IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

GENENTECH, INC. and CITY OF HOPE, *Plaintiffs and Counterclaim Defendants*, v. AMGEN INC., *Defendant and Counterclaim Plaintiff.*	Civ. No. 18-924-CFC
GENENTECH, INC. and CITY OF HOPE, *Plaintiffs and Counterclaim Defendants*, v. SAMSUNG BIOEPSIS CO., LTD., *Defendant and Counterclaim Plaintiff.*	Civ. No. 18-1363-CFC

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MEMORANDUM OPINION

June 14, 2019

Wilmington, Delaware

CONNOLLY, UNITED STATES DISTRICT JUDGE

This action arises under the Biologics Price Competition and Innovation Act ("BPCIA"), 42 U.S.C. § 262, and involves biosimilar versions of Herceptin®, a drug used to treat breast cancer. Pending before me is the matter of claim construction pursuant to *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996). Plaintiffs Genentech, Inc. and City of Hope (collectively, "Genentech") and Defendants Amgen, Inc. ("Amgen") and Samsung Bioepsis Co., Ltd. ("Samsung," and collectively with Amgen, "Defendants") have asked me to construe the meaning of terms set forth in U.S. Patent Nos. 7,993,834 ("the '834 patent"); 8,076,066 ("the '066 patent"); 8,574,869 ("the '869 patent"); 8,512,983 ("the '983 patent"); and 7,390,660 ("the '660 patent"). D.I. 60; D.I. 121.[1]

I held a *Markman* hearing on April 24, 2019.[2] D.I. 182. I ruled from the bench with respect to one of the disputed terms. *See Id.* at 12:3-14:14 (adopting Genentech's proposed construction of "A method for increasing likelihood of

[1] All citations are to the docket for C.A. No. 18-924 unless stated otherwise.

[2] Two of the terms at issue in this case are also at issue in *Genentech v. Amgen*, C.A. 17-1407 (the "Avastin case"). Oral argument on the overlapping terms was held in the Avastin case on April 2, 2019 and April 23, 2019. *See* C.A. 17-1407, D.I. 340 at 5:8-83:10 ("following fermentation") and D.I. 345 at 18:18-96:21 ("glutamine-free"). Samsung appeared in the Avastin case to state that it has "the same position as Amgen" on glutamine-free, "so we don't need to … argue it on [April] 24th." D.I. 345 at 96:5-8.

effectiveness of breast cancer treatment with humanized anti-ErbB2 antibody huMAb4D5-8"). The parties also agreed during the hearing that I could assign another disputed term ("Pre-Harvest [Culture Fluid]") its plain and ordinary meaning. *See id.* at 90. I address in this Memorandum Opinion the remaining disputed terms.

I. STANDARD OF REVIEW

"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).[3]

The court may also consider extrinsic evidence, which "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Phillips*, 415 F.3d at 1317.

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[3] 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."

"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. CONSTRUCTION OF DISPUTED TERMS

A. "Wherein The Patient's Cancer Cells Express HER2 At A 0 Or 1+ Level By Immunohistochemistry" ('066 patent)[4]

Genentech's Construction	"wherein the patient's cancer cells have an antigen level corresponding to a 0 or 1+ score for HER2 by any immunohistochemistry test"
Amgen's Construction	"wherein the patient's cancer cells have been found to express HER2 at a 0 or 1+ level by any immunohistochemistry test"
Court's Construction	"wherein the patient's cancer cells have been found to express HER2 at a 0 or 1+ level by any immunohistochemistry test"

1. Background

Claim 1 of the '066 patent, reformatted for clarity, recites:

> A method of identifying and treating a breast cancer patient disposed to respond favorably to a HER2 antibody, huMAb4D5-8,
>
> which method comprises detecting her2 gene amplification in cancer cells in a breast tissue sample from the patient and treating the patient

[4] This term is not at issue in the case between Genentech and Samsung.

with her2 gene amplification with the HER2 antibody in an amount effective to treat the breast cancer,

wherein the patient's cancer cells express HER2 at a 0 or 1+ level by immunohistochemistry.

'066 patent at 22:22-64 (emphasis added).

Some technical background is helpful in understanding the intrinsic evidence. Trastuzumab, the active ingredient in Herceptin®, is an antibody that binds to the protein HER2, a receptor on the surface of a cell, and slows the growth of "HER2-positive" cancer cells. The HER2 protein is encoded by the HER2 gene. A normal cell has two copies of the HER2 gene. In patients with certain types of breast cancer, cells have extra copies of the HER2 gene. The relevant field of art refers to the extra copies of the HER2 *gene* as "amplification." Having extra copies of the HER2 gene results in a higher than normal level (i.e., "overexpression") of the HER2 protein. Thus, amplification of the HER2 *gene* is said to result in the overexpression of the HER2 *protein.*

At the time of the invention, there were two ways to test a sample of breast cancer tissue: (i) immunohistochemistry ("IHC") tests, which measured antigen levels (i.e., overexpression of the HER2 protein), and (ii) fluorescence in-situ hybridization ("FISH") tests, which measured the number DNA copies of the HER2 gene (i.e., amplification). In general, pathologists evaluated IHC assays using a 0, 1+, 2+, and 3+ scoring system. A score of 0 to 1+ was considered

HER2-negative. A score of 2+ was considered "borderline" or "equivocal." A score of 3+ was considered HER2-positive. At the time of the invention, it was known in the art that IHC tests could yield false negative results that excluded patients from treatment who might otherwise have benefitted from it.

2. Analysis

Genentech and Amgen dispute the meaning of "wherein the patient's cancer cells express HER2 at a 0 or 1+ level by immunohistochemistry." The crux of the dispute is whether this "wherein" clause requires that an IHC test be performed as a step in the claimed method. Amgen argues that an IHC test is required. Genentech contends the test is not necessary. I agree with Amgen.

First, claim 1 describes a "method of *identifying* and treating a breast cancer patient disposed to respond favorably to a HER2 antibody ... wherein the patient's cancer cells express HER2 at a 0 or 1+ level by immunohistochemistry." *Id.* at 22:22 (emphasis added). To identify a patient with an IHC score of 0 or 1+, an IHC test has to be performed on that patient's cancer cells.

Genentech admits that the "wherein" clause is "a substantive claim requirement" and that infringement of claim 1 requires "that the patient's cancer cells express HER2 at a zero or one-plus level." D.I. 182 at 43:19-20. It argues, however, that

> [t]here are multiple ways that one might determine that. One might do a test and one might go back and look at patient samples as patients who were screened using FISH and who were then treated with Herceptin and determine what the IHC result for those patients would be. One might also perform a statistical analysis, which is common in patent cases in evaluating the scope of infringement.

Id. at 24:22-25:3.

There are two problems with this argument. First, conducting an IHC test after a patient's treatment effectively reads "identifying" out of the claimed method. "[I]t is well settled that claims are not to be interpreted so as to render claim language meaningless." *Dade Behring Marburg GmbH v. Biosite Diagnostics, Inc.*, 1998 WL 552962, at *15 (D. Del. July 24, 1998). If "identifying ... a breast cancer patient disposed to respond favorably to a HER2 antibody" is to have meaning, the identification of the patient must be part of the claimed method. And if the "wherein" clause is, as Genentech admits, a substantive requirement, then the ascertainment of the patient's HER2 level "*by* immunohistochemistry" must be part of the identification.

Second, the claim calls for the identification and treatment of "*a* breast cancer patient." This reference to the singular patient makes clear that the method does not contemplate the use of statistical analysis of "samples [of] patients who were screened using FISH." Genentech may be correct that "around 9 to 10

percent" of patients with a FISH+ test result "will score a 0 or 1+ by [ICH]." D.I. 121 at 58. But that does not mean that a *particular* patient with a FISH+ test result will have an ICH score of 0 or 1+. Indeed, accepting Genentech's cited statistic as true, the odds are that a particular patient with a FISH+ score will *not* have an ICH score of 0 or 1+.

The patent's written description also largely supports Amgen's reading of claim 1. It states that "[a] particular advantage of the invention is that it permits selection of patients for treatment who, based on immunohistochemical criteria, would be excluded." '066 patent at 3:22-24; *id.* at 21:65-67. This sentence makes clear that the invention is directed towards the identification (i.e., selection) of patients whose ICH scores (i.e., immunohistochemical criteria) would hitherto have excluded them from treatment because of false-negative ICH test results. The fact that the written description repeatedly refers to an ICH "0 or 1+ level" as "a score," *see, e.g.*, *id.* at 3:26, 4:2, 18:24, and equates scores with "results," *see, e.g.*, *id.* at 18:54, provides further evidence that the patent contemplates the selection of a patient based on the results determined by an actual ICH test.

The prosecution history also makes clear that the claimed method requires the performance of an IHC test. Claim 1 originally did not have the "wherein" clause and, therefore, described a method that relied solely on FISH to "detect[ ]

HER2 gene amplification" in a breast tissue sample taken from the patient. D.I. 60-5 at J.A. 1719. The Examiner rejected the claim as obvious in light of Baselga, Pauletti, and Persons. *Id.* at J.A. 1729-30. Baselga taught that breast cancer patients "should be screened for overexpression of Her2 *before* treatment." *Id.* at 1730 (emphasis added). Pauletti and Persons taught that "detection of Her2 gene amplification using FISH is superior to immunochemistry [sic] for assessing Her2 status in patients with breast cancer." *Id.* Thus, the Examiner concluded that one would have been motivated to use FISH instead of IHC to assess HER2 status before treatment, because both Pauletti and Persons taught the advantages of the FISH technique. *Id.* Genentech overcame the rejection by adding the "wherein" clause to claim 1. *Id.* at J.A. 1735-36. The Examiner accepted Genentech's amendment, because the "wherein" clause "chang[ed] the scope of the claims to a method for treating patients that express HER2 at 0 or 1+ level *by immunohistochemistry* and also have a HER2 gene amplification." *Id.* at J.A. 1740-41 (emphasis added).

In its remarks to the Examiner, Genentech stated that support for the amendment could be found in the written description's statement that "[i]dentification of FISH+ patients in the 1+ and 0 sub-groups might identify subjects who, though failing the IHC criteria for HERCEPTIN® treatment, would

likely benefit from HERCEPTIN® treatment." *See Id.* at J.A. 1736 (asserting that the "wherein" clause amendment is "supported ... by page 28, line 27-29" of the original specification, which ultimately became lines 19:42-47 of the '066 patent). Thus, Genentech specifically linked patients who received a failing IHC score to the disputed claim limitation. Having disclaimed a method that did not require IHC testing, Genentech cannot now recapture claim scope it relinquished during prosecution. *See Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1323 (Fed. Cir. 2003) ("The doctrine of prosecution disclaimer . . . preclud[es] patentees from recapturing through claim interpretation specific meanings disclaimed during prosecution.").

Genentech relies heavily on the following excerpt from the written description:

> [T]he present invention is a powerful adjunct to IHC assays for target protein expression level-based selection of patients. *It can also be employed on its own*, i.e., without IHC, to provide initial screening and selection of patients.

D.I. 138 at 50 (citing '066 patent at 4:34-37) (emphasis added). This statement, however, was in the original written description before Genentech added the "wherein" clause to overcome the Examiner's obviousness rejection just discussed. *See* D.I. 60-5 at J.A. 1469. Thus, the "present invention" referred to in the quoted

passage describes the method taught by claim 1 *before* the claim was amended—i.e., a method claim that required only FISH testing and not IHC testing.

I also do not find compelling Genentech's two claim differentiation arguments. First, Genentech argues that language in dependent claim 3 of the '066 patent would be rendered surplusage under Amgen's construction of independent claim 1. D.I. 138 at 51. It points specifically to claim 3's requirement that "the patient's breast cancer cells *ha*[*ve*] *been subjected* to immunohistochemistry assay and *found* to express HER2 at 0 and 1+ level." '066 patent at 23:2-4 (emphasis added). The doctrine of claim differentiation, however, does not apply when other claim language distinguishes the claim scope. *Mantech Envtl. Corp. v. Hudson Envtl. Servs., Inc.*, 152 F.3d 1368, 1376 (Fed. Cir. 1998). Dependent claim 3 states in its entirety: "the method of claim 1 *wherein a formaldehyde-fixed tissue sample containing the patient's breast cancer cells* has been subjected to immunohistochemistry assay and found to express HER2 at a 0 or 1+ level." '066 patent at 23:1-4. Thus, dependent claim 3 is distinguished from and narrower than independent claim 1 based on the use of a formaldehyde-fixed tissue sample. *Id.* at 1:30-44, 2:21-35.

Second, Genentech argues that the difference between claim 2 of the related '834 patent—which includes a "wherein" clause that expressly states that a

patient's cells "have been found to express" HER2 at a 0 or 1+ level—and claim 1 of the '066 patent—which does not include the past tense language "have been found"—means that the '066 patent does not require that the patient's cells were "found to express" such ICH test results. *See* D.I. 121 at 68. But the "wherein" clauses of both patents were added by Genentech in response to same objection by the patent examiner. *Compare* D.I. 60-5 at J.A. 1526, 1531-34 (the '834 patent) *with* D.I. 60-6 at J.A. 2147-49 (the '066 patent). Thus, the slight difference in wording between the two "wherein" clauses should not be interpreted to suggest different meanings. *See Multiform Desiccants, Inc. v. Medzam, Ltd.* 133 F.3d 1473, 1480 (Fed. Cir. 1998) ("[T]he doctrine of claim differentiation cannot broaden claims beyond their correct scope, determined in light of the specification and the prosecution history and any relevant extrinsic evidence."). The common written description and prosecution history of the '834 and '066 patents suggest that both sets of claims are properly construed to cover the same subject matter. *See Nystrom v. TREX Co., Inc.,* 424 F.3d 1136, 1143 (Fed. Cir. 2005) ("Different terms or phrases in separate claims may be construed to cover the same subject matter where [the intrinsic evidence indicates] that such a reading of the terms or phrases is proper.").

Accordingly, I will adopt Amgen's proposed construction. The disputed claim limitation in claim 1 of the '066 patent, which states "wherein the patient's cancer cells express HER2 at a 0 or 1+ level by immunohistochemistry," means "wherein the patient's cancer cells have been found to express HER2 at a 0 or 1+ level by any immunohistochemistry test."

B. "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"
Samsung's construction	"after all the steps that occur in the production fermenter"
Court's construction	I am unable to construe the limitation 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 (emphasis added). As stated, the goal of the invention is to prevent the reduction of disulfide bonds in the antibody expressed in a recombinant host cell.

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 phrase does not "provide clear guidance for when 'fermentation' ends and 'following fermentation' begins[.]" D.I. 121 at 68. 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. Samsung defines "fermentation" as "the steps that occur in the production fermenter." *Id.* at 63. Genentech equates "fermentation" with "the cell growth and antibody production phases." *Id.*

Although the '869 patent has a lengthy section titled "Definitions," it does not provide definitions for "fermentation," "fermenter,"[5] or "production."

[5] "Fermenter" does not appear in the patent. The patent uses but does not define "fermentor."

Language in column 9 of the patent suggests that "fermentation" 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). The use of the words "following fermentation" immediately after a description of the "production phase" in another portion of the patent's written description 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." This sloppy language is unfortunately typical of the patent. Because of its two references to "reduction," the 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 teaches a method to achieve the prevention of "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 patent only adds to the confusion over the relationship between fermentation and production:

> 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*.

Id. 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.[6] And 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 a convene a hearing to determine if "following fermentation" can be construed by resort to extrinsic evidence or is invalid for indefiniteness.

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[6] 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)).

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

Genentech's Construction:	"A production culture medium that is essentially free of glutamine"
Defendants' 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, like trastuzumab, 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

Defendants assert that "a glutamine-free production culture medium" refers to a cell culture medium used in the production phase of the antibodies that omits glutamine from the formulation of the base media and/or feed media. D.I. 121 at 91. Genentech takes the position that "a glutamine-free production culture medium" refers to the concentration of glutamine in the bioreactor at any point during the production phase. *Id.* Because cells themselves can produce glutamine during the production phase, a glutamine-free production 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." *Id.*

I find that Defendants' proposed construction better aligns with the patent's intrinsic evidence and I will construe the limitation similarly to, though not exactly, the way Defendants do. 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 taught a "glutamine-free medium." D.I. 60-9 at 3231-35. In its response to the non-final rejection, Genentech agreed that Nagle, Tomei, and Kurano each taught a "glutamine-free" culture medium.[7] *Id.* at 3247-52. 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

[7] Genentech overcame the objection by amending the claims to add a limitation based on the concentration of asparagine. D.I. 60-9 at J.A. 3241, 3247-48.

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. 108-3, Ex. 17 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 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. 108-3, Ex. 18 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 was one that 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. 108-3, Ex. 19 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." *Id.* at 114-15 (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 would use 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."

D. "Wherein Said Citric Acid Or Citrate Is Maintained At A Concentration Of About 1 To 50 mmol/L During Cultivation" And "Is Not Bound In A Chelate Complex With Iron Or Another Transition Metal Ion" ('660 patent)[8]

Genentech's construction	"the concentration of citric acid or citrate that is not bound in a chelate complex with iron or another transition metal ion is kept between approximately 1 and approximately 50 mmol/l while the cells are cultivated"
Samsung's construction	"the concentration of citric acid or citrate in the culture medium is maintained within the claimed range during cultivation; excludes concentrations below 1 mmol/l. None of the citric acid is bound in a chelate complex with iron or another transition metal ion."
Court's construction	"during the cultivation of the cells the citric acid or citrate is maintained at a concentration of between approximately 1 and approximately 50 mmol/l and is not bound in a chelate complex with iron or another transition metal ion"

1. Background

Claim 1 of the '660 patent, reformatted for clarity, provides:

> A method for reducing glucose consumption during cultivation of CHO, myeloma, or hybridoma cells, comprising
>
> cultivating CHO, myeloma, or hybridoma cells in culture medium in the presence of citric acid or citrate
>
> *wherein said citric acid or citrate is maintained at a concentration of about 1 to 50 mmol/l during cultivation* and
>
> *wherein said citric acid or citrate is not bound in a chelate complex with iron or another transition metal ion.*

[8] This term is not at issue in the case between Genentech and Amgen.

'660 patent at 6:30-37.

2. Analysis

Genentech and Samsung dispute the meaning of both "wherein" clauses of claim 1. They disagree about the meaning of "about 1 to 50 mmol/l" in the first "wherein" clause. And they dispute whether the second "wherein" clause requires that *all* the citric acid and citrate in the presence of which the CHO, myeloma, or hybridoma cells are cultivated must be "not bound in a chelate complex with iron."

a. "About 1 to 50 nmol/l"

Samsung asks me to construe "about 1 mmol/l" as having a strict cutoff that "exclude[s] concentrations below 1 mmol/L." D.I. 121 at 124. It is well-established, however, that "use of the word 'about,' avoids a strict numerical boundary." *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217 (Fed. Cir. 1995). Instead, the claim term "about" encompasses amounts slightly above or below the specified numerical range. *See Ferring B.V. v. Watson Labs., Inc.-Fla.*, 764 F.3d 1382, 1389 (Fed. Cir. 2014) ("about" means "approximately"). In this case, there is no support in the intrinsic evidence for deviating from the ordinary meaning of "about."

Samsung identifies two examples in the written description that use 2.4 mmol/l citrate. D.I. 121 at 129 (citing '660 patent at 4:27, 4:61, 6:20). But

nothing about the specific amount used in the examples suggests that the word "about" should be written out of claim 1. Samsung also relies on a declaration submitted during prosecution wherein the inventor stated that "[d]uring the experiments, the amount of citrate was adjusted by adding citrate to the production bioreactor to maintain a certain level of citrate 1 - 50 mmol/L." D.I. 121 at 130 (citing D.I. 60-13, J.A. 4508 at ¶ 6). This declaration, however, was directed to a different claim limitation that is not present in the issued claim. D.I. 60-13, J.A. 4499-50 (addressing limitations reciting "adjusting the amount of the bicarbonic acid or tricarbonic or salt thereof, if necessary, to achieve a reduction in the rate of glucose consumption by at least about 40%"). Thus, there is nothing about the declaration that suggests that Genentech was making a clear and unmistakable disclaimer of "about 1 mmol/l" in the present claim limitation. Because nothing in the intrinsic record suggests a strict cutoff, I will not adopt Samsun's construction of "about 1 mmol/l." Instead, I will give the term its plain and ordinary meaning—i.e., "approximately."

b. "not bound in a chelate complex with iron"

Genentech asks that I construe the second "wherein" clause as restricting the first "wherein" clause, and thus read the "not bound in a chelate complex with iron" limitation as applying only to the citric acid and citrate that is kept in a

concentration of about 1 to 50 nmol/l during cultivation. The problem with this construction is that it conflicts with the plain language of the claim. It is clear from the claim's plain language that both "wherein" clauses are restrictive clauses that modify (i.e. get their antecedent basis from) the first mention of "citric acid or citrate" in the claim, i.e., the citric acid or citrate in the presence of which the CHO, myeloma, or hybridoma cells are cultivated. Thus, the citric acid or citrate in which the cultivation is performed must be *both* (1) in a concentration of about 1 to 50 nmol/l *and* (2) not bound in a chelate complex with iron. Accordingly, I agree with Samsung's construction that "[n]one of the citric acid is bound in a chelate complex with iron or another transition metal ion."

In support of its position, Genentech points to the following language in the written description:

> The cultivation is performed in the presence of one or more bi- or tricarbonic acids or their salts ... at a concentration of about 1 to 50 mmol/1. Specifically, where the di- or tricarbonic acid or salt is citric acid or citrate, *this amount* of citric acid or citrate is not bound in chelate complex with iron or another transition metal ion.

'660 patent at 2:9-16 (emphasis added). Genentech is correct that "this amount" refers to the citric acid and citrate that are at a concentration of about 1 to 50 mmol/1. But the quoted passage does not say that *other amounts* of citric acid or citrate are bound (or not bound) in chelate complex with iron. Thus, it does not contradict or conflict with the plain language of the claim. On the contrary, the

quoted passage is entirely consistent with giving both "wherein" clauses of claim 1 their plain meaning and reading them each as limiting the citric acid or citrate in which the cultivation of the CHO, myeloma, or hybridoma cells occurs.

The evidence that most strongly favors Genentech's position is the specification's description of one of at least three embodiments identified in the patent as "preferred":

> Bi- and tricarbonic acids are *preferably* added as an alkali metal or alkaline metal salt or as free acid at a concentration of about 1 to 50 mmol/1. This acid is *preferably* not bound to a chelate complex with iron or another transition metal. However, the medium may *preferably* contain an additional amount of a bi- and tricarbonic acid or a citrate salt thereof in a chelate complex with iron.

Id. at 2:58-64 (emphasis added). The first two sentences in this passage describe the preferred embodiment as having unbound citric acid in a concentration of 1 to 50 mmol/l. The last sentence suggests that either *this* preferred embodiment or *a different* preferred embodiment may contain an additional amount of citric acid or citrate that is bound.

Although a "claim construction that would exclude the preferred embodiment is rarely, if ever, correct and would require highly persuasive evidentiary support," *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1342 (Fed. Cir. 2001) (internal quotation marks and citation omitted), the disclosure of this

latter embodiment does not alter my conclusion to adopt Samsung's construction of the "not bound" limitation. My reasoning is threefold.

First, the embodiment at issue is not "*the* preferred embodiment," but rather one of at least three and possibly four embodiments identified by the patent as preferred. '660 patent at 2:58-64. Second, during the prosecution of the patent, the Applicant disclaimed a culture medium that contained bound citrate. The Applicant added the "not bound" limitation to overcome a rejection that was based on the Examiner's conclusion that a prior art reference (WO93/00423) anticipated the patent's independent claims that did not include a "not bound" limitation. WO93/00423 disclosed a culture medium that contained *both* chelated (i.e., bound) and free citrate. Because the Applicant disclaimed during the patent's prosecution a culture medium that contained bound citric acid, Genentech cannot now recapture that relinquished claim scope. *See Omega*, 334 F.3d at 1323. Third, the claim language itself is clear, and "it is the *claims*, not the written description, which define the scope of the patent right." *Laitram Corp v. NEC Corp.*, 163 F.3d 1342, 1347 (Fed. Cir. 1998) (emphasis in the original) (citations omitted).

Finally, citing an expert's declaration, Genentech argues that requiring all of the citric acid and citrate to be not bound is "inconsistent with the real-world conditions necessary for cell growth[,]" as "it was well understood [when the

patent was prosecuted] that cells require trace amounts of iron and other transition metals to survive in culture." D.I. 121 at 126. Such extrinsic evidence, however, "in general [i]s less reliable than the patent and its prosecution history in determining how to read claim terms." *Phillips*, 415 F.3d at 1318. Moreover, "a court should discount any expert testimony that is clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history." *Id.* (internal quotation marks and citation omitted). In this case, the plain language of the claim and the prosecution history make clear that the Applicant did not pursue claims covering trace amounts of citrate or citric acid bound in a chelated complex with iron.

Accordingly, I will construe the "not bound" limitation as applying to all the citric acid or citrate used during cultivation and will construe the two "wherein" clauses of claim 1 to mean: "during the cultivation of the cells the citric acid or citrate is maintained at a concentration of between approximately 1 and approximately 50 mmol/l and is not bound in a chelate complex with iron or another transition metal ion."

III. CONCLUSION

I will construe the disputed terms as explained above.

The Court will issue an Order consistent with the Memorandum Opinion.