UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

96-1440

GENENTECH, INC.,

Plaintiff-Appellee,

v.

NOVO NORDISK, A/S, NOVO NORDISK OF NORTH AMERICA, INC.

and NOVO NORDISK PHARMACEUTICALS, INC.,

Defendants-Appellants.

Leora Ben-Ami, Rogers & Wells, of New York, New York, argued for plaintiff-appellee. With her on the brief were John E. Kidd, Nicholas L. Coch, Joseph Ferraro, Philip E. Roux, and Gerard P. Norton. Of counsel was Ryan Trainer, Rogers & Wells, of Washington, D.C.

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Appealed from: U.S. District Court for the Southern District of New York

Senior Judge Motley

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DECIDED: March 13, 1997

Before ARCHER, Chief Judge, LOURIE, and BRYSON, Circuit Judges.

LOURIE, Circuit Judge.

Novo Nordisk A/S, Novo Nordisk of North America, Inc., and Novo Nordisk Pharmaceuticals, Inc. (collectively "Novo") appeal from the order of the United States District Court for the Southern District of New York, issuing a preliminary injunction in favor of Genentech, Inc., enjoining Novo from importing, marketing, using, selling, offering for sale or distributing its Norditropin®-brand recombinant human growth hormone (hGH) product. Genentech, Inc. v. Novo Nordisk A/S, 935 F. Supp. 260 (S.D.N.Y. 1996). Because the district court's conclusion that Genentech had demonstrated a likelihood of success on the merits was based on an error of law and because its remaining findings were premised on this error, we vacate the injunction.

BACKGROUND

This consolidated patent infringement action was first brought in the United States District Court for the Southern District of New York on November 30, 1994. On May 12, 1995, Genentech moved for a preliminary injunction under U.S. Patent 4,601,980 to prevent Novo from importing, marketing, using, selling, offering for sale or distributing in the United States its Norditropin®-brand recombinant hGH product. The district court granted Genentech's motion and issued an injunction. Novo Nordisk of North Am., Inc. v. Genentech, Inc., No. 94 Civ. 8634 (CBM), 1995 U.S. Dist. LEXIS 12588, 1995 WL 512171 (S.D.N.Y. Aug. 28, 1995).

On appeal this court vacated the injunction. Novo Nordisk of North Am., Inc. v. Genentech, Inc., 77 F.3d 1364, 37 USPQ2d 1773 (Fed. Cir. 1996). We held that the district court clearly erred in finding that Genentech established a likelihood of proving infringement of the '980 patent because that finding was based on an improper construction of claim 2 of the patent. Based upon the specification and prosecution history, we concluded that because the claim used the phrase "human growth hormone unaccompanied by . . . other extraneous protein," it was limited to processes for directly expressing either hGH or met-hGH. Id. at 1371, 37 USPQ2d at 1779. Because the parties agreed that Novo did not use direct expression to produce these proteins, we concluded that Novo did not infringe the patent. Id.

Upon returning to the district court, Genentech asserted its newly issued U.S. Patent 5,424,199. The '199 patent has the same specification as the '980 patent and contains a single claim directed to:

[a] method of producing a protein consisting essentially of amino acids 1-191 of human growth hormone comprising:

(a) expressing in a transformant bacterium, DNA coding for a human growth hormone conjugate protein, which conjugate protein consists essentially of amino acids 1-191 of human growth hormone as set forth in combined Figs. 1 and 3 unaccompanied by the leader sequence of human growth hormone or other extraneous protein bound thereto and an additional amino acid sequence which is specifically cleavable by enzymatic action, and

(b) cleaving extracellularly said conjugate protein by enzymatic action to produce said protein consisting

essentially of amino acids 1-191 of human growth hormone.

This claim differs from the claim adjudicated in the prior case in reciting that the encoded protein has an additional amino acid sequence and includes the step of cleaving this conjugate protein. This process of expressing a DNA encoding a conjugate protein and using an enzyme to cleave off an undesired portion of that protein is generally known as cleavable fusion expression. The parties agree that Novo uses cleavable fusion expression to produce hGH. Id.

On June 27, 1996, after conducting a twelve-day evidentiary hearing, the district court again issued a preliminary injunction, this time based upon the '199 patent, enjoining Novo from importing, marketing, using, selling, offering for sale, or distributing in the United States its Norditropin®-brand recombinant hGH product. Genentech v. Novo Nordisk A/S, 935 F. Supp. 260 (S.D.N.Y. 1996). The district court based its decision upon, inter alia, a finding that Genentech would likely overcome Novo's defense that the '199 patent was invalid for lack of an enabling disclosure under 35 U.S.C. § 112, 1 (1994).

Novo appeals to this court, challenging the grant of the preliminary injunction. 1 We have jurisdiction pursuant to 28 U.S.C. § 1292(c) (1994).

DISCUSSION

The grant or denial of a preliminary injunction pursuant to 35 U.S.C. § 283 is within the discretion of a district court. We Care, Inc. v. Ultra-Mark Int'l Corp., 930 F.2d 1567, 1570, 18 USPQ2d 1562, 1564 (Fed. Cir. 1991). Accordingly, a trial court's decision granting a preliminary injunction will be overturned on appeal only upon a showing that the court abused its discretion. Joy Techs., Inc. v. Flakt, Inc., 6 F.3d 770, 772, 28 USPQ2d 1378, 1380 (Fed. Cir. 1993). Such an abuse of discretion may be established by showing that the court made a clear error of judgment in weighing relevant factors or exercised its discretion based upon an error of law or clearly erroneous factual findings. Id.

As the moving party, Genentech had to establish its right to a preliminary injunction in light of four factors: (1) a reasonable likelihood of success on the merits; (2) irreparable harm if the injunction were not granted; (3) the balance of the hardships; and (4) the impact of the injunction on the public interest. Nutrition 21 v. United States, 930 F.2d 867, 869, 18 USPQ2d 1347, 1348-49 (Fed. Cir. 1991); Hybritech Inc. v. Abbott Lab., 849 F.2d 1446, 1451, 7 USPQ2d 1191, 1195 (Fed. Cir. 1988).

A. Likelihood of Success on the Merits

In order to demonstrate that it has a likelihood of success, Genentech must show that, in light of the presumptions and burdens that will inhere at trial on the merits, (1) it will likely prove that Novo infringes the '199 patent and (2) its infringement claim will likely withstand Novo's challenges to the validity and enforceability of the '199 patent. See New England Braiding Co. v. A.W. Chesterton Co., 970 F.2d 878, 882-83, 23 USPQ2d 1622, 1625-26 (Fed. Cir. 1992). In other words, if Novo raises a "substantial question" concerning validity, enforceability, or infringement (i.e., asserts a defense that Genentech cannot show "lacks substantial merit") the preliminary injunction should not issue. Id. More specifically, with regard to Novo's validity defenses, the question on appeal is whether there is substantial merit to Novo's assertion that the '199 patent claim fails to meet the requirements of 35 U.S.C. § 112, 1 (1994).

Novo argues that the district court's findings regarding validity under § 112, 1, are clearly erroneous because

it presented clear and convincing evidence that the patent specification would not have enabled a person of ordinary skill in the art to practice the claimed invention without undue experimentation. Novo also argues that the specification fails to contain a written description of the claimed invention. Regarding enablement, Novo argues that the patent is invalid because it does not contain sufficient detail concerning the practice of the claimed method. Novo argues that the mere generic statement of the possibility of cleavable fusion expression, along with the DNA sequence encoding hGH, a single enzyme (trypsin) for cleaving undisclosed conjugate proteins, and a statement of that enzyme's cleavage sites as being potential amino acid extensions conjugated to hGH is not an enabling disclosure commensurate in scope with the claim. Genentech responds that all of the district court's factual findings regarding enablement are supported by the record. More specifically, Genentech argues that those skilled in the art of recombinant protein expression and purification at the time of filing, July 5, 1979, would have been able to use cleavable fusion expression to produce hGH without undue experimentation by using the teachings of the specification along with methods and tools well known in the art. We conclude that Novo has raised more than a substantial question concerning the validity of the '199 patent. In fact, it has shown that the patent is invalid.

Section § 112, 1, provides, in relevant part that:

[t]he specification shall contain a written description of the invention, and the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . .

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); see also Amgen Inc. v. Chugai Pharms. Co., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) ("[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."). Whether making and using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a legal conclusion based upon several underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-37, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988).

The question before us is whether the specification would have enabled a person having ordinary skill in the art at the time of filing to use cleavable fusion expression to make hGH without undue experimentation. There is no dispute that the portion of the specification chiefly relied upon by Genentech and by the district court, column 7, lines 29-59, does not describe in any detail whatsoever how to make hGH using cleavable fusion expression. For example, no reaction conditions for the steps needed to produce hGH are provided; no description of any specific cleavable conjugate protein appears. The relevant portion of the specification merely describes three (or perhaps four) applications for which cleavable fusion expression is generally well-suited and then names an enzyme that might be used as a cleavage agent (trypsin), along with sites at which it cleaves ("arg-arg or lys-lys, etc."). Thus, the specification does not describe a specific material to be cleaved or any reaction conditions under which cleavable fusion expression would work.

Notwithstanding this limited disclosure, Genentech argues (and the district court found) that those of ordinary skill in the art would have been able to practice the claimed invention without undue experimentation. Essentially, Genentech's argument is that the knowledge of one skilled in the art was sufficient to provide all of the missing information and, more specifically, that the disclosure of a DNA encoding hGH, when

combined with prior art cleavable fusion expression techniques applied to non- human proteins, would enable the practice of the claimed method. In support of this argument, Genentech points to the testimony of Dr. Ravetch, who testified as to the knowledge of one skilled in the art, to the extensive description of enzymes in the reference textbook Methods in Enzymology, and to the specification's explicit reference to British Patent 2008123-A, which more fully details the potential use of trypsin in cleavable fusion expression.

In response to these arguments, Novo asserts that at the time of filing, trypsin and other like enzymes were used only to digest proteins, not to specifically and precisely cleave conjugate proteins to yield intact, useful proteins, and that the British patent explicitly indicates that trypsin would not be useful for the cleavable fusion expression of arginine-containing proteins such as hGH. Novo further argues that neither the specification nor the references cited by Genentech suggest a single amino acid sequence, out of the virtually infinite range of possibilities, that would yield hGH in a useful form when cleaved from the conjugate protein.

We agree with Novo. Genentech's arguments, focused almost exclusively on the level of skill in the art, ignore the essence of the enablement requirement. Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. That requirement has not been met in this specification with respect to the cleavable fusion expression of hGH.

It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

The specification indicates that it purports to solve a problem. That problem is summarized at column 3, line 65, through column 4, line 8:

[A] need has existed for new methods of producing hGH and other polypeptide products in quantity and that need has been particularly acute in the case of polypeptides too large to admit to organic synthesis or, for that matter, microbial expression from entirely synthetic genes. Expression of mammalian hormones from mRNA transcripts . . . has permitted only microbial production of bio-inactive conjugates from which the desired hormone could not practically be cleaved.

The problem thus was the difficulty of obtaining hGH from a precursor containing added protein material. This problem was solved by the description of a method of obtaining hGH unaccompanied by a leader

sequence or other extraneous proteins, as claimed in the '980 patent. However, the specification for the '199 patent, which is the same as the specification for the '980 patent, does not provide a specific enabling disclosure concerning what the new claim recites, viz., obtaining hGH by cleaving an hGH- containing conjugate protein. That was the problem avoided by the invention claimed in the '980 patent. The present specification contains no more disclosure than the '980 specification, but this patent now purports to claim the unresolved problem that the '980 patent overcame. Genentech is attempting to bootstrap a vague statement of a problem into an enabling disclosure sufficient to dominate someone else's solution of the problem. This it cannot do.

Genentech's arguments in favor of enablement are unavailing. While Genentech's witness, Dr. Ravetch, did state that it would have been possible for a skilled artisan to create a DNA sequence coding for arg-arg-hGH or lys-lys-hGH, he did not discuss the experimentation needed for the creation of DNA coding for more extensive sequences, such as those that have proved necessary to the production of hGH via cleavable fusion expression. Likewise, the description of a wide range of enzymes in Methods in Enzymology, by itself, does not render routine the determination of an enzyme-conjugate protein combination. Rather, as Novo argues and the record reflects, various combinations of conjugate protein sequences, cleaving enzymes, and reaction conditions needed to be studied to establish a process for producing hGH in useful form. Finally, the British patent cited in the specification actually works against Genentech's position by explicitly teaching that trypsin would not work well to produce hGH. The specification does not even acknowledge any of the known difficulties associated with using trypsin on an hGH conjugate protein. This specification is so lacking with respect to the limitation of paragraph (b) of claim 1 that providing testimony regarding the skill in the art has been an exercise in futility.

The limited testimony regarding the knowledge of one skilled in the art offered by Genentech at the preliminary injunction hearing, and relied upon by the district court, is further undermined by the fact that no one had been able to produce any human protein via cleavable fusion expression as of the application date. If, as Genentech argues, one skilled in the art, armed only with what the patent specification discloses (a DNA sequence encoding a human protein, in this case, hGH, and a single example of an enzyme and its cleavage site), could have used cleavable fusion expression to make a human protein without undue experimentation, it is remarkable that this method was not used to make any human protein for nearly a year, see Shine et al., 285 Nature 456 (June 1980), or to make hGH for five years. See Belagaje et al., 3 DNA 120 (1984). Certainly, DNAs encoding desirable human proteins were known at the time of filing (e.g., insulin, described in the British patent), and a great many researchers were attempting to produce human proteins using recombinant DNA technology. This failure of skilled scientists, who were supplied with the teachings that Genentech asserts were sufficient and who were clearly motivated to produce human proteins, indicates that producing hGH via cleavable fusion expression was not then within the skill of the art. The contrary testimony offered by Genentech's witnesses, who hypothesized about the skill of the art more than fifteen years earlier, does not demonstrate the incorrectness of Novo's arguments. See In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("[A]n expert's opinion on the ultimate legal issue [of enablement] must be supported by something more than a conclusory statement.").

Moreover, it stands to reason that if the disclosure of a useful conjugate protein and the method for its cleavage were so clearly within the skill of the art, it would have been expressly disclosed in the specification, and in the usual detail. Patent draftsmen are not loath to provide actual or constructive examples, with details, concerning how to make what they wish to claim. In addition, as indicated above, the specification of this patent was clearly drafted to claim the invention of obtaining hGH unaccompanied by extraneous protein, the

cleavage of which was identified by the specification as a problem in this field. Genentech's inventors knew how to enable that which they had invented. These facts underline the inadequacy of the specification in enabling that which it provided only a means to avoid.

The record does not support the district court's implicit finding that the disclosure of trypsin and its cleavage site enables the production of any conjugate protein from which hGH can practically be cleaved and thus produced in useful form; the record indicates that determination of these features required further undue experimentation. None of the expert testimony relied upon by Genentech or by the district court suggests otherwise. Where, as here, the claimed invention is the application of an unpredictable technology in the early stages of development, an enabling description in the specification must provide those skilled in the art with a specific and useful teaching. Genentech has not shown that the '199 patent provides that teaching.

Under the circumstances, we are compelled to conclude that the district court made an error of law in ruling that Genentech showed a likelihood of success on enablement. See In re Epstein, 32 F.3d 1559, 1568, 31 USPQ2d 1817, 1823 (Fed. Cir. 1994) ("[E]nablement is a question of law . . . which may involve subsidiary questions of fact."). Furthermore, since we are able to review the record and to read the specification, there is no reason why we should limit our decision here to reversing the grant of the preliminary injunction. Rather, because the parties agreed at oral argument that the enablement issue had been thoroughly ventilated by the extensive arguments before the district court and that court's extensive analysis, we deem it appropriate to rule on the merits of Novo's defense of invalidity. See 28 U.S.C. § 2106 (1994) ("The Supreme Court or any other court of appellate jurisdiction may . . . direct the entry of such appropriate judgment, decree, or order, or require such further proceedings to be had as may be just under the circumstances."); Chicago Observer, Inc. v. City of Chicago, 929 F.2d 325, 329 (7th Cir. 1991) (reversing preliminary injunction and instructing district court to enter judgment in favor of defendant because the plaintiff "has not suggested that it holds more evidence it could offer at trial and we cannot imagine what additional evidence could aid its cause. Litigation is costly not only for the litigants but also for parties in other cases waiting in the queue for judicial attention. Once it becomes clear that additional proceedings are pointless, the court should bring the case to a close."). We therefore hold that claim 1 and hence the '199 patent are invalid as a matter of law for failure of the specification to enable the practice of the claimed method.

Novo has also argued that the '199 patent is invalid for lack of a written description of the claimed invention and that it is not infringed by Novo. Given our decision on the enablement question, we need not reach these issues.

B. Other Factors

Novo also challenges the district court's findings that irreparable harm, the equities, and the public interest favored Genentech. In view of our conclusion concerning the invalidity of the '199 patent, we need not consider these other findings.

CONCLUSION

The court abused its discretion by granting the preliminary injunction based upon an error of law. The district court's error was in finding that Genentech had shown a likelihood of success on the merits since the '199 patent is invalid for failure of the specification to meet the enablement requirement of § 112, 1. Accordingly, we vacate the injunction and instruct the district court to dismiss Genentech's claim for infringement of the '199 patent on the ground that the patent is invalid.

VACATED

Footnotes

1 On July 3, Novo moved for an emergency stay of the injunction pending disposition of this appeal. On August 1, we denied Novo's motion and reinstated the injunction. However, after having heard oral argument in this case, we reconsidered the motion and reinstated the stay of the injunction.

2 A patent is presumed valid, 35 U.S.C. § 282 (1994), and a party challenging validity must prove invalidity by clear and convincing evidence. "However, the presumption does not relieve a patentee who moves for preliminary injunction from carrying the normal burden of demonstrating that it will likely succeed on all disputed liability issues at trial, even when the issue concerns the patent's validity." New England Braiding, 970 F.2d at 882, 23 USPQ2d at 1625 (citing Nutrition 21, 930 F.2d at 869, 18 USPQ2d at 1349).

3 At column 7, lines 52-58, the specification states: "At least in the latter three applications [of the four applications that are disclosed], the synthetic adaptor molecular [sic] employed to complete the coding sequence of the mRNA transcript can additionally incorporate codons for amino acid sequences specifically cleavable, as by enzymatic action. For example, trypsin will cleave specifically at arg-arg or lys- lys, etc."

4 Novo's witness, Dr. Villa- Komaroff, merely stated on cross-examination that, assuming arg-arg-hGH was initially produced and successfully extracted from the transformed cell, that "[u]nder the best condition, approximately five percent of the time there will be in the [post-digestion] mix [hGH]." This statement, characterized by Genentech as an admission, was made in the limited context of partial trypsin digests of isolated arg-arg-hGH, but none of the necessary experimentation is described in the specification, which is where it should be if it is to contribute to an enabling disclosure.

5 Genentech stated that it would introduce new evidence at a full trial only in response to new arguments and new defenses raised by Novo. Novo revealed that it had no intention of raising any new arguments or defenses, stating that the "full and complete record" on appeal gave this court "the benefit of everything it really needs" to reach ultimate issues of validity. Thus, considerations that would normally dictate that we limit our decision to reversing the grant of the preliminary injunction are not present. See University of Texas v. Camenisch, 451 U.S. 390, 395 (1981) (stating that it is generally inappropriate to render a final judgment on the merits at the preliminary injunction stage because "a preliminary injunction is customarily granted on the basis of procedures that are less formal and evidence that is less complete than in a trial on the merits.") (citations omitted) (emphasis added).

A patent is presumed valid, 35 U.S.C. § 282 (1994), and a party challenging validity must prove invalidity by clear and convincing evidence. "However, the presumption does not relieve a patentee who moves for preliminary injunction from carrying the normal burden of demonstrating that it will likely succeed on all disputed liability issues at trial, even when the issue concerns the patent's validity." New England Braiding, 970 F.2d at 882, 23 USPQ2d at 1625 (citing Nutrition 21, 930 F.2d at 869, 18 USPQ2d at 1349). At column 7, lines 52-58, the specification states: "At least in the latter three applications [of the four applications that are disclosed], the synthetic adaptor molecular [sic] employed to complete the coding sequence of the mRNA transcript can additionally incorporate codons for amino acid sequences specifically cleavable, as by enzymatic action. For example, trypsin will cleave specifically at arg-arg or lys-lys, etc." Novo's witness, Dr. Villa-Komaroff, merely stated on cross-examination that, assuming arg-arg-hGH was

initially produced and successfully extracted from the transformed cell, that "[u]nder the best condition, approximately five percent of the time there will be in the [post-digestion] mix [hGH]." This statement, characterized by Genentech as an admission, was made in the limited context of partial trypsin digests of isolated arg-arg-hGH, but none of the necessary experimentation is described in the specification, which is where it should be if it is to contribute to an enabling disclosure. Genentech stated that it would introduce new evidence at a full trial only in response to new arguments and new defenses raised by Novo. Novo revealed that it had no intention of raising any new arguments or defenses, stating that the "full and complete record" on appeal gave this court "the benefit of everything it really needs" to reach ultimate issues of validity. Thus, considerations that would normally dictate that we limit our decision to reversing the grant of the preliminary injunction are not present. See University of Texas v. Camenisch, 451 U.S. 390, 395 (1981) (stating that it is generally inappropriate to render a final judgment on the merits at the preliminary injunction stage because "a preliminary injunction is customarily granted on the basis of procedures that are less formal and evidence that is less complete than in a trial on the merits.") (citations omitted) (emphasis added).