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

REVISED PETITIONER'S REPLY

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EXHIBITS

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1001	U.S. Patent No. 9,073,987 to Fischkoff et al. ("the '987 patent").
1002	U.S. Prosecution History of the '135 patent.
1003	Kempeni, "Preliminary results of early clinical trials with the fully human TNFα monoclonal antibody D2E7," *Ann. Rheum. Dis.,* vol. 58, pp. 170-72 ("Kempeni").
1004	van de Putte et al., "Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis," *Arthritis & Rheum.* 42(S9):S400 (abstract 1977) (1999) ("van de Putte 1999").
1005	Rau et al., "Effective Combination of the Fully Human Anti-TNF Antibody D2E7 and Methotrexate in Active Rheumatoid Arthritis," *Ann. Rheum. Dis.,* 217, No. 907 (1999) ("Rau #907").
1006	Declaration of Dr. Sharon Baughman.
1007	Declaration of Dr. James O'Dell.
1008	U.S. Patent No. 6,090,382 to Salfeld et al. ("Salfeld").
1009	Rau et al., "Long-term treatment with the fully human anti TNF alpha-antibody D2E7 slows radio-graphic disease progression in rheumatoid arthritis," *Arthritis & Rheum.,* 42 (S9):S400, No. 1978, Sept. 1999 ("Rau #1978").
1010	Dorland's Illustrated Medical Dictionary, p. 4-5 (1988).
1011	Etanercept/ENBREL® label (1998).
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1013	Richard G. Hamilton, The Human IgG Subclasses (2001).

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1014	Methotrexate (Rheumatrex, Trexall, Otrexup, Rasuvo), American College of Rheumatology, http://www.rheumatology.org/I-Am-A/Patient-Caregiver/Treatments/Methotrexate-Rheumatrex-Trexall (Mar. 2015).
1015	"Updated consensus statement on tumour necrosis factor blocking agents for the treatment of rheumatoid arthritis and other rheumatic diseases." (April 2001).
1016	Guidance for Industry, Clinical Development Programs for Drugs, Devices and Biological Products for the Treatment of Rheumatoid Arthritis (1999).
1017	van de Putte et al., "A Single Dose Placebo Controlled Phase I Study of the Fully Human Anti-TNF Antibody D2E7 in Patients with Rheumatoid Arthritis," *Arthritis & Rheum.,* 41(S9):S57, No. 148 (1998) ("van de Putte 1998").
1018	Rau et al., "Long-Term Efficacy and Tolerability of Multiple I.V. Doses of the Fully Human Anti-TNF-Antibody D2E7 in Patients with Rheumaoid [sic] Arthritis," *Arthritis & Rheum.,* 41(Suppl.):S55, No. 137 (1998) ("Rau 1998").
1019	Schattenkirchner et al., "Efficacy and Tolerability of Weekly Subcutaneous Injections of the Fully Human Anti-TNF-Antibody D2E7 in Patiens [sic] with Rheumatoid Arthritis-Results of a Phase I Study," *Arthritis & Rheum.,* 41(S9):S57, No. 149 (1998) ("Schattenkirchner").
1020	ENBREL® Summary Basis of Approval (1998).
1021	REMICADE® Summary Basis of Approval (1999).
1022	WO98/004281.
1023	Weisman et al., "A dose escalation study designed to demonstrate the safety, tolerability and efficacy of the fully human anti-TNF antibody, D2E7, given in combination with

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	methotrexate (MTX) in patients with active RA," *Arthritis & Rheum.,* vol. 43 (9 Suppl. 1):S391, abstract 1948 ("Weisman 2000").
1024	van de Putte et al., Arthritis & Rheum., vol. 42(9 Suppl.):S269 (2000) ("van de Putte 2000").
1025	Declaration of Dr. Brian Reisetter.
1026	Exhibit L to Declaration of Medgar Williams submitted during prosecution of the '135 patent.
1027	Certolizumab/CIMZIA® label (Revised July 2010).
1028	Golimumab/SIMPONI® label (Revised Dec. 2011).
1029	Larry Dobrow, "MM&M 2014 Large Pharma Marketing Team of the Year: Humira," *Medical Marketing & Media* (Jan. 1, 2014).
1030	Larry Dobrow, "DTC Report – DTC Gets Smart," *Medical Marketing & Media* (Apr. 1, 2014).
1031	CVS/caremark™ Performance Drug List (Oct. 2015).
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1041	Martin et al., "Pediatric Psychopharmacology Principles: Principles and Practice," *Oxford University*, 2011
1042	Mouton et al., "Comparative Pharmacokinetics of the Carbapenems: Clinical Implications," *ClinPharmacokinet* 2000 Sep, 39(3), 185-201
1043	Yaffe et al., "Neonatal and Pediatric Pharmacology: Therapeutic Principles in Practice, Third Edition," *Lippincott Williams & Wilkins*, 2005
1044	Rosen et al., "Review Article: Applying Pharmacokinetics to Optimise Dosing of Anti-TNF Biologics in Acute Severe Ulcerative Colitis," *AP&T Alimentary Pharmacology and Therapeutics*, 2015
1045	Biotech, "Birth of a Blockbuster: Abbott mounts Humira's marketing campaign," *Boston Business Journal*, October 20, 2003
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1050	van Gestel et al., "Development and Validation of the European League Against Rheumatism Response Criteria for Rheumatoid Arthritis," *Arthritis & Rheumatism*, Vol, 39, No. 1, January 1996, pp 34-40
1051	Figure 2 of the van Gestel Chart
1052	"Optimizing Clinical Outcomes in Rheumatoid Arthritis: An Expert Interview With Dr. Allan Gibofsky," *Neurosciencecme.com*, November 16, 2011
1053	Allan Gibofsky, "Current Therapeutic Agents and Treatment Paradigms for the Management of Rheumatoid Arthritis," *AJMC.com*, May 2014
1054	Deposition transcript of Brian E. Harvey, M.D.
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I. INTRODUCTION

AbbVie essentially asks the Board to ignore all of its own studies published before the '135 patent was filed, including the conclusions of the '135 and '987 patents' inventor. AbbVie would now have the Board believe (1) the only way to design a safe and effective dosing regimen was to develop a pharmacokinetic model; and (2) a number of concerns, including C_{min} and the potential development of anti-drug antibodies ("ADAs"), would have dissuaded a POSA from developing the claimed dosing regimen in 2001.

AbbVie's prior admissions, both in its 2001-era publications and in the '135 patent's prosecution history, squarely contradict AbbVie's current arguments. AbbVie published the results of many of its early empirical studies describing D2E7 dosing before filing the '135 patent. Those publications include van de Putte (EX.1004) and Kempeni (EX.1003). van de Putte discloses administering a total body dose of 20, 40, and 80 mg of D2E7 subcutaneously on a weekly basis to treat rheumatoid arthritis ("RA"), and concludes that "[f]or all efficacy parameters studied, all doses of D2E7 were statistically significantly superior to placebo ($p < 0.001$)." EX.1004, p.1. Kempeni (a named inventor of the '135 and '987 patents) summarized a number of intravenous and subcutaneous dosing studies using a wide range of D2E7 doses and intervals to treat RA and concluded that

subcutaneous delivery of D2E7 is "safe and effective" whether administered alone or in combination with methotrexate. EX.1003, p.3.

Nowhere did van de Putte or Kempeni discuss modeling, nor did they discuss the safety and efficacy concerns that AbbVie now raises. Both state precisely the opposite –that D2E7 was safe and effective. With the van de Putte and Kempeni roadmap in hand, a POSA following standard practice would have been motivated to explore dosing D2E7 subcutaneously 40 mg every other week and would have reasonably expected it to be safe and effective in reducing the signs and symptoms of RA.

AbbVie tries to sidestep its own publications by asking the Board to credit a new model created by its expert, Dr. Vinks, a pharmacologist who has never designed a dosing regimen. EX.1055, 61:15-63:5. Dr. Vinks' model rests on a number of faulty assumptions that do not apply to D2E7. For example, Dr. Vinks treated a 20 mg weekly dose of D2E7 as if it represented the lowest therapeutically effective dose. *See* EX.2069, ¶¶17-18. This is not true. Before the '135 patent's filing date, there was no evidence that lower doses would not have reduced the signs and symptoms of RA. The therapeutic "floor" of D2E7 simply was not known. *See* EX.2003, ¶53 n.2 (lowest effective dose for D2E7 "was undefined in June 2001"). Dr. Vinks also assumed that because fluctuations between C_{min} and

C_{max} for a 40 mg every other week dosing regimen were greater than for a 20 mg weekly dosing regimen, the 40 mg every other week dosing raised efficacy and safety concerns. EX.2069, ¶17. This also is not true. Large fluctuations are a potential issue with drugs that have a narrow therapeutic window. D2E7 has a wide window.

AbbVie criticizes Dr. Baughman's use of half-life to design dosing regimens. That criticism is misplaced, and at odds with AbbVie's statements during prosecution. There, AbbVie's PK expert, Dr. Mould, acknowledged that half-life is a factor that POSAs considered when designing dosing regimens. EX.2003, ¶78. Pharmacokinetic textbooks agree. *See* EX.2119, pp.9, 41; EX. 2049, p.8. Dr. Vinks himself stated in multiple publications that half-life informed dosing regimens. EX.1055, 122:2-123:8; EXS.1041, 1042.

AbbVie's alleged concerns regarding ADAs are exaggerated. Not all ADAs are harmful. HUMIRA®, REMICADE®, and ENBREL® all produce ADAs in some patients, yet FDA approved each of them. AbbVie's expert, Dr. Gibofsky, admitted that clinicians did not routinely test for ADAs as of 2001. EX.1058, 104:5-10. The scientific literature established that methotrexate, a drug that rheumatologists had been prescribing since the 1980s, was readily available to POSAs in 2001 to reduce the risks associated with any ADAs. *See* EX.2024, pp.13-15.

As such, the alleged "problem" of ADAs would not have dissuaded a POSA from exploring the claimed 40 mg bi-weekly subcutaneous dosing regimen.

AbbVie has created an artificial protocol for designing a dosing regimen that AbbVie tries to substitute for the empirical approach that its own scientists and POSAs actually used. AbbVie uses this protocol to justify ignoring its own pre-filing date publications, including van de Putte and Kempeni, that provided a roadmap for the claimed D2E7 dosing regimen, and to exaggerate the unpredictability involved in designing the claimed dosing regimen. Viewed in the context of the state of the art as it existed before the '135 patent's filing date, the '135 dosing claims are unpatentable as obvious.

II. ARGUMENT

A. POSAs Would Have Relied On Published Clinical Data, Not Theoretical PK Modeling, to Design a D2E7 Dosing Regimen

Before the '135 patent's filing date, POSAs designed dosing regimens empirically by testing different doses and dosing intervals in human clinical studies and recording how the patients reacted. *See* EX.2119, p.8. This is how AbbVie developed the 40 mg bi-weekly s.c. dosing regimen for D2E7 that the '135 patent claims. *See* EX.2006, ¶¶12-15, 24 and EX.1002, pp.970-72 (describing the early Phase I clinical trials used to develop the D2E7 dosing regimen). Dr. Mould, AbbVie's PK expert during prosecution, confirmed that to predict the effect of lengthening the dosing interval of D2E7, a POSA would have conducted a clinical

trial testing different dosages. EX.2003, ¶62. Dr. Mould also suggested, as an alternative, developing a PK/PD model if the relevant data were available from multiple later-stage Phase II and III clinical studies. *Id.,* ¶¶62-64. Those data were not available until years after AbbVie had filed the '135 patent. *See* EX.1002, pp.970-72 (Appendix G timeline of D2E7 clinical trials); EX.1006, ¶62. The fact that AbbVie itself developed the claimed dosing regimen without the PK/PD correlation discredits AbbVie's arguments that C_{min} values and PK/PD modeling were "essential" for designing a dosing regimen. EX.1055, 66:1-12, 70:6-15.

Not only did AbbVie develop the claimed dosing regimen empirically, but it published the results of many of the clinical studies before filing the '135 patent application. Dr. Kupper was AbbVie's Study Director "who approved the final study reports for the D2E7 Phase I clinical trials DE001, DE003, DE004, and DE010, and the Phase II clinical trial DE007 …." EX.2006, ¶1. Appendix G included in Dr. Kupper's declaration that AbbVie submitted during prosecution describes the timeline for the Phase I, II, and III clinical trials. EX.1002, pp.970-72.

As Appendix G illustrates, the Phase I studies and some of the Phase II studies took place before the '135 patent's filing date. Kempeni summarized several of the Phase I studies (DE001/003, DE004, and DE010). *See* EX.1003, pp.2-3. Kempeni describes the results of those studies as "very encouraging" and

states that D2E7 was "well tolerated" over a wide range of doses. *See id.* Kempeni further characterizes s.c. dosing as a "promising approach for D2E7 delivery" and concludes that D2E7 is "safe and effective." *Id.,* p.3. The next steps, according to Kempeni, involve "further defin[ing] optimal use of this model treatment." *Id.*

One of the Phase II studies is described in van de Putte (EX.1004). van de Putte describes 20, 40 and 80 mg weekly dosing of D2E7 as "statistically significantly superior to placebo" and "nearly equally efficacious when given s.c. in patients with active RA." EX.1004, p.1.

A POSA seeking to develop a dosing regimen for D2E7 would have read the results of the Phase I and II clinical studies published before the '135 patent's filing date, including Kempeni and van de Putte. These studies narrowed the available options for viable D2E7 dosing regimens that could successfully treat the signs and symptoms of RA. *See* EX.1006, ¶73; EX.1007, ¶33. A POSA would not have ignored these studies in favor of creating a PK/PD model once the later-stage data were available. The data from AbbVie's published studies, including Kempeni and van de Putte, would have motivated a POSA to stretch van de Putte's 20 mg weekly dosing to 40 mg bi-weekly dosing with the reasonable expectation that it would treat the signs and symptoms of RA. EX.1006, ¶¶73, 74.

Another flaw in AbbVie's modeling theory is the assumption that a POSA

would have been motivated solely to design the most efficacious dosing regimen possible. *See* Response, pp.7, 19. Maximum efficacy is not the only goal of a dosing regimen. When designing a regimen, a POSA would balance therapeutic efficacy with factors such as safety and patient preference, as reflected in frequency of administration, to arrive at a dosing regimen for treating the disease. EX.2006, ¶23; EX.1006, ¶¶49-55, 64-65; EX.1007, ¶¶20-22; EX.2119, p.67 (convenience matters for patient compliance).

AbbVie's efforts in designing a dosing regimen for D2E7 (later marketed as HUMIRA®) illustrate this principle. AbbVie's scientists concluded that the most therapeutically effective s.c. dosing regimen was 40 mg ***weekly***. It was ***not*** 40 mg bi-weekly. EX.2021, pp.9-10. Nevertheless, AbbVie opted to proceed with 40 mg bi-weekly dosing for HUMIRA®.

AbbVie's pre-filing publications, including van de Putte and Kempeni, tell the real story. They show that the claimed dosing regimen represented no more than optimization of the previously published D2E7 dosing studies.

B. POSAs Relied On Half-Life When Designing Dosing Regimens

AbbVie takes the remarkable position that half-life is effectively irrelevant when designing a dosing regimen. Response, pp.6, 44-45. Echoing AbbVie's position, Dr. Vinks testified that he "would not rely on [terminal half-life] in any way." EX.1055, 64:18-65:10.

Dr. Vinks' own publications contradict his testimony and AbbVie's theory regarding half-life in designing dosing regimens. Dr. Vinks wrote in "Development Principles of Pharmacokinetics:"

> The ***elimination half-life can be useful when determining frequency of dosing and dosing interval*s**. When a drug is dosed at regular intervals, it is the plasma half-life that determines the plasma steady state concentration.

EX.1041, p.12 (emphasis added).

When asked about this statement, Dr. Vinks agreed with it. EX.1055, 122:2-123:8. In another paper, Dr. Vinks similarly tied half-life to dosing interval:

> The ***increased half-life*** of the newer carbapenems ***will probably lead to less frequent administration*** although continuous infusion may still be the optimal mode of administration for these drugs.

EX.1042, p.2 (emphasis added).

Dr. Vinks' published statements support Petitioner's reference to D2E7's half-life as an important consideration in developing the claimed bi-weekly dosing regimen, and are inconsistent with the position that AbbVie and Dr. Vinks now urge.

Before June 2001 (and still today), POSAs routinely relied on half-life as a factor when designing a dosing regimen. EX.1006, ¶¶65-66 ("the half-life can be

used informally to map out a treatment regimen and to predict what dosing intervals would likely be efficacious"); EX.2003, ¶78 (half-life "is of course a necessary parameter in any model"); EX.2119, p.60. For this reason, Dr. Baughman's declaration contains a table illustrating the general concept of half-life dosing as it would have been applied to D2E7 following administration of a single dose. EX.1006, ¶¶67-68; EX.2072, 62:16-65:18. As stated in her declaration, the purpose of the table was to show that because D2E7 was known to have a relatively long half-life (11.6-13.7 days), a POSA reasonably could have expected successful treatment by stretching van de Putte's 20 mg weekly dosing to 40 mg bi-weekly dosing. Kempeni's observations that D2E7 was safe and efficacious over a wide range of doses and dosing intervals confirmed this expectation. *See* EX.1003, p.3.

AbbVie attacks the relevance of Dr. Baughman's half-life table. *See e.g.,* Response, pp.22-26. However, such tables are commonly used to assess the potential influence of half-life on dosing regimen. AbbVie and Dr. Vinks rely on Aulton (EX.2049) to illustrate relevant considerations for developing dosing regimens (EX.2069, ¶¶35, 39 citing EX.2049). Aulton includes a table illustrating the half-life concept for a drug having a half-life of 4 hours:

Table 19.1 Relationship between the amount of drug eliminated and the number of half-lives elapsed

Number of half-lives elapsed	Percentage of drug eliminated
0.5	29.3
1.0	50.0
2.0	75.0
3.0	87.5
3.3	90.0
4.0	94.0
4.3	95.0
5.0	97.0
6.0	98.4
6.6	99.0
7.0	99.2

Aulton explains that half-life is an "important factor that influences the plasma concentration-time curve" in a ***multi-dose*** regimen. EX.2049, p.8. Aulton validates the use of Dr. Baughman's table to illustrate the concept of half-life and its influence on choice of dosing regimen for D2E7.

AbbVie argues that because some other drugs are not dosed in strict accordance with their half-lives, a POSA would not use D2E7's half-life in designing a dosage regimen. Response, p.47. However, this does not mean that half-life has no bearing on dosing regimen design. *See, e.g.,* EX.2003, ¶78. As Dr. Baughman testified, the half-life of D2E7 reported in Kempeni (11.6 to 13.7 days), along with the other published clinical trial results showing safety and efficacy, would have motivated a POSA to stretch van de Putte's 20 mg weekly dosing to 40 mg bi-weekly dosing and provided a reasonable expectation that it would have reduced the signs and symptoms of RA. EX.1006, ¶¶65-68.

C. AbbVie's PK Modeling Based On C_{min} Is Wrong

In addition to being inconsistent with how POSAs actually designed dosing regimens, Dr. Vinks' IPR-inspired theoretical modeling, which relies on C_{min} of the 20 mg bi-weekly dose from van de Putte as the critical parameter, is wrong.

First, at the time of filing no one knew that C_{min} was the correct parameter to use. Dr. Baughman testified that C_{min} "might be" the best parameter but that other parameters, including Area Under the Curve (AUC) or $C_{max,}$ might be the relevant parameter. EX.1006, ¶62. Dr. Vinks agreed that for some drugs C_{max} and AUC can be important parameters. EX.1055, 186:21-187:8; 191:12-21. Dr. Vinks made clear he had not concluded that C_{min} was the critical parameter: "I don't think in my declaration that I interpreted that is the best parameter." *Id.,* 185:9-10. Likewise, during prosecution Dr. Mould identified C_{min}, C_{max}, and peak:trough ratios as potentially important parameters. EX.2003, ¶73. AbbVie simply assumes, without support, that C_{min} is ***THE*** critical parameter for designing a D2E7 dosing regimen.

Even if C_{min} were the critical parameter, there is no evidence that the C_{min} value for a 20 mg weekly dose was the appropriate C_{min} value to use as the therapeutic floor. AbbVie makes that assumption and Dr. Vinks' modeling turns on it. Dr. Vinks admitted that he used the C_{min} value of van de Putte's 20 mg weekly dose only because that was the question he was asked to opine upon.

EX.1055, 200:13-201:19; 231:13-18. Dr. Vinks was unable to offer an opinion on whether a 20 mg weekly subcutaneous dose was safe or effective or, for that matter, whether a 10 mg weekly subcutaneous dose would be safe and effective. *Id.,* 203:1-205:8. Dr. Vinks was simply asked to compare the C_{min} values of a 20 mg weekly dose and a 40 mg bi-weekly dose. Unless one knows that C_{min} is the critical parameter and knows the value above which C_{min} must be maintained, however, that comparison is not useful. The record does not provide either piece of information.

No expert identifies C_{min} as the critical parameter. No expert identifies a floor value above which C_{min} must be maintained. Dr. Mould explicitly states that the "lowest effect [sic] dose" for D2E7 "was undefined in June 2001." EX.2003, ¶53 n.2. This directly contradicts the assumption AbbVie asked Dr. Vinks to base his model upon and upon which he based his conclusions. Indeed, AbbVie admits that "[i]n June 2001, however, the minimum drug concentration [i.e. C_{min}] of D2E7 needed to induce a therapeutic response was unknown." Response, p.21. Choosing the 20 mg weekly dose for the point of comparison was arbitrary and inappropriate.

Dr. Baughman's testimony is consistent on this point. During her deposition, she was asked:

> 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.

EX.2072, 68:15-20.

AbbVie cites Dr. Baughman's testimony as proof that POSAs designed dosing regimens based upon C_{min}. Dr. Baughman made clear that this is true ***if you have data*** showing the C_{min} is the important parameter and the minimum value for safe and effective dosing regimens. In the absence of data (as was the case in June 2001 for D2E7), a POSA would rely on empirical data taken from published studies of patients actually dosed with D2E7.[1]

Dr. Vinks and AbbVie wrongly argue that a POSA would have been dissuaded from dosing 40 mg bi-weekly because fluctuations in serum concentration are harmful. Response, pp.27-28; EX.2069, ¶¶148-149. There is no evidence that this is true for D2E7. Fluctuations are a problem with drugs that

[1] Dr. Vinks' statements (EX.2069, ¶¶115-116) regarding the importance of measuring drug levels at the site of action contradict his PK/PD model because the latter only looks at serum levels.

have narrow therapeutic windows and short half-lives. *See* EX.2049, p.11.[2] D2E7 has a wide therapeutic window and a relatively long half-life. The floor is unknown but it is at least as low as 20 mg weekly. The ceiling is high because, per Kempeni, patients were dosed up to 10 mg/kg bi-weekly (approximately 400 mg weekly average) with no long term adverse effects. *See* EX.1003, p.2. Therefore, the C_{min}-C_{max} ratio for the therapeutic window for D2E7 is at least 20, compared to "narrow" therapeutic windows with C_{min}-C_{max} ratios of only 2-3. *See* EX.2119, p.29. Likewise, many of the drugs described in EX.2119 have half-lives on the order of minutes or hours, while D2E7's half-life is almost 2 weeks.[3]

Dr. Vinks agreed that "when the window is narrow and the drug is eliminated rapidly, small doses must be given often to achieve therapeutic success." EX.1055, 74:11-75:4. That is not true in all cases; Dr. Vinks agreed that in some cases fluctuations can be desirable. *Id.,* 133:8-134:2; *see also* EX.2119, 34 ("Sometimes a fluctuating concentration is more desirable."). Here, D2E7 has a

[2] Dr. Vinks, who has never designed a dosing regimen for an investigational drug except for individual patients (EX.1055, 61:15-63:5), testified that determining a therapeutic range was irrelevant to his opinion. *Id.,*104:8-105:20.

[3] Dr. Vinks' description of his antibiotic model is irrelevant. Dr. Vinks makes clear that each model is specific to the particular drug at issue. *See* EX.1055, 79:16-80:5.

wide therapeutic window, long half-life, and no evidence suggesting that fluctuations are undesirable. Therefore, a POSA would not have been dissuaded from stretching van de Putte's subcutaneous dosing regimen from 20 mg weekly to 40 mg bi-weekly.

More fundamentally, models are simply attempts to predict how patients will react to a dosing regimen. EX.2119, p.25 ("Ultimately, however, the value of a dosing regimen must be assessed by the therapeutic and toxic responses produced."). Dr. Vinks acknowledged that those patient responses are typically validated through clinical trials. EX.1055, 84:4-85:13. Here, AbbVie ran clinical trials and published the results. A POSA would rely upon those results to determine the next steps for optimizing a dosing regimen for D2E7.

D. Up-Dosing From 0.5 mg/kg Bi-Weekly Would Not Have Dissuaded a POSA From 40 mg Bi-Weekly Dosing

AbbVie argues that up-dosing of the 0.5 mg/kg bi-weekly dose described in Kempeni shows that this dose was "***insufficient*** for treating RA across the patient population," (Response, p.12 (emphasis in original)), leading AbbVie to conclude that "Kempeni teaches away from the fixed dosing regimen of the claims," (Response, p. 49).

AbbVie's argument is based on a false premise – namely, that "[i]n all trials that evaluated the 0.5mg/kg dose, some patients had to be up-dosed to higher doses

due to ***inadequate clinical response***." Response, p.50 (emphasis added). However, the criteria for up-dosing was not based on "inadequate clinical response." Rather, per the study protocol, even patients who obtained a reduction in the signs and symptoms of RA were up-dosed. With that proper understanding of the trial protocol as a backdrop, Kempeni's conclusion—that the 0.5 mg/kg dose given to patients bi-weekly was "safe and effective"—is correct.[4]

The DE003 study that Kempeni describes used the DAS criteria to score patient response. EX.1003, p.3 (n.12). The DAS criteria characterizes a patient's response as: (1) "good;" (2) "moderate;" or (3) "non-responder." *See* EX.1050, pp.3-4 (providing an overview of the DAS criteria as used and cited by Kempeni), and Fig. 2. In describing the DE003 protocol, Kempeni states that a "[p]ositive response was defined as a decrease of at least 1.2 (compared with baseline) in the DAS." EX.1003, p. 2. In other words, "positive response" was a "good" or "moderate" DAS response. Kempeni then states that "D2E7 was administered every two weeks until the response could be rated as 'good,' defined as an absolute DAS of < 2.4." *Id.* AbbVie's clinician expert, Dr. Gibofsky, agreed that a patient achieving a "moderate" DAS response would see an overall reduction in the signs and symptoms of RA. EX.1058, 80:9-81:3.

[4] Dr. Vinks admitted that a 0.5 mg/kg dose is equivalent to a fixed dose of 40 mg for an 80 kg adult. EX.1055, 149:7-17; 159:4-160:1.

There is no basis for AbbVie and its experts to argue that patients on the bi-weekly 0.5mg/kg dose who failed to elicit a "good" response, as measured by the DAS, were up-dosed because the drug was not working. In the DE003 study (as Dr. Kupper, AbbVie's prosecution expert, explained), patients administered 0.5 mg/kg bi-weekly were up-dosed if they did not exhibit a "good" response, ***even if they exhibited a "moderate" response.*** *See* EX.1003, p.2; EX.2006, ¶13 (emphasis added).

Dr. Kupper's testimony aligns with Rau 2000 (EX.2218), which disclosed that patients given bi-weekly doses of 0.5mg/kg D2E7 elicited treatment responses by week 12 that were comparable to a "moderate" DAS response. Figure 4 from Rau 2000 (unannotated) is reproduced below:

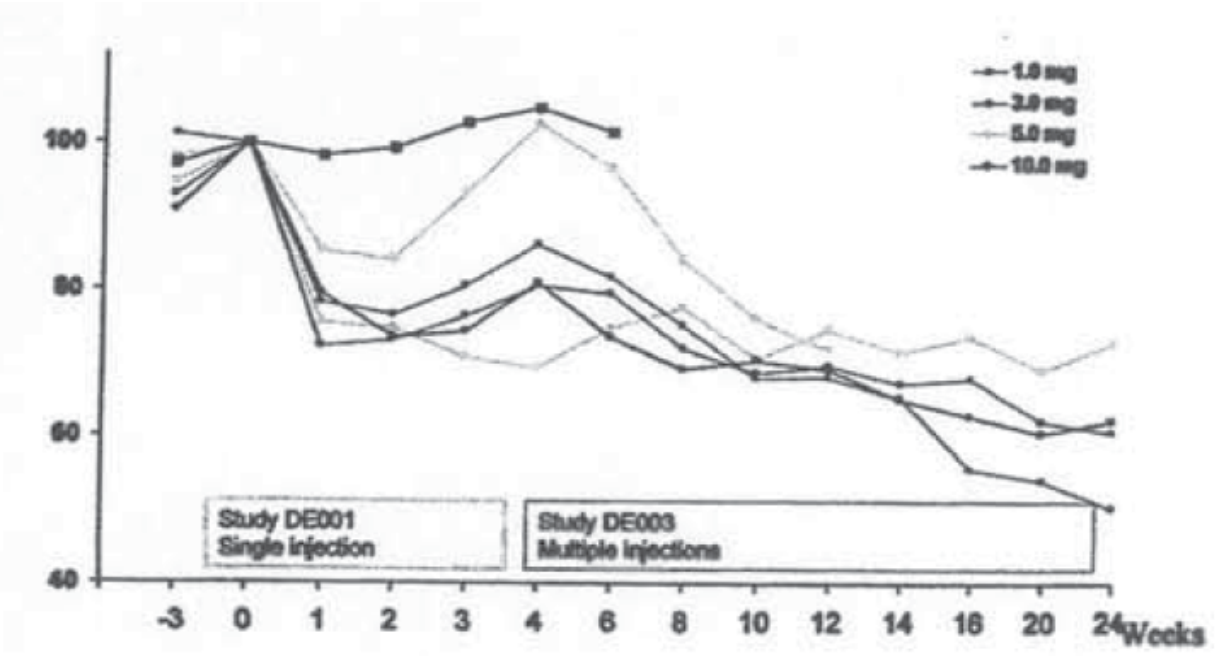

Abb. 4 Mittelwerte des DAS während der Studie. Ausgangswert = 100 %.

Figure 4 shows that the 0.5mg/kg dose was nearly as effective as higher doses (and more effective than the 5.0 mg/kg dose) in reducing DAS scores after 12 weeks.[5] In fact, the initial median DAS score (which Rau 2000 reports is 5.3) was reduced by approximately 30% or more in patients receiving the 0.5 mg/kg dose. Notably, Dr. Gibofsky testified that a reduction of this magnitude would be a "moderate" DAS response, with patients seeing an overall reduction in the signs

[5] Figure 5 from Rau 2000 shows the 0.5mg/kg as the most effective dose in lowering ESR, which is a measure of inflammation.

and symptoms of RA. EX.1058, 80:9-81:3. In line with these results, Rau 2000 summarized that D2E7 was safe and effective:

> In summary, it can be established that the completely human TNFα antibody D2E7 is quickly (within the space of days) effective in the majority of patients, and has not lost its efficacy in the course of long-term treatment over, up to now, two and one-half years. D2E7, with a half-life of 12 days, can be administered every two weeks as an intravenous injection over 3-5 minutes or subcutaneously. D2E7 is well tolerated and must be called a therapeutic step forward.

EX.2114, p.8.

AbbVie and Dr. Vinks misunderstand the published study results. For example, Dr. Vinks testified that all of DE003 patients receiving the 0.5 mg/kg therapy were up-dosed because they did not meet the ***ACR20*** criteria. EX.1055, 253:4-256:1 ("That's my understanding. That's what I also express in my opinion.").[6] But the up-dosing criteria in DE003 had nothing to do with achieving an ACR20 response. The decision to up-dose was based on a patient's DAS response.

Kempeni and Rau 2000 both teach that the 0.5 mg/kg bi-weekly dose was "sufficient" and reduced the signs and symptoms of RA in patients even if it

[6] Dr. Vinks admitted not reviewing Kupper's declaration in forming his understanding. EX.1055, 40:19-21.

resulted in only a "moderate" DAS response.[7] These references do not teach away from the challenged claims. A POSA reviewing the published results would conclude that the next logical step would be a study of bi-weekly 40 mg subcutaneous dosing, and would reasonably expect that dose to treat the signs and symptoms of RA. *See, e.g.,* EX.1006, ¶73; EX.1007, ¶33.

E. The Risk of ADAs Would Not Have Dissuaded a POSA From 40 mg Biweekly Dosing

The risk of developing ADAs would not have prevented a POSA from pursuing a 40 mg bi-weekly dosing regimen. FDA guidance shows that ADAs, even if present, may have little or no impact on safety or efficacy. EX.2082, p.37; EX.1056, 44:1-22. Before the '135 patent's filing date, FDA found

[7] While AbbVie argues that the construction of "for a time period sufficient to treat the rheumatoid arthritis" should be changed, the trial record does nothing to change the rationale of the Institution Decision—that AbbVie's proposed construction "introduces ambiguity into the claims where none exists." Institution Decision, p.9. Dr. Gibofsky testified that under AbbVie's proposed construction, "a time period sufficient to treat rheumatoid arthritis" would differ from patient to patient based on the drug the physician is using and the timeframe for therapeutic administration. EX.1058, 85:4-7; 148:6-150-7.

REMICADE® and ENBREL® to be safe and efficacious despite the knowledge that some patients using these products developed ADAs. *See* EX.1011, p.4 (ENBREL®) (16% of patients developed ADAs; "No apparent correlation of antibody development to clinical response or adverse events was observed. The long term immunogenicity of ENBREL is unknown."); EX.1012, p.7 (REMICADE®) (13% of patients developed ADAs); EX.2069, ¶64; EX.1055, 218:15-220:3; EX.1056, 33:5-16.

Whether assays for detecting ADAs were known and reliable prior to the '135 filing date is irrelevant. ADAs only matter if they compromise efficacy or patient safety. Dr. Gibofsky testified that clinicians do not routinely test for ADAs. EX.1058, 104:5-10. According to Dr. Gibofsky, clinicians are interested in loss of efficacy or adverse events, not whether the patient has ADAs. *Id.,* 116:19-117:7.

Kempeni unequivocally states that D2E7 was safe and efficacious over a wide range of doses. EX.1003, p.3. A POSA would have relied upon Kempeni's statements, which were based on clinical data, in assessing the safety or efficacy of the therapy.[8] Moreover, D2E7 was the first, fully-human anti-TNF antibody.

[8] Mr. Sailstad had no knowledge of when assays for detecting ADAs to D2E7 were available or performed. *See, e.g.,* EX.1056, 38:21-25. Mr. Sailstad admitted that he was unable to assess Kempeni's clinical conclusions. *Id.*, 75:2-17.

Kempeni described the expectation that D2E7, being fully human, may have advantages in "minimizing antigenicity in humans." EX.1003, p.1. Kempeni contrasts D2E7 (fully human) with infliximab/REMICADE® (mouse/human chimeric) and etanercept/ENBREL® (fusion protein arranged in an unnatural configuration). As a result, POSAs would have expected D2E7 to be less immunogenic and less likely to develop ADAs than either REMICADE® or ENBREL®. EX.1003, p.1; EX.1056, 56:8-57:22.

Likewise, a POSA would note that no D2E7 prior art references identify any safety or efficacy problems attributable to ADAs. *See* EX.1056, 76:6-20; 78:7-80:13. The prior art says repeatedly that D2E7 therapy was safe, well-tolerated, and efficacious over every dosing regimen tested. *See, e.g.,* EX.1003, pp.2-3. We now know that some patients treated with HUMIRA® develop ADAs. *See* EX.1034, p.9 (HUMIRA® label) (12% of RA patients treated with HUMIRA® developed ADAs). Some of the patients in van de Putte's studies developed ADAs. *See* EX.2021, p.9. Even with knowledge of these ADAs, FDA found HUMIRA® safe and effective, approving HUMIRA® in 2002. *See* EX.1056, 90:17-91:22.

AbbVie argues that "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." Response, p.18. Thus, by AbbVie's own admission, a biologic can be safe and efficacious despite the presence of ADAs.

A POSA also would have known in 2001 that tools existed to minimize any risks associated with ADAs. Studies on REMICADE® had shown that co-administration of methotrexate could reduce ADAs. *See* EX.2024, pp.13-15. HUMIRA® itself proves the point: 12% of RA patients receiving HUMIRA® as a monotherapy develop ADAs but that number drops to 1% when methotrexate is co-administered. *See* EX.1034, p.9.

With all this knowledge, the speculative risk of developing harmful ADAs in some patients would not have dissuaded a POSA from pursuing the claimed dosing regimen. *See* EX.1006, ¶71.

F. AbbVie's Evidence of Secondary Considerations Is Insufficient

AbbVie points to three alleged "real-world" factors it contends support a finding of non-obviousness. All three factors fall short.

1. AbbVie's Generalized Reference to "A Need For New RA Therapies" Does Not Establish Long-Felt Need

AbbVie argues that "there was a long-felt but unmet need for new RA therapies." Response, p.55. It is undisputed that AbbVie's HUMIRA®, which was approved in 2001, was the *third* anti-TNFα RA medication to the market, following ENBREL® (1998) and REMICADE® (1999). As of the '135 patent's

filing date and since, ENBREL® and REMICADE® have successfully treated hundreds of thousands of RA patients. It is unclear what need was either "long-felt" or "unmet" at the time of HUMIRA®'s introduction.

AbbVie has made no attempt to connect the alleged long-felt need to the specific dosing regimen the '987 patent claims. *See Merck v. Gnosis*, S.P.A., 808 F.3d. 829, 838 (Fed. Cir. 2015) (long-felt need "not sufficiently connected with the novel elements of the asserted claims."). AbbVie's primary evidence of a long-felt and unmet need is conclusory testimony from Dr. Gibofsky that does not discuss the claimed dosing regimen at all. *See* EX.2065, ¶¶90-91. To the extent AbbVie is claiming that HUMIRA® was the first drug to put patients in remission, Petitioner's expert, Dr. O'Dell, testified that HUMIRA® did not meet this particular problem, which remains unresolved to this day. *See* EX.2074, 45:25-46:2.

AbbVie's generalized evidence falls short of showing that the claimed dosing regimen solved any long-felt or unmet need. *See Coalition for Affordable Drugs II Inc. v. NPS Pharms., Inc.*, IPR 2015-01093, Paper 67 at 32-33 (Oct. 21, 2016) (rejecting Patent Owner's argument when "the record before us does not sufficiently indicate that the claimed subject matter itself satisfied a long-felt need").

2. AbbVie's Publications Contradict Its "Unexpected Results" Argument

There was nothing "unexpected" about the effectiveness of the claimed dosing regimen. Before the June 2001 priority date, AbbVie repeatedly touted the safety and efficacy of all elements of the dosing regimen that '987 patent claims. *See, e.g.,* EXs.1003, 1004, 2114. Despite this, AbbVie now argues that the claimed dosing regimen "has unexpectedly been one of the most effective treatments for RA." Response, p.57.

AbbVie's unexpected results argument is a naked attempt to disavow its repeated prior statements regarding the safety and efficacy of the therapy. AbbVie's citations to (1) lower C_{min}; (2) the alleged "up-dosing" in prior art trials; and (3) ADAs all rely on faulty premises, as discussed above.

Dr. Gibofsky's generalized testimony regarding the effectiveness of HUMIRA® in treating patients also does not establish that the claimed dosing regimen would have been unexpected. While Dr. Gibofsky discusses the advantages of "one size fits all" dosing for HUMIRA® (EX.2065, ¶84), it is undisputed that fixed dosing was known in the prior art, including with ENBREL®. Because AbbVie has not established unexpected results relative to the prior art, this argument should be rejected. *See Mylan Pharms., Inc. v. Yeda*

Research and Dev. Co., Ltd, IPR 2015-00830, Paper 85 at 24 (Dec. 2, 2016) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.") (citation omitted).

3. HUMIRA® Is Successful For Reasons Other Than The Claimed Dosing Regimen

HUMIRA® has been commercially successful, but for reasons unrelated to the claimed dosing regimen.

AbbVie has conceded that other factors have driven HUMIRA®'s commercial success. In a different IPR involving its 9,114,166 patent, AbbVie argued that it was the ***formulation*** of HUMIRA® claimed in the 9,114,166 patent that allowed HUMIRA® to be "stable enough to be commercially viable," which in turn "yield[ed] this commercial success." *See* EX.1046, pp.61-62.

AbbVie has obtained numerous additional patents that cover HUMIRA®'s formulation and manufacture. AbbVie's economist expert, Dr. Hausman, conceded that he had not considered these patents in his analysis. *See* EX.1057, 120:7-14; EX.1047. Such a failure provides grounds to reject AbbVie's commercial success argument. *See Coalition,* IPR 2015-01093, Paper 67 at 32-33 (rejecting patent owner's commercial success argument because it was not clear which patent might be responsible for sales).

Dr. Hausman also conceded that AbbVie's heavy marketing of HUMIRA® has played a role in driving its sales. In 2015, for example, AbbVie spent $357 million marketing HUMIRA®, the highest amount of marketing for any pharmaceutical drug in the United States that year. *See* EX.1049. While Dr. Hausman admitted that AbbVie's marketing initiatives led to additional sales of HUMIRA®, he did not know how many additional sales resulted from AbbVie's marketing expenditures. EX.1057, 131:10-20.

Other factors driving sales of HUMIRA® include: (1) AbbVie pricing HUMIRA® "25 to 30 percent less" than REMICADE® at launch (EX.1045); (2) HUMIRA®'s syringe and auto-injection pen designs (EX.1026; EX.1057, 123:2-16); and (3) AbbVie's ability to maintain "Tier 2" status on pharmaceutical formularies and the relative importance of having "Tier 2" status over other anti-TNF drugs. *See* EX.2159; EX.1057, 74:20-24.

Given all of the other factors that admittedly drive sales of HUMIRA® and for the reasons discussed in Dr. Reisetter's declaration (EX.1025), Petitioner has rebutted any nexus that HUMIRA®'s sales are due to the dosing features claimed in the '987 patent. *See Mylan,* IPR 2015-0830, Paper 85 at 26 ("[W]e cannot conclude from the evidence before us whether the sales are due to the merits of the invention or due to pricing and marketing initiatives.").

III. CONCLUSION

For the reasons set forth in Petitioner's Petition and Reply, the '987 claims are unpatentable as obvious over van de Putte in view of Kempeni.

Respectfully submitted,

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/Dorothy P. Whelan/
Dorothy P. Whelan, Reg. No. 33,814
W. Chad Shear, Reg. No. 47,938
Fish & Richardson P.C.
P.O. Box 1022
Minneapolis, MN 55440-1022
T: 612-337-2509
F: 612-288-9696

Louis E. Fogel, Reg. No. 54,731
Steven R. Trybus, Reg. No. 32,760
Jenner & Block LLP
353 North Clark Street
Chicago, IL 60654
(312) 222-9350
lfogel@jenner.com
Attorneys for Petitioner

(Case No. IPR2016-00189)

CERTIFICATION UNDER 37 CFR § 42.24(d)

Under the provisions of 37 CFR § 42.24(d), the undersigned hereby certifies that the word count for the foregoing Petitioner's Response totals 5,459, which is less than the 5,600 allowed under 37 CFR § 42.24(c)(i).

Respectfully submitted,

Date:/January 23, 2017/

/ Dorothy P. Whelan/
Dorothy P. Whelan, Reg. No. 33,814
W. Chad Shear, Reg. No. 47,938
Fish & Richardson P.C.
P.O. Box 1022
Minneapolis, MN 55440-1022
T: 612-337-2509
F: 612-288-9696

Louis E. Fogel, Reg. No. 54,731
Steven R. Trybus, Reg. No. 32,760
Jenner & Block LLP
353 North Clark Street
Chicago, IL 60654
(312) 222-9350
lfogel@jenner.com
Attorneys for Petitioner

(Case No. IPR2016-00189)

CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§ 42.6(e)(4) and 42.205(b), the undersigned certifies that on January 23, 2017, a complete and entire copy of Petitioner Coherus BioSciences Inc.'s Revised Reply is provided via electronic service, to the Patent Owner by serving the correspondence address of record as follows:

Steven P. O'Connor, Ph.D.
Finnegan, Henderson, Farabow, Garrett & Dunner, LLP
Two Freedom Square
11955 Freedom Drive
Reston, VA 20190-5675

William B. Raich, Ph.D.
Finnegan, Henderson, Farabow, Garrett & Dunner, LLP
901 New York Avenue
Washington, DC 20001-4413

Scott E. Kamholz, M.D., Ph.D.,
Foley Hoag LLP 1717 K St., NW
Washington, DC 20006-5350

Charles E. Lipsey, Back-up Counsel
Finnegan, Henderson, Farabow, Garrett & Dunner, LLP
Two Freedom Square
11955 Freedom Drive
Reston, VA 20190-5675

John M. Williamson, Back-up Counsel
Finnegan, Henderson, Farabow, Garrett & Dunner, LLP
901 New York Avenue, NW
Washington, DC 20001-4413

William G. McElwain
Wilmer Cutler Pickering Hale and Dorr LLP
1875 Pennsylvania Avenue, NW
Washington, DC 20006

Amy K. Wigmore
Wilmer Cutler Pickering Hale and Dorr LLP
1875 Pennsylvania Avenue, NW
Washington, DC 20006

E-mail: steven.oconnor@finnegan.com
william.raich@finnegan.com
skamholz@foleyhoag.com
charles.lipsey@finnegan.com
john.williamson@finnegan.com
william.mcelwain@wilmerhale.com
amy.wigmore@wilmerhale.com

/Jessica K. Detko/

Jessica K. Detko
Fish & Richardson P.C.
60 South Sixth Street, Suite 3200
Minneapolis, MN 55402
(612) 337-2516