NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

AMGEN INC., AMGEN MANUFACTURING LIMITED,
Plaintiffs-Appellants

v.

APOTEX INC., APOTEX CORP.,
Defendants-Appellees

2017-1010

Appeal from the United States District Court for the Southern District of Florida in Nos. 0:15-cv-61631-JIC, 0:15-cv-62081-JIC, Judge James I. Cohn.

Decided: November 13, 2017

NICHOLAS P. GROOMBRIDGE, Paul, Weiss, Rifkind, Wharton & Garrison LLP, New York, NY, argued for plaintiffs-appellants. Also represented by JENNIFER GORDON, ARIELLE K. LINSEY, STEPHEN ACCURSIO MANISCALCO, CATHERINE NYARADY, PETER SANDEL, ERIC ALAN STONE, JENNIFER H. WU; JOHN F. O'SULLIVAN, ALLEN P. PEGG, JASON STERNBERG, Hogan Lovells US LLP, Miami, FL; LOIS M. KWASIGROCH, KIMBERLIN L.

MORLEY, WENDY A. WHITEFORD, Amgen Inc., Thousand Oaks, CA.

BARRY P. GOLOB, Cozen O'Connor, Washington, DC, argued for defendants-appellees. Also represented by WILLIAM BLAKE COBLENTZ, AARON S. LUKAS, KERRY BRENDAN MCTIGUE.

Before LOURIE, O'MALLEY, and TARANTO, *Circuit Judges*.

TARANTO, *Circuit Judge*.

Amgen Inc. and Amgen Manufacturing Limited (collectively, Amgen) own U.S. Patent No. 8,952,138, which describes and claims methods of refolding recombinant proteins expressed in non-mammalian cells, such as bacteria and yeast. '138 Patent, col. 1, lines 10–20; col. 2, lines 52–61. Amgen also holds Biologics License Application Nos. 125031 and 103353, approved by the Food and Drug Administration (FDA), for therapeutic products made from the recombinant proteins pegfilgrastim (Neulasta®) and filgrastim (Neupogen®).

Apotex Inc. and Apotex Corp. (collectively, Apotex) filed abbreviated Biologics License Applications Nos. 761026 and 761027 under 42 U.S.C. § 262(k) of the Biologics Price Competition and Innovation Act (BPCIA), seeking permission from the FDA to market biosimilar versions of pegfilgrastim and filgrastim products, and listing Neulasta® and Neupogen®, respectively, as the reference products. Apotex and Amgen then engaged in the information exchange described in the BPCIA, 42 U.S.C. § 262(*l*)(3). After Apotex provided Amgen with copies of its applications, Amgen identified the '138 patent as a patent that the Apotex-proposed products would infringe, and Apotex replied by sending Amgen a detailed statement describing, claim by claim, the factual and

legal basis for its opinion that it did not infringe. Amgen responded with its contrary, detailed view of infringement. Amgen eventually filed two infringement suits against Apotex, one for each of Apotex's applications, pursuant to 35 U.S.C. § 271(e)(2)(C), (a) and (g).

The two suits were consolidated. The district court held a bench trial in July 2016, and it issued findings of fact and conclusions of law on September 6, 2016. The court found that Amgen had failed to prove that Apotex's proposed commercial marketing of the two products, pursuant to Apotex's applications, would infringe the '138 patent, either literally or under the doctrine of equivalents.

Amgen appeals. We have jurisdiction under 28 U.S.C. § 1295(a)(1). We affirm.

I

A

The '138 patent explains that when recombinant proteins are formed in non-mammalian expression systems, such as bacterial cells, they can precipitate into limited-solubility aggregates of misfolded proteins called "inclusion bodies." '138 patent, col. 1, lines 20–24. To obtain properly folded proteins from inclusion bodies, practitioners developed various methods to accomplish refolding. *Id.*, col. 1, lines 36–38. Those methods, the patent explains, commonly include steps of (1) extracting the inclusion bodies from the expression system; (2) solubilizing the inclusion bodies in a solubilization buffer, which disassembles the inclusion bodies into individual protein chains and unfolds the proteins; and (3) diluting or washing the unfolded proteins in a refolding buffer, which causes the proteins to refold in the proper manner. *Id.*, col. 1, lines 38–51.

Industry faced a challenge in producing certain refolded proteins on an industrial scale. *Id.*, col. 1, lines 55–

60. For larger, complicated molecules (*e.g.*, antibodies and peptibodies, which often have between 8 and 24 disulfide bonds), the refolding mixture used for the process had to be maintained at a relatively low protein concentration, typically 0.01–0.5 g/L. *Id.*, col. 1, lines 51–54; col. 2, lines 10–16. As a result, a very large volume of the mixture was required to produce a large amount of the desired protein. *Id.*, col. 1, lines 55–60; *see also id.*, col. 1, lines 64–67.

The '138 patent purports to solve this problem by using a carefully controlled reduction-oxidation (redox) reaction to refold proteins—even large, complicated protein molecules—at a higher concentration than was possible in the prior art. Claim 1, the '138 patent's only independent claim, reads as follows:

> 1. A method of refolding a protein expressed in a non-mammalian expression system and present in a volume at a concentration of 2.0 g/L or greater comprising:
>
> (a) contacting the protein with a refold buffer comprising a redox component comprising a final thiol-pair ratio having a range of 0.001 to 100 and a redox buffer strength of 2 mM or greater and one or more of:
>
> (i) a denaturant;
>
> (ii) an aggregation suppressor; and
>
> (iii) a protein stabilizer;
>
> to form a refold mixture;
>
> (b) incubating the refold mixture; and
>
> (c) isolating the protein from the refold mixture.

Id., col. 17, lines 47–59.

B

Claim 1, in its preamble (which all agree is limiting), calls for protein present in "a volume at a concentration of 2.0 g/L or greater." *Id.*, col. 17, line 49. During claim construction, Amgen argued that the claimed "volume" was the volume of protein before, not after, the contact with the refolding buffer that forms the refold mixture. Amgen also argued, based on the specification, that the "refold mixture," as a matter of claim construction, must have a protein concentration at or above about 1.0 g/L. Apotex, for its part, contended that the claim 1 "volume" refers to the refold mixture, so that the claimed refold mixture must have a protein concentration of 2.0 g/L or more. The district court agreed with Amgen on both points, construing "a protein . . . present in a volume at a concentration of 2.0 g/L or greater" to mean "a protein as it existed in a volume before contacting the volume with a refold buffer" and construing "refold mixture" to have a "high protein concentration[] . . . at or above about 1 g/L."

C

For the 1.0 g/L claim requirement, Amgen alleged only literal infringement, not infringement under the doctrine of equivalents. In seeking to prove that Apotex's accused processes meet this claim requirement, Amgen relied at trial on the fact that Apotex's abbreviated Biologics License Applications identified an "inclusion body concentration" of 0.9–1.4 g/L for the refold mixture in its processes for refolding filgrastim and pegfilgrastim. J.A. 23–24, 5594, 5902. In the BPCIA information exchange that occurred before this suit was filed, Apotex had sent Amgen several "pre-litigation" letters, at least one with respect to the filgrastim application and one with respect to the pegfilgrastim application. In both letters, Apotex stated that it did not infringe the '138 patent because its "concentration of [filgrastim or filgrastim critical intermediate] in the refold buffer" was limited to 0.9–1.4 g/L

(*i.e.*, the "inclusion body concentration" listed on the applications).

At trial, however, Apotex's fact witness, Dr. Jason Dowd, presented evidence that the maximum concentration of *protein* in its refold mixture would actually be 0.708 g/L. Dr. Dowd testified, during cross examination, that the statements in Apotex's pre-litigation letters were factually inaccurate. He explained that the inclusion bodies in Apotex's process were not pure protein, but, rather, were a paste of which about two-thirds was water. In addition, to resolve any potential ambiguity created by the numbers presented on the face of its application, Apotex presented two "batch records" showing the actual data from the manufacturing process of its filgrastim product. According to Dr. Dowd, those records showed that the protein (not the inclusion-body) concentration in the refold mixture never exceeded about 0.56 g/L. Both that figure and the 0.708 g/L figure are well below the 1.0 g/L minimum level required under the Amgen-urged and court-adopted claim construction.

The court ruled in favor of Apotex on this issue. It found that Amgen had failed to prove by a preponderance of the evidence that Apotex's processes would meet the 1.0 g/L requirement of claim 1 of the '138 patent. For that reason, the court found, Amgen failed to prove direct infringement.

On Amgen's appeal, we affirm that finding. We therefore need not and do not reach Amgen's challenge to the district court's other, independent ground for finding no infringement, which involves the claim term "2mM or greater." In particular, we do not decide the correctness or incorrectness of the district court's construction of that claim term.

II

Amgen challenges the district court's finding of no direct infringement of the '138 patent on three grounds: (1) that the district court erred in finding Apotex's pre-litigation letters to lack probative value; (2) that the district court erred in not treating "protein concentration" as interchangeable with "inclusion body concentration"; and (3) that the district court erred in not finding the required 1.0 g/L protein concentration based on what Apotex's abbreviated Biologics License Applications permit. We review the finding of non-infringement for clear error, *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006), and we decide any legal issues de novo, *Jack Guttman, Inc. v. Kopykake Enters., Inc.*, 302 F.3d 1352, 1356 (Fed. Cir. 2002).

A

Amgen first focuses on the pre-litigation letters sent by Apotex to Amgen during the information exchange conducted before the litigation pursuant to the BPCIA. Amgen does not argue that Apotex is legally bound by its statements about protein concentration in those letters; indeed, both in the district court and in this court, Amgen has disclaimed such an argument. *See* J.A. 3807; Reply Br. 17–18. Rather, Amgen argues that the district court, acting as fact-finder during the bench trial, erred by disregarding those letters.

We do not question the general legal principle that Amgen asserts: we agree that a district court cannot ignore letters sent during the BPCIA's information exchange if properly offered into evidence. Indeed, the pre-litigation information exchange is part of the BPCIA's "carefully calibrated scheme for preparing to adjudicate, and then adjudicating, claims of infringement." *Sandoz Inc. v. Amgen Inc.*, 137 S. Ct. 1664, 1670 (2017). The purpose of the exchange is "to identify relevant patents and to flesh out the legal arguments that the[] [parties]

might raise in future litigation." *Id.* at 1671. Through the information exchange, the BPCIA seeks to facilitate the efficient resolution of patent disputes. The statements in the pre-litigation letters are party admissions and therefore have *some* probative weight. The district court's statement that the letters "are not probative on the issue of protein concentration," J.A. 24 ¶ 39, is therefore an overstatement to the extent it suggests that the letters lack probative value as a matter of law.

We read the district court's statement in context, however, to mean only that the letters are not *sufficiently* probative to outweigh other evidence presented at trial indicating that the information in the letters was inaccurate. Indeed, the district court did not ignore the pre-litigation letters. Rather, it first concluded that the letters were not binding on Apotex, a conclusion that Amgen does not dispute, and it then found that the letters lacked probative value in light of the other evidence presented at trial. Thus, the court gave the letters their evidentiary due. We do not believe that the court's phrasing reflects an error in the approach it actually took to reach its findings or calls the court's ultimate conclusion into question.

The letters do not render the finding of fact regarding the protein concentration clearly erroneous. The district court found that the letters were "not probative on the issue of protein concentration" because they were "factually incorrect," J.A. 24, and it had a sufficient basis in the evidence to make that finding. On direct examination, Dr. Dowd testified that the inclusion bodies produced by the Apotex process are wet—*i.e.*, a paste. He then testified that, based on the description of the refolding process given in Apotex's abbreviated Biologics License Applications, the maximum protein concentration that could occur in Apotex's process is 0.708 g/L. On cross examination, when asked about the pre-litigation letters, Dr. Dowd stated that the letters were factually incorrect.

That is, he reiterated that his calculation of a 0.708 g/L protein concentration was accurate and that the 0.9–1.4 g/L mentioned in the letter was not. Amgen did not attempt to challenge the accuracy of Dr. Dowd's statements regarding the pre-litigation letters during cross-examination. Amgen also did not present any evidence, other than the pre-litigation letters themselves, to contradict Dr. Dowd's statements.

On this record, we conclude that the district court did not err by crediting Dr. Dowd's testimony and finding that the factually inaccurate letters were not probative on the issue of the protein concentration.

B

Amgen argues, as a matter of claim construction, that "protein concentration" in the claims of the '138 patent is interchangeable with "washed-inclusion-body concentration." We review this claim-construction argument, which rests entirely on intrinsic evidence, de novo. *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015). We reject the argument.

Amgen's argument depends on its equating of inclusion bodies with protein. Only on that basis does Amgen then treat the concentration of one as necessarily identical to the concentration of the other. But the specification pervasively disproves rather than supports the equation of inclusion bodies with proteins.

The specification repeatedly makes clear that the proteins are not the same as, but instead are "in" or "deposit[ed] . . . into" or "disposed in," the "aggregates" called "inclusion bodies." *See*, *e.g.*, '138 patent, col. 1, lines 23–25 ("the precipitation of the expressed proteins in limited-solubility intracellular precipitates typically referred to as inclusion bodies"); *id.*, col. 9, lines 44–46 ("Often the cells will deposit the recombinant proteins into large insoluble or limited solubility aggregates called inclusion bodies.");

id., col. 10, lines 43–44 ("disposed in"); *id.*, col. 1, lines 23, 38–44; *id.*, col. 7, line 59–60; *id.*, col. 9, line 50; *id.*, col. 12, line 61–62. Amgen's own description reflects that fact. Appellant's Br. at 9 ("The misfolded proteins precipitate within the bacterial cells *in* aggregates called 'inclusion bodies.'" (emphasis added)). The specification also makes clear that it is individual proteins, disaggregated from the inclusion bodies, that are refolded. *See* '138 patent, col. 1, lines 35–51 (background describing methods "for obtaining correctly folded proteins from bacterial inclusion bodies" by, *e.g.*, "solubilizing the inclusion bodies," "which unfolds the proteins and disassembles the inclusion bodies into individual protein chains," allowing the "refolding"); *id.*, col. 2, line 52 (summary: "[a] method of refolding *a* protein" (emphasis added)); *id.*, col. 6, lines 13–14 ("the term 'refolding' means a process of reintroducing secondary and tertiary structure to *a* protein" (emphasis added)). Amgen's description reflects that fact as well. Appellant's Brief at 9 ("The inclusion bodies must be isolated and solubilized so that the incorrectly folded proteins are unfolded and subsequently refolded to form the proper three-dimensional conformation.").

Amgen argues otherwise by first pointing to the Background of the '138 patent, which, according to Amgen, shows that "the patent specification contemplates that, for purposes of calculating concentration, the protein . . . and the inclusion bodies are one and the same." Appellant's Brief at 52 (internal quotation marks omitted). But the Background material, quoted above, does not support that characterization. Indeed, it speaks of proteins "in" inclusion bodies; it does not equate them. And it does not mention concentration at all, or give any indication that the patent contemplates calculating the concentration from the total mass of the inclusions bodies rather than from the amount of protein contained in the inclusion bodies.

Amgen next points to the specification's description of an embodiment of the claimed refolding method, which states that "[w]hen the protein is disposed in inclusion bodies, the inclusion bodies can be harvested . . . , washed, concentrated and refolded." '138 Patent, col. 10, lines 39–44. Amgen contends that the passage teaches the folding and washing of inclusion bodies and therefore must be equating inclusion bodies with proteins. But even this passage speaks of a protein "disposed in" inclusion bodies, thereby recognizing the distinction—as does the usage throughout the specification cited above. In this context, we read the second half of the sentence as nothing more than a somewhat imprecise shorthand reference to a process that the rest of the patent makes clear involves refolding the proteins, not the aggregates called "inclusion bodies." Accordingly, no inference of equating proteins with the aggregates of proteins that are inclusion bodies can fairly be drawn from this passage. And the passage gives no indication that protein concentration should be derived from the concentration of inclusion bodies rather than from the proteins contained within the inclusion bodies.

Amgen's final basis for its contention is no more persuasive. A specification passage states that "the disclosed method is particularly useful for proteins expressed in bacterial expression systems[] . . . in which the protein is expressed in the form of inclusion bodies." *Id.*, col. 12, lines 54–57. But the language of "expressed in the form of" does not imply interchangeability, but refers instead to the problem of agglomeration that the method is meant to help solve: "the precipitation of the expressed proteins in limited-solubility intracellular precipitates typically referred to as inclusion bodies," *id.*, col. 1, lines 22–24, which must be disassembled to "unfold[] the proteins" contained in them, *id.*, col. 1, line 43, where doing so at an industrial scale is challenging. It is not reasonable to read the particular language Amgen cites to mean, coun-

ter to the specification as a whole, that inclusion bodies *are* the proteins inside them, even though there also is water and other non-protein content inside them. In particular, that reading is wrong in a context of identifying concentration levels, where the distinction might well (and does here) matter.

Thus, we reject Amgen's proposed claim construction of "protein concentration" as interchangeable with "washed-inclusion-body concentration."

C

Amgen argues that the district court's non-infringement finding rests on too restrictive a view of Apotex's FDA applications. It challenges that view as contrary to this court's decision in a Hatch-Waxman Act case, *Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc.*, 731 F.3d 1271 (Fed. Cir. 2013), under which, Amgen argues, the district court here was required to assess infringement based on the full range of processes that would be consistent with Apotex's applications. Apotex does not challenge the importation of *Sunovion*'s analysis into the BPCIA context, but it does dispute *Sunovion*'s applicability to the facts of this case. We agree with Apotex.

Sunovion involved an abbreviated new drug application that, on its face, authorized the applicant to engage in actions that would, in fact, infringe the patent in question. *Sunovion*, 731 F.3d at 1274–75. The district court had granted summary judgment of non-infringement because the defendant had "certified" that it did not actually intend to run its process in an infringing manner and presented evidence of internal manufacturing guidelines showing non-infringement. *Id.* This court reversed, reasoning that internal guidelines and a certification were insufficient to avoid a finding of infringement when the application itself authorized the activity that would infringe. *Id.* at 1280.

Here, in contrast, the district court had a sufficient basis for reading Apotex's applications as not authorizing processes that infringe, indeed, as constraining the processes to non-infringing levels. The district court credited the testimony of Dr. Dowd, based on the numbers in the applications, that the maximum protein concentration possible in the refold mixtures of Apotex's applications is 0.708 g/L. J.A. 3618–20. Dr. Dowd arrived at this calculation using the high-end of the "key process parameter" range for solubilized inclusion bodies, 11.8 mg/mL, and the minimum 75 percent purity of the target protein (*i.e.*, filgrastim or pegfilgrastim) specified by the applications. Amgen argues that the key process parameters do not prevent Apotex from infringing the '138 patent because they are not absolute limits. But the applications indicate that close adherence to the key process parameters is critical to the function of the process. J.A. 6725 (noting that key process parameters must be "carefully controlled within a narrow range and are essential for process performance"); J.A. 6728 (identifying the 11.8 mg/ml figure as a "qualified upper limit"). Consistent with this description, Dr. Dowd testified at trial that Apotex needs to maintain its process within the key process parameters in order "for the batch to be acceptable," and that, if those ranges are exceeded, "the batch would be thrown out." J.A. 3622–23. The district court found this testimony credible. J.A. 26. In light of the evidence, we see no basis for deeming the district court's finding as to the constraints in Apotex's applications to be clearly erroneous.

At oral argument in this court, Amgen pointed to the fact that Apotex's applications contain a "dash" in the "Acceptance Criterion" column of the solubilized inclusion body concentration parameters. *See* J.A. 5595. Amgen argued that the lack of an explicit acceptance criterion means that there is effectively no upper bound for the concentration of solubilized inclusion bodies—and therefore protein—that can be used in the process. But Amgen

has given us no evidence to justify setting aside the district court's contrary reading of the applications. The dash in Apotex's applications is not on its face an affirmative statement authorizing the infringing levels, contrary to the other evidence recited above. And Amgen has pointed us to no evidence that the dash would be understood as such an authorization. In these circumstances, the content of the applications does not bring this case within *Sunovion*.

Even if we did not read the applications as affirmatively constraining the processes in the way at issue here, the most that we could conclude about the applications is that they are silent on the point. In such a case, this court's reasoning in *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562 (Fed. Cir. 1997), is applicable. In *Glaxo*, the court looked to extrinsic evidence, such as the samples and data submitted to the FDA, to resolve a question of infringement left open by the abbreviated new drug application. *Id*. at 1569. In this case, Apotex submitted batch records of its actual manufacturing process to resolve any question of infringement left open by Apotex's application. Between the two batch records submitted by Apotex, the maximum protein concentration observed in the process was roughly 0.56 g/L—even further from infringing levels than the 0.708 g/L level derived from the applications. J.A. 3645; J.A. 4512.

Amgen disputes the probative value of the batch records, arguing that Apotex failed to provide batch records for the other 89 times it has run the process. But it was not Apotex's burden to prove non-infringement. *Glaxo*, 110 F.3d at 1567. It was Amgen's burden to prove that Apotex's processes would infringe the '138 patent. Amgen presents us with no challenge to a restriction on discovery or an exclusion of evidence. In these circumstances, we see no basis in the mere existence of other records for disturbing the district court's finding that Amgen failed to provide adequate evidence to prove infringement.

III

For the foregoing reasons, we affirm the judgment of the district court.

AFFIRMED