United States Court of Appeals for the Federal Circuit

AMGEN INC., AMGEN MANUFACTURING LTD.,
Plaintiffs-Appellants

v.

COHERUS BIOSCIENCES INC.,
Defendant-Appellee

2018-1993

Appeal from the United States District Court for the District of Delaware in No. 1:17-cv-00546-LPS, Chief Judge Leonard P. Stark.

Decided: July 29, 2019

NICHOLAS P. GROOMBRIDGE, Paul, Weiss, Rifkind, Wharton & Garrison LLP, New York, NY, argued for plaintiffs-appellants. Also represented by JENNIFER GORDON, GOLDA LAI, PETER SANDEL, JACOB WHITT, JENNIFER H. WU; LOIS M. KWASIGROCH, KIMBERLIN L. MORLEY, WENDY A. WHITEFORD, Amgen Inc., Thousand Oaks, CA.

ADAM G. UNIKOWSKY, Jenner & Block LLP, Washington, DC, argued for defendant-appellee. Also represented by BRADFORD PETER LYERLA, AARON A. BARLOW, LOUIS FOGEL, SUSAN O'BRIEN, Chicago, IL.

Before REYNA, HUGHES, and STOLL, *Circuit Judges*.

STOLL, *Circuit Judge*.

Amgen Inc. and Amgen Manufacturing Ltd. (collectively, "Amgen") sued Coherus BioSciences Inc. for patent infringement in the District of Delaware. The district court dismissed Amgen's complaint for failure to state a claim, and Amgen appeals. Because prosecution history estoppel bars Amgen from succeeding on its infringement claim under the doctrine of equivalents, we affirm the order of the district court.

BACKGROUND

I

Recombinant therapeutic proteins are a class of biologic medicines that are manufactured inside living cells. Before a protein can be therapeutically useful, it must first be purified from contaminants. Amgen's U.S Patent No. 8,273,707 claims methods of purifying proteins using hydrophobic interaction chromatography ("HIC"). A HIC column contains a solid, hydrophobic matrix and "is used to separate proteins on the basis of hydrophobic interactions between the hydrophobic moieties of the protein and insoluble, immobilized hydrophobic groups on the matrix." '707 patent col. 1 ll. 36–39. In a HIC purification, a buffered salt solution containing the desired protein and associated impurities is first poured onto a HIC column. *Id.* at col. 1 ll. 40–41. This is known as the "loading" step. The salt in the buffer exposes the hydrophobic regions of the protein and causes them to adsorb (*i.e.*, attach) onto the hydrophobic groups on the column matrix. *See id.* at col. 1 ll. 41–44. The impurities are then washed out of the column with a buffered salt solution while the desired protein remains attached to the matrix. *See id.* at col. 4 ll. 27–29. Finally, molecules of the desired protein are detached (or "eluted") by pouring a buffer solution with a lower salt concentration through the column. *See id.* at col. 1 ll. 44–49.

"Usually, a decreasing salt gradient is used to elute proteins from a column. As the ionic strength decreases, the exposure of the hydrophilic regions of the protein increases and proteins elute from the column in order of increasing hydrophobicity." *Id.* at col. 1 ll. 45–49.

During the loading step, only a finite amount of protein can bind to the matrix. If too much protein is loaded on the column, "'breakthrough' or loss of protein to the solution phase before elution" will occur. *Id.* at col. 3 ll. 40–41. The '707 patent claims a process that reduces breakthrough, or in other words, increases the "dynamic capacity" of a HIC column. Dynamic capacity refers to "the maximum amount of protein in solution which can be loaded onto a column without significant breakthrough or leakage of the protein into the solution phase of a column before elution." *Id.* at col. 3 l. 65–col. 4 l. 3.

Prior art methods of increasing a HIC column's dynamic capacity included using a higher salt concentration in the buffer solution. *See id.* at col. 3 ll. 37–38. This resulted in other problems, however, as "high salt can be detrimental to protein stability. High salt increases the viscosity of a solution, results in increased formation of aggregates, results in protein loss due to dilution and filtration of the protein after elution from the column, and can lead to reduced purity." *Id.* at col. 3 ll. 41–45. Instead of increasing the concentration of a single salt, the '707 invention:

> provides combinations of salts useful for increasing the dynamic capacity of an HIC column compared with the dynamic capacity of the column using separate salts alone. These combinations of salts allow for a decreased concentration of at least one of the salts to achieve a greater dynamic capacity, without compromising the quality of the protein separation.

Id. at col. 2 ll. 9–15. All of the '707 claims require a salt combination chosen from one of three pairs: citrate and sulfate, citrate and acetate, or sulfate and acetate. Representative claim 1 recites:

> 1. A process for purifying a protein on a hydrophobic interaction chromatography column such that the dynamic capacity of the column is increased for the protein comprising
>
> mixing a preparation containing the protein with a combination of a first salt and a second salt,
>
> loading the mixture onto a hydrophobic interaction chromatography column, and eluting the protein,
>
> wherein the first and second salts are selected from the group consisting of citrate and sulfate, citrate and acetate, and sulfate and acetate, respectively, and
>
> wherein the concentration of each of the first salt and the second salt in the mixture is between about 0.1 M and about 1.0.

Id. at col. 15 ll. 8–18.

II

During prosecution, the examiner rejected the then-pending '707 claims as obvious in view of U.S. Patent No. 5,231,178 ("Holtz"). J.A. 174–75. The examiner noted that Holtz disclosed several salts for improving hydrophobic interactions between a protein and the column matrix. J.A. 174. According to the examiner, it would have been obvious for a person of ordinary skill to routinely optimize Holtz to achieve the claimed invention. J.A. 175.

On January 26, 2011, Amgen responded to the examiner's rejection, pointing out that "the pending claims recite a particular *combination* of salts. No combinations of salts

[are] taught nor suggested in the Holtz et al. patent, nor [are] the *particular* combinations of salts recited in the pending claims taught nor suggested in this reference." J.A. 182. Amgen further noted that the claimed invention is directed to increasing dynamic capacity of a HIC column and Holtz does not teach dynamic capacity at all. *See id*. It also attached a declaration from '707 patent inventor Anna Senczuk ("Declaration") for support. The Declaration states that the inventors discovered that using a sulfate/citrate or sulfate/acetate salt combination resulted in substantial increases in the dynamic capacity of a HIC column as compared to using a single salt. *See* J.A. 187 ¶ 3. It further explains that using a sulfate/citrate, sulfate/acetate, or acetate/citrate combination reduced purification costs on a commercial scale as compared to using only a single salt. *See* J.A. 187–88 ¶ 4. The Declaration did not discuss any salt pairs other than sulfate/citrate, sulfate/acetate, and acetate/citrate—the only claimed pairs in the '707 patent. Amgen's response highlighted the particular salt pairs disclosed in the Declaration:

> As pointed out in paragraph 4 of the Declaration, "The improvement resulting from the use of dual salts in HIC goes beyond merely optimizing a column to best suit a particular protein. Use of *this particular combination of salts* greatly improves the cost-effectiveness of commercial manufacturing by reducing the number of cycles required for each harvest and reducing the processing time for each harvest."

J.A. 183 (emphasis added) (quoting J.A. 188 ¶ 4).

On April 7, 2011, the examiner again rejected the claims. The examiner stated that "[a]pplicant contends that the instant claims recite a particular combination of salts. However, the examiner contends that the cited reference does disclose salts used in a method of purification" and that adjustment of conditions was within the skill of

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