



DEPARTMENT OF HEALTH & HUMAN SERVICES

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

February 5, 1999

Our Reference Number: 97-1325

Jill P. Hillier, Ph.D.
Seragen, Inc.
97 South Street
Hopkinton, Massachusetts 01748

Dear Dr. Hillier:

This letter hereby issues Department of Health and Human Services U.S. License No. 1258 to Seragen, Inc., Hopkinton, Massachusetts in accordance with the provisions of Title III Part F of the Public Health Service Act, as amended November 21, 1997 (FDAMA; Public Law 105-115), controlling the manufacture and sale of biological products. This license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license you are authorized to manufacture the product Denileukin diftitox. Denileukin diftitox is indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor.

Under this authorization, you are approved to manufacture Denileukin diftitox at Marathon Biopharmaceuticals, Inc. in Hopkinton, Massachusetts.

In accordance with approved labeling, your product will be distributed by Ligand Pharmaceuticals Inc. in San Diego, California, will bear the tradename Ontak, and will be marketed in single-use vials containing 300 ug of Denileukin diftitox.

You are not currently required to submit samples of future lots of Denileukin diftitox to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specifications.

The dating period for this product shall be 12 months from the date of manufacture when stored frozen at or below -10°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated product. The purified bulk Denileukin diftitox may be stored for up to 36 months at -80 °C. Results of ongoing stability studies should be submitted throughout the dating period as they become available including the results of stability studies

from the first three production lots. The stability protocol in your license application is considered approved for the purpose of extending the expiration dating period of your drug substance and drug product as specified in 21 CFR 601.12.

Any changes in the manufacture, testing, packaging or labeling of the product, or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

As requested in your letter of December 5, 1997, marketing approval of this product is granted under the accelerated approval of biological products regulations, 21 CFR 601.40-46. These regulations permit the use of certain surrogate endpoints or an effect on a clinical endpoint other than survival or irreversible morbidity as a basis for approvals of products intended for serious or life-threatening illnesses or conditions.

Approval of Denileukin diftitox under these regulations has been based on objective tumor responses and requires, among other things, that you demonstrate through adequate and well-controlled studies that treatment results in clinical benefits such as relief in tumor related symptoms, diminished use of rescue medications, and prolonged time to progression. Such studies must be carried out with due diligence. As stated in 21 CFR 601.43, if you fail to meet these requirements the Agency may, following a hearing, withdraw or modify approval.

Granting of this approval is contingent upon completion of the blinded, placebo-controlled study, Protocol 93-04-11 with amendments as submitted on February 2, 1999 and submission of the results within 12 months of entry of the last patient, as outlined in your commitment of February 3, 1999. An amended protocol will be submitted within one month of February 5, 1999. Please submit annual updates on accrual and progress of the ongoing study. It is understood that, to fulfill the requirements of accelerated approval, these studies must be conducted with due diligence and must verify that clinical benefit is associated with the surrogate endpoint.

We acknowledge your additional written commitments of February 3, 1999 and February 4, 1999 which include the following:

1. To complete the crossover study, Protocol 93-04-14 with amendments as submitted on February 2, 1999, and to submit results within 12 months of entry of the last patient. To include under Protocol 93-04-14 an evaluation of the effectiveness of ONTAK in patients with CTCL whose malignant cells do not express CD25 at the level required for entry into Protocol 93-04-10 and 93-04-11 (CD25 membrane expression in $\leq 20\%$ of cells by —
_____ The amended clinical protocol under which these patients will be enrolled and data collected will be submitted within one month of the date of this letter. The total number of patients to be studied will be determined following

discussion with the agency but must be sufficient to determine the overall response rate with sufficient precision to assess clinical utility and evaluate whether the rate is significantly different from that observed in patients whose malignant cells express CD25 (the indicated population).

2. To collect data under Protocols 93-04-11 and 93-04-14 in order to expand the pharmacokinetic profile for ONTAK by determining pharmacokinetic parameters following the infusion on Day 1 of Course 1, 3, 5, and 7, and by measuring antibody levels on Day 1 of Courses 1, 3, 5 and 7. The protocol will be submitted within one month of the date of this letter.
3. To evaluate the question of optimal duration of therapy Seragen will conduct, in a group of lymphoma patients to be determined; a randomized trial designed to examine the relative efficacy and safety of utilizing either _____ courses of therapy as an initial treatment regimen. To conduct a randomized trial in CD25 positive, ONTAK-naïve patients with lymphoma, where the primary objective is to determine whether a long course _____ is significantly more effective than a short course _____ of ONTAK therapy. If conducted in a population other than CTCL, where the immunogenicity profile (and thus the pharmacokinetic profile) may be different, pharmacokinetics and antibody responses will be collected for correlation with clinical outcome. The clinical protocol under which these patients will be enrolled and data collected will be submitted within three months of the date of this letter.
4. To retrospectively evaluate the correlation of response and expression of CD122 by immunohistochemistry on screening samples from Protocol 93-04-10, and to prospectively evaluate the predictability of CD122 expression for response in samples from patients enrolled in Protocols 93-04-11 and 93-04-14. The retrospective evaluation will be initiated within 30 days of completion of the study described in item 6 and the prospective testing will begin upon implementation of the amendments to Protocols 93-04-11 and 93-04-14.
5. To retrospectively evaluate the correlation of response and expression of CD25 and/or CD122 by semi-quantitative PCR on screening samples from Protocol 93-04-10, and to compare the results from PCR to those from immunohistochemistry. A detailed protocol will be submitted within six weeks of February 5, 1999.
6. To further validate the CD25 immunohistochemistry method at _____ by completing a reproducibility/concordance study. The data will be analyzed in a report to be submitted by April 30, 1999.

7. To improve the purification process to increase product purity. Material from the improved process will be available to initiate preclinical assessments in Q2 2000. A protocol will be submitted no later than Q4 1999 and will not be initiated until it has been determined to be adequate by the agency. The proposed study will evaluate the pharmacokinetic profile and establish whether there is pharmacokinetic equivalence between the current and modified process-derived product. In this proposed preclinical study and/or in additional preclinical studies, immunogenicity and toxicity of the purer product will be characterized. Additional clinical studies (in humans) may be required.
8. To submit data from every drug product lot manufactured (either released or not) and associated purified drug substance lots. These data will be submitted at the time of final release/reject by Quality Assurance and will include previously agreed upon scans or actual photographs. These data will be used to periodically reassess the current exemption from CBER lot release under 21 CFR 610.2.
9. To submit for review and approval all promotional materials to be used within 120 days following today's date.

It is requested that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

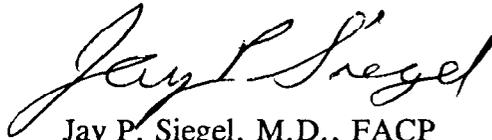
Please submit three copies of all final printed labeling at the time of use and include part II of the label transmittal form (FDA Form 2567) with completed implementation information. In addition, as specified in 21 CFR 601.45, any additional advertising and promotional labeling to be disseminated after 120 days following today's date should be submitted to the Advertising and Promotional Labeling Staff, HFM-202, Center for Biologics Evaluation and Research, Food and Drug Administration, Document Control (HFM-99) 1401 Rockville Pike, Rockville, MD 20852-1448, for review and approval at least 30 days prior to the initial publication of any advertisement or to the initial dissemination of any promotional labeling.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other similar products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

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Please acknowledge receipt of the enclosed biologics license to the Director, Division of Application Review and Policy (HFM-585), Center for Biologics Evaluation and Research.

Sincerely yours,

A handwritten signature in black ink, reading "Jay P. Siegel". The signature is written in a cursive style with a large, prominent "J" and "S".

Jay P. Siegel, M.D., FACP

Director

Office of Therapeutics

Research and Review

Center for Biologics

Evaluation and Research