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January 2, 2008

BY CM/ECF

REDACTED – PUBLIC VERSION

The Honorable Gregory M. Sleet
U.S. District Court for the District of Delaware
J. Caleb Boggs Federal Building
844 N. King Street, Lockbox 19
Wilmington, DE 19801

Re: *Elan Pharma Int'l Ltd. v. Abraxis BioScience, Inc.*, C.A. No. 06-438-GMS

Dear Chief Judge Sleet:

Abraxis requests permission to move for summary judgment of noninfringement of U.S. Patent No. 5,399,363 (the "'363 patent"), as Elan has failed to provide any evidence under the Court's claim construction that the particles in the accused product, Abraxane®, "consist[ ] essentially of" the recited components. This motion would dispose of all infringement claims for the '363 patent.

By email dated December 21, 2007, Elan notified Abraxis that it is no longer prosecuting its claim for infringement under U.S. Patent No. 5,834,025, the second patent-in-suit, in view of the Court's claim construction. Accordingly, Abraxis is not requesting leave to file a motion for summary judgment of non-infringement on that patent.

Introduction

Elan's infringement case for the '363 patent is premised on its application of the Court's construction of the transitional phrase "consisting essentially of" to permit the claimed particles to include amorphous medicament. Expert discovery has now closed, and Elan has no evidence

of literal infringement that is consistent with proper application of the Court's construction. Further, Elan's disclaimers in the prosecution history foreclose invocation of the doctrine of equivalents. Even under Elan's preferred application of "consisting essentially of," Elan's evidence is so deficient that no reasonable jury could find infringement.

Argument

A. Elan Has No Infringement Case Under A Proper Application Of The Court's Construction Of The Transitional Phrase "consisting essentially of."

Claim 1, from which all asserted claims depend, recites in pertinent part:

> Particles consisting essentially of 99.9-10% by weight of a crystalline medicament useful in treating cancer susceptible to treatment with said medicament, said medicament having a solubility in water of less than 10 mg/ml, and having a non-crosslinked surface modifier adsorbed on the surface thereof in an amount of 0.1-90% by weight . . .

(D.I. 144, Joint Appendix at A0001-A0010, '363 patent, claim 1; April 25, 2006 Certificate of Correction (emphases added).)

As previously explained in Abraxis's Rule 11 Motion[1] and its supporting papers (including internal Elan documents), the "medicament" (paclitaxel) in Abraxane is not "crystalline" as required by the claims, but rather is amorphous. Indeed, as explained below in Section B, despite striving mightily to establish crystallinity, Elan's experts could opine only that "crystalline paclitaxel [in Abraxane]. . . measured at levels between 3.5% and 12% of the total paclitaxel present."[2] (Expert Report of Eric Munson ("Munson Report") ¶¶ 18-24 and 27.C.) (Ex. A)

In light of such data, Elan's experts focused exclusively on proving infringement under a loose reading of the transitional phrase "consisting essentially of" that would allow the claimed particles to "also contain a non-crystalline, or amorphous, component" so as to include up to "90% by weight of an amorphous medicament." (Expert Report of Harry Brittain ("Brittain Report") ¶ 31) (emphasis added) (Ex. B) Such an infringement theory, however, is foreclosed under the Court's construction.

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[1] (D.I. 78, Abraxis's Motion for Sanctions Pursuant to Federal Rule of Civil Procedure 11, filed March 20, 2007, *denied by* D.I. 345, Order, issued September 24, 2007)

[2] As discussed at n. 5, below, Abraxis disputes the admissibility of Elan's testing, and hence whether Elan has *any* evidence of crystalline paclitaxel in Abraxane. Abraxis's evidence, moreover, is to the contrary: the paclitaxel in Abraxane is entirely amorphous. For purposes of deciding this application, however, the Court need not wade into that controversy.

The Court construed the transitional phrase "particles consisting essentially of" to mean that "the particles, composed of crystalline medicament and surface modifier, may also include other ingredients that do not affect their basic and novel properties, and are essentially free of solvent and other contaminants." (D.I. 271, Order Construing the Terms of U.S. Patent Nos. 5,399,363 and 5,834,025 ("Markman Order") at 1) (emphasis added) But the specification of the '363 patent explicitly distinguishes crystalline from amorphous particles,[3] and the applicants repeatedly relied on that distinction to overcome prior art and secure issuance of both the '363 patent and its parent.[4] It is thus hard to imagine an ingredient that would "affect the[ ] basic and novel properties" of the claimed particles more than an amorphous medicament. *See, e.g., Atlas Powder Co. v. E. I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1574 (Fed. Cir. 1984) ("The '978 claims exclude the presence of nitric acid because the essence of the claimed composition is the elimination of nitric acid and the claim phrase 'consisting essentially of' excludes ingredients that would 'materially affect the basic and novel characteristics' of the claimed composition.").

Furthermore, the Court previously rejected Elan's attempt to expand the claim language to require that merely "a portion" of the medicament be crystalline, "find[ing] no support in the claim language, the specification, or the prosecution history for reading this limitation ['a portion'] into the claim . . . ." (Markman Order (D.I. 271) at 2, n. 4.)

Accordingly, summary judgment of noninfringement should be granted on the basis that an amorphous medicament is excluded from the scope of the claims as delimited by the "consisting essentially of" transitional phrase, especially where, as here, the presence of amorphous medicament was disclaimed and distinguished from crystalline medicament during prosecution. *See, e.g., Talbert Fuel Sys. Patents Co. v. Unocal Corp.*, 275 F.3d 1371, 1375 (Fed. Cir. 2002), *vacated and remanded on other grounds*, 537 U.S. 802 (U.S. 2002), *affirmed on remand*, 347 F.3d 1355 (Fed. Cir. 2003) (affirming grant of summary judgment of noninfringement by rejecting patentee's interpretation of "consisting essentially of" as being inconsistent with prosecution history: "The phrase 'consisting essentially of' thus cannot negate

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[3] *See, e.g.*, D.I. 144, Joint Appendix at A0001-A0010, '363 patent, col. 2:28-31 ("The anticancer agent is present in one or more discrete crystalline phases. The crystalline phase differs from an amorphous i.e., non-crystalline phase...").

[4] *See, e.g.*, D.I. 144, Joint Appendix at A0236, '105 App. (from which U.S. Patent No. 5,145,684 issued, which is the parent of the '363 patent) Nov. 18, 1991 Amendment at 9 ("The crystalline phase differs from non-crystalline and amorphous phases. The crystalline particles of this invention exhibit improved stability compared to particles containing a drug substance in an amorphous phase."); D.I. 144, Joint Appendix at A0161, '125 App., (from which the '363 patent issued) Oct. 29, 1992 IDS at 3 ("amorphous materials and formulations tend to exhibit unacceptably poor stability and/or short shelf lives."); D.I. 144, Joint Appendix at A0169, '125 App., Sept. 13, 1993 Amendment at 5 ("Furthermore, there is no suggestion in the cited references or in the art as a whole of the unexpected advantageous properties associated with the claimed crystalline anticancer particles.").

the limiting effect of . . . , a limitation added in acquiescence to the examiner's requirement for specificity.").

In addition, as the prosecution history reflects that Elan's patentability arguments were premised on limiting the claimed subject matter to crystalline medicament, Elan is estopped to reach, by way of the doctrine of equivalents, particles of amorphous medicament. *See, e.g.*, *Talbert Fuel Sys. Patents Co. v. Unocal Corp.*, 347 F.3d 1355, 1358-60 (Fed. Cir. 2003) (affirming grant of summary judgment of noninfringement under doctrine of equivalents for subject matter surrendered by patentee for patentability purposes).

Therefore, under a proper application of the Court's construction of the term "particles consisting essentially of," the asserted claims of the '363 patent cannot be infringed, either literally or under the doctrine of equivalents, by particles that are amorphous, even if they include incidental crystalline medicament.

B. Elan Has No Infringement Case Under Its Preferred Application of The Transitional Phrase "consisting essentially of."

Even under Elan's application of the Court's construction, however, it cannot prove infringement. In Elan's view, the "consisting essentially of 99.9-10% by weight of a crystalline medicament" limitation is met if at least 10% of the weight of the particles is "crystalline medicament," regardless of the presence of amorphous medicament in the particles. Assuming for purposes of this letter brief the admissibility of Elan's expert evidence,[5] Elan cannot establish that at least 10% by weight of the Abraxane particles is crystalline paclitaxel.

First, Elan has no actual measurements showing that the particles in Abraxane are at least 10% by weight crystalline paclitaxel. Elan's only affirmative evidence on the purported amount of crystallinity in Abraxane was provided by Elan's expert, Dr. Eric Munson, who claimed that 7% and 8% of the paclitaxel in two samples derived from Abraxane is crystalline. Munson further claimed that 50% error rates in these determinations meant that the paclitaxel in Abraxane could be as little as 3.5% or up to 12% crystalline. (Munson Report ¶¶ 18-24 and 27.C.) (Ex. A)

Because Munson's actual "measurements" indicated less than 10% crystallinity, he had to rely on the 50% error rate to reach 10%. But Elan cannot carry its burden of proof on infringement by relying on an error rate. Here, moreover, the error rate is itself the product of speculation, which Munson admitted by testifying at his deposition that this was his "best guess

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[5] Abraxis can – and, if necessary, will – establish that Elan's expert testimony and associated testing evidence fails admissibility standards because: (a) Elan refused to produce much of its testifying experts' work, including other tests on Abraxane that *its testifying experts* performed, claiming it was shielded by the work-product doctrine; (b) Elan failed to comply with its expert disclosure obligations even for those tests it did disclose; and (c) the testimony and testing do not meet basic standards for reliability and general acceptance.

estimate" at the amount of "error." (Expert Report of Eric Munson ¶ 24 (Ex. A); 11/29/07 Munson Dep. at 230:18-232:8 (Ex. C).) Munson's "best guess estimate" is rank speculation that has no probative value; accordingly his testimony cannot support the burden of proof by the preponderance of the evidence that Elan bears on infringement. *See Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 249-250 (U.S. 1986) ("If the evidence is merely colorable, or is not significantly probative, summary judgment may be granted.") (internal citations omitted).

Second, Munson's speculation that 12% of the paclitaxel in Abraxane may be crystalline answers the wrong question. Under the plain language of the claims, the issue is not whether 10% of the *paclitaxel* in Abraxane is crystalline; rather, the question is whether 10% of the *particles* by weight is crystalline medicament. Answering that question requires consideration not only of the paclitaxel in the particles but of the particles' entire weight, including the adsorbed surface modifier. Neither Munson, nor any other Elan expert, made that calculation. *See PharmaStem Therapeutics v. ViaCell, Inc.*, 491 F.3d 1342, 1353-4 (Fed. Cir. 2007) (affirming finding of noninfringement for failure of proof where "having chosen not to try to prove that particular cord blood samples or categories of samples contained sufficient stem cells to effect hematopoietic reconstitution of an adult, PharmaStem took the risk that the court would conclude that it had failed to prove that any of the defendants' cryopreserved samples infringed."). Abraxis's data, which Elan has not controverted,

REDACTED of the Abraxane particles by weight is allegedly crystalline paclitaxel, which falls short of the 10% minimum recited by the claims.

Thus, even under Elan's preferred application of the transitional phrase "consisting essentially of," Elan's evidence of infringement is speculative, ignores the "by weight" limitation, and falls short of the recited range. Further, the doctrine of equivalents will not help Elan for the reasons discussed above and because Elan has not contended that crystallinity of less than 10% is equivalent to 10%. For these reasons, no reasonable jury can find infringement.

Conclusion

Expert discovery has now confirmed what Abraxis had argued in its Rule 11 motion: Elan's crystalline nanoparticle patent cannot cover Abraxis's amorphous nanoparticle cancer treatment. Abraxis respectfully requests that the Court allow it to end Elan's infringement claims on summary judgment.

Respectfully submitted,

Karen E. Keller

Karen E. Keller (#4489)

Attachments

cc: Clerk of Court (by CM/ECF)
John G. Day, Esq. (redacted version by CM/ECF)
Steven J. Balick, Esq. (redacted version by CM/ECF)
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EXHIBIT A

EXPERT REPORT OF ERIC J. MUNSON

Elan Pharma International Ltd. versus Abraxis BioScience Inc., Civil Action Number 06-438-GMS, District of Delaware

1. I reside at 1324 Lawrence Avenue, Lawrence, Kansas 66049. I hold a B.A. degree in Chemistry and Physics from Augustana College, Sioux Falls, SD (1987) and a Ph.D. in Chemistry from Texas A&M University (1993). I was a Postdoctoral Associate at the University of California, Berkeley, from 1993-94.

2. Since 2006, I have been employed as a Professor in the Department of Pharmaceutical Chemistry at the University of Kansas. From 2001 to 2006 I was employed as an Associate Professor in the Department of Pharmaceutical Chemistry at the University of Kansas at Lawrence. From 1994 to 2001 I was employed by the University of Minnesota, Twin Cities, where I successively held the titles of Assistant Professor and Associate Professor in the Department of Chemistry.

3. I currently serve on the Editorial Board of *the Journal of Pharmaceutical Science.* I have published more than 65 articles in refereed journals, including more than a dozen concerning the characterization of pharmaceutical solids. My area of expertise includes solid-state Nuclear Magnetic Resonance (NMR) spectroscopy and other techniques to characterize solid pharmaceuticals.

4. Based on my experience, in particular, my expertise in spectroscopic and other analytical techniques and through extensive collaborations with experts in the field of pharmaceutical solids, I have developed considerable expertise in the analysis of active pharmaceutical ingredients. More specifically, I have expertise in using spectroscopic and other analytical techniques to differentiate and identify different forms of active pharmaceutical ingredients, as well as formulated products of such active pharmaceutical ingredients. I have published more than a dozen articles on the analysis of different forms of pharmaceutical compounds using solid-state NMR

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18. The solid-state NMR spectrum of the lyophilized sample is shown in Appendix G. The spectrum is very similar to that of the amorphous paclitaxel spectrum. However, there is a shoulder on the peak centered at 204 ppm. This indicates that the material may contain a phase of paclitaxel other than amorphous paclitaxel.

19. The solid-state NMR spectrum of the air-dried sample is shown in Appendix H. The spectrum is also very similar to that of the amorphous paclitaxel spectrum. However, there is also a shoulder on the peak centered at 204 ppm. This indicates that the material may contain a phase of paclitaxel other than amorphous paclitaxel.

20. In order to determine the nature of the peak at 204 ppm, which is due to C9 in the numbering scheme of paclitaxel shown in Appendix I, the spectrum of the amorphous paclitaxel was deconvoluted into two and only two components. Shown in Appendix J is the spectrum of amorphous paclitaxel deconvoluted into its two components. The spectrum of amorphous paclitaxel is shown in red. The peak for C9 in amorphous paclitaxel is located in the region between 198 ppm and 213 ppm. Outside of this region is noise. In the top spectrum is the deconvolution showing the smaller of the two peaks, and in the bottom spectrum is the deconvolution showing the larger of the two peaks. The sum of those two peaks is shown in the blue line which closely follows the red line of the spectrum. The difference between the blue line (i.e. deconvoluted spectrum) and the red line (i.e. the actual spectrum) is shown in the blue noise between 200 and 210 ppm. This noise should be identical to that of the noise outside of the region between 198 ppm and 213 ppm, and that is clearly the case. This demonstrates that the spectrum of amorphous paclitaxel can be simulated into just two peaks.

21. This deconvolution process was repeated for the sample prepared using the lyophilization method. In order to deconvolute the spectrum, the exact same

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parameters that were used to deconvolute the spectrum of amorphous paclitaxel were used for the sample prepared using the lyophilization method. Those two components are shown in the bottom and middle spectra of Appendix K. However, when the spectrum of the sample prepared using the lyophilization method was deconvoluted using those two peaks, a third peak appeared. The third peak is located at approximately 207 ppm, and is considerably narrower than the peaks used to deconvolute the spectrum of the amorphous material. The area of this third peak was approximately 4%.

22. The deconvolution process was repeated for the sample prepared using the air-dried method. As before, the exact same parameters that were used to deconvolute the spectrum of amorphous paclitaxel were used for the sample prepared using the air-dried method. Those two components are shown in the bottom and middle spectra of Appendix L. As before, when the spectrum of the sample prepared using the air-dried method was deconvoluted using those two peaks, a third peak appeared. This third peak has the same location and line width as used in the deconvolution of the sample prepared using the lyophilization method. The area of this third peak was approximately 3.5 %.

23. The nature of the third peak at 207 ppm was investigated. There is no peak in the spectrum of crystalline anhydrous paclitaxel at 207 ppm. However, there is a peak at approximately 207 ppm in the spectrum of the crystalline dihydrate paclitaxel. This peak indicates two things. First, it strongly suggests that the dihydrate sample is not pure dihydrate, but rather is a mixture of two different crystalline forms. The line widths of the peaks at 209 and 207 ppm are both relatively narrow, consistent with a crystalline form. One of the forms is likely the dihydrate, which is probably the larger peak at 209 ppm. The second peak at 207 ppm is likely a different crystalline form that is very similar in its conformation and arrangement to that of the crystalline form of the dihydrate. This peak is very similar in its chemical shift to that of the peak observed in the deconvoluted spectra. Moreover, the other peaks in the spectrum are

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also very similar to the dihydrate. This suggests that this crystalline form is very similar structurally to that of the crystalline dihydrate form.

24. The peak at 204 ppm in both the anhydrate and the dihydrate form are very similar, and representative of one of the two molecules in the asymmetric unit. The peak around 206 ppm in the anhydrate form is not split. However, the two peaks at 207-209 ppm in the dihydrate spectrum indicate that different crystalline forms exist, and that the chemical shift of the peak at about 207 ppm is representative of one of the two molecules in the crystal lattice. The other molecule in the crystalline form is present at 204 ppm. Therefore, the deconvoluted peak at 207 ppm represents only half of the intensity of C9. The actual intensity of the crystalline form indicated by the peak at 207 ppm in the deconvoluted spectrum is twice that of the integrated area. So for the peak in the spectrum of the sample prepared using the lyophilization method, the actual area for the crystalline form represented by the peak at 207 ppm is 8 %. The error associated with measurement is estimated to be 50% of the determined value, so the total amount of the form represented by the peak at 207 ppm in the deconvoluted spectrum is between 4% to 12%. Correspondingly, the deconvolution of the spectrum of the sample prepared using the air-dried method, which contained 3.5% of the peak at 207 ppm, would correspond to 7 % of the total sample, and therefore have a range of 3.5% to 10.5%.

25. Solid-state NMR spectroscopy measures the fraction of each phase present in the sample. However, the sample itself consists of particles that contain a range of paclitaxel phases. Samples that are on average from 3.5 to 12% crystalline, such as those discussed above, include individual particles that are mostly crystalline.

26. This crystalline form is present in both samples prepared using the lyophilization method and the air-dried method in roughly equal intensity. This strongly suggests that this form was present in the initial Abraxane formulation from the vial and this crystalline form remained unchanged during the isolation process.

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Moreover, the processing steps used to isolate the particles likely produces some amorphous paclitaxel, and therefore the actual level of crystalline paclitaxel in the Abraxane product is likely higher than what was measured. This is consistent with the solid-state NMR spectrum of the initial Abraxane formulation from the vial.

27. I have formed the following opinions and hold these opinions to a reasonable degree of scientific certainty:

A. The solid-state NMR spectra of amorphous paclitaxel and the crystalline anhydrate and dihydrate forms of paclitaxel are very different.

B. The peak at 207 ppm is diagnostic of the presence of a crystalline phase of paclitaxel.

C. Crystalline paclitaxel was measured at levels between 3.5% and 12% of the total paclitaxel present in the samples prepared using the lyophylization method and the air-dried method.

D. These samples consist of particles that contain a range of paclitaxel phases. Samples that are on average from 3.5 to 12% crystalline, such as those discussed above, include individual particles that are mostly crystalline.

E. The actual level of paclitaxel that is crystalline in the initial Abraxane formulation out of the vial is likely higher than the levels measured in the samples prepared using the lyophylization method and the air-dried method.

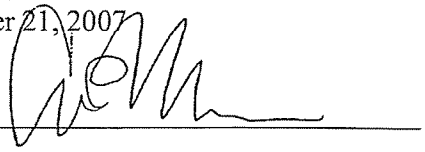
F. It follows that the paclitaxel that is crystalline in the reconstituted formulation of Abraxane is at least equal or higher than the levels

measured in the samples prepared using the lyophylization method and the air-dried method.

G. It is my opinion that Abraxane contains particles consisting essentially of 99.9%-10% by weight of a crystalline medicament useful in treating cancer susceptible to treatment with a said medicament, said medicament having a solubility in water of less than 10 mg/ml, where "particles consisting essentially of" is construed to mean "the particles, composed of crystalline medicament and surface modifier, may also include other ingredients that do not affect their basic and novel properties, and are essentially free of solvent and other contaminants," and where "crystalline medicament useful for treating cancer" is construed to mean "a medicament suitable for treating cancer that has a regular arrangement of atoms or molecules in a space lattice, as distinguished from amorphous". The paclitaxel in Abraxane is present in one or more discrete crystalline phases.

H. It is my opinion that Abraxane contains particles consisting essentially of from about 0.1 to about 99.9% by weight of a crystalline organic drug substance having a solubility in water of less than 10 mg/ml, where "particles consisting essentially of" is construed to mean "the particles, composed of crystalline medicament and surface modifier, may also include other ingredients that do not affect their basic and novel properties, and are essentially free of solvent and other contaminants," and where "organic drug substance" is construed to mean "a crystalline carbon-based therapeutic or diagnostic agent suitable for administration to a mammal."

Dated: September 21, 2007

Signed: 

Eric Munson

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EXHIBIT B

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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

EXPERT REPORT OF HARRY G. BRITTAIN, PhD, FRSC

I. Summary of Credentials and Professional Experience

1. I am presently the Institute Director of the Center for Pharmaceutical Physics in Milford, New Jersey, a private consulting company I established in 1999. My areas of research are best described as being in the fields of physical pharmacy, with special concentration on preformulation, formulation design, and substance characterization. I received a bachelor's degree in 1970 and a master's degree in 1972 from Queens College, New York and a Ph.D. in physical chemistry from the City University of New York in 1975. Between 1975 and 1976 I was a Postdoctoral Research Fellow at the University of Virginia (Charlottesville, Virginia).

2. From 1996 to 1999 I was Vice-President of Pharmaceutical and Chemical Development at Discovery Laboratories Inc. (located in Doylestown, Pennsylvania), where I was responsible for the non-clinical aspects of drug development and management of all analytical,

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stated that "Stable pipsulfan nanoparticles were also prepared using bovine serum albumin as the surface modifier" ['363 patent, column 9, lines 44-45], which provides ample demonstration that BSA is fully capable of functioning as a surface modifying agent capable of stabilizing particles consisting of substances having low water solubility.

29. A correction to Claim 1 of the '363 patent was issued on April 25, 2006, and with that correction, Claim 1 reads:

> 1. Particles consisting essentially of 99.9%-10% by weight of a crystalline medicament useful in treating cancer susceptible to treatment with said medicament, said medicament having a solubility in water of less than 10 mg/ml, and having a non-crosslinked surface modifier adsorbed on the surface thereof in an amount of 0.1-90% by weight and sufficient to maintain an average effective particle size of less than 1000 nm, wherein said medicament is selected from the group consisting of alkylating agents selected from the group consisting of alkylating agents having a bis-(2-chloroethyl)-amine group, alkylating agents having a substituted aziridine group, alkyl sulfonates, and N-alkyl-N-nitrosoureas; antimetabolites; natural products selected from the group consisting of vinca alkaloids, epipophylotoxins, adriamycine, daunomycine, doctinomycine, daunorubicin, doxorubicin, mithramycin, bleomycin, mitomycin, enzymes, biological response modifiers, camptothecin, taxol and retinoids; hormones and antagonists: radiosensitizers; platinum coordination complexes; anthracenediones; and adrenocortical suppressants. ['363 patent, column 14, lines 7-28]

The scope of Claim 1 can be more readily understood by one of ordinary skill if the claim is divided into five elements so that they may be discussed in turn.

B1. Element (a) of claim 1 of the '363 patent

30. Element (a) of claim 1 reads "Particles consisting essentially of 99.9%-10% by weight of a crystalline medicament useful in treating cancer susceptible to treatment with said medicament …" ['363 patent, column 14, lines 7-9] In its order construing the terms of the '363 patent, the court defined the term "particles consisting essentially of" as "the particles, composed of crystalline medicament and surface modifier, and also include other

ingredients that do not affect their basic and novel properties, and are essentially free of solvent and other contaminants". The Court also defined the term "crystalline medicament useful in treating cancer" as "a medicament suitable for treating cancer that has a regular arrangement of atoms or molecules in a space lattice, as distinguished from amorphous." This latter definition infers that an amorphous material would be one that is characterized by a lack of "regular arrangement of atoms or molecules in a space lattice".

31. This claim element therefore identifies the solid-state characteristics of the drug substance used to treat cancer, namely where individual medicament particles are characterized by a degree of crystallinity (*i.e.*, the percentage of molecules arranged in a space lattice) in the amount of 99.9% to 10% by weight. Therefore, the literal meaning of this claim element is that if two or more particles contain a degree of crystallinity in the range of 99.9% to 10% by weight, then those particles would necessarily also contain a non-crystalline, or amorphous, component. Therefore, element (a) of claim 1 encompasses particles that consist essentially of 0.1% to 90% by weight of an amorphous medicament.

32. In order to fully understand element (a) of claim 1, one must understand how an individual particle could contain 0.1% to 90% by weight of an amorphous component. It is well known to crystallographers that a perfect crystal (*i.e.*, a crystal consisting entirely of molecules arranged in a space lattice) is difficult to obtain, and that the majority of crystalline solids actually contain regions of crystalline defect. These defective regions are themselves characterized by a lack of long range order, that is, no type of space lattice can be used to define the structure. Crystalline solids therefore consist of zones of crystallinity that are assembled to obtain the solid itself. Sir Lawrence Bragg, who with his father, developed the science of x-ray diffraction for structure elucidation, discussed the imperfect

structure of real crystals in his 1955 book, "The Crystalline State: A General Survey" (see Exhibit D), commenting:

> The quantitative treatment of diffraction by the whole crystal would at first sight appear to be an extremely complex problem. An ideal case for mathematical treatment would be that of a parallel monochromatic beam falling upon an absolutely perfect crystal. In actual fact, crystals rarely approach this condition. They almost invariably consist of a mosaic of small crystalline blocks, which are inclined at small angles to each other so that there is necessarily an interruption of the regular pattern at the intervening boundaries.

33. Obviously, as the content of disorder between the crystalline blocks increases in a solid, the degree of crystallinity of that solid necessarily decreases. Therefore, the element (a) of claim 1 that encompasses particles consisting essentially of 99.9% to 10% by weight of a crystalline medicament (or, alternatively, 0.1% to 90% by weight of an amorphous medicament) speaks specifically to real particles that are composed of sufficient crystalline and amorphous regions so that the overall crystalline composition of individual particles averages in the range of 99.9% to 10% by weight.

34. While the determination of degree of crystallinity in micrometer-sized particle can easily be performed using X-ray powder diffraction, the question arises as to how one can perform such determinations on nanometer-sized particles. In the 4th edition of his book, "Applied X-Rays" (published in 1955), Clark provided an answer to this question (see Exhibit E). Discussing the diffraction of colloids, Clark notes that

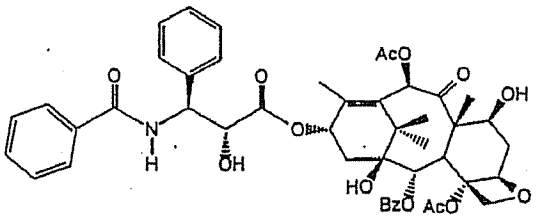
> Diffraction by Colloids. A single crystal subjected to analysis by the pinhole method produces a Laue diffraction pattern characterized by a symmetrical array of spots, lying on a series of ellipses. As the size decreases and more individuals lie in the path of the beam, this symmetrical pattern gives way to a random" peppering" of spots. As the size decreases and the number increases still further, these small spots begin to assemble on a series of concentric rings. Finally the spots become so small and numerous that they merge into uniformly intense concentric rings, the so-called" powder" pattern. The maximum range of grain diameter over which these sharp rings are registered

> is 10^{-3} to 10^{-5} cm. It is clearly evident that a sharp interference effect can take place only with a certain minimum number of parallel diffracting planes in each particle. As this number falls below the minimum, in other words, as the particle size decreases below about 10^{-5} cm, it follows that interference is less perfect and that the diffraction rings (or lines by the Hull-Debye-Scherrer method) will become broader in proportion to decreasing size until in the neighborhood of 10^{-8} cm atomic dimensions are reached. Conceivably these" halos" might merge, and the pattern would then be classed as amorphous. A measurement of line breadth in the colloidal range will therefore allow calculation of particle size. The question arises of how small a particle can be and still produce a diffraction pattern upon which maxima may be detected. Levi in his study of metallic catalysts reports that particles only about five times as large as the unit crystal cell (in other words, 10 or 15 parallel planes) will produce resolved diffraction maxima, even though these are very diffuse.
>
> Now it must be noted that diffuse diffraction maxima must be the consequence of any crystal grating which is imperfect in the sense of having too few parallel planes or of having these planes, ordinarily sufficient in number, distorted, bent, or imperfectly aligned. In other words, it is conceivable that an assemblage of fairly large colloidal particles might yield very diffuse patterns simply because molecules which may themselves be very large are not oriented in regular fashion. This condition is observed in the colloidal gels and is particularly interesting in the light of the prediction that simple mechanical stretching might tend to pull these diffracting units into parallel position and thus permit them to act as a diffraction grating.

35. One key feature of this discussion is that a lower limit in particle size exists for obtaining sharp-line X-ray powder patterns, and that for particles smaller than this, the lines would be unacceptably broad. According to Clark, this limit corresponds to where the size of the diffracting particles is in the range of 10^{-5} cm, which is equivalent to 0.1 μm or 100 nm. In addition, Clark notes that colloidal sized particles typically yield vary diffuse patterns. Consequently, one must conclude that X-ray powder diffraction is not a useful technique for determining the degree of crystallinity of particles that are in the nanometer size range.

B2. Element (b) of claim 1 of the '363 patent

36. Element (b) of claim 1 reads "… said medicament having a solubility in water of less than 10 mg/ml …" ['363 patent, column 14, lines 9-11] This claim element specifies that the



45. The Abraxane® product Package Insert also supplies a small amount of information regarding the physical properties of the paclitaxel active ingredient:

> Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.91. It is highly lipophilic, insoluble in water, and melts at approximately 216°C to 217°C.

REDACTED

REDACTED

REDACTED

N. The Abraxis Product Known as Abraxane® Falls within the Scope of Claim 17 of United States Patent 5,399,363 Under the Doctrine of Equivalents

151. Dependent claim 17 of the '363 patent states "The particles of claim 1 wherein said surface modifier is present in an amount of 10 to 30% by weight based on the total weight of the dry particle." As discussed above in paragraph 51,

REDACTED

152. Since the Abraxane® product has already been shown to fall within the scope of claim 1 of the '363 patent under the Doctrine of Equivalents, the product is also shown to fall within the scope of claim 17 of the '363 patent under the Doctrine of Equivalents.

I am continuing my study and analysis of the information I have considered in preparing this report. From time to time, I may refine, expand, or supplement my opinions during the course of that further study. Also, I reserve the right to alter my opinions in the event that additional information is brought to my attention.

Signed,

Harry G. Brittain

Date: September 28, 2007

Harry G. Brittain, PhD, FRSC

EXHIBIT C

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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

ORAL VIDEOTAPED DEPOSITION

ERIC J. MUNSON, Ph.D.

NOVEMBER 29, 2007

ORAL VIDEOTAPED DEPOSITION OF ERIC J. MUNSON, Ph.D., produced as a witness at the instance of the Plaintiff and duly sworn, was taken in the above-styled and numbered cause on the 29th day of November, 2007, from 9:07 a.m. to 7:15 p.m., before Melinda Barre, Certified Shorthand Reporter in and for the State of Texas, reported by computerized stenotype machine at the offices of Baker Botts, 910 Louisiana, 32nd Floor, Houston, Texas, pursuant to the Federal Rules of Civil Procedure and the provisions stated on the record or attached hereto.

one of those variables, the T-1 Rho value, the T-1 Rho value is different even slightly between them. You can actually get slightly different intensities associated with their relative peak intensities.

So the downside to that is with the differences in the relative peak intensities, that's just one component. So you need to consider that, as I said, in the case of Neotame, that that could end giving instead of a 50/50, you end up with a 60/40.

So when you add in that parameter associated with the T-1 Rho -- or TCH values and possible relative intensities associated with the CSA parameters, also when you add in the parameters associated with the potentially different T-1 Rho values, these are all things that need to be considered.

Now, to get to your second question --

Q. I still haven't had an answer. Where did you get 50 percent? I haven't heard anything about 50 percent. Where did you get this 50 percent?

A. Okay. So, like I said --

Q. How did you calculate 50 percent? Where did that number come from exactly in, you know, a hundred words or less?

MR. SULLIVAN: Object.

Q. (By Ms. Evans) Come on. Hopefully you can answer that question in less than ten minutes, Dr. Munson.

MR. SULLIVAN: Object.

A. Well, one of the things that, for example, we've done is if you look at our quantitation paper that we published as specifically related to Neotame, that paper is approximately 12 pages long; and it describes a lot of the details associated with all this. So from that particular perspective, you know, I'm trying to explain the very complex type of system in terms of estimating some of the errors that are going to be associated with quantitation. So one of the things I need to do is to understand how each of the various components can be.

Now, when you look at it, relatively speaking, you know, what are the parameters that you know? Well, you don't necessarily know what the TCH value is. You don't necessarily know what the T-1 Rho value is. You don't necessarily know what the T-1 values are. So all of these are potential errors associated with it. So what you need to do is come up with what I call a best guess estimate.

So, once again, I know, for example, differences in T-1 Rho values can lead to something

clearly on the order of 20 to 30 percent depending upon those values. Also potential differences in the T-1s can also matter. Slight differences in the CSA powder patterns can make a slight difference.

So all of them, when you add them up together -- I considered 50 percent to be sort of a conservative estimate in terms of the amount of error that could potentially be present in this.

Q. So looking at paragraph 14 of your report, you say that the various relaxation parameters of these forms, referring to paclitaxel, anhydrate crystals, crystalline paclitaxel, dihydrate and amorphous paclitaxel, were also measured; and it was found that the proton T-1 and T-1 Rho values were similar. Do you see that?

A. I do see that.

Q. Is that correct? Is that a true statement?

A. So you're referring specifically to the samples that were stated to be crystalline paclitaxel, anhydrate crystalline paclitaxel, dihydrate and amorphous paclitaxel?

Q. Yes.

A. So within the context of simply stating that, the fact that you're looking at these particular values and these representations of the

UNITED STATES DISTRICT COURT
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ELAN PHARMA INTERNATIONAL LIMITED, Plaintiff,	)	
vs.	)	Case No. 06-438-GMS
ABRAXIS BIOSCIENCE, INC., Defendant.	)	

REPORTER'S CERTIFICATE

ORAL VIDEOTAPED DEPOSITION OF ERIC J. MUNSON, PH.D.

NOVEMBER 29, 2007

I, Melinda Barre, Certified Shorthand Reporter in and for the State of Texas, hereby certify to the following:

That the witness, ERIC J. MUNSON, Ph.D., was duly sworn and that the transcript of the deposition is a true record of the testimony given by the witness;

That the deposition transcript was duly submitted on _____ to the witness or to the attorney for the witness for examination, signature, and return to me by _____.

That pursuant to information given to the deposition officer at the time said testimony was taken, the following includes all parties of record and the amount of time used by each party at the time of the

deposition:

Emily Evans (7h32m)
Attorney for Plaintiff
Jeffrey D. Sullivan (0h8m)
Attorney for Defendant

That a copy of this certificate was served on all parties shown herein on _____ and filed with the Clerk.

I further certify that I am neither counsel for, related to, nor employed by any of the parties in the action in which this proceeding was taken, and further that I am not financially or otherwise interested in the outcome of this action.

Further certification requirements pursuant to Rule 203 of the Texas Code of Civil Procedure will be complied with after they have occurred.

Certified to by me on this 12th day of December, 2007.

_____

Melinda Barre, Texas CSR 2192
Expiration Date: December 31, 2008
Firm Registration No. 189

EXHIBIT D

REDACTED IN ITS ENTIRETY