutaneous administration of D2E7.

Nor is there any logical reason why a POSA would have been led to a dosing interval that is the same as the terminal half-life of a drug. In the absence of additional data, a dosing interval that is the same as a drug's terminal half-life ensures substantial, usually undesirable, fluctuations in drug levels. Moreover, the evidence shows that for therapeutic monoclonal antibodies, half-life is not a reliable predictor of dosing interval. Approved prior art therapeutic antibodies were dosed more frequently and less frequently than their terminal half-lives.

In short, the evidence before the Board refutes the factual underpinnings of the obviousness theory on which the Petition is based. The known clinical and PK data, including half-life, would not have "led" a POSA to the claimed invention—they would have taught away. A POSA would not have been motivated to try a dosing regimen that was likely to be less efficacious—if it worked at all—than the known dosing regimens in van de Putte, particularly when that regimen carried an increased risk of ADAs and when experience with weight-based doses indicated that the claimed dosing regimen would be inadequate. And even if a POSA had tried the claimed invention, there would have been no reasonable expectation that it would be sufficient to treat RA. For these reasons alone, Petitioner has failed to carry its burden of demonstrating that the challenged claims are unpatentable. *In re Magnum Oil Tools, Int'l, Ltd.*, --F.3d--, 2016 WL 3974202, at *10 (Fed. Cir.

2016) ("[T]he Board must base its decision on arguments that were advanced by a party, and to which the opposing party was given a chance to respond.").

Nonetheless, in addition to the declarations of Dr. Vinks and Mr. Sailstad, Patent Owner also submits the declarations of Drs. Allan Gibofsky, Jerry Hausman, and Brian Harvey. These declarations show that the development of an antibody-based dosing regimen in Phase II and III clinical studies was anything but "routine" and that the claimed invention—the first approved dosing regimen for the most successful pharmaceutical product in the world—produced unexpected results, satisfied a long-felt need where others had failed, and is directly responsible for the enormous success of the commercial embodiment of D2E7 in treating RA. This additional evidence confirms the patentability of the challenged claims.

II. FACTUAL STATEMENT

A. The Prior Art

In June 2001, biologic agents designed to block TNFα activity were a new class of drugs that had shown promise for treating RA. Ex. 1003, 1; Ex. 2069 ¶53. At that time, there were two FDA-approved anti-TNFα biologics: ENBREL® (a TNFα receptor fusion protein) and REMICADE® (a chimeric monoclonal antibody that contains both murine and human sequences). Ex. 2065 ¶¶30-32; Ex. 2069 ¶54. D2E7 (HUMIRA®) is also a monoclonal antibody but was developed from

human genetic material. Ex. 2069 ¶77. It was the first such antibody to be approved by the FDA and the first antibody of any kind approved by FDA for subcutaneous administration.[2] Ex. 2066 ¶11; Ex. 2069 ¶59; Ex. 2027, 10-12.

Clinicians in 2001 were faced with a number of promising options for the treatment of RA, but there was significant confusion and unanswered questions about how to apply the available therapies. Ex. 2061, 1; Ex. 2065 ¶¶15, 38, 58-59; Ex. 2074, 104:3-106:6. With respect to anti-TNFα biologics in particular, there were significant safety concerns as of 2001 and "studies to elucidate the optimal degree of TNF inhibition that [was] safe and effective in each patient [were] crucial." Ex. 2063, 2; *see also* Ex. 2068 ¶¶18, 35-37; Ex. 2074, 152:17-24, 152:25-155:21; Ex. 2069 ¶53, 62.

The prior art pertaining to D2E7 contained preliminary data from four Phase I clinical trials and one Phase II trial. *See* Ex. 2065 ¶¶42-50; Ex. 2069 ¶78, 91, 94. Limited information about these early trials was published in abbreviated form in review articles and conference abstracts, including van de Putte (Ex. 1004) and Kempeni (Ex. 1003). *See also* Exs. 1005; 1009; 1017; 1018; 1019; 1023; 1024;

[2] The use of monoclonal antibodies as therapeutic agents was in its infancy in 2001. Only 11 such antibodies had been approved, most for acute rather than chronic conditions. Ex. 2066 ¶11.

2020. Collectively, the D2E7 prior art discussed a variety of dosing strategies involving different routes of administration, dosing schedules, dosing amounts, and response rates. Ex. 2065 ¶16.

The clinical trials that led to the claimed invention did ***not*** constitute the exercise of "routine optimization" of a dosing regimen. Developing a clinical trial for an investigational new drug is a complex and unpredictable endeavor. Ex. 2074, 124:11-21; Ex. 2066 ¶¶7-8, 13, 15-18. As explained by Petitioner's rheumatology declarant Dr. O'Dell, "[c]onfounding factors include funding for clinical research, patient recruitment, which drugs to use and in what combination, duration of the study, accepted end points to measure efficacy, dosage of the medication, numbers and kinds of control groups needed, and the numbers of patients in each study needed to show real efficacy differences." Ex. 2062, 2; Ex. 2074, 111:14-113:10. Clinical trials of a biologic product—particularly an investigational new drug that has not yet been approved for human use—require an enormous investment of resources and face a high risk of failure. Ex. 2066 ¶¶8, 17-18, 20; Ex. 2074, 106:7-19; *see also id*., 30:18-20 (a POSA "can't assume that a dose or an interval is going to be effective or appropriate until you've actually studied it.")

Notably, biologics routinely fail to advance towards approval at even the later phases of clinical trials for any number of reasons, including because of the

failure of a drug's dosing regimen. Ex. 2066 ¶9, 20-21. Indeed, poor dose selection was identified as ***the leading reason*** for delay and denial of FDA approval based on a review of NDAs submitted between 2000 and 2012. *Id*. ¶19; Ex. 2182, 4, 6.

1. Kempeni

Kempeni discloses several early "weight-based" D2E7 prior art trials. Ex. 1003, 2-3; Ex. 2069 ¶78; Ex. 2065 ¶¶ 43-46, 75. The first Phase I study (DE001) examined 120 total patients, divided into 5 groups, who received placebo or a single intravenous dose of D2E7 based on weight (0.5 to 10mg/kg). Ex. 1003, 2; Ex. 2069 ¶79-80, 84. This study was followed by an open-label extension (DE003) in which patients continued to receive intravenous injections based on their body-weight. Ex. 1003, 2; Ex. 2069 ¶86. In the second Phase I study (DE004), just 24 patients received weekly subcutaneous weight-based doses of either placebo or 0.5mg/kg D2E7 for three months. Ex. 1003, 2-3; Ex. 2069 ¶¶87-88. The third Phase I study reported in Kempeni (DE010) involved a head-to-head comparison of a single, 1mg/kg weight-based dose of D2E7 administered either subcutaneously or intravenously. Ex. 1003, 3; Ex. 2069 ¶89.

In each of the trials reported in Kempeni, patients who received a weight-based dose of 0.5mg/kg had to be up-dosed to maintain their responder status. This need to up-dose indicated that a 0.5mg/kg dose is ***insufficient*** for treating RA

across the patient population. *See* Ex. 2065 ¶¶44-45, 47; Ex. 2069 ¶¶154-155. The claimed 40mg dosing regimen—which Petitioner equates with the Kempeni dose by multiplying the 0.5mg/kg dose by an assumed average patient weight of 80kg—therefore also would have been insufficient to treat RA. *See* Pet. 26 (Table). Moreover, the prior art disclosed up-dosing in patients administered 0.5mg/kg ***intravenously***. Ex. 2065 ¶¶44, 47. Compared to that method, ***subcutaneous*** administration decreases the bioavailability of the administered drug. Accordingly, the claimed 40mg dosing regimen would have been understood to result in lower concentrations of drug than those resulting from intravenous administration of a 0.5mg/kg dose to an 80kg patient. Ex. 2069 ¶¶31-34, 72-74, 126-127; *see also* Ex. 2017, 29; Ex. 2119, 19-20.[3]

[3] Reporting on a study lacking an intravenous arm (DE004), Kempeni states "preliminary data" shows that D2E7 blood levels after multiple SC doses were "comparable" to those obtained following intravenous administration. Ex. 1003, 3. No information was provided as to the PK parameters being considered, the concentration levels of D2E7, or the number of subcutaneous administrations of D2E7 needed to achieve "comparable" concentration levels. Ex. 2069 ¶88.; Ex. 2072, 79:6-22.

There is nothing in Kempeni that teaches or suggests a fixed dose of D2E7 or every-other-week dosing. All of the doses were weight-based, and the purportedly "biweekly" phase of the DE003 study actually involved a mean dosing interval of 2.5 weeks in a weight-based, intravenously administered regimen. Ex. 1003, 2-3.

Kempeni also reports substantial variability in the effect of the drug on patients (called pharmacodynamic ("PD") responses) following single administration. Ex. 2069 ¶152. Specifically, in the three highest dose groups of the DE001 trial, "40-70% of patients achieved DAS and ACR20 response status at 24 hours to 29 days" post-treatment, indicating significant patient-to-patient variability both with respect to whether the drug would work and how long it would take.[4] Ex. 1003, 2

2. van de Putte

The van de Putte abstract is a conference abstract that reports preliminary data from the first Phase II trial of D2E7. Ex. 1004; Ex. 2065 ¶ 48; Ex. 2069 ¶91. This trial, called DE007, featured a three-month placebo-controlled study in which

[4] DAS (Disease Activity Score) and ACR20 (American College of Rheumatology) refer to composite criteria used to measure the effectiveness of RA treatments. Ex. 1003, 1-2; Ex. 2065 ¶¶40-41; Ex. 2112, 1.

patients received a fixed dose of 20, 40, or 80mg D2E7 administered subcutaneously on a weekly schedule. Ex. 1004; Ex. 2069 ¶92. DE007 was the first fixed dose trial; all of the previous trials had used weight-based dosing. Ex. 2065 ¶¶42, 61.

A total of 283 patients were randomized equally into the four arms. Ex. 1004. The study was not powered to provide statistically meaningful comparisons between doses, but only to determine the statistical significance of each of the doses compared to placebo. Ex. 2065 ¶64. The data showed that while the 40 and 80mg doses were numerically superior to the 20mg dose, each dose was statistically superior to placebo. *Id.* ¶¶64-66; Ex. 2069 ¶93. Although the authors concluded that "20, 40 and 80 mg/week were nearly equally efficacious," this statement was based on a comparison of each group to placebo, not to each other. Ex. 1004.

Additional information about the DE007 trial exists in the prior art, although it is not addressed by Petitioner. After 3 months, patients receiving placebo were switched to a 40mg weekly dose. Ex. 2129; Ex. 2069 ¶94. Those patients showed greater improvement in the same 3 clinical outcome measures (ACR20, SJC, CRP)

after just 3 months of 40mg weekly dosing compared to patients who received 20mg weekly for 6 months.[5] *Id.*; Ex. 2065 ¶67.

	Percent Response or Improvement	
	Placebo/40mg 3 mos./6 mos.	20mg 3 mos./6 mos.
ACR20	10/**59**	49/**56**
SJC (median)	16/**56**	42/**54**
CRP (median)	01/**67**	54/**59**

The difference between 20mg and the higher weekly doses becomes even more evident at 12 months. For example, the ACR50 for the 20mg weekly group remains essentially the same between 3 and 12 months. Ex. 1024. The 40mg and 80mg weekly groups, on the other hand, experience a 60% increase in percentage of patients achieving ACR50. *Id.* In fact, at 12 months, the percentage of patients receiving 40 and 80mg weekly doses was numerically superior for every clinical measure outcome compared to 20mg weekly. *Id.*; Ex. 2065 ¶68.

	Percent Response or Improvement		
	20mg 3 mos./12 mos.	40mg 3 mos./12 mos.	80mg 3 mos./12 mos.
ACR20	49/**46**	59/**60**	56/56
ACR50	24/**25**	27/**43**	19/31
TJC (median)	52/**51**	57/**60**	53/60
SJC (median)	39/**52**	56/**65**	54/59
CRP (median)	53/**55**	61/**64**	64/60

[5] SJC refers to Swollen Joint Count; CRP refers to C reactive protein, a biomarker of inflammation. Ex. 2065 ¶¶40, 48.

Other contemporaneous reports of the same clinical study do not even mention the efficacy of 20mg weekly dosing, indicating that the 40mg weekly regimen was preferred among the three regimens. Ex. 2020; Ex. 2065 ¶69. Moreover, in the full-length, peer-reviewed article reporting the data, the authors stated that "[i]n most measures of efficacy at week 12, adalimumab [D2E7] ***40 mg was associated with better results than the other doses***." Ex. 2130, 9 (emphasis added); Ex. 2065 ¶70; Ex. 2069 ¶95.

B. The PK Data in Kempeni

Kempeni reports three PK parameters: (1) mean total serum clearance, (2) steady-state volume of distribution, and (3) an "estimated mean terminal half-life" of 11.6 to 13.7 days. Ex. 1003, 2; Ex. 2069 ¶80. These three metrics are reported as ranges in Kempeni, which does not report any patient-specific PK information. Ex. 2069 ¶133.

Clearance refers to the rate at which a drug is eliminated from the body and is typically expressed as mL/min. Ex. 2069 ¶30. Volume of distribution refers to the theoretical volume over which the drug is distributed. It is typically expressed as L/kg, where kg is the weight of the patient. *Id.*

Terminal half-life, a calculated value, refers to the time taken for the concentration of the drug in the blood to fall by 50% during the elimination phase of a PK profile (the period when the rate of drug elimination due to excretion

and/or metabolism predominates). Ex. 2069 ¶¶29, 109. Terminal half-life provides no information about the "absorption" phase (the period when the drug moves from the site of administration to the blood) or "distribution" phase (the period in which the drug is distributed to other areas in the body). *Id.* ¶¶25-26, 32, 109; *see also* Ex. 2017, 14-19. Thus, in the case of a subcutaneously administered drug, the terminal half-life does not reflect how long the drug is in the body, nor does it provide any information about how long the drug is at the site of action. *Id.* ¶¶25-26, 32, 34. Finally, half-life does not itself reveal any information about the concentration of drug in the blood, the PK parameter of primary importance for designing a dosing regimen. *Id.* ¶¶36, 107, 108, 110; Ex. 2119, 41.

Kempeni does not report key exposure metrics such as C_{min}, C_{max}, or AUC. Ex. 1006 ¶62; Ex. 2069 ¶¶79-80, 86-89. C_{max} and C_{min} respectively refer to the peaks and troughs of a concentration-time curve that graphs exposure to a drug. Ex. 2069 ¶35, 39. AUC is the total area under a PK curve and reflects overall exposure to a drug. *Id.* ¶35. According to Dr. Baughman, "many in the industry believed that the C_{min} parameter (e.g., the lowest blood level observed between doses) might be the best parameter to indicate the threshold of efficacy"). Ex. 1006 ¶62.

C. The ’987 Patent

The ’987 patent claims priority to an application filed June 8, 2001. Ex. 1001, (60). It contains two claims directed to methods of reducing signs and symptoms in a patient with moderately to severely active RA involving administering an anti-TNFα antibody having the six CDRs and heavy chain constant region of D2E7. *Id.*, 59:38-60:46. The claims cover the first-approved dosing regimen for HUMIRA®. Each of the claims requires administering a total body dose of 40mg subcutaneously once every 13-15 days. *Id.*

D. HUMIRA®

HUMIRA® was first approved for the treatment of RA at the end of December 2002. Ex. 2065 ¶39; Ex. 2094; Ex. 2095. As Petitioner concedes, HUMIRA® has been a commercial success in the treatment of RA. Ex. 2070, 38:2-19; 144:22-145:7.

As Petitioner’s expert also concedes, the success of HUMIRA® is largely attributable to its safety and efficacy, which is inextricably bound up with the invention of a safe and efficacious dosing regimen. *See* Ex. 2070, 23:4-18, 254:14-255:3. Beyond its safety and efficacy, moreover, HUMIRA® also satisfied the need for an anti-TNFα therapy that could be safely self-administered at home, that did not require weight-based calculations of dose amount, and that maximized

patient comfort and convenience by limiting the number of injections. Ex. 2065 ¶¶90-91. Each of these features results from the claimed invention as a whole.

III. INSTITUTION DECISION

The Board instituted *inter partes* review of claims 1-2 of the '987 patent over the combination of Kempeni and van de Putte under 35 U.S.C. §103. Paper 8, 22.

The POSA was defined as possessing the skill sets of both a physician treating RA patients and a pharmacokineticist with experience in monoclonal antibodies. *Id.*, 5, n.5.

The Board determined that the phrase "a method of reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis" is not limiting. *Id.*, 9. Resolution of the IPR does not turn on the construction of this phrase, both because the prior art teaches away and because a POSA would have been motivated to pursue the most effective treatment possible. *See Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (expectation that modification of compound would have achieved "baseline level" of functionality insufficient to show motivation). Nevertheless, Patent Owner addresses the Board's interpretation in §IV.E below.

IV. THE CHALLENGED CLAIMS WOULD NOT HAVE BEEN OBVIOUS OVER VAN DE PUTTE AND KEMPENI

To show obviousness, there must be evidence of a reason or motivation to modify the prior art and a reasonable expectation of success. *Procter & Gamble Co. v. Teva Pharms. USA, Inc*., 566 F.3d 989, 994 (Fed. Cir. 2009); *see also Arendi S.A.R.L v. Apple Inc.*, --F.3d--, 2016 WL 4205964, at *5 (Fed. Cir. 2016) (common sense "cannot be used as a wholesale substitute for reasoned analysis and evidentiary support"). Here, Petitioner cannot satisfy either requirement. A POSA would not have been motivated to modify the van de Putte dosing regimens to arrive at the claimed invention because of well-founded concerns that the drug concentrations resulting from the claimed dosing regimen would be insufficient to treat RA and would generate ADAs. Indeed, the evidence as a whole taught away from the claimed dosing regimen. *Syntex (U.S.A.) LLC v. Apotex, Inc*., 407 F.3d 1371, 1380 (Fed. Cir. 2005) ("Under the proper legal standard, a reference will teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention."). And, far from there being a "reasonable expectation of success," it would have been ***unexpected*** that the claimed dosing regimen would be sufficient to treat RA as effectively as HUMIRA® because a POSA would have predicted that trough concentrations associated with the claimed dosing regimen would be substantially lower than those produced by the 20mg weekly van de Putte regimen.

A. The Available Pharmacokinetic Data, Including Half-Life, Would Not Have Provided The Requisite Motivation And Expectation Of Success

It is undisputed that a dosing regimen having too low a C_{min} would raise concerns about safety and efficacy. Indeed, Dr. Baughman concedes that "many in the industry believed that the C_{min} parameter (e.g., the lowest blood level observed between doses) might be the best parameter to indicate the threshold of efficacy." Ex. 1006 ¶62; *see also* Ex. 2069 ¶¶18, 21, 41, 123. In June 2001, however, the minimum drug concentration of D2E7 needed to induce a therapeutic response was unknown. Ex. 1006 ¶62.

It is also undisputed that underdosing correlated with the formation of ADAs. As stated by Dr. Baughman:

> An additional consideration in "underdosing" is whether the amount of antibody circulating between doses (C_{min}) could be so low as to induce the body to make anti-drug antibodies. In other words, if the C_{min} were low enough, it is possible the body would treat D2E7 as an antigen and generate antibodies that would bind it and prevent it from exerting its anti-TNFα activity.

Ex. 1006 ¶71; *see also* Ex. 2072, 65:22-66:14; Ex. 2069 ¶¶69-71; Ex. 2068 ¶¶15-17. Nonetheless, she dismisses any concerns about efficacy based on her PK analysis, which concludes that the C_{min} of the claimed invention is higher or similar to the C_{min} of the prior art. Ex. 1006 ¶71; Ex. 2072, 66:19-67:9.

As demonstrated in the declaration of Dr. Vinks, this analysis is deeply flawed. Ex. 2069 ¶¶16-17, 120. Far from motivating a POSA to try the claimed invention and providing a reasonable expectation of success, both fundamental pharmacokinetic principles and the available PK data, including half-life, would have discouraged a POSA from the claimed dosing regimen because it would have suggested that a 40mg every-other-week dose would have delivered too low a dose of D2E7 to be safe and effective. *Id.* ¶¶18, 122. In particular, a POSA would have expected that the C_{min} of the claimed invention would be substantially ***lower*** than the C_{min} of the prior art van de Putte regimens, not higher as Dr. Baughman's declaration suggests. *Id.* ¶¶42-44.

1. Dr. Baughman's calculation of serum drug levels is wrong

The table on which Dr. Baughman's opinion is based is reproduced below.

D2E7 Dose Administered	D2E7 Circulating One Week After Injection	D2E7 Circulating Two Weeks After Injection
20mg	15mg	10mg
40mg	30mg	20mg
80mg	60mg	40mg

Ex. 1006 ¶67. According to Dr. Baughman, these calculations demonstrate that "at the end of the second week after dosing 40mg, the C_{min} would be greater than or similar to the C_{min} at the end of the first week after dosing 20mg, which was

already tested in van de Putte 1999's Phase II study without reported anti-drug antibody concerns." Ex. 1006 ¶71.

The Board relied on the calculations from Dr. Baughman's table in describing Petitioner's arguments:

> [A] skilled artisan would have been led to biweekly dosing based on the known 11.6 to 13.7 day half-life of D2E7. Pet. 33; Ex. 1006 ¶¶ 48, 56-57, 63-68. Pointing to the clinical results reported in van de Putte, ***Petitioner explains that a skilled artisan would have recognized that at least 30 mg of D2E7 would have remained circulating in a patient's blood one week after administration of a 40 mg dose, and that this amount is greater than the 20 mg dose van de Putte disclosed as efficacious when administered weekly***.

Paper No. 8, 17-18 (emphasis added). But the numbers in Dr. Baughman's table are incorrect, and she is looking at the wrong time period.

First and foremost, Dr. Baughman analyzed the wrong time interval, inappropriately imparting significance to drug levels after a single administration of D2E7. *Id.* ¶¶16, 20, 121-123; *see* Ex. 2072, 92:22-24. RA is not treated with a single dose. It is a chronic disease requiring long-term, usually life-long, treatment. Ex. 2065 ¶24; Ex. 2132, 3; Ex. 2069 ¶37. This is why van de Putte analyzed efficacy at 3 months after 12 weekly injections, not following a single administration. Ex. 2069 ¶121.

Given the nature of the disease and the claims, it is irrelevant (as well as incorrect[6]) "that a skilled artisan would have recognized that at least 30 mg of D2E7 would have remained circulating in a patient's blood one week after administration of a 40 mg dose[.]" Paper 8, 18. The question relevant to a POSA seeking to treat RA would be the profile of a drug over multiple administrations where the course of treatment has reached a steady-state (in other words, when the trough (C_{min}) and peak (C_{max}) drug levels are no longer increasing). Ex. 2017, 3; Ex. 2069 ¶¶38-40; *see generally* Ex. 2119, Chapter 7. Dr. Baughman's declaration and the Petition fail to address this critical question, and the result is an analysis that is fundamentally misleading. *See* § IV.A.2-.5.

Second, Dr. Baughman's assumption of a 14 day half-life inappropriately rounds up a range (11.6 to 13.7 days) that itself is an "estimated mean." Ex. 1003, 2; *see also* Ex. 2072, 72:10-13. Dr. Baughman does not explain why it is appropriate to assume a half-life that is almost 20% longer than the lower end of the range reported in Kempeni. Had Dr. Baughman used the reported half-lives

[6] As explained below the values in Dr. Baughman's table are incorrect even for a first injection. Ex. 2069 ¶124; *see* Ex. 2072, 82:22-83:11 (amount lost to absorption).

instead of rounding up, the numbers in her table would have been lower. Ex. 2072, 72:15-21; Ex. 2069 ¶125.

Third, Dr. Baughman's table assumes 100% bioavailability of D2E7 in the blood, as would be true of an intravenous dose. Ex. 2072, 76:16-19. But the claims require subcutaneous administration. The administration of a drug subcutaneously was known to cause a variable, frequently significant reduction in the amount of drug absorbed into the bloodstream. Ex. 2018, 8-9; Ex. 1022, 4, 10; Ex. 2069 ¶¶23, 31, 34, 126. This means that following administration of a subcutaneous dose, only a fraction of the total antibody administered reaches the blood. *Id.* ¶126. Post-filing data shows that for D2E7 only about 64% of the antibody is bioavailable after subcutaneous administration. *Id.*; Ex. 1034, 14. Dr. Baughman's analysis fails to account for this loss of dose when D2E7 is administered subcutaneously. *See* Ex. 2072, 76:16-23. Had she accounted for the loss of drug during the absorption phase, the numbers in her table would have been lower. Ex. 2072, 82:22-83:11; *see also* Ex. 2069 ¶126.

Fourth, the table incorrectly assumes that drug is immediately bioavailable after administration of a subcutaneous dose. Ex. 2069 ¶127. But, unlike intravenous dosing, subcutaneous dosing was known to require an additional absorption period when the drug moves from the site of injection to the blood. *Id.* ¶¶32, 127; Ex. 2072, 33:4-7. For protein drugs, such as monoclonal antibodies,

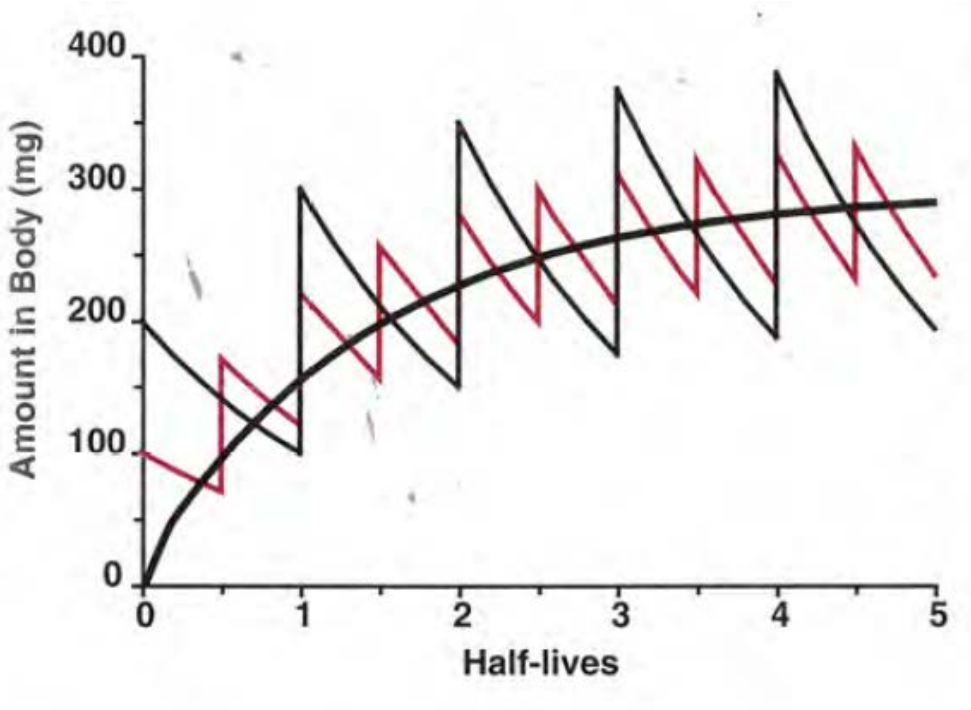
absorption could take several days, and would be highly variable among patients. Ex. 2069 ¶¶33, 128; Ex. 2099, 9. This means that following administration of a subcutaneous dose, there is a substantial delay before the antibody is available to contribute to efficacy. Dr. Baughman fails to account for such delays. Ex. 2072, 75:17-19.

2. A POSA would have expected the steady-state trough levels of the claimed dosing regimen to be substantially lower than those of the 20mg weekly van de Putte regimen

Given the implications for Petitioner's obviousness theory, it is not surprising that the Petition erroneously focused on drug levels after only a single administration instead of steady-state drug concentrations. A basic principle of pharmacokinetics is that increasing the dosing interval of a drug while maintaining the total exposure to the drug (*e.g.*, doubling both the dose amount and the interval between doses) will result in higher peaks and lower troughs of drug concentration in the body. Ex. 2069 ¶¶16-17, 42-44, 120. This is shown in prior art textbooks and articles and is conceded by Dr. Baughman to be a fundamental pharmacokinetic principle. Ex. 2119, 57-58; Ex. 2170, 7; *see also* Ex. 2049, 13; Ex. 2120, 11; Ex. 2072, 88:15-89:6, 90:20-91:3.

The figure below, extracted from a well-known pharmacokinetics textbook, illustrates this principle. Ex. 2120, 11. The figure shows the PK profiles for a drug given either as 200mg once every half-life (black line) versus a drug given as

100mg twice every half-life (red line). Ex. 2069 ¶43. Administration of double the dose and double the dosing interval results in higher peak (C_{max}) and lower trough (C_{min}) concentrations. As explained by the authors, "the less frequent the administration, the greater is the fluctuation." Ex. 2120, 11.



Id., Figure 11-3.

Applying this basic pharmacokinetic principle to D2E7, at steady-state, a POSA would have expected the claimed dosing regimen to produce higher peak concentrations, lower trough concentrations, and greater fluctuations between peaks and troughs than the 20mg weekly van de Putte regimen. Ex. 2069 ¶122. This would have discouraged a POSA from pursuing the claimed dosing regimen

in view of the available clinical data and the known threat of ADAs. *See* §§IV.A.5, C.

3. In her deposition, Dr. Baughman agreed that the C_{min} of the claimed dosing regimen would have been expected to be lower than a 20mg weekly dose and that a POSA would have sought to design a dosing regimen to avoid that result

Dr. Baughman does not address the C_{min} of the claimed dosing regimen or the van de Putte dosing regimens at a steady-state. Ex. 2069 ¶121. But in her deposition, she grudgingly conceded that, as a matter of pharmacokinetic principles, a POSA would have expected the C_{min} of the claimed invention to be less than the 20mg weekly van de Putte regimen once a steady-state was reached:

> Q. So, in general, at a steady state, C_{max} would have been expected to be greater for the claimed dosing regimen than the 20 milligram van de Putte regimen?
>
> MR. KANE: Objection, lack of foundation.
>
> THE WITNESS: Based on pharmacokinetic principles, I would say, yes.
>
> BY MR. RAICH:
>
> Q. For those two dosing regimens, the 20 milligram weekly regimen in van de Putte --
>
> A. Uh-huh.
>
> Q. -- and the claimed 40 milligram every other week dosing regimen, when a steady state is reached, a person of skill in the art would have expected the troughs of the 40 milligram every other week dosing regimen to be lower than the troughs of the 20 milligram weekly regimen, correct?

A. I can’t state that.

Q. Why?

A. I don’t have the data.

Q. Why would it be true for the peaks, but you can’t be certain one way or the other for the troughs?

A. Repeat the question. Why would what be true for the peaks?

Q. Why would the peaks for the 40 milligram every other week dosing regimen be higher than the peaks for the 20 milligram weekly dosing regimen --

A. Okay.

Q. -- but you can’t say one way or the other whether the troughs for the 40 milligram every other week dosing regimen would be lower than the troughs for the 20 milligram regimen?

MR. KANE: Object, mischaracterizes.

THE WITNESS: On pharmacokinetic principles, one might assume that.

BY MR. RAICH:

Q. On pharmacokinetic principles, one might assume that the troughs would be lower for the 40 milligram every other week dosing regimen than the troughs of the 20 milligram weekly regimen?

A. It's a possibility, yes.

Q. So under pharmacokinetic principles, at steady state, C_{min} would have been expected to be lower for the claimed dosing regimen than the 20 milligram van de Putte regimen?

A. I can't state -- say for certain, but it’s a possibility.

> Q. That would be your expectation as a matter of pharmacokinetic principles?
>
> A. In a perfect world, yes.

Ex. 2072, 88:24-91:3.

Dr. Baughman also admitted that a POSA would have sought to design dosing regimens to avoid this result.

> Q. . . . So to avoid underdosing, a person of skill in the art who wanted to design a new dosing regimen would design that regimen so that its C_{min} would be at or above the C_{min} of other regimens shown to be safe and effective?
>
> A. If you have the data, yes.

Id., 68:15-20. Under Federal Circuit precedent, the Board need go no further. *Magnum Tools*, 2016 WL 3974202, at *10 ("[T]he Board must base its decision on arguments that were advanced by a party, and to which the opposing party was given a chance to respond.") Focusing on the first dose instead of steady-state conditions, Petitioner argued that a POSA would have expected that the claimed dosing regimen would have been safe and effective because it purportedly would have produced trough concentrations that were higher than the van de Putte 20mg regimen. Pet. 35; Ex. 1006 ¶¶67-68, 71. But the undisputed evidence shows that at the relevant time, as a matter of pharmacokinetic principles, exactly the opposite would be true.

4. The available PK and clinical data would have taught away from the claimed invention

While unnecessary to resolve the dispute, the available PK and clinical information for D2E7 further suggest that the trough concentrations for the claimed dosing regimen would have been expected to be too low. Ex. 2069 ¶131.

a. The PK data

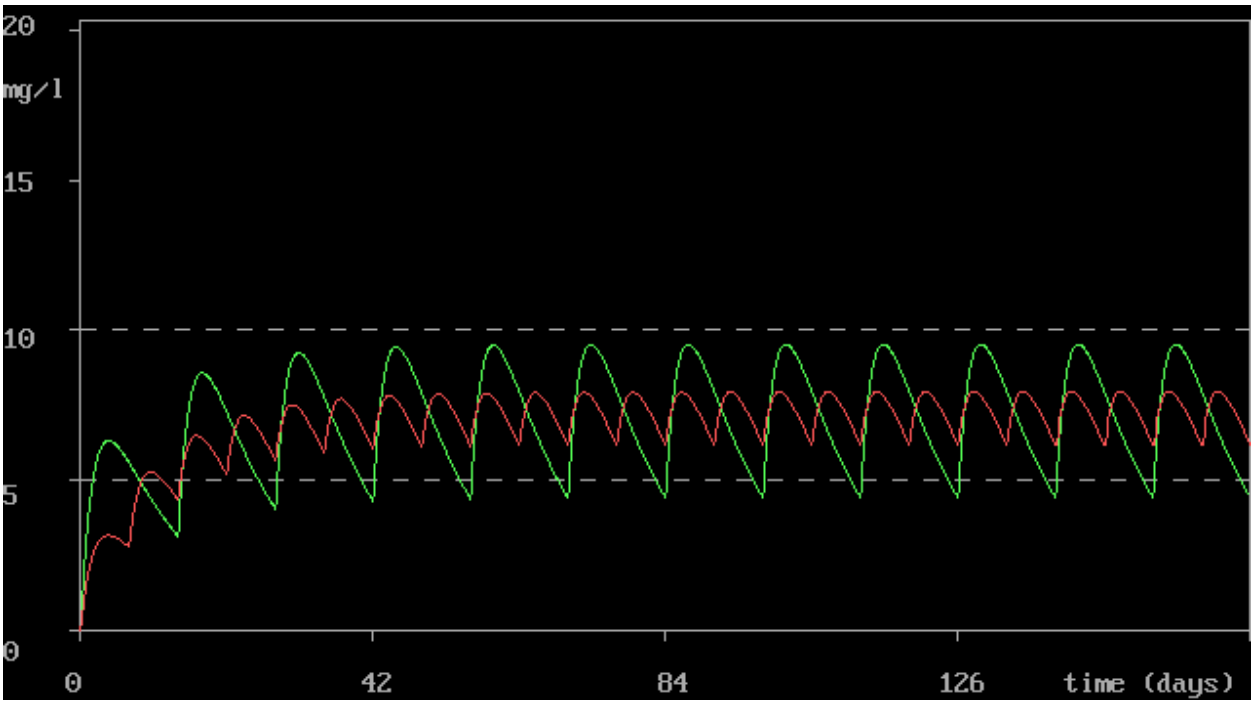
A POSA in June 2001 designing a new multiple-dose regimen would have analyzed actual drug concentrations from specific patients resulting from existing dosing regimens and correlated that information with specific safety and efficacy results from those patients (a PK/PD correlation). Ex. 2069 ¶130; *see also id.* ¶¶19, 46-48; Ex. 2119, 10; Ex. 2170, 1-2, 6. That information would have been informative in designing a dosing regimen that would have been predicted to achieve those target blood concentrations (*e.g.*, C_{min}) in the patient population. Ex. 2069 ¶¶52, 114; Ex. 2119, 10. This could not have been done for D2E7 based on the limited amount of publicly available information available in June 2001. *Id.* ¶133; *see also In re Cyclobenzaprine Hydrochloride Extended Release Capsule Patent Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012) (claims to therapeutically effective dosage forms non-obvious because of the lack of a known PK/PD relationship).

But even if a POSA had relied on the existing PK information (as Dr. Baughman argues), that information taught away from the claimed dosing regimen

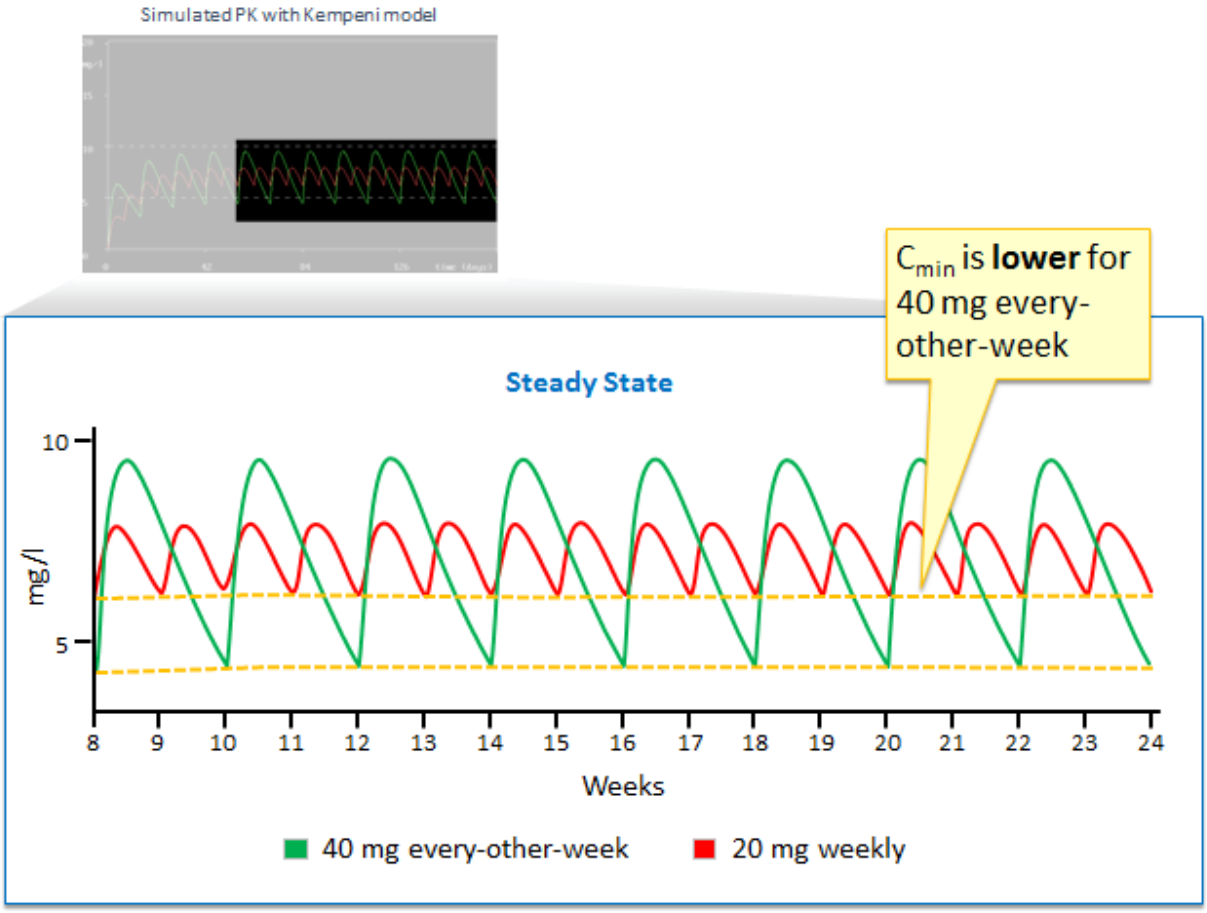
because it suggested, consistent with pharmacokinetic principles, that the steady-state trough concentrations for the 40mg every-other-week dosing regimen would have been substantially lower than the trough concentrations for the 20mg weekly regimen. Ex. 2069 ¶¶131, 149.

This difference in expected steady-state trough levels is shown in modeling performed by Dr. Vinks using methods available to a POSA. *Id.* ¶132. To perform his modeling, Dr. Vinks had to make certain conservative assumptions because of the lack of data. *Id.* ¶133. He assumed that the absorption rate for D2E7 could be approximated by using data from another subcutaneously administered protein; he assumed 100% bioavailability (even though bioavailability would have been expected to be lower for a subcutaneously administered protein); and he used the modeling software's standard patient default of a 55 year-old, 70kg male with normal renal function. *Id.* ¶¶136-138. Dr. Vinks then used the mean clearance (CL) and volume of distribution (Vd) information reported in Kempeni to model predicted concentrations over time for both the claimed invention and those resulting from the 20mg weekly regimen of van de Putte. *Id.* ¶¶134-135; *see* Ex. 2109; Ex. 2135.

The results of this simulation are shown below. *See also id.* ¶139. The green line shows the PK curve for the claimed 40mg every-other-week regimen and the red line shows the PK curve for the van de Putte 20mg weekly regimen.



As expected, at steady-state, the claimed regimen (in green) shows ***higher peak concentrations*** and ***lower trough concentrations*** than the 20mg weekly van de Putte regimen (in red). *Id.* ¶140-141. This is illustrated in the demonstrative below, which is a blow-up of the steady-state portion of the curve shown above.



As can be seen, at steady-state, the claimed dosing regimen results in substantially greater fluctuations between C_{max} and C_{min} than the 20mg weekly regimen. *Id.* ¶142. Such fluctuations were known to be potentially hazardous. Ex. 2049, 11; Ex. 2069 ¶¶43, 123, 148-149; *see also* Ex. 2170, 6.

To address the effect of dose-stretching across the patient population, Dr. Vinks modeled multiple combinations of the mean clearances and distribution volumes reported in Kempeni (testing each possible combination using the high and low ends of the reported ranges). Ex. 2069 ¶143. At steady-state, every combination he modeled resulted in greater fluctuations for the 40mg every-other-

week regimen versus the 20mg weekly van de Putte regimen. *Id.* ¶147. Further, at steady-state, every combination he modeled resulted in lower predicted C_{min} values for the claimed 40mg every-other-week regimen versus the 20mg weekly van de Putte regimen. *Id.* ¶144.

In each case, the predicted differences are substantial. *Id.* ¶145. For example, the percent difference in predicted steady-state trough levels ranged up to 41%, meaning that certain patients could experience trough levels that were much lower under the 40mg every-other-week regimen compared to the 20mg weekly regimen. Moreover, in each model, for four consecutive days out of the fourteen day dosing interval—more than half a week—patients receiving the 40mg every-other-week regimen would have less drug in their system than at any point in the 20mg weekly regimen. *Id*. ¶146. This could be the difference between a drug working and a drug not working. *Id.* ¶45; Ex. 2170, 6.

But even this model substantially underrepresents the actual variability in C_{min} levels that would have been expected among different patients in the population for at least two reasons. First, Kempeni does not report standard deviations for these PK parameters (Ex. 1003, 2), so the variability is based only on estimated mean values and does not reflect the true variability among different patients in the population. Ex. 2069 ¶150.

Second, for subcutaneously administered D2E7, a POSA would have expected additional variability among different patients based on the rate of absorption and the extent of bioavailability (the Kempeni values are based on an intravenous dose). *Id.* These additional sources of variability would have increased the distribution of values around the average C_{min} levels, particularly for the claimed 40mg regimen. *Id.* Consequently, more patients would experience lower than average C_{min} levels in the 40mg every-other-week regimen than in the 20mg weekly regimen. *Id.* This would have been a particular concern for a fixed-dose regimen (as claimed), rather than weight-based regimen.

b. The clinical data

The clinical data that was available highlighted the need for administering doses higher than 40mg or at intervals more frequent than once every-other-week. *Id.* ¶¶154-155. For example, every prior art trial that tested the purportedly comparable dose of 0.5mg/kg (*e.g.*, a dose of 40mg for an 80kg patient) reported up-dosing patients to higher doses such as 1mg/kg (equivalent to 80mg for an 80kg patient) and 3mg/kg (equivalent to 240mg for an 80kg patient). Ex. 1003, 2-3; Ex. 1018, 1; Ex. 2114, 4 (reporting "long-lasting reduction of disease activity . . . with all doses > 1 (3) mg/kg"); Ex. 2065 ¶¶44-45, 47. This up-dosing occurred even in trials involving intravenous administration, where absorption and bioavailability

would not have been concerns. Ex. 1003, 2-3; Ex. 1018, 1; Ex. 2065 ¶¶44, 47; Ex. 2069 ¶31.

The trend of better efficacy with higher or more frequent doses was also observed in van de Putte 1999. Ex. 2065 ¶¶17, 64-66; Ex. 2069 ¶93. As explained above, the 20mg weekly dose appeared to be less effective than the 40mg and 80mg weekly doses. Ex. 1004, 1. The two later van de Putte abstracts reporting 6-month and 1-year data similarly showed that the 20mg weekly dose was numerically inferior to the 40mg weekly dose.[7] Ex. 2129, 1; Ex. 1024, 1; Ex. 2069 ¶¶94-95; Ex. 2065 ¶¶67-68. As with the up-dosed patients, these data indicate that the 20mg weekly van de Putte regimen was a sub-optimal dose. Ex. 2065 ¶¶69-71.

Thus, based on the clinical data, a POSA would have been unlikely to pursue the 20mg weekly dose of van de Putte and would have been discouraged from making changes to that dosing regimen that would be expected to decrease its efficacy. Ex. 2069 ¶¶153, 156; Ex. 2065 ¶¶71-72. Instead, a POSA seeking to

[7] Rheumatologists routinely rely on numerical trends, even if not statistically validated. Ex. 2065 ¶71. For example, in support of a proposed combination therapy, Dr. O'Dell explained that "[i]t is also important to note that [the] . . . ACR 20 and 50[] responses were numerically better, but not statistically different from those patients who received mono-therapy . . . ." Ex. 2026, 18.

design a fixed dosed regimen would have sought a dosing regimen that produced trough levels higher than the 20mg weekly dose. Ex. 2069 ¶¶123, 157; *see also* Ex. 2106, 9. Indeed, the goal of a POSA engaged in the design of a D2E7 dosing regimen would not have been to obtain mere superiority over placebo or to achieve marginal efficacy. Ex. 2065 ¶¶71, 92-93; Ex. 2074, 48:24-49:1 (treating a patient's symptoms is not a sufficient form of treatment). The goal would have been to eliminate disease activity or reduce it to the fullest extent possible. Ex. 2065 ¶¶71, 92-93; Ex. 2025, 3; Ex. 2074, 64:18-65:12. *See Yamanouchi*, 231 F.3d at 1345 (expectation that modification of compound would have achieved "baseline level" of functionality insufficient to show motivation).

As Dr. Vinks's PK model shows, the claimed dosing regimen would not have been expected to satisfy these criteria because the trough levels would have been expected to be lower than that of the suboptimal 20mg weekly dose. Collectively, the available PK and clinical information thus taught away from the claimed invention. *See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1378 (Fed. Cir. 2006) (finding teaching away exists where prior art would have suggested to a person of ordinary skill that a lead compound should not have been developed further because it did not possess the chemical structure thought necessary for efficacy); *Tec Air, Inc. v. Denso Mfg. Michigan Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999) (teaching away where reference would have led a POSA "in

a direction divergent from the path taken by the applicant"). The factual underpinnings of Petitioner's motivation theory are thus without foundation.

5. The lower C_{min} of an every-other-week regimen would have raised concerns about anti-drug antibodies

The lower expected trough levels for the 40mg every-other-week regimen would have been of particular concern to a POSA due to the risk of developing ADAs. Ex. 2065 ¶¶19, 34, 77-78; Ex. 2068 ¶¶10, 13-14, 19-24; Ex. 2069 ¶¶158-159. ADAs were known to cause a range of adverse effects, including serious reactions such as anaphylaxis. *See, e.g.*, Ex. 1012, 7; Ex. 1011, 3; Ex. 2069 ¶67; Ex. 2072, 48:1-7, 98:20-99:8, 100:8-13; Ex. 2068 ¶¶19-20; Ex. 2081, 6; Ex. 2082, 38; *see also* Ex. 2177, 5 (Deputy Commissioner of FDA testifying in 2007 that immune responses to therapeutic proteins can impact safety and effectiveness and remain a serious concern). ADAs also have the potential to lessen or destroy a biologic's efficacy by increasing clearance of the administered biologic and/or interfering with the biologic's ability to bind to its target. Ex. 1016, 5, 14; Ex. 2068 ¶21-24; Ex. 2072, 38:5-39:17, 47:5-21; Ex. 2069 ¶68; Ex. 2024, 6; *see also* Ex. 2082, 37; Ex. 2105, 7; Ex. 2121, 9; Ex. 2123, 4; Ex. 2177, 5. In other words, ADAs have the potential to abolish efficacy entirely.

It was known that the risk of developing ADAs increased as serum concentrations of the biologic decreased. Ex. 2068 ¶¶15-17; Ex. 2024, 12, 14; Ex. 2126, 6, 8; Ex. 2125, 4; Ex, 2100, 9; Ex. 2069 ¶¶69-70; *see also* Ex. 2121, 9.

Clinical data with REMICADE®, for example, showed an ***inversely*** proportional relationship between dose and ADA formation, with lower doses resulting in higher levels of ADAs. Ex. 2024, 12; Ex. 2068 ¶15; Ex. 2065 ¶77. This inverse relationship is consistent with the immune system's typical response of producing antibodies after intermittent exposure to foreign antigens—lower antibody doses translate into lower serum concentrations, which mirror intermittent antigen exposure. *See, e.g.*, Ex. 2069 ¶71; Ex. 2068 ¶¶15-17. Because lengthening the dosing interval was known to cause lower trough concentrations, it carried an increased risk of developing ADAs. Ex. 2069 ¶159; Ex. 2068 ¶¶15-17.

It was also appreciated that biological drugs administered subcutaneously often display greater immunogenicity than drugs administered intravenously. Ex. 2068 ¶18; Ex. 2046, 16; Ex. 2072, 36:20-37:10; Ex. 2069 ¶72; Ex. 2117, 3, 8; Ex. 2045, 14; *see also* Ex. 2079, 4, 17; Ex. 2078, 3; Ex. 2118, 9. This was believed to occur because subcutaneous administration exposes the drug to antigen-presenting cells in the extravascular space, which in turn stimulates ADAs. Ex. 2068 ¶18.

Dr. Baughman admits that "[p]eople working in the field knew that developing ADAs was a possibility" from underdosing. Ex. 1006 ¶71. Yet she dismisses this concern based on her estimates of drug levels following a single injection and the lack of mention of such antibodies in the D2E7 publications she reviewed. *Id.*; *see also* Ex. 1007 ¶¶39-41. As discussed above, her PK analysis is

incorrect. Because the C_{min} of the claimed 40mg every-other-week dosing regimen at steady-state would be ***lower*** than for the van de Putte 20mg weekly dosing regimen, the concern about ADAs she acknowledges would have been triggered, not ameliorated, by a proposed dose stretching. Ex. 2069 ¶162.

Petitioner's attempt to dismiss concerns about ADAs based on the lack of reports in the literature is equally flawed. *Id.* ¶163. The FDA had specifically identified the development of ADAs "following repeated courses of treatment" as a "particular concern with biological agents" used to treat RA. Ex. 1016, 14; Ex. 2069 ¶164. Petitioner's assertion that a POSA would not have been concerned about ADAs for D2E7 ignores the prior art's experience with REMICADE®, ENBREL®, and the anti-TNFα agent lenercept (abandoned as of June 2001 because of ADAs). Ex. 2024, 12, 14; Ex. 2116, 102; Ex. 1011, 3; Ex. 1012, 7; Ex. 2100, 9; Ex. 2045, 20.

That the existing literature about D2E7 did not report the actual detection of ADAs is both unsurprising and of no probative value. As an initial matter, the D2E7 prior art warned that allergic reactions could be caused by "idiotypical epitopes," which are portions of antibodies that differ among patients that can stimulate the body's immune response. Ex. 2068 ¶13; Ex. 2069 ¶66. More fundamentally, as of June 2001, the techniques for detecting ADAs were limited, typically requiring long washout periods to prevent the drug from interfering with

the assays. Ex. 2068 ¶¶11, 28-35; Ex. 2084, 22; Ex. 2092, 6; Ex. 2072, 105:24-107:10; Ex. 2074, 172:19-175:3; *see also* Ex. 2024, 12; Ex. 2082, 37; Ex. 2104, 4-5, 7; Ex. 2105, 19. Because the D2E7 prior art trials were ongoing, there was no opportunity for the long washout periods needed to detect ADAs. Thus, a POSA would not have assumed from the meager record of prior clinical trials that ADAs did not pose a risk. Ex. 2068 ¶¶12, 36-38; *see also* Ex. 2074, 171:2-173:10 (acknowledging that ADAs could be responsible for prior art non-responders and stating that the study of ADAs was problematic in 2001); Ex. 2069 ¶163; Ex. 2051, 7.

Petitioner's reliance on the absence of evidence of ADAs in the D2E7 prior art is also illogical. The claimed dosing regimen is different from any regimen tested in the prior art, would have been expected to repeatedly produce lower trough levels, and consequently would have been expected to be more vulnerable to development of ADAs. That less vulnerable regimens might have avoided the problem would not have ameliorated concern over this new treatment.

Although not in their declarations, Drs. Baughman and O'Dell suggested in their depositions that there would have been decreased concerns about D2E7 immunogenicity because it is fully human. Ex. 2072, 50:2-51:22; Ex. 2074, 162:24-167:13. While some at the time speculated that this would be the case, serious concerns remained. Ex. 2068 ¶¶25-27; Ex. 2045, 19; Ex. 2080, 4-5, 7; Ex.

2077, 15. Both ENBREL® and lenercept, completely human anti-TNFα fusion proteins, generated ADAs. Ex. 2068 ¶¶14, 23; Ex. 1011, 3; Ex. 2069 ¶¶64-65; Ex. 2085, 3; Ex. 2086, 2. Indeed, ADAs were reported to contribute to lenercept's abandonment. Ex. 2045, 20; *see also* Ex. 2068 ¶14; Ex. 2069 ¶¶65, 75.[8]

6. Doubling both the dose and interval between doses can abolish efficacy

A POSA would have known that doubling both the dose and the interval between doses could abolish efficacy entirely. Ex. 2069 ¶45. AbbVie's own experience with an 80mg monthly D2E7 dosing regimen demonstrates the inherent unpredictability of the art and the unreliability of the analysis undertaken by Dr. Baughman. Extending Dr. Baughman's analysis, there would be no difference between dosing subcutaneous D2E7 at 20mg weekly, 40mg every-other-week, or 80mg once every four weeks, because the trough concentrations four weeks after administering an 80mg dose would be greater than or equal to those obtained two weeks after administering a 40mg dose or one week after administering a 20mg dose. *See* Ex. 1006 ¶¶67, 71. But in an actual clinical study, subcutaneous injection of 80mg D2E7 on a monthly basis was found to be no better than placebo

[8] When studies of D2E7 were finally published in a peer reviewed journal, they confirmed the existence of anti-D2E7 antibodies and their link to sub-therapeutic serum drug levels. Ex. 2021, 9; Ex. 2023, 5; *see also* Ex. 2016, 29.

for ACR20, the primary outcome measure of the study. Ex. 2015, 6. Specifically, "***superiority*** of adalimumab [D2E7] 80 mg compared with placebo ***could not be claimed***" because no difference was observed in the primary efficacy endpoint (ACR20). *Id.*, 5 (emphasis added); Ex. 2065 ¶82.

Although failed experiments and clinical results are frequently unreported, other examples of this sort of unpredictability exist in the art. For example, a 2000 publication authored by Dr. Vinks modeled the effect of two different dosing regimens of the same antibiotic on bacterial killing—5mg/kg administered every 12 hours versus 10mg/kg administered every 24 hours. Ex. 2069 ¶45; Ex. 2170, 6. The 5mg/kg dose administered every 12 hours resulted in bacterial eradication. Ex. 2069 ¶45. In contrast, the 10mg/kg dose administered every 24 hours permitted bacterial regrowth. *Id.* In other words, doubling the dose and interval between doses resulted in the study drug becoming ineffective.

7. Half-life does not provide sufficient information to design a dosing regimen

Concern about low blood levels is not the only consideration that would have counseled against relying on terminal half-life in devising a dosing regimen. Such reliance also would have been at odds with what was known in the art about the relevance of terminal half-life to developing a dosing regimen. Ex. 2069 ¶¶111-112.

In particular, terminal half-life does not impart any information about drug concentration, the key determinant of safety and efficacy. *Id.* ¶107. A POSA would have designed a dosing regimen based on the concentration-response relationship of the drug in the body, taking into consideration the site of drug action. *Id.* ¶108; Ex. 2049, 9 ("The aim of drug therapy is to achieve promptly and maintain a ***concentration of drug*** at the appropriate ***site(s) of action*** which is both clinically efficacious and safe for the desired duration of treatment") (emphases added). The terminal half-life does not provide information about drug concentrations in the blood or at the site of action, nor does it provide any information as to how those concentrations correlate to safety and efficacy. Ex. 2069 ¶108.

Both the Federal Circuit and the Board have acknowledged the importance of complete PK/PD data when assessing the obviousness of a dosing regimen. *See In re Cyclobenzaprine*, 676 F.3d at 1070; *see also Avanir Pharms., Inc. v. Actavis S. Atl, LLC,* 36 F. Supp. 3d 475, 487, 506 (D. Del. 2014) (holding non-obvious patent claims that recited two ranges of drug components and stating that efficacy cannot be predicted "based on in vivo or in vitro pharmacokinetic studies when the dose-effect relationship was unknown"), *aff'd*, *Avanir Pharms. Inc. v. Par Pharm., Inc.*, 612 F. App'x 613 (Fed. Cir. 2015) (affirmance via Rule 36); *Dr. Reddy's Labs., Ltd. v. Galderma Labs., Inc.*, IPR2015-01782, Paper 10, 20-21 (Feb. 16,

2016) (denying institution despite prior art's disclosure of drug half-life because petitioner failed to address the PK/PD relationship between peak drug levels and therapeutic effects).

Indeed, terminal half-life (what is reported in Kempeni) does not even tell a POSA how long the drug remains in the body. Ex. 2069 ¶¶109-110. It is a measure of drug elimination ***after*** the absorption and distribution phases—phases that can last days in the case of a subcutaneous administration. *Id*. ¶¶32, 109; Ex. 2017, 31. And terminal half-life does not provide any information about how long a drug lasts ***at the site of action***. *Id.* ¶115. In June 2001, it was uncertain whether, in treating RA, D2E7 would act on TNFα in the blood and/or at the site of inflammation, *e.g.*, in the synovial fluid of the joints. *Id.* ¶116; *see also* Ex. 2127, 9; Ex. 2101, 2. It was also unknown whether measurements of drug levels in blood would correlate with concentrations in synovial fluid. Ex. 2069 ¶¶116-117. Thus, the terminal half-life values reported in Kempeni would not have informed a POSA about how long D2E7 would last in synovial fluid. *Id*. ¶118; *see also* Ex. 2072, 135:7-138:25, 147:2-17 (explaining that half-life is not relevant if the measurement site differs from the biological site of action).

There is, moreover, no logical or scientific principle that would suggest that a dosing interval should be the same as the terminal half-life of a drug. Ex. 2069 ¶¶111-113; *see also* Ex. 2110, 6; Ex. 2074, 169:22-171:1. On the contrary, in the

absence of additional PK or PD data, designing a dosing regimen to be the same as a drug's half-life ensures substantial fluctuations of drug concentrations, which are often undesirable. Ex. 2069 ¶43.

As of June 2001, the experience with other therapeutic antibodies also would have suggested that half-life alone could not be used as a surrogate or predictor for establishing dosing interval in any periodic dosing regimen. Ex. 2069 ¶¶112, 115; *see also* Ex. 2110, 5. The lack of correlation between half-life and dosing interval, ignored entirely by Petitioner and its experts, is shown by these prior art FDA-approved antibodies:

- REMICADE® is dosed about once every 3 to 6 half-lives (Ex. 1012, 2, 12; Ex. 2072, 96:22-97:3);
- RITUXAN® is dosed about once every 2.8 half-lives (Ex. 2007, 1, 2; Ex. 2072 , 140:24-141:5);
- MYLOTARG® is dosed about once every 5 half-lives (Ex. 2013, 3, 17); and
- ZENAPAX® is dosed about once every 0.6 half-lives (Ex. 2010, 1, 2).

Because these prior art therapeutic antibodies were dosed both more and less frequently than their half-lives, a POSA would have understood that other factors must be considered when determining dosing intervals for antibodies such as D2E7. Ex. 2069 ¶113.

Before this proceeding, Dr. Baughman also acknowledged that half-life alone cannot meaningfully inform the choice of dosing interval. Half-life was notably missing from the parameters she identified as being associated with the efficacy of biologics in a presentation to the American Chemical Society Drug Metabolism Discussion Group. Ex. 2046, 31. Instead, Dr. Baughman taught that "PD [is] generally associated with C_{min} or AUC" (*id.*; Ex. 2072, 40:16-41:12), consistent with her declaration in this proceeding. *See* Ex. 1006 ¶62 ("[M]any in the industry believed that the C_{min} parameter (e.g., the lowest blood level observed between doses) might be the best parameter to indicate the threshold of efficacy.").

Likewise, when half-life was mentioned in the context of one of Dr. Baughman's own patent applications, it was listed as only one among a myriad of factors that inform the choice of a dosing regimen. There, the applicant argued that "the feasibility of a particular route of administration, such as subcutaneous delivery, depends on a number of factors, such as pharmacokinetic profile (including half-life and clearance mechanism), bioavailability, local reaction, and immunogenicity, just to mention a few." Ex. 2029, 7-8. As Dr. Baughman indicates, this additional information was unavailable for D2E7 in June 2001. Ex. 1006 ¶62.

B. "Biweekly" Dosing In Kempeni Would Not Have Provided The Requisite Motivation And Expectation Of Success

According to the Petition, the motivation to convert van de Putte's weekly dosing regimen into an every-other-week regimen also comes from Kempeni's description of "studies investigating biweekly dosing of D2E7," which "demonstrated that it was a viable treatment protocol." Pet. 34. This argument is based on a misreading of Kempeni and the DE001/DE003 study it describes.

Patients in the DE001/DE003 study received intravenous, weight-based doses according to a variety of different dosing schedules, depending on their responses. Ex. 1003, 2. During the "biweekly" phase of the DE003 study, treatment was discontinued once a response was rated as "good" and patients were retreated "only upon disease flare up." *Id.* Positive response rates involved a mean dosing interval of 2.5 weeks. *Id.* The bare bones description of the "biweekly" phase of Kempeni thus fails to disclose subcutaneous dosing, a 40mg dose specifically or fixed-weight dosing generally, or even a biweekly dosing regimen that was sustained over a defined period of time. Indeed, in its focus on personalized doses and schedules, Kempeni teaches away from the fixed dosing regimen of the claims. *See, e.g.*, Ex. 2065 ¶¶83-85.

Nonetheless, Petitioner alleges that the 0.5mg/kg weight-based ***intravenous*** dose disclosed in Kempeni can be equated to a 40mg ***subcutaneous*** dose (by multiplying the 0.5mg/kg dose by an assumed 80kg patient). Pet. 26 (Table). But

this intravenous dose would have delivered substantially more drug than a 40mg subcutaneous dose because only a fraction of the subcutaneous dose is absorbed in the blood stream. Ex. 2069 ¶34. And regardless of whether a POSA would have accepted this purported equivalence, a POSA would not have understood the study as suggesting that a 40mg every-other-week regimen would be effective to treat RA. In all trials that evaluated the 0.5mg/kg dose, some patients had to be up-dosed to higher doses due to inadequate clinical response. Ex. 1003, 2-3; Ex. 1023. During the DE003 trial, patients were up-dosed to as high as 3mg/kg, which, according to Petitioner's calculations, would correspond to a fixed dose of ***240mg*** for an average 80kg patient. Ex. 1003, 2. One prior art reference emphasized that D2E7 doses ***greater*** than 1mg/kg resulted in long-lasting reduction of disease activity. Ex. 2114, 4. The prior art as a whole therefore taught away from using a 0.5mg/kg dose (or even a 1mg/kg dose) across all patients, and instead favored higher doses. As a result, a POSA would have considered a 40mg fixed dose too low to serve as a "one-size-fits-all" dose.

C. Petitioner's Claim That The Invention Represents "Routine Optimization" Of A Prior Art Therapy Does Not Satisfy Its Burden Of Proof

Although not presented as an independent argument in support of the Petition, Petitioner repeatedly suggests that dose-stretching "represents no more than the 'routine optimization' of the therapy outlined in the van de Putte 1999 and

Kempeni references." Pet. 20; *see also id.*, 2, 37. These suggestions are apparently based on Dr. O'Dell's opinion that clinicians would have been motivated to "stretch out" recommended dosing levels for a drug to provide an optimal treatment regimen for individual RA patients. Ex. 1007 ¶¶20-21, 33. Petitioner's arguments and Dr. O'Dell's reasoning about "routine optimization" are flawed on multiple grounds.

First, an incantation of "routine optimization" cannot substitute for evidence showing a reason or motivation to modify the prior art and a reasonable expectation of success. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (first finding a motivation to modify the prior art and a reasonable expectation of success ***before*** discussing "routine optimization" in the context of "obvious to try").

Nor are the facts here similar to those in *BioMarin Pharm. Inc. v. Genzyme Therapeutic Products Ltd.*, IPR2013-00534, Paper 81 (Feb. 23, 2015). Unlike *BioMarin*, in which the claimed dosing regimen had been used in the prior art for treating a different disorder (*id.*, 11, 17, 22), the dosing regimen claimed in the '987 patent was ***not*** taught in the prior art. Unlike *BioMarin*, in which the Board determined that there were not "numerous parameters to try" (*id.*, 17), the dosing regimen claimed in the '987 patent involves multiple parameters, including the route of injection, the schedule, and the amount dosed, all of which were still being

investigated and were unsettled in the prior art. Ex. 1006 ¶30; Ex. 2072, 119:21-120:2. And unlike in *BioMarin*, the available D2E7 PK/PD information taught away from the claimed invention. *See supra* §IV.A.4.

Second, "routine optimization" requires something to optimize. *See* Ex. 2074, 130:21-132:4; *see also* Ex. 2065 ¶73; Ex. 2096, 20. In June 2001, HUMIRA® had yet to be approved, and the only evidence of efficacy or safety were in abbreviated reports of early clinical studies. Ex. 2065 ¶¶73-76; *see also id.* ¶80. Given the small number of patients involved and the minimal data reported in the prior art publications, a POSA would not have been able to form any firm conclusions about whether the tested regimens would prove safe and efficacious across a larger patient population over extended periods of time. Ex. 2065 ¶¶62-63, 74-76.

Third, determining a safe and efficacious dosing regimen of a new biologic during clinical trials is anything but routine. *See* Ex. 2062, 2; Ex. 2074, 111:14-113:10; Ex. 2066 ¶¶7-8, 11, 13, 15-16, 20; *see also* Ex. 2065 ¶80. Poor dose selection was identified as the leading reason for delay and denial of FDA approval for new drug products. Ex. 2182, 4, 6; Ex. 2066 ¶19. Sponsors are frequently forced to abandon once promising new biologics in the later stages of clinical trials even after years of development. Ex. 2066 ¶9, 20-21. As acknowledged in one of Dr. Baughman's patent applications, "[t]he determination of the dosing schedule of

a drug, such as a therapeutic antibody, . . . is very complex going far beyond routine optimization." Ex. 2029, 7.

Fourth, even if a clinician felt free to "adjust the dose, route of administration, and dosing frequency" of a known regimen, as Dr. O'Dell suggests (*see* Ex. 1007 ¶20), there would have been many possible combinations to try. Ex. 2065 ¶¶58-60. Based on the D2E7 clinical trials in the prior art, which tested different doses, routes of administration, and dosing frequencies, a large range of different dosing regimens could have been tried. *Id.* Even if one were to restrict these variables to those reported in the prior art (*i.e.*, route of administration: intravenous or subcutaneous; dose: 0.5mg/kg, 1mg/kg, 3mg/kg, 5mg/kg, 10mg/kg, 20mg, 40mg, 80mg; interval: weekly, every-other-week, when response status is lost; co-administration: with methotrexate or without), there are 96 dosing regimens possible. *Id.* If one adds additional variables, like a loading dose, co-administration with other agents, or doses and dosing intervals other than those previously reported, the options increase exponentially. *Id*.

In fact, Dr. O'Dell's "stretching" theory, which seeks to provide optimal treatment regimens for individual patients (Ex. 1007 ¶¶20-21), is the antithesis of what is claimed. The inventors discovered a method of administering D2E7 for treating RA that could be applied across a diverse and highly variable patient population. The challenged claims recite this discovery, *i.e.*, a method of treating

RA involving administering to a patient a fixed dose ("a total body dose") of 40mg of antibody. Ex. 1001, 59:41. Thus, it is irrelevant whether Dr. O'Dell was custom-tailoring anti-TNFα dosing regimens in June 2001 for the benefit of individual patients treated with approved drugs such as ENBREL® or REMICADE®. Even assuming he did so, that approach was the opposite of what is claimed. Ex. 2065 ¶85.

Finally, Dr. O'Dell's "stretching" theory ignores the significant risks a POSA would have understood to be associated with dose-stretching. As discussed above, those skilled in the art in June 2001 would have understood that stretching a 20mg weekly dosing schedule to a 40mg every-other-week schedule would result in lower trough concentrations. Ex. 2069 ¶44. A POSA would have had concerns both about the development of ADAs and about reduced effectiveness—if the trough concentration is too low, then a patient can experience between-dose symptomatic breakthrough. *See* Ex. 2065 ¶¶77-79; Ex. 2128, 12-13; Ex. 2069 ¶69. Because RA is a painful, disabling, and disfiguring disease, patients will gladly endure more frequent injections to obtain relief. Ex. 2065 ¶81. Dr. O'Dell's dose stretching theory completely ignores the risks associated with lengthening the interval between doses.

D. Objective Indicia Support the Nonobviousness of the Challenged Claims

Real-world evidence demonstrates the patentability of the challenged claims. Objective indicia "are not just a cumulative or confirmatory part of the obviousness calculus but constitute[ ] independent evidence of nonobviousness." *Leo Pharm. Prods., Ltd., v. Rea,* 726 F.3d 1346, 1358 (Fed. Cir. 2013) (internal quotation omitted). "[T]he objective indicia of nonobviousness are crucial in avoiding the trap of hindsight," *id*., a trap into which Petitioner repeatedly falls.

1. There was a long-felt but unmet need for new RA therapies

As of June 2001, there was an unmet need for new treatments for RA. Ex. 2074, 45:19-46:3; Ex. 2065 ¶¶90-91. Prior to the introduction of anti-TNFα biologics, traditional remedies were inadequate to treat moderate-to-severe RA. Ex. 2065 ¶¶21-29. The gold standard was methotrexate, an immunosuppressant with substantial side effects. *Id.* ¶29; *see also* Ex. 2133, 10. Few patients achieved complete remission using traditional therapies. Ex. 2065 ¶29; *see also* Ex. 2103, 25; Ex. 2090, 3

Anti-TNFα agents represented a breakthrough in treatment, but only two were approved as of 2001—ENBREL® and REMICADE®. Ex 2065 ¶¶30, 32. Both drugs were dosed, as Petitioner admits, in a manner with significant clinical disadvantages. ENBREL® required patients to inject themselves twice a week. *Id.* ¶38. REMICADE® was administered intravenously, requiring patients to travel to

a doctor's office for each administration of the drug. *Id.* Moreover, neither drug was effective in all patients. *Id.* A need thus existed for additional biologics with more advantageous dosing regimens. *Id*.

Others companies tried and failed to satisfy this need. Ex. 2065 ¶¶86-89; *see also* Ex. 2086, 2; Ex. 2124, 11; Ex. 2108, 3; Ex. 2107, 4. Roche failed with an anti-TNFα fusion protein, lenercept, the dosing regimen of which generated unacceptable levels of ADAs. Ex. 2065 ¶87; Ex. 2086, 2. Celltech failed with a humanized anti-TNFα antibody that also produced ADAs. Ex. 2065 ¶86; Ex. 2124, 11 In contrast, D2E7 succeeded because the scientists who developed it designed a safe and effective dosing regimen for RA that has been successfully used to treat hundreds of thousands of patients. Ex. 2065¶¶84-85.

2. Despite low predicted trough levels, the claimed invention is unexpectedly effective

As detailed above, fundamental PK principles and the available PK information would have suggested to a POSA that the claimed dosing regimen would have been insufficient to treat RA because the predicted steady-state trough concentrations (C_{min}) were substantially lower than those of the van de Putte regimens. Ex. 2069 ¶149. Given the predicted lower trough levels, a POSA also would have been concerned about the formation of ADAs and their associated effects on both safety and efficacy. *Id.* ¶¶73-74, 158-159. Inter-patient variability among the RA patient population would have exacerbated these concerns. Ex.

2063, 2; Ex. 2074, 150:9-152:7; Ex. 2069 ¶¶49, 51, 151-152; *see also* Ex. 2119, 13; Ex. 2083, 6.

The available PD information also taught away from any dosing regimen that would have been expected to produce trough levels lower than those predicted for the 20mg weekly van de Putte regimen. Ex. 2069 ¶154. Indeed, the PD data that was available highlighted the need for administering doses higher than 40mg or at intervals more frequent than once every-other-week. *Id.* ¶155. As detailed above, every prior art trial that tested the purportedly comparable dose of 0.5mg/kg (*e.g.*, a dose of 40mg for an 80kg patient) reported up-dosing patients to higher doses such as 1mg/kg (equivalent to 80mg) and 3mg/kg (equivalent to 240mg). *See supra* §IV.A.4.b. This up-dosing occurred in trials involving ***intravenous*** administration, where absorption and bioavailability would not have been concerns. *Id*.

Yet since its introduction in 2003, the claimed dosing regimen has unexpectedly been one of the most effective treatments for RA. Ex. 2069 ¶¶165-166; Ex. 2065 ¶¶83-85. HUMIRA® is indicated for reducing signs and symptoms of RA, including major clinical response, and improving physical function in adult patients with moderately to severely active disease. Ex. 1034, 1; Ex. 1016, 5-9. As explained by Dr. Gibofsky, the claimed methods, featuring a "one-size-fits-all" dose of 40mg every-other-week, works remarkably well for a wide variety of

patients. Ex. 2065 ¶¶83-85; *see* Ex. 2074, 61:24-62:13. Patients experience an improved overall health-related quality of life. Ex. 2065 ¶¶83-85. This evidence further confirms the patentability of the claims.

3. The claimed invention was a commercial success as a result of its efficacious and safe dosing regimen

HUMIRA® is the most successful pharmaceutical product in the world. Petitioner's expert concedes that HUMIRA® "has been commercially successful since its introduction in 2003" when it was first approved only for RA. Ex. 1025 ¶9; *see also* Ex. 2067 ¶¶8-9. This is remarkable because when it launched in 2003, HUMIRA® was the third anti-TNFα biologic introduced into the RA market, coming several years after the market leaders, Amgen's ENBREL® and J&J's REMICADE®. Ex. 1025 ¶11; Ex. 2067 ¶10.

It is undisputed that the ability of HUMIRA® to break into an already-established market is attributable to at least (1) the safety and efficacy of the RA treatment when dosed as claimed in the '987 patent, Ex. 2067 ¶¶12-13, and (2) the features of the treatment that differentiate it from the established competition, *id.* ¶¶14-25. *See* Ex. 2070, 23:4-13, 89:22-90:17, 254:14-255:3. The safety and efficacy of HUMIRA's® dosing regimen, as well as its differentiation from ENBREL® and REMICADE®, are due to the claimed invention as a whole—a regimen that specifies the biological agent (D2E7), the method of administration (subcutaneous), the dose (40mg fixed dose) and the dosing interval (13-15 days).

Ex. 2067 ¶¶12-13, 23. Because the safety, efficacy, and dosing superiority of HUMIRA® for RA are attributable to all of these elements in combination, there is a "nexus" between the commercial success and the claimed invention. *See WBIP, LLC v. Kohler Co.*, --F.3d--, 2016 WL 3902668, at *7 (Fed. Cir. 2016) ("it is the claimed combination as a whole that serves as a nexus for the objective evidence"). Moreover, a nexus between the claimed invention and commercial success is presumed to exist where, as here, "the patentee shows both that there is commercial success, and that the thing (product or method) that is commercially successful is the invention disclosed and claimed in the patent." *Demaco Corp. v. F. Von Langsdorff Licensing, Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988); *Innopharma Licensing, Inc. v. Senju Pharm. Co.*, IPR2015-00903, Paper 82, 17-18 (July 28, 2016).

Petitioner's commercial success expert contravenes these principles, improperly evaluating the commercial success of specific claim elements, particularly the 40mg dose amount, in isolation. Ex. 2070, 202:18-203:18. Petitioner's expert offers several additional alleged reasons for HUMIRA's® success including marketing efforts, contracting strategies, and syringe design. But this approach is factually and legally erroneous. Ex. 2067 ¶¶29-37. Huge numbers of RA patients would not continue to use HUMIRA® for RA in accordance with the '987 patent claims if it did not work well, and an invention need not be the sole

and exclusive reason for a product's commercial success. *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991). Petitioner's position is also flawed because HUMIRA's® competition—Amgen and J&J—have the same relative level of resources and sophistication as AbbVie, leaving no one company with a true competitive advantage based on amorphous "marketing" or "contracting" strategies. Ex. 2067 ¶¶33, 36-37. Rather, HUMIRA® cracked an entrenched market for RA on the merits of the product itself—its safety, efficacy, and convenience flowing from the claimed invention of the '987 patent. Ex. 2067 ¶¶12-13, 20-25, 28. Petitioner's plan to market and sell a biosimilar product to D2E7 having the same dosing regimen as the claimed invention also belies its argument that the success of the invention is due to specific AbbVie marketing or contracting strategies. *Innopharma*, IPR2015-00903, Paper 82, 21.

Finally, Petitioner's cursory mention of blocking patents is insufficient to prove lack of nexus. Pet. 29. The Federal Circuit in *Galderma* and *Merck* did not, as Petitioner suggests, broadly hold that commercial success has no probative value where there is another patent blocking market entry. Rather, in both *Galderma* and *Merck*, the claimed inventions were modifications of already-marketed dosages. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013); *Merck & Co., v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005). Here, by contrast, there was no approved D2E7 dosage, there was

fierce competition among competing anti-TNFα biologics, including prior market entrants, and HUMIRA® distinguished itself on the basis of a unique and superior treatment method for RA claimed in the '987 patent. *See* Ex. 2067 ¶¶20-25, 28.

E. The Claims Require a Therapeutically Meaningful Level of Efficacy

Given the evidence before the Board, the proper interpretation of the claims and the level of efficacy they require is irrelevant to resolving the IPR. As shown above, the evidence does not support the half-life theory advanced by Petitioner, and consequently Petitioner has failed to carry its burden of proving that the claims are unpatentable under the theory underlying the Petition.

In any event, the claim terms at issue necessarily require both administering to a patient with moderate to severe RA and a therapeutically meaningful level of efficacy. In its Institution Decision, the Board concluded that the claim language "method for reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis" is not limiting. Paper 8, 9. As of June 2001, a treating physician who satisfied the definition of a POSA would have understood the claims to require meaningful therapeutic efficacy. Ex. 2065 ¶¶20, 92-93. No clinician would consider himself or herself to be reducing signs and symptoms of RA if there were no therapeutically meaningful reduction in the patient's signs and symptoms. *Id.*; *see* Ex. 2025, 3; Ex. 2074, 64:18-65:12, 48:24-49:1. If that were the case, then anything that had any effect on a patient's symptoms, no matter how

minimal or short-lived (for example, an analgesic or intoxicant), would constitute "reducing signs and symptoms." Ex. 2065 ¶¶92-93. That is simply not how a physician seeking to reduce the signs and symptom of RA would understand his or her clinical objective (both then and now). *Id.*

However, to the extent the Board believes the claims do not require meaningful therapeutic efficacy, Patent Owner respectfully requests reconsideration. Instead of interpreting the claims as embracing marginal efficacy, the Board should adopt a construction consistent with the specification, which discloses that administration of D2E7 produces a meaningful improvement in a variety of clinical outcome measures such as ACR20, ACR50, and SJC. Ex. 1001, Figs. 1b, 2, 3, 30:25-28. The specification further states that biweekly dosing refers to "the time course of administering a substance (e.g., an anti-TNFα antibody) to a subject to achieve a therapeutic objective (e.g., the treatment of a TNFα-associated disorder)." *Id*. at 6:26-29. A POSA would have recognized that the specification provides clinically meaningful outcome parameters for the treatment of RA. Ex. 2065 ¶¶92-93. Those same parameters are reported in the February 1999 FDA guidance for industry, which explained that new claims for RA could be established by reducing the signs and symptoms of validated composite endpoints such as ACR20. *See* Ex. 1016, 5-6; Ex. 2065 ¶92. Patent

Owner's proposed construction is consistent with the teachings of the specification as they would have been understood by a POSA in June 2001.

V. CONCLUSION

For these reasons, Petitioner has not met its burden of showing, by a preponderance of the evidence, that claims 1-2 of the '987 patent would have been obvious based on a combination of the van de Putte abstract and Kempeni. The Board should therefore order that claims 1-2 of the '987 patent have not been shown to be unpatentable.

Date: September 13, 2016

By: /Steven P. O'Connor/

Steven P. O'Connor, Reg. No. 41,225
William B. Raich, Reg. No. 54,386
Charles E. Lipsey, Reg. No. 28,165
John M. Williamson, Reg. No. 48,275
Finnegan, Henderson, Farabow,
Garrett & Dunner, LLP

Scott E. Kamholz, M.D., Ph.D., Reg. No. 48,543
Foley Hoag LLP

William G. McElwain (admitted *pro hac vice*)
Amy K. Wigmore (admitted *pro hac vice*)
Wilmer Cutler Pickering Hale and Dorr LLP

Counsel for Patent Owner
AbbVie Biotechnology Ltd.

CERTIFICATE OF COMPLIANCE

The undersigned hereby certifies that the foregoing PATENT OWNER'S RESPONSE contains 13,818 words, excluding those portions identified in 37 C.F.R. §42.24(a), as measured by the word-processing system used to prepare this paper.

Dated: September 13, 2016 By: /Steven P. O'Connor/
Steven P. O'Connor
Reg. No. 41,225

CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Response** was served electronically via email on September 13, 2016, in its entirety on the following:

Dorothy P. Whelan
Fish & Richardson, P.C.
3200 RBC Plaza
60 South Sixth Street
Minneapolis, MN 55402

Louis E. Fogel
Jenner & Block LLP
353 North Clark Street
Chicago, IL 60654

W. Chad Shear
Fish & Richardson, P.C.
3200 RBC Plaza
60 South Sixth Street
Minneapolis, MN 55402

Steven R. Trybus
Jenner & Block LLP
353 North Clark Street
Chicago, IL 60654

Michael J. Kane
Fish & Richardson P.C.
3200 RBC Plaza
60 South Sixth Street
Minneapolis, MN 55402

Petitioner has consented to electronic service by email to IPR40299-0014IP1@fr.com.

/Steven P. O'Connor/
Steven P. O'Connor
Reg. No. 41,225