IN THE 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

PLAINTIFF ELAN PHARMA INTERNATIONAL LIMITED'S ANSWERING BRIEF IN OPPOSITION TO ABRAXIS'S 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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I. INTRODUCTION

Abraxis fought to submit the ultimate question of inequitable conduct to the jury. At the May 15, 2008 pre-trial hearing, the Court granted Abraxis's request to submit this question to the jury over Elan's objections. Although Abraxis first proposed instructions stating that the jury's findings on inequitable conduct would be "advisory," Abraxis modified those jury instructions and deleted the "advisory" language. Now that the jury has returned findings in favor of Elan, Abraxis refuses to accept those findings. Abraxis is precluded from seeking to set aside the jury's findings on inequitable conduct due to estoppel and because it waived its right. Elan requests that the Court deny Abraxis's motion and accept the jury's findings that the '363 and '025 patents are not unenforceable for inequitable conduct. However, if the Court chooses to enter findings of fact and conclusions of law on this issue, Elan urges it to adopt the proposed findings of fact and conclusions of law submitted herewith.

II. NATURE AND STAGE OF PROCEEDINGS

Following an eight day trial, the jury returned a verdict in Elan's favor, finding that Abraxis infringed Elan's '363 patent, and also finding that both the '363 and '025 patents are not invalid or unenforceable due to inequitable conduct. The Court entered judgment on June 16, 2008.

III. SUMMARY OF ARGUMENT

Abraxis had the burden to show by clear and convincing evidence that Elan withheld material information from the United States Patent and Trademark Office ("PTO") during prosecution of the '363 and '025 patents, with intent to deceive the PTO. Abraxis did not meet its burden. Through its motion, Abraxis seeks to retry its defense with evidence not presented

during trial[1] and new allegations concerning Elan's conduct. Even considering Abraxis's new allegations and evidence, Abraxis still cannot meet its burden of proof.

First, Abraxis has not proven that the inventors of the '363 and '025 patents or their attorneys made false statements or withheld *material* information from the PTO. Second, Abraxis has no evidence that the inventors or their attorneys withheld material information with the intent to deceive the PTO. The patents' co-inventors, Drs. Gary and Elaine Liversidge, testified on facts relating to inequitable conduct. The jury heard the evidence, weighed the credibility of the witnesses, and found in favor of Elan. The jury's findings were correct—Elan did not engage in inequitable conduct during the patents' prosecution. The Court should not disturb these findings.

IV. FACTUAL BACKGROUND

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

V. LEGAL STANDARD

"A party seeking to have a patent declared unenforceable has a heavy burden to meet." *Hoffman-La Roche, Inc. v. Promega Corp.*, 323 F.3d 1354 1359 (Fed. Cir. 2003). "Inequitable conduct entails a two-step analysis: first, a determination of whether the withheld reference meets a threshold level of materiality and intent to mislead, and second, a weighing of the materiality and intent in light of all of the circumstances to determine whether the applicant's conduct is so culpable that the patent should be unenforceable." *Juicy Whip, Inc. v. Orange Bang, Inc.*, 292 F.3d 728, 744 (Fed. Cir. 2002). Each of the elements "must be shown by clear and convincing evidence." *Hoffman-La Roche*, 323 F.3d at 1359.

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[1] For example, in support of its inequitable conduct claim for the '363 Patent, Abraxis now cites to exhibits DX228 and DX320, which were not presented to the jury during trial, and for its inequitable conduct claim for the '025 allegations it cites to exhibits DX254 and JX087, which also were not presented to the jury at trail.

"Materiality is defined by what a reasonable examiner would have considered important in deciding whether to allow a patent application." *Innogenetics v. Abbott Labs.*, 512 F.3d 1363, 1378 (Fed. Cir. 2008). "Materiality does not presume intent, which is a separate and essential component of inequitable conduct." *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1351 (Fed. Cir. 2002). "Intent is a subjective inquiry into whether the inventor knew the information was material and chose not to disclose it." *Liquid Dynamics Corp. v. Vaughan Co.*, 449 F.3d 1209, 1227 (Fed. Cir. 2006). "[S]imple negligence, oversight, or an erroneous judgment made in good faith is not sufficient to satisfy the intent element." *Hycor Corp. v. Schlueter Co.*, 740 F.2d 1529, 1540 (Fed. Cir. 1984) "[T]he 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." *Kingsdown Med. Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 876 (Fed. Cir. 1988).

VI. ARGUMENT

A. Abraxis is Precluded from Challenging the Jury's Findings on Inequitable Conduct

In the preliminary pre-trial order, Abraxis sought to submit inequitable conduct to the jury over Elan's objections. During the pre-trial conference, the Court overruled Elan's objections and agreed to submit this issue to the jury. Abraxis never asked the Court for advisory jury findings. (*See* Pre-trial Hearing Tr. at 124:19-125:25.)

Abraxis drafted the proposed verdict form. That form requested the jury decide the ultimate question of inequitable conduct, without calling for subsidiary findings on whether material information was withheld from the PTO, nor did it ask the jury to make findings on whether patent applicants or their agents and representatives acted with an intent to deceive the PTO—prerequisites of Abraxis's defense. For both the '363 and '025 patents, Abraxis's form

simply asked if "Abraxis has proven by clear and convincing evidence, that [the patent] is unenforceable due to inequitable conduct." (Verdict Form at 4 (D.I. 613).) This form of submission contrasts with, *e.g.*, the AIPLA model instructions, which provide that "[t]he court should consider whether to charge the jury in detail, to charge the jury solely on materiality, or to retain the issue solely for itself, and should consider using a verdict form that breaks out materiality, intent, and/or balancing." Am. Intellectual Property Law Ass'n, *Model Patent Jury Instructions*, at 45 (2007).

The jury instructions Abraxis submitted in the preliminary pre-trial order expressly indicated that the jury's findings were advisory:

> Although the question of whether there has been inequitable conduct is one that I will decide, I will ask for your findings so that I can consider them in making my decision. You should make determinations on this issue as you would for any other issue in this case because I will consider them seriously in making my decision.

(Ex. 12 to Proposed Joint Pre-trial Order (Parties Proposed Jury Instructions) at 139 (D.I. 509).)[2] However, on June 12, 2008, the day before the instructions were read to the jury, Abraxis filed a revised version. The "advisory" language was deleted. (*See* Parties' Proposed General Jury Instructions, at 53 (D.I. 608).) This instruction, without the advisory language, was ultimately read to the jury. (Tr. 1678:23-1681:23.) Abraxis's deletion was not accidental. Abraxis initially proposed similar advisory language in its jury instruction for unclean hands; that language was not deleted from the unclean hands instructions Abraxis later filed.[3] In contrast, Abraxis

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[2] This language is the suggested language from the Federal Circuit Bar Ass'n, *Model Patent Jury Instructions* (Jan. 12, 2008).

[3] *Compare* Ex. 12 to Proposed Joint Pre-trial Order, at 140 (D.I. 509) ("Although the question of whether Elan's claims are barred by unclean hands is one that I will decide . . . ."), *with* Parties' Proposed General Jury Instructions, at 54 (D.I. 608) ("Although the question of whether Elan's claims are barred by unclean hands is one that I will decide . . . .").

recognized and intended that the ultimate question of inequitable conduct be submitted to the jury, and the jury answered that question in Elan's favor.

Abraxis must accept the jury's findings as final, because Abraxis requested them. Abraxis created a judicial estoppel by urging the Court to adopt a ruling and then turning around and challenging that ruling. *See Data Gen. Corp. v. Johnson*, 78 F.3d 1556, 1565 (Fed. Cir. 1996) ("The doctrine of judicial estoppel is that where a party successfully urges a particular position in a legal proceeding, it is estopped from taking a contrary position in a subsequent proceeding where its interests have changed."). As explained above, Abraxis took action to force inequitable conduct before the jury with instructions that removed any reference to an advisory verdict. Judicial estoppel bars a party from "creating" what it later argues is an error.

The Federal Circuit has also held that a party's failure to object to the submission of the ultimate question of inequitable conduct to the jury waives its ability to challenge the jury instruction. *Modine Mfg. Co. v. Allen Group*, 917 F.2d 538, 542 (Fed. Cir. 1990). If mere failure to object affects a waiver, then affirmative advocacy of the instruction (*i.e.*, Abraxis's conduct) must affect a waiver, too.

B. Abraxis Failed to Prove Elan Engaged in Inequitable Conduct During the Prosecution of the '363 Patent.

1. Abraxis Failed to Prove Material Information Was Withheld or that any Intentional Misrepresentations Regarding Contamination Were Made to the PTO

(a) Abraxis Introduced No Evidence at Trial that the "Particles" of the '363 Patent Were Contaminated or that Statements Made by Applicants to the PTO were False

Abraxis is deliberately confusing Elan's product development history with the specific advantages identified in the '363 patent. Specifically, Abraxis is attempting to prove inequitable conduct by contrasting two distinct categories of statements—(1) those relating to whether

certain grinding media are believed to provide particles having acceptable levels of contamination for preparation of pharmaceutical compositions, and (2) those relating to the advantages of the claimed particles of the '363 patent over particles made by, *e.g.*, solvent precipitation techniques. None of Abraxis's evidence proves that anything said to the PTO was false.

i. ***Statements About Grinding Media***

The '363 patent proposes that "zirconium 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 6:23-27.) Inventor Gary Liversidge testified that in drug development, "[a]cceptable means the [contamination] levels are acceptable to regulatory authorities and are safe." (Tr. 427:21-22.) He also testified that the '684 patent (parent to the '363 patent) disclosed levels of contamination that are all within regulatory limits. (Tr. 425:5-10; JX082 10:40-11:37 (examples 4 and 5).) Contrary to Abraxis's assertion that the particles formulated by the teaching of the '363 patent contain unacceptable levels of contamination, Drs. Gary and Elaine Liversidge both testified that FDA has never reported a contamination problem with any product formulated by the milling technology taught by the '363 patent. (Tr. 303:12-304:2; Tr. 535:5-11.) The jury weighed the credibility of that testimony and, apparently, accepted it.

Against this unambiguous and unexculpatory inventor testimony, Abraxis offers DX243, a 1990 memo authored by one Raymond Fabian, opining that "zirconium oxide/zirconium silicate are [not] acceptable [media] because there is one report which suggests that zirconium accumulates in certain organs, such as the ovaries." (DX243; Tr. 424:13-22.) Mr. Fabian is not an inventor. Moreover, Mr. Fabian also wrote (in a portion of the exhibit which Abraxis ignores) that "[t]he bottom line is that I can't tell you that a particular grinding media is acceptable by

scanning the list of chemicals that make up the residue. We need to know how much is in the final product . . . ." *Id.*

Inventor Dr. Gary Liversidge did not think Mr. Fabian had raised a credible issue of contamination. In a memo he authored the next day, Dr. Liversidge wrote:

> Ray Fabian has conducted a literature search that had not uncovered any reports on toxicity following oral administration of zirconium oxide. . . . There was one abstract in the literature on oral administration of ZrO that gave no data only qualitative statements indicating that Zr was poorly absorbed but accumulated in the ovaries, lung and bone of rats following repeated oral administration. *In contrast to the abstract on accumulation of Zr in organs of the rat, ZrO particles are used in humans as a bone cement with no reports of detrimental toxicological consequences.*

(DX244, at ELANP0092628 (emphasis added).)

Dr. Liversidge also testified that zirconium was not a heavy metal listed in the U.S. Pharmacopia ("USP"), and therefore, the heavy metal contamination limits set by the USP do not apply to zirconium. (Tr. 431:19-22; 433:10-15.) None of the evidence relied upon by Abraxis at trial (or now in its brief) proves that the '363 patent's claim that "zirconium 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" is false. Dr. Liversidge certainly thought it was true; and it is his belief, not Mr. Fabian's, that is relevant to Abraxis's defense.

ii. ***Statements About Prior Art***

Abraxis next proposes that Elan's inventors falsely represented that "unlike the prior art, the particles that resulted from the '363 patent's net milling technique were free from unacceptable contamination." As with the contamination issue address above, the jury heard (and apparently credited) testimony that this statement is true.

Dr. Liversidge testified that "U.S. Patent No. 5,049,322 discloses a solvent precipitation technique for preparing nanocapsules," and that "[p]articles prepared by solvent precipitation techniques provide *particles which are contaminated with solvent*." (JX039 at 280 (emphasis added).) He also noted that "[s]uch solvents are often pharmaceutically unacceptable and can be difficult, if not impossible, to adequately remove to pharmaceutically acceptable levels to be practical." (*Id.*) That testimony is consistent with what Elan's patent counsel, Mr. William Davis, represented to the PTO: "solvent precipitation techniques such as [that] described in U.S. Patent No. 4,826,689 for preparing particles tend to provide *solvent contaminated particles*," which are "often toxic and can be very difficult, if not impossible, to adequately remove to pharmaceutically acceptable levels for diagnostic imaging." (*Id.* at 0576 (emphasis added).)

Abraxis has not proffered a scintilla of evidence that would suggest that any of these representations were either false or relevant to patentability. Abraxis's evidence is silent on solvent contamination in general; it certainly does not suggest a solvent contamination problem with particles. Abraxis did not even question Dr. Gary Liversidge about the statements he made to the PTO during prosecution of the '363 patent or its parent, the '684 patent. Nor did Abraxis present testimony from Mr. Davis, despite designating portions of his deposition testimony in the pre-trial order. Having failed with the jury, Abraxis wants this Court to review this evidence, which it did not bother to offer at trial, to determine if either Dr. Liversidge (who testified) or Mr. Davis lied to the PTO. The Court should decline Abraxis's invitation.

(b) Abraxis Failed to Prove that Material Information Was Withheld from the PTO During Prosecution of the '363 Patent

Contrary to Abraxis's assertions, the documents on which Abraxis relies was withheld from the PTO are far from "unambiguous." Rather than submit hard data from laboratory notebooks and experiments from those with a duty of candor to try to meet its burden, Abraxis

relies on general, ambiguous statements from presentations and memoranda authorized by others. These exhibits are not relevant to the '363 patent invention or its patentability, and do not meet Abraxis's clear and convincing evidentiary burden.[4]

The claims of the '363 patent has been construed by this Court to cover particles that are essentially free of solvent and other contaminants. (Markman Order, at 1 (D.I. 217).) The patent describes stabilized zirconium oxide media believed to provide particles free of unacceptable contamination and proposes that contamination by media erosion is optimized by controlling the viscosity of the premix. (JX081 6:8-14.) The '363 patent also teaches processes of preconditioning the milling media (JX081 8:44-47), which Dr. Liversidge testified reduces contamination (Tr. 435:20-436:4), and milling process durations of less than one day for media milling and up to five days or longer for ball milling. (JX081 6:32-40.)

Abraxis has not shown that any of the "contaminated" materials described in its exhibits were prepared by these methods. Exhibit JX053 at ELANP0018468, which Abraxis fancies as a smoking gun, provides no information on the milling process media or the premix viscosity, on whether the media were pre-cleaned as taught in the '363 patent, or on the duration of milling. This exhibit actually corroborates Dr. Liversidge's testimony that pre-cleaning the media as

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[4] None of the cases Abraxis cites found materiality based on vague statements in presentations and memoranda. Rather, materiality was found when the infringor proved the applicant either withheld data conflicting with its representations to the PTO or failed to actually generate the data presented to the PTO. *See Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359, 1364 (Fed. Cir. 2007) (finding materiality for a report containing test data and additional oven test data that directly contradicted representations to the PTO); *Purdue Pharma L.P. v. Endo Pharm., Inc.*, 438 F.3d 1123, 1129-33 (Fed. Cir. 2006) (finding materiality based on repeated representations about efficacy in humans made to the PTO when it was undisputed that applicant did not have the clinical data in humans to support the claims); *Hoffman-La Roche, Inc. v. Promega Corp.*, 323 F.3d 1354, (Fed. Cir. 2003) (finding materiality based on false statements in a declaration in support of an example when the evidence demonstrated that the experiment outlined in the example had never actually been conducted; *Merck & Co. v. Danbury Pharmacal, Inc.*, 873 F.2d 1418 (Fed. Cir. 1989) (finding materiality based on representations to the PTO that were directly contradicted by applicant's submission to FDA and by applicant's own data).

taught by the '363 patent reduces contamination! (*See id.* at ELANP0018478 & 490 ("Reducing Contamination Optimize media preconditioning.").)

Exhibit JX054 does not support Abraxis's allegation that material information was withheld from the PTO, either. Nowhere in this memo are zirconium oxide beads or the stabilized zirconium oxide media of the sort taught in the '363 patent. Further, the memo notes that glass media are acceptable, with the exception of large volume oral suspensions, which are not anticancer drugs or relevant to the '363 patent.

Even further removed from relevance to the '363 patent are Exhibits DX238 and DX607, which are general presentations on technology development, the origin and dissemination of which were not established at trial (or in Abraxis's motion). Neither exhibit mentions contaminated *particles* (or contaminated anticancer particles—embodiments of the '363 patent). Both exhibits are silent as to whether contamination resulted after applying the '363 patent's teachings (i.e., whether the premix had the viscosity taught by the '363 patent to reduce contamination or whether the media were pre-cleaned). The exhibits do not even mention whether the grinding media was 95% ZrO stabilized by magnesia or zirconium silicate, as disclosed in the '363 patent. Nor do they indicate the duration of the milling time, *i.e.*, "less than 1 day" as taught by the '363 patent for media milling. (JX081 6:32-40.)

Finally, Abraxis relies upon a presentation dated April 13, 1993, Exhibit JX055, as proof that Elan's milling with zirconium oxide resulted in unacceptable contamination levels exceeding 10 parts per million ("ppm").[5] However, these data actually prove that zirconium silicate media (taught by the '363 patent) yield low levels of contamination (JX055 ELANP0083675 (reporting contamination of 2.8 and 3.8 ppm for zirconium silicate)), much

[5] This exhibit is also silent as to whether contamination resulted after applying the '363 patent's teachings.

lower than Elan's "internal goal" of 10 ppm, as Dr. Liversidge testified. (Tr. 432:5-7; 433:12-15.)

(c) Abraxis's New Evidence Regarding Contamination from "Yttria Beads" Is Not Relevant or Material to the '363 Patent

To bolster a case it did not prove at trial, Abraxis offers more evidence, Exhibits DX228 and DX320, that was not before the jury. After reading these exhibits, Elan understands why Abraxis did not bother using them at trial. Both are dated after the '363 patent issued; neither can represent material information withheld from the patent office. Thus, the inquiry should end here.

Also, both exhibits refer to milling with "yttria beads," not zirconium beads as Abraxis alleges in its brief. The '363 patent does not propose "yttria beads" as a milling media. Although the '363 Patent discloses zirconium oxide stabilized by yttrium (JX081 6:27-31), Abraxis cannot credibly claim that the yttria beads of these exhibits are the same as zirconium oxide stabilized by yttrium, as taught in the patent. Nor do these documents indicate whether the yttria beads were pre-cleaned before milling or whether the particles are contaminated.[6]

2. Abraxis Failed to Prove By Clear and Convincing Evidence that the Inventors (or the Patent Attorney) Had the Requisite Intent to Deceive the PTO

Abraxis offered no evidence that the applicants intended to make misrepresentations to the PTO or to withhold material information from the PTO. Abraxis presented no evidence that anyone with a duty of candor believed that zirconium oxide, such as 95% zirconium oxide stabilized by magnesia, zirconium silicate and glass grinding media provided particles having unacceptable levels of contamination. Abraxis would basically have this Court ignore (in a way

[6] DX320 analyzes the final formation, not the particles, and the stated purpose of the experiment in DX228 is to "reduce the contamination level in plantery milled formulations" through filtration, centrifugation, and dialysis.

the jury likely did not) Dr. Gary Liversidge's testimony explaining why the contamination in the milling dispersion was not "unacceptable." Dr. Liversidge explained that he did not believe the contamination issue was material because it would not keep a product from going to market. (Tr. 428:22-429:2.) He explained that "unacceptable" is an issue for FDA drug approval; and that contamination has never been an issue with regard to FDA approval. (Tr. 427:19-24.) Dr. Gary Liversidge testified that the '363 patent discloses a method of cleaning the milling media to reduce contamination and that he did not believe contamination was an issue once that procedure was used. (Tr. 435:17-436:4; Tr. 463:18-464:2.) That testimony is corroborated by both the data in the '363 patent specification and by DX244.

Contrary to proving intent, the evidence and testimony provide clear and convincing proof that Elan did not intentionally withhold information from the PTO. Finally, both Gary and Elaine Liversidge testified that they did not withhold any material information with an intent to deceive the PTO. (Tr. 467:10-16; 499:14-18.) The jury credited the Liversidges' testimony because it was right and corroborated by other evidence. While Abraxis offered the opinions of Dr. Mansoor Amiji to dispute these points, it was within the jury's province to discount or ignore Dr. Amiji's opinions.

Apparently recognizing they have no proof of Drs. Gary and Elaine Liversidge's intent to deceive the PTO, Abraxis "empty chairs" Elan's patent attorney, William Davis. Abraxis seems to forget which party had the burden of proving intent by clear and convincing evidence. Abraxis did not ask a single question at trial about Mr. Davis's prosecution of the '363 patent, nor did Abraxis introduce the testimony Abraxis designated from Mr. Davis's deposition. Perhaps it is Abraxis that should "explain" why this Court should allow it, on post-trial motions, a second chance of proving its affirmative defenses with evidence it did not use at trial.

3. Abraxis Failed to Prove that Elan Withheld Material Information from the PTO Regarding the Screening Process Taught in the '363 Patent

Abraxis accuses Elan's inventors of reporting successful combinations of drug and surface modifiers to the PTO and withholding failures. Only a cursory review of the '363 patent contradicts Abraxis's assertions. The '363 patent incorporates the disclosure of the '684 patent, its parent. The '684 patent expressly states that "[a]s indicated by the following examples, not every combination of surface modifier and drug substance provides the desired results." (JX082 7:21-23.) Further, examples 13 and 22 of the '363 patent disclose "failures" resulting from flocculation and aggregates. (JX081 12:67, 13:58.)

To make a case for inequitable conduct where none exists, Abraxis ignores these disclosures and cites screening tests conducted to identify compatible surface modifiers for particular drugs. The very essence of the '363 patent is stable particles. However, as the inventor recognized and taught, not every surface modifier will stabilize every drug. Thus, the '363 patent teaches a "simple screening process" to enable one of ordinary skill in the art to identify compatible surface modifiers for a particular drugs. (JX081 7:5-8.) Dr. Mark Manning testified that the disclosed screening process allows one skilled in the art to determine whether a surface modifier can keep particles from associating. (Tr. 1586:25-1588:4.)

Elan truthfully represented that "a wide variety of surface modifiers are useful." The '363 patent disclose 23 examples of various classes of anticancer drugs using a variety of different surface modifiers. (JX081 8:20-13:68.) The '684 patent, which is incorporated by reference, discloses an additional 14 examples. (JX082 8:36-13:52.) The Rule 132 declaration in the '684 patent's file history discloses an additional 35 examples of successful nanoparticles with various surface modifiers. (DX016 000134-140.)

The success of the '363 patent's teachings is undisputed. Dr. Gary Liversidge testified that every anticancer drug that Elan attempted to formulate as nanoparticles was so formulated. (Tr. 230:14-24.) Dr. Elaine Liversidge testified that she uses the disclosed screening process on approximately ten new chemical entities that Elan receives each week from various clients. (Tr. 489:3-11.) She also testified that Elan has had a 98% success rate in finding compatible surface modifiers for drug compounds. (Tr. 491:1-5.)

Even Elan's "failure" with piposulfan, the only example Abraxis can muster, is not; Abraxis mischaracterizes the evidence. Their contention that Elan could only stabilize piposulfan with specific combinations of two surfactants, Tween and Span, "despite 20 years of effort" confuses "failures" and "adverse testing" with screens utilized to identify compatible surface modifier-drug combinations for particulate drug formulations. Exhibit DX193, which Abraxis relies upon for its argument reports the results as "[s]tabilizers tested during *feasibility studies*." (DX193 at ELANP0010903 (emphasis added).)

Even in the case of piposulfan, the screens worked and compatible surface modifiers were identified. In addition to the four examples of successful piposulfan-surface modifier combinations disclosed in the '363 patent (JX081 8:20-9:45), testimony and exhibits presented at trial show piposulfan was also stabilized by surface modifiers. Among these were human serum albumin ("HSA"), bovine serum albumin, and HSA and tyloxapol combinations and HSA and F-108 combinations. (Tr. 532:4-6; PX717 at ELANP0014823; JX069 at ELANP018338, JX068 at 18019; PX717 at ELANP0014832, ELANP 0014827.)

In *Atlas Power Co. v. E.I. DuPont de Nemours & Co.*, 750 F.2d 1529 (Fed. Cir. 1984), DuPont made allegations similar to the ones now made by Abraxis in an effort to challenge a patent disclosing numerous salts, fuels and emulsifiers for use in claimed emulsions. *Id.* at 1576.

DuPont argued that 40 percent of the 300 experiments Atlas conducted before filing the patent failed for some reason. *Id.* at 1577. The court recognized that listing an experiment as a failure or unsatisfactory "was misleading" because experiments were designated as failures because "they were not optimal under all conditions." *Id.* The court rejected DuPont's inequitable conduct allegations based on failure to disclose these "failure" because DuPont failed to prove that any of the emulsions were inoperative. *Id.* at 1578.

Abraxis's case is even worse than DuPont's. The experiments Abraxis characterizes as "failures" are merely drug candidate screens, as opposed to concerted efforts to match drugs and modifiers per the teachings of the patent. Further, most of the documents by Abraxis are silent on the criteria or endpoints, for determining success or failure. DX238 and DX607, for example, merely state that "[f]ew surfactants meet criteria necessary for a successful drug NanoCrystal formulation." Although the document lists criteria of "[s]ize, stability, safety, & efficacy," there is no indication of the desired size or stability endpoints—is it an average effective particle size of 1000 nm, 400 nm, or 300 nm as claimed in the '363 patent or an average effective particle size of 50 nm. (DX238 at ELANP0085240.)

Abraxis cites DX190, a memo to Dr. Elaine Liversidge from William Bosch for the proposition that "[b]y 1994 Elan still had not identified a 'surfactant of choice' for use in parenteral (IV) formulations." Abraxis's Brief, at 15. But during trial, Abraxis chose not to question Dr. Elaine Liversidge about the context of this memo. Instead, Abraxis only questioned Dr. Manning about it, and he testified that he did not know its context. (Tr. 1591:3-12.)

4. Abraxis Failed to Prove By Clear and Convincing Evidence that the Inventors (or the Patent Attorney) Had the Requisite Intent to Deceive the PTO

In any screening process, some surface modifiers will not stabilize a particular drug to the claimed average effective particle size. That's why these materials are screened, to determine

which modifiers are potentially compatible with the drug. *See, e.g.*, *In re Wands*, 858 F.2d 731, 740 (Fed. Cir. 1988) (noting that "[t]he nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics" and "[p]ractitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody"). The '363 patent teaches a screening process to identify compatible surface modifier-drug combinations for the development of nanoparticulate compositions. Abraxis's suggestion that specific incompatibilities identified by the screening process taught by the '363 patent (regardless of whether the person identifying the incompatible surface modifier even had a duty of candor to the PTO) should have been disclosed to the PTO falls far short of clear and convincing evidence.

And Abraxis has no evidence that any inventor ever considered this information important enough to "conceal" it. "Intent to deceive cannot be inferred solely from the fact that information was not disclosed; there must be a factual basis for finding a deceptive intent." *Herbert v. Lisle Corp.*, 99 F.3d 1109, 1116 (Fed. Cir. 1996). Further, Abraxis's attempt to demonstrate an intent to deceive the PTO by Mr. Davis fares no better on this issue than on contamination. Abraxis also did not introduce any evidence at trial that demonstrated Mr. Davis had knowledge of any material information or made false statements to the PTO.

C. Abraxis Failed to Prove Elan Engaged in Inequitable Conduct During the Prosecution of the '025 Patent.

Abraxis argues that Elan knew the hemodynamic effects from administration of nanoparticles were species-specific and only applicable to dogs. That claim is not supported by the evidence. As with contamination, Abraxis points to ambiguous statements twisted out of context. The jury saw through this tactic, so should this Court.

1. Abraxis Failed to Prove that Elan Withheld Material Information from the PTO During the Prosecution of the '025 Patent.

(a) Abraxis Mischaracterizes Its Evidence Regarding "Species Specific" Observations.

The '025 patent was issued based on canine experiments. Dr. Elaine Liversidge testified that dogs were used as a "very classic model" to study cardiovascular issues and that all the data in the '025 patent was based on the dog model. (Tr. 496:16-25; 524:8-10.) Dr. Gary Liversidge explained why testing in dogs is applicable to humans: "[T]he dog is used pretty typically as a species for, as a model for the human. If you see this in a dog it is a huge red flag. You have got to really proceed with caution." (Tr. 450:11-13.) Abraxis has no evidence to contradict the Liversidges' testimony that experiments in a classic dog model to determine hemodynamic effects are not applicable to other species, including humans. The examiner did not request additional studies before issuing the patent, nor did Abraxis present any evidence that Elan withheld such studies from the PTO. Abraxis did not even call its expert witness, Dr. Johnson Tai Wong, who authored an expert report directed, in part, to this very issue.

(b) The Statements Abraxis Cites in Elan's Documents Do Not Prove Material Evidence Was Withheld from the PTO

None of the statements or reports Abraxis cites demonstrate that a person with a duty of candor had knowledge that contradicted a representation made to the PTO. Indeed, Abraxis can point to no experimental data that contradict any of Elan's representations.

All Abraxis's documentary evidence is to a similar effect: "[c]ardiovascular depressant effects have not been observed in other animal species studied: rat, rabbit and monkey." (DX248; DX297; DX301.) Dr. Gary Liversidge explained that this meant only that cardiovascular effects had not been observed in these species because they had not been measured in those species. (Tr. 449:15-450:1.) When questioned about this same exhibit, Dr. Elaine Liversidge corroborated his testimony. (Tr. 497:11-23.) She also explained that "[b]y 'observing' it means an animal or rodent might have been dosed, but the idea of the heart rate

and blood pressure were never measured in these other species." (Tr. 525:3-7.) She further explained that "seeing is not measuring" and the '025 patent is about measuring the cardiovascular response, measuring the blood pressure, measuring the heart rate. (Tr. 526:3-5.) Dr. Elaine Liversidge testified that measuring hemodynamic effects is a very complicated process requiring a "carefully designed study." (Tr. 495:23-496:10.) Elan did not conduct these studies in other species; nor did the PTO request that Elan provide data from other species to establish patentability. Yet Abraxis argues that Elan committed inequitable conduct by failing to provide this nonexistent data.

Dr. Elaine Liversidge offered another explanation of why hemodynamic effects had not been "observed" in monkeys, rabbits, mice, and rats by Elan or its clients. First, she testified that to her knowledge none of the clients measured hemodynamic effects during the dosing studies. (Tr. 527:17-529:2.) But she also added that hemodynamic effects had not been observed in any testing in species or humans after 1996 because both Elan and its clients administered nanoparticles following the methods taught by the '025 patent. (*Id.*)

(c) Abraxis's New Evidence Regarding the '025 Patent Is Not Material

Exhibits DX259 and JX087, cited in Abraxis's brief, were not presented to the jury during trial, and for good reason, Exhibit DX259 was created after the '025 patent issued.[7] Nor does it prove what Abraxis alleges. Instead, it merely recites the observation that nanocrystals have been administered to mice, rats, rabbits, baboons and monkeys without any incidence of adverse reactions. JX087, dated July 2, 1992, is a report on rabbits authored by one of the named inventors of the '025 patent, Dr. Lawrence de Garavilla. Abraxis chose not to call Dr. de

[7] Although the memo is undated, a footnote reference contains a publication from 1999, which allows the inference that the memo was created no earlier than 1999. The '025 patent issued in 1998.

Garavilla to the stand during trial, despite compelling his appearance via subpoena. Abraxis also chose not to question Drs. Gary and Elaine Liversidge about this report during trial, for good reason. There is no evidence that the Liversidges knew of this report's existence during the time the '025 patent was prosecuted; Dr. Elaine Liversidge testified that she only recently leaned about this report. Tr. 498:2-8. *See FMC Corp. v. Manitowoc Co.*, 835 F.2d 1411, 1415 (Fed. Cir. 1987) (noting that an inference of intent can be rebutted by demonstrating the applicant had no knowledge of the withheld material).

Dr. Elaine Liversidge also offered a credible explanation why this report may not have been disclosed by Dr. de Garavilla:

> If you go back and look at those early '90 studies, those early '90 studies were not paying attention to the critical find of the '025 patent, which is, Is one controlling the rate in which those particles are being infused in those animals? They were dosed, the two 1990 studies were based upon the weight of the animal. A dog is ten times heavier than a laboratory rabbit. The dog was given ten times more medication than the rabbit. The dog and the rabbit were infused at the same rate. So, hence, it's more than likely that the rabbit was actually infused with the teachings of the '025 patent.

(Tr. 498:17-499:3.) She concluded by explaining that "those 1990 studies are actually what caused Larry to come back to us in 1995 and say, Hey, we have this real confusing observation; what can we do to sort it out and figure out how best to dose nanoparticles?" (Tr. 499:4-7.)

2. Abraxis Failed to Prove that Elan Had the Requisite Intent to Deceive the PTO During the Prosecution of the '025 Patent.

Abraxis's theory of intent is simply that because documents were material (which they were not), intent must be assumed. But that is not the law. "Materiality does not presume intent, which is a separate and essential component of inequitable conduct." *Allen Eng'g Corp.*, 299 F.3d at 1351. To support a finding of inequitable conduct, "there must be evidence sufficient to show, clearly and convincingly, the intent to withhold material information in order to deceive or

mislead the examiner." *Jazz Photo Corp. v. U.S. Int'l Trade Comm'n*, 264 F.3d 1094, 1110 (Fed. Cir. 2001).

The law is also clear that a plausible or credible explanation can demonstrate that the lack of requisite intent. *See Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1354 (Fed. Cir. 2005). The Liversidges both provided credible explanations. Both Dr. Gary Liversidge and Dr. Elaine Liversidge explained that hemodynamic effects had not been observed in other species because they had not been measured. In summary, Elan had not conducted studies in other species, and therefore, did not have any data on the hemodynamic effects in other species. Dr. Elaine Liversidge explained that hemodynamic effects had not been observed in any studies by Elan or its clients after 1996 because nanoparticles had been administered in accordance with the teachings of the '025 patent. Finally, both Dr. Gary Liversidge and Dr. Elaine Liversidge testified that they never knowingly withheld or misrepresented any information from the PTO regarding the '025 Patent. (Tr. 467:17-20; Tr. 499;14-17.) The jury considered the Liversidges' testimony and weighed their credibility. The jury found that Elan did not engage in inequitable conduct during the prosecution of the '025 patent. The jury's findings are correct and should not be set aside.

VII. CONCLUSION

Abraxis fought, and prevailed, to submit the ultimate question of inequitable conduct to the jury. But after the jury returned findings in favor of Elan, Abraxis rejects those findings. Abraxis, through its actions, is estopped from challenging them. Elan respectfully requests that the Court find Abraxis precluded from seeking to set aside the jury's verdict. In the alternative, Elan respectfully requests that the Court deny Abraxis's motion and accept the jury's findings that the '363 and '025 patents are not unenforceable for inequitable conduct.

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