UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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

DECLARATION OF DIANA B. KRUZE IN SUPPORT OF DEFENDANT'S REPLY BRIEF IN SUPPORT OF DEFENDANT'S MOTION FOR SANCTIONS PURSUANT TO FED. R. CIV. P. 11

Josy W. Ingersoll (No. 1088)
jingersoll@ycst.com
Elena C. Norman (No. 4780)
enorman@ycst.com
Karen E. Keller (No. 4489)
kkeller@ycst.com
YOUNG CONAWAY STARGATT & TAYLOR, LLP
The Brandywine Building, 17th Floor
1000 West Street
Wilmington, DE 19801
302-571-6600

Attorneys for Defendant ABRAXIS BIOSCIENCE, INC.

Dated: April 10, 2007

I, Diana B. Kruze, declare as follows:

1. I am an attorney admitted to practice in the State of California, and I am admitted *pro hac vice* in the above-captioned action. I am an associate with the law firm of Morrison & Foerster LLP, attorneys for Abraxis BioScience, Inc. ("Abraxis") in the above captioned action. I submit this declaration in support of Defendant's Reply in Support of Defendant's Motion for Sanctions Pursuant to Federal Rule of Civil Procedure 11. I have personal knowledge of the matters set forth herein, and if called upon to do so, I could and would competently testify thereto.

2. On March 23, 2007, before Elan filed its Opposition to the instant Rule 11 Motion, Abraxis produced an entire 83-page report, entitled "Characterization of ABI-007: Nanoparticle Paclitaxel for Injection." This report includes the 11-page document showing that the paclitaxel in Abraxane is amorphous, which is referenced by Elan in its Opposition at page 12.

3. Attached hereto as Exhibit A is a true and correct copy of U.S. Patent No. 5,399,363.

4. Attached hereto as Exhibit B is a true and correct copy of excerpts from the prosecution history of U.S. Patent No. 5,399,363.

5. Attached hereto as Exhibit C is a true and correct copy of Abraxis's Responses to Elan's First Set of Requests for Admission, served January 25, 2007.

6. Attached hereto as Exhibit D is a true and correct copy of ABRX 0003273, a document produced by Abraxis on January 31, 2007.

7. Attached hereto as Exhibit E is a true and correct copy of ABRX 0076740, a document produced by Abraxis on January 31, 2007.

8. Attached hereto as Exhibit F is a true and correct copy of ABRX 0117565 – ABRX 0117566, a document produced by Abraxis on March 23, 2007.

9. Attached hereto as Exhibit G is a true and correct copy of Elan's Second Amended Responses to Abraxis's First Set of Interrogatories, served March 2, 2007.

10. Attached hereto as Exhibit H is a true and correct copy of the proof of service of Abraxis's Rule 11 Motion and supporting papers, indicating they were served on Elan's counsel on February 26, 2007.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed this 10th day of April, 2007 at Palo Alto, California.

Diana B. Kruze

CERTIFICATE OF SERVICE

I, Josy W. Ingersoll, Esquire, hereby certify that on April 17, 2007, I caused to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF, which will send notification that such filing is available for viewing and downloading to the following counsel of record:

Steven J. Balick, Esquire
ASHBY & GEDDES
500 Delaware Avenue, 8th Floor
Wilmington, DE 19801

I further certify that on April 17, 2007**,** I caused a copy of the foregoing document to be served by hand delivery on the above-listed counsel of record and on the following non-registered participants in the manner indicated:

BY E-MAIL

Stephen Scheve, Esquire
BAKER BOTTS L.L.P.
One Shell Plaza
910 Louisiana Street
Houston, TX 77002-4995
steve.scheve@bakerbotts.com

Paul F. Fehlner
BAKER BOTTS L.L.P.
30 Rockefeller Plaza
New York, NY 10112-4498
paul.fehlner@bakerbotts.com

William J. Sipio, Esquire
1375 Brentwood Road
Yardley, PA 19067
sipz25@aol.cm

YOUNG CONAWAY STARGATT
& TAYLOR, LLP

/s/ *Josy W. Ingersoll*

Josy W. Ingersoll (No. 1088)
jingersoll@ycst.com
Elena C. Norman (No. 4780)
enorman@ycst.com
Karen E. Keller (No. 4489)
kkeller@ycst.com
The Brandywine Building
1000 West Street, 17th Floor
Wilmington, Delaware 19899
(302) 571-6600
Attorneys for Defendant
ABRAXIS BIOSCIENCE, INC.

EXHIBIT A

US005399363A

United States Patent [19]

Liversidge et al.

[11] Patent Number: 5,399,363

[45] Date of Patent: Mar. 21, 1995

[54] **SURFACE MODIFIED ANTICANCER NANOPARTICLES**

[75] Inventors: **Gary G. Liversidge; Elaine Liversidge**, both of West Chester; **Pramod P. Sarpotdar**, Malvern, all of Pa.

[73] Assignee: **Eastman Kodak Company**, Rochester, N.Y.

[21] Appl. No.: **908,125**

[22] Filed: **Jul. 1, 1992**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 647,105, Jan. 25, 1991, Pat. No. 5,145,684.

[51] **Int. Cl.**[6] **A61K 9/14**

[52] **U.S. Cl.** **424/490**; 424/489

[58] **Field of Search** 424/490, 487; 514/352

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,671,750	3/1954	Macek	514/179
3,881,020	4/1975	Nakamura et al.	514/619
4,107,288	8/1978	Oppenheim	424/22
4,225,581	9/1980	Kreuter et al.	424/88
4,269,821	5/1981	Kreuter et al.	424/489
4,540,602	9/1985	Motoyama	427/213.31
4,826,689	5/1989	Violanto	424/489
4,851,421	7/1989	Iwasaki et al.	514/352
5,049,322	9/1991	Devissaguet	424/490
5,091,188	2/1992	Haynes	424/450
5,118,525	6/1992	Fessi	424/487
5,124,338	6/1992	King	514/352

FOREIGN PATENT DOCUMENTS

262560	9/1987	European Pat. Off. .
411629	2/1991	European Pat. Off. .
499299	1/1992	European Pat. Off. .
2118987	4/1972	France .
3772837	7/1987	Germany .
2282330	11/1990	Japan .
2185397	7/1987	United Kingdom .
2200048	7/1988	United Kingdom .
8400294	7/1983	WIPO .
9115193	6/1989	WIPO .
9015593	6/1990	WIPO .
9203380	8/1990	WIPO .
9106292	11/1990	WIPO .

OTHER PUBLICATIONS

Lachman et al., "The Theory and Practice of Industrial Pharmacy", Chapter 2 (1986).

Remington's Pharmaceutical Sciences, 17th Edition, Chapter 20, Schott, H., "Colloidal Dispersions".

Goodman and Gilman, "The Pharmacological Basis of Therapeutics", Eighth Edition, pp. 68–69.

Primary Examiner—Thurman K. Page

Assistant Examiner—William E. Benston, Jr.

Attorney, Agent, or Firm—Arthur H. Rosenstein

[57] **ABSTRACT**

Dispersible particles consisting essentially of a crystalline anticancer agent having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 1000 nm. Anticancer compositions comprising the particles exhibit reduced toxicity and/or enhanced efficacy, and can be administered by IV bolus injection.

17 Claims, No Drawings

SURFACE MODIFIED ANTICANCER NANOPARTICLES

CROSS REFERENCED TO RELATED APPLICATION

This application is a continuation-in-part of U.S. patent application Ser. No. 647,105, filed Jan. 25, 1991, now U.S. Pat. No. 5,145,684, the disclosure of which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

1. Field of Invention

This invention relates to anticancer agents in the form of particles, to anticancer compositions comprising the particles, and to methods employing the particles.

2. Description of the Prior Art

The therapeutic index is a measure of how selective a drug is at producing its desired effects and can be defined as the ratio of the median lethal dose to the median effective dose, i.e., (LD_{50}/ED_{50}) (see Goodman and Gilman, *The Pharmacological Basis of Therapeutics,* Eight Edition, p. 68–69). Virtually all anticancer agents have a low therapeutic index, e.g., less than about 1.0. Increasing the therapeutic index, e.g., by reducing toxicity or enhancing efficacy would provide more latitude to physicians in their duty of administering anticancer drugs to patients in need thereof. Consequently, methods to reduce toxicity and/or enhance efficacy of anticancer drugs and thus increase the therapeutic indices of such drugs would be of great value in the treatment of cancers.

In addition, poorly water-soluble drugs, such as poorly water-soluble anticancer agents, are not readily injectable via an intravenous (IV) bolus injection. The creation of injectable forms of poorly soluble drugs represents a formidable problem. It would be highly desirable to be able to provide poorly soluble drugs, such as poorly soluble anticancer agents, in an IV bolus injectable form.

SUMMARY OF THE INVENTION

We have discovered that anticancer compositions comprising anticancer agents in the form of surface modified nanoparticles exhibit reduced toxicity and/or enhanced efficacy.

More particularly, in accordance with this invention, there are provided particles consisting essentially of a crystalline anticancer agent having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 1000 nm.

This invention further provides an anticancer composition comprising the above-described particles.

In another embodiment of the invention, there is provided a method of treating a mammal comprising administering to the mammal the above-described anticancer composition.

In yet another embodiment of the invention, there is provided a method of enhancing the efficacy and/or reducing the toxicity of an anticancer agent which includes the step of administering the agent in the form of the above-described particles.

It is an advantageous feature of this invention that anticancer compositions are provided exhibiting reduced toxicity.

It is another advantageous feature of this invention that anticancer compositions are provided exhibiting improved efficacy.

Yet another advantageous feature of this invention is that compositions are provided featuring poorly soluble anticancer agents that can be administered by IV bolus injection.

Still another advantageous feature of this invention is that compositions are provided containing poorly soluble anticancer agents exhibiting prolonged circulation in the blood pool after IV bolus injection.

Other advantageous features will become readily apparent upon reference to the following descriptions of preferred embodiments.

DESCRIPTION OF PREFERRED EMBODIMENTS

This invention is based partly on the discovery that surface modified anticancer nanoparticles exhibit reduced toxicity and/or enhanced efficacy. While the invention is described herein primarily in connection with its preferred class of drugs, i.e., anticancer agents including immunosuppressive agents, it is also useful in conjunction with poorly water soluble drugs, particularly those with low therapeutic indices, from other classes of drug substances.

The particles of this invention comprise an anticancer agent. The anticancer agent is present in one or more discrete crystalline phases. The crystalline phase differs from an amorphous, i.e., non-crystalline phase which results from conventional solvent precipitation techniques for the preparation of particles in the submicron size range, such as described in U.S. Pat. No. 4,826,689.

The invention can be practiced with a wide variety of anticancer agents. However, the anticancer agent must be poorly soluble and dispersible in at least one liquid medium. By "poorly soluble", it is meant that the drug substance has a solubility in the liquid dispersion medium, e.g., water, of less than about 10 mg/ml, and preferably, of less than 1 mg/ml at processing temperature, e.g., room temperature. The preferred liquid dispersion medium is water. However, the invention can be practiced with other liquid media in which the anticancer agent is dispersible including, for example, aqueous salt solutions, safflower oil, and solvents such as ethanol, t-butanol, hexane, and glycol. The pH of the aqueous dispersion media can be adjusted by techniques known in the art.

The anticancer agent preferably is selected from alkylating agents, antimetabolites, natural products, hormones and antagonists, and miscellaneous agents, such as radiosensitizers.

Examples of alkylating agents include alkylating agents having the bis-(2-chloroethyl)-amine group such as, for example, chlormethine, chlorambucile, melphalan, uramustine, mannomustine, extramustinephoshate, mechlore-thaminoxide, cyclophosphamide, ifosfamide, and trifosfamide;

alkylating agents having a substituted aziridine group such as, for example, tretamine, thiotepa, triaziquone and mitomycine;

alkylating agents of the alkyl sulfonate type, such as, for example, busulfan, piposulfan, and piposulfam;

alkylating N-alkyl-N-nitrosourea derivatives, such as, for example, carmustine, lomustine, semustine, or streptozotocine; and alkylating agents of the mitobronitole, dacarbazine and procarbazine type.

Examples of antimetabolites include folic acid analogs, such as, for example, methotrexate;

pyrimidine analogs such as, for example, fluorouracil, floxuridine, tegafur, cytarabine, idoxuridine, and flucytosine; and

purine derivatives such as, for example, mercaptopurine, thioguanine, azathioprine, tiamiprine, vidarabine, pentostatin, and puromycine.

Examples of natural products include vinca alkaloids, such as, for example, vinblastine and vincristine;

epipodophylotoxins, such as, for example, etoposide and teniposide;

antibiotics, such as, for example, adriamycine, daunomycine, doctinomycin, daunorubicin, doxorubicin, mithramycin, bleomycin, and mitomycin;

enzymes, such as, for example, L-asparaginase;

biological response modifiers, such as, for example, α-interferon;

camptothecin;

taxol; and

retinoids, such as retinoic acid.

Examples of hormones and antagonists include adrenocorticosteroids, such as, for example, prednisone;

progestins, such as, for example, hydroxyprogesterone caproate, medroxyprogesterone acetate and megestrol acetate;

estrogens, such as, for example, diethylstilbestrol and ethinyl estradiol;

antiestrogens, such as, for example, tamoxifen;

androgens, such as, for example, testosterone propionate and fluoxymesterone;

antiandrogens, such as, for example, flutamide;

and gonadotropin-releasing hormone analogs, such as, for example leuprolide.

Examples of miscellaneous agents include radiosensitizers, such as, for example, 1,2,4-benzotriazin-3-amine 1,4-dioxide (SR 4889) and 1,2,4-benzotriazine-7-amine 1,4-dioxide (WIN 59075);

platinum coordination complexes such as cisplatin and carboplatin;

anthracenediones, such as, for example, mitoxantrone;

substituted ureas, such as, for example, hydroxyurea;

and adrenocortical suppressants, such as, for example, mitotane and aminoglutethimide.

In addition, the anticancer agent can be an immunosuppressive drug, such as, for example, cyclosporine, azathioprine, sulfasalazine, methoxsalen and thalidomide.

The anticancer agents useful in the practice of this invention are known compounds and/or can be prepared by techniques known in the art.

The anticancer agent can be used alone or in combination with one or more anticancer agents.

The particles of this invention contain an anticancer agent as described above having a surface modifier adsorbed on the surface thereof. Useful surface modifiers are believed to include those which physically adhere to the surface of the anticancer agent but do not chemically bond to the anticancer agent.

Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants. Representative examples of excipients include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available Tweens™, polyethylene glycols, polyoxyethylene stearates, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP). Most of these excipients are described in detail in the *Handbook of Pharmaceutical Excipients,* published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986. The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two or more surface modifiers can be used in combination.

Particularly preferred surface modifiers include polyvinylpyrrolidone, tyloxapol, polaxomers, such as Pluronic™ F68, F108 and F127, which are block copolymers of ethylene oxide and propylene oxide available from BASF, and poloxamines, such as Tetronic™ 908 (T908), which is a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine available from BASF, dextran, lecithin, Aerosol OT™ (AOT), which is a dioctyl ester of sodium sulfosuccinic acid, available from American Cyanamid, Duponol™ P, which is a sodium lauryl sulfate, available from DuPont, Triton™ X-200, which is an alkyl aryl polyether sulfonate, available from Rohm and Haas, Tween 20, 40, 60 and 80, which are polyoxyethylene sorbitan fatty acid esters, available from ICI Speciality Chemicals, Span 20, 40, 60 and 80, which are sorbitan esters of fatty acids, Arlacel 20, 40, 60 and 80, which are sorbitan esters of fatty acids, available from Hercules, Inc., Carbowax™ 3550 and 934, which are polyethylene glycols available from Union Carbide, Crodesta™ F-110, which is a mixture of sucrose stearate and sucrose distearate, available from Croda Inc., Crodesta SL-40, which is available from Croda, Inc., hexyldecyl trimethyl ammonium chloride (CTAC), bovine serum albumin and SA90HCO, which is $C_{18}H_{37}$ CH_2 (CON (CH_3) CH_2 $(CHOH)_4CH_2OH)_2$. Surface modifiers which have been found to be particularly useful include polyvinylpyrrolidone, Pluronic F-108, polyvinyl alcohol and gum acacia.

The surface modifier is adsorbed on the surface of the anticancer agent in an amount sufficient to maintain an effective average particle size of less than about 1000 nm. The surface modifier does not chemically react with the anticancer agent or itself. Furthermore, the individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages.

As used herein, particle size refers to a number average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art, such as sedimentation field flow fractionation, photon correlation spectroscopy, or disk centrifugation. By "an effective average particle size of less than about 1000 nm" it is meant that at least 90% of the particles have a number average particle size of less than about 1000 nm when measured by the above-noted tech-

niques. In particularly preferred embodiments of the invention, the effective average particle size is less than about 400 nm. In some embodiments of the invention, the effective average particle size is less than about 300 nm. With reference to the effective average particle size, it is preferred that at least 95% and, more preferably, at least 99% of the particles have a particle size of less than the effective average, e.g., 1000 nm. In particularly preferred embodiments, essentially all of the particles have a size less than 1000 nm.

Motoyama et al, U.S. Pat. No. 4,540,602 disclose that a solid drug can be pulverized in an aqueous solution of a water-soluble high molecular substance, and that as a result of such wet grinding, the drug is formed into finely divided particles ranging from 0.5 μm or less to 5 μm in diameter. However, there is no suggestion that particles having an average particle size of less than about 1 μm can be obtained. Attempts to reproduce the wet grinding procedures described by Motoyama et al resulted in particles having an average particle size of much greater than 1 μm.

The particles of this invention can be prepared by a method comprising the steps of dispersing an anticancer agent in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the anticancer agent to an effective average particle size of less than about 1000 nm. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

A general procedure for preparing the particles of this invention is set forth below. The anticancer agent selected is obtained commercially and/or prepared by techniques known in the art in a conventional coarse form. It is preferred, but not essential, that the particle size of the coarse anticancer agent selected be less than about 100 μm as determined by sieve analysis. If the coarse particle size of the anticancer agent is greater than about 100 μm, then it is preferred that the particles of the anticancer agent be reduced in size to less than 100 μm using a conventional milling method such as airjet or fragmentation milling.

The coarse anticancer agent selected can then be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of the anticancer agent in the liquid medium can vary from about 0.1–60% and preferably is from 5–30% (w/w). It is preferred, but not essential, that the surface modifier be present in the premix. The concentration of the surface modifier can vary from about 0.1 to about 90% and preferably is 1–75%, more preferably 20–60%, by weight based on the total combined weight of the drug substance and surface modifier. The apparent viscosity of the premix suspension is preferably less than about 1000 centipoise.

The premix can be used directly by subjecting it to mechanical means to reduce the average particle size in the dispersion to less than 1000 nm. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, the anticancer agent and, optionally, the surface modifier, can be dispersed in the liquid medium using suitable agitation, e.g., a roller mill or a Cowles type mixer, until a homogeneous dispersion is observed in which there are no large agglomerates visible to the naked eye. It is preferred that the premix be subjected to such a premilling dispersion step when a recirculating media mill is used for attrition.

The mechanical means applied to reduce the particle size of the anticancer agent conveniently can take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, a planetary mill, media mills such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the intended result, i.e., the desired reduction in particle size. For media milling, the apparent viscosity of the premix preferably is from about 100 to about 1000 centipoise. For ball milling, the apparent viscosity of the premix preferably is from about 1 up to about 100 centipoise. Such ranges tend to afford an optimal balance between efficient particle fragmentation and media erosion.

The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in form having an average size less than about 3 mm and, more preferably, less than about 1 mm. Such media desirably can provide the particles of the invention with shorter processing times and impart less wear to the milling equipment. The selection of material for the grinding media is not believed to be critical. However, zirconium oxide, such as 95% ZrO stabilized with magnesia, zirconium silicate, and glass grinding media provide particles having levels of contamination which are believed to be acceptable for the preparation of pharmaceutical compositions. Further, other media, such as stainless steel, titania, alumina, and 95% ZrO stabilized with yttrium, are expected to be useful. Preferred media have a density greater than about 2.5 g/cm^3.

The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For ball mills, processing times of up to five days or longer may be required. On the other hand, processing times of less than 1 day (residence times of one minute up to several hours) have provided the desired results using a high shear media mill.

The particles must be reduced in size at a temperature which does not significantly degrade the anticancer agent. Processing temperatures of less than about 30°–40° C. are ordinarily preferred. If desired, the processing equipment can be cooled with conventional cooling equipment. The method is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process. For example, ambient processing pressures are typical of ball mills, attritor mills and vibratory mills. Processing pressures up to about 20 psi (1.4 kg/cm^2) are typical of media milling.

The surface modifier, if it was not present in the premix, must be added to the dispersion after attrition in an amount as described for the premix above. Thereafter, the dispersion can be mixed, e.g., by shaking vigorously. Optionally, the dispersion can be subjected to a sonication step, e.g., using an ultrasonic power supply. For example, the dispersion can be subjected to ultrasonic energy having a frequency of 20–80 kHz for a time of about 1 to 120 seconds.

The relative amount of the anticancer agent and surface modifier can vary widely and the optimal amount of the surface modifier can depend, for example, upon the particular anticancer agent and surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, the surface area of the anticancer agent, etc. The surface modifier preferably is present in an amount of about 0.1–10 mg per square

meter surface area of the anticancer agent. The surface modifier can be present in an amount of 0.1–90%, preferably 0.5–80% and more preferably 1–60% by weight based on the total weight of the dry particle.

A simple screening process has been developed whereby compatible surface modifiers and anticancer agents can be selected which provide stable dispersions of the desired particles. First, coarse particles of an anticancer agent are dispersed in a liquid in which the anticancer agent is essentially insoluble, e.g., water at 2% (w/v) and milled for 120 hours in a roller mill under the following milling conditions:

Grinding vessel: 8 oz. (250 ml) glass jar
Available volume of grinding vessel: 250 ml
Media volume: 120 ml
Media type: 1.0 mm pre-cleaned zirconium oxide beads (distributed by Zircoa, Inc.)
Milling time: 120 hours
Slurry volume: 60 ml
RPM: 92
Room Temperature

The slurry is separated from the milling media by conventional means, e.g., by pouring the slurry out of the vessel, or by using a pipette. The separated slurry is then divided into aliquots and surface modifiers are added at a concentration of between 2 and 50% by weight based on the total combined weight of the anticancer agent and surface modifier. The dispersions are then sonicated (1 minute, 20 kHz) or vortexed using a multitubed vortexer for one minute, to disperse agglomerates and subjected to particle size analysis, e.g., by photon correlation spectroscopy (PCS) and/or by examination under an optical microscope (1000× magnification). If a stable dispersion is observed, then the process for preparing the particular anticancer agent surface modifier combination can be optimized in accordance with the teachings above. By stable it is meant that the dispersion exhibits no flocculation or particle agglomeration visible to the naked eye and, preferably, when viewed under the optical microscope at 1000×, at least 15 minutes, and preferably, at least two days or longer after preparation. In addition, preferred particles exhibit no flocculation or agglomeration when dispersed in 0.1N HCl and/or phosphate buffered saline, pH 7.4 (PBS) or rat plasma.

The resulting dispersion is stable and consists of the liquid dispersion medium and the above-described particles. The dispersion of surface modified anticancer agent nanoparticles can be spray coated onto sugar spheres or onto a pharmaceutical excipient in a fluid-bed spray coater by techniques well known in the art.

Anticancer pharmaceutical compositions according to this invention include the particles described above and a pharmaceutically acceptable carrier therefor. Suitable pharmaceutically acceptable carriers are well known to those skilled in the art. These include non-toxic physiologically acceptable carriers, adjuvants or vehicles for parenteral injection, for oral administration in solid or liquid form, for rectal administration, nasal administration, intramuscular administration, subcutaneous administration, and the like.

A method of treating a mammal in accordance with this invention comprises the step of administering to the mammal in need of treatment an effective amount of the above-described anticancer composition. The selected dosage level of the anticancer agent for treatment is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage can be readily determined by one skilled in the art and depends upon the particular anticancer agent, the desired therapeutic effect, the route of administration, the desired duration of treatment and other factors.

It is a particularly advantageous feature that the anticancer compositions of this invention exhibit reduced toxicity and/or enhanced efficacy as illustrated in the examples that follow. Further, the particles of this invention exhibit prolonged circulation in the blood pool.

Moreover, anticancer agents which heretofore could not be administered by injection, when prepared as nanoparticles and formulated in anticancer compositions according to this invention, can be effectively administered by injection, e.g., by an intravenous bolus injection.

The following examples further illustrate the invention.

EXAMPLES 1–4 Nanoparticulate Piposulfan

EXAMPLE 1

Piposulfan (purchased from Eastman Kodak) was milled in a mixture of 0.33% polyoxyethylene sorbitan monooleate, Tween 80, (ICI Americas, Inc., Wilmington, Del.) and 0.67% sorbitan monooleate, Span 80, (ICI) using 1 mm zirconium oxide beads for about 96 hours to produce particles approximately 240 nm in diameter. The final piposulfan concentration in the suspension was 10 mg/mL. The particles were stable to flocculation/aggregation in rat plasma.

Milling Conditions: A coarse suspension of piposulfan was prepared by adding 300 mg of the drug to a 4 oz. (120 mL) amber bottle which was previously filled with 60 mL of 1 mm precleaned zirconium oxide beads (Zircoa Inc., Solon, Ohio) and 30 mL of 1% Tween 80/Span 80 (1 to 2 ratio) solution. The surfactant solution was prepared by accurately weighing 333 mg of Tween 80 and 667 mg of Span 80 in a volumetric flask followed by addition of sterile water for injection to dissolve/disperse the surfactants. Sufficient quantity of water was added to make the final volume 100 mL. Zirconium oxide beads were cleaned by first rinsing in 1N sulfuric acid followed by several rinses with deionized water. The media was dried in a vacuum oven at about 100° C. overnight.

The sealed primary container was loaded into a secondary padded aluminium containment can to ensure a tight fit. It was milled on a roller mill (US Stoneware, Mawah, N.J.) at 144 RPM for about 96 hours. At the end of the milling time the slurry was separated from the media and particle size was measured using a PCS device. Stability of these particles to rat plasma was assessed by optical microscopy at 1000× magnification. The final pH of the formulation was 6.

Control A (unmilled), a coarse suspension containing 40 mg of bulk piposulfan was dispersed in water in the presence of 3% ethanol and 1% Tween 80. This suspension could not be injected IV.

Example 1 was evaluated for efficacy studies in female mice (avg. wt. 22 g) which were implanted with early stage Mammary Adenocarcinoma #16/C on day 0. The formulation was injected starting from day 1 for several days. The antitumor activity was assessed by monitoring tumor weight and comparing it to the control animals. The results were as follows:

Treatment	Route of Adm.*	Total Dose (mg/kg)	% Wt. Loss	T/C %	Log10 Cell Kill
Control	—	—	+5.5	—	—
Example 1	IV	356	−5.5	0	2.75
(243 nm)	IV	220	−5.5	2	2.75
	IV	137	−1.8	2	2.25
	IV	85	0	18	1.0
Control A	SC	800	−10.8	0	2.1

*Administration - IV Intravenous; SC Subcutaneous

Example 1 could be injected directly as 10 mg/ml suspension. There was no acute toxicity after injection of 78 mg/kg single dose.

T/C=Tumor weight in treated animals divided by the tumor weight of the control animals, reported as percent value. Lower value indicates better efficacy, 0% suggests cures. <10% is considered highly active, 10 to 42% is moderately active formulation. >42% is considered inactive.

Log Kill=(T−C)/3.32 (Td), where T is the time in days for the median tumor to reach 1000 mg mass in treated animals, C is the time in days for the median tumor to reach 1000 mg in control animals and Td is the tumor volume doubling time in days. Cures (tumor free animals) are excluded from (T−C) calculations.

Example 1 demonstrates that a composition of this invention exhibited reduced toxicity and enhanced efficacy compared to a prior art composition and could be administered by IV bolus injection.

EXAMPLES 2–4

The milling procedure described in Example 1 was repeated except that the ratio of Tween 80 to Span 80 was 2:1. The resulting average particle size was 297 nm.

The milling procedure described in Example 1 was repeated except that the ratio of Tween 80 to Span 80 was 1:1. The resulting average particle size was 380 nm.

The milling procedure described in Example 1 was repeated except that the surface modifier was a 1:1 ratio of Tween 60 and Span 60. The resulting average particle size was 301 nm.

Stable pipsulfan nanoparticles were also prepared using bovine serum albumin as the surface modifier.

EXAMPLES 5–7 Nanoparticulate Camptothecin

EXAMPLE 5

Approximately 60 mL of precleaned zirconium oxide beads (1 mm) were placed in a 120 mL wide mouth round amber bottle. To it was added 0.35 g of Tetronic 908 (BASF) followed by 0.35 g of Camptothecin (Sigma Chemicals, 95% pure). To the above mixture, 35 mL of water for injection (Abbott) was added. The bottle was sealed and mounted on a roller mill. Milling was effected by rotating the bottle at 100 RPM for 7 days.

At the end of milling, an aliquot (100 μL) was checked for particle size using a Malvern Zetasizer. The particles were determined to have an average particle size of 240 nm.

EXAMPLE 6

Example 5 was repeated except that the Tetronic 908 was replaced by polyvinyl alcohol (MW 30 to 70K). The final particle size was 256 nm.

EXAMPLE 7

Example 5 was repeated except that Tetronic 908 was replaced by gum acacia. The final particle size was 298 nm.

Nanocamptothecin formulations were evaluated for efficacy in two murine tumor models, i.e., Mammary Adenocarcinoma #16/C and Pancreatic Ductal Adenocarcinoma #03. The antitumor activity was assessed by monitoring tumor weight from experimental and control animals.

1. Efficacy Studies in Pancreatic Ductal Adenocarcinoma #03:

Example	Route	Dose mg/kg	Wt % Loss	Drug Deaths	T/C %
Control B	SC	60	−24.1	6/6	—
	SC	40.2	−21.8	5/5	—
	SC	26.7	−18.2	5/5	—
	SC	18	−10.9	1/5	62
6	IV	83.1	−16.7	1/4	14
	IV	78.2	−14.6	1/4	55
	IV	48.6	−8.3	0/4	0
	IV	24.3	−4.2	0/4	18
PVA Control	IV	—	+6.3	0/4	100
7	IV	93.5	−16.7	1/4	7
	IV	46.8	−14.6	0/4	17
	IV	23.4	−8.3	0/4	11
Cum Acacia Control	IV	—	0.0	0/4	60

The Control B formulation consisted of 1% coarse camptothecin in 3% ethanol, and 1% Tween 20. Control B could only be administered subcutaneously and even at the lowest SC dose (18 mg/kg) was inactive. Control B was toxic to 1/5 animals tested. In contrast, doses of the nanocamptothecin formulations of this invention ranging from 24–93 mg/kg were administered intravenously (IV) and were shown to be safe and efficacious.

2. Efficacy Studies in Mammary Adenocarcinoma #16/C Murine Tumor Model

Example	Route	Dose mg/kg	% Wt Loss	Drug Deaths	T/C %
Control B	SC	60	−23.5	5/5	—
	SC	30	−20.9	5/5	—
	SC	15	−18.3	3/5	14**
5	IV	65	−17.4	0/5	23
	IV	33	−18.7	1/5	33
	IV	16	−2.2	0/5	63
T908 Control	IV	—	+4.3	0/2	100
6	IV	65	−21.7	5/5	—
	IV	33	−15.7	0/5	100
PVA Control	IV	—	+4.3	0/2	100

**% T/C for the control animals was determined from the surviving animals, N = 2.

The T908 and PVA controls consisted of 1% aqueous solutions of the respective surface modifiers. The Control B was injected subcutaneously, and it was toxic at all doses tested. Efficacious doses of the nanocamptothecin formulations of this invention were administered intravenously.

3. Blood and Tumor Clearance

To determine if the increased efficacy was related to alterations in pharmacokinetic properties, blood clear-

ance and tumor distribution were studied in the Mammary adenocarcinoma #16/C murine tumor model.

Tumor bearing mice were injected via the tail vein with 10 mg/ml of camptothecin formulated as described in Examples 5 and 6 and a control which was 5 mg/ml camptothecin solubilized by the addition of 0.1N NaOH. At various times after injection, i.e., 5 min., 30 min., 60 min., 2 hrs., 4 hrs., 8 hrs., 16 hrs., 24 hrs. and 48 hrs., animals were euthanized and a blood sample was collected and the tumor excised. Concentrations of drug samples were quantified using HPLC. Results show that the compositions of this invention affect the clearance of the drug from the circulating pool of blood and the tumor.

	$T_{\frac{1}{2}}$ Blood and Tumor	
Formulation	Blood	Tumor
Example 6	18 hrs.	>48 hrs.
Example 5	13 hrs.	>48 hrs.
Control	1.6 hrs.	13.5 hrs.

When formulated in accordance with this invention, the elimination half-life and the residence time of camptothecin in the tumor were prolonged significantly. It was concluded that pharmacokinetic parameters of the nanoparticulate formulation of camptothecin are directly related to the improved performance of the drug.

EXAMPLES 8–10 Nanoparticulate Etoposide

EXAMPLE 8

Example 5 was repeated except that 1.7 g of etoposide was combined with 1.7 g of PVA and the milling time was 14 days. The final particle size was 310 nm. The particles were stable in acid and plasma.

EXAMPLE 9

Example 8 was repeated except that the PVA was replaced by Pluronic F-108 (BASF). The final particle size was 312 nm. The particles were stable in acid and plasma.

EXAMPLE 10

Etoposide (2%) was milled in sterile water for 7 days. A 1:1 mixture of the milled slurry was prepared with 2% Pluronic F127 solution. The mixture was vortexed before measuring particle size. The final size was 277 nm. The slurry was stable in simulated gastric fluid, PBS (pH 7.4) and rat plasma.

EFFICACY STUDIES

Nanoetoposide formulations were evaluated in two separate efficacy studies in pancreatic ductal adenocarcinoma #03 (PANC #03). Control C was a 2% nonaqueous etoposide solution prepared using the formula described on pages 741–743 of the 46th Edition of the Physicians' Desk Reference. As described above, antitumor activity was assessed by monitoring tumor weight from experimental and control animals. These studies demonstrate that the etoposide compositions of this invention provide a means to deliver high doses of the drug without evidence of severe toxic reaction.

1. Efficacy Studies for Nanoetoposide in PANC #03 Murine Tumor Model

Example	Route	Dose mg/kg	% Wt Loss	Drug Deaths	T/C %
Control C	IV	120	−24.0	0/5	4.0
	IV	75	−4.0	0/5	20.0
7	IV	160	−12.0	0/5	18.0
	IV	100	0.0	0/5	32.0
	IV	62	2.0	0/5	42.0
8	IV	160	−12.0	0/5	26.0
	IV	100	+2.0	0/5	35.0
	IV	62	+4.0	0/5	35.0
9	IV	170	−18.5	1/5	16
	IV	85	−2.0	0/5	35
	IV	43	+2.5	0/5	41

EXAMPLES 11–16 Nanoparticulate Taxol

EXAMPLE 11

Approximately 18 mL of precleaned zirconium oxide media (1 mm) was added to a 30 mL amber jar. To it was added 240 mg of taxol (Sigma Chemicals) and 180 mg of Tween 20. Finally, 12 mL of water for injection was added to the jar, it was sealed and mounted on a roller mill for 11 days. The final particle size was 327 nm. The formulation was stable when exposed to PBS (pH 7.4) and rat plasma.

EXAMPLE 12

Example 11 was repeated except that the Tween 20 was replaced with PVA (MW 30 to 70 k). The final particle size was 365 nm.

The above samples were evaluated in efficacy studies in mice bearing early stage mammary adenocarcinoma #16/C. The antitumor activity was assessed by comparing tumor weights of taxol treated animals with the tumor weights of untreated animals. The toxicity was assessed by dose ranging studies with death and weight loss as end points. All samples were injected IV.

Example	Dose mg/kg	% Wt Loss	Deaths	Median Tumor on Day 11	T/C %
Control D	—	+6.1	—	1539 mg	—
Example 11	108.5	−1.5	0/5	1528	13
Example 12	108.5	−3.0	0/5	201	99

A control sample of taxol (NCI) was not available. However, a single dose of taxol formulated in Cremophore EL causes immediate deaths at 25 mg/kg total dose. However, taxol formulated in compositions of this invention could be injected at a dose of 88 mg/kg with no apparent adverse effects.

A taxol suspension prepared in a manner similar to Example 11 was treated separately with several surface modifiers. After addition of the new surface modifier the mixture was vortexed and evaluated for particle size and fluid stability. All the suspensions contained 1% taxol and 0.75% Tween 20. The results are as follows.

Example/ Surface Modifier	Concentration %	Size (nm)	Fluid Stability PBS	Fluid Stability Rat Plasma
13 CTAC	0.25	364	OK	Flocculation
14 AOT	0.25	322	SA*	SA
15 F68	0.5	297	SA/OK	SA/OK

-continued

Example/ Surface Modifier	Concentration %	Size (nm)	Fluid Stability PBS	Fluid Stability Rat Plasma
16 T908	0.5	313	SA/OK	SA/OK

*SA = Slight Aggregation

EXAMPLES 17–18 Nanoparticulate WIN 59075

Approximately 60 mL of precleaned zirconium oxide (1 mm) media was transferred into a 4 oz amber jar. It was followed by addition of 1.5 g of WIN 59075 and 28.5 mL of water for injection. The jars were sealed, loaded onto a roller mill and cascaded at 95 RPM for 48 hrs. PCS analysis determined the particle size to be 322 nm, however, the presence of larger particles was suggested. Milling was continued for 5 additional days.

Studies were conducted by mixing 0.5 mL of the WIN 59075 slurry prepared above with 0.5 mL of 6% surface modifier solutions. The final concentration of the drug was 2.5% and that of the surface modifiers was 3%. The surface modifier stabilized nanosuspensions of WIN 59075 were then treated with either PBS (pH 7.0) or 0.1N HCl (pH 1). Optical microscopic observations were made to determine fluid stability. The results are as follows;

Example	Surface Modifier	Stability pH 1	Stability pH 7	Human Plasma
17	PVP (12K) (BASF)	Fine	Fine	Fine
18	Gum Acacia (Aldrich)	—	SA/OK	SA/OK

It was concluded that stable nanoparticles of WIN 59075 could be prepared.

EXAMPLES 19–22 Nanoparticulate SR 4889

7.5 mL of precleaned zirconium oxide media (1 mm) was transferred into a 15 mL amber jar along with 18.75 mg of SR 4889 and 3.75 mL of water. After 11 days of milling the nanosuspension was separated from the media. To each of the 100 μL aliquots of the suspension, 100 μL of a surfactant solution (2%) was added giving a final concentration of 0.25% drug and 1% surfactant. The mixture was vortexed and analyzed for particle size. Fluid stability was assessed microscopically by mixing 10 μL of the suspension with 90 μL of rat plasma. The results are as follows:

Example	Surface Modifier	Particle Size (nm)	Fluid Stabilty Rat Plasma
19	PVP (12K)	134	Fine
20	Gum Acacia	344	SA/OK
21	Tween 80	128	Fine
22	T908	130	Aggregates

EXAMPLE 23 Nanoparticulate Retinoic Acid

30 mL of precleaned zirconium oxide media was transferred to a 60 mL amber jar. To it was added 1 g of transretinoic acid (Sigma), 470 mg of tyloxapol and 15 mL of water. The mixture was milled on a roller mill for 15 days. The final particle size was 140 nm. The nanosuspension was stable when exposed to either rat plasma or simulated gastric fluid.

The invention has been described in detail with particular reference to certain preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

What is claimed:

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

2. The particles of claim **1** having an average effective particles size of less than 400 nm.

3. The particles of claim **1** having an average effective particle size of less than 300 nm.

4. The particles of claim **1** wherein said surface modifier is present in an amount of 1 to 75% by weight.

5. The particles of claim **1** wherein said anticancer agent is selected from the group consisting of piposulfan, piposulfam, camptothecin, etoposide, taxol, 1,2,4-benzotriazin-3-amine 1,4-dioxide, 1,2,4-benzotriazin-7-amine 1,4-dioxide and retinoic acid.

6. The particles of claim **1** wherein said surface modifier is selected from the group consisting of polyvinyl alcohol, a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine, gum acacia, a block copolymer of ethylene oxide and propylene oxide, a polyoxyethylene sorbitan fatty acid ester, and a sorbitan ester of a fatty acid.

7. The particles of claim **1** wherein said anticancer agent is taxol and said surface modifier comprises a polyoxyethylene sorbitan fatty acid ester.

8. An anticancer composition comprising the particles of claim **1**.

9. A method of treating a mammal comprising administering to the mammal an effective amount of the anticancer composition of claim **8**.

10. In a method of treating a mammal comprising administering to the mammal an effective amount of an anticancer agent, the improvement wherein the efficacy of said anticancer agent is increased by administering said anticancer agent in the form of the particles of claim **1**.

11. In a method of treating a mammal comprising administering to the mammal an effective amount of an anticancer agent, the improvement wherein the toxicity of said anticancer agent is reduced by administering said anticancer agent in the form of the particles of claim **1**.

12. The particles of claim **1** wherein said surface modifier is a surfactant.

13. The particles of claim 1 wherein said surface modifier is a nonionic surfactant.

14. The particles of claim 1 wherein said surface modifier is an anionic surfactant.

15. The particles of claim 1 wherein said surface modifier is selected from the group consisting of gelatin, casein, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinyipyrrolidone, poloxomers, tyloxapol, poloxamines, dextran, a dioctyl ester of sodium sulfosuccinic acid, sodium lauryl sulfate, an alkyl aryl polyether sulfonate, a mixture of sucrose stearate and sucrose distearate, hexyldecyl trimethyl ammonium chloride, bovine serum albumin and $C_{18}H_{37}CH_2(CON(CH_3)CH_2(CHOH)_4CH_2OH)_2$.

16. The particles of claim 1 wherein said surface modifier is present in an amount of 10 to 60% by weight based on the total weight of the dry particle.

17. The particles of claim 1 wherein said surface modifier is present in an amount of 10 to 30% by weight based on the total weight of the dry particle.

* * * * *

EXHIBIT B

MAIL ROOM OCT 29 1992 PAT. & TRADEMARK OFF.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#2 R. Gassaway 11-17-92

RECEIVED NOV 12 1992 GROUP 1500

In re Application of
Elaine Liversidge et al

Serial No. : 07/908,125 : Group Art Unit: ~~1205~~

Filed: July 1, 1992 :

: Malvern, Pennsylvania 19355

Title: Surface Modifier Anticancer Nanoparticles :

CERTIFICATE UNDER 37 CFR 1.8 (a)
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks Washington, D.C 20231, on 26 Oct. 1992
(Date of Deposit)
William Davis 30744
(Reg. No.)
William Davis 26 Oct 1992
(Date of Signature)

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

INFORMATION DISCLOSURE STATEMENT
PURSUANT TO 37 CFR 1.97 - 1.99

For the convenience of the Patent Office, record is made below to published art for consideration by the Office in connection with the above-identified application. No representation is made or intended that a search has been made, or, if made, was complete, or that no more pertinent art than that listed is available. It is expected that the Patent Office will conduct independently a complete search for relevant prior art.

In compliance with MPEP Sec. 609 and 37 CFR 1.97 through 1.99, accompanying each citation is a discussion indicating and including reference to specifically identified portions (e.g., page and line) of the above-identified application, where appropriate. Unless otherwise indicated, a full text copy of the entire item of published art and, in the case of references not in English, a translation thereof is attached. Where specifically indicated, an equivalent

English language patent or publication is attached in lieu of a translation.

In accordance with the Patent Office Notice (998 OG 9) dated August 15, 1980, also enclosed is a completed form PTO-1449.

CITED ART

AA — U.S. Patent 2,671,750 relates to an aqueous suspension of cortisone acetate and a method for the preparation thereof which comprises milling an aqueous vehicle and cortisone acetate. However, the aqueous vehicle contains a surface active agent, which functions to prevent individual particles from coalescing (column 4, lines 25-28), a suspending agent and a bacteriological preservative. Moreover, suspensions reported contain a substantial percentage of particles greater than 5 microns (5,000 nm) in size.

AB — U.S. Patent 4,107,288 describes particles in the size range from 10 to 1,000 nm containing a biologically or pharmacodynamically active material. However, the particles comprise a cross-linked matrix of macromolecules having the active material supported on or incorporated into the matrix.

AC — U.S. Patent No. 4,540,602 discloses that a solid drug can be pulverized in an aqueous solution of a water-soluble high

molecular substance, and that as a result of such wet grinding, the drug is formed into finely divided particles ranging from 0.5 µm or less to 5 µm in diameter. However, there is no suggestion that particles having an average particle size of less than about 400 nm can be obtained. Indeed, attempts on behalf of the applicants to reproduce the wet grinding procedures described in U.S. Patent No. 4,540,602 resulted in particles having an average particle size of much greater than 1 µm.

AD U.S. Patent No. 4,826,689 discloses a method of making uniformly sized non-crystalline amorphous particles from water-insoluble organic compounds wherein the organic compound is dissolved in an organic solvent. However, solvent precipitation techniques such as described in U.S. Patent No. 4,826,689 for preparing particles tend to provide solvent contaminated particles. Such solvents are often toxic and can be very difficult, if not impossible, to adequately remove to pharmaceutically acceptable levels for diagnostic imaging. Additionally, amorphous materials and formulations tend to exhibit unacceptably poor stability and/or short shelf-lives.

AE U.S. Patent No. 4,851,421 describes an agricultural suspension containing a

biocidal fine powder and a specific adjuvant, but does not suggest applicants' surface modified anticancer nanoparticles.

AL EPO 411,629 (indicating a publication date of February 6, 1991, after the applicants' priority date) discloses a process for micronizing slightly soluble drugs by subjecting a mixture of the drug and a sugar or sugar alcohol to high speed stirring comminution or impact comminution. There is no suggestion of the applicants' claimed particles or method.

AM Japanese Patent Application 2,282,330 relates to a danazol composition containing danazol microcrystals prepared by solvent precipitation, a surfactant and optionally a carrier. There is no suggestion of applicants' claimed particles or method.

AN U.K. Patent Application 2,185,397 discloses a drug delivery system wherein particles of drug are directed away from the reticuloendothelial system by the use of a surface coating which prevents the take up of the composite particles.

AO U. K. Patent Application 2,200,048 discloses pharmaceutical colloidal hydrosols for injection. The hydrosols are formed by a solvent precipitation

technique (page 11, lines 8-14), and thus exhibit the problems, e.g., solvent contamination, associated with particles prepared by solvent precipitation techniques such as described in U.S. Patent 4,826,689. U.K. Patent Application 2,200,048 suggests that it is not possible to completely remove the solvent, noting that the suspension contains residual organic solvent after solvent removal in a rotary evaporator (page 11, lines 11-14). There is no suggestion of applicants' claimed particles or method.

AP

EPO 275,796 describes the production of colloidally dispersible systems comprising a substance in the form of spherical particles smaller than 500 nm. However, the method involves a precipitation effected by mixing a solution of the substance and a miscible non-solvent for the substance and results in the formation of non-crystalline nanoparticle. Furthermore, precipitation techniques for preparing particles tend to provide particles contaminated with solvents. Such solvents are often toxic and can be very difficult, if not impossible, to adequately remove to pharmaceutically acceptable levels to be practical.

AR
AS

These publications provide a background on industrial milling and colloidal dispersions but do not suggest applicants' surface modified anticancer nanoparticles.

AT

See applications page 1.

Respectfully submitted,

William J. Davis

Date: 26 October 1992

William J. Davis
Registration No. 30,744
Attorney for Applicants
(215) 889-8802

Address:
Patent Department
Sterling Winthrop Inc.
81 Columbia Turnpike
Rensselaer, NY 12144

WJD:mmm

#6/A
10/5/93

MAIL ROOM SEP 15 1993 PAT & TRADEMARK OFF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	
Liversidge et al	:	Group Art Unit: 1502
	:	
Title: SURFACE MODIFIED ANTICANCER NANOPARTICLES	:	Examiner: W. Benston, Jr.
	:	
Serial No.: 07/908,125	:	Malvern, Pa 19355
	:	
Filed: July 1, 1992	:	

RECEIVED
SEP 15 1993
GROUP 1500

Honorable Commissioner of Patents and Trademarks
Washington, DC 20231

AMENDMENT

Sir:

In response to the Office Action mailed March 11, 1993, the period for response having been extended by 3 months to expire on September 11, 1993, by the petition and fee authorization enclosed herewith, please amend this application, without prejudice, as follows:

In the Claims

Please rewrite claim 1 as follows:

1. (Amended) Particles consisting essentially of 99.9-10% by weight of a crystalline anticancer agent having a solubility in water of less than 10 mg/ml, said anticancer agent having a non-crosslinked surface modifier adsorbed on the surface thereof in an amount of 0.1-90% by weight and sufficient to maintain an average effective particle size of less than about 1000 nm.

P 30133 10/06/93 07908125 19-4325 030 103 132.00CH

Please add claims 28-33 as follows:

~~28~~ 12. The particles of claim 1 wherein said surface modifier is a surfactant.

~~29~~ 13. The particles of claim 1 wherein said surface modifier is a nonionic surfactant.

~~30~~ 14. The particles of claim 1 wherein said surface modifier is an anionic surfactant.

~~31~~ 15. The particles of claim 1 wherein said surface modifier is selected from the group consisting of gelatin, casein, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose,hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, poloxomers, tyloxapol, poloxamines, dextran, a dioctyl ester of sodium sulfosuccinic acid, sodium lauryl sulfate, an alkyl aryl polyether sulfonate, a mixture of sucrose stearate and sucrose distearate, hexyldecyl trimethyl ammonium chloride, bovine serum albumin and $C_{18}H_{37}CH_2(CON(CH_3)CH_2(CHOH)_4CH_2OH)_2$.

~~32~~ 16. The particles of claim 1 wherein said surface modifier is present in an amount of 10 to 60% by weight based on the total weight of the dry particle.

33. The particles of claim 1 wherein said surface modifier is present in an amount of 10 to 30% by weight based on the total weight of the dry particle.

REMARKS

Claims 1-27 are pending in this application. Claims 7-15 and 17-23 have been withdrawn from consideration. Claims 28-33 have been added by this amendment. The present application is a continuation-in-part of U.S. Patent Application Ser. No. 647,105 filed January 25, 1991, now U.S. Patent No. 5,145,684. Favorable reconsideration of this application is respectfully requested in view of this amendment and the accompanying remarks.

Applicants' claims are directed to particles consisting essentially of a crystalline anticancer agent having a non-crosslinked surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 1000 nm. Applicants' claims are further directed to anticancer compositions comprising such particles and to methods of treating mammals comprising administering the particles, whereby the efficacy of the anticancer agent is enhanced and/or the toxicity of the agent is reduced. The particles are prepared by wet grinding coarse crystals of the anticancer agent in the presence of fine grinding media and in conjunction with a surface modifier.

The rejection of claims 1-6, 16 and 24-27 under 35 U.S.C. § 103 as being unpatentable over King (U.S. Patent No. 5,124,338) in view of Devissaguet et al (U.S. Patent No. 5,049,322) is respectfully traversed. It is respectfully submitted that applicants' claims are patentable over these references taken individually or in combination.

King describes potentiating agents, i.e., specific acrivatine esters, which enhance the efficacy of antineoplastic agents. However, the pharmaceutical formulations of King are conventional, i.e., they are prepared by methods known in the

art (column 5, lines 55-58). Consequently, as noted in the Office Action, King does not suggest a particulate anticancer agent having an average effective particle size of less than 1000 nm.

Devissaguet et al describe a process for preparing nanocapsules. However, the nanocapsules described by Devissaguet et al are radically different than applicants' particles. The Devissaguet et al nanocapsules feature a wall of film-forming polymer (substance A) and a core (substance B), which can be a medicinal. On the other hand, applicants' claimed particles consist essentially of a crystalline anticancer agent and a non-crosslinked surface modifier adsorbed on the surface thereof. Moreover, the only medicinal containing nanocapsules described by Devissaguet et al are prepared by a precipitation technique, i.e., substance B is first dissolved in a solvent. For example, as illustrated in Example 2 therein, indomethecin is dissolved in acetone. Such solvent precipitation techniques provide non-crystalline, e.g., amorphous, cores which are contaminated with solvent. Such solvents are often toxic and can be very difficult, if not impossible, to adequately remove to pharmaceutically acceptable levels to be practical. On the other hand, applicants' crystalline particles, prepared by wet grinding, a technique entirely different than the technique of Devissaguet et al, are essentially free of solvent contamination.

Thus, it is urged that the references individually do not suggest applicants' claimed particles. Furthermore, applicants' respectfully submit that the combined teachings of the references in no way suggest the claimed invention. Nothing in the cited references or the prior art as a whole offers any suggestion that the teachings could be so modified and combined to yield anything resembling applicants' claimed particles of a crystalline anticancer agent. Devissaguet et al disclose nanocapsules, radically different than applicants' crystalline particles, of a size embraced by the range specified in applicants' claims. However, there is no reason for one skilled

in the art to expect that the claimed crystalline particles could be prepared according to the teaching of Devissaguet et al. Nor does King, teaching conventional pharmaceutical formulation preparation techniques, remedy the deficiency in the teaching of Devissaguet et al. Even if the teaching of Devissaguet et al were applied to the anticancer agents listed by King, the resulting nanocapsules, as discussed above, would be radically different than the claimed crystalline particles.

method of manufacture

Further, applicants' crystalline nanoparticles are obtained by a specific wet grinding technique which is not disclosed or suggested in the prior art. As stated in EPO 411,629 (cited in applicants' disclosure statement) "preparation of submicron particles of less than 1 μm in diameter is almost impossible". The reason for this is the inherent tendency of such particles to agglomerate, aggregate, solidify and/or adhere to the particle size decreases. Additionally, as discussed in the instant specification, applicants' attempts to reproduce the closest prior art wet grinding technique described by Motoyama et al in U.S. Patent No. 4,540,602 resulted in particles having an average particle size of much greater than 1 micron. Thus, the prior art as a whole does not disclose or suggest, and cannot be construed to disclose or suggest, applicants' claimed crystalline particles having an average effective particle size of less than 1000 nm.

Furthermore, there is no suggestion in the cited references or in the art as a whole of the unexpected advantageous properties associated with the claimed crystalline anticancer particles. The particles of this invention have been formulated into anticancer compositions which demonstrate enhanced efficacy and/or reduced toxicity and which can be administered by IV bolus injection. These advantages are illustrated in the working examples set forth on pages 13-22 of the instant specification.

To further evidence the nonobviousness of the claimed particles, applicants' proffer herewith the attached Rule 132 Declaration of Gary G. Liversidge, Ph.D., pointing out that the

above-noted differences between the particles of the claimed invention and particles prepared by prior art techniques, such as solvent precipitation techniques, are commercially significant.

For all the reasons set forth above, it is respectfully urged that all of the applicants' claims are patentable over the prior art. It is therefore requested that the rejection under § 103 be withdrawn.

Claim 1 has been amended consonant with the amendment to the claims in parent U.S. Patent No. 5,145,684 for reasons discussed fully in the parent relating to the § 112 rejection and prior art cited therein. More specifically, claim 1 has been amended to recite minimal and maximal amounts of the crystalline anticancer agent and surface modifier present, that the surface modifier is non-crosslinked, and that the anticancer agent has a specific, i.e., low, solubility in water. Ample support for such amendments can be found, e.g., on page 9, lines 1-5; page 7, lines 19-21; and page 3, lines 23-29 of the instant specification.

non-crosslinked

New claims 28-33 added by this amendment are directed to various embodiments of the surface modifier component of the particles of this invention. Ample support for such claims can be found, e.g., on page 5, line 32 - page 7, line 5 of the instant specification. The new claims are dependent from claim 1 and thus are patentable over the prior art for the reasons discussed above.

In conclusion, applicants' claimed invention is nonobvious over the prior art because the art does not suggest the invention or its unexpected, advantageous properties. In view of the foregoing amendment, remarks and the attached Rule 132 Declaration, it is respectfully asserted that the Examiner's rejection cannot be sustained and should be withdrawn. It is respectfully urged that claims 1-6, 16 and 24-33 are patentable and in condition for allowance. Notice of Allowance or early action to that end is earnestly solicited.

In the event that the Examiner believes that a telephone and/or personal interview would be helpful in resolving any remaining issues, it is requested that the Examiner telephone applicants' undersigned attorney.

Respectfully submitted,

William J Davis

William J. Davis
Attorney for Applicants
Reg. No. 30,744

Sterling Winthrop Inc.
9 Great Valley Parkway
Malvern, PA 19355
Tele: (215) 889-8802

CERTIFICATE UNDER 37 CFR 1.8(a)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks Washington, D.C 20231, on September 10, 1992
(Date of Deposit)

William J Davis 30,744
(Reg. No.)

September 9, 1992
(Date Signature)

#1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

MAIL ROOM SEP 13 1993 PAT. & TRADEMARK OFF.

In re Application of	:	
Liversidge et al	:	Group Art Unit: 1502
	:	
Title: Surface Modified	:	Examiner: W. Benston, Jr.
Anticancer Nanoparticles	:	
	:	
Serial No.: 07/908,125	:	Malvern, PA 19355
	:	
Filed: July 1, 1992	:	

.. ..

Honorable Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

RULE 132 DECLARATION

I, Gary G. Liversidge, hereby say and declare that:

1) I am currently employed by Sterling Winthrop Inc. as Director of Oral Products. My primary responsibilities include managing research and development work associated with pharmaceutical sciences including drug delivery. I received a B. Pharm. degree in Pharmacy from the University of Bradford in 1978, and a Ph.D. degree in Pharmaceutical Chemistry from the University of Nottingham in 1981.

2) I am a coinventor of the subject matter disclosed and claimed in U.S. Patent Application Serial No. 908,125.

3) I have read and understood and I am quite familiar with the teaching and subject matter of U.S. Patent No. 5,049,322 of Devissaguet et al.

4) U.S. Patent No. 5,049,322 discloses a solvent precipitation technique for preparing nanocapsules. Solvent precipitation techniques ordinarily result in the formation of non-crystalline or amorphous particles. Particles prepared by solvent precipitation techniques provide particles which are contaminated with solvent. Such solvents are often pharmaceutically unacceptable and can be difficult, if not impossible, to adequately remove to pharmaceutically acceptable levels to be practical. This problem is noted in U.K. Patent Application 2,200,048 of record which suggest that it is not possible to completely remove solvent by conventional techniques.

5) The crystalline particles described in U.S. Patent Application Serial No. 908,125 are essentially free of solvent contamination. Such essentially solvent free particles prepared according to the method described in U.S. Patent Application Serial No. 908,125 and parent U.S. Patent No. 5,145,684 provide a significant commercial advantage compared to the solvent contaminated particles prepared according to the teaching of Devissaguet et al and other prior art solvent precipitation techniques such as those described in U.S. Patent No. 4,826,689 of record.

6) Example 7 in U.S. Patent No. 5,049,322 describes nanocapsules of a polymer containing an inorganic mineral solid, i.e., particulate silicon carbide. However, there is no exemplification of a particulate organic medicine. Moreover, I believe that the prior art does not teach one skilled in the art how to prepare crystalline particles of organic medicines, e.g., anticancer agents, in the size range specified in U.S. Patent No. 5,049,322.

7) Furthermore, laboratory work has demonstrated that particles prepared according to the teaching of U.S. Patent Application Serial No. 908,125 have exhibited unexpected

advantageous properties, e.g., with respect to toxicity and/or efficacy.

8) All statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and

9) These statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

9/8/93
Date

Gary G. Liversidge, Ph.D.

CERTIFICATE UNDER 37 CFR 1.8 (a)
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks Washington, D.C 20231, on September 10, 1993
(Date of Deposit)
William J Davis 30,744
(Reg. No.)
September 9 1993
(Date Signature)

EXHIBIT C

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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

RESPONSE OF ABRAXIS BIOSCIENCE, INC. TO ELAN PHARMA INTERNATIONAL LIMITED'S FIRST SET OF REQUESTS FOR ADMISSION

Pursuant to Rule 36 of the Federal Rules of Civil Procedure, Abraxis BioScience, Inc. hereby submits the following responses and objections to Elan Pharma International Limited's First Set of Requests for Admission.

RESPONSE TO ELAN'S DEFINITIONS

A. "Abraxane:" Abraxis objects to Elan's definition of the term "Abraxane" as incorrect. For the purposes of its Responses, Abraxis will interpret the term to mean the human albumin-bound paclitaxel product that is sold by Abraxis.

B. "ABI-007:" Abraxis objects to Elan's definition of the term "ABI-007" as incorrect. Among other things, American Pharmaceutical Partners, Inc. did not sponsor the clinical trials that tested ABI-007. For the purposes of its Responses, Abraxis will interpret the term to mean the various formulations of human albumin-bound paclitaxel that were tested in clinical trials sponsored by American BioScience, Inc.

C. "Toxicity occurrence:" Abraxis objects to Elan's definition of the term "toxicity occurrence" as vague, ambiguous, and compound. *See, e.g., Fulhorst v. United Tech.*

Automotive, Inc., No. 96-577-JJF, 1997 U.S. Dist. LEXIS 22290, at *3-4 (D. Del. Nov. 17, 1997) (citation omitted) ("A party is not required to respond to a request that contains vague or ambiguous statements.").

D. "Solvent-free:" Abraxis objects to Elan's definition of the term "solvent-free" as vague and ambiguous. *See, e.g., Fulhorst v. United Tech. Automotive, Inc.*, No. 96-577-JJF, 1997 U.S. Dist. LEXIS 22290, at *3-4 (D. Del. Nov. 17, 1997) (citation omitted) ("A party is not required to respond to a request that contains vague or ambiguous statements."). In particular, the degree to which the "chemical … dissolves paclitaxel" is not specified.

REQUESTS FOR ADMISSION

REQUEST FOR ADMISSION NO. 1:

Admit that American Pharmaceutical Partners, Inc. ("APP") and American Bio[S]cience, Inc. merged to form Abraxis Bio[S]cience, Inc.

RESPONSE TO REQUEST FOR ADMISSION NO. 1:

Admitted.

REQUEST FOR ADMISSION NO. 2:

Admit that APP tested ABI-007 in clinical trials.

RESPONSE TO REQUEST FOR ADMISSION NO. 2:

Denied.

REQUEST FOR ADMISSION NO. 3:

Admit that on September 24, 2003, APP issued a press release regarding ABI-007 (the "September 2003 Press Release").

RESPONSE TO REQUEST FOR ADMISSION NO. 3:

Abraxis admits that on September 24, 2003, APP and another entity issued a press release referring to "ABI-007." Except as expressly admitted, the Request is denied.

REQUEST FOR ADMISSION NO. 4:

Admit that the September 2003 Press Release stated that there was "an absence of severe hypersensitivity reactions despite no routine pre-medication in patients receiving ABI-007."

RESPONSE TO REQUEST FOR ADMISSION NO. 4:

Abraxis admits that a September 2003 press release stated that a finding of a Phase III clinical trial was that there was an "[a]bsence of severe hypersensitivity reactions despite no routine pre-medication in patients receiving ABRAXANE." Except as expressly admitted, the Request is denied.

REQUEST FOR ADMISSION NO. 5:

Admit that ABI-007 is now marketed as Abraxane.®

RESPONSE TO REQUEST FOR ADMISSION NO. 5:

Abraxis admits that it now markets Abraxane and that it has at times referred to clinical trial versions of Abraxane as "ABI-007." Except as expressly admitted, the Request is denied.

REQUEST FOR ADMISSION NO. 6:

Admit that Abraxane® is solvent-free.

RESPONSE TO REQUEST FOR ADMISSION NO. 6:

Abraxis objects that the term "solvent-free" is vague and ambiguous as used in this Request. *See, e.g., Fulhorst v. United Tech. Automotive, Inc.*, No. 96-577-JJF, 1997 U.S. Dist. LEXIS 22290, at *3-4 (D. Del. Nov. 17, 1997) (citation omitted) ("A party is not required to respond to a request that contains vague or ambiguous statements.").

Subject to and without waiving Abraxis's objection, if Elan intends "solvent-free" in the Request to mean completely devoid of any chemical that dissolves paclitaxel to any degree, then the Request is denied. Except as expressly admitted, the Request is denied.

REQUEST FOR ADMISSION NO. 7:

Admit that Abraxis recommends a dose reduction to 180 mg/m^2 of Abraxane® for patients who experience a second toxicity occurrence.

RESPONSE TO REQUEST FOR ADMISSION NO. 7:

Abraxis objects that the term "toxicity occurrence" is vague, ambiguous, and compound as used in this Request. *See, e.g., Fulhorst v. United Tech. Automotive, Inc.*, No. 96-577-JJF, 1997 U.S. Dist. LEXIS 22290, at *3-4 (D. Del. Nov. 17, 1997) (citation omitted) ("A party is not required to respond to a request that contains vague or ambiguous statements.").

Due to the ambiguity and vagueness of the term "toxicity occurrence" as used in this Request, Abraxis denies having knowledge or information sufficient to admit or deny this Request and therefore denies it.

REQUEST FOR ADMISSION NO. 8:

Admit that if Grade 3 sensory neuropathy develops in a patient undergoing Abraxane® treatment, Abraxis recommends that further Abraxane® treatment be withheld.

RESPONSE TO REQUEST FOR ADMISSION NO. 8:

Abraxis admits that the Abraxane package insert states that "[f]or grade 3 sensory neuropathy hold treatment until resolution to grade 1 or 2." Except as expressly admitted, the Request is denied.

REQUEST FOR ADMISSION NO. 9:

Admit that if a patient's Grade 3 sensory neuropathy resolves to a Grade 1 or 2 sensory neuropathy after Abraxane treatment has been withheld, Abraxis recommends a dose reduction from 260 mg/m^2 for subsequent courses of Abraxane®.

RESPONSE TO REQUEST FOR ADMISSION NO. 9:

Abraxis admits that the Abraxane package insert states that "[f]or grade 3 sensory neuropathy hold treatment until resolution to grade 1 or 2, followed by a dose reduction for all subsequent courses of ABRAXANE." Except as expressly admitted, the Request is denied.

REQUEST FOR ADMISSION NO. 10:

Admit that if a patient develops severe neutropenia (<500 $cells/mm^3$ for seven days or more) during a course of Abraxane® therapy, Abraxis recommends a dose reduction from 260 mg/m^2 for subsequent courses of therapy.

RESPONSE TO REQUEST FOR ADMISSION NO. 10:

Abraxis admits that the Abraxane package insert states as follows:

> Patients who experience severe neutropenia (neutrophil <500 cells/mm³ for a week or longer) . . . during ABRAXANE therapy should have dosage reduced to 220 [milligrams of paclitaxel per meter squared] for subsequent courses of ABRAXANE.

Except as expressly admitted, the Request is denied.

REQUEST FOR ADMISSION NO. 11:

Admit that each single use vial of Abraxane® contains 100 mg of paclitaxel and 900 mg human serum albumin ("HSA").

RESPONSE TO REQUEST FOR ADMISSION NO. 11:

Abraxis admits that, prior to reconstitution, each single-use vial of Abraxane contains approximately 100 milligrams of non-crystalline, amorphous paclitaxel and approximately 900 milligrams of human albumin. Except as expressly admitted, the Request is denied.

REQUEST FOR ADMISSION NO. 12:

Admit that each single use vial of Abraxane® contains 10% paclitaxel and 90% HSA by weight.

RESPONSE TO REQUEST FOR ADMISSION NO. 12:

Abraxis admits that, prior to reconstitution, each single-use vial of Abraxane contains approximately 10% non-crystalline, amorphous paclitaxel and approximately 90% human albumin by weight. Except as expressly admitted, the Request is denied.

REQUEST FOR ADMISSION NO. 13:

Admit that Abraxis recommends reconstituting each vial of Abraxane® by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.

RESPONSE TO REQUEST FOR ADMISSION NO. 13:

Abraxis admits that the Abraxane package insert states: "[R]econstitute each vial [of Abraxane] by injecting 20 mL of 0.9% Sodium Chloride Injection, USP." Except as expressly admitted, the Request is denied.

REQUEST FOR ADMISSION NO. 14:

Admit that 0.9% Sodium Chloride Injection, USP is a pharmaceutically acceptable carrier for intravenous administration of Abraxane®.

RESPONSE TO REQUEST FOR ADMISSION NO. 14:

Abraxis objects that the term "pharmaceutically acceptable carrier" is vague and ambiguous as used in this Request. *See, e.g., Fulhorst v. United Tech. Automotive, Inc.*, No. 96-577-JJF, 1997 U.S. Dist. LEXIS 22290, at *3-4 (D. Del. Nov. 17, 1997) (citation omitted) ("A party is not required to respond to a request that contains vague or ambiguous statements."). Abraxis further objects to the Request as an improper attempt to seek an admission relating to claim construction. *Id.* at *4-8 (improper to seek admission on issue that involves claim construction).

Subject to and without waiving its objections, Abraxis admits that Abraxane is administered intravenously and that a vial of Abraxane may be reconstituted with 0.9% Sodium Chloride Injection, USP. Except as expressly admitted, the Request is denied.

REQUEST FOR ADMISSION NO. 15:

Admit that reconstituted Abraxane® remains stable for up to 8 hours if refrigerated and protected from exposure to light.

RESPONSE TO REQUEST FOR ADMISSION NO. 15:

Abraxis objects that the term "stable" is vague and ambiguous as used in this Request. *See, e.g., Fulhorst v. United Tech. Automotive, Inc.*, No. 96-577-JJF, 1997 U.S. Dist. LEXIS 22290, at *3-4 (D. Del. Nov. 17, 1997) (citation omitted) ("A party is not required to respond to a request that contains vague or ambiguous statements."). Abraxis further objects that this Request calls for an admission of a statement that is neither reasonably related to a claim or defense in this litigation, nor reasonably calculated to lead to the discovery of admissible evidence. Abraxis also objects because it appears that this Request was interposed for an improper purpose.

Due to the ambiguity and vagueness of the term "stable" as used in this Request, Abraxis denies having knowledge or information sufficient to admit or deny this Request and therefore denies it.

REQUEST FOR ADMISSION NO. 16:

Admit that the active agent in Abraxane® is paclitaxel.

RESPONSE TO REQUEST FOR ADMISSION NO. 16:

Abraxis admits that the active agent in Abraxane is non-crystalline, amorphous paclitaxel. Except as expressly admitted, the Request is denied.

REQUEST FOR ADMISSION NO. 17:

Admit that Abraxane is manufactured using paclitaxel, which is a white to off-white crystalline powder.

RESPONSE TO REQUEST FOR ADMISSION NO. 17:

Abraxis objects to this Request as being vague and ambiguous in that it does not distinguish between the state of paclitaxel as a raw material used in the manufacture of Abraxane and the state of paclitaxel as it exists in Abraxane. *See, e.g., Fulhorst v. United Tech. Automotive, Inc.*, No. 96-577-JJF, 1997 U.S. Dist. LEXIS 22290, at *3-4 (D. Del. Nov. 17, 1997) (citation omitted) ("A party is not required to respond to a request that contains vague or ambiguous statements.").

Subject to and without waiving its objection, Abraxis admits that Abraxane is manufactured using paclitaxel and that the paclitaxel used as a raw material in the manufacture of Abraxane is a white to off-white crystalline powder. Abraxis avers that the paclitaxel in Abraxane is non-crystalline and amorphous and denies that the paclitaxel in Abraxane is crystalline. Except as expressly admitted, the Request is denied.

REQUEST FOR ADMISSION NO. 18:

Admit that the term "proteins," as created in cells, refers to polypeptides or polymers of amino acids of any length.

RESPONSE TO REQUEST FOR ADMISSION NO. 18:

Abraxis objects to this Request as calling for an admission of a statement that is neither reasonably related to a claim or defense in this litigation, nor reasonably calculated to lead to the discovery of admissible evidence. Abraxis also objects because it appears that this Request was interposed for an improper purpose.

Subject to and without waiving Abraxis's objection, the Request is denied.

REQUEST FOR ADMISSION NO. 19:

Admit that Abraxane is an [sic] nanoparticulate composition consisting of paclitaxel and a carrier protein, such as human serum albumin.

RESPONSE TO REQUEST FOR ADMISSION NO. 19:

Abraxis objects that the terms "carrier protein" and "nanoparticulate" are vague and ambiguous as used in this Request. *See, e.g., Fulhorst v. United Tech. Automotive, Inc.*, No. 96-577-JJF, 1997 U.S. Dist. LEXIS 22290, at *3-4 (D. Del. Nov. 17, 1997) (citation omitted) ("A party is not required to respond to a request that contains vague or ambiguous statements."). Abraxis also objects that this Request calls for an admission of a statement that is neither reasonably related to a claim or defense in this litigation, nor reasonably calculated to lead to the discovery of admissible evidence. Abraxis also objects because it appears that this Request was interposed for an improper purpose.

Subject to and without waiving its objections, Abraxis admits that Abraxane is a human albumin-bound form of non-crystalline, amorphous paclitaxel with a mean particle size of approximately 130 nanometers. Except as expressly admitted, the Request is denied.

REQUEST FOR ADMISSION NO. 20:

Admit that Human serum albumin as used in Abraxane is Human albumin USP.

RESPONSE TO REQUEST FOR ADMISSION NO. 20:

Abraxis admits that Albumin (Human), USP is one of the raw materials used in the manufacture of Abraxane. Except as expressly admitted, the Request is denied.

REQUEST FOR ADMISSION NO. 21:

Admit that paclitaxel is stabilized in an aqueous suspension if it remains suspended in an aqueous medium without visible precipitation or sedimentation for an extended period of time.

RESPONSE TO REQUEST FOR ADMISSION NO. 21:

Abraxis objects that the terms "stabilized" and "extended period of time" are vague and ambiguous as used in this Request. *See, e.g., Fulhorst v. United Tech. Automotive, Inc.*, No. 96-577-JJF, 1997 U.S. Dist. LEXIS 22290, at *3-4 (D. Del. Nov. 17, 1997) (citation omitted) ("A party is not required to respond to a request that contains vague or ambiguous statements."). Abraxis also objects that this Request calls for an admission of a statement that is neither reasonably related to a claim or defense in this litigation, nor reasonably calculated to lead to the discovery of admissible evidence. Abraxis also objects because it appears that this Request was interposed for an improper purpose.

Due to the ambiguity and vagueness of the terms "stabilized" and "extended period of time" as used in this Request, Abraxis denies having knowledge or information sufficient to admit or deny this Request and therefore denies it.

REQUEST FOR ADMISSION NO. 22:

Admit that Abraxane is a formulation of paclitaxel stabilized with human serum albumin USP.

RESPONSE TO REQUEST FOR ADMISSION NO. 22:

Abraxis objects that the term "stabilized" is vague and ambiguous as used in this Request. *See, e.g., Fulhorst v. United Tech. Automotive, Inc.*, No. 96-577-JJF, 1997 U.S. Dist. LEXIS 22290, at *3-4 (D. Del. Nov. 17, 1997) (citation omitted) ("A party is not required to respond to a request that contains vague or ambiguous statements."). Abraxis further objects that this Request calls for an admission of a statement that is neither reasonably related to a claim or defense in this litigation, nor reasonably calculated to lead to the discovery of admissible evidence. Abraxis also objects because it appears that this Request was interposed for an improper purpose.

Subject to and without waiving its objections, Abraxis admits that Abraxane contains non-crystalline, amorphous paclitaxel and human albumin. Due to the ambiguity and vagueness of the term "stabilized" as used in this Request, Abraxis denies having knowledge or information sufficient to otherwise admit or deny this Request and therefore, except as expressly admitted, denies it.

REQUEST FOR ADMISSION NO. 23:

Admit that Abraxane forms a stable colloidal suspension of paclitaxel when dispersed in an aqueous medium such as 0.9% sodium chloride.

RESPONSE TO REQUEST FOR ADMISSION NO. 23:

Abraxis objects that the terms "stable," "colloidal suspension," and "aqueous medium such as ..." are vague and ambiguous as used in this Request. *See, e.g., Fulhorst v. United Tech. Automotive, Inc.*, No. 96-577-JJF, 1997 U.S. Dist. LEXIS 22290, at *3-4 (D. Del. Nov. 17, 1997) (citation omitted) ("A party is not required to respond to a request that contains vague or ambiguous statements."). Abraxis further objects that this Request calls for an admission of a statement that is neither reasonably related to a claim or defense in this litigation, nor reasonably calculated to lead to the discovery of admissible evidence. Abraxis also objects because it appears that this Request was interposed for an improper purpose.

Due to the ambiguity and vagueness of the terms "stable," "colloidal suspension," and "aqueous medium" as used in this Request, Abraxis denies having knowledge or information sufficient to admit or deny this Request and therefore denies it.

REQUEST FOR ADMISSION NO. 24:

Admit that bovine serum albumin could be used as a carrier protein for paclitaxel in an [sic] nanoparticle composition.

RESPONSE TO REQUEST FOR ADMISSION NO. 24:

Abraxis objects that the terms "carrier protein," "nanoparticle," and "could be used" are vague and ambiguous as used in this Request. *See, e.g., Fulhorst v. United Tech. Automotive, Inc.*, No. 96-577-JJF, 1997 U.S. Dist. LEXIS 22290, at *3-4 (D. Del. Nov. 17, 1997) (citation

omitted) ("A party is not required to respond to a request that contains vague or ambiguous statements."). Abraxis also objects that, without further definition or context, the entire Request is vague and ambiguous, as it is unclear what use is intended for such a composition. Abraxis also objects that this Request calls for an admission of a statement that is neither reasonably related to a claim or defense in this litigation, nor reasonably calculated to lead to the discovery of admissible evidence. Abraxis also objects because it appears that this Request was interposed for an improper purpose.

Subject to and without waiving Abraxis's objections, the Request is denied.

REQUEST FOR ADMISSION NO. 25:

Admit that paclitaxel is a medicament useful for treating cancer.

RESPONSE TO REQUEST FOR ADMISSION NO. 25:

Abraxis admits that certain paclitaxel formulations are useful for the treatment of certain cancers in certain patients. Except as expressly admitted, the Request is denied.

REQUEST FOR ADMISSION NO. 26:

Admit that breast cancer is susceptible to treatment with paclitaxel.

RESPONSE TO REQUEST FOR ADMISSION NO. 26:

Abraxis objects that the term "susceptible to treatment with paclitaxel" is vague and ambiguous as used in this Request. *See, e.g., Fulhorst v. United Tech. Automotive, Inc.*, No. 96-577-JJF, 1997 U.S. Dist. LEXIS 22290, at *3-4 (D. Del. Nov. 17, 1997) (citation omitted) ("A party is not required to respond to a request that contains vague or ambiguous statements.").

Subject to and without waiving its objection, Abraxis admits that certain paclitaxel formulations are useful for the treatment of certain breast cancers in certain patients. Except as expressly admitted, the Request is denied.

Dated: January 25, 2007

Josy W. Ingersoll (#1088)
Elena C. Norman (#4780)
Karen E. Keller (#4489)
YOUNG CONAWAY STARGATT & TAYLOR, LLP
The Brandywine Building
1000 West Street, 17th Floor
Wilmington, DE 19801
(302) 571-6672 Telephone
(302) 576-3301 Facsimile
jingersoll@ycst.com
enorman@ycst.com
kkeller@ycst.com

Michael A. Jacobs
MORRISON & FOERSTER, LLP
425 Market Street
San Francisco, CA 94105-2482
(415) 268-7000 Telephone
(415) 268-7522 Facsimile
MJacobs@mofo.com

Emily A. Evans
MORRISON & FOERSTER, LLP
755 Page Mill Road
Palo Alto, CA 94304-1018
(650) 813-5600 Telephone
(650) 494-0792 Facsimile
EEvans@mofo.com

Attorneys for Defendant
ABRAXIS BIOSCIENCE, INC.

CERTIFICATE OF SERVICE

I, Elena C. Norman, Esquire, hereby certify that on January 25, 2007, I caused copies of the foregoing document to be served upon the following counsel in the manner indicated:

BY E-MAIL AND HAND DELIVERY

Steven J. Balick, Esquire
ASHBY & GEDDES
500 Delaware Avenue
Wilmington, DE 19801

BY E-MAIL

Stephen Scheve, Esquire
BAKER BOTTS L.L.P.
One Shell Plaza
910 Louisiana Street
Houston, TX 77002-4995
steve.scheve@bakerbotts.com

Paul F. Fehlner
BAKER BOTTS L.L.P.
30 Rockefeller Plaza
New York, NY 10112-4498
paul.fehlner@bakerbotts.com

William J. Sipio, Esquire
1375 Brentwood Road
Yardley, PA 19067
sipz25@aol.cm

YOUNG CONAWAY STARGATT & TAYLOR, LLP

/s/ Elena C. Norman
Elena C. Norman (No. 4470)
enorman@ycst.com
The Brandywine Building
1000 West Street, 17th Floor
Wilmington, Delaware 19899
(302) 571-6600
Attorneys for Defendant
ABRAXIS BIOSCIENCE, INC.

EXHIBITS D – F

REDACTED IN THEIR ENTIRETY

EXHIBIT G

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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

PLAINTIFF ELAN PHARMA INTERNATIONAL LIMITED'S SECOND AMENDED RESPONSES AND OBJECTIONS TO DEFENDANT ABRAXIS'S FIRST SET OF INTERROGATORIES (No. 1)

Pursuant to Rule 33 of the Federal Rules of Civil Procedure, Plaintiff Elan Pharma International Limited ("Elan"), by and through its undersigned counsel, hereby submits its Second Amended Responses and Objections to Defendant Abraxis Bioscience, Inc.'s ("Abraxis"), First Set of Interrogatories to Elan, served on November 3, 2006.

OBJECTIONS TO INTERROGATORY NO. 1

1. Elan objects to Abraxis's Interrogatory No. 1 to the extent that it seeks information that is protected by the attorney-client privilege and/or attorney work-product doctrine, or is otherwise immune from discovery. Elan does not intend to waive any applicable protections or privileges by supplying information in response to Abraxis's Interrogatory. On the contrary, Elan specifically intends to preserve all applicable protections or privileges.

2. Elan objects to Abraxis's Interrogatory No. 1 to the extent that it purports to impose obligations on Elan beyond those or different from the obligations imposed by the Federal Rules of Civil Procedure, the Federal Rules of Evidence, and the Local Civil Rules of this Court.

3. Elan objects to Abraxis's Interrogatory No. 1 as premature insofar Elan has not yet received sufficiently complete discovery responses from Abraxis and, reserves the right to supplement its response at a later date, as appropriate.

4. Elan objects to Abraxis's Interrogatory No. 1 as seeking impermissible legal conclusions to the extent that they call for information relating to the interpretation of the claims of the asserted patents, U. S. Patent Nos. 5,399,363 and 5,834,025, where the Court has not yet held a *Markman* hearing. *See Tulip Computers Int'l B.V. v. Dell Computer Corp.*, 210 F.R.D. 100, 108 (D. Del. 2002) ("Requests directed toward applying the claims of the patent or requiring application of the claims prior to any *Markman* ruling are not the application of law to facts relevant to the case, but in reality are requests for legal conclusions and therefore, improper.").

5. Elan objects to Abraxis's Interrogatory No. 1 to the extent that it prematurely requests expert testimony.

6. Elan objects to Abraxis's Interrogatory No. 1 to the extent that it is unduly burdensome because it seeks information that is in the public domain, and, as such, is equally accessible to Abraxis.

7. Elan is answering Abraxis's Interrogatory No. 1 without waiving or intending to waive, but on the contrary, preserving and intending to preserve: (a) the right to object, on the grounds of competency, privilege, relevance or materiality, or any other proper grounds, to the use of such information for any purpose, in whole or in part, in any subsequent proceedings, in this action or in any other action; (b) the right to object on all grounds, at any time to interrogatories, requests or other discovery procedures involving or relating to the subject of the Interrogatory to which Elan has responded herein; and (c) the right at any time to revise, correct, add to or clarify Elan's answer herein.

8. Elan reserves the right to supplement its answers and to raise any additional objections deemed necessary and appropriate in light of the results of any further review.

INTERROGATORY NO. 1:

Please explain in detail why Elan contends that Abraxis infringes U.S. Patent Nos. 5,399,363 and 5,834,025. Please provide an element-by-element claim chart including your contentions and references to the documents and other evidence on which Elan relies.

ANSWER TO INTERROGATORY NO. 1:

Subject to the foregoing objections, Elan contends that Abraxis infringes at least the claims of U.S. Patent Nos. 5,399,363 and 5,834,025 that are identified in the charts attached as Exhibit A (the "Asserted Claims"). Attached hereto as Exhibit A are element by element claim charts including Elan's contentions to date.

Elan contends that Abraxis infringes one or more of the Asserted Claims of U.S. Patent No. 5,399,363 pursuant to 35 U.S.C. §§ 271(a),(b) and/or (c). Elan also contends that Abraxis indirectly infringes one or more of the Asserted Claims of U.S. Patent No. 5,834,025 pursuant to 35 U.S.C. § 271(b).

In the unlikely event it is determined that Abraxis does not literally infringe the Asserted Claims of either U.S. Patent No. 5,399,363 or U.S. Patent No. 5,184,025, Elan contends that Abraxis infringes the Asserted Claims under the doctrine of equivalents.

ASHBY & GEDDES

Steven J. Balick (I.D. #2114)
John G. Day (I.D. #2403)
Tiffany Geyer Lydon (I.D. #3950)
500 Delaware Avenue, 8th Floor
P.O. Box 1150
Wilmington, DE 19899
(302) 654-1888
sbalick@ashby-geddes.com
jday@ashby-geddes.com
tlydon@ashby-geddes.com

Attorneys for Plaintiff
Elan Pharma International Limited

Of Counsel:

Stephen Scheve
BAKER BOTTS LLP
One Shell Plaza
910 Lousiana Street
Houston, TX 77042-4995
Telephone: (713) 229-1659

Paul F. Fehlner
BAKER BOTTS LLP
30 Rockefeller Plaza
New York, NY 10112-4498
Telephone: (212) 408-2527

William J. Sipio
1375 Brentwood Road
Yardley, PA 19067
Telephone: (215) 801-3625
Facsimile: (866) 317-2059

Dated: March 2, 2007
178453.1

Elan Pharma International Limited vs. Abraxis BioScience, Inc.
Preliminary Infringement Contentions For U.S. Patent Nos. 5,399,363 & 5,834,025

U.S. Patent No. 5,399,363 Claim 1	Abraxane®
Particles consisting essentially of	Abraxane® is a formulation of particles. *See, e.g.*, Abraxane NDA 21-660[1] Chemistry Review at 7, *available at* http://www.fda.gov/cder/foi/nda/2005/21660_ABRAXANE_chemr.PDF (last accessed February 28, 2007). The particles are made up of paclitaxel and human serum albumin ("HSA"). *See, e.g., id.*
99.9 -10% by weight of a crystalline medicament useful in treating cancer susceptible for treatment with said medicament,	Each single-use vial of Abraxane® contains approximately 100 mg of paclitaxel in 1000 mg of material. *See, e.g.*, Abraxane Prescribing Information[2] ¶ 1, *available at* http://abraxane.com/resources/Abraxane_Healthcare_Professional_Prescribing_Information.pdf. (last accessed February 28, 2007). Paclitaxel is a white to off-white crystalline powder. *See, e.g., id.* ¶ 4. Paclitaxel is present for the treatment of breast cancer. *See, e.g., id.*
said medicament having a solubility in water of less than 10 mg/ml,	Paclitaxel is insoluble in water. *See, e.g., id.* ¶ 3.
and having a non-cross-linked surface modifier adsorbed on the surface thereof	HSA is adsorbed on the paclitaxel. *See, e.g.*, Abraxane NDA 21-660 Chemistry Review at 7. The HSA in Abraxane® is HSA, USP. *See, e.g.*, Abraxane NDA 21-660 Clinical Review at 10; United States Patent App. No. 20060263434 ¶ 174 to Desai et al. The HSA is non-cross-linked. *See, e.g.*, "Abraxane: Nanoparticle platform delivers improved antitumor activity" presentation given by Michael Hawkins, M.D., Chief Medical Officer American Bioscience, Inc. on January 24, 2006 at the National Institutes of Health in Bethezda, Maryland. (the HSA "binding is non-covalent . . . similar to the kind of protein binding that occurs for drugs following their administration when they get into the plasma.").

[1] "Abraxane NDA 21-660" refers to the New Drug Application No. 21-660 submitted to the U.S. Food and Drug Administration for Abraxane.
[2] "Abraxane Prescribing Information" refers to the Abraxane Prescribing Information approved by the U.S. Food and Drug Administration, dated January 7, 2005.

Elan Pharma International Limited vs. Abraxis BioScience, Inc.
Preliminary Infringement Contentions For U.S. Patent Nos. 5,399,363 & 5,834,025

U.S. Patent No. 5,399,363 Claim 1	Abraxane®
in an amount of 0.1-90% by weight	Abraxane® has approximately 900 mg HSA in 1000 mg of material. *See, e.g.,* Abraxane Prescribing Information ¶ 1.
and sufficient to maintain an average effective particle size of less than 1000 nm,	The particles in Abraxane® have a mean particle size of approximately 130 nm. *See, e.g., id.* ¶ 1.
wherein said medicament is selected from the group consisting of alkylating agents selected from the group consisting of alkylating agents having a bis-(2-chloroethyl)-amine group, alkylating agents having a substituted aziridine group, alkyl sulfonates, and N-alkyl-N-nitrosoureas; antimetabolites; natural products selected from the group consisting of vinca alkaloids, epipophylotoxins, adriamycine, daunomycine, doctinomycine, daunorubicin, doxorubicin, mithramycin, bleomycin, mitomycin, enzymes, biological response modifiers, camptothecin, taxol and retinoids; hormones and antagonists: radiosensitizers; platinum coordination complexes; anthracenediones; and adrenocortical suppressants.	Abraxane® contains the medicament paclitaxel, otherwise known as taxol. *See, e.g., id.* ¶ 1.

Elan Pharma International Limited vs. Abraxis BioScience, Inc.
Preliminary Infringement Contentions For U.S. Patent Nos. 5,399,363 & 5,834,025

U.S. Patent No. 5,399,363 Claim 2	Abraxane®
The particles of claim 1, having an average effective particle size of less than 400 nm.	The particles in Abraxane® have a mean particle size of approximately 130 nm. *See, e.g.*, Abraxane Prescribing Information ¶ 1.

Elan Pharma International Limited vs. Abraxis BioScience, Inc.
Preliminary Infringement Contentions For U.S. Patent Nos. 5,399,363 & 5,834,025

U.S. Patent No. 5,399,363 Claim 3	Abraxane®
The particles of claim 1, having an average particle size of less than 300 nm.	The particles in Abraxane® have a mean particle size of approximately 130 nm. *See, e.g.,* Abraxane Prescribing Information ¶ 1.

Elan Pharma International Limited vs. Abraxis BioScience, Inc.
Preliminary Infringement Contentions For U.S. Patent Nos. 5,399,363 & 5,834,025

U.S. Patent No. 5,399,363 Claim 5	Abraxane®
The particles of claim 1, wherein said anticancer agent is selected from the group consisting of piposulfan, piposulfam, camptothecin, etoposide, taxol, 1,2,4-benzotriazin-3-amine 1,4-dioxide, 1,2,4-benzotriazin-7-amine 1,4-dioxide and retinoic acid.	Each single-use vial of Abraxane® contains the anticancer agent paclitaxel, otherwise known as taxol. *See, e.g.,* Abraxane Prescribing Information ¶¶ 1-3.

Elan Pharma International Limited vs. Abraxis BioScience, Inc.
Preliminary Infringement Contentions For U.S. Patent Nos. 5,399,363 & 5,834,025

U.S. Patent No. 5,399,363 Claim 8	Abraxane®
An anticancer composition comprising the particles of claim 1.	Abraxane® is formulation of particles. *See generally* Abraxane NDA 21-660; Abraxane Prescribing Information.

Elan Pharma International Limited vs. Abraxis BioScience, Inc.
Preliminary Infringement Contentions For U.S. Patent Nos. 5,399,363 & 5,834,025

U.S. Patent No. 5,399,363 Claim 9	Abraxane®
A method of treating a mammal comprising administering to the mammal an effective amount of the anticancer composition of claim 8.	An effective amount of reconstituted Abraxane® is intravenously administered to humans for the treatment of cancer. *See generally* Abraxane NDA 21-660; Abraxane Prescribing Information. Abraxis instructs others to intravenously administer reconstituted Abraxane®. *See, e.g.*, Abraxane Prescribing Information at 3.

Elan Pharma International Limited vs. Abraxis BioScience, Inc.
Preliminary Infringement Contentions For U.S. Patent Nos. 5,399,363 & 5,834,025

U.S. Patent No. 5,399,363 Claim 10	Abraxane®
In a method of treating a mammal comprising administering to the mammal an effective amount of an anticancer agent,	An effective amount of reconstituted Abraxane® is intravenously administered to humans for the treatment of cancer. *See generally* Abraxane NDA 21-660; Abraxane Prescribing Information. Abraxis instructs others to intravenously administer reconstituted Abraxane®. *See, e.g.*, Abraxane Prescribing Information at 3.
the improvement wherein the efficacy of said anticancer agent is increased by administering said anticancer agent in the form of the particles of claim 1.	The efficacy of paclitaxel is increased by administering paclitaxel in the form of Abraxane®. *See, e.g.*, Abraxane NDA 21-660 Clinical Review at 16-17, 40-48, 59-60, *available at* http://www.fda.gov/cder/foi/nda/2005/21660_ABRAXANE_medr.PDF (last accessed February 28, 2007); Abraxane Prescribing Information, Table 1.

Elan Pharma International Limited vs. Abraxis BioScience, Inc.
Preliminary Infringement Contentions For U.S. Patent Nos. 5,399,363 & 5,834,025

U.S. Patent No. 5,399,363 Claim 11	Abraxane®
In a method of treating a mammal comprising administering to the mammal an effective amount of an anticancer agent,	An effective amount of reconstituted Abraxane® is intravenously administered to humans for the treatment of cancer. *See generally* Abraxane NDA 21-660; Abraxane Prescribing Information. Abraxis instructs others to intravenously administer reconstituted Abraxane®. *See, e.g.*, Abraxane Prescribing Information at 3.
the improvement wherein the toxicity of said anticancer agent is reduced by administering said anticancer agent in the form of the particles of claim 1.	The toxicity of paclitaxel is reduced by administering paclitaxel in the form of Abraxane®. *See, e.g.*, Abraxane NDA 21-660 Clinical Review at 60-61, 78.

Elan Pharma International Limited vs. Abraxis BioScience, Inc.
Preliminary Infringement Contentions For U.S. Patent Nos. 5,399,363 & 5,834,025

U.S. Patent No. 5,399,363 Claim 12	Abraxane®
The particles of claim 1, wherein the surface modifier is a surfactant.	HSA is known in the art as a surfactant. *See, e.g.,* Bazile et al., "Body distribution of fully biodegradable [14C]-poly(lactic acid) nanoparticles coated with albumin after parenteral administration," *Biomaterials* 13/15:1093-1102 (1992) [produced as ELAP0006925-35] (describing HSA as surfactant). Bazile et al. is cited on the face of U.S. Patent Nos. 6,753,006, 6,506,405 and 6,537,579, assigned to Abraxis Bioscience, Inc.

Elan Pharma International Limited vs. Abraxis BioScience, Inc.
Preliminary Infringement Contentions For U.S. Patent Nos. 5,399,363 & 5,834,025

U.S. Patent No. 5,399,363 Claim 15	Abraxane®
The particles of claim 1 wherein said surface modifier is selected from the group consisting of gelatin, casein, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinyipyrrolidone, poloxomers, tyloxapol, poloxamines, dextran, a dioctyl ester of sodium sulfosuccinic acid, sodium lauryl sulfate, an alkyl aryl polyether sulfonate, a mixture of sucrose stearate and sucrose distearate, hexyldecyl trimethyl ammonium chloride, bovine serum albumin and $C_{18}H_{37}CH_2(CON(CH_3)CH_2(CHOH)_4CH_2OH)_2$.	Human serum albumin is an equivalent of bovine serum albumin. The amino acid sequences of human serum albumin and bovine serum albumin have at least seventy-six percent identity and Abraxis even publicly admits that bovine serum albumin is contemplated as a replacement for human serum albumin. *See*, U.S. Patent Publication No. 2006/0263434.

Elan Pharma International Limited vs. Abraxis BioScience, Inc.
Preliminary Infringement Contentions For U.S. Patent Nos. 5,399,363 & 5,834,025

U.S. Patent No. 5,834,025 Claim 1	Abraxane®
A method of administering a nanoparticle composition to a mammal	Abraxis instructs others to reconstitute and intravenously administer Abraxane®, a formulation of nanoparticles, to humans. *See generally* Abraxane Prescribing Information.
without eliciting adverse hemodynamic effects comprising	Abraxis has noted that during clinical trials, cardiovascular events such as hypotension occurred in 5% of patients and bradycardia occurred in <1% of patients, and severe cardiovascular events occurred in only 3% of patients. *See, e.g., id.* at 2, Table 2.
intravenously administering to said mammal	Abraxis instructs others to intravenously administer Abraxane®. *See, e.g., id.* at 1.
an effective amount of a nanoparticulate drug composition	An effective amount of Abraxane® is administered to humans for the treatment of cancer. *See generally id.*
at an infusion rate not exceeding 10 mg/min,	Abraxis instructs others to administer a defined amount of Abraxane® over a specified period of time. For example, Abraxis instructs a reduction in dosage to 180 mg/m^2 over 30 minutes for recurrences of severe neutropenia or severe sensory neuropathy. *See, e.g., id.* at 3.
wherein said drug comprises (a) particles consisting essentially of	Abraxane® is a formulation of particles. *See, e.g.*, Abraxane NDA 21-660 Chemistry Review at 7. The particles are made of paclitaxel and human serum albumin ("HSA"). *See, e.g., id.*
from about 0.1 to about 99.9% by weight of a crystalline organic drug substance	Each single-use vial of Abraxane® contains approximately 100 mg of paclitaxel in 1000 mg of material. *See, e.g.,* Abraxane Prescribing Information[3] ¶ 1. Paclitaxel is a white to off-white crystalline powder. *See, e.g., id.* ¶ 4. Paclitaxel is present for the treatment of breast cancer. *See, e.g., id.*
having a solubility in water of less than 10 mg/ml	Paclitaxel is insoluble in water. *See, e.g., id.* ¶ 3.
(b) a surface modifier adsorbed on the surface of the drug substance	HSA is adsorbed on the paclitaxel. *See, e.g.*, Abraxane NDA 21-660 Chemistry Review at 7.

[3] "Abraxane Prescribing Information" refers to the Abraxane Prescribing Information approved by the U.S. Food and Drug Administration, dated January 7, 2005.

in an amount of from about 0.1 to about 99.9% by weight and	Abraxane® has approximately 900 mg HSA in 1000 mg of material. *See, e.g.,* Abraxane Prescribing Information ¶ 1.
sufficient to maintain an effective average particle size of from about 50 to about 1000 nm; and	The particles in Abraxane® have a mean particle size of approximately 130 nm. *See, e.g.,* Abraxane Prescribing Information ¶ 1.
(c) a pharmaceutically acceptable carrier therefor.	Abraxis instructs others to reconstitute the Abraxane® lyophilized powder with 20 mL of 0.9% Sodium Chloride Injection, USP, a pharmaceutically acceptable carrier. *See, e.g., id.* at ¶ 1 and p. 3.

Elan Pharma International Limited vs. Abraxis BioScience, Inc.
Preliminary Infringement Contentions For U.S. Patent Nos. 5,399,363 & 5,834,025

U.S. Patent No. 5,834,025 Claim 2	Abraxane®
The method of claim 1, wherein the effective average particle size of said drug is from about 50 to about 400 nm.	The particles in Abraxane® have a mean particle size of approximately 130 nm. *See, e.g.*, Abraxane Prescribing Information ¶ 1.

Elan Pharma International Limited vs. Abraxis BioScience, Inc.
Preliminary Infringement Contentions For U.S. Patent Nos. 5,399,363 & 5,834,025

U.S. Patent No. 5,834,025 Claim 3	Abraxane®
The method of claim 1, wherein said drug is an organic therapeutic substance.	Paclitaxel is an organic therapeutic substance. *See generally* Abraxane NDA 21-660; Abraxane Prescribing Information.

Elan Pharma International Limited vs. Abraxis BioScience, Inc.
Preliminary Infringement Contentions For U.S. Patent Nos. 5,399,363 & 5,834,025

U.S. Patent No. 5,834,025 Claim 13	Abraxane®
A method of administering a nanoparticulate composition to a mammal	Abraxis instructs others to reconstitute and intravenously administer Abraxane®, a formulation of nanoparticles, to humans. *See generally* Abraxane Prescribing Information.
without eliciting adverse hemodynamic effects comprising	Abraxis has noted that during clinical trials, cardiovascular events such as hypotension occurred in 5% of patients and bradycardia occurred in <1% of patients, and severe cardiovascular events occurred in only 3% of patients. *See, e.g., id.* at 2, Table 2.
intravenously administering to said mammal	Abraxis instructs others to intravenously administer Abraxane®. *See, e.g., id.* at 1.
an effective amount of a nanoparticulate drug composition	An effective amount of Abraxane® is administered to humans for the treatment of cancer. *See generally id.*
at an infusion rate not exceeding 10 mg/min,	Abraxis instructs others to administer a defined amount of Abraxane® over a specified period of time. For example, Abraxis instructs a reduction in dosage to 180 mg/m^2 over 30 minutes for recurrences of severe neutropenia or severe sensory neuropathy. *See, e.g., id.* at 3.
wherein said drug composition comprises: (a) particles	Abraxane® is a formulation of particles. *See, e.g.*, Abraxane NDA 21-660 Chemistry Review at 7. The particles are made of paclitaxel and HSA. *See, e.g., id.*
having an effective average particle size of from about 50 to about 1000 nm and	The particles in Abraxane® have a mean particle size of approximately 130 nm. *See, e.g.*, Abraxane Prescribing Information ¶ 1.
consisting essentially of from about 0.1 to about 99.9% by weight of an organic drug substance	Each single-use vial of Abraxane® contains approximately 100 mg of paclitaxel in 1000 mg of material. *See, e.g., id.* Paclitaxel is an organic drug substance. *See, e.g., id.* ¶ 4.
entrapped in from about 99.9 to about 0.1% by weight of liposome or a colloidal polymeric material; and	The paclitaxel in Abraxane® is entrapped in HSA, a colloidal polymeric material. *See, e.g.*, United States Patent App. No. 20060263434 ¶¶ 165, 174 to Desai et al. Abraxane® has approximately 900 mg HSA in 1000 mg of material. *See, e.g., id.*
(b) a pharmaceutically acceptable carrier therfor.	Abraxis instructs others to reconstitute the Abraxane® lyophilized powder with 20 mL of 0.9% Sodium Chloride Injection, USP, a pharmaceutically acceptable carrier. *See, e.g., id.* at ¶ 1 and p. 3.

Elan Pharma International Limited vs. Abraxis BioScience, Inc.
Preliminary Infringement Contentions For U.S. Patent Nos. 5,399,363 & 5,834,025

U.S. Patent No. 5,834,025 Claim 14	Abraxane®
The method of claim 13 wherein the effective average particle size of said drug is from about 50 to about 400 nm.	The particles in Abraxane® have a mean particle size of approximately 130 nm. *See, e.g.*, Abraxane Prescribing Information ¶ 1.

Elan Pharma International Limited vs. Abraxis BioScience, Inc.
Preliminary Infringement Contentions For U.S. Patent Nos. 5,399,363 & 5,834,025

U.S. Patent No. 5,834,025 Claim 15	Abraxane®
The method of claim 13, wherein said drug is an organic therapeutic substance.	Paclitaxel is an organic therapeutic substance. *See generally* Abraxane NDA 21-660; Abraxane Prescribing Information.

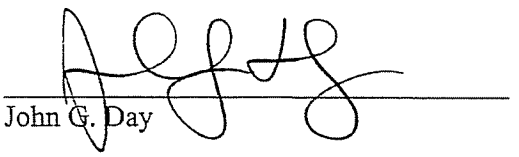
CERTIFICATE OF SERVICE

I hereby certify that on the 2nd day of March, 2007, the attached **PLAINTIFF ELAN PHARMA INTERNATIONAL LIMITED'S SECOND AMENDED RESPONSES AND OBJECTIONS TO DEFENDANT ABRAXIS'S FIRST SET OF INTERROGATORIES (No. 1)** was served upon the below-named counsel of record at the addresses and in the manner indicated:

Josy W. Ingersoll, Esquire — HAND DELIVERY
Young, Conaway, Stargatt & Taylor
The Brandywine Building
1000 West Street, 17th Floor
Wilmington, DE 19801

Michael A. Jacobs, Esquire — VIA ELECTRONIC MAIL
Morrison & Foerster, LLP
425 Market Street
San Francisco, CA 94105-2482

Emily A. Evans, Esquire — VIA ELECTRONIC MAIL
Morrison & Foerster, LLP
755 Page Mill Road
Palo Alto, CA 94304-1018



John G. Day

173077.1

EXHIBIT H

CERTIFICATE OF SERVICE

I, Elena C. Norman, Esquire, hereby certify that on February 26, 2007, I caused copies of the foregoing document to be served upon the following counsel in the manner indicated:

BY E-MAIL AND HAND DELIVERY

Steven J. Balick, Esquire
ASHBY & GEDDES
500 Delaware Avenue
Wilmington, DE 19801

BY E-MAIL

Stephen Scheve, Esquire
BAKER BOTTS L.L.P.
One Shell Plaza
910 Louisiana Street
Houston, TX 77002-4995
steve.scheve@bakerbotts.com

Paul F. Fehlner
BAKER BOTTS L.L.P.
30 Rockefeller Plaza
New York, NY 10112-4498
paul.fehlner@bakerbotts.com

William J. Sipio, Esquire
1375 Brentwood Road
Yardley, PA 19067
sipz25@aol.cm

YOUNG CONAWAY STARGATT & TAYLOR, LLP

/s/ Elena C. Norman
Elena C. Norman (No. 4780)
enorman@ycst.com
The Brandywine Building
1000 West Street, 17th Floor
Wilmington, Delaware 19899
(302) 571-6600
Attorneys for Defendant
ABRAXIS BIOSCIENCE, INC.