UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

ABBOTT LABORATORIES, ABBOTT BIORESEARCH CENTER, INC., and ABBOTT BIOTECHNOLOGY LTD.,	)	**Civil No. 09-40002-FDS**
Plaintiffs/Counterclaim Defendants,	)	
v.	)	
BAYER HEALTHCARE LLC,	)	
Defendant/Counterclaim Plaintiff,	)	
BAYER HEALTHCARE LLC,	)	**Civil No. 09-40061-FDS**
Plaintiff,	)	
v.	)	
ABBOTT LABORATORIES, ABBOTT BIORESEARCH CENTER, INC., and ABBOTT BIOTECHNOLOGY LTD.,	)	
Defendant.	)	

MEMORANDUM AND ORDER ON CLAIM CONSTRUCTION

SAYLOR, J.

These are consolidated actions alleging patent infringement. The dispute involves a composition that is used in pharmaceuticals to combat autoimmune diseases—specifically, an antibody that binds to human tumor necrosis factor alpha ("TNFα"). Plaintiff Bayer HealthCare LLC holds the patent at issue; defendants Abbott Laboratories, Abbott Bioresearch Center, Inc.,

and Abbott Biotechnology Ltd. (collectively, "Abbott") manufacture an allegedly infringing product under the trade name Humira. After Bayer accused Abbott of infringing its patent, Abbott filed a countersuit for a declaratory judgment of noninfringment.

The parties' respective allegations hinge on the construction of the claims of Bayer's U.S. Patent No. 5,654,407 (the "'407 patent"). The Court conducted a *Markman* hearing with respect to the construction of claim 1, which the parties agree is the relevant claim to be construed. The claim reads as follows:

> A composition comprising human monoclonal antibodies that bind specifically to human tumor necrosis factor alpha.

Abbott and Bayer dispute all three sets of terms in this claim: (1) "composition," (2) "human monoclonal antibodies," and (3) "bind specifically to human tumor necrosis factor alpha."

I. Background

The '407 patent was filed by Bayer in 1995 as a continuation of an application filed in 1993. It is directed to certain antibodies that are designed to attach to a naturally occurring protein in the human body called tumor necrosis factor alpha ("TNFα"). TNFα is involved in regulation of the immune system, a role it performs by triggering inflammation in response to invasion by a foreign entity. Overproduction of TNFα can lead to excessive inflammation that can result in tissue damage. This occurs in diseases such as rheumatoid arthritis, Crohn's disease, and psoriasis, which are known as autoimmune diseases because of the way the body's own immune system – in this case, through TNFα – targets healthy human tissue instead of foreign contaminants.

Antibodies are proteins that target harmful foreign substances, or "antigens," such as

viruses or bacteria. Antibodies attach themselves to an antigen by binding with a portion of the antigen called an "epitope." Bayer invented an antibody that binds to TNFα. By occupying TNFα's epitopes, this antibody, which Bayer named "B5," prevents TNFα from binding to receptors in tissues where it can cause damage. This process is known as "neutralization" of TNFα.

In order for an antibody to effectively neutralize TNFα, it must attach to TNFα with sufficient strength. The strength of an antibody's interaction with an antigen is called its "affinity" for the antigen. An important quality of therapeutic antibodies is the "specificity" of the agent for a target antigen. If an antibody is not specific to its target antigen, it will bind to other proteins, which has a number of negative consequences. Among other things, the targeting of other proteins can cause unintended side effects, and reduces the number of antibodies reaching and neutralizing the actual target, thus weakening its effect.

In its specification to the '407 patent, Bayer discloses that it was successful only in producing low-affinity antibodies for TNFα that do not neutralize the protein. This was a consequence, among other things, of the fact that the inventors used a technique to produce antibodies called the "human hybridoma" method. This technique, developed in the 1970s, utilizes native human antibody-producing cells called "B cells." By exposing B cells to TNFα as an antigen, the cells would begin producing antibodies to combat it. However, this method's reliance on native B cell populations is a critical weakness that ultimately limits this technique's suitability for generating high-affinity, neutralizing anti-TNFα antibodies. Healthy humans, like other animals, generally do not possess circulating B cells that generate high-affinity, neutralizing antibodies to their own proteins. There is limited clinical use for antibodies that attach to TNFα

with only low affinity and do not neutralize it.

Genetic engineering techniques – which existed, but were essentially in their infancy, and therefore not commonplace in 1993 when the parent application of the '407 patent was filed – avoid the weaknesses of the human hybridoma methods. The most common of these techniques are phage display and transgenic mouse techniques. Both of these techniques involve splicing and recombining DNA. The resultant antibodies produced are known as "recombinant antibodies."

The allegedly infringing product, Abbott's biologic drug Humira ("biologic" refers to drugs developed using biotechnology), is created with phage display techniques and contains antibodies that exhibit high affinity and specificity for TNFα.

II. Analysis

A. Legal Framework of Claim Construction

"[T]he construction of a patent, including terms of art within its claim, is exclusively within the province of the court." *Markman v. West View Instruments, Inc.*, 517 U.S. 370, 372 (1996).

In *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005), the Federal Circuit clarified the proper approach to claim construction and set forth principles for determining the hierarchy and weight of the definitional sources that give the patent its meaning. These sources include "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Id.* at 1314 (citing *Innova Pure Water Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)).

The claims of a patent "define the invention to which the patentee is entitled the right to

exclude." *Phillips*, 415 F.3d at 1312 (citing *Innova*, 381 F.3d at 1115). The words of a claim are to be given their "ordinary and customary meaning" as a person of ordinary skill in the art in question would understand them. *Phillips*, 415 F.3d at 1312-13 (citing *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)).

In some cases, claim construction "involves little more than the application of the widely accepted meaning of commonly understood words." *Id.* at 1314. However, the Court may also look to other sources because terms may have "a particular meaning in a field of art" and patentees "frequently use terms idiosyncratically." *Id.*

One such source is the claims themselves. Because claim terms are normally used consistently throughout the patent, the meaning of the term in one claim is likely the meaning of that same term in another. *Id.* Further, a term used in another claim may help define the disputed term; for example, "the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim." *Id.* at 1314-15.

The claim should also be read "in the context of the entire patent, including the specification." *Phillips*, 415 F.3d at 1313. In other words,

> [t]he claims . . . do not stand alone. Rather, they are part of 'a fully integrated written instrument,' consisting principally of a specification that concludes with the claims. For that reason, claims 'must be read in view of the specification, of which they are a part.'

Id. at 1315 (internal citations omitted); *see Network, LLC. v. Centraal Corp*., 242 F.3d 1347, 1352 (Fed. Cir. 2001) ("[t]he claims are directed to the invention that is described in the specification; they do not have meaning removed from the context from which they arose."). Thus, "the specification 'is always highly relevant to the claim construction analysis. Usually, it is

dispositive; it is the single best guide to the meaning of a disputed term.'" *Phillips*, 415 F.3d at 1315 (citing *Vitronics*, 90 F.3d at 1582). "[T]he specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess." *Id.* at 1316.

However, reading claims "in view of their specification" generally means "using the specification to interpret the meaning of a claim," not "importing limitations from the specification into the claim"– a distinction that "can be a difficult one to apply in practice." *Id.* at 1323. "Words or expressions of manifest exclusion or explicit disclaimers in the specification are necessary to disavow claim scope." *Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1375 (Fed. Cir. 2005) (internal quotations omitted).

A patent's "claims, not specific embodiments, define the scope of patent protection." *Kara Tech. Inc. v. Stamps.com Inc.*, 582 F.3d 1341 (Fed. Cir. 2009); *see also Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363 (Fed. Cir. 2009) ("embodiments appearing in the written description will not be used to limit claim language that has broader effect.") (internal quotations omitted). Nevertheless, "[c]laims cannot be of broader scope than the invention that is set forth in the specification." *On Demand Mach. Corp v. Ingram Indus., Inc.*, 442 F.3d 1331, 1340 (Fed. Cir. 2006). Therefore, if the specification reveals a disavowal or disclaimer of claim scope, the claims are to be construed in way which makes them consistent with their specification. *Phillips*, 415 F.3d at 1316 ("claims must be construed so as to be consistent with the specification, of which they are a part") (internal quotations omitted).

B. Construction of the '407 Patent Claims

As stated above, for claim construction purposes, the parties dispute the terms (1)

"composition," (2) "human monoclonal antibodies," and (3) "bind specifically to human tumor necrosis factor alpha."

1. "Composition"

Bayer contends that the term "composition" needs no construction. Abbott proposes the following construction: "a mixture of elements or ingredients that is neither intended for use nor used as a therapeutic agent."

The Court notes at the outset that "composition" is a term of art in patent law, and is not a term that normally requires interpretation. *See PIN/NIP, Inc. v. Platte Chem. Co.*, 304 F.3d 1235, 1244 (Fed Cir. 2002) ("the basic definition of the term 'composition' is well-established as 'a mixture'"). Section 101 states as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or *composition of matter*, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

35 U.S.C. § 101 (emphasis added). Bayer's use of the term "composition" was thus required in order to indicate to the examiner the statutory category of utility into which the proposed patent fell.

Abbott's argument, however, is essentially based on the doctrine of prosecution disclaimer, rather than the purported ambiguity of the term. According to Abbott, the prosecution history shows that Bayer disclaimed antibodies directed to therapeutic uses, and therefore cannot now claim that the patent covers such uses.

Bayer's application, as originally filed, included two claims (4 and 5) that claimed

therapeutic use of the invention.[1] The patent examiner rejected those claims for lack of utility under § 101 on the ground that without clinical trials, "there is no evidence in the specification to establish that the anti-TNFα antibodies can be used for therapy." (Office Action of Apr. 19, 1994). At the time, the PTO had a practice of requiring human clinical data in order to satisfy the utility requirement for specific pharmaceutical applications. In response to that rejection, Bayer requested that those two claims "be cancelled without prejudice until the PTO has made a formal determination of whether human clinical studies are needed to support pharmaceutical composition claims." (Feb. 14, 1995 Request for Amendment After Final, p. 2, Stoffelmayr Response Decl. Ex. 3). The examiner then cancelled the claims without prejudice.

Shortly thereafter, in *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), the Federal Circuit held that human clinical data was not required to show the utility of a pharmaceutical invention, and that laboratory results may be sufficient to establish utility. *See also In re '318 Patent Infringement Litigation*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) ("human trials are not required for a therapeutic invention to be patentable"). Bayer did not, however, make any further attempt to patent claims 4 and 5.

An explicit disclaimer ordinarily is found where an applicant amends claims (for example, by adopting a narrow interpretation) to overcome a rejection. *See Omega Eng'g., Inc. v. Raytek Corp.*, 334 F.3d 1314, 1324 (Fed. Cir. 2003) ("[W]here the patentee has unequivocally disavowed a certain meaning to obtain his patent, the doctrine of prosecution disclaimer attaches and narrows the ordinary meaning of the claim congruent with the scope of the surrender.").

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[1] Claim 4 was for "[t]he composition of claim 1 in a pharmaceutically acceptable carrier" and claim 5 was for "[t]he composition of claim 1 wherein the antibodies are suitable for intravenous administration."

Such a disclaimer, however, must be "clear and unmistakable." *See, e.g., Sandisk Corp. v. Memorex Prods., Inc.*, 415 F.3d 1278, 1287 (Fed. Cir. 2005); *Golight, Inc. v. Wal-Mart Stores, Inc.*, 355 F.3d 1327, 1332 (Fed. Cir. 2004).

Under the circumstances presented here, the Court does not find that the standard for prosecution disclaimer has been met. First, composition claims are not restricted to a particular use of the invention. *See Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 809 (Fed. Cir. 2002) ("a patent grants the right to exclude others from making, using, selling, offering to sell, or importing the claimed apparatus or composition for any use of that apparatus or composition"). Nor is there anything in the prosecution history to suggest that Bayer intended, or the patent examiner understood, that claim 1 would receive a narrow or restrictive meaning as a result of the cancellation of claims 4 and 5. Put another way, in this case broad claims were not withdrawn in order to preserve a narrow claim; rather, narrow claims were withdrawn, leaving the relatively broad claim untouched.[2] Finally, and in any event, the claims were cancelled without prejudice in order to give Bayer an opportunity to re-file them once the legal standard had been changed or clarified; this is not a situation in which the integrity of the patent application process is implicated, or concerns of fundamental fairness require that disclaimer should be found. Accordingly, Bayer will not be held to have made an "unequivocal disavowal" of therapeutic use under the doctrine of prosecution disclaimer.

2. "Human Monoclonal Antibodies"

The second disputed term is "human monoclonal antibodies." Bayer contends that the

[2] The specification of the patent and the description in the patent of the invention's utility indicate that its useful features are principally for human medical therapy.

term "human" needs no construction, and that the term "monoclonal antibodies" means "antibodies with substantially identical amino acid sequences." Abbott's proposed construction is "human antibodies originating from a single human B lymphocyte, wherein such antibodies are low affinity and non-neutralizing."

It is uncontested that the antibody disclosed in the '407 patent was created using the human hybridoma technique, and that it exhibited a low affinity for, and did not effectively neutralize, TNFα. The parties essentially contest three issues. First, they dispute whether the claim term "monoclonal antibodies" should be mean "antibodies with amino acid sequences that are identical." Second, they dispute whether the term "human monoclonal antibodies" – which, on its face, does not describe how the antibodies were created – should be limited to antibodies created by the hybridoma process used by Bayer. Abbott contends that the claim does not cover antibodies created using recombinant techniques; Bayer contends that the claim language allows for no such limitation. Third, they dispute whether the claim should be limited to antibodies that are low-affinity and non-neutralizing. Abbott contends that only antibodies with the effectiveness of Bayer's B5 line – and not more effective antibodies – fall within the scope of the claimed invention; Bayer contends that the claim language does not describe the effectiveness of the antibodies, and should not be so limited.

a. <u>"Substantially Identical Amino Acid Sequences"</u>

The parties agree that the term "monoclonal antibodies," as used by a person of ordinary skill in the art, normally refers to antibodies with identical amino acid sequences. The problem is that the statement is not quite literally true, as there may be minor changes at the end of an amino acid chain without any change in the binding properties of the antibodies. It is unclear whether

the distinction is material, but Bayer has proposed a construction in its reply brief that takes that circumstance into account. As Abbott does not appear to oppose that construction, the Court will accept it.

Accordingly, the term "monoclonal antibodies" shall mean (subject to further refinement, as noted below) "antibodies with amino acid sequences that are identical, apart from post-translational events that result in minor modifications in amino acid sequences at the ends of amino acid chains and that do not affect the antibodies' binding characteristics."

b. Antibodies Created with Hybridoma Methods

The '407 patent is for a composition, not a process, and the claim itself is silent as to whether the monoclonal antibodies were to be created by hybridoma process (or any other process). Normally, the process by which a product is made is irrelevant. *Vanguard Products Corp. v. Parker Hannifin Corp.*, 234 F.3d 1370, 1372-73 (Fed. Cir. 2000) ("A novel product that meets the criteria of patentability is not limited to the process by which it was made."); *Outlast Technologies, Inc. v. Frisby Technologies, Inc.*, 128 Fed.Appx. 122, 127 (Fed. Cir. 2005) ("[A]bsent clear and unambiguous evidence to the contrary, a product claim is not limited to, or does not exclude, products made by a particular process."); *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338 (Fed. Cir. 2008).

Abbott, however, contends that in 1993, the effective filing date of the '407 patent, persons of ordinary skill in the art would have interpreted "monoclonal antibodies" only to mean those created by the hybridoma method. In support of that position, Abbott cites external sources that describe "monoclonal antibodies" only in the context of hybridoma techniques and make no mention of recombinant techniques. In response, Bayer cites various external sources from 1993

that show that researchers in the art did not limit the term "monoclonal antibodies" to monoclonal antibodies created with hybridoma methods. Given that recombinant technologies were not commonly used in 1993, there is no reason to believe that the descriptions set forth in Abbott's sources were meant to be exclusive. In fact, one source Abbott actually cites supports Bayer's position; it states that "recent developments suggest that recombinant DNA technology can replace cell fusion [*i.e.*, hybridoma methods] as a means of generating monoclonal antibodies." (Abbott Reply Br. at 6-7).

Abbott argues that recombinant technologies in 1993 were in their infancy, and were not yet capable of producing high-affinity human TNFα antibodies. That may be true, but the evidence does not suggest that a person of ordinary skill in the art would exclude antibodies created by recombinant technologies from the claim term "monoclonal antibodies," or would refer to such antibodies by some other term. The composition at issue here thus falls under the general rule: a patent for a product is not limited to a particular process by which the product is made.

Accordingly, the Court concludes that the claim term "human monoclonal antibodies" will not be limited to monoclonal antibodies created with hybridoma methods.

c. <u>Antibodies That Are Low Affinity and Non-Neutralizing</u>

The specification of the '407 patent discloses that the invented antibodies have low affinity. (col. 20, l. 29 (" . . . B5 appears to bind with low affinity . . . "); col. 8, ll. 55-57 ("attempts to measure the binding constant of B5 mAb revealed an affinity too low to calculate by conventional methods")). The specification also discloses that the antibodies do not neutralize TNFα. (col. 9, l. 15 ("B5 mAb does not neutralize the cytotoxicity of rhTNFα") ; col. 9, ll. 21-22 ("At no concentration of B5 . . . was any neutralization of rhTNFα observed"); col. 18, ll. 31-33

("Previous experiments . . . have shown that B5 does not neutralize TNFα"); col. 19, ll.56-57 ("B5 mAb does not neutralize rhTNFα")).

Furthermore, the inventors acknowledge in the specification that it may not be possible to develop high-affinity or neutralizing antibodies with the techniques used. ('407 patent, col. 19, l. 66 to col. 20, l. 2 ("The biological effects of TNFα, especially its ability to promote Ig secretion, may preclude the generation of a high affinity neutralizing human anti-TNFα autoantibody by the techniques used")).

Abbott contends that the claim should be construed so that it is limited to antibodies that are low-affinity and non-neutralizing. It raises, in substance, three arguments as to this issue. First, it contends that the specification disclaimed any claim that the invention covers antibodies that are high-affinity and neutralizing. Second, it contends that even in the absence of a disclaimer, only a narrow construction of the claim would be faithful to the terms of the specification. Third, it contends that the patent should be construed narrowly, as it would be invalid for failure to meet the enablement requirement of 35 U.S.C. § 112 if construed to cover low-affinity, non-neutralizing antibodies. Bayer opposes those arguments, and contends that the doctrine of claim differentiation requires that the construction not be so limited.

(1) Disclaimer

Abbott's first argument may be disposed of quickly. It is true that where there are "[w]ords or expressions of manifest exclusion or explicit disclaimers in the specification," courts may limit the scope of a claim, even if the claim language alone appears broader. *Gillette Co.*, 405 F.3d at 1375. Such a disclaimer may also be inferred from the language of the specification – for example, where the specification clearly states that a particular embodiment is unsuitable, even

if within the literal terms of the claim. *See, e.g., Honeywell Int'l, Inc. v. ITT Industries, Inc.*, 452 F.3d 1312, 1319-20 (Fed. Cir. 2006) (noting that "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 of the patent, even though the language of the claims, read without reference to the specification, might be considered broad enough to encompass the feature in question." In *Honeywell*, the embodiments of the invention, a fuel filter system, not only incorporated metal fibers but explained that carbon fibers were unsuitable. The court held that carbon fibers were therefore disclaimed, noting that "[i]f the written description could talk, it would say, 'Do not use carbon fibers.'"). *Id.* at 1319. Nothing of the sort is present here; the specification does not state or suggest that the claimed invention was not intended to include high-affinity, neutralizing antibodies. The doctrine of specification disclaimer accordingly does not apply.

(2) Narrow Construction Based on Specification

Abbott's second contention — that only a narrow construction of the claim would be faithful to the specification — is on a far more secure footing. Seemingly broad claim terms may be interpreted narrowly when such a construction is the only approach that is faithful to the specification. *See, e.g., Decisioning.com, Inc. v. Federated Dep't Stores, Inc.*, 527 F.3d 1300 (Fed. Cir. 2008) (holding that the phrase "remote interface" in claim, when interpreted in light of the specification, did not encompass consumer-owned personal computers); *Andersen Corp. v. Fiber Composites LLC*, 474 F.3d 1361 (Fed. Cir. 2007) ("While nothing on the face of the asserted claims states that the term 'composite composition' is limited to a mixture that is in pellet or linear extrudate form, the specifications make clear that the term, as used in the [asserted] patents, must be construed to be limited in that manner."); *On Demand*, 442 F.3d at 1340

(holding that the term "customer" was limited to retail customers only; "the entire focus of the [inventor's] patented invention is that the 'customer' is . . . the ultimate consumer," and the "specification repeatedly reinforce[d] its usage of the term'customer' as the retail customer"); *Biovail Labs. Int'l SRL v. Impax Labs., Inc.*, 433 F. Supp. 2d 501, 512 (E.D. Pa. 2006) ("[B]ecause the . . . patent, as set forth in the specification, does not teach any means of controlling the release of [a drug] other than by a special coating, I cannot construe the patent to cover tablets in which the release is not controlled by a coating . . . ."). The Court must be careful, however, not to simply import limitations from preferred embodiments in the specification into the claim. *See Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1381 (Fed Cir. 2009); *Kara Tech, Inc. v. Stamps.com Inc.*, 582 F.3d 1341, 1348 (Fed Cir. 2009).

Here, the specification only describes antibodies that are low-affinity and non-neutralizing. It is clear that both (a) a high affinity for TNFα and (b) the ability to neutralize TNFα are desirable characteristics of antibodies. But the patent nowhere describes an antibody with those characteristics. More importantly, nowhere does it indicate (directly or indirectly) *how* to create such an antibody, and indeed suggests that such an antibody could not be created with the technology employed. In other words, a person of ordinary skill in the art, reading the patent in its entirety, would not be able to create a high-affinity, neutralizing antibody for TNFα by employing the methodology described.

Under the circumstances, the claim must be construed narrowly, in light of the specification, to include only low-affinity and non-neutralizing antibodies. Without that limitation, the claim would include antibodies that were not created by the inventors, that were not disclosed in the specification, and that the inventors apparently did not know how to create.

The claim will therefore be read narrowly to include only low-affinity, non-neutralizing antibodies.

(3) Lack of Enablement

Abbott's third argument is that the claim must also be read narrowly to avoid invalidity on the ground of lack of enablement. In substance, Abbott argues that the patent cannot be construed to cover high-affinity, neutralizing antibodies, because it does not explain how to create them; that the reason it does not is because it was not possible to do so with the methods disclosed; and therefore Bayer's position would permit it to hold a patent on a product that did not exist and that it did not know how to make.[3]

The enablement requirement of 35 U.S.C. § 112 does not allow patentees to claim an invention that cannot be practiced by one skilled in the art upon reading the specification. *See ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010) ("To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'") (quoting *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997)). A patentee may choose narrow or broad claims, but "[a] patentee who chooses broad claim language must make sure the broad claims are fully enabled. The scope of the claims must be less than or equal to the scope of the enablement." *Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 999 (Fed. Cir. 2008) (internal quotations omitted). "Enabling the full scope of each claim is part of the *quid pro quo* of the patent bargain." *Id.*

[3] According to Abbott, even today no one has been able to develop a high-affinity neutralizing antibody for TNFα using the human hybridoma method. (Larrick Decl. ¶ 51). Bayer disputes whether, as a matter of science, the human hybridoma method is necessarily incapable of producing high-affinity neutralizing antibodies for TNFα. But the issue is not whether it is possible to create such antibodies, but whether the patent discloses how to do so.

Enablement analysis is distinct from claim construction, and is not normally addressed at the claim construction stage. *See Phillips*, 415 F.3d 1303, 1327 ("we have certainly not endorsed a regime in which validity analysis is a regular component of claim construction"). Nonetheless, a patent should be construed narrowly when possible to avoid potential invalidity issues. *See Wang Labs., Inc. v. America Online, Inc.*, 197 F.3d 1377, 1383 (Fed. Cir. 1999) ("claims should be construed, when feasible, to sustain their validity"). It is clear from the foregoing discussion that Bayer's construction of the claim language would include a purported invention (a high-affinity, neutralizing antibody) that the specification does not teach those skilled in the art how to make. For that reason, the claim should be construed narrowly to avoid inclusion of high-affinity and neutralizing antibodies.

(4) Claim Differentiation

Notwithstanding the above, Bayer argues that the doctrine of claim differentiation compels the conclusion that Claim 1 includes neutralizing antibodies. Under the doctrine of claim differentiation, "the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim." *Phillips*, 415 F.3d at 1315. If the independent claim contained all of the same requirements as the dependent claim, it would be as narrow as the dependent claim and the separate dependent claim would serve no purpose. Claim differentiation is "based on the common sense notion that different words or phrases used in separate claims are presumed to indicate that the claims have different meanings and scope," so "limitations stated in dependent claims are not to be read into the independent claim from which they depend." *Karlin Tech., Inc. v. Surgical Dynamics, Inc.*, 177 F.3d 968, 971-72 (Fed. Cir. 1999).

The rule applies only to negate a proposed construction that in fact would render two claims identical. *See Sinorgchem Co. v. Int'l Trade Comm'n*, 511 F.3d 1132, 1140 (Fed. Cir. 2007) (a construction "present[s] no claim differentiation problem" when "the claims are not rendered identical"); *Sealed Air Corp. v. Int'l Packaging Sys., Inc.*, No. 86-0365-R, 1987 WL 44350, at *21 (E.D. Va. July 24, 1987) (dependent claims that are "not identical in coverage" to an independent claim "do not offend any notions of claim differentiation").

Claim differentiation is a rebuttable presumption that cannot supplant the clear import of the specification. *Regents of the Univ. of Cal. v. Dakocytomation Cal., Inc.*, 517 F.3d 1364, 1375 (Fed. Cir. 2008); *Curtiss-Wright Flow Control Corp. v. Velan, Inc.*, 438 F.3d 1374, 1380-81 (Fed. Cir. 2006); *see also Invisible Fence, Inc. v. Perimeter Techs., Inc.*, No. 1:05-CV-361, 2006 WL 1443399, at *12 n.20 (N.D. Ind. May 25, 2006) (the presumption of claim differentiation is "easily overcome").

Here, the relevant claims of the '407 patent state as follows:

> 1. A composition comprising human monoclonal antibodies that bind specifically to human tumor necrosis factor alpha.
>
> 5. The composition of claim 1 wherein the antibodies can bind to non-neutralizing epitopes of tumor necrosis factor alpha.

According to Bayer, the scope of claim 1 is not limited (like claim 5) to antibodies that can bind to non-neutralizing epitopes. Claim 1, therefore, must also include antibodies that do not bind to non-neutralizing epitopes but that instead bind to neutralizing epitopes—that is, neutralizing antibodies. Otherwise, claim 1 and claim 5 would have exactly the same scope.

The Court disagrees. First, the disputed term ("human monoclonal antibodies") has been construed by the Court to mean antibodies that bind with low affinity and are non-neutralizing.

That construction includes both (1) antibodies that bind to neutralizing epitopes and (2) antibodies that bind to non-neutralizing epitopes. In other words, epitopes can be either neutralizing or non-neutralizing. But it does not follow that binding to a neutralizing epitope necessarily results in neutralization. An antibody's affinity affects whether the antibody is able to neutralize the antigen. A low-affinity antibody may not neutralize an antigen even if it binds to a neutralizing epitope, because such an antibody will fall off before neutralization occurs. (*See* Larrick Decl. ¶¶ 2-5 & Exs. 21-22).

Furthermore, and in any event, claim differentiation simply creates a presumption; it is not a rigid rule. If high-affinity, neutralizing antibodies were not actually invented; if the patent does not disclose the invention of such antibodies; and if the patent does not disclose any means by which such antibodies could be created, the claim must be construed accordingly, and the presumption created by the claim differentiation doctrine has been overcome.

* * *

In summary, based on the disclosure of only low-affinity and non-neutralizing antibodies and the lack of description as to how to manufacture any other kind of antibody, the Court concludes that low-affinity and non-neutralizing antibodies are the only invention covered by the claims. Accordingly, the claim term "human monoclonal antibodies" will be limited to antibodies that attach to TNFα with low affinity and without neutralizing properties.

3. <u>"Bind Specifically to Human Tumor Necrosis Factor Alpha"</u>

The third disputed term is "bind specifically to human tumor necrosis factor alpha." Abbott's proposed construction is "bind to human TNFα, including the 17 kD and 26 kD forms of human TNFα, and do not bind to other human proteins."

The term "specificity" refers to the extent to which an antibody binds preferentially to a particular antigen rather than to other antigens. (Ravetch Decl. ¶ 39). A "polyreactive" antibody has low specificity and can bind with similar strength to a wide variety of antigens. (*Id.*). A highly specific antibody binds to a particular antigen with a certain strength and only much more weakly to other antigens. (*Id.*).

The patent discloses that the B5 antibody bound specifically to TNFα; did not bind to a similar human protein called TNFβ; and did not bind to certain identified antigens to which polyreactive antibodies often bind. Thus, the inventors reported that the B5 antibody of the patent "binds specifically to TNFα and fails to bind to any of the antigens tested . . . . Hence, B5 appears to be monospecific and is not polyreactive." ('407 patent, col. 20, ll. 34-36).

Part of Abbott's proposed construction may be disposed of quickly. Abbott's proposed construction requires that an antibody bind to human TNFα in both 17kD and 26kD forms. Abbott's proposal refers to the molecular weight (measured in kilodaltons or kD) of TNFα at different points in its lifecycle. While TNFα is still connected to the cell that produced it (transmembrane TNFα), it has a molecular weight of about 26kD. After it is released from the cell that produced it (soluble TNFα), TNFα has a molecular weight of about 17kD. Because different epitopes on TNFα may be exposed depending on whether it is still in the transmembrane stage or has become soluble, an antibody might bind to TNFα in one form but not the other. There is no evidence that monospecificity toward a particular antigen requires that an antibody bind to such antigen at all points in its lifestyle, nor is this required for the B5 antibody by the '407 patent's specification. That construction will therefore be rejected.

The remaining contentions require more extended discussion. Abbott contends that the

’407 patent uses the terms “monospecific” and “bind specifically” interchangeably and synonymously, and that a “monospecific” antibody (as understood by a person of ordinary skill in the art) would bind only to a specific antigen and not to any others. In other words, Abbott contends that an antibody that binds to any antigen other than human TNFα, in any circumstances whatsoever, falls outside the scope of the claim.

Bayer contends that Abbott’s construction should be rejected on the grounds that “[v]irtually any antibody will begin to show non-specific binding to a wide variety of antigens at sufficiently high concentrations,” and that “[i]nterpreting the claim language in such absolute terms would create an impossible standard for specificity,” requiring testing against every known antigen in the world. (Bayer Br. at 17-18; *see* Ravetch Decl. ¶ 41). Bayer accordingly proposes a construction that defines monospecificity to TNFα with “materially greater affinity” than to certain other antigens, including certain antigens that are “commonly recognized” by polyreactive natural autoantibodies.

Bayer further contends that Abbott’s construction is inaccurate because the patent discloses that antibody B5 binds to mouse TNFα as well as human TNFα: “We have made monoclonal human antibodies which bind to both human and mouse TNFα. . . . Specificity analyses indicate that the human IgM autoantibody binds to both human and mouse recombinant TNFα, but not to other antigens commonly recognized by polyreactive natural IgM autoantibodies.” (’407 patent, col. 2, ll. 14-26).

Abbott contends that Bayer’s use of the phrases “materially greater” and “commonly recognized” are vague, and would introduce further ambiguity. It also contends that the phrase “materially greater” would not be self-defining to a person of ordinary skill in the art, and might

be interpreted to include antibodies that are classified as polyreactive but nevertheless attach to TNFα to a materially greater degree than to other antigens. Abbott acknowledges that requiring absolute monospecificity is unfeasible, but maintains that its construction is not meant to be so strict. Rather, according to Abbott, "monospecificity must be assessed under physiologically relevant conditions." (Abbott Reply Br. at 16).

Abbott further contends that with respect to the B5 antibody's ability to bind to mouse proteins, there is no evidence that this prevents the antibody from being classified as monospecific. As the '407 patent itself discloses, "B5 *appears to be monospecific* and is not polyreactive. B5 seems to bind specifically to an epitope, most likely a linear epitope, shared by mouse and human TNFα." ('407 patent, col. 20, ll. 33-36 (emphasis added)).

Put in simple terms, Bayer contends that Abbott's construction is unduly restrictive and absolute; Abbott contends that Bayer's construction is unduly vague and ambiguous. The Court concludes that Abbott's construction should be rejected, as it indeed involves a standard that is unnecessarily restrictive. Abbott's position is in fact undermined by the testimony of its own expert, who indicated that a person of ordinary skill in the field of immunology would not interpret "monospecific" to require proof that the antibody attach to no other antigens, but that "an antibody can be considered monospecific if it is shown not to bind to other antigens it is likely to encounter." (Abbott Reply Br. at 17; *see* Larrick Decl. ¶ 87-89 & n. 7; Supp'l Larrick Decl. ¶ 9). The use of the phrase "likely to encounter" obviously suggests something less than absolute certainty, which is what Abbott's proposed construction would require.

Bayer's proposed construction, however, is far from perfect. In particular, it cannot be stated with complete confidence that any ambiguity has been entirely eliminated, as the

construction relies on the phrases "materially greater" and "commonly recognized," which do not create precise boundaries. Nonetheless, the use of such phrases is not without precedent. *See, e.g., Playtex Prods., Inc. v. Procter & Gamble Co.*, 400 F.3d 901, 909 (Fed. Cir. 2005) ("conclud[ing] that '*substantially* flattened surfaces' means surfaces, including flat surfaces, materially flatter than the cylindrical front portion of the applicator") (emphasis added); *Collett v. Piper's Saw Shop, Inc.*, 4 Fed. Appx. 904, 906 (Fed. Cir. 2001) (district court construed claimed alloy for saws to permit inclusion of an additional compound "that does not *materially* affect the ability of the cutting tip to resist shattering") (emphasis added). Nor are such terms without meaning. For something to be "material," it must have genuine significance or importance; not every antibody that shows a greater affinity for a particular antigen will be "materially" greater. For something to be "common," it must occur with substantial frequency; not every antigen that is recognized by polyreactive natural autoantibodies will be "commonly" recognized. Finally, and in any event, no more precise definition has been offered to the Court, and none is suggested by the record. Under the circumstances, the Court will adopt Bayer's proposed construction.

Accordingly, the claim term "bind specifically to human tumor necrosis factor alpha" will be interpreted to mean "bind to human tumor necrosis factor alpha with materially greater affinity than (i) to human tumor necrosis factor beta and (ii) to antigens commonly recognized by polyreactive natural autoantibodies (*i.e.*, by naturally occurring antibodies known to bind to a variety of antigens, including antigens naturally found in humans)."

III. Conclusion

For the foregoing reasons, the following are the constructions of the disputed claim terms: the term "composition" needs no construction;

the term "human monoclonal antibodies" means "human monoclonal antibodies (that is, 'antibodies with amino acid sequences that are identical, apart from post-translational events that result in minor modifications in amino acid sequences at the ends of amino acid chains and that do not affect the antibodies' binding characteristics') that are low-affinity and non-neutralizing"; and

the term "bind specifically to human tumor necrosis factor alpha" means "is monospecific for human tumor necrosis factor alpha and does not bind to other human proteins under physiologically relevant conditions."

So Ordered.

/s/ F. Dennis Saylor
F. Dennis Saylor IV
Dated: October 20, 2010 United States District Judge