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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

STN/BLA 125075/0

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

OCT 27 2003

Our STN: BL 125075/0

Genentech Incorporated
Attention: Robert L. Garnick, Ph.D.
Senior Vice President
Regulatory Affairs, Quality and Compliance
1 DNA Way, MS#48
South San Francisco, CA 94080-4990

Dear Dr. Garnick:

We have approved your biologics license application (BLA) for Efalizumab effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Efalizumab under your existing Department of Health and Human Services U.S. License No. 1048. Efalizumab is indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Under this authorization, you are approved to manufacture Efalizumab at your facility in South San Francisco, CA. Your product will bear the proprietary name RAPTIVA™ and will be marketed in single-use vials containing 150 mg of lyophilized product designed to deliver 125 mg Efalizumab/1.25 mL upon reconstitution with 1.3 mL of the supplied sterile water for injection (non-USP).

The dating period for Efalizumab shall be 24 months from the date of manufacture when stored at 2°-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be 24 months when stored at -20°C. We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

You currently are not required to submit samples of future lots of Efalizumab to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of Efalizumab, or in the manufacturing facilities.

FDA's Pediatric Rule at 21 CFR 314.55 and 21 CFR 601.27 was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and barred FDA from enforcing it. Therefore the provision in the regulation allowing the FDA to grant or deny waivers and deferrals no longer exists. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party intervenors have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage and specific requirements of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

We acknowledge your written commitments as described in your letter of October 24, 2003 as outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

1. To conduct a multicenter (approximately 500 sites) prospective five year surveillance study of 5000 patients with moderate to severe plaque psoriasis who have received at least one dose of Efalizumab in order to assess the incidence of serious adverse events including all malignancies, serious infections, psoriasis related serious adverse events, inflammatory and autoimmune mediated adverse events, thrombocytopenia, and serious hepatic adverse events. All enrolled study subjects will be followed for at least five years. The final study protocol will be submitted by June 30, 2004. Patient accrual will be completed by June 30, 2008, the study will be completed by June 30, 2013, and the final study report will be submitted by March 31, 2014.

2. To conduct a study of approximately 20 Efalizumab treated patients with new onset NCI CTCAE v3.0 grade 3/4 thrombocytopenia (TCP) to evaluate, through laboratory testing for anti-platelet antibodies, the role of Efalizumab. The final protocol will be submitted by June 30, 2004, the study will be completed by June 30, 2013, and a final study report will be submitted by March 31, 2014.

3. To develop and validate an assay that can detect the presence of neutralizing antibodies to Efalizumab to be used to analyze archived patient samples, and to conduct an Efalizumab immunogenicity study of approximately 245 patients in order to evaluate and explore the incidence and association of anti-Efalizumab antibodies in patients who discontinue Efalizumab secondary to a serious adverse event or due to an apparent loss of response. The final protocol will be submitted by June 30, 2004, the study will be completed by June 30, 2013, and a final study report will be submitted by March 31, 2014.

- Of the 2589 subjects treated with SC efalizumab,19 (0.7%) had a serious adverse event of psoriasis (including psoriatic erythroderma and pustular psoriasis). In the first exposure of controlled clinical trials of efalizumab, adverse events of psoriasis occurred in more subjects receiving efalizumab (2.4%, n=22) than placebo (1.1%, n=5).
- Thrombocytopenia consisting of platelets < 52,000 cells/cmm occurred in a total of 8 efalizumab-treated patients. Clinical response to treatment with systemic corticosteroids suggests an immune-mediated thrombocytopenia. One patient had clinically significant bleeding requiring hospitalization.
- Rare cases of serious inflammatory and/or potentially autoimmune events (e.g. transverse myelitis, pneumonitis, idiopathic hepatitis, serum sickness) have occurred in efalizumab-treated patients.
- Laboratory abnormalities
    - Inflammation-associated laboratory analytes were higher in efalizumab-treated patients as compared to placebo. These included C reactive protein, fibrinogen and C3a and C5a.
    - Hematologic changes included increases in mean total white blood cell counts, approximate doubling of mean lymphocyte counts and smaller degrees of elevations in absolute eosinophil and neutrophil counts.
    - Elevations in alkaline phosphatase levels which are mostly unassociated with elevations in other hepatic tests. Both the intestinal and hepatic fractions are shown to be elevated.
- Efalizumab has been associated with anti-human antibody (HAHA) in 6.3% of patients. There is no apparent decrease in clinical efficacy associated with HAHA positivity. The clinical significance with regard to safety is under investigation.

11 RECOMMENDATIONS

Efalizumab is an immunosuppressive biologic that interferes with the binding of LFA-1 to ICAM-1 and thus inhibits the activation and migration of T lymphocytes. It has shown reproducible clinical efficacy in the treatment of moderate to severe chronic plaque psoriasis in four phase 3 clinical trials.

Additional studies are needed in the post-marketing phase to explore the following issues

- Safety and efficacy of long-term exposure, including the risk of malignancy and immunogenicity
- Risk of serious infections and infections with an atypical course or presentation
- The risk of thrombocytopenia
- Safety of discontinuation of Efalizumab with respect to worsening of psoriasis/rebound
- Laboratory abnormalities, including the potential for cumulative toxicity and reversibility of deviations in laboratory values
- Efficacy in the treatment of psoriasis variants and psoriatic arthritis
- Safety in special populations such as women who are pregnant

4. To submit a final study report for the 516 patient study ACD2391g, "An Open-label, Multicenter Study to Evaluate the Efficacy and Safety of 1.0 mg/kg Subcutaneously Administered Efalizumab Followed by Efalizumab Taper in Adults with Plaque Psoriasis Previously Enrolled in Study ACD2390g." This study addresses the safety of discontinuation of Efalizumab with respect to the occurrence of worsening of psoriasis, and of psoriasis rebound. The final study protocol was submitted October 26, 2001, as amendment 113 to [redacted]. The study was initiated April 15, 2002, and the study was completed on April 9, 2003. The final study report will be submitted by February 27, 2004.

5. To complete the 130 patient study, HUPS300 "A Phase IIIb, Open-label, Multicenter Study to Evaluate the Transition from Subcutaneous Efalizumab Therapy to Approved Systemic and/or Phototherapy Psoriasis Treatments in Adults with Moderate to Severe Plaque Psoriasis" that addresses the appropriate use of other anti-psoriasis therapies that may be used as follow-on therapies after the discontinuation of Efalizumab therapy. The protocol was submitted November 1, 2002, and cross-referenced by [redacted]. The study will be completed by December 31, 2003, and the final study report will be submitted by February 27, 2004.

6. To complete the 30 patient study, ACD2244g "A Randomized, Placebo-controlled, Single-Blind, Parallel-Group Study to Evaluate the Effects of 12 Weekly Subcutaneous Doses of 1.0 mg/kg Efalizumab on Immune Responses in Subjects With Moderate Plaque Psoriasis," that evaluates the following:

   a. The effect of Efalizumab on percentages of lymphocytes including $CD3^+$, $CD4^+$, $CD8^+$ as well as B and NK cells and the associated CD11a expression and binding site saturation;

   b. The effect of Efalizumab on neoantigen immunization with respect to interval from dosing and the potential for induction of tolerance and assessment of tolerance using a series of two booster immunizations post-Efalizumab clearance;

   c. The effect of Efalizumab on recall antigen responses in a chronic dosing situation including the levels of antibody to the recall antigen and the ability of a booster immunization to raise antibody levels; and,

   d. Patient responses to a neovaccination (pneumococcal vaccine) after withdrawal of Efalizumab treatment;

   The final study protocol will be submitted by November 30, 2003, patient accrual will be completed by March 15, 2004, the study will be completed by March 31, 2004, and the final study report will be submitted by August 31, 2004.

5. To conduct a prospective, observational registry study of women with moderate to severe plaque psoriasis exposed to Efalizumab during pregnancy or within six weeks prior to conception. This study will assess the outcomes in the offspring born to those women who were exposed to Efalizumab during pregnancy and breastfeeding relative to background risk in similar patients not exposed to Efalizumab. These outcomes will include adverse effects on immune system development, platelets, major birth defects (congenital anomalies), minor birth defects, and spontaneous abortion and will be assessed in the first year after birth for infants exposed prenatally and again at one year post-weaning for infants exposed through breast milk. A final protocol will be submitted by October 31, 2004 that will include the revised draft labeling with the inclusion of the pregnancy registry telephone number. The study will be initiated by January 31, 2005. Patient accrual will be completed by January 31, 2010, and the study will be completed by January 31, 2011. The final study report will be submitted by September 30, 2011.

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70

6. To manufacture and perform testing for three additional Efalizumab validation runs, consisting of (b)(4) of the Genentech Parenteral Manufacturing Facility, using (b)(4) in order to obtain full load (b)(4) validation data on Efalizumab. The final process validation reports will be submitted by March 31, 2004.

7. To perform a reevaluation of the Efalizumab (b)(4) drug product release specification after obtaining data for 30 commercial manufacturing runs and to submit these data and reevaluation to the agency as a CBE-30 manufacturing supplement.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this BLA, STN BL125075. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA, STN BL 125075. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Protocol**
- **Postmarketing Study Final Report**
- **Postmarketing Study Correspondence**
- **Annual Report on Postmarketing Studies**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment;
- the original schedule for the commitment;

- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publically disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cber/gdlns/post040401.htm) for further information.

We acknowledge your written agreement of October 27, 2003, to place the first full-scale lot reprocessed for viral filtration on the full stability testing program as described within the BLA.

Under 21 CFR 201.57(f)(2), patient labeling must be reprinted at the end of the package insert. We request that the text of information distributed to patients be printed in a minimum of 10-point font.

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to the Center for Drug Evaluation and Research, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81). You should submit distribution reports to CBER Document Control Center, Attn: Office of Therapeutics Research and Review, Suite 200N (HFM-99), 1401 Rockville Pike, Rockville, Maryland 20852-1448

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate promptly all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication (HFD-42), 5600 Fishers Lane,

Rockville, MD 20857. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cber/transfer/transfer.htm and http://www.fda.gov/OHRMS/DOCKETS/98fr/03-16242.html. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

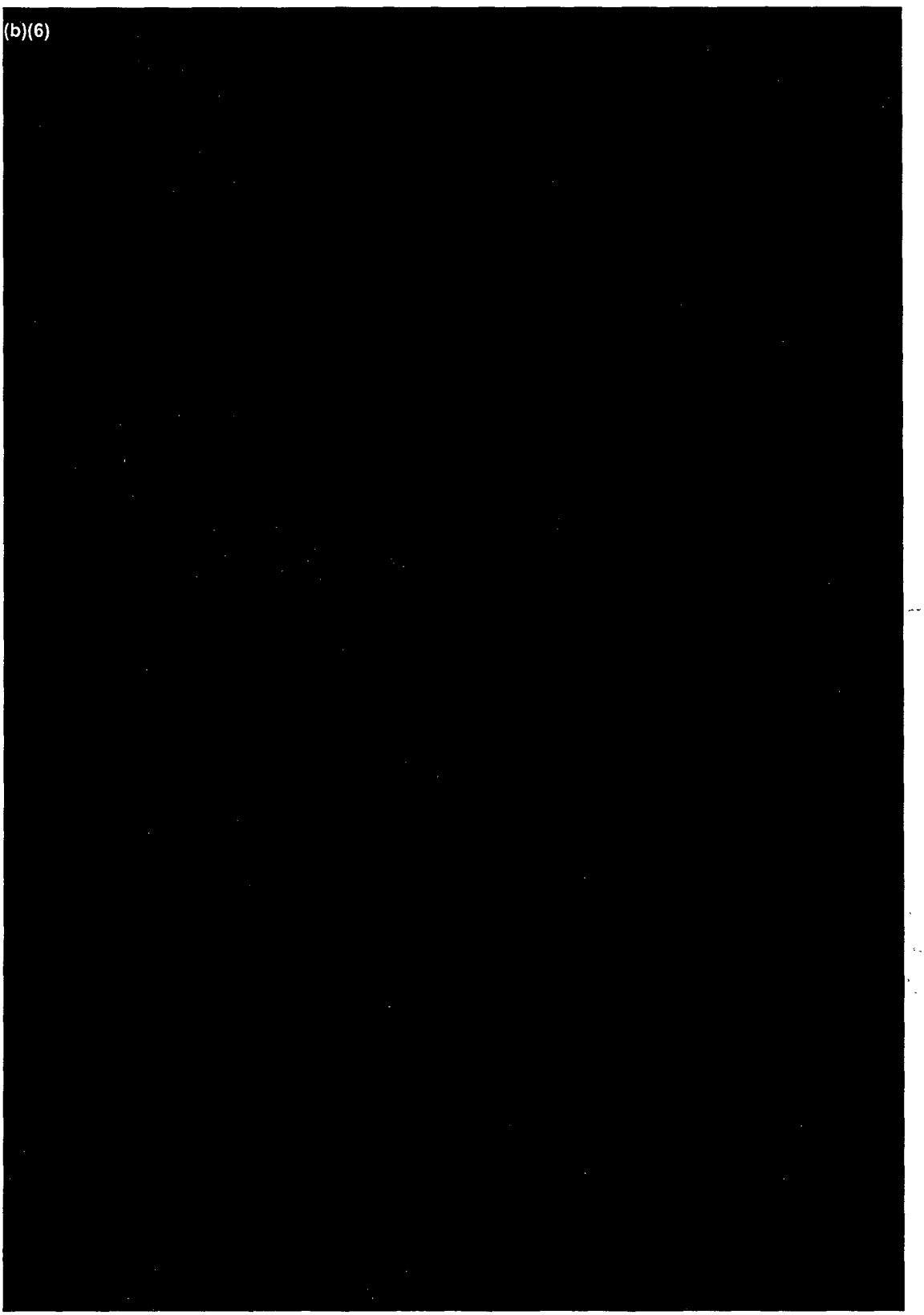
Sincerely,

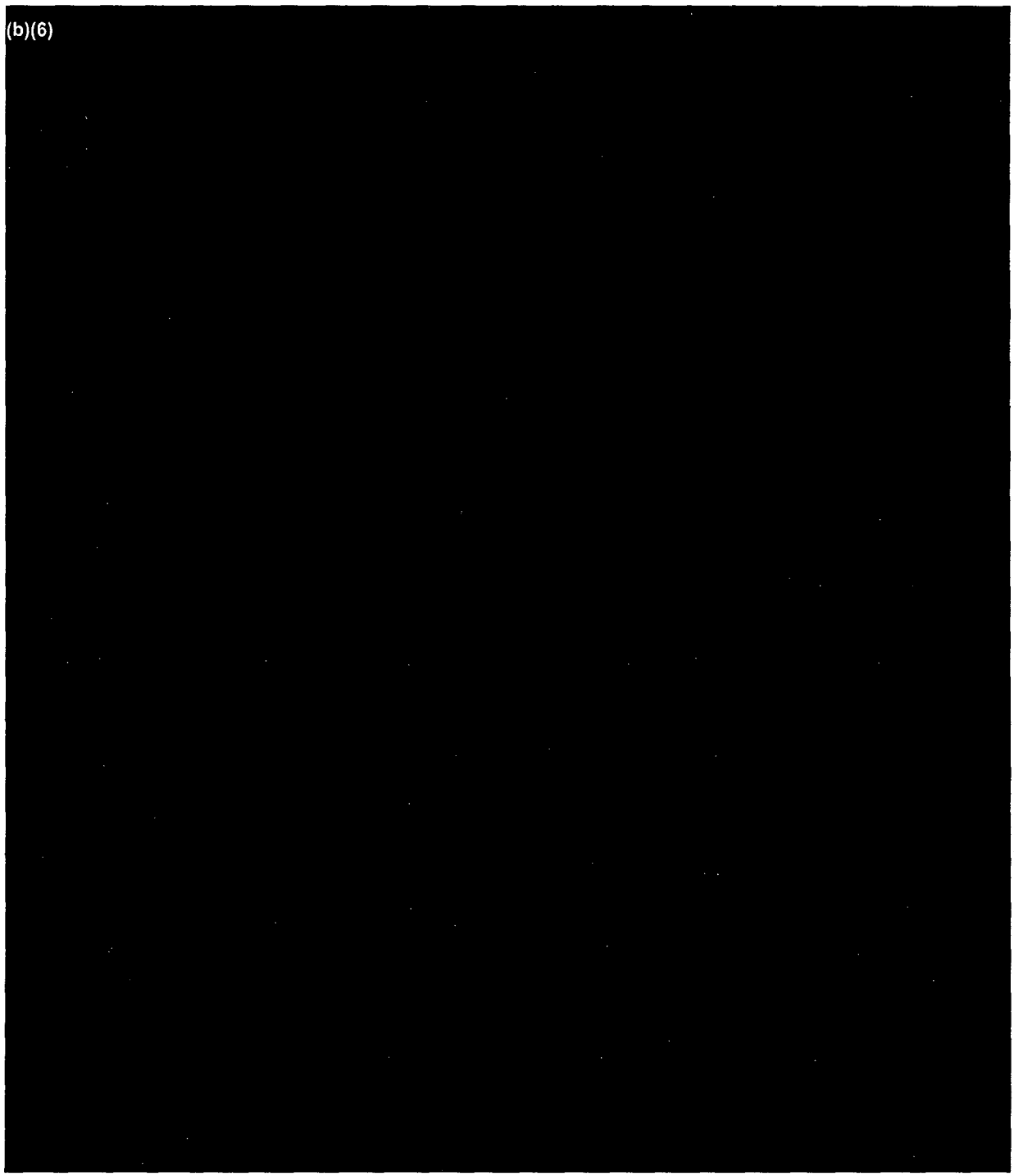
(b)(6)

Karen D. Weiss, M.D.
Director
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

Concurrence Page

(b)(6)

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