

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
21-248**

ADMINISTRATIVE DOCUMENTS

from ORIGINAL
3-27-00 SUBMISSION

NDA 21-248

(arsenic trioxide injection)

ITEM 13

PATENT INFORMATION

Cell Therapeutics, Inc.
March 2000

ITEM 13: PATENT INFORMATION

None of the patent applications owned by or licensed to Cell Therapeutics, Inc. for compositions, formulations, processes of preparation, or methods of use of (arsenic trioxide injection) for cancer treatment have issued.

APPEARS THIS WAY
ON ORIGINAL

FROM ORIGINAL
3-27-00 SUBMISSION

NDA 21-248

(arsenic trioxide injection)

ITEM 14

PATENT CERTIFICATION

Cell Therapeutics, Inc.
March 2000

ITEM 14: PATENT CERTIFICATION

No patent certification is required for this application, as the application does not reference a Reference Listed Drug (RLD) in the Orange Book.

APPROVED FOR SIGNATURE

d) Did the applicant request exclusivity?

YES / / NO / /

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

Seven years (Orphan Drug Exclusivity)

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

YES / / NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /_X_/

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

NDA # _____

NDA # _____

NDA # _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA # _____

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

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

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

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

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

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

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

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

YES /___/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

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

YES /___/ NO /___/

If yes, explain: _____

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

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____
 NDA # _____ Study # _____
 NDA # _____ Study # _____

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

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

Investigation #1	:	
IND # _____	YES /___/	NO /___/ Explain: _____
	:	_____
	:	_____
Investigation #2	:	
IND # _____	YES /___/	NO /___/ Explain: _____
	:	_____
	:	_____

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

Investigation #1	:	
YES /___/ Explain _____	:	NO /___/ Explain _____
_____	:	_____
_____	:	_____
Investigation #2	:	
YES /___/ Explain _____	:	NO /___/ Explain _____
_____	:	_____
_____	:	_____

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

YES /___/ NO /___/

If yes, explain: _____

ISI

Signature of Preparer
Title: Project Manager _____

9-1-00
Date

ISI

Signature of Office or Division Director

9/18/00
Date

cc:
Archival NDA 21-248
HFD-150/Division File
HFD-150/D.Spillman
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347

FROM ORIGINAL
3-27-00 SUBMISSION

NDA 21-248

(arsenic trioxide injection)

ITEM 16

DEBARMENT CERTIFICATION

**Cell Therapeutics, Inc.
March 2000**

(arsenic trioxide injection)
NDA 21-248

Item 16
Debarment Certification

ITEM 16: DEBARMENT CERTIFICATION

Cell Therapeutics, Inc. hereby certifies that it did not and will not use in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Jennie A. Jewell, Director, Regulatory Affairs and Compliance
Cell Therapeutics, Inc.

March 27, 2000
Date

NDA 21-248

ACTION PACKAGE TAB:

Division Director's Memo

**See Tab for
Group Leader's Memo**

CLINICAL TEAM LEADER AND DIVISION DIRECTOR
EXECUTIVE SUMMARY OF NDA

NDA 21248

DRUG Trisenox (Arsenic Trioxide Injection)

APPLICANT Cell Therapeutics, Inc.

DATE RECEIVED March 28, 2000

PROPOSED INDICATION "second-line therapy in patients with relapsed or refractory acute promyelocytic leukemia"

BACKGROUND

Several chemotherapeutic agents are approved for initial treatment of acute myelogenous leukemia (AML). Acute promyelocytic leukemia (APL) is a subgroup of AML. All Trans Retinoic Acid (ATRA) is approved for second-line treatment of APL. In practice most patients have both cytotoxic chemotherapy and ATRA as part of their initial treatment for APL.

CLINICAL TRIALS WITH TRISENOX

Clinical data is submitted from two single arm clinical studies on a total of 52 patients with relapsed or refractory APL treated with Trisenox. All patients had prior treatment with cytotoxic chemotherapy and ATRA. Patients in the single center study at MSKI (n=12) received Trisenox doses ranging from 0.06 to 0.20 mg/kg/day and patients in the multicenter study (n=40) received Trisenox doses of 0.15 mg/kg/day intravenously over 1 to 2 hours daily until the bone marrow was cleared of leukemia cells up to a maximum of 60 days. Patients with complete remission received consolidation with Trisenox for 25 additional doses over up to a five-week period. Consolidation began within 3-8 weeks after induction in the MSKI study and within 3-6 weeks after induction in the multicenter study.

In the MSKI study 9 of 12 Trisenox treated patients (75%) had a complete response (CR). Two of two children had a CR. In the multicenter study 28 of 40 Trisenox treated patients (70%) had a CR. Three of five children had a CR. No children under the age of five years were treated in either study.

In the multicenter study 18 of 24 patients (75%) who had their last ATRA < 1 year prior to Trisenox had a CR and 10 of 18 patients (56%) who had their last ATRA > 1 year prior to Trisenox had a CR. Generally patients who have not received ATRA for at least a year have a good chance of another CR with ATRA while patients who have received ATRA within less than a year have much less chance of another CR with ATRA.

In the multicenter study following induction and consolidation 18 patients received further Trisenox as maintenance therapy and 15 patients had bone marrow transplantation. At last follow-up 27 of 40 patients were alive with a median follow-up time of 484 days (range 280-755) and 23 of 28 complete responders remained in complete response with a median follow-up time of 483 days (range 280-755).

As an historical control the Applicant submits results of retreatment with ATRA in 27 patients at MSKI who are relapsed or refractory to prior treatment with cytotoxic chemotherapy and ATRA. Complete responses were seen in 6 of 27 patients (22%). Insufficient information is submitted on these historical control patients to assess their comparability to the Trisenox treated patients.

As a further point of comparison the CR rate in Trisenox treated patients is slightly better than the CR rate in APL patients who are refractory or relapsed after prior treatment with cytotoxic chemotherapy and are receiving ATRA for the first time.

Insufficient data is submitted on maintenance to assess this. Additional data may be submitted later. The present approval is limited to induction and consolidation.

Trisenox has a wide variety of adverse effects, but relatively few dose limiting or life-threatening adverse effects compared to other acute leukemia induction and consolidation regimens. Perhaps the most remarkable is QTc interval prolongation. In the 42 patients who received Trisenox at the recommended dose of 0.15 mg/kg/day, 16 (38%) had at least one QTc interval greater than 500 msec. One patient on concomitant amphotericin B had torsade de pointe during induction, but it did not recur during consolidation. The review team has worked with the FDA Cardiorenal Division to develop revised labeling with adequate precautions for managing patients with this problem.

CONCLUSION

Trisenox achieves a complete response rate of 70% at the recommended dose in patients with refractory or relapsed APL after prior treatment with cytotoxic chemotherapy and ATRA. The complete responses are durable. Toxicity is acceptable for this patient population.

RECOMMENDATION

This NDA is approvable with labeling revisions. See labeling revised by the FDA review team.

The Applicant has agreed to several Phase 4 Biopharm requirements.

ISI *MD*

Richard Pazdur, M.D.
Division Director DOPD
September 12, 2000

ISI

John R. Johnson, M.D.
Clinical Team Leader DOPD
September 12, 2000

cc NDA 21248
Division File
Hirschfeld
IbrahimA
Spillman
Pazdur

from ORIGINAL
3.27.00 SUBMISSION

(arsenic trioxide injection)
NDA 21-248

Item 19
Other

19.2 FINANCIAL DISCLOSURE

19.2.1 Form FDA 3454

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

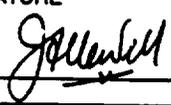
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached sheet	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME		TITLE	
Jennie Allewell		Director, Regulatory Affairs and Compliance	
FIRM/ORGANIZATION			
Cell Therapeutics, Inc.			
SIGNATURE		DATE	
		March 27, 2000	

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

LIST OF INVESTIGATORS

Principle Investigator Name and Address	Subinvestigators	Studies No.	# Patients Enrolled / # with CR ²
Steven Coutre, MD Stanford University Medical Ctr Division of Hematology S-161 300 Pasteur Drive Stanford, CA 94305-5112	Lenn Fechter, RN Thai Cao, MD Kathleen Dugan, MD	PLRXAS01	1 / 1
		PLRXAS02	1
Dan Douer, MD USC/Norris Comprehensive Cancer Ctr 1441 Eastlake Avenue, Room 3436 Los Angeles, CA 90033	Brahma Khonda, MD Sandeep Rajan, MD Renato Yuzon, MD Maria Sanchez, MD Alexandra M Levine, MD Ann F. Mohrbacher, MD	PLRXAS01	4 / 1
		PLRXAS02	1
Stanley R. Frankel, MD Georgetown University Medical Center Lombardi Cancer Center 3800 Reservoir Road, NW Washington, DC 20007	Harvey Luksenburg, MD Phillip Cohen, MD Craig Kessler, MD Carl Freter, MD	PLRXAS01	7 / 4
		PLRXAS02	3
Matthew Kalaycio, MD Director, Leukemia Program Cleveland Clinic Foundation 9500 Euclid Avenue T40 Cleveland, OH 44195	Alan Lichtin, MD Brad Pohlman, MD John Tate, MD	PLRXAS01	2 / 2
Hagop M. Kantarjian, MD MD Anderson Cancer Center Department of Hematology 1515 Holcombe Boulevard Houston, TX 77030-4095	Steven Kornblau, MD Elihu H. Estey, MD Sima C. Jeha, MD Miloslav Beran, MD Michael J. Keating, MD Moshe Talpaz, MD Susan O'Brien, MD Michael Andreef, MD Francis Giles, MD Emil J. Freireich, MD Jorge Cortes, MD Charles Koller, MD	PLRXAS01	3 / 3
		PLRXAS02	2
		DM98-211	5
Nikhil Munshi, MD Myeloma and Transplant Research Ctr Arkansas Cancer Research Ctr Univ. of Arkansas for Medical Sciences Little Rock, AR 72205	Bart Barlogie, MD, PhD Elais Anaissie, MD Raman K. Desikan, MD Maurizio Zangari, MD Seema Singhal, MD Jayesh Mahta, MD	UARK98-033	9
David A. Scheinberg, MD, PhD Memorial Sloan-Kettering Cancer Center 1275 York Avenue New York, NY 10021	Steven Soignet, MD Elizabeth Calleja, MD	97-66	12 / 9
		98-13	5
		PLRXAS01	14 / 11
		PLRXAS02	5
Eric Sievers, MD Fred Hutchinson Cancer Research Center 1100 Fairview Avenue North Seattle, WA 98024	Kathleen Shannon-Dorcy, MN, RN Frederick Appelbaum, MD	98-23	22
		PLRXAS01	2 / 1

Principle Investigator Name and Address	Subinvestigators	Studies No.	# Patients Enrolled / # with CR ^a
St en Soignet, MD Memorial Sloan-Kettering Cancer Center 1275 York Avenue New York, NY 10021	Elizabeth Calleja, MD Nai-Kong Cheug, MD, PhD David Spriggs, MD	98-46	28
Richard M. Stone, MD Dana-Farber Cancer Institute Room Dana 314 44 Binney Street Boston, MA 02115-6084	Holcombe Grier, MD Daniel De Angelo, MD Philip Amrein, MD	PLRXAS01	3 / 2
Martin S. Tallman, MD Northwestern University Medical School Div. of Hematology/Oncology, Suite 700 233 East Erie Street Chicago, IL 60611	Mir Yousuf Ali, MD Leo I. Gordon, MD Jane N. Winter, MD	PLRXAS01	4 / 3
		PLRXAS02	2

^a Number of patients with confirmed CR in the pivotal studies only

APPROVED
ON ORIGINAL

(arsenic trioxide injection)
NDA 21-248

Item 19
Other

19.2.2 FDA Form 3455

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Other

[redacted] was a subinvestigator for the clinical trials, Study No. [redacted] and [redacted]. Since the efficacy data collected is quantitative, it is concluded that there is minimum potential for bias of the clinical study results. Additionally, as a subinvestigator [redacted] generally was not directly involved in the collection of primary efficacy or safety data for these studies. Therefore the potential for bias is minimal.

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 9/25/00 4:10:48 PM
From: Karen Storms (STORMSK)
To: See Below
Subject: Inspection Summary for NDA-21-248

Hi Linda,

Please find attached the inspection summary for NDA 21-248. Hard copy to follow.

Should the EIR should contain additional information regarding this NDA you will be notified.

Per the field investigator, no objectionable conditions were noted that would prevent the use of the data from Dr. [REDACTED] site.

Thanks,
Karen

To: Linda Carter (CARTERL)
Cc: Dianne Spillman (SPILLMAND)
Cc: Dotti Pease (PEASE)
Cc: Gerald Hajarjian (HAJARIAN)
Cc: Antoine El Hage (ELHAGEA)
Cc: Robert Young (YOUNGR)



Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: September 25, 2000

TO: Diane Spillman, Regulatory Project Manager
Steven Hirschfeld, M.D., Clinical Reviewer
Division of Oncology Drug Products, HFD-150

THROUGH: Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

FROM: Gerald R. Hajarian

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 21-248

APPLICANT: Cell Therapeutics, Inc.

DRUG: Trisenox® (arsenic trioxide) Injection

CHEMICAL CLASSIFICATION: Type 1

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of acute promyelocytic leukemia

CONSULTATION REQUEST DATE: April 20, 2000

ACTION GOAL DATE: September 28, 2000

I. BACKGROUND:

Inspection assignments were issued on May 2, 2000 for two domestic clinical investigators and on May 12, 2000 for the sponsor, for the purpose of validating data in support of pending NDA 21-248.

II. RESULTS (by site):

NAME	CITY	STATE or COUNTRY	ASSIGNED DATE	EIR RECEIVED	CLASSIFICATION
[REDACTED]	[REDACTED]	[REDACTED]	5/2/00	6/00	VAI
[REDACTED]	[REDACTED]	[REDACTED]	5/2/00		VAI *
Cell Therapeutics	Seattle	WA	5/12/00	6/00	NAI

A. [REDACTED]

Dr. Stanley Frankel was the original principal investigator for this study. However, Dr. Frankel is no longer employed at Georgetown, and [REDACTED] who was a sub-investigator [REDACTED] assumed responsibility as principal investigator.

Seven subjects were enrolled and all 7 subjects' records were audited. Four of the 7 completed the study. One was lost to follow-up, one refused treatment, and one did not respond. Five of the 7 subjects did not sign the current version of the informed consent; case report forms were not always accurate and complete; and the IRB was not notified within 72 hours of 3 serious adverse events. Monitoring reports revealed protocol violations and deficiencies in test article accountability records. Subsequent monitoring reports confirmed that corrective action was generally taken.

Although various objectionable conditions were noted, the data appear to be acceptable.

B. [REDACTED]

- Classification of this site is based on telephone call with the field investigator. Form FDA 483 is being issued with minor violations per field investigator.

C. Cell Therapeutics, Inc.

Cell Therapeutics, Inc. was established in September, 1991 and acquired PolaRx Biopharmaceuticals, Inc. and the rights to Trisenox® in January, 2000. The inspection revealed a signed contract with a contract research organization (CRO), [REDACTED]

[REDACTED] The contract called for a pre-study initiation visit, interim visits, and a close out visit by [REDACTED]

[REDACTED] The procedures for selecting clinical investigators and the SOPs for monitoring clinical

studies were adequate. The monitoring reports were reviewed and were adequate. Several minor discrepancies in reporting adverse events were noted. No Form FDA 483 was issued.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS:

Although there were minor deficiencies noted in the conduct of [redacted] study which are described above, the data from the two clinical investigator sites and the results of the sponsor inspection appear acceptable for use in support of pending NDA 21-248. As noted above, this summary is based partially on the Form FDA 483 and a teleconference with the FDA investigator regarding [redacted] study. Should the EIR for [redacted] contain significant additional findings, you will be notified.

- * Should the EIR for [redacted] contain additional information that would change our recommendation regarding study data, you will be informed.

Key to Classifications

NAI = No deviation from regulations. Data acceptable

VAI = Minor deviations(s) from regulations. Data acceptable

VAIr= Deviation(s) form regulations, response requested. Data acceptable

OAI = Significant deviations for regulations. Data unreliable

Pending = Inspection not completed

/S/

Gerald R. Hajarian
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

/S/

Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

DISTRIBUTION:

NDA 21-248 Division File
HFD-45/Program Management Staff (electronic copy)
HFD-47/Young/Hajarian
HFD-47/GCP II Branch Chief
HFD-45/RF



DEPARTMENT OF HEALTH & HUMAN SERVICES

Spillman

Food and Drug Administration
Rockville MD 20857

JUL 27 2000

Dear Dr. [redacted]

Between June 1-7, 2000, Ms. Melanie M. Mayor, representing the Food and Drug Administration (FDA), met with representatives of ([redacted]) to review your conduct of a clinical study (protocol ([redacted])) of the investigational drug arsenic trioxide, performed for ([redacted]). This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Ms. Mayor presented and discussed with representatives of your institution the items listed on Form FDA 483, Inspectional Observations. The discussion included, but was not limited to, informed consent, record keeping, and the non-reporting of adverse events. We understand that the items noted on Form FDA 483 pre-date your involvement as a principal investigator in this study.

We appreciate the cooperation shown Investigator Mayor during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me by letter at the address listed below.

Sincerely yours,


Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

FEI: 3003035944

Field Classification: VAI

Headquarters Classification:

1)NAI

2)VAI-no response required

3)VAI-response requested

If Headquarters classification is a different classification, explain why:

Deficiencies noted:

inadequate informed consent

inadequate drug accountability

failure to adhere to protocol

inadequate records

failure to report adverse events to IRB within 72 hours, as required

other:

cc:

HFA-224

HFC-230

HFD-150/Div. Dir./Mazdur

HFD-150/MO/Hirschfeld

HFD-150/PM/Spillman

HFD-150/Doc. Rm. NDA 21-248

HFR-CE250/DIB/Draper

HFR-CE250/Mayor

HFR-CE250/BIMO Monitor/Glasgow

HFD-45 r/f

HFD-47

HFD-47/Young/Hajarian

r/d:GRH:7/26/00

revised 7/27/00

Note to Rev. Div. M.O.

7 subjects enrolled

All 7 medical charts audited

1 lost to follow up, 1 refused treatment, 1 failed to respond

Although minor deficiencies were noted, the data appear to be acceptable.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Spillman

Food and Drug Administration
Rockville MD 20857

James A. Bianco, M.D.
President/CEO
Cell Therapeutics, Inc.
201 Elliott Avenue West, Suite 400
Seattle, Washington 98119

JUL 12 2000

Dear Dr. Bianco:

Between May 30 and June 2, 2000, Mr. Carl A. Anderson, representing the Food and Drug Administration (FDA), met with you and your staff to review your firm's monitoring practices and procedures of clinical studies. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections of sponsors/contract research organizations/monitors, designed to ensure the proper conduct of clinical studies for submission to the FDA, and to assure that the rights and welfare of the human subjects of those studies have been protected.

This inspection focused on protocol #PLRXAS01: "Multicenter Study of Arsenic Trioxide in Relapsed or Refractory Acute Promyelocytic Leukemia". Monitoring of this study was conducted by [redacted] under contract to PolaRx Biopharmaceuticals, Inc., which was purchased by your firm in January, 2000, including the rights to the investigational drug.

From our evaluation of the inspection report and the documents submitted with the report, we conclude that Cell Therapeutics, Inc./RTL adhered to pertinent federal regulations governing sponsor/contract research organization/monitor responsibilities for the conduct of clinical studies and the protection of human subjects.

We appreciate the cooperation shown Investigator Anderson during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me in writing at the address below.

Sincerely yours,

[Signature]
Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Page 2 - James A. Bianco, M.D.

Field Classification: NAI

Headquarters Classification:

- 1) NAI
- 2) VAI-no response required
- 3) VAI-response requested

If Headquarters classification is a different classification, explain why:

Deficiencies noted: None

- inadequate informed consent
- inadequate drug accountability
- failure to adhere to protocol
- inadequate records
- failure to report ADRS _____
- other: inadequate documentation of monitor training and training files

cc:

HFA-224
HFC-230
HFD-150/Director/Pazdur
HFD-150/MO/Hirschfeld
HFD-150/PM/Spillman
HFD-150/Doc. Rm. NDA 21-248
HFD-45 r/f
HFD-47 c/r/s
HFD-47 Young/Hajarian
HFR-PA350/DIB/Corcoran
HFR-PA350/Anderson
HFR-PA3540/BIMO Monitor/Mattson

r/d:GRH:7/7/00

Note to Review M.O.

Procedures for selecting clinical investigators and for monitoring studies were adequate.
No Form FDA was issued.

8.1 LIST OF INVESTIGATORS AND IND NUMBERS

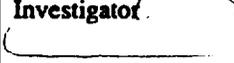
Table 8.1.1 List of Investigators

Investigator Name and Address	Studies Conducted	# Patients Enrolled / # with CR ^a	Location of Data Listings	Location of CRFs
Edwin Alyea, MD Dana-Farber Cancer Institute Boston, MA	Compassionate Use Study E99-5209	1	None	None
Giuseppe Avvisati, MD, Ph.D. Ematologia Universita La Sapienza Via Benevento 6 00161 Rome, Italy	Compassionate Use (using protocol PLRXAS01)	7	None	None
Jules Blank, MD St. Vincent Hospital Wisconsin	Compassionate Use Study E99-5194	1	None	None
Joseph Eugene Briere, MD Louisiana Oncology Associates 601 West St. Mary Blvd. Suite 100 Lafayette, LA 70506	PLRXAS02	1	None	None
Steven Coutre, MD Stanford University Medical Ctr Division of Hematology S-161 300 Pasteur Drive Stanford, CA 94305-5112	PLRXAS01	1 / 1	Item 11 Vol. 2 & 3	Item 12 Vol. 17
	PLRXAS02	1	None	None
	Extension Treatment Investigator (98-13)	1	None	None
Dan Douer, MD USC/Norris Comprehensive Cancer Ctr 1441 Eastlake Avenue, Room 3436 Los Angeles, CA 90033	PLRXAS01	4 / 1	Item 11 Vol. 2 & 3	Item 12 Vol. 9, 10, 15, 16, 19
	PLRXAS02	1	None	None
Stanley R. Frankel, MD, Georgetown University Medical Center Lombardi Cancer Center 3800 Reservoir Road, NW Washington, DC 20007	PLRXAS01	7 / 4	Item 11 Vol. 2 & 3	Item 12 Vol. 7-8, 11, 12, 14-16
	PLRXAS02	3	None	None
Steven D. Gore, MD Johns Hopkins Hospital Department of Oncology 600 N. Wolfe Street Onc 2-109 Baltimore, MD 21287	PLRXAS01 no patients enrolled	0	None	None

Table 8.1.1 List of Investigators

Investigator Name and Address	Studies Conducted	# Patients Enrolled / # with CR ^a	Location of Data Listings	Location of CRFs
Leonard T. Heffner, MD Emory University School of Medicine Winship Cancer Center 1365B Clifton Road, NE, Suite 4100 Atlanta, GA 30322	PLRXAS01 no patients enrolled	0	None	None
Charles Hess, MD University of Virginia Virginia	Compassionate Use Study E99-5121	1	None	None
Matthew Kalaycio, MD Director, Leukemia Program Cleveland Clinic Foundation 9500 Euclid Avenue T40 Cleveland, OH 44195	PLRXAS01	2 / 2	Item 11 Vol. 2 & 3	Item 12 Vol. 18-20
	Compassionate Use Study E99-5246	1	None	None
Arthur N. Kales, MD Fairfax-Prince William Hemat./Oncology 3289 Woodburn Road Suite 230 Annandale, VA 22003	Extension Use Investigator.	1	None	None
Hagop M. Kantarjian, MD MD Anderson Cancer Center Department of Hematology 1515 Holcombe Boulevard Houston, TX 77030-4095	PLRXAS01	3 / 3	Item 11 Vol. 2 & 3	Item 12 Vol. 9-11, 16-17
	PLRXAS02	2	None	None
	DM98-211	5	None	None
A. Kung, MD Dana-Farber Cancer Institute Boston, MA	Compassionate Use Study E99-5221	1	None	None
Charles Linker, MD University of California, San Francisco School of Medicine 400 Parnassus Avenue, Room A-502 San Francisco, CA 94143	PLRXAS01 no patients enrolled	0	None	None
Harvey Luksenburg, MD Georgetown University Medical Center Lombardi Cancer Center 3800 Reservoir Road, NW Washington, DC 20007	Has assumed responsibility for patients enrolled by S. Frankel	0	None	None
Ken Miller, MD New England Medical Center Boston, MA	Compassionate Use Study E99-5255 Study E99-5262	2	None	None

Table 8.1.1 List of Investigators

Investigator Name and Address	Studies Conducted	# Patients Enrolled / # with CR ^a	Location of Data Listings	Location of CRFs
Nikhil Munshi, MD Myeloma and Transplant Research Ctr Arkansas Cancer Research Ctr Univ. of Arkansas for Medical Sciences Little Rock, AR 72205	UARK98-033 (Patients with multiple myeloma)	9	None	None
Kazunori Ohnishi, MD Department of Medicine III Hamamatsu Univ. School of Medicine 3600 Handa-cho, Hamamatsu, 431-3192 Japan	Compassionate Use (using protocol PLRXAS01)	4 / 3	None	None
David L. Porter, MD Univ. of Pennsylvania, Dept of Medicine Hematology-Oncology Division 6 PennTower 3400 Spruce Street Philadelphia, PA 19104	Extension Use Investigator 	1 1	None	None
Memorial Sloan-Kettering Cancer Center 1275 York Avenue New York, NY 10021	97-66	12 / 9	Item 11 Vol. 1	Item 12 Vol. 1-7
	98-13	5	None	None
	PLRXAS01	14 / 11	Item 11 Vol. 2 & 3	Item 12 Vol. 7-13, 15, 17, 19-21
	PLRXAS02	5	None	None
	98-23	22 (12 PK)	Item 11 Vol. 4	Item 12 Vol. 23-25
Gary J. Schiller, MD UCLA School of Medicine Hematology/Oncology Div., Room 42-121 Center for Health Sciences Los Angeles, CA 90024	PLRXAS01 no patients enrolled	0	None	None
Harvey Segal, MD Eastern Maine Medical Center Bangor, ME	Compassionate Use Study E99-5193	1	None	None
Ronald Sham, MD Rochester General Hospital Dept. of Hematology, Box 266 Rochester, NY 14621	Extension Use Investigator 	1	None	None
Eric Sievers, MD Fred Hutchinson Cancer Research Center 1100 Fairview Avenue North Seattle, WA 98024	PLRXAS01	2 / 1	Item 11 Vol. 2 & 3	Item 12 Vol. 19-22

We request that the inspections be performed and the Inspection Summary Results be provided by June 30, 2000. We intend to make a regulatory decision on this application by July 28, 2000, possibly earlier. Any modifications to our review schedule will be communicated to you through e-mail by the project manager, Dianne Spillman

Should you require any additional information please contact Jennie Allewell, Cell Therapeutics Inc. Regulatory Affairs and Compliance Director, at (206) 270-8424.

The reviewing medical officers for this application are

Steve Hirschfeld, M.D., Ph.D.....(301) 827-1532* -- primary contact
Amna Ibrahim, M.D.....(301) 827-1539

The project manager for this application is Dianne Spillman, (301) 594-5746.

The division's action goal date is July 28, 2000, or earlier. Dianne Spillman, project manager, will communicate any modifications to the review schedule after the next team meeting scheduled for May 12, 2000.

ATTACHMENT (6 pages)

cc: ORIG. NDA 21-248
Div. File
HFD-344/R.Young
HFD-150/S.Hirschfeld
/A.Ibrahim
HFD-150/D.Spillman/4-20-00

Table 8.1.1 List of Investigators

Investigator Name and Address	Studies Conducted	# Patients Enrolled / # with CR ^a	Location of Data Listings	Location of CRFs
Samuel Smith, MD Greenville Memorial Hospital 701 Grove Road Greenville, SC 29605	Extension Use Investigator (PLRXAS02)	1	None	None
Steven Soignet, MD Memorial Sloan-Kettering Cancer Center 1275 York Avenue New York, NY 10021	98-46 (In patients with advanced hematologic malignancy)	28 (22 PK)	Item 11 Vol. 5	Item 12 Vol. 25
Richard M. Stone, MD Dana-Farber Cancer Institute Room Dana 314 44 Binney Street Boston, MA 02115-6084	PLRXAS01	3 / 2	Item 11 Vol. 2 & 3	Item 12 Vol. 17, 18, 21
Martin S. Tallman, MD Northwestern University Medical School Div. of Hematology/Oncology, Suite 700 233 East Erie Street Chicago, IL 60611	PLRXAS01	4 / 3	Item 11 Vol. 2 & 3	Item 12 Vol. 12-14, 17, 18
	PLRXAS02	2	None	None
Connie Uzel, MD Division of Hematology University of South Alabama 307 University Boulevard CCCB, Room 414 Mobile, AL 36688	Extension Use Investigator (PLRXAS02)	1	None	None
George Jay Weiner, MD Univ. of Iowa Hospital and Clinics Cancer Center Administration 200 Hawkins Drive Room 5970 JPP Iowa City, IA 52242	PLRXAS02	1	None	None

^a Number of patients with confirmed CR in the pivotal studies only

Table 8.1.2 List of INDs

STUDY NUMBER	INVESTIGATOR NAME
97-66	
98-13	
98-23	
98-46	Steven Soignet, MD

Table 8.1.2 List of INDs

STUDY NUMBER	INVESTIGATOR NAME	
(transferred to Cell Therapeutics, Inc. in March 2000)		
PLRXAS01	Steven Coutre, MD Dan Douer, MD Stanley R. Frankel, MD Matthew Kalaycio, MD Hagop M. Kantarjian, MD Eric Sievers, MD Richard M. Stone, MD Martin S. Tallman, MD	
PLRXAS02	Joseph E. Brierre, MD Dan Douer, MD Hagop M. Kantarjian, MD Harvey Luksenburg, MD Martin S. Tallman, MD George J. Weiner, MD	
UARK 98-033	Nikhil Munshi, MD	
DM 98-211	Hagop M. Kantarjian, MD	
Compassionate Use, Italy	Giuseppe Avvisati, MD	
Compassionate Use in Patients with APL		
NCI Monitor: Anthony Murgo, MD; NSC Number: 706363		
Study E99-5121	Charles Hess, MD	
Study E99-5193	Harvey Segal, MD	
Study E99-5194	Jules Blank, MD	
Study E99-5209	Edwin Alyea, MD	
Study E99-5221	A. Kung, MD	
Studies E99-5255 E99-5262	Ken Miller, MD	
Study E99-5246	Matthew Kalaycio, MD	
Individual Investigator for extension treatment of patients with CR in prior ATO studies		
IND Number	Protocol Number	Investigator
	98-13	Arthur N. Kales, MD
	98-13	David L. Porter, MD
	98-13	Steven Coutre, MD
	98-13	Ronald Sham, MD
	PLRXAS02	Connie Uzel, MD
	98-13	David L. Porter, MD
	PLRXAS02	Samuel Smith, MD

10 STUDY PATIENTS

This study was conducted at nine centers in the United States during the 15 months from April 22, 1998 to July 5, 1999. The last followup contact for the 29 surviving patients was on December 31, 1999. Table 2 shows the number of patients, and the patient numbers, enrolled by each center.

Table 2. Patient Enrollment by Center

PolaRx Site #	Investigator Name and Institution	Number of Patients Enrolled	Patient Numbers Enrolled
7	Memorial Sloan-Kettering Cancer Center New York, NY	14	1013 1027 1014 1028 1016 1032 1017 1039 1020 1044 1023 1047 1026 1049
1	Stanley R. Frankel, MD Georgetown University Medical Center Washington, DC	7	1015 1031 1022 1033 1024 1035 1030
8	Daniel Douer, MD USC/Norris Cancer Center Los Angeles, CA	4	1019 1036 1034 1045
5	Martin S. Tallman, MD Northwestern University Medical School Chicago, IL	4	1025 1038 1029 1042
3	Hagop Kantarjian, MD M.D. Anderson Cancer Center Houston, TX	3	1018 1021 1037
6	Richard M. Stone, MD Dana-Farber Cancer Institute Boston, MA	3	1041 1050 1051
16	Matthew Kalaycio, MD Cleveland Clinic Foundation Cleveland, OH	2	1043 1048
15	Eric Sievers, MD Fred Hutchinson Cancer Research Center Seattle, WA	2	1046 1052
11	Steven Coutre, MD Stanford University Medical Center Stanford, CA	1	1040

APR 20 2000

MEMORANDUM

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

DATE: April 20, 2000

FROM: Richard Pazdur, M.D. *R Pazdur*
Director
Division of Oncology Drug Products, HFD-150

TO: David LePay, M.D.
Director, Division of Scientific
Investigations, HFD-340

SUBJECT: Request for Clinical Inspections for NDA 21-248
(arsenic trioxide injection)
PDUFA goal date is September 28, 2000

Indication: for the induction of remission and consolidation in patients with relapsed or refractory acute promyelocytic leukemia (APL), characterized by the presence of the t(15;17) translocation and/or the presence of the PML/RAR-alpha gene who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, or for whom anthracycline-based chemotherapy is contraindicated.

We have identified the following study as being pivotal to the approval of this application and have selected the following specific sites to be audited.

STUDY Number (site ID, investigator/address)

PLRXAS01: sites # 7 and 1 (see attached pages: 8 vol 1 P001-005 and 8 vol 3 P101)

1. Site # 1

Stanley R. Frankel, M.D. 
Georgetown University Medical Center
Lombardi Cancer Center
3800 Reservoir Road, N.W.
Washington, DC 20007

2. Site #7

David A Scheinberg, M.D., Ph.D.
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10021

FROM ORIGINAL
3.27.00 SUBMISSION

NDA 21-248

..... (arsenic trioxide injection)

ITEM 18

USER FEE FORM

Cell Therapeutics, Inc.
March 2000

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Cell Therapeutics, Inc.
201 Elliott Avenue west
Suite 400
Seattle, WA 98119

3. PRODUCT NAME

..... (arsenic trioxide injection)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE
AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY
REFERENCE TO _____

(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(206) 282-7100

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER

21-248

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT
APPROVED UNDER SECTION 505 OF THE FEDERAL
FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN
EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,
Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT
QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of
the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL
GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED
COMMERCIALY
(Self Explanatory)

FOR BIOLOGICAL PRODUCTS ONLY

WHOLE BLOOD OR BLOOD COMPONENT FOR
TRANSFUSION

A CRUDE ALLERGENIC EXTRACT PRODUCT

AN APPLICATION FOR A BIOLOGICAL PRODUCT
FOR FURTHER MANUFACTURING USE ONLY

AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT
LICENSED UNDER SECTION 351 OF THE PHS ACT

BOVINE BLOOD PRODUCT FOR TOPICAL
APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

IS/

TITLE

Director, Regulatory Affairs
and Compliance

DATE

March 27, 2000

from ORIGINAL
3-27-00 SUBMISSION

¹ (arsenic trioxide injection)
NDA 21-248

Item 19
Other

ITEM 19: OTHER

19.1 ORPHAN DESIGNATION

Pursuant to 21 U.S.C. § 360bb, PolaRx Biopharmaceuticals, Inc. received orphan drug designation for arsenic trioxide for the treatment of relapsed APL. See FDA letter dated March 3, 1998 attached in Section 19.1.1.

In a letter to the Office of Orphan Drug Products dated March 10, 2000, PolaRx Biopharmaceuticals, Inc. requested that the orphan designation of TM (arsenic trioxide injection) be transferred to Cell Therapeutics, Inc. This letter is attached as Section 19.1.2.

Cell Therapeutics, Inc. has notified the Office of Orphan Drug Products of our intention to exercise the statutory period of seven years of orphan drug exclusivity if we are the first sponsor to obtain market approval for arsenic trioxide for the treatment of relapsed APL.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: May 15, 2000

DUE DATE: June 30, 2000

OPDRA CONSULT #: 00-0150

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

THROUGH: Dianne Spillman, Project Manager
HFD-150

PRODUCT NAME:

(Arsenic Trioxide Injection)
1 mg/mL, 10 mL ampule

Alternate Name:
Trisenox

NDA #: 21-248

MANUFACTURER: Cell Therapeutics, Inc.

SAFETY EVALUATOR: Carol Holquist, R.Ph.

SUMMARY: In response to a consult from the Division of Oncology Drug Products (HFD-150), OPDRA conducted a review of the proposed proprietary names [redacted] and "Trisenox" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: From a safety perspective, OPDRA has no objections to the use of the name "Trisenox". We do not recommend use of the name [redacted]. We have also made recommendations for labeling revisions to minimize potential errors with the use of this product. See the checked box below.

- FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.
- FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from this date forward.
- FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDAs from this date forward.

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/

Peter Honig, M.D.
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 20, 2000

NDA NUMBER: 21-248

NAME OF DRUG: (Arsenic Trioxide Injection) 1 mg/mL, 10 mL ampule

NDA HOLDER: Cell Therapeutics, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Oncology Drug Products (HFD-150) for assessment of the tradenames [redacted] and Trisenox. The sponsor previously submitted the name [redacted] however following a legal search, the sponsor determined the name was unacceptable and has since revised it to [redacted]. The container labels, carton and insert labeling provided for review and comment reflect the old name [redacted].

PRODUCT INFORMATION

[redacted] /Trisenox (Arsenic Trioxide Injection) is indicated for induction of remission and consolidation in patients with relapsed or refractory acute promyelocytic leukemia (APL), characterized by the presence of the t(15;17) translocation and/or the presence of the PML/RAR-alpha gene who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, or for whom anthracycline-based chemotherapy is contraindicated.

[redacted] Trisenox will be supplied as a sterile, clear, colorless solution in 10 mL glass single use ampules. The product contains no preservatives and should be diluted immediately with 100 to 250 mL 5% Dextrose Injection. The drug is administered at a fixed dose of 0.15 mg/kg daily, however the total number of days of administration differs based on the treatment schedule. During the induction treatment schedule the drug is administered until the bone marrow is cleared of leukemia cells not to exceed 60 days and during the consolidation and maintenance schedule the drug is administered for 25 days.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{i,ii,iii} as well as several FDA databases^{iv} for existing drug names which sound alike or look alike to [redacted] or **Trisenox** to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted^v. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

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

1. *Trisenox*

There were no proprietary names for currently marketed U.S. products identified by the Expert Panel that were believed to have significant look-alike, sound-alike properties.

2. [redacted]

A few product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with [redacted]. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

Confusion of [redacted] with Atropen (Atropine, emergency kit) seems unlikely, given differences in dosing schedule, packaging configuration, and usual dosing schedule. However, significant concerns were raised in connection with potential confusion between [redacted] and Ativan when written.

ⁱ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference, London: Pharmaceutical Press, Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

ⁱⁱ American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

^{iv} COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

^v WWW location <http://www.uspto.gov/tmdb/index.html>.

TABLE 1

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
	Injection, Arsenolite 1 mg/mL, (Oncology)	0.15 mg/kg daily	
Ativan	Lorazepam (Rx, benzodiazepine) Oral tablet – 0.5 mg, 1 mg and 2 mg Injection (IV/IM) - 1 mg/0.5 mL, 2 mg/mL and 4 mg/mL	Oral: Varies with indication, the usual range is 2 to 6 mg/day given in divided doses Injection: Varies with indication, i.e., status epilepticus 4 mg; preanesthetic 0.05 mg/kg	S/A, L/A per OPDRA
Atropen	Injection. (Rx, atropine sulfate)	Prefilled automatic injection device	S/A, L/A per OPDRA
		*Frequently used, not all-inclusive.	**L/A (look-alike), S/A (sound-alike)

A. STUDY CONDUCTED BY OPDRA

1. Methodology

A separate study was conducted within FDA for each proposed proprietary name to determine the degree of confusion of [redacted] and Trisenox with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 92 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote inpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for [redacted] or Trisenox (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal inpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
<i>Inpatient:</i> Start [redacted] 10 mg in 250 mL D5W over 2 hrs	<i>Inpatient:</i> Start [redacted] 10 mg in 250 mL D5W over 2 hrs
<i>Inpatient:</i> Start [redacted] 10 mg in 250 mL D5W, give over 2 hrs	
TRISENOX	
<i>Inpatient:</i> D/C Trisenox after the last dose today	<i>Inpatient:</i> D/C Trisenox after the last dose today
<i>Inpatient:</i> DC Trisenox after dose today	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Atrisen" or "Trisenox" response	Other response
Written: Inpatient	31	22 (71%)	11 (50%)	11 (50%)
Inpatient	31	13 (42%)	13 (100%)	0 (0%)
Verbal: Inpatient	30	8 (27%)	0 (0%)	8 (27%)
Total:	92	43 (47%)	24 (56%)	19 (44%)
TRISENOX				
Written: Inpatient	31	22 (71%)	17 (77%)	5 (23%)
Inpatient	31	13 (42%)	13 (100%)	0 (0%)
Verbal: Inpatient	30	8 (27%)	1 (13%)	7 (88%)
Total:	92	43 (47%)	31 (72%)	12 (28%)

a.

Among participants in the written prescription studies, 11 of 35 respondents (31%) interpreted the name incorrectly. *Two respondents interpreted the name as "Ativan".*

Among verbal prescription study participants, 8 of 8 (100%) of the study participants interpreted the name incorrectly. Most of the incorrect name interpretations were phonetic variations of _____.

b. *Trisenox*

Among participants in the written prescription studies, 5 of 35 (14%) of the respondents interpreted the name incorrectly. *One respondent interpreted the name as "Tussionex". The remaining responses were phonetic variations of "Trisenox".*

Among verbal prescription study participants, 7 of 8 (88%) of the respondents interpreted the name incorrectly. Most of the incorrect name interpretations were phonetic variations of "Trisenox".

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Trisenox	Injection, Arsenolite 1 mg/mL, (Oncology)	0.15 mg/kg daily	
Tussionex	Extended-release Oral Suspension (Rx, Hydrocodone polistirex and Chlorpheniramine polistirex)	Adult – 5 mL (1 teaspoonful) every 12 hours Children – 2.5 mL (1/2 teaspoonful every 12 hours)	S/A, L/A per OPDRA
		*Frequently used, not all-inclusive.	**L/A (look-alike). S/A (sound-alike)

A. SAFETY EVALUATOR RISK ASSESSMENT

1. [redacted]

In reviewing the proprietary name "[redacted]" the primary concerns raised were related to a couple of sound-alike, look-alike names that already exist in the U.S. marketplace. One product, Ativan (an Rx product, lorazepam) was believed to be the most problematic in terms of medication error prevention.

We conducted prescription studies to simulate the prescription ordering process. *In this case, there was confirmation that [redacted] could be confused with Ativan, as this name had two respondents provide this interpretation in handwritten prescriptions.* [redacted] and Ativan are both injectable products, which will be ordered on a mg/kg basis. The names contain almost the same number of characters (6 vs. 7) and are a couple of letters off. When scripted [redacted] looks very similar to Ativan. Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretations with these drug products. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

For these reasons, we do not recommend use of the name [redacted]

2. *Trisenox*

In reviewing the alternate proprietary name "Trisenox", there were no names identified in the Expert Panel Discussion that were believed to have significant sound-alike, look-alike properties.

We conducted prescription studies to simulate the prescription ordering process. In this case, Trisenox was confused with the prescription drug "Tussionex". "Tussionex" is a combination narcotic antitussive and analgesic oral solution. We recognize that a positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. However, prescriptions for Tussionex will most likely be written for 1 teaspoonful or ½ teaspoonful rather than a "mg" amount. In addition, Tussionex is a narcotic and would have special handling. Trisenox and Tussionex are different dosage forms and will have different dosing schedules (daily vs. q12h). The written prescription that was misinterpreted as Tussionex contained no dosing information because it was an order to discontinue the drug.

For these reasons, we do not object to the use of the alternate proposed proprietary name "Trisenox".

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the container labels, carton labeling, and draft package insert for [redacted] Trisenox, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user error.

A. CONTAINER LABEL (10 mL) and CARTON LABELING (10 x 10 mL)

1. The expression of strength should be revised on all labels and labeling to indicate the total contents of the ampule. We suggest the following:

10 mg/10 mL
(1 mg/mL)

2. Important information such as the drug name and strength should have the greatest prominence on the container labels and carton labeling. The company logo "cti" appears to have greater prominence on the labels and labeling than the proprietary and established names. We suggest the labels and labeling be revised to decrease the amount of space devoted to the corporate logo.

IV. RECOMMENDATIONS

1. From a safety perspective, OPDRA has no objections to the use of the proprietary name "Trisenox". We do not recommend use of the name _____
2. We have made recommendations for labeling revisions to minimize potential errors with the use of this product.

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Holquist, R.Ph. at 301-827-3244.



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6/23/00

Concur:



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6/24/2000