DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

July 2, 1999

Tung Koh
Director, Regulatory Affairs
Nexell Therapeutics, Inc.
9 Parker
Irvine, CA 92718-1605

Re: BP 97-0001
Product: Isolex 300 Magnetic Cell Selection System
Filed: February 24, 1997
Amended: See appended list

Re: BP 97-0001/01
Product: Isolex 300i Magnetic Cell Selection System
Filed: February 3, 1998
Amended: See appended list

Dear Ms. Koh:

The Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) and supplement for the Isolex 300 Magnetic Cell Selection System and for the Isolex 300i Magnetic Cell Selection System, respectively. These devices are indicated for processing autologous peripheral blood progenitor cell (PBPC) products to obtain a CD 34+ cell enriched population intended for hematopoietic reconstitution after myeloablative therapy in patients with CD 34-negative tumors. We are pleased to inform you that the PMA and supplement are approved subject to the conditions described below and in the "Conditions of Approval" (enclosed here and previously communicated to you in a letter dated January 7, 1999). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device, the device is further restricted within the meaning

of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order; and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the post-approval requirements in the enclosure, the post-approval reports must include the following information:

1. You have agreed to conduct the post-marketing studies detailed below. An outline of the protocols for these studies are to be provided to CBER within three weeks of receipt of this letter to be followed, within 3 months, by more detailed protocols and plans for implementation, including timelines for completion.

a. Laboratory Studies:

i. Full scale studies using apheresis products to determine the effect of leukocyte counts, total nucleated cell counts and platelet counts on yield, purity and viability of CD34+ selected cells. These studies will be designed to determine the level (absolute number, relative percentage) of granulocytes, platelets, and/or other cellular elements which will result in a higher risk/incidence of performance failure.

ii. Full scale studies using apheresis products to determine the effects of anti-coagulant concentration (ACD-A to cell ratio) and the composition of suspension and wash solutions used for prior apheresis collection on yield, purity and viability of CD34+ selected cells and to assess factors which will result in a higher incidence of performance failure.

iii. Full scale studies using apheresis products to determine the effect of paraprotein levels, over a range expected to be observed in subjects with multiple myeloma and other monoclonal gammopathies, on yield, purity and viability of CD34+ selected cells.

iv. Full scale studies using apheresis products to determine the effect of prior freezing and thawing on yield, purity and viability of CD34+ selected cells.

v. Full scale studies using apheresis products to explore approaches for maximum recovery of CD34+ cells from the non-target cell collection under conditions of separation/selection failure.

b. Surveillance Study:

Provide a plan for a surveillance study for performance failures for each device which will capture critical information using case report forms (CRFs) and describe suitable follow-up measures. This reporting study should capture data on the specific causes of performance failures or problems, including but not limited to, the contribution of all of the above factors (see laboratory studies). The reporting period should be the first three years post-approval, and, once the data are analyzed, to discuss with the FDA whether the study should be continued or closed.

The CRFs should capture information regarding the absolute number and relative percentage of: total nucleated cells, granulocytes, and platelets in the apheresis product, and the yield of CD34+ cells after selection; ACD-A anticoagulant to cell ratio; presence (and if present immunoglobulin subtype and serum level) of paraproteins; and information regarding cryopreservation of the cellular products prior to selection. The plan for evaluation of performance failures and CRFs are to be provided within three weeks of the receipt of this letter.

2. As stated in your commitment dated June 22, 1999, we acknowledge that you will:

a. improve the information contained in the lot release certificates of analysis, specifically: to include a specification for pH range for the Dynabeads M-450 Sheep Anti-Mouse IgG and to include the actual values obtained for the LAL tests for each component of the Reagent Kit;

b. include two additional lots of the Anti-CD34-Monoclonal Antibody in your ongoing stability studies;

c. establish a limit for aggregates observed during the SDS-PAGE analysis of the Anti-CD34-Monoclonal Antibody;

d. monitor the temperature in shipments of Dynabeads-M-450 Sheep Anti Mouse IgG from Norway to California by inclusion of a temperature recording device;

We acknowledge your commitment dated June 22, 1999, to assure that all outstanding issues associated with the inspection of your production facilities are satisfactorily resolved and corrective actions completed.

Expiration dating for the components of the Reagent Kit has been established and approved as follows: at 18 months for the Anti-CD34-Monoclonal Antibody (murine) when stored at 2-8°C; at 30 months for the Dynabeads M-450 Sheep Anti-Mouse IgG when stored at 2-8°C; at 36 months for the PR 34+ Stem Cell Releasing Agent when stored at 2-8°C. The dating period for the disposable sets has been established and approved at 24 months when stored at ambient temperature. This is to advise you that, with the exception of the Anti-CD34-Monoclonal Antibody, the protocols you used to establish these expiration dating periods are considered approved protocols for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

CBER will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

Document Control Center (HFM-99)
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852-1448

If you have any questions concerning this approval order, please contact Terrye G. Zaremba at(301) 827-5103.

Sincerely,

Jay P. Siegel, M.D.,FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Enclosure