IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

GENENTECH, INC. and CITY OF HOPE, *Plaintiffs*, v. AMGEN INC., *Defendant*.	Civ. No. 17-1407- CFC, Consol.

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MEMORANDUM OPINION

June 17, 2019

Wilmington, Delaware

CONNOLLY, UNITED STATES DISTRICT JUDGE

Pending before me are competing proposed claim constructions in this consolidated patent infringement action brought pursuant to the Biologics Price Competition and Innovation Act ("BPCIA"), 42 U.S.C. § 262 by Plaintiffs Genentech, Inc. and City of Hope (collectively, "Genentech") against Defendant Amgen, Inc. ("Amgen"). Genentech has accused Amgen of infringing 26 patents.

The parties initially asked me to construe the meaning of ten claim limitations in seven of the asserted patents. I reviewed the parties' claim construction briefing and held a *Markman* hearing that spanned two days. D.I. 340; D.I. 345. By the conclusion of the *Markman* hearing, only seven claim terms in six of the asserted patents remained in dispute.[1] I address in this Memorandum those disputed terms.

The disputed terms appear in the following patents: U.S. Patent Nos. 8,512,983 ("the '983 patent"); 9,441,035 ("the '035 patent"); 8,574,869 ("the '869 patent"); 6,884,879 ("the '879 patent"); 7,169,901 ("the '901 patent"); and 7,060,269 ("the '269 patent"). D.I. 225; D.I. 325. These patents cover a wide range of complex technologies. Accordingly, I write primarily for the parties and,

[1] During or shortly before the *Markman* hearing, the parties agreed to the meaning of the terms "cystine," "grade III hypertensive event," and "without altering the dosage regimen." *See* D.I. 340 at 83:11-84:9, 85:3-92:6; D.I. 345 at 147:3-10.

to a large degree, presume familiarity with the underlying technology. In general, however, the '983 patent, '035 patent, and '869 patent relate to various aspects of manufacturing proteins, particularly antibodies, using a cell culture process. D.I. 226 at 326, 381, 476. The '879 patent, '901 patent, and '269 patent disclose humanized and variant anti-VEGF antibodies and various uses of those antibodies. *Id.* at 69, 157, 240.

I. LEGAL STANDARDS

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005). "'[T]here is no magic formula or catechism for conducting claim construction.' Instead, the court is free to attach the appropriate weight to appropriate sources 'in light of the statutes and policies that inform patent law.'" *SoftView LLC v. Apple Inc.*, 2013 WL 4758195, at *1 (D. Del. Sept. 4, 2013) (quoting *Phillips*, 415 F.3d at 1324). Construing the claims in a patent is a question of law. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 977–78 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370, 388–90 (1996).

Unless a patentee acts as his own lexicographer by setting forth a special definition or disavows the full scope of a claim term, the words in a claim are to be given their ordinary and accustomed meaning. *Thorner v. Sony Comput. Entm't*

Am. LLC, 669 F.3d 1362, 1365 (Fed. Cir. 2012). "[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips*, 415 F.3d at 1313. A person of ordinary skill in the art ("POSITA") "is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Id.* at 1313. "[T]he 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." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).[2]

The court may also consider extrinsic evidence, which "consists of all evidence external to the patent and prosecution history, including expert and

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[2] Section 112(b) of Title 35 provides that "[t]he specification shall conclude with one or more claims[.]" This language makes clear that the specification includes the claims asserted in the patent, and the Federal Circuit has so held. *See Markman*, 52 F.3d at 979 ("Claims must be read in view of the specification, of which they are part"). The Federal Circuit and other courts, however, have also used "specification" on occasion to refer to the written description of the patent as distinct from the claims. *See, e.g., id.* ("To ascertain the meaning of claims, we consider three sources: The claims, the specification, and the prosecution history."). To avoid confusion, I will refer to the portion of the specification that is not the claims as "the written description."

inventor testimony, dictionaries, and learned treatises." *Phillips*, 415 F.3d at 1317. "Extrinsic evidence is to be used for the court's understanding of the patent, not for the purpose of varying or contradicting the terms of the claims." *Markman*, 52 F.3d at 981. "The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998).

II. ANALYSIS OF DISPUTED TERMS

A. "a glutamine-free production culture medium" ('983 patent)

Genentech's Construction: "A production culture medium that is essentially free of glutamine"
Amgen's Construction: "culture medium used in the production phase that does not contain glutamine when formulated"
Court's Construction: "a culture medium used in the production phase that is not formulated or supplemented with glutamine"

1. Background

Claim 1 of the '983 patent, reformatted for clarity, teaches:

> A process for producing a polypeptide in a mammalian host cell expressing said polypeptide,
>
> comprising culturing the mammalian host cell in a production phase of the culture in *a glutamine-free production culture medium* containing asparagine,

wherein the asparagine is added at a concentration in the range of 7.5 mM to 15 mM.

'983 patent at 49:12-17 (emphasis added).

Antibodies are polypeptides, manufactured by culturing genetically-engineered cells inside tanks called bioreactors. The cells in the bioreactor are suspended in a solution called a "cell culture medium," which supplies, among other things, various nutrients for the cells to consume. Cell culture media are comprised of "base media" (also sometimes called "basal media") and "feed media." *Id.* at 1:33-36. A base medium is the initial medium added to the bioreactor. Feed media are periodically added to the bioreactor to supplement (or replenish) the nutrients in the base medium. Base media and feed media are "formulated" (i.e., made or prepared).

The amino acid glutamine is a nutrient frequently used in the formulation of base and feed media. Cells not only consume glutamine, they also produce their own glutamine. As a result, the concentration of glutamine in a cell culture medium is dynamic, as cells are continually consuming and adding to the glutamine in the cell culture medium and a manufacturer can also add glutamine at any time through feed media.

2. Analysis

Amgen argues that "a glutamine-free production culture medium" refers to a cell culture medium used in the production phase of antibodies that omits glutamine as an ingredient in the formulation of the culture medium's base media and/or feed media. Genentech takes the position that "a glutamine-free production culture medium" refers to the concentration of glutamine measured in the bioreactor at any point during the production phase. Because cells themselves can produce glutamine during the production phase, a glutamine-free culture medium would not exist in the production phase if "-free" means "the absence of glutamine" or "zero glutamine." Thus, not surprisingly, Genentech proposes that "glutamine-free" allow for some amount of glutamine and asks me to construe "-free" to mean "essentially free." D.I. 325 at 2.

I find that Amgen's proposed construction better aligns with the patent's intrinsic evidence and I will construe the limitation similarly to, though not exactly, the way Amgen does. Specifically, I will construe "a glutamine-free production culture medium" to mean "a culture medium used in the production phase that is not formulated or supplemented with glutamine." My reasoning is threefold.

First, the written description of the patent states that "the culture media of the present invention can be based [on] any of the media described in [certain prior art] *provided that glutamine is omitted as an ingredient.*" '983 patent at 29:5-12 (emphasis added). The words "omitted" and "ingredient" connote preparing a formulation, not measuring a sample of a cell culture medium.

Second, the patent links the term "glutamine-free" with media "formulated with" zero glutamine. It describes, for example, Figure 4 as presenting certain "[e]ffect[s] of asparagine *under glutamine-free ... conditions*," and the caption to Figure 4 is: "Cases *formulated with 0mM Glutamine*, 0mM or 5mM Glutamate, 10mM Aspartate." *Id.* at 4:59-60 and Figure 4 (emphasis added). Similarly, Figures 1 through 3 and Example 1 provide the results of a study designed to test the production of polypeptides in a production medium formulated with various concentrations of glutamine, including "0" glutamine. *Id.* at Figures 1-3; *id.* at 44:26-46:61. As noted above, because cells themselves produce glutamine, a cell culture medium (which, by definition, contains cells) cannot have "zero" glutamine. Only the base or feed media—which do not contain cells—can be said to have zero or an absence of glutamine.

Third, during the prosecution history, both the Patent Examiner and Genetech used "glutamine-free" to describe media that omitted glutamine as an

ingredient in their formulations. The Patent Examiner rejected claim 1 of the '983 patent as anticipated by Nagle, Tomei, and Kurano, because each of these references taught a "glutamine-free medium." D.I. 228 at 1044-48. In its response to the rejection, Genentech agreed that Nagle, Tomei, and Kurano each taught a "glutamine-free" culture medium.[3] *Id.* at 1060-65. As a result, how Nagle, Tomei, and Kurano defined a glutamine-free medium informs how Genentech and the Examiner understood the meaning of the term. *See Am. Radio LLC v. Qualcomm Inc.*, 578 F. App'x 975, 980 (Fed. Cir. 2014) (stating that prior "can often help to demonstrate how a disputed term is used by those skilled in the art" (quoting *Vitronics*, 90 F.3d at 1584)). A review of Nagle, Tomei, and Kurano shows that each of them taught the formulation of a cell culture medium that omits glutamine as an ingredient.

Nagle states: "The primary intent of this paper was to present the *formulation* of a heat-stable chemically defined medium that supported increased populations of several cell lines." D.I. 326-8, J.A. 2526-2531, at 261 (emphasis added). The composition of the medium presented in Nagle "differ[ed] from that previously reported by the omission of glutamine." *Id.* at 260. Thus, Nagle's

[3] Genentech overcame the objection by amending the claims to add a limitation based on the concentration of asparagine. D.I. 228 at 1054, 1060-61.

formulation of a cell culture medium differed from that previously reported precisely because it omitted glutamine as an ingredient.

Tomei describes growing mammalian cells in a "glutamine-free ... chemically defined medium." D.I. 326-8, J.A. 2532-2537, at 2:8-12. "The composition of the particular medium used for [Tomei's] invention is shown in Table 1," which omits glutamine as one of the "components." *Id.* at 2:52-55, Table 1. Tomei further states that the composition set forth in Table 1 "does not necessarily represent a critical formulation because other formulations may also be used." *Id.* at 2:55-57. Accordingly, Tomei taught that a glutamine-free cell culture medium omitted glutamine as a component of the formulation.

Lastly, Kurano "investigated whether the cells were able to grow on glutamine free medium or not." D.I. 326-5, J.A. 2110-2125, at 122. To conduct the investigation, Kurano compared a "medium A," which was a "standard MEM-α medium ... purchased from Gibco" to a "medium B," which was "prepared" using the "same components" as medium A "*other than* glucose, *glutamine* and asparagine." D.I. 228 at 1087-89 (emphasis added). Thus, Kurano described a glutamine-free cell culture medium as prepared without glutamine as a component.

The repeated references in the prior art to the terms "components" and "formulations" makes clear that those skilled in the art at the time of the invention

used the term "glutamine-free" to refer to a culture medium that was not formulated or supplemented with glutamine. Those references are consistent with the intrinsic evidence cited above, and accordingly, I will construe "a glutamine-free production culture medium" as "a culture medium used in the production phase that is not formulated or supplemented with glutamine."

B. "wherein the cystine is at a concentration of from 1.25 mM to 2.5 mM" ('035 patent)

Genentech's construction: "Plain and ordinary meaning. The recited cystine concentration is the concentration of cystine in the bioreactor."
Amgen's construction: "wherein the cystine is at a concentration of from 1.25 mM to 2.5 mM calculated when the cell culture medium is formulated"
Court's construction: "wherein the cystine is at a concentration of from 1.25 mM to 2.5 mM calculated when the cell culture medium is formulated"

1. Background

Claim 1 of the '035 patent, reformatted for clarity, recites:

> A method of producing bevacizumab, or a fragment thereof,
>
> comprising the step of culturing a Chinese hamster ovary (CHO) cell comprising a nucleic acid encoding bevacizumab or fragment thereof in a cell culture medium,
>
> wherein the cell culture medium comprises copper, insulin, and cystine,
>
> *wherein the cystine is at a concentration of from 1.25 mM to 2.5 mM*, and

wherein the cell produces bevacizumab, or a fragment thereof.

'035 patent at 46:14-21 (emphasis added).

2. Analysis

The parties disagree on whether the cystine concentration in the cell culture medium is calculated at the time of formulation (Amgen's position) or measured in the bioreactor at any single point in time (Genentech's position). I will adopt Amgen's construction, as it better aligns with the intrinsic evidence.

First, the patent's written description discusses the use of cystine in a manner consistent with its use as a component in a formulation. Specifically, it describes a cell culture medium "prepared" by combining two or more "components" selected from copper, insulin, and cystine "in an amount to provide" a certain concentration in the cell culture medium. '035 patent at 25:46-54; *see also id.* at 5:26-36. The terms "prepared" and "components" suggest a formulation. In addition, the phrase "in an amount *to provide*" is forward-looking and thus consistent with Amgen's position that the determination of the amount of cystine is made when the base or feed media is formulated, not after the base or feed media is added to the cell culture medium.

Second, prior art cited during the patent's prosecution demonstrates that a POSITA would understand that the concentration of cystine in the cell culture

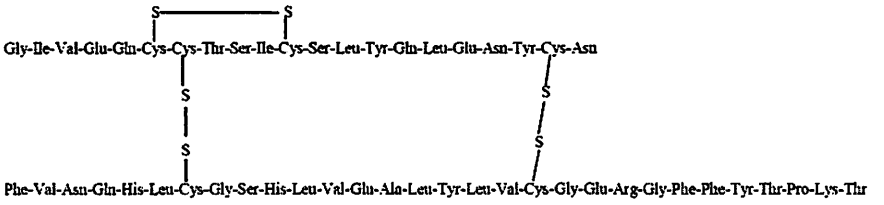
medium is calculated at the time of the media's formulation. The Patent Examiner initially rejected claim 1 of the '035 patent as anticipated by four prior art references, because each reference taught a cell culture medium that contained cystine. D.I. 228 at 1193-95, 1199, 1205. Genentech overcame the rejection by amending the claims to specify a concentration of cystine that was outside the range taught by the prior art. *Id.* at 1212, 1227-29, 1233, 1236. As a result, how those prior art references—Mather, Gawlitzek, Knudsen, and Valamehr—used cystine informs how Genentech and the Examiner understood the meaning of the disputed term. *See Am. Radio LLC*, 578 F. App'x at 980 (stating that prior art "can often help to demonstrate how a disputed term is used by those skilled in the art" (quoting *Vitronics*, 90 F.3d at 1584)). A review of the prior art shows that it taught a concentration of cystine at the time of formulation.

Mather teaches cystine at the time of formulation because it describes "prepar[ing]" the cell culture media by "weigh[ing] out" the "necessary amount of each of the solid ingredients in the medium," "combin[ing]" the ingredients to form a mixture termed the "basal medium powder," and then adding the basal medium powder to the purified water. D.I. 326-4, J.A. 1751-1762 at 1:9-11, 2:48-68, 4:52-11:15, 5:21-24, 10:10, 10:23-38. Gawlitzek, which is the patent application that resulted in the '983 patent, concerns the formulation of a cell

culture medium for the reasons stated in connection with my construction of "glutamine-free production culture medium" in Section II(A)(2) above. *See* D.I. 326-4, J.A. 1781-833 (application); D.I. 326-1, J.A. 1-55 (patent). In Knudsen, Table 3a and Table 3b set forth the "mg/L" (milligrams per liter) for the "component[s]" used in "a composition of a medium suitable for use in the present invention." D.I. 326-4, J.A. 1834-1849, at 9. Because milligrams is a solid measurement and liters is a liquid measurement, use of the words "mg/L" and "component" suggest mixing dry ingredients to formulate a base or feed medium. Finally, Valamehr mentions cystine twice: in Table 1, which sets forth the amino acids that "may ... be added to the basal medium," and in Table 2, which provides the "cell culture media components for basal media" and each component concentration ("mg/L"). D.I. 326-4, J.A. 1763-1780, at 7-8. References to "basal medium" (i.e., a base medium), "components," which are the ingredients of a formulation, and "mg/L," which is an amount of solid per liquid, strongly suggest that the concentration of cystine is calculated when the media is formulated.

In light of the foregoing intrinsic evidence, I will construe the disputed phrase "wherein the cystine is at a concentration of from 1.25 mM to 2.5 mM" to mean, as Amgen proposes, "wherein the cystine is at a concentration of from 1.25 mM to 2.5 mM calculated when the cell culture medium is formulated."

C. "insulin" ('035 patent)

Genentech's construction: "Plain and ordinary meaning. The claim is not limited to human insulin."
Amgen's construction: "hormone with the amino acid sequence in Appendix A to the Joint Claim Construction Chart. (D.I. 225-1)" 
Court's construction: "Plain and ordinary meaning. The claim is not limited to human insulin."

1. Background

Again, claim 1 of the '035 patent recites:

> A method of producing bevacizumab, or a fragment thereof,
>
> comprising the step of culturing a Chinese hamster ovary (CHO) cell comprising a nucleic acid encoding bevacizumab or fragment thereof in a cell culture medium,
>
> wherein the cell culture medium comprises copper, *insulin*, and cystine,
>
> wherein the cystine is at a concentration of from 1.25 mM to 2.5 mM, and
>
> wherein the cell produces bevacizumab, or a fragment thereof.

'035 patent at 46:14-21 (emphasis added).

2. Analysis

Genentech argues that "insulin" should be given its plain and ordinary meaning and not be limited to human insulin. Amgen argues that "insulin" should be defined as the amino acid sequence of human insulin.

The '035 patent does not define "insulin." Nor does it limit "insulin" to any particular species or even suggest that "insulin" must be human insulin.

Amgen argues that the prosecution history supports its position, because Genentech amended its claims to overcome the Examiner's rejection of the claims "in view of a prior art reference ("Gawlitzek") that disclosed, among other things, 'human insulin.'" D.I. 267 at 46. But nothing in the amended claims Genentech proposed to overcome the rejection or in Genentech's communications with the Examiner about the rejection suggest that Genentech intended to limit "insulin" to "human insulin." Accordingly, I will give "insulin" its plain and ordinary meaning and not limit it to human insulin.

D. "following fermentation" ('869 patent)

Genentech's construction: "After the end of the cell growth and antibody production phases (which is indicated by a change in the cell culture environment that substantially ends cell growth and antibody production)"
Amgen's construction: "steps starting with initiation of purification"
Court's construction: The Court will not construe the term at this time.

1. Background

Claim 1 of the '869 patent, reformatted for clarity, teaches

> [a] method for the prevention of the reduction of a disulfide bond in an antibody expressed in a recombinant host cell,
>
> comprising, *following fermentation*, sparging the pre-harvest or harvested culture fluid of said recombinant host cell with air,
>
> wherein the amount of dissolved oxygen (dO2) in the pre-harvest or harvested culture fluid is at least 10%.

'869 patent at 107:44-49. As stated, the goal of the invention is to prevent the reduction of disulfide bonds in the antibody expressed in a recombinant host cell. *Id.* at 107:44-45.

2. Analysis

The construction of "following fermentation" involves two questions. First, what is "fermentation?" And second, when does "fermentation" end?

Amgen dodges the first question. It argues that "following fermentation" is indefinite because the specification does not "provide clear guidance for when 'fermentation' ends and 'following fermentation' begins[.]" D.I. 325 at 60. Amgen does not say that the term "fermentation" itself is indefinite; and although Amgen argues that the '869 patent "does not use 'fermentation' in the ordinary way," *id.*, it makes no attempt to explain "the way" the patent does use the term.

For its part, Genetech equates "fermentation" with "the cell growth and antibody production phases." *Id.* at 54.

The '869 patent does not define "fermentation." Language in column 9 of the patent suggests that the term is synonymous with "production":

> It is emphasized that *the fermentation, recovery and purification methods* described herein are only for illustration purposes. The methods of the present invention can be combined with any manufacturing process developed for *the production, recovery and purification of recombinant proteins*.

'869 patent at 29:4-8 (emphasis added). In another portion of the patent's written description, the use of the words "following fermentation" immediately after a description of the "production phase" provides further evidence that the patentee understood "fermentation" and "production" to mean the same thing. *See id.* at 26:29-41.

Language in column 22 of the patent, however, suggests that fermentation is not synonymous with production. Specifically, lines 10 through 13 of column 22 provide that "non-specific methods can also be used to prevent the reduction [sic] of disulfide bond reduction [sic] following fermentation during the recombinant production of recombinant proteins." *Id.* at 22:10-13. This sloppy language is unfortunately typical of the '869 patent. Because of its two references to "reduction," the quoted sentence describes an invention that does the exact

opposite of what is described in the patent's Abstract and taught by claim 1—that is, the sentence literally refers to a method to prevent "the reduction of the reduction" of disulfide bonds. I assume, therefore, that either the phrase "the reduction of" that precedes "disulfide bond" or the word "reduction" that follows "disulfide bond" is a typographical error.

Correcting that error, however, does not cure the sentence's ambiguities. The corrected sentence (i.e., with only one reference to "reduction") can be read in two different ways with respect to the relationship between fermentation and production: either (1) the prevention of disulfide bond reduction occurs during a production process that comes after fermentation, or (2) the prevention of disulfide bond reduction occurs after the completion of a fermentation process that itself occurs and is completed during production. In the first case, fermentation occurs *before* production. In the second case, fermentation occurs *during* production. In both cases, fermentation is neither coterminous with nor the same thing as production.

Language in Column 1 of the '869 patent only adds to the confusion over the relationship between fermentation and production. That column states in relevant part:

> Usually, to begin *the production cycle*, a small number of transformed recombinant host cells are allowed to grow

> in culture for several days (see, e.g., FIG. 23). *Once the cells have undergone several rounds of replication, they are transferred to a larger container where they are prepared to undergo fermentation.* The media in which the cells are grown and the levels of oxygen, nitrogen and carbon dioxide that exist during *the production cycle* may have a significant impact on *the production process*.

'869 at 1:52-2:9 (emphasis added). It is clear from this quoted passage that fermentation occurs after "several rounds of replication" and that "replication" refers to the initial growing "in culture for several days" of a small number of transformed recombinant host cells. Because of the ambiguous phrase "to begin the production cycle," however, it is unclear whether this replication is the beginning of the production cycle or whether it precedes (and lays the foundation for) the production cycle. Thus, it is not clear whether the production cycle begins before fermentation takes place. To compound the confusion, the quoted passage refers in one sentence to "the production cycle" and "the production process," and it does not make clear whether these terms refer to the same thing. The confusion is further compounded because the patent variably uses "production" throughout

its written description.[4] And finally, although the passage describes the transfer of cells to a larger container where they are "*prepared* to undergo fermentation," it does not indicate when fermentation begins, let alone when it ends or what it encompasses.

In sum, the patent neither defines fermentation nor allows for a cogent inference of the term's meaning. Moreover, the parties have not identified any prior art cited in the patent or anything from the prosecution history that would enable me, based solely on the intrinsic evidence, to construe reasonably the meaning of "fermentation" (and, consequently, the meaning of "following fermentation"). Accordingly, I cannot construe the term based on the intrinsic evidence and, therefore, will convene a hearing to determine whether "following

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[4] For example, at times, the patent equates "production" with "manufacturing." *Compare* '869 Patent at 2:17-19 (referring to a "*manufacturing*, recovery and purification process" (emphasis added)) *with id.* at 25:40-41, 28:38-39 (referring to a "*production*, recovery and purification" process (emphasis added)). At other times, the patent describes "production" as encompassing "manufacturing" and other processes. *See, e.g., id.* at 2:13-19 ("[D]uring the recombinant *production* of polypeptides ..., it is essential to protect and retain the disulfide bonds throughout the *manufacturing*, recovery and purification process." (emphasis added)). And at other times the patent describes "manufacturing" as encompassing "production" and other processes. *See, e.g., id.* at 29:6-8 (stating that "[t]he methods of the present invention can be combined with any *manufacturing* process developed for the *production*, recovery and purification of recombinant proteins" (emphasis added)).

fermentation" can be construed by resorting to extrinsic evidence or whether it should be found invalid for indefiniteness.

E. "Said Humanized Variant" ('879 patent) / "Said Humanized anti-VEGF Antibody" ('901 patent)

Genentech's construction: "The humanized anti-vascular endothelial growth factor (VEGF) antibody recited at the beginning of claim 1."
Amgen's construction: "anti-VEGF antibody created by humanization of a parent anti-VEGF antibody"
Court's construction: "The humanized anti-vascular endothelial growth factor (VEGF) antibody recited at the beginning of claim 1."

1. Background

The parties dispute the meaning of "said humanized variant" and "said humanized anti-VEGF antibody," which appear, respectively in the '879 patent and '901 patent. D.I. 325 at 96. The parties' respective arguments regarding the meaning of each of these claim limitations are the same and the patents share a common written description. D.I. 325 at 96-104; '879 patent; '901 patent. For convenience, therefore, I will refer only to "said humanized variant" and the '879 patent.

Claim 1 of the '879 patent, reformatted for clarity, provides:

> Isolated nucleic acid encoding a humanized variant of a parent anti-VEGF antibody which parent antibody comprises non-human variable domains,

> wherein *said humanized variant* binds human VEGF and comprises the following heavy chain Complementary Determining Region (CDR) amino acid sequences: SEQ ID NO:128 as CDRH1, SEQ ID NO:2 as CDRH2 and SEQ ID NO:129 as CDRH3.

'879 patent at 131:2-9 (emphasis added).

2. Analysis

The parties' dispute over the term "said humanized variant" boils down to whether "humanized" is a process limitation or a structural limitation. Amgen argues that "humanized" is a process limitation, and that an antibody is "humanized" only if it is produced by a process "wherein small sections of a human antibody are replaced with non-human sections." D.I. 325 at 98. Genentech argues that "humanized" refers to the antibody's structure and that an antibody is "humanized" if its sequence of amino acids corresponds in part to a human antibody and in part to a non-human antibody, and the manner or means by which that sequence is created is of no consequence. *Id.* at 97. I agree with Genentech.

"[W]ords of limitation that can connote with equal force a structural characteristic of the product or a process of manufacture are commonly and by default interpreted in their structural sense, unless the patentee has demonstrated otherwise." *3M Innovative Prop. Co. v. Avery Dennison Corp.*, 350 F.3d 1365, 1371 (Fed. Cir. 2003). For that reason, the Federal Circuit has "in numerous

instances held such limitations to convey structure even when they also describe[d] a process of manufacture." *In re Nordt Dev. Co., LLC*, 881 F.3d 1371, 1375-76 (Fed. Cir. 2018) (citations omitted).

In this case, the patent is replete with references to and examples of the structural characteristics of "humanized." For example, in a section titled "definitions," the written description recites: "'Humanized' forms of non-human (e.g., murine) antibodies are chimeric antibodies which contain minimal sequence [of amino acids] derived from non-human immunoglobulin." '879 patent at 9:19-21. "Chimeric" antibodies are in turn defined by their sequence as antibodies "in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species ..., while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species ...." *Id.* at 9:7-18. The written description further provides that

> [i]n general, the humanized antibody will comprise all or substantially all of at least one, and typically two, variable domains, in which all or substantially all the hypervariable regions correspond to those of a non-human immunoglobulin and all or substantially all of the [framework regions] are those of a human immunoglobulin sequence."

Id. at 9:33-38.

The first sentence under the heading "Summary of Invention" states that the "application describes humanized anti-VEGF antibodies and anti-VEGF antibody variants with desirable properties from a therapeutic perspective." '879 patent at 2:15-17. The written description then explains that the anti-VEGF antibodies with the desirable properties will have heavy and light chain variable domains with specifically identified amino acid sequences. *Id.* at 2:33-3:64. In addition, the written description states that the "preferred embodiment" of the invention will have heavy and light chain hypervariable regions with specifically identified amino acid sequences. *Id.* at 14:34-16:7.

The figures in the written description and the patent's claims are also largely directed to the structure of antibodies. Several figures in the '879 patent compare the amino acid sequences of heavy and light chain variable domains for humanized antibodies, murine antibodies, and human antibodies. *See Id.* at Fig. 1A, 1B, 5A, 5B, 9A, 9B, 10A, 10B, 4:25-36, 4:66-5:15, 5:34-64. Independent claim 1 and the claims that depend from it are also directed to antibodies with a particular structure. The specification sets forth over 90 amino acid sequences, each identified by a particular sequence number ("SEQ ID NO"). '879 patent at col. 55-129. These amino acid sequences are a key limitation in independent claim 1, which requires that the three complimentary determining regions of the heavy

chain (CDRH1, CDRH2, and CDRH3) have SEQ ID NO 128, SEQ ID NO 2, and SEQ ID NO 129 respectively. *Id.* at 131:2-8. In addition, the sole limitation for six of the seven claims depending from claim 1 is a heavy and/or light chain variable domain with the SEQ ID NO identified. *Id.* at 131:9-132:23 (*see* dependent claims 6, 9, 11, 12, 13, 14).

In short, the '879 patent repeatedly refers to the amino acid sequences that comprise a humanized antibody. Moreover, neither claim 1 nor any of its dependent claims mention a "process." In contrast, independent claim 4 covers "a process of producing a humanized anti-VEGF antibody." *Id.* at 131:11-13. Accordingly, I will adopt Genentech's construction for "said humanized variant" and "said humanized anti-VEGF antibody."

F. Preamble of Claim 2: "A method for inhibiting VEGF-induced angiogenesis in a subject" ('269 patent)

Genentech's construction: Plain and ordinary meaning. The preamble is not limiting.
Amgen's construction: The preamble is limiting.
Court's construction: Plain and ordinary meaning. The preamble is not limiting.

1. Background

Claim 2 of the '269 patent, reformatted for clarity, provides:

A method *for inhibiting VEGF-induced angiogenesis* in a subject,

> comprising administering to said subject an effective amount of a humanized anti-VEGF antibody which binds human VEGF with a Kd value of no more than about lxl0-8M,
>
> said humanized anti-VEGF antibody comprising a heavy chain variable domain sequence of SEQ ID N0:7 and a light chain variable domain sequence of SEQ ID N0:8.

'269 patent at 128:23-30.

2. Analysis

The parties dispute whether "inhibiting VEGF-induced angiogenesis" in the preamble of claim 2 is an affirmative limitation. Language in a preamble limits a claim where it "recites essential structure or steps" or is "necessary to give life, meaning, and vitality" to the claim. *Catalina Mktg Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed Cir. 2002) (quoting *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999)). But language in a preamble is not limiting where "a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention." *Catalina Mktg.*, 289 F.3d at 808 (quoting *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997)).

The term "subject" in the preamble to claim 2 provides antecedent basis for "said subject" in the body of the claim and, therefore, the preamble is limiting to that extent. But otherwise, the preamble is not limiting for two reasons. First, the body of claim 2 recites a structurally complete invention (i.e., "administering to [a]

subject an effective amount of a humanized anti-VEGF antibody"). Second, the preamble merely recites the purpose of the invention (i.e., "*for* inhibiting VEGF-induced angiogenesis in a subject"). *See TomTom, Inc. v. Adolph,* 790 F. 3d 1315, 1322-24 (Fed. Cir. 2015) (holding that portion of preamble may be limiting while remainder, which "only states the intended use of the invention," was not).

Accordingly, I will adopt Genentech's construction of the disputed claim term. The phrase "a method for inhibiting VEGF-induced angiogenesis in a subject" in the preamble of claim 2 of the '269 patent is given its plain and ordinary meaning and is not limiting.

G. "binds human VEGF with a Kd value of no more than about 1 x 10-8 M" ('269 patent)

Genentech's construction: Plain and ordinary meaning. The limitation does not require a Kd determination "in a subject."
Amgen's construction: "binds human VEGF in a subject with a Kd value of no more than about 1 x 10 –8 M"
Court's construction: Plain and ordinary meaning. The limitation does not require a Kd determination "in a subject."

1. Background

Again, claim 2 of the '269 patent provides:

> A method for inhibiting VEGF-induced angiogenesis in a subject,
>
> comprising administering to said subject an effective amount of a humanized anti-VEGF antibody which *binds*

human VEGF with a Kd value of no more than about lxl0-8M,

said humanized anti-VEGF antibody comprising a heavy chain variable domain sequence of SEQ ID N0:7 and a light chain variable domain sequence of SEQ ID N0:8.

'269 patent at 128:23-30 (emphasis added).

2. Analysis

"Kd value" measures "binding affinity" between an antibody and an antigen. *See* '269 patent at 6:66-67, 58:56. The lower the Kd value the stronger the binding affinity. *Id.* at 3:32-37. Amgen's proposed construction inserts the words "in a subject" into the disputed claim limitation so that it reads: "binds human VEGF *in a subject* with a Kd value of no more than about l x l0-8M." D.I. 325 at 108 (emphasis added). Genentech argues for the plain and ordinary meaning of the limitation. *Id.* Thus, the crux of the dispute is whether the Kd value recited in claim 2 is measured inside a subject (Amgen's position) or inside a laboratory (Genentech's position).

The intrinsic evidence supports Genentech's proposed construction. The patent's written description teaches multiple methods for measuring binding affinity in a laboratory and no method for measuring binding affinity in a subject. *See, e.g.,* '269 patent at 17:50-53 ("The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson et

al., Anal. Biochem., 107:220 (1980)"); *id.* at 36:45-48 (describing an assay for "measuring the VEGF binding activity of F(ab)s," which is the antigen-binding region of the antibody); *id.* at 37:3-5 (stating that "VEGF binding of the humanized and chimeric F(ab)s were compared using a BIAcore™ biosensor"); *id.* at 44:18-32 (describing how to measure binding affinity by using "surface plasmon resonance"). Accordingly, I will adopt Genentech's proposed construction for "binds human VEGF with a Kd value of no more than about l x l0-8M."

III. CONCLUSION

I will construe the disputed terms as explained above. The Court will issue an order consistent with this Memorandum Opinion.