UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ELAN PHARMA INTERNATIONAL LIMITED, Plaintiff, v. ABRAXIS BIOSCIENCE, INC., Defendant.	C.A. No. 06-438-GMS

ABRAXIS'S OPENING BRIEF IN SUPPORT OF MOTION TO AMEND THE JUDGMENT AND ENTER FINDINGS THAT ELAN ENGAGED IN INEQUITABLE CONDUCT IN PROCURING THE '363 AND '025 PATENTS

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Dated: July 14, 2008

TABLE OF CONTENTS

Page

I. NATURE AND STAGE OF THE PROCEEDING....1

II. SUMMARY OF ARGUMENT....1

III. STATEMENT OF FACTS....3

IV. ABRAXIS IS ENTITLED TO JUDGMENT OF INEQUITABLE CONDUCT....3

A. Legal Standards....3

B. Elan Intentionally Misrepresented and Withheld Material Information....6

1. Elan Intentionally Misrepresented that its Invention Resolved Issues of Contamination....6

2. Elan Misrepresented and Withheld Material Information Regarding Drug/Surface Modifier Combinations....13

3. Elan Misrepresented and Withheld Material Information Regarding the Scope of the '025 Patent....17

V. CONCLUSION....20

TABLE OF AUTHORITIES

CASES

Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs. Ltd., 394 F.3d 1348 (Fed.Cir. 2005) 5

Cargill, Inc. v. Canbra Foods, Ltd., 476 F.3d 1359 (Fed. Cir. 2007) ..... passim

Ferring B.V. v. Barr Labs., Inc., 437 F.3d 1181 (Fed. Cir. 2006) 4, 17

Hayes v. Community Gen. Osteopathic Hospital, 940 F.2d 54 (3d Cir. 1991) 5

Hoffman-LaRoche, Inc. v. Promega Corp., 323 F.3d 1354 (Fed. Cir. 2003) 3, 4, 9

Impax Labs., Inc. v. Aventis Pharms., Inc., 468 F.3d 1366 (Fed. Cir. 2006) 4

LaBounty Mfg., Inc. v. U.S. Int'l Trade Comm'n, 958 F.2d 1066 (Fed. Cir. 1992) 4

McKesson Info. Solutions, Inc. v. Bridge Med., Inc., 487 F.3d 897 (Fed. Cir. 2007) 3

Merck & Co., Inc. v. Danbury Pharmacal, 873 F.2d 1418 (Fed. Cir. 1989) 9

Monsanto Co. v. Bayer BioScience N.V., 514 F.3d 1229 (Fed. Cir. 2008) 3

Purdue Pharma L.P. v Endo Pharm., Inc., 438 F.3d 1123 (Fed. Cir. 2006) 9

Refac Int'l, Ltd. v. Lotus Dev. Corp., 81 F.3d 1576 (Fed.Cir. 1986) 4

Transmatic, Inc. v. Gulton Indus., Inc., 53 F.3d 1270 (Fed. Cir. 1995) 5

RULES

37 C.F.R. 1.56 ..... 1, 2

Fed. R. Civ. P. 52(a) 1, 5

Fed. R. Civ. P. 59(e) 1

I. NATURE AND STAGE OF THE PROCEEDING

In this patent case, the jury returned a verdict in favor of Elan on infringement of the '363 patent (but not willfulness) and validity of the '363 and '025 patents, and for $55,230,000. The jury rendered an advisory verdict in Elan's favor on inequitable conduct in the prosecution of the '363 and '025 patents. The Court entered judgment on June 16, 2008, which included judgment of no inequitable conduct in the prosecution of the patents-in-suit without specific findings of fact or conclusions of law. D.I. 613; D.I. 614.

II. SUMMARY OF ARGUMENT

Abraxis timely moved under Federal Rules of Civil Procedure 52(a) and 59(e) to amend the judgment to enter proposed findings of fact and conclusions of law that Elan engaged in inequitable conduct before the PTO such that its asserted patents are unenforceable. D.I. 634. This memorandum is offered in support of that motion pursuant to the briefing schedule entered by the Court. D.I. 632. Abraxis is concurrently filing proposed findings of fact and conclusions of law on the issue of inequitable conduct.

Abraxis relies on the following legal propositions in this memorandum:

(1) PTO Rule 56, 37 C.F.R. 1.56, imposes on those involved in patent prosecution a duty of candor and good faith, including a duty to disclose information material to patentability;

(2) A breach of this duty may constitute inequitable conduct, which can arise from an affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive or mislead the PTO.

The evidence at trial demonstrated clearly and convincingly that Elan's patent applicants[1] engaged in inequitable conduct by making false statements and failing to disclose material information with intent to deceive. Elan represented that the '363 patent's grinding technique was superior to the prior art because it resulted in anti-cancer formulations with acceptable levels of contamination, but it knew that contamination was plaguing its approach. Elan represented that its experiments supported the multitude of anti-cancer drug and surface modifier combinations claimed in the '363 patent, but in fact Elan experienced numerous failed experiments and recognized internally that its choice of surface modifiers potentially useful for purposes of the patent was severely limited. And Elan represented that its infusion rate discovery claimed in the '025 patent applied to all mammals, despite knowing it in fact applied only to dogs.

Unambiguous documentary evidence directly contradicted what Elan was representing to the PTO about its claimed inventions. While Drs. Gary and Elaine Liversidge disclaimed any intentional misconduct, they never denied knowledge of the documents. Nor did Elan bring its patent attorney, Mr. William Davis, to testify at trial and explain his conduct. In view of the high degree of materiality, the clear evidence that persons involved in the prosecution knew of the falsity of the representations, and the failure to adequately explain them, there can be no other conclusion but that the false representations occurred with the requisite level of intent. Balancing materiality and intent, the compelling evidence of both warrants a finding of inequitable conduct.

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[1] For concision, we refer to the persons subject to Rule 56's disclosure requirements as "Elan."

III. STATEMENT OF FACTS

The pertinent facts are discussed in the Argument sections, as appropriate.

IV. ABRAXIS IS ENTITLED TO JUDGMENT OF INEQUITABLE CONDUCT

A. Legal Standards

A patent is unenforceable for inequitable conduct if one with a duty of candor and good faith withholds or misrepresents information, or submits false information, that is material to the examination of the patent application, with an intent to deceive or mislead the patent office. *See, e.g., Monsanto Co. v. Bayer BioScience N.V.*, 514 F.3d 1229, 1233-34 (Fed. Cir. 2008).

Information or statements are material if they contradict or refute a position the applicant took when making an argument to the examiner that the invention was patentable or when opposing an argument by the examiner that the patent was not patentable. *Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359, 1364 (Fed. Cir. 2007) (quoting 37 C.F.R. § 1.56(b)). Information or statements are also material if they establish, alone or in combination with other information, that the invention sought to be patented more likely than not failed to satisfy one or more requirements for a patent. *Id.* (quoting 37 C.F.R. § 1.56(b)).

However, information "may be material even though it would not invalidate the patent." *McKesson Info. Solutions, Inc. v. Bridge Med., Inc.*, 487 F.3d 897, 913 (Fed. Cir. 2007). Indeed, materiality is "not limited to matters reflected in the claims of the patent." *Hoffman-LaRoche, Inc. v. Promega Corp.*, 323 F.3d 1354, 1367 (Fed. Cir. 2003). There need only be "a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent."

Cargill, 476 F.3d at 1364 (quoting 37 C.F.R. §1.56(a) (1991)). Information that is cumulative to other information before the examiner is not material. *Id.*

"[A]ffirmative misrepresentations ... in contrast to misleading omissions, are more likely to be regarded as material." *Hoffman-LaRoche*, 323 F.3d at 1367 (misrepresentations about purity of material); *see also Refac Int'l, Ltd. v. Lotus Dev. Corp.*, 81 F.3d 1576, 1583 (Fed.Cir. 1986) (submission of a false affidavit may be "inherently material"). It is well established that adverse testing data, as well as the applicant's interpretation of that data, are material if directly relevant to an important issue of patentability. *Cargill*, 476 F.3d at 1365-66.

Although not necessary to decide this case, the Federal Circuit has made clear that "[c]lose cases should be resolved by disclosure, not unilaterally by the applicant." *Cargill*, 476 F.3d at 1367 (quoting *LaBounty Mfg., Inc. v. U.S. Int'l Trade Comm'n*, 958 F.2d 1066, 1076 (Fed. Cir. 1992)).

"The intent element of inequitable conduct requires that '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.'" *Cargill*, 476 F.3d at 1364 (quoting *Impax Labs., Inc. v. Aventis Pharms., Inc.*, 468 F.3d 1366, 1374-75 (Fed. Cir. 2006)). Direct evidence of an intent to deceive or mislead the patent office is rarely available, and deceptive intent can be inferred from the surrounding circumstances and evidence. *Id.* "[I]n the absence of a credible explanation, intent to deceive is generally inferred from the facts and circumstances surrounding a knowing failure to disclose material information." *Ferring B.V. v. Barr Labs., Inc.*, 437 F.3d 1181, 1191 (Fed. Cir. 2006) (quoting *Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs. Ltd.*,

394 F.3d 1348, 1354 (Fed.Cir. 2005)). Indeed, even summary judgment of intent is appropriate if there has been a failure to supply highly material information and if "(1) the applicant knew of the information; (2) the applicant knew or should have known of the materiality of the information; and (3) the applicant has not provided a credible explanation for the withholding." *Id.*

Once it is demonstrated that material information was withheld from the PTO, the Court must balance materiality and intent. In other words, where the materiality of the withheld information is high, the requisite showing of intent is lower, and vice versa. *Cargill*, 476 F.3d at 1364.

Abraxis has the burden of proving inequitable conduct by clear and convincing evidence.

"When, as here, trial is held before the district court with an advisory jury, the court must find the facts specially just as it would when conducting a bench trial without an advisory jury." *Transmatic, Inc. v. Gulton Indus., Inc.*, 53 F.3d 1270, 1275 (Fed. Cir. 1995); Fed. R. Civ. P. 52(a); *see also* D.I. 592, Pretrial Hearing Tr. 124:19-125:25 (Court states that "[n]othing prevents me from rejecting [the jury's] finding" on inequitable conduct). "[F]indings of fact satisfy Rule 52(a) when they are sufficiently comprehensive and pertinent to the issue in dispute to form a basis for the district court's decision." *Transmatic, Inc.*, 53 F.3d at 1276. "A trial court has full discretion to accept or reject the findings of an advisory jury." *Hayes v. Community Gen. Osteopathic Hospital*, 940 F.2d 54, 57 (3d Cir. 1991).

B. Elan Intentionally Misrepresented and Withheld Material Information

1. Elan Intentionally Misrepresented that its Invention Resolved Issues of Contamination.

The '363 patent teaches making nanoparticles through wet milling techniques. The patent generally describes mixing a surface modifier with a crystalline medicament in the presence of a liquid and then milling until small crystalline particles of drug and surface modifier are obtained. JX081 at 5:43-6:14 (A485). Several different grinding media are referenced. *Id.* at 6:15-31.

Elan sought to distinguish its claimed invention by asserting that, unlike the prior art, the particles that resulted from the '363 patent's wet milling technique were free from unacceptable contamination. Elan represented to the PTO that "[t]he selection of material for the grinding media is not believed to be critical." JX081 at 6:21-23 (A485). Elan also represented that zirconium oxide and glass grinding media were believed to provide acceptable levels of contamination for drugs:

> [Z]irconium oxide, such as 95%ZrO stabilized with magnesia, zirconium silicate, and glass grinding media provide particles having levels of contamination which are believed to be acceptable for the preparation for pharmaceutical compositions.

JX081 at 6:23-27 (A485).

Zirconium oxide grinding media featured prominently in the remainder of the patent application. Indeed, in the '363 patent's working examples, zirconium oxide is the only grinding medium referenced. *See, e.g.*, JX081 at 8:27-28 (A486), 9:34-43, 9:50-58, 9:66-67, 10:3-4 (A487).

The '684 patent, incorporated by reference into the '363 patent (JX-081 at 1:8-11 (A483)), also represented that the disclosed methods, including the recommended

zirconium oxide grinding media, led to acceptable levels of contamination. Right in the "Summary of the Invention," Elan stated:

> It is an advantageous feature that a wide variety of surface modified drug nanoparticles *free of unacceptable contamination* can be prepared in accordance with this invention.

JX082 at 2:63-66 (emphasis added). In urging patentability, Elan emphasized freedom from contamination as an unexpected result: "it was surprising that stable drug particles of such a small effective average particle size *and free of unacceptable contamination* could be prepared by the method of this invention." *Id.* at 8:29-32 (emphasis added). It also touted lack of contamination as an "advantageous feature" of the patented invention. *Id.* at 2:62-66.

These representations were false. Far from being unimportant, Elan knew that the selection of grinding media was critical. Far from providing acceptable levels of contamination, Elan knew that its grinding methods resulted in unacceptable contamination. And far from being a suitable grinding media, Elan knew that zirconium and glass beads were unusable because they generated unsafe contamination levels.

Elan's internal reports before filing and during prosecution expressed alarm at the "undesirable" and "unacceptable" contamination that resulted from the wet milling techniques disclosed in the patent. In September 1990, Elan's toxicology department reported concerns with the use of zirconium grinding media because zirconium contamination could accumulate in the ovaries. DX243. Dr. Gary Liversidge was copied on this memorandum. Thus, Elan's statements in the '684 and '363 patent applications that the wet milling process resulted in "acceptable" contamination were directly contrary to what its toxicology department had told Dr. Liversidge before filing.

While the '363 application was being prosecuted, Elan continued to be plagued with high levels of contamination when using the patent's wet milling method. During a series of development retreats in 1993, Elan grappled with the problems of "unacceptable" and "undesirable" contamination using the zirconium and glass beads recommended in the '363 patent. DX607 at ELANP0085236; DX238 at ELANP0085240. Repeated internal reports of high levels of contamination were sent to Elan's inventors throughout the period when Elan was prosecuting the '363 patent. *Id.*; *see also* JX053 at ELANP0018457, 468, 478, 491; JX055 at ELANP0083635, 673,675, 685,687; DX243. Dr. Gary Liversidge was copied on a 1993 memorandum reporting that the toxicology department had recommended the non-use of zirconium grinding media due to concerns about unsafe contamination. JX054 at ELANP033711. The same memorandum also highlighted problems due to contamination from glass grinding media. *Id.*

During prosecution, Elan never corrected the false statements in its patent applications. To the contrary, it repeatedly distinguished its supposedly uncontaminated particles from the "unacceptable contamination" it said resulted from prior art methods such as dry milling, polymerization and solvent precipitation. *See, e.g.*, JX084 ('684 patent file history), Amendment dated November 18, 1991 at 5 ("[p]olymerization techniques require the arduous removal of contaminants, such as unreacted monomers and/or initiator, which can be toxic."); *id.* at 6 ("conventional dry milling techniques often cause unacceptable levels of dust"); JX039 at 0280 (A161) ('363 patent file history), Rule 132 Declaration of Gary G. Liversidge ¶ 4, dated September 8, 1993 ("Particles prepared by solvent precipitation techniques provide particles which are

contaminated with solvent[s]. Such solvents are often pharmaceutically unacceptable and can be difficult, if not impossible, to [ ] remove to pharmaceutically acceptable levels to be practical."); JX039 (A156-7) at 275-76, Amendment dated September 15, 1993.

That Elan's misrepresentations and omissions regarding contamination are material is incontrovertible. As the Court has confirmed in its claim construction, the claims require that the nanoparticles be "essentially free of solvent *and other contamina[tion]*." J.I. 4.2.3(l)(1) (emphasis added). Elan's internal documents demonstrate that the techniques disclosed in the '363 patent result in particles contaminated with unacceptable amounts of zirconium and other materials. Thus, Elan falsely represented that the disclosed methods enabled production of the claimed nanoparticles essentially free of contaminants. Courts have had no difficult finding materiality even where the misinformation was less directly tied to issues of patentability. *Purdue Pharma L.P. v Endo Pharm., Inc.,* 438 F.3d 1123, 1129-33 (Fed. Cir. 2006) (representation that inventors had "discovered" that drug had efficacy over four-fold dosage range rather than eight-fold range of prior art was material misrepresentation where based on "insight" rather than scientific evidence); *Cargill*, 476 F.3d at 1365-66 (failure to disclose adverse testing data material even if obtained under "unusual conditions"); *Hoffmann-La Roche, Inc. v. Promega Corp.*, 323 F.3d 1354, 1367-68 (Fed. Cir. 2003) (affirming finding of materiality for misrepresentations about "purity" even though purity not a limitation of the claims and statements about purity were not the principal focus of office action response); *Merck & Co., Inc. v. Danbury Pharmacal*, 873 F.2d 1418, 1421-22 (Fed. Cir. 1989) (misrepresentation about side effects material even where lack of side effects not a claim limitation). Moreover, the unacceptable

contamination that resulted from the patent's methods directly contradicted Elan's repeated statements that these methods resulted in particles free of unacceptable contamination, which it contrasted with the contaminated particles of the prior art.

The evidence of intent far exceeds clear and convincing. The undisputed evidence is that Elan desired the broadest possible patent coverage to prevent competition. DX244. Given the clear documentary record of contamination problems receiving significant attention from the inventors, including in multiple memoranda and even at development retreats, Elan could not and did not claim that its inventors were unaware of the contamination problems. Both Drs. Gary and Elaine Liversidge admitted knowing of internal reports regarding unacceptable levels of contamination using glass and zirconium oxide beads. Tr. 429:5-20, 431:7-9, 507:19-508:2; DX607 at ELANP0085236. Elan did not bring its patent attorney to explain the many false statements made in the patent application and file history. Nor did it offer any testimony from Dr. Elaine Liversidge to justify the false statements regarding supposedly "acceptable" levels of contamination.

Instead, Elan responded with testimony by Dr. Gary Liversidge, who claimed that the contamination problems did not need to be disclosed because they were (eventually) resolved by the development of new milling media. Tr. 507:19-508:6. However, that Elan had to develop new "polymeric" milling media not taught by the '363 patent only emphasizes the importance of the false representations that *the '363 patent* enabled skilled artisans at the time of filing to make anti-cancer nanoparticles free from excessive contamination. Moreover, the development of new grinding media does not even begin

to address the false statements that use of the zirconium and glass media taught in the patent were believed to result in acceptable contamination.

Elan's other excuses also don't square with the unchallenged documentary record. When confronted with a 1993 development retreat document reporting "undesirable contamination" with glass and zirconium beads, Dr. Gary Liversidge claimed he did not think it was necessary to report undesirable contamination to the PTO because of a supposed distinction between the "undesirable" contamination reported internally at Elan, and "unacceptable" contamination:

> I think there is a misunderstanding. Acceptable and undesirable have very different meanings in our field. Acceptable means the levels are acceptable to regulatory authorities and are safe. Undesirable, I want the purest product possible. And to me, any level of contamination, whether it's a regulatory acceptable, is undesirable.

Tr. 427:19-24; 428:11-15.

Dr. Liversidge admitted, however, that he understood that "unacceptable" contamination was a very serious concern:

> Q. Let me stop you there. Do you think it would have been important to tell the Patent Office that you had undesirable levels of contamination in cancer products that were going to be given to patients?
>
> A. *I think unacceptable is a far, far greater concern that undesirable.* (emphasis added).

Tr. 428:16-21.

Dr. Liversidge was then shown another internal report from a November 1993 Development Retreat, which confirmed that Elan considered the levels of contamination to be "unacceptable." DX607 at ELANP0085236; Tr. 429:5-20; 431:7-9. He admitted that this document accurately reflected Elan's internal conclusions.

Dr. Liversidge then changed his testimony, and claimed that one of the examples in the patent (Example 1) supposedly showed a method for cleaning the zirconium beads. Tr. 435:14-23. This excuse does not withstand even minimal scrutiny. The "pre-cleaning" procedure disclosed in the patent is, by its own terms, for *pre-cleaning* media before milling, not cleaning the contaminated particles. JX081 at 8:44-47 (A486) (zirconium oxide beads pre-cleaned with sulfuric acid and de-ionized water, and dried overnight). Elan could not point to anything in the '363 patent that would permit cleaning contaminated particles to acceptable levels. Moreover, Elan's internal documents showed that it continued to be plagued by contamination long after July 1992, by which time it had developed its method for pre-cleaning the zirconium beads. DX607; JX053; JX055; DX228; DX238; DX320. As Dr. Amiji explained in unchallenged testimony, the pre-cleaning could do nothing to address contamination, which resulted from fragments of beads chipping off during the milling process. Tr. 1431:13-1432:6.

Comparing what Elan told the PTO with what it knew internally, Elan should have written its patent application as follows:

The selection of grinding media is not believed to be critical.	Proper selection of grinding media is critical to the techniques disclosed in this application
Zirconium oxide and glass grinding media are believed to produce particles with acceptable levels of contamination using the methods taught by the '363 patent.	Zirconium oxide and glass are not acceptable as grinding media because they results in dangerous levels of contamination. We have not yet found an acceptable grinding medium and cannot yet formulate with reduced contamination or toxicity.

There is no question that the truth – that using the methods disclosed in the patent resulted in unacceptable contamination – would have been important to a reasonable examiner, i.e., was material. The claims are directed to particles "essentially free" of

contamination, as well as to methods of treatment that result in increased efficacy (claim 10) and reduced toxicity (claim 11). Indeed, Elan distinguished the prior art based on unacceptable levels of contamination. Had the truth been known, a reasonable examiner would certainly have considered this important to deciding whether Elan was entitled to such broad claims, or instead should be limited to something much narrower, such as its screening method.

It is equally clear that the intent element is met. Despite signing an inventor's oath attesting to the truth of the statements in the '363 patent application, Elan's inventors falsely stated that the use of the zirconium and glass beads taught in the application led to acceptable levels of contamination, while reporting internally the opposite. No Elan inventor even attempted to contradict the unambiguous documentary record showing that they were well aware of the extent of the contamination problem. The only explanations offered – by Dr. Gary Liversidge – do not withstand scrutiny. Based on Elan's admitted knowledge of unacceptable contamination, and the lack of any reasonable explanation for its false statements, the only reasonable inference is that it made intentional misrepresentations in order to obtain broad patent claims to block competition.

2. Elan Misrepresented and Withheld Material Information Regarding Drug/Surface Modifier Combinations.

Elan also made intentional material misrepresentations and omissions regarding the surface modifier/drug combinations that were supposedly enabled by the wet milling and screening method taught by the patent. The '363 patent claims crystalline nanoparticles representing a wide variety of drug/surface modifier combinations, and asserts that these particles can be used in injectable anti-cancer formulations to improve efficacy or reduce toxicity of the anti-cancer drug.

Elan's claims are sweeping in breadth. For example, claims 10 and 11 claim the use of a stunningly broad range of drug and surface modifier combinations to make crystalline nanoparticles with improved efficacy or reduced toxicity. To persuade the PTO to issue these broad claims, Elan made misrepresentations about the scope of its alleged invention, and provided the PTO with favorable test results while concealing its failures.

During prosecution of the '363 patent, the PTO rejected the broad claims sought by Elan. For example, the examiner stated that the application supported only limited claims using several specific surface modifiers exemplified. JX039 at 0348-49 (A164-5). In response, Elan represented that the patent taught that a "wide variety of surface modifiers are useful":

> Applicants' specification teaches that a wide variety of surface modifiers are useful. Indeed, Applicants have shown that the invention can be practiced with a wide variety of surface modifiers. In addition to the numerous surface modifiers exemplified in Applicants' specification and working examples, additional surface modifiers tested in varying amounts have been demonstrated to be useful.

JX039 at 428-29 (A168-9).

Indeed, Elan represented that the specification "readily enables" persons skilled in the art to select surface modifiers for any medicament. *Id.* Elan summarized:

> The evidence demonstrates conclusively that the instant invention can be practiced with a wide variety of surface modifiers. Thus, one skilled in the art is readily able to practice the claimed invention .... (*Id.*)

At the same time Elan was telling the PTO that the evidence "*conclusively*" established that skilled artisans could practice the claimed invention with a "wide variety" of surface modifiers, internally it was bemoaning its failures with the "wide

variety" of surface modifiers claimed. For example, during development retreats in 1993, Elan acknowledged that only a small number of surface modifiers could obtain the requisite size, stability, efficacy and toxicity. DX238 at ELANP0085240; DX607 at ELANP0085230. These are, of course, precisely the features Elan claimed to have invented in the '363 patent. By 1994, Elan still had not identified a surfactant of choice for use in parenteral (IV) products. DX190. Thus, while Elan was able to stabilize some drug/surface modifiers combinations, in many instances the combinations failed and Elan was left without useful injectable anti-cancer formulations.

While reporting only its successful experiments, Elan failed to inform the PTO about its numerous failures. These were not merely a normal part of the experimental process, as Elan claimed. Rather, the evidence demonstrated that the wet milling process taught by the '363 patent simply did not work for many surface modifier/drug combinations. Thus, just as the PTO initially stated in its office action, Elan's invention was much narrower than it had claimed.

The evidence regarding piposulfan, which is described in four "examples" in the '363 patent (JX081 at 8:20-9:45 (A486-7)), is illustrative. Although the patent claims *all* combinations of surface modifiers with the crystalline drugs specified, despite 20 years of effort, the only way Elan could stabilize piposulfan with any degree of consistency was to use specific combinations of two surfactants, Tween and Span. JX055 at ELANP0083673 (despite extensive milling studies "a viable back-up stabilizer has not been identified"). These combinations were of questionable value since these were not surfactants that had been proven usable in humans in injectable form. DX286; *see also* JX055.

Elan disclosed only the formulations of piposulfan that worked, while concealing its failures. For example, a memorandum summarizing the exact same set of experiments that underlie examples 1 through 4 in the patent states that many combinations "failed to reduce the average particle size." JX081; DX193; Tr. 1404:1-1405:25. Elan reported in the patent application the examples that reduced particle size, but failed to disclose the other combinations from the same memorandum that failed. Surface modifiers listed as "particularly preferred" in the patent actually resulted in unacceptable piposulfan formulations. *Id.* Indeed, even the slightest variations of the patent examples, such as "[c]ombinations of Tween 20/Span 20 and Tween 40/Span 40[,] failed." DX193. Adverse "test[ing] data that is directly related to an important issue of patentability," such as enablement, is "material information." *Cargill*, 476 F.3d at 1366. Elan's selective disclosure of only favorable results from the exact same set of experiments given to the patent office is classic inequitable conduct.

Elan claims that its misstatements should be forgiven because it stated in the '684 patent that "not every combination of surface modifier and drug substance provides the desired results" (JX082 at 7:21-23) and that the '684 patent was incorporated by reference into the '363 patent. Elan's later statements that "a wide variety of surface modifiers are useful" and that "additional surface modifiers tested in varying amounts" were useful, were false and misleading given the extent of failures and the resulting conclusion that there were only a small number of surface modifiers that were could be used in the anticancer particles and methods of treatment claimed in the '363 patent.

Again comparing what Elan told the PTO with what it said internally shows the following:

"The evidence demonstrates conclusively that the instant invention can be practiced with a wide variety of surface modifiers. Thus, one skilled in the art is readily able to practice the claimed invention …."	The evidence demonstrates that the instant invention can be practiced, if at all, only with a limited number of surface modifiers. Whether one skilled in the art will be able to practice the claimed invention has not been established.

The truth – that the surface modifiers/drug combinations were much more limited than Elan represented – was certainly material. The examiner rejected the claims as too broad precisely on this ground. A reasonable examiner informed of the truth is likely to have limited the claims to drug/surface modifier combinations that could be developed using the disclosed methods, rather than the millions of possible combinations, many of which could not be made using the techniques disclosed in the patent.

As for the intent element, Elan never called its patent attorney to explain why the false statements were made, and why failures were not reported in the '363 application or during prosecution. Nor did Drs. Elaine or Gary Liversidge offer any reasonable explanation. In the absence of any credible explanation, the only reasonable inference is that Elan's false statements and omissions regarding the scope of the alleged invention were made with the intent to deceive the examiner, as part of Elan's business plan to obtain broad claims to block competition. DX244; *Ferring B.V.*, 437 F.3d at 1191 (intent to deceive generally inferred from knowing failure to disclose material information absent credible explanation).

3. Elan Misrepresented and Withheld Material Information Regarding the Scope of the '025 Patent.

The '025 patent claims a monopoly on the intravenous administration of crystalline nanoparticles, in all mammals, below a specified infusion rate of 10 mg/min, so long as that administration does not result in adverse hemodynamic effects.

In support of these broad claims, Elan had data from only one specific experiment injecting polystyrene beads into dogs. Elan's claims were directed to infusions to mammals generally, and the specification stated that in addition to dogs, there existed other "sensitive" species, including humans. DX015 at 2:66-67. Moreover, to overcome an obviousness rejection during prosecution, Elan alleged that the claimed infusion rate (10 mg/min) was a "**critical** parameter" to avoiding hemodynamic effects. JX040 at 0058 (emphasis in original).

Elan's internal documents tell a starkly different tale. Document after document introduced at trial demonstrates that from the very beginning, Elan believed that the effect observed in dogs occurred only in dogs, and hence was "species specific." Elan based this belief in part on tests that were conducted in other species, including rats, rabbits and monkeys. DX248; DX291; DX259; JX087.

Elan's excuse for failing to disclose its understanding that the effect was limited to dogs is that the testing on other animals was not conclusive. Tr. 496:15-499:7. This is a non-sequitur. Elan's internal documents consistently demonstrate that Elan itself believed that the effect occurred only in dogs. DX248; DX291; DX259; DX297; DX301. Elan's own understanding of these experiments at the time is that the effect reported in the '025 patent was limited to dogs. Yet Elan represented to the PTO that humans were also "sensitive" species and directed its claims to mammals generally.

Again, comparing what Elan told the PTO with what it would have said had it accurately reported its own conclusions from the results of its experiments on hemodynamic effects:

The claimed infusion rate (10 mg/min) is "a critical parameter."	The claimed 10 mg/min infusion rate is not believed to be relevant to species other than

	dogs.
"As used herein, mammals preferably means a dog and other sensitive species including human species"	The effects observed are believed to be specific to dogs; in other words, dogs are the only known sensitive species.

There is no question that Elan's interpretation of its own experiments was material. *Cargill*, 476 F.3d at 1365-67 (interpretation of tests can be material). It showed that, at best, the evidence supported a claim that hemodynamic effects existed in dogs, not in other mammals. This evidence goes to the very heart of the claims – the extension of the patent from dogs to use of intravenous drugs in humans and all other mammals. Armed with the knowledge that the effect was believed by Elan to be species-specific, a reasonable examiner certainly would, at a minimum, have had serious reservations about extending the claims to other mammals. Moreover, as discussed above, the examiner rejected the claims on the grounds of obviousness. JX040 at 48-49. And, indeed, as was clear at trial, it was well known to reduce rates of infusion to avoid deleterious side effects from infusion of anti-cancer drugs; in fact this was routinely done for drugs such as Taxol. Tr. 445:17-446:12. Elan's statement to the examiner to overcome the rejection that the claimed infusion rate (10 mg/min) was a "critical parameter" to avoiding hemodynamic effects was thus the key to its obtaining the patent (JX040 at 0058). The truth – that this infusion rate was relevant, if at all, only to dogs and not to other mammals, was inconsistent with Elan's statement to the examiner and therefore material.

The evidence of intent is also overwhelming. As the documents at trial made clear, the issue of hemodynamic effects garnered significant attention from the patent's inventors as well as management, as evidenced by discussion of the topic with Elan's Board of Scientific Medical Advisors (BOSMA). DX248. Moreover, from the outset

Elan was keenly focused on the species-specific nature of the effect, as reflected in multiple internal documents on the subject. *See, e.g.*, DX291, DX259; JX087. Elan's failure to report the documented conclusions of its own inventors that the effects observed were specific to dogs, while seeking claims to humans and other mammals cannot reasonably be believed to be the result of an oversight.

V. CONCLUSION

The evidence at trial showed that Elan, plagued with contamination problems, blithely told the PTO just the opposite: that nanoparticles made using the methods disclosed in the '363 patent were free from unacceptable contamination. To obtain broad patent coverage, it also withheld failed experiments and falsely represented that the evidence "conclusively" demonstrated that the patent's methods worked with a wide variety of surface modifiers. The pattern was similar for the '025 patent. To obtain claims covering infusion of certain nanoparticles to *any* mammal, so long as the infusion rate is below 10 mg/min, Elan falsely represented that humans were "sensitive" species and that 10 mg/min was a "critical" parameter, while failing to disclose its internal belief that the effects reported in the patent were species-specific and occurred only in dogs.

These facts present clear and convincing evidence that the '363 and '025 patents are unenforceable for inequitable conduct. Abraxis requests that the Court so find, and that it enter the proposed findings of fact and conclusions of law that are filed herewith.

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CERTIFICATE OF SERVICE

I, Karen E. Keller, Esquire, hereby certify that on July 14, 2008, I caused to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF, which will send notification that such filing is available for viewing and downloading to the following counsel of record:

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