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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 IPR2017-00822
U.S. Patent No. 9,085,619

PATENT OWNER'S PRELIMINARY RESPONSE

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2001	Wang, "Instability, Stabilization, and Formulation of Liquid Protein Pharmaceuticals*," Int'l J. Pharmaceutics 185*, 129-188 (1999)
2002 - 2003	*Not Used*
2004	Declaration of Mark C. Manning, Ph.D. dated May 6, 2016 from IPR2016-01018, Ex. 1002.
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I. Introduction

In four separate Petitions, Coherus Biosciences Inc. ("Petitioner") challenges claims 16-19 and 24-30 of AbbVie Biotechnology Ltd.'s ("AbbVie") U.S. Patent No. 9,085,619 ("the '619 patent") directed to high concentration (50-200 mg/ml) aqueous pharmaceutical formulations comprising adalimumab (the active ingredient in HUMIRA®) without a buffering system. (IPR2017-00822, IPR2017-00823, IPR2017-01008, IPR2017-01009.) Each of the Petitions is flawed and should be denied for the reasons set forth in Patent Owner's respective preliminary responses.

Here, Petitioner presents two proposed grounds of unpatentability: (1) anticipation by Int'l Pat. Pub. WO 2006/138181 ("Gokarn PCT") (Ex. 1003); and (2) obviousness over Gokarn PCT in view of the *Physicians' Desk Reference* (58th ed. 2004) entry for HUMIRA ("HUMIRA Label") (Ex. 1005). The Board should deny the Petition in its entirety because both grounds are factually unsupported and legally deficient. Gokarn PCT does not render the challenged claims unpatentable, either alone or in combination with the HUMIRA Label.

Petitioner's anticipation argument requires one to (i) choose HUMIRA (adalimumab) from a virtually limitless list of proteins and categories of proteins in Gokarn PCT, (ii) then choose without guidance at which concentration to formulate adalimumab, and (iii) also choose whether to use a buffering system.

Gokarn PCT refers to "HUMIRA (Adalimumab)" in a voluminous list of *potentially* "self-buffering" proteins (proteins that may provide sufficient buffering capacity at high enough concentrations). The list is *silent* as to any threshold adalimumab concentration needed in a formulation lacking a buffering system. Gokarn PCT also discloses a broad range of possible protein concentrations and formulation options, including both *buffered* and non-buffered formulations. Petitioner does not address this incredibly large number of possible choices and combinations, much less show that Gokarn PCT discloses each of the claim elements as arranged in the '619 claims as required by law. Gokarn PCT does not. Failing this, Petitioner improperly relies on a second prior-art reference (the HUMIRA Label) in asserting that one would have immediately "envisaged" the claims based on Gokarn PCT.

Nor does the asserted combination of Gokarn PCT and the HUMIRA Label render the claims obvious. First, Petitioner fails to establish that a skilled artisan would have been motivated to combine these references to generate a high concentration (50-200 mg/ml) aqueous adalimumab pharmaceutical formulation without a buffering system. In fact, Petitioner does not identify *any* problem with HUMIRA that would have motivated a skilled artisan to remove its buffering system described in its label. This is a fatal deficiency in the Petition.

Petitioner also fails to establish that one of ordinary skill would have had any reasonable expectation of success in achieving the claimed invention. Given the lack of any examples involving adalimumab and the absence of any other meaningful guidance in Gokarn PCT, the high level of unpredictability associated with removing a buffering system from an antibody formulation, and the well-established unpredictability in applying the formulation for one antibody to another, one of ordinary skill would have had no reasonable expectation of success.

For these reasons, which are explained in more detail below, Petitioner has not shown that it is likely to prove that any challenged claim is unpatentable. The Board should therefore deny institution of the Petition.

II. Background

A. The Asserted Prior Art

1. Gokarn PCT

Gokarn PCT, cited in the Petition as 35 U.S.C. § 102(a) and/or 35 U.S.C. § 102(e) (pre-AIA) prior art, was filed on June 8, 2006, and published on December 28, 2006.[1] (Ex. 1003, 1.)[2] The U.S. national stage entry of Gokarn PCT

[1] For purposes of this Preliminary Response only, Patent Owner will assume that Gokarn PCT is prior art to the '619 patent. In the unlikely event that the Board institutes an IPR, Patent Owner will antedate Gokarn PCT by showing that the

application was cited as a reference during prosecution of the '619 patent. (Ex. 1001, 2 (citing U.S. Pat. Pub. No. 2008/0311078).)

Gokarn PCT concerns "self-buffering protein formulations." (Ex. 1003, 1.) It states that proteins, depending on their concentration, *could* have enough buffer capacity to maintain a formulation without additional buffering agents. (*Id.*, 27:4-9.) However, Gokarn PCT recognizes that maintaining the correct pH of a pharmaceutical protein formulation is "critical[]" to its effectiveness and emphasizes the importance of determining a protein's buffer capacity in assessing whether a protein can buffer a pharmaceutical formulation. (*Id.*, 1:15-19, 28:12-18.) It states that *empirically* determining buffer capacity is a "crucial aspect of formulating self-buffering compositions" and that theoretical calculations of buffer capacity for any given protein "will be of less utility and less accurate than empirical determinations of protein buffer capacity." (*Id.*, 38:10-14, 40:15-19.) Thus, Gokarn PCT devotes several pages to the need for empirical testing, methods for performing those tests, the preparation of buffer-capacity standards, and the

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inventors of the '619 patent invented the claimed subject matter before the earliest asserted date of Gokarn PCT.

[2] All citations herein refer to the exhibits' native page numbers, except IPR page numbers are used where the exhibits do not include native page numbers.

need to titrate individual proteins to empirically determine their buffer capacities. (*Id.*, 28:12-36:6.) But it does not apply those empirical methods to adalimumab. (*Id.*)

Gokarn PCT purports to describe a vast number of proteins and categories of proteins that potentially may provide sufficient buffer capacity to maintain pH. (*Id.*, 40:20-23.) This speculative disclosure extends for over a dozen pages, and is not limited to antibodies. (*Id.*, 40:20-52:9.) It broadly encompasses stem cell factors, ligands, and many other categories and sub-categories of proteins and incorporates by reference several U.S. patents for their equally broad listings of proteins. (*Id.*) Adalimumab is included only once in the list, among numerous other commercial protein products that vary widely in structure, sequence, and function. (*Id.*, 51:15-52:8.) But Gokarn PCT provides no examples with adalimumab or any buffer capacity calculations for adalimumab (or for most of the proteins encompassed by its broad disclosure). Instead, it provides examples only for four different proteins: Ab-hOPGL, Ab-hB7RP1, Ab-hCD22, and Ab-hIL4R. (*Id.*, 74:19-80:24.)

Recognizing that it may not be possible or desirable to formulate any particular protein without a separate buffer, Gokarn PCT discloses including a separate buffer as appropriate, depending on a protein's buffering capacity. (*See id.*, 57:28-33.) In fact, Gokarn PCT teaches that a separate buffer may provide as much

as 45% of the total buffering capacity; depending on the protein and the formulation, Gokarn speculates that the protein may provide any of "approximately 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99%, or 99.5% of the buffer capacity of the composition." (*Id.*) Gokarn PCT provides no guidance as to which protein(s) require more or less separate buffer or which proteins could be formulated to provide which percentage of the buffer capacity. As to adalimumab, for example, Gokarn PCT fails to calculate or estimate adalimumab's buffer capacity or provide any formulation examples.

Gokarn PCT also provides a generic range of potential protein concentrations, broadly extending from 20-400 mg/ml, but it does not tie this range of possible concentrations to any particular protein, much less adalimumab. (*Id.*, 58:1-5.) Gokarn PCT does not address the viscosity or opacity of any protein formulation.

2. The HUMIRA Label

The HUMIRA Label (Ex. 1005, 470) concerns AbbVie's HUMIRA pharmaceutical adalimumab product, initially approved in 2002 for treating moderately to severely active rheumatoid arthritis. HUMIRA's prescribing information was cited during prosecution of the '619 patent. (Ex. 1001, 3.) The HUMIRA Label states that adalimumab is a recombinant human IgG1 human monoclonal antibody that binds specifically to TNF-alpha. (Ex. 1005, 470.) (*Id.*) It

states that 40 mg adalimumab is administered subcutaneously with a single-use, pre-filled syringe containing 0.8 ml of product. (*Id*., 472.)

The HUMIRA Label describes the composition of AbbVie's marketed HUMIRA product, which is *buffered* with a dual citrate-phosphate buffering system. The HUMIRA Label does not disclose formulations that do not contain a buffering system, nor does it identify any need to reduce or eliminate buffers.

B. The State Of The Art

The buffered adalimumab formulation of HUMIRA was a breakthrough in the field of antibody therapeutics when it was approved in 2002. (Ex. 2042.) HUMIRA was the first commercialized high-concentration, liquid antibody formulation for subcutaneous administration. (*Id.*) HUMIRA was successfully formulated as a buffered pharmaceutical formulation and is one of the top selling drugs in the world. (Ex. 1005, 470; Ex. 2042, 1.) At the time of the invention of the '619 patent, HUMIRA was the only monoclonal antibody formulation approved for subcutaneous administration that was liquid rather than lyophilized—a testament to its remarkable formulation. (*See, e.g.,* Ex. 2047, 2-4 (Table 1).)

Like HUMIRA, all of the fifteen approved aqueous monoclonal antibody products available between 2003 and 2007 were provided with a buffering system. (Ex. 2047, 2-4; Ex. 2055, 852.) The same held true as late as 2015. (Ex. 2051, 94-101 (Table 4.1); Ex. 2055, 852.)

At the time of the '619 patent invention, those skilled in the art used buffering systems because it was extremely difficult to make stable (*e.g.,* non-aggregated, non-fragmented, non-degraded, non-denatured, *etc.*), liquid pharmaceutical formulations of antibodies, particularly at high concentrations. (Ex. 2047, 5, 14; *see, e.g.*, Ex. 1001, 2:56-62 ("difficulties with the aggregation, insolubility, and degradation of proteins generally increase as protein concentrations in formulations are raised").) Even after HUMIRA's introduction, the scientific literature reported the use of buffering systems, such as citrate, to produce a successful formulation. (*See* Ex. 2028, 271.) The initial formulation of ERBITUX, for example, had antibody aggregation problems, which those skilled in the art addressed by empirically optimizing conditions and using citrate buffer. (*See id.*; *see also* Ex. 1001, 3:66-4:2 (stating that traditional formulations use buffering systems).)

The complexity and unpredictability of formulating antibodies resulted, at least in part, because a formulation designed for one antibody would not reasonably have been expected to be successfully applied to a different antibody. Indeed, it was well established by 2007 that antibodies had to be evaluated *individually* when developing a liquid formulation because of their differing structures and properties. (Ex. 2047, 5, 14, 21.) This was true even for antibodies

with similar sequences and among antibodies of the same class (*e.g.*, IgG or IgG1). (*Id.*; Ex. 2021, 690.)

C. The ’619 Patent

The ’619 patent details the surprising discovery that adalimumab formulated in water at high concentrations *without* a buffering system may be used as a pharmaceutical formulation. (*See* Ex. 1001, 3:29-33.) Contrary to the traditional approaches for monoclonal antibody formulation, the ’619 patent describes and claims high concentration (50-200 mg/ml) aqueous pharmaceutical formulations comprising adalimumab without a buffering system. (*See, e.g.*, *id.*, 60:47-62:32, Table 12 & claims 16-18.)

While conducting experiments for a different but related purpose, the inventors made several observations that led them to use diafiltration techniques to produce adalimumab in pure water at concentrations ranging from 10 mg/ml to above 200 mg/ml. (*See, e.g.*, *id.*, 51:47-54:18, 60:47-62:32.) The ’619 patent describes the resulting formulations as unexpectedly non-opalescent. (*See, e.g.*, *id.*, 60:6-16, 68:37-49.) That is, surprisingly, the formulations were clear, with no solution haziness or precipitation. (*Id.*, 44:47-57, 60:25-36.) The formulations were also “surprisingly stable,” with only minimal protein aggregation even at adalimumab concentrations of 200 mg/ml and “virtually no instability phenomena” were observed. (*Id.*, 67:30-45; 68:52-55.) The ’619 patent also discloses that

adalimumab formulations without a buffering system had low viscosity at concentrations up to 200 mg/ml—a key property for a subcutaneously administered formulation. (*Id.*, 3:1-7; 60:17-20.) The patent contrasts the low viscosity of the adalimumab formulations without a buffering system with another protein (human serum albumin) formulation without a buffering system, which exhibited a six-fold *increase* in viscosity compared to a buffered formulation. (*Id.*, 65:1-10 (concluding that viscosity "may depend on the individual protein").)

The '619 patent claims are directed to the disclosed high-concentration adalimumab pharmaceutical formulations lacking a buffering system, which achieved the unexpected properties of low aggregation, low opalescence, low viscosity, and high solubility. (*Id.*, 151:9-152:65.) Independent claim 16 defines an aqueous pharmaceutical formulation comprising an antibody having the complementarity determining region (CDR) amino acid sequences of adalimumab, an antibody concentration of 50-200 mg/ml, and water, in which the formulation does not comprise a buffering system. (*Id.*, 152:15-32.)

At the time of AbbVie's invention, *no one* had successfully developed a commercial high concentration aqueous monoclonal antibody pharmaceutical formulation without a buffering system.

III. Level Of Ordinary Skill In The Art

For the limited purpose of this Preliminary Response, Patent Owner does not contest Petitioner's proposed level of ordinary skill in the art. (Pet., 18-19.)

IV. Claim Construction

Patent Owner believes that construction of the phrase "does not comprise a buffering system" is unnecessary at this stage. For purposes of this Preliminary Response only, Patent Owner does not dispute Petitioner's proposed construction: "contains no more than a *de minimis* amount of extrinsic buffer." (*Id.*, 19-20.)

V. Ground 1: Petitioner Fails To Establish That Gokarn PCT Anticipates The Challenged Claims

Petitioner's anticipation challenge improperly requires making selections from the vast disclosures of Gokarn PCT. (Pet., 26-29.) In an attempt to arrive at the claimed invention, Petitioner points to only two places where Gokarn PCT lists "HUMIRA (Adalimumab)" among a countless number of potential proteins, and then makes additional selections from at least two other categories of options (*e.g.*, amount of buffer; protein concentrations) that are not tied to any particular protein.[3] (*See id.*; Ex. 1003, 9:25, 51:24.) This is not anticipation. *Akzo N.V. v. USITC*, 808 F.2d 1471, 1480 (Fed. Cir. 1986) (affirming holding of no anticipation

[3] For dependent claims 24-30, Petitioner needs to make yet another selection of pH.

where the prior art required picking and choosing among different disclosed compounds, solvents, and ranges of viscosities); *Volkswagen Grp. of Am., Inc. v. Emerachem Holdings, LLC*, No. IPR2014-01556, Paper 57 at 27-29 (P.T.A.B. Jan. 22, 2016) (finding no anticipation were one would not envisage a combination of catalyst and absorber from thousands described in the prior art reference).

Petitioner's attempt to remedy these deficiencies by reaching to extrinsic evidence is insufficient under Section 102. *Sanofi-Synthelabo v. Apotex, Inc*., 550 F.3d 1075, 1083 (Fed. Cir. 2008) ("To anticipate, the reference 'must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements arranged as in the claim.'") (internal quotations omitted) (citation omitted); *Net MoneyIN*, *Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008). For example, Petitioner attempts to rely on the 50 mg/ml adalimumab concentration of Patent Owner's HUMIRA product. (Pet., 26.) But that concentration is nowhere described in Gokarn PCT, which refers only to the *protein* in HUMIRA (adalimumab), and is silent regarding HUMIRA's formulation or concentration. (Ex. 1003, 8-9 ("wherein the protein is selected from the group consisting of").) Because Gokarn PCT does not disclose each and every limitation of the challenged claims as arranged in the claims, the Board should deny Ground 1.

A. Gokarn PCT Does Not Disclose All Of The Claim Elements

Recognizing Gokarn PCT's lack of disclosure, Petitioner resorts to asserting that a person of ordinary skill would "at once envisage" the claimed adalimumab formulations without a buffering system based on Gokarn PCT. (Pet., 25.) A reference does not anticipate, however, when the number of disclosed combinations is so large that one could not "at once envisage" the claimed combination. *Volkswagen*, IPR2014-01556, Paper 57 at 27-29 (citation omitted). Here, Gokarn PCT discloses such an immense number of different combinations of proteins, additional buffer amounts, and protein concentrations that it cannot anticipate the claimed combination of a high-concentration formulation of adalimumab in water without a buffering system. *In re Arkley*, 455 F.2d 586, 587-88 (C.C.P.A. Feb. 13, 1963).

Gokarn PCT purports to describe "any protein" that provides sufficient buffering capacity. (Ex. 1003, 40:21-23.) It broadly defines "protein" as "a polypeptide or a complex of polypeptides." (*Id*., 25:10-22.) It discloses innumerable possible protein choices spanning *more than a dozen pages*. (*Id*., 7-10, 40:20-52:8.) Its section on "Target Binding Proteins," for example, contains dozens of broad categories of possible target protein categories, including any and all CD proteins, HER receptor family proteins, cell adhesion molecules, growth factors, insulin and insulin-related proteins, coagulation and coagulation-related

proteins, colony stimulating factors, blood and serum proteins, receptor and receptor-associated proteins, neurotrophic factors, interferons, interleukins, among many others. (*Id.*, 45:1-46:29.) Gokarn PCT also incorporates by reference several other U.S. patents for their equally broad listings of proteins. (*Id.*, 47:16-48:14, 51:4-13.) Its broad disclosure of so many categories and sub-categories makes it impossible to even count the number of proteins encompassed. (*See id*., 7-10, 40:20-52:8.) Further, even its section on "Particular Illustrative Proteins" contains innumerable potentially acceptable pharmaceutical proteins spanning six pages. Many of those proteins are not antibodies at all, much less previously known formulations of high-concentration antibodies. (*Id*., 46:31-52:8.) Finally, it includes a lengthy section identifying virtually all known commercially available protein products. (*Id*., 51:15-52:8.) Gokarn PCT does not identify adalimumab in any example or as a preferred antibody. Accordingly, to select adalimumab from Gokarn PCT, one would have had to select it from among a vast number of disclosed proteins. This is not anticipation. *Arkley*, 455 F.2d at 587-88 ("picking and choosing . . . has no place in the making of a 102, anticipation rejection.")

Petitioner's reliance on Gokarn PCT's claims fares no better. Claim 23 of Gokarn PCT, for example, recites the same extensive list of commercial proteins that appears in the specification. (*See* Ex. 1003, claim 23.) The preceding claims broadly encompass many categories of non-antibody proteins, such as

receptibodies, peptibodies, and growth factors, similar to the extensive lists disclosed in the specification. (*Id.*, claims 17-22.) The subsequent claims are directed to only three of the four specifically exemplified antibodies in the specification: Ab-hOPGL, Ab-hIL4R, and Ab-hB7RP1. (*Id.*, claims 24-29.) Thus, Gokarn PCT's claims add no specificity to its disclosure and no preference or direction to choose adalimumab.

To arrive at the claimed invention, in addition to selecting adalimumab, a skilled artisan also would have had to select a formulation without a buffering system. Gokarn PCT discloses multiple options for the amount of additional buffer to be used in a protein's formulation. (*Id.*, 5:30-33.) Gokarn PCT speculates, for example, that a protein could provide 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99%, or 99.5% of a formulation's buffering capacity (at least thirteen options). (*Id*.) But it fails to say which of the countless proteins could provide which listed percentage of total buffer capacity. In addition, the sole independent claim in Gokarn PCT is not directed to formulations without a buffering system, but encompasses other components that can provide buffering capacity. (*Id.*, 81:2-11.) Therefore, there is nothing in the wide array of options disclosed in Gokarn PCT pointing a skilled artisan toward a formulation of adalimumab without a buffering system. *Arkley*, 455 F.2d at 587-88.

There is also nothing that would have directed a skilled artisan to the claimed antibody concentration of 50-200 mg/ml, particularly because this range is not explicitly disclosed in Gokarn PCT. Rather, Gokarn PCT speculates that the protein concentration range could be as broad as 20-400 mg/ml without specifying which proteins could be successfully formulated at which of these concentrations without experiencing aggregation or other problems associated with high-concentration protein formulations. (Ex. 1003, 6:4-8, 81:19-22.) Gokarn PCT also states that an appropriate "self-buffering" concentration should be *empirically* determined *for each protein*. (*Id.*, 31:18-28, 36:10-14 (empirical measurements are preferred because a "complete description" of contributing factors to buffer capacity "is beyond the reach of current theoretical and computational methods").) Yet Gokarn PCT presents no information about adalimumab's buffering capacity or the relationship between adalimumab's concentration and its buffering capacity. Gokarn PCT therefore is not anticipatory but instead is, at best, merely an invitation to investigate a concentration range. *See Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004) (finding no anticipation where the prior art disclosed a broad genus and invited experimentation).

Because Gokarn PCT purports to list every conceivable protein through many pages of broad categories of proteins of widely varying structures and

functions, encompasses at least thirteen different options for the amount of buffer capacity the protein might possibly contribute to the formulation, and speculates about a wide range of potential protein concentrations, the number of possible choices and combinations described is so large that the claimed adalimumab formulations at 50-200 mg/ml in water without a buffering system would not have been disclosed to one skilled in the art. *See Sanofi-Synthelabo,* 550 F.3d at 1083; *Net MoneyIN*, 545 F.3d at 1371 (holding that an anticipatory reference must disclose the claimed invention arranged or combined in the same way as the claim).

Notably, neither Petitioner nor Dr. Radtke addresses the size or breadth of the combinations disclosed by Gokarn PCT. Instead, they dismiss the countless other listed proteins simply because adalimumab is also listed. (*See* Pet., 25.) But the mere mention of "HUMIRA (Adalimumab)" among innumerable *potential* proteins is not enough. *Sanofi-Synthelabo*, 550 F.3d at 1083-84; *Akzo*, 808 F.2d at 1480.

Unlike Gokarn PCT's vast number of possible combinations, Petitioner's cited anticipation cases all concern a prior art reference with only a small number of possible combinations. In *Kennametal, Inc. v. Ingersoll Cutting Tool Co*., 780 F.3d 1376, 1380-83 (Fed. Cir. 2015), for example, the Court found that substantial evidence supported the Board's finding that the prior art described only fifteen combinations of PVD coatings and metal binders, one of which anticipated the

claim at issue. In *Blue Calypso, LLC v. Groupon Inc*., 815 F.3d 1331, 1344 (Fed. Cir. 2016), the Federal Circuit affirmed the Board's finding of anticipation based on prior art that disclosed only a "limited number" of tools for internet-based communication systems, including the claimed tools, and also suggested their combination. In *Perricone v. Medicis Pharmaceutical Corporation*, 432 F.3d 1368, 1376-77 (Fed. Cir. 2005), the prior art disclosed only a "handful" of different cosmetic compositions, one of which anticipated the claims. Similarly, in *Wm. Wrigley*, the prior art stated that the claimed WS-23 was one of only three preferred cooling agents and identified the claimed combination of WS-23 with menthol, which was identified as the most suitable flavoring agent. *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361-62 (Fed. Cir. 2012). Finally, *In re Gleave*, 560 F.3d 1331, 1338 (Fed. Cir. 2009), did not involve combining different sections of a prior-art disclosure; rather, the prior art explicitly disclosed the claimed composition.

Here, the number of possible combinations in Gokarn PCT is far greater than the "limited" number of combinations at issue in Petitioner's cited cases. By failing to even address this large number of combinations, or explain why a skilled artisan would have immediately envisioned the claimed invention, Petitioner fails to prove that Gokarn PCT discloses each of the individual elements arranged as in the claims. *See Volkswagen*, IPR2014-01556, Paper 57 at 27-29 (finding no

anticipation because one would not envisage the claimed catalyst/absorber combination from the thousands described in the prior art); *see also Akzo*, 808 F.2d at 1480.

B. Petitioner's Attempt To Import Missing Elements From The Prior Art Is Improper

Petitioner's anticipation argument is legally flawed for the additional reason that it improperly seeks to import limitations that are missing from the allegedly anticipatory reference. Gokarn PCT does not disclose an adalimumab formulation without a buffering system at all, let alone at the claimed concentration and pH.

1. Gokarn PCT does not disclose a "bufferless" adalimumab formulation

Petitioner is not asserting that a skilled artisan would have selected an adalimumab formulation without a buffering system from Gokarn PCT's disclosure because no such formulation is disclosed. Rather, Petitioner improperly relies on *Kennametal* to contend that a skilled artisan would have picked commercially available "HUMIRA (Adalimumab)" (which contains a citrate-phosphate buffer) out of a long list of possible protein products, and then would have at once "envisage[d]" removing the buffering system from HUMIRA. (Pet., 25.) But Petitioner stretches *Kennametal* far beyond its holding because Gokarn PCT does not disclose such an adalimumab formulation lacking a buffering system, let alone at the claimed concentration and pH.

The Federal Circuit clarified the limited scope of *Kennametal* in *Nidec Motor Corporation v. Zhongshan Broad Ocean Motor Co*., 851 F.3d 1270, 1274-75 (Fed. Cir. 2017). In that case, the court reversed the PTAB's ruling that Nidec's claims were anticipated, holding that *Kennametal* addresses whether disclosure of a *limited* number of possibilities discloses one of the possible combinations—which is not the case here. Further, the court explained that "*Kennametal* does not permit the Board to fill in missing limitations simply because a skilled artisan would immediately envision them." *Id*. Petitioner and Dr. Radtke are doing exactly what the Federal Circuit held in *Nidec* was improper: (1) picking and choosing among a vast number of different possibilities, and (2) using *Kennametal* to fill in a missing limitation by alleging that a skilled artisan would have envisioned it. Accordingly, Petitioner has failed to show a reasonable likelihood that it can prevail on its anticipation challenge.

2. Gokarn PCT does not disclose the claimed adalimumab concentration

Because Gokarn PCT does not disclose the HUMIRA formulation, Petitioner attempts to add that missing information to Gokarn PCT through extrinsic evidence (*i.e.*, the HUMIRA Label). (Pet., 27.) But the use of extrinsic evidence to establish a specific prior art teaching not found in the allegedly anticipatory reference (Gokarn PCT) is contrary to the law of anticipation.

Studiengesellschaft Kohle, m.b.H. v. Dart Indus., 726 F.2d 724, 726-27 (Fed. Cir. 1984).

Petitioner nevertheless argues that a skilled artisan would have understood the mention of "HUMIRA" to disclose adalimumab at a specific concentration of 50 mg/ml. (Pet., 27.) This is incorrect. Gokarn PCT refers only to the *protein* in HUMIRA (adalimumab), and is silent as to HUMIRA's formulation or concentration. (Ex. 1003, 9:16, 9:25, 46:30-34, 51:24; *see also* Pet., 25 ('"HUMIRA (Adalimumab)' is specifically identified as a suitable *protein* for use in the self-buffering formulation.").)[4] Indeed, Gokarn PCT cannot be pointing to the concentration or formulation of adalimumab in HUMIRA for a formulation that lacks a buffering system because *HUMIRA is a buffered formulation*. (Pet., 27 n.3.)

Petitioner's reliance on *In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991), is misplaced. (Pet., 27.) In *Baxter*, the Court relied on an inherent property of the expressly disclosed prior art bags. 952 F.2d at 390. Here, Petitioner is not using extrinsic evidence to establish adalimumab's inherent properties (*e.g.,* its structure or molecular weight). Instead, it is relying on extrinsic evidence concerning HUMIRA's *buffered* formulation to establish adalimumab's concentration in a formulation *without a buffering system*. But Petitioner has not

[4] In this paper, all emphases are added unless otherwise indicated.

shown these concentrations would *necessarily* be the same. Accordingly, Gokarn PCT's disclosure of "HUMIRA (Adalimumab)" does not anticipate the claimed concentration.

Petitioner also asserts that even if Gokarn PCT's reference to "HUMIRA" did not disclose 50 mg/ml, Gokarn PCT's disclosure of generic concentration ranges of 20-250 mg/ml and 20-400 mg/ml (not tied to any particular protein or antibody) anticipates the claimed adalimumab concentration range of 50-200 mg/ml. (Pet., 28.) But the disclosure of a genus does not necessarily disclose every species within that genus. *Wasica Fin. GmbH v. Cont'l Auto. Sys.*, *Inc.,* 853 F.3d 1272, 1285-86 (Fed. Cir. 2017) (citing *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006)) (affirming PTAB's finding of patentability because Petitioner failed to address the size of the prior art genus or identify any of its species); *Sanofi-Synthelabo*, 550 F.3d at 1084. Instead, whether a genus anticipates a claimed range depends on the particular facts. *OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 706 (Fed. Cir. 2012) (holding that how one "would understand the relative size of a genus or species in a particular technology is of critical importance"). Here, Petitioner's conclusory analysis does not establish that Gokarn PCT describes the claimed concentration range with sufficient specificity to anticipate. *Atofina*, 441 F.3d at 999.

Petitioner asserts that many commercially available formulations had low protein concentrations and thus did not have sufficient protein to lack a buffering system. (Pet., 12.) However, at least two commercial formulations (other than HUMIRA) available prior to 2007 had protein concentrations within the disclosed range of 20-400 mg/ml—yet were still formulated with a buffer system. (Ex. 2047, 2-4.) This demonstrates that the prior art used buffer systems even when protein concentrations were within Gokarn PCT's disclosed range of 20-400 mg/ml. Thus, this range lacks the legally required specificity to anticipate the range of '619 patent claim 16.

Petitioner does not address the breadth of Gokarn PCT's concentration ranges or the difference between Gokarn PCT's concentration ranges and the claimed range *within the technology of pharmaceutical antibody formulations* and therefore cannot establish that Gokarn PCT anticipates the claimed adalimumab concentration. *See OSRAM*, 701 F.3d at 705-06 (vacating summary judgment of anticipation because, within the invention's field of technology, disclosure of an air pressure of "approximately 1 torr or less" may not disclose "less than 0.5 torr"). This omission is critical, as increasing the concentration of antibodies was known at the time of the invention to reduce their physiochemical stability, causing a high tendency to aggregate and increase viscosity. (Ex. 2025, 6109; Ex. 2047, 14.) Indeed, concentration-dependent antibody aggregation was characterized as "the

greatest challenge to developing protein formulations at higher concentrations." (Ex. 2047, 8, 14-15.)

Petitioner also fails to show that the broad concentration range disclosed in Gokarn PCT would identify the concentration necessary for adalimumab to "self-buffer." As Petitioner recognizes, a protein's ability to "self-buffer" depends on its concentration (among other factors). (Pet., 12; Ex. 1002, ¶46.) Yet Gokarn PCT does not disclose adalimumab's buffer capacity, and Petitioner fails to calculate or estimate it based on any information available in the prior art. Because Petitioner has failed to even address the relationship between adalimumab concentration and buffering capacity, it has not shown that Gokarn PCT's broad concentration ranges disclosed the claimed range with sufficient specificity to anticipate. *See Moses Lake Indus. v. Enthone, Inc.*, No. IPR2014-00246, Paper 6 at 14-15 (P.T.A.B. June 18, 2014) (finding no anticipation where (as here) a reference disclosing a broad range did not suggest reducing it to the narrower claimed range, and Petitioner's expert did not explain how the reference suggested the narrower range).

The *Ineos* and *ClearValue* cases cited by Petitioner do not support a finding of anticipation, as they involved different facts. In *Ineos*, the court affirmed a finding of anticipation of a claimed lubricant concentration based on a prior-art disclosure of an overlapping amount of that lubricant because no evidence indicated that the selection of lubricant was critical to the "operability or

functionality of the claimed invention." *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 870-72 (Fed. Cir. 2015). In *ClearValue*, the court affirmed a finding of anticipation of a claim directed to clarifying water with an alkalinity of less than 50 ppm based on prior art disclosing clarifying water with an alkalinity of less than 150 ppm. *ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1344-45 (Fed. Cir. 2012). Nothing indicated that the water treatment would not work for both the broad prior-art range and the narrower claimed range. *Id*. at 1345. In contrast, the protein formulation technology at issue here *directly links* antibody concentration to its buffering capacity, which Gokarn PCT states is "crucial" to the ability to formulate the antibody without a buffering system. (Ex. 1003, 37:21-25 (buffer capacity is "a function of concentration"), *id.,* 38:10-14 (determining buffer capacity is a "crucial" aspect of formulating self-buffering compositions.).) Petitioner fails to establish that one would have understood Gokarn PCT's broad concentration range to disclose the concentration range effective for adalimumab to "self-buffer" in an aqueous pharmaceutical formulation. *See OSRAM*, 701 F.3d at 705-06.

Because Gokarn PCT does not disclose all of the claim elements as arranged in the challenged claims, including the claimed adalimumab concentration range of 50-200 mg/ml, the Board should deny institution of Ground 1.

VI. Ground 2: Petitioner Fails To Establish That The Asserted References Render The Claimed Invention Obvious

Petitioner fails to establish that a skilled artisan would have been motivated to combine Gokarn PCT with the HUMIRA Label. The HUMIRA Label concerns the commercially available 50 mg/ml *buffered* formulation of adalimumab, which uses a citrate-phosphate buffering system. (Ex. 1005, 470; *see supra* Section II.A.2.) Gokarn PCT and the HUMIRA Label, however, do not describe *any* known problem with HUMIRA that would have motivated one of ordinary skill to modify the highly successful adalimumab formulation of HUMIRA. (Ex. 1005, 470.) Indeed, the Petition identifies *no problem* that would have motivated one of ordinary skill to attempt to modify HUMIRA at all.

Petitioner also does not establish any reasonable expectation of success of achieving the claimed invention. It was well established that one could not reasonably expect a formulation that worked for one antibody (such as one of the exemplified Ab-hOPGL, Ab-hB7RP1, Ab-hCD22, and Ab-hIL4R antibodies in Gokarn PCT) to work for any other antibody, such as adalimumab.

A. Petitioner Fails To Establish A Motivation To Combine Gokarn PCT With The HUMIRA Label

1. Petitioner does not identify any problem with HUMIRA

HUMIRA, one of the top selling drugs in the world, is used by hundreds of thousands of patients to treat rheumatoid arthritis and other inflammatory

conditions. (Ex. 2042, 1.) When it was initially approved in 2002, HUMIRA was successfully formulated with a multi-component citrate-phosphate buffering system. (Ex. 2047, 2; *see also* Ex. 1005, 470.) Indeed, at the time of the invention, this groundbreaking buffered formulation was the only approved monoclonal antibody formulation intended for subcutaneous injection that was not lyophilized, meaning that it could be administered directly without reconstitution. (*See*, *e.g.*, Ex. 2047, 2-4.) Despite HUMIRA representing a significant achievement in the formulation of high-concentration monoclonal antibodies, Petitioner asserts that one of ordinary skill would have been motivated to modify this formulation to remove its buffering system. (Pet., 39-40.)

But Petitioner has not identified *any* problem with HUMIRA that would have led one of ordinary skill to remove its buffer. This is a fatal deficiency in the Petition. *Novartis Pharm. Corp. v. Watson Labs., Inc.*, 611 F. App'x 988, 995-96 (Fed. Cir. 2015) (finding no motivation to modify a pharmaceutical formulation where the prior art did not unambiguously identify a known problem). Rather, Petitioner simply recites the components of HUMIRA from its label, and then cites Gokarn PCT as identifying "HUMIRA (Adalimumab)" as "a protein for use in a self-buffering formulation." (Pet., 39.)

The fact that Gokarn PCT lists "HUMIRA (Adalimumab)" is not sufficient motivation to modify HUMIRA to achieve the claimed formulation. Obviousness

concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention. *InTouch Techs., Inc. v. VGo Commc'ns, Inc.*, 751 F.3d 1327, 1352 (Fed. Cir. 2014). Even as late as 2014, buffering systems were frequently used. (Ex. 2028, 271 (reporting that the initial formulation of ERBITUX encountered antibody aggregation, which was addressed by "empirically optimiz[ing]" conditions and employing citrate buffer).) By failing to establish any reason to reformulate the successful HUMIRA formulation, Petitioner's obviousness allegations are necessarily based on impermissible hindsight. *See, e.g., Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1354 (Fed. Cir. 2013) (holding that because the prior art did not recognize or disclose a stability problem, one of ordinary skill would not have attempted to improve upon that prior art).

Notably, from HUMIRA's introduction in 2003 through the 2007 filing date of the '619 patent, only two other commercially available monoclonal antibody products were formulated for subcutaneous administration, but both were lyophilized (freeze-dried). (Ex. 2047, 2-4.) In the same time period, commercially available liquid formulations existed for fifteen other monoclonal antibody products, and all were provided with a buffering system. (*Id.*; *See also* Ex. 2055, 852.) Petitioner accordingly fails to establish that persons skilled in the art had any reason to remove buffering systems from existing antibody formulations.

Table 1. Commercially Available Antibody Formulations (2007) [5]

Antibody Product	Delivery	Form
AVASTIN®	IV	Buffered Liquid
BEXXAR®	IV	Buffered Liquid
CAMPATH®	IV	Buffered Liquid
ERBITUX®	IV	Buffered Liquid
HUMIRA®	SC	Buffered Liquid
LUCENTIS®	Intravitreal	Buffered Liquid
ONCOSCINT®	IV	Buffered Liquid
ORTHOCLONE®	IV	Buffered Liquid
PROSTASCINT®	IV	Buffered Liquid
REOPRO®	IV	Buffered Liquid
RITUXAN®	IV	Buffered Liquid
TYSABRI®	IV	Buffered Liquid
VERLUMA®	IV	Buffered Liquid
ZENAPAX®	IV	Buffered Liquid
ZEVALIN®	IV	Buffered Liquid
RAPTIVA®	SC	Lyophilized (Buffered)
XOLAIR®	SC	Lyophilized (Buffered)

The history of commercial antibody formulations subsequent to the disclosure of Gokarn PCT confirms that those of ordinary skill in the art were not,

[5] Table adapted from Wang 2007 (Ex. 2047, 2-4 (Table 1); *see also* Ex. 2055, 852.)

in fact, motivated to exclude buffers. Even as late as 2015, *all* commercially available aqueous monoclonal antibody formulations were provided with a buffering system. (Ex. 2051, 94-101 (Table 4.1); Ex. 2055, 852.)

At the time of the invention, it was extremely difficult to make stable (*e.g.,* non-aggregated, non-fragmented, non-degraded, non-denatured, *etc.*), liquid pharmaceutical formulations of antibodies, particularly at the high concentration that permits HUMIRA to be delivered in the small injection volume needed for single-dose subcutaneous administration. (*See, e.g.*, Ex. 2047, 14 ("Among all the commercial antibody products, about half are stable enough to be formulated in a liquid form.").) The same held true even several years later. (*See, e.g.,* Ex. 2028, 271 ("[a] considerable proportion of human monoclonal antibody candidates *fail formulation studies*"); Ex. 2020, 612; Ex. 2026, 82.) Petitioner's failure to identify a motivation to eliminate buffers from HUMIRA is dispositive, particularly in view of the demonstrated success of the HUMIRA formulation. *Leo Pharm.*, 726 F.3d at 1354; *InTouch*, 751 F.3d at 1352.

2. There would have been no motivation to choose adalimumab from the broad disclosure of Gokarn PCT

Petitioner fails to establish that a skilled artisan would have been motivated to select adalimumab from Gokarn PCT's immense number of *potentially* suitable proteins and protein categories spanning *more than a dozen pages*. (Ex. 1003, 7-10,

40:20-52:8.) Those categories are not limited to antibodies. Rather, they broadly encompass growth factors, coagulation-related proteins, peptibodies, stem cell factors, ligands, and many other unrelated categories of proteins. (*See, e.g.*, *id.*, 51 (further incorporating by reference other U.S. patents for their broad listings of proteins).)

Petitioner's assertion that Gokarn PCT discloses adalimumab as a "most preferred embodiment" is factually inaccurate. (Pet., 29.) Gokarn PCT never describes adalimumab as a most preferred protein. (Ex. 1003.) Gokarn PCT's section on "Particular Illustrative Proteins" includes innumerable potentially acceptable proteins and categories of proteins, spanning six pages. (Ex. 1003, 46:31-52:9.) Many of these proteins are not antibodies at all. (*Id.* (describing myostatin binding agents, peptibodies, stem cell factors, ligands, *etc.*) In the final paragraph of this lengthy disclosure, "HUMIRA (Adalimumab)" is mentioned as just one possibility among virtually all known other commercial protein products. (*Id.,* 51:15-52:9.) While Petitioner inaccurately asserts that the alleged "most preferred embodiment" of adalimumab would provide 99% of a composition's buffer capacity, Gokarn PCT never discloses the buffer capacity of adalimumab in any formulation or concentration. (*See id.*; Pet., 29.) Out of the vast number of possibilities of all known proteins, Gokarn PCT provides no disclosure that would have guided a skilled artisan toward adalimumab. *In re Baird*, 16 F.3d 380, 382-83

(Fed. Cir. 1994) (reversing obviousness where a reference required choosing from an extensive array of options without any guidance to arrive at the claimed invention).

Instead of pointing toward adalimumab, Gokarn PCT discusses and includes example solutions for four different antibodies: Ab-hOPGL (Ex. 1003, 47:12-15, 75:25-77:33), Ab-hB7RP1 (*id.*, 50:15-17, 78:1-79:13), Ab-hCD22 (*id.*, 49:14-17, 79:15-27), and Ab-hIL4R (*id.*, 48:4-6, 79:29-80:24). Gokarn PCT describes experiments relating to these four proteins, reporting data on the buffering capacity of their preparations at various concentrations, including certain preparations that were purportedly "self-buffered." (*Id.*, Examples 1-17 & Figs. 4-15.) At most, Gokarn PCT focuses on these four proteins—none of which is adalimumab—and the Petition does not contend that any of them would have led a skilled artisan to select adalimumab from the innumerable alternative proteins and protein categories listed across *a dozen pages*. (*See, e.g.*, Ex. 1003, 40:20-52:8.) Indeed, the Petition provides no information regarding how these four exemplified proteins' characteristics would have compared to adalimumab. The Petition therefore fails to establish any motivation to select adalimumab from Gokarn PCT's broad disclosure of proteins and antibodies. *Baird*, 16 F.3d at 383 (finding specific diphenol compound nonobvious "given the vast number of diphenols"

encompassed by the reference and the fact that its "preferred" diphenols differed from the claimed compound).

Petitioner therefore fails to establish that one of ordinary skill would have had any reason or motivation to eliminate the buffering system from HUMIRA's successful commercial formulation. For at least this reason alone, the Board should deny institution of Ground 2.

3. Petitioner previously alleged that a skilled artisan would have been motivated to use a buffering system with adalimumab

Petitioner's failure to provide any rationale for eliminating the buffering system from the commercially successful HUMIRA product is unsurprising given previous positions taken by Petitioner before this Board on the importance of buffers in formulating adalimumab. For example, in a previous IPR Petition, Petitioner asserted that buffers *should be included* in adalimumab formulations because they maintain the solution pH and affect the stability of the antibody. *See*, *e.g., Coherus Biosciences, Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2016-01018 ("*Coherus* IPR), Paper 1 at 33 (P.T.A.B. May 9, 2016) ("A POSA would have been motivated to prepare a stable liquid formulation of [adalimumab] *with a buffer system* . . . .").) Petitioner's expert in that proceeding testified, for example, that adalimumab should be formulated with a buffer because buffered formulations were the "standard in the industry." (Ex. 2004, ¶64.) He specifically identified

citrate and phosphate buffer systems, used in other commercial products, as useful and appropriate. (*Id.*, ¶143.) And he testified that it "was a given" that an adalimumab formulation should include a buffer. (*Id.*, ¶156.)

Petitioner cannot retreat from its previous representations to the Board in support of aqueous adalimumab formulations that include a buffering system, such as a citrate or phosphate buffering system. Petitioner itself continues to pursue *at least a dozen* patents and patent applications filed in 2012, almost *five years after* the priority date of the '619 patent having claims directed to *buffered* adalimumab formulations. (*See, e.g.,* U.S. Pat. Nos. 9,340,611; 9,340,612; 9,346,880; and U.S. Pat. Pub. Nos. 2014/0186361; 2015/0190513; 2016/0039926; 2016/0031982; 2016/0256545; 2016/0256546; 2016/0256547; 2016/0263226; 2017/0072054.) This includes pursuing claims directed to adalimumab formulations that are specifically *phosphate*-buffered (*see*, *e.g.*, U.S. Pat. Pub. No. 2016/0039926 and 2016/0031982) or *citrate*-buffered (*see, e.g.,* U.S. Pat. Pub. No. 2016/0031982).

B. Petitioner Fails To Demonstrate A Reasonable Expectation Of Successfully Achieving An Adalimumab Formulation Without A Buffering System

Petitioner also fails to establish that one of ordinary skill would have had any reasonable expectation of successfully reformulating HUMIRA by removing its buffering system, much less at the high protein concentration (50-200 mg/ml) claimed in the '619 patent.

1. A formulation designed for one antibody would not have been expected to apply to a different antibody

Petitioner asserts that one of ordinary skill would have reasonably expected success in formulating adalimumab at 50 mg/ml and pH 5.2 without a buffering system, because Gokarn PCT discloses doing so. (Pet., 40.) But as discussed above, this is incorrect. (*See supra* Section V.) Gokarn PCT does not tie adalimumab to any particular concentration or pH. (Pet., 39-40.) Petitioner also relies on Dr. Radtke's conclusory assertion that one would have expected such a formulation to work, "since this pH is within the range disclosed by Gokarn PCT and is the same as the pH of the Humira® commercial formulation." (*Id.*; Ex. 1002, ¶103.) Such conclusory statements do not prove a reasonable expectation of success. *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016) ("To satisfy its burden of proving obviousness, a petitioner cannot employ mere conclusory statements.").

Petitioner also asserts that one would have expected success in reformulating adalimumab without a buffering system based on Gokarn PCT's examples with different antibodies. (Pet., 41.) But Petitioner fails to address the well-established unpredictability in applying a formulation that works with one antibody to a different antibody.

Indeed, in 2007, there was a general consensus in the art that a formulation that worked for one antibody (such as Ab-hOPGL, Ab-hB7RP1, Ab-hCD22, or Ab-hIL4R of Gokarn PCT) would *not* be predicted to work for a different antibody (such as adalimumab). For example, the Wang 2007 review article (Ex. 2047) explained the complexities involved in formulating different antibodies:

> Development of commercially viable antibody pharmaceuticals has, however, not been straightforward. This is because the behavior of antibodies seems to vary, even though they have similar structures.

(*Id.*, 5.)

Rather, Wang and others explained that antibodies had to be evaluated *individually* when developing a liquid formulation because of their differing structures and properties. (*See id.*, 21.) Persons skilled in the art rejected the notion that a formulation useful for one antibody could reasonably be expected to be successfully applied to other similar antibodies. (Ex. 2021, 690 (each IgG1 antibody "seems to have a unique personality related to its requirements for stability" arising from even small differences in protein folding and solvent-exposed amino acid residues).) Therefore, the assumption by Petitioner and its declarant that "substantial identity" among amino acid sequences in IgG antibodies would lead to similar buffering capacities and formulation requirements is unsupported. (Pet., 40); 37 C.F.R. § 42.65(a); (*see* Ex. 2028, 271 (reporting in 2014 that "[d]espite recent advances, the identification of suitable formulation

conditions for a specific monoclonal antibody remains challenging and *cannot be determined from its amino acid sequence*").). Rather, different proteins need to be evaluated individually using only trial-and-error. (*See*, *e.g.*, Ex. 2001, 130.) In fact, Petitioner's argument is contradicted by Gokarn PCT, which concedes that the buffering capacities of a protein's amino acid residues "can vary dramatically" due to protein folding, and therefore that empirical experimentation is "a crucial aspect of formulating self-buffering compositions." (Ex. 1003, 38:10-14, 38:26-39:2.)

Accordingly, to produce a formulation for a particular antibody, one had to identify the appropriate ionic strength, pH, and buffer type needed to minimize precipitation and other adverse events (*e.g.*, deamidation). (Ex. 2016, 1333.) Yet even a skilled artisan's "best efforts" at developing antibody formulations were unpredictable and not reasonably expected to succeed, as a result of inherent limitations of antibodies themselves. (Ex. 2021, 701.) Even as recently as 2014, the scientific literature reported the use of buffering systems, such as citrate, to produce a successful formulation. (Ex. 2028, 271.)

Moreover, it was well known that liquid antibody formulations suffered from problems such as aggregation, which were more likely to occur as the antibody concentration increased. (*See*, *e.g.,* Ex. 2047, 9 ("Increasing the concentration of antibodies often increases the aggregation tendency of the protein."); Ex. 2009, 1929; Ex. 2021, 693; Ex. 2001, 152.) Similar problems

continued to be reported after the priority date. (*See*, *e.g.,* Ex. 2025, 6109 ("[I]ncreasing immunoglobulin (IgG) concentration increases self association of these molecules").) Petitioner does not provide any evidence regarding the properties of adalimumab or any analysis of the aggregation tendencies of adalimumab in a formulation without a buffering system. Instead, Petitioner overgeneralizes and merely alleges that one of ordinary skill knew "for decades" that proteins could provide buffer capacity at high concentrations. (Pet., 11.) Petitioner therefore has not established any reasonable expectation of success in obtaining an adalimumab formulation without a buffering system at 50 mg/ml.

Notably, in prior IPRs concerning claims directed to adalimumab formulations, the Board recognized that a formulation for one antibody could not provide a reasonable expectation of success in obtaining a similar formulation for a different antibody. For example, with reference to Wang 2007 (Ex. 2047), which was published the *same year* as the earliest claimed priority date of the '619 patent, the Board explained:

> Wang 2007 also states that "[d]evelopment of commercially viable antibody pharmaceuticals has, however, not been straight forward. This is because the behavior of antibodies seems to vary, *even though they have similar structures*." Despite acknowledging the similarity in structures, Wang 2007 repeatedly states that the differences among antibody sequences

> affect the stability of antibody pharmaceuticals . . . . Finally, Wang 2007 concludes that one of the "major issues in antibody formulation [that is] apparently challenging and need[s] significant attention in the coming years [includes] development of stable high concentration formulations.". . . Taken together, we are not persuaded that structural similarity of 95% amongst IgG_1 antibodies necessarily means a person of ordinary skill in the art would have expected all IgG_1 antibodies to behave similarly. Nor, for similar reasons, are we persuaded that Petitioner has shown sufficiently that a person of ordinary skill in the art would have had a reasonable expectation of success in formulating a stable, liquid, high concentration D2E7 [adalimumab] formulation, as required by the claims.

Coherus IPR, Paper 12 at 3-4 (Decision Denying Request for Rehearing) (Feb. 2, 2017) (citing Ex. 2047, 5, 14, 21) (citations omitted; emphasis in original). The Board in the *Coherus* IPR was not alone in reaching the conclusion that one would not have a reasonable expectation of success in attempting to formulate one antibody based on formulations designed for different antibodies. *See*, *e.g.*, *Amgen, Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2015-01514, Paper 9 (Decision Denying Institution) (P.T.A.B. Jan. 14, 2016); *Amgen, Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2015-01517, Paper 9 (Decision Denying Institution) (P.T.A.B. Jan. 14, 2016).

2. Petitioner fails to establish that all IgG antibodies have "highly similar" buffering capacities

Petitioner alleges that the total number of contributing charged amino acid residues that create buffering capacity is relatively constant for a given class of monoclonal antibodies. (Pet., 40 (quoting Ex. 1004, 3:1-8; citing Ex. 1003, 1:3-5).) Petitioner further alleges that Gokarn PCT teaches that different antibodies within the IgG class would have similar buffering capacity because of "the substantial identity of amino acid sequences and tertiary structures across all IgG antibodies." (*Id.*) But the contemporaneous scientific literature contradicts these assertions.

Petitioner focuses on the similarity among the constant regions of human IgG antibodies, while omitting the contribution to buffer capacity of the variable regions. (Pet., 8.) Yet the variable regions make up a substantial portion of the antibody and contain the most sequence diversity. (*See* Ex. 2047, 5 ("The variable (V) regions of both [heavy and light] chains cover approximately the first 110 amino acids [and the] N-terminal sequences of both the heavy and light chains vary greatly between different antibodies.")

Because the buffering capacity of any particular antibody is mainly attributed to its solvent-exposed amino acid residues, differences in amino acid sequences, particularly in the binding regions, are important. (Ex. 2021, 690; Ex. 2041, 3062.) As explained in Gokarn PCT, this is one of the reasons empirical

measurements of protein buffer capacities are preferred. (Ex. 1003, 36:10-14.) Petitioner ignores these differences in solvent-exposed residues and thus fails to establish that one skilled in the art would have expected different antibodies within the IgG class to have similar buffering capacities.

Petitioner also fails to account for structural differences between the exemplified antibodies in Gokarn PCT and adalimumab that could affect key properties of the antibody in an aqueous formulation. By the time of the invention, it was known that small changes in antibody amino acid sequence could significantly affect a given formulation. (*See, e.g.,* Ex. 2047, 14, 21 ("Due to the significant difference in the primary sequence among different antibodies, the relative severity of . . . degradation pathways can be significantly different."); *see also* Ex. 2027, 2079.) A 2006 article stated that because of differences in amino acid sequences, the interfacial surface of each antibody drug is unique, meaning that formulations for one antibody cannot reasonably be expected to be successfully applied to other antibodies. (Ex. 2021, 690.) As explained in Wang 2007, an excipient suitable for one antibody may not be suitable for another because of differences in their sequences. (*See, e.g.,* Ex. 2047, 14, 21; Ex. 2028, 271 (suitable formulation conditions "cannot be determined from [an antibody's] amino acid sequence").)

For at least these reasons, one of ordinary skill would not have had a reasonable expectation of success in obtaining the claimed adalimumab formulations based on Gokarn PCT's formulation of antibodies other than adalimumab.

3. Petitioner fails to address the potential consequences of removing HUMIRA's buffering system

Petitioner argues that it was desirable to remove an "extraneous buffering system," relying on Gokarn PCT for the proposition that a buffering system would be unnecessary for HUMIRA. (Pet., 40-41.) But Petitioner fails to address the consequences of eliminating HUMIRA's buffering system.

Buffers were known to affect protein formulations in ways beyond simply maintaining pH. (*See*, *e.g.*, Ex. 2009, 1939 ("[U]nusually high viscosity [results from] concentrated monoclonal antibody in low ionic strength buffers" that can have "a major impact on important pharmaceutical properties.").) Indeed, removing the buffering system from a protein formulation could change the chemistry, stability, and physical characteristics of the overall formulation. (*See*, *e.g.*, Ex. 2033, 9690, 9691; Ex. 2034, 420, 422; Ex. 2035, E3; Ex. 2036, 1581; Ex. 2038, 9871.) *See Nichia Corp. v. Everlight Ams., Inc.*, Nos. 2016-1585/-1618, 2017 WL 1521595, at *7 (Fed. Cir. Apr. 28, 2017) (affirming nonobviousness where "artisans in this field face myriad design challenges because small design changes

may cause unpredictable results and because design considerations often pull in multiple directions"). For example, "there are cases where conditions that minimize chemical degradation foster physical damage and vice versa." (Ex. 2039, 969 (internal citations omitted); *see also, e.g.*, Ex. 2013, 110 ("[S]ometimes there are conflicting conditions (e.g., pH) needed to slow sufficiently multiple degradation pathways in aqueous solution."); Ex. 2001, 164.)

Only with improper hindsight, therefore, would one of ordinary skill have had any reasonable expectation of success. One would not have reasonably predicted the effects of eliminating the buffering system from the HUMIRA formulation, which could negatively affect the overall formulation (*e.g.*, cause aggregation or cloudiness). Thus, Petitioner has not established a reasonable expectation of success in achieving the claimed aqueous adalimumab pharmaceutical formulations without a buffering system.

4. The cited references do not disclose adalimumab's buffer capacity

Petitioner asserts that one would have concluded from Gokarn PCT and the HUMIRA Label that 50 mg/ml of adalimumab without an additional buffer could maintain pH of 5.2 during storage. (Pet., 2, 41.) This assertion is unsupported, especially because the cited references do not disclose the buffer capacity of adalimumab, and Petitioner fails to calculate or otherwise establish that one would

have expected the buffer capacity of adalimumab to be high enough to "self-buffer" at the claimed concentrations.

Gokarn PCT states that for a protein to be "self-buffering" it must provide sufficient buffer capacity to maintain pH. (Ex. 1003, 27:4-7.) It states that it is therefore important to determine a protein's buffer capacity when developing a "self-buffering" protein formulation. (*Id.*, 28:12-13, 37:21-23 ("It is a particular aspect of the invention to determine the buffer capacity of proteins as a function of concentration in solution.").) Gokarn PCT also discloses that buffer capacity depends, in part, on protein concentration. (*Id.*, 37:21-23.)

Gokarn PCT emphasizes that protein buffer capacity cannot be estimated accurately based on amino acid sequences but must be *empirically* determined. (Ex. 1003, 38:10-14, 36:10-14.) In particular, Gokarn PCT explains that none of the methods for estimating the buffer capacity of a given protein is "complete or entirely accurate." (*Id.*, 39:21-25; *see also id.*, 40:9-18 ("Such estimates often will be too high, since some residues usually are sequestered in regions of the protein not accessible to the solvent, and, therefore, do not contribute to its actual buffer capacity.").) For this reason, Gokarn PCT stresses that "empirical determinations of protein buffer capacity" are preferred. (*Id.*, 40:15-18.) Even as late as 2008, a publication by Gokarn acknowledged that one of ordinary skill in the art would have understood that buffering capacity of a protein is difficult to predict and

determined by multiple factors. (Ex. 2041, 3062.) This reference states that predicting an antibody's buffering capacity is *nontrivial* and extremely resource-intensive. (*Id*.)

Despite Gokarn PCT's emphasis on the importance of empirically determining a protein's buffer capacity when developing a "self-buffering" protein formulation, it does not disclose the buffer capacity of adalimumab or of most of the vast number of potential proteins disclosed. Petitioner also fails to identify (or even estimate) the buffer capacity of adalimumab or establish that a skilled artisan would have expected that buffer capacity to be high enough for adalimumab to "self-buffer" at the claimed concentrations. Petitioner's assertion that one would have expected that adalimumab could "self-buffer" is therefore unsupported.

Finally, even if one of ordinary skill in the art could determine a protein's buffer capacity that does not mean that one would arrive at an antibody concentration of 50-200 mg/ml. For example, the provisional application leading to Gokarn PCT discloses solutions involving a monoclonal antibody called "EMAB." (Ex. 1004, 4-5.) Although the applicant attempted to predict by extrapolation EMAB's buffer capacity, its EMAB formulations became cloudy at concentrations less than 50 mg/ml. (*Id*., 4-5, 8-12.) Neither Petitioner nor its declarants address the inability to formulate this monoclonal antibody at a concentration higher than 46 mg/ml.

Because Petitioner failed to prove any reason or motivation to remove HUMIRA's buffering system, much less provide the requisite evidence to support its claim that one of ordinary skill would have had a reasonable expectation of success in doing so, the Board should not institute Ground 2.

VII. Conclusion

Petitioner fails to show that Gokarn PCT anticipates any challenged claim or that any challenged claim would have been obvious over Gokarn PCT in view of the HUMIRA Label. For these reasons, the Petition fails to establish a reasonable likelihood that any challenged claim is unpatentable. The Board should therefore deny institution of the Petition.

Dated: June 11, 2017

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

I, the undersigned, certify that the above Preliminary Response to Petition complies with the applicable type-volume limitations of 37 C.F.R. § 42.24(b)(1). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a), this Preliminary Response, including footnotes, contains 9,621 words, as counted by the word count function of Microsoft Word. This is less than the limit of 14,000 words as specified by 37 C.F.R. § 42.24(a)(1)(i).

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that I caused to be served on the counsel for Petitioner a true and correct copy of the foregoing Patent Owner's Preliminary Response by electronic means on June 11, 2017 at the following email addresses of record:

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