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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 IPR2017-01009
U.S. Patent No. 9,085,619

PATENT OWNER'S PRELIMINARY RESPONSE

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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 a single proposed ground of unpatentability: obviousness over the *Physicians' Desk Reference* (58th ed. 2004) entry for HUMIRA ("HUMIRA Label") (Ex. 1305) in view of Fransson (Ex. 1304) and the *Physicians' Desk Reference* (56th ed. 2002) entry for the GAMIMUNE N, 5% Label ("GAMIMUNE Label") (Ex. 1307.) The Board should deny the Petition because the sole ground presented is factually unsupported and legally deficient.

First, Petitioner fails to establish that one of ordinary skill in the art would have been motivated to combine the HUMIRA Label with Fransson and the GAMIMUNE Label to generate a high concentration (50-200 mg/ml) aqueous adalimumab pharmaceutical formulation without a buffering system. The HUMIRA Label discloses a *buffered* adalimumab formulation. Although the

HUMIRA Label mentions injection site pain, there were a multitude of potential contributors to such pain, and an even larger number of potential avenues to address each one. Nothing in the HUMIRA Label or other cited references would have provided any motivation to modify the already highly successful HUMIRA formulation to address such pain by removing HUMIRA's buffering system.

Fransson makes no mention of HUMIRA. It instead reports an investigation into tolerance of subcutaneous injection site pain with *buffered* formulations of human insulin-like growth factor 1 (hIGF-1). No reason existed to combine these *buffered* protein formulations with the GAMIMUNE Label to try to arrive at a pharmaceutical formulation of adalimumab *without a buffering system*. Moreover, the GAMIMUNE Label concerned a different mixture of proteins and a different route of administration (*i.e.*, intravenous infusion, rather than subcutaneous injection) than HUMIRA or Fransson.

Second, even if combined, the cited references would not have led to the claimed invention. Critically, Fransson never discloses or suggests removing a buffering system. Rather, Fransson proposes to address injection site pain by using a different buffer, decreasing (but not eliminating) the buffer concentration, or changing the solution's pH. In fact, Fransson reports that no further reduction in injection pain was observed when the buffer concentration of the solution was decreased below a certain threshold. Fransson also points to some of the dozens of

other known potential causes of injection site pain, including injection volume, speed of injection, injection site, the size and quality of the injection needle, and other factors. Therefore, Petitioner's hindsight-driven assertion that Fransson would have motivated a skilled artisan to remove HUMIRA's buffering system is refuted by Fransson's disclosure.

Third, Petitioner fails to establish that the cited references are properly combinable or that there would have been any reasonable expectation of success in removing the buffering system from HUMIRA. Petitioner relies on GAMIMUNE as an alleged example of a pharmaceutical formulation without a buffering system. But GAMIMUNE is a *polyclonal* antisera product (a collection of immunoglobulin molecules and other proteins), which does not contain adalimumab and is administered by *intravenous infusion*. HUMIRA, by contrast, is a *monoclonal* antibody product, which contains only adalimumab and is administered by *subcutaneous injection*. Monoclonal antibodies have unique formulation challenges not shared by plasma-derived polyclonal antibody populations, such as a tendency to self-associate, particularly at high concentrations. Petitioner disregards these fundamental differences, offering no evidence that one of ordinary skill in the art would have looked to the formulation of an intravenous polyclonal antisera, such as GAMIMUNE, when formulating a subcutaneous monoclonal antibody such as adalimumab. In fact, the prior art emphasized the distinct nature

of polyclonal and monoclonal antibodies, as well as the significantly different pharmaceutical formulations used for intravenous infusions versus subcutaneous preparations.

In addition, as the Board found in prior IPR decisions, the scientific literature in 2007 was replete with evidence showing that a formulation designed for one antibody (much less a heterogeneous polyclonal antibody population such as GAMIMUNE) could not reasonably be expected to be successfully applied to a different monoclonal antibody, such as adalimumab. The positions that Petitioner advocates here regarding buffers and the state of the art also cannot be reconciled with positions it has taken before this Office in prosecuting Petitioner's own patent applications, which also purport to cover formulations of adalimumab. Thus, Petitioner does not present a viable obviousness theory.

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. The HUMIRA Label

The HUMIRA Label (Ex. 1305, 470) [1] 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. 1301, 3.) The HUMIRA Label states that adalimumab is a recombinant human IgG1 human monoclonal antibody that binds specifically to TNF-alpha. (Ex. 1305, 470.) 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.

The HUMIRA Label lists adverse events experienced in rheumatoid arthritis clinical trials, including respiratory, gastro-intestinal, laboratory testing, and

[1] 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.

"other" events, including injection site pain. (*Id.*, 472.) The only listed adverse events leading to discontinuation of HUMIRA treatment are "clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%)." (*Id.*) The HUMIRA Label states that most injection site reactions were described as mild and did not necessitate discontinuation. (*Id*.) The HUMIRA Label does not identify any cause of injection site reactions or suggest any connection with the buffering system.

2. The GAMIMUNE Label

The GAMIMUNE Label was published in *Physicians' Desk Reference* (56th ed. 2002). (Ex. 1307, 925.) It concerns the GAMIMUNE immune globulin product, approved for treating or preventing infectious diseases in patients with primary humoral immunodeficiency, idiopathic thrombocytopenic purpura, and pediatric HIV, as well as patients undergoing bone marrow transplantation. (*Id.*, 925-26.)

The GAMIMUNE Label states that GAMIMUNE is only administered as an intravenous infusion. (*Id.*, 925; *see id.*, 926 (the subcutaneous route has "not been evaluated").) An infusion "usually lasts several hours." (*Id.*, 925.) The GAMIMUNE Label states that the infusion rate may range from 0.01 to 0.08 ml/kg per minute. (*Id.*, 927.) The total administered dosage may range from 100 mg/kg to 1000 mg/kg of bodyweight. (*See id.*)

Due to the large infusions required, the GAMIMUNE Label states that doctors should carefully consider the "acid load" of a GAMIMUNE infusion. (*Id.*,

925.) The GAMIMUNE Label warns that a patient's blood will not necessarily neutralize GAMIMUNE's acid load, particularly for patients having compromised acid-base compensatory mechanisms. (*Id.*) The GAMIMUNE Label does not attribute the buffering capacity of GAMIMUNE to any particular component(s) of its formulation.

The exact composition of GAMIMUNE is not disclosed. (*See id.*, 925.) For example, the GAMIMUNE Label does not describe the presence or absence of any specific antibodies in GAMIMUNE. (*Id.*, 925-26 (similarly noting that the mechanisms of action for indicated treatments are "unknown").) Rather, it states that GAMIMUNE supplies a "broad spectrum of opsonic and neutralizing IgG antibodies for the prevention or attenuation of a wide variety of infectious diseases." (*Id.*, 925.) The GAMIMUNE Label states that GAMIMUNE is prepared by processing "large pools of human [blood] plasma" with cold ethanol fractionation. (*Id.*)

Similarly, the GAMIMUNE Label provides few details about the GAMIMUNE formulation. It states that each milliliter of GAMIMUNE contains approximately 50 mg of "protein." (*Id.*) Without identifying any of the specific proteins included, the GAMIMUNE Label states that 98% of the protein "has the electrophoretic mobility of gamma globulin." (*Id.*) Maltose is included to achieve

isotonicity. (*Id.*) The GAMIMUNE Label does not discuss including or excluding buffering systems.

The GAMIMUNE Label states that one should inspect the product "visually for particulate matter and discoloration prior to administration." (*Id.*, 927.) The percentage of monomer content of the IgG antibodies present in GAMIMUNE may be as low as 90%. (*Id.*, 925.) Potential adverse events of GAMIMUNE treatment include acute renal failure. (*Id.*, 927.)

3. Fransson

Fransson is a journal article titled "Local Tolerance of Subcutaneous Injections." (Ex. 1304, 1012.) It reports the results of a ten-subject study on how pH and buffer concentration might affect local tolerance to subcutaneous injection of solutions of hIGF-1, but says nothing about formulation or injection of antibodies, much less HUMIRA. (*Id.*, 1012-13.)

Fransson analyzes eight hIGF-1 solutions having a varying pH (6.0 or 7.0) and varying concentrations of phosphate buffer: 5 mM, 10 mM, 50 mM. (*Id.*, 1013 (Table 2 listing formulations A-H).) Fransson used phosphate buffer as an alternative to citrate, stating that "citrate buffer causes pain." (*Id.*, 1012.) Fransson also points to some of the many other known potential causes of injection pain, including injection volume, speed of injection, injection site, the size and quality of the injection needle, and other factors. (*Id.*)

Compared to the higher 50 mM phosphate-buffered solutions of hIGF-1, Fransson reports that the intermediate 10 mM phosphate-buffered solutions generated less injection pain. (*Id.*, 1014.) Further reduction to 5 mM phosphate, however, "did not reduce pain further." (*Id.*) Fransson does not disclose or suggest eliminating buffer to minimize injection pain. Fransson also reports that increasing pH reduces injection pain, with solutions at a pH of 6.0 causing more pain than those at a pH of 7.0. (*Id.*, 1014-15.)

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. 1305, 470; Ex. 2042.) 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. 1378, 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. 1378, 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. 1378, 5, 14; *see, e.g.*, Ex. 1301, 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; Ex. 2020, 612; Ex. 2026, 82.) 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. 1301, 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. 1378, 5, 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. 1301, 3:29-33.) Contrary to the traditional approaches for protein 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 formulation 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.*, 151:9-152:66.) 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 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., 22-23.)

IV. Claim Construction

Patent Owner believes 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." (Pet., 23-24.)

V. The Challenged Claims Would Not Have Been Obvious Over The HUMIRA Label In View Of Fransson And The GAMIMUNE Label

Petitioner contends that it would have been obvious to achieve the claimed adalimumab formulation without a buffering system because one of ordinary skill in the art allegedly would have been motivated to remove the citrate-phosphate buffering system from the highly successful HUMIRA formulation to avoid injection pain and eliminate "unnecessary excipients." (Pet., 2, 27, 32.) Petitioner further contends that a skilled artisan would have had a reasonable expectation of success in arriving at the claimed formulations. (Pet., 34-42.) These theories, however, are unsupported by the cited references and tainted by hindsight reasoning. Petitioner therefore fails to establish a reasonable likelihood that the challenged claims are unpatentable as obvious.

A. Petitioner Fails To Establish Any Motivation To Remove HUMIRA's Buffering System

1. Petitioner does not establish that injection site pain would have motivated one of ordinary skill in the art to eliminate the buffering system from HUMIRA

Although Petitioner asserts that the "self-buffering" capabilities of proteins were known "for decades" (*Id.*, 14, 36), as of 2007, *all* commercially available aqueous monoclonal antibody pharmaceutical formulations were provided with a buffering system. (Ex. 1378, 2-4; *see also* Ex. 2055, 852.) The same held true as late as 2015. (Ex. 2051, 94-101 (Table 4.1); *see also* Ex. 2055, 852.)

HUMIRA, for example, was initially approved in 2002 and was successfully formulated with a multi-component citrate-phosphate buffering system. (Ex. 1378, 2; *see also* Ex. 1305, 470.) Indeed, at the time of the '619 patent 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. 1378, 2-4.)

Petitioner nevertheless alleges that one of ordinary skill in the art would have been motivated to eliminate HUMIRA's buffering system because the HUMIRA Label discloses that 12% of patients in clinical trials reported injection site pain. (Ex. 1305, 472.) Petitioner further alleges that this injection site pain caused "compliance issues." (Pet., 29.) The HUMIRA Label, however, does not

identify injection site pain as an adverse event leading to discontinuation. (Ex. 1305, 472.) Rather, it states that the most common adverse events leading to discontinuation were clinical flare reaction (0.7%), rash (0.3%), and pneumonia (0.3%). (*Id*.)

Petitioner's declarant, Dr. Sherry, cites no documentary evidence of compliance issues for HUMIRA resulting from injection site pain. (Ex. 1303, ¶¶21-23 (basing opinions on what he "heard" about the "patient experience," rather than any published literature).) The Board should disregard this unsupported testimony. 37 C.F.R. § 42.65(a) (unsupported testimony is entitled to "little or no weight"); *see also TRW Auto. US LLC v. Magna Elecs., Inc.,* No. IPR2014-00258, Paper 18 at 11 (P.T.A.B. Aug. 27, 2014) (the Board has "well-established discretion to give little weight to conclusory, unsupported expert testimony"). Indeed, Petitioner offers no tangible evidence that injection site pain affected patient use of HUMIRA, one of the most successful drug products of all time. (Ex. 2042, 1.)

Accordingly, Petitioner's assertion that injection site pain would have motivated one of ordinary skill in the art to modify the highly successful HUMIRA formulation is without merit.

a. Petitioner ignores the multitude of other factors that contribute to injection site pain

Even *if* pain injection site pain was a perceived problem, contrary to Petitioner's conclusory assertion, a skilled artisan had far more than "[a]t most" two predictable solutions available to reduce such pain (*i.e.,* selecting a different buffering system or eliminating the buffering system entirely). (Pet., 31-32.) Instead, one of ordinary skill in the art would have been aware of the multitude of potential contributors to injection site pain, and the numerous potential avenues to address each one.

Fransson, for example, discloses several causes of injection pain, including injection volume, injection speed, osmolality, pH, injection site, needle size, needle quality, presence of irritating substances, and temperature. (Ex. 1304, 1012.) Brazeau 1998 lists twenty injection-pain factors, which were "by no means inclusive." (Ex. 2003, 672-73.) In fact, the art described many possible causes of injection site pain, including:

i. Intrinsic properties of the active ingredient. (Ex. 2003, 673.)

ii. High concentrations of the active ingredient. (*Id.*)

iii. Protein aggregation. (*Id.*)

iv. Greater formulation viscosity. (Ex. 2009, 1929.)

v. pH. (Ex. 1304, 1012; Ex. 1319, 218; Ex. 2049, 585; Ex. 2002, 730.)

vi. Anatomical site of injection. (Ex. 2008, 679; Ex. 1304, 1012.)

vii. Temperature at injection site. (Ex. 2005, 57; Ex. 1304, 1012.)

viii. Injection volume. (Ex. 2002, 730.)

ix. Injection technique. (Ex. 2003, 673.)

x. Speed and rate of injection. (*Id.*)

xi. Needle size and length. (Ex. 2006, 175; Ex. 1304, 1012.)

xii. Tonicity. (Ex. 2003, 673.)

xiii. Buffer concentration. (Ex. 1304, 1014.)

xiv. Preservatives. (Ex. 2002, 730.)

xv. Osmolality. (*Id.*; Ex. 1304, 1012.)

xvi. Osmolarity. (Ex. 2003, 673.)

xvii. Frequency of injection. (Ex. 1319, 218.)

xviii. Individual patient characteristics. (*Id.*)

Petitioner disregards these other known causes of injection site pain. Petitioner also ignores known effective, low-tech solutions for reducing injection pain such as applying ice to the skin. (Ex. 2005, 57 (applying ice to the skin before injection "decreases the pain perception considerably").)

Petitioner's selective focus on the buffering system of HUMIRA reflects hindsight bias and an improper obvious-to-try rationale. Where, as here, the prior art does not indicate which parameters are critical or which of many possible

choices would likely succeed, an invention is not obvious to try. *Unigene Labs., Inc. v. Apotex, Inc*., 655 F.3d 1352, 1361 (Fed. Cir. 2011); *see also BioDelivery Scis. Int'l, Inc. v. MonoSol Rx, LLC*, No. IPR2015-00167, Paper 6 at 19-20 (P.T.A.B. May 20, 2015) (denying institution of ground where prior art merely suggested varying all parameters or trying each of numerous possible choices until possibly arriving at successful result).

b. Fransson does not suggest removing a buffering system

Notwithstanding the numerous recognized causes of injection site pain, Petitioner asserts that the citrate-phosphate buffer in HUMIRA was "the most likely cause" of injection site pain reported in the HUMIRA Label. (Pet., 30-32.) Petitioner relies on Fransson's disclosure that "citrate buffer causes pain" (*see, e.g.,* Pet., 13, 30 (*citing* Ex. 1304, 1012) as allegedly motivating one of ordinary skill in the art to remove HUMIRA's entire buffering system to alleviate this pain. (*Id.*, 31-34.)

As an initial matter, Fransson was published in 1996, more than a decade before the 2007 priority date of the '619 patent. Fransson does not disclose or concern *any* antibody, much less HUMIRA, but is instead directed to solutions of a globular protein (hIGF-1). (Ex. 1304, 1012.)

Moreover, Fransson does not disclose omitting a buffering system or describe any formulation without a buffering system, which Petitioner fails to acknowledge. (*See* Pet., 26.) Rather, each of the eight solutions Fransson tested *contained phosphate buffer* in varying concentrations. (Ex. 1304, 1013.) Petitioner attempts to read more into Fransson than it actually discloses, using the challenged claims as a template to reconstruct the invention with improper hindsight. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1354 (Fed. Cir. 2013) (reversing obviousness determination as improperly based on hindsight). Fransson cannot motivate what it does not disclose. *Redline Detection, LLC v. Star Envirotech, Inc.*, 811 F.3d 435, 453 (Fed. Cir. 2015) (affirming nonobviousness because one of ordinary skill in the art would not have looked to a reference teaching use of an inert gas to modify another reference requiring the presence of oxygen).

Instead of removing a buffer, Fransson *uses a buffer* (specifically, sodium phosphate) in *all* of its disclosed solutions. (Ex. 1304, 1013.) Petitioner's focus on Fransson's limited discussion of citrate buffers ignores Fransson's express endorsement of sodium phosphate, one of the buffers used in HUMIRA. (Ex. 1305, 470.) Petitioner does not (and cannot) explain why Fransson would have motivated one of ordinary skill in the art to *remove* the very buffer that Fransson *used*. Moreover, Fransson's mention of pain caused by a *citrate* buffer does not suggest any motivation to entirely remove the two-component (*phosphate and citrate*)

buffering system from AbbVie's highly successful, FDA-approved HUMIRA product.

Petitioner argues that Fransson's suggestion to keep buffer strength "*as low as possible*" suggests eliminating HUMIRA's buffering system. (Pet., 30-31 (emphasis in original).) But Fransson's disclosure does not support this assertion. Fransson discloses that an intermediate buffer concentration (10 mM) minimizes injection pain, and that *continuing to lower the concentration provides no further benefit*. (Ex. 1304, 1013-14 (reporting decreased injection pain when lowering buffer concentration from 50 mM to 10 mM, but no further reduction in pain when further lowering buffer concentration to 5 mM).) Fransson's disclosure that no additional benefit is achieved when reducing phosphate buffer concentration below a particular threshold refutes any alleged motivation to *eliminate* HUMIRA's citrate-phosphate buffering system.

Petitioner does not even establish that Fransson would have motivated a person of ordinary skill in the art to *reduce* the phosphate component of HUMIRA's buffering system. Petitioner does not evaluate how HUMIRA's citrate-phosphate buffering system compares with the 50 mM, 10 mM, or 5 mM sodium phosphate buffer concentrations in the Fransson solutions. Thus, Petitioner does not demonstrate that Fransson would have guided or motivated one to reduce

the phosphate concentration of HUMIRA's buffering system, much less remove the entire citrate-phosphate buffering system altogether.

c. Other buffering systems were not known to be associated with injection site pain

Petitioner also does not establish that one of ordinary skill in the art would have eliminated the citrate-phosphate buffering system of HUMIRA instead of choosing a different buffering system. As discussed above, for example, Fransson proposed substituting a phosphate buffering system—*i.e.,* one of the buffer components of HUMIRA—instead of a citrate buffering system. (Ex. 1304, 1012.) Other studies similarly advised replacing citrate buffer with phosphate buffer to reduce pain. (*See, e.g.,* Ex. 1319, 219; Ex. 2011, 41; Ex. 2012, 341.) Histidine, a known alternative to citrate buffers, was associated with no pain on injection. (*See, e.g.,* Ex. 1316, 299; Ex. 1319, 218.)

In addition to suggesting buffer *substitution* instead of *removal*, the literature downplayed the connection between buffering systems and injection site pain. For example, while comparing citrate- and phosphate-buffered epoetin-alpha (EPO) solutions, Veys *et al.* noted the limitations of adjusting buffer systems to address pain: "the presence of citrate . . . is not the only culprit of local discomfort." (Ex. 2011, 44.) Accordingly, the scientific literature does not support Petitioner's heavy

reliance on alleged buffer-related injection pain to justify eliminating the buffering system from the highly successful HUMIRA formulation.

Notably, Petitioner's own declarant admits that subcutaneous injections of phosphate-buffered protein preparation were "rarely described as being particularly painful" and instead were "largely attributed to the injection itself (i.e., the needle stick)." (Ex. 1303, ¶26.)

d. "Buffer-free" formulations cited by Petitioner cause injection site pain

Petitioner contends that commercially available human plasma-derived immunoglobulin products were formulated at high concentrations without a separate buffering system. (*See, e.g.,* Pet., 38-40; Ex. 1302, ¶¶47-48, 101-03 (citing Exs. 1307, 1309, 1323, 1332, 1339, 1349-1354).) As an initial matter, Petitioner does not show that any of these products are similar to HUMIRA. None of them is a monoclonal antibody product like HUMIRA, and HUMIRA is administered by subcutaneous injection (Ex. 1305, 470) whereas the cited products are generally administered using either intramuscular injections or, more commonly, lengthy intravenous infusions. (*See, e.g.,* Ex. 1307, 925; Ex. 1323, 558, 805, 914-19; Ex. 1351, 1; Ex. 1339, 872; *see also infra* Section V.B.1.)

Moreover, the labels for these allegedly "buffer-free" products describe *pain on injection* and other injection site reactions. The NABI-HB label, for example,

reported that 12% of patients had local pain associated with administration—the same percentage as HUMIRA. (Ex. 1323, 2296; Ex. 1305, 472.) IMOGAM RABIES had "*tenderness, pain, soreness* or stiffness of the muscles [that] may occur at the injection site." (Ex. 1323, 806)[2]; *see also* VIVAGLOBIN (Ex. 1349, 7 (reporting that 92% of subjects had "adverse events at the injection site")); RHOGAM (Ex. 1323, 2524 ("swelling, induration, redness and mild *pain* at the site of injection")); BAYGAM (*Id*., 915 ("*pain and tenderness* at the injection site")); BAYHEP B (*Id*., 916 ("*pain and tenderness* at the injection site")); BAYRAB (*Id*., 918 ("*[s]oreness* at the site of injection")); BAYRHO-D (*Id*., 922 ("*soreness* at the site of injection")); BAYTET (*Id*., 924 ("*soreness* at the site of injection")); and GAMMAGARD LIQUID (Ex. 1351, 3 (indicating that infusion site events occurred in 13.1% of the subjects).)

Petitioner does not explain why one of ordinary skill would have removed the buffering system of HUMIRA instead of pursuing the plethora of possible ways to address injection site pain, particularly when these allegedly "buffer-free" commercial products failed to solve the alleged problem of injection site pain.

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

2. Petitioner fails to show that regulatory or processing cost concerns would have motivated one skilled in the art to remove HUMIRA's buffering system

Petitioner asserts that regulatory authorities "expect exclusion of unnecessary excipients." (Pet., 32.) Petitioner fails to prove, however, that this would have motivated one skilled in the art to remove *any* particular excipient—much less the buffering system—from the *FDA-approved* and highly successful formulation of HUMIRA. (Ex. 1311, 1, 3.) Consistent with the Gokarn textbook chapter quoted by Petitioner (Pet., 32), the safety and tolerability of HUMIRA's buffered formulation was already established through development studies, resulting in its FDA approval. (*See* Ex. 1311, 1-3.) As discussed in Section V.B.3 below, Petitioner fails to prove that HUMIRA's buffering system was "unnecessary" or "extraneous" (Pet., 34) such that one would have been motivated to remove it. (*See also, e.g., infra* Section V.A.3. & V.B.1.) Indeed, given this alleged expectation that only appropriate excipients will be included, the FDA's approval of HUMIRA as a buffered formulation suggests that a buffering system was viewed as "*essential* in imparting a desired pharmaceutical effect (*i.e.,* stability or delivery)." (Pet., 32 (emphasis in original) (quoting Ex. 1316, 294-295).) Petitioner's argument is also contradicted by the regulatory approval of dozens of other liquid monoclonal antibody products in *buffered* solutions. (Ex. 2051, 94-101 (Table 4.1); *see also* Ex. 2055, 852.)

Petitioner also argues that eliminating HUMIRA's buffering system would "simplify manufacturing and quality control processes." (Pet., 34.) The Petition does not cite any evidence, however, concerning HUMIRA's manufacturing or quality control processes. (*Id.*; *see also* Ex. 1302, ¶92.) Dr. Radtke's assertions regarding "cost savings" are not specific to HUMIRA and should therefore be disregarded as conclusory and unsupported. (Ex. 1302, ¶92); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) (a lack of objective support for expert opinion may render the testimony of little probative value). Petitioner and Dr. Radtke also fail to account for the processing controls and manufacturing steps required to prepare a formulation *without a buffering system*. (Pet., 34; *see also* Ex. 1302, ¶92.) Thus, Petitioner's "cost savings" position is unsupported and hindsight-driven. *See, e.g., Leo Pharm.*, 726 F.3d at 1354.

Petitioner therefore has not proven that any regulatory or processing cost concerns would have motivated one of ordinary skill to remove the buffering system of HUMIRA.

3. Petitioner previously argued that one of ordinary skill would have included a buffer with adalimumab

Petitioner's arguments concerning the purported motivation to eliminate buffers from HUMIRA are also contradicted by its own prior arguments to the

Board. In a previous IPR Petition, Petitioner asserted that buffers *should be included* in formulations of adalimumab because they maintain the solution pH and affect 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; *see also id.*, ¶¶103, 107, 149, 156, 166, 170.)

And while Petitioner now attempts to 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. Nos. 2016/0039926 and 2016/0031982) or *citrate*-buffered (*see, e.g.,* U.S. Pat. Pub. No. 2016/0031982).

Accordingly, Petitioner fails to establish that HUMIRA's injection site pain would have motivated one of ordinary skill in the art to entirely remove the buffering system from HUMIRA. For at least this reason alone, institution should be denied.

B. Petitioner Fails To Demonstrate A Reasonable Expectation Of Successfully Formulating Adalimumab Without A Buffering System

Petitioner also fails to establish that one of ordinary skill would have had any reasonable expectation of success of obtaining an aqueous adalimumab pharmaceutical formulation at a concentration of 50-200 mg/ml without a buffering system, as claimed in the '619 patent.

1. One of ordinary skill in the art attempting to improve the HUMIRA formulation would not have looked to the GAMIMUNE Label for guidance

Petitioner asserts that "[a] POSA would have looked to . . . existing high-concentration IgG products when formulating a high-concentration monoclonal antibody like adalimumab" and would have specifically turned to the GAMIMUNE Label. (Pet., 4.) HUMIRA comprises a recombinantly produced

monoclonal antibody, adalimumab (Ex. 1305, 470.) GAMIMUNE comprises a heterogeneous mixture of many different antibodies (termed "polyclonal") and other proteins derived from pooled human sera. (Ex. 1307, 925.)

These products are so different that any alleged connection is pure hindsight. Indeed, Petitioner's declarant identifies no supporting documentation for the assertion that one would look to the GAMIMUNE Label or understand, without any supporting calculations or analysis, that GAMIMUNE and adalimumab would have similar buffer capacities. (Pet., 4 (citing Ex. 1302 ¶¶100-101, 106); *see* Ex. 2041, 3062 (Gokarn publication stating that, even as of 2008, calculating an antibody's buffering capacity was *nontrivial* and extremely resource-intensive).)

a. GAMIMUNE and HUMIRA have different dosages and routes of administration

GAMIMUNE and HUMIRA have different dosages and routes of administration that uniquely impact formulation considerations. GAMIMUNE is administered by intravenous infusion at a dose of 100-1000 mg/kg bodyweight, which equals *120-1200 ml* 5% GAMIMUNE for a 60 kg patient. (Ex. 1307, 925-27.) By contrast, the HUMIRA formulation is administered subcutaneously at a dose of 40 mg in a *0.8 ml* volume. (Ex. 1305, 470, 472.) Accordingly, a 60 kg patient receiving GAMIMUNE potentially receives an infusion of *over one liter*

(1200 ml) of GAMIMUNE—a *1500-fold increase* in volume over the 0.8 ml amount of the HUMIRA formulation.

Petitioner ignores the formulation considerations required by such different administration volumes. For example, the GAMIMUNE Label cautions that the high volumes of its product impose a significant acid load on patients. (Ex. 1307, 925 ("In patients with limited or compromised acid-base compensatory mechanisms, consideration should be given to the effect of the additional acid load Gamimune N, 5% might present.").) In contrast, the HUMIRA Label does not mention acid load, and Petitioner offered no evidence to show such a concern existed with HUMIRA.

Nevertheless, Petitioner simply assumes that one of ordinary skill would have "ideally" removed the "extraneous" buffering system of HUMIRA based on the problem of acid load with GAMIMUNE. (Pet., 33-34.) This problem of acid load is one of Petitioner's own making, stemming from its impermissible hindsight choice of the GAMIMUNE Label, not from what was known in the art about HUMIRA. Indeed, the prior art illustrates that such a concern would not exist at the low volume administered to a patient with the HUMIRA formulation. (*See, e.g.,* Ex. 1316, 297 (comparing intravenously and subcutaneously administered formulations and stating that "[f]or formulations that are administered by direct IV infusion, the total amount of buffer (and any other formulation component) needs

to be monitored.").) Petitioner fails to explain how this particular concern for GAMIMUNE would have possibly applied to HUMIRA. Thus, any attempts to extend the GAMIMUNE Label to adalimumab at a high concentration without a buffering system are without merit.

Petitioner admitted as much to this Office during prosecution of its own patent portfolio. In prosecuting a patent application directed to formulations of adalimumab filed in 2012, *nearly five years after* the earliest priority date of the '619 patent, Petitioner recently argued that a publication directed to formulations of different (non-adalimumab) antibodies did not apply to its claimed formulations of adalimumab:

> [WO 1996/056418 to Lam] is not directed to adalimumab formulations, nor does it even mention adalimumab . . . . *Since WO '418 discloses different formulations for different antibodies, it does not support the Office Action conclusion "the antibody formulation of the '418 publication is suitable for any antibodies."*

(Ex. 2043, 5; *see also* Ex. 2044, 3; Ex. 2045, 6 ("Zolton teaches immunoglobulins in general, which would not lead [one of ordinary skill in the art] to combine the teachings of Zolton with those" relating to adalimumab).)

Petitioner's representations to the Office contradict its position here, and Petitioner cannot have it both ways. The GAMIMUNE Label discloses a different formulation for a different mixture of plasma-derived polyclonal antibodies,

intended to be administered via a different (intravenous) route of administration and in vastly different volumes. Therefore, Petitioner's assertion that one would have looked to such plasma-derived IgG products when formulating high-concentration monoclonal antibodies like adalimumab is without merit. (Pet., 4, 35.)

b. Monoclonal antibodies like HUMIRA present complicated and unpredictable formulation challenges not found with plasma-derived polyclonal antibody populations like GAMIMUNE

Monoclonal antibody formulations have unique formulation challenges not shared by heterogeneous population of plasma-derived polyclonal antibodies. (*See*, *e.g.*, Ex. 2054, 6.) As compared to polyclonal antibodies, monoclonal antibodies were known to be more sensitive to changes in pH and salt concentration. (*See, e.g.,* Ex. 2050, 261 ("PAbs are also more stable over a broad pH and salt concentration, whereas MAbs can be highly susceptible to small changes in both.").)

Monoclonal antibodies tend to self-associate, especially at high concentrations. (*See*, *e.g.,* Ex. 1378, 9 ("Increasing the concentration of antibodies often increases the aggregation tendency of the protein."); Ex. 2009, 1939 (Monoclonal antibody "self-association can have a major impact on important pharmaceutical properties.").) Self-association can result in high viscosity formulations that pose a challenge especially for subcutaneous administration. (Ex. 2009, 1929 ("High viscosity of a protein formulation can also make it more

difficult to administer the protein drug by injection, particularly for SC delivery.").) High viscosity due to self-aggregation of monoclonal antibodies was known to result from reducing the ionic strength or buffer in the formulation. (*Id.*, 1939.) To successfully minimize protein aggregation and stabilize the protein against attractive intermolecular forces, the prior art taught one of ordinary skill in the art to vary ionic strength, pH, and buffer type. (Ex. 2016, 1333.)

One of ordinary skill in the art would not have considered a formulation strategy that was used for the polyclonal antibodies of GAMIMUNE to be "suitable for a wide variety of high concentration IgG antibodies, including adalimumab," as Petitioner contends. (*See* Pet., 35.) In fact, one would not have looked to a formulation for *any* polyclonal antibodies, much less GAMIMUNE, with a reasonable expectation of successfully applying it to *any* monoclonal antibody formulation, much less adalimumab, because the skilled artisan would have appreciated the additional risk of reducing ionic strength in promoting monoclonal antibody self-association and in increasing the viscosity of the formulation. (*See also* Ex. 1302, ¶29 (acknowledging that the buffering system in the HUMIRA formulation constitutes ionic excipients).)

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

Notwithstanding the distinct properties and formulation challenges associated with monoclonal antibodies, Petitioner fails to address the recognized unpredictability in attempting to apply a formulation from one antibody to another. (*See, e.g.*, Ex. 2021, 690.) Accordingly, Petitioner fails to establish that one of ordinary skill would have reasonably expected to succeed in preparing a high concentration aqueous pharmaceutical formulation of adalimumab without a buffering system based on the GAMIMUNE Label and the other cited references.

Indeed, in 2007, there was general consensus in the art that a formulation that worked for one monoclonal antibody, *much less* a polyclonal antibody product such as GAMIMUNE, would *not* be predicted to work for another monoclonal antibody, such as adalimumab. For example, the Wang 2007 review article (Ex. 1378) 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.

(Ex. 1378, 5.)

Rather, Wang and others explained that each antibody 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 assumptions by Petitioner and its declarant that "sequence and structural similarity" among IgG antibodies would lead to similar buffering capacities and formulation requirements are unsupported. (Pet., 36-37; Ex. 1302, ¶¶33-36); 37 C.F.R. § 42.65(a); (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.)

Accordingly, to produce a formulation for a particular antibody, one had to identify the appropriate ionic strength, pH, and buffer type so as 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 monoclonal antibody formulations suffered from problems such as aggregation, which were more likely to occur as the antibody concentration increased. (*See*, *e.g.,* Ex. 1378, 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 ("increasing 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 be "self-buffering" at high concentrations. (Pet., 3, 14, 36.) Petitioner therefore does not establish any reasonable expectation of success in obtaining an adalimumab formulation without a buffering system at 50 mg/ml.

Petitioner also attempts to distinguish the Board's earlier decision in IPR2016-01018, which recognized that a formulation for one antibody would not have reasonably been expected to succeed for a different antibody, adalimumab. (Pet., 44-45); *Coherus* IPR, Paper 10 (Decision Denying Institution) (P.T.A.B. Nov. 7, 2016); *Coherus* IPR, Paper 12 (Decision Denying Request for Rehearing) (P.T.A.B. Feb. 2, 2017). Petitioner argues that the state of the art in the earlier

Coherus IPR was "very different" because the challenged patent was effectively filed in 2002, five years before the '619 patent's 2007 priority date. (Pet., 44.) In denying Coherus's Request for Rehearing, however, the Board relied on the same Wang 2007 reference discussed above, which is contemporaneous with the filing of the '619 patent. The Board concluded:

> Wang 2007 also states that "development 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 needs 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 (emphasis in original) (*citing* Ex. 1378, 5, 14, 21).

Here, Petitioner's proposed obviousness challenge is similar to the one denied in the earlier *Coherus* IPR. Petitioner again purports to make sweeping inferences about the entire category of IgG antibodies (including polyclonal antibodies), and then apply those inferences to one specific monoclonal antibody, adalimumab. (*See, e.g.,* Pet., 4, 35.) Petitioner's reliance on the GAMIMUNE Label's description of a heterogeneous population of plasma-derived polyclonal antibodies to try to arrive at a formulation for adalimumab, a monoclonal antibody, similarly runs afoul of the Board's finding in the *Coherus* IPR that one would not have expected all IgG1 antibodies to behave similarly. (*Id.*); *Coherus* IPR, Paper 12 at 3-4. Petitioner's current obviousness challenge merely repackages deficient theories previously rejected by the Board.

The Board in the *Coherus* IPR was not alone in reaching the conclusion that one would not have had a reasonable expectation of success in attempting to formulate one antibody based on formulations designed for different antibodies. For instance, in IPR2015-01514, the Board denied a petition filed against another AbbVie patent filed in 2002. *Amgen, Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2015-01514, Paper 9 at 15-16 (Decision Denying Institution) (P.T.A.B. Jan. 14, 2016). Citing another Wang article (Ex. 2001) containing similar teachings as Wang 2007, the Board concluded that petitioner failed to establish a reasonable expectation of success because, among other things, "structural differences among

different proteins are so significant that generalization of universal stabilization strategies has not been successful." *Id.* at 15 ("Wang suggests a high degree of *un*predictability in the antibody formulation art.") (quoting Ex. 2001, 130). The Board reached a similar conclusion in another Amgen-filed IPR, again citing Ex. 2001 and denying the petition. *Amgen, Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2015-01517, Paper 9 at 16-17 (Decision Denying Institution) (P.T.A.B. Jan. 14, 2016).

Thus, as discussed above, the scientific literature before and after the '619 patent's 2007 filing date was replete with evidence showing that a formulation designed for one antibody could not reasonably be expected to be successfully applied to a different antibody. The Board has acknowledged this fact in at least three IPR decisions denying institution.

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

Petitioner alleges that the total number of contributing amino acid residues that create buffering capacity is relatively constant for a given class of monoclonal antibodies. (Pet., 37.) Petitioner further alleges that one of ordinary skill in the art would have recognized that the proteins in GAMIMUNE would have similar buffering capacity as adalimumab because "amino acid sequences and tertiary

structure of human IgG antibodies are very similar." (Pet., 36-37.) But the contemporaneous scientific literature contradicts these assertions.

As an initial matter, while the GAMIMUNE Label describes the buffering capacity of GAMIMUNE, it does not attribute the buffering capacity to any particular component(s) of the GAMIMUNE product, nor does it purport to characterize the buffering capacity of any of the many antibodies or other proteins that GAMIMUNE contains. (*See, e.g.*, Ex. 1307 at 3 (stating that GAMIMUNE contains a "broad spectrum" of unidentified antibodies).) In fact, Petitioner fails to establish that the buffer capacity of GAMIMUNE is attributable to IgG alone, particularly given the presence of other formulation components that may also serve to buffer the solution. The GAMIMUNE Label does not disclose the exact composition of the GAMIMUNE product (Ex. 1307 at 3), and Petitioner fails to show the absence of other buffering components in GAMIMUNE. For example, while the GAMIMUNE Label states that 98% of the total protein "has the electrophoretic mobility of gamma globulin," it does not limit such proteins to IgG proteins. (*Id.*) Petitioner has not established the extent to which these remaining 2% of protein components present in GAMIMUNE contribute to its buffer capacity.

Petitioner focuses on the similarity among the constant regions of human IgG antibodies, while omitting the contribution to buffer capacity of the variable regions. (*Id.*; *see also id.*, 10-11.) Yet the variable regions make up a substantial

portion of the antibody and contain the most sequence diversity. (*See* Ex. 1378, 5 ("The variable (V) regions of both chains cover approximately the first 110 amino acids, forming the antigen-binding (Fab) regions . . . . 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. 2041, 3062.) This is one of the reasons empirical measurements of protein buffer capacities are preferred. (Ex. 1361, [0200] ("[A] complete description of the hydrogen ion equilibria of a protein in a given environment is beyond the reach of current theoretical and computational methods. Empirical measurements of protein buffer capacities, thus are preferred.").) 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 any structural differences between adalimumab and the plethora of different antibodies in the pooled plasma-derived polyclonal gamma globulin population in GAMIMUNE, much less those 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. 1378, 14, 15, 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. 1378, 14, 21; Ex. 2028, 271 (suitable formulation conditions "cannot be determined from [an antibody's] amino acid sequence.").)

For at least these reasons, Petitioner has not shown a reasonable expectation of success in obtaining the claimed adalimumab formulations without a buffering system based on the formulation of pooled plasma-derived gamma globulin polyclonal antibodies in GAMIMUNE, which are not a recombinant monoclonal antibody population like adalimumab.

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

Petitioner argues that it was desirable to remove "unnecessary excipients," relying on the GAMIMUNE Label for the proposition that a buffering system

would be unnecessary for HUMIRA. (Pet. 32-33.) However, as discussed above, HUMIRA is a single recombinantly produced monoclonal antibody, whereas GAMIMUNE is a mixture of polyclonal antibodies and other proteins derived from pooled human sera. Thus, these two products are so different that any alleged connection is pure hindsight. Moreover, Petitioner does not address the potential consequences of eliminating HUMIRA's buffering system.

Contrary to Petitioner's allegations (*see, e.g.,* Pet., 11-12), 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 a 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; *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, could there be any reasonable expectation of success. One of ordinary skill in the art 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 an aqueous adalimumab formulation that does not comprise a buffering system.

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

Petitioner and its declarant assert that one of ordinary skill would have concluded from the GAMIMUNE Label and the HUMIRA Label that 50 mg/ml of adalimumab without an additional buffer could maintain pH of 5.2 during storage. (Pet., 42 (citing Ex. 1302 ¶¶109-11).) This assertion is unsupported, especially because the cited references do not calculate or otherwise determine the buffer capacity of adalimumab. 37 C.F.R. § 42.65(a).

The importance of determining buffer capacity when developing a formulation was known. (Ex. 1361, [0150], [0158], [0204].) However, contemporaneous scientific publications made clear that protein buffer capacity

cannot be estimated accurately based on amino acid sequences but must be *empirically* determined. (*Id.*, [0215].) In particular, it was known that none of the methods for estimating the buffer capacity of a given protein was "complete or entirely accurate." (*Id.*, [0212]; *see also id.,* [0214] ("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, "empirical measurements of protein buffer capacities" were preferred. (*Id.*, [0200], [0204].)

In fact, it was known that the pKa of the amino acids that determine the buffering capacity of a protein can "*vary dramatically*" depending on the microenvironment, and that the self-buffering capacity of a protein at weakly acidic pH (pH 4 to 6) is mostly determined by solvent-accessible aspartic acid and glutamic acid residues. (*Id.*, [0209]-[0211].) But none of the cited references, Petitioner, or its experts identify (or even estimate) how many such residues are present in adalimumab (or even in GAMIMUNE as a basis for comparison), nor does Petitioner argue that such information was known or obtainable by a skilled artisan at the time of the invention.

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 the known importance of empirically determining a protein's buffer capacity when developing a self-buffering protein formulation, Petitioner and the cited references do not identify or even estimate the buffer capacity of adalimumab or establish that a skilled artisan would have expected its buffer capacity to be high enough for adalimumab to "self-buffer" at the claimed concentrations. Petitioner's assertion that one of ordinary skill in the art would have reasonably expected that adalimumab could "self-buffer" is therefore unsupported and should be disregarded. 37 C.F.R. § 42.65(a). 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. Because Petitioner failed to prove any motivation to remove HUMIRA's buffering system, much less the requisite evidence to support its claim that one skilled in the art would have had a reasonable expectation of success in doing so, the Petition's proposed grounds should not be instituted.

VI. Conclusion

Petitioner fails to establish any motivation to combine the asserted references or any reasonable expectation of success. For these reasons, and those discussed above, Petitioner fails to establish a reasonable likelihood that any challenged claim is unpatentable. The Board should therefore deny institution.

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 9,339 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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