IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ABBVIE INC. and ABBVIE BIOTECHNOLOGY LTD, Plaintiffs, v. BOEHRINGER INGELHEIM INTERNATIONAL GMBH, BOEHRINGER INGELHEIM PHARMACEUTICALS, INC., AND BOEHRINGER INGELHEIM FREMONT, INC. Defendants.	Civil Action No. 17-cv-01065-MSG

PLAINTIFFS' OPENING CLAIM CONSTRUCTION BRIEF

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I. Introduction

This is a patent infringement action under the Biologics Price Competition and Innovation Act ("BPCIA"). Pursuant to the BPCIA, Boehringer seeks to market a biosimilar version of AbbVie's pharmaceutical product, HUMIRA®. HUMIRA® belongs to a category of drugs known as biologics, and contains the antibody adalimumab as its active pharmaceutical ingredient. Unlike traditional drugs that are manufactured by chemical synthesis, adalimumab is created in and purified from living organisms.

Adalimumab is a genetically engineered antibody that was created in the mid-1990s. Following its creation, AbbVie's scientists worked for years to obtain FDA approval for HUMIRA®. During that time, AbbVie studied adalimumab in the lab and in the clinic, learning how to formulate it to remain stable during storage and use, how to administer it to be both effective and convenient, and how to manufacture it in quantities sufficient to treat thousands. The clinical and lab work did not end on approval. AbbVie continued its research and investment, ultimately discovering how adalimumab could be used to treat more than a dozen conditions. The manufacturing work continued as well, with AbbVie developing, studying, and learning how to make millions of doses consistently, to supply HUMIRA® to patients around the world. As a reward for its many years of research and investment AbbVie has been granted dozens of patents. The patents claim inventions concerning how to make adalimumab, how to effectively use it in different diseases, and how to formulate it in useful and stable form. But AbbVie's patents are more notable for their strength than their numbers. Numerous companies seeking to sell biosimilar versions of HUMIRA® have sought to invalidate AbbVie's patents in *inter partes* review ("IPR") proceedings in the United States Patent and Trademark Office. Yet AbbVie has prevailed in 15 IPRs on nine patents despite the lower burden of proving unpatentability in IPR proceedings and the high success rates of petitioners in IPRs generally.

Eight of AbbVie's patents are at issue in this lawsuit. Pursuant to the BPCIA, when AbbVie received notice of Boehringer's application to make a HUMIRA® biosimilar, AbbVie provided Boehringer with a list of over 70 patents for which it believed a claim of patent infringement could reasonably be asserted (AbbVie's "3A List"). (D.I. 208, Ex. 1 Boehringer Am. Answer at ¶ 7.) However, the BPCIA gave Boehringer the ability to cap the number of patents from this list that would be subject to a lawsuit prior to Boehringer providing a notice of its intent to commercially produce a biosimilar product (which it has not yet done). 42 U.S.C. § 262(l)(5)(A). Boehringer chose to cap that number at five patents selected per side, resulting in the eight patents in suit (with two patents appearing on both parties' chosen lists of patents). (D.I. 208, Ex. 1 Boehringer Am. Answer at ¶ 7.)

After the Court-mandated process of disclosures, the parties present here two claim terms from three patents that they believe need construction by the Court. The first of those patents, U.S. Patent No. 9,272,041 ("the '041 patent"), is directed to formulations of adalimumab. The other patents involve methods of manufacturing adalimumab: U.S. Patent Nos. 9,018,361 ("the '361 patent") and 9,090,867 ("the '867 patent").

AbbVie's proposed constructions of the two terms at issue are grounded in the intrinsic evidence. The disputes have arisen from Boehringer's attempts to seek overbroad constructions that stray from how a person of ordinary skill in the art would have understood the terms in the context of these patents, presumably in an attempt to bolster its invalidity defenses. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (*en banc*) ("A court construing a patent claim seeks to accord a claim the meaning it would have to a person of ordinary skill in the art at the time of the invention.").

II. Summary of Argument

The parties seek construction of the term "stable" from the '041 patent directed to formulations of adalimumab. The term "stable" should be construed as "a formulation in which the antibody therein essentially retains its physical stability, and/or chemical stability, and/or biological stability upon storage and use as a pharmaceutical formulation" consistent with the construction given the identical term in related patents challenged by various biosimilar makers in IPR proceedings at the Patent Trial and Appeal Board ("PTAB") in the United States Patent and Trademark Office. This construction was formulated by the PTAB, after its expert analysis of the issues related to this claim term as part it its decisions rejecting petitions seeking to hold AbbVie's formulation patents unpatentable. Boehringer's construction would remove the requirement that stability be considered by reference to the drug's "use as a pharmaceutical formulation." Boehringer has not identified, nor can it, any reason to deviate from the PTAB's well-reasoned construction.

The term "Protein A" in the '361 patent and the '867 patent should be construed as a "protein containing the five IgG binding domains of native protein A." This construction corresponds to the structure of Protein A described in the '361 patent, the experiments disclosed in the '361 patent, and the commercial Protein A resins used in the '361 patent. In contrast, Boehringer's purely functional construction ("protein used for . . .") is overbroad, ambiguous, and inconsistent with the disclosure of the patents.

III. Legal Standard

The construction of patent claim terms is a question of law. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996). The Court must focus primarily on the intrinsic evidence of record, which consists of the claims, the patent specification, and the prosecution history. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576,

1582 (Fed. Cir. 1996). Claim terms "are generally given their ordinary and customary meaning" and must be read in the context of the patent specification, which is the "primary basis for construing the claims" and is usually "the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315 (citations omitted). In addition to the specification, "the prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution." *Id.* at 1317.

IV. U.S. Patent No. 9,272,041: "Stable"

A. The '041 Patent

The '041 patent belongs to a family of related patents (the "Krause Patents") concerning formulations of adalimumab, all of which claim priority to an application filed in 2002 and share the same specification. The claims of the '041 patent each recite a "stable liquid aqueous pharmaceutical formulation" containing certain ingredients. Claim 1 reads as follows:

> 1. A ***stable*** liquid aqueous pharmaceutical formulation comprising
> (a) a human IgGl anti-human Tumor Necrosis Factor alpha (TNFα) antibody at a concentration of 50 mg/ml,
> (b) a polyol,
> (c) a polysorbate, and
> (d) a buffer system comprising acetate and having a pH of 4 to 8,
> wherein the antibody is D2E7, and
> wherein the formulation is suitable for subcutaneous injection.
>
> (D.I. 245-3, '041 patent at 39:11-22 (emphasis added).)

The formulations in the Krause Patents were revolutionary at the time the priority application was filed. While other commercial injectable formulations for antibodies were known in 2002, they were either lower concentration or lyophilized (freeze-dried), making them more difficult to administer and less convenient for patients, particularly those suffering from

rheumatoid arthritis with limited dexterity. (Ex. 1, Decision Denying Institution, IPR2015-01517 ("Amgen '517 IPR").) AbbVie's stable liquid formulations of adalimumab were unlike anything else on the market.

B. The PTAB's Previous Construction of "Stable" Is Correct

In prior IPR proceedings before the PTAB, three different biosimilar manufacturers—Amgen Inc. ("Amgen"), Coherus BioSciences Inc. ("Coherus"), and Sandoz Inc. ("Sandoz")—tried and failed to establish unpatentability of four other members of the Krause family (U.S. Pat. Nos. 8,802,100; 8,916,157; 8,916,158; and 9,114,166). Despite the lower burden of proof in that forum (IPRs require the challenger to show unpatentability by a preponderance of the evidence, rather than clear and convincing evidence) and despite the PTAB's application of a broader claim construction doctrine at the time (i.e., the broadest reasonable interpretation), the PTAB denied institution of ***all four*** of those petitions—that is, the PTAB found not one petition had established it was likely to succeed in proving that any claims of those patents were unpatentable. (*See* Ex. 2 Decision Denying Institution, IPR2015-01514 ("Amgen '514 IPR") and Ex. 1 Decision Denying Institution, IPR2015-01517 ("Amgen '517 IPR") (collectively, the "Amgen IPRs"); Ex. 3 Decision Denying Institution IPR2016-01018 ("Coherus IPR"); Ex. 4 Decision Denying Institution, IPR2017-01823 ("Sandoz IPR").)

In denying institution of those four prior IPR petitions, the PTAB construed the term "stable" as used in the Krause Patents and explained its rationale in doing so.

Because of the PTAB's unique technical and patent-related expertise, courts have valued its guidance in claim construction. *See, e.g., PPC Broadband, Inc. v. Corning Gilbert, Inc.*, No. 5:12-CV-0911 (GLS/DEP), 2014 WL 12599388, at *5 (N.D.N.Y. Mar. 13, 2014) ("While the court will not be bound by [the PTAB's] statements regarding claim construction, they can certainly prove informative, and thus should be carefully considered in light of the PTAB's

expertise."). In particular, PTAB constructions provided in IPR proceedings are considered intrinsic evidence. *See, e.g., Fairfield Indus., Inc. v. Wireless Seismic, Inc.*, No. 4:14-CV-2972, 2015 WL 1034275, at *5 (S.D. Tex. Mar. 10, 2015). Thus, when the PTAB's reasoning is sound, courts—including courts in this jurisdiction—have adopted the PTAB's prior construction. *See, e.g., Centrak, Inc. v. Sonitor Techs., Inc.*, No. CV 14-183-RGA, 2015 WL 9595999, at *4 (D. Del. Dec. 30, 2015) ("[W]hile not controlling, I find the PTAB's construction of this term in its decision not to institute *inter partes* review of '909 patent to be well-reasoned and persuasive."); *see also Star Envirotech, Inc. v. Redline Detection, LLC*, No. SACV 12-01861-JGB (DFMx), 2015 WL 12743875, at *6 (C.D. Cal. Apr. 30, 2015) ("Defendants have not identified anything in the intrinsic record, nor have they submitted extrinsic evidence, to show that the PTAB's reasoning is incorrect or that this Court's decision should be different from the PTAB's conclusion."); *Karl Storz Endoscopy-Am., Inc. v. Stryker Corp.*, No. 14-CV-00876-RS, 2016 WL 3597426, at *3 (N.D. Cal. July 5, 2016).

The PTAB's construction of "stable" is **"a formulation in which the antibody therein essentially retains its physical stability, and/or chemical stability, and/or biological stability upon storage *and use as a pharmaceutical formulation*."** (Ex. 3 Coherus IPR at 6 (emphasis added); Ex. 4 Sandoz IPR at 9; *see also* Ex. 1 Amgen '517 IPR; Ex. 2 Amgen '514 IPR.) This PTAB construction remained substantially the same throughout all four IPR proceedings. It was (and remains, in this proceeding) AbbVie's proposed construction.[1]

In rendering its construction of "stable," the PTAB focused on the specification's

[1] The PTAB determined that as of August 16, 2002, a person of ordinary skill in the art would have had a Pharm.D. or Ph.D. in biology, biochemistry, or chemistry and at least two years of experience preparing stable formulations of therapeutic protein drugs. (Ex. 4 Sandoz IPR at 7; *see also* Ex. 3 Coherus IPR at 4.) AbbVie agrees with this level of ordinary skill in the art.

definition. (*See* D.I. 245-3, '041 patent at 7:26-28.) The PTAB adopted the phrase "and use as a pharmaceutical formulation," explaining that the phrase clarifies that stability should be considered in the context of the formulation's intended use. (*See* Ex. 2 Amgen '514 IPR at 7-8; Ex. 1 Amgen '517 IPR at 7-8; *see also* Ex. 3 Coherus IPR at 6; Ex. 4 Sandoz IPR at 8-9.) The phrase "and use as a pharmaceutical formulation" also serves to exclude an erroneous interpretation of the term "stable" (proposed by Petitioner Amgen) that a "stable" formulation could be "stab[le] upon storage ***for any period of time, no matter how short***." (Ex. 2 Amgen '514 IPR at 7-8; Ex. 1 Amgen '517 IPR at 7-8 (emphasis added); *see also* Ex. 4 Sandoz IPR at 9 ("We clarified in the Coherus IPR that 'the formulation must be sufficiently stable for use when administered subcutaneously to a human.") (citing Ex. 3 Coherus IPR at 6).)

C. The Parties' Dispute

Term	AbbVie's Proposed Construction	Boehringer's Proposed Construction
"stable"	"a formulation in which the antibody therein essentially retains its physical stability, and/or chemical stability, and/or biological stability upon storage and use as a pharmaceutical formulation"	"a formulation in which the antibody therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage"

AbbVie's proposed construction for the term "stable" in this proceeding adopts in its entirety the PTAB's construction of "stable" from the related IPR proceedings for U.S. Patent Nos. 9,114,166 and 8,802,100, which share the same specification as the '041 patent. (*See* Ex. 4 Sandoz IPR at 7-9; Ex. 3 Coherus IPR at 5-6.)[2] Like Boehringer's proposed construction for "stable," the PTAB's construction draws from the definition for "stable" in the '041 patent specification. (*See* D.I. 245-3, '041 patent at 7:26-28.) But the PTAB construction further

[2] These PTAB decisions relied upon the prior decisions in the Amgen '514 IPR and Amgen '517 IPR. (*See* Ex. 4 Sandoz IPR at 7-9; Ex. 3 Coherus IPR at 5-6.)

clarifies that the formulation's stability must be retained upon both storage "and use as a pharmaceutical formulation." (*See* Ex. 4 Sandoz IPR at 7-9; Ex. 3 Coherus IPR at 5-6; *see also* Ex. 2 Amgen '514 IPR at 6-8; Ex. 1 Amgen '517 IPR at 6-8.)

The competing proposals—Boehringer, and AbbVie/PTAB—appear substantively very similar. But Boehringer proposes stripping the clarifying clause that the PTAB adopted from the construction. The PTAB explained that its construction is consistent in the context of the claim language, where the term "stable" modifies the phrase "pharmaceutical formulation." (*See* Ex. 2 Amgen '514 IPR at 7; Ex. 1 Amgen '517 IPR at 7-8; D.I. 245-3, '041 patent at Claim 1 (claiming "a stable liquid aqueous pharmaceutical formulation"); *see also IGT v. Bally Gaming Int'l, Inc.*, 659 F.3d 1109, 1117 (Fed. Cir. 2011) ("Extracting a single word from a claim divorced from the surrounding limitations can lead construction astray."); *ACTV, Inc. v. Walt Disney Co.*, 346 F.3d 1082, 1088 (Fed. Cir. 2003) ("While certain terms may be at the center of the claim construction debate, the context of the surrounding words of the claim also must be considered in determining the ordinary and customary meaning of those terms.").)

The PTAB's construction also aligns with the specification, which describes the invention of the '041 patent as a "pharmaceutical formulation" and describes the need in the art for a stable high concentration liquid formulation with an extended shelf life. (*See* Ex. 2 Amgen '514 IPR at 7; Ex. 1 Amgen '517 IPR at 7; D.I. 245-3,'041 patent at 3:16-23; *see also id.* at 3:50-6:54, 6:58-7:5, 17:48-18:7, 20:21:49-50 (describing the invention as a pharmaceutical formulation).) Prior to HUMIRA®, the only antibody formulations for commercial use at the time were either: (1) low-concentration liquid formulations, or (2) lyophilized (i.e., freeze-dried) formulations. (*See* Ex. 2 Amgen '514 IPR at 14-15; Ex. 1 Amgen '517 IPR at 15-16.) It is in this context that the '041 patent describes that there was "a need for a *stable* aqueous pharmaceutical

formulation with an extended shelf life, comprising an antibody suitable for therapeutic use which is easily administered and contains a high protein concentration." (D.I. 245-3, '041 patent at 3:19-23 (emphasis added).)

When it construed "stable," the PTAB applied the "broadest reasonable interpretation" standard. The PTAB definition is therefore the high-water mark for claim breadth. And yet Boehringer's proposal deletes the phrase "and use as a pharmaceutical formulation." To the extent Boehringer is seeking to broaden the claims, a claim construction under the *Phillips* standard required for litigation cannot be broader than the broadest reasonable interpretation. *See Facebook, Inc. v. Pragmatus AV, LLC*, 582 F. App'x 864, 869 (Fed. Cir. 2014), *reh'g denied* (Oct. 30, 2014) ("The broadest reasonable interpretation of a claim term may be the same as or broader than the construction of a term under the *Phillips* standard. But it cannot be narrower.").

AbbVie's proposed construction is tried and tested: The PTAB carefully considered this very same claim term during four prior IPR proceedings and arrived at the broadest reasonable interpretation. To the extent Boehringer seeks a construction that is arguably broader, without explaining whether it views the difference as material, AbbVie's proposed construction is more consistent with the claim language, the specification, and the state of the art, and properly anchors the requirement of stability to the reality of the field: stability, to have meaning to one of skill, must provide for the storage and use of a pharmaceutical formulation.

V. U.S. Patent No. 9,018,361: "Protein A"

A. The '361 Patent

Pharmaceutical antibodies are made in genetically engineered living cells through processes that yield a mixture of the target antibody and undesirable impurities that must be separated from the antibody before it can be administered to a patient. (*See* D.I. 245-3, '361 patent at 19:44-20:46.) One technique used to purify antibodies is called affinity

chromatography, which involves pouring the antibody mixture into a column (e.g., a tall tube that is open at the top and bottom) packed with a resin that attracts (i.e., has an affinity for) and binds the antibody while many impurities flow through the column and can be discarded. (*See id.*) To recover the antibody bound to the resin, the antibody is then eluted from the column—that is, a different solution is poured into the column that changes the chemical conditions so that the resin and antibody no longer bind, and the antibody flows through the column and can be collected and subjected to further purification. (*See id.*)

The '361 patent has an effective filing date of October 20, 2008, and is titled "Isolation and Purification of Antibodies using Protein A Affinity Chromatography." The '361 patent discloses and claims an innovative method for purifying a specific antibody, adalimumab, using a specific technique, Protein A affinity chromatography, using specific pH elution conditions. Protein A is a bacterial protein that comprises five binding domains, A, B, C, D, and E, each of which is capable of binding to a variety of different antibodies, including IgGs—the most common antibody type in humans. (Ex. 5 at 1; Ex. 6 at 637; Ex. 7 at para. [0005].)[3]

Claim 1 is the sole independent claim and recites as follows:

> 1. A process for purifying adalimumab from a fermentation harvest of a Chinese Hamster Ovary (CHO) cell culture expressing said adalimumab, said process comprising:
> a) binding adalimumab from said fermentation harvest to a ***Protein A*** resin,
> b) eluting the bound adalimumab at an elution pH of 3.6-4, and
> c) incubating the eluted adalimumab for 1 to 3 hours.

(D.I. 245-3, '361 patent at Claim 1 (emphasis added).) Claim 1 therefore requires binding adalimumab, the active ingredient in HUMIRA®, to Protein A, while many unbound impurities

[3] In its native state, Protein A also comprises domains S, X, and M. But these domains do not bind to antibodies and are typically removed for ease of recombinant production (i.e., producing Protein A in another organism). (D.I. 245-3, '361 patent at 19:58-61; Ex. 8 at 36; Ex. 7 at para. [0003]; Ex. 9 at 3.)

are washed away. Adalimumab is then separated from the Protein A (i.e., eluted) by changing the pH of the column. (*Id.*, '361 patent at 20:33-46.)

The '361 patent describes specific examples using Protein A to purify adalimumab. (*Id.*, '361 patent at 49:56-53:67 and Figures 11 & 12.) For example, the patent reports that adalimumab can be eluted from a Protein A resin under a variety of different conditions, including using an elution pH of 3.6-4. (*Id.*) The patent reports that using these conditions had benefits, including high yields and formation of few undesirable aggregates. (*Id.*)

B. The Parties' Dispute

1. Overview of the dispute

Term	AbbVie's Proposed Construction	Boehringer's Proposed Construction
"Protein A"	"protein containing the five IgG binding domains of native protein A"	"a protein used in affinity chromatography to purify antibodies, particularly IgG1, IgG2, and IgG4 antibodies, based on its ability to bind to the Fc region of those antibodies"

AbbVie's proposed construction is structural. It is based on the chemical structure of Protein A. It relies on the definition of "Protein A" provided in the '361 patent and is supported by intrinsic and extrinsic evidence. (*See, e.g.*, D.I. 245-3, '361 patent at 19:56-64 ("Protein A has five IgG binding domains.").)

Boehringer's proposed construction is functional. It is based on what Protein A may be useful for, rather than what Protein A actually is. This attempt to construe the term by what a molecule *does*, rather than what it *is*, creates needless ambiguity. For example, as explained below, there are proteins other than Protein A that *do* what Protein A does (i.e., can be used to purify antibodies) but are *not* what the '361 patent describes as Protein A. Boehringer's

construction would improperly include those proteins, in conflict with the '361 patent claims and specification.

2. AbbVie's proposed construction

AbbVie's proposed construction is consistent with the intrinsic and extrinsic evidence. The '361 patent states as follows:

> Protein A is a bacterial cell wall protein that binds to mammalian IgGs primarily through their Fc regions. In its native state, ***Protein A has five IgG binding domains*** as well as other domains of unknown function. ***There are several commercial sources for Protein A resin. One suitable resin is MabSelect™ from GE Healthcare***.

(D.I. 245-3, '361 patent at 19:58-64 (emphases added).) Thus, the patent explains that Protein A has the five IgG binding domains of native Protein A and identifies MabSelect™ as an exemplary Protein A resin. MabSelect™ contains the five IgG binding domains of native protein A. (D.I. 245-3, '361 patent at 19:60-64; Ex. 7 at paras. [0005], [0085]-[0086].) So does Poros A™, a second commercial resin identified in the '361 patent. (*See, e.g.*, D.I. 245-3, '361 patent at 19:60-64 & 51:32-33; Ex. 7 at paras. [0005], [0085]-[0086].)

All of the data reported in the '361 patent were generated using a Protein A resin that contains the five IgG binding domains of native Protein A. (D.I. 245-3, '361 patent at 49:56-53:67; Ex. 7 at paras. [0005], [0085]-[0086].) This data includes the pH elution conditions recited in claim 1 that were determined using a protein comprising the ***five*** IgG binding domains of native Protein A. The patent identifies no commercial resin containing something other than the five IgG binding domains of native Protein A, and likewise reports no data from experiments using any other resin. (*See, e.g.*, D.I. 245-3, '361 patent at 19:60-64 & 51:32-33; Ex. 7 at paras. [0005], [0085]-[0086].)

Claims should be construed to "tether the claims to what the specifications indicate the inventor actually invented." *Retractable Techs., Inc. v. Becton, Dickinson & Co.*, 653 F.3d 1296,

1305 (Fed. Cir. 2011). One of the core innovations of the '361 patent was the determination of an elution pH at which adalimumab could be effectively separated from a protein that specifically contains the five IgG binding domains of native Protein A. Protein A should be construed consistent with that innovation.

3. Boehringer's proposed construction

In contrast to AbbVie's structural construction, Boehringer proposes that Protein A should be construed to mean "a protein used in affinity chromatography to purify antibodies, particularly IgG1, IgG2, and IgG4 antibodies[4], based on its ability to bind to the Fc region of those antibodies." This construction is derived from a non-limiting discussion in the '361 patent about what Protein A may be "useful for." (D.I. 245-3, '361 patent at 19:56-58.) It would define Protein A purely by its function (rather than by its structure), and consequently encompasses other proteins or mutant proteins that are unrelated to and have different characteristics than Protein A, including those excluded by the specification.

Because Boehringer's proposed construction sweeps in every protein that has the ability to bind to the Fc region of antibodies, it would encompass other proteins that do not have the structure the '361 patent identifies for Protein A, but nonetheless are used for the same purpose as Protein A. As discussed below, Boehringer's construction would include Protein G, which is listed as a distinct alternative to Protein A in the patent; Protein LG, a distinct fusion protein; and Protein Z, a mutant protein that does not share the same five binding domains of Protein A

[4] The phrase "particularly IgG_1, IgG_2, and IgG_4 antibodies" is vague and adds nothing to Boehringer's proposed construction, as it fails to foreclose use of Protein A to purify IgG_3 antibodies or other types of antibodies. *See Paragon Sols., LLC v. Timex Corp.*, 566 F.3d 1075, 1091 (Fed. Cir. 2009) (criticizing a construction that "confuses rather than clarifies, frustrates the ability of both the patentee and potential infringers to ascertain the propriety of particular activities, and is inconsistent with the notice function central to the patent system.").

described in the patent. Each of these proteins is used in affinity chromatography to purify antibodies by binding the antibodies' Fc region. None of these proteins is what the patent describes as Protein A. Accordingly, Boehringer's overbroad construction should be rejected.

First, Boehringer's proposed construction is inappropriate because it encompasses Protein G, which is described by the patent as a distinct alternative to Protein A. Protein G was also used in affinity chromatography to purify antibodies based on its ability to bind to the Fc region of those antibodies. (*See* Ex. 10 at 49 (Proteins A and G are "[i]mmobilized bacterial surface proteins that interact with the Fc portion of IgG.") But Protein G is a different molecule, which shares "neither sequence nor structural homology" with Protein A (*id.*), was isolated from a different bacterial species than Protein A and comprises only "two or three domains that bind to the constant Fc region of most [IgGs]" (Ex. 11 at 265). The '361 patent describes that Protein A, in contrast, has *five* binding domains. (D.I. 245-3, '361 patent at 19:56-64.)

As a consequence, the '361 patent distinguishes Protein A from Protein G, listing them as distinct alternatives. (D.I. 245-3, '361 patent at 19:50-53 ("examples of such chromatographic material include: Protein A, Protein G").) "Where the specification makes clear that the invention does not include a particular feature, that feature is deemed to be outside the reach of the claims." *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1341 (Fed. Cir. 2001). Boehringer's overbroad construction, which encompasses Protein G, cannot be correct at least because it is inconsistent with the patent specification, which describes Protein A and Protein G as alternatives.

Boehringer's construction also inappropriately encompasses fusion proteins such as Protein LG that are distinct from Protein A, and engineered derivatives like Protein Z. Both of these are distinct from Protein A, but were used in affinity chromatography to purify antibodies

by binding to their Fc region. (*See* Ex. 10 at 46; Ex. 12 at 25586; Ex. 13 at 234 (Protein Z is "widely used in affinity chromatography systems. . . . [and] binds to the Fc-part of IgG from various species.").) Protein LG is an engineered protein that fuses portions of Protein G to portions of Protein L (another unrelated protein). (*See* Ex. 12 at 25583.) Protein Z is a "synthetic protein" engineered from only *one* of the five domains of native Protein A, i.e., the B domain. (*See, e.g.*, Ex. 13 at 234; Ex. 14 at 109; Ex. 15 at 3191.) Boehringer's construction would inappropriately include this distinct fusion protein and mutant protein, which are nowhere described or contemplated by the patent.

Boehringer's overbroad construction also captures ***further*** engineered derivatives of Protein Z. For example, a Superior Resistance ("SuRe") resin includes four copies of Protein Z, but does not have ***any*** of the five binding domains of native Protein A. (*See, e.g.*, Ex. 5 at 1; Ex. 16 at 1 & 24; Ex. 17 at cols. 1-5.] GE Healthcare, which manufacturers both MabSelect™ (i.e., Protein A) and MabSelect SuRe™, highlights the different structures between the two resins in its own publications. (*See, e.g.*, Ex. 5 at 1 ("The novel MabSelect SuRe ligand was developed by protein engineering of one of the IgG binding domains of protein A . . . The final construct is a tetramer [i.e., four copies] of the engineered domain [as shown in Fig. 1]"); *see also* Ex. 18 at 1-3 & 7-14.)

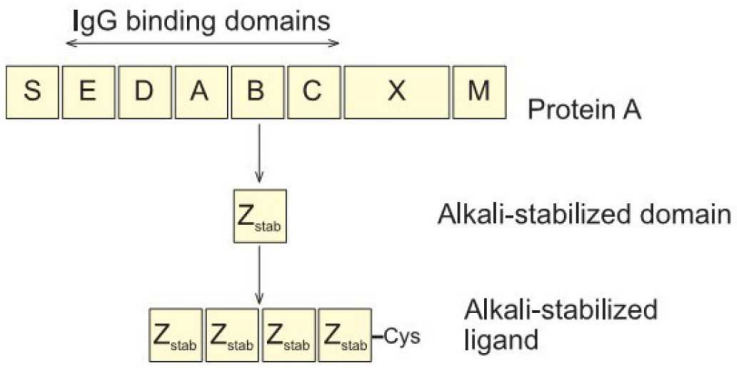

Fig 1. Site-specific mutagenesis of protein A yields an alkali-stabilized tetramer variant.

GE Healthcare Technical Note, Figure 1

As a result of its different structure, the strength of SuRe binding to and separation from antibodies is different than Protein A. (*See, e.g.,* Ex. 19 at 34; Ex. 20 at 48.) "[E]ach term must be construed to implement the invention described in the specification." *On Demand Mach. Corp. v. Ingram Indus., Inc*., 442 F.3d 1331, 1344 (Fed. Cir. 2006); *see Phillips*, 415 F.3d at 1316 (the construction that "most naturally aligns with the patent's description of the invention will be, in the end, the correct construction."). The '361 patent is directed to innovation surrounding the effective elution pH for separating adalimumab from a protein comprising five IgG binding domains of native Protein A. Adopting Boehringer's overbroad construction to encompass entirely distinct proteins, fusion proteins, and mutant and derivative proteins that have different structures and display different elution profiles than Protein A would be inconsistent with the intrinsic evidence.

Boehringer's reliance on extrinsic evidence that groups mutant and derivative proteins together with Protein A resins does not change the disclosure of the '361 patent. "Although extrinsic evidence may be useful, 'it is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence.'" *Sciele Pharma Inc. v.*

Lupin Ltd., No. 09-0037, 2011 WL 4351672, at *5 (D. Del. Sept. 15, 2011) (quoting *Phillips*, 415 F.3d at 1319).

For example, Boehringer cites to excerpts from extrinsic evidence where the term Protein A is used colloquially to refer to multiple proteins, including in particular MabSelect SuRe™. This same evidence, however, carefully distinguishes Protein A from mutant proteins with different structures and different functional properties. For example, Frey 2005 describes SuRe as a "***variant*** of Protein A with increased alkaline stability." (Ex. 21 at 558 (emphasis added).) Similarly, the GE HiTrap brochure states that SuRe is an "alkali-stabilized protein A-***derived*** ligand" that displays ***different properties*** than Protein A. (Ex. 22 at 1 (emphasis added).) Gronberg 2007 contrasts MabSelect, which contains "recombinant protein A," with SuRe, which contains "an alkali-stabilized protein A-***derived*** ligand that can withstand harsh cleaning agents." (Ex. 20 at 48 (emphasis added).) Gronberg further emphasizes that the elution profile observed with SuRe (a derivative) is different than that obtained from MabSelect (recombinant Protien A). (*Id*. ("A more generic elution for a broad range of [antibodies] has also been observed on MabSelect SuRe [than that obtained with Protein A]").) Shukla 2007 explains that SuRe is an "***engineered***" protein consisting "solely of the B domain of Protein A." (Ex. 19 at 34 (emphasis added).) This evidence confirms that "Protein A" does not encompass all proteins that perform the same function.

Boehringer may also attempt to cite statements or documents from AbbVie scientists, made outside the context of the '361 patent, that categorize derivatives such as SuRe as a Protein A. But unlike this extrinsic evidence, the '361 patent ***never*** extends Protein A to cover "variants," "derivatives," or "engineered" ligands. Indeed, the patent uses the term "Protein A" over 100 times, but ***never*** once refers to "derivatives," "mutants," "engineered proteins," or

"variants" such as SuRe. Nor does the patent mention SuRe, or any other similarly engineered resin. "Consistent use of a term in a particular way in the specification can inform the proper construction of that term." *Wi-LAN USA, Inc. v. Apple Inc.*, 830 F.3d 1374, 1382 (Fed. Cir. 2016). Boehringer's overbroad construction renders superfluous the naming convention of affinity chromatography resins altogether. Under Boehringer's proposed construction, Protein G, Protein LG, Protein Z, and SuRe are all "Protein A" even though they have radically different structures and materially different properties. The Court should reject Boehringer's litigation-inspired construction as overbroad and inconsistent with the intrinsic evidence, and instead adopt AbbVie's proposed construction of a "protein containing the five IgG binding domains of native protein A."

VI. U.S. Patent No. 9,090,867: "Protein A"

Although obtained in a separate patent family that is directed to a different invention, Boehringer contends that the term "Protein A" in dependent claims 16 and 30 of the '867 patent requires construction.

For at least the reasons explained above with respect to the '361 patent, AbbVie proposes the same construction of "Protein A": a protein containing the five IgG binding domains of native protein A. While Boehringer proposes the same, overbroad, functional construction of Protein A that it proposed for the '361 patent, the '867 patent never uses the term "Protein A" to refer to any mutated, engineered, or derivatized protein.

Boehringer's proposed construction again conflicts with the text of the patent. Like the '361 patent, the '867 patent characterizes Protein A and Protein G as distinct alternatives. (D.I. 245-3, '867 patent at 42:7-9 ("[o]ther types of affinity purification steps can be a Protein A or a Protein G column, which affinity agents bind to proteins that contain Fc domains").) Yet Boehringer's proposed construction of Protein A is so broad as to encompass Protein G.

Accordingly, the Court should adopt AbbVie's proposed construction, which is based on the structure of Protein A and supported by intrinsic and extrinsic evidence.

VII. Conclusion

For all of the foregoing reasons, AbbVie respectfully requests that the Court adopt its proposed constructions of the disputed terms in the '041, '361, and '867 patents.

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