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.
GENENTECH, INC. and CITY OF HOPE, *Plaintiffs*, v. AMGEN INC., *Defendant.*	Civ. No. 18-924-CFC

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MEMORANDUM OPINION

March 9, 2020
Wilmington, Delaware

CONNOLLY, UNITED STATES DISTRICT JUDGE

Genentech, Inc. and City of Hope (collectively, Genentech) brought these patent infringement actions against Amgen, Inc. pursuant to the Biologics Price Competition and Innovation Act (BPCIA), 42 U.S.C. § 262. Pending before me is the matter of the construction of the disputed claim term "following fermentation" in United States Patent Number 8,574,869 (the Kao or #869 patent). The Kao patent teaches methods and means of preventing disulfide bond reduction during the manufacturing of therapeutic antibodies. #869 patent at 1:17–22.

I initially heard argument on the meaning of "following fermentation" and other disputed claim terms at two *Markman* hearings convened in April 2019. C.A. No. 17-1407, D.I. 340; C.A. No. 18-924, D.I. 182.[1] In memorandum opinions issued in June 2019, I explained that I was unable to construe "following fermentation" based solely on the intrinsic evidence, and I ordered a hearing "to determine if 'following fermentation' can be construed by resort to extrinsic evidence or is invalid for indefiniteness." D.I. 256 at 19.[2]

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

[2] Identical documents were usually filed in both cases. In addition, the memorandum opinions' discussions of "following fermentation" are identical. Accordingly, all citations are to the docket for C.A. No. 18-924 unless otherwise noted.

The parties thereafter presented me with extrinsic evidence in the form of affidavits, treatises, articles, reports, and competing expert testimony at an evidentiary hearing on October 16, 2019. D.I. 372; D.I. 373. Based on the extrinsic evidence and my reconsideration of the intrinsic evidence in light of that extrinsic evidence, I have concluded that a person of ordinary skill in the art (POSITA) would understand "following fermentation" to mean "after the earlier of harvesting or purification has begun," and I will construe the term accordingly.

I set forth the legal standards that govern claim construction in my earlier memorandum opinions. *See* D.I. 256 at 3–5. Rather than repeat those standards here, I incorporate by reference the earlier memorandum opinions. I write primarily for the parties and, to a large degree, presume familiarity with the underlying technology.

I.

Claim 1 of the Kao patent 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 (reformatted for clarity and emphasis added). As I explained in my earlier memorandum opinions, the construction of "following fermentation" involves two questions. First, what is "fermentation?" And second, when does "fermentation" end? D.I. 256 at 15.

Unfortunately, as I also discussed in my earlier memorandum opinions, the Kao patent neither defines fermentation nor allows for a cogent inference of fermentation's meaning, let alone when it ends. The patent is plagued by typographical errors and sloppy language; it suggests at times that fermentation is synonymous with "production" and "manufacturing" and at other times that fermentation is distinct from these concepts. *Id.* at 16, 19 n.6. To add to the confusion, the patent does not consistently use or assign meaning to "production" and "manufacturing." *Id.* at 19 n.6. As Genentech's counsel conceded (to his credit) at oral argument, "certain words like manufacturing and production may not be used quite as precisely as one would like in the Kao patent." C.A. No. 17-1407, D.I. 340 at 25:20–22. Resort to extrinsic evidence is therefore necessary. *See Digital Biometrics, Inc. v. Identix, Inc.*, 149 F.3d 1335, 1344 (Fed. Cir. 1998) ("[I]f after consideration of the intrinsic evidence there remains doubt as to the exact meaning of the claim terms, consideration of extrinsic evidence may be necessary to determine the proper construction.").

II.

Genentech argues that "fermentation" refers to "the growing of the cells and the producing of the protein [i.e., antibody]" in the manufacturing process. D.I. 528 at 13:20–22; *see also id.* at 66:13–22.[3] Amgen insists that I should reject this definition, D.I. 373 at 4, but it has used "fermentation" in the context of antibody manufacturing to mean exactly what Genentech says the term means. Specifically, in its 2011 Annual Report, Amgen stated that the "[b]ulk manufacturing" of its biological products "includes fermentation and/or cell culture, *processes by which our proteins are produced.*" D.I. 376-2 at Appx. 449 (emphasis added). In addition, Amgen's expert, Dr. Glacken, admitted during cross-examination at the evidentiary hearing that "[w]ithin the context of the Kao patent, the person of ordinary skill would understand the term fermentation to refer to cell culture processes for making antibodies." D.I. 528 at 145:14–19; *see also id.* at 152:7–9 (Glacken) (admitting that "using fermentation synonymous[ly] with mammalian cell culture is becoming more common").

Genentech's proposed definition of fermentation is well supported by other extrinsic evidence. For instance, Kemp states that therapeutic antibodies "are produced ... via mammalian cell fermentation." D.I. 376 at Appx. 248. And

[3] The parties used "protein" and "antibody" interchangeably, and I will therefore do the same.

Geigert states that "fermentation" is used interchangeably with "cell culture," which the parties equate with cell growth and antibody production. *See* C.A. No. 17-1407, D.I. 271-2, Ex. 9 at 119 (Geigert) ("In this CMC book, the terms 'fermentor' and 'bioreactor' will be used interchangeably; as well as the terms 'fermentation' and 'cell culturing.'"); D.I. 374 ¶ 1 (Hauser) (stating that "cell culture technology is "the science of isolating cells from their natural environment and growing them in a controlled, artificial environment" and that "cell culture processes [are] used to manufacture biotherapeutics, such as therapeutic antibodies"); D.I. 375 at ¶ 56 (Glacken) (noting that for some skilled artisans "[t]he term 'fermentation' refers to a process in which organisms growing in a liquid or solid medium produce an industrial product." (quoting U.S. Patent Appl. 2007/0141687A1)).

Support for Genentech's proposed definition of fermentation can also be found in the written description of the Kao patent. *See* #869 patent at 29:4–8 (discussing "fermentation, recovery and purification" in the sentence that immediately precedes discussion of "production, recovery and purification," thereby suggesting that fermentation and production are synonymous); *id.* at 26:29–41 (using "following fermentation" immediately after a description of the "production phase," thereby suggesting that fermentation and production are

synonymous). Therefore, I will adopt Genentech's definition of "fermentation"—i.e., the growing of the cells and producing of the protein.

III.

Neither side was able to point me to a treatise, dictionary, or other reference that expressly defines when fermentation ends in the antibody manufacturing process. Both parties, however, effectively conceded that "harvesting" marks the end of fermentation for proteins secreted into the cell culture fluid. I will therefore construe "following fermentation" for those antibodies to mean "after harvesting has begun."

Amgen's expert, Dr. Glacken, testified that "following fermentation is just harvest, really. If [the term] comes up at all, that's the context it comes up in." D.I. 528 at 165:6–9.

For its part, Genentech describes the end of fermentation as being coterminous with the end of antibody production. *See id.* at 13:20–23 (Genentech's counsel explaining that "[f]ermentation includes both the growing of the cells and the producing of the protein, and so in context, the end of production and the end of fermentation are coterminous, at the same time."). And Genentech describes the manufacture of therapeutic antibodies secreted from cells as follows:

> Therapeutic antibodies . . . are manufactured by growing or "culturing" genetically engineered cells inside large tanks called "bioreactors" (or "production fermenters" as referred to by [a defendant in a related civil case]). The

> cells produce the antibody and then secrete it into the surrounding culture fluid. ***Once the antibodies have been produced in sufficient quantity, the culture fluid containing the antibodies is "harvested"*** and then the antibodies are purified from the fluid.

D.I. 121 at 62 (citations omitted) (emphasis added). Thus, Genentech concedes that in the manufacture of antibodies secreted by the cells in the culture fluid, harvesting immediately follows fermentation.

That harvesting immediately follows—and thus can be said to mark the end of—fermentation, is supported by the extrinsic evidence. Wurm, for example, states that "the timing of the termination (that is, harvest) of a culture is driven mainly by plant capacity and productivity kinetics." D.I. 375-4, Ex. 5 at 1397. And the inventors of the Kao patent, along with other Genentech employees, acknowledged in a 2009 article that "[a]t the end of the production phase, the feedstock is usually harvested by disc stacked centrifugation followed by depth filtration or by tangential flow microfiltration." D.I. 376 at Appx. 130.

Construing "following fermentation" for secreted proteins to mean "after harvesting has begun" also finds support in the intrinsic evidence. The patent's written description, for example, explains that "[w]hen the cells grow to sufficient numbers, they are transferred to large-scale production tanks to begin the production phase, and grown for a longer period of time. *At this point in the process*, the recombinant protein can be harvested." #869 patent at 1:64–67

(emphasis added). Figure 23 of the patent similarly depicts "harvest" as the step that immediately follows cell growth and antibody production:

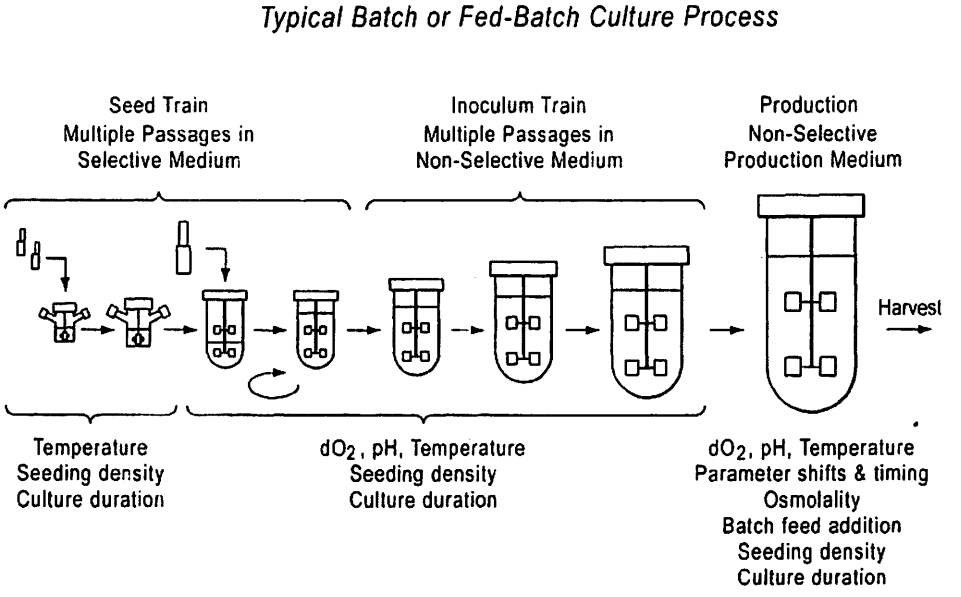

FIG. 23

The parties agree that for proteins that are secreted by the cells into the culture fluid, "harvesting" is, to use Genentech's words, "the process of separating the culture fluid (which contains antibody) from cells or cellular debris." D.I. 449 at 1 (citations omitted); *see also* C.A. No. 17-1407, D.I. 325 at 61 (Amgen acknowledging that "[w]hen 'the cells are engineered to secrete the [antibody] into the cell culture media, . . . the first step in the purification process is to separate the cells from the media,' which is harvesting") (quoting #869 patent at 1:67–2:4) (second alteration and ellipses in original)). And although the extrinsic evidence showed that there is no universal first step for every harvesting process, Genentech

agrees that a POSITA "readily could determine the first step of harvest in that process." D.I. 449 at 2. Accordingly, it makes sense to define the end of fermentation for proteins secreted into the cell culture fluid in terms of the beginning of harvesting.

Genentech argues that my construction is erroneous for two reasons. First, it states that

> [r]ather than address the meaning of 'following fermentation,' [my] construction elides it, substituting a distinct concept, the beginning of harvest. When something ends and when something else begins are not necessarily the same thing. History "following World War II" is defined by the end of the conflict known by that name (1945), not the beginning of, for example, the Cold War that followed (1947).

D.I. 514 at 1. It is of course true that "when something ends and when something begins are not necessarily the same thing." But sometimes they are the same thing, and we often meaningfully define the end of something with the beginning of something else. A marriage ends when a spouse dies or obtains a divorce. A pregnancy ends when a birth, miscarriage, or abortion occurs. And, most relevant here, crops end their growth when they are harvested. Genentech's World War II analogy misses the point. The end of World War II *is* defined by the beginning of another event—the surrender of Japan in August 1945. It is (clearly) *not* defined by the beginning of the Cold War two years after that surrender.

Second, Genentech argues that my construction "impermissibly nullifies one of the two embodiments the claims explicitly recite—the method of sparging a 'pre-harvest culture fluid' following fermentation." D.I. 514 at 3. But the premise of this argument—that "sparging of 'pre-harvest cell culture fluid' obviously cannot occur 'after harvesting has begun," *id.*—is neither obvious nor correct. Sparging of pre-harvest culture fluid *can* occur after harvesting of secreted antibodies has begun. If, for example, a harvesting were initiated by moving into another vessel culture fluid containing cells that had secreted their proteins directly into the fluid and then sparging were immediately begun in the new vessel, a pre-harvest fluid would be sparged after harvesting had begun.

IV.

There remains the issue of construing "following fermentation" when the antibodies are not made by secretion into the cell culture but are instead produced "intracellularly." *See* #869 patent at 26:43–45 (distinguishing antibodies "secreted directly from the cell into the surrounding growth media" from antibodies "made intracellularly"); *see also* C.A. No. 17-1407, D.I. 271-2, Ex. 9 at 119 (same).

The written description of the Kao patent states that "[f]ollowing fermentation proteins are purified," and it states further that when proteins are "made intracellularly . . . the first step of a purification process involves lysis of

cells." #869 patent at 26:41–47.[4] But the specification does not state expressly whether purification immediately follows fermentation.

Certain language in the written description could be read to suggest that purification does not immediately follow fermentation. The patent, for example, speaks of "the fermentation, recovery and purification methods described herein." #869 patent at 29:4–5; *see also id.* at 25:40–41 (describing "protocol for the production, recovery and purification of recombinant antibodies"); *id.* at 28:38–39 (referring to "[m]ethods for the production, recovery and purification of recombinant proteins"). Genentech cites this clause as evidence that the "antibody manufacturing process involves three steps," D.I. 325 at 65, and it argues that purification is the third step and is temporally separated from the first step (fermentation) by the second step (recovery, which the parties agree is the same thing as harvest), *id.* at 65–67; C.A. No. 17-1407 at 11:12–14; *id.* at 25:18–19; *id.* at 58:6–7 ("Well, Your Honor, so I think we agree that recovery is harvest.").

But other language in the written description can be read to suggest that harvesting is part of, not separate from, purification. Specifically, the written description provides:

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[4] Lysis refers to processes that disrupt the cell wall or membrane, thereby releasing the entire contents of the cell, including the proteins, into the culture medium. #869 patent at 26:43–45. Lysis can be done by a variety of methods, including mechanical shear, osmotic shock, or enzymatic treatments. *Id.*

> When the cells grow to sufficient numbers, they are transferred to large-scale production tanks and grown for a longer period of time. At this point in the process, the recombinant proteins can be harvested. Typically, the cells are engineered to secrete the [antibody] into the cell culture media, ***so the first step in the purification process is to separate the cells from the media.*** Typically, harvesting includes centrifugation and filtration to produce a Harvested Cell Culture Fluid (HCCF). The media is then subjected to additional purification steps that remove any cellular debris, unwanted proteins, salts, minerals, or other undesirable elements. At the end of the purification process, the recombinant [antibody] is highly pure and is suitable for human therapeutic use.

#869 patent at 1:64–2:9 (italics and underlining added).

Both sides agree that the italicized language describes "harvesting." *See* D.I. 449 at 1 (Genentech citing sentence containing italicized language in support of its proposed definition of "harvest" as "the process of separating the culture fluid (which contains the antibody) from cells or cellular debris"); C.A. No. 17-1407, D.I. 325 at 61 (Amgen citing sentencing containing italicized language in support of its contention that "harvesting" is the "first step in the purification process" and involves the "separat[ion] [of] the cells from the media."). And thus, they agree that harvesting is the first step in the purification process for proteins secreted from the cells into the culture fluid. The written description's subsequent reference to "additional purification steps" confirms that "harvesting" is a purification step. #869 patent at 2:5–6.

If harvesting is deemed to be part of purification, then the antibody manufacturing process consists of two steps, not three steps, as Genentech argues.

And if antibody manufacturing consists of only two steps—fermentation and purification—then it can be said that fermentation ends when purification begins.

Like the Kao patent, the extrinsic evidence adduced by the parties does not uniformly describe the steps of the antibody manufacturing process. *See, e.g.,* D.I. 376 at Appx. 179 (Fahrner) (describing antibody manufacturing process as "cell banking and cell culture, recovery, filling ..., finishing, and packaging."); *id.* at Appx. 214 (Birch) (describing antibody manufacturing process as "inoculum prep," "production," "clarification," and "purification"); C.A. No. 17-1407, D.I. 271-1 at 530 (Dwiveldi) (referring to the antibody manufacturing steps as "cell expansion," "fermentation," "harvest," "cell free harvest," and "concentration"); *id.* at 562 (Nelson) (identifying the basic steps of the antibody manufacturing process as "inoculum prep," "production," "recovery," "purification," and "bulk fill"); C.A. No. 17-1407, D.I. 271-2, Ex. 9 at 117 (Geigert) (identifying the steps of the antibody manufacturing process as "expansion of master/working bank aliquot," "expression of the biopharmaceutical," "harvest"). Nor does the extrinsic evidence uniformly use the terms "purification" or "recovery" (which the parties agree is synonymous with harvesting). *See, e.g.,* C.A. No. 17-1407, D.I. 271-1 at 442 (Bates) (stating that "initial purification" involves "filtration, centrifugation, precipitation, [and] large-bead adsorption chromatography"); *id.* at 566 (Nelson) (stating that purification is "typically a mixture of chromatography and ultrafiltration"); D.I. 376 at Appx. 179

(Fahrner) (stating that "[p]roduct recovery includes harvest ..., chromatography for antibody purification, and formulation by tangential flow filtration."); C.A. No. 17-1407, D.I. 271-1 at 442 (Bates) (describing the entire downstream process as "recovery," and depicting "recovery" as the steps of "initial purification," "intermediate processing," and "final polishing"); *id.* at 565 (Nelson) (stating that "recovery operations clarify and remove cell debris," and that "[c]larification operations may be done using centrifugation, depth filtration, dead-end sterile filtration, or tangential flow microfiltration.").

In sum, the intrinsic and extrinsic evidence is conflicting. But my overall impression of the evidence taken as a whole is that a POSITA would understand for purposes of the Kao patent that harvesting is part of purification and that antibody manufacturing consists of two steps—fermentation (i.e., cell culturing or antibody production) and purification. I find three things especially informative.

First, as noted above, the Kao patent describes both harvesting and lysing as "the first step" of purification, depending on whether the proteins are made by secretion or intracellularly. This suggests that the inventors ultimately viewed antibody manufacturing as consisting of two main processes—fermentation and purification. Second, Genentech's expert, Dr. Hauser, conceded at his deposition that POSITAs use "purification" in "a broad sense" to describe the "downstream processing" in the manufacturing of antibodies. *See* D.I. 326-4 at J.A. 1600,

138:10–12) ("I admit that people sometimes use 'purification' in a broad sense, like downstream processing"); *id.* at 139:2–4 ("purification is from time to time used in a very general way that [is] identical [to] or identically understood [as] downstream processing"). As there is only an upstream and a downstream, this concession also suggests a two-step manufacturing process. Third, the same sentence in Amgen's 2011 Annual Report cited by Genentech as evidence that Amgen understands "fermentation" to mean what Genentech says it means also makes clear that Amgen understands the "bulk manufacturing" of antibodies to consist of two steps: fermentation and purification. *See* D.I. 376-2 at Appx. 449 ("Bulk manufacturing includes fermentation and/or cell culture, processes by which our proteins are produced, and also includes purification of the proteins to a high quality.").

Accordingly, I will construe "following fermentation" for the proteins made intracellularly in terms of the beginning of purification. Furthermore, because claim 1 of the patent (in which "following fermentation" appears) applies to proteins made by either secretion or intracellularly and because of the inconsistent and overlapping uses of "harvest" (or recovery) and "purification" in the Kao patent and the extrinsic evidence, I will construe "following fermentation" to mean "after the earlier of harvesting or purification has begun."

V.

Genentech proposes that I construe "following fermentation" to mean "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)." D.I. 121 at 63–64. This definition is problematic for five reasons.

First, it is essentially a tautology. It defines the end of fermentation (i.e., cell growth and antibody production) as a change that "substantially ends" fermentation (i.e., cell growth and antibody production).

Second, nothing in the patent's claims, figures, or written description suggests that fermentation ends when cell growth and antibody production *substantially* end.

Third, the prosecution history contradicts Genentech's construction. Substantially means largely, but not wholly; and thus Genentech's construction would allow for continued cell growth following fermentation. But during prosecution, in overcoming a non-final rejection by the patent examiner, Genentech stated that a prior art reference did not anticipate the claims in question because the reference "describes sparging the culture medium *during the cell growth*" but "does not describe sparging the pre-harvest or harvested culture fluid of the recombinant host cell with air *following fermentation.*" C.A. No. 17-1407,

D.I. 326-2 at J.A. 612 (emphasis added) (underlines removed). Thus, Genentech disclaimed the possibility of cell growth following fermentation. *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.").

Fourth, nothing in the patent teaches a POSITA how to determine when cell growth and antibody production *substantially* ends. "When a word of degree is used the district court must determine whether the patent's specification provides some standard for measuring that degree." *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 4351 (Fed. Cir. 2005). The Kao patent provides no standard to ascertain when the end of cell growth and antibody production has been substantially reached.

And finally, Genentech's expert admitted that the analytical methods by which Genentech proposes to measure the substantial end of cell growth and antibody production are "theoretical[]" and that he is unaware of any occasion when such methods were actually used in an antibody manufacturing process. D.I. 106-5, Ex. 12 at 85:17–86:11; *see also* D.I. 528 at 81:6–10.

VI.

Wherefore, for the reasons discussed above, I will construe "following fermentation" in the Kao patent to mean "after the earlier of harvesting or purification has begun."

The Court will issue an order consistent with this Memorandum Opinion.