IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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

PLAINTIFF'S OFFER OF PROOF
REGARDING TESTIMONY OF DR. CORY J. BERKLAND

WHEREAS, it its Order Regarding Abraxis' Motions in Limine Nos. 1 and 4 (D.I. 567) the Court ruled that Dr. Cory J. Berkland could not offer expert opinion at trial critiquing Abraxis' XRPD testing; and

WHEREAS, during a telephone conference with the parties on May 29, 2008, the Court granted defendant Abraxis Bioscience, Inc.'s ("Abraxis") oral motion to strike the Supplemental Expert Report of Cory J. Berkland ("Berkland Supplemental Expert Report"), submitted in response to the deposition testimony of Katherine Melody, the Supplemental Expert Report of Jerry L. Atwood, and the Court's May 19, 2008 Order (D.I. 569) clarifying its August 17, 2007 claim construction Order (D.I. 271);

NOW COMES plaintiff Elan Pharma International Ltd. ("Elan"), and submits the following offer of proof: If Cory J. Berkland had been permitted to testify at trial concerning the criticisms of Abraxis' XRPD testing that were set forth in the Expert Report of Cory Berkland (attached hereto as Exhibit A), and concerning the facts underlying, and basis for the conclusions

set forth in, the Berkland Supplemental Expert Report (attached hereto as Exhibit B), his testimony would have been as follows:

PXRD Is Not Sufficient to Detect
Paclitaxel Nanoparticle Crystallinity in Abraxane

1. In light of the newly produced documents and the deposition testimony of Katherine Melody, the lack of sensitivity of PXRD to detect crystallinity in the paclitaxel nanoparticles in Abraxane is confirmed. Furthermore, the omission of critical experiments and information that I believe should have been requested of Micron in order to properly quantify crystalline content of paclitaxel nanoparticles in Abraxane is verified by Ms. Melody's testimony and further calls into question the conclusions Abraxis draws from her testing. Finally, new questions have arisen as to the methodology used to generate PXRD data. These questions are based not on the general technical qualifications and competencies of Ms. Melody or Micron, which I do not question, but on the fact that they appear to have been given inadequate guidance as a vendor when Abraxis asked them to test Abraxane.

2. Selected lab notebook entries provided by Ms. Melody (ABRX 0537237) and email correspondence with Dr. Selvaraj (ABRX 0151402 and others) indicate that Micron received instructions to follow standard operating procedure (SOP) XRD002 Rev.001. This SOP indicates adherence to the U.S. Pharmacopeia specifications on X-ray diffraction, which is also verified in e-mail correspondence between Dr. Selvaraj and Micron and in the multiple reports provided by Micron to Abraxis that I have reviewed. Unfortunately, several key points from the U.S. Pharmacopeia section on X-ray diffraction were not adhered to in the studies Abraxis commissioned for Abraxane.

3. The mass of material analyzed can cause limitations in quantifying crystalline content using PXRD. PXRD is similar to most analytical techniques in that sensitivity and

accuracy depend upon the amount of material that is analyzed. For example, as the amount of total material in a sample decreases, one would expect a corresponding decrease in detectability (e.g. the intensity of peaks would decrease). As the amount (mass) of sample decreases below a threshold level, there is a corresponding decrease in peak intensity relative to "noise" of the spectrum peaks obtained by PXRD for that sample. It is surprising to me that the mass of material that was analyzed at Micron was never recorded in the documents I viewed, which included lab notebook excerpts, email correspondence between Micron and Abraxis, and reports. When questioned about the mass used for experiments, Ms. Melody did not recall how much material was tested. Since the amount of material analyzed was not quantified, a quantitative assessment of the amount of crystalline material would not be possible either. The U.S. Pharmacopeia states "In quantitative analyses of materials, a *known amount* of standard usually is added to a *weighed amount* of specimen to be analyzed" (my emphasis). Therefore, one cannot conclusively determine the crystalline content of paclitaxel from the PXRD data provided by Micron. Further, testing a small amount of material (which we cannot rule out given that Micron was not instructed to record sample size) would limit the detection of crystalline content.

4. The fact that Abraxane is a mixture can cause limitations in quantifying crystalline content using PXRD. Several problems can arise when analyzing mixtures using PXRD. The U.S. Pharmacopeia states:

> "The absorption of the radiation by any specimen is determined by the number and kinds of atoms through which the X-ray beam passes." "Therefore, it is important in quantitative studies that standard curves relating amount of material to the [peak] intensity…be determined in a matrix similar to that in which the substance will be analyzed." "The standard used should have approximately the same density as the specimen and similar absorption characteristics. More important, its diffraction pattern should not overlap to any extent with that of the material to be analyzed."

Recall that Abraxane is a mixture of paclitaxel and human albumin, with the albumin being present in a nine-fold excess by weight relative to the paclitaxel particles. Tests performed by Micron have not verified the density or X-ray absorption characteristics of paclitaxel or albumin. In other words, using a physical mixture of paclitaxel and albumin is not validated as an adequate standard due to potential differences in the respective density or X-ray absorption of these two materials within the mixture. In addition, there is an overlap between the amorphous "humps" in the albumin diffraction pattern and the diffraction pattern of paclitaxel, which further confounds any quantitative assessment of crystallinity benchmarked by the physical mixture.

5. The small particle size in Abraxane can cause limitations in quantifying crystalline content of the paclitaxel particles using PXRD. Referring to using PXRD as an analytical tool for nanoparticles, Ms. Melody indicated in her deposition that "the peaks are wider" (Melody deposition, 108:3 and see 41:1-7) in comparison to the peaks associated with larger particles. This, again, confirms statements in my previous report that a decrease in crystal particle size leads to a reduction in peak height (e.g. as a result of peak broadening). The extremely small particle size in Abraxane (~130 nm) continues to make this an important point concerning the sensitivity of PXRD for quantifying crystallinity in this product. Conversely, the particle size for the crystalline paclitaxel standard (raw material) was significantly larger (5-500 microns as reported in US Pat. No. 6,749,868, Col. 31, L. 64-65). Crystals of this size and shape are known to exhibit "preferred orientation" effects, which can influence (e.g. amplify) peak intensity according to the U.S. Pharmacopeia. Thus, Micron recommends that the particle size be less than 10 microns (Melody Deposition, Exhibit 4), a specification which evidently was not followed.

6. Preparation of the samples can also affect the measure of crystalline or amorphous character of particles analyzed using PXRD. I have reviewed Micron records and have heard testimony from Ms. Melody indicating that the Micron testing involved prior mechanical homogenization of the sample and chopping it with a razor blade under non-sterile conditions (Melody deposition, 53:22-57:8). This type of physical manipulation of a sample can induce "phase changes" that would affect the degree of crystallinity or amorphousness that subsequent PXRD would detect. Not only is it possible that such a phase change (including, possibly, a reduction in the apparent degree of crystallinity) could have been induced by Micron's sample preparation methods, but it is impossible to estimate what degree of such change may have occurred, because Micron did not conduct a PXRD assay of the Abraxane sample prior to its homogenization and chopping (Melody deposition, 53:22-54:5). Such a pre-homogenization reference pattern would be necessary (and is recommended by U.S. Pharmacopeia protocol) in order for the post-homogenization PXRD results to be relied upon with any scientific certainty. When questioned, Ms. Melody confirmed that it would have been advisable to check the diffraction pattern of the sample prior to grinding (Melody deposition, 53-55 and 63). This is another reason I would not place scientific reliance on the PXRD results reported by Micron and relied on by Dr. Atwood in reaching any conclusion regarding the presence or prevalence of crystalline particles within Abraxane.

7. The relative amount of material in a mixture can cause limitations in quantifying crystalline content using PXRD. Reducing the mass of material reduces the ability to detect that material. The relative mass of crystalline material being examined can be further reduced if it is mixed with another material, such as albumin. This dilution of the material of interest (e.g. paclitaxel) further limits the detection of crystalline content (e.g. 100 mg of Abraxane contains

only 10% paclitaxel). The U.S. Pharmacopeia states regarding PXRD "In favorable cases, amounts of crystalline materials as small as 10% may be determined in solid matrices." This excerpt indicates that, if a large mass of Abraxane were analyzed (we are not sure of the mass analyzed) and if this were a "favorable case", the 10% paclitaxel would have to be near 100% crystalline to be detectable in Abraxane.

8. Each of these limitations (paragraphs 2-7) for using PXRD to detect crystallinity sheds serious doubt on the effectiveness of this analytical technique Abraxis relied upon for determining the crystallinity of paclitaxel nanoparticles in Abraxane. I am convinced that the PXRD results Ms. Melody reports are scientifically insufficient to draw a reliable conclusion. The conclusions that Dr. Atwood reached regarding the crystallinity of Abraxane based on this data are, therefore, nullified. In her deposition testimony, Ms. Melody expressed similar doubts:

> Q. I'm trying to understand, if we take all these factors we've been talking about today...are you comfortable with someone making a conclusion, based on your data of the samples that Abraxis provided, that the material in the nanoparticles is crystalline or amorphous, or would you want to see some further testing done to nail down some of these variables?
>
> * * *
>
> A. I would like to see some more testing done.

Melody deposition, 110:1-10; see also Melody deposition, 104:13-105:1

> Q: Is the x-ray powder diffraction work that you did for Abraxis sufficient enough to make a conclusion about the nanoparticles in Abraxane, whether they're crystalline or amorphous?
>
> * * *
>
> A: I'm still not sure I understand whether they are crystalline or amorphous.

The proper method to assess whether PXRD may be used to quantify crystalline content in Abraxane is clearly described in the U.S. Pharmacopeia, which states:

> "In quantitative analyses of materials, a known amount of standard usually is added to a weighed amount of specimen to be analyzed. This enables the amount of the substance to be determined relative to the amount of

> standard added. The standard used should have approximately the same density as the specimen and similar absorption characteristics. More important, its diffraction pattern should not overlap to any extent with that of the material to be analyzed. Under these conditions a linear relationship between line intensity and concentration exists. In favorable cases, amounts of crystalline materials as small as 10% may be determined in solid matrices."

9. Standards are necessary to quantify crystallinity, as further verified on Micron's website (Melody deposition, Exh. 4) and by Ms. Melody in her deposition (e.g., Melody deposition, 106, 107)). Ms. Melody testified that she believes it may be possible to detect amounts of crystalline material in a mixture when it is present in a quantity below 10% of the mixture. (Melody deposition, 53:2-11; 70:3-21; 71:11-15; and 72:3). However, as Ms. Melody correctly pointed out, in order to know whether this is in fact possible, one must first determine the limits of detection of the particular system under evaluation. To determine limits of detection for materials, one performs reference experiments with those materials (Melody deposition, 72:11-16); however, Ms. Melody, Micron's designated PXRD technologist, was not instructed to perform such reference experiments to establish the limits of detection in her work with Abraxane samples (Melody deposition, 72:17-21). Ms. Melody even goes so far as to recommend the additional experiments that would she would like to see to test the limit of detection for a mixture of paclitaxel and albumin and to assess the ability of PXRD to quantify crystalline content (Melody deposition, 110-112).

10. Taken comprehensively, I am convinced that the paclitaxel medicament portion of nanoparticles in Abraxane cannot be qualified as entirely or even mostly amorphous based on the PXRD studies conducted by Micron and the data Micron supplied based on these studies. Ms. Melody confirms that crucial data regarding the experimental protocol were not recorded and that the proper tests and data were not demanded or received by Abraxis or its expert and hence

no tests were conducted in order to quantify crystallinity and, perhaps more importantly, to establish a limit for paclitaxel crystallinity detection. In addition, pre-manipulation PXRD patterns of Abraxane were not collected as a reference to confirm that the physical chopping and homogenization Micron carried out had not induced changes in phase/crystallinity. Even supposing the most favorable conditions for paclitaxel crystal detection, the conclusion that paclitaxel nanoparticles in Abraxane are amorphous by Jerry Atwood is accordingly unfounded.

Abraxis's Criticisms Of Elan's Record Keeping Are Unfounded

11. Jerry Atwood in his Supplemental Report stated:

> "The failure of Drs. Munson, Barich, Shi, Berkland, and Winkler to keep a laboratory notebook of the experiments they performed for this litigation is contrary to standard scientific practice. Due to their lack of proper record keeping, Elan's experiments are not reproducible."

I was very surprised at this assertion and what it implied. The asserted "failure" to keep a laboratory notebook in a manner commensurate with cited texts (the first sentence quoted above) implied a lack of proper record keeping (the second sentence quoted above). The second proposition does not flow from the first, and Dr. Atwood's assertion is unsupported by standard practices in science generally, and in our laboratory in particular. In reality, lab notebooks may be one technique for recording data in support of a scientific method. Important information about experimental protocols is often also provided by or evident from various other sources, such as the existence of "standard operating procedures" (SOP), reference to scientific texts or standards (e.g. the U.S. Pharmacopeia), a user's manual for a piece of equipment, materials safety data sheets for chemicals used, electronic databases, etc. In addition, details may not be recorded at all if a procedure is habitually conducted in the same manner or if a piece of equipment is dedicated to a certain task and programmed to run consistently.

12. In the current day, scientists often keep records electronically, which can be more convenient and reliable than keeping a paper laboratory notebook. Some technical personnel still keep laboratory notebooks, but there is a clear trend toward storing more and more data electronically. This is true, for instance, of the raw data relating to the ssNMR tests performed by Dr. Munson on Abraxane samples prepared in our lab. This raw data, including considerable data relating to not only the returned spectra, but the settings used for the assay, was recorded on the instrument itself, and thus it would have been a waste of time to document it in a redundant paper notebook since any skilled technician conversant with ssNMR could readily have accessed and analyzed the computer data files. The validation of this multi-sourced and comprehensive, type of "proper record keeping" is evident in the acceptance of paper publications, presentations, reports, or other similarly communicated, peer-reviewed work.

13. Methods used for the sample preparation and analyses of the nanoparticle component of Abraxane reported on by myself and Dr. Munson *have* been reported in a manner that would allow reproduction of the experiments. Lab notebooks were not a necessary component to accurately communicate these methods since we employed a routine procedure using dedicated pieces of equipment in a laboratory where experts in this technology routinely perform and report on such testing. For comparison, the lab notebooks provided by Abraxis Biosciences typically do not offer reproducible methods. Abraxis Biosciences' formal report of methods to the FDA does, however, offer an organized and comprehensible report format illustrative of the methods used to analyze Abraxane. A final demonstration of this point is the lab notebook excerpts provided by Micron (Melody deposition, Exhibit 2), which would also not allow reproduction of the work conducted if consulted alone.

Abraxis's PXRD Testing Results Are Unreliable

14. As I understand the Court's clarification of the claim construction, the Court has now instructed that the claimed crystalline medicament particles must contain only crystalline paclitaxel. For all the reasons set forth above, I believe that Ms. Melody's experimental PXRD techniques, the records that she kept (or, in some cases, was not instructed to keep), or Dr. Atwood's conclusions based on them, are insufficient to say with any scientific reliability that Abraxane as sold and/or as administered lacks particles of paclitaxel in which the entirety of the paclitaxel medicament is essentially crystalline in nature. Therefore, I would not place scientific reliance on such testing or conclusions in determining whether Abraxane meets the language of the Elan '363 Patent as construed by the Court.

15. Subject to the many limitations on the reliability of the PXRD data that I have identified above, certain of the peaks in the PXRD spectra Ms. Melody obtained may be, in my opinion, consistent with crystalline peaks. However, I believe it unnecessary to consider at length whether these peaks definitively establish the presence of particles containing purely crystalline medicament, because Dr. Munson's ssNMR testing and the conclusions he has drawn are considerably more reliable bases for reaching a conclusion as to the essentially crystalline nature of the medicament contained within many or most of the particles within Abraxane.

16. Abraxis's testing of Abraxane also conclusively demonstrates that human serum albumin does not crosslink with paclitaxel (ABRX 0117420 at 0117504 and 0117547). Accordingly, in Abraxane, the individually adsorbed molecules of human serum albumin are essentially free of intermolecular crosslinkages.

17. Abraxis's testing also confirms that Abraxane is essentially free of intermolecular crosslinkages between molecules of human serum albumin. Early versions of the Abraxane formulation, at the time called Capxol, were tested for multimeric forms of human serum

albumin (ABRX0117143 at 0117373 and 0117385). Capxol appears to be formulated using a similar method and under similar conditions as Abraxane is now formulated (ABRX0117143 at ABRX0117245). The human serum albumin in Capxol was about 80% monomeric (ABRX0117143 at: 0117383; 0117388-0117390; 0117396; 0117401; 0117417). Later testing of Abraxane (ABI-007) demonstrated the same amounts of monomeric human serum albumin (ABRX0151870 at 0151921-27). Putting aside whether these tests are sufficient to demonstrate crosslinking between human serum albumin molecules, 80% monomeric human serum albumin is certainly "essentially free" of crosslinks.

18. Abraxis appears to have made a cursory investigation concerning the potential for disulfide bonds between human serum albumin molecules in reconstituted Abraxane (ABRX0274492). The human serum albumin (starting material) used in formulating Abraxane was reported to be 95% monomer. The majority of the forms of human serum albumin in Abraxane and the separated nanoparticle portion were shown by Abraxane's own documents to be of lower order (monomeric or dimeric). These data show that the formulation process results in small changes in the human serum albumin form in Abraxane compared to the starting human serum albumin, mostly represented by an increase in dimer. Abraxis reports that the human serum albumin contained in the nanoparticle fraction exhibits slightly more dimer and more "polymer" compared to human serum albumin in Abraxane. The number of assembled human serum albumin molecules required to form the "oligomer" and "polymer" fractions was unclear. Reduction (*i.e.* disruption or cleavage) of disulfide bonds did not reduce the "polymer" content in the human serum albumin contained in the nanoparticle fraction; therefore, Abraxis's own documents indicate that the polymeric portion is not crosslinked by disulfide bonds.

19. When human serum albumin is processed during Abraxane formulation, the

human serum albumin is exposed to shear, heat, hydrophobic interfaces, freeze drying, *etc.*, each of which have the ability to transform monomeric human serum albumin to dimeric, trimeric, and higher order molecular assemblies (referred to in Abraxis's documents as "oligomer" and "polymer"). For example, simply freeze drying human serum albumin or exposing human serum albumin to an organic solvent induces the formation of dimeric, trimeric, and higher order molecular assemblies (ABRX0171908). The processing conditions used during Abraxane formulation are known to drive the formation of dimeric, trimeric, and higher order molecular assemblies by causing the proteins to partially unfold and expose hydrophobic domains. The exposure of the hydrophobic protein domains, which are usually hidden on the inside of the protein's three dimensional structure, drives protein aggregation. In my opinion, protein aggregation as a result of processing is not crosslinking as construed by the court. In any event, such aggregates are an expected byproduct of processing a solution containing proteins.

20. Other testing by Abraxsis provides additional evidence that the human serum albumin is "essentially free of intermolecular crosslinkages". Abraxis's documents contain data that reflect the use of dynamic light scattering, which is a technique commonly used to characterize the size of large molecules, aggregates, and nanoparticles. The human serum albumin starting material was reported to possess "a lot" of particles that gave a persistent "background" signal around ~10 nm (ABRX0279513). One would expect this background signal at ~10 nm to shift to larger values if intermolecular crosslinking of human serum albumin occurred. To my knowledge, the peak associated with the background signal was not reported in Abraxis's documents when Abraxane was analyzed. Data showing the dissolution of paclitaxel nanoparticles as a function of the paclitaxel concentration in reconstituted Abraxane was reported. Paclitaxel nanoparticles dissolved quickly at paclitaxel concentrations less than ~50

μg/mL and, upon dissolution, a residual background signal was detected at ~10 nm. The ~10 nm background particle size in Abraxane after paclitaxel nanoparticle dissolution was reported to be the same as the ~10 nm background particle size in the human serum albumin starting material; therefore, Abraxis's own data suggests that the human serum albumin in Abraxane is "essentially free of intermolecular crosslinkages" (ABRX0123712 at 0123717; Neil Desai FDA Nanotechnology Presentation, Oct. 10, 2006).

21. I have reviewed several of the techniques used in the characterization of Abraxane for the FDA. Some of the conclusions drawn by Abraxis from the data obtained by these techniques are unfounded. In particular, the XRPD studies were insufficient to conclude that "nanoparticles of ABI-007 are amorphous" (ABRX0117420 at 0117484). Further, assertions that electron microscopy techniques are adequate to determine the presence of crystals exaggerate what can be learned from this technique (Selvaraj Tr. 145:1-25).

22. Abraxis's documents report the use of transmission electron microscopy (TEM) and cryo-TEM as techniques to characterize the nanoparticle size, morphology, and crystallinity of Abraxane and of the nanoparticle fraction of Abraxane (ABRX0117420; ABRX0151870). Contrary to Abraxis's reliance on TEM images to characterize the paclitaxel nanoparticles (Neil Desai FDA Nanotechnology Presentation, Oct. 10, 2006; Selvaraj Tr. 171:20-172:4), TEM techniques do not provide direct evidence of nanoparticle crystallinity. Although faceted, angular surface structures are suggestive of crystalline material and rounded surfaces are suggestive of amorphous material observed using TEM, the lack of faceted, angular structures does not necessarily disprove the existence of crystallinity. In Abraxis's own documents, nanoparticle morphology (*i.e.* shape) obtained from TEM images was often used to identify the paclitaxel nanoparticles in Abraxane as amorphous. TEM images of Abraxane and nanoparticles

separated from Abraxane in Abraxis's own documents show particles that possess rounded morphology (ABRX0117420 at 0117491) and particles that possess angular morphology (ABRX0117420 at 0117492; ABRX0532455-74), which would suggest that both amorphous and crystalline nanoparticles are present. Abraxis's documents identify paclitaxel as the darker portion of the particles and human serum albumin as the lighter portion of the particles (ABRX0151870 at 0151886), usually surrounding the darker portion. In some cases, the lighter, human serum albumin portion of the particle appears round, while the darker, paclitaxel portion on the inside is angular (ABRX0532455-74). Thus, the TEM images depict morphologies suggestive of both crystalline and amorphous paclitaxel, but are not conclusive of either (Selvaraj Tr. 160:4-6).

23. X-Ray Powder Diffraction Spectroscopy (XRPD) is a rapid and nondestructive method to determine crystallinity. The inherent molecular order of crystalline materials causes x-rays to diffract in regular ways. Detection of the regularly scattered x-rays in crystalline material produces sharp, narrow spectral peaks. In contrast, the molecular disorder of amorphous materials causes more random x-ray diffraction and the appearance of broad, smooth spectral peaks. As an example, XRPD spectra of human serum albumin (lyophilized starting material) presented in Abraxis's documents possessed broad smooth peaks while crystalline paclitaxel (raw material) possessed sharp, distinct peaks of much greater magnitude (ABRX0117420 at 0117485 and 0117486). The intensity of the peaks in crystalline materials is a function of the degree of crystallinity of the material, the crystal size, and the relative concentration. Less crystallinity, smaller crystal size, and lower relative concentration will reduce the peak height and may increase peak broadening in the XRPD spectra. In some of the reviewed spectra, the highest peaks in the paclitaxel spectra (*e.g.* at ~12.5 degrees) exhibit a

height corresponding to of 6,000-7,000 counts per second (CPS). When the physical mixture of crystalline paclitaxel and human serum albumin was analyzed, most paclitaxel peaks are obscured by the human serum albumin except for a few of the highest peaks that have decreased in height to 600-700 CPS because the physical mixture is only 10% paclitaxel (the crystalline paclitaxel peak decreases to approximately one tenth of the original peak height). Even the highest peaks are partially obscured by the presence of human serum albumin. Based on the XPRD data, conservative estimates would suggest that if the paclitaxel particle size and concentration in the physical mixture was the same as the physical mixture (100 mg in approximately 900 mg human serum albumin), XPRD would not detect paclitaxel crystallinity below 50%. In other words, the most pronounced paclitaxel peaks would be totally obscured by the human serum albumin even if 50% of the paclitaxel was crystalline in the physical mixture. 48. In addition, the crystal size in the crystalline paclitaxel (raw material) was significantly larger (5-500 μm as reported in US Pat. No. 6,749,868, Col. 31, L. 64-65) than the paclitaxel nanoparticles in Abraxane (~130 nm). Paclitaxel nanoparticles in Abraxane are 50-5000 times smaller, which would significantly reduce the peak intensity in comparison to the crystalline paclitaxel (raw material) and physical mixture, thus, rendering XRPD an especially insensitive technique for deducing the crystalline content of paclitaxel nanoparticles in Abraxane.

24. Additionally, I am concerned about the presentation of XRPD data. It is common practice to apply a mathematical algorithm to smooth the raw XRPD data, subtract any spectral elements associated with background (*i.e.* spectra not associated with the sample), and to remove the Kα2 doublet. The data supplied to Abraxis often show all of these plots (*e.g.* ABRX0151363). In many Abraxis reports, only the raw XRPD data is shown (ABRX0117420; ABRX0296424), which obscures small, but significant spectral differences. Additionally,

presentation of solely the raw, unprocessed data is concerning because complete processing of XRPD data as described above revealed peaks that were not assigned to human serum albumin for certain lots of ABI-007 (ABRX0151417 at 0151441-42; ABRX0151512 at 0151519-20; ABRX0151528 at 0151533-34). These peaks appear near the most intense peaks for crystalline paclitaxel (~5.5 and ~12.5 degrees) in spite of the low relative paclitaxel concentration and small nanoparticle size in ABI-007.

25. Also of note is Neil Desai's comments in his presentation at the FDA's nanotechnology meeting, he quotes from the National Nanotechnology Initiative: "At the nanoscale, the physical, chemical, and biological properties of materials differ in fundamental and valuable ways from the properties of individual atoms and molecules or bulk matter." Abraxis seems to have ignored this in relying solely only XRPD and electron microscopy to characterize the crystallinity of paclitaxel in Abraxane (Selvaraj Tr. 145:1-25).

26. In my opinion, Abraxis's XRPD testing of Abraxane is inadequate to determine the crystallinity of paclitaxel in Abraxane.

27. In my opinion, Abraxis's electron microscopy (TEM and cryo-TEM) of Abraxane is inadequate to determine the crystallinity of paclitaxel in Abraxane.

ASHBY & GEDDES

/s/ *John G. Day*

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Dated: June 2, 2008

EXHIBIT A

Expert report of Cory Berkland

Elan Pharma International Ltd. v. Abraxis Bioscience, Inc.,
No. 06-438-GMS, District of Delaware

1. I, Cory Berkland, Ph.D., provide this report in the above-captioned case. The opinions expressed herein are my own and I have personal knowledge of the facts stated herein. If called as a witness, I could testify competently to the facts and opinions herein.

I. Background

A. QUALIFICATIONS

2. I reside at 18329 Northwind Drive, Lawrence, Kansas, 66044. I hold a B.S. degree in Chemical Engineering from Iowa State University (Ames), a M.S. degree in Chemical Engineering from the University of Illinois (Urbana-Champaig n) and a Ph.D. in Chemical and Biomolecular Engineering from the University of Illinois (Urbana-Champaig n). I was a Postdoctoral Associate at the University of Illinois (Urbana-Champaig n) from 2003 to 2004.

3. Since 2004, I have been employed as an Assistant Professor in the Department of Chemical and Petroleum Engineering and the Department of Pharmaceutica l Chemistry (50% appointment in each department) at the University of Kansas (Lawrence). My area of expertise includes nanoparticulate drug formulation, microencapsulati on of pharmaceuticals, and controlled release drug delivery. Through extensive collaborations with industrial and academic partners and close relationships with experts in particle sciences, I have developed considerable expertise in the formulation and character ization of pharmaceutica l nanoparticles and microencapsulate d therapeutics. My qualifications are further detailed on my CV (Appendix A).

B. COMPENSATION

4. For my work related to this case, I am compensated at the rate of $350.00 per hour, and $450.00 per hour for time spent in depositio ns or at trial. My compensation is not being affected by the outcome of this case.

C. PUBLICATIONS

5. A list of the papers I have co-authored in the past ten years is set forth in my CV attached as Appendix A.

D. PREVIOUS TESTIMONY

6. None.

E. SCOPE OF EXPERT REPORT

7. Elan, through their counsel, has asked me to review documents and testimony related to this case. I have also examined United States Patent Nos. 5,399,363 (363 patent), 5,145,684 (684 patent), and 5,834,025. I have been asked to offer opinions on whether Abraxis's pharmaceutical product Abraxane (also referred to as ABI-007) meets certain claim limitations in the '363 patent. I have also been asked to offer opinions on analytical techniques used in the reviewed materials.

F. INFORMATION CONSIDERED

8. I have reviewed the documents listed in Appendix B in reaching my opinions.

G. BASES FOR OPINIONS EXPRESSED

9. My opinions are based on my education and my work experience as set forth Section A of this report, and the documents listed in Section F of this report.

H. ONGOING NATURE OF ANALYSIS

10. I am continuing my study and analysis of the information that I have considered in preparing this report. From time to time, I may refine or expand on 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.

II. Expert Opinions

A. ASSUMPTIONS

11. I have been asked to make assumptions regarding the interpretation of certain language in the claims. Those assumptions are illustrated in the several orders of the court. I am not opining on the interpretation of patent claims.

B. LEGAL BACKGROUND

12. I understand that a patent claim is literally infringed if each limitation of the claim is found in an accused product or process that is made, used, sold, offered for sale, or imported.

13. I understand that if a patent claim is not literally infringed, the claim may be infringed under the doctrine of equivalents. Infringement under the doctrine of equivalents occurs where the accused product or process contains an element that performs substantially the same function in substantially the same way to achieve substantially the same result as that of a claim limitation, or if there is an insubstantial difference between the claim limitation and a corresponding element in the accused product or process. I have been asked to give opinions as to whether Defendants literally infringe or, in the alternative, infringe under the doctrine of equivalents.

C. PARTICLE ISOLATION

14. Since the application of nanoparticle technology has emerged in pharmaceutical products, it has become important to thoroughly characterize the nanoparticle component of pharmaceutical formulations without overshadowing the nanoparticle properties as a result of the presence of other ingredients. The handling of nanoparticles requires careful consideration of the particle physicochemical attributes so as to determine conditions for proper handling and sample preparation that will mitigate changes in particle properties while facilitating selective characterization of nanoparticles or other chemicals included in the formulation. In addition, good laboratory practices are necessary to nullify potential sources of sample contamination. With this in mind, the nanoparticle components of samples of Abraxane were isolated in our lab and transferred to Prof. Eric Munson of the Pharmaceutical Chemistry Department at the University of Kansas for analysis.

15. Several vials of Abraxane were provided by Elan's counsel. Abraxane contains 100 mg of paclitaxel and approximately 900 mg of human serum albumin according to the package insert (Appendix C). Abraxane was reconstituted according to the package insert, but

replacing saline with deionized water from a Barnstead EASYPure RoDi water purification system. Deionized water was used instead of sodium chloride to eliminate the presence of salt during analysis. Using sterile techniques, the metal seal and rubber stopper were removed and ~20 mL of deionized water was slowly added to the contents of each vial, taking precautions not to inject directly onto the lyophilized powder. After injection, the contents were allowed to sit for a minimum of five minutes, and then gently swirled for at least two minutes to completely resuspend the product. The contents were transferred to centrifuge tubes, which were centrifuged at 12,000 rpm (15,950 g) for approximately 45 minutes using a Thermo Scientific, IEC Multi RF centrifuge with rotor type 8850. The centrifuge temperature was set at 4°C. These conditions are commonly used to isolate nanoparticles ~100 nm in diameter. Centrifugation conditions were selected so as to offer the combination of low forces for long times at low temperature that are appropriate for mitigating changes in the physicochemical properties of the nanoparticle portion of Abraxane The centrifuge tubes were removed from the centrifuge and the supernatants were gently decanted so as not to disturb the pellets. Two methods were employed to remove the remaining water from the pellets. In the lyophilization method, the centrifuge tubes were transferred to a flask connected to a Labconco Freezone 1. Samples were lyophilized for a minimum of 24 hours. After lyophilization , the centrifuge tubes were transferred to Prof. Eric Munson. In the air-dried method, the pellets were removed from the centrifuge tubes and transferred to a piece of weighing paper using a clean spatula. The paper was placed in a hood and the samples were allowed to dry overnight at room temperature (~23°C). The samples were transferred to Petri dishes, which were sealed with paraffin film and transferred to Prof. Eric Munson for analysis.

D. INFRINGEMENT OF CERTAIN CLAIM LIMITATIONS

16. Abraxane is a nanoparticulate formulation of paclitaxel onto which human serum albumin is adsorbed (ABRX 0279352). Abraxane is packaged as a lyophilized (freeze-dryed) powder. Abraxane's package insert instructs health care professionals to reconstitute Abraxane with saline prior to administration to a patient. I have been asked to evaluate whether Abraxane meets certain claim limitations in the 363 and 025 patents.

17. **Non-crosslinked**

18. The court has construed the term "non-crosslinked" to mean "the individually adsorbed molecules of the surface modifier are essentially free of intermolecula r crosslinkages." In the 363 patent, the surface modifier is not crosslinked to the anticancer agent or another surface modifier molecule.

19. Typically, the term "crosslinked" is applied to linkages that hold together multiple polymers. In contrast, the term "aggregate" is typically used to describe the interaction of two or more molecules (*e.g.* polymers) as distinguished from "crosslinking", which generally refers to the bonding of multiple molecules (*e.g.* polymers). Proteins, like human serum albumin, are made up of amino acid residues covalently linked together by peptide bonds into a linear, unbranched polypeptide chain (polymer). Individua l protein molecules can crosslink with other molecules. Proteins can also aggregate.

20. Abraxis, and others (ABRX0478762 at 0478764), have described the human serum albumin in Abraxane as "unmodified":

- "*nab* process **does not alter either the drug or the protein**" (ABRX0224829 at 0224837)
- "binding to the **unmodified albumin** allows use of endogenous albumin pathways" (ABRX0224829 at 0224837)
- "Abraxane is formed using the company's proprietary nanoparticle albumin bound (nab™) technology that combines water insoluble compounds, such as paclitaxel, with **human albumin without altering either component or forming covalent bonds**. . . . we believe the albumin particles disassociate into individual albumin molecules and then circulate with the paclitaxel still attached (ABRX0123712 at 0123717)
- "The active pharmaceutical ingredient of Abraxane, paclitaxel, is identical to that of Taxol. The formulation components differ between Taxol and Abraxane in that the solvents Cremophor-EL and ethanol in Taxol are replaced with **unmodified human albumin** as an excipient." (ABRX0123712 at 0123747)

These statements indicate that human serum albumin is not crosslinked, either to paclitaxel nanoparticles or other molecules of human serum albumin. Crosslinking is a modification to any molecule.

21. Abraxis's testing of Abraxane also conclusively demonstrates that human serum albumin does not crosslink with paclitaxel (ABRX 0117420 at 0117504 and 0117547). Accordingly, in Abraxane, the individually adsorbed molecules of human serum albumin are essentially free of intermol ecular crosslinkages.

22. Abraxis's testing also confirms that Abraxane is essentially free of intermolecular crosslinkages between molecules of human serum albumin. Early versions of the Abraxane formulation, at the time called Capxol, were tested for multimeric forms of human serum albumin (ABRX0117143 at 0117373 and 0117385). Capxol appears to be formulated using a similar method and under similar conditions as Abraxane is now formulated (ABRX0117143 at ABRX0117245). The human serum albumin in Capxol was about 80% monomeric (ABRX0117143 at: 0117383; 0117388-0117390; 0117396; 0117401; 0117417). Later testing of Abraxane (ABI-007) demonstrated the same amounts of monomeric human serum albumin (ABRX0151870 at 0151921-27). Putting aside whether these tests are sufficient to demonstrate crosslinking between human serum albumin molecules, 80% monomeric human serum albumin is certainly "essentially free" of crosslinks.

23. Abraxis appears to have made a cursory investigation concerning the potential for disulfide bonds between human serum albumin molecules in reconstituted Abraxane (ABRX0274492). The human serum albumin (starting material) used in formulating Abraxane was reported to be 95% monomer. The majority of the forms of human serum albumin in Abraxane and the separated nanoparticle portion were shown by Abraxane's own documents to be of lower order (monomeric or dimeric). These data show that the formulation process results in small changes in the human serum albumin form in Abraxane compared to the starting human serum albumin, mostly represented by an increase in dimer. Abraxis reports that the human serum albumin contained in the nanoparticle fraction exhibits slightly more dimer and more "polymer" compared to human serum albumin in Abraxane. The number of assembled human serum albumin molecules required to form the "oligomer" and "polymer" fractions was unclear. Reduction (*i.e.* disruption or cleavage) of disulfide bonds did not reduce the "polymer" content in the human serum albumin contained in the nanoparticle fraction; therefore, Abraxis's own documents indicate that the polymeric portion is not crosslinked by disulfide bonds.

24. When human serum albumin is processed during Abraxane formulation, the human serum albumin is exposed to shear, heat, hydrophobic interfaces, freeze drying, *etc.*, each of which have the ability to transform monomeric human serum albumin to dimeric, trimeric, and higher order molecular assemblies (referred to in Abraxis's documents as "oligomer" and "polymer"). For example, simply freeze drying human serum albumin or exposing human serum albumin to an organic solvent induces the formation of dimeric, trimeric, and higher order

molecular assemblies (ABRX0171908). The processing conditions used during Abraxane formulation are known to drive the formation of dimeric, trimeric, and higher order molecular assemblies by causing the proteins to partially unfold and expose hydrophobic domains. The exposure of the hydrophobic protein domains, which are usually hidden on the inside of the protein's three dimensional structure, drives protein aggregation. In my opinion, protein aggregation as a result of processing is not crosslinking as construed by the court. In any event, such aggregates are an expected byproduct of processing a solution containing proteins.

25. Other testing by Abraxsis provides additional evidence that the human serum albumin is "essentially free of intermolecular crosslinkages". Abraxis's documents contain data that reflect the use of dynamic light scattering, which is a technique commonly used to characterize the size of large molecules, aggregates, and nanoparticles. The human serum albumin starting material was reported to possess "a lot" of particles that gave a persistent "background" signal around ~10 nm (ABRX0279513). One would expect this background signal at ~10 nm to shift to larger values if intermolecular crosslinking of human serum albumin occurred. To my knowledge, the peak associated with the background signal was not reported in Abraxis's documents when Abraxane was analyzed. Data showing the dissolution of paclitaxel nanoparticles as a function of the paclitaxel concentration in reconstituted Abraxane was reported. Paclitaxel nanoparticles dissolved quickly at paclitaxel concentrations less than ~50 µg/mL and, upon dissolution, a residual background signal was detected at ~10 nm. The ~10 nm background particle size in Abraxane after paclitaxel nanoparticle dissolution was reported to be the same as the ~10 nm background particle size in the human serum albumin starting material; therefore, Abraxis's own data suggests that the human serum albumin in Abraxane is "essentially free of intermolecular crosslinkages" (ABRX0123712 at 0123717; Neil Desai FDA Nanotechnology Presentation, Oct. 10, 2006).

26. **Surface modifier**

27. The court has construed the term "surface modifier" to mean "a substance that modifies the surface properties of the crystalline medicament." In the 363 patent, surface modifiers are used to stabilize the small size of nanoparticles. By modifying surface properties, surface modifiers inhibit the agglomeration of nanoparticles, which otherwise would cause an undesirable increase in particle size. The human serum albumin adsorbed on paclitaxel nanoparticles in Abraxane modifies the surface properties of the paclitaxel nanoparticles.

Abraxis has stated to the FDA that "[h]uman albumin functions as a surface-active polymer providing charge and steric stabilization to the paclitaxel nanoparticles to prevent aggregation." (ABRX0117420 at 0117442 and 0117480-81). Dr. Selvaraj, an Abraxis formulation scientist, also confirms that human serum albumin stabilizes paclitaxel nanoparticles in Abraxane (Selvaraj Tr. 55:1-56:20). Dr. Desai, Vice President for Research and Development at Abraxis, states: "The other aspect about stability is that we have -- due to the albumin coating that we have, the biocompatible human albumin on the nanoparticles, at neutral pH these particles are negatively charged. We heard some things about negatively charged particles and their lack of toxicity earlier this morning. They resist agglomeration and further more due to the presence of the polymer albumin, which is a large molecule, you get steric-stabilization that keeps these nanoparticles stable." (Neil Desai Presentation FDA Nanotechnology Final Oct 10 2006 at 183-4).

28. In Abraxane, the human serum albumin is adsorbed onto the paclitaxel nanoparticles thereby modifiying its surface properties to prevent agglomeration and maintain a particle size less than 1,000 nm. Accordingly, the human serum albumin in Abraxane is a "surface modifier".

29. **Adsorbed on the surface**

30. The court has construed the term "adsorbed on the surface" to mean "a molecule retained at the surface of the crystalline medicament that does not chemically bond with such medicament." Human serum albumin in Abraxane is a "surface-active polymer" that "adsorbs onto the surface of the nanoparticles." (ABRX0117420 at 0117480). By definition, surface-active molecules have a propensity to adsorb on surfaces. For example, albumins, in particular, are often used as blocking agents in biological assays to prevent the adsorption of other proteins onto surfaces, such as the plastic containers commonly used in the lab. Further, human serum albumin does not bond or chemically react with paclitaxel (ABRX0117420 at 0117504, 0117509, 0117514; Selvaraj Tr. 96:12-98:19). Accordingly, the human serum albumin in Abraxane is a surface modifier that is "adsorbed on the surface" of paclitaxel nanoparticles.

31. **Surfactant**

32. The court has construed the term "surfactant" to mean "a stabilizing agent that reduces interfacial tension between oil and water." In the 363 patent, surfactants are one type of surface modifier. Surfactants are also known as "surface-active agents" (Dictionary of Scientific

and Technical Terms). Surfactants, or surface-active agents, stabilize nanoparticle size by preventing agglomeration. Hydrophobic (water-hating) drugs, like paclitaxel, tend to agglomerate in aqueous (water) environments, but not in organic (oil) environments. Surfactants prevent agglomeration of hydrophobic drugs in aqueous environments by reducing the tension between aqueous and organic surfaces.

33. In Abraxane, the human serum albumin adsorbed onto paclitaxel nanoparticles "functions as a surface-active polymer and stabilizes the paclitaxel nanoparticles." (ABRX0117420 at 0117440). Human serum albumin is known to be a surfactant that reduces interfacial tension (Bazile, et al., Biomaterials 13/15:1093-1102 (1992) [ELANP0006925]). Accordingly, the human serum albumin in Abraxane is a "surfactant".

34. **Colloidal polymeric material**

35. The court has construed the term "colloidal polymeric material" to mean "a polymer capable of forming a suspension of the organic drug substance." Human serum albumin in Abraxane is a protein, and proteins are polymers of amino acids. When reconstituted, "Abraxane forms a stable colloidal suspension of paclitaxel." (Pat. App. Pub. No. 2006/0263434 ¶ 0174). It follows that the human serum albumin-bound paclitaxel nanoparticles in Abraxane represent a "colloidal polymeric material."

36. **Bovine serum albumin**

37. In the 363 patent, bovine serum albumin is a specific type of surface modifier. In my opinion, bovine serum albumin is equivalent to the human serum albumin in Abraxane. The differences between bovine serum albumin and human serum albumin are insubstantial and both perform substantially the same function in substantially the same way to achieve substantially the same result.

38. In the 363 patent, bovine serum albumin functions as a surface modifier that stabilizes the small size of nanoparticles by inhibiting nanoparticles from clumping. Human serum albumin in Abraxane has the same function (Selvaraj Tr. 55:1-56:20); it "functions as a surface-active polymer and stabilizes the paclitaxel nanoparticles" (ABRX0117420 at 0117440) by "providing charge and steric stabilization to the paclitaxel nanoparticles to prevent aggregation." (ABRX0117420 at 0117442 and 0117480-81). Furthermore, in the pharmaceutical industry, bovine serum albumin and human serum albumin are commonly used to perform the same function of stabilizing particles (Selvaraj Tr. 105:25-106:21; ABRX0117420 at 0117480).

39. The way in which human serum albumin and bovine serum albumin stabilize nanoparticles is also the same. In the 363 patent, bovine serum albumin stabilizes nanoparticles through adsorption, without chemical bonding, to the nanoparticle anticancer agent (363 patent, col. 3, ll. 57-60). This is the same way human serum albumin stabilizes paclitaxel nanoparticles in Abraxane (ABRX0117420 at 0117504, 0117509, 0117514; Selvaraj Tr. 96:12-98:19).

40. In the 363 patent, use of bovine serum albumin as a surface modifier results in stabilizing the size of the nanoparticle to below 1,000 nm (363 patent, col. 4, ll. 53-55). In Abraxane, the result of using human serum albumin is a particle size less than 1,000 nm (ABRX0117420 at 0117547). Because bovine serum albumin and human serum albumin perform the same function in the same way to achieve the same result, bovine and human serium albumins are equivalent.

41. Bovine serum albumin is also equivalent to the human serum albumin in Abraxane because their differences are insubstantial. Bovine and human albumins are substantially identical in all respects with the exception of their source. Bovine serum albumin is derived from cows, while human serum albumin is derived from humans. This difference in source, however, does not mean the two albumins are non-equivalent. In fact both human and bovine albumins have almost identical properties. The properties of any particular protein are largely determined by the physical and chemical properties of its topologically and chemically varied surface.

42. Both bovine and human serum albumins are polymers of amino acids (proteins). They have the essentially the same order of amino acids and these amino acids are arranged in essentially the same three-dimensional conformation (Selvaraj Tr. 104:13-105:7). So, topologically and chemically, bovine and human serum albumins are equivalent. Moreover, Abraxis itself has also recognized the interchangeability of human and bovine albumins (Pat. App. Pub. No. 2006/0263434 ¶ 0165).

E. ANALYTICAL TECHNIQUES

43. I have reviewed several of the techniques used in the characterization of Abraxane for the FDA. Some of the conclusions drawn by Abraxis from the data obtained by these techniques are unfounded. In particular, the XRPD studies were insufficient to conclude that "nanoparticles of ABI-007 are amorphous" (ABRX 0117420 at 0117484). Further, assertions that

electron microscopy techniques are adequate to determine the presence of crystals exaggerate what can be learned from this technique (Selvaraj Tr. 145:1-25).

44. **Electron microscopy**

45. Abraxis's documents report the use of transmission electron microscopy (TEM) and cryo-TEM as techniques to characterize the nanoparticle size, morphology, and crystallinity of Abraxane and of the nanoparticle fraction of Abraxane (ABRX0117420; ABRX0151870). Contrary to Abraxis's reliance on TEM images to characterize the paclitaxel nanoparticles (Neil Desai FDA Nanotechnology Presentation, Oct. 10, 2006; Selvaraj Tr. 171:20-172:4), TEM techniques do not provide direct evidence of nanoparticle crystallinity. Although faceted, angular surface structures are suggestive of crystalline material and rounded surfaces are suggestive of amorphous material observed using TEM, the lack of faceted, angular structures does not necessarily disprove the existence of crystallinity. In Abraxis's own documents, nanoparticle morphology (*i.e.* shape) obtained from TEM images was often used to identify the paclitaxel nanoparticles in Abraxane as amorphous. TEM images of Abraxane and nanoparticles separated from Abraxane in Abraxis's own documents show particles that possess rounded morphology (ABRX0117420 at 0117491) and particles that possess angular morphology (ABRX0117420 at 0117492; ABRX0532455-74), which would suggest that both amorphous and crystalline nanoparticles are present. Abraxis's documents identify paclitaxel as the darker portion of the particles and human serum albumin as the lighter portion of the particles (ABRX0151870 at 0151886), usually surrounding the darker portion. In some cases, the lighter, human serum albumin portion of the particle appears round, while the darker, paclitaxel portion on the inside is angular (ABRX0532455-74). Thus, the TEM images depict morphologies suggestive of both crystalline and amorphous paclitaxel, but are not conclusive of either (Selvaraj Tr. 160:4-6).

46. **X-Ray Powder Diffraction Spectroscopy**

47. X-Ray Powder Diffraction Spectroscopy (XRPD) is a rapid and nondestructive method to determine crystallinity. The inherent molecular order of crystalline materials causes x-rays to diffract in regular ways. Detection of the regularly scattered x-rays in crystalline material produces sharp, narrow spectral peaks. In contrast, the molecular disorder of amorphous materials causes more random x-ray diffraction and the appearance of broad, smooth spectral peaks. As an example, XRPD spectra of human serum albumin (lyophilized starting

material) presented in Abraxis's documents possessed broad smooth peaks while crystalline paclitaxel (raw material) possessed sharp, distinct peaks of much greater magnitude (ABRX0117420 at 0117485 and 0117486). The intensity of the peaks in crystalline materials is a function of the degree of crystallinity of the material, the crystal size, and the relative concentration. Less crystallinity, smaller crystal size, and lower relative concentration will reduce the peak height and may increase peak broadening in the XRPD spectra. In some of the reviewed spectra, the highest peaks in the paclitaxel spectra (*e.g.* at ~12.5 degrees) exhibit a height corresponding to of 6,000-7,000 counts per second (CPS). When the physical mixture of crystalline paclitaxel and human serum albumin was analyzed, most paclitaxel peaks are obscured by the human serum albumin except for a few of the highest peaks that have decreased in height to 600-700 CPS because the physical mixture is only 10% paclitaxel (the crystalline paclitaxel peak decreases to approximately one tenth of the original peak height). Even the highest peaks are partially obscured by the presence of human serum albumin. Based on the XPRD data, conservative estimates would suggest that if the paclitaxel particle size and concentration in the physical mixture was the same as the physical mixture (100 mg in approximately 900 mg human serum albumin), XPRD would not detect paclitaxel crystallinity below 50%. In other words, the most pronounced paclitaxel peaks would be totally obscured by the human serum albumin even if 50% of the paclitaxel was crystalline in the physical mixture.

48. In addition, the crystal size in the crystalline paclitaxel (raw material) was significantly larger (5-500 μm as reported in US Pat. No. 6,749,868, Col. 31, L. 64-65) than the paclitaxel nanoparticles in Abraxane (~130 nm). Paclitaxel nanoparticles in Abraxane are 50-5000 times smaller, which would significantly reduce the peak intensity in comparison to the crystalline paclitaxel (raw material) and physical mixture, thus, rendering XRPD an especially insensitive technique for deducing the crystalline content of paclitaxel nanoparticles in Abraxane.

49. Additionally, I am concerned about the presentation of XRPD data. It is common practice to apply a mathematical algorithm to smooth the raw XRPD data, subtract any spectral elements associated with background (*i.e.* spectra not associated with the sample), and to remove the Kα2 doublet. The data supplied to Abraxis often show all of these plots (*e.g.* ABRX0151363). In many Abraxis reports, only the raw XRPD data is shown (ABRX0117420; ABRX0296424), which obscures small, but significant spectral differences. Additionally, presentation of solely the raw, unprocessed data is concerning because complete processing of

XRPD data as described above revealed peaks that were not assigned to human serum albumin for certain lots of ABI-007 (ABRX0151417 at 0151441-42; ABRX0151512 at 0151519-20; ABRX0151528 at 0151533-34). These peaks appear near the most intense peaks for crystalline paclitaxel (~5.5 and ~12.5 degrees) in spite of the low relative paclitaxel concentration and small nanoparticle size in ABI-007.

50. Also of note is Neil Desai's comments in his presentation at the FDA's nanotechnology meeting, he quotes from the National Nanotechnology Initiative: "At the nanoscale, the physical, chemical, and biological properties of materials differ in fundamental and valuable ways from the properties of individual atoms and molecules or bulk matter." Abraxis seems to have ignored this in relying solely only XRPD and electron microscopy to characterize the crystallinity of paclitaxel in Abraxane (Selvaraj Tr. 145:1-25).

III. Conclusions

51. It is my opinion that Abraxane contains human serum albumin that is essentially non-crosslinked where the court has construed the term "non-crosslinked" to mean "the individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages."

52. It is my opinion that Abraxane contains a surface modifier where the court has construed the term "surface modifier" to mean "a substance that modifies the surface properties of the crystalline medicament."

53. It is my opinion that Abraxane contains human serum albumin adsorbed on the surface where the court has construed the term "adsorbed on the surface" to mean "a molecule retained at the surface of the crystalline medicament that does not chemically bond with such medicament."

54. It is my opinion that human serum albumin in Abraxane is a surfactant in full knowledge that the court has construed the term "surfactant" to mean "a stabilizing agent that reduces interfacial tension between oil and water."

55. It is my opinion that human serum albumin in Abraxane is equivalent to bovine serum albumin.

56. It is my opinion that Abraxane contains paclitaxel particles "entrapped in from about 99.9 to about 0.1% by weight of liposome or a colloidal polymeric material" where the

court has construed the term "colloidal polymeric material" to mean "a polymer capable of forming a suspension of the organic drug substance."

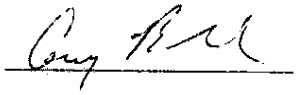
57. In my opinion, Abraxane meets the claim limitation: "a non-crosslinked surface modifier adsorbed on the surface thereof in an amount of 0.1-90% by weight and sufficient to maintain an average particle size of less than 1000 nm".

58. In my opinion, Abraxis's XRPD testing of Abraxane is inadequate to determine the crystallinity of paclitaxel in Abraxane.

59. In my opinion, Abraxis's electron microscopy (TEM and cryo-TEM) of Abraxane is inadequate to determine the crystallinity of paclitaxel in Abraxane.

DATED: September 28, 2007

Respectfully submitted,



Cory Berkland, Ph.D.

Appendix A

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Education

Ph.D. Chemical and Biomolecular Engineering, University of Illinois, Urbana-Champaign , IL	May 2003
M.S. Chemical Engineering, University of Illinois, Urbana, IL	May 2001
B.S. Chemical Engineering, Iowa State University, Ames, IA	December 1998

Awards

Teaching Achievement Recognition, Center for Teaching Excellence, Lawrence, KS	2007
Miller Professional Development Award for Research, School of Engineering, Lawrence, KS	2006
Selected as an Outstanding Reviewer for the Journal of Pharmaceutica l Science	2005
Genencor Outstanding Consumer & Diversified Products Paper Award, Controlled Release Society, Honolulu, HI	2004
Best Presentation, Chemical and Biomolecular Engineering Symposium, Urbana, IL	2003
Graduate College Travel Award, Urbana, IL	2003
Highlights of Student Posters Award, Controlled Release Society, Seoul, Korea	2002
Whitaker Award, American Chemical Society, Particles meeting, Orlando, FL	2002
Featured Technology, University of Illinois Technology Showcase, Urbana, IL	2001
Best Poster, Cell and Molecular Biology Training Grant Symposium, Urbana, IL	2001
Graduate College Travel Award, Urbana, IL	2000
Cell and Molecular Biology Training Grant, National Institutes of Health, Urbana, IL	1999-2000
Dorothy and Maurice Clark Scholarship, Ames, IA	1997-1998
Transfer Student Scholarship, Ames, IA	1996-1997

Research Experience

Postdoctoral Research Associate , University of Illinois, Urbana, IL — 2003-2004
Advisors: Daniel W. Pack and Kevin Kyekyoon Kim (Electrical and Computer Engineering)

- Studied thermodynamic phenomena of phase separation in ternary (polymer I, polymer II, water) systems and drug partitioning. Developed microencapsulati on projects and directed several graduate students.

Graduate Research Assistant , University of Illinois, Urbana, IL — 1999-2003
Advisors: Daniel W. Pack and Kevin Kyekyoon Kim

- Developed PPF technology for producing monodisperse microspheres and microcapsules encapsulating therapeutics. Organized and advised projects of six undergraduate researchers.

Undergraduate Research Assistant , Iowa State University, Ames — 1996-1998
Advisor: Charles Glatz

- Studied the crystallization of lysozyme using pressure as a probe to determine protein structural mutations that promoted or hindered crystallization.

Teaching Experience

Chemical Engineering	Fall 2006

CPE 111 Introduction to Chemical Engineering

Chemical Engineering — Fall 2006
CPE 800 Graduate Seminar

Pharmaceutical Chemistry — Fall 2006
PHCH 510 Emerging Trends in Pharmaceutical Chemistry

Chemical Engineering/Pharmaceutical Chemistry — Fall 2005
CPE/PHCH 715 Drug Delivery — Fall 2007
Coordinated and taught a new graduate-level course in drug delivery principles.

Chemical Engineering — Spring 2005
CPE 732 Advanced Transport Phenomena II — Spring 2006
Coordinated and taught the mass transport course to graduate students. — Spring 2007

Publications

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C. Berkland, E.J. Pollauf, N. Varde, D.W. Pack, and K. Kim (2007) "Monodisperse liquid-filled biodegradable microcapsules" *Pharmaceutical Research*, 24(5):1007-1013

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Patents

C. Berkland, L. Stehno-Bittel , and T. Siahaan "Templated Islet Cells and Small Islet Clusters for the Diabetes Treatment." filed October 30, 2006, U.S. Provisional Application

C. Berkland, M. Cordova, J.T. Liang, and P. Willhite "Polyelectrolyte Complexes for Oil and Gas Applications." filed September 5, 2006, U.S. Patent Application and PCT filing

L. Shi and C. Berkland, "Nanoclusters for Delivery of Therapeutics." filed December 16, 2005, U.S. Patent Application and PCT filing

K. Kim, D.W. Pack, C. Berkland, "Microparticles ." filed August 15, 2001, U.S. Patent #6,669,961

Invited Presentations

C. Berkland "Pharmaceutical Applications of Nanoparticle Technology" Presented at Cima Labs, Brooklyn Park, Minnesota, August 27, 2007

C. Berkland "Engineering Nanoparticles for Biomedicine" Presented at the National Institute of Standards and Technology, Gaithersburg, Maryland, May 4, 2007

M. Cordova, M. Cheng, P.G. Willhite, J. Liang, and C. Berkland "Polyelectrolyte complexes for oil and gas field applications" Presented at Conoco Phillips, Bartlesville, Oklahoma, March 13, 2007

C. Berkland "Nanoparticles for Targeted Angiogenesis: Potential Applications in Heart Disease and Spinal Cord Injury" Presented at Genentech, South San Francisco, California, November 14, 2006

C. Berkland "Engineering Pharmaceutical Nanoparticles" Presented at the Globalization of Pharmaceutics Education Network, Lawrence, Kansas, October 26, 2006

C. Berkland "Nanoparticle Agglomeration for Dry Po wder Formulation" Presented at Schering Plough's Pharmaceutical Science Seminar Series in Product Development, Kenilworth, New Jersey, September 27, 2006

C. Berkland "Nanoparticle Technolog y in the Pharmaceutical Industry" Presented at AAPS Kansas City Discussion Group, Kansas City, Kansas, August 8, 2006

C. Berkland "Nanoclusters as a Unique Drug Delivery Platform" Presented at ACS Particles Meeting, Orlando, Florida, May 16, 2006

C. Berkland "Designing Particulate Vaccine Delivery Systems" Mannkind Corporation, Valencia, California, January 24, 2006

C. Berkland "Precision Particle Fabrication Technology" Southwest Research Institute, San Antonio, Texas, January 11, 2006

C. Berkland "Engineering Therapeutic Particles" guest lecturer in senior Biochemical Engineering course at Vanderbilt University, Nashville, Tennessee, November 7, 2005

C. Berkland "API Particle Engineering" 47th Annual International Industrial Pharmaceutical Research & Development Conference: Emerging Practices for Advancing Drug Development, Merrimac, Wisconsin, June 7, 2005

C. Berkland "Engineering micro- and nanoparticles for enhanced drug delivery performance" University of Kansas, Department of Chemistry, Lawrence, Kansas, March 7, 2005

C. Berkland "Improvements in Delivery Strategies Using Particulate Technologies to Treat Infectious Diseases" 3rd Annual Great Plains Infectious Disease Meeting, Lawrence, Kansas, September 18, 2004

C. Berkland, K. Kim, and D.W. Pack "Novel Techniques for Controlling Size of Micro- and Nano-Particles Used in Drug Delivery" Cell and Molecular Biology Training Grant meeting, Urbana-Champaign , Illinois, March 15, 2000

Other Presentations

L. Shi and C. Berkland "Acid-Degradable Poly(N-vinylformamide)/Polyvinylamine Nanogel Capsules" Presented at the Controlled Release Society annual meeting, Long Beach, CA, July 11, 2007 (selected)

M. Huang, S.N. Vitharana, J. Huang, M. Bilgen, and C. Berkland "MRI Contrast Enhanced Polyelectrolyte Complexes for Traceable VEGF Delivery" Presented at the Controlled Release Society annual meeting, Long Beach, CA, July 9, 2007 (selected)

N. Zhang, L. Shi, T. Siahaan, and C. Berkland "Nanoparticles targeting intercellular cell-adhesion molecules" Presented at American Institute of Chemical Engineers annual meeting, San Francisco, California, November 16, 2006

L. Shi and C. Berkland "pH-Induced Dispersion of Nanoparticle Clusters" Presented at American Institute of Chemical Engineers annual meeting, San Francisco, California, November 15, 2006

M. Huang, S. Vitharana, L. Peek, T. Coop, and C. Berkland "Nanoparticle delivery of stabilized angiogenic growth factors" Presented at American Institute of Chemical Engineers annual meeting, San Francisco, California, November 15, 2006

C. Berkland "What do Chemical Engineers do?" Presented to high school girls visiting the School of Engineering, University of Kansas, February 4, 2006

M. Arnold and C. Berkland "Monodisperse Powders for Controlled Release Inhalation Therapy" Presented at American Institute of Chemical Engineers annual meeting, Cincinnati, OH, November 2, 2005

C. Berkland, K. Kim, and D.W. Pack "Pulsatile release of macromolecules from aqueous core PLG microcapsules" American Institute of Chemical Engineers annual meeting, San Francisco, California, November 9, 2004

C. Berkland, E. Pollauf, N. Varde, K. Kim, and D.W. Pack "Monodisperse microcapsules of controlled shell thickness and composition" American Institute of Chemical Engineers annual meeting, San Francisco, California, November 9, 2004

C. Berkland "Designing materials to enhance drug delivery performance" University of Kansas, Department of Pharmaceutical Chemistry, Lawrence, Kansas, September 7, 2004

C. Berkland, E. Pollauf, K. Kim, and D.W. Pack "Control of Drug Delivery from Core-Shell Microparticles" American Institute of Chemical Engineers annual meeting, San Francisco, California, November 19, 2003

C. Berkland, E. Pollauf, K. Kim, and D.W. Pack "Visual Tracking of Protein Release from Uniform PLG Microspheres" American Institute of Chemical Engineers annual meeting, San Francisco, California, November 19, 2003

C. Berkland, K. Kim, and D.W. Pack "Uniform biodegradable polymer microparticles for improved drug delivery" Chemical and Biomolecular Engineering Biannual Symposium, Urbana-Champaign , Illinois, April 1, 2003

C. Berkland, K. Kim, and D.W. Pack "Precision fabrication of polymer-based drug delivery devices for enhanced control of drug release kinetics" Cell and Molecular Biology Training Grant Symposium, Urbana-Champaign , Illinois, October, 25, 2002 (selected)

C. Berkland, K. Kim, and D.W. Pack "Modeling drug release from uniform PLG microspheres" American Institute of Chemical Engineers annual meeting, Indianapolis, Indiana, November 8, 2002

C. Berkland, M. King, A. Cox, K. Kim, and D.W. Pack "Modulation of release profiles through microsphere size control" Controlled Release Society annual meeting Highlights of Student Posters Session, Seoul, Korea, July 20, 2002 (selected)

C. Berkland, K. Kim, and D.W. Pack "Controlled electrohydrodynamic spraying to produce precision micro- and nanostructures" Particles 2002, Orlando, Florida, April 22, 2002

C. Berkland, K. Kim, and D.W. Pack "Fabrication of Polymer Microshells with Controlled Core Diameter and Shell Thickness" American Institute of Chemical Engineers annual meeting, Reno, Nevada, November 7, 2001

Posters

L.J. Peek, L. Roberts and C. Berkland "Flocculated PLG Nanoparticles for Inhaled Vaccine Delivery" Presented at the Controlled Release Society annual meeting, Long Beach, CA, July 9, 2007

L. Shi and C. Berkland "Acid-Labile Polyvinylamine Nanovesicles" Presented at the American Association of Pharmaceutical Scientists: Drug Delivery meeting, San Antonio, TX, October 31, 2006

L. Shi and C. Berkland "pH-Triggered Dispersion of Nanoparticle Clusters" Presented at the American Association of Pharmaceutical Scientists: Drug Delivery meeting, San Antonio, TX, October 31, 2006

C. Berkland, E. J. Pollauf, K. Kim, and D.W. Pack "Modulating protein release from monodisperse aqueous-core microcapsules with a defined PLG shell" Presented at the Controlled Release Society annual meeting, Honolulu, HI, June 13, 2004

C. Berkland, E. J. Pollauf, N.K. Varde, K. Kim, and D.W. Pack "Uniform polymer, oil, or aqueous core microcapsules of controlled biodegradable shell thickness" Presented at the American Association of Pharmaceutical Scientists: Drug Delivery meeting, Philadelphia, PA, June 7, 2004

C. Berkland, K. Kim, and D.W. Pack "Controlled release from uniform two polymer microcapsules" Presented at the Controlled Release Society annual meeting, Glasgow, United Kingdom, July 21, 2003

C. Berkland, M. King, A. Cox, K. Kim, and D.W. Pack "Modulation of release profiles through microsphere size control" Presented at the Controlled Release Society annual meeting, Seoul, Korea, July 20, 2002

C. Berkland, K. Kim, and D.W. Pack "Improved techniques for the production of precision micro and nanoparticles" Presented at Particles 2002, Orlando, Florida, April 22, 2002

C. Berkland, K. Kim, and D.W. Pack "Fabrication of Polymer Microshells with Controlled Core Diameter and Shell Thickness" Presented at Cell and Molecular Biology Training Grant meeting, Urbana-Champaign, Illinois, November 17, 2001

C. Berkland, K. Kim, and D.W. Pack "Novel Techniques for Controlling Size of Micro- and Nano-Particles Used in Drug Delivery" Presented at Cell and Molecular Biology Training Grant meeting, Urbana-Champaign , Illinois, November 4, 2000

C. Berkland, K. Kim, and D.W. Pack "Biodegradable Polymer Nanoshells for Drug Delivery: The pursuit of an artificial virus" Presented at Cell and Molecular Biolog y Training Grant meeting, Urbana-Champaign , Illinois, October 30, 1999

Professional Activities

Lawrence High School, Lawrence, KS – Technology Depart ment Advisory Board. Serving to develop/impro ve curriculum for pre-engineering training of local junior high and high schools.

Societies – American Institute of Chemical Engineers, American Chemical Society, American Association of Pharmaceutical Scientists, Controlled Release Society

Journal reviewer – Advanced Materials, Expert Opinion in Drug Delivery, Biomaterials, Journal of Pharmaceutica l Sciences, Journal of Controlled Release, Pharmaceut ical Research, Chemical Engineering Communications

Organized short course entitled "Polymers in Drug deliver y: Nanocarriers and implantable polymeric drug delivery systems" for the Globalizati on of Pharmaceutics Education Network meeting, Lawrence, KS

Co-Founder of the Nanomedicine Research Group, a collabo rative effort between KUMC and KU (2006-present)

Appendix B

No	Document	Beginning Bates No
1.	Abraxane ODAC briefing package, 09/07/2006	N/A
2.	*Pharmaceutical Forum* Vol 31, No. 5 (September-Oct ober 2005) [Also labeled NYC ECOPY]	N/A
3.	Stipulated Protective Order	N/A
4.	Court's Markman Order	N/A
5.	US Pat No. 6753006	N/A
6.	Abraxis Power Point Presentatio n: "Nanoparticle albumin bound (*nab*) technology : A nanotechnology platform for biologically interactive drug delivery and targeting" by Neil P. Desai, PhD Vice President, Research and Development Abraxis BioScience, Inc.	N/A
7.	Sugio, et al. "Crystal structure of human serum albumin at 2.5 A Resolution." *Protein Engineering* vol. 12 no. 6 (1999) pp. 439-446.	N/A
8.	Laboratory Notebook 24076	ABRX0150543.003
9.	7/27/2007 Selvaraj Deposition Transcript with Exhibits	
10.	VivoRX Pharmaceuticals: Capxol Chemistry, Manufacturing and Controls Information	ABRX0117143
11.	Interaction of taxol with human serum albumin	ABRX0074262
12.	FDA nano meeting transcript	
13.	Lab Notebook 28315 (excerpt pp. 26 - 43)	ABRX0153522
14.	American BioScience, Inc. "II. Drug Product, Components and Composition"	ABRX0117420
15.	Tarelli, et al. "Rocombinate human albumin as a stabilizer for biological materials and for the preparation of international reference reagents." *Biologicals* 1998 (26).	ABRX0222760
16.	Curry, et al. "Crysteal structure of human serum albumin complexed with fatty acid reveal s an asymetric distribution of binding sites." *Nature Structural Biology*. Vol. 5 No. 9 (September 1998).	ABRX0223454
17.	Colmenarajo, G. "In silico Prediction of Drug-Binding Strengths to Human Serum Albumin." *Medicial Research Reviews*. Vol. 23 No. 3 (2003)	ABRX0267158

18.	Slideshow - Binding of Paclitaxel to Albumin	ABRX0267439
19.	Excerpt from Abraxane report	ABRX0279352
20.	American Pharmaceuticals Partners, Inc. chart re: Albumin and Paclitaxel	ABRX0153692
21.	Investigation of disulfide bond induced in human serum albumin (HSA) in nab-formulations	ABRX0168408
22.	Carter, Daniel C. "Structure of Serum Albumin." *Advances in Protein Chemistry* Vol. 45. 1994 Academic Press.	ABRX0171833
23.	Lin, Jen-Jen, et al. "Stability of human serum albumin during biopreocessing: denaturation and aggregation during processing of albumin paste." *Pharmaceutical Research*. Vo. 17, No. 4, 2000.	ABRX0171908
24.	Lund, Martin. "Structural hetergeneity of the binding sites of HSA for phenyl-groups and medium-chain fatty acids." *European Journal of Biochemistry* 260. (1999).	ABRX0171928
25.	The Merck Index 1996	ABRX0171970
26.	Paal, Krisztina. "High affinity binding of paclitaxel to human serum albumin." *European Journal of Biochemistry* 268. (2001).	ABRX0171974
27.	Gradishar, W. J.. "Aluminum-Bound Paclitaxel: a next generation taxane." *Expert Opinion* 2006, 7(8).	ABRX0478762
28.	Lab Notebook 29	ABRX0527865
29.	APP HA Pellet Chromatographs	ABRX0532496
30.	APP Experiment Abstract - Standard Operating Procedure 10-08-03-6183	ABRX0533089
31.	"Co-Rapporteur - Quality"	ABRX0291998
32.	Abraxis Research Study Report	ABRX0296424
33.	E-mail correspondence between Tapas De and Neil Desai regarding Abraxane particle dissolution	ABRX0279496
34.	E-mail correspondence between Zachary Yim and Neil Desai regarding Abraxane particle dissolution	ABRX0279513
35.	Appendix A: Chemistry Manufacturing and Controls	ABRX0151870
36.	Narrative on SEM of Capxol	ABRX0266516
37.	U.S. Patent 5,399,363 Certification of Correction	N/A
38.	Dr. Hawkins Deposition Transcript	N/A
39.	Grant, D.J.W. "Theiry and Origin of Polymorphism"	N/A

40.	Smith, Deane K. "Particle statistics and whole-pattern methods in quantitative X-ray powder diffraction analysis." Department of Geosciences, Penn State University. 2001.	N/A
41.	James, R.W. *The Optical Principles of the Diffraction of X-Rays*. OX Bow Press: Woodbridge, CT. 1982.	N/A
42.	Munson Report	N/A
43.	Banyopadhyay, et al. "Application of Powder X-Ray Diffraction in Studying the Compaction Behavior of Bulk Pharmaceutical Powders," Michigan Pharmaceutical Sciences. March 9, 2005.	N/A
44.	McGraw Hill Dictionary of Scientific and Techincal Terms (excerpt)	N/A
45.	US Pat Pub No 2007/0092563	N/A
46.	US Pat No 5,145,684	N/A
47.	Nov. 10, 1994 Lab Notebook	ABRX0148725
48.	Mar. 6, 2000 Lab Notebook	ABRX0148693

Appendix C

Case 1:06-cv-00438-GMS Document 597 Filed 06/02/2008 Page 46 of 61

LOT 301699
EXP 08-10

Abraxane
for Injectable Suspension
(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

Cytotoxic agent.

Sterile, Lyophilized

Each vial contains: 100 mg paclitaxel and approximately 900 mg human albumin.

Reconstitute with 20 mL of Sodium Chloride Injection, USP resulting in a suspension containing 5 mg/mL of paclitaxel.

Note:
An albumin-bound form of paclitaxel.
See package insert for dosage formulation.

ABRAXIS
ONCOLOGY

A Division of American Pharmaceutical Partners, Inc
Schaumburg, IL 60173

ABRAXIS

AVOID ERRORS, READ CAREFULLY.

Store vial in original carton at controlled room temperature 20°C to 25°C (68°F to 77°F) (see USP Controlled Room Temperature).

Store reconstituted suspension in the original carton at 2°C to 8°C (36°F to 46°F) to protect from bright light.

Use reconstituted suspension within 8 hours. Discard any unused portion.

STOP Verify dosage and infusion rate.

ABRAXIS
ONCOLOGY

[redacted]

NDC 68817-134-50 103450

Read all sides of carton.

Abraxane
for Injectable Suspension
(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

100 mg

Single Use Vial

For IV Use Only
Rx only

Functional properties differ from other paclitaxel products. DO NOT SUBSTITUTE.

ABRAXIS
ONCOLOGY

ABRAXIS

Abraxane
for Injectable Suspension
(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

3 68817-134-50 0

Abraxane
for Injectable Suspension
(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

62813

ABRAXIS ONCOLOGY

451031 Issued January 2005

Abraxane® for Injectable Suspension

Rx only

(paclitaxel protein-bound particles for injectable suspension) (albumin bound)

(Patient Information Enclosed)

WARNING

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

ABRAXANE therapy should not be administered to patients with metastatic breast cancer who have baseline neutrophil counts of less than 1,500 cells/mm³. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE.

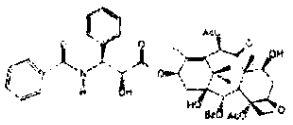
Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.

DESCRIPTION:

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. ABRAXANE is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. ABRAXANE is free of solvents.

The active agent in ABRAXANE is paclitaxel, a natural product with antitumor activity. Paclitaxel is obtained from *Taxus media*. The chemical name for paclitaxel is 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

Paclitaxel has the following structural formula:



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.

CLINICAL PHARMACOLOGY:

Mechanism of Action

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Human Pharmacokinetics

The pharmacokinetics of total paclitaxel following 30- and 180-minute infusions of ABRAXANE at dose levels of 80 to 375 mg/m² were determined in clinical studies. Following intravenous administration of ABRAXANE, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline representing distribution to the peripheral compartment and the slower second phase representing drug elimination. The terminal half-life was about 27 hours.

The drug exposure (AUCs) was dose proportional over 80 to 375 mg/m² and the pharmacokinetics of paclitaxel for ABRAXANE were independent of the duration of administration. At the recommended ABRAXANE clinical dose, 260 mg/m², the mean maximum concentration of paclitaxel, which occurred at the end of the infusion, was 18,741 ng/mL. The mean total clearance was 15 L/hr/m². The mean volume of distribution was 632 L/m²; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetic data of 260 mg/m² ABRAXANE administered over 30 minutes was compared to the pharmacokinetics of 175 mg/m² paclitaxel injection over 3 hours. The clearance of ABRAXANE was larger (43%) than for the clearance of paclitaxel injection and the volume of distribution of ABRAXANE was also higher (53%). Differences in C_{max} and $C_{1\mu}$ corrected for dose reflected differences in total dose and rate of infusion. There were no differences in terminal half-lives.

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicate that between 89% to 98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

After a 30-minute infusion of 260 mg/m² doses of ABRAXANE, the mean values for cumulative urinary recovery of unchanged drug (4%) indicated extensive non-renal clearance. Less than 1% of the total administered dose was excreted in urine as the metabolites 6α-hydroxypaclitaxel and 3'-*p*-hydroxypaclitaxel. Fecal excretion was approximately 20% of the total dose administered.

In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by CYP2C8 and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4 (see **PRECAUTIONS: *Drug Interactions***). The effect of renal or hepatic dysfunction on the disposition of ABRAXANE has not been investigated.

Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

CLINICAL STUDIES:

Metastatic Breast Carcinoma

Data from 106 patients accrued in two single arm open label studies and from 460 patients enrolled in a randomized comparative study were available to support the use of ABRAXANE in metastatic breast cancer.

Single Arm Open Label Studies

In one study, ABRAXANE was administered as a 30-minute infusion at a dose of 175 mg/m² to 43 patients with metastatic breast cancer. The second trial utilized a dose of 300 mg/m² as a 30-minute infusion in 63 patients with metastatic breast cancer. Cycles were administered at 3 week intervals. Objective responses were observed in both studies.

Randomized Comparative Study

This multicenter trial was conducted in 460 patients with metastatic breast cancer. Patients were randomized to receive ABRAXANE at a dose of 260 mg/m² given as a 30-minute infusion, or paclitaxel injection at 175 mg/m² given as a 3-hour infusion. Sixty-four percent of patients had impaired performance status (ECOG 1 or 2) at study entry; 79% had visceral metastasis and 76% had > 3 sites of metastases. Fourteen percent of the patients had not received prior chemotherapy, 27% had received chemotherapy in the adjuvant setting, 40% in the metastatic setting and 19% in both metastatic and adjuvant settings. Fifty-nine percent received study drug as second or greater than second-line therapy. Seventy-seven percent of the patients had been previously exposed to anthracyclines.

In this trial, patients in the ABRAXANE treatment arm had a statistically significantly higher reconciled target lesion response rate (the trial primary endpoint) of 21.5% (95% CI: 16.2% to 26.7%), compared to 11.1% (95% CI: 6.9% to 15.1%) for patients in the paclitaxel injection treatment arm. See Table 1.

		ABRAXANE 260 mg/m²	Paclitaxel Injection 175 mg/m²
Reconciled Target Lesion Response Rate (primary endpoint)[a]			
All randomized patients	Response Rate (95% CI)	50/133 (37.6%) (29.1% to 46.7%)	25/127 (19.7%) (13.0% to 28.0%)
	P value[b]	0.001	
Patients with had received neoadjuvant chemotherapy or relapsed within 6 months of adjuvant chemotherapy	Response Rate (95% CI)	20/129 (15.5%) (9.6% to 23.3%)	12/123 (9.8%) (5.1% to 16.8%)

[a] Confirmed Target Lesion Response Rate (TLRR) is the prospectively defined primary efficacy endpoint. Source of independent radiology assessment (central vs. investigator) and all investigator responses are based on RECIST (Response Evaluation Criteria in Solid Tumors). The reconciled TLRR was lower than the investigator Response Response Rate, which was based on 6 cycles of therapy.

[b] Cochran-Mantel-Haenszel test stratified by hormone receptor status.

INDICATION:
ABRAXANE™ for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

CONTRAINDICATIONS:
ABRAXANE should not be used in patients who have baseline neutrophil counts of < 1,500 cells/mm³.

WARNINGS:
Bone marrow suppression (primarily neutropenia) is dose dependent and a dose limiting toxicity. ABRAXANE should not be administered to patients with baseline neutrophil counts of < 1,500 cells/mm³. Frequent monitoring of blood counts should be instituted during ABRAXANE treatment. Patients should not be retreated with subsequent cycles of ABRAXANE until neutrophils recover to a level > 1,500 cells/mm³ and platelets recover to a level > 100,000 cells/mm³.

The use of ABRAXANE has not been studied in patients with hepatic or renal dysfunction. In the randomized controlled trial, patients were excluded for baseline serum bilirubin >1.5 mg/dL or baseline serum creatinine >2 mg/dL.

Pregnancy – Teratogenic Effects: Pregnancy Category D
ABRAXANE can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel protein-bound particles to rats on gestation days 7 to 17 at doses of 6 mg/m² (approximately 2% of the daily maximum recommended human dose on a mg/m² basis) caused embryo- and fetotoxicity as indicated by intrauterine mortality, increased resorptions (up to 5 fold), reduced numbers of litters and live fetuses, reduction in fetal body weight and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations such as eye bulge, folded retina, microphthalmia, and dilation of brain ventricles. A lower incidence of soft tissue and skeletal malformations were also exhibited at 3 mg/m² (approximately 1% of the daily maximum recommended human dose on a mg/m² basis).

There are no adequate and well controlled studies in pregnant women using ABRAXANE. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with ABRAXANE.

Use in Males
Men should be advised to not father a child while receiving treatment with ABRAXANE (see **PRECAUTIONS: *Carcinogenesis, Mutagenesis, Impairment of Fertility*** for discussion of effects of ABRAXANE exposure on male fertility and embryonic viability).

Albumin (Human)
ABRAXANE contains albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Drug Interactions
No drug interaction studies have been conducted with ABRAXANE.

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering ABRAXANE (paclitaxel protein-bound particles for injectable suspension) concomitantly with known substrates or inhibitors of CYP2C8 and CYP3A4 (see **CLINICAL PHARMACOLOGY**).

Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (such as ritonavir, saquinavir, indinavir and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

Hematology
ABRAXANE therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm³. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE. Patients should not be retreated with subsequent cycles of ABRAXANE until neutrophils recover to a level > 1,500 cells/mm³ and platelets recover to a level > 100,000 cells/mm³. In the case of severe neutropenia (< 500 cells/mm³) for seven days or more) during a course of ABRAXANE therapy, a dose reduction for subsequent courses of therapy is recommended (see **DOSAGE AND ADMINISTRATION**).

Nervous System
Sensory neuropathy occurs frequently with ABRAXANE. The occurrence of grade 1 or 2 sensory neuropathy does not generally require dose modification. If grade 3 sensory neuropathy develops, treatment should be withheld until resolution to grade 1 or 2 followed by a dose reduction for all subsequent courses of ABRAXANE (see **DOSAGE AND ADMINISTRATION**).

Injection Site Reaction
Injection site reactions occur infrequently with ABRAXANE and were mild in the randomized clinical trial. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of ABRAXANE has not been studied.

Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). ABRAXANE was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel protein-bound particles to male rats at 42 mg/m² on a weekly basis (approximately 16% of the daily maximum recommended human exposure on a mg/m² basis) for 11 weeks prior to mating with untreated female rats resulted in significantly reduced fertility accompanied by decreased pregnancy rates and increased loss of embryos in mated females. A low incidence of skeletal and soft tissue fetal anomalies was also observed at doses of 3 and 12 mg/m²/week in this study (approximately 1 to 5% of the daily maximum recommended human exposure on a mg/m² basis). Testicular atrophy/degeneration has also been observed in single-dose toxicology studies in rodents administered paclitaxel protein-bound particles at 54 mg/m² and dogs administered 175 mg/m² (see **WARNINGS**).

Pregnancy – Teratogenic Effects: Pregnancy Category D
(See **WARNINGS** section).

Nursing Mothers
It is not known whether paclitaxel is excreted in human milk. Following intravenous administration of carbon-14 labeled paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving ABRAXANE therapy.

Pediatric Use
The safety and effectiveness of ABRAXANE in pediatric patients have not been evaluated.

Geriatric Use
Of the 229 patients in the randomized study who received ABRAXANE, 11% were at least 86 years of age and < 2% were 75 years or older. No toxicities occurred notably more frequently among elderly patients who received ABRAXANE.

(See **Patient Information Leaflet**).

ADVERSE REACTIONS:
The following table shows the frequency of important adverse events in the randomized comparative trial for the patients who received either single-agent ABRAXANE or paclitaxel injection for the treatment of metastatic breast cancer.

Table 2: Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Study on an Every-3-Weeks Schedule

	Percent of Patients	
	ABRAXANE 260 mg/m²[b] (n = 229)	Paclitaxel Injection 175 mg/m²[c] (n = 225)
Bone Marrow		
Neutropenia		
< 2.0 x 10⁹/L	80	47
< 0.5 x 10⁹/L	9	22
Thrombocytopenia		
< 100 x 10⁹/L	4	2
< 50 x 10⁹/L	1	1
Anemia		
< 11 g/dL	93	79
< 8 g/dL	4	4
Infection	24	20
Febrile Neutropenia	2	1
Bleeding	2	2
Hypersensitivity Reaction[d]		
All	4	12
Severe	1	2
Cardiovascular		
Vital Sign Changes		
Bradycardia	4	1
Hypotension	3	6
Severe Cardiovascular Events	3	3
Abnormal ECG		
All patients	66	52
Patients with Normal Baseline	55	50
Respiratory		
Cough	6	6
Dyspnea	12	11
Sensory Neuropathy		
Any Symptoms	71	35
Severe Symptoms	10	3
Myalgia/Arthralgia		
Any Symptoms	36	40
Severe Symptoms	2	3
Asthenia		
Any Symptoms	47	38
Severe Symptoms	8	3
Fluid Retention/Edema		
Any Symptoms	10	8
Severe Symptoms	2	1
Gastrointestinal		
Nausea		
Any symptoms	40	47
Severe symptoms	1	2
Vomiting		
Any symptoms	19	18
Severe Symptoms	3	2
Diarrhea		
Any Symptoms	34	37
Severe Symptoms	4	4
Mucositis		
Any Symptoms	7	8
Severe Symptoms	1	1
Alopecia	80	94
Hepatic (Patients with Normal Baseline)		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	41
AST (SGOT) Elevations	39	32
Injection Site Reaction	1	0

[a] Based on worst grade.
[b] ABRAXANE dose in mg/m² delivered as a 30-minute infusion.
[c] Paclitaxel injection dose in mg/m² delivered as a 3-hour infusion; patients premedicated.
[d] Includes treatment related events related to hypersensitivity (e.g. flushing, dyspnea, chest pain, hypotension). Most occur on day of dosing.
[e] Severe events are defined as at least grade 3 severity.
[f] During study drug dosing.

Myelosuppression and sensory neuropathy were dose related.

Adverse Event Experiences by Body System
Unless otherwise noted, the following discussion refers to the primary safety database of 229 patients with metastatic breast cancer treated with single-agent ABRAXANE in the randomized

controlled trial. The frequency and severity of important adverse events for the study are presented above in tabular form. In some instances, rare severe events observed with paclitaxel injection may be expected to occur with ABRAXANE.

Hematologic
Neutropenia, the most important hematologic toxicity, was dose dependent and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm³ (Grade 4) in 9% of the patients treated with a dose of 260 mg/m² compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m².

In the randomized metastatic breast cancer study, infectious episodes were reported in 24% of the patients treated with a dose of 260 mg/m² given as a 30-minute infusion. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications. Febrile neutropenia was reported in 2% of patients in the ABRAXANE arm and 1% of patients in the paclitaxel injection arm.

Thrombocytopenia was uncommon. In the randomized metastatic breast cancer study, bleeding episodes were reported in 2% of the patients in each treatment arm.

Anemia (Hb < 11 g/dL) was observed in 33% of patients treated with ABRAXANE in the randomized trial and was severe (Hb < 8 g/dL) in 1% of the cases. Among all patients with normal baseline hemoglobin, 31% became anemic on study and 1% had severe anemia.

Hypersensitivity Reactions (HSRs)
In the randomized controlled metastatic breast cancer study, Grade 1 or 2 HSRs occurred on the day of ABRAXANE administration and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all <1%). The use of ABRAXANE in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Cardiovascular
Hypotension, during the 30 minute infusion, occurred in 5% of patients in the randomized metastatic breast cancer trial. Bradycardia, during the 30-minute infusion, occurred in <1% of patients. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation.

~~Severe cardiovascular events possibly related~~ to single-agent ABRAXANE occurred in approximately 3% of patients in the randomized trial. These events included chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary embolism, and hypertension. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported rarely.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 60% of patients in the metastatic breast cancer randomized trial. Among patients with a normal ECG prior to study entry, 35% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia.

Respiratory
Reports of dyspnea (12%) and cough (6%) were reported after treatment with ABRAXANE in the randomized trial. Rare reports (<1%) of pneumothorax were reported after treatment with ABRAXANE. Rare reports of interstitial pneumonia, lung fibrosis, and pulmonary embolism have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment. Rare reports of radiation pneumonitis have been received in paclitaxel injection patients receiving concurrent radiotherapy. There is no experience with the use of ABRAXANE with concurrent radiotherapy.

Neurologic
The frequency and severity of neurologic manifestations were influenced by prior and/or concomitant therapy with neurotoxic agents.

In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent ABRAXANE. In the randomized trial, sensory neuropathy was observed in 71% of patients (10% severe) in the ABRAXANE arm and in 56% of patients (2% severe) in the paclitaxel injection arm. The frequency of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of ABRAXANE discontinuation in 7/229 (3%) patients in the randomized trial. In the randomized comparative study, 24 patients (10%) treated with ABRAXANE developed Grade 3 peripheral neuropathy, of these patients, 14 had documented improvement after a median of 22 days; 10 patients resumed treatment at a reduced dose of ABRAXANE and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy.

No incidences of grade 4 sensory neuropathies were reported in the clinical trial. Only one incident of motor neuropathy (grade 1) was observed in either arm of the controlled trial.

Reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of paclitaxel injection safety.

Ocular/visual disturbances occurred in 13% of all patients (n = 366) treated with ABRAXANE in single arm and randomized trials and 1% were severe. The severe cases (keratitis and blurred vision) were reported in patients in a single arm study who received higher doses (than those recommended (300 or 375 mg/m²). These effects generally have been reversible. However, rare reports in the literature of abnormal visual evoked potentials in patients treated with paclitaxel injection have suggested persistent optic nerve damage.

Arthralgia/Myalgia
Forty-four percent of patients treated in the randomized trial experienced arthralgia/myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred two or three days after ABRAXANE administration, and resolved within a few days.

Hepatic
Among patients with normal baseline liver function treated with ABRAXANE in the randomized trial, 7%, 36%, and 39% had elevations in bilirubin, alkaline phosphatase, and AST (SGOT), respectively. Grade 3 or 4 elevations in GGT were reported for 14% of patients treated with ABRAXANE and 10% of patients treated with paclitaxel injection in the randomized trial.

Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment.

Renal
Overall 11% of patients experienced creatinine elevation, 1% severe. No discontinuations, dose reductions, or dose delays were caused by renal toxicities.

Gastrointestinal (GI)
Nausea/vomiting, diarrhea, and mucositis were reported by 33%, 27%, and 7% of ABRAXANE treated patients in the randomized trial.

Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment. Rare reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were observed in patients treated with paclitaxel injection alone and in combination with other chemotherapeutic agents.

Injection Site Reaction
Injection site reactions have occurred infrequently with ABRAXANE and were mild in the randomized clinical trial. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site, i.e., "recall" has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been received as part of the continuing surveillance of paclitaxel injection safety. In some cases the onset of the injection site reaction in paclitaxel injection patients either occurred during a prolonged infusion or was delayed by a week to ten days.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Asthenia
Asthenia was reported in 47% of patients (8% severe) treated with ABRAXANE in the randomized trial. Asthenia included reports of asthenia, fatigue, weakness, lethargy and malaise.

Other Clinical Events
Rare cases of cardiac ischemia/infarction and thrombosis/embolism possibly related to ABRAXANE treatment have been reported. Alopecia was observed in almost all of the patients. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon. Edema (fluid retention) was infrequent (10% of randomized trial patients); no patients had severe edema.

The following rare adverse events have been reported as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment: skin abnormalities related to radiation recall as well as reports of maculopapular rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, conjunctivitis, and increased lacrimation.

Accidental Exposure
No reports of accidental exposure to ABRAXANE have been received. However, upon inhalation of paclitaxel, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported. Following topical exposure, events have included tingling, burning, and redness.

OVERDOSAGE:
There is no known antidote for ABRAXANE overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

DOSAGE AND ADMINISTRATION:
After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen for ABRAXANE for Injectable Suspension (paclitaxel protein bound particles for injectable suspension) is 260 mg/m² administered intravenously over 30 minutes every 3 weeks.

Hepatic Impairment
The appropriate dose of ABRAXANE for patients with bilirubin greater than 1.5 mg/dL is not known.

Dose Reduction
Patients who experience severe neutropenia (neutrophil < 500 cells/mm³ for a week or longer) or severe sensory neuropathy during ABRAXANE therapy should have dosage reduced to 220 mg/m² for subsequent courses of ABRAXANE. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m². For grade 3 sensory neuropathy hold treatment until resolution to grade 1 or 2, followed by a dose reduction for all subsequent courses of ABRAXANE.

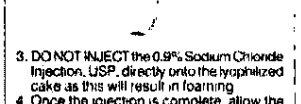
Preparation and Administration Precautions
ABRAXANE is a cytotoxic anticancer drug and as with other potentially toxic paclitaxel compounds, caution should be exercised in handling ABRAXANE. The use of gloves is recommended. If ABRAXANE (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If ABRAXANE contacts mucous membranes, the membranes should be flushed thoroughly with water.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Limiting the infusion of ABRAXANE to 30 minutes as directed, reduces the likelihood of infusion-related reactions (see **PRECAUTIONS: *Injection Site Reaction***).

No premedication to prevent hypersensitivity reactions is required prior to administration of ABRAXANE.

Preparation for Intravenous Administration
ABRAXANE is supplied as a sterile lyophilized powder for reconstitution before use. **AVOID ERRORS, READ ENTIRE PREPARATION INSTRUCTIONS PRIOR TO RECONSTITUTION.**

1. Aseptically reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
2. Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL.



3. DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming.
4. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.
5. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam.
6. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel.

Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient. Dosing volume (mL) = Total dose (mg)/5 (mg/mL)

The reconstituted sample should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use.

Inject the appropriate amount of reconstituted ABRAXANE into an empty, sterile, polyvinyl chloride (PVC) type IV bag. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer ABRAXANE infusions. The use of an in-line filter is not recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Stability

Unopened vials of ABRAXANE are stable until the date indicated on the package when stored between 20°C to 25°C (68°F to 77°F), in the original package. Reconstituted ABRAXANE should be used immediately, but may be refrigerated at 2°C to 8°C (36°F to 46°F) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion. Neither freezing nor refrigeration adversely affects the stability of the product. Some settling of the reconstituted suspension may occur. Ensure complete resuspension by mild agitation before use. Discard the reconstituted suspension if precipitates are observed. The suspension for infusion prepared as recommended in an infusion bag is stable at ambient temperature (approximately 25°C) and lighting conditions for up to 8 hours.

HOW SUPPLIED:

Product No.	NDC No.	
103450	68817 134-50	100 mg in a single use vial, individually packaged in a carton

Storage

Store the vials in original cartons at 20°C to 25°C (68°F to 77°F). Retain in the original package to protect from bright light.

Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

U.S. Patent Numbers: 5,439,686; 5,498,421; 5,560,933; 5,665,382; 6,096,331; 6,506,405; 6,537,579; 6,749,868; 6,753,006

REFERENCES:

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ABRAXIS ONCOLOGY

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451031
Issued: January 2005

EXHIBIT B

CONTAINS RESTRICTED CONFIDENTIAL MATERIAL

SUPPLEMENTAL EXPERT REPORT OF CORY J. BERKLAND

In Response to the Testimony Of Katherine Melody, the Supplemental Expert Report of Jerry L. Atwood , and the Court's Claim Construction Clarification

Elan Pharma International Ltd. v. Abraxis Biosciences, Inc.

1. I, Cory J. Berkland, Ph.D., hereby provide this Supplemental Expert Report with respect to the case referenced above. The opinions expressed are my own and, if called as a witness, I would and could attest to the facts and opinions stated herein.

2. I am the same Cory Berkland who provided an Expert Report served on September 28, 2007.

3. This Supplemental Expert Report is submitted in response to the deposition of Katherine Melody recently authorized by the Court and held on May 22, 2008, which I attended in person, and a transcript of which I reviewed. It is also submitted as a response to the Supplemental Expert Report of Jerry Atwood served on February 29, 2008 and to the Court's Claim Construction Clarification Order dated May 19, 2008, both of which I have reviewed. I understand that the Court has very recently authorized the use of Dr. Atwood's late-submitted Supplemental Expert Report, which is my basis for now tendering my own responsive supplementation.

4. I am submitting this document at this time in order to supplement and clarify certain matters contained in my Expert Report and/or new issues raised by the Melody deposition, the Supplemental Atwood Report, and the Court's clarification.

5. I have relied on or will refer to several documents in preparing this Supplemental Report. Among other documents, I have reviewed the deposition transcript of Ms. Melody in its entirety with Exhibits; Dr. Atwood's Supplemental Expert report; and I have also reviewed certain documents produced by Abraxis in this litigation, including DX 041 (ABRX015402-535), DX 141 (ABRX0537237-238), ABRX015935-966, ABRX015298-347, ABRX053533066-075, ABRX0533101-120, ABRX0151402-507, and ABRX015445.

CONTAINS RESTRICTED CONFIDENTIAL MATERIAL

PXRD Is Not Sufficient to Detect Paclitaxel Nanoparticle Crystallinity in Abraxane

6. Powder X-ray diffraction ("PXRD") represents an historical analytical technique to assess the presence of crystallinity in particulate materials; however, multiple sources have validated my previous criticisms of this technique as a method to quantify the crystallinity of paclitaxel in Abraxane. In light of the recent deposition of Ms. Katherine Melody, an employee of Abraxis's technical vendor Micron, and of information that I understand has emerged in discovery since I prepared my Expert Report, I hereby supplement my Expert Report to address Micron's use of this technique as it applies (and was applied by Abraxis) to the analysis of Abraxane formulations. The testimony of Ms. Melody confirms my former assertions and provides additional information that should be addressed. In light of the newly produced documents and Ms. Melody's testimony, the lack of sensitivity of PXRD to detect crystallinity in the paclitaxel nanoparticles in Abraxane is, again, confirmed. Furthermore, the omission of critical experiments and information that I believe should have been requested of Micron in order to properly quantify crystalline content of paclitaxel nanoparticles in Abraxane is verified by Ms. Melody's testimony and further calls into question the conclusions Abraxis draws from her testing. Finally, new questions have arisen as to the methodology used to generate PXRD data. These questions are based not on the general technical qualifications and competencies of Ms. Melody or Micron, which I do not question, but on the fact that they appear to have been given inadequate guidance as a vendor when Abraxis asked them to test Abraxane.

7. Selected lab notebook entries provided by Ms. Melody (ABRX 0537237) and email correspondence with Dr. Selvaraj (ABRX 0151402 and others) indicate that Micron received instructions to follow standard operating procedure (SOP) XRD002 Rev.001. This SOP indicates adherence to the U.S. Pharmacopeia specifications on X-ray diffraction, which is also verified in e-mail correspondence between Dr. Selvaraj and Micron and in the multiple reports provided by Micron to Abraxis that I have reviewed. Unfortunately, several key points from the U.S. Pharmacopeia section on X-ray diffraction were not adhered to in the studies Abraxis commissioned for Abraxane. Details of my concerns regarding the PXRD studies are delineated below.

8. The mass of material analyzed can cause limitations in quantifying crystalline content using PXRD. PXRD is similar to most analytical techniques in that sensitivity and accuracy depend upon the amount of material that is analyzed. For example, as the amount of total material in a sample decreases, one would expect a corresponding decrease in detectability (e.g. the intensity of peaks would decrease). As the amount (mass) of sample decreases below a threshold level, there is a corresponding decrease in peak intensity relative to "noise" of the spectrum peaks obtained by PXRD for that sample. It is surprising to me that the mass of material that was analyzed at Micron was never recorded in the documents I viewed, which included lab notebook excerpts, email correspondence between Micron and Abraxis, and reports. When questioned about the mass used for experiments, Ms. Melody did not recall how much material was tested. Since the amount of material analyzed was not quantified, a quantitative assessment of the amount of crystalline material would not be possible either. The U.S. Pharmacopeia states "In quantitative analyses of materials, a *known amount* of standard usually is added to a *weighed amount* of specimen to be analyzed" (my emphasis). Therefore, one cannot conclusively determine the crystalline content of paclitaxel from the PXRD data provided by Micron. Further, testing a small amount of material (which we cannot rule out given that Micron was not instructed to record sample size) would limit the detection of crystalline content.

9. The fact that Abraxane is a mixture can cause limitations in quantifying crystalline content using PXRD. Several problems can arise when analyzing mixtures using PXRD. The U.S. Pharmacopeia states:

> "The absorption of the radiation by any specimen is determined by the number and kinds of atoms through which the X-ray beam passes." "Therefore, it is important in quantitative studies that standard curves relating amount of material to the [peak] intensity…be determined in a matrix similar to that in which the substance will be analyzed." "The standard used should have approximately the same density as the specimen and similar absorption characteristics. More important, its diffraction pattern

should not overlap to any extent with that of the material to be analyzed."

Recall that Abraxane is a mixture of paclitaxel and human albumin, with the albumin being present in a nine-fold excess by weight relative to the paclitaxel particles. Tests performed by Micron have not verified the density or X-ray absorption characteristics of paclitaxel or albumin. In other words, using a physical mixture of paclitaxel and albumin is not validated as an adequate standard due to potential differences in the respective density or X-ray absorption of these two materials within the mixture. In addition, there is an overlap between the amorphous "humps" in the albumin diffraction pattern and the diffraction pattern of paclitaxel, which further confounds any quantitative assessment of crystallinity benchmarked by the physical mixture.

10. The small particle size in Abraxane can cause limitations in quantifying crystalline content of the paclitaxel particles using PXRD. Referring to using PXRD as an analytical tool for nanoparticles, Ms. Melody indicated in her deposition that "the peaks are wider" (Melody deposition, 108:3 and see 41:1-7) in comparison to the peaks associated with larger particles. This, again, confirms statements in my previous report that a decrease in crystal particle size leads to a reduction in peak height (e.g. as a result of peak broadening). The extremely small particle size in Abraxane (~130 nm) continues to make this an important point concerning the sensitivity of PXRD for quantifying crystallinity in this product. Conversely, the particle size for the crystalline paclitaxel standard (raw material) was significantly larger (5-500 microns as reported in US Pat. No. 6,749,868, Col. 31, L. 64-65 as previously noted in my Expert Report). Crystals of this size and shape are known to exhibit "preferred orientation" effects, which can influence (e.g. amplify) peak intensity according to the U.S. Pharmacopeia. Thus, Micron recommends that the particle size be less than 10 microns (Melody Deposition, Exhibit 4), a specification which evidently was not followed.

11. Preparation of the samples can also affect the measure of crystalline or amorphous character of particles analyzed using PXRD. For instance, I have reviewed Micron records and have heard testimony from Ms. Melody indicating that the Micron testing involved prior mechanical homogenization of the sample and chopping it with a razor blade under non-sterile conditions (Melody deposition, 53:22-57:8). This type of

physical manipulation of a sample can induce "phase changes" that would affect the degree of crystallinity or amorphousness that subsequent PXRD would detect. Not only is it possible that such a phase change (including, possibly, a reduction in the apparent degree of crystallinity) could have been induced by Micron's sample preparation methods, but it is impossible to estimate what degree of such change may have occurred, because Micron did not conduct a PXRD assay of the Abraxane sample prior to its homogenization and chopping (Melody deposition, 53:22-54:5). Such a pre-homogenization reference pattern would be necessary (and is recommended by U.S. Pharmacopeia protocol) in order for the post-homogenization PXRD results to be relied upon with any scientific certainty. When questioned, Ms. Melody confirmed that it would have been advisable to check the diffraction pattern of the sample prior to grinding (Melody deposition, 53-55 and 63). This is another reason I would not place scientific reliance on the PXRD results reported by Micron and relied on by Dr. Atwood in reaching any conclusion regarding the presence or prevalence of crystalline particles within Abraxane.

12. The relative amount of material in a mixture can cause limitations in quantifying crystalline content using PXRD. As stated above, reducing the mass of material reduces the ability to detect that material. The relative mass of crystalline material being examined can be further reduced if it is mixed with another material, such as albumin. This dilution of the material of interest (e.g. paclitaxel) further limits the detection of crystalline content (e.g. 100 mg of Abraxane contains only 10% paclitaxel). The U.S. Pharmacopeia states regarding PXRD "In favorable cases, amounts of crystalline materials as small as 10% may be determined in solid matrices." This excerpt indicates that, if a large mass of Abraxane were analyzed (we are not sure of the mass analyzed) and if this were a "favorable case", the 10% paclitaxel would have to be near 100% crystalline to be detectable in Abraxane.

13. Each of these limitations (paragraphs 6-12) for using PXRD to detect crystallinity sheds serious doubt on the effectiveness of this analytical technique Abraxis relied upon for determining the crystallinity of paclitaxel nanoparticles in Abraxane. I am convinced that the PXRD results Ms. Melody reports are scientifically insufficient to draw a reliable conclusion. The conclusions that Dr. Atwood reached regarding the

crystallinity of Abraxane based on this data are, therefore, nullified. In her testimony, Ms. Melody expresses similar doubts:

> Q. I'm trying to understand, if we take all these factors we've been talking about today...are you comfortable with someone making a conclusion, based on your data of the samples that Abraxis provided, that the material in the nanoparticles is crystalline or amorphous, or would you want to see some further testing done to nail down some of these variables?
>
> * * *
>
> A. I would like to see some more testing done.

Melody deposition, 110:1-10; see also Melody deposition, 104:13-105:1

> Q: Is the x-ray powder diffraction work that you did for Abraxis sufficient enough to make a conclusion about the nanoparticles in Abraxane, whether they're crystalline or amorphous?
>
> * * *
>
> A: I'm still not sure I understand whether they are crystalline or amorphous.

The proper method to assess whether PXRD may be used to quantify crystalline content in Abraxane is clearly described in the U.S. Pharmacopeia, which states:

> "In quantitative analyses of materials, a known amount of standard usually is added to a weighed amount of specimen to be analyzed. This enables the amount of the substance to be determined relative to the amount of standard added. The standard used should have approximately the same density as the specimen and similar absorption characteristics. More important, its diffraction pattern should not overlap to any extent with that of the material to be analyzed. Under these conditions a linear relationship between line intensity and concentration exists. In favorable cases, amounts of crystalline materials as small as 10% may be determined in solid matrices."

14. Standards are necessary to quantify crystallinity, as further verified on Micron's website (Melody deposition, Exh. 4) and by Ms. Melody in her deposition (e.g., Melody deposition, 106, 107)). Ms. Melody testified that she believes it may be possible to detect amounts of crystalline material in a mixture when it is present in a quantity below 10% of the mixture. (Melody deposition, 53:2-11; 70:3-21; 71:11-15; and 72:3).

15. However, as Ms. Melody correctly pointed out, in order to know whether this is in fact possible, one must first determine the limits of detection of the particular system under evaluation. To determine limits of detection for materials, one performs reference experiments with those materials (Melody deposition, 72:11-16); however, Ms. Melody, Micron's designated PXRD technologist, was not instructed to perform such reference experiments to establish the limits of detection in her work with Abraxane samples (Melody deposition, 72:17-21). Ms. Melody even goes so far as to recommend the additional experiments that would she would like to see to test the limit of detection for a mixture of paclitaxel and albumin and to assess the ability of PXRD to quantify crystalline content (Melody deposition, 110-112).

16. Taken comprehensively, I am convinced that the paclitaxel medicament portion of nanoparticles in Abraxane cannot be qualified as entirely or even mostly amorphous based on the PXRD studies conducted by Micron and the data Micron supplied based on these studies. Ms. Melody confirms that crucial data regarding the experimental protocol were not recorded and that the proper tests and data were not demanded or received by Abraxis or its expert and hence no tests were conducted in order to quantify crystallinity and, perhaps more importantly, to establish a limit for paclitaxel crystallinity detection. In addition, pre-manipulation PXRD patterns of Abraxane were not collected as a reference to confirm that the physical chopping and homogenization Micron carried out had not induced changes in phase/crystallinity. Even supposing the most favorable conditions for paclitaxel crystal detection, the conclusion that paclitaxel nanoparticles in Abraxane are amorphous by Jerry Atwood is accordingly unfounded.

Criticisms of Record Keeping were Unfounded

17. Jerry Atwood in his Supplemental Report states:

> "The failure of Drs. Munson, Barich, Shi, Berkland, and Winkler to keep a laboratory notebook of the experiments they performed for this litigation is contrary to standard scientific practice. Due to their lack of proper record keeping, Elan's experiments are not reproducible."

I was very surprised at this assertion and what it implied. The asserted "failure" to keep a laboratory notebook in a manner commensurate with cited texts (the first sentence quoted above) implied a lack of proper record keeping (the second sentence quoted above). The second proposition does not flow from the first, and Dr. Atwood's assertion is unsupported by standard practices in science generally, and in our laboratory in particular. In reality, lab notebooks may be one technique for recording data in support of a scientific method. Important information about experimental protocols is often also provided by or evident from various other sources, such as the existence of "standard operating procedures" (SOP), reference to scientific texts or standards (e.g. the U.S. Pharmacopeia), a user's manual for a piece of equipment, materials safety data sheets for chemicals used, electronic databases, etc. In addition, details may not be recorded at all if a procedure is habitually conducted in the same manner or if a piece of equipment is dedicated to a certain task and programmed to run consistently.

18. In the current day, scientists often keep records electronically, which can be more convenient and reliable than keeping a paper laboratory notebook. Some technical personnel still keep laboratory notebooks, but there is a clear trend toward storing more and more data electronically. This is true, for instance, of the raw data relating to the ssNMR tests performed by Dr. Munson on Abraxane samples prepared in our lab. This raw data, including considerable data relating to not only the returned spectra, but the settings used for the assay, was recorded on the instrument itself, and thus it would have been a waste of time to document it in a redundant paper notebook since any skilled technician conversant with ssNMR could readily have accessed and analyzed the computer data files. The validation of this multi-sourced and comprehensive, type of "proper record keeping" is evident in the acceptance of paper publications, presentations, reports, or other similarly communicated, peer-reviewed work.

19. Methods used for the sample preparation and analyses of the nanoparticle component of Abraxane reported on by myself and Dr. Munson in my previous document *have* been reported in a manner that would allow reproduction of the experiments. Lab notebooks were not a necessary component to accurately communicate these methods since we employed a routine procedure using dedicated pieces of equipment in a laboratory where experts in this technology routinely perform and report on such testing.

For comparison, the lab notebooks provided by Abraxis Biosciences typically do not offer reproducible methods. Abraxis Biosciences' formal report of methods to the FDA does, however, offer an organized and comprehensible report format illustrative of the methods used to analyze Abraxane; a format that is similar to the Expert Report I provided. A final demonstration of this point is the lab notebook excerpts provided by Micron (Melody deposition, Exhibit 2), which would also not allow reproduction of the work conducted if consulted alone.

Conclusion Based on Court's Claim Construction Clarification

20. As I understand the Court's clarification of the claim construction, the Court has now instructed that the claimed crystalline medicament particles must contain only crystalline paclitaxel. For all the reasons set forth above, I believe that Ms. Melody's experimental PXRD techniques, the records that she kept (or, in some cases, was not instructed to keep), or Dr. Atwood's conclusions based on them, are insufficient to say with any scientific reliability that Abraxane as sold and/or as administered lacks particles of paclitaxel in which the entirety of the paclitaxel medicament is essentially crystalline in nature. Therefore, I would not place scientific reliance on such testing or conclusions in determining whether Abraxane meets the language of the Elan '363 Patent as construed by the Court.

21. Subject to the many limitations on the reliability of the PXRD data that I have identified above, certain of the peaks in the PXRD spectra Ms. Melody obtained may be, in my opinion, consistent with crystalline peaks. However, I believe it unnecessary to consider at length whether these peaks definitively establish the presence of particles containing purely crystalline medicament, because Dr. Munson's ssNMR testing and the conclusions he has drawn based on it in his Expert Report, Supplemental Expert Report, and Second Supplemental Expert Report, are considerably more reliable bases for reaching a conclusion as to the essentially crystalline nature of the medicament contained within many or most of the particles within Abraxane.

CONTAINS RESTRICTED CONFIDENTIAL MATERIAL

Cory J. Berkland, Ph.D.
May 28, 2008