CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-660

CORRESPONDENCE

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc.	**From:**	Sheila Ryan, Pharm.D.
Fax:	310-998-8553	**Fax:**	(301) 827-4590
Phone:	310-883-3141	**Phone:**	(301) 594-5779
Pages (including cover):	1	**Date:**	January 4, 2005
Re:	NDA 21-660 Abraxane: Request for commitment to Phase 4 commitments		

■ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

Mitch,

The Division requests American BioScience, Inc. to commit to the following Phase 4 commitment requests. Please provide an estimated timeline for completion of commitment #1 and review the suggested protocol submission, study start, and final report submission dates for commitment #2.

1. Survival data and analysis results should be submitted from randomized study CA012-0 when 80% of the patients have died.

2. You should evaluate Abraxane safety and pharmacokinetics in subjects with hepatic impairment, to allow the determination of dosing adjustment for this population.

   Protocol Submission: April 2005
   Study Start: November/December 2005
   Final Report Submission: December 2006

Please provide your commitment in writing via facsimile as soon as possible.

Please call should you have any questions.

American BioScience, Inc.

January 4, 2005

Attention: Dr. Sheila Ryan
Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901 Ammendale Road, Unit B
Beltsville, MD 20705
Tel: (301) 210 2885
Fax: (301) 594 0498

Via facsimile and
Federal Express

New Drug Application

NDA# 21-660

Abraxane™ for Injectable Suspension

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

Amendment to a Pending Application:

Response to FDA Request for Information

Dear Dr. Ryan,

Reference is made to our pending New Drug Application for Abraxane™, (NDA 21-660). Reference is also made to a facsimile from Dr. Ryan dated January 4, 2005 requesting American BioScience to commit to two Phase 4 commitment requests. The Agency requested an estimated timeline for completion of commitment #1 and to review and commit to the protocol submission, study start, and final report submission dates for commitment #2. The Agency's Phase 4 commitment requests are detailed below in bold text and American BioScience's response follows.

1. **Survival data and analysis results should be submitted from randomized study CA012-0 when 80% of the patients have died.**

   American BioScience commits to provide survival data and analysis results from randomized study CA012-0 when 80% of the patients have died. We estimate that these data will be available for submission on or before June 1, 2005.

2. **You should evaluate Abraxane safety and pharmacokinetics in subjects with hepatic impairment, to allow the determination of dosing adjustment for this population.**

   Protocol Submission: April 2005
   Study Start: November/December 2005
   Final Report Submission: December 2006

   We hereby commit to evaluate the safety and pharmacokinetics of ABRAXANE in subjects with hepatic impairment, to allow the determination of dose adjustment for this population. We commit to conduct the study in accordance with the timeframes described above.

The archival copy of the submission is provided on a compact disc (CD) with a file size of approximately 334.0 kb along with a paper copy bearing original signatures. The CD has the following specifications:

1. CD media: Office Depot single side CD-R; 700MB.
2. CD drive used to create the CD: Dell PC Burner Single Drive 48X CD-RW ROM Combo Drive
3. Backup software used to create the CD: EZ CD Creator V5.0

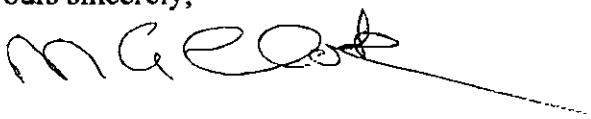
This submission is certified as virus free based on a scan of the electronic media using Symantec Norton Anti-Virus Corporate Edition-Version 9.0.0.338.

The following is a list of the information provided in this submission:

- Cover letter
- Form FDA 356h

Please do not hesitate to contact me on 310 883 3141 if you have any questions concerning this submission.

Yours sincerely,



Mitchall G. Clark, B. Pharm, MRPharmS.
Vice President, Regulatory Affairs
American BioScience, Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
American BioScience, Inc.	01/04/05
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
310 883 1300	310 998 5830
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
2730 Wilshire Boulevard, Suite 110 Santa Monica, CA 90403	Not Applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(if previously issued)* 21-660

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
(proposed)	Abraxane™ (paclitaxel albumin nanoparticle for injectable suspension)

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
5B,-20-epoxy-1,2a,4,7B,13a,-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-n-benzoyl-3-phenylisoserine	ABI-007

DOSAGE FORM	STRENGTHS:	ROUTE OF ADMINISTRATION:
Lyophilized Cake For Injectable Suspension	100 mg/Vial	Intravenous Infusion

(PROPOSED) INDICATION(S) FOR USE:

PLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☒ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Taxol (paclitaxel) Injection Holder of Approved Application Bristol Myers Squibb Company

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Amendment to an NDA. Submission in Response to FDA Request for Information-Phase 4 commitment.

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Drug Substance Manufacturer (Paclitaxel):

Albumin Human, USP manufacture and testing :

Drug Product Manufacture and testing :

erican Pharmaceutical Partners, Inc. 2020 Ruby Street, Melrose Park, Illinois, 60160 and 2045 N. Cornell Avenue, Melrose Park, 0160. Contact Tina Perkins 708 486 2078;

Sites are ready for inspection.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 55,974; Indena DMF #12876; Instituto Grifols, PLA/ELA #1181 for Albumin Human USP; Stelmi DMF #s 4258 and 12343 for vial stoppers; Kimble Glass DMF#14106, for glass vials; The Glass Group, DMF 9645 for glass vials.

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8 Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20 OTHER *(Specify)* American BioScience, Inc. submission in response to FDA request received Jan 04, 2005

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	Mitchall G. Clark Vice President, Regulatory Affairs	1/4/05

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2730 Wilshire Boulevard, Suite 110, Santa Monica, CA 90403	(310) 883 3141

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing ructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. id comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	January 7, 2005
Re:	NDA 21-660 for Abraxane		

■ **Urgent** ■ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660). Please note that the following reference should be included in the final printed labeling for this application:

> ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice Pittsburgh, Pa: Oncology Nursing Society; 1999:32-41.

Please contact me should you have any questions.

WS 1-7-05

Sincerely,

Sheila Ryan
Project Manager
Division of Oncology Drug Products

From: Ryan, Sheila
Sent: Wednesday, January 05, 2005 9:33 AM
To: 'Mitchall Clark'; 'Monica Batra'
Subject: NDA 21-660 Response to fax dated 12-29-04

Mitch,

Please refer to your facsimile dated December 29, 2004 for ABRAXANE. Regarding your proposed changes to the Clinical Pharmacology section of the labeling, we have the following response:

Our concern with both proposals described in your recent fax transmission is that they do not appear to add to insight on how one might use this drug/formulation in a practical setting.

For these reasons our recommendation is to avoid such language.

Please contact me should you have any questions.

Thank you,
Sheila

Sheila Ryan, PharmD
Regulatory Project Manager
Division of Oncology Drug Products
Phone: 301-594-5771
Fax: 301-594-0498
Email: ryans@cder.fda.gov

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark	**From:**	Amy Baird, CSO
Fax:	310-998-8553	**Fax:**	301-827-4590
Phone:	310-883-3141	**Phone:**	301-594-5779
Pages (including cover):	1	**Date:**	December 30, 2004
Re:	NDA 21-660 Abraxane.		

• **Urgent** • **For Review** ☐ **Please Comment** • **Please Reply** ☐ **Please Recycle**

• **Comments:**

Per the request of the clinical review team:

You have provided us with summary data and narratives for patients who died while on study. Please provide us with this information for any additional patients who ***died within 28 days of study drug*** for each treatment arm of Study CA012-0.

Please call should you have any questions.

Thank you,

Amy Baird

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

/s/

Amy Baird
12/30/04 11:49:38 AM
CSO

DRS 12-17-04

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	December 16, 2004
Re:	NDA 21-660 for Abraxane-information requests		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your new drug application for Abraxane (NDA 21-660). Please provide the following information as soon as possible to facilitate our review of this application:

1. Please provide your analysis for both treatment arms of the incidence of motor neuropathy, grade 1-2 and 3-4.
2. Please comment on Item 10 in the study protocol which states "After study treatment administration, grade 1 and grade 2 laboratory abnormalities will not be recorded as adverse events unless considered clinically significant by the investigator. All grade 3 and 4 laboratory abnormalities will be recorded as adverse events." Does this mean that we have significant under-reporting of gr 1-2 laboratory abnormalities?
3. Please clarify/justify why the proposed label — certain toxicities for which the clinical trial specified decrease to 220 mg/m2, and subsequently to 180 mg/m2.
4. In the PI (label) you have provided data for asthenia for patients in all of the trials. What was the incidence in the arms of the randomized trials? Please provide your analysis for "asthenia" and AEs that constitute asthenia for the 2 treatment arms in the randomized trial, grade 1-2 and 3-4.

Please contact me should you have any questions.

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	2	**Date:**	December 13, 2004
Re:	NDA 21-660 for Abraxane-information request		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660). Included in this facsimile are information requests regarding this application from the clinical review team. Please provide the requested information as soon as possible to facilitate our review of this application.

Please contact me as soon as possible should you have any questions.

Sincerely,

Sheila Ryan

Sheila Ryan

DFS 12-13-04

REQUESTS:

1. We request your analysis for the incidence of neutropenic fever by grade and by treatment arm for study CA012-0.

   The ADEX dataset indicates the following incidence of grade 3/4 febrile neutropenia when we searched for events which *contain* the NCI-CTC preferred term febrile neutropenia.

   Incidence of febrile neutropenia by treatment arm (CA012-0)

	ABI-007 (n=229)	Taxol (n=225)
Grade 3-4	11 (4.8%)	8 (3.6%)

   We also conducted a search for all grade events which *contain (as an NCI preferred term)* the term febrile neutropenia with the following results:

	ABI-007 (n=229)	Taxol (n=225)
All grades	55 (24.0%)	42 (18.7%)

   We note that CTC version 3 includes definitions only for grade 3 or higher febrile neutropenia. Please provide an explanation for these inconsistencies. Did the term "febrile neutropenia" capture additional events such as neutropenia in the absence of fever, etc?

2. In the Adverse Event table (5) in the PI, please clarify what is contained in the definition of "infection." Is this any infection, regardless of ANC? Please provide the incidence of "infection" for each treatment arm in study CA012-0 according to "all" vs. "grade 3-4."

3. For the AE "Fluid Retention," we found 24 patients in the ABI-007 arm with grade 1or 2, compared with your report of 22 patients. Can you explain this discrepancy?

4. Regarding incidence of AEs in the proposed labeling, please clarify if any of the numbers are derived from a treatment-emergent approach. If so, what rules were employed if patients had worsening of pre-existing baseline findings?

5. Regarding in-text table 65 (treatment exposure by cycle and dose) from the study report of CA012-0, the protocol provides for step dose-reductions either to 220 or 180 mg/m^2 for toxicity. Please clarify why the first column specifies an ABI-007 dose of 208 mg/m^2 (instead of 180).

DFS 12-7 04

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	2	**Date:**	December 7, 2004
Re:	NDA 21-660 for Abraxane-established name		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660). Attached are comments regarding the established name for this application.

Please contact me as soon as possible should you have any questions.

Thank you,

Sheila Ryan
Regulatory Project Manager

The Division of Oncology Drug Products with the concurrence from Center for Drug Evaluation (CDER) Labeling and Nomenclature Committee recommend the following established name for the ABI-007 drug product:

"Paclitaxel Protein Bound Particles for Injectable Suspension"

To further differentiate Abraxane from currently marketed paclitaxel drug products, you have the option to add a parenthetical statement underneath the name of the drug product, for example: (Cremophor EL™ free)" or "(albumin bound)". Therefore, the ABI-007 drug product name would read:

Abraxane for Injectable Suspension
(Paclitaxel Protein Bound Particles for Injectable Suspension)
(Cremophor EL™ free)

or

Abraxane for Injectable Suspension
(Paclitaxel Protein Bound Particles for Injectable Suspension)
(albumin bound)

Please make appropriate labeling changes. If you have any questions, please contact me as soon as possible.

DFS12-04

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	December 2, 2004
Re:	NDA 21-660 for Abraxane-information requests		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your new drug application for Abraxane (NDA 21-660). Please clarify the following regarding the safety data from study CA012-0 which appears in your table 5 (AEs) of the proposed label:

1. What terms are included under the AE "hypersensitivity reaction?" Please provide a table with the incidence of each component for grade 3 or 4 and for grade 1 and 2.

2. Are you able to provide data which shows grade 3 or 4 vs. grade 1 or 2 elevation of transaminases, alkaline phosphatase, and bilirubin?

3. What terms are included under the AE "fluid retention?" What is the incidence for grade 3-4 vs. grade 1-2 and overall?

4. The incidence is given for AE Nausea *and* Vomiting. Does this include both N and V, or either one? Can you distinguish grade 1-2 vs. 3-4 for each of the components and overall?

Please contact me should you have any questions.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DFS
11-30-04

From: Ryan, Sheila
Sent: Tuesday, November 30, 2004 3:25 PM
To: 'Mitchall Clark'
Subject: RE: NDA 21-660 Abraxane
Mitch,

We have additional requests regarding this response:

1. Please explain how the two variables WCINPD and WCINPDDT in data sets resp and resp_ are defined.
2. Please submit the SAS program that defines these two variables.

Please submit this information as soon as possible to facilitate our review of the application.

Please contact me should you have any questions.

Thank you,
Sheila

Sheila Ryan, PharmD
Regulatory Project Manager
Division of Oncology Drug Products
Phone: 301-594 5771
Fax: 301 594 0498
Email: ryans@cder.fda.gov

-----Original Message-----

From: Mitchall Clark [mailto:MClark@AmericanBioScience.com]
Sent: Tuesday, November 16, 2004 4:51 PM
To: Ryan, Sheila
Subject: FW: NDA 21-660 Abraxane

Dear Sheila

Reference is made to your e-mail from yesterday in which you requested information concerning the datasets provided in NDA 21-660 for Abraxane.

Provided below is our response. Your questions are provided in bold font, followed by our response:

FDA Question 1

You specify in the study report section 10.2 that there were 3 (2 ABI and 1 Taxol) patients randomized, but did not meet eligibiity criteria, and were not treated. In your fax October 20, you indicate that 6 patients were

randomized but not treated. For these patient numbers, please specify the patient numbers, treatment arm, and specific eligibility problem or other reason for no therapy. In addition, from dataset "elig", please clarify the specific criteria which rendered patient 437 ineligible and whether she was actually treated as randomized on the Abraxane arm.

ABI Response:

Provided in the table below is a listing of patients who were randomized but not treated, including the reasons for not receiving treatment. In addition, the reason for patient 437 violating an eligibility criterion is described. This patient did receive treatment.

Patient Site/Subject	Randomized Treatment	Treated? (Yes/No)	Eligibility Violation	Reason Not Treate
320/314	ABI-007	No	Patient enrolled under protocol amendment 1 which required patient to have failed prior chemotherapy in adjuvant or metastatic setting (consistent with Taxol indication). This patient did not receive chemotherapy in either the adjuvant or metastatic setting and thus was ineligible.	Ineligible p
120/109	Taxol	No	Patient enrolled under protocol amendment 1 which required patient to have failed prior chemotherapy in adjuvant or metastatic setting (consistent with Taxol indication). This patient did not receive chemotherapy in either the adjuvant or metastatic setting and thus was ineligible.	Ineligible F
312/290	ABI-007	No	NA	Patient witl consent in baseline p prior to firs of study dr
160/184	Taxol	No	NA	Patient witl consent in Baseline p prior to firs of study dr
113/171	ABI-007	No	Patient was a screen failure and was randomized in error by the site. End of study reason noted as "incl/excl not met".	Ineligible F
321/504	ABI-007	No	Patient was randomized in error; incomplete baseline evaluations (FACT, EORTC, ECG, CBC, and clinical chemistry not done).	Eligibility c not be con - CBC, CX clinical che not done.

227/437	ABI-007	Yes	Patient did not complete two week washout of hormonal therapy prior to study drug administration. Patient last took Arimidex on Aug 28, 2002 and had their first dose of study drug on Aug 29, 2002.	Patient wa: treated

FDA Question #2

In some of your SAS programs (such as dur_response_rec.sas and dur_response_o_rec.sas), the variables "wcinpd" and "wcinpddt" are called for logrank test. However, these two variables are not in the referred data sets. In addition, the program dur_response_rec.sas intends to analyze duration of response on responders as defined by reconciled target lesion response, whereas dur_response_o_rec.sas is for responders as defined by reconciled overall response. Why are the same "progression date" variable and "censoring indicator" variable used in both programs? Please provide these two variables for each such analysis to reproduce the corresponding tables.

ABI Response:

The variables WCINPD and WCINPDDT were inadvertently dropped when preparing the analysis datasets for FDA. Enclosed are the table production analysis dataset RESP and FDA analysis dataset RESP_A with these two variables included. The data defintion table for RESP_A is also enclosed which includes the definition of WCINPD and WCINPDDT.

Per RECIST, overall progression occurred if there was progression of a target lesion, unequivocal growth of a non-target lesion and/or the development of a new lesion. As per the RECIST tumor response criteria, one of the criteria for progression of a target lesion is the development of a new lesion; the target lesion response when there was non-target lesion progression was not specifically addressed in the RECIST criteria publication (attached). However, conceptually there was no reason to distinguish progression due to a new lesion from progression due to growth of non-target lesions. Therefore, for consistency, we extended the definition of target lesion progression to include progression of non-target lesions.

Therefore, for response assessment datasets, if progression occurred, the target lesion response was coded as progressive disease (PD) regardless of the target lesion tumor measurements. As specified in our data handling rules (i.e., Data Handling Rules for Response Assessment Reconciliation of Investigator and Independent Radiology Laboratory Datasets), the occurrence of non-target lesion

PD for whatever cause resulted in the coding of the target lesion response as PD as well. Thus within each dataset, the occurrence and date of progression based on overall response or target lesion response are the same and therefore we used variables based on overall response in the analyses of duration of response.

FDA Question #3:

Some other SAS programs (such as dur_response_inv.sas and dur_response_inv_bc6.sas) intend to analyze duration of response on responders as defined by investigator's assessment of target lesion response. However, the progression date (variable "inpddt") and the censoring indicator (variable "inpd") appear to be derived from the overall response rather than the target lesion response. Please clarify this and provide these two variables for each such analysis.

ABI Response:

As mentioned in our response to Question #2, if progression occurred, the target lesion response was coded as PD regardless of the target lesion tumor measurements and thus the occurrence and date of progression based on overall response or target lesion response are the same. Therefore we used variables based on overall response in the analyses of duration of response.

Please do not hesitate to contact me if you have any further questions.

Kind regards,

Mitchall G. Clark B.Pharm, MRPharmS
Vice President, Regulatory Affairs
American BioScience, Inc.
Tel. 310 883 3141
Fax. 310 998 8553

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	November 17, 2004
Re:	NDA 21-660 for Abraxane-information request		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your new drug application for Abraxane (NDA 21-660), specifically your email dated November 16, 2004. Please provide the following additional information regarding this submission as soon as possible to facilitate our review of this application:

Please provide specific information about the following patients who were said to have significant protocol violations of inclusion/exclusion criteria. What were the specific criteria for the patients listed by number below and were they treated/which arm?

- 138
- 183
- 289
- 535

Please contact me should you have any questions.

Sincerely,

Sheila Ryan

Sheila Ryan

DFS 11-17-04

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	2	**Date:**	November 15, 2004
Re:	NDA 21-660 for Abraxane-information requests		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660). Please provide the following information as soon as possible to facilitate our review of this application:

1. You specify in the study report section 10.2 that there were 3 (2 ABI and 1 Taxol) patients randomized, but did not meet eligibility criteria, and were not treated. In your fax of Oct. 20, you indicate that 6 patients were randomized but not treated. For these patients, please specify the patient numbers, treatment arm, and specific eligibility problem or other reason for no therapy. In addition, from data set "elig", please clarify the specific criteria which rendered patient 437 ineligible and whether she was actually treated as randomized on the Abraxane arm.

2. In some of your SAS programs (such as dur_response_rec.sas and dur_response_o_rec.sas), the variables "wcinpd" and "wcinpddt" are called for logrank test. However, these two variables are not in the referred data sets. In addition, the program dur_response_rec.sas intends to analyze duration of response on responders as defined by reconciled target lesion response, whereas dur_response_o_rec.sas is for responders as defined by reconciled overall response. Why are the same "progression date" variable and "censoring indicator" variable

DFS 11-15-04

used in both programs? Please provide these two variables for each such analysis and reproduce the corresponding tables.

3. Some other SAS programs (such as dur_response_inv.sas and dur_response_inv_bc6.sas) intend to analyze duration of response on responders as defined by investigator's assessment of target lesion response. However, the progression date (variable "inpddt") and the censoring indicator (variable "inpd") appear to be derived from the overall response rather than the target lesion response. Please clarify this and provide these two variables for each such analysis.

Please contact me should you have any questions.

Sincerely,

Sheila Ryan

From: Ryan, Sheila
Sent: Wednesday, November 03, 2004 11:53 AM
To: 'Mitchall Clark'
Subject: NDA 21-660 request

Mitch,

We have the following request regarding NDA 21-660 for Abraxane:

Was the variable "date of randomization" included in the data base in the NDA submission? If so, please indicate the names of the variable and the data set. If not, please submit it as soon as possible.

Please contact me as soon possible should you have any questions.

Thank you,
Sheila

Sheila Ryan, PharmD
Regulatory Project Manager
Division of Oncology Drug Products
Phone: 301-594-5771
Fax: 301-594-0498
Email: ryans@cder.fda.gov

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/s/

Sheila Ryan
11/4/04 12:12:19 PM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchell Clark—American Bioscience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover): 2		**Date:**	November 1, 2004
Re:	NDA 21-660 for Abraxane- CMC requests/generic name comments		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660). Attached are information requests pertaining to the chemistry, manufacturing, and controls section of the application. Also attached are comments regarding the established names that were proposed in your October 12, 2004 submission.

Please submit the requested information as soon as possible to facilitate our review of the application.

Please contact me should you have any questions.

Thank you,

Sheila

DFS 11-1-04

The following comments/requests pertain to the paclitaxel drug substance specifications:

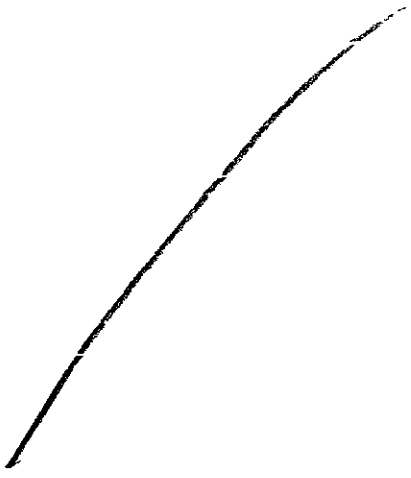
1. You have considered the proposed limit of NMT — for — qualified based on the report that this — impurity was present in the majority of paclitaxel lots used in non-clinical and clinical trials (page 51, under I. Drug Substance). However, the observed level of — in your supporting data [Taxol (lot 2C65657)] does not support the proposed limit of — Please provide justifications for the proposed limit or lower the limit to a level supported by safety data.

2. The proposed limit of — is above the ICH qualification threshold. Available batch analysis data of paclitaxel drug substance indicated that this — impurity was usually found at levels — . Please provide safety data to support the proposed limit or lower the limit for this impurity to a level below the ICH threshold of qualification.

The following comments pertain to the established name:

The rationale behind the rejection of the recommended names was given as concerns about "potentially serious consequences for the safe use of the drug" due to "Inadvertently dispensing Taxol® (paclitaxel) ***Injection*** *or its generic equivalent instead of Abraxane™..."*

The Labeling and Nomenclature Committee (LND) does not agree with this rationale for the following reasons:



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DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

DFS 10/29

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):		**Date:**	October 29, 2004
Re:	NDA 21-660 for Abraxane-clinical requests		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660). Please provide the following information as soon as possible to facilitate our review of this application:

Please refer to the proposed limit for — in the paclitaxel drug substance specifications. You have reported that — was present in the majority of lots used in non-clinical and clinical trials and is therefore considered qualified (page 51, under I. Drug Substance). However, the observed level of — in Taxol (lot 2C65657) does not support the proposed limit of NMT —n the drug substance acceptance specifications. Please provide justifications for the proposed limit or lower the limit to a level supported by safety data.

Thank you,

Sheila

From: Ryan, Sheila
Sent: Wednesday, October 27, 2004 1:01 PM
To: 'Mitchall Clark'
Subject: NDA 21-660

Dear Mitch,

Please refer to my October 15, 2004 facsimile in which we requested a table with *rec*TLRR by treatment arm (request #1 of the facsimile). We have the following additional request in regards to this item.

Please also provide the SAS program which derived whether or not patients met the criteria "after failure of combination chemotherapy for metastatic disease or relapse within 6 month of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated (Taxol indication)" Please also submit the data set in .xpt format that includes the derived indicator variable.

Please contact me should you have any questions.

Thank you,
Sheila

Sheila Ryan, PharmD
Regulatory Project Manager
Division of Oncology Drug Products
Phone: 301-594-5771
Fax: 301-594-0498
Email: ryans@cder.fda.gov

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/s/

Sheila Ryan
10/27/04 01:08:19 PM
CSO

Fax

DFS 10-26-04

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Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	2	**Date:**	October 26, 2004
Re:	NDA 21-660 for Abraxane-information requests/comments		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660). Included in this facsimile are information requests and comments from the review team regarding this application. Please submit the requested information as soon as possible to facilitate our review of your application.

Please contact me should you have any questions.

Sincerely,

Sheila Ryan
Project Manager
Division of Oncology Drug Products

The following requests pertain to the statistical analysis of the ABI-007 drug product stability data:

1. You have provided all statistical analysis plots on time scales of 100 months or longer, based on stability data of — Please re-draw the graphs using a — scale.

2. It is not clear why the regression analysis on the — impurity was performed using a 2 sided approach. Please provide a one-side analysis for this degradation product.

3. Please confirm that all confidence limits are one-sided and have 95% coverage.

The following comments pertain to the proposed drug product specification of individual and total limits:

1. The proposed limits of — at release and — of shelf-life for — are not supported by batch analysis data and stability data of ABI-007 drug product. The proposed limits are above the ICH recommended qualification threshold as well. Please provide justifications for the proposed limits for — or lower the limits to reflect the levels actually found in the drug product.

2. Similarly, the proposed limits for impurities — are above the ICH recommended qualification threshold. They are not supported by drug product batch analysis data and stability data, either. Test results of stability studies indicated that the levels of these impurities in the drug product exhibit/stability batches did not increase over storage. Please provide justifications for the proposed limits for — or lower the limits to reflect the levels actually found in the drug product.

3. The proposed limits for impurities — are not supported by drug product batch analysis data and stability data.. Test results of stability studies indicated that the levels of these impurities in the drug product exhibit/stability batches did not increase over storage. It is recommended that you consider lowering the proposed limits for these individual impurities as more data accumulate.

4. Additionally, the proposed limit for total impurities should be lowered to a level supported by batch analysis/stability data.

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):		**Date:**	October 20, 2004
Re:	NDA 21-660 for Abraxane-clinical requests		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660). Please provide the following information as soon as possible to facilitate our review of this application:

1. Please provide us with the site and patient ID numbers for the patients who were randomized but not treated for each arm of the study.

2. Please clarify whether you calculated TTP from date of randomization or date of initiation of therapy.

Also, I will be out of the office on Thursday and Friday of this week. If you are able to respond to these requests before Monday, please send the response to the attention of Dotti Pease at 301-827-4590 (fax).

Thank you,

Sheila

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

DFS 10-15-04

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	2	**Date:**	October 15, 2004
Re:	NDA 21-660 for Abraxane-clinical requests		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660). Please provide the following information as soon as possible to facilitate our review of this application:

1. Please provide a table with the *rec*TLRR by treatment arm for all randomized patients, and for first line patients, and for patients "after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated." [Taxol indication]

2. For your analysis of prognostic factors (In-Text Table 44 of CA012-0 study report), you have used *inv*ORR as the end-point. We request that you provide a similar analysis of response in the 2 treatment arms related to prognostic factors, but use the primary efficacy endpoint, Reconciled Target Lesion Response Rate *(recTLRR).*

3. Please explain the basis for the reconciled Target Lesion Response (*Rec*TLR) for the patients listed in the following table:

Patients Treated with ABI-007

Site #	Pt #	*Rec*TLR (6 cycles)	*Inv*TLR (6 cycles)	*WC*TLR (6 cycles)	FDA TLR	Comment
309	342	CR	CR	--	Not evalu-able	We could not verify measurable disease at baseline to assess response. WC did not assess response. Investigator cited 17mm axillary lesion on CT resolved.
302	303	PR	PR	--	PD	We identified a response in the sum of measurable lesions on CT, apparently confirmed [redacted] Baseline liver CT (limited study) showed no lesions, but no repeat until [redacted] when apparently new disease seen.
335	430	PR	SD	PR	PD	Although sum of TLs decreased from baseline through week 12, there appear to be new nonTLs in liver, suspicious week 5, confirmed week 9.
308	161	PR	PR	--	SD	Multiple small lung nodules, probably no change over time. Investigator lung lesions 11mm + 18mm, decreased to 8+8 mm
318	225	PR	PR	--	SD	Poor quality films. We saw one stable left lung lesion. WC reported nonTL left lung decreased. Investigator says 1 TL on CT chest 27mm, decreased to 8mm

Please contact me should you have any questions.

Sincerely,

Sheila

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchell Clark—American BioScience	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	October 6, 2004
Re:	NDA 21-660 generic name comments		

■ **Urgent** ■ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Mitch,

Please refer to NDA 21-660 for Abraxane (paclitaxel albumin nanoparticle for injectable suspension). I have attached recommendations from our Labeling and Nomenclature Committee (LNC) regarding the proposed established name for this application.

Please contact me should you have any questions.

Sincerely,

DFS 10·6·04

Sheila Ryan
Project Manager
Division of Oncology Drug Products

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

From: Ryan, Sheila
Sent: Monday, October 04, 2004 2:14 PM
To: 'Mitchall Clark'
Subject: NDA 21-660 CMC request

Mitch,

Please refer to NDA 21-660 for Abraxane. Please provide the following information as soon as possible to facilitate our review of this application:

You have reported that during the [redacted] of the drug product manufacturing process, [redacted] to below the ICH limits. However, the testing of levels of [redacted] in the [redacted] is not included in the in-process tests. Please provide a detailed description of the [redacted] and provide data/evidence to demonstrate that the levels of [redacted] are within acceptable limits.

Please contact me should you have any questions.

Thank you,
Sheila

Sheila Ryan, PharmD
Regulatory Project Manager
Division of Oncology Drug Products
Phone: 301-594-5771
Fax: 301-594-0498
Email: ryans@cder.fda.gov

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/s/

Sheila Ryan
10/4/04 02:28:34 PM
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Fax

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Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	2	**Date:**	October 1, 2004
Re:	NDA 21-660 for Abraxane-information requests		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660). Please provide the following information as soon as possible to facilitate our review of this application:

1. We have the study reports for these two trials (CA005-0 and CA008-0). For CA008-0, we can not find the synopsis in the electronic record or detailed information about the study population besides Table 1 in your CA008-0 report. Please provide us with the synopsis of protocol CA008-0, which includes how patients were selected for study CA008-0, inclusion/exclusion criteria, study site, and previous chemotherapy for cancer patients.
2. Please provide the analytical reports BPPAC7 and ARPAC7.
3. Please verify that the In-Text Figure 18 Patient assessment of Sensory Neuropathy Based on FACT-Taxane (Version 4) "additional Concerns" Questionnaire by Cumulative Dose was generated by analysis of the Subject Assessment of Peripheral Neuropathy Dataset. Please also describe how this analysis was generated. Were all 16 items/questions included and how did you derive the score in relation to the 15 point scale represented on the y-axis of Figure 18? How did you deal with missing data?

DFS 10-4-04

4. Please provide the following analyses from the Subject Analysis of Peripheral Neuropathy Dataset:

    a. Overall incidence of peripheral neuropathy as reported by patients in each arm (any reported complaint from "a little bit" to "very much"), without adjustment for cumulative dose of drug.
    b. Breakdown, for each treatment arm, the incidence of the following reports overall and by severity:

    numbness in hands
    numbness in feet
    discomfort in hands
    discomfort in feet
    trouble buttoning buttons
    trouble feeling small objects
    trouble walking
    pain in fingertips

Please contact me should you have any questions.

Sincerely,

Sheila Ryan

From: Ryan, Sheila
Sent: Friday, September 10, 2004 8:49 AM
To: 'Mitchall Clark'
Subject: NDA 21-660 information request

Mitch,

Please refer to NDA 21-660 for Abraxane. Please clarify the following two items:

1. With reference to the clinical study report, Appendix 16.3, list 4 (patients with confirmed target lesion response per "recTLRR"), page 25163, patient designated as ID# 315/PK07:
There is no patient contained in the datasets of study CA012-0 with ID# PK07. What is the actual ID number for this responder?

2. In PK study CA008-0, Appendix I, Table 3, the patients are designated with identifying numbers 101 through 127. These numbers do not correspond to the unique identifying numbers assigned to patients in CA012-0. For the PK patients please list the study sites and ID numbers from study CA012-0, which correspond to PK patients numbers 101-127.

Also, I found the update labeling. I am sorry for the confusion. Our electronic document room was down yesterday and I couldn't find the labeling when I called you. It is up and running again today and I located the submission.

Thank you,
Sheila

Sheila Ryan, PharmD
Regulatory Project Manager
Division of Oncology Drug Products
Phone: 301-594-5771
Fax: 301-594-0498
Email: ryans@cder.fda.gov

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/s/

Sheila Ryan
9/10/04 01:23:16 PM
CSO

From: Ryan, Sheila
Sent: Thursday, August 26, 2004 10:54 AM
To: 'Mitchall Clark'
Subject: NDA 21-660 clarification

Mitch,

We have received your response to our inquiry about the product codes and lot numbers used in trials CA012-0 and CA008-0. There seems to be a discrepancy in your response regarding CA008-0, for which you have specified product code 103450 and lot number C102-004. In Amendment I of your submission (Table II page 6 of 83), lot number C102-004 seems to correspond to product code 103350. Please clarify.

Thank you,
Sheila

Sheila Ryan, PharmD
Regulatory Project Manager
Division of Oncology Drug Products
Phone: 301-594-5771
Fax: 301-594-0498
Email: ryans@cder.fda.gov

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/s/

Sheila Ryan
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Fax

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Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	August 25, 2004
Re:	NDA 21-660 for Abraxane-clinical requests		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660). Please provide the following information as soon as possible to facilitate our review of this application:

Please provide the product code numbers and lot numbers of study drug used in the following trials:

a. CA008-0
b. CA012-0

Please contact me should you have any questions.

Sincerely,
Sheila Ryan

DFS 8-25-04

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

BFS
p2
8/12/4

To: Mitchall Clark/ABS	From: Paul Zimmerman for Sheila Ryan
Fax: 310-998-8553	Fax: 301-594-0498
Phone:	Phone: 301-594-5724
Pages, including cover sheet: 1	Date: August 12, 2004
Re: NDA 21-660 for Abraxane	

☐ **Urgent** ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

The following concern NDA 21-660.

It appears that the raw data (tumor measurements) as assessed by WorldCare are contained in datasets "WCLESN" and "WCLESION."

The source of the tumor assessments in raw datasets "TARG" (Target Lesion Measurement Form Dataset Variables) and "NTLE" (Non-Target Lesion Evaluation Form Dataset Variables) is not labeled. Please clarify if these measurements are investigator assessments and the designations of any other datasets which may contain tumor measurements.

Thank you for your early response.

DFS 7-29-04

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	July 29, 2004
Re:	NDA 21-660 for Abraxane-clinical requests		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660). Please provide the following information as soon as possible to facilitate our review of this application:

1. Clarify if the appearance of new lesions was considered in the assessment of the target lesion response. Did the target lesion response take into consideration progression elsewhere?

2. From your April presentation to DODP, please provide the slide of "Prognostic Factors by Country."

3. Please provide us with a table of target lesion response (TLS) and overall response (OR) by country for each treatment arm. Present the results for all (ITT) patients, and for first line metastatic and greater than first line patients.

Please contact me should you have any questions.

Sincerely,
Sheila Ryan

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	July 28, 2004
Re:	NDA 21-660 for Abraxane-CMC request for clarification		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660). Please provide the following information regarding the chemistry, manufacturing, and controls as soon as possible to facilitate our review of this application:

> You have stated that drug product of Product Code 103450 is the product intended for marketing and lots of this formulation have been manufactured and used in drug product stability studies. Please clarify whether any batches of Product Code 103450 have been used in clinical trials.

Please contact me if you have any questions.

Sincerely,

Sheila Ryan
Project Manager
Division of Oncology Drug Products

DFS 7-26-04

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	2	**Date:**	July 26, 2004
Re:	NDA 21-660 for Abraxane		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660). Please provide the following information regarding the chemistry, manufacturing, and controls as soon as possible to facilitate our review of this application:

b.

2. In the — formulation of the 100 mg presentation, each vial contains 100 mg paclitaxel and approximately 900 mg human albumin. When the drug product is reconstituted with 20 mL NaCl (0.9%) for Injection, a paclitaxel nanoparticle suspension is obtained. This suspension is composed of paclitaxel/human albumin nanoparticles in equilibrium with human albumin molecules in solution. Please specify the average weight by weight ratio of paclitaxel to human albumin of the nanoparticles.

Please contact me if you have any questions.

Sincerely,

Sheila Ryan
Project Manager
Division of Oncology Drug Products

From: Ryan, Sheila
Sent: Friday, July 23, 2004 10:04 AM
To: 'Mitchall Clark'
Subject: Toxicology question for NDA 21-660

Good Morning Mitch,

Please refer to NDA 21-660 for Abraxane. Please provide the following clarifications to facilitate our review of this application.

1. Was a toxicology bridging study conducted for Abraxane? If one was conducted, please describe where the study results can be found in the NDA submission.

2. Please explain the status of our request for updated pharmacokinetic data/pharmacodynamic data for study CA005-0.

Thank you,
Sheila

Sheila Ryan, PharmD
Regulatory Project Manager
Division of Oncology Drug Products
Phone: 301-594-5771
Fax: 301-594-0498
Email: ryans@cder.fda.gov

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/s/

Sheila Ryan
7/23/04 10:11:28 AM
CSO

DFS 6-25-04

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	2	**Date:**	June 25, 2004
Re:	NDA 21-660 for Abraxane		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660). Please provide the following information as soon as possible to facilitate our review of this application:

1. Please provide the following items for Trial CA012-0:
   a. SAS programs that produced all derived efficacy variables based on submitted raw data and the resulting SAS data sets (in .xpt format). The following are examples of derived variables: response status based on (a) investigator assessment, (b) WorldCare assessment, (c) reconciled assessment, and by (a) target lesions, (b) non-target lesions, (c) target and non-target lesions; date of response; time to progression, the variable indicating whether patients were censored or not, date of disease progression; overall survival with a censoring variable.
   b. SAS programs that produced all efficacy results in the study report.

2. Please provide the location in the electronic submission of a list of response status (confirmed CR or PR, SD, PD in target lesions) by ID and treatment as assessed by:
   b. Investigators
   c. Worldcom
   d. Reconciled

   If this is information is not already in the electronic submission, please provide this type of list in .xpt format and text file.
3. Please provide a similar list for non-target lesions and the secondary efficacy endpoint: **overall** CR or PR, SD, PD.
4. Please provide any updated pharmacokinetic/pharmacodynamic data from study CA005-0.
5. Please provide the charter for radiological review.

Please contact me should you have any questions.

Sincerely,

Sheila Ryan
Project Manager
Division of Oncology Drug Products

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	May 7, 2004
Re:	NDA 21-660 for Abraxane		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660). Please provide the following information as soon as possible to facilitate our review of this application:

> Please provide the telephone and facsimile numbers for the 8 top-enrolling Russian/Ukraine study sites for which you recently provided us with summary response data (#313, #311, #312, #308, 3309, #315, #304, and #305).

Please contact me should you have any questions.

DFS 5-7-04

Sincerely,

Sheila Ryan
Project Manager
Division of Oncology Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-660

American BioScience, Inc.
Attention: Mitch Clark, Vice President
Regulatory Affairs
2730 Wilshire Boulevard, Suite 110
Santa Monica, CA 90403

Dear Mr. Clark:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: —— Paclitaxel for Injectable Suspension)

Date of Submission: June 30, 2003

Date of Receipt: July 1, 2003

Our Reference Number: NDA 21-660

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete. Please cite the NDA number assigned to this application at the top of the first page of every communication concerning this application.

Address all additional presubmissions as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room, 3067
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150

Attention: Division Document Room, 3067
1451 Rockville Pike
Rockville, Maryland 20852

Send the submission that completes this application and is intended to start the review clock to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Ave.
Rockville, Maryland 20852-1833

If you have any questions, call Sheila Ryan, Regulatory Project Manager, at (301) 594-5771.

Sincerely,

{See appended electronic signature page}

Dotti Pease, Chief
Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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
7/14/03 08:31:00 AM
signing for Dotti Pease

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-660

American BioScience, Inc.
Attention: Mitchall G. Clark
Vice President, Regulatory Affairs
2730 Wilshire Boulevard
Santa Monica, CA 90403

Dear Mr. Clark:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Abraxane (*nab* paclitaxel) for injectable suspension

Review Priority Classification: Standard (S)

Date of Application: March 4, 2004

Date of Receipt: March 8, 2004

Our Reference Number: NDA 21-660

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 7, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 8, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room

5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Document Room 3067
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, call Sheila Ryan, Pharm.D., Regulatory Project Manager, at (301) 594-5771.

Sincerely,

{See appended electronic signature page}

Dotti Pease, Chief
Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Amy Baird
5/7/04 04:52:18 PM
for Dotti Pease

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-660

American Bioscience, Inc.
Attention: Mitchall Clark
Vice President Regulatory Affairs
2730 Wilshire Boulevard
Santa Monica, CA 90403

Dear Mr.Clark:

Please refer to your March 4, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abraxane (*nab* paclitaxel) for Injectable Suspension.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on May 7, 2004 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Sheila Ryan, Pharm.D., Regulatory Project Manager, at (301) 594-5771.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Richard Pazdur
5/7/04 05:10:43 PM

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	May 5, 2004
Re:	NDA 21-660 for Abraxane--submission date 2-19-04		

☐ **Urgent** ■ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660), specifically submission dated February 19, 2004. We have the following comment regarding your proposal for the 120 day safety update:

> We have reviewed your proposals for the submission of the 120-day safety update for Abraxane (NDA 21-660). The proposed data cut-off date of March 29, 2004 and the categories of information you plan to submit seem appropriate.

Please contact me should you have any questions.

DFS 5-5-04

Sincerely,

Sheila Ryan
Project Manager
Division of Oncology Drug Products

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchell Clark---American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	May 4, 2004
Re:	NDA 21-660 for Abraxane/imaging component		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660). We have the following comments regarding the system to review tumor images:

> We are considering an audit approach whereby we remotely access a database that contains your digitized radiological images. We would like feedback on whether this approach could be a possibility. Also, if it would it be helpful, we would be willing to schedule a teleconference to discuss this issue in more detail.

Please contact me should you have any questions.

Sincerely,

Sheila Ryan
Project Manager
Division of Oncology Drug Products

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/s/

Sheila Ryan
5/4/04 09:27:20 AM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Mitchell G. Clark	From: Sheila Ryan, Pharm.D.
Fax: 310-998-8553	Fax: 301-594-0498
Phone: 310-883-3141	Phone: 301-594-5771
Pages, including cover sheet: 2	Date: April 23, 2004

Re: NDA presentation for Abraxane (NDA 21-660)—FDA attendees

- Dear Mitch,

Per your request, I have attached the FDA attendees for your presentation for Abraxane (NDA 21-660) that was held on April 22, 2004.

Please contact me should you have any questions.

Thank you,

Sheila Ryan, Pharm.D.
Regulatory Project Manager

DFS 5-4-04

ATTENDEES:

NDA 21-660 Review Team:

Richard Pazdur, MD, Division Director, Division of Oncology Drug Products (DODP)
Grant Williams, MD, Deputy Director, DODP
Ramzi Dagher, MD, Medical Team Leader
Nancy Scher, MD, Medical Reviewer
Yung-Ao Hsieh, PhD, Chemistry Reviewer
Margaret Brower, PhD, Pharmacology Reviewer
Brian Booth, PhD, Biopharmaceutics Team Leader
Sophia Abraham, PhD, Biopharmacuetics Reviewer
Rajeshwari Sridhara, PhD, Statistical Team Leader
Peiling Yang, PhD, Statistical Reviewer
Stephen Langille, Microbiology Reviewer
David Gan, PhD, Division of Scientific Investigation
Susan Lu, RPh, Office of Drug Safety
Sheila Ryan, PharmD, Project Manager

Other Attendees:

Lilia Talarico, MD, Associate Director, DODP
Atiqur Rahman, PhD, acting Deputy Director, Division of Pharmaceutical Evaluation I
Kooros Mahjoob, PhD, Supervisory Staticisan, Division of Biometrics I
Maitreyee Hazarika, MD, Medical Reviewer, DODP
Buhupinder Mann, MD, Medical Reviewer, DODP
Kevin Ridenhour, MD, Medical Reviewer, DODP
Qin Ryan, Medical Reviewer, DODP
Dianne Spillman, Special Assistant to Division Director, DODP

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall Clark—American BioScience, Inc	**From:**	Sheila Ryan, PharmD
Fax:	(310) 998-8553	**Fax:**	(301) 594-0498
Phone:	(310) 883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	April 22, 2004
Re:	NDA 21-660 for Abraxane		

■ **Urgent** ■ **For Review** ■ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Mitch,

Please refer to your new drug application for Abraxane (NDA 21-660). Please provide the following information to facilitate our review of this application:

1. A table with each of the study sites listed by center name and location that shows the number of patients accrued.

2. Response rate by treatment for the eight largest sites.

Please contact me should you have any questions.

DTS 4-22-04

Sincerely,

Sheila Ryan
Project Manager
Division of Oncology Drug Products

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Mitchall G. Clark	From: Sheila Ryan, Pharm.D.
Fax: 310-998-8553	Fax: 301-594-0498
Phone: 310-883-3141	Phone: 301-594-5771
Pages, including cover sheet: 1	Date: April 7, 2004

Re: NDA 21-660 for Abraxane

● Dear Mitch,

Please refer to your NDA 21-660 for Abraxane, specifically your email dated April 2, 2004. This email explained issues that have arisen during the inspection of your manufacturing facility for Abraxane. We have the following comments regarding these issues:

1. Please clarify whether the stability batches were filled with a —
2. We have not begun the full review of the application. We understand the omission regarding output of data from the 'Data –Loggers' was not intentional. We will request this information/data should the need arise during the review of the application.

Please contact me should you have any questions.

Thank you,

Sheila Ryan, Pharm.D.
Regulatory Project Manager

DFS 4-9-04

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Mitchell G. Clark	From: Sheila Ryan, PharmD
Fax: 310-998-8553	Fax: 301-594-0498
Phone: 310-883-3141	Phone: 301-594-5771
Pages, including cover sheet: 2	Date: March 19, 2004

Re: NDA presentation for Abraxane (NDA 21-660)

- Dear Mitch,

Please refer to your NDA 21-660 for Abraxane. We have tentatively scheduled your NDA presentation regarding this application for April 22, 2004 at 12:30 pm EST. The presentation will take place here at WOCII, 1451 Rockville Pike, Rockville, MD. Please confirm this date with me by facsimile or phone as soon as possible. The presentation should provide a brief summary of the pharmacology/toxicology, chemistry/manufacturing/controls, statistical, clinical and biopharmaceutical sections of the NDA to the Division. Please allow time for a question and answer period at the end of the presentation.

I have also attached the anticipated FDA attendees for the presentation. Please provide me with a list of attendees from your company prior to the presentation date.

Please contact me should you have any questions.

Thank you,

Sheila Ryan, Pharm.D.
Regulatory Project Manager

DFS 3-19-04

March 19, 2004

Anticipated Attendees:

Richard Pazdur, MD, Division Director, Division of Oncology Drug Products
Grant Williams, MD, Deputy Director, Division of Oncology Drug Products
Ramzi Dagher, MD, Medical Team Leader
Patricia Cortazar, MD, Medical Reviewer
Rebecca Wood, PhD, Chemistry Team Leader
Yung-Ao Hsieh, PhD, Chemistry Reviewer
John Leighton, PhD, Pharmacology Team Leader
Margaret Brower, PhD, Pharmacology Reviewer
Atiqur Rahman, PhD, Biopharmaceutics Team Leader
Sophia Abraham, PhD, Biopharmacuetics Reviewer
Rajeshwari Sridhara, PhD, Statistical Team Leader
Peiling Yang, PhD, Statistical Reviewer
Peter Cooney, PhD, Microbiology Team Leader
Stephen Langille, Microbiology Reviewer
Sheila Ryan, PharmD, Project Manager

In addition, the following people have been invited to attend:

Robert Temple, MD, Director, Office of Drug Evaluation I
Joseph Grillo, PharmD, Division of Drug Marketing, Advertising, and Communication
Khin U, PhD, Division of Scientific Investigation
David Gan, PhD, Division of Scientific Investigation
Leslie Ball, Division of Scientific Investigation
Robert Kang, Office of Drug Safety
Kim Colangelo, Office of New Drugs

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchell G. Clark	**From:**	Sheila Ryan, PharmD
Fax:	310-998-8553	**Fax:**	(301) 594-0498
Phone:	310-883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	2	**Date:**	February 24, 2004
Re:	NDA 21-660 for ABRAXANE		

■ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

Mitch,

Please refer to the chemistry portion of your rolling submission of NDA 21-660 for Abraxane. Included in this facsimile are deficiencies and comments from the microbiology review team. These deficiencies and comments need to be addressed in writing as soon as possible.

Please call me if you have any questions.

Sincerely,

Sheila Ryan
Project Manager

FS 2-24-04

DEFICIENCIES AND COMMENTS:

1. Please describe how the

2. Please provide the following information with regard to

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/s/

Sheila Ryan
2/24/04 11:09:44 AM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchell G. Clark	**From:**	Sheila Ryan, PharmD
Fax:	310-998-8553	**Fax:**	(301) 594-0498
Phone:	310-883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	3	**Date:**	February 18, 2004
Re:	NDA 21-660 for ABRAXANE initial proprietary name review		

☐ **Urgent** ■ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Mitch,

Please refer to NDA 21-660 for Abraxane, specifically your November 17, 2003 request for an initial proprietary name review. Attached are comments from our Division of Medication Errors and Technical Support (DMETS) within the Office Of Drug Safety (ODS) regarding the proposed proprietary name and labeling.

Please call me if you have any questions.

Sincerely,

Sheila Ryan
Project Manager

PROPIETARY NAME RECOMMENDATIONS:

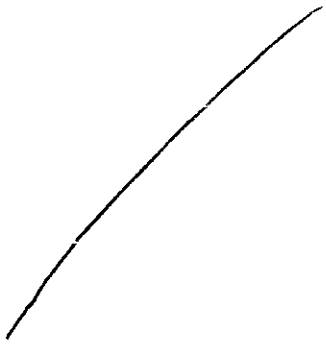
1. DMETS has no objections to the use of the proprietary name Abraxane. This is considered a tentative decision. This name with its associated labels and labeling **must be re-evaluated approximately 90 days prior to the expected action of the NDA.** A re-evaluation of the proprietary name prior to the NDA action will rule out any objections based upon approval of other proprietary names or established names from the date of this document.
2. Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the proprietary name Abraxane acceptable from a promotional perspective.

LABELING RECOMMENDATIONS:

GENERAL COMMENT

1. The draft labels and labeling submitted to DMETS do not include the artwork and font sizes that will be used in the final printed labels and labeling. Therefore, it is not possible to fully assess the safety of the labels and labeling based upon these drafts.

CONTAINER LABEL (100 mg in 50 mL Single Dose vial)



CARTON LABELING

INSERT LABELING

2. PRECAUTIONS

Include a subsection of this section entitled "Information for Patients" and refer to the patient information to be printed in full at the end of the professional insert labeling. We refer you to CFR 21 201.57(f)(2) for guidance.

PATIENT INFORMATION

1. See comment 2. under INSERT LABELING above.

EDUCATION

Because of post-marketing experience of medication errors resulting from introduction of modified formulations of injection drug products, DMETS recommends the sponsor plan a vigorous education campaign to accompany the launch of this product. A videotape might be helpful to deliver important safety messages for this product and for explanation of the proper method of product preparation. The education campaign should include the following components at a minimum:

1. Education for health care providers about special precautions to be taken for the preparation and administration of this cytotoxic product. Because of the unique reconstitution directions for this product and its cytotoxic nature, education for health care providers including special precautions to be taken for its preparation and administration should be provided.
2. Education to alert practitioners of the dangers of inadvertent substitution between intravenous paclitaxel formulations.

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/s/

Sheila Ryan
2/18/04 12:00:56 PM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchell G. Clark	**From:**	Sheila Ryan, PharmD
Fax:	310-998-8553	**Fax:**	(301) 594-0498
Phone:	310-883-3141	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	January 30, 2004
Re:	NDA 21-660 for ABRAXANE		

☐ **Urgent** ■ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Mitch,

Please refer to the chemistry portion of your rolling submission of NDA 21-660 for Abraxane. The following is a comment from the Chemistry, Manufacturing, and Controls review team.

> We wish to inform you that the — drug product stability data provided are not adequate to support the requested expiration dating of — The data indicated that the stability studies were initiated in — (lots 0102073B and C) and — (lot 0102073D), full term stability data should have become available. Please submit the updated stability data for review.

Additional comments may be provided as our review continues.

Please call me if you have any questions.

Sincerely,

Sheila Ryan
Project Manager

DFS
11-4-04

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Mitchall G. Clark	**From:**	Dianne Spillman
Fax:	(708) 343-4269	**Fax:**	(301) 594-0499
Phone:	(708) 547-3618	**Phone:**	(301) 594-5746
Pages (including cover):	12	**Date:**	May 1, 2001
Re:	IND 55,974 – Bullets for May 3, 2001 EOP2 follow-up meeting		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• Comments:

Mitch –

Attached are the FDA answers to your questions.

We will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we may not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan, for which you would like FDA feedback, should be submitted as a new meeting request.

Regards,

Dianne Spillman
Project Manager, Oncology Drugs

☑ Checked in DFS 5-10-01...IND 55,974/n-058 (MR)
c:\...\55974\faxes\010501a-fax-p2fu-oh-n058.doc

1. Please confirm that the proposed Phase III study protocol (CA012-0) will fulfill the requirement for inclusion of a non-inferiority study in the NDA 505(b)(2)* submission for the breast carcinoma indication.

   FDA: The design of your proposed phase III protocol (CA012-0), if amended according to FDA statistical comments in subsequent questions, is acceptable to demonstrate non-inferiority of ABI-007 to Taxol in the treatment of breast cancer.

*Please refer to the February 5, 2001 EOP2 meeting minutes. The Oncology Division would accept this application as a 505(b)(2) because ABI-007 and Taxol have the same active ingredient. Consequently, the Division would accept a single randomized, non-inferiority phase 3 study, maintaining at least 75% of the Taxol effect, with response rate as a primary endpoint. This phase 3 study, along with phase 2 data showing similar activity, would support approval of ABI-007 in a second line metastatic breast cancer setting.

2. Please confirm that the CA012-0 protocol design is acceptable for the proposed Phase III, non-inferiority study.

FDA: Clinical - See previous answer to question 1.

Statistical

- **Sample size calculations could not be confirmed. We estimate 307 patients/arm.**

- **Please specify any stratification factors that will be considered for randomized stratification (e.g., country; prior chemotherapy; interval from breast cancer diagnosis to recurrence < 1 year; site of relapse: visceral versus bone/soft tissue; hormone receptor status; and number of metastatic sites: 0-1 versus 2 or more).**

3. The primary endpoint for CA012-0 is response rate and secondary endpoints include time to disease progression and survival. This is the sponsor's understanding based on discussions with the FDA in a previous meeting on February 5 and 6, 2001. Please confirm these endpoints for CA012-0.

   FDA: The proposed endpoints for the Phase III trial are acceptable.

4. Non-inferiority of ABI-007 compared to Taxol: Based on the discussions with the FDA in a previous meeting on February 5 and 6, 2001, it was agreed that for approval of ABI-007, it would be essential to demonstrate "non-inferiority" of ABI-007 compared to Taxol. "Non-inferior" was defined as ABI-007 having a response rate at least 75% of that of Taxol. Please confirm that achieving non-inferiority for ABI-007, as defined herein, will be sufficient for approval of ABI-007.

   FDA: If the proposed Phase III trial shows the non-inferiority margin for ABI-007 preserves at least 75% of the Taxol effect, ABI-007 could be approved for second line treatment of metastatic breast cancer. See answer to question 1.

5. Sample size/Statistical design/Interim analysis: The current study has been designed for a maximum of 265 evaluable patients per treatment arm. This sample size would provide at least 80% power at alpha level of .04 (making an assumption that TAXOL response rate is 30%, and ABI-007 response rate is only 33%), to prove that ABI-007 is not inferior to TAXOL, that is, having a response rate of at least 75% of that of TAXOL. The alpha level is chosen at .04 so that an interim analysis can be performed at alpha level of .01 and the overall type-one error is still less than .05. An interim analysis will be performed after 148 evaluable patients per arm have been treated for a minimum of two treatment cycles in each treatment arm, and have undergone the necessary tumor evaluations for the assessment of protocol response. Please confirm that this design for the Phase III trial is appropriate.

FDA: Sample size calculations could not be confirmed. We estimate 307 patients/arm.

Please clarify whether overall type I error is one-sided or two-sided. The alpha allocated for interim analysis appears to be large. We recommend use of O'Brien-Fleming boundary for spending alpha; however, see our answer to question 6.

6. The sponsor understands that if the interim analysis demonstrates non-inferiority of ABI-007 (as defined above) over Taxol, the Phase III study may be terminated and ABI-007 will be in condition for approval based on results of the interim analysis. Please confirm.

   FDA: This is a review issue. However, it is unlikely that in a single non-inferiority trial the size will be enough to establish equivalence or non-inferiority at interim analysis. We do <u>not</u> recommend conducting an interim analysis for efficacy in non-inferiority trials.

7. The Sponsor's (American BioScience, Inc.) understanding, based on the meeting with the FDA on February 5 and 6, 2001, is that the clinical data consisting of the 5 IND studies described in the clinical plan, with three studies being pivotal for the NDA 505(b)(2) submission (DM97-123, CA002-0 and CA012-2) is sufficient as a basis of approval for ABI-007. The IND clinical plan is summarized in Attachment 3 (Table 1 and Table 2) of the March 16, 2001 briefing document. Please confirm that DODP agrees with the above clinical plan.

FDA: Assuming that, upon review, we find that the phase III trial (CA012-0) was an adequately conducted study with internal consistency, the results from this trial plus those from study CA002 (a phase II trial) could provide sufficient evidence to support approval under 505(b)(2) if

(1) you study a sufficient subset of patients (at least 100 treated with ABI-007) in Taxol's approved indication ("TAXOL is indicated for treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated."),

and

(2) results from the single-arm study are supportive,

and

(3) ABI-007 is not more toxic than Taxol.

OTHER FDA COMMENTS:

A. CLINICAL

1. A comparison of toxicities between ABI-007 and Taxol will be important. A comparison of quality of life on the ABI-007 and Taxol arms is not likely to support labeling changes. We suggest instead that you evaluate symptoms known to occur after treatment with taxanes. For instance, we suggest that all patients fill out a peripheral neuropathy form at baseline and at each visit to document:

    1) no neuropathic symptoms

    2) paresthesias without functional changes

    3) neuropathic symptoms leading to mild changes in function (give list of functions to choose from)

    4) neuropathic sympoms leading to major changes in function (give list to choose from)

2. Also, you should carefully document duration and reversibility of neurotoxicity.

B. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

1. We recommend that you increase the sample size, for pharmacokinetic assessment of ABI-007, from 8 to 12 patients.

C. REGULATORY

1. **Final Protocols**

    Please submit final protocol(s) to the IND for FDA review.

2. **Submission Of Clinical Trials To NIH Public Access Data Base**

    Section 113 of the Food and Drug Modernization Act requires that specific information on clinical trials of drugs for serious or life-threatening diseases conducted under FDA's IND regulations (21

CFR part 312) be made available to the public in a public access data base. In response to this law, the National Institutes of Health (NIH), through its National Library of Medicine (NLM), developed the Clinical Trials Data Bank and is implementing it in a phased approach. The first version of the Clinical Trials Data Bank was made available to the public on February 29, 2000 at http://clinicaltrials.gov.

FDA published draft guidance entitled "*Information Program on Clinical Trials for Serious or Life-Threatening Diseases: Establishment of a Data Bank*" in the Federal Register on March 29, 2000 (65 FR 16620) at http://www.fda.gov/cder/guidance/3585dft.htm. The draft guidance stated that an implementation plan, addressing procedural issues, would be available later and include information on how to submit protocols to the Clinical Trials Data Bank. FDA and NIH are currently developing the implementation plan.

The clinical trial information for the NIH data bank should include the purpose of the trial, the patient eligibility criteria, the location of the trial sites and, a contact for patients wanting to enroll in the trial.

Until a final guidance issues, please contact Theresa Toigo at (301) 827-4460 or ttoigo@ oc.fda.gov who will explain the submission procedure for entering your clinical trial in the NIH Clinical Trial Data Bank.

3. **Financial Disclosure Final Rule**

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective, or that makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at http://www.fda.gov/oc/guidance/financialdis.html.

4. **Pediatric Final Rule**

Please note that you will need to address the December 2, 1998 Pediatric Rule (63 FR 66632) when you submit your NDA unless your product/indication has been designated an Orphan Drug. You may be eligible for a waiver under 21 CFR 314.55(c). Please refer to http://www.fda.gov/ohrms/dockets/98fr/120298c.txt.

5. **Pediatric Exclusivity**

Under the Food and Drug Administration Modernization Act, you have the opportunity for an exclusivity extension if ABI-007 is appropriate for an indication in pediatrics. If you choose to pursue pediatric exclusivity, your plans for a pediatric drug development, in the form of a Proposed Pediatric Study Request (PPSR), should be submitted so that we can consider issuing a Written Request.

Please refer to the "*Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505 A of the Federal Food, Drug and Cosmetic Act*" at Drug Information Branch (301) 827-4573 or http://www.fda.gov/cder/guidance/index.htm. You should also refer to our division's specific guidance on pediatric oncology Written Requests which is at http://www.fda.gov/cder/guidance/3756dft.htm.

UNRESOLVED ISSUES REQUIRING FURTHER DISCUSSION:

1.

2. APPEARS THIS WAY ON ORIGINAL

3.

ACTION ITEMS:

Item	Responsible Person	Due Date	Completion Date
1. Provide copy of FDA minutes to ABI.	D.Spillman, FDA		_____
2.			_____
3. APPEARS THIS WAY ON ORIGINAL			_____
4.			_____
5.			_____

The meeting concluded at approximately _____ a.m.

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

/s/

Dianne Spillman
5/10/01 05:11:05 PM
CSO
fax sent 5-1-01; checked in DFS 5-10-01