CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-660

ADMINISTRATIVE DOCUMENTS

American BioScience, Inc.

Patent Certification

Paragraph II Certification

In the opinion and to the best knowledge of American BioScience, Inc., there are no unexpired patents that claim the listed drug [Taxol® (paclitaxel) Injection] referred to in this application or that claim a use of the listed drug.

MG Clark 11/6/03

Mitchall G. Clark
Vice President, Regulatory Affairs

Date

2730 Wilshire Blvd., Suite 110 Santa Monica, California 90403 Tel: (310) 883-1300 Fax: (310) 998-8553

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER: 21-660

NAME OF APPLICANT / NDA HOLDER: American BioScience, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Abraxane*TM* (*nab* Paclitaxel) for Injectable Suspension

ACTIVE INGREDIENT(S)	STRENGTH(S)
Paclitaxel	100 mg/vial

DOSAGE FORM
Sterile powder for injectable suspension

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,537,579	3/25/2003	2/22/2013

d. Name of Patent Owner	Address *(of Patent Owner)*	
American BioScience, Inc.	2730 Wilshire Boulevard, Suite 110	
	City/State: Santa Monica, CA	
	ZIP Code: 90403	FAX Number *(if available)*: 310 998 8553
	Telephone Number: 310 883 1300	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
☞ N/A	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

FORM FDA 3542a (7/03) Page 1

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.		
2. Drug Substance (Active Ingredient)		
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No
3. Drug Product (Composition/Formulation)		
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No
4. Method of Use		
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 1-6, 10-15, 22-27, 30-42, 49-51	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Claims 10-15 - Abraxane (*nab* paclitaxel) for injectable suspension is a nanoparticle albumin-bound (*nab*) form of paclitaxel. *See Description.* Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. *See Description.* This formulation is free from solvents. *See Description.* Abraxane (*nab* paclitaxel) for injectable suspension is indicated for the treatment of [redacted] breast cancer. *See Indication.* Abraxane does not contain Cremophor-EL, therefore hypersensitivity reactions to Abraxane are rare. *See Adverse Reactions: Hypersensitivity Reactions (HSRs).* For metastatic breast cancer, Abraxane (*nab* paclitaxel for injectable suspension) at a dose of 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks has been shown to be effective. *See Dosage and Administration.* Claims 22-27, 32-34, 39-42, and 49-51 - Abraxane (*nab* paclitaxel) for injectable suspension is a nanoparticle albumin-bound (*nab*) form of paclitaxel. *See Description.* Abraxane is supplied as a white to yellow, sterile, lyophilized powder intended for reconstitution with 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. *See Description.* Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. *See Description.* Abraxane (*nab* paclitaxel) for injectable suspension is indicated for the treatment of [redacted] breast cancer. *See Indication.* For metastatic breast cancer, Abraxane (*nab* paclitaxel for injectable suspension) at a dose of 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks has been shown to be effective. *See Dosage and Administration.* Abraxane is supplied as a sterile lyophilized powder for reconstitution before use. *See Dosage and Administration: Preparation for Intravenous Administration.* Reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP. *See Dosage and Administration: Preparation for Intravenous Administration.* Each mL of the reconstituted nanoparticle formulation will contain 5 mg/mL paclitaxel. *See Dosage and Administration: Preparation for Intravenous Administration.* Claim 30 - Abraxane (*nab* paclitaxel) for injectable suspension is a nanoparticle albumin-bound (*nab*) form of paclitaxel. *See Description.* Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. *See Description.* This formulation is free from solvents. *See Description.* Abraxane (*nab* paclitaxel) for injectable suspension is indicated for the treatment of [redacted] breast cancer. *See Indication.* Neutropenia, the most important hematologic toxicity, was dose dependent and was generally rapidly reversible. *See Adverse Reactions: Hematologic.* Grade 4 (<500 cells/mm^3) neutropenia occurred in 12% of patients treated with Abraxane. *See Adverse Reactions: Hematologic.* Among patients treated in the Phase 3 metastatic breast cancer study, neutrophil counts declined below 500 cells/mm^3 (Grade 4) in 9% of the patients treated with a dose of 260 mg/m^2 compared to 22% in patients receiving Cremophor-based paclitaxel injection at a dose of 175 mg/m^2. *See Adverse Reactions: Hematologic.* Among patients Abraxane does not contain Cremophor-EL, therefore hypersensitivity reactions to Abraxane are rare. *See Adverse Reactions: Hypersensitivity Reactions (HSRs).* For metastatic breast cancer, Abraxane (*nab* paclitaxel for injectable suspension) at a dose of 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks has been shown to be effective. *See Dosage and Administration.* Abraxane is supplied as a sterile lyophilized powder for reconstitution before use. *See Dosage and Administration: Preparation for Intravenous Administration.* Reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP. *See Dosage and Administration: Preparation for Intravenous Administration.* Claim 31 - Abraxane (*nab* paclitaxel) for injectable suspension)is a nanoparticle albumin-bound (*nab*) form of paclitaxel. *See Description.* Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. *See Description.* Abraxane (*nab* paclitaxel) for injectable suspension is indicated for the treatment of [redacted] breast cancer. *See Indication.* In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent Abraxane. *See Adverse Reactions: Neurologic.* Peripheral neuropathy was observed in 64% of all patients (10% severe). *See Adverse Reactions: Neurologic.* Peripheral neuropathy was the cause of Abraxane discontinuation in 13/366 (4%) of all patients. *See Adverse Reactions: Neurologic.* Sensory symptoms have usually improved or resolved within 22 days of interrupting Abraxane therapy. *See Adverse Reactions: Neurologic.* Pre-existing neuropathies resulting from prior therapies are not a contraindication for Abraxane therapy. *See Adverse Reactions: Neurologic.* No incidences of grade 4 peripheral neuropathies were reported in the clinical trial. *See Adverse Reactions: Neurologic.* Other than peripheral neuropathy, serious neurologic events following Abraxane administration have been rare (<1%) and have included ischemic stroke, metabolic encephalopathy, confusion, dizziness/lightheadedness, and mood alteration/depression. *See Adverse Reactions: Neurologic.* For metastatic breast cancer, Abraxane (*nab* paclitaxel for injectable suspension) at a dose of 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks has been shown to be effective. *See Dosage and Administration.* Abraxane is supplied as a sterile lyophilized powder for reconstitution before use. *See Dosage and Administration: Preparation for Intravenous Administration.* Reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP. *See Dosage and Administration: Preparation for Intravenous Administration.*

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Claims 36 and 38 - Abraxane (*nab* paclitaxel) for injectable suspension is a nanoparticle albumin-bound (*nab*) form of paclitaxel. *See Description.* Abraxane is supplied as a white to yellow, sterile, lyophilized powder intended for reconstitution with 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. *See Description.* Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. *See Description.* Two studies were conducted in 106 patients previously treated with a maximum of one prior chemotherapeutic regimen. *See Clinical Studies: Breast Carcinoma: Phase 2 open label studies.* Abraxane was administered in these two trials as a 30 minute infusion at doses of 175 mg/m^2 or 300 mg/m^2 without steroid premedication or planned G-CSF support. *See Clinical Studies: Breast Carcinoma: Phase 2 open label studies.* Abraxane (*nab* paclitaxel for injectable suspension) is indicated for the treatment of [redacted] breast cancer. *See Indication.* For metastatic breast cancer, Abraxane (*nab*-paclitaxel for injectable suspension) at a dose of 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks has been shown to be effective. *See Dosage and Administration.* Abraxane is supplied as a sterile lyophilized powder for reconstitution before use. *See Dosage and Administration: Preparation for Intravenous Administration.* Reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP. *See Dosage and Administration: Preparation for Intravenous Administration.* No premedication is required prior to the administration of Abraxane. *See Dosage and Administration: Preparation and Administration Precautions.*

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
Patrick Soon-Shiong, MD, CEO, American Bioscience, Inc.	13 Feb 2009

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name American BioScience, Inc.	
Address 2730 Wilshire Boulevard, Suite 110	City/State Santa Monica, CA
ZIP Code 90403	Telephone Number 310 883 1300
FAX Number *(if available)* 310 998 8553	E-Mail Address *(if available)*

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER: 21-660

NAME OF APPLICANT / NDA HOLDER: American BioScience, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Abraxane™ (*nab* Paclitaxel) for Injectable Suspension

ACTIVE INGREDIENT(S)	STRENGTH(S)
Paclitaxel	100 mg/vial

DOSAGE FORM
Sterile powder for injectable suspension

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,506,405	1/14/2003	2/22/2013

d. Name of Patent Owner	Address *(of Patent Owner)*	
American BioScience, Inc.	2730 Wilshire Boulevard, Suite 110	
	City/State: Santa Monica, CA	
	ZIP Code: 90403	FAX Number *(if available)*: 310 998 8553
	Telephone Number: 310 883 1300	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
☞ N/A	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

FORM FDA 3542a (7/03) Page 1

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 13-22, 24-34, 36-40, 44, 46, 48, 52, 54, 56, 58, 60	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Claims 13-22, 24-26, 33-34, 36, 37-40, 44, 46, 48, 54, and 56 - Abraxane (*nab* paclitaxel) for injectable suspension is a nanoparticle albumin-bound (*nab*) form of paclitaxel. *See Description.* Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. *See Description.* This formulation is free from solvents. *See Description.* Abraxane (*nab* paclitaxel) for injectable suspension is indicated for the treatment of [redacted] breast cancer. *See Indication.* Abraxane does not contain Cremophor-EL, therefore hypersensitivity reactions to Abraxane were rare. *See Adverse Reactions: Hypersensitivity Reactions (HSRs).* For metastatic breast cancer, Abraxane (*nab*-paclitaxel for injectable suspension) at a dose of 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks has been shown to be effective. *See Dosage and Administration.* No premedication is required prior to the administration of Abraxane. *See Dosage and Administration: Preparation and Administration Precautions.* Claims 27-29 - Abraxane (*nab* paclitaxel) for injectable suspension is a nanoparticle albumin-bound (*nab*) form of paclitaxel. *See Description.* Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. *See Description.* This formulation is free from solvents. *See Description.* Abraxane (*nab* paclitaxel for injectable suspension) is indicated for the treatment of [redacted] breast cancer. *See Indication.* Abraxane does not contain Cremophor-EL, therefore hypersensitivity reactions to Abraxane were rare. *See Adverse Reactions: Hypersensitivity Reactions (HSRs).* Neutropenia, the most important hematologic toxicity, was dose dependent and was generally rapidly reversible. *See Adverse Reactions: Hematologic.* Grade 4 (<500 cells/mm^3) neutropenia occurred in 12% of patients treated with Abraxane. *See Adverse Reactions: Hematologic.* Among patients treated in the Phase 3 metastatic breast cancer study, neutrophil counts declined below 500 cells/mm^3 (Grade 4) in 9% of the patients treated with a dose of 260 mg/m^2 compared to 22% in patients receiving Cremophor-based paclitaxel injection at a dose of 175 mg/m^2. *See Adverse Reactions: Hematologic.* For metastatic breast cancer, Abraxane (*nab* paclitaxel for injectable suspension) at a dose of 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks has been shown to be effective. *See Dosage and Administration.* Claims 30-32 - Abraxane (*nab* paclitaxel) for injectable suspension is a nanoparticle albumin-bound (*nab*) form of paclitaxel. *See Description.* Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. *See Description.* This formulation is free from solvents. *See Description.* Abraxane (*nab* paclitaxel) for injectable suspension is indicated for the treatment of [redacted] breast cancer. *See Indication.* In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent Abraxane. *See Adverse Reactions: Neurologic.* Peripheral neuropathy was observed in 64% of all patients (10% severe). *See Adverse Reactions: Neurologic.* Peripheral neuropathy was the cause of Abraxane discontinuation in 13/366 (4%) of all patients. *See Adverse Reactions: Neurologic.* Sensory symptoms have usually improved or resolved within 22 days of interrupting Abraxane therapy. *See Adverse Reactions: Neurologic.* Pre-existing neuropathies resulting from prior therapies are not a contraindication for Abraxane therapy. *See Adverse Reactions: Neurologic.* No incidences of grade 4 peripheral neuropathies were reported in the clinical trial. *See Adverse Reactions: Neurologic.* Other than peripheral neuropathy, serious neurologic events following Abraxane administration have been rare (<1%) and have included ischemic stroke, metabolic encephalopathy, confusion, dizziness/lightheadedness, and mood alteration/depression. *See Adverse Reactions: Neurologic.* Abraxane does not contain Cremophor-EL, therefore hypersensitivity reactions to Abraxane were rare. *See Adverse Reactions: Hypersensitivity Reactions (HSRs).* For metastatic breast cancer, Abraxane (*nab* paclitaxel) for injectable suspension at a dose of 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks has been shown to be effective. *See Dosage and Administration.* Claim 52 - Abraxane (*nab* paclitaxel) for injectable suspension is a nanoparticle albumin-bound (*nab*) form of paclitaxel. *See Description.* Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. *See Description.* This formulation is free from solvents. *See Description.* Abraxane (*nab* paclitaxel) for injectable suspension is indicated for the treatment of [redacted] breast cancer. *See Indication.* Abraxane does not contain Cremophor-EL, therefore hypersensitivity reactions to Abraxane were rare. *See Adverse Reactions: Hypersensitivity Reactions (HSRs).* For metastatic breast cancer, Abraxane (*nab* paclitaxel for injectable suspension) at a dose of 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks has been shown to be effective. *See Dosage and Administration.* No premedication is required prior to the administration of Abraxane. *See Dosage and Administration: Preparation and Administration Precautions.* Neither freezing nor refrigeration adversely affects the stability of the product. *See Dosage and Administration: Stability.* Claim 58 - Abraxane (*nab* paclitaxel)for injectable suspension is a nanoparticle albumin-bound (*nab*) form of paclitaxel. *See Description.* Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. *See Description.* This formulation is free from solvents. *See Description.* Abraxane (*nab* paclitaxel) for injectable suspension is indicated for the treatment of [redacted] breast cancer. *See Indication.* Abraxane does not contain Cremophor-EL, therefore hypersensitivity reactions to Abraxane were rare. *See Adverse Reactions: Hypersensitivity Reactions (HSRs).* For metastatic breast cancer, Abraxane (*nab*-paclitaxel for injectable suspension) at a dose of 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks has been shown to be effective. *See Dosage and Administration.* No premedication is required prior to the administration of Abraxane. *See Dosage and Administration: Preparation and Administration Precautions.* Inject the appropriate amount of reconstituted Abraxane into an empty, sterile, polyvinyl chloride (PVC) type IV bag. *See Dosage and Administration: Preparation for Intravenous Administration.* The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer Abraxane infusions. *See Dosage and Administration: Preparation for Intravenous Administration.*

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Claim 60 - Abraxane (*nab* paclitaxel) for injectable suspension is a nanoparticle albumin-bound (*nab*) form of paclitaxel. *See Description.* Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. *See Description.* This formulation is free from solvents. *See Description.* Abraxane (*nab* paclitaxel) for injectable suspension is indicated for the treatment of [redacted] breast cancer. *See Indication.* Abraxane does not contain Cremophor-EL, therefore hypersensitivity reactions to Abraxane were rare. *See Adverse Reactions: Hypersensitivity Reactions (HSRs).* For metastatic breast cancer, Abraxane (*nab* paclitaxel for injectable suspension) at a dose of 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks has been shown to be effective. *See Dosage and Administration.* No premedication is required prior to the administration of Abraxane. *See Dosage and Administration: Preparation and Administration Precautions.*

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
Patrick Soon-Shiong, MD, CEO, American Bioscience, Inc.	13 Feb 2008

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name American BioScience, Inc.	
Address 2730 Wilshire Boulevard, Suite 110	City/State Santa Monica, CA
ZIP Code 90403	Telephone Number 310 883 1300
FAX Number *(if available)* 310 998 8553	E-Mail Address *(if available)*

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER: 21-660

NAME OF APPLICANT / NDA HOLDER: American BioScience, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Abraxane™ (*nab* paclitaxel) for Injectable Suspension

ACTIVE INGREDIENT(S)	STRENGTH(S)
Paclitaxel	100 mg/vial

DOSAGE FORM
Sterile powder for injectable suspension

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,096,331	8/1/2000	2/22/2013

d. Name of Patent Owner	Address *(of Patent Owner)*	
American BioScience, Inc.	2730 Wilshire Boulevard, Suite 110	
	City/State: Santa Monica, CA	
	ZIP Code: 90403	FAX Number *(if available)*: 310 998 8553
	Telephone Number: 310 883 1300	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
☞ N/A	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

FORM FDA 3542a (7/03) Page 1

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2

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 1-2, 5-19, 26, 28, 40, 43-47, 49, 52-57	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Claims 1-2, 5-6, 19, 26, 28, 40, 43, 49, 52, 54, and 56 – Abraxane (*nab* paclitaxel) for injectable suspension is a nanoparticle albumin-bound (*nab*) form of paclitaxel. *See Description.* Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. *See Description.* This formulation is free from solvents. *See Description.* Abraxane (*nab* paclitaxel) for injectable suspension is ind cated for the treatment of [redacted] breast cancer. *See Indications.* Abraxane does not contain Cremophor-EL, therefore hypersensitivity reactions to Abraxane were rare. *See Adverse Reactions: Hypersensitivity Reactions (HSRs).* For metastatic breast cancer, Abraxane (*nab* paclitaxel for injectable suspension) at a dose of 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks has been shown to be effective. *See Dosage and Administration.* No premedication is required prior to administration of Abraxane. *See Dosage and Administration: Preparation and Administration Precautions.* Claims 7-14, 44, 53, 55, and 57 – Abraxane (*nab* paclitaxel) for injectable suspension is a nanoparticle albumin-bound (*nab*) form of paclitaxel. *See Description.* Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. *See Description.* This formulation is free from solvents. *See Description.* Abraxane (*nab* paclitaxel) for injectable suspension is indicated for the treatment of [redacted] breast cancer. *See Indications.* Pharmacokinetic parameters of paclitaxel following 30- and 180 minute infusions of Abraxane at dose levels of 80-375 mg/m^2 were determined in two phase 1 clinical studies and a phase 3 randomized study in adult cancer patients and are summarized in the following table [Table 1]. *See Clinical Pharmacology.* Abraxane does not contain Cremophor-EL, therefore hypersensitivity reactions to Abraxane were rare. *See Adverse Reactions: Hypersensitivity Reactions (HSRs).* For metastatic breast cancer, Abraxane (*nab* paclitaxel for injectable suspension) at a dose of 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks has been shown to be effective. *See Dosage and Administration.* No premedication is required prior to administration of Abraxane. *See Dosage and Administration: Preparation and Administration Precautions.* Claims 15-16 and 45 - Abraxane (*nab* paclitaxel) for injectable suspension is a nanoparticle albumin-bound (*nab*) form of paclitaxel. *See Description.* Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. *See Description.* This formulation is free from solvents. *See Description.* Abraxane (*nab* paclitaxel) for injectable suspension is indicated for the treatment of [redacted] breast cancer. *See Indications.* Neutropenia, the most important hematologic toxicity, was dose dependent and was generally rapidly reversible. *See Adverse Reactions: Hematologic.* Grade 4 (<500 cells/mm^3) neutropenia occurred in 12% of patients treated with Abraxane. *See Adverse Reactions: Hematologic.* Among patients treated in the Phase 3 metastatic breast cancer study, neutrophil counts declined below 500 cells/mm^3 (Grade 4) in 9% of the patients treated with a dose of 260 mg/m^2 compared to 22% in patients receiving Cremophor-based paclitaxel injection at a dose of 175 mg/m^2. *See Adverse Reactions: Hematologic.* Abraxane does not contain Cremophor-EL, therefore hypersensitivity reactions to Abraxane were rare. *See Adverse Reactions: Hypersensitivity Reactions (HSRs).* For metastatic breast cancer, Abraxane (*nab* paclitaxel for injectable suspension) at a dose of 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks has been shown to be effective. *See Dosage and Administration.* Claims 17-18 and 46-47 - Abraxane (*nab* paclitaxel) for injectable suspension is a nanoparticle albumin-bound (*nab*) form of paclitaxel. *See Description.* Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. *See Description.* This formulation is free from solvents. *See Description.* Abraxane (*nab* paclitaxel) for injectable suspension is indicated for the treatment of [redacted] breast cancer. *See Indications.* Abraxane does not contain Cremophor-EL, therefore hypersensitivity reactions to Abraxane were rare. *See Adverse Reactions: Hypersensitivity Reactions (HSRs).* In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent Abraxane. *See Adverse Reactions: Neurologic.* Peripheral neuropathy was observed in 64% of all patients (10% severe). *See Adverse Reactions: Neurologic.* Peripheral neuropathy was the cause of Abraxane discontinuation in 13/366 (4%) of all patients. *See Adverse Reactions: Neurologic.* Sensory symptoms have usually improved or resolved within 22 days of interrupting Abraxane therapy. *See Adverse Reactions: Neurologic.* Pre-existing neuropathies resulting from prior therapies are not a contraindication for Abraxane therapy. *See Adverse Reactions: Neurologic.* No incidences of grade 4 peripheral neuropathies were reported in the clinical trial. *See Adverse Reactions: Neurologic.* Other than peripheral neuropathy, serious neurologic events following Abraxane administration have been rare (<1%) and have included ischemic stroke, metabolic encephalopathy, confusion, dizziness/lightheadedness, and mood alteration/depression. *See Adverse Reactions: Neurologic.* For metastatic breast cancer, Abraxane (*nab* paclitaxel for injectable suspension) at a dose of 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks has been shown to be effective. *See Dosage and Administration.*

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Patrick Soon-Shiong, MD, CEO, American Bioscience, Inc.	13 febra

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name American BioScience, Inc.	
Address 2730 Wilshire Boulevard, Suite 110	City/State Santa Monica, CA
ZIP Code 90403	Telephone Number 310 883 1300
FAX Number *(if available)* 310 998 8553	E-Mail Address *(if available)*

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-660

NAME OF APPLICANT / NDA HOLDER
American BioScience, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Abraxane™ (*nab* paclitaxel) for Injectable Suspension

ACTIVE INGREDIENT(S)	STRENGTH(S)
Paclitaxel	100 mg/vial

DOSAGE FORM
Sterile powder for injectable suspension

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,498,421	3/12/1996	3/12/2013

d. Name of Patent Owner	Address *(of Patent Owner)*	
American BioScience, Inc.	2730 Wilshire Boulevard, Suite 110	
	City/State: Santa Monica, CA	
	ZIP Code: 90403	FAX Number *(if available)*: 310 998 8553
	Telephone Number: 310 883 1300	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
☞ N/A	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

FORM FDA 3542a (7/03) Page 1

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☒ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 27, 29	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Claim 27 – Abraxane (*nab* paclitaxel) for injectable suspension is a nanoparticle albumin-bound (*nab*) form of paclitaxel. *See Description.* Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. *See Description.* Abraxane (*nab* paclitaxel) for injectable suspension is indicated for the treatment of [redacted] breast cancer. *See Indications.* For metastatic breast cancer, Abraxane (*nab* paclitaxel for injectable suspension) at a dose of 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks has been shown to be effective. *See Dosage and Administration.* Claim 29 - Abraxane (*nab* paclitaxel) for injectable suspension is a nanoparticle albumin-bound (*nab*) form of paclitaxel. *See Description.* Abraxane is supplied as a white to yellow, sterile, lyophilized powder intended for reconstitution with 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. *See Description.* Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. *See Description.* Abraxane (*nab* paclitaxel) for injectable suspension is indicated for the treatment of [redacted] breast cancer. *See Indications.* For metastatic breast cancer, Abraxane (*nab* paclitaxel for injectable suspension) at a dose of 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks has been shown to be effective. *See Dosage and Administration.* ABRAXANE is supplied as a sterile lyophilized powder for reconstitution before use. *See Dosage and Administration: Preparation for Intravenous Administration.* Reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP. *See Dosage and Administration: Preparation for Intravenous Administration.*

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Patrick Soon-Shiong, MD, CEO, American Bioscience, Inc.	13 Feb 2008

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name American BioScience, Inc.	
Address 2730 Wilshire Boulevard, Suite 110	City/State Santa Monica, CA
ZIP Code 90403	Telephone Number 310 883 1300
FAX Number *(if available)* 310 998 8553	E-Mail Address *(if available)*

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER: 21-660

NAME OF APPLICANT / NDA HOLDER: American BioScience, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Abraxane™ (*nab* paclitaxel) for Injectable Suspension

ACTIVE INGREDIENT(S)	STRENGTH(S)
Paclitaxel	100 mg/vial

DOSAGE FORM
Sterile powder for injectable suspension

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,439,686	8/8/1995	2/22/2013

d. Name of Patent Owner	Address *(of Patent Owner)*	
American BioScience, Inc.	2730 Wilshire Boulevard, Suite 110	
	City/State: Santa Monica, CA	
	ZIP Code: 90403	FAX Number *(if available)*: 310 998 8553
	Telephone Number: 310 883 1300	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
N/A	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

FORM FDA 3542a (7/03) Page 1

PSC Media Arts (301) 443-1090 EF

7

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Patent Claim Number *(as listed in the patent)* — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. — Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
Patrick Soon-Shiong, MD, CEO, American Bioscience, Inc.	13 Feb 2002

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name American BioScience, Inc.	
Address 2730 Wilshire Boulevard, Suite 110	City/State Santa Monica, CA
ZIP Code 90403	Telephone Number 310 883 1300
FAX Number *(if available)* 310 998 8553	E-Mail Address *(if available)*

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY FOR NDA # 21-660 SUPPL #_____

TradeName ABRAXANE for Injectable Suspenion

Generic Name paclitaxel protein-bound particles for injectable suspension

Applicant NameAmerican BioScience, Inc.

HFD # 150

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /__X__/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /__X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /__X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

___3 years_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /__X__/ NO /__X__/ stat Sorry

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__X__/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /__X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20262 Taxol

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered ``NO'' for original approvals of new molecular entities.) IF ``YES'' GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___X/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's

conclusion? If not applicable, answer NO.

YES /___/ NO /__X__/

If yes, explain:

---

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /__X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Phase 3 study (Protocol CA012-0) comparing paclitaxel protein-Particles 260 mg/m^2 to 175 mg/m^2 of Taxol®.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency

to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /__X__/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /__X__/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Protocol CA012-0 _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or

its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 55974 YES /X/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /__X__/

If yes, explain: _____

_____

Signature Date
Title: Sheila Ryan, Pharm.D. 01/ /2005

Signature of Office/ Date
Division Director

Richard Pazdur, M.D. 01/07/2005

Form OGD-011347 Revised 05/10/2004

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Grant Williams
1/7/05 11:39:56 AM
For Dr. Pazdur

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-660 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: March 8, 2004 **Action Date:** January 8, 2005

HFD 150 **Trade and generic names/dosage form:** Abraxane (*nab* paclitaxel) for Injectable Suspension [redacted]/mL)

Applicant: American Biosciene, Inc. **Therapeutic Class:** 5S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: [redacted]

Is there a full waiver for this indication (check one)?

X **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
X **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Sheila Ryan, Pharm.D.
Regulatory Project Manager

cc: NDA 21-660
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A
(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: N/A

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ___Partial Waiver ___Deferred ___Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Sheila Ryan, Pharm.D.
Regulatory Project Manager

NDA 21-660
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sheila Ryan
5/7/04 12:41:28 PM

American BioScience, Inc.

DEBARMENT CERTIFICATION

American BioScience, Inc. certifies that in support of this NDA for Abraxane™ (*nab* paclitaxel) for Injectable Suspension (company code ABI-007), the company did not and will not employ in any capacity the services of any person debarred under section 306 of the Food, Drug, and Cosmetic Act in connection with this application.

MG Clark

Mitchall G. Clark
Vice President, Regulatory Affairs

1/26/04

Date

2730 Wilshire Blvd., Suite 110 Santa Monica, California 90403 Tel: (310) 883-1300 Fax: (310) 998-8553

AMERICAN PHARMACEUTICAL PARTNERS, INC.

DEBARMENT CERTIFICATION

American Pharmaceutical Partners, Inc. certifies that in support of this NDA for ABI-007, the company did not and will not employ in any capacity the services of any person, listed under http://www.fda.gov/ora/compliance_ref/debar/default.htm, who are debarred under subsections (a) or (b) [section 306(a) or (b)] of the Generic Drug Enforcement Act of 1992, and listed under

Mia Igyarto
Vice President, Human Resources

2/27/03
Date

1101 PERIMETER DRIVE, SUITE 300
SCHAUMBURG, ILLINOIS 60173-5837

TO AMERICAN BIOSCIENCE, INC. SANTA MONICA, CA 90403 (AMERICAN PHARMACEUTICAL PARTNERS):

certifies that:

, did not and will not employ in any capacity the services of any person listed under http://www.fda.gov/ora/compliance_ref/debar/default.htm who are debarred under section 306 of the Food, Drug, and Cosmetic Act in connection its approved application for Albumin Human, USP.

April 25, 2003

DEBARMENT CERTIFICATION

— certifies that in support of this NDA for ABI-007, the company did not and will not employ in any capacity the services of any person listed under http.://www.fda.gov/ora/compliance_ref/debar/default.htm, who are debarred under section 306 of the Food, Drug, and Cosmetic Act in connection with this application.

[redacted]

July 22, 2003

Mr. Mitchall Clark
American BioScience, Inc.
2730 Wilshire Boulevard, Suite 110
Santa Monica, CA 90403

Dear Mr. Clark:

[redacted] is a supplier of services to the pharmaceutical industry in general as well as to American BioScience, Inc. in particular. [redacted] carries out its operations in compliance with the current policies, guidelines and regulations promulgated by the Food and Drug Administration (FDA) under requirements of the Federal Food, Drug, and Cosmetic Act and related Acts.

Inasmuch as [redacted] provides pharmaceutical services to American BioScience, Inc., the results of those services (records and data) may be used by American BioScience, Inc. in applications to the FDA seeking marketing approval [redacted] now wishes to fulfill its obligation to American BioScience, Inc. by attesting to compliance with the Generic Drug Enforcement Act of 1992. Specifically:

1. [redacted], certifies that, in the course of supplying pharmaceutical services to American BioScience, Inc. in support of any of its drug marketing applications, it did not and will not use in any capacity the services of any person or firm debarred under subsections (a) or (b) of section 306 of the Generic Drug Enforcement Act of 1992.

2. [redacted], certifies that, to the best of its knowledge, no person in the firm or affiliated with the firm and responsible for the development or submission of records or data in support of any abbreviated drug application for American BioScience, Inc. has been convicted within the last five years of any crime described in subsections (a) and (b) of section 306 of the Generic Drug Enforcement Act of 1992.

[redacted], stands ready to provide American BioScience, Inc. with any additional information that may be required in support of the above certifications.

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA **21-660**	Efficacy Supplement Type SE-	Supplement Number	
Drug: **Abraxane (paclitaxel protein bound particles) for Injectable Suspension**		Applicant: **American BioScience, Inc.**	
RPM: **Sheila Ryan**		HFD-**150**	Phone # **301-594-5771**

Application Type: ( ) 505(b)(1) (√) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** (√) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): **NDA 20-262 Taxol (paclitaxel) Injection**

❖ Application Classifications:	
• Review priority	(√)Standard ( ) Priority
• Chem class (NDAs only)	**5**
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	**1-08-05**
❖ Special programs (indicate all that apply)	( ) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) (√) Fast Track (√) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(√) Paid UF ID number 4554
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (√) No

Version: 6/16/2004

• This application is on the AIP	( ) Yes (√) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(√) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(√) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) (√) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(√) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	( ) Yes ( ) No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).*	( ) Yes ( ) No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No

Version: 6/16/2004

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary	√
• Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	**No**
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (√) No
Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	**Filing Review 5-18-04**

Version: 6/16/2004

General Information	
Actions	
• Proposed action	(√) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	**N/A**
• Status of advertising (approvals only)	(√) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(√) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(√) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	√
• Most recent applicant-proposed labeling	√ **12-20-04**
• Original applicant-proposed labeling	√ **3-4-04**
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	**DDMAC: 10-14-04** **DMETS: 11-16-04** **DSRCS: 1-5-05**
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	**N/A**
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	√
• Applicant proposed	**6-21-04**
• Reviews	**See CMC and DMETS reviews**
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	**1-4-05**
• Documentation of discussions and/or agreements relating to post-marketing commitments	**1-4-05**
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	√
❖ Memoranda and Telecons	√ **(see outgoing correspondence)**
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	**5-3-01**
• Pre-NDA meeting (indicate date)	**3-19-03 and 11-21-03**
• Pre-Approval Safety Conference (indicate date; approvals only)	**N/A**
• Other	**Filing meeting 5-7-04**
❖ Advisory Committee Meeting	
• Date of Meeting	**N/A**
• 48-hour alert	**N/A**
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	**N/A**

Summary Application Review	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	**Div. Director Memo: 2-7-05**
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	**1-7-05**
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	**N/A**
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	**1-7-05**
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	**N/A**
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	**5/7/04**
❖ Demographic Worksheet *(NME approvals only)*	**N/A**
❖ Statistical review(s) *(indicate date for each review)*	**12-3-04**
❖ Biopharmaceutical review(s) *(indicate date for each review)*	**1-4-05**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	**N/A**
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	**N/A**
• Bioequivalence studies	**1-10-05**
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	**12-7-04**
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	**12-7-04**
• Review & FONSI *(indicate date of review)*	**N/A**
• Review & Environmental Impact Statement *(indicate date of each review)*	**N/A**
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	**2-20-04 and 5-24-04**
❖ Facilities inspection (provide EER report)	Date completed: **8-2-04** (√) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (√) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**12-20-04**
❖ Nonclinical inspection review summary	**N/A**
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	**N/A**
❖ CAC/ECAC report	**N/A**

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

14 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 5, 2005

TO: Richard Pazdur, M.D., Director
Division of Oncologic Drug Products
HFD-150

VIA: Sheila Ryan, Regulatory Health Project Manager
Division of Oncologic Drug Products
HFD-150

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for Abraxane (paclitaxel albumin nanoparticle for injectable suspension), NDA 21-660

Background and Summary

The sponsor submitted draft patient labeling June 21, 2004, and revised draft patient labeling on December 22, 2004 for Abraxane (paclitaxel albumin nanoparticle for injectable suspension), NDA 21-660. Abraxane is a cancer chemotheraputic agent that is prepared in a healthcare facility and administered intravenously only by healthcare care professionals. The main purpose of FDA approved patient labeling is to provide information to patients on the safe and effective use of a drug product that is primarily used on an outpatient basis without direct supervision by a healthcare professionals. Medication Guides (for products with serious and significant health concerns, primarily for outpatient prescriptions used without direct medical supervision) and Patient Package Inserts (PPIs) for estrogen-containing products and oral contraceptives are required patient labeling that must be dispensed by a pharmacist with outpatient prescriptions. All other PPIs are voluntary and generally do not reach the patient unless they are packaged in unit-of-use packages with outpatient prescriptions dispensed directly to the patient. There is no requirement to print voluntary PPIs and no mechanism for the dispensing of any patient information in supervised medical settings. For these reasons it is unlikely that patients receiving Abraxane will receive FDA approved patient labeling.

Comments and Recommendations

We have the following comments and recommendations:

1. The sponsor should state the purpose of a PPI for Abraxane and the mechanism for getting it to the patient.

2. The PRECAUTIONS section, Information for Patients subsection of the PI refers prescribers to the Patient Information Leaflet. Voluntary PPIs are not required to be appended to the product labeling [21 CFR 201.57(f)(2)]. The Information for Patients subsection should contain specific counseling information for prescribers to provide to patients regarding the safe and effective use of the product [21 CFR 201.57(f)(2)].

3. Revise the Patient Package Insert (PPI) to a question and answer format with the content ordered similarly to Medication Guides. This format is known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. Alternate formats are discouraged without supportive data for their communication effectiveness from studies such as label comprehension testing. Place any brief information regarding the Disease state at the end of the leaflet or provide a separate sheet for the disease. The purpose of patient information is to provide the information regarding the safe and effective use of the drug product.

4. Simplify the vocabulary and sentence structure for lower literacy readers. A 6 to 8th grade reading comprehension level is optimal for all patient information with a reading ease score of at least 60% (a 60% reading score correlates with an 8th grade reading level). Approximately 50% of U.S. adults function at a lower literacy level and read at less than an 8th grade level. The Flesch-Kincaid Reading Level of the draft PPI for Abraxane is 9.7 with a Flesch Reading Ease Score of 51.1%. There are many opportunities to simplify complex words and statements in this draft PPI.

5. Avoid the use of all UPPER CASE lettering to emphasize important information (the tradename is an exception). Upper case lettering is difficult to read. Bold, underline, or increase the font size of the word or statement for emphasis.

Please call us if you have any questions.

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/s/

Jeanine Best
1/5/05 01:10:05 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
1/5/05 01:48:16 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 9/10/04 **DATE OF DOCUMENT:** 3/4/2004	**DESIRED COMPLETION DATE:** 12/04 **PDUFA DATE:** 1/8/05	**ODS CONSULT #:** 03-0303-1

TO: Richard Pazdur, MD
Director, Division of Oncology Drug Products
HFD-150

THROUGH: Sheila Ryan, Division of Oncology Drug Products
Project Manager
HFD-150

PRODUCT NAME: **Abraxane™** (Paclitaxel for Injectable Suspension) 100 mg/vial **NDA#: 21-660**	**NDA SPONSOR:** American BioScience, Inc.

SAFETY EVALUATOR: Felicia Duffy, RN

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Abraxane provided that only one name, Abraxane (NDA 65-053) or [redacted] is approved. We recognize the Division may overturn this decision based on preliminary discussions concerning the differentiating product characteristics. However, despite these product differences, the names are extremely similar in sound and thus we anticipate numerous potential error reports based on this similarity alone. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name and its associated labels and labeling must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Abraxane acceptable from a promotional perspective.

4. We recommend consulting Guirag Poochikian, Acting Chair, of the CDER Labeling and Nomenclature Committee for the proper designation of the established name.

Carol Holquist, RPh
Director, Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

APPEARS THIS WAY
ON ORIGINAL

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 4, 2004

NDA# 21-660

NAME OF DRUG: Abraxane™
(Paclitaxel for Injectable Suspension)
100 mg/vial

NDA HOLDER: American BioScience, Inc.

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Oncology Drug Products (HFD-150), for a re-review of the proprietary name, "Abraxane", regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment. DMETS previously reviewed this proprietary name in ODS consult #03-0303 on January12, 2004 and found the name acceptable.

PRODUCT INFORMATION

Abraxane is the proprietary name proposed for Paclitaxel Albumin for Injection, a nanoparticle albumin bound (nab) formulation of paclitaxel. The nab formulation allows administration of paclitaxel without the toxicities associated with the solvent, cremophor, present in currently marketed products. Paclitaxel Injection 6 mg/mL is currently marketed under the proprietary name, Taxol, and by generic manufacturers. Abraxane is indicated for treatment of breast cancer after failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. The recommended dosage for Abraxane in this indication is 260 mg/m^2 every three weeks, in contrast to Paclitaxel Injection which is dosed at 175 mg/m^2 every three weeks. Abraxane may also be infused over a 30 minute time period as compared to the three hour infusion time required for currently marketed paclitaxel injection products. Abraxane is available in single dose vials containing 100 mg of paclitaxel and 900 mg of human albumin. When reconstituted with 20 mL of 0.9% sodium chloride, each mL contains 5 mg of paclitaxel.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Abraxane to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Abraxane. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Abraxane acceptable from a promotional perspective.

2. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with Abraxane. These products are listed in table 1 (see page 4), along with the dosage forms available and usual dosage.

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

5 Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Abraxane	Paclitaxel for Injectable Suspension Lyophilized powder: 100 mg single dose vial	260 mg/m^2 given intravenously over 30 minutes every 3 weeks.	
Blenoxane	Bleomycin Sulfate Powder for Injection: 15 units/vial, 30 units/vial	0.25 to 0.5 units/kg (10 -20 units/m^2) administered IV, IM, or SC once or twice weekly	LA

*Frequently used, not all-inclusive.
**LA (look-alike), SA (sound-alike)
***Name pending approval. Not FOI releasable.**

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Abraxane were discussed by the Expert Panel (EPD).

C. SAFETY EVALUATOR RISK ASSESSMENT

Since the initial review, two additional names were identified as having phonetic and orthographic similarities to Abraxane. The primary concerns related to look-alike and sound-alike confusion with — and Blenoxane.

2. Blenoxane may look similar to Abraxane when scripted. Blenoxane contains bleomycin sulfate and is indicated for the treatment of Hodgkin and non-Hodgkin lymphoma, head and neck squamous cell carcinoma, testicular cancer and malignant pleural effusions. The usual dose for Blenoxane is 10-20 units/m^2. It is administered either intravenously, intramuscularly, or subcutaneously. Blenoxane is available as a powder for injection. Blenoxane powder must be refrigerated, however it is stable at room temperature after reconstitution. Blenoxane and Abraxane may look similar because they both share the same ending ("xane"). In addition, the letters "a" and "o" preceding "xane" may look similar when scripted. Contrarily, the prefix of both names differ when scripted ("Blen" vs. "Abr"). Product similarities between Blenoxane and Abraxane include indication for use (cancer), route of administration (intravenous), dosage form (injectable), and prescriber population (oncologist). Despite the overlapping characteristics, both product differ in strength (15 units/vial and 30 units/vial vs. 100 mg vial), usual dosage (10-20 units/m^2 vs. 260 mg/m^2), frequency of administration (once or twice weekly vs. once every 3 weeks), and storage conditions (refrigeration vs. room temperature). Although Blenoxane and Abraxane share a few overlapping product characteristics, the differentiating product characteristics including strength, usual dosage, frequency of administration, storage conditions, and the lack of strong orthographic similarities help to minimize the potential for medication errors.

Blenoxane	Abraxane

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Abraxane, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

DMETS notes the sponsor has used technology within the established name, " In addition, the word appears above the proprietary name. Please delete the word as it is not a part of the proprietary or established name. We recommend consulting Guirag Poochikian, Acting Chair, CDER Labeling and Nomenclature Committee for the proper designation of the established name.

B. CONTAINER LABEL (100 mg vial)

C. CARTON LABELING (100 mg vial)

emphasize its importance

D. PACKAGE INSERT LABELING

Preparation for Intravenous Administration

In the second to last paragraph, the following statement exists: "The use of an in-line filter is not recommended." DMETS questions if the filter has a negative effect on the product and if so, what are the implications? The next sentence reads:

' This statement is contradictory to the previous statement that does not recommend the use of a filter?

E. PATIENT PACKAGE INSERT

No comment.

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name Abraxane provided that only one name, Abraxane (NDA 65-053) or , is approved. We recognize the Division may overturn this decision based on preliminary discussions concerning the different product characteristics. However, despite these product differences, the names are extremely similar in sound and thus we anticipate numerous potential error reports based on this similarity alone. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name and its associated labels and labeling must be re-evaluated. A re-review of the name will rule out any objection based upon approval of other proprietary or established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C DDMAC finds the proprietary name Abraxane acceptable from a promotional perspective.

D. We recommend consulting Guirag Poochikian, Acting Chair, of the CDER Labeling and Nomenclature Committee for the proper designation of the established.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Felicia Duffy, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Felicia Duffy
11/16/04 01:26:32 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/16/04 04:06:47 PM
DRUG SAFETY OFFICE REVIEWER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-660 Supplement # n/a SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: Abraxane
Generic Name: *nab* paclitaxel for injectable suspension
Strengths: —*g*/mL
Applicant: American BioScience, Inc

Date of Application: March 4, 2004
Date of Receipt: March 8, 2004
Date clock started after UN: n/a
Date of Filing Meeting: May 7, 2004
Filing Date: May 7, 2004
Action Goal Date (optional): User Fee Goal Date: January 8, 2005

Indication(s) requested: Metastatic breast cancer

Type of Original NDA: (b)(1) _____ (b)(2) ___x_____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S ___X___ P _____
Resubmission after withdrawal? ___No_____ Resubmission after refuse to file? NO_____
Chemical Classification: (1,2,3 etc.) ___5_____
Other (orphan, OTC, etc.) ___Fast track and rolling review_

User Fee Status: Paid ___Yes_____ Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

Form 3397 (User Fee Cover Sheet) submitted: YES
User Fee ID # ___4554_____
Clinical data? YES ___X___ Also, Referenced to NDA # __20-262___

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

NO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? NO
Taxol has orphan exclusivity until 8-4-04 for AIDs related Kaposi's sarcoma.

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? NO

Is the application affected by the Application Integrity Policy (AIP)? NO
If yes, explain.

Version: 9/25/03

If yes, has OC/DMPQ been notified of the submission? N/A

- Does the submission contain an accurate comprehensive index? YES

- Was form 356h included with an authorized signature? YES
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES
  If no, explain:

- If an electronic NDA, does it follow the Guidance? YES
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A

- Is it an electronic CTD? NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- Patent information submitted on form FDA 3542a? YES

- Exclusivity requested? YES, ____3___ years
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., *"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."* Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
  Applicant submitted 3454. Form 3455 is not applicable The company certified none of the investigators had financial interests.

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? YES

- List referenced IND numbers: 55,974

- End-of-Phase 2 Meeting(s)? Date(s) 2-5, 2-6, and 5-3-01
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meetings? Dates: 3-19-03 and 11-21-03
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A

- Has DOTCDP been notified of the OTC switch application? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
  If no, did applicant submit a complete environmental assessment? N/A
  If EA submitted, consulted to Nancy Sager (HFD-357)? In progress

- Establishment Evaluation Request (EER) submitted to DMPQ? YES

- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #: Taxol® (paclitaxel) Injection, NDA 20-262

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

  This application provides for a change in formulation, dosage form, and administration rate.

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  NO

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

  __x__ 21 CFR 314.50(i)(1)(ii): No relevant patents.

  ____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

  ____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES
  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES
  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    YES
  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES
  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES
  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    IND # 55,974

    NO

    OR

    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application? YES, contacted James Cross and Kim Colangelo on 3-25-04.

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/s/

Sheila Ryan
5/18/04 05:07:42 PM
CSO

MINUTES OF FILING MEETING

DATE: May 7, 2004 **TIME:** 12:00 PM **ROOM:** B

NDA: 21-660 **DRUG:** Abraxane (*nab* paclitaxel for injectable suspension)

BACKGROUND:

American Bioscience has submitted an electronic rolling NDA for Abraxane (*nab* paclitaxel for injectable suspension) for . The pharmacology and chemistry sections were submitted on June 30, 2003. The final piece (clinical) was submitted on March 4, 2004.

ATTENDEES:

Ramzi Dagher, M.D., Medical Team Leader
Nancy Scher, M.D., Medical Reviewer
Peiling Yang, Ph.D., Statistical Reviewer
Brian Booth, Ph.D., Acting Biopharmaceutics Team Leader
Angela Men, Ph.D., Biopharmaceutics Reviewer
Yung Ao Hsieh, Ph.D., Chemistry Reviewer

ASSIGNED REVIEWERS:

Discipline	Reviewer	Team Leader
Medical:	Nancy Scher, M.D.	Ramzi Dagher, M.D.
Statistical:	Peiling Yang, M.D.	Rajeshwari Sridhara, Ph.D.
Pharmacology:	Margaret Brower, Ph.D.	John Leighton, Ph.D.
Chemistry:	Yung Ao Hsieh, Ph.D.	Rebecca Wood, Ph.D.
Biopharmaceutical:	Angela Men, Ph.D.	Brian Booth, Ph.D.
Microbiology:	Stephen Langille, Ph.D.	Peter Cooney, Ph.D.
DSI:	David Gan, M.D.	
Regulatory Project Management:	Sheila Ryan, Pharm.D.	

Per reviewers, are all parts in English or English translation? **YES**
If no, explain:

CLINICAL FILE ___X___ REFUSE TO FILE _____

- Clinical site inspection needed: **YES**
- Advisory Committee Meeting needed? **NO**

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A

CLINICAL MICROBIOLOGY	FILE __X__	REFUSE TO FILE _____
STATISTICS	FILE __X__	REFUSE TO FILE _____
BIOPHARMACEUTICS	FILE __X__	REFUSE TO FILE _____
PHARMACOLOGY	FILE __X__	REFUSE TO FILE _____
CHEMISTRY	FILE __X__	REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES
- Microbiology YES

ELECTRONIC SUBMISSION: Initially, the final submission could not be loaded into the EDR, because the tape that the sponsor submitted was not readable. All issues have been resolved as of March 19, 2004.

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ This application is unsuitable for filing. Explain why:

__X__ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

__X__ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

OTHER DISCUSSION:

1. Identified patient consultant as —
2. Nancy to identify breast cancer consultant(s).
3. DSI memo: Nancy to pick sites for inspection.
4. Secure email: Established
5. Target Date for completion: prior to Christmas
6. EA and EER: Yung Ao will complete.
7. DDMAC, tradename, and ODS: Sheila will complete.
8. Generic name consult: pending.
9. Radiologist: Dr — , clearance pending
10. Microbiology review will be done shortly.

11. Imaging Update: The sponsor is willing to establish remote access to allow the review team to view imaging database. However, the logistics still need to be worked out. A teleconference will be scheduled to work out logistics ASAP. Additional training will still be needed in the future.
12. Schedule first team meeting in 6 weeks. Timelines to be established at this meeting.

ACTION ITEMS:

1. Sheila to start clearance of patient consultant. **Pending: with Joann Minor as of 5-7-04.**
2. Nancy to identify breast cancer consultant. **Completed: Dr. — unavailable. Dr. Edith Perez pending SGE approval 5-14-04.**
3. Nancy to identify sites for clinical inspection and Sheila to draft/circulate memo. **Completed: memo sent to DSI, 5-11-04.**
4. Yung Ao to complete EA and EER consults.
5. Sheila to complete DDMAC consult: **Completed: 5-10-04.**
6. Sheila to complete ODS and tradename consults.
7. Sheila to complete acknowledgement letter. **Completed: sent to sponsor, 5-7-04.**
8. Sheila to draft FG letter. **Completed: final sign off and sent to sponsor, 5-7-04.**
9. Sheila to schedule teleconference with sponsor regarding remote access to imaging database. **Done: scheduled for 5-17-04 at 4 pm in B.**
10. Sheila to schedule first team meeting. **Completed: scheduled for 6-23-04 at 3 pm in B.**

Sheila Ryan, Pharm.D.
Regulatory Project Manager, HFD-150

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/s/

Sheila Ryan
5/17/04 03:47:26 PM

MEETING MINUTES

MEETING DATE: Nov. 21, 2003 **TIME:** 2:30 **LOCATION:** G

IND/NDA: 55,974/NDA 21-660 **Meeting Request Submission Date:** 10-1-03
FDA Response Date: 10-03-03
Briefing Document Submission Date: 10-20-03

DRUG: Abraxane (*nab*-paclitaxel for inj. susp.) **INDICATION:** —

SPONSOR: American BioScience, Inc. **TYPE of MEETING:** pre-NDA

FDA PARTICIPANTS: Richard Pazdur, M.D. Dir., DODP
Ramzi Dagher, M.D., Medical Team Leader, DODP
Patricia Cortazar, M.D., Medical Officer, DODP
Rebecca Wood, Ph.D., Chemistry Team Leader, DODP
Yung-Ao Hsieh, Ph.D., Chemistry Reviewer, DODP
Margaret Brower, Ph.D., Pharmacologist, DODP
Atik Rahman, Ph.D., Clin. Phar./Biopharm. Team Leader, DODP
Sophia Abraham, Ph.D., Clin. Pharm. Reviewer, DODP (pre-mtg)
Ning Li, Ph.D., Acting Stat. Team Leader, DODP
Raji Sridhara, Ph.D., Statistician, DODP (pre-mtg)
Roswitha Kelly, M.S., Statistician
Dotti Pease for Sheila Ryan, Project Manager, DODP

SPONSOR: Mitchall Clark, VP Reg. Affairs, American BioScience, Inc. (ABI)
Patrick Soon Shiong, M.D., CEO, ABI
Michael Hawkins, M.D., Medical Dir., ABI
N. Dat, Ph.D., VP Clinical Operations, ABI
Neil Desai, Ph.D., VP Res. and Dev., ABI
Paul Bhar, Statistician

MEETING OBJECTIVES: Discuss sponsor's questions re: upcoming NDA clinical submission

BACKGROUND: The pharmacology/toxicology portion of this rolling NDA was submitted on June 30, 2003; the chemistry/manufacturing/controls on August 21, 2003. This meeting was scheduled to discuss the clinical submission scheduled for December/January.

FDA's responses to the questions were faxed to the sponsor on November 20. Italics indicate the discussion at the meeting.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Clinical

1) Analysis of the efficacy data from the Phase 3 randomized clinical study (Protocol CA012-0, ATTACHMENT 3) was performed in accordance with the Statistical Analysis Plan (SAP) provided in ATTACHMENT 4. The results for target lesion response rates and time to tumor progression showed statistical non-inferiority, as well as superiority of ABRAXANE compared to Taxol (ATTACHMENT 5,Table 6, 7, 8, and 11.) Assuming FDA concurs with the data following its review of the NDA, please confirm that we have achieved our efficacy endpoint for response.

   FDA Response: This will be a review issue. The following concerns should be noted :

   The basis for review is a single unblinded trial evaluating response rate, a surrogate endpoint for efficacy. For a single trial to be the primary basis of approval, results must be robust and compelling even after a rigorous examination of trial design, trial conduct, and data quality.

   We note that the response rate observed in the Taxol arm (11.1% with CI 7-15.22) is significantly lower than that expected based on prior clinical experience (30%). Therefore, the characteristics of the patient population in relation to the proposed indication will need to be carefully evaluated, and the study arms need to be carefully evaluated to assure that randomization was successful in balancing important prognostic factors.

   We also note that approximately 38% of patients had an initial histology reported as 'other'. Please provide more detail regarding the histologic diagnosis for these patients as part of the NDA submission.

   Sponsor - we will address these in the submission. The histologies were primarily infiltrating and ductal carcinoma and adenocarcinoma. Reconciled target lesion response rate is not a relevant statistic when compared to other studies in the literature.
   Sponsor - The investigator overall responses were comparable to that reported in the literature (see attached table).

   FDA - we would like an analysis of the prognostic factors by country.

2) The clinical database was locked in September 2003. Only limited survival data is therefore available. ABI proposes to update the proposed labeling with survival data during the labeling review. Please concur.

   FDA Response: Evaluation of survival data will be a component of the review process.

We agree that survival data should be updated during the review process.

3) Provided in ATTACHMENT 5, Section 3 is an overall analysis of safety data from the Phase III clinical study (Protocol CA012-0). Assuming FDA agrees with the data following its review of the NDA, please concur that based on the above considerations, the results meet the requirement to demonstrate that ABRAXANE is not more toxic than Taxol.

FDA Response: This is a review issue, but FDA does not generally make generalizations about one drug being more or less toxic than another. The toxicities observed in the individual study arms will be described.

4) Sensory peripheral neuropathy is a well recognized, cumulative toxicity to taxanes, as described in the Taxol Package Insert (ATTACHMENT 6) and the results from CALGB study 9342 (ATTACHMENT 7), and Mamounis et. al. (ATTACHMENT 8). While the incidence of sensory peripheral neuropathy was higher in the Abraxane arm, the toxicity was qualitatively similar to that seen with Taxol. Sensory peripheral neuropathy was safely managed without the development of grade 4 toxicity using standard treatment guidelines (i.e. dose interruption and reduction). Based on these results, we propose t

Please concur.

FDA Response: FDA comments on the specifics of labeling will be determined after detailed review of the data.

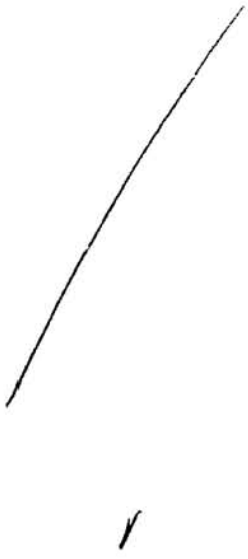
5) ABI believes that it has achieved its protocol- defined endpoints, and that the results demonstrate a meaningful benefit of ABRAXANE over Taxol. Further, although the phase 3 study did not compare ABRAXANE with Taxotere® we believe that the safety profile is improved over that described in Taxotere's package insert (ATTACHMENT 9).

Do the results justify an accelerated review of the NDA for ABRAXANE when filed?

Further, does the Agency have resources and time available to initiate the review of Items 4 and 5 of the NDA which were pre-submitted along with user fees in June 2003? The sponsor anticipates that the full NDA will be submitted in Late January/early February 2004.

FDA Response: The decision regarding standard versus priority review will be made at the time of NDA submission.

6) We believe that the results of the phase 3 clinical study described in this package of information, along with results from two previously reported phase 2 studies of ABRAXANE support the conclusion that ABRAXANE will provide a benefit compared to existing second-line treatments for MBC. Based on the pre-planned statistical analysis (a copy of the statistical analysis plan is provided in ATTACHMENT 4) ABI has demonstrated superiority of ABRAXANE over Taxol in response rates for first and second-line treatment of MBC. Therefore,



7) At a March 19, 2003 meeting with the FDA, the Division requested that we provide tumor images from patients who responded to treatment in the phase 3 study (protocol CA012-0). Provided in ATTACHMENT 11 is a compact disc containing sample images from three responding patients, along with print-outs of the images. Each file name identifies the site, and patient number. Each image is bookmarked for its week of assessment.

   a. Please advise us if these images are acceptable with regard to image quality and image identification.
   b. In which section of the NDA do you wish us to provide these images?
   c. Are the file names and bookmarks acceptable to facilitate navigation?

FDA Response: Image quality and image identification appear to be appropriate.

FDA needs to verify the response rates on both study arms. Because this is a comparative study, this will involve evaluating not only responders (especially in the ABRAXANE arm) but also the non-responders (especially in the TAXOL arm). This may require submission of all radiologic studies for all patients. We suggest additional discussions between ABI and FDA regarding how FDA can verify your response rate findings.

Labeling

1) ABI understands that proposed proprietary and non-proprietary names undergo a formal evaluation by the Agency at the time of NDA submission. However, the sponsor wishes to introduce its preferred names in scientific communications prior to the launch of the drug product. Within the limits of this communication with the Division, and understanding that any opinion offered by the Agency is not binding at this time, can the Agency offer informal comments on the acceptability of:

ABRAXANE™ as the trade name, and

/

Will the Agency accept a formal approach for a review of the acceptability of the names prior to the filing of the full NDA?

FDA Response: An initial review of the name can be done now to provide feedback of generic and tradename prior to filing the full NDA. We have forwarded this consult to our tradename review group. Please note that this review is not final and we can not give a final answer on acceptability of names at this time. An additional final tradename review will be done 90 days prior to the action date of the NDA. Use of your tradename publicly at this point may result in confusion should you have to change it before marketing.

Pharmacokinetics

1) The phase 3 study required that 12 patients receiving ABRAXANE be evaluated for blood, urine, and fecal levels of paclitaxel and metabolites. The blood and urine assay methods for paclitaxel and metabolites were fully validated. Feces sample collection was complicated by a number of patients suffering from constipation. In addition, despite reasonable efforts on the part of ABI, it was not practical to fully validate the fecal assay methods for paclitaxel as well as metabolites due to limited availability of standards. This resulted in a large variation in the percent of total dose recovered from feces.

For completeness we propose to present blood, urine, and fecal data in the NDA, but will provide an explanation for why we believe the fecal assay data are unreliable. We will report only blood and urine data in the package insert.

Please concur.

FDA Response: Inclusion in the NDA your explanation for why you believe that the fecal assay data are unreliable is acceptable. We expect fully validated assay methods for all biological samples as well as data from these samples (blood, urine, and feces) in the NDA. All data from blood, urine and feces should be included in the package insert.

The Agency expects that the disposition of paclitaxel from ABRAXANE is completely evaluated and reported in the NDA submission.

Sponsor - we can not do a fecal assay/validation.

FDA - present what you did in the application and your proposal for labeling. We would also review and comment on a pre-submission proposal of how to address this. This issue will not hold up approval.

Chemistry, Manufacturing, and Controls

1) ABRAXANE is a lyophilized form of nanoparticles of paclitaxel stabilized with human albumin. American BioScience is preparing to qualify an alternate supplier of Human Albumin. We also wish to qualify a source of paclitaxel which is supplied by the current manufacturer —, but which is — — (Taxus media) as is the current procedure. The Human Albumin — will be sourced from — and is a FDA approved product. The paclitaxel is from the same plant species as the current material, and has been demonstrated analytically to be equivalent to material from —.

Due to the expense of the raw materials, and their known chemical equivalence with the currently used materials, ABI is proposing the matrix described in ATTACHMENT 12 for the drug product stability lots necessary to support a supplement to change the source/supplier of raw materials. Please confirm that the matrix is adequate for the manufacture of stability lots to support a supplemental NDA for the approval of the alternate supplier of Human Albumin, and the alternate source of paclitaxel. If the Agency does not agree with the proposed matrix, please provide guidance on the requirements for the stability batches to support the supplemental application.

FDA Response: The Division considers the proposed stability protocol inadequate. As changes of sources of the paclitaxel and the human albumin are being introduced, the sponsor should provide long-term storage data on drug product batches described below, following the proposed testing schedule specified in

Attachment 12:

No. of Batches	Paclitaxel Source	Human Albumin Source
2	—	—
3	—	—

For accelerated testing, — data of — or each of — — should be provided.

Additionally, Data to demonstrate the equivalency between the current source of paclitaxel and the alternate source of paclitaxel should be submitted for review.

Additional comment on Drug Product Validation (stability) Batches:

Please specify the sources of paclitaxel and human albumin that will be used to manufacture the drug product validation (stability) batches.

Sponsor - Both will be the current source —and albumin supplier.

2) Due to the limited availability of paclitaxel —, and the known stability of Abraxane, we propose to file the NDA supplement described above immediately upon approval of the original NDA, but with not less than six months of stability data.

Please concur.

FDA Response: No, — data, at a minimum, should be submitted for the NDA supplement review.

For the material available from the current source —, how long do you expect this material to last?

ADDITIONAL FDA COMMENTS:

PHARMACOLOGY/TOXICOLOGY

You have proposed a change in the biosource material from — *Taxus Media* and a change in the human serum albumin source from — You will need to demonstrate adequate assurance of equivalency for these changes, which may be based on a pre-clinical GLP bridging study in a single species. Since peripheral neurotoxicity is accumulative, a multiple cycle study would be preferred.

Sponsor - will do bridging study.

ACTION ITEMS:

Sponsor will include in the clinical pharmacology submission an explanation of what was done to develop a fecal assay and why it did not work.
Sponsor will submit a proposal for expanded access before beginning such a program.
A bridging study will be provided when the biosource is changed.

Dotti Pease
Chief, Project Management Staff

Concurrence Chair: signed off via email/12-1-03
Patricia Cortazar, M.D.
Medical Officer

Attachment: Sponsor presentation (4 pages)

Taxol (175 mg/m^2, q3wk) Overall Response Rates (ORR) Pharma studies

STUDY	Sympto-matic PS>0	Visceral disease	Prior Adjuvant	Prior Metastatic	Prior Anthra-cycline	Tumor response Criteria	ORR (95% CI)	TTP (months
CA012 Ph III ABI-007 vs Tax N=225	64	81%	43%	60%	78%	RECIST	19% (14-24)	3.7
BMS TAXOL PI 135 vs 175 N=236	60%	72%	61%	70%	67%	WHO	28% (20-36)	4.2
Aventis TAX311 Taxotere vs Tax N=222	-	75%	68%	53%	98%	WHO	25% (19-31)	3.6
CA012 Ph III ABI-007 vs Tax N=89	-	70%	-	0	-	RECIST	27% (18-36)	3.7
Lilly Gem/Tax vs Tax N=262	-	73%	-	0	-	WHO	25.6% (20-31)	3.5

CA012 Study Results

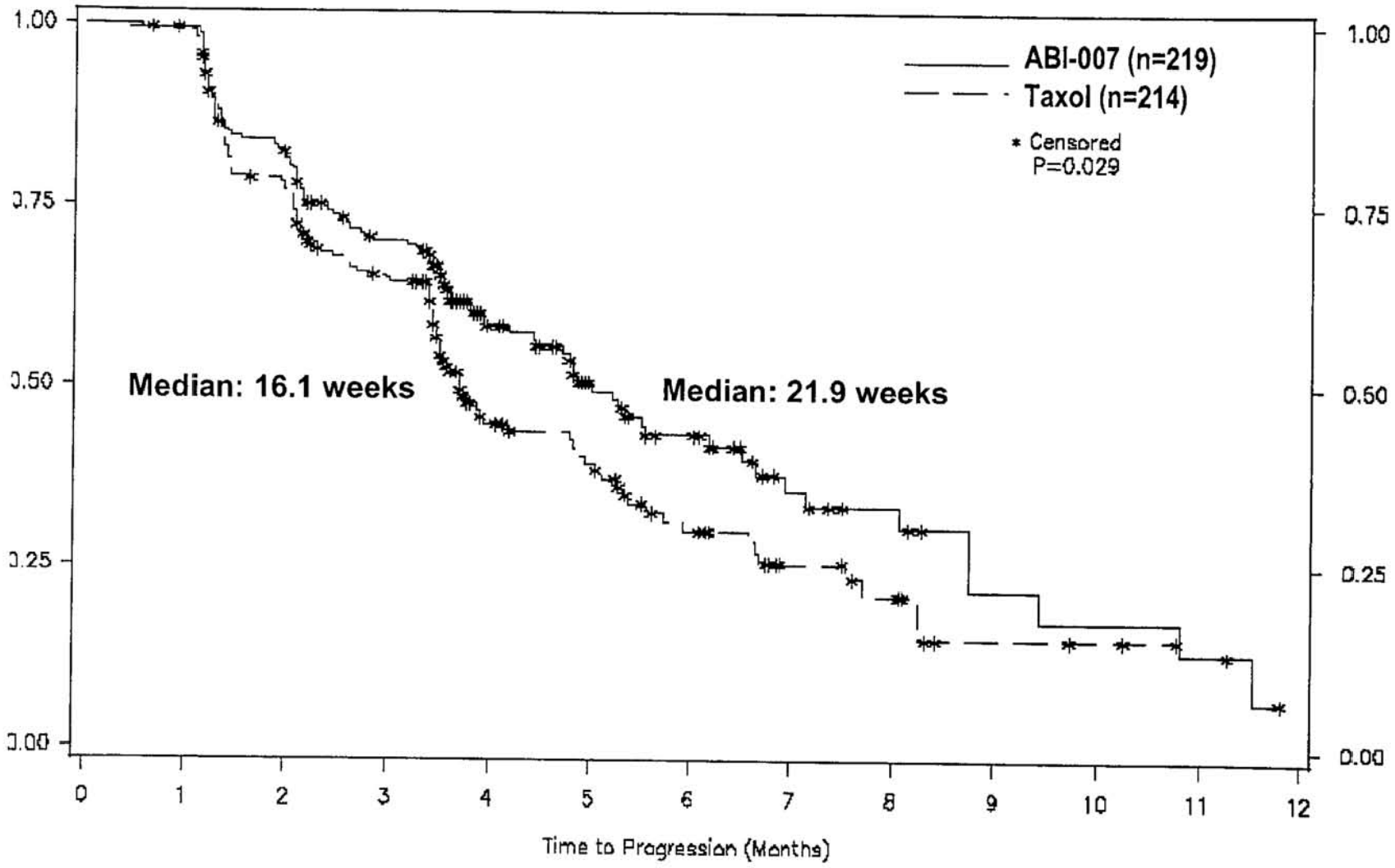
In this Phase III trial ABI-007 had significant advantages over Taxol as treatment for metastatic breast cancer

- **30 min infusion with no prophylactic steroid premedication**
- **No severe hypersensitivity reactions**
- **Higher Overall Response Rate and Longer Time to Tumor Progression**
- **Greater Antitumor Activity whether analyzed using Investigator, Independent radiology review or Reconciled data sets**
  - **All treated patients**
  - **First line patients**
  - **Patients with prior anthracycline exposure**
- **Less neutropenia despite higher dose of paclitaxel**
- **More rapid recovery makes peripheral neuropathy easier to manage**

Investigator Response Rates (ORR) for CA012

	ABI-007	TAXOL	P value
All Patients	n=229 33% (27-39)	N=225 19% (14-24)	<0.001
Anthracycline exposed (Metastatic)	N=115 27% (19-35)	N=130 14% (8-20)	0.011
First Line	N=97 42% (32-52)	N=89 27% (18-36)	0.029
Anthracycline exposed (Adj or Meta)	N=176 34% (27-41)	N=175 18% (13-24)	0.002

Time to Tumor Progression



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/s/

Patricia Cortazar
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_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

MEETING MINUTES

MEETING DATE: March 19, 2003 **TIME:** 9:30 am **LOCATION:** WOC2/R5006

IND: 55,974 **Meeting Request Submission Date:** 1-16-03 (sn 206)
Briefing Document Submission Date: 2-18-03 (sn 217)

DRUG: ABI-007

SPONSOR: American BioScience, Inc.

TYPE OF MEETING:

Pre-NDA meeting

FDA PARTICIPANTS:

Richard Pazdur, M.D.	-	Director, Division of Oncology Drug Products (DODP)
Grant Williams, M.D.	-	Deputy Director, DODP
Lilia Talarico, M.D.	-	Associate Director, DODP
Ramzi Dagher, M.D.	-	Clinical Team Leader, DODP
Patricia Cortazar, M.D.	-	Clinical Reviewer, DODP
Rebecca Wood, Ph.D.	-	Chemistry Team Leader, DODP
Yung-Ao Hseih, Ph.D.	-	Chemistry Reviewer, DODP
John Leighton, Ph.D.	-	Pharmacology Team Leader, DODP
Margaret Brower, Ph.D.	-	Pharmacology Reviewer, DODP
Atik Rahman, Ph.D.	-	Clin Pharm and Biopharm Team Leader, DODP
Sophia Abraham, Ph.D.	-	Clin Pharm and Biopharm Reviewer, DODP
Rajeshwari Sridhara, Ph.D.	-	Statistics Reviewer, DODP
Caroline Currier, Ph.D.	-	Div of Scientific Investigation, DODP
Dotti Pease	-	Chief, Project Management Staff, DODP
Sheila Ryan, Pharm.D.	-	Project Manager, DODP

INDUSTRY PARTICIPANTS:

Patrick Soon Shiong, M.D.	-	Chief Executive Officer, ABI
Michael Hawkins, M.D.	-	Chief Medical Officer, ABI
Mitchell Clark	-	VP, Regulatory Affairs, ABI
Neil Desai, Ph.D.	-	VP, Research, ABI
Nguyen Dat, Ph.D.	-	VP, Clinical Research, ABI
Aaron Van Etten	-	Medical Writer
Rajesh Kapoor, Ph.D.	-	VP, QA/QC, American Pharmaceutical Partners
Lynn Samuel	-	Project Manager, APP
/	-	Consultant Statistician
	-	Consultant Pharmacokineticist

MEETING OBJECTIVE:

To discuss and receive guidance prior to submitting NDA.

BACKGROUND:

ABI-007 is nanoparticle cremophor-free formulation of paclitaxel. As such, it is considered a 505(b)(2) application since FDA will rely, in some part, on the approved Taxol paclitaxel application; however, the clinical studies are only being done in metastatic breast cancer and this will be the only ABI-007 indication. Meetings were previously held with the sponsor on February 5, February 6, and May 3, 2001. Sponsor proposes to submit their NDA electronically as a Rolling Submission with the CMC/pre-clinical sections coming in the 2nd quarter of 2003 and the clinical/biopharmaceutics portions in the 3rd quarter. This meeting was scheduled to address specific cross-discipline questions from the sponsor. FDA responses were faxed to the sponsor on 3-12-03 and sponsor elected to have the face-to-face meeting for clarification of several of the responses. Meeting discussion is indicated by italics.

COMMENTS FOR DISCUSSION AND FDA RESPONSES:

1. The sponsor will provide the following information as hard copy documents in addition to electronic PDF files in the electronic submission.

   Certifications bearing Original signature
   cGMP certificates (Originals)
   Debarment Certificates (Original)
   Field Copy Certification (Originals)
   OVI Certifications (Originals)
   Environmental Assessment Waiver (Original)
   Patent Certification (Originals)
   Patent Information (Originals)
   User Fee Cover Sheet (Originals)
   Financial Disclosures (Copies, originals to be maintained by ABI)
   Form FDA 356h

   Does the FDA agree that paper copies of other sections of the application (e.g. analytical methods) will not be required?

   FDA Response: Yes. Also, we request 4 paper copies of the clinical study report (without appendices) and pivotal and supporting pre-clinical study text (not including detailed tables or individual data).

2. Financial disclosures will be provided for principle and sub-investigators for the following covered completed clinical study:

   CA012 (Controlled Phase III comparative study of ABI-007 and Taxol)

   Financial Disclosures will not be provided in the submission for all other phase I and II studies because, under the Agency's definition of covered clinical studies, they generally do not include phase I tolerance studies or pharmacokinetics studies, most clinical pharmacology studies, large open label safety studies conducted at multiple sites, treatment protocols and parallel track protocols.

   ABI proposes therefore that the following studies are not 'covered clinical studies' under the

Agency's definition:
DM97-123 (Phase I tolerance and pharmacokinetics study).
CA005-0 (ongoing Phase I tolerance and pharmacokinetics study in patients with solid tumors – weekly dosing schedule)
CA002-0 (open label, Phase II safety and initial efficacy study in metastatic breast cancer)
CA002-0LD (open label, Phase II safety and initial efficacy study in metastatic breast cancer)
CA013-0 (Weekly dosing, Phase II safety and initial efficacy study in patients who have failed taxane treatment for metastatic breast cancer)

Does the FDA agree that Financial Disclosures for investigators participating in the studies listed above will not be required?

FDA Response: No; you will need financial disclosure information for studies CA002-0 and CA002-OLD. You may wish to contact Lee Ripper (301, 827-5920), Associate Director for Regulatory Affairs, Office of Drug Evaluation II, for confirmation.

3. Provided in Attachment 3 is an overview of the status of all open and closed clinical studies of ABI-007.

Data Analysis Plans

On December 9, 2002, ABI submitted the Statistical Analysis Plan (SAP) (Serial #198) for the analysis of the safety and efficacy data from Phase III protocol CA012-0. A copy of Protocol CA012-0 is provided in Attachment 4. A copy of the SAP is provided in Attachment 5.

Provided in Attachments 6 and 7 are the SAPs for Phase II clinical studies CA002-0LD and CA002-0 respectively.

Provided in Attachments 8 and 9 are outlines for the ISS and ISE. These plans have been written following the principles agreed with the FDA during meetings and exchange of correspondence in 2001.

Does the FDA agree with the plans for analysis and data presentation described in these documents?

FDA Response: We have previously conveyed statistical comments to Protocol CA012-0 Statistical Analysis Plan. Outlines for ISS and ISE appear to be adequate. As previously discussed with the Sponsor, an essential element of the 505(b)(2) submission is that ABI007 study population should be similar to the one for Taxol's approved metastatic breast cancer indication. Therefore, it is important to document that the patient population from the Phase 3 trial CA012-0 have failed combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy. Previous chemotherapy should have included an anthracycline unless contraindicated. The NDA submission should include the following information:

- **Detailed previous chemotherapy for metastatic breast cancer**
- **Detailed previous chemotherapy for adjuvant breast cancer**

- **If no previous therapy for metastatic breast cancer include data on time to relapse after adjuvant therapy or if patient relapse while receiving adjuvant chemotherapy.**
- **If patients did not have previous anthracycline, indicate reason why not.**

Sponsor wanted clarification that 100 patients/arm on anthracyclines would be adequate.

FDA's response was that it probably would be adequate, assuming the two patient populations were similar enough. We agreed that the asymptotic confindence interval (CI) was likely to be valid for pA/pT given the sample size of 460 patients.

4. Provided in the Statistical Analysis Plans are examples of tables and listings to support the application. Does the FDA concur with our choice and presentation of the data?

   FDA Response: Listings appear to be adequate. However, tables should include Taxol arm. It will be helpful if we can take a look at a sample of the data sets before the NDA submission. Submission of all primary data sets in a usable format is a critical element of the electronic submission.

5. Provided is a listing of the clinical studies conducted to date, and our proposal for the order of presentation in Item 8, ClinStat. All study reports will be presented in the format described in ICH (E2B (M)) Harmonized Tripartite Guideline (E3) - Structure and Content of Clinical Study Reports. Synopses will be written as described in Guidance for Industry, Submission of Abbreviated Reports and Synopses in Support of Marketing Applications (August 1999). Does the FDA concur with the proposed order of presentation?

   FDA Response: Order of presentation is acceptable.

6. Assuming that the order and means (full study reports and synopses) of reporting the clinical study data as described above are acceptable, ABI proposes to provide the information described in Attachment 10 (regarding safety and efficacy studies) and Attachment 11 (regarding human pharmacokinetics studies) of this information package to support each study. Does the FDA agree with this proposal?

   FDA Response: Yes.

7. ABI proposes not to include a folder for 'patient profiles' in the ClinStat folder. The individual patient data that are usually contained in this folder will be available in the data sets in Item 11 (Case Report Tabulations) for the completed studies and will be available as SAS transport files for retrieval by the reviewer as well as in various data listings of the study reports. Creation of 'patient profiles' will require a considerable use of resources to present information, which as described, is easily accessible within the electronic submission. Does the FDA agree with this proposal?

   FDA Response: Yes.

8. One phase I/II clinical study (DM97-123), two supportive phase II studies (CA002, CA002-0LD), and one controlled phase III clinical study (CA012-0) will be included in the NDA as direct support

of submission. Are Case Report Forms required for any patients who died or dropped out of study because of serious adverse events other than in studies DM97-123, CA002, CA002-0LD, and CA012-0?

FDA Response: At the time of the NDA submission you do not need to send CRFs from additional studies. However, you should be ready to submit additional information including CRFs from the other studies if during the NDA review we find it necessary.

9. Will additional CRFs be required for patients in the Phase III Study CA012-0) to support the review process other than those who have died or dropped-out of the study because of serious adverse events?

FDA Response: Please submit narratives, CRFs and CRTs from:

- **All patients who died during the study or within 30 days after the last dose of study drug or whose death was related to study drug. deaths and adverse events for our review.**
- **All patients with serious adverse events during the study or within 30 days after the last dose, regardless of relationship to study drug.**
- **Patients withdrawn from the study due to adverse events**

Please submit CRFs from all responders.

We would like to discuss with you the possibility of obtaining selected x-rays to aid us in evaluating response.

FDA clarified that we would probably like to see the x-rays for responders in order to confirm response rate. Sponsor has them available digitally in the same format as the Xeloda x-rays were submitted.

10. All case report domains will be provided as SAS data sets. Is it sufficient to provide SAS data sets that cover all data presented in the data listings proposed in the SAPs (Attachments 5, 6, and 7)?

FDA Response: Yes. Please include SAS raw and analysis data sets.

11. The efficacy assessment performed by the investigators will be confirmed by an independent group, with the readers being blinded to study drug treatment. A detailed summary of the methodology for lesion response analysis is provided in Attachment 12 of this information package. Does the Agency have any comments on the planned methodology for the evaluation of lesion response?

FDA Response: Response rate should include only complete and partial response in both the ABI-007 and Taxol treated arms.

12. Safety data will be evaluated in a similar manner to that used by Bristol Myers Squibb (BMS) to support their approval of Taxol for the treatment of metastatic breast cancer. Specifically, data from each treatment arm from the first cycle and the worst cycle of chemotherapy for each type of toxicity will be compared. Cochran-Mantel-Haenszel (CMH) Test will be used to compare AE severity grade of relevant AEs. Toxicities that are statistically significantly different will be reviewed for clinical relevance and significance.

be a clinical judgment based on these comparative analyses and clinical significance of the adverse events. A summary of the methodology for safety evaluation is provided in Attachment 8 of this meeting package. The method of safety data collection is described in Attachment 13. Does the Agency have any comments on the proposed analysis of safety data?

FDA Response: The proposed analysis provided in Attachment 8 and 13 appears to be acceptable.

13. ABI intends to file the NDA with — , of accelerated stability data (40°C±2°C/75%±5%RH) on — :ots of finished product. In addition, supportive data on batches of drug product used in clinical lots will also be provided. These data, which will also be included in the application, show that the product is stable for up to — when stored at room temperature. We anticipate, based on available data that the product will be stable for in excess of — . Does the FDA concur that the initial NDA may be filed with — of accelerated and room temperature stability data?

FDA Response: Yes, the initial NDA may be filed with — of accelerated and room temperature stability data. However, we wish to remind you that the shelf life is established based on the quality and quantity of the stability data of the drug product under the recommended long-term storage conditions. The batches should be of the same formulation and dosage form in the container/closure system proposed for marketing. — batches should be at least pilot scale (Please refer to Guideline for Industry: Stability Testing of New Drug Substances and Products, ICH – Q1A, September, 1994).

14. The labeling will recommend that reconstituted ABI-007 be used immediately. However, we have generated data which demonstrates that the product remains stable for up to 8 hours after reconstitution with 0.9% Sodium Chloride Injection, USP. In order to provide sufficient time for use should there be an unavoidable delay in administering the drug to the patient, we propose to also recommend that if it is not possible to use immediately, the reconstituted drug product may be stored in the refrigerator at 2 – 8°C for up to 8 hours. Is this an acceptable instruction when supported by data showing physical and chemical stability under these conditions?

FDA Response: Yes.

15. May ABI file the CMC Item (Item 4) in advance of the final complete Application? It is anticipated that Item 4, containing — of accelerated stability data will be complete in April/May 2003.

FDA Response: Yes, we accept pre-submissions. Whether the pre-submission will be reviewed depends on our workloads and time available.

16. As recommended by the Agency in a meeting held in February 2001, ABI is seeking approval for only one commercial supplier of active pharmaceutical ingredient (— . Chemistry, Manufacturing, and Controls information will be provided by reference to — Type II DMF for paclitaxel. During early clinical development (up to phase II clinical trials), two other manufacturers — , supplied ABI with paclitaxel. A table identifying the API source used in each clinical trial to be presented in the NDA is provided in Attachment 14. ABI proposes to identify these suppliers (Names and Addresses will be provided) in the NDA, and will provide comparative test data for the API and the finished product lots used in all pre-clinical and clinical trials. These data show that the materials are of comparable quality. Will further information on the suppliers and drug substance from — be required in the NDA?

FDA Response: (Pharm/Tox) In order to justify your statement of biosource comparability, please provide comparative individual impurity and degradation specification for the — — and natural biosource paclitaxel used in pivotal and supportive clinical and pre-clinical studies with ABI-007 from — suppliers. In addition, please provide specification comparison of ABI-007 and Taxol for pivotal and supportive studies, as well as a list of the biosource used for all pre-clinical and clinical studies. Please refer to our concerns regarding comparability in meetings and documentation from 2001 and 2002 (facsimile of 7/29/02).
APP/ABI data may be acceptable if these data specifically address the items listed in response to this question, namely:

a. ***comparative individual impurity specification for — and natural biosourse paclitaxel from differing suppliers***
b. ***Biosourse used for all preclinical and clinical studies***

(Chemistry) Paclitaxel batches obtained from different sources exhibit somewhat different impurity profiles — — — . We will not be able to comment on this question before information and data supporting the equivalency of paclitaxel batches from — (natural source), — are submitted and reviewed.

Sponsor requested confirmation that this could be satisfied by providing specifications and test data for ABI-007 and certificates of analysis for Taxol. ***FDA concurred with this clarification:***

The impurity profie of paclitaxel isolated from one source is considered equivalent to the paclitaxel obtained from another source when the test data demonstrate that:

a. ***No new — impurities are observed at or above the threshold. This is defined as 0.1% for qualification of impurities as described in the ICH guidance Q3A.***
b. ***Existing impurities, including residual solvents, are within the stated limits or (if not specified) are at or below the upper statistical limit of historical data.***
c. ***Total impurities are within the stated limits or (if not specified) are at or below the upper statistical limit of historical data.***

17. Provided in Attachment 14 is a brief overview of pertinent information relevant to the understanding of important aspects of the chemistry, manufacturing, and control of ABI-007. Also provided in Attachment 15 is a detailed list of the specific documents to be included in the NDA. Does the Agency have any concerns or advice relative to the specific content of the CMC section of the NDA?

FDA Response: We will not be able to comment on content until detailed information and data are submitted and reviewed.

18. Albumin Human, USP used in the manufacture of the ABI-007 drug product is commercially available finished product manufactured by — Although the albumin is used as an excipient, it was discussed in our February 2001 end of phase II with the Agency that more technical information will be required in the NDA than is typically used to support the use of a 'standard' excipient

ABI will therefore provide full chemistry, manufacturing, and controls information in the NDA by providing information on the source plasma obtained from — Master file, and by permission from — to cross-refer to their approved BLA for Albumin Human, USP. Test data from the drug manufacturer, APP will also be provided.

Will this information will suffice to support the NDA for ABI-007? If not, please advise what additional information will be required.

FDA Response: (Pharm/Tox) Please indicate ratios of Human Albumin to paclitaxel in non-clinical and clinical studies by study number.

(Chemistry) Yes. This information supports the use of the Albumin Human, USP in the proposed formulation of the drug product.

19. An outline of the overall content and organization of the 505(b)(2) NDA is summarized in Attachment 15. Does the Agency have any comments on the proposed content of the submission?

FDA Response: (Clinical) The proposed NDA format and content provided in Attachment 15 appear to be acceptable.

(Bioph.) The contents of the Human Pharmacology/Bioavailability/Bioequivalency section (Studies DM97-123 and CA012-0) appears adequate, however, you also should address the following issues in your anticipated NDA submission.

a. **Pharmacokinetic information on the use of ABI-007 in the target patient population (patients with metastatic breast cancer) at the proposed labeling dosing regimen (260 mg/m^2 every 3 weeks). Please confirm that you will submit the pharmacokinetic study report from your Phase 3 Study CA012-0 in the NDA.** ***Sponsor confirmed this.***
b. **Comparative pharmacokinetic information on paclitaxel administered as ABI-007 and Taxol® from your proposed Study CA008-0. We recommend that you submit Study CA008-0 in your NDA.**

   This study was not performed as FDA had told ABI that it would not be required in the 5-3-01 meeting.

   FDA had stated that the study might not be required for filing, but the study was still recommended. FDA explained that this study would support much of the clinical pharmacology section of the labeling; if the pk of ABI-007 is very similar to that of Taxol, then the labeling could be borrowed from the Taxol package insert. If the pk is not similar, additional studies might be indicated for ABI-007. This study should be in at least 15 patients and may be a parallel or crossover design of 260 mg or 175 mg ABI-007 (30 minute infusion) vs. 175 mg Taxol (3 hours infusion). Diagnosis for the patients is not an issue. The source for the data can be taken from plasma samples alone.

c. **Information on the use of ABI-007 in special populations such as elderly, renally impaired patients, and hepatically impaired patients.** *Sponsor is not planning to do these special population studies but to use the wording from Taxol's labeling.* ***FDA concurred with the qualification that the pk study described above demonstrated that ABI-007 and Taxol have similar pharmacokinetics. For elderly patients, FDA concurred that data***

obtained from Phase 3 trials with 60 patients over 65 years of age would be sufficient. FDA wants efficacy and toxicity analysis in these patients.

d. Information on possible drug-drug interactions between ABI-007 and commonly administered co-mediations in patients with metastatic breast cancer. ***Same sponsor clarification as "c."***

20. How does the Agency wish ABI to provide the word processing version of the labeling text? Please advise us of the word processing format and version currently being used by the Center.

FDA Response: We are currently using Word 97. Proposed draft labeling should be submitted in Word as well as PDF for the electronic submission. You should provide a statement that these two versions are exactly the same.

21. American BioScience, Inc has conducted phase I, II, and III clinical studies to support the safety and efficacy of ABI-007, and to define the pharmacokinetics of the product. There will therefore be extensive differences in text between the labeling for ABI-007 and that of the Reference Listed Drug. Does the FDA agree that a side-by-side comparison with the reference listed drug (Taxol) labeling will not be required?

FDA Response: (Clinical/Bioph) We strongly recommend you have a side by side comparison of ABI 007 and Taxol for efficacy and safety.

22. Because paclitaxel is not a new drug substance, and because it is a potent agent for the treatment of non-hematological cancers, it is not appropriate or necessary to conduct human pharmacology and pharmacokinetics studies in volunteers. ABI has however performed pharmacokinetics studies in patients enrolled into Phase I/II (DM97-123) and a Phase III (CA012-0) safety and/or safety and efficacy studies. In accordance with the guideline for providing regulatory submissions in electronic format, the Summary of Human Pharmacology and Bioavailability/bioequivalence, Assays, and Publications will be included in the hpbio folder. However, rather than providing the separate study reports in this folder we will provide hyperlinks to the full clinical study reports in Item 8 which contain the individual reports of the pharmacokinetics portions of these studies. Does the FDA agree with this proposal?

FDA Response: This proposal is acceptable.

23. It is anticipated that Item 5 will be complete in April 2003. Provided in Attachment 15 is an overview of the proposed organization of the NDA, including Item 5. Also provided, in Attachment 16 is a table summarizing in more detail the studies that will be presented in the non-clinical section (Item 5) of the submission. May ABI file the Non-Clinical Item (Item 5) in advance of the final complete application? Does the Agency have any specific requirements or questions concerning this Item which may assist in the review of the application?

FDA Response: (Clin.) Yes, you can pre-submit Item 5. We currently do not have any questions concerning this Item. *Sponsor confirmed that Study NP0011106 will be included in the NDA.*

(Pharm/Tox) In 2001 and 2002, we indicated that pharmacokinetic equivalence should be demonstrated in animals between paclitaxel sources, and if pharmacokinetic equivalence cannot be demonstrated, a pre-clinical bridging study would be needed in rodents comparing the natural source paclitaxel proposed for the NDA with th[redacted] sources. Your listing of ongoing pre-clinical studies, submitted in April, 2002 (serial #130) included Protocol #NP001106: Blood kinetics study on three formulations of ABI-007 following a single intravenous dose in the rat at 50 mg/kg. This study does not appear to be included in your overview of non-clinical studies included in Attachment 16 of the current submission. In addition, a pre-clinical bridging study does not appear to have been conducted. Please indicate if these studies have been completed. *Sponsor will be conducting the bioequivalence study in rats to demonstrate the BE of drug product from each paclitaxel source.*

The non-clinical section of the NDA may be filed in advance of the complete application; *however, the section should be complete when submitted, i.e., all study reports included.*

24. Although the content and format of the proposed NDA will comply with relevant guidelines for an e-NDA, we would like to format the Item 5 summary in the format described in the Common Technical Document Guidelines. General feedback from the FDA suggests that this format is well received by reviewers and is preferred to the format described in the 1987 Guidelines for the Format and Content of the Non-clinical Pharmacology/Toxicology Section of an Application. Does the Agency concur that the CTD format may be used for the summary document?

    FDA Response: Yes, the CTD format may be used.

ACTION ITEMS:

1. Sponsor will submit a time table for rolling submissions for FDA concurrence.
2. Sponsor will consider FDA's comments when preparing the NDA.

The meeting concluded at 10:45 am.

(see appended electronic signature page)

Sheila Ryan
Project Manager

(see appended electronic signature page)

Concurrence chair: _____

Patricia Cortazar, M.D.
Medical Officer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ramzi Dagher
4/16/03 09:26:04 AM