United States Court of Appeals for the Federal Circuit

00-1372

HOFFMANN-LA ROCHE, INC.,
and ROCHE MOLECULAR SYSTEMS, INC.,

Plaintiffs-Appellants,

v.

PROMEGA CORPORATION,

Defendant-Appellee.

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Appealed from: United States District Court for the Northern District of California

Judge Vaughn R. Walker

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DECIDED: March 31, 2003

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

Opinion for the court filed by Circuit Judge BRYSON. Dissenting opinion filed by Circuit Judge NEWMAN.

I

The polymerase chain reaction (PCR) allows scientists, beginning with a small amount of deoxyribonucleic acid (DNA), to generate many copies of that DNA in a short period of time. The ability of PCR to synthesize DNA rapidly has led to significant advances in molecular biology and has been particularly useful in pathology and in the identification of trace materials such as blood and hair.

In the first stage of PCR, a segment of DNA is separated at high temperature into its two component strands. Then, at a lower temperature, small pieces of synthetic DNA called "primers" are annealed to specific locations on the separated strands. Enzymes known as DNA polymerases then "extend" the primers by attaching a complementary nucleotide to each nucleotide in the template strand. In this manner, the polymerase creates two identical double-stranded DNA helices from the two separated single strands of the original helix. The process of strand separation, primer annealment, and extension is then performed repeatedly, resulting in the production of a large number of identical DNA strands.

When PCR was first developed, the high temperatures associated with strand separation destroyed the polymerase that was used to drive the reaction. Accordingly, new polymerase had to be added at the beginning of each cycle of the reaction, which was cumbersome. It was subsequently discovered that the DNA polymerase of the Thermus aquaticus, or "Taq," bacterium, which is found in geysers and hot springs, was stable and active at high temperatures and therefore could withstand the rigors of PCR. Thus, Taq needed to be added to the reaction mixture only once, which resulted in making the PCR process much faster and more efficient.

On June 17, 1987, Cetus Corporation, the predecessor of appellants Hoffmann-La Roche, Inc., and Roche Molecular Systems, Inc. (collectively, "Roche"), filed U.S. Patent Application No. 07/063,509 ("the '509 application"), which was

directed to a purified thermostable enzyme. The '509 application named Dr. David Gelfand, the Cetus scientist most knowledgeable about the Taq enzyme, and Ms. Susanne Stoffel, Dr. Gelfand's technician, as inventors. The broadest originally filed claim was not limited to the Taq enzyme.

In an office action dated November 1, 1988, the examiner rejected all the submitted claims on a variety of grounds. The rejections included an anticipation/obviousness rejection based on journal articles by Chien, et al., and Kaledin, et al., both of which disclosed a DNA polymerase derived from the Taq bacterium. The examiner noted that the applicants included molecular weight limitations in dependent claims and that those limitations differed from the estimates of Taq's molecular weight reported by Chien and Kaledin. The examiner suggested that "some proteins behave anomalously when subjected to SDS page," the technique used by the applicants to estimate molecular weight. For that reason, the examiner concluded that "[i]t is not clear whether or not the molecular weight an[d] pH range of activity claimed by applicants for the instant enzyme is a result of experimental parameters or an enzyme activity different than the [enzyme] previously described in the literature."

On March 17, 1989, the inventors responded to the examiner's rejection, canceling all pending claims and entering three new claims, the broadest of which provided as follows:

1. Purified thermostable Thermus aquaticus DNA polymerase that migrates on a denaturing polyacrylamide gel faster than phosphorylase B and more slowly than does bovine serum albumin and has an estimated molecular weight of 86,000-90,000 daltons when compared with a phosphorylase B standard assigned a molecular weight of 92,500 daltons.

U.S. Patent No. 4,889,818, col. 44, ll. 46-52.

In remarks accompanying the amendment, the applicants made a two-part argument for patentability. First, they asserted that the claimed enzyme was distinct from the prior art enzyme, citing differences in molecular weight, specific activity, and fidelity. Second, they contended that even if, contrary to their belief, the claimed and prior art enzymes were identical, the claimed enzyme would still be patentable because it was "far more pure" than the enzyme of the Chien and Kaledin preparations. To support that assertion, the inventors cited a portion of the application indicating that the claimed enzyme had a specific activity ten times that of the prior art enzyme.

The examiner allowed the amended claims without further comment. The '509 application therefore issued as U.S. Patent No. 4,889,818 ("the '818 patent") on December 26, 1989.

Cetus licensed the '818 patent to Promega Corporation in June 1990. After Cetus sold the '818 patent to Roche, Promega allegedly breached the license agreement. Roche filed suit, alleging patent infringement and breach of contract. Promega counterclaimed, asserting inter alia that the '818 patent was unenforceable due to inequitable conduct, a claim that soon became the focus of the litigation.

In August 1996, the district court held on summary judgment that the inventors had made four material misrepresentations during the prosecution of the '818 patent. After a bench trial, the court held that the '818 patent was unenforceable based on eight separate misrepresentations and omissions, including three of the ones the court had addressed at the summary judgment stage. Roche appeals the court's order holding the patent unenforceable.

II

A party seeking to have a patent declared unenforceable has a heavy burden to meet. Inequitable conduct requires misrepresentation or omission of a material fact, together with an intent to deceive the PTO. Both of those distinct elements must be shown by clear and convincing evidence. See Manville Sales Corp. v. Paramount Sys., Inc., 917 F.2d 544, 552, 16 USPQ2d 1587, 1593 (Fed. Cir. 1990); Kingsdown Med. Consultants, Ltd. v. Hollister Inc., 863 F.2d 867, 872, 9 USPQ2d 1384, 1389 (Fed. Cir. 1988). Once the requisite levels of materiality and intent are shown, the district court must determine whether the equities warrant a conclusion that the patentee has engaged in inequitable conduct. Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178, 33 USPQ2d 1823, 1827 (Fed. Cir. 1995).

While it is difficult to prove inequitable conduct, a district court's ruling on inequitable conduct is reviewed deferentially. The court's findings on materiality and intent are reviewed for clear error, and thus will not be overturned in the absence of a "definite and firm conviction" that a mistake has been made. Molins, 48 F.3d at 1178, 33 USPQ2d at 1827. The district court's assessment of the equities is reviewed for an abuse of discretion. Id.

The district court in this case based its inequitable conduct ruling on its finding that the inventors made various material misrepresentations and related omissions, which can be grouped into three categories: (1) representations regarding the difference in molecular weight between the claimed and prior art Taq enzymes; (2) representations that the inventors had performed Example VI, one of the procedures described in the specification, and that they had achieved the described results; and (3) representations concerning the comparative fidelity and template dependence of the claimed enzyme and the prior art enzymes.

We analyze each of the three categories of asserted inequitable conduct below, upholding the district court's findings as to two of the three and overturning the court's findings as to the third. The dissent, which would overturn the district court's findings with respect to all three categories, criticizes us for failing to apply the clear and convincing standard of proof in assessing the evidence of materiality and intent. While we recognize the standard of proof that applies to those factual issues, we also note that our task as a reviewing court is not to make those factual determinations in the first instance but to determine whether the district court's findings on those issues are clearly erroneous or are infected with legal error. With that standard of review in mind, we turn to each of the grounds on which the district court based its ruling.

A. Molecular Weight

In their response to the examiner's office action, the inventors argued that the claimed enzyme was different from the enzyme described in the cited references. Their argument focused principally on the disparity in the molecular weight values reported for the prior art enzymes and the claimed enzyme. The inventors noted that claim 1 of the '509 application recited an enzyme with a molecular weight of 86,000 to 90,000 daltons, while the Chien and Kaledin references described enzymes with molecular weights of 63,000-68,000 daltons and 60,000-62,000 daltons, respectively. The inventors proffered an explanation for the discrepancy: they believed that, at most, Chien and Kaledin had isolated a "crude preparation of degraded Taq polymerase." The district court, however, concluded on summary judgment that the inventors had withheld information from the PTO that tended to show that the enzymes Chien and Kaledin had isolated were not simply degraded fragments of Taq polymerase and thus made it less clear that the Chien and Kaledin enzymes were distinguishable from the enzyme described in the application.

1. The Stoffel Experiment

The dispute over the disparity in reported molecular weights relates in part to an experiment that Ms. Stoffel performed, in which she applied a protein sample to a phosphocellulose column. She observed that a Taq fragment with a molecular weight of 62,000 daltons did not bind to the phosphocellulose column. According to the district court, the results of that experiment undercut the inventors' statement in the March 17, 1989, office action response that the Chien article referred to a degraded form of Taq. In the district court's view, the fact that the Taq fragment did not bind to Ms. Stoffel's phosphocellulose column indicated that a similar fragment would have been "lost" in the experiment described by Chien, because that experiment also used a column of phosphocellulose. The district court therefore concluded that the Stoffel experiment suggested that the enzyme described in the prior art references was not a degraded form of Taq, as the inventors contended. For that reason, the court determined that the inventors should have replicated the prior art experiment before characterizing it as producing a Taq fragment with a lower molecular weight.

Roche argues that there were genuine issues of material fact regarding the materiality of the Stoffel experiment, and that the issue should not have been decided on summary judgment. We agree. Two key facts are undisputed. First, the ability of a particle to bind to a phosphocellulose column depends upon the initial salt concentration of the buffer in which the phosphocellulose column is suspended. Promega's expert, Dr. Mosbaugh, concurred with Roche's evidence on that point. Second, the initial salt concentration of the Stoffel experiment (80 mM) differed significantly from that described in the Chien reference (10 mM). Because the Stoffel experiment was conducted under conditions very different from those described in the Chien reference, it is not clear that the results of the Stoffel experiment were pertinent to the inventors' characterization of the prior art enzyme. Because the district court improperly concluded as matter of law that the Stoffel experiment was material, the portion of the district court's summary judgment order relating to the materiality of the Stoffel experiment cannot be sustained.

We also must reverse the district court's finding of intent with respect to the Stoffel experiment. Following trial, the court found that the inventors intended to deceive the PTO when they failed to disclose the results of the Stoffel experiment to the examiner. Roche characterizes that finding as clearly erroneous, and we agree. The evidence does not demonstrate that the inventors intended to deceive the PTO by suppressing the results of the Stoffel experiment. Instead, it shows that they believed that the initial salt concentration in such an experiment was critical to the capacity of the fragment to bind to the column and that the low initial salt concentration used in the Chien experiment rendered the Stoffel experiment not comparable and the results of the Stoffel experiment not pertinent to patentability.

The evidence showed, for example, that when one of Dr. Gelfand's colleagues had difficulty with an enzyme sticking to the column, he called Dr. Gelfand, who concluded that it was possible the colleague had encountered a fragment and suggested reducing the salt concentration to around 40 mM. The colleague stated that "[t]he suggestion from Dr. Gelfand was that the salt concentration of the load in this column was probably too high. And in order to get that material to stick to the column, one needed to lower the salt concentration by dialyzing." Similarly, Ms. Stoffel testified that experiments showed that the fragment did not bind when it was loaded at a salt concentration of 80 mM, but that "it stuck but it eluted earlier in the gradient" at a salt concentration of 10 mM—the concentration in Chien's experiment. When the inventors noted that the proteolyzed enzyme did not bind to phosphocellulose, they included a reference to the restriction "at 80 mM salt," indicating that they considered the salt concentration significant to the failure to bind. Thus, the record reflects that the enzyme's ability to bind to the column is dependent on the initial salt concentration and that the inventors knew of that dependence and deemed it significant. This evidence as to the inventors' state of mind stands as unrebutted proof that they did not think the results of the Stoffel experiment had any bearing on whether Chien had isolated a fragment of the Taq enzyme. Accordingly, we conclude that the district court committed clear error in finding clear and convincing evidence of intent to deceive in the inventors' failure to disclose the Stoffel experiment.

2. Size Exclusion Chromatography

The district court also ruled that the inventors improperly withheld four pieces of information that suggested that the technique Chien used to determine molecular weight—size exclusion chromatography—was inaccurate and produced results underestimating the true molecular weight of Chien's Taq. In the district court's view, that information would have weakened the inventors' argument that the claimed enzyme was distinct from the enzyme of the prior art, as evidenced by a difference in molecular weight.

In the size exclusion chromatography procedure in question, a sample of the protein whose weight is to be estimated is introduced into a column filled with porous beads (sometimes referred to as a "matrix"). A buffer solution is run through the column. The proteins in the sample that are larger than the pore size of the beads will flow around the beads and out the bottom of the column. The smaller proteins will enter the pores between the beads, thus retarding their progress through the column. As a result, the speed at which a protein "elutes," or moves through the column, corresponds to its molecular weight. The faster a protein moves through the column, the greater its molecular weight. If, however, a protein that otherwise would pass quickly through the matrix because of its large size has a chemical affinity for the matrix, it may move through the column more slowly than would be expected, resulting in an underestimation of its molecular weight.

According to the district court, the inventors had information suggesting that the Taq enzyme would have bound to the matrix used by Chien in her size exclusion procedure. The district court therefore concluded that the inventors knew that Chien's molecular weight value was potentially too low, and that the difference between the claimed and prior art enzymes was less than the inventors asserted.

The information to which the district court pointed consisted of (1) the results of a purification experiment by Ms. Stoffel; (2) a sizing experiment by Dr. Drummond, another Cetus employee; (3) data concerning Taq's hydrophobicity (its tendency to avoid interacting with water); and (4) an internal memorandum by Mr. Raymond, a Cetus employee. Roche argues that the information marshaled by the district court does not constitute evidence that Taq would have bound to the matrix used by Chien in her sizing experiment and that the district court improperly ruled in Promega's favor on this issue. We agree. None of the information cited by the district court tends to prove that Taq would have bound to the particular type of matrix used by Chien, a product known as Sephadex G-100.

The experiments conducted by Dr. Drummond and Ms. Stoffel used types of gels (Zorbax and Ultrogel) that differed from the type of gel used by Chien. Promega's expert on this subject, Dr. Burgess, conceded that the phenomenon of a protein binding to a matrix is dependent upon the specific chemistry between the matrix and the protein in question. Promega introduced no evidence that the experiments that were conducted with Zorbax and Ultrogel shed any light on the manner in which Sephadex and Taq interact. The evidence therefore did not show that the experiments indicated that Chien's Taq would have bound to the matrix and produced inaccurate results. Accordingly, the district court improperly held that the failure to disclose those experiments was a material omission.

The district court also ruled that the inventors' knowledge of Taq's hydrophobicity was material to determining whether Chien's sizing experiment was accurate. Roche contests that ruling, claiming that Taq's hydrophobicity is not probative of whether it would interact with a matrix composed of Sephadex.

It is undisputed that a protein's interaction with a particular sizing matrix depends not only on the properties of the protein, but also on those of the matrix itself. In reaching the conclusion that Taq's hydrophobicity would make it likely that it would

have bound to Sephadex, the district court did not consider the chemical properties of Sephadex. That omission is critical. The only evidence adduced at trial on that point was from Roche's expert Dr. Chamberlin, who testified that the chemical composition of Sephadex would make it unlikely to bind to a hydrophobic enzyme such as Taq, because Sephadex is hydrophilic rather than hydrophobic. Thus, the record does not support the district court's conclusion that Taq's hydrophobic nature makes it likely that Chien's sizing experiment produced inaccurate molecular weight estimates, because there is no proof that Taq is likely to bind to a matrix composed of Sephadex G-100. The court's finding on that issue is clearly erroneous.

Finally, the district court ruled on summary judgment that the Raymond memorandum was material. That memorandum indicates that Taq "migrates differently on sorbax [sic: Zorbax] or other sizing columns" and that a different technique, SDS-PAGE, is needed to get an accurate determination of molecular weight. Again, however, the Raymond memorandum does not indicate whether Taq would interact with Sephadex G-100. The possibility that the Raymond memorandum was referring to Sephadex when it mentioned "other sizing columns" is remote, because there is no evidence that Cetus ever conducted any sizing experiments with that type of gel. Furthermore, Roche contends that because Sephadex has a significantly different chemistry than the types of gels Cetus used, extrapolating from the Raymond memorandum in the manner that the district court did is improper. We conclude that, at a minimum, there is a genuine dispute of material fact on this issue, and we therefore hold that it was inappropriate for the district court to resolve this question on summary judgment. In sum, we reverse the district court's inequitable conduct ruling to the extent that it relies on representations and omissions regarding the respective molecular weights of the prior art and the claimed enzymes.

B. Example VI

Following trial, the district court found that the inventors committed inequitable conduct by erroneously stating that they had performed a particular purification protocol and had obtained certain results. Example VI is a procedure described in the '509 application for repeatedly refining, or fractionating, a bacterial culture of the Taq enzyme through a variety of techniques, including column chromatography. According to Example VI, the last of these "fractions" is the purified version of the claimed enzyme. Example VI concludes:

Active fractions with no detectable nuclease(s) were pooled and run on a silver stained SDS-page mini gel. The results show a single ~88 kd band with a specific activity of ~250,000 units/mg.

> This specific activity is more than an order of magnitude higher than that claimed for the previously isolated Taq polymerase and is at least an order of magnitude higher than that for E. coli polymerase I.

'818 patent, col. 41, ll. 12-20. The inventors further stated that "[t]he Taq polymerase purified as described above in Example VI was found to be free of any contaminating Taq endonuclease and exonuclease activities." '818 patent, col. 41, ll. 23-25.

1. Misrepresentations

Example VI is written in the past tense. The inventors state, for example, that a certain quantity of cells "were resuspended in 75 ml of a buffer," that the cells "were lysed in a French press," '818 patent, col. 39, ll. 3-7, after which 300 ml of Tris-EDTA "were added." Each step of the example, over more than two columns of the patent, is described in the same fashion, using the past tense. Indeed, the past tense is used to describe the steps of Example VI on more than 75 occasions. E.g., "These steps were repeated and the protein suspension was dialyzed extensively"; "The polymerase activity was assayed"; "An assay . . . was performed"; "Active fractions with no detectable nuclease(s) were pooled, and run on a silver stained SDSPAGE mini gel." '818 patent, col. 39, ll. 61-62; col. 41, ll. 3-4, 6-14. From the language used, a reader of the patent would conclude that the protocol was performed and that the following results were actually achieved: (1) the refined enzyme possessed "single-band purity"; (2) the purified enzyme was free from nuclease activity; (3) the enzyme had a specific activity of approximately 250,000 units/mg; and (4) the specific activity of the enzyme was at least ten times that of the prior art enzyme.

As a threshold matter, Roche suggests that the description of Example VI in the past tense is not actually a misrepresentation, and therefore that we need not inquire into the issues of intent and materiality. The district court, however, specifically found that Example VI had not been performed as written, and in light of the testimony adduced at trial, that finding cannot be held to be clearly erroneous.

Dr. Gelfand admitted that Example VI was never performed as described:

Q. Well, if you thought this was the best way, when did you ever do Example 6 from start to finish exactly as written? You never have done Example 6 from start to finish as written, have you, ever?

A. Susanne Stoffel and I, that is correct, Susanne Stoffel and I never carried out Example 6 from start to finish as laid out.

Ms. Stoffel's testimony was similar. Since Example VI was never performed, the inventors never obtained the described results.

Roche notes that the last sentence in the description of the procedure purportedly used in Example VI is in the present tense ("The results show a single ~88 kd band with a specific activity of ~250,000 units/mg."). Because that sentence is in the present tense, Roche argues, a reader would understand that Example VI was a prophetic example, and was not actually performed. That argument is entirely unpersuasive. After having described in great detail the process purportedly used in the experiment and the results obtained—all in the past tense—the use of the present tense in the single quoted sentence would be understood as a present characterization of results actually obtained in the past, not as the inventors' prediction of what such an experiment would show if it were performed.

Roche next suggests that the use of the past tense in Example VI is not really a misrepresentation since all of the steps in that procedure were purportedly part of two procedures that Roche did perform, Prep 3 and Prep 4. Specifically, Dr. Gelfand stated that four of the five column steps of Example VI were completed in Prep 4 and the remaining step was performed at some point in Prep 3.

The district court, however, rejected the argument that Example VI was in effect performed through the combination of Prep 3 and Prep 4. The court noted that Gelfand and Stoffel had "combined steps from [Prep 3 and Prep 4] to arrive at Example VI," but the court made clear that it did not regard the combination of steps from those two preparations as constituting the performance of Example VI. In fact, the court explained that the representation "that Example VI yielded a single ~88 kd band on an SDS PAGE mini-gel was necessarily a misstatement because the inventors had not, in fact, performed Example VI of the patent."

While Promega's expert witness, Dr. Linn, conceded that the inventors did each of the column steps at some point, he also noted that they were not done in the order specified in Example VI. Moreover, Dr. Mosbaugh testified that the order of the steps is important and that the addition or deletion of a step would affect the collection of proteins, a significant result. He stated that "it's not just a matter of doing five steps. It's important what those five steps are, the order in which they're carried out." Dr. Mosbaugh examined the details of the steps and noted that there were many differences in how the two final columns in Prep 4 were "handled and evaluated relative to what the patent says" in Example VI. When asked about the predictive value of Prep 3 and 4 with regard to Example VI, Dr. Mosbaugh stated that one "cannot fuse these together and get any prediction as to what the outcome would be." He concluded that "they didn't do Example 6 as reported in the patent; [ ] what they did do, that is [Prep] 3 and [Prep] 4, will not get you, in my opinion, to Example 6." Roche offered no evidence contradicting the importance of the order of the steps, the differences within the steps, and the conclusion that the results of Prep 3 and Prep 4 would not provide an accurate representation of the results of a procedure conducted according to Example VI. Accordingly, although Roche attempts to convert the district court's finding that the inventors generated Example VI by combining steps from Prep 3 and Prep 4 into a finding that by performing Prep 3 and Prep 4 they had in effect performed Example VI, that effort runs headlong into the district court's repeated findings that Example VI was never performed. And, as noted, that finding was supported by evidence and cannot be deemed clearly erroneous.

Nor is there force to Roche's argument that the results reported in Example VI are consistent with the results of other experiments that had actually been performed. With respect to the assertion in Example VI that the inventors derived an enzyme exhibiting single-band purity, Dr. Mosbaugh stated that even improved protocols for purity failed to achieve single-band purity. He also noted that when outside contractors performed Example VI, they encountered multiple bands. Roche's expert witness, Dr. Chamberlin, testified that he did not see a gel from either Prep 3 or Prep 4 with only a single band. Additionally, while Ms. Stoffel asserted that she achieved a single band in Prep 4, Dr. Gelfand conceded that in Prep 4 they obtained a major band, but that "it was not the only band. There were some other very faint bands." Based on that testimony, the district court permissibly concluded that the representation that Example VI yielded a single band was a significant deviation from the information known to the inventors.

The district court reached a similar conclusion with respect to the assertion in the specification that Example VI resulted in a nuclease-free preparation. In particular, the court found that the representations that "[a]ctive fractions with no detectable nuclease(s) were pooled and run on a silver stained SDS PAGE mini-gel" and that "[t]he Taq polymerase purified as described above in Example VI was found to be free of any contaminating Taq endonuclease and exonuclease activities" were false. The court noted that while the inventors relied on the results of Prep 4 to support those claims, Ms. Stoffel and

Roche's expert admitted that the enzyme that resulted from that procedure was not nuclease-free. Roche's expert, Dr. Chamberlin, testified that there was detectable endonuclease activity. Ms. Stoffel testified that Prep 4 contained only a "very small" or "minimal" amount of nucleases, but Promega's expert witness Dr. Linn characterized the contamination of that preparation as substantial. In light of this testimony, on which the district court relied, it was not clearly erroneous for the district court to conclude that the inventors did not achieve a nuclease-free polymerase in any experiment that they actually conducted.

The district court was also justified in concluding that the inventors' assertion that they had achieved an enzyme with a specific activity of approximately 250,000 units/mg was false. Example VI specifically states that a "unit" is equal to "10 nM of product in 30 minutes." The court found at the summary judgment stage, however, that the 250,000 value corresponded to a different definition of a "unit," and it held that under the definition set forth in Example VI, the correct value should have been recited as 100,000 units/mg. The district court noted that Dr. Gelfand gave conflicting accounts of the source of the specific activity value reported in Example VI. In a declaration submitted to the court, Dr. Gelfand asserted that the value was obtained according to the conditions recited in Example VI. In a prior declaration submitted to the PTO, however, Dr. Gelfand stated that the results of Example VI were obtained from an experiment based on the assay conditions listed in Example I (also in the '509 application). In reality, neither of those statements was true, for it appears that the 250,000 number was based on an experiment performed by Ms. Stoffel, in which she obtained a result of 248,000 units/mg.

The Stoffel experiment does not, however, prove that the specific activity result of Example VI is grounded in an actual experimental result. Although Dr. Gelfand testified that Ms. Stoffel's result was 200,000 units/mg "under the new unit definitions," that testimony does not prove that the new unit definition was the same as the one used in Example VI, nor does it prove that the Stoffel experiment was conducted under conditions equivalent to those described in Example VI. Roche's claim that another experiment measured a specific activity of approximately 390,000 units/mg also fails for similar reasons, because there is no proof that that experiment was performed under conditions equivalent to Example VI with a per milligram specific activity value approaching 250,000 "units," as that term is defined in Example VI. Thus, Roche has not met its burden of demonstrating that the district court clearly erred in determining that the inventors' stated specific activity result was a misrepresentation.

Finally, the evidence supports the court's finding that the inventors' comparison of the specific activity of the claimed and prior art enzymes was deceptive. The application stated that the specific activity of the claimed enzyme, as purified according to Example VI, was at least ten times that of the prior art enzyme. The inventors repeated that argument in the March 17, 1989, office action response as an alternative argument for patentability. Based on Dr. Mosbaugh's testimony, however, the court found that the comparison was invalid because the two enzymes were not assayed under the same conditions. The court also found that the contrary testimony of Roche's witness, Dr. Chamberlin, was not credible. There is no clear error in that determination.

2. Intent

Misrepresentations by themselves are not enough to render a patent unenforceable; the misrepresentations must be intentional and they must be material to patentability. With regard to the element of intent, Roche has not demonstrated clear error in the district court's finding. The inventors attested that all statements made in the '509 application were true. There was no suggestion by Roche that the use of the past tense in Example VI was an oversight—Dr. Gelfand admitted he understood that, at least in a scientific publication, the use of the past tense means that an experiment was actually performed. He provided no reasonable explanation as to why a different principle would apply in a patent application. Nor did Roche introduce any other evidence to explain why the past tense was used to describe an experiment that was not performed. Accordingly, the district court did not clearly err in determining that the inventors' use of the past tense in Example VI was knowingly false.

Roche contends that Example VI was included in the application because it represented the best mode of practicing the invention, disclosure of which is required by 35 U.S.C. § 112. The best mode requirement, however, does not entitle the inventor to suggest that the best mode has been performed when it has not, and to report results that have not actually been observed.

Roche attaches great significance to the fact that the district court found that the inventors had a good faith belief that they had discovered a different enzyme than that described in the prior art, arguing that "[b]ecause one cannot intentionally deceive by representing what one honestly believes, the district court's judgment cannot stand." Roche misapprehends the import of that finding by the district court. The inventors may indeed have believed they had discovered a novel enzyme, but that belief does not permit them to make misrepresentations in seeking to persuade the examiner to issue a patent for that enzyme. Thus, the district court's finding that the inventors had a good faith belief in the novelty of their invention is not incompatible with a finding of deceptive intent.

3. Materiality

As to the materiality element of inequitable conduct, Roche argues that because the '818 patent did not include claim limitations directed to purity, representations about purity made in the application cannot be material. Materiality, however, is not limited to matters reflected in the claims of a patent. See PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc., 225 F.3d 1315, 1322, 56 USPQ2d 1001, 1006 (Fed. Cir. 2000). Rather, information is material when there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue. Id. at 1321, 56 USPQ2d at 1006. Moreover, the information at issue with respect to Example VI consisted of affirmative misrepresentations, not omissions, as was the case with respect to the issue of molecular weight. This court has held that affirmative misrepresentations by the patentee, in contrast to misleading omissions, are more likely to be regarded as material. Rohm & Haas Co. v. Crystal Chem. Co., 722 F.2d 1556, 1571, 220 USPQ 289, 300 (Fed. Cir. 1983).

In the office action response, the inventors argued that even if the claimed enzyme was not distinct from the prior art enzyme, "[a]pplicants would still be entitled to a patent because the present preparations are far more pure" than the prior art enzyme, citing the comparison of specific activity made in the patent application. Purity was therefore a prominent (albeit an alternative) argument in favor of patentability. Indeed, the prosecuting attorney testified that the argument regarding purity was made in order to allow amendments in the event that the examiner did not allow the existing claim. The district court based its finding of materiality on that ground: "Since Cetus argued that the patent could issue based on the asserted purity limitation, a reasonable examiner would have considered important information which indicated that Cetus had overstated the level of purity of the claimed enzyme."

The court's determination is not clearly erroneous. The fact that the examiner did not have to rely on the purity representations in issuing the patent is not inconsistent with a finding of materiality. See Merck & Co. v. Danbury Pharmacal, Inc., 873 F.2d 1418, 1421, 10 USPQ2d 1682, 1686 (Fed. Cir. 1989) (rejecting a "but for" standard of materiality). Although the inventors' statements regarding purity were not the principal focus of the office action response, they were clearly an important aspect of it. Under the circumstances, a reasonable examiner would have wanted to know that the patentability argument based on purity was unsupported by the experimental results cited by the inventors.[1] Thus, the purity results reported in Example VI and the reference to them in the office action response were central enough to the prosecution to be "within a reasonable examiner's realm of consideration." Id.[2]

C. Comparison of Fidelity

The district court next focused on the inventors' comparison of the fidelity and template dependency of the claimed enzyme and the prior art enzymes. A DNA polymerase is said to be "template dependent" if it has the ability to read the identity of a nucleotide in the template strand of DNA and then synthesize the appropriate complementary base pair. Fidelity relates to the accuracy of the DNA polymerase in adhering to the complementary base-pairing during synthesis. A polymerase exhibits a higher fidelity when it experiences fewer misincorporation events, which are mistaken base-pairings. A template-dependent, high fidelity DNA polymerase will exhibit little or no activity when one of the four types of nucleotides is absent from the reaction mixture. The polymerase will incorporate nucleotides until it encounters a position on the template for which the corresponding complement is not available. At that point, the polymerase will effectively stop working because it cannot perform the synthesis operation correctly, causing experimental results of less than one hundred percent incorporation.

In the '509 application, the inventors posited that their claimed enzyme exhibited high fidelity while the prior art enzyme experienced misincorporation. The inventors stated that:

> when only one or more nucleotide triphosphates were eliminated from a DNA polymerase assay reaction mixture, very little, if any, activity was observed using the enzyme herein, and the activity was consistent with the expected value, and with an enzyme exhibiting high fidelity. In contrast, the activity observed using the Kaledin et al. (supra) enzyme is not consistent with the expected value, and suggests misincorporation of nucleotide triphosphate(s).

'818 patent, col. 30, ll. 23-31. The inventors made a similar assertion in their March 17, 1989, office action response:

> The data in the . . . [prior art references] would lead one of ordinary skill in the art to conclude that the enzymes described in these references are not suitable for template-directed in vitro DNA synthesis, because the enzymes have a rather substantial promiscuous ability to synthesize DNA on a natural DNA template in the absence of one of the four deoxynucleoside triphosphates.
> The Taq polymerase of the present invention has an activity quite different from and superior to the activity of the polymerase described by [the prior art references]. On page 47, lines 6-12, of the specification,

> Applicants point out that the purified Taq polymerase of the invention has little or no activity in a DNA polymerase assay reaction mixture that does not contain one of the four deoxynucleoside triphosphates.

That assertion was made to support the contention that the claimed enzyme was different from the prior art enzyme cited by the examiner. The claim of greater fidelity was therefore intended to demonstrate, along with the purported difference in molecular weight, that the claimed enzyme was not the same as the enzyme described in the prior art references and accordingly was patentable.

While it appears that the applicants' statements about the fidelity of their own enzyme were accurate, the district court found that the statements characterizing the activity of the prior art enzymes and comparing it to that of the claimed enzyme were inaccurate. That finding is not clearly erroneous. Promega's expert witness Dr. Kunkel testified that the Kaledin and Chien experiments are "not indicative of an enzyme that is not suitable for template-directed in vitro synthesis," but instead indicate just the opposite. Dr. Kunkel also addressed the applicants' representations that the prior art enzyme had a substantial promiscuous ability, which in the field of fidelity measurements suggests misincorporation, and that the reported activity levels indicated misincorporation.[3] Dr. Kunkel explained how Kaledin's and Chien's levels of incorporation recorded in the absence of one of the nucleotides did not reflect misincorporation events, but rather that the enzyme was incorporating until the missing nucleotide was needed for a base-pairing. Based on an examination of the structure of the template used by Kaledin, Dr. Kunkel reported that the results that Kaledin obtained were as anticipated, given the nature of the experiment, and that the experiment in no way indicated misincorporation.

According to Dr. Kunkel, the differing results referred to by the inventors in the office action response related to differences in experimental conditions (specifically, differences in the DNA templates used), and not to differences in the properties of the enzymes. For example, Dr. Kunkel explained that the template used by Kaledin and Chien was a mixture of double- and single-stranded DNA with various short, single-stranded gaps and that the synthesis began at a different point in each molecule. Therefore, there were as few as 21 total incorporation events in one example. In a particular instance, Dr. Kunkel testified, a gap may not even require the missing nucleotide and would incorporate fully, adhering to the complementary base-pairing and not misincorporating. This would result in activity levels closer to 100%. In contrast, the template used by Dr. Gelfand is a long single-strand that the enzyme must copy with synthesis starting at the same point on all the molecules and approximately 7000 incorporation events. A low percentage of the total incorporation is likely then to occur before the missing nucleotide is needed, resulting in lower activity levels than in Kaledin, but not necessarily indicating a higher fidelity. Dr. Kunkel explained that the results illustrated that both of the polymerases were template-dependent, that Kaledin's and Dr. Gelfand's results were as anticipated, and that the percent incorporation relative to the control is a function of the nature of the DNA. In addition, Dr. Kunkel described an experiment he conducted in which the same enzyme produced varying activity levels when different templates were used. According to Dr. Kunkel, that experiment demonstrated that the different activity levels found by Kaledin and by the inventors resulted from the use of different templates, "illustrating the well-known principles taught in the literature that the difference in incorporation values that one gets are a function of the DNA template that was used[,] not a function of the polymerase that was used." Dr. Kunkel testified that misincorporation could not be an explanation for the activity levels that Kaledin and Chien were observing. Roche did not offer expert testimony to contradict Dr. Kunkel's statements.

Roche responds to the district court's analysis of this issue by arguing that the inventors and Dr. Kunkel simply differed over how to interpret the results of the experiments involving the prior art and claimed enzymes, and that a dispute of that sort cannot give rise to a finding of inequitable conduct. Roche, however, failed to make a persuasive showing that there was a legitimate difference of scientific opinion on that issue and that the district court therefore committed clear error in its findings.

In its brief, Roche argues that a portion of Dr. Kunkel's cross-examination, together with a passage from the Chien reference itself, supports the claim that the comparison between the enzymes was sound. Roche argues that Chien explained that her activity level results were related to the nature of the enzyme, rather than to the template used. Chien stated that the incorporation she observed with one nucleotide omitted is "higher than those reported for most bacterial polymerases but is similar to certain mammalian DNA polymerases. The incorporation probably represents the addition of two or three dTTP's to complementary ends." However, Dr. Kunkel stated that Chien's use of the term "complementary" implies correct matching of base-pairs, rather than misincorporation. Thus, Chien fails to provide the requisite evidence that the district court committed clear error in rejecting Dr. Gelfand's statement that the activity suggests misincorporation. Roche's argument and citation to Chien fall far short of rebutting Dr. Kunkel's detailed testimony on which the district court relied. The court therefore did not clearly err in finding that the inventors misrepresented the prior art enzyme and its activity as compared to that of the claimed enzyme.[4]

We likewise uphold the district court's finding of materiality with respect to the fidelity issue. The statement in the office action response was made in an effort to support the inventors' primary argument for patentability—that the claimed enzyme

was different from the prior art enzyme. The most prominent evidence cited by the inventors in this regard was a difference in molecular weight, but the alleged difference in fidelity was also argued at some length. Given the prominence of that argument in the office action response, the district court did not clearly err in concluding that the misrepresentation made as part of that argument was material.

The district court found that the statements about fidelity were intentionally deceptive, based primarily on testimony from Dr. Kunkel, who worked with Dr. Gelfand and Cetus. Dr. Kunkel stated that he was aware of Dr. Gelfand's knowledge of template dependency and fidelity and that Dr. Gelfand could not possibly believe that the experiments indicated that the prior art enzyme was promiscuous and not suitable for template-directed synthesis. Dr. Kunkel testified that he did not believe that a scientist aware of the information in the Cetus records could truthfully make the statements found in the specification and office action response and that Dr. Gelfand was knowledgeable about that information. Stating that the experiment done in the prior art had nothing to do with fidelity or misincorporation and did not indicate that the prior art enzyme was not suitable for template-directed in vitro synthesis, Dr. Kunkel noted that such information was "well known to persons who studied polymerases in the '70's and '80's." In Dr. Kunkel's words, "with respect to fidelity, the issue that I was just speaking to, I feel very strongly that the – that Dr. Gelfand knew better."

Roche asserts that Dr. Kunkel's testimony is not probative of intent and that the finding of intent cannot stand because neither the inventors nor the prosecuting attorney were asked about that issue. Intent, however, is typically proved inferentially, Molins PLC v. Textron, Inc., 48 F.3d 1172, 1180, 33 USPQ2d 1823, 1828 (Fed. Cir. 1995), and a finding of intent does not require a confession from the stand by the inventor or the prosecuting attorney. The district court's reliance on Dr. Kunkel's testimony was entirely permissible. Dr. Kunkel is an expert in enzyme fidelity and was invited by Dr. Gelfand to visit Cetus, where he presented a seminar on the fidelity of Taq. Dr. Kunkel had discussions with Dr. Gelfand on that subject both at Cetus and at conferences where Dr. Kunkel presented. Accordingly, he was well positioned to testify as to Dr. Gelfand's knowledge of fidelity and misincorporation. While Dr. Kunkel did not testify that he and Dr. Gelfand spoke about the specific subject of the impact of a template on the percentage incorporation occurring in the absence of one of the nucleotides, it was permissible for the district court to infer that Dr. Gelfand understood that relationship on the record before it. Dr. Kunkel's testimony provided a sufficient basis for the district court's conclusion that Dr. Gelfand had sufficient information to understand the import of the statements made in the specification and the office action response. The district court did not clearly err in finding the requisite intent.

We note that Roche did not put forward evidence to contradict Dr. Kunkel as to whether the inventors' interpretation was reasonable, even though inaccurate. For example, Roche did not put forward testimony by another scientist, in a position similar to Dr. Gelfand, that a scientist studying polymerases could have misunderstood the data to indicate that the prior art enzymes were misincorporating and exhibiting a lower fidelity than the claimed enzyme. In particular, Dr. Gelfand did not testify about his knowledge of fidelity or that he believed the statements made in the specification and in the office action response. We therefore have no evidentiary basis from which to conclude that it was clearly erroneous for the district court to find that the assertions regarding fidelity were not legitimate or reasonable, and that the inventors therefore intentionally sought to deceive the PTO.

III

As we have explained, an important step in the judicial resolution of inequitable conduct claims is for the court to determine whether the material misrepresentations or omissions in question are sufficiently serious in light of the evidence of intent to deceive, under all the circumstances, to warrant the severe sanction of holding the patent unenforceable. That determination is committed to the trial court's discretion. In this case, the trial court did not expressly address this step in the inequitable conduct analysis. For that reason, and because we have not upheld all of the grounds on which the court found inequitable conduct in this case, we vacate the court's order of unenforceability and remand the case to the district court for it to determine, in the exercise of its judgment, whether under all the circumstances, the incidents of inequitable conduct that we have sustained are such as to justify the sanction of rendering the '818 patent unenforceable.

Each party shall bear its own costs for this appeal.

VACATED and REMANDED.

United States Court of Appeals for the Federal Circuit

00-1372

HOFFMANN-LA ROCHE, INC.,

and ROCHE MOLECULAR SYSTEMS, INC.,

Plaintiffs-Appellants,

v.

PROMEGA CORPORATION,

Defendant-Appellee.

NEWMAN, Circuit Judge, dissenting.

Litigation-induced assaults on the conduct of science and scientists, by aggressive advocates intent on destruction of reputation and property for private gain, produced the past "plague" of charges of "inequitable conduct." A successful attack on the inventor or his lawyer will destroy the patent, no matter how valid the patent and how sound the invention. The uncertainties of the processes of scientific research, the vagaries of the inductive method, the complexities of patent procedures, and the twists of hindsight, all provided grist for this pernicious mill. Indeed, the prevalence of accusations of inequitable conduct in patent cases led judges to suspect that all scientists are knaves and all patent attorneys jackals. Today this court revives that misbegotten era.

The Federal Circuit, having observed the ease with which ordinary actions in scientific research or patent prosecution can be distorted by zealous attack, established the requirement that the attacker make clear and convincing showings of both material misrepresentation and deceptive intent. See Kingsdown Medical Consultants, Ltd. v. Hollister Inc., 863 F.2d 867, 876, 9 USPQ2d 1384, 1392 (Fed. Cir. 1988) (there must be clear and convincing evidence that material information was known to the inventor and was misrepresented or withheld for the purpose of deceiving or misleading the examiner into granting the patent). See also, e.g., Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 1570, 43 USPQ2d 1398, 1407 (Fed. Cir. 1997); Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1582, 18 USPQ2d 1001, 1014-15 (Fed. Cir. 1991). Today the court casts this safeguard aside, finds misrepresentation in correct science, infers malevolence from verb tense, and grounds intent to deceive on personal slurs by a hostile witness.

These inventors made the discovery that the Thermus aquaticus enzyme has a quite different molecular weight and specific activity than had been reported in scientific publications of a decade earlier. The Taq enzyme isolated and characterized by Dr. Gelfand and Ms. Stoffel had an activity over ten times that of the Taq enzyme previously reported. This discovery led Cetus to commercial development of this important invention, with Promega obtaining a license. Now attempting to destroy the patent, Promega attacks the competence as well as the integrity of the inventors.

The patentability and validity of this discovery is not challenged. Instead, Promega charges the inventors with inequitable conduct in obtaining the patent, focused on two areas. First, Promega asserts that more experiments should have been done by the inventors than were done, particularly with respect to reproducing the prior art. Although Promega's witnesses conceded that the inventors drew the correct conclusions, Promega argued successfully in the district court that they should have performed certain additional experiments and that their failure to do so established omission, misrepresentation, and deceptive intent. Although the majority opinion properly rejects these attacks with respect to molecular weight, they have accepted them with respect to other properties.

Second, the panel majority finds grounds of inequitable conduct in the presentation in the patent application of a specific example that was a combination of two chromatographic purification procedures but did not say so. It is undisputed

that the example works as written and that it was included in the patent application because it was the best mode known to the inventors, who had previously distributed the procedure of this example to potential manufacturers. The panel majority holds that because the example was not written entirely in the present tense and identified as "prophetic," this establishes, without more, both material misrepresentation and deceptive intent.

This case illustrates the ease of opportunistic challenge to the conduct of experimental science in patent context. My colleagues have distorted the patent process, and the science it supports, into a game of high stakes hindsight that few patents can survive. This additional risk to those who create valuable advances of science and technology has no countervailing public benefit, for the only beneficiary is the infringer who destroys the patent. I must, respectfully, dissent.

I

MOLECULAR WEIGHT

The panel majority has reversed the district court's rulings of inequitable conduct based on molecular weight.[5] I concur in the majority's decision with respect to this aspect, and remark only that this record well illustrates the litigation tactic of probing the hundreds if not thousands of experimental details, scrutinizing every experiment performed and not performed, criticizing everything done or undone, and then charging that the research process was somehow fraudulent, although there was no evidence of either misrepresentation or intent to deceive, and the validity of the claims is not challenged.

II

EXAMPLE VI

Example VI describes a five-column chromatographic purification procedure for the Taq enzyme. This five-column procedure had been distributed to potential contractors for commercial production, and was added to the specification in a continuation-in-part application in order to comply with the best mode requirement. There is no challenge to the district court's finding that "Gelfand and Stoffel combined the steps from purifications numbered three and four to arrive at Example VI, which they considered the best method for purifying Taq."

A. Example VI is Scientifically Accurate

Example VI as written was a combination of the chromatographic columns of two purification sequences designated as Prep 3 and Prep 4. Prep 3 was the three-column purification of the Taq enzyme through a phosphocellulose column, a heparin sepharose column, and a hydroxyapatite column. These are columns 1, 2, and 3 of Example VI. The product of Prep 3 had a specific activity of ~248,000 units/mg. Prep 4 used the same first two columns of Prep 3 plus a

DEAE-Trisacryl column and a CM-Trisacryl column; these are columns 1, 2, 4, and 5 of Example VI. The product of Prep 4 had a specific activity of ~390,000 units/mg. Thus Example VI combined the three columns of Prep 3 with the four columns of Prep 4 to form a five-column purification procedure, and described the product as having the properties of the preparations that it embodied. At the time of filing of the patent application, Example VI had not been run by the inventors as it was written.

The fatal flaw, according to the panel majority, is that the entire Example VI was not written in the present tense, the code for "prophetic" or "paper" examples in the Manual of Patent Examining Procedure. The Manual states that "simulated or predicted test results and prophetical examples (paper examples) are permitted," and that the past tense should not be used for paper examples. MPEP §608.01(p) (8th ed., 2001).[6] Example VI was written in the past tense for the five chromatographic columns, and concluded by reporting some properties of the Taq enzyme in the present tense. E.g., "The results show a single ~88 kd band with a specific activity of ~250,000 units/mg." My colleagues rule that the use of the past tense, without more, is a material misrepresentation with deceptive intent.

Example VI is a faithful representation of the purification columns that were actually run. At trial Roche offered extensive evidence comparing the inventors' experimental data to Example VI. There was no evidence, or suggestion, that Example VI did not work as stated. Promega's expert Dr. Mosbaugh compared Prep 3 and Prep 4 to Example VI; he concluded that the inventors performed each of the chromatographic steps of Example VI, but stated that "it's not just a matter of doing five steps. It's important what those five steps are, the order in which they're carried out." Dr. Mosbaugh testified that he could not predict how such a combination of chromatographic steps would perform, although he did not disagree with Dr. Chamberlin (expert witness for Roche) and Dr. Linn (expert witness for Promega), both of whom testified that the five-column purification procedure, using the third columns of Prep 3 with the four columns of Prep 4, would reasonably be expected to produce a product at least as pure as the four columns alone.

My colleagues simply err in stating that there was "no evidence" that Example VI was accurately projected from Preps 3 and 4. Indeed, the district court made no such finding. Although Dr. Mosbaugh stated that he was not capable of this projection, this admission, compared with the testimony of other witnesses including an expert for Promega, cannot be clear and convincing evidence that the inventors made a material misrepresentation for the purpose of deception, in making the accurate projection. The inventors believed, and so testified, that the combination of Preps 3 and 4 would be an optimum procedure, and added it to the disclosure because it was their best mode. The issue before the court was not whether Example VI had been performed in complete sequence; the issue was whether there was a misrepresentation material to patentability, and whether the misrepresentation was made in order to deceive the examiner into granting the patent. The ascribed material misrepresentation is not the data in the example, but only the use of the past tense. It was not disputed that the procedure and results of Example VI were supported by Roche's experimental data.[7] There was no proffered evidence of deceptive intent,

or basis for such an inference, and no contradiction to the evidence that Example VI was added because the inventors believed it to be the best mode.

The panel majority has selected some parameters from Example VI that it describes as "Misrepresentations." Inspection negates this description. For example, the panel majority designates as misrepresentations the statements that "a certain quantity of cells 'were resuspended in 75 ml of a buffer,' that cells 'were lysed in a French press,' after which 300 ml. of Tris-EDTA 'were added.'" Maj. op. at 14. In Prep 3 the cells "were resuspended in 75 ml of a buffer," the cells were "lysed in a French press," and 395 ml of Tris-EDTA were added. The other criticisms by the panel majority are equally trivial, and at trial were devoid of even the accusation, much less proof, of deceptive intent.

Example VI was a protocol that had been written for use by manufacturers, and had been given to those manufacturers as instructions for commercial scale purification of Taq polymerase. The inventors explained that Example VI was the best mode and had already been distributed, explaining why Example VI was added to the specification. Evidence of the reason why an action was taken is highly relevant when fraudulent intent is charged. See Kingsdown, 863 F.2d at 876, 9 USPQ2d at 1392 (good faith must always be considered). The district court erred in ruling that "the fact that Example VI may have been a superior method of purification is irrelevant," for it was the superior method that led the inventors to include it in the patent.

The panel majority finds that the purity values in Example VI were not actually obtained because Example VI was not actually run, and therefore challenges as fraudulent the statement that the product of Example VI has a specific activity of approximately 250,000 units/mg. As I have mentioned, the product of Prep 3 had a specific activity of about 248,000 and the product of Prep 4 had a specific activity of about 390,000 units/mg. Although the majority questions how specific activity was measured, it was undisputed that these activities are comparable and that the specific activity of the product of the Example VI procedure is at least as high as reported in Example VI.

It was also undisputed that the inventors' statement to the examiner that "the present preparations [of Taq] are far more pure than the Chien et al. and Kaledin et al. preparations" was a true statement. The evidence was that Dr. Gelfand and Ms. Stoffel achieved approximately 8900-fold purification of Taq from the crude T. aquaticus extracts, whereas Kaledin described 140-fold purification of his enzyme. Comparison with Chien was complicated by the addition of stabilizing protein in her final step, and her final fold purification was not calculated, but Chien had achieved less than 50-fold purification prior to her final column. Dr. Chamberlin testified that a 100-fold increase in purity in a single step -- which would still leave Chien at less than half the purity of Gelfand -- was greater than any effect he had seen. Promega did not challenge Roche's evidence that Chien's preparation could not possibly have reached the purity levels of the inventors. Although the panel majority disputes the statement that the Example VI purity is "more than an order of magnitude [ten times] higher than that

claimed for the previously isolated Taq polymerase and at least an order of magnitude higher than that for E. coli polymerase," '818 patent, col. 41, lines 17-20, the prior art activities of 118.7 units/mg for the Chien Taq polymerase and 7,658 units/mg for the Kaledin Taq polymerase were conceded by Promega's witnesses to be less than one tenth that of the product of Example VI, however activity was calculated. And there was no challenge to the accuracy of the inventors' statement comparing the activity of the Example VI Taq polymerase with that of E. Coli polymerase.

The district court found that the examiner "did not indicate in any way that she considered the greater purity of the Cetus enzyme to be a basis for patentability." Nonetheless, the statement of "single band purity" of the product of Example VI is raised by the panel majority as grounds of inequitable conduct. The district court found that Prep 4 "very nearly yielded a single band," and referred to the evidence that "faint bands" evident in these preparations are not contaminating proteins but are shorter forms of the Taq enzyme that are artifacts of the purification process. The evidence that these procedures achieved "essentially a pure protein" stands undisputed. Also, someone of skill in this art would understand the statement that the purified fractions were "nuclease free" to indicate that nuclease was not detected over background levels, according to Promega's expert Dr. Linn, who explained that he instructs his graduate students to state nuclease activity as "less than" a particular value to avoid the phrase "nuclease free." I take note that nuclease activity was not an issue during prosecution, and that for these properties there was no evidence of material misrepresentation with intent to deceive the examiner.

B. Constructive Reduction to Practice

Example VI is not really a "paper example," as the term is normally used, for Example VI is a combination of actual experiments. However, even if any example that was not performed precisely as written were deemed to be a "paper example," such examples have long been accepted in patent documents, unlike their prohibition in scientific articles. Paper examples meet the practical need of compliance with the requirement for specific embodiments of every invention, as well as with aspects of patent law such as the need to provide a full range of variables or to describe and enable alternatives or equivalents. To fulfill their legal purpose, such examples must be enabling of specific embodiments. For some inventions the detailed embodiments can be described and enabled by the inventor without conducting full laboratory experiments or building entire machines. The patent law authorizes that an invention may be constructively reduced to practice by filing a patent application, whether the embodiments were actually made or are constructed in the patent application.

"Constructive reduction to practice" is a legal status unique to the patent art. Unlike the rules for scientific publications, which require actual performance of every experimental detail, patent law and practice are directed to teaching the invention so that it can be practiced. The inclusion of constructed examples in a patent application is an established method of providing the technical content needed to support the conceived scope of the invention. The Manual of Patent

Examining Procedure implements this legal status and purpose, in its explicit recognition that "simulated or predicted test results and prophetic examples (paper examples) are permitted." MPEP §608.01(p). Although the MPEP states that the present tense should be used for such examples, see n.2 supra, patentability does not depend on whether the example was actually conducted. The presentation of accurate "constructive" descriptive and enabling information in the specification, whether or not marked as "prophetic," is not material misrepresentation with culpable intent. Indeed, were there negligence on the part of the inventors in presenting most of Example VI in the past tense, it is established law that negligence alone, even gross negligence, does not establish inequitable conduct. Kingsdown, 863 F.2d at 876, 9 USPQ2d at 1392.

It is not scientifically improper to gather knowledge from separate experiments and to draw scientific conclusions based thereon; that is the methodology of science. It is not a legal misrepresentation to fuse knowledge from various sources, drawing on one's skill and experience. Although Dr. Mosbaugh testified that: "As an enzymologist, I cannot fuse these [Prep 3 and Prep 4] together and get any prediction as to what the outcome would be," these inventors did fuse them and did predict the outcome. It is not inequitable conduct to have superior knowledge and experience, and to use them to successfully predict the scientific result. Precedent recognizes that whether an example was performed precisely as written does not establish materiality or deceptive intent. In Regents v. Eli Lilly the court considered specific examples (written in the past tense) that differed from the experiments actually performed, but found no inequitable conduct despite the applicant's modification of the experimental details. 119 F.3d at 1570, 43 USPQ2d at 1407 ("There is no reason to believe that a reasonable examiner would have made any different decision if UC had framed Examples 4 and 5 as constructive examples.") In Atlas Powder Co. v. E. I. du Pont de Nemours & Co., 750 F.2d 1569, 1578, 224 USPQ 409, 415 (Fed. Cir. 1984) the entire text of the patent is in the present tense (including all examples), the court holding that when "all but one of the examples were based on actual experiments and only slightly modified to reflect the inventor's notion of the most effective formulation," the inventor's "failing to tell the examiner that the examples were 'prophetic'" is not inequitable conduct. The district court agreed that the properties of the Taq polymerase described in Example VI were not significantly different from the properties of the products of Prep 3 or Prep 4. There was no evidence that the examiner might have decided differently as to patentability had the examiner known the origin of Example VI.

Even were Example VI deemed not to be in impeccable compliance with the protocol of the Manual of Patent Examining Procedure, this is not material misrepresentation and deceptive intent. Inventors Gelfand and Stoffel were interrogated at length concerning their use of verb tense. They testified that they were not aware of the protocol of using the present tense in patent examples, and that Example VI was provided to comply with the best mode requirement. The panel majority misconstrues this testimony: Dr. Gelfand did not state that he knew of (and thus deliberately violated) the patent protocol of past and present tense, as he distinguished scientific writing from the "arcaneness" of patent documents. Dr. Gelfand was persistently asked, over many pages of the trial transcript, whether he understood the significance of verb tense

in scientific publications, as Promega attempted to impugn the scientific integrity of the inventors. The following exchanges are typical:

Mr. Troupis (Promega's attorney): So when you used the term "was" or "were," you understood, did you not, that that communicates that you had done it? You understood that; did you not, Dr. Gelfand?

Dr. Gelfand: We're coming to an area that deals with prophetic examples and arcaneness, and I B

Mr. Troupis: I'm not coming to anything with regard to the law. I'm coming to the facts, Dr. Gelfand. I'm simply asking you: when you used those terms, "was," "were," or the like, you mean you actually did it; don't you? When you used those terms as a scientist, that's what you mean, you did it?

Dr. Gelfand: We did many, many of the things described. The "was" is absolutely correct. . . .

* * *

Mr. Troupis: I want this record to be clear. No one did Example VI before June of 1987 -- That's a "yes" or "no" question, Dr. Gelfand -- isn't that right?

Dr. Gelfand: I believe that's correct.

Mr. Troupis: Yet you put in the patent that you or somebody had done it; isn't that right?

Dr. Gelfand: We put in the patent in the description, in Example VI, what I believed to be the best way to go about isolating Taq DNA polymerase at the time.

Mr. Troupis: You used the tense, the past tense, in Example VI indicating you had done it, and in a scientific publication that means you did it, it doesn't mean you hoped for it, it means you did it; doesn't it, Dr. Gelfand?

Dr. Gelfand: In a scientific publication, yes.

* * *

Mr. Troupis: You chose at that time not to tell the patent office what you had done, but chose to tell them something you had not done? You just indicated you made a conscious decision to tell them something you had not done and tell them in a way as if it had been done; isn't that right?

Dr. Gelfand: No. It was my understanding that we had an obligation to tell the Patent Office what we believed to be the best way of [purifying Taq] drawing on the experience from the third prep, drawing on the experience from the fourth prep and describing for the Patent Office, for the world, the best way we thought to go about doing it. That's what I believed.

Ms. Stoffel was similarly interrogated. The panel majority now faults the inventors for not explaining why a different principle applies in patent applications than in scientific articles. Indeed, the differences between scientific and patent practice are commonly misunderstood. However, the patent use of constructed examples is not a material misrepresentation, whether or not the examples are designated as constructed; and the provision of accurate science in the wrong verb tense does not establish deceptive intent. Such findings, which require the elements of common law fraud, are measured by objective reasonableness. Telling the truth, even in the past tense, cannot be a material misrepresentation or

clear and convincing evidence of deceptive intent.

III

FIDELITY AND ACTIVITY

The panel majority also finds grounds of inequitable conduct because the inventors, in comparing their Taq polymerase with the Chien and Kaledin published properties of the prior art Taq, did not repeat the prior art procedures. Indeed, it is facile to ascertain what experiments were not done, and then to argue that they should have been done, on risk of invalidating the patent for inequitable conduct. My colleagues hold that the inventors should not have stated that their products were superior, in activity and in fidelity, to the products reported in the publications of Chien and Kaledin, because the inventors should not have relied on the data in those publications without duplicating them. The publications of Chien and Kaledin included the specific activities of their products as well as the molecular weights, and the methods of measurement. There was no evidence that these data were incorrect; the only charge was that the prior art could not "legitimately" be compared.

There was no evidence that the published assays of Chien and Kaledin were incorrect for their products, or should have been suspected to be materially different from the published values. Indeed, the evidence was undisputed that the Chien and Kaledin products were degraded, as Gelfand and Stoffel discovered, and that the properties reported for this early work were for degraded products. There was no evidence that the improvements in assay conditions over the ensuing decade would have altered the dramatic difference between the activities of 118.7 units/mg and 7,658 units/mg reported by Chien and Kaledin respectively, and the activities found by Gelfand and Stoffel for their undegraded enzyme. Indeed, the examiner did not question the inventors' comparisons of activity with the prior art, although the examiner did question the molecular weight comparisons. While Promega places emphasis on the evolution of precision in measurement of Taq polymerase activity, and on an apparent uncertainty in Ms. Stoffel's recollection at trial of the details of assay procedures used at various times, it is not disputed that the magnitude of the claimed differences in activity was correct.[8] No information is asserted to have been withheld from the examiner. The findings of materiality and deceptive intent in the comparison of activity are devoid of any support.

Similarly, the panel majority challenges the comparisons of fidelity and template dependency. The only evidence on this issue was the testimony of Promega's expert Dr. Kunkel. He testified that it was scientifically unacceptable for Dr. Gelfand to have compared his results with the prior art. Dr. Kunkel stated that "[the results] don't lead me, and I don't think they would lead any correct-thinking scientist, to conclude that those results can be fairly compared to what was done with activated DNA. It simply is not a scientifically valid comparison to make." Dr. Kunkel testified that "It is certainly not a scientifically-valid statement to say that based on this information, that the patented enzyme was far superior to the prior art

in this regard. . . . It's simply not correct scientific principles." He compared the statements in the patent concerning fidelity to "scientific misconduct," and designated them as "intentional misrepresentations." He stated that the inventors should have duplicated the prior art in order to conduct a side-by-side comparison. The district court asked:

The court: In your view is Dr. Gelfand a fraud?

Dr. Kunkel: Yes. In B on the issues related to this case, yes. . . . And he knew better.

Thus the witness challenged the inventors' integrity and competence, although it was undisputed that their conclusions were correct.[9] My colleagues adopt these specious charges of scientific fraud although neither inaccuracy nor falsity of any data was shown. It is not a material misrepresentation with intent to deceive, for an inventor to use his/her knowledge and experience to reach a reasonable conclusion.

The panel majority appears to misunderstand the statements in the specification and during prosecution. The patent states that the inventors' results "are consistent with" a high fidelity polymerase, and that the activity reported by Kaledin "is not consistent with the expected value and suggests misincorporation of nucleotide triphosphate(s)." The inventors explained to the examiner that Chien and Kaledin's data "would lead one of ordinary skill in the art to conclude that" the prior products "are not suitable for template-directed in vitro DNA synthesis" and "have a rather substantial promiscuous ability to synthesize DNA in the absence of one of the four deoxynucleoside triphosphate." Response, March 17, 1989. It is undisputed that the inventors' data were accurately presented. Dr. Kunkel's charge that Dr. Gelfand "knew better" is mysterious indeed, when despite this inflammatory testimony, the district court found as fact that: "Evidence adduced by the inventors led them to believe that the prior art had generated something other than that which the inventors purified." No error has been asserted in this finding. A hostile witness' flashy challenge to the inventor's personal integrity is not probative of anything.

IV

THE NEW PLAGUE

Of course patent applicants must conduct themselves with honesty and integrity. However, unwarranted charges of inequitable conduct can infect the entire body of invention and inventors. As illustrated in this case, every experiment done and not done, every scientific inference, every judgment or belief, is fair game for opportunistic attack. Such attacks feed upon the complexities of science and technology, and it is rare indeed that some flaw cannot be found. In this case, straightforward scientific and patent activity were distorted until judicial suspicions were raised, despite the absence of any significant error or misstatement. The actions challenged herein, even if viewed in their worst light (whatever that might be) do not establish material misrepresentation and intent to deceive. The need for attention to the burden of proof and its requirement of clear and convincing evidence of both material misrepresentation and deceptive intent, is forcefully illustrated.

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[1] Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), relied on by the dissent, is inapposite, because the misidentification of a plasmid in the patent examples did not make the examples inoperative; rather, the procedures described in the examples "worked to yield the intended results irrespective of" whether the actual plasmid was used, making the "misidentification of the plasmid . . . not material to patentability." Id. at 1570-71, 43 USPQ2d at 1408. In this case, not only did the applicants fail to practice the example as written, but they also failed to achieve the stated results. The dissent's reliance on Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984), is also misplaced. In that case, the examples were written in the present tense to conform with the PTO requirements on prophetic examples, and the appellant's claim was that the patentee should have informed the patent examiner that the examples written in the present tense were prophetic. We held that it was not clear error for the district court to find no materiality or intent to deceive under those circumstances. Not only were those facts—use of the present tense when it was proper to do so—wholly different from the facts of this case, but in Atlas Powder we applied the "clearly erroneous" standard of review to uphold the district court's findings, as opposed to rejecting the district court's findings as the dissent would have us do here.

[2] Under the current standard for materiality, there would be no question that the inventors' representations would be material. See 37 C.F.R. § 1.56(b)(2) (2002) ("[I]nformation is material to patentability when . . . [i]t refutes, or is inconsistent with, a position the applicant takes in . . . [a]sserting an argument of patentability."). Although the current standard was not in effect at the time of the prosecution of this patent, the new standard was not intended to constitute a significant substantive break with the previous standard. See 57 Fed. Reg. 2021, 2023 (Jan. 17, 1992) (explaining that the amendment to § 1.56 was intended to clarify the lack of certainty in the previous materiality standard).

[3] Roche contends that the language at issue is merely a statement of belief, which cannot constitute a material misrepresentation. We disagree. The applicants did not in any way indicate that they were simply conveying their personal beliefs; instead, the language used by the applicants indicated that they were offering the representations as statements of fact.

[4] We do not suggest that an applicant is required to repeat the experiments of the prior art; an applicant, however, may not knowingly misrepresent those experiments or their results.

[5] Only molecular weight is included in the claims. Claim 1 follows:

> **1.** Purified thermostable Thermus aquaticus DNA polymerase that migrates on a denaturing polyacrylamide gel faster than phosphorylase B and more slowly than does bovine serum albumin and has an estimated molecular weight of 86,000-90,000 daltons when compared with a phosphorylase B standard assigned a molecular weight of 92,500 daltons.

[6] '**608.01(p).** Simulated or predicted test results and prophetical examples (paper examples) are permitted in patent applications. Working examples correspond to work actually performed and may describe tests which have actually been conducted and results that were achieved. Paper examples describe the manner and process of making an embodiment of the invention which has not actually been conducted. Paper examples should not be represented as work actually done. No results should be represented as actual results unless they have actually been achieved. Paper examples should not be described using the past tense.

[7] Roche's expert witness Dr. Chamberlin was comparing Prep 4 to Example VI when the district court cut off the testimony:

> The court: This whole line of questioning you've shown the consistency between the notebooks and what's on the flowchart, and what's on the flowchart and the patent. And so what's the point you're making?
>
> Roche Attorney: That this fourth purification scheme in fact leads to a preparation that meets the purity levels that were already to the Patent Office.
>
> The court: And I ask you again, what is the significance of that?

Roche Attorney: That the inventors had, in fact, performed a purification run where they obtained preparations of significantly high purity, that they could make the arguments that they made to the Patent Office, your honor.

The court: All right. Well, I think you've made your point without belaboring it.

[8] The district court re-calculated the specific activity data to accord with the definition of "unit" in Example VI. The Chien and Kaledin publications both define "unit" in accordance with the inventors' raw data, supporting the inventors' activity number of ~250,000 units/mg. By any of the calculation methods presented at trial, whether that of Cetus, Promega, or the district court, there was at least a ten-fold improvement of unit activity, as described in the patent in suit.

[9] In support of Dr. Kunkel's charges of scientific fraud based on his asserted personal knowledge of what Dr. Gelfand knew of the science, the panel majority reports that Dr. Kunkel "worked with Dr. Gelfand and Cetus" during 1986-1989. When cross-examined, Dr. Kunkel admitted that the extent of his contact with Cetus was a single visit in 1988 to deliver a seminar.