DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-248

SEP 25 2000

Cell Therapeutics, Inc
201 Elliot Avenue West #400
Seattle, WA 98119

Attention: Jennie Allewell
Director
Regulatory Affairs and Compliance

Dear Ms. Allewell:

Please refer to your new drug application (NDA) dated March 27, 2000, received March 28, 2000, and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trisenox™ (arsenic trioxide) injection, 10 mg/10 mL (1 mg/mL) ampule.

We acknowledge receipt of your submissions dated April 12, 17, 18, 26, and 28, June 2, 23, 26, and 27, July 10, 11, 12, 17, 18, 19, 21, and 27, August 1, 18, and 24, and September 5, 2000.

This new drug application provides for the use of Trisenox (arsenic trioxide) injection for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 21-248." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submission dated August 18, 2000. These commitments, along with any completion dates agreed upon, are to:

1. [ ].

2. Conduct an *in vitro* study to assess the inhibition potential of arsenic trioxide on the major cytochrome P-450 isoenzymes.

   As you agreed in your August 18, 2000 submission, you anticipate starting this study by the end of the year 2000.

3. Develop additional pediatric pharmacokinetic data. From the limited pediatric pharmacokinetic information provided in this NDA (n=3), it appears possible that pediatric patients may experience greater exposure to arsenic trioxide than adults. Since the drug is approved for a patient population down to the age of 5 and the pharmacokinetics of arsenic trioxide in the pediatric population is as yet poorly described, a formal pharmacokinetic study should be conducted in an appropriate number of children to adequately characterize the pharmacokinetics of arsenic trioxide in the pediatric population. Alternatively, this information could be obtained from a pediatric efficacy trial using a prospectively planned population pharmacokinetic approach. We refer you to our published document titled "*Guidance for Industry, Population Pharmacokinetics*".

   As you agreed in your August 18, 2000 submission, you will evaluate the pharmacokinetics of arsenic trioxide in an appropriate number of pediatric patients with cancer for whom arsenic trioxide is an appropriate therapy when the assay methods for arsenic trioxide are available.

4. Characterize the pharmacokinetics of arsenic trioxide after administration of 0.15 mg/kg/day of arsenic trioxide in APL patients. Control patients enrolled in the renal and hepatic impaired patient study (see below) may also provide this information.

   As you agreed in your August 18, 2000 submission, you will characterize the pharmacokinetics of arsenic trioxide after administration of 0.15 mg/kg/day of arsenic trioxide to selected APL patients using the assays discussed in item 1 above. Additionally, you will initiate this activity as soon as the assay methods for arsenic trioxide are available.

5. Obtain further pharmacokinetic data in patients with impaired renal function. Because inorganic and organic arsenic are primarily excreted via the kidneys, patients with renal impairment are likely to have a different disposition pattern than the patients with normal renal function. A pharmacokinetic study of arsenic trioxide in patients with varying degrees of renal function is therefore needed. We refer you to our published document titled "*Guidance for Industry, Pharmacokinetics in Patients with Impaired Renal Function*" for guidance on

study design, categories of renal impairment, and data analysis for conducting such study. Please submit your protocol to the Agency for review.

As you agreed in your August 18, 2000 submission, after you develop the validated assays, you will assess the pharmacokinetics of arsenic trioxide for patients having varying degrees of renal function who are appropriate candidates for treatment with arsenic trioxide. Additionally, you will submit a protocol for this study for Agency review around the time the arsenic trioxide assays are available.

6. Obtain further pharmacokinetic data in patients with impaired hepatic function. Since liver is the major site of methylation (detoxification) reactions for arsenic trioxide, accumulation of arsenic trioxide in hepatically impaired patients may occur with chronic administration of the drug. A pharmacokinetic study in hepatically impaired cancer patients is therefore needed. We refer you to our draft document titled "*Guidance for Industry, Pharmacokinetics in Patients with Impaired Liver Function*" for guidance on study design, categories of renal function, and data analysis for conducting such study. Please submit your protocol to the Agency for review.

   As you agreed in your August 18, 2000 submission, after you develop the validated assays, you will assess the pharmacokinetics of arsenic trioxide for patients having varying degrees of hepatic function who are appropriate candidates for treatment with arsenic trioxide. Additionally, you will submit a protocol for this study for Agency review around the time the arsenic trioxide assays are available.

7. Analyze data from all the pharmacokinetic studies conducted as a Phase 4 commitment to evaluate the influence of age, gender, and race on the pharmacokinetics of arsenic trioxide.

   As you agreed in your August 18, 2000 submission, you will stratify patients according to age, gender, and race for whom pharmacokinetic data are available from the studies conducted for the Phase 4 commitment in an attempt to evaluate the influence of age, gender, and race on the pharmacokinetics of arsenic trioxide.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Oncology Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Dianne Spillman, Project Manager, at (301) 594-5746.

Sincerely,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure