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] PUBLIC VERSION FILED: October 14, 2019
GENENTECH, INC., *Plaintiff and Counterclaim Defendant*, v. AMGEN INC., *Defendant and Counterclaim Plaintiff*.	C.A. No. 18-924-CFC [redacted]

GENENTECH'S LETTER-BRIEF CONCERNING
CONSTRUCTION OF "FOLLOWING FERMENTATION"

The Kao patent's claimed methods improve antibody manufacturing processes by adding a step "following fermentation," a term Genentech proposes to construe as "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)." The Court observed correctly that construction of this term involves two questions: (1) what is fermentation; and (2) when does it end? D.I. 401 at 16. The patent provides the POSA clear answers to both questions. Genentech's construction is therefore definite.

1. Kao describes how cells are grown and used to produce antibody proteins. Kao at 25:43-26:41. The next line describes steps taken "Following fermentation . . .," indicating that the preceding activities are "fermentation." In the examples, Kao describes a small-scale "fermentation process" during which cells were grown to produce antibodies. Kao at 48:30-41. And in the background, Kao describes preparing cells to "undergo fermentation" in a container where parameters are controlled to ensure "optimal growth and production conditions." Kao at 1:54-63.

Kao's use of "fermentation" is consistent with the term's ordinary meaning. In the biotechnology context, "fermentation" refers to the growth of cells and the production (manufacture) by those cells of a product. Hauser ¶ 53; Appx220 (Webster's 3d) ("any of various controlled aerobic or anaerobic processes used for

the manufacture of certain products . . .”). FDA defines “fermentation” as a “bioprocess” and notes that “[t]he fermentation process is used also in the production of monoclonal antibodies.” Appx227.

The scientific literature confirms this usage. Dr. Hauser identifies several publications using “fermentation” to describe a process for growing cells to produce proteins—its ordinary meaning in the antibody context to the POSA and to Amgen’s prior expert, whom Amgen replaced after he acknowledged that reality. Hauser ¶¶ 54-63; Appx417-418 (Chalmers Tr. 25:15-26:5), Appx421-423 (29:14-31:23), Appx440-443 (48:1-51:1).[1]

Amgen also understands “fermentation” in this way. Its 10-K Annual Report explains that “Bulk manufacturing includes *fermentation* and/or cell culture, *processes by which our proteins are produced*.” Appx449. [redacted].

The Court’s opinion asked whether “fermentation” and “production” are synonymous. D.I. 401 at 17-20. They are not, though they are related. “Production” refers to making a product, or it can modify another term to indicate

[1] The question of whether “fermentation” is limited to the production phase or also includes the cell growth phase—when fermentation *begins*—is irrelevant to construing the claimed methods to sparging *following* fermentation.

a relationship to making a product (*e.g.*, the "production cycle"). Hauser ¶¶ 71-72.[2] "Fermentation" *results in* the production of proteins, but it generally is understood to include the process in which cells grow and produce proteins.

2. "Fermentation" ends when the cells stop growing and stop making their product. Genentech proposed that this "is indicated by a change in the cell culture environment that substantially ends cell growth and antibody production." D.I. 401 at 12. This is consistent with the patent's disclosure and the POSA's understanding that phases of the manufacturing process are defined by the imposed conditions, Kao at 1:60-63, 26:34-37, and absent changed conditions, cells will continue fermenting, Hauser ¶ 75. The adverb "substantially" reflects that biological systems, such as a typical culture of 100 trillion cells, cannot be turned "on/off" like a lightbulb. Hauser ¶¶ 82-84. For example, chilling cells to certain temperatures will cease cell growth and antibody production. Hauser ¶¶ 76-78. Cells under such conditions are no longer fermenting, a fact that can be confirmed readily by conducting the patent's testing of cell growth rate and titer (antibody production). Kao at 48:49-53; Hauser ¶ 82.

This construction "inform[s] those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments, Inc.*,

[2] "Production" also is used in "production phase," which is *part* of fermentation. Hauser ¶ 72.

572 U.S. 898, 910 (2014). This standard recognizes that "absolute precision" in language is "unattainable," and not required. *Id.* Definiteness requires only what is "reasonable" for the particular technical field. *Id.* at 910-11. As Dr. Hauser explains, the POSA is "reasonably certain" when fermentation has ended using their experience and the testing described in Kao. Hauser ¶ 82.

The Federal Circuit's decision in *Enzo Biochem v. Applera* is instructive. 599 F.3d 1325, 1336 (Fed. Cir. 2010).[3] The claims there concerned "hybridization," the binding of two "nucleic acid" molecules (e.g., DNA). *Id.* at 1333-34. Because the POSA could measure hybridization, the claim was definite: "the binding strength of a DNA strand will depend on the length and sequence of the strand, not on the subjective opinion of the particular chemist performing the hybridization." *Id.* at 1336. Claim language that depends upon objective, measurable parameters, like the end of cell growth and antibody production, is definite. Because those parameters can be measured as described in the patent, they are entirely unlike subjective criteria held indefinite in other cases. *E.g.*, D.I. 141, *HIP, Inc. v. Hormel Foods Corp.*, No. 18-615-CFC (D. Del. June 24, 2019) ("resembling a pan-fried bacon product").

[3] The Federal Circuit continues to cite *Enzo* post-*Nautilus*. *E.g.*, *Guangdong Alison Hi-Tech Co. v. ITC*, 2019 WL 4019880, at *4-*6 (Fed. Cir. Aug. 27, 2019).

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