

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125156

MICROBIOLOGY REVIEW



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Date: 27 June 2006
To: Administrative File, STN 125156/0
From: Patricia F. Hughes, Ph.D., CDER/OC/DMPQ/TRFB, HFD-328
Through: Brenda Uratani, Ph.D., Acting Branch Chief, CDER/OC/DMPQ/TRFB, HFD-328
Subject: New Biologic License Application (BLA)
US License # 1048
Applicant Genentech, Inc.
Facilities Novartis Pharma Stein AG, Stein Switzerland, FEI 3002653483
Novartis Pharma AG, Basel, Switzerland, FEI 3002807772
Product Lucentis™ (ranibizumab)
Indication Treatment of neovascular age-related macular degeneration
Dosage: Liquid single use vial for intravitreal injection (—— 10 mg/mL)
Due date: 01 July 2006

PH 6/27/06
Brenda Uratani
6/27/06

Recommendation: The data and information related to the aseptic manufacturing of ranibizumab at Novartis Stein AG and drug product sterility assurance has been reviewed from a microbiology product quality perspective. The submission, as amended, is recommended for approval.

Review Summary

Genentech, Inc. has submitted this BLA for ranibizumab a drug intended for the treatment of neovascular age-related macular degeneration. The application contains CMC information in an eCDT format.

This review evaluates sterility assurance information included in the submission in support of the —— process for drug product manufacturing. The information is found in part in the following sections of the BLA under 3.2.P Drug Product: 3.2.P.1 Description and Characterization, 3.2.P.2 Pharmaceutical Development, 3.2.P.3 Manufacture, 3.2.P.4 Control of Excipients, 3.2.P.5 Control of Drug Product, 3.2.P.7 Container Closure, 3.2.P.8 Stability and 3.2.A.1, Drug Product Facilities and Equipment and 3.2.R Method Validation. All other information should be evaluated by the assigned reviewers in OBP/DMA.

An amendment to the BLA was submitted on June 27, 2006 and reviewed here.

Ranibizumab drug product is manufactured at []
[] (manufacturing QC, and primary packaging) and at []
[] (QC). Both these facilities have an acceptable compliance
status and the pre-approval inspections were not conducted. Secondary packaging occurs in the
USA at Genentech, Inc. SSF.

Drug Product (3.2.P)

Ranibizumab is a recombinant, humanized antibody antigen-binding fragment (Fab) that neutralizes vascular endothelial growth factor-A. The recombinant protein has molecular weight of ranibizumab is approximately 48 kDa.

Description and Composition of the drug product (3.2.P.1)

Ranibizumab drug product is a liquid formulation supplied in [] configurations, []
10 mg/ml ranibizumab. [] dosage forms are supplied in single-use vials containing a sterile,
aqueous, preservative-free solution for intravitreal injection. Each vial of []
10 mg/mL dosages contain [] per vial.

[] The 10 mg/mL formulation consists of 10 mg/ml
ranibizumab in 10 mM histidine HCl, 10% (w/v) a,a-trehalose dihydrate, 0.01% (w/v)
polysorbate 20, pH 5.5.

*Review comment: The information provided is sufficient for the evaluation of the
manufacturing process.*

Satisfactory

20 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

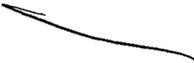
Environmental Assessment

In accordance with 21 CFR 25.31(c), an Environmental Assessment is not required for this submission. Action on this submission will not alter significantly the concentration or distribution of the substance, its metabolites, or its degradation products in the environment. _____ is in compliance with the categorical exclusion criteria listed in 21 CFR 25.31(c), and no extraordinary circumstances exist.

cGMP Status

"The Investigations and Pre-approval Compliance Branch has completed the review and evaluation of the Therapeutic Biologic-EER request below. There are no pending or ongoing compliance actions to prevent approval of STN 125156/0 at this time."

The following is the current status for the submitted sites:

| Manufacturer | FEI # | Profile Class | Profile Status | EIR Classification |
|---|-------|---|----------------|---|
|  | |  | |  |

Conclusion

- I. The data and information related to the aseptic manufacturing of ranibizumab at _____ and drug product sterility assurance has been reviewed from a microbiology product quality perspective. The application, as amended, is recommended for approval.
- II. The remainder of the information and data in the application not related to drug product sterility assurance was not evaluated here.
- III. A decision was made to waive the pre-approval inspection for the _____. _____ The waiver is attached to this review.

Cc: HFD-328, Uratani
HFD-328, Clark-Stuart
HFD-520, Gorski
HFD-328, Harper-Velazquez
HFD-320, Famulare
HFD-328, TFRB Blue Files (STN 125156)

drug substance



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Date: June 9, 2006
To: Administrative File, STN 125156/0
From: Patricia F. Hughes, Ph.D., CDER/OC/DMPQ TFRB, HFD-328
Through: Brenda Uratani, Ph.D., Actg. Branch Chief, CDER/OC/DMPQ/TRFB, HFD-328
Subject: Review of Biological License Application (BLA): New BLA
US License: 1048
Applicant: Genentech, Inc.
Product: Lucentis™ (ranibizumab, recombinant humanized anti-VEGF mAb, rhuFab V2)
Facility: For Drug Substance, Genentech, Inc. South San Francisco, CA FEI 2917293
Indication: Treatment of neovascular age-related macular degeneration
Dosage: Liquid single use vial for intravitreal injection (— 10 mg/mL)
PDUFA: 01 Jul 2006

PP 6/9/06

Recommendation: The drug substance section of the application (3.2.S) was reviewed from a microbiology product quality perspective. The application is recommended for approval.

Review Summary

Genentech Inc. submitted this BLA in support of the manufacturing of ranibizumab, a humanized IgG1 monoclonal antibody Fab fragment that binds to human vascular endothelial growth factor (VEGF) and inhibits its activity. Ranibizumab is produced from a recombinant *Escherichia coli* expression system. The drug substance is manufactured at Genentech, Inc. in South San Francisco, CA and the drug product is manufactured at Novartis Pharma Stein AG.

The drug substance CMC sections of the BLA were evaluated in this review for adequacy from a microbiology product quality perspective. The sections evaluated include in part 3.2.S.2, 3.2.S.4, 3.2.S.6 and 3.2.S.7.

An inspection of the facility(s) was waived by OC/DMPQ/TFRB (see Inspection Waiver Memo, dated January 27, 2006). However, a targeted inspection was nonetheless conducted by Ray T. Oji, lead investigator, San Francisco District Office, Michelle R. Frazier-Jessen, Ph.D., product specialist, OBP/DMA and Joseph Kutza, Ph.D., product specialist, OPS/DMA to clarify product related CMC review issues. No 483 observation were made

Review Narrative

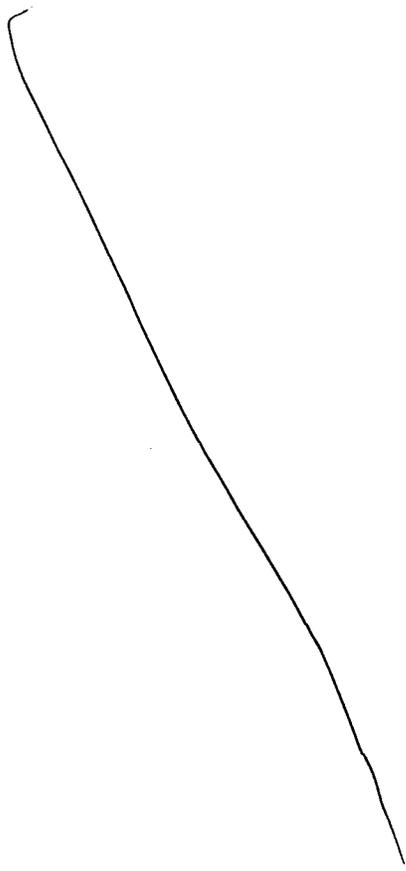
Drug Substance

Manufacturer - 3.2.S.2

The manufacturer of the drug substance is:

Genentech Inc.
1 DNA Way
South San Francisco, CA
94080-4990, USA
FEI 2917293

Description of Manufacturing Process and Process Controls, 3.2.S.2.2



8 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process