IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENENTECH, INC. and CITY OF HOPE, *Plaintiffs*, v. AMGEN INC., *Defendant*.	)	C.A. No. 17-1407-CFC (CONSOLIDATED) [redacted]
GENENTECH, INC., *Plaintiff and Counterclaim Defendant*, v. AMGEN INC., *Defendant and Counterclaim Plaintiff*.	)	C.A. No. 18-924-CFC

GENENTECH'S LETTER-BRIEF ADDRESSING
THE COURT'S POST-HEARING QUESTIONS

I. The First Step of Harvesting

"Harvest" is the process of separating the culture fluid (which contains the antibody) from cells or cellular debris. Kao at 2:1-5; No. 18-1363, D.I. 81 ¶¶ 42-43 & Ex. 6 at 301-02. Amgen appears to agree with this understanding of harvest. *See* No. 1407, D.I. 325 at 61.[1]

The "first step" in harvest therefore is the first step in the process of separating the antibody from cells and debris; its exact nature will depend upon how a company implements its manufacturing process. The antibody manufacturing process depicted in Figure 3 in the Birch paper from Lonza shows, in the second row, centrifugation as the first step in the harvest process. No. 1407, D.I. 516 at Appx213. The Kao patent's examples likewise involve centrifugation followed by filtration, Kao at 48:61-49:3, and the written description deems this sequence of harvest operations typical, *id.* at 2:3-4; *see also* 4/24/19 *Markman* Hrg. Tr. at 60:1-21. But other harvest implementations may separate the antibody from cells and debris using a first step other than centrifugation. Kao states that "harvesting by centrifugation, filtration *or* similar separation methods" can be used, Kao at 22:4-5 (emphasis added), and the review paper cited in Kao suggested harvesting by filtration *or* centrifugation, No. 18-1363, D.I. 81, Ex. 6 at 301-02.

[1] The parties also agree that "harvest" is used synonymously with "recovery" in Kao. *See* 4/24/19 *Markman* Hrg. Tr. at 57:18-58:11.

Thus, while centrifugation typically is the first step, there is no universal first step for every process of separating the antibody-containing culture fluid from the cells. However, given a particular manufacturing process, the POSA readily could determine the first step of harvest in that process.

All of the previous examples involve mammalian cells in which the antibody was secreted by the cells into the culture fluid. Other cells, for example bacteria, typically do not secrete proteins, so it is necessary to "lyse," or rupture, the cells to release any antibody trapped inside. Kao at 28:40-52. Depending upon the technique used (enzymatic treatment, osmotic shock, mechanical shear, etc., *see* Kao at 26:47-49), lysis may occur inside or outside of the bioreactor. After lysis, antibody expressed by bacterial cells may be harvested, including by the techniques discussed above. No. 1407, D.I. 325 at 62.

Whether the antibody is expressed in mammalian or bacterial cells, the patent is clear that harvest occurs after (but not necessarily immediately after[2]) the end of antibody production. *See* Kao at 25:40-42.

II. "Pre-Harvest Culture Fluid"

"Pre-harvest culture fluid" was a disputed term in the Genentech/Samsung Bioepis Herceptin litigation. The parties agreed during the *Markman* argument

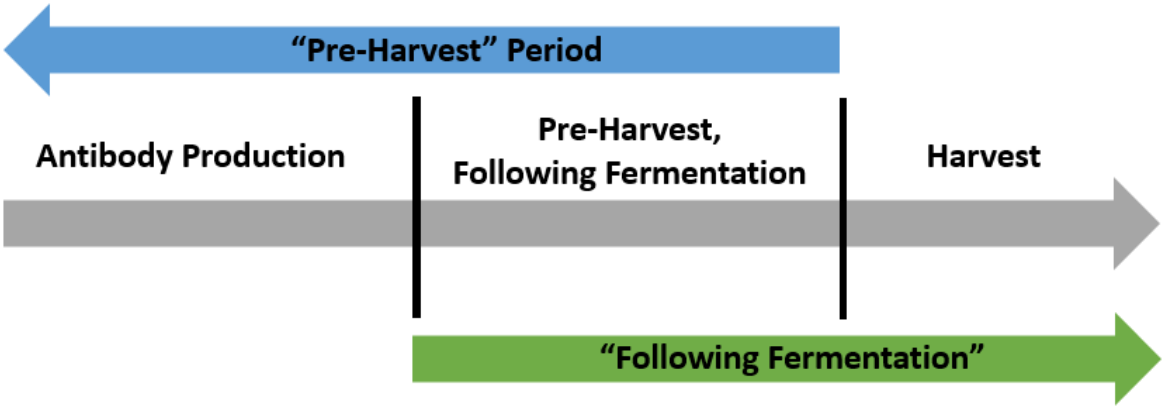
[2] As discussed below, a manufacturer can take steps to prepare to harvest after fermentation. Amgen agrees that harvest does not need to occur immediately after fermentation. *See* No. 1407, D.I. 325 at 61-62.

that its plain and ordinary meaning would suffice, No. 18-1363, D.I. 182 at 90, and the Court entered that construction, No. 18-1363, D.I. 257 at 2.

The plain and ordinary meaning of "pre-harvest culture fluid" is culture fluid that will be harvested. Kao explains how disulfide bond reduction can be inhibited by applying sparging "following completion of the cell culture processes, preferably to CCF [cell culture fluid] prior to harvest . . . ." Kao at 23:54-58. The "CCF prior to harvest" is pre-harvest culture fluid—culture fluid that will be harvested.

Kao's prosecution history reinforces that "pre-harvest" culture fluid is fluid that will be harvested. The Examiner issued a rejection over "Reeves," a reference disclosing sparging the bioreactor before harvest to support cell growth. No. 18-1363, D.I. 81 ¶¶ 62-63. Genentech did not dispute the Examiner's conclusion that Reeves disclosed sparging of "pre-harvest" culture fluid; rather, it responded by adding the "following fermentation" limitation to clarify that the claims concerned sparging at a different point in manufacturing.

"Following fermentation" thus limits when the claimed sparging occurs. It does *not* limit *where* the claimed sparging takes place. In some processes steps are taken in the bioreactor to prepare for harvest, *e.g.*, chilling the culture fluid. As shown below, if antibody production has ended at this juncture, any sparging in the bioreactor will be both "pre-harvest" and "following fermentation."



In other cases, the manufacturer may choose to proceed immediately to harvest at the end of fermentation.[3]

The POSA has no trouble understanding the meaning of "pre-harvest."

[redacted]

confirms that the POSA could understand "pre-harvest" culture fluid with the

[3] Though "pre-harvest" is a temporal rather than spatial limitation, the pre-harvest culture fluid, following fermentation, typically is located between the bioreactor and the centrifuge (inclusive of both locations). Dr. Hauser's testimony that the pre-harvest fluid in Figure 3 of Birch is the material between "the tank" and the centrifuge reflects this. *See* 10/16/19 Hrg. Tr. at 112:11-18.

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