UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

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

DEFENDANT ABRAXIS BIOSCIENCE, INC.'S REPLY BRIEF IN SUPPORT OF ITS 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

In its opening brief, Abraxis showed that Elan repeatedly engaged in inequitable conduct in pursuit of its business plan to obtain broad patent claims to block competition. The evidence is much stronger than in the typical inequitable conduct case, as the misconduct here involves not merely failures to disclose information, but affirmative false representations in the patent applications and prosecution filings. Proof that the inventors knew the statements were false lies in contemporaneous documents showing that what Elan had concluded internally was the exact opposite of what it told the PTO. These documents include not just internal memoranda and emails, but important planning documents from development retreats and meetings with outside scientific advisors. They show that the very subjects at issue in this motion were the subject of significant attention and concern at Elan. The '363 and '025 patent inventors were closely involved in those deliberations, and admitted that they knew what these documents reported.

Although the evidence cited in Abraxis's brief is extensive, a few documents illustrate the stark contrast between what Elan was telling the PTO to obtain issuance of the patents, and what it was saying internally:

The selection of material for the grinding media is not believed to be critical. However, 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 of pharmaceutical compositions. JX081 6:21-27	Problem: Roller & media milling using zirconium or glass beads generates unacceptable contamination levels and pH shifts. DX607 at ELANP0085236

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 .... JX039 at 0429	**Problem:** Few surfactants meet criteria necessary for a successful drug NanoCrystal formulation. – size, stability, safety & efficacy DX607 at ELANP0085230
Also, as used herein, mammal preferably means a dog and other sensitive species including human species. DX015 at 2:66-67	*One of the key issues NanoSystems has had to deal with is the severe hypotensive effect of particles administered to dogs. We believe this effect is species dependent and can be avoided in the dog by slow peripheral injection.* DX248 at ELANP0117903

Elan argues that the statements in its internal documents are "vague" but they could not be more clear, and could not be more diametrically opposed to what Elan told the PTO to gain issuance of the patents. Because the contemporaneous documents contradicted its inventors' attempts at trial to justify its false statements regarding the '363 patent, Elan largely abandons those excuses for others made up out of whole cloth, with no supporting trial testimony or evidence. The evidence of materiality and intent is overwhelming. The Court should find that Elan engaged in inequitable conduct, and that both patents are unenforceable.

II. ARGUMENT

A. The Jury's Verdict Was Advisory

Ignoring the relevant rule, Elan argues Abraxis is estopped from taking the position that the jury's verdict on inequitable conduct was advisory. But Fed. R. Civ. P. 39(c)(2) requires both parties' consent for a jury to render the ultimate verdict on an issue where a jury trial is not a matter of right. There can be no dispute that there was no such mutual consent here – Elan admits that it objected to the jury deciding the issue. D.I. 665

("Elan Br.") at 3. While Elan's pretrial objection alone is dispositive, Abraxis requested only an advisory verdict, as can be seen from Abraxis's opposition to Elan's request to bifurcate (D.I. 490, Abraxis Opp. to MIL 2 at 4-5) and its proposed jury instructions (Elan Br. at 4).

Elan also ignores that at the pretrial conference, the Court decided to seek an advisory verdict. D.I. 643 ("Opening Br.") at 5, citing 5/29/08 Hearing Tr. 124:19-125:25. Abraxis's later acceptance of a jury instruction that did not inform the jury of its advisory role is not the consent required by Rule 39(c)(2). *See ISCO Intl., Inc. v. Conductus, Inc.* 279 F. Supp. 2d 489, 499-500 (D. Del. 2003) (inequitable conduct jury verdict advisory where parties did not expressly consent to jury deciding issue). Indeed, the AIPLA Model Instructions, the source of that instruction, note that it can be used with an advisory jury.[1] *See* AIPLA Model Patent Jury Instructions § 11.3 (2008).

B. Elan Engaged in Inequitable Conduct

1. Elan Intentionally Misrepresented That Its Invention Resolved Issues of Contamination

Elan has no response to Abraxis's evidence that it made a series of intentional misrepresentations to the PTO regarding the supposed lack of contamination associated with the '363 patent's grinding methodology. Elan does not contest that it affirmatively represented to the PTO that the prior art particles were contaminated but particles made using the '363 patent's process were not; that the choice of grinding media did not matter;

[1] For the sake of completeness, Abraxis notes that it was *Elan* not Abraxis, that proposed the final inequitable conduct instruction based on the AIPLA model. Declaration of Matthew S. Chen in Support of Defendant's Motion to Amend the Judgment and Enter Findings that Elan Engaged in Inequitable Conduct in Procuring the '363 and '025 Patents ("Chen Decl.") ¶¶ 2-4.

and that zirconium and glass grinding media led to particles "free of unacceptable contamination." Nor does it contest that zirconium oxide grinding media features prominently throughout the '363 patent and is the only medium used in the examples.

As for what Elan was actually finding in its laboratories, it does not challenge the evidence at trial that (1) its formulations using zirconium oxide and glass grinding media were plagued by contamination, leading Elan ultimately to abandon those media in favor of less contaminating approaches; and (2) its inventors were aware of these problems during prosecution of the '363 patent and, indeed, that the toxicology department had reported problems with zirconium media as early as 1990 and had recommended its non-use by 1993. Nonetheless, they told the PTO precisely the opposite in order to persuade it that the claims had utility and were superior to the prior art.

Elan's arguments in defense represent a continuation of its misleading disclosure to the PTO. Elan argues that it did not need to report the contamination because the '363 patent discloses a method for cleaning the grinding media. Elan Br. at 9-10. As Abraxis demonstrated and Elan does not address, this argument is conclusively refuted by Elan's documents showing "unacceptable" contamination continuing long after the cleaning procedure was disclosed in the patent. Opening Br. at 12. Elan points to no document suggesting that use of this cleaning method resulted in contamination-free particles. That Elan was forced to develop new grinding media and phase out zirconium further refutes the argument that a "simple" cleaning procedure fixed the contamination problem.

Similarly, Elan's argument that the FDA did not complain about contamination ignores that for its commercial products, Elan phased out the grinding media disclosed in the patent in favor of polymeric grinding media. Opening Br. at 10-11.

Elan also argues there is insufficient evidence of intent because Dr. Gary Liversidge supposedly disbelieved the toxicology department's assessment of the risks associated with zirconium contamination. Elan Br. at 7. Dr. Liversidge never testified, however, to any such disbelief. In fact, as Abraxis explained (Opening Br. at 11-12) and Elan does not challenge, after initially defending his decision not to tell the PTO about Elan's contamination problems because of a supposed distinction between "undesirable" and "unacceptable" contamination, Dr. Liversidge eventually conceded knowing that the contamination was "unacceptable." The 1990 document Elan cites does not show otherwise; it simply mentions that in one unrelated application (zirconium oxide in bone cement), contamination problems had not been reported. DX244.

Elan argues that there is no evidence tying the contamination to the '363 patent's teachings, which it says include specific milling times, particular types of zirconium oxide media, or particular premix viscosities. Elan Br. at 9-10. This argument is unsupported by any trial testimony and has not been advanced before, for good reason. Elan's internal documents are clear and unequivocal: zirconium and glass beads result in unacceptable contamination. Elan's toxicology department recommended completely abandoning zirconium media (Opening Br. at 8), and said nothing about alternatives such as using zirconium only under certain conditions. Moreover, Elan misstates the teachings of the '363 patent. The patent teaches the general use of zirconium oxide media, a fact Dr. Gary Liversidge repeatedly admitted at trial. *E.g.*, Tr. 424:5-12, 426:14-23. The patent does not teach that ball milling be limited to 5 days, but can last "five days *or longer*." JX081 at 6:32-39 (emphasis added). In fact, nearly all of the '363 patent examples report milling times exceeding 5 days. JX081 at 9:55-58, 9:66-68, 10:3-5,

11:35-37, 11:42-44, 11:48-50, 12:24-26, 12:31-34, 12:56-58, 13:11-18, 13:43-45, 13:65-66 (milling for 7, 11, 14 or 15 days).

Elan's argument that it did not engage in inequitable conduct because the contamination supposedly is not inside the particles (Elan Br. at 10) is equally disingenuous. Elan broadly represented to the PTO that its particles are "free of unacceptable contamination" and that its particles have levels of contamination "believed to be acceptable for the preparation for pharmaceutical compositions." Opening Brief at 6-7. Elan never suggested to the PTO that the particles are free of internal contamination but contaminated on the outside. The Court's claim construction requires the particles to be "essentially free" of contamination (Opening Br. at 9), and is not limited to contamination within isolated particles. Also, the particles are useful only if they can be administered, and their safety depends on being free of contamination inside or outside the particles. Claims 10 and 11 highlight this point, as they are directed to methods of treatment using the claimed particles, to which toxic contamination is plainly relevant.

The evidence of intent exceeds clear and convincing, and is reinforced by the demonstration that Elan made affirmative false statements (not just omissions) that were directly contradicted by its internal documents. The controlling authority Abraxis cited (Opening Br. at 4-5), and Elan did not contest, makes clear that in the absence of a reasonable explanation, the only possible conclusion is that Elan intended to deceive the PTO.[2]

[2] Elan complains that Abraxis did not call Elan's attorney, Mr. Davis, to testify on intent. But it was Elan's choice not to bring him to trial and defend the prosecution of the patents. The trial record shows statements to the PTO that were directly contradicted by information known to the inventors. Absent a credible explanation from anyone, the only possible conclusion is that Elan intended to deceive the PTO. Opening Br. at 4-5.

2. Elan Made Intentional Misrepresentations Regarding Drug/Surface Modifier Combinations

Elan does not contest that it represented to the PTO that the evidence "conclusively" demonstrated that the claimed invention worked with a "wide variety of surface modifiers" and that the patent "readily enable[d]" making the claimed particles. Opening Br. at 14. Nor does it challenge that it failed to disclose numerous failed attempts to make nanoparticles using a variety of surface modifiers; that despite extensive efforts, its internal conclusion was that only a few surface modifiers could obtain the requisite size, stability, toxicity and efficacy; and that it could not identify a surface modifier of choice for injectable (parenteral) formulations.

Elan's response ignores the facts and mischaracterizes its duty of candor. Elan points to the '363 and '684 patent examples and a declaration it submitted to the PTO to support its argument that it was "successful" with a range of drugs and surface modifiers. But Elan does not contest that the Examiner was concerned about the claims' breadth, having rejected them except for certain preferred surface modifiers. *Id.* The Examiner should have had the necessary information available – the successes *and* the failures – to decide the appropriate scope of the claims. Rather than provide the full truth, Elan falsely told him only what it wanted him to hear.

Elan does not challenge that its inventors were aware of the failed experiments and internal documents bemoaning the shortage of potentially useable surface modifiers. Elan attempts to justify not disclosing this information with new excuses none of its witnesses raised at trial. Elan does not contest that it concluded that few surfactants met the size, stability, efficacy and toxicity criteria necessary for "successful" nanoparticles. *Id.* at 15. It speculates that its internal documents may have referred to different size

particles than those claimed in the patent (Elan Br. at 15) but no witness at trial so testified, and its conclusion that only a few surfactants could successfully make nanoparticles flatly contradicts its representation to the PTO that a "wide variety" of surface modifiers could be used. Elan also suggests that perhaps the failures resulted from use of the patent's screening method, not "concerted efforts to match drugs and modifiers per the teaching of the patent." *Id.* But this argument is nonsensical, as the screen is the method the patent teaches, and there is nothing in the patent pointing to the need for "concerted efforts."

Elan's arguments regarding piposulfan are also flawed. Elan says the patent contains "four" successful piposulfan examples, and claims others are shown by its laboratory notebooks. Elan ignores that it failed to disclose to the PTO a multitude of failures – roughly *30* documented failed attempts to make piposulfan nanoparticles by August 1992. *See* DX258 at ELANP0145863 (concluding "single surfactant" suspensions unstable based on tests of 30 surface modifiers); DX193 at ELANP0010903 (33 surface modifiers tested, all failed). Moreover, what Elan characterizes as "four" different piposulfan examples in reality are all related Tween/Span formulations – three concentrations of the Tween 80/Span 80 combination, with the "fourth" a Tween 60/Span 60 mixture. Elan does not challenge Abraxis's showing that Elan did not disclose a long list of failed combinations, including even other Tween/Span combinations from the same experiments reported in the patent. Opening Br. at 14-15.

The notebooks Elan cites in fact show more failures. *E.g.*, PX717 at ELANP014824, 825, 835 (HSA combinations aggregated "so stability may be an issue"); JX068 at ELANP0018025 (BSA failed due to "terrible foaming"). Elan has no answer to

its own document showing that after years of trying and dozens of failures, Elan could not find a single back-up stabilizer, and it acknowledged internally that its single "success" had not been shown usable in injectable formulations. Opening Br. at 15.

Elan argues that the evidence of intent is insufficient. But Elan does not even respond to the controlling authority cited in Abraxis's Opening Brief (at 4-5) holding that intent will generally be inferred where there is a lack of a credible explanation for failing to disclose material information. Here, the evidence is even stronger as the issue is not merely withholding information; it is Elan's affirmative false representations, including in a declaration to the PTO. Under these circumstances, the intent element is clearly met.

3. Elan Intentionally Misrepresented the Applicability of the '025 Patent to Mammals Other than Dogs

Elan is silent on most of the issues raised in Abraxis's opening brief regarding the species-specific nature of the hemodynamic effects reported in the '025 patent. Elan does not address its false statements to the PTO that the 10 mg/min infusion rate was a "**critical** parameter" (double emphasis in original) when it knew that this rate applied, if at all, only to dogs.[3] Opening Br. at 17-18. Nor does it justify its false statement to the PTO that humans are "sensitive species." *Id.* The reason for this silence is clear. Elan has no explanation for these falsehoods, nor can it dispute their materiality as they related directly to the issuance of broad claims that applied to all mammals, not just dogs.

Elan is also silent on its failure to report to the PTO its internal conclusion that the hemodynamic effects it observed in dogs were species specific. As Abraxis explained

[3] Elan also does not contest that its inventors admitted that it was well-known to reduce infusion rates to avoid hemodynamic effects, or that Elan overcame an obviousness rejection by falsely representing that the 10 mg/min rate was a magic number that avoided hemodynamic effects. Opening Br. at 17.

and Elan does not contest, Elan's own documents created before and during the pendency of the '025 patent application reflect this belief. Opening Br. at 17-19.

Elan does not contest that it knew of testing intravenous administration of nanoparticles in species other than dogs, and based on those tests believed the effects were species-specific. Elan argues that its knowledge was nonetheless insufficient to require any disclosure; in a memorable phrase, it says, "seeing is not measuring." Elan Br. at 18. But Elan cites no authority for the proposition that only *measurements* need be reported, but other observations and conclusions from experiments need not be. The contemporaneous documents showed that Elan observed no deleterious hemodynamic effects when administering nanoparticulate compositions to species other than dogs, and based on these observations had formed a conclusion that the effects were specific to dogs. Moreover, Dr. de Garavilla *did* take measurements with rabbits without observing any hemodynamic effects using "a similar protocol" to that used for the dog experiments. JX088 at ELANP0059375; *see also* JX087. Whether the other inventors knew about the actual data or not is irrelevant; they were well aware of and shared the conclusion that the effect was species-specific. Opening Br. at 17-20. Nonetheless, Elan falsely informed the PTO that humans, like dogs, were a sensitive species, falsely stated that the 10 mg/min infusion rate it knew was relevant only to dogs was a "**critical** parameter" and sought broad claims applicable to all species without informing the PTO that the effects were unique to dogs. It is hard to imagine a clearer case of inequitable conduct.

III. CONCLUSION

For the reasons stated above, the Court should enter findings that Elan engaged in inequitable conduct during prosecution of the '363 and '025 patents.

Dated: August 18, 2008

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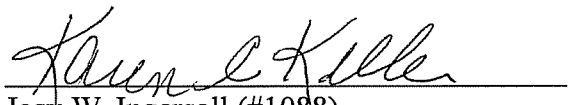

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