Nanocrystalline Pharmaceutical Patent Litigation: The First Case

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ABSTRACT

Nanotechnology promises to have a major impact on health care. Indeed, one of the first major product success stories to come out of this emerging field is a nanoparticle-based drug for cancer therapy. Abraxane, manufactured by Abraxis, uses albumin nanoparticles to enhance the effectiveness and reduce the side effects of paclitaxel, a chemotherapy drug used for treating breast cancer. In July 2006, Elan Pharmaceuticals filed a complaint alleging that the Abraxane infringes two of Elan's patents regarding nanoparticle formulation technology. After two years of discovery battles, the dispute has finally gone before a jury, which rendered a verdict in favor of Elan for $55.2 million. In this article, IP lawyers William Prendergast and Heather Schafer provide a background of the dispute, summarize the case, and draw conclusions regarding its implications for nanotechnology patent litigation.

I. INTRODUCTION

On June 13, 2008, a Delaware jury delivered a $55.2 million dollar jury verdict to Plaintiff Elan Pharmaceutical International, Ltd. ("Elan") in the first patent infringement trial involving pharmaceuticals and nanotechnology. In July 2006, Elan Pharmaceutical International, Ltd. ("Elan") filed a complaint in the U.S. District Court for the District of Delaware alleging that the cancer treatment, "Abraxane," manufactured by Abraxis Bioscience, Inc. ("Abraxis"), infringes two of Elan's patents.[1] After almost two years of discovery battles, the dispute went before a jury on June 2, 2008.[2]

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1 Elan Pharma. Int'l, Ltd. v. Abraxis Biosci., Inc., No. 06-438 (D. Del. filed July 19, 2006), at Complaint at 3.

2 *Id*. at Minute Entry of Nov. 6, 2006.

II. BACKGROUND OF THE DISPUTE

Abraxane is in a category of its own when it comes to nanotechnology.[3] It is a nanopharma reformulation of the traditional breast cancer treatment, paclitaxel (Taxol).[4] However, there are no nanotubes, fullerenes or other nanoscale delivery devices involved in this treatment.[5] Abraxane has the attention of the nano-community primarily because it is a very small thing, a 130-nanometer albumin-bound form of the traditional breast cancer treatment paclitaxel.[6] The drug represents a growing trend of pharmaceutical nanoengineering—improving the bioavailability of non-soluble pharma compounds by making them smaller and linking them to proteins such as human albumin.[7] Abraxane represents the first of these protein nanoparticles to achieve FDA approval.[8]

Protein nanoparticles, such as Abraxane, are a solution to a long-standing dilemma inherent in non-water soluble cancer treatments such as paclitaxel. Humans cannot absorb these non-soluble compounds unless they are enhanced with a "solvent vehicle."[9] The solvent vehicle used to improve solubility of paclitaxel is cremophor.[10] However, like other solvent vehicles, cremophor is associated with almost as many drawbacks as advantages.[11] The cremophor solvent transforms an otherwise effective cancer-fighting compound, paclitaxel, into a compound preparation having potentially dangerous side effects.[12] Patients infused with cremophor-paclitaxel preparations often experience serious hypersensitivity reactions, increased susceptibility to infections due to lowered white blood cells count, and nerve damage.[13] As a result, the delivery of cremophor-paclitaxel requires premedication with corticosteroids and antihistamines to ward off hypersensitivity reactions; furthermore, administration is prolonged (3 hours) and it requires special intravenous tubing.[14] Abraxane has none of these drawbacks and can therefore be used at higher—and more effective—doses.[15]

In March 2005, the United States Food and Drug Administration (FDA) approved Abraxane for the treatment of breast cancer.[16] The FDA approved Abraxane for use in patients only after they experienced a failure of combination chemotherapy or had a relapse within six months of adjuvant chemotherapy and only where prior therapies included an anthracycline.[17] Although approved for a seemingly specific and limited patient population, the drug caught on fast with doctors and achieved $134 million in sales during its first year on the market.[18]

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[3] *See* Howard Lovy, *A Spoonful of Nano Helps the Medicine Go Down: FDA Approves Hybrid Protein-Nanoparticle Anticancer Drug*, THE SCIENTIST, Mar. 28, 2005, at 35.

[4] Michael J. Hawkins, Patrick Soon-Shiong & Neil Desai, *Protein Nanoparticles as Drug Carriers in Clinical Medicine*, 60 DRUG DELIVERY REV. 876, 877 (2008).

[5] *See* supra note 3.

[6] *See* supra note 4 at 878.

[7] *See id.*

[8] *Id.*

[9] Charity D. Scripture, William D. Figg & Alex Sparreboom, *Paclitaxel Chemotherapy: From Empiricism to a Mechanism-Based Formulation Strategy*, 1 THERAPEUTICS & CLINICAL RISK MGMT. 107, 107-08 (2005), *available at* http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1661618&blobtype=pdf.

[10] *See id* at 108-09.

[11] *See supra* note 4 at 877.

[12] *See id.*

[13] *See id.*

[14] *See id.*

[15] *See id* at 877-88.

[16] *See supra* note 1 at Answer and Countercl., Aug. 22, 2006.

[17] *See id.*

[18] *See supra* note 16.

III. SUMMARY OF THE CASE

Elan filed suit against Abraxis in the United States District Court of Delaware in July 2006, just over one year after Abraxane reached the United States market. Elan owns two patents claiming a nanoparticle formulation technology aimed at enhancing the delivery of poorly water-soluble compounds. Elan's complaint alleges that Abraxis directly infringes two of its patents by making and selling Abraxane and by teaching medical professionals how to administer the treatment.[19] Elan also alleges, under theories of contributory and inducing infringement, that Abraxis is liable for the direct infringement by medical professionals who administer Abraxane to patients.[20]

When the complaint was filed, Elan asserted infringement of two patents, U.S. Patent Nos. 5,399,363 and 5,834,025. The '363 patent claims "surface modified nanoparticles."[21] The claims of that patent define the invention as particles "consisting essentially of . . . a non-crosslinked surface modifier . . . and a crystalline medicament."[22] The '025 patent claims a method of reducing adverse physiological reactions associated with administering nanoparticle compositions.[23] That patent claims a "method of administering a nanoparticle composition to a mammal . . . at an infusion rate not exceeding 10 mg/min."[24] Elan's complaint requests injunctive relief, treble damages, and attorneys fees.[25] Abraxis denied that Abraxane infringes Elan's patents and challenged the validity of both the '363 and '025 patents.[26] Abraxis alleges that the patents are invalid because they were rendered obvious by prior art patent references.[27] Abraxis further alleges that the Elan patents are unenforceable because the inventors and their attorneys committed fraud on the patent office by failing to cite a critical reference.[28]

Most of the early discovery by the parties focused on one word: "crystalline." Abraxis attempted to bring the case to an early halt by asserting that Abraxane was an amorphous compound, not a crystalline compound.[29] Elan was unsatisfied by Abraxis' pre-approval FDA documents and scientific publications that support that assertion.[30] Elan persisted in its conviction that, at some point in the manufacture and/or reconstitution of lyophilized Abraxane, the paclitaxel exists in a crystalline form and in an amount sufficient to infringe the '363 patent.[31] Elan's claims are premised on an FDA-approved label that states that paclitaxel is known to be a "crystalline" material as well as statements in Abraxis' patent applications which claim that the paclitaxel in Abraxane may be "amorphous, crystalline, or both."[32] Finally, Elan asserts that even an amorphous paclitaxel composition infringes under the doctrine of equivalents.[33]

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19 *See supra* note 1.
20 *See id.*
21 U.S. Patent No. 5,399,363 (issued Mar. 21, 1995).
22 *Id.* at col. 14, ll: 7-11.
23 U.S. Patent No. 5,834,025 (issued Nov. 10, 1998).
24 *Id.* at col. 16, ll: 56-60.
25 *See supra* note 1 at Complaint at 5.
26 *See supra* note 17.
27 *See supra* note 1 at Am. Answer (Redacted) at ¶ 33, Apr. 6, 2007.
28 *See id.*
29 *See id* at Defs.'s Mot. for Sanctions, Mar. 20, 2007. Crystalline solids are arranged in fixed geometric patterns or lattices; they have orderly arranged units, and show definite melting points. Amorphous solids are solids with random, unoriented molecules that do not have definite melting points. *See* Univ. of Tenn., http://www.utmem.edu/physpharm/.038.html (last visited May 14, 2008).
30 *See supra* note 1 at Pl.'s Answer Brief. in Opp'n to Def.'s Mot. for Sanctions.
31 *See id.*
32 *See id.*
33 *See id.*

Elan made extensive discovery requests for Abraxis documents regarding Abraxane, including requests for detailed information about Abraxis' manufacturing procedures.[34] Abraxis, however, did not give up its trade secret manufacturing processes easily. Abraxis acknowledged that, due to the proximity of the competing technologies, this was only the beginning of a "brewing, long-term battle" between the parties.[35] Abraxis also characterized the current lawsuit as a "fishing expedition" and expressed concern both that Elan doesn't have a good faith basis for its present claims and that Elan is attempting to illicit admissions in this case that can be used in future litigation.[36] The parties' discovery disputes were the subject of numerous discovery conferences with Chief Judge Gregory M. Sleet.

Abraxis also filed a Rule 11 Motion for Sanctions alleging that Elan did not have a good faith basis for filing the lawsuit. The motion was premised upon a statement by Elan's attorney that "until [Elan's experts] see how [Abraxane] is made, they are really shooting in the dark."[37] Abraxis asserted that Elan filed its complaint before conducting a reasonable inquiry into Abraxane's composition and continues to violate Rule 11 by refusing to abandon its claims in the face of evidence that Abraxane is not crystalline and therefore non-infringing.[38]

Elan characterized the Rule 11 Motion as an effort by Abraxis to insert its interpretation of the claims into the proceedings prior to the Court's claim construction.[39] Elan stated that, under the circumstances, it had ample support to form a reasonable belief of infringement.[40] Elan further stated that "the morphology of nanoparticulate compositions is not easily ascertained by known techniques."[41] Judge Sleet denied Abraxis' Motion for Sanctions, stating simply that "defendant's counterclaims for declaratory judgment belie its assertion that the plaintiff did not sufficiently investigate the substantive basis for its claims and that the plaintiff filed its complaint for an improper purpose."[42]

The focus of the case changed considerably after Judge Sleet issued his claim construction order. Elan withdrew its claims of infringement of the '025 patent, as construed by the Court. Elan continues to assert that Abraxis infringes the '025 and that they withdrew the claims only to expedite the trial. Elan persists in its effort to get the '025 patent before the Federal Circuit.[43] To that end, they asked Abraxis to stipulate to a judgment on the claims of the '025 patent to provide grounds for them to appeal the Court's claim construction.[44] Abraxis declined.[45]

After the claim construction, the controversy narrowed and the direction of the litigation took on an interesting turn. After the first claim construction Order was submitted, it became clear that, at trial, Elan's position would be that the alleged amorphous compound, Abraxane, is embraced by the claim language "particles consisting essentially of . . . a crystalline medicament . . . ." On May 19, just two weeks before trial, Judge Sleet issued an Order clarifying his claim construction Order.[46] In that Order, the Court concluded that a largely amorphous product could not infringe the claim term "crystalline

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[34] *See supra* note 30.
[35] *See supra* note 1 at Teleph. Conf. before Hon. Gregory M. Sleet, (attached as Ex. C to Def.'s Mot. for Sanctions) p. 5, 11: 17-21.
[36] *See supra* note 30.
[37] *See supra* note 30.
[38] *See supra* note 30.
[39] *See supra* note 31 at 22.
[40] *See id.*
[41] *See id.*
[42] *See supra* note 1 at Order Den. Def.'s Mot. for Sanctions, Sept. 25, 2007.
[43] *See supra* note 1 at Elan's Letter Req. Permission to File and Br. Mot. for Summ. J. (Redacted), Jan. 2, 2008.
[44] *See supra* note 1 at Elan's Letter Req. Permission to File and Br. Mot. for Summ. J. (Redacted), Jan. 2, 2008.
[45] *See id.*
[46] Order (May 19, 2008), Elan Pharma. Int'l, Ltd. v. Abraxis Biosci., Inc., No. 06-438 (D. Del. filed July 19, 2006).

medicament."[47] Elan asserted in a Motion for Reconsideration that the Court's construction foreclosed its infringement case, under any theory, but specifically under the doctrine of equivalents.[48] On June 2, 2008, a jury was confronted with determining whether Abraxane's drug literally infringed the '363 patent and also with determining the validity of both patents and reviewing an assertion of inequitable conduct.[49] On June 13, 2008, after 10 days of trial, the jury delivered a verdict finding the '363 patent infringed and awarding damages of $55.2 million based on a reasonable royalty rate of 6%. The jury also rejected defenses based on lack of enablement, lack of adequate written description and inequitable conduct.

IV. CONCLUSIONS

The *Elan* case is important to those following nanotechnology patent litigation. First, this case raises an important procedural issue regarding summary judgment motions in patent litigation. Presiding Judge Sleet has been quoted as disfavoring such summary judgment motions in patent litigation matters.[50] In this case, while both parties requested permission to file motions for summary judgment, permission was never granted. According to Judge Sleet, summary judgment motions can be a significant waste of time and money in cases where parties have experts that are willing to dispute the underlying facts. Because patent cases often involve a disagreement over the facts, there is a growing trend to limit the use of summary judgment motions by requiring permission for filing such motions from the presiding judge—a permission that may not be as freely granted as in the past. The outcome of this case is also a poignant example of Judge Sleet's theory regarding the central role of experts in patent cases. The parties relied heavily on expert testimony regarding the composition of Abraxane to establish their respective positions.

Second, those companies obtaining and defending against nanotechnology patents will be interested to see how the jury determined and applied the facts of the present case to the interpreted claims as this may have implications on their own patent drafting and product clearance work. The *Elan* case may also have important implications regarding the preparation of other legal and non-legal documents to the extent they describe or characterize a nanotechnology based material. However, in the end, the final word on the verdict in this case may still be far off as there will mostly likely be numerous post-trial motions and an appeal to the Federal Circuit.

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47 *Id.*

48 Elan's Motion for Reconsideration, Filed May 22, 2008.

49 Order of May 21, 2008.

50 Sara Stefanini, *Judges Top Four Pet Peeves In Patent Litigation*, *IP LAW 360*, May 13, 2008 ("'Generally in these cases, both parties have experts who are ready, willing and able to come to court and dispute the facts,' said Chief Judge Gregory M. Sleet of the U.S. District Court in Delaware. 'It can be a significant waste of time and money to bring a summary judgment motion.' ").