United States Court of Appeals for the Federal Circuit

2008-1480, -1481

ASTRAZENECA PHARMACEUTICALS LP and ASTRAZENECA UK LIMITED,

Plaintiffs-Appellees,

v.

TEVA PHARMACEUTICALS USA, INC.
and TEVA PHARMACEUTICAL INDUSTRIES, LTD.,

Defendants-Appellants,

and

SANDOZ, INC.,

Defendant-Appellant.

Henry J. Renk, Fitzpatrick Cella, Harper & Scinto, of New York, New York, argued for plaintiffs-appellees. With him on the brief were Bruce C. Haas; Charles E. Lipsey, Finnegan, Henderson, Farabow Garrett & Dunner, LLP, of Reston, Virginia, and Thomas A. Stevens, AstraZeneca Pharmaceuticals LP, of Wilmington, Delaware.

Ira J. Levy, Goodwin Proctor LLP, of New York, New York, argued for defendants-appellants Teva Pharmaceuticals USA, Inc., et al. With him on the brief were Henry C. Dinger, Daryl L. Wiesen and John T. Bennett, of Boston, Massachusetts.

Douglass C. Hochstetler, Schiff Hardin LLP, of Chicago, Illinois, argued for defendant-appellant Sandoz, Inc. With him on the brief were Jason G. Harp; and Beth D. Jacob, of New York, New York.

Appealed from: United States District Court for the District of New Jersey

Judge Joel A. Pisano

United States Court of Appeals for the Federal Circuit

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SANDOZ, INC.,

Defendant-Appellant.

Appeal from the United States District Court for the District of New Jersey in consolidated Case Nos. 05-CV-5333, 06-CV-1528, 07-CV-1632, and 07-CV-3001, Judge Joel A. Pisano.

DECIDED: September 25, 2009

Before NEWMAN, RADER, and PROST Circuit Judges.

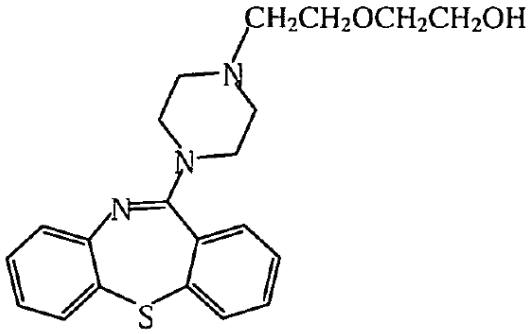
NEWMAN, Circuit Judge.

Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., and Sandoz, Inc. appeal from the grant, by the United States District Court for the District of New Jersey, of AstraZeneca Pharmaceuticals LP and AstraZeneca UK Limited's motion for summary

judgment of no inequitable conduct.[1] The district court ruled that the Appellants had not presented evidence sufficient for a reasonable jury to find that, in prosecution of the subject patent application in the Patent and Trademark Office ("PTO"), AstraZeneca made a misrepresentation of material fact or an omission of material fact, with intent to deceive or mislead the patent examiner into granting the patent. We affirm the district court's ruling.

BACKGROUND

AstraZeneca is the assignee of United States Patent No. 4,879,288 ("the '288 patent") which claims the antipsychotic drug quetiapine, having the following structural formula:



Quetiapine

AstraZeneca markets quetiapine under the brand name "SEROQUEL®." The '288 patent explains that this product is an "atypical" antipsychotic drug, which means that, unlike "typical" antipsychotics, it does not produce involuntary body movements including torsion spasms, muscle spasms and dystonia of the face, neck, or back with protrusion of

[1] AstraZeneca Pharm. LP v. Teva Pharm. USA, 567 F. Supp. 2d 683 (D.N.J. 2008).

the tongue, and tonic spasms of the limbs (dyskinesias). Such undesirable side effects were not unusual for antipsychotic drugs. An earlier atypical antipsychotic drug, clozapine, had become available in the 1970s, but it was withdrawn from the market after it was discovered to cause a potentially deadly reduction in white blood cell count known as agranulocytosis. The AstraZeneca product quetiapine was approved by the FDA in 1997. The '288 patent expires on September 26, 2011.

Teva and Sandoz each filed abbreviated new drug applications ("ANDAs") for approval to sell their production of quetiapine under 21 U.S.C. §355(j), certifying under "paragraph IV" that the '288 patent is invalid and/or not infringed. Paragraph IV certifications are, by statute, an act of technical patent infringement designed to permit litigation of patent issues for products subject to federal regulatory approval. 35 U.S.C. §271(e)(2)(A). In accordance with the statutory procedures, AstraZeneca filed infringement suits against Teva and Sandoz; the suits were consolidated in the District Court for the District of New Jersey. See 21 U.S.C. §355(j)(5)(B)(iii).

The district court granted summary judgment that there was no inequitable conduct in prosecution of the '288 patent application. That is the only issue of this appeal.

DISCUSSION

The grant of summary judgment receives plenary review on appeal. Innogenetics, N.V. v. Abbott Labs., 512 F.3d 1363, 1378 (Fed. Cir. 2008). "Although the premises of inequitable conduct require findings based on all the evidence, a procedure that may preclude summary determination, a motion for summary judgment may be granted when, drawing all reasonable factual inferences in favor of the non-movant, the evidence is such that the non-movant can not prevail." ATD Corp. v. Lydall, Inc., 159 F.3d 534, 547 (Fed.

Cir. 1998) (citation omitted). On appellate review, we accordingly consider the evidence and all reasonable factual inferences, in light of the applicable law and the burdens and standards of proof. Id. at 540.

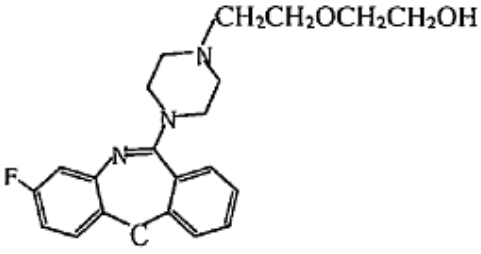
The issue presented in this case relates to the extent to which the patent applicant, having fully disclosed the relevant prior art and having provided comparative data to the satisfaction of the patent examiner, must also present any additional unpublished information in the applicant's possession concerning other less structurally similar compounds, and must also synthesize additional compounds for comparative testing. The district court reviewed the evidence in the dual contexts of the materiality of any withheld or omitted information, and whether deceptive intent had been established. These are the essential factual underpinnings of the charge of inequitable conduct, and both materiality and deceptive intent must be established by clear and convincing evidence. See Kingsdown Medical Consultants, Ltd. v. Hollister Inc., 863 F.2d 867, 872 (Fed. Cir. 1988) (en banc) (both materiality and deceptive intent must be shown). Intent to deceive cannot be inferred from a high degree of materiality alone, but must be separately proved to establish unenforceability due to inequitable conduct. Id. at 876; see Star Scientific, Inc. v. R.J. Reynolds Tobacco Co., 537 F.3d 1357, 1366 (Fed. Cir. 2008) ("[T]he fact that information later found material was not disclosed cannot, by itself, satisfy the deceptive intent element of inequitable conduct.").

If both materiality and deceptive intent are established, the court shall balance these findings, with cognizance of the underlying facts, and determine whether, in the specific case, there was inequitable conduct in the prosecution of the patent application. Star Scientific, 537 F.3d at 1365. Upon determining that there was inequitable conduct in

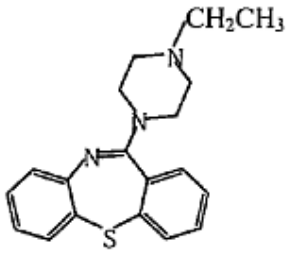
obtaining the patent, the district court may in its discretion declare the patent permanently unenforceable. Kingsdown, 863 F.2d at 876.

The Prior Art

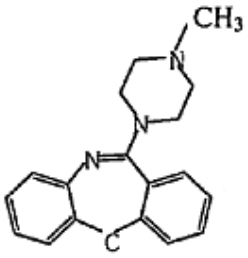
The references on which the Appellants base their argument of withholding comparative data were all before the PTO. After filing of the '288 patent application, before the examiner's first Office Action, AstraZeneca filed an Information Disclosure Statement ("IDS") listing several references including those described below, and stated: "Enclosed herewith . . . is a list of references believed to be relevant to the subject matter of the invention[.]" The relevant compounds in these references are Compound 21076, described in the German-language publication Research Disclosure (1980) ("Research Disclosure"); Compound 24028, described in U.S. Patent No. 3,539,573 to Schmutz et al. ("Schmutz II"); Perlapine, described in U.S. Patent No. 3,389,139 to Schmutz et al. ("Schmutz I"); and Fluperlapine, described in U.S. Patent No. 4,308,207 to Hunziker et al. ("Hunziker"). These four compounds have the structural formulae shown below:



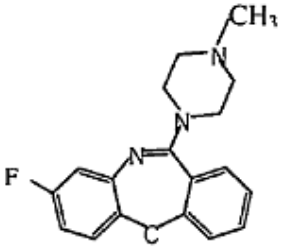
Compound 21076



Compound 24028



Perlapine

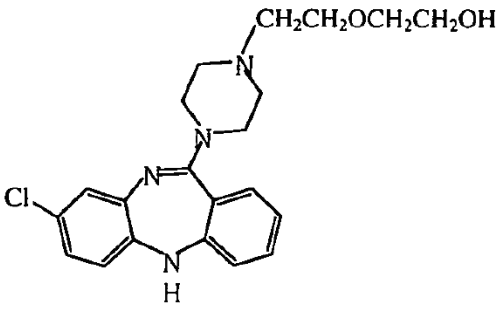


Fluperlapine

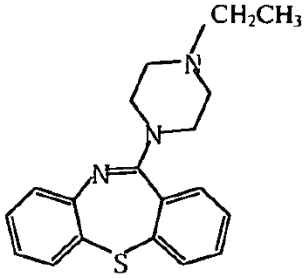
AstraZeneca had internal test data for these four compounds as well as for many other compounds; data that were generated in the course of the research leading to quetiapine. This internal information was not included in its IDS—that is the main basis of the Appellants' inequitable conduct argument, for they argue that AstraZeneca's data showed that some prior art compounds potentially exhibited atypical antipsychotic activity, and that this information should have been reported to the patent examiner.

The examiner, in the first Office Action, cited several references showing compounds of close structural similarity to quetiapine. The examiner cited Schmutz II as the primary reference, in view of U.S. Patent No. 4,097,597 to Horrom ("Horrom"), which was another reference included in AstraZeneca's IDS, and other combinations of secondary references. In particular, the examiner identified a compound described in Schmutz II to which the

parties refer as “Schmutz X,” and a compound described in Horrom. These structures are as follows:



Horrom Compound



Schmutz X

During the prosecution the applicant and the examiner discussed the prior art compounds, for it was not disputed that the structural differences were small among these various compounds. The examiner based the rejection on structural similarity alone, and the applicant in response pressed the unpredictability of the critical physiological property of atypicality, and that the prior art provided no reason to make the particular compound quetiapine for the purpose of obtaining atypical antipsychotic properties. AstraZeneca pointed to the long-felt need for such a drug, because the use of clozapine was severely limited and no suitable replacement was available in the United States.

The examiner persisted in the rejection, stating that in accordance with the law of obviousness as to the claimed structure it is not necessary that the prior art described or suggested that a specific structure would impart a specific property, if in fact the prior art product had the desired property. The examiner stated that in order to overcome the structural obviousness rejection AstraZeneca must provide proof that the prior art compounds:

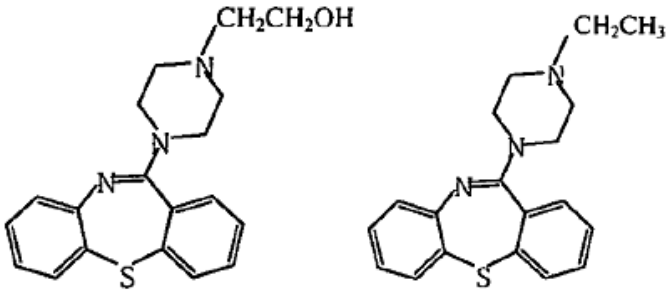
> do not necessarily or inherently possess the characteristics of the claimed product. . . . In other words, once a condition of prima facie structural obviousness has been made out, it must be overcome by a side-to-side comparison with the closest art compound(s). In this case, one would test both the prior art species ([Horrom compound] and [Schmutz X]) and the claimed specie for their ability to avoid e.g. tardive dyskinesia (or whatever undesirable side effect applicant wishes to focus on).

PTO Paper No. 10, December 2, 1988. The examiner referred to the IDS and stated:

> [T]he cited references are noted. None disclose [sic] compounds closer than the species already discussed.

Id.

In response to the examiner's position, AstraZeneca submitted the Declaration of one of the inventors, Dr. Migler, with data for the Horrom compound and a Schmutz compound. The prosecuting attorney explained that AstraZeneca did not have psychotic test data for Schmutz X, and that such data would be "very expensive to generate now," and as a substitute AstraZeneca offered pre-existing internal data for Schmutz B, which the inventors believed was closer structurally than Schmutz X because the hydroxyethyl side-chain of Schmutz B is more similar to quetiapine's side-chain than is the ethyl side-chain of Schmutz X. These structures are:



Schmutz B **Schmutz X**

Dr. Migler's declaration contained psychotic test data showing that the Horrom compound's antipsychotic properties were "typical." The declaration also contained

psychotic test data for Schmutz B, and showed that it too was "typical." Dr. Migler also included test data for another compound described in Schmutz II that the parties call Schmutz A, which differs from quetiapine in that Schmutz A's left benzene ring is substituted with chlorine (whereas quetiapine's left ring is unsubstituted), and Schmutz A's side chain is methyl (as compared to quetiapine's hydroxyethoxyethyl). The test data showed that Schmutz A was inactive for antipsychotic activity; AstraZeneca explained that in light of this inactivity no test for atypical side-effects was conducted for Schmutz A.

The Appellants' inequitable conduct arguments before the district court, and again before this court, focus on the fact that AstraZeneca did not submit to the PTO its internal test data for perlapine, fluperlapine, compound 21076, and compound 24028, shown supra. The Appellants state that it was a material withholding to provide test data only for the compounds on which the examiner relied, stating that AstraZeneca's internal test data showed that compounds other than quetiapine possessed potential atypical antipsychotic activity. Thus, the Appellants argued that the Migler Declaration was deliberately misleading.

The district court found that AstraZeneca properly addressed the closest prior art, in response to the examiner's specific requests, and that the premises of the factual allegations of material withholding with deceptive intent had not been shown sufficiently to avoid the grant of summary judgment, citing that inequitable conduct in patent prosecution requires proof by clear and convincing evidence of both (1) an affirmative misrepresentation of material fact, a failure to disclose material information, or submission of false material information, and (2) an intent to deceive the examiner by such material falsity.

AstraZeneca, 567 F. Supp. 2d at 691 (citing Cargill, Inc. v. Canbra Foods, Ltd., 476 F.3d 1359, 1364 (Fed. Cir. 2007)).

Materiality

Several standards for establishing the fact of materiality in connection with patent prosecution have been proposed. See, e.g., Litton Indus. Products, Inc. v. Solid State Systems Corp., 755 F.2d 158, 166 n.19 (Fed. Cir. 1985) (identifying "four tests: (1) objective 'but for'; (2) subjective 'but for'; (3) 'but it may have been'; (4) PTO Rule 1.56(a), i.e., whether there is a substantial likelihood that a reasonable examiner would have considered the omitted reference or false information important in deciding whether to allow the application to issue as a patent.") While a uniform standard has not been rigorously applied in the courts, the fourth test of whether a reasonable examiner would have considered the information important in deciding whether to grant the patent, even when the omitted information does not negate patentability, is most often employed. See, e.g., Upjohn Co. v. Mova Pharm. Corp., 225 F.3d 1306, 1312 (Fed. Cir. 2000). "However, a reference need not be provided to the examiner if it is merely cumulative to or less material than other references before the examiner." Id.

Appellants contend that AstraZeneca misrepresented that the atypical properties of quetiapine were unexpected, stating that AstraZeneca presented internal test data about similar compounds that were typical while omitting internal test data about similar compounds that were potentially atypical. AstraZeneca states that it properly focused on the prior art compounds that were structurally closest to quetiapine and that its internal test data show that these closest compounds were not atypical. AstraZeneca states that this is the comparison requested by the examiner, and the comparison most directly in line with

the applicable law. AstraZeneca states that it never represented to the examiner that quetiapine's atypical properties made it completely unique among structurally similar compounds, and points out that in its IDS AstraZeneca identified the references describing the compounds that the Appellants here assert are potentially atypical antipsychotics, i.e., perlapine, fluperlapine, compound 24028, and compound 21076.

No relevant reference is asserted to have been withheld. Various references stated that certain prior art compounds were known to be atypical antipsychotics, such as clozapine and fluperlapine. For example, the cited Hunziker reference identifies fluperlapine as a "non-classical neuroleptic" (i.e., antipsychotic) "like clozapine."[2] U.S. Patent No. 4,308,207 col.3 ll.5-9. AstraZeneca points out that since the Hunziker reference describes fluperlapine as having atypical properties, AstraZeneca's internal test data on whether fluperlapine is atypical is, at most, cumulative information.

With all of the references before him, the Examiner made a prima facie obviousness rejection based on the structural similarity between quetiapine and the two prior art compounds that he identified as structurally closest to quetiapine; that is, Schmutz X and the Horrom Compound. As we have discussed, AstraZeneca responded that it had test data for the Horrom Compound, but that it did not have test data for Schmutz X, and provided test data for Schmutz B; AstraZeneca told the examiner that the test data on Schmutz X would be "very expensive to generate now" and that Schmutz B was actually

[2] AstraZeneca requests that we take judicial notice that Sandoz, in a document filed in a separate proceeding before the United States District Court for the District of New Jersey, acknowledged that the Hunziker patent describes fluperlapine as an atypical antipsychotic. AstraZeneca Pharm. LP v. Sandoz, Inc., Civil Action No. 09-CV-870 (JAP) (TJB) (D.N.J. 2009). We take judicial notice of this statement, which merely confirms an uncontested fact, as Sandoz's brief already states "Hunziker described fluperlapine as being a non-classical antipsychotic like clozapine."

structurally closer to quetiapine than Schmutz X. Appellants charge that both of these statements to the examiner are material misrepresentations. AstraZeneca replies that both statements are accurate and true.

First, the Appellants argue that AstraZeneca falsely stated that generating test data on Schmutz X would be "very expensive." Appellants contend that expense was mere pretext, asserted because AstraZeneca believed that Schmutz X was atypical based on the structural similarity between Schmutz X and Compound 24028, which AstraZeneca knew to have potential atypical properties. Appellants do not assert that AstraZeneca had data for Schmutz X and withheld it; nor do they argue that Schmutz X is in fact atypical, and no data are presented to this effect. Instead the Appellants seem to argue that because of the structural similarity between Schmutz X and Compound 24028, Schmutz X could be atypical, and thus should have been synthesized and its antipsychotic properties tested. The Appellants' position appears to be that AstraZeneca's failure to do so was a material withholding or omission, with deceptive intent.

Although there may be situations in which the failure to conduct specific tests of specific compounds can be criticized, in this case there was no evidence that the information gleaned, if such tests had been conducted, would have been material to patentability. It was not disputed that it was unpredictable whether a given compound would exhibit atypical antipsychotic properties. The record demonstrates that structural similarity is not a predictor of whether antipsychotic behavior would be typical or atypical. As AstraZeneca points out, the properties of these structurally similar compounds vary significantly with minor structural changes.[3] The Appellants made no showing as to

[3] During the course of this litigation, the district court collaterally estopped Teva

whether the structural similarity between Schmutz X and Compound 24028 would establish whether Schmutz X would have atypical properties. In the context of the knowledge in this field, as reflected in the various references, AstraZeneca's provision of its existing test data for Schmutz B, instead of preparing and testing Schmutz X, cannot constitute a material misrepresentation. The district court correctly so held.

The Appellants also argue that AstraZeneca should have submitted to the examiner its existing test data for Compound 24028 because Compound 24028 and Schmutz B are "equally close" to quetiapine. The Appellants state that the data should have been submitted although not identified or requested by the examiner.

To ascertain what is "equally close," in identifying the structurally closest prior art, the compounds are viewed as they would be perceived by persons experienced in the particular field of science. Precedent suggests that as a starting point it is useful to ascertain the common elements of the claimed invention and the prior art. See In re Merchant, 575 F.2d 865, 868 (CCPA 1978) (determining the common elements). Thus the Appellants point out that Compound 24028, Schmutz B, and quetiapine differ only in their respective side chains. That is correct. However, AstraZeneca is also correct in pointing out that Schmutz B's hydroxyethyl side chain is structurally closer to quetiapine's hydroxyethoxyethyl side chain, both in length of the chain and in the hydroxyl end group, than is Compound 24028's methyl side chain, as shown below:

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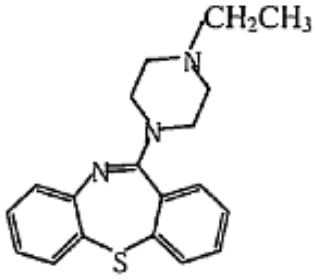
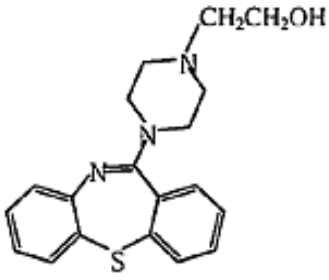
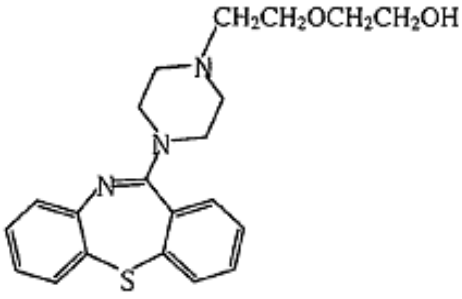
from challenging the unpredictability of atypical antipsychotic properties because Teva had agreed to be bound by the decision of the district court in Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 364 F. Supp. 2d 820, 831 ¶14 (S.D. Ind. 2005), which involved many of the same issues regarding the development of an atypical antipsychotic. See AstraZeneca Pharm. LP v. Teva Pharm. USA, Civil Action No. 05-CV-05333 (JAP) (TJB), Order Granting Motion for Summary Judgment Based on Collateral Estoppel (D.N.J. Oct. 12, 2007).



Compound 24028



Schmutz B



Quetiapine

The patent examiner did not dispute AstraZeneca's scientific position, and accepted the proffered data on Schmutz B as the closest prior art. Accordingly, AstraZeneca's substitution of Schmutz B in place of Schmutz X was not a material misrepresentation, and the non-provision of the data on Compound 24028, which is structurally less similar to quetiapine, was not a material omission.

The appellants also argue that AstraZeneca's submission of its internal test data of Schmutz B along with its internal test data of Schmutz A was an implied misrepresentation because it omitted other internal test data of potentially atypical compounds including fluperlapine, perlapine, Compound 21076, and Compound 24028. We agree with the district court that the Migler declaration, which was directed to the closest prior art compounds, was not an implied misrepresentation. AstraZeneca has not asserted that no prior art compound is atypical. Rather, AstraZeneca demonstrated, as the examiner required, that the structurally closest prior art compounds did not possess the same properties as quetiapine. The prosecuting attorney explained that Schmutz A was on the same list of antipsychotics as Schmutz X. A reasonable examiner would not have understood the Migler declaration as stating that no prior art product had the atypical property shown by quetiapine, for it was known that other atypical antipsychotics existed,

including fluperlapine and clozapine. A reasonable examiner would understand AstraZeneca's statements to refer to the closest prior art compounds, not all prior art compounds. AstraZeneca's inclusion of the Schmutz A data is not an "implied" misrepresentation.

We conclude, as did the district court, that the evidence cannot support a finding that AstraZeneca misrepresented or omitted material information.

Deceptive Intent

Intent to deceive is an independent element of inequitable conduct, and must be independently established by clear and convincing evidence. Star Scientific, 537 F.3d at 1365; Cargill, 476 F.3d at 1364; see Molins PLC v. Textron, Inc., 48 F.3d 1172, 1181 (Fed. Cir. 1995) ("[C]lear and convincing evidence must prove that an applicant had the specific intent to accomplish an act that the applicant ought not to have performed, viz., misleading or deceiving the PTO. In a case involving nondisclosure of information, clear and convincing evidence must show that the applicant made a deliberate decision to withhold a known material reference."); Allen Organ Co. v. Kimball Int'l, Inc., 839 F.2d 1556, 1567 (Fed. Cir. 1988) ("[m]ateriality does not presume intent, which is a separate and essential component of inequitable conduct").

Appellants state that they have shown a "high degree of materiality," and that they therefore need a proportionally lesser showing of intent to deceive to establish the requisite threshold level of intent. That is incorrect. Evidence of mistake or negligence, even gross negligence, is not sufficient to support inequitable conduct in patent prosecution. Kingsdown, 863 F.2d at 876. To establish the requisite deceptive intent, "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." Id. While the court must, as the final step, weigh and balance the findings of materiality and intent, this presupposes that a threshold level of both of these elements has already been established by clear and convincing evidence. See Manville Sales Corp. v. Paramount Systems, Inc., 917 F.2d 544, 551 (Fed. Cir. 1990) ("Inequitable conduct requires proof by clear and convincing evidence. A threshold showing of both materiality and intent to mislead or deceive must be first established, and then those fact-findings are balanced to make the determination whether 'the scales tilt to a conclusion that inequitable conduct occurred.'").

The only evidence of intent offered by the Appellants is AstraZeneca's internal knowledge of certain compounds of this structural class that were atypical, without including this information in the IDS. The Appellants argue that it is irrelevant that the omitted compounds are not the closest structural analogs, and irrelevant that the patent examiner asked for comparative data for other, closer compounds. The Appellants offer no evidence or suggestion of deceptive intent, other than the fact that this information was not provided. The law is clear that "inequitable conduct requires not intent to withhold, but rather intent to deceive. Intent to deceive cannot be inferred simply from the decision to withhold [information] where the reasons given for the withholding are plausible." Dayco Products, Inc. v. Total Containment, Inc., 329 F.3d 1358, 1367 (Fed. Cir. 2003). As argued by Appellants, an applicant would not know how much of its research effort must be filed with the PTO, although of no interest to the examiner, or run the risk of accusation of wrongdoing no matter where the line is drawn.

As we have discussed, the omitted test data were not material because the compounds were not the structurally closest compounds, whereas AstraZeneca and the

examiner focused on the structurally closest compounds. Although the Appellants argue that this is an inadequate reason, no evidence of bad faith has been proffered concerning the omission of data for the less similar compounds, AstraZeneca presented plausible reasons for its presentation of arguments and data during the prosecution, and although the Appellants dispute AstraZeneca's reasoning, intentional withholding for the purpose of deceiving the examiner is unsupported by evidence sufficient to avert summary judgment.

We reach the same conclusion as did the district court, that the Appellants have not provided evidence sufficient to establish the threshold facts of material withholding with the intent to deceive. The grant of summary judgment of no inequitable conduct is affirmed.

COSTS

Each party shall bear its own costs.

AFFIRMED.