United States Court of Appeals for the Federal Circuit

2007-1280

AVENTIS PHARMA S.A. and AVENTIS PHARMACEUTICALS, INC.,

Plaintiffs-Appellants,

v.

AMPHASTAR PHARMACEUTICALS, INC.,

Defendant-Appellee,

and

TEVA PHARMACEUTICALS USA, INC.,

Defendant-Appellee.

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

Senior Judge Mariana R. Pfaelzer

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Appeal from the United States District Court for the Central District of California in case no. 03-CV-887, Senior Judge Mariana R. Pfaelzer.

DECIDED: May 14, 2008

Before RADER, PROST, and MOORE, Circuit Judges.

Opinion for the court filed by Circuit Judge PROST. Dissenting opinion filed by Circuit Judge RADER.

PROST, Circuit Judge.

This infringement case returns to us for the second time after remand to the district court on the issue of whether Aventis committed inequitable conduct before the United States Patent and Trademark Office ("PTO"). In our earlier opinion, we held that the dosage of the prior art composition used in half-life comparisons with the patented

composition was information material to patentability, but we remanded to the district court to determine whether there was an intent to deceive by Aventis in failing to disclose the dosage. After a trial on the matter, the district court found that there was intent to deceive and held the patents unenforceable for inequitable conduct. Because we find no abuse of discretion by the district court in its holding of inequitable conduct, we affirm.

I

Aventis is the owner of U.S. Patent No. RE 38,743 ("the '743 patent") and U.S. Patent No. 5,389,618 ("the '618 patent"), which was surrendered upon the issuance of the '743 Patent. The patents are directed to a composition comprising low molecular weight heparins ("LMWHs"). Claim 1 of the '618 patent recites:

> A heterogeneous intimate admixture of sulfated heparinic polysaccharides, such sulfated polysaccharides having a weight average molecular weight less than that of heparin and said admixture consisting essentially of
>
> from 9% to 20% of polysaccharide chains having a molecular weight less than 2,000 daltons
>
> from 5% to 20% of polysaccharide chains having a molecular weight greater than 8,000 daltons, and
>
> from 60-86% of polysaccharide chains having a molecular weight of between 2,000 and 8,000 daltons,
>
> the ratio between the weight average molecular weight and the number average molecular weight thereof ranging from 1.3 to 1.6
>
> said admixture (i) exhibiting a bioavailability and antithrombotic activity greater than heparin and (ii) having an average molecular weight of between approximately 3,500 and 5,500 daltons.

The drug is marketed as Lovenox® in the United States and Clexane® in Europe and is effective in preventing thromboses (blood clotting) while minimizing the possibility of hemorrhaging, especially during high-risk surgery. According to the specification, the

advantage of the claimed LMWHs as compared to heparin is that they exhibit a longer half-life, excellent bioavailability, higher rate of absorption, low clearance, resistance to degradation, increased residence time, and reduced sensitivity to serum factors. '618 patent, col. 2, l. 55-col. 3, l. 26.

A

The prosecution history of the '618 patent is germane to the issue of inequitable conduct. Original claim 1 of the '618 patent application recited as follows:

> A heterogeneous intimate admixture of sulfated heparinic polysaccharides, such sulfated polysaccharides having a weight average molecular weight less that that of heparin and which comprise from 9% to 20% of polysaccharide chains having a molecular weight less than 2,000 daltons and from 5% to 20% of polysaccharide chains having a molecular weight greater than 8,000 daltons, the ratio between the weight average molecular weight and the number average molecular weight thereof ranging from 1.3 to 1.6.

In the first office action, the patent examiner rejected the claims under 35 U.S.C. §§ 102(b)/103 over several references, including European Patent 40,144 ("EP '144"). The examiner stated that each of the prior art references teaches sulfated heparinic admixtures within the molecular weight ("MW") range of the claims and is considered to be inherently the same as the claimed admixtures. In particular, the examiner explained that

> the Patent and Trademark Office does not have facilities for testing and comparing various products, and where the prior art teaches a product which is identical or nearly identical to that claimed, it is incumbent upon the Applicant to convincingly demonstrate that the claimed product provides some unexpected or unobvious property not demonstrated by the prior art products.

(Emphases added).

In response to the office action, Aventis independently addressed the anticipation and obviousness portion of the rejection.[1] With respect to anticipation, Aventis argued that EP '144 does not expressly state that the mixture contains two types of polysaccharides, one with a MW less than 2,000 daltons and one with a MW greater than 8,000 daltons, nor does it state the number average/weight average MW ratio. Presuming, therefore, that the examiner's anticipation rejection rested on inherency, Aventis argued that the evidence in the specification rebuts inherency. In particular, Aventis pointed to example 6 in the specification, which provides in relevant part:

> This example illustrates the increase in stability, in vivo, of the mixtures of the invention, expressed by their plasma half-life.
>
> . . . .
>
> (1) From the mixtures produced in Examples 3 and 4:
>
> 40 mg dose: in 75% of the cases, the half-life was longer than 4 hours, and was even longer than 4½ hours in approximately 45% of the cases;
>
> 60 mg dose: in 75% of the cases, the half-life was longer than 3.7 hours.
>
> . . . .
>
> (3) When the product was prepared according to the process described in European Patent EP 40,144, the half-life was longer than 4½ hours in 17% of the cases.

'618 patent, col. 9, ll. 33-58 (emphases added). Example 6 was prepared with the assistance of Dr. André Uzan, a French chemist who was a non-inventor. Based on the example, Aventis argued that the claimed LMWHs exhibit a significantly longer half-life than formulations prepared in accordance with EP '144. Aventis went on to explain that, because it is well established that compounds are inseparable from their properties, the evidence of a difference in a property, i.e., half-life, serves as evidence of a difference in

[1] All responses by Aventis were made by its outside counsel, Mr. Robert Schulman.

structure. With regard to the obviousness portion of the rejection, Aventis contended that, under 35 U.S.C. § 103, the prior art must suggest the modification to one of skill in the art, yet EP '144 provides absolutely no suggestion to select the particular combination of oligosaccharide chains of specified lengths as claimed.

The examiner was not convinced and issued a second (final) office action, maintaining the prior 102/103 rejection "for the reasons of record in the last Office action." The examiner reiterated that the MW requirements of the claimed compounds are within the range of the compounds disclosed in EP '144 and that any properties would be inherent in the prior art compounds because they have the same structure as the claimed compounds.[2]

Thereafter, Aventis amended claim 1 to read:

> A heterogeneous intimate admixture of sulfated heparinic polysaccharides, such sulfated polysaccharides having a weight average molecular weight less that that of heparin and said admixture comprising[3]
>
> from 9% to 20% of polysaccharide chains having a molecular weight less than 2,000 daltons
>
> from 5% to 20% of polysaccharide chains having a molecular weight greater than 8,000 daltons, and
>
> from 60-86% of polysaccharide chains having a molecular weight of between 2,000 and 8,000 daltons,
>
> the ratio between the weight average molecular weight and the number average molecular weight thereof ranging from 1.3 to 1.6,

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[2] The examiner also reiterated that

> the Patent and Trademark Office does not have facilities for testing and comparing various products, and where the prior art teaches a product which is identical or nearly identical to that claimed, it is incumbent upon the Applicant to convincingly demonstrate that the claimed product provides some unexpected or unobvious property not demonstrated by the prior art products.

(Emphases added).

[3] Upon filing a continuing application "comprising" was changed to "consisting essentially of," which is how the claim read when it issued.

> said admixture (i) exhibiting a bioavailability and antithrombotic activity greater than heparin and (ii) having an average molecular weight of between approximately 3,500 and 5,500 daltons.

Aventis also submitted a declaration from Dr. Uzan ("first Uzan declaration"). In ¶ 8 of the declaration, Dr. Uzan distinguished the claimed formulations from the formulations in EP '144. First, he noted that the half-life of the claimed formulation is greater than 4½ hours 45% of the time, as compared to the EP '144 formulation which achieved such a half-life only 17% of the time. He remarked, "This represents an increase in 250% in the half life and is very significant because it enables the same effect to be achieved with lower dosages." Further, Dr. Uzan stated that he analyzed the EP '144 product and found that 21% of the chains had a MW lower than 2,000; 6% of the chains had a MW greater than 8,000; and 73% of the chains had a MW between 2,000 and 8,000. Id. Finally, he concluded that "the formulations of [EP '144] are clearly outside the scope of the present invention." Aventis relied on example 6 and the first Uzan declaration to address the anticipation rejection, arguing that the compounds disclosed in EP '144 are not inherently the same as the claimed compounds because the claimed compounds have a longer half-life and because compounds prepared in accordance with EP '144 fall outside the scope of the claims. With respect to obviousness, Aventis argued that the claimed compounds are non-obvious over EP '144 because the compositions in EP '144 did not exhibit the unexpected properties of the claimed combination of MW chains.

In the third office action (first office action in the continuing application), the examiner affirmatively withdrew several 102/103 rejections over other prior art references. The examiner continued to reject the claims under 35 U.S.C. § 103 over EP

’144 “for the reasons of record in” the second office action. According to the examiner, EP ’144 teaches “admixtures of sulfated heparinic polysaccharides having molecular weight ranges which are not patentably distinct from those of the instant claims.”[4] The examiner explained that “the instant molecular weight requirements are highly similar to those of the prior art molecular weight ranges,” and that no evidence has been presented that the claimed compounds would have “any properties or activities not necessarily inherent [in] the prior art compounds.” With respect to the half-life comparisons between the claimed compounds and EP ’144, the examiner stated that the “[a]pplicant has failed to provide evidence that the alleged difference between the half-life of the [EP ’144] product and that of the [claimed] mixture is statistically significant.” Further, the examiner contended that the first Uzan declaration showed that the differences in composition based on MW were minimal and there was no showing of any unexpected results. Aventis responded by submitting another declaration from Dr. Uzan (“second Uzan declaration”). In ¶ 3 of the declaration, Dr. Uzan referenced five tables comprising the raw data from the half-life comparisons between the claimed compound and the EP ’144 compound, which tables were attached to the declaration.[5] Dr. Uzan also provided results from a statistical analysis

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[4] The examiner reiterated the statement, in a slightly modified form, that

> the Patent and Trademark Office does not have facilities for testing and comparing various products, and where the prior art teaches a product which is nearly identical to that claimed, it is incumbent upon the Applicant to convincingly demonstrate that the claimed product provides some unexpected or unobvious property not demonstrated by the prior art products.

(Emphases added).

[5] Half-life data for the patented compound were contained in Tables I, X, and XI. Half-life data for the EP ’144 compound were contained in Tables A and III.

showing a statistically significant difference between the mean half-life for the claimed compound and that of the EP ’144 compound. Specifically, Dr. Uzan reported, “For the claimed compound $T_{½}$ was 4.36 ± 1.07. For the compound of [EP ’144], $T_{½}$ was 3.33 ± 0.2,” and the statistical analysis showed that 4.36 and 3.33 were statistically significant. The mean half-life of 4.36 for the claimed compound was taken from Table X, which indicated the dosage to be 40 mg. The mean half-life of 3.33 for the EP ’144 compound was taken from Table III, which did not mention the dosage.

Aventis argued, in its response, that EP ’144 does not suggest compounds containing polysaccharides of the claimed MW in the claimed proportions and that the examiner improperly relied on inherency to reject the claimed compounds over EP ’144. Referring to the second Uzan declaration, Aventis asserted that different half-lives are obtained with the claimed preparation as compared to the preparation of EP ’144. Therefore, Aventis averred, the claimed compounds have been shown to differ from the compounds of EP ’144 in both their structure and properties.

Thereafter, the ’618 patent application was allowed.

B

Amphastar Pharmaceuticals, Inc. (“Amphastar”) and Teva Pharmaceuticals USA, Inc. (“Teva”) each filed an Abbreviated New Drug Application (“ANDA”) with the FDA to obtain approval to a market generic version of Lovenox®. The ANDA contained a paragraph IV certification challenging the two Aventis patents.

Aventis sued both Teva and Amphastar for infringement of the ’618 patent in the United States District Court for the Central District of California. Aventis Pharma S.A. v.

Amphastar Pharms., Inc., 390 F. Supp. 2d 936, 938 (C.D. Cal. 2005) ("Aventis I"). Amphastar filed a motion for summary judgment on its affirmative defense and counterclaim that the '618 patent is unenforceable due to inequitable conduct. Id. at 938-39. Specifically, Amphastar averred that Dr. Uzan engaged in inequitable conduct by failing to disclose that the half-life studies comparing the patented compound to the EP '144 compound were at different doses. Id. at 941, 944.

The district court determined that the representation by Aventis that the patented compound had an improved half-life as compared to the EP '144 compound was material to patentability because Aventis referred to the improved half-life at least four times during prosecution and the examiner ultimately allowed the '618 patent application after the final representation that the difference in mean half-life was statistically significant. Id. at 950-51. The court found a strong inference of intent to deceive because it could find no credible explanation for comparing half-lives at different doses and because comparisons at the same dose showed little difference in half-life. Id. at 951-52. After weighing the evidence of materiality and intent, the court found weighty uncontroverted evidence establishing inequitable conduct. Id. at 952. It, therefore, granted summary judgment against Aventis and held the '618 patent unenforceable.[6] Id.

[6] One day prior to issuance of the district court's order, Aventis surrendered the '618 patent to the PTO pursuant to reissue proceedings in the '743 patent application. Aventis Pharma S.A. v. Amphastar Pharms., Inc., 390 F. Supp. 2d 952, 954 (C.D. Cal. 2005). In a subsequent order, the district court granted Aventis's motion to substitute the '743 patent for the '618 patent, and amended its earlier holding of unenforceability to apply also to the '743 patent. Id. at 957. In so holding, the district court relied on the well-settled principle articulated in Hoffman-La Roche Inc. v.

On appeal, Aventis argued that the district court erred in finding materiality because if the dose information were material to patentability, the examiner would have requested it because: she was presented with half-life data that enabled her to compare various doses, Dr. Uzan informed the examiner that the half-life comparison was done at different doses, those of skill in the art frequently compare half-lives at different doses, and half-life is independent of dose. Aventis Pharma S.A. v. Amphastar Pharms., Inc., 176 Fed. Appx. 117, 120 (Fed. Cir. 2006) ("Aventis II"). To support the argument that Dr. Uzan informed the examiner that the half-life comparisons were done at different doses, Aventis relied on the statement in the first Uzan declaration that "[t]his represents an increase in 250% in the half life and is very significant because it enables the same effect to be achieved with lower dosages," and Dr. Uzan's deposition testimony stating that he believed this to mean "that the comparison is a comparison between two doses of which one is lower than the other." Id. at 120-21 (emphasis added) (internal quotations omitted). Aventis relied on this same statement to argue that Dr. Uzan did not intend to deceive the examiner. Id. at 123. Aventis further argued lack of intent based on the fact that Dr. Uzan submitted half-life data for the claimed compound at 60 mg, as well as at 40 mg. Id.

With regard to materiality, this court held that it was not plausible to read the statement in the first Uzan declaration as indicating to the examiner that the half-life comparison was done at different doses and, therefore, there was no genuine issue of

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Lemmon Co., 906 F.2d 684 (Fed. Cir. 1990), that a reissue proceeding cannot rehabilitate a patent held to be unenforceable due to inequitable conduct. Id. at 688. Thus, contrary to the assertion by the dissent, slip op. at 7, the district court was fully aware of the reissue proceeding, yet recognized that any holding of unenforceability in the original application extended to the reissue application.

material fact that Dr. Uzan did not disclose that the comparison was made using data for the two compounds at different doses. Id. at 121. We also rejected Aventis's explanation for nondisclosure that using different doses in half-life comparisons was common practice in the field because, in contrast to the references cited in support of this proposition, Aventis did not disclose the actual doses. Id. Further, this court did not accept the explanation that the half-life data were dose independent because the evidence clearly suggested otherwise. Id. at 121-22. Therefore, we concluded that the withholding of the EP '144 dosage information prevented the examiner from considering information important to patentability and constituted a failure to disclose material information. Id. at 122.

While this court found that the dosage of the EP '144 composition was indeed information material to patentability, we held that the district court erred in finding intent to deceive on summary judgment. Id. In particular, we held that the reasonableness of the comparison at different doses is relevant to determining whether there was an intent to deceive in withholding the dosage of the EP '144 composition. Id. at 122-23. This court reasoned:

> [T]he district court . . . ultimately concluded that the facts supported a strong inference of intent to deceive. The district court's inference was reasonable—by failing to disclose that the EP 40,144 data was at a 60 mg dose, Aventis may have been painting the rosiest picture possible as to the half-life improvement of its claimed compounds in an attempt to deceive the examiner. . . . However, there is another reasonable inference—namely, as Aventis argues, if the comparison between different doses was reasonable, the failure to disclose may have been due purely to inadvertence.

Id. at 123. Accordingly, this court reversed the grant of summary judgment of unenforceability of the '618 patent and '743 patent, and remanded to the district court for determination of whether there was intent to deceive. Id.

Following remand, the district court held a bench trial limited to the issue of intent. Aventis Pharma S.A. v. Amphastar Pharms., Inc., 475 F. Supp. 2d 970, 975 (C.D. Cal. 2007) ("Aventis III"). Thereafter, the court issued its opinion, considering the principle explanations proffered by Aventis for Dr. Uzan's failure to disclose the dose of the EP '144 composition in its half-life comparisons. These explanations were that: (1) comparison of half-lives at different doses was reasonable because it was customary to compare the half-lives of different drugs at the "clinically relevant dose," i.e., the dose presenting the best efficacy-safety ratio, and the half-life comparisons were intended to show a difference in therapeutic properties, not a compositional difference; (2) comparison of half-lives at different doses was reasonable because half-lives are dose independent; and (3) the failure to disclose was due merely to inadvertence. Id. at 977-92.

The district court found Dr. Uzan's clinical relevance justification implausible because such a justification presumed a compositional difference between the compounds being compared, yet the issue of inherency was repeatedly raised by the examiner during prosecution. Id. at 977-82. The court noted that the examiner recognized that a compound's properties, e.g., half-life, are inherent in its composition and thereby rejected the claims as anticipated by the EP '144 compound under 35 U.S.C. § 102. Id. Therefore, the court was not persuaded that Dr. Uzan presented the half-life comparisons to show only a difference in property and not also a difference in

composition. Id. The court was similarly unpersuaded by Aventis's dose-independence argument because the evidence did not establish that the half-lives were dose-independent, given the high intra-subject variability. Id. at 984-86.

Furthermore, the court rejected Dr. Uzan's clinically-relevant dose justification on the grounds that it was incredible because: (1) there was no statistical difference in half-lives when the 60 mg dose of EP '144 composition was compared to the patented composition at a 20 mg, 60 mg or 80 mg dose, i.e., there was a statistical difference only when a 40 mg dose of the patented composition was compared; (2) the '618 patent was not limited to safe and effective doses for particular therapeutic indications; (3) there were a number of preferred therapeutic doses for the patented composition; and (4) Aventis offered no corroborating evidence to support Dr. Uzan's clinically relevant dose justification. Id. at 986-89.

Finally, the court declined to find that Dr. Uzan's failure to disclose the difference in doses could be justified based on inadvertence because it was not credible that a scientist with Dr. Uzan's qualifications could have committed, and failed to correct during a lengthy prosecution, such an egregious error, and there was a complete absence of evidence suggesting negligence throughout prosecution. Id. at 989-92.

Based on the totality of the facts and circumstances, the court determined that but for Dr. Uzan's intentional omissions, the probability was high that the '618 patent would not have issued. Id. at 994. Accordingly, the court held the '618 patent and the '743 patent unenforceable due to inequitable conduct. Id.

Aventis appeals the district court's finding of intent to deceive and holding of inequitable conduct. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

II

We review a district court's finding of intent to deceive for clear error. Monsanto Co. v. Bayer Bioscience N.V., No. 2007-1109, 2008 WL 200027, at *3 (Fed. Cir. Jan. 25, 2008); Cargill, Inc. v. Canbra Foods, Ltd., 476 F.3d 1359, 1364 (Fed. Cir. 2007). A finding of intent will not be overturned "in the absence of a 'definite and firm conviction' that a mistake has been made." Hoffman La-Roche, Inc. v. Promega Corp., 323 F.3d 1354, 1359 (Fed. Cir. 2003) (quoting Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178 (Fed. Cir. 1995)). We review the district court's ultimate holding of inequitable conduct for abuse of discretion. Monsanto, 2008 WL 200027, at *3; Cargill, 476 F.3d at 1365. We will overturn a holding of inequitable conduct only if it is based on clearly erroneous findings of fact or a misapplication or misinterpretation of relevant law or if the holding evidences a clear error of judgment. Kingsdown Med. Consultants, Ltd. v. Hollister, Inc., 863 F.2d 867, 876 (Fed. Cir. 1988) (en banc in relevant part). Decisions by the district court concerning the admission or exclusion of evidence are reviewed for abuse of discretion. United States v. Curtin, 489 F.3d 935, 943 (9th Cir. 2007) (en banc); DSU Med. Corp. v. JMS Co., 471 F.3d 1293, 1310 (Fed. Cir. 2006).

"To satisfy the intent to deceive element of inequitable conduct, '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.'" Impax Labs., Inc. v. Aventis Pharms. Inc., 468 F.3d 1366, 1374-75 (Fed. Cir. 2006) (quoting Kingsdown, 863 F.2d at 876). Given that direct evidence is often unavailable, intent is generally inferred from surrounding facts and circumstances. Id. at 1375. The district court, upon finding materiality and intent, shall "balance the equities to determine

whether the patentee has committed inequitable conduct that warrants holding the patent unenforceable." Id. (quoting Monsanto Co. v. Bayer Bioscience N.V., 363 F.3d 1235, 1239 (Fed. Cir. 2004)). "The more material the omission or misrepresentation, the less intent that must be shown to elicit a finding of inequitable conduct." Id.

III

A

Now, on its second time on appeal, Aventis offers a new justification for Dr. Uzan's failure to disclose the dosage information in his half-life comparisons.[7] According to Aventis, Dr. Uzan's half-life comparisons were intended to show a difference in properties in response to the obviousness rejection under 35 U.S.C. § 103, not to demonstrate a compositional difference to address the anticipation rejection under 35 U.S.C. § 102, as the district court concluded. Aventis's argument is premised on the fact that while a half-life comparison must be done using equivalent doses to establish a compositional difference, a half-life comparison may be done using different doses if the purpose is to establish a difference in property. In fact, Aventis argues, it is more appropriate to use the "clinically relevant dose" of each compound to demonstrate a difference in property.

As a preliminary matter, it appears that Aventis's argument would require us, at least in part, to revisit our prior holding on materiality. The essence of Aventis's argument is that the reason that Dr. Uzan did not disclose the dosage of the prior art

[7] We note that in its first appeal, Aventis argued only that Dr. Uzan did not have deceptive intent in failing to disclose the dosage information because he thought he informed the examiner that the comparisons were done at different doses, and because he did provide half-life data for the claimed compound at 60 mg as well as at 40 mg. Aventis II, 176 Fed. Appx. at 123.

compound in his half-life comparisons is that the comparisons were not being used to show a compositional difference and, therefore, the dosage information was not material. We have previously determined, however, that the dosage information was material to patentability. Aventis II, 176 Fed. Appx. at 122. Nevertheless, because materiality and intent to deceive are necessarily intertwined, Kimberly-Clark Corp. v. Johnson & Johnson, 745 F.2d 1437, 1455 (Fed. Cir. 1984), we will consider the merits of Aventis's argument with respect to deceptive intent.

Aventis contends that the district court made two clearly erroneous findings of fact: (1) that the central question relating to patentability was compositional differences, and (2) that the purpose of Dr. Uzan's half-life comparisons was to show compositional differences. According to Aventis, coursing throughout the district court's opinion is the notion that the central question relating to patentability was compositional differences. During oral argument, Aventis emphasized that the district court referred to compositional differences nineteen times in its opinion. Oral Arg. at 3:9-3:17, available at http://www.cafc.uscourts.gov/oralarguments/mp3/2007-1280.mp3. As an example, Aventis quoted the court:

> Thus, the central question throughout the prosecution of the '618 patent was whether the [claimed] and [the] EP '144 LMWH products were compositionally different.

Id. at 10:50-11:03; see Aventis III, 475 F. Supp. 2d at 982. Aventis thus contends that the district court erroneously concluded that anticipation was the only rejection of record, even though there was an obviousness rejection present throughout prosecution. Moreover, Aventis asserts that the district court erred in concluding that

the "issue of obviousness necessarily folds into, and is subsumed, by inherency." Aventis III, 475 F. Supp. 2d at 982 n.10.

We find nothing in the district court's opinion to suggest that it did not recognize the existence of the obviousness rejection, or that it believed the anticipation rejection to be the only rejection of record. Indeed, several statements in the opinion clearly indicate that the court was aware of the obviousness rejection. Id. at 980 ("It also relied on [the claimed composition's] properties to rebut obviousness."), ("[B]ecause the ratio identified by [the claimed] LMWH exhibited superior properties over EP '144, the inventive formulation could neither be inherent nor obvious."), ("This signaled to Aventis that its reliance on biochemical properties held promise for overcoming both the [primary examiner's] inherency and obviousness rejections.") (emphases added). Although the court incorrectly suggested, in a footnote, that obviousness is subsumed by inherency, we see this as merely a recognition by the court that the notion of inherency was part and parcel of the examiner's rejections. Id. at 979. In other words, the properties of a compound are inherent in its composition and, therefore, a difference in property could successfully demonstrate a difference in composition. Id. The court understood that, based on the information available to her, the examiner viewed the patented composition and the EP '144 composition to be inherently the same, or nearly the same, and, because the Patent Office did not have the facilities to test the products, the examiner invited Aventis to provide evidence of a difference in property to show a compositional difference. Id. at 980; see In re Best, 562 F.2d 1252, 1255 (CCPA 1977). We find no clear error in the district court's ultimate conclusion.

Aventis next contends that the district court clearly erred in finding that the purpose of Dr. Uzan's half-life comparison was to show compositional differences to address the anticipation rejection under 35 U.S.C. § 102. Instead, Aventis argues, the MW distribution analysis in the first Uzan declaration, showing a difference between the claimed compounds and those disclosed in EP '144 in the proportion of chains of a given MW, was directed to the anticipation rejection; the half-life comparisons were directed to the obviousness rejection. Further, Aventis contends, Dr. Uzan's statement at the end of the declaration that "the formulations of [EP '144] are outside the scope of the claimed invention," was based on the MW distribution analysis, not the half-life comparisons. According to Aventis, the district court improperly concluded that Aventis could not establish compositional differences with the MW distribution analysis, so it relied instead on the half-life comparisons to show that the compounds were not identical. In support, Aventis quotes the court's opinion:

> But Aventis could not successfully distinguish [the patented compound] merely by appealing to [its] ratio of number average and weight average molecular weights. The EP '144 patent is not limited by a specific ratio of constituents. Rather it employs open claim language "comprising various proportions of particular molecular weight products." Therefore, Aventis attacked sameness based on a difference in properties.

Oral Arg. at 14:21-14:52 (quoting Aventis III, 475 F. Supp. 2d at 980).

We cannot agree that the district court clearly erred in its determination that the half-life comparisons were, at least in part, intended to show compositional differences. Nothing in example 6 suggests that the half-life comparison was designed to show only non-obviousness and not lack of identity. The beginning of the example merely states: "This example illustrates the increase in stability, in vivo, of the mixtures of the invention, expressed by their plasma half-life." '618 patent, col. 9, ll. 33-35. Moreover,

the first Uzan declaration does not clearly delineate between evidence intended to address the anticipation rejection and evidence intended to address the obviousness rejection. All of the evidence directed to the EP '144 reference appears in ¶ 8 of the declaration, without distinction between the § 102 and the § 103 aspects of the rejection, and there is no basis for concluding that the final statement in ¶ 8—"Thus, the formulations of [EP '144] are clearly outside the scope of the present invention"—refers only to the MW distribution data and not to the half-life data. We likewise reject Aventis's contention that the court did not recognize that the half-life comparisons were, in part, intended to demonstrate nonobviousness. In fact, immediately following the portion of the opinion quoted by Aventis, the court continued: "It also relied on [the claimed composition's] properties to rebut obviousness." Aventis III, 475 F. Supp. 2d at 980. In addition, the court, in reference to a statement by the examiner in the second office action, observed, "This signaled to Aventis that its reliance on biochemical properties held promise for overcoming both the [primary examiner's] inherency and obviousness rejections." Id. Therefore, we conclude that the district court properly found that the half-life comparisons were intended to address both the anticipation and obviousness rejections, and, to the extent that they were intended to address the anticipation rejection, the failure to disclose the dosage information evidenced intent to deceive.[8]

[8] Aventis further argues that the district court erroneously imputed to Dr. Uzan arguments made by Aventis's attorney, Mr. Schulman, in response to the examiner's rejections. While it is indeed true that Mr. Schulman represented to the examiner that the difference in half-life indicated that the compositions were different, we find nothing to suggest that the district court relied entirely, or in large part, on Mr.

Aventis further contends that, in the third office action, the examiner withdrew the § 102 rejection and maintained only the § 103 rejection over EP '144. Yet, Aventis asserts, it was not until the second Uzan declaration, which was submitted after the third office action, that Dr. Uzan provided a statistical analysis showing that the half-life differences were statistically significant. Hence, Aventis urges, the examiner clearly withdrew the § 102 rejection based on the MW distribution data, and the half-life data in the second Uzan declaration was intended only to overcome the § 103 rejection. Aventis thus avers that the district court erred in concluding that the anticipation rejection was still pending at the time of the third office action.

The court apparently came to the conclusion that the anticipation rejection was still pending because the rejection had not been expressly withdrawn.[9] Id. at 982 n.9. Although the court may have erred in concluding that the anticipation rejection was still pending in the third office action, that conclusion was not critical to the court's ultimate determination that there was intent to deceive. In fact, as explained by the court:

> Even if the Court were to accept as true Aventis'[s] unlikely contention that, by the time of Dr. Uzan's Second Declaration, the [primary examiner] had conceded that the [claimed] and EP '144 products were different, there can be no question that inherency was the central, dispositive question up to that point.

Schulman's statements in determining that Dr. Uzan intended to deceive the examiner by his failure to disclose the dosage information in his half-life comparisons. Instead, we find that the court's conclusion rested almost entirely on example 6 of the specification and on the first Uzan declaration.

[9] Notably, the examiner did expressly withdraw other prior art rejections. Also, the examiner stated that the rejection over EP '144 was "repeated for the reasons of record," and reiterated that any properties were considered to be inherent in the prior art compounds, making the record somewhat ambiguous.

Id. at 982. Therefore, even if anticipation were not at issue at the time of the third office action, the court still concluded, based on evidence prior to the third office action, that there was deceptive intent. Any error by the court in concluding that anticipation was still at issue in the third office action does not override the evidence of intent to deceive based on the failure to disclose dosage information in the half-life comparisons in example 6 of the specification and in the first Uzan declaration, both of which were submitted prior to the third office action. We cannot agree that the court clearly erred in its factual findings prior to the third office action and in its determinations with respect to intent to deceive based thereon.

In sum, we find that the district court did not clearly err in determining that the half-life comparisons were, in part, intended to show compositional differences to address the anticipation rejection under 35 U.S.C. § 102 and, therefore, rejecting Aventis's argument that they were intended only to show differences in property, such that dosage information was immaterial.

B

Aventis next argues that the district court clearly erred in excluding evidence that comparison of half-lives at different doses was the standard practice in the LMWH field. The "clinically relevant dose," Aventis avers, is the standard dose for comparison of half-lives, and every contemporaneous publication comparing half-lives did so at the clinically relevant doses, even though those doses may have differed. Aventis contends that Dr. Uzan selected the 40 mg dose for the patented compound and the 60 mg dose for the EP '144 compound because they were the clinically relevant doses. According to Aventis, the 40 mg dose for the patented compound was the approved dose for its

most important indication, namely, prevention of deep venous thrombosis ("DVT") during high-risk orthopedic surgery.

The district court excluded the evidence of industry practice because it determined that such evidence was irrelevant to the reasonableness of Dr. Uzan's non-disclosure. Id. at 975 n.6. We find no abuse of discretion by the court's exclusion of the evidence. First, evidence of industry practice of clinically-relevant doses would only be pertinent if there was a finding that the half-life comparisons were used to address obviousness, and not anticipation, because Aventis has conceded that half-life comparisons must be at the same dose to show compositional differences. Here, however, the district court found, and we have affirmed, that the half-life comparisons were at least in part intended to show compositional differences to address the anticipation rejection.

Furthermore, the district court, after examining all of the evidence, found it simply incredible that Dr. Uzan selected the clinically relevant doses for his half-life comparisons. In particular, the court noted that neither the claims nor the specification were limited to prevention of DVT in high-risk surgical patients and that the patented

composition could be used at several different doses for several different indications;[10] that there was not nearly as significant a difference, or no difference at all, in half-life when any other dose (i.e., 20 mg, 60 mg, or 80 mg) of the patented compound was compared to the 60 mg dose of EP '144; and that there was no evidence corroborating Dr. Uzan's testimony that he selected the 40 mg dose due to its efficacy in preventing DVT.[11] Id. at 986-89. Evidence of industry practice using clinically relevant doses would have no impact on the court's credibility determination with respect to whether Dr. Uzan intended the clinically relevant doses in this case.

Therefore, we cannot agree that the district court abused its discretion in excluding evidence that comparison of half-lives at different doses to demonstrate a difference in property was routine practice in the LMWH field.

C

Aventis advances several additional arguments focused on whether Dr. Uzan really had deceptive intent. First, Aventis argues that the court erred in not considering exculpatory testimony by Dr. Uzan indicating that he believed that he informed the examiner that he was comparing half-lives at different doses when he stated, in the first

[10] Aventis disputes this finding by the district court, relying on In re Chupp, 816 F.2d 643, 646 (Fed. Cir. 1987), for the proposition that a compound need not excel over a prior art compound in all properties to be patentable. However, whether a superior property need be demonstrated throughout the entire claim scope in order to show nonobviousness of a claimed product over a prior art product is a separate question from whether there was deceptive intent in failing to disclose material dosage information in a comparison between the claimed product and the prior art product when there is nothing in the claims or specification to suggest that the dosage of the claimed product was the dosage used for a particular purpose.

[11] The court further noted that the 60 mg dose of the EP '144 composition was the only dose for which there was half-life data available. Aventis III, 475 F. Supp. 2d at 984.

Uzan declaration: "[T]his represents an increase in 250% in the half life and is very significant because it enables the same effect to be achieved with lower dosages." This court already concluded in the prior appeal, "that there is no genuine issue of material fact that Dr. Uzan did not disclose in this statement that the comparison was made using data from different doses." Aventis II, 176 Fed. Appx. at 121. We left open the possibility, however, that Dr. Uzan may have intended by this statement to convey to the examiner that the half-life comparisons were done at different doses. Id. at 121 n.2. The district court heard Dr. Uzan's testimony and considered it along with all other evidence relevant to deceptive intent, yet determined that it did not outweigh the cumulative evidence evincing an intent to deceive. We cannot find that the district court clearly erred in concluding that other evidence outweighed Dr. Uzan's testimony that he intended by this statement to inform the examiner that the half-life comparisons were done at different doses.

Next, Aventis avers that Dr. Uzan did not fail to disclose the dosage information for the patented compound to the examiner. In example 6, Aventis urges, Dr. Uzan provided half-life data for the patented compound at 60 mg as well as at 40 mg; and, in the second Uzan declaration, he attached the raw half-life data for the patented compound in Table XI, which showed that the half-life of the patented compound was less at a 60 mg dose than at the 40 mg dose that was used in the comparison with the EP '144 compound. Even if we acknowledge that half-life data at other doses for the patented compound were provided to the examiner, the data were provided in a very misleading way. Paragon Podiatry Lab., Inc. v. KLM Labs., Inc., 984 F.2d 1182, 1191 (Fed. Cir. 1993) (inference of deceptive intent may arise from misleading character of

affidavit); accord B.F. Goodrich Co. v. Aircraft Braking Sys. Corp., 72 F.3d 1577, 1585 (Fed. Cir. 1996). In example 6, half-life data for the patented compound at the 4½ hour cut-off, which could be readily compared to the 4½ hour cut-off data for the EP '144 compound, were only provided at the 40 mg dose. In the first Uzan declaration, reference was made only to the half-life comparison at the 4½ hour cut-off, without reference to the dosage of the patented compound. Moreover, Dr. Uzan failed to disclose, in either example 6 or the first Uzan declaration, the dosage information for the EP '144 compound. Accordingly, we cannot conclude that the district court's finding that Dr. Uzan failed to disclose the dosage information was clearly erroneous.

Lastly, Aventis contends that Dr. Uzan's failure to disclose the dosage information was purely due to inadvertence. In support, Aventis relies on other evidence of inadvertent and benign mistakes made during prosecution of the '618 patent application, suggesting that its omission of the dose of the EP '144 compound was likewise inadvertent. For example, Aventis points out that the first Uzan declaration mistakenly stated that the claimed compound had 1.5% of chains below a specified MW, whereas the remarks by Aventis in its response stated 31.5% of the chains. Here, however, in contrast to any inadvertent omissions made during prosecution, there is sufficient evidence of concealment to warrant a determination that the dose information was intentionally withheld. The fact that Aventis made other inadvertent errors during prosecution has no bearing on this material failure to disclose. Therefore, we cannot agree that the district court clearly erred by not concluding that Dr. Uzan's failure to disclose the dosage information was due to mere inadvertence.

IV

For the foregoing reasons, we affirm the district court's finding of inequitable conduct and holding of unenforceability of the '618 and '743 patents.

AFFIRMED

United States Court of Appeals for the Federal Circuit

2007-1280

AVENTIS PHARMA S.A. and AVENTIS PHARMACEUTICALS, INC.,

Plaintiffs-Appellants,

v.

AMPHASTAR PHARMACEUTICALS, INC.,

Defendant-Appellee,

and

TEVA PHARMACEUTICALS USA, INC.,

Defendant-Appellee.

Appeal from the United States District Court for the Central District of California in case no. 03-CV-887, Senior Judge Mariana R. Pfaelzer.

RADER, Circuit Judge, dissenting.

This court today affirms the unenforceability of a patent due to inequitable conduct. To my eyes, this record does not show clear and convincing evidence of intent to deceive the United States Patent and Trademark Office (USPTO). Moreover, my reading of our case law restricts a finding of inequitable conduct to only the most extreme cases of fraud and deception.

Without doubt, candor and truthful cooperation are essential to an ex parte examination system. With burgeoning application rates, the USPTO must rely on applicant submissions to narrow the prior art search. And, of course, those submissions must be reliable. The threat of inequitable conduct, with its "atomic bomb" remedy of unenforceability, ensures that candor and truthfulness.

Although designed to facilitate USPTO examination, inequitable conduct has taken on a new life as a litigation tactic. The allegation of inequitable conduct opens new avenues of discovery; impugns the integrity of patentee, its counsel, and the patent itself; excludes the prosecuting attorney from trial participation (other than as a witness); and even offers the trial court a way to dispose of a case without the rigors of claim construction and other complex patent doctrines. This court has even observed a number of cases, such as this one, that arrive on appeal solely on the basis of inequitable conduct where the trial court has apparently elected to try this issue in advance of the issues of infringement and validity. See, e.g., Frazier v. Roessel Cine Photo Tech, Inc., 417 F.3d 1230 (Fed. Cir. 2005); Semiconductor Energy Lab. Co. v. Samsung Elecs. Co., 204 F.3d 1368 (Fed. Cir. 2000).

This phenomenon is not new or unprecedented. At an earlier time, the Federal Circuit also observed that inequitable conduct as a litigation strategy had become a "plague." Burlington Indus. v. Dayco Corp., 849 F.2d 1418, 1422 (Fed. Cir. 1988). In response, this court took a case to reduce abuse of inequitable conduct. Kingsdown Med. Consultants, Ltd. v. Hollister, Inc., 863 F.2d 867, 876 (Fed. Cir. 1988) (en banc).

In light of the rejuvenation of the inequitable conduct tactic, this court ought to revisit occasionally its Kingsdown opinion. Kingsdown claimed a two-piece ostomy device. Id. at 869. The examiner rejected claim 50 as indefinite. Id. at 870. In response, Kingsdown amended claim 50. Id. Then, later in the prosecution, Kingsdown copied the rejected claim 50, not the amended version, into a continuation application as new claim 43. Id. at 870-71. The once rejected, now recopied claim 43 matured into claim 9 of U.S. Patent No. 4,460,363. Id. at 871. On the basis of this error that certainly

called into question the integrity of the examination system, the district court found inequitable conduct. Id. at 871-72. This court, en banc, reversed. Id. at 877.

In Kingsdown, this court clearly conveyed that the inequitable conduct was not a remedy for every mistake, blunder, or fault in the patent procurement process. Even mistakes that struck at the heart and integrity of the process—like repeatedly recopying and acquiring rights to a rejected claim—did not amount to inequitable conduct. Instead this court required "culpable" conduct supported by clear and convincing evidence of intent to deceive the USPTO. Halliburton Co. v. Schlumberger Tech. Corp., 925 F.2d 1435, 1443 (Fed. Cir. 1991) (citing Consol. Aluminum Corp. v. Foseco Int'l Ltd., 910 F.2d 804, 809 (Fed. Cir. 1990)). At the same time, it is hard to imagine a more material mistake than reasserting claims to rejected subject matter. Materiality of any undisclosed or misleading information, of course, is the other prong of an inequitable conduct analysis. Cargill, Inc. v. Canbra Foods, Ltd., 476 F.3d 1359, 1363 (Fed. Cir. 2007). In sum, Kingsdown properly made inequitable conduct a rare occurrence.

More recently, however, the judicial process has too often emphasized materiality almost to the exclusion of any analysis of the lofty intent requirement for inequitable conduct. Merging intent and materiality at levels far below the Kingsdown rule has revived the inequitable conduct tactic. For example, in Nilssen v. Osram Sylvania, Inc., 504 F.3d 1223 (Fed. Cir. 2007), one of the reasons this court upheld a judgment of unenforceability for an exaggerated claim of small entity status. Nilssen entered into agreements with Philips Electronics North America Corp. ("Philips") to license the patents in suit. Id. at 1227-28. Because Phillips had more than 500 employees, the district court found that Nilssen had made several improper small entity

maintenance fee payments to the USPTO. Id. at 1228. This court affirmed, stating: "[w]e therefore affirm the district court's decision finding that all of the patents in suit are unenforceable due to inequitable conduct in improperly claiming small entity status." Id. at 1233. In General Electro. Music Corp. v. Samick Music Corp., 19 F.3d 1405 (Fed. Cir. 1994), this court upheld unenforceability under circumstances that are even harder to reconcile with the en banc Kingsdown rule. The mistake in that case involved a petition to make special. Id. at 1407.

The applicant sought expedited examination of its application on the ground that the claimed invention was being infringed. Id. At that time, such a request required an oath or declaration that the applicant made a careful and thorough search of the prior art. Id. The applicant submitted that declaration, but later conceded that it actually had only conducted an informal search as opposed to a formal search. Id. This process did not result in the issuance of rejected claims, but involved nothing more than an expedited examination. Still this miscarriage rendered the entire patent unenforceable. Id. at 1412.

While the case at bar does not feature small entity status or expedited examination, the record still does not, in the context of Kingsdown, show a clear and convincing intent to deceive. We are cognizant of the high standard of review. To overturn a discretionary ruling of a district court, the appellant must establish that the ruling is based upon clearly erroneous findings of fact or a misapplication or misinterpretation of applicable law or that the ruling evidences a clear error of judgment. Kingsdown, 863 F.2d at 876. While the standard of review is high, it is not

insurmountable. Where the district court made clear error of fact, this court must overturn such a determination.

In this case, Dr. Uzan, Associate Director of Biological Research at Aventis, assisted in the prosecution of the application that led to U.S. Patent No. 5,389,618 ('618) covering a low molecular weight heparin mixture invented by Roger Debrie (Debrie LMWH). Specifically, Dr. Uzan assembled data from various clinical studies comparing the half-lives of the Debrie LMWH to a prior art LMWH invented by Mardiguian (Mardiguian LMWH). Dr. Uzan submitted this data, from the Duchier study and the Foquet study respectively, as example 6 of the patent. In submitting the data, Dr. Uzan did not draw attention to the different doses in those studies.

Without question, Dr. Uzan should have disclosed the dosage of the Mardiguian LMWH in example 6 subsection 3. Unfortunately, the Forquet study chart that Dr. Uzan used did not show the dosage information. Dr. Uzan neglected to add the information. To make it clear, Dr. Uzan did not attempt to conceal data that were otherwise present. Rather he just submitted the study without adding to the disclosure. This omission, even if negligent, is hardly Kingsdown's culpable intent to deceive. Moreover this omission strikes less at the integrity of the system than issuance of a rejected claim, which Kingsdown sanctioned.

Likewise, Dr. Uzan ought to have disclosed to the USPTO that he compared the 60 mg dose of the prior art Mardiguian LMWH to the 40 mg dose of the Debrie LMWH in the declaration he submitted on March 29, 1993. Dr. Uzan testified that the different dose "did not come to his mind." In context, this explanation has merit. Dr. Uzan was asked to compare the superior pharmacokinetic properties of the Debrie LMWH over

the Mardiguian LMWH prior art compound. Comparison of drug properties at their clinically relevant (and different) dosages is, of course, completely appropriate. Again, this oversight may have been careless, but hardly culpable. To my eyes, Dr. Uzan's negligence does not rise to the level of intent to deceive, particularly in comparison with Kingsdown.

Even a cursory review of example 6 shows no dosage indications. The Debrie LMWH in subsection 1 indicates two dosages. Dosage is an element in subsections 2 and 4 as well. Thus, the absence of a dosage in subsection 3 is blatantly obvious. Surely if Dr. Uzan had intended to deceive the USPTO, he would not have made this omission so conspicuous. Moreover, I find it difficult to fathom that a scientist of Dr. Uzan's caliber and reputation would engage in such deception. As the district court points out, Dr. Uzan has had a magnificent fifty year career with Aventis, has published over 350 scientific articles and has received numerous prestigious awards including the Galien Research Prize, France's highest award for drug discovery. This world-class scientist would hardly risk his reputation and tarnish his brilliant career for a single example in the prosecution of a patent for an invention in which he was not even involved.

The inadvertence in this case presents another difficulty for a finding of intent to deceive. The omissions and prosecution errors were committed by two individuals, Dr. Uzan and Mr. Schulman, Aventis' prosecuting attorney. Collective actions call into question any showing of intent for inequitable conduct. 37 C.F.R. § 1.56 refers to the duty of candor and good faith possessed by "[e]ach individual associated with the filing and prosecution of a patent application." (emphasis added). Mr. Schulman did not

know that the doses of the Debrie LMWH and the Mardiguian LMWH were different. Dr. Uzan admitted that he inadvertently neglected to add that information to the graphs. The dosage information was not on the original Foquet chart submitted to the Aventis patent department and Dr. Uzan neglected to add it. Mr. Schulman had no way of knowing that the comparison was at two different doses and therefore the impropriety of using that data to demonstrate compositional difference. Mr. Schulman's arguments also carry the markings of a good faith mistake.

Most important, Dr. Uzan himself revealed the error. This candor is inconsistent with deceptive intent. He submitted all of the underlying data to the patent office with his second declaration on June 9, 1994. Thus, unlike the situation in Kingsdown, Dr. Uzan corrected the mistake before it resulted in an issued patent. In Dr. Uzan's second declaration, he clearly articulated that the half-life data showed superior properties of the Debrie LMWH over the prior art Mardiguian LMWH. Still, with all information before the USPTO, the examiner allowed the patent. Lastly, in early 2003, before filing its infringement suit, Aventis filed a reissue application for the '618 patent. The patent reissued on June 14, 2005 with all of the original independent claims, but without example 6. The half-life data were apparently not even necessary for patentability. The USPTO determined that the Debrie LMWH was inventive over the prior art Mardiguian LMWH without relying on the controversial half-life data from example 6.

The USPTO granted the reissue a day before the district court judge granted Teva and Amphastar's summary judgment motion that the '618 patent was unenforceable. Aventis did not have the opportunity to make this argument to the trial judge. This record does not prevent this court, however, from considering all this

information in evaluating the inequitable conduct finding. Thus, both materiality and intent seem suspect on this record. In sum, read in the context of Kingsdown, I would reverse the district court's determination of inequitable conduct.