United States Court of Appeals for the Federal Circuit

CORRECTED: October 5, 2005 at 1:00 PM

04-1581

NOVO NORDISK PHARMACEUTICALS, INC.,
and NOVO NORDISK A/S,

Plaintiffs-Appellants,

v.

BIO-TECHNOLOGY GENERAL CORP. and
TEVA PHARMACEUTICALS USA, INC.,

Defendants-Appellees.

Steven E. Lipman, Darby & Darby, P.C., of New York, New York, argued for plaintiffs-appellants. Of counsel were James Edward Hanft, Paul M. Zagar, Jay P. Lessler, Kevin L. Reiner, Robert Schaffer and Joseph R. Robinson.

John W. Bateman, Kenyon & Kenyon, of Washington, DC, argued for defendants-appellees. On the brief was Richard L. DeLucia, of New York, New York. Of counsel were Steven J. Lee, and Thomas J. Meloro, of New York, New York, and Kenneth R. Corsello, of Washington, DC.

Appealed from: United States District Court for the District of Delaware
.
Chief Judge Sue L. Robinson

United States Court of Appeals for the Federal Circuit

04-1581

NOVO NORDISK PHARMACEUTICALS, INC.
and NOVO NORDISK A/S,

Plaintiffs-Appellants,

v.

BIO-TECHNOLOGY GENERAL CORP. and
TEVA PHARMACEUTICALS USA, INC.,

Defendants-Appellees.

DECIDED: October 5, 2005

Before SCHALL, Circuit Judge, ARCHER, Senior Circuit Judge, and BRYSON, Circuit Judge.

SCHALL, Circuit Judge.

Novo Nordisk Pharmaceuticals, Inc. and Novo Nordisk A/S (collectively, "Novo") appeal from the final judgment of the United States District Court for the District of Delaware in their suit for patent infringement against Bio-Technology General Corp. and Teva Pharmaceuticals USA, Inc. The district court held the two claims of Novo Nordisk A/S's U.S. Patent No. 5,633,352 ("the '352 patent") invalid by reason of anticipation

under 35 U.S.C. § 102(a). The court also held the patent unenforceable due to inequitable conduct. Novo Nordisk Pharms., Inc. v. Bio-Technology Gen. Corp., No. 1:02-CV-00332-SLR (D. Del. Aug. 3, 2004) ("Opinion"). We affirm the judgment of invalidity with respect to claim 1 of the '352 patent, as well as the judgment that the patent is unenforceable. We vacate the judgment of invalidity with respect to claim 2 of the patent.

BACKGROUND

I.

Novo Nordisk Pharmaceuticals, Inc. and Novo Nordisk A/S are research-based pharmaceutical manufacturers. Novo Nordisk A/S is the assignee of the '352 patent, which is entitled "Biosynthetic Human Growth Hormone." The '352 patent is directed to a process for producing "ripe" human growth hormone ("hGH") protein in *E.Coli* bacteria through the use of recombinant DNA techniques. Novo Nordisk Pharmaceuticals, Inc. is the U.S. healthcare affiliate of Novo Nordisk A/S.

The hGH protein has a specific sequence of 191 amino acids and is secreted by the anterior pituitary gland. The protein, which plays a central role in cell growth and metabolism, is therapeutically useful to treat, among other conditions, growth hormone deficiencies and infertility. It also is useful in wound care. Until the mid-1980's, hGH for therapeutic purposes could be obtained only from the pituitary gland of a human cadaver (known as "pituitary-derived hGH"). However, the use of pituitary-derived hGH carried a high risk of contamination and infection for the patient.

Prior to the '352 patent, numerous attempts were made to produce biosynthetic hGH that would function in vivo in the same manner as pituitary-derived hGH. One

such attempt, set forth in U.S. Patent No. 4,342,832, resulted in hGH protein with 192 amino acids, instead of the 191 amino acids found in pituitary-derived hGH. '352 patent col. 1, ll. 20-25. The additional amino acid residue, methionine, resulted in a hGH protein variant that does not function in the same way in vivo as pituitary-derived hGH. Accordingly, there was a need for a method to produce "pure" hGH, or hGH containing the 191 amino acid sequence identical to that of pituitary-derived hGH.

II.

As noted, the '352 patent discloses the production of ripe hGH protein via recombinant DNA techniques. Recombinant DNA techniques make it possible to transfer DNA segments (genes) that code for a human protein to bacteria, such as *E. coli*, for the purpose of protein synthesis.

Bacteria such as *E. coli* normally will not recognize a human gene sequence and, thus, will not synthesize the corresponding human protein. However, transferring the gene sequence for a "fusion protein"[1] into *E. coli*, in effect, "tricks" the bacteria into synthesizing the human protein. The gene sequence for the fusion protein contains, in a side-by-side relationship: (1) the gene sequence for a bacterial protein and (2) the gene sequence for a human protein, such as hGH. The *E. coli* recognizes the portion of the gene sequence that encodes the bacterial protein and, as a result, synthesizes the entire fusion protein. The fusion protein is made up of: (1) the amino acid sequence for the bacterial protein and (2) the amino acid sequence for the human protein. In order to isolate the desired human protein, the bacterial amino acid sequence, or "pro-sequence," must be removed from the fusion protein. This process can be

accomplished through the use of a proteolytic enzyme.[2] The proteolytic enzyme cleaves the bond between the pro-sequence and the amino acid sequence for the human protein.

The '352 patent discloses a process whereby a proteolytic enzyme, preferably the enzyme dipeptidyl aminopeptidase I (DAP I), cleaves a pre-hGH fusion protein in order to produce "ripe" hGH protein. '352 patent col. 1, l. 56 – col. 2, l. 2. First, the gene sequence for the hGH protein is combined with the gene sequence for a bacterial protein. Id. col. 4, ll. 53-67. This DNA sequence is then introduced into *E. coli*. Id. col. 5, ll. 1-10. This results in a pre-hGH fusion protein being produced by the *E. coli* bacteria. The resulting pre-hGH fusion protein is made up of: (1) the 191-amino-acid sequence for the hGH protein; and (2) a variable amino acid sequence with an even number of amino acids that is formulated to take advantage of the cleavage specificity of DAP I. When DAP I is then added, it works to cleave, or cut, the fusion protein at the junction of the two amino acid sequences described above. Id. col. 5, ll. 24-25. This results in "ripe" hGH protein, or hGH protein containing the correct 191 amino acid sequence.

III.

The '352 patent traces priority back through a series of continuation applications to Application Ser. No. 640,081, filed on December 9, 1983, as PCT Application PCT/DK83/001118 ("the 1983 PCT application"). The 1983 PCT application, in turn,

(Cont'd. . . .)

[1] A "fusion protein" is coded for by genes that have been combined together in vitro from two or more sources.

traces priority back to a 1982 Danish patent application filed on December 10, 1982. The 1983 PCT application was directed to "A Process for Preparing Ripe Proteins from Fusion Proteins, Synthesized in Pro- or Eukaryotic Cells." Unlike the '352 patent, which discloses the use of the proteolytic enzyme DAP I, the 1983 PCT application discloses leucine aminopeptidase (LAP) as the preferred cleavage enzyme to produce ripe hGH protein from a pre-hGH fusion protein.

On November 12, 1992, Novo filed U.S. Application No. 07/959,856 ("the '856 application"), directed to "A Process for Preparing a Desired Protein." The '856 application discloses a process for producing hGH protein from a fusion protein using the DAP I enzyme. The '856 application was the first in a series of applications that claimed a priority date of December 10, 1982, based on the 1983 PCT application. The final application in the chain was U.S. Application Ser. No. 402,286 ("the "286 application"), filed on March 10, 1995. The '352 patent issued from the '286 application on May 27, 1997.

The '352 patent has two claims:

> 1. Biosynthetic ripe human growth hormone free of contaminants from pituitary derived human growth hormone.
>
> 2. Biosynthetic ripe human growth hormone produced by expressing an amino terminal extended human growth hormone fusion protein in a microorganism capable of such expression, enzymatically cleaving the amino terminal extension and recovering the biosynthetically produced ripe human growth hormone.

(Cont'd. . . .)

[2] Proteolytic enzymes are unique proteins that catalyze the cleavage of peptide bonds (the bonds linking the chains of amino acids that make up proteins). Many proteolytic enzymes exhibit specificity with respect to the bonds that they cleave.

IV.

On July 7, 2000, the Board of Patent Appeals and Interferences ("Board") of the United States Patent and Trademark Office ("PTO") declared an interference involving Novo's '352 patent and Bio-Technology General Corp.'s[3] U.S. Application Ser. No. 09/023,248 ("the '248 application"). Blumberg v. Dalbøge, Interference No. 104,422 (Bd. Pat. App. Int. Mar. 12, 2002) ("Board Decision"). The '248 application is directed to a biosynthetic hGH protein produced via recombinant DNA techniques. In declaring the interference, the Board accorded the '352 patent the benefit of priority of the August 8, 1984 filing date of U.S. Patent Application Ser. No. 06/640,081 ("the '081 application").[4]

In due course, Novo filed a preliminary motion in the interference seeking the benefit, for purposes of priority, of the filing date of the 1983 PCT application. Board Opinion, slip op. at 9. Bio-Technology General Corp., in turn, moved to deny Novo the benefit of the filing date of the 1983 PCT application, as well as the benefit of the filing date of the '081 application. It argued that DAP I was not disclosed in the 1983 PCT application, and that the LAP enzyme that was disclosed in the application was not effective to produce ripe hGH protein. Board Decision, slip op. at 11.

On March 12, 2002, the Board issued its final decision, awarding priority to Novo. The Board noted that during prosecution of its applications resulting in the '352 patent, Novo had made contradictory statements regarding whether the 1983 PCT application enabled the production of ripe hGH protein. However, the Board concluded: "[W]e do not find the evidence relied upon by [Bio-Technology General Corp.] . . . to establish

[3] Bio-Technology General Corp. develops, manufactures, and markets biopharmaceutical products.

that pure LAP would not work to produce ripe hGH in the methods described in the '081 and [1983] PCT applications to be convincing." Board Decision, slip op. at 33.

On April 1, 2002, pursuant to 35 U.S.C. § 146, Bio-Technology General Corp. appealed the final decision of the Board to the United States District Court for the District of Delaware. The district court eventually reversed the Board's decision awarding Novo priority with respect to the invention claimed in the '352 patent. Bio-Technology Gen. Corp. v. Novo Nordisk A/S, No. 02-235-SLR, slip op. at 59 (D. Del. Aug. 3, 2004) ("Priority Decision"). In doing so, the court ruled that the 1983 PCT application was not enabled because one of ordinary skill in the art would not have been able to produce ripe hGH protein at the time the application was filed using the information disclosed in the application. Id. at 49. The court based this determination, in part, on a finding that Novo itself had been unable to synthesize ripe hGH protein using the disclosure of the 1983 PCT application. Id. at 56. The court remanded the case to the Board for consideration of two preliminary motions by Novo that the Board had dismissed as moot.[5]

V.

On April 30, 2002, Novo filed a complaint in the District of Delaware against Bio-Technology General Corp. and Teva Pharmaceuticals USA, Inc. (collectively, "Bio-Technology") for infringement of the '352 patent and for injunctive relief to prevent the

(Cont'd. . . .)

[4] The '081 application is the U.S. counterpart of the 1983 PCT application. As far as this appeal is concerned, it is identical in substance to that application.

[5] As of the time of this appeal, remand proceedings before the Board still are pending.

sale of Tev-Tropin®, a recombinant hGH protein product.[6] On June 7, 2002, the district court issued a preliminary injunction, which was vacated by this court on November 26, 2002. Novo Nordisk A/S v. Bio-Technology Gen. Corp., No. 02-1447, 52 Fed. Appx. 142 (Fed. Cir. Nov. 26, 2002). On June 12, 2002, Bio-Technology filed its answer to the complaint and asserted a counterclaim for a declaratory judgment that the '352 patent is invalid and unenforceable.

Prior to trial, Bio-Technology admitted infringement of claim 1 of the '352 patent. Opinion, slip op. at 5. Thereafter, from August 4, 2003, to August 8, 2003, the district court construed the claims of the '352 patent and held a bench trial on the issues of: (1) invalidity of claim 1 of the '352 patent by reason of anticipation; and (2) unenforceability of the '352 patent due to inequitable conduct.

Following the trial, the district court found that claim 1 of the '352 patent was anticipated by a December 1981 article by George N. Pavlakis, published in the journal Biochemistry and entitled "Expression of two human growth hormone genes in monkey cells infected by simian virus 40 recombinants" ("the 1981 Pavlakis article"). Opinion, slip op. at 80. Based upon that finding, the court ruled claims 1 and 2 invalid under 35 U.S.C. § 102(a). Id. In addition, the court held that the '352 patent was unenforceable based on inequitable conduct during prosecution of the '856 application and during the interference proceeding before the Board. Id.

[6] Teva Pharmaceuticals USA, Inc. develops, manufactures and markets generic pharmaceutical products. It has entered into an agreement with Bio-Technology General Corp. to market and sell Bio-Technology General Corp.'s biosynthetic hGH protein in the United States under the name Tev-Tropin®.

Novo now appeals the district court's decision. We have jurisdiction pursuant to 35 U.S.C. § 1295(a)(1).

DISCUSSION

I.

We review a district court's decision following a bench trial for errors of law and clearly erroneous findings of fact. SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1337 (Fed. Cir. 2005) (citing Allen Eng'g Corp. v. Bartell Indus., Inc., 299 F.3d 1336, 1343-44 (Fed. Cir. 2002)). "A factual finding is clearly erroneous when, 'although there is evidence to support [the finding], the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed.'" Tegal Corp. v. Tokyo Electron Am., Inc., 257 F.3d 1331, 1338-39 (Fed. Cir. 2001) (quoting United States v. United States Gypsum Co., 333 U.S. 364, 395 (1948)). However, "[w]here the record viewed in its entirety renders the district court's account of the evidence plausible or discloses two permissible readings of the evidence, the fact-finder has committed no clear error." King Instruments Corp. v. Perego, 65 F.3d 941, 943 (Fed. Cir. 1995) (citation omitted).

On appeal, Novo challenges the district court's rulings with respect to both validity and inequitable conduct. We address its contentions in turn, starting with the validity issue.

II.

A.

As noted above, the district court ruled that the '352 patent was invalid by reason of anticipation based upon the 1981 Pavlakis article. In the article, Pavlakis describes a

method of producing hGH protein with monkey kidney cells using what is known as the secretion approach.[7] The article discusses using the secretion approach with two different hGH genes, identified as hGH1 and hGH2. The hGH1 gene encodes for the 191 amino acid sequence of pituitary-derived hGH. The hGH2 gene is a variant of the hGH1 gene, containing fourteen amino acid substitutions. The article describes a variety of tests performed on the two resulting proteins, using (1) gel electrophoresis; (2) isoelectric focusing and nonequilibrium pH gradient electrophoretic gels; and (3) cell surface receptor binding studies involving IM-9 culture human lymphocytes and pregnant rabbit liver membranes.[8] Based on these tests, Pavlakis comes to the conclusion that the "hGH1 protein, as predicted from the DNA sequence, appears identical in all respects to the major form of pituitary hGH. In contrast, the hGH2 protein differs from authentic hGH both in its behavior on isoelectric focusing gels and in its low immunoreactivity, yet it binds to hGH receptors quite efficiently."

In its anticipation analysis, the district court construed the term "ripe" hGH in claim 1 of the '352 patent to mean "a protein produced by recombinant DNA techniques composed of a 191 amino acid sequence identical to that of hGH produced by the human pituitary gland with the full biological activity of hGH produced by the human pituitary gland, and free of the contaminants present in hGH produced by the human

---

[7] The secretion approach, based on recombinant DNA techniques, involves the steps of transforming a host organism (such as a monkey kidney cell) to express a pre-protein consisting of the desired protein and a "leader" or "signal" sequence. The leader sequence causes the pre-protein to be transported across the cell membrane. In the process of transport across the cell membrane, a specialized enzyme clips off the leader sequence. As a result, the desired protein is secreted from the cell of the host organism.

[8] An understanding of the details of these tests is not necessary for purposes of this appeal.

pituitary gland." Opinion, slip op. at 45. The court determined that the 1981 Pavlakis article discloses each limitation of claim 1 of the '352 patent. Id. at 64. The court stated:

> First, the Pavlakis article describes a method to produce hGH . . . using . . . recombinant DNA techniques. Second, the Pavlakis 1981 article specifically discusses experimental tests used to characterize the hGH product. Gel electrophoresis, isoelectric focusing, and nonequilibrium pH gradient electrophoresis analyses all revealed that the hGH product was indistinguishable from pituitary-derived hGH. . . . This collective data establishes that the hGH product necessarily must be composed of the same 191 amino acid residues as the pituitary-derived hGH. Third, the Pavlakis 1981 article discloses through receptor binding assay data that the hGH1 product exhibited the same receptor binding affinity as pituitary-derived hGH in both the human lymphocyte line IM-9 and the pregnant rabbit liver membranes. From this, the court concludes that the hGH1 product has the full biological activity of hGH produced by the human pituitary gland. Finally, the aforementioned data inherently establishes that the hGH product is free of contaminants present in hGH produced by the human pituitary gland. Accordingly, the court concludes that the 1981 Pavlakis article clearly and convincingly discloses all of the limitations of claim 1 of the '352 patent.

Id. at 64-65. The court also determined that the Pavlakis article was enabled. Id.

B.

On appeal, Novo argues that the 1981 Pavlakis article cannot anticipate claim 1 of the '352 patent because the article does not disclose the second and third limitations of the claim (a protein that is composed of a 191-amino acid sequence identical to that of pituitary-derived hGH and that has the full biological activity of pituitary-derived hGH). Novo argues that the test results disclosed in the article do not demonstrate conclusively that the hGH1 protein discussed is identical in these respects to pituitary-derived hGH.

Novo also argues that the district court committed reversible error when it stated that "[p]rior art references are presumed to be enabling," Opinion, slip op. at 66, given that the 1981 Pavlakis article is a non-patent publication. Novo acknowledges our decision in Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1355 (Fed. Cir. 2003), in which we held that "a presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled," but in which we did not decide whether the presumption applies to non-patent publications. See id. at 1355 n.22 ("We note that by logical extension, our reasoning here might also apply to prior art printed publications as well, but as Sugimoto is a patent we need not and do not so decide today."). Novo argues that, in the case of a non-patent prior art reference, however, the burden of proving enablement of the prior art reference by clear and convincing evidence should remain on an alleged infringer.

Bio-Technology responds that the district court correctly determined that the 1981 Pavlakis article discloses each limitation of claim 1. Bio-Technology also argues that the district court correctly held that the 1981 Pavlakis article is presumed to be enabled. Lastly, Bio-Technology urges that even if the article is not presumptively enabled, the district court held on separate grounds that it enabled the subject matter of claim 1.

C.

A patent claim is invalid by reason of anticipation if "the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent . . . ." 35 U.S.C. § 102(a). Anticipation based on a printed publication under section 102(a)

requires the presence in the publication of each and every limitation of the claimed invention. Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1272, 1282 (Fed. Cir. 2000) (citation omitted). However, "a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing feature is necessarily present, or inherent, in the single anticipating reference." SmithKline Beecham, 403 F.3d at 1343 (quoting Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1377 (Fed. Cir. 2003)). "What a prior art reference discloses in an anticipation analysis is a factual determination that we review under the clearly erroneous standard." Tegal Corp., 257 F.3d at 1345-46 (citing In re Graves, 69 F.3d 1147, 1151 (Fed. Cir. 1995)).

In order to anticipate, a prior art disclosure must also be enabling, such that one of ordinary skill in the art could practice the invention without undue experimentation. SmithKline Beecham, 403 F.3d at 1342. The standard for enablement of a prior art reference for purposes of anticipation under section 102 differs from the enablement standard under 35 U.S.C. § 112. Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1325 (Fed. Cir. 2005) (citation omitted). While section 112 "provides that the specification must enable one skilled in the art to 'use' the invention," id. (quoting In re Hafner, 410 F.2d 1403, 1405 (CCPA 1969)), "section 102 makes no such requirement as to an anticipatory disclosure," id. Significantly, we have stated that "anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabled to one of skill in the art." Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1379 (Fed. Cir. 2001) (citing In re Donhue, 766 F.2d 531, 533 (Fed. Cir. 1985) ("It is not, however, necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the

enablement requirement.”)). “Whether a prior art reference is enabling is a question of law based upon underlying factual findings.” SmithKline Beecham, 403 F.3d at 1342-43 (citation omitted).

D.

We see no error in the district court’s finding that the 1981 Pavlakis article discloses the second and third limitations of claim 1 of the '352 patent. These limitations require that the hGH protein be composed of a 191-amino acid sequence identical to that of pituitary-derived hGH and that the protein have the full biological activity of pituitary-derived hGH. In that regard, the article states that “[t]he hGH1 protein, as predicted from the DNA sequence, appears identical in all respects to the major form of pituitary hGH.” (emphasis added). Further, the article discusses experimental tests used to characterize the hGH product. These tests were designed in order to determine whether the hGH1 protein had the same amino acid sequence and biological activity as pituitary-derived hGH. The article’s discussion of the tests provides strong support for the district court’s conclusion that the 1981 Pavlakis article discloses the subject matter of claim 1. Gel electrophoresis tests reported in the article demonstrated that the hGH1 protein co-migrated with pituitary-derived hGH on the gel and that hGH1 thus was of the same overall size as pituitary-derived hGH. At the same time, the results from tests using isoelectric focusing and nonequilibrium pH gradient electrophoresis gels showed that the hGH1 protein co-migrated with pituitary-derived hGH on a pH gradient and that it thus had the same charge as pituitary-derived hGH. Finally, the results of radioreceptor assays with both the human lymphocyte IM-9 line and pregnant rabbit liver membranes showed that hGH1 was indistinguishable from

pituitary-derived hGH, indicating that hGH1 had an identical ability to bind to cell surface receptors. Thus, the test results disclosed in the Pavlakis article indicated that the hGH1 protein had the same structure and chemical properties as pituitary-derived hGH. In other words, the test results indicated that the hGH1 protein contained the same 191 amino acid sequence and biological activity as pituitary-derived hGH. Accordingly, we hold that the article discloses a ripe hGH protein.

As far as enablement is concerned, in our view, a fair reading of the district court's opinion is that the court did not rely solely on the Amgen presumption in finding that the 1981 Pavlakis article was enabled. See Koito Mfg. v. Turn Key Tech., 381 F.3d 1142, 1151 (Fed. Cir. 2004) ("At trial, [the declaratory judgment plaintiff (potential infringer)] . . . failed to provide any testimony or other evidence that would demonstrate . . . how that reference [JP '082, a Japanese unexamined application] met the limitations of the claim in the '268 patent or how the reference enabled one of ordinary skill in the art to practice the claimed invention."). In that regard, the court determined that Bio-Technology affirmatively established enablement of the 1981 Pavlakis article. The court stated:

> Moreover, the Pavlakis 1981 article offers particular materials and methodology to produce hGH. The court has no reason to doubt that this information will not lead to the successful production of hGH. Indeed, Dr. Pavlakis actually made the subject matter of claim 1 using the disclosed materials and methodology set forth in the Pavlakis 1981 article.

Opinion, slip op. at 67-68.

The critical inquiry is whether the 1981 Pavlakis article discloses in an enabling manner the production of ripe hGH. See SmithKline, 403 F.3d at 1344 ("Thus, whether

it was actually possible to make pure PCH anhydrate before the critical date of the '723 patent is irrelevant. The '196 patent suffices as an anticipatory prior art reference if it discloses in an enabling manner the production of PHC hemihydrate."); see also Rasmusson, 413 F.3d at 1326; Bristol-Myers Squibb, 246 F.3d at 1379; In re Donhue, 766 F.2d at 533. The 1981 Pavlakis article discloses the production of ripe hGH protein in an enabling manner because it discusses particular materials and a particular methodology (the secretion approach) to produce the hGH protein. In other words, the article relies on standard recombinant DNA techniques that would have been understood by one of ordinary skill in the art at the time of its publication. We see no reason to disturb the district court's conclusion that the 1981 Pavlakis article is sufficiently enabling to serve as an anticipating reference. We therefore affirm the district court's ruling that claim 1 of the '352 patent is anticipated by the 1981 Pavlakis article.[9]

The district court's order, dated August 3, 2004, states that "[the '352 patent] is invalid under 35 U.S.C. § 102." However, as Novo points out, the validity of claim 2 was not litigated at trial. Accordingly, we vacate the portion of the district court's order relating to claim 2 of the '352 patent.

[9] Because we affirm the district court's ruling that claim 1 of the '352 patent is invalid as anticipated by the 1981 Pavlakis article, we need not address Bio-Technology's alternative arguments that the district court erred in construing claim 1, and that under Bio-Technology's proposed construction, U.S. Patent No. 4,775,622 to Hitzeman would anticipate claim 1.

III.

A.

We turn next to Novo's argument that the district court erred in holding the '352 patent unenforceable due to inequitable conduct during prosecution of the '856 application and during the interference proceedings before the Board. The following additional facts relating to prosecution of the '856 application are relevant to the inequitable conduct issue:

As noted above, the '352 patent claims priority based on the 1983 PCT application. The 1983 PCT application, in turn, claims priority to the Danish Patent application filed on December 10, 1982.

The 1983 PCT application discloses the use of the LAP enzyme to produce ripe hGH from a pre-hGH fusion protein. Example 1 of the application describes the production, purification, and evaluation of a fusion protein. It also describes treatment of the fusion protein with the LAP enzyme in order to obtain ripe hGH. Finally, Example 1 states that standard tests indicated that the disclosed methodology produced ripe hGH protein that was 98% pure. Speaking in the past tense, the example states that "[t]he fusion product <u>was purified</u> from this extract," 1983 PCT application at 10 (emphasis added), that "[t]he purified fusion protein <u>was evaluated</u> to be more than 98% pure," <u>id.</u> (emphasis added), and that "[t]his . . . product <u>was then treated</u> with leucine aminopeptidase," <u>id.</u> (emphasis added).

The district court found, however, and it is undisputed, that when the 1983 PCT application was filed on December 10, 1983, the inventors had not successfully prepared hGH with LAP using recombinant DNA technology. <u>Priority Decision</u>, slip op.

at 20. For five months after the 1983 PCT application was filed, Novo's scientists attempted unsuccessfully to use LAP enzyme to synthesize hGH. Finally, on March 7, 1984, Novo successfully synthesized hGH using commercial LAP purchased from a company called Sigma. Id. at 21. However, unbeknownst to Novo at the time, the particular batch of LAP contained the DAP I enzyme. Id. at 22. At a meeting on October 18, 1984, Novo scientists concluded that "the active component in Sigma LAP presumably is not LAP but a 'contaminating' substance." Id. at 23. The discovery that this "contaminating" substance was DAP I led to the filing, on February 6, 1986, of PCT/DK86/00014 ("the 1986 PCT application"). The 1986 PCT application, entitled "A Process for Producing Human Growth Hormone," disclosed a process for producing hGH from a fusion protein using the DAP I enzyme. Id.

On October 3, 1986, Novo filed U.S. Patent Application Ser. No. 06/910,230 ("the '230 application"), entitled "Process for Producing Human Growth Hormone." Priority Decision, slip op. at 24. The '230 application did not claim priority to the 1983 PCT application, but instead claimed priority to the 1986 PCT application. During prosecution of the '230 application, the originally filed claims were rejected under 35 U.S.C. § 103 as obvious over U.S. Patent No. 4,532,207 to Brewer[10] in view of U.S. Patent No. 4,543,329 to Daum.[11] On April 11, 1990, in a response to a final rejection,

[10] The application that resulted in the Brewer '207 patent was filed on March 3, 1983. Its European counterpart was published on September 28, 1983. The examiner read the Brewer patent as disclosing a method of producing a protein using a sequence of charged amino acids and a cleavage enzyme.

[11] The application that resulted in the Daum '329 patent was filed on July 6, 1982, claiming priority to an application filed on May 29, 1980. The Daum patent discloses the use of LAP enzyme to cleave a fusion protein. '329 patent col. 9, ll. 60-62.

Novo argued that the Daum patent was distinguishable from the invention in the '230 application. Novo stated:

> Daum mentions . . . that with LAP it is possible to "split off N-terminal methionine from foreign proteins[.]"
>
> Although applicants have tested LAP with bacterially produced HGH, LAP has been shown <u>not</u> to be effective. The effectiveness of LAP seems to disappear as soon as peptides greater than about 50 amino acids are involved.

(emphasis in original).

In addition, on September 12, 1990, Novo filed a declaration on behalf of Jorli Ringsted, John Pendersen, and Thorkild Christensen, all of whom are named inventors on the '352 patent (the "1990 declaration"). The 1990 declaration described the ability of the LAP enzyme to remove a pro-sequence from a fusion protein to produce hGH. After describing an experiment in which the scientists compared LAP preparations from several different suppliers, the inventors stated:

> It is shown that essentially only LAP-preparations from Sigma contain enzymatic activity able to convert Ala-Glu-hGH to mature hGH. LAP-preparations from Merck, Serva, and Worthington did not contain such enzymatic activity at all. It is thus likely that an enzymatic activity different from LAP-activity is contained in the Sigma preparations . . . , which can convert Ala-Glu-hGH to mature hGH.

The Novo scientists went on to conclude:

> The experiments show clearly that a pure LAP-preparation will not convert amino extended hGH to mature hGH. Only LAP-preparations with relevant impurities will have some effect depending upon the nature and amount of the impurity and of course this can lead to misunderstanding about the effect of LAP.

Thus, during prosecution of the '230 application, Novo sought to overcome the prior art rejection based upon Daum by arguing that the LAP enzyme disclosed in Daum was not effective in the production of hGH protein.

Unable to overcome the examiner's rejections under section 103, Novo eventually abandoned the '230 application. Over the next several years, Novo filed a number of U.S. applications describing the use of the DAP I enzyme to produce ripe hGH and claiming priority to the 1986 PCT application. Then, on November 12, 1992, Novo filed the '856 application, directed to "A Process for Preparing a Desired Protein." As seen above, the '856 application disclosed a process for producing hGH from a fusion protein using the DAP I enzyme. In a preliminary amendment, filed on October 13, 1992, Novo amended the specification of the '856 application to indicate that the application was entitled to a priority date of December 10, 1982, based upon the 1983 PCT application claiming priority back to the 1982 Danish application. Novo specifically pointed out that the December 10, 1982 priority date of the 1983 PCT application—based upon that application's claim of priority to the priority date of the 1982 Danish patent application—preceded the 1983 priority date of the Brewer patent.

The examiner did not immediately accept the new priority claim, and on September 22, 1993, rejected the two pending claims as obvious under 35 U.S.C. § 103 in view of several references, including the Brewer patent. On January 7, 1994, the examiner held a personal interview with Cheryl Agris, a Novo in-house patent attorney, Poul Eisten Petterson, a Novo in-house patent advisor, and Thorkild Christensen and Henrik Dalbøge, two of the named inventors on the '856 application. The examiner's interview-summary record indicates that the Brewer patent was one of the prior art

items that was discussed at the conference and states in relevant part: "The priority date should be 1982. [Cheryl Agris] will point out where in priority documents the enablement is present."

Novo followed up the interview with an amendment, on January 20, 1994, which addressed the issue of whether the 1983 PCT application was enabled. The issue of whether the 1983 PCT application was enabled was critical to the prosecution because, if the application was not enabled, Novo would not be able to rely upon the application's priority date to overcome the Brewer patent. Novo pointed to the 1983 PCT application as providing "the general concept of adding an amino-terminal extension with an aminopeptidase, and isolation of mature hGH." Novo also pointed to Example 1 of the 1983 PCT application as being "specifically directed to hGH." Novo was ultimately able to claim priority to the 1983 PCT application. Upon allowance, the examiner stated:

> [T]he amendment of abandoned files to recite additional parent history places the effective filing date of the instant invention to December 9, 1983, and foreign priority to December 10, 1982. Therefore, the Brewer et al. reference, published September 28, 1983, does not appear to be prior art against the invention.

As seen, the '352 patent issued on May 27, 1997 from the '286 application, the final application in the chain of applications that resulted in the patent.

B.

Inequitable conduct occurs when a patent applicant breaches his or her "duty of candor and good faith" to the PTO. 37 C.F.R. § 1.56(a) (2004); Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd., 394 F.3d 1348, 1351 (Fed. Cir. 2005). Inequitable conduct includes "affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information, coupled with

an intent to deceive." CFMT, Inc. v. YieldUp Int'l Corp., 349 F.3d 1333, 1340 (Fed. Cir. 2003) (quoting Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178 (Fed. Cir. 1995)). Materiality and intent must be established by clear and convincing evidence. Id. Once materiality and intent have been established, the district court must weigh these factors in light of all of the circumstances to determine whether a finding that inequitable conduct occurred is warranted. Dayco Prods., Inc. v. Total Containment, Inc., 329 F.3d 1358, 1363 (Fed. Cir. 2003) (citing Purdue Pharma L.P. v. Boehringer Ingelheim GMBH, 237 F.3d 1359, 1366 (Fed. Cir. 2001)). We have stated that "when balanced against high materiality, the showing of intent can be proportionally less." Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc., 326 F.3d 1226, 1234 (Fed. Cir. 2003) (citation omitted).

We review the district court's factual findings with respect to materiality and intent for clear error. Perspective Biosystems, Inc. v. Pharmacia Biotech, Inc., 225 F.3d 1315, 1319 (Fed. Cir. 2000) (citation omitted). We review the ultimate determination of inequitable conduct, however, under an abuse of discretion standard. Id. (citations omitted). Thus, we may reverse a district court's decision on inequitable conduct only if the decision is based upon "clearly erroneous findings of fact or on a misapplication or misinterpretation of applicable law, or evidences a clear error of judgment on the part of the . . . court." Elk Corp. of Dallas v. GAF Bldg. Materials Corp., 168 F.3d 28, 30 (Fed. Cir. 1999) (citation omitted).

The district court based its finding of inequitable conduct with respect to prosecution of the '856 application on Novo's failure to disclose to the PTO that Example 1 of the 1983 PCT application had never actually been performed. Id. at 76.

Referring to Example 1 being worded in the past tense, the court found that "Novo did not alert the examiner that the cleavage and purification steps had not been performed or that the purity result was merely a prediction." Id. The district court found the requirement of materiality satisfied because the examiner relied upon Example 1 in deciding whether the 1983 PCT application enabled the invention of the '856 application and thus was entitled to a priority date earlier than that of the Brewer patent. Id.

Next, the court found the inequitable conduct intent requirement satisfied because "Novo, nine years after it first submitted Example 1 to the PTO, knew or should have known that the examiner would have considered the fact that Example 1 contained prophetic data important in evaluating whether the ['081 application, the U.S. counterpart of the 1983 PCT application,] enabled the invention of the '856 application, particularly in light of the fact that Novo never successfully produced ripe hGH using the methodology described in Example 1." Priority Decision, slip op. at 76.

The district court found inequitable conduct with respect to the interference proceedings before the Board based again upon Novo's failure to inform the Board that it was ultimately unable to produce ripe hGH using the methodology described in Example 1 of the 1983 PCT application. Priority Decision, slip op. at 79. First, the district court found the materiality element satisfied because the Board "looked to Example 1 and reviewed expert testimony related to . . . whether the steps described therein enabled one of ordinary skill in the art to produce ripe hGH." Id. With respect to the intent element, the court noted that, before the Board, Novo presented extensive expert testimony from Dr. Villa-Romaroff about Example 1, knowing that Example 1 had never been successfully performed. The court found that "Novo knew or should have

known that the Board would consider both Example 1 and Dr. Villa Romaroff's expert opinion material to the question of enablement, particularly since this question was the sole focus of the interference." Id. at 80. Moreover, the court found that following the interference proceeding, Novo failed to offer any explanation for its silence, merely asserting that "it was not required to provide the PTO with a running update of its efforts to make hGH." Id.

C.

On appeal, Novo argues that the district court's finding that Novo was unable to make ripe hGH according to the methodology of Example 1 is clearly erroneous. Pointing to the experiment performed on March 7, 1984, during which Novo used commercial grade LAP enzyme purchased from the Sigma company in order to produce ripe hGH, Novo asserts that it was able to produce ripe hGH according to the methodology of Example 1. Thus, Novo argues, because the methodology did work, there can be no culpable failure to say that it did not work.

The district court did not commit clear error in determining that Novo was unable to make ripe hGH according to the methodology of Example 1. It is undisputed that on March 7, 1984, Novo unintentionally used LAP from the Sigma company which happened to be "contaminated" with DAP I. Priority Decision, slip op. at 56-57. Moreover, at oral argument, counsel for Novo conceded that Novo was never able to produce ripe hGH through the use of "pure" LAP enzyme. Example 1 is directed to the production of ripe hGH through the use of LAP enzyme. We are not prepared to accept the proposition that simply because fate interceded and Novo scientists unintentionally

used LAP "contaminated" with DAP I, Novo produced ripe hGH according to the methodology of Example 1.

Novo also assigns error to the district court's finding that Novo acted with deceptive intent in failing to disclose the prophetic nature of Example 1 to the PTO or the Board. According to Novo, the district court never made a finding that anyone had actual knowledge that Example 1 of the PCT application was prophetic and that Novo never successfully produced ripe hGH using the methodology described in Example 1. Specifically, Novo contends that there is no evidence that Dr. Christensen, the co-inventor who wrote Example 1, subsequently learned that the drafting of a prophetic example in the past tense was not a good procedure at the PTO, or that he subsequently told any of Novo's attorneys that Example 1 was prophetic.[12] Thus, Novo asserts, because it is impossible to disclose the unknown, the district court's finding of inequitable conduct is reversible error under FMC Corp. v. Manitowoc Co., Inc., 835 F.2d 1411, 1415 (Fed. Cir. 1987) (stating that an "[a]pplicant must be chargeable with knowledge of the existence of the prior art or information, for it is impossible to disclose the unknown"). Novo also asserts that the district court's finding of inequitable conduct amounts to a finding of misconduct based on an imputation of gross negligence, contrary to our holding in Kingsdown Medical Consultants, Ltd. v. Hollister, Inc., 863 F.2d 867, 876 (Fed. Cir. 1988) ("We adopt the view that a finding that particular conduct

[12] The district court found that, at the time of filing the '081 application, Dr. Christensen did not intentionally breach his duty of candor and good faith. Rather, the court concluded "that Mr. Christensen's use of past tense was merely an oversight on his part, likely due to the fact that Dr. Christensen is trained as a scientist, not as a patent attorney familiar with the teachings of the MPEP." Priority Decision, slip op. at 75. However, the district court did not extend this finding to actions taken by Dr. Christensen during prosecution of the '856 application and thereafter.

amounts to ‘gross negligence’ does not of itself justify an inference of intent to deceive; the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive.”).

Bio-Technology responds that Dr. Christensen was aware that Example 1 was prophetic, and because “knowledge of the law is chargeable to the inventor,” and “inventors represented by counsel are presumed to know the law,” the district court’s inference of deceptive intent was not clearly erroneous. See Brasseler, U.S.A. I, L.P. v. Stryker Sales Corp., 267 F.3d 1370 (Fed. Cir. 2001).

We agree with Bio-Technology. It is undisputed that Dr. Christensen was aware that Example 1 was prophetic and that Novo never successfully produced ripe hGH through the use of “pure LAP” enzyme. It also is undisputed that, during prosecution of the '856 application, Dr. Christensen was one of four Novo representatives present during the January 7, 1994 interview with the examiner, during which one of the issues addressed was enablement of the 1983 PCT application, of which the ’081 application was the U.S. counterpart. As noted, other representatives included Novo’s in-house patent attorney and in-house patent advisor. Thus, Novo asks us to hold, on the one hand, that the failure of Dr. Christensen and his co-inventors to disclose the truth about Example 1 to Novo’s attorneys absolves them of their duty to disclose this information to the PTO or the Board, because without their attorney’s consultation, they could not have known that this information was material. At the same time, Novo asks us to hold that its counsel’s failure to disclose the truth about Example 1 to the PTO or Board is excused because the inventors failed to fully inform them of the details surrounding Example 1. As we have done in similar situations in the past, we reject the “circular

logic" of this request. See Brasseler, 267 F.3d at 1380 ("We refuse to pursue the circular logic of Brasseler's request and decline to carve out an exception to the inequitable conduct law to shield those guilty of inequitable conduct from responsibility for their actions."); see also Molins, 48 F.3d at 1178 (stating that the knowledge and actions of an applicant's representatives are chargeable to the applicant (citing FMC Corp., 835 F.2d at 1415 n.8)). Accordingly, the district court correctly concluded that Novo knew or should have known that the PTO and the Board would have considered the information relating to Example 1 important in evaluating whether the 1983 PCT application was enabled.

Finally, Novo argues that the withheld information about Example 1 cannot be material as a matter of law because it was cumulative of what was already before the examiner, or because it is less relevant than information about the Example 1 methodology that was disclosed. See Regents of Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1574-75 (Fed. Cir. 1997) ("[E]ven where an applicant fails to disclose an otherwise material prior art reference, that failure will not support a finding of inequitable conduct if the reference is 'simply cumulative to other references,' i.e., if the reference teaches no more than what a reasonable examiner would consider to be taught by the prior art already before the PTO.") (citing Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1582 (Fed. Cir. 1991) ("A reference that is simply cumulative to other references does not meet the threshold of materiality that is predicate to a holding of inequitable conduct.") (citation omitted)).

In making this argument, Novo points to the 1990 declaration, which it describes as showing that pure LAP enzyme did not work, while commercial LAP from Sigma did

work. However, the withheld information concerning Example 1 was not merely cumulative of information already before the examiner; nor was the withheld information less relevant than information already before the examiner. First, the testing conditions in Example 1 of the 1983 PCT application differ from the testing conditions used in the examples in the 1990 declaration. The 1990 declaration does not indicate that pure LAP enzyme is not effective to produce ripe hGH under the methodology and testing conditions of Example 1 of the 1983 PCT application. In addition, an inventor's failed attempts to practice an invention are relevant evidence of non-enablement. See AK Steel Corp. v. Sollac, 344 F.3d 1234, 1244-45 (Fed. Cir. 2003) ("[G]iven the specification's teaching away from the subject matter that was eventually claimed and AK Steel's own failures to make and use the later claimed invention at the time of the application, the district court correctly concluded that there was no genuine issue of material fact relating to undue experimentation as it relates to enablement."); Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1372 (Fed. Cir. 1999) ("The court noted that the record is replete with the inventor's own failed attempts to control the expression of other genes in prokaryotes or eukaryotes using antisense technology."). We see no error in the district court's finding that the withheld information concerning Example 1 was material. We therefore affirm the district court's ruling that the '352 patent is unenforceable due to inequitable conduct.

CONCLUSION

In sum, we affirm the district court's holding that claim 1 of the '352 patent is invalid based on anticipation under 35 U.S.C. § 102(a), as well as its holding that the '352 patent is unenforceable due to inequitable conduct. However, we vacate the

court's ruling that claim 2 of the '352 patent is invalid based on anticipation under 35 U.S.C. § 102(a).

COSTS

Each party shall bear its own costs.

AFFIRMED-IN-PART and VACATED-IN-PART