

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125156Orig1s110

Trade Name: LUCENTIS

Generic or Proper Name: ranibizumab

Sponsor: Genentech Inc.

Approval Date: October 13, 2016

Indication: Lucentis, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of patients with

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPLICATION NUMBER:

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APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125156/S-110

SUPPLEMENT APPROVAL

Genentech, Inc.
Attention: Key Kang, M.Sc.
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Mr. Kang:

Please refer to your Supplemental Biologics License Application (sBLA), dated June 16, 2016, received June 16, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for Lucentis (ranibizumab injection).

This Prior Approval supplemental biologics application proposes the addition of a Lucentis 0.5 mg prefilled syringe (PFS).

We also acknowledge receipt of the [REDACTED] (b) (4) [REDACTED] (b) (4) will require a separate prior approval supplement.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling text for the package insert and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 3134 Perform a shipping study designed to confirm stability of Lucentis drug product during shipping under conditions and through a route that are representative of commercial drug product shipping. The study will include testing of pre- and post-shipping samples for product quality (container closure integrity, purity by SEC, nrCE-SDS, IE-HPLC, sub-visible particles, and potency of ranibizumab).

The timetable you submitted on October 10, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/16
Study/Trial Completion:	06/17
Final Report Submission:	08/17

Submit clinical protocols to your IND 008633 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Lois Almoza, M.S., Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
10/13/2016

**CENTER FOR DRUG EVALUATION AND
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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LUCENTIS safely and effectively. See full prescribing information for LUCENTIS.

LUCENTIS® (ranibizumab injection)

Intravitreal Injection

Initial U.S. Approval: 2006

-----**RECENT MAJOR CHANGES**-----

Dosage and Administration, Preparation for Administration (2.6) XX/2016
Dosage and Administration, Administration (2.7) XX/2016

-----**INDICATIONS AND USAGE**-----

LUCENTIS, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)
- Diabetic Macular Edema (DME) (1.3)
- Diabetic Retinopathy in patients with DME (1.4)

-----**DOSAGE AND ADMINISTRATION**-----

For Ophthalmic Intravitreal Injection Only (2.1)

Neovascular (Wet) Age-Related Macular Degeneration (AMD) (2.2)

LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Although not as effective, patients may be treated with 3 monthly doses followed by less frequent dosing with regular assessment.

Although not as effective, patients may also be treated with one dose every 3 months after 4 monthly doses. Patients should be assessed regularly.

Macular Edema Following Retinal Vein Occlusion (RVO) (2.3)

- LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in patients with Diabetic Macular Edema (2.4, 2.5)

- LUCENTIS 0.3 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

-----**DOSAGE FORMS AND STRENGTHS**-----

Single-use prefilled syringe designed to provide 0.05 mL for intravitreal injections:

- 10 mg/mL solution (LUCENTIS 0.5 mg) (3)

Single-use glass vial designed to provide 0.05 mL for intravitreal injections:

- 10 mg/mL solution (LUCENTIS 0.5 mg) (3)
- 6 mg/mL solution (LUCENTIS 0.3 mg) (3)

-----**CONTRAINDICATIONS**-----

- Ocular or periocular infections (4.1)
- Hypersensitivity (4.2)

-----**WARNINGS AND PRECAUTIONS**-----

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be monitored following the injection (5.1).
- Increases in intraocular pressure (IOP) have been noted both pre- and post-intravitreal injection (5.2).
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors (5.3).
- Fatal events occurred more frequently in patients with DME and DR at baseline, who were treated monthly with LUCENTIS compared with control (5.4).

-----**ADVERSE REACTIONS**-----

- The most common adverse reactions (reported more frequently in LUCENTIS-treated subjects than control subjects) are conjunctival hemorrhage, eye pain, vitreous floaters, and increased IOP (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: XX/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- 1.2 Macular Edema Following Retinal Vein Occlusion (RVO)
- 1.3 Diabetic Macular Edema (DME)
- 1.4 Diabetic Retinopathy in patients with DME

2 DOSAGE AND ADMINISTRATION

- 2.1 General Dosing Information
- 2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- 2.3 Macular Edema Following Retinal Vein Occlusion (RVO)
- 2.4 Diabetic Macular Edema (DME)
- 2.5 Diabetic Retinopathy in patients with DME
- 2.6 Preparation for Administration
- 2.7 Administration

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- 4.2 Hypersensitivity

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- 5.2 Increases in Intraocular Pressure
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* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUCENTIS is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (Non Proliferative Diabetic Retinopathy (NPDR), Proliferative Diabetic Retinopathy (PDR)) in patients with Diabetic Macular Edema (DME)

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

LUCENTIS 0.5 mg (0.05 mL of 10 mg/mL LUCENTIS solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Although not as effective, patients may be treated with 3 monthly doses followed by less frequent dosing with regular assessment. In the nine months after 3 initial monthly doses, less frequent dosing with 4-5 doses on average is expected to maintain visual acuity while monthly dosing may be expected to result in an additional average 1-2 letter gain. Patients should be assessed regularly [*see Clinical Studies (14.1)*].

Although not as effective, patients may also be treated with one dose every 3 months after 4 monthly doses. Compared with continued monthly dosing, dosing every 3 months over the next 9 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average. Patients should be assessed regularly [*see Clinical Studies (14.1)*].

2.3 Macular Edema Following Retinal Vein Occlusion (RVO)

LUCENTIS 0.5 mg (0.05 mL of 10 mg/mL LUCENTIS solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

In Studies RVO-1 and RVO-2, patients received monthly injections of LUCENTIS for 6 months. In spite of being guided by optical coherence tomography and visual acuity re-treatment criteria, patients who were then not treated at Month 6 experienced on average, a loss of visual acuity at Month 7, whereas patients who were treated at Month 6 did not. Patients should be treated monthly [*see Clinical Studies (14.2)*].

2.4 Diabetic Macular Edema (DME)

LUCENTIS 0.3 mg (0.05 mL of 6 mg/mL LUCENTIS solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

2.5 Diabetic Retinopathy in patients with Diabetic Macular Edema

LUCENTIS 0.3 mg (0.05 mL of 6 mg/mL LUCENTIS solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

2.6 Preparation for Administration

LUCENTIS 0.3 mg (0.05 mL of 6 mg/mL LUCENTIS solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

2.6 Preparation for Administration

Prefilled Syringe:

To prepare LUCENTIS for intravitreal administration, please adhere to these instructions for use. Read all the instructions carefully before using the prefilled syringe.

How to store LUCENTIS:

- LUCENTIS should be refrigerated at 2°-8°C (36°-46°F). **Do not** freeze.
- **Do not** use beyond the expiration date stamped on the label.
- LUCENTIS prefilled syringes should be protected from light and stored in a dark place.
- **Do not** open the sealed tray until time of use.

The prefilled syringe is for single use only. The prefilled syringe is sterile. **Do not** use the product if the packaging is damaged or has been tampered with.

The opening of the sealed tray and all subsequent steps should be done under aseptic conditions.

For the intravitreal injection, a 30-gauge x ½ inch sterile injection needle should be used (not provided).

Note: the dose must be set to 0.05 mL.

Device description

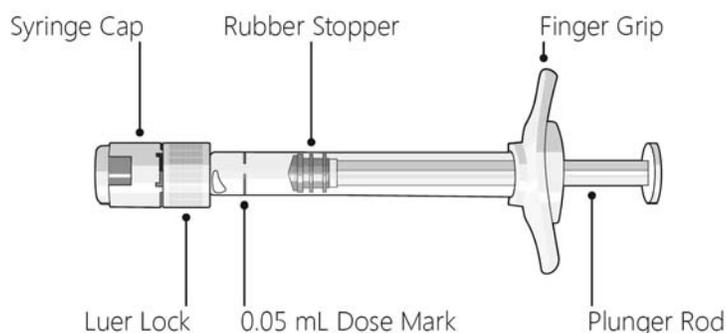


Figure 1

Step 1: Prepare

- Make sure that your pack contains a sterile prefilled syringe in a sealed tray.

- Peel the lid off the syringe tray and, using aseptic technique, remove the syringe.

Step 2: Inspect syringe

- LUCENTIS should be colorless to pale yellow.
- **Do not** use the prefilled syringe if:
 - the syringe cap is detached from the Luer lock.
 - the syringe is damaged.
 - particulates, cloudiness, or discoloration are visible.

Step 3: Remove syringe cap

- Snap off (**do not** turn or twist) the syringe cap (see Figure 2).

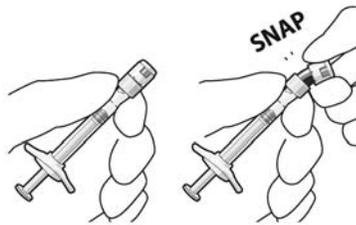


Figure 2

Step 4: Attach needle

- Attach a 30G x ½ inch sterile injection needle firmly onto the syringe by screwing it tightly onto the Luer lock (see Figure 3).
- Carefully remove the needle cap by pulling it straight off.

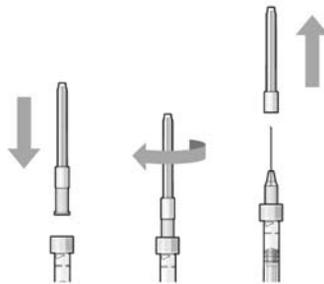


Figure 3

Note: Do not wipe the needle at any time.

Step 5: Dislodge air bubbles

- Hold the syringe with the needle pointing up.
- If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 4).

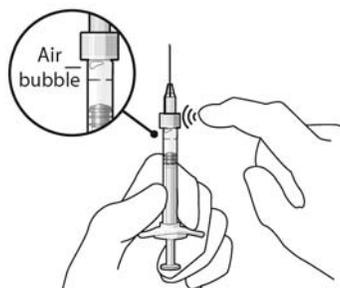


Figure 4

Step 6: Expel air and adjust drug dose

- Hold the syringe at eye level, and carefully push the plunger rod until the **edge below the dome** of the rubber stopper is aligned with the 0.05 mL dose mark (see Figure 5).

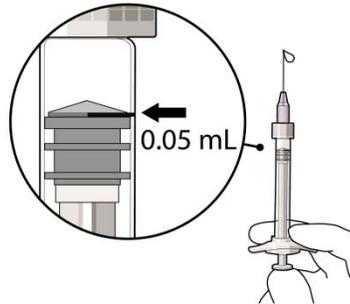


Figure 5

Note: The plunger rod is not attached to the rubber stopper – this is to prevent air being drawn into the syringe.

Step 7: Inject

- The injection procedure should be carried out under aseptic conditions.
- Insert the needle into the injection site.
- Inject slowly until rubber stopper reaches the bottom of the syringe to deliver the volume of 0.05 mL.
- After injection, **do not** recap the needle or detach it from the syringe. Dispose of the used syringe together with the needle in a sharps disposal container or in accordance with local requirements.

Vial:

Using aseptic technique, all of the LUCENTIS vial contents are withdrawn through a 5-micron, 19-gauge filter needle attached to a 1-cc tuberculin syringe. The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The filter needle should be replaced with a sterile 30-gauge x 1/2-inch needle for the intravitreal injection. The contents should be expelled until the plunger tip is aligned with the line that marks 0.05 mL on the syringe.

2.7 Administration

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection.

Prior to and 30 minutes following the intravitreal injection, patients should be monitored for elevation in intraocular pressure using tonometry. Monitoring may also consist of a check for perfusion of the optic nerve

head immediately after the injection [*see Warnings and Precautions (5.2)*]. Patients should also be monitored for and instructed to report any symptoms suggestive of endophthalmitis without delay following the injection [*see Warnings and Precautions (5.1)*].

Each prefilled syringe or vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new prefilled syringe or vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter needle (vial only), and injection needles should be changed before LUCENTIS is administered to the other eye.

No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

3 DOSAGE FORMS AND STRENGTHS

Single-use prefilled syringe designed to provide 0.05 mL for intravitreal injection.

- 10 mg/mL solution (LUCENTIS 0.5 mg)

Single-use glass vial designed to provide 0.05 mL for intravitreal injection.

- 10 mg/mL solution (LUCENTIS 0.5 mg)
- 6 mg/mL solution (LUCENTIS 0.3 mg)

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

LUCENTIS is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity

LUCENTIS is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored following the injection to permit early treatment should an infection occur [*see Dosage and Administration (2.6, 2.7)* and *Patient Counseling Information (17)*].

5.2 Increases in Intraocular Pressure

Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately [*see Dosage and Administration (2.7)*].

5.3 Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

Neovascular (Wet) Age-Related Macular Degeneration

The ATE rate in the three controlled neovascular AMD studies (AMD-1, AMD-2, AMD-3) during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 of 441) in patients from the control arms [see *Clinical Studies (14.1)*]. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 of 435) in patients in the control arms (odds ratio 2.2 (95% confidence interval (0.8-7.1))).

Macular Edema Following Retinal Vein Occlusion

The ATE rate in the two controlled RVO studies during the first 6 months was 0.8% in both the LUCENTIS and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 of 260 in the control arms) [see *Clinical Studies (14.2)*]. The stroke rate was 0.2% (1 of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 of 260) in the control arms.

Diabetic Macular Edema and Diabetic Retinopathy

Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline [see *Clinical Studies (14.3, 14.4)*].

In a pooled analysis of Studies D-1 and D-2 [see *Clinical Studies (14.3)*], the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.

5.4 Fatal Events in Patients with DME and DR at baseline

Diabetic Macular Edema and Diabetic Retinopathy

Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline [see *Clinical Studies (14.3, 14.4)*].

A pooled analysis of Studies D-1 and D-2 [see *Clinical Studies (14.3)*], showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the *Warnings and Precautions (5)* section of the label:

- Endophthalmitis and Retinal Detachments

- Increases in Intraocular Pressure
- Thromboembolic Events
- Fatal Events in patients with DME and DR at baseline

6.1 Injection Procedure

Serious adverse reactions related to the injection procedure have occurred in < 0.1% of intravitreal injections, including endophthalmitis [*see Warnings and Precautions (5.1)*], rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

6.2 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3, and 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg LUCENTIS in 250 patients with DME and DR at baseline [*see Clinical Studies (14)*].

Safety data observed in Study AMD-4 were consistent with these results. On average, the rates and types of adverse reactions in patients were not significantly affected by dosing regimen.

Ocular Reactions

Table 1 shows frequently reported ocular adverse reactions in LUCENTIS-treated patients compared with the control group.

Table 1
Ocular Reactions in the DME and DR, AMD, and RVO Studies

Adverse Reaction	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg Control	n=250 n=250	LUCENTIS 0.5 mg Control	n=379 n=379	LUCENTIS 0.5 mg Control	n=440 n=441	LUCENTIS 0.5 mg Control	n=259 n=260
Conjunctival hemorrhage	47%	32%	74%	60%	64%	50%	48%	37%
Eye pain	17%	13%	35%	30%	26%	20%	17%	12%
Vitreous floaters	10%	4%	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	18%	7%	24%	7%	17%	5%	7%	2%
Vitreous detachment	11%	15%	21%	19%	15%	15%	4%	2%
Intraocular inflammation	4%	3%	18%	8%	13%	7%	1%	3%
Cataract	28%	32%	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	10%	5%	16%	14%	13%	10%	7%	5%
Eye irritation	8%	5%	15%	15%	13%	12%	7%	6%
Lacrimation increased	5%	4%	14%	12%	8%	8%	2%	3%
Blepharitis	3%	2%	12%	8%	8%	5%	0%	1%
Dry eye	5%	3%	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	8%	4%	18%	15%	13%	10%	5%	3%
Eye pruritis	4%	4%	12%	11%	9%	7%	1%	2%
Ocular hyperemia	9%	9%	11%	8%	7%	4%	5%	3%
Retinal disorder	2%	2%	10%	7%	8%	4%	2%	1%
Maculopathy	5%	7%	9%	9%	6%	6%	11%	7%
Retinal degeneration	1%	0%	8%	6%	5%	3%	1%	0%
Ocular discomfort	2%	1%	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	1%	2%	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	4%	3%	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	1%	0%	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions

Non-ocular adverse reactions with an incidence of $\geq 5\%$ in patients receiving LUCENTIS for DR, DME, AMD, and/or RVO and which occurred at a $\geq 1\%$ higher frequency in patients treated with LUCENTIS compared to control are shown in Table 2. Though less common, wound healing complications were also observed in some studies.

Table 2
Non-Ocular Reactions in the DME and DR, AMD and RVO Studies

Adverse Reaction	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg n=250	Control n=250	LUCENTIS 0.5 mg n=379	Control n=379	LUCENTIS 0.5 mg n=440	Control n=441	LUCENTIS 0.5 mg n=259	Control n=260
Nasopharyngitis	12%	6%	16%	13%	8%	9%	5%	4%
Anemia	11%	10%	8%	7%	4%	3%	1%	1%
Nausea	10%	9%	9%	6%	5%	5%	1%	2%
Cough	9%	4%	9%	8%	5%	4%	1%	2%
Constipation	8%	4%	5%	7%	3%	4%	0%	1%
Seasonal allergy	8%	4%	4%	4%	2%	2%	0%	2%
Hypercholesterolemia	7%	5%	5%	5%	3%	2%	1%	1%
Influenza	7%	3%	7%	5%	3%	2%	3%	2%
Renal failure	7%	6%	1%	1%	0%	0%	0%	0%
Upper respiratory tract infection	7%	7%	9%	8%	5%	5%	2%	2%
Gastroesophageal reflux disease	6%	4%	4%	6%	3%	4%	1%	0%
Headache	6%	8%	12%	9%	6%	5%	3%	3%
Edema peripheral	6%	4%	3%	5%	2%	3%	0%	1%
Renal failure chronic	6%	2%	0%	1%	0%	0%	0%	0%
Neuropathy peripheral	5%	3%	1%	1%	1%	0%	0%	0%
Sinusitis	5%	8%	8%	7%	5%	5%	3%	2%
Bronchitis	4%	4%	11%	9%	6%	5%	0%	2%
Atrial fibrillation	3%	3%	5%	4%	2%	2%	1%	0%
Arthralgia	3%	3%	11%	9%	5%	5%	2%	1%
Chronic obstructive pulmonary disease	1%	1%	6%	3%	3%	1%	0%	0%
Wound healing complications	1%	0%	1%	1%	1%	0%	0%	0%

6.3 Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%-5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-9% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in patients with DME and DR at baseline, or RVO patients with the highest levels of immunoreactivity.

6.4 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of LUCENTIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

7 DRUG INTERACTIONS

Drug interaction studies have not been conducted with LUCENTIS.

LUCENTIS intravitreal injection has been used adjunctively with verteporfin photodynamic therapy (PDT). Twelve (12) of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (\pm 2 days) after verteporfin PDT.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There are no studies of LUCENTIS in pregnant women. An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 13 times higher than predicted C_{max} levels with single eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

Animal reproduction studies are not always predictive of human response. It is also not known whether ranibizumab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab [*see Clinical Pharmacology (12.1)*], treatment with LUCENTIS may pose a risk to embryo-fetal development (including teratogenicity) and reproductive capacity. LUCENTIS should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether ranibizumab is excreted in human milk. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of LUCENTIS in pediatric patients have not been established.

8.5 Geriatric Use

In the clinical studies, approximately 79% (2387 of 3005) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 54% (1636 of 3005) were ≥ 75 years of age [*see Clinical Studies (14)*]. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure.

10 OVERDOSAGE

More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

11 DESCRIPTION

LUCENTIS[®] (ranibizumab injection) is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use. Ranibizumab binds to and inhibits the biologic activity of human vascular endothelial growth factor A (VEGF-A). Ranibizumab, which lacks an Fc region, has a molecular weight of approximately 48 kilodaltons and is produced by an *E. coli* expression system in a nutrient medium containing the antibiotic tetracycline. Tetracycline is not detectable in the final product.

LUCENTIS is a sterile, colorless to pale yellow solution in a single-use prefilled syringe or a single-use glass vial. LUCENTIS is supplied as a preservative-free, sterile solution in a single-use container designed to deliver 0.05 mL of 10 mg/mL LUCENTIS (0.5 mg dose prefilled syringe or vial) or 6 mg/mL LUCENTIS (0.3 mg dose vial) aqueous solution with 10 mM histidine HCl, 10% α,α -trehalose dihydrate, 0.01% polysorbate 20, pH 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ranibizumab binds to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, VEGF₁₁₀. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion and is thought to contribute to pathophysiology of neovascular AMD, macular edema following RVO, DR and DME. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

12.2 Pharmacodynamics

Increased retinal thickness (i.e., center point thickness (CPT) or central foveal thickness (CFT)), as assessed by optical coherence tomography (OCT) is associated with neovascular AMD, macular edema following RVO, and DME. Leakage from choroidal neovascularization (CNV) as assessed by fluorescein angiography (FA) is associated with neovascular AMD. Microvascular retinal changes and neovascularization, as assessed by color fundus photography, are associated with diabetic retinopathy.

Neovascular (Wet) Age-Related Macular Degeneration

In Study AMD-3, CPT was assessed by time domain (TD)-OCT in 118 of 184 patients. TD-OCT measurements were collected at baseline, Months 1, 2, 3, 5, 8, and 12. In patients treated with LUCENTIS, CPT decreased, on average, more than in the sham group from baseline through Month 12. CPT decreased by Month 1 and decreased further at Month 3, on average. In this study, CPT data did not provide information useful in influencing treatment decisions [*see Clinical Studies (14.1)*].

In Study AMD-4, CFT was assessed by spectral domain (SD)-OCT in all patients; on average, CFT reductions were observed beginning at Day 7 following the first LUCENTIS injection through Month 24. CFT data did not provide information capable of predicting final visual acuity results [*see Clinical Studies (14.1)*].

In patients treated with LUCENTIS, the area of CNV leakage, on average, decreased by Month 3 as assessed by FA. The area of CNV leakage for an individual patient was not correlated with visual acuity.

Macular Edema Following Retinal Vein Occlusion

On average, CPT reductions were observed in Studies RVO-1 and RVO-2 beginning at Day 7 following the first LUCENTIS injection through Month 6. CPT was not evaluated as a means to guide treatment decisions [*see Clinical Studies (14.2)*].

Diabetic Macular Edema

On average, CPT reductions were observed in Studies D-1 and D-2 beginning at Day 7 following the first LUCENTIS injection through Month 36. CPT data did not provide information useful in influencing treatment decisions [*see Clinical Studies (14.3)*].

Diabetic Retinopathy in patients with Diabetic Macular Edema

Improvements from baseline in DR severity as assessed on fundus photography were observed in Studies D-1 and D-2 at Month 3 (first scheduled DR photographic assessment after randomization) through Month 36 [*see Clinical Studies (14.4)*].

12.3 Pharmacokinetics

In animal studies, following intravitreal injection, ranibizumab was cleared from the vitreous with a half-life of approximately 3 days. After reaching a maximum at approximately 1 day, the serum concentration of ranibizumab declined in parallel with the vitreous concentration. In these animal studies, systemic exposure of ranibizumab was more than 2000-fold lower than in the vitreous.

In patients with neovascular AMD, following monthly intravitreal administration of 0.5 mg LUCENTIS, mean (\pm SD) maximum ranibizumab serum concentrations were 1.7 (\pm 1.1) ng/mL. These concentrations were below the concentration range of ranibizumab (11 to 27 ng/mL) that was necessary to inhibit the biological activity of VEGF-A by 50%, as measured in an in vitro cellular proliferation assay (based on human umbilical vein endothelial cells (HUVEC)). No significant change from baseline was observed in the mean plasma VEGF concentrations following three monthly 0.5 mg intravitreal injections. The maximum observed serum concentration was dose proportional over the dose range of 0.05 to 2 mg/eye. Serum ranibizumab concentrations in RVO and DME and DR patients were similar to those observed in neovascular AMD patients.

Based on a population pharmacokinetic analysis of patients with neovascular AMD, maximum serum concentrations are predicted to be reached at approximately 1 day after monthly intravitreal administration of

LUCENTIS 0.5 mg/eye. Based on the disappearance of ranibizumab from serum, the estimated average vitreous elimination half-life was approximately 9 days. Steady-state minimum concentration is predicted to be 0.22 ng/mL with a monthly dosing regimen. In humans, serum ranibizumab concentrations are predicted to be approximately 90,000-fold lower than vitreal concentrations.

In pharmacokinetic covariate analyses, 48% (520/1091) of patients had renal impairment (35% mild, 11% moderate, and 2% severe). Because the increases in plasma ranibizumab exposures in these patients are not considered clinically significant, no dosage adjustment is needed based on renal impairment status.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity data are available for ranibizumab injection in animals or humans.

No studies on the effects of ranibizumab on fertility have been conducted. Although systemic exposure following ocular administration is expected to be low, effects on female fertility are possible due to the anti-VEGF mechanism of action for ranibizumab [*see Clinical Pharmacology (12.1)*].

14 CLINICAL STUDIES

Unless otherwise noted, visual acuity was measured at a distance of 4 meters.

14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The safety and efficacy of LUCENTIS were assessed in three randomized, double-masked, sham- or active-controlled studies in patients with neovascular AMD. A total of 1323 patients (LUCENTIS 879, control 444) were enrolled in the three studies.

Studies AMD-1 and AMD-2

In Study AMD-1, patients with minimally classic or occult (without classic) CNV lesions received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections. Data are available through Month 24. Patients treated with LUCENTIS in Study AMD-1 received a mean of 22 total treatments out of a possible 24 from Day 0 to Month 24.

In Study AMD-2, patients with predominantly classic CNV lesions received one of the following: 1) monthly LUCENTIS 0.3 mg intravitreal injections and sham PDT; 2) monthly LUCENTIS 0.5 mg intravitreal injections and sham PDT; or 3) sham intravitreal injections and active verteporfin PDT. Sham PDT (or active verteporfin PDT) was given with the initial LUCENTIS (or sham) intravitreal injection and every 3 months thereafter if fluorescein angiography showed persistence or recurrence of leakage. Data are available through Month 24. Patients treated with LUCENTIS in Study AMD-2 received a mean of 21 total treatments out of a possible 24 from Day 0 through Month 24.

In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at 12 months compared with baseline. Almost all LUCENTIS-treated patients (approximately 95%) maintained their visual acuity. Among LUCENTIS-treated patients, 31% to 37% experienced a clinically significant improvement in vision, defined as gaining 15 or more letters at 12 months. The size of the lesion did not significantly affect the results. Detailed results are shown in Table 3, Table 4, and Figure 1 below.

Table 3
Visual Acuity Outcomes at Month 12 and Month 24 in Study AMD-1

Outcome Measure	Month	Sham n=229	LUCENTIS 0.5 mg n=230	Estimated Difference (95% CI) ^a
Loss of <15 letters in visual acuity (%)	12	60%	91%	30% (23%, 37%)
	24	56%	89%	33% (26%, 41%)
Gain of ≥15 letters in visual acuity (%)	12	6%	31%	25% (18%, 31%)
	24	4%	30%	25% (18%, 31%)
Mean change in visual acuity (letters) (SD)	12	-11.0 (17.9)	+6.3 (14.1)	17.1 (14.2, 20.0)
	24	-15.0 (19.7)	+5.5 (15.9)	20.1 (16.9, 23.4)

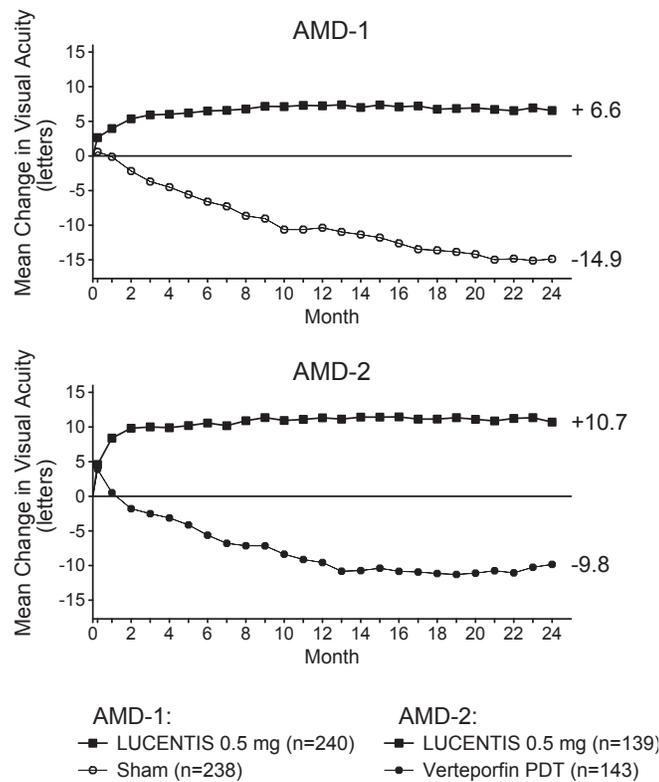
^aAdjusted estimate based on the stratified model; p < 0.01

Table 4
Visual Acuity Outcomes at Month 12 and Month 24 in Study AMD-2

Outcome Measure	Month	Verteporfin PDT n=141	LUCENTIS 0.5 mg n=139	Estimated Difference (95% CI) ^a
Loss of <15 letters in visual acuity (%)	12	66%	98%	32% (24%, 40%)
	24	65%	93%	28% (19%, 37%)
Gain of ≥15 letters in visual acuity (%)	12	11%	37%	26% (17%, 36%)
	24	9%	37%	29% (20%, 39%)
Mean change in visual acuity (letters) (SD)	12	-8.5 (17.8)	+11.0 (15.8)	19.8 (15.9, 23.7)
	24	-9.1 (18.7)	+10.9 (17.3)	20 (16.0, 24.4)

^aAdjusted estimate based on the stratified model; p < 0.01

Figure 1
Mean Change in Visual Acuity from Baseline to Month 24 in Study AMD-1 and Study AMD-2



Visual acuity was measured at a distance of 2 meters

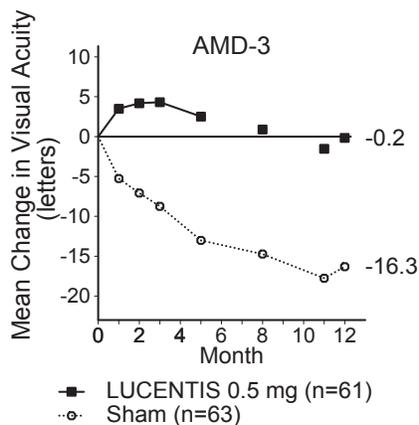
Patients in the group treated with LUCENTIS had minimal observable CNV lesion growth, on average. At Month 12, the mean change in the total area of the CNV lesion was 0.1-0.3 disc areas (DA) for LUCENTIS versus 2.3-2.6 DA for the control arms. At Month 24, the mean change in the total area of the CNV lesion was 0.3-0.4 DA for LUCENTIS versus 2.9-3.1 DA for the control arms.

Study AMD-3

Study AMD-3 was a randomized, double-masked, sham-controlled, two-year study designed to assess the safety and efficacy of LUCENTIS in patients with neovascular AMD (with or without a classic CNV component). Data are available through Month 12. Patients received LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or sham injections once a month for 3 consecutive doses, followed by a dose administered once every 3 months for 9 months. A total of 184 patients were enrolled in this study (LUCENTIS 0.3 mg, 60; LUCENTIS 0.5 mg, 61; sham, 63); 171 (93%) completed 12 months of this study. Patients treated with LUCENTIS in Study AMD-3 received a mean of 6 total treatments out of a possible 6 from Day 0 through Month 12.

In Study AMD-3, the primary efficacy endpoint was mean change in visual acuity at 12 months compared with baseline (see Figure 2). After an initial increase in visual acuity (following monthly dosing), on average, patients dosed once every 3 months with LUCENTIS lost visual acuity, returning to baseline at Month 12. In Study AMD-3, almost all LUCENTIS-treated patients (90%) lost fewer than 15 letters of visual acuity at Month 12.

Figure 2
Mean Change in Visual Acuity from Baseline to Month 12 in Study AMD-3



Study AMD-4

Study AMD-4 was a randomized, double-masked, active treatment-controlled, two-year study designed to assess the safety and efficacy of LUCENTIS 0.5 mg administered monthly or less frequently than monthly in patients with neovascular AMD. Patients randomized to the LUCENTIS 0.5 mg less frequent dosing arm received 3 monthly doses followed by monthly assessments where patients were eligible to receive LUCENTIS injections guided by pre-specified re-treatment criteria. A total of 550 patients were enrolled in the two 0.5 mg treatment groups with 467 (85%) completing through Month 24. Data are available through Month 24. Clinical results at Month 24 remain similar to that observed at Month 12.

From Month 3 through Month 24, visual acuity decreased by 0.3 letters in the 0.5 mg less frequent dosing arm and increased by 0.7 letters in the 0.5 mg monthly arm (see Figure 3). Over this 21 month period, patients in the 0.5 mg less frequent dosing and the 0.5 mg monthly arms averaged 10.3 and 18.5 injections, respectively. The distribution of injections received in the less frequent dosing arm is shown in Figure 4.

Figure 3

Mean Change in Visual Acuity from Baseline to Month 24 in Study AMD-4

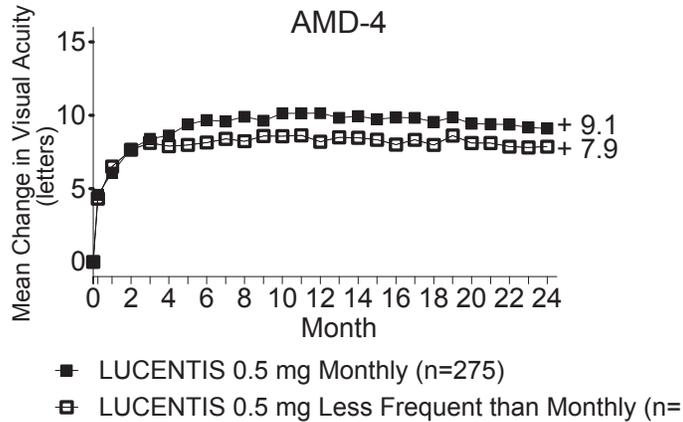
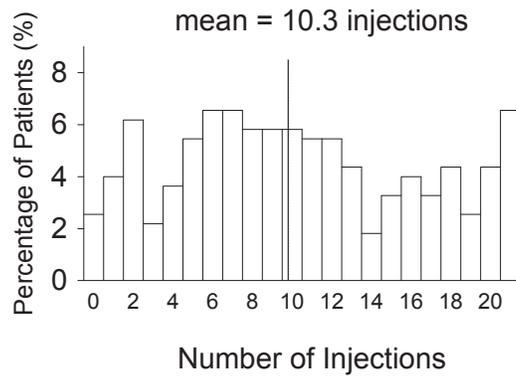


Figure 4

Distribution of Injections from Month 3 to Month 24 in the Less Frequent Dosing Arm in Study AMD-4



14.2 Macular Edema Following Retinal Vein Occlusion (RVO)

The safety and efficacy of LUCENTIS were assessed in two randomized, double-masked, 1-year studies in patients with macular edema following RVO. Sham controlled data are available through Month 6. Patient age ranged from 20 to 91 years, with a mean age of 67 years. A total of 789 patients (LUCENTIS 0.3 mg, 266 patients; LUCENTIS 0.5 mg, 261 patients; sham, 262 patients) were enrolled, with 739 (94%) patients completing through Month 6. All patients completing Month 6 were eligible to receive LUCENTIS injections guided by pre-specified re-treatment criteria until the end of the studies at Month 12.

In Study RVO-1, patients with macular edema following branch or hemi-RVO, received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections for 6 months. All patients were eligible for macular focal/grid laser treatment beginning at Month 3 of the 6-month treatment period. Macular focal/grid laser treatment was given to 26 of 131 (20%) patients treated with 0.5 mg LUCENTIS and 71 of 132 (54%) patients treated with sham.

In Study RVO-2, patients with macular edema following central RVO received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections for 6 months.

At Month 6, after monthly treatment with 0.5 mg LUCENTIS, the following clinical results were observed:

Table 5
Visual Acuity Outcomes at Month 6 in Study RVO-1 and Study RVO-2

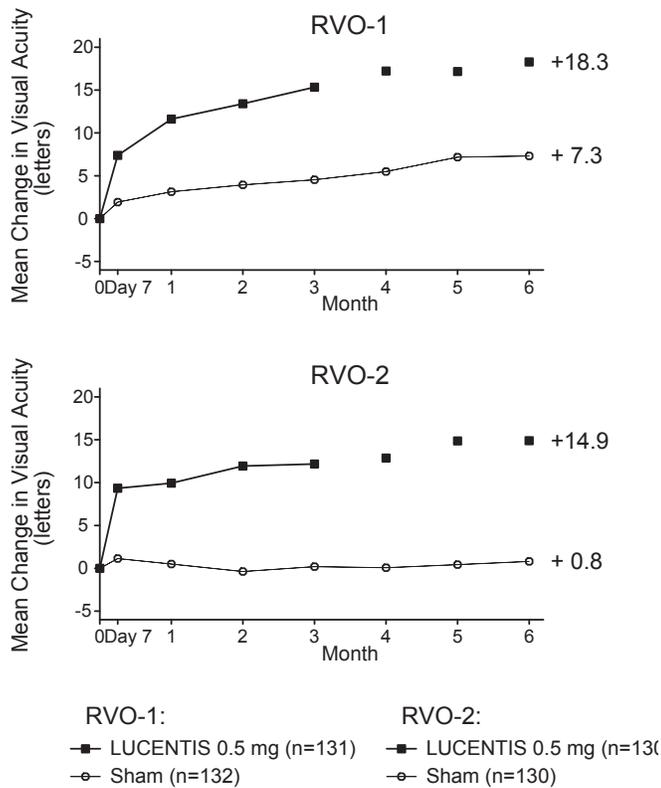
Outcome Measure	Study ^a	Sham	LUCENTIS 0.5 mg	Estimated Difference (95% CI) ^b
Gain of ≥15 letters in visual acuity (%)	RVO-1	29%	61%	31% (20%, 43%)
Gain of ≥15 letters in visual acuity (%)	RVO-2	17%	48%	30% (20%, 41%)

^a RVO-1: Sham, n=131; LUCENTIS 0.5 mg, n=132

RVO-2: Sham, n=130; LUCENTIS 0.5 mg, n=130

^b Adjusted estimate based on stratified model; p < 0.01

Figure 5
Mean Change in Visual Acuity from Baseline to Month 6 in Study RVO-1 and Study RVO-2



$p < 0.01$ for all time points

14.3 Diabetic Macular Edema

Efficacy and safety data of LUCENTIS are derived from studies D-1 and D-2 (See Section 14.4 Diabetic Retinopathy below). All enrolled patients had DR and DME at baseline.

The safety and efficacy of LUCENTIS were assessed in two randomized, double-masked, 3-year studies. The studies were sham-controlled through Month 24. Patient age ranged from 21 to 91 years, with a mean age of 62 years. A total of 759 patients (LUCENTIS 0.3 mg, 250 patients; LUCENTIS 0.5 mg, 252 patients; sham, 257 patients) were enrolled, with 582 (77%) completing through Month 36.

In Studies D-1 and D-2, patients received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections during the 24-month controlled treatment period. From Months 25 through 36, patients who previously received sham were eligible to receive monthly LUCENTIS 0.5 mg and patients originally randomized to monthly LUCENTIS 0.3 mg or 0.5 mg continued to receive their assigned dose. All patients were eligible for macular focal/grid laser treatment beginning at Month 3 of the 24-month treatment period or panretinal photocoagulation (PRP) as needed. Through Month 24, macular focal/grid laser treatment was administered in 94 of 250 (38%) patients treated with LUCENTIS 0.3 mg and 185 of 257 (72%) patients treated with sham; PRP was administered in 2 of 250 (1%) patients treated with LUCENTIS 0.3 mg and 30 of 257 (12%) patients treated with sham.

Compared to monthly LUCENTIS 0.3 mg, no additional benefit was observed with monthly treatment with LUCENTIS 0.5 mg. At Month 24, after monthly treatment with LUCENTIS 0.3 mg, the following clinical results were observed:

Table 6
Visual Acuity Outcomes at Month 24 in Study D-1 and D-2

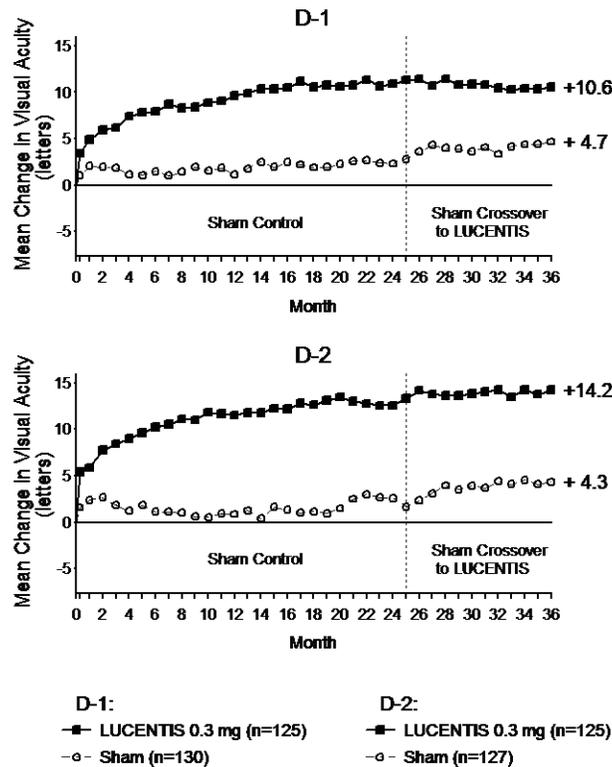
Outcome Measure	Study ^a	Sham	LUCENTIS 0.3 mg	Estimated Difference (95% CI) ^b
Gain of ≥15 letters in visual acuity (%)	D-1	12%	34%	21% (11%, 30%)
	D-2	18%	45%	24% (14%, 35%)
Loss of <15 letters in visual acuity (%)	D-1	92%	98%	7% (2%, 13%)
	D-2	90%	98%	8% (2%, 14%)
Mean change in visual acuity (letters)	D-1	2.3	10.9	8.5 (5.4, 11.5)
	D-2	2.6	12.5	9.6 (6.1, 13.0)

^a D-1: Sham, n=130; LUCENTIS 0.3 mg, n=125

D-2: Sham, n=127; LUCENTIS 0.3 mg, n=125

^b Adjusted estimate based on stratified model; p ≤ 0.01

Figure 6
Mean Change in Visual Acuity from Baseline to Month 36 in Study D-1 and Study D-2



$p < 0.01$ for all time points comparing LUCENTIS 0.3 mg to sham through Month 24

VA outcomes observed at Month 24 in patients treated with LUCENTIS 0.3 mg were maintained with continued treatment through Month 36 in both DME studies. Patients in the sham arms who received LUCENTIS 0.5 mg beginning at Month 25 achieved lesser VA gains compared to patients who began treatment with LUCENTIS at the beginning of the studies.

In Studies D-1 and D-2, patients received monthly injections of LUCENTIS for 12 or 36 months, after which 500 patients opted to continue in the long-term follow-up study. Of 298 patients who had at least 12 months of follow-up from Month 36, 58 (19.5%) patients maintained vision with no further therapy. The remaining 202 patients were followed for less than 12 months.

14.4 Diabetic Retinopathy in patients with Diabetic Macular Edema (DME)

Efficacy and safety data of LUCENTIS are derived from studies D-1 and D-2 (See Section 14.3 Diabetic Macular Edema above). All enrolled patients had DR and DME at baseline.

Of the 759 patients enrolled, 746 patients had a baseline assessment of fundus photography. Patients had baseline Early Treatment Diabetic Retinopathy Study (ETDRS) Retinopathy Severity Scores (ETDRS-RSS) ranging from 10 to 75. At baseline, 62% of patients had NPDR (ETDRS-RSS less than 60) and 31% had PDR (ETDRS-RSS greater than or equal to 60).

The ETDRS-RSS could not be graded in 5% of patients at baseline, and 2% of patients had absent or questionable DR at baseline. Approximately 20% of the overall population had prior PRP.

After monthly treatment with LUCENTIS 0.3 mg, the following clinical results were observed (Table 7; Figure 7):

Table 7
≥3-step and ≥2-step improvement at Month 24 in
Study D-1 and Study D-2

Outcome Measure	Study ^a	Sham	LUCENTIS 0.3 mg	Estimated Difference (95% CI) ^b
≥3-step improvement from baseline in ETDRS-DRSS ^c	D-1	2%	17%	15% (7%, 22%)
	D-2	0%	9%	9% (4%, 14%)
≥2-step improvement from baseline in ETDRS-DRSS ^d	D-1	4%	39%	35% (26%, 44%)
	D-2	7%	37%	31% (21%, 40%)

^a D-1: Sham, n=124; LUCENTIS 0.3 mg, n=117

D-2: Sham, n=115; LUCENTIS 0.3 mg, n=117

^b Adjusted estimate based on stratified model

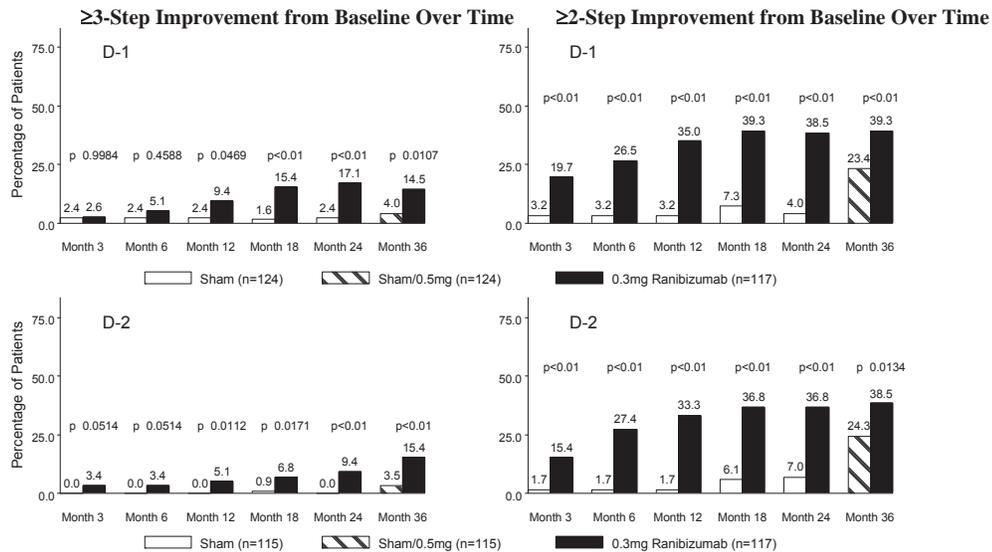
^c p < 0.05 for all time points comparing LUCENTIS 0.3 mg to sham from
Month 12 through Month 24

^d p < 0.05 for all time points comparing LUCENTIS 0.3 mg to sham from
Month 3 through Month 24

At Month 24, DR improvement by ≥3-steps in ETDRS-RSS from baseline in subgroups examined (e.g., age, gender, race, baseline visual acuity, baseline HbA1c, prior DME therapy at baseline, baseline DR severity (NPDR, PDR)) were generally consistent with the results in the overall population.

The difference in the proportion of patients treated with LUCENTIS 0.3 mg compared to sham who achieved DR improvement based on the ETDRS-RSS was observed as early as Month 3 for ≥2-step improvement or at Month 12 for ≥3-step improvement.

Figure 7
Proportion of Patients with ≥ 3 -Step and ≥ 2 -Step Improvement from Baseline in ETDRS Diabetic Retinopathy Severity Level over Time in Study D-1 and Study D-2



16 HOW SUPPLIED/STORAGE AND HANDLING

- Each LUCENTIS 0.5 mg carton (NDC 50242-080-03) contains a single-use, prefilled syringe designed to deliver 0.05 mL of 10 mg/mL ranibizumab. The prefilled syringe has a non-retractable plunger stopper and a syringe cap consisting of a tamper-evident rigid seal with a rubber tip cap including a Luer lock adapter. The prefilled syringe has a plunger rod and a CLEAR finger grip. The prefilled syringe is sterile and is packed in a sealed tray.
- Each LUCENTIS 0.5 mg carton (NDC 50242-080-01) contains a single-use, 2-cc glass vial with a BLUE CAP designed to deliver 0.05 mL of 10 mg/mL ranibizumab. Also contains one 5-micron, 19-gauge x 1-1/2-inch filter needle for withdrawal of the vial contents; one 30-gauge x 1/2-inch injection needle for the intravitreal injection
- Each LUCENTIS 0.3 mg carton (NDC 50242-082-01) contains a single-use, 2-cc glass vial with a WHITE CAP designed to deliver 0.05 mL of 6 mg/mL ranibizumab. Also contains one 5-micron, 19-gauge x 1-1/2-inch filter needle for withdrawal of the vial contents; one 30-gauge x 1/2-inch injection needle for the intravitreal injection

EACH CARTON IS FOR SINGLE-EYE USE ONLY.

LUCENTIS should be refrigerated at 2°-8°C (36°-46°F). DO NOT FREEZE. Do not use beyond the date stamped on the label. Protect LUCENTIS prefilled syringe and vials from light and store in a dark place. Keep LUCENTIS prefilled syringe in the sealed tray until time of use.

17 PATIENT COUNSELING INFORMATION

Advise patients that in the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist [see Warnings and Precautions (5.1)].

LUCENTIS® [ranibizumab injection]	
Manufactured by: Genentech, Inc. A Member of the Roche Group 1 DNA Way South San Francisco, CA 94080-4990	LUCENTIS® is a registered trademark of Genentech, Inc. ©2016 Genentech, Inc.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125156Orig1s110

MEDICAL REVIEW(S)

Medical Officer's Review of BLA 125156
Prior Approval Supplement (PAS)
Review #2

BLA 125156/S-110
SDN-828

Submission Date: 10/7/16
Received Date: 10/7/16
Review Date: 10/13/16

Sponsor:

Genentech, Inc.
1 DNA Way, MS 321B
South San Francisco, CA 94080-4990

Drug:

Lucentis (ranibizumab injection)

Pharmacologic Category:

VEGF inhibitor

**Dosage Form and
Route of Administration:**

intravitreal injection

Indication:

Treatment of patients with treatment of patients with neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), and diabetic retinopathy in patients with DME

Submitted:

This supplemental application proposes the addition of a Lucentis 0.5 mg prefilled syringe (PFS) with associated changes to the labeling. A Type C meeting (teleconference) had previously been held on May 19, 2015, to discuss a change in the presentation of Lucentis 0.5mg from a single-use vial to a single-use pre-filled syringe. This PFS product is considered a biologic and not a combination product.

This submission provide for revised Labeling Artwork for the (b) (4).

Reviewer's Comments:

The package insert (submitted 9/22/16) and the carton labeling and syringe labeling (submitted 6/16/16) were previously found to be acceptable. See Clinical review dated 10/11/16 in DARRTS.

(b) (4)

Office of Biotechnology Products Labeling Review

The Office of Biotechnology Products labeling review was completed on 10/7/16. Per an email exchange between DTOP and OBP labeling on 10/6/16:

We have the following comments regarding your proposed prescribing information (PI), container labels, and carton labeling submitted on June 6, 2016.

A. Prescribing Information

1. Add your U.S. License Number 1048 to appear with the manufacturer information at the bottom of the PI to fulfill 21 CFR 610.61(b).

[DTOP] The manufacturer license number information on the carton appears to satisfy 21 CFR 610.61(b), “The following items shall appear on the label affixed to each package containing a product...” Correct?

[OBP] The definition of package in 21 CFR 600.3(cc) “means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers.” Therefore, we consider the PI part of the “package” ask Applicant’s to add it to all articles of labeling including the PI.

[DTOP] 21 CFR 610.61(b) specifically refers to the package label, not the package. We would not require the U.S. License Number on the PI if it is on the carton. DTOP

B. Carton Labeling

1. What regulation are you attempting to fulfill with the statement “Made in Singapore” that appears with the manufacturer information?

[DTOP] Many states require the “Made in” statement. Is there a regulation prohibiting its inclusion?

[OBP] There is no regulation prohibiting its inclusion. Sometimes Applicants place “Made in Country X” it on the labeling to fulfill Country of Origin regulations 19 CFR 134.11 (enforced by US Customs Border and Protection). But I was unsure in this case.

[DTOP] We have no objection to “Made in Singapore” on the carton as proposed.

C. Prefilled Syringe Container Label and (b) (4) Labeling

1. Revise the display of the proprietary name and proper name to appear on two separate lines, similar to the presentation on all other Lucentis container labels and carton labeling. For example:

[DTOP] This appears to be a preference, not a requirement under regulation. Correct?

[OBP] Correct. But to explain why we make this recommendation...

21 CFR 610.62 states the proper name should appear above the proprietary name...

However specified biologics (mAb like ranibizumab) are exempt from this regulation. Therefore, our practice is the reverse for specified biologics (proprietary name appear above proper name). There is no regulation for this but we consistently take this approach for specified biologics. The Applicant has agreed to this with all their other specified biologics.

[DTOP] If there is no requirement under regulation, we would not request revision of the prefilled syringe container label and (b) (4) labeling.

Office of Biotechnology Products, Division of Biotechnology Review and Research I (DBRRI)

Office of Biotechnology Products, Division of Biotechnology Review and Research I (DBRRI) completed their review on 10/12/16 and recommends approval. For details, see that completed review.

The Office of Biotechnology Products requested a postmarketing commitment (PMC) to confirm stability of Lucentis drug product during shipping. The applicant agreed to this PMC in their 10/11/16 submission:

PMC #1: Perform a shipping study designed to confirm stability of Lucentis drug product during shipping under conditions and through a route that are representative of commercial drug product shipping. The study will include testing of pre- and post-shipping samples for product quality (container closure integrity, purity by SEC, nrCE-SDS, IE-HPLC, sub-visible particles, and potency of ranibizumab).

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Table P.5.1-3 Blister Integrity Testing Performed on the Finished PFS

Analytical Procedure	Acceptance Criterion at Release	Acceptance Criterion at End of Shelf Life
Blister Integrity (Dye Leak) ^a	NA	No leakage detected

Abbreviations: NA= not applicable; PFS= prefilled syringe.

^a Tested to end of shelf life using the finished PFS (see [Table P.5.1-1](#)).

Office of Pharmaceutical Quality, Division of Microbiology Assessment (DMA), Branch IV

Office of Pharmaceutical Quality, Division of Microbiology Assessment (DMA) completed their review on 10/13/16 and recommends approval. For details, see that completed review.

Reviewer's Comments:

There is an incorrect statement on page 23 of the review. The proposal to file this change in a Changes Being Effective in 30 Days (CBE-30) supplement would not be acceptable. A [REDACTED] (b) (4),

[REDACTED] (b) (4)

Recommended Regulatory Action:

The package insert (submitted 9/22/16) and the carton labeling and syringe labeling (submitted 6/16/16) are acceptable.

The [REDACTED] (b) (4) Labeling submitted 10/7/16 is acceptable.

Office of Biotechnology Products, Division of Biotechnology Review and Research I (DBRRI) recommends approval.

Office of Pharmaceutical Quality, Division of Microbiology Assessment (DMA) recommends approval.

CDRH (Office of Device Evaluation Division of Anesthesiology, General Hospital, Respiratory, Infection Control, and Dental Devices) recommends approval.

This supplemental application with its associated labeling (see Appendix this review) is recommended for approval.

William M. Boyd, M.D.
Clinical Team Leader

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/s/

WILLIAM M BOYD
10/13/2016

WILEY A CHAMBERS
10/13/2016

Medical Officer's Review of BLA 125156
Prior Approval Supplement (PAS)

BLA 125156/S-110

SDN-798

Submission Date: 6/16/16

Received Date: 6/16/16

SDN-816

Submission Date: 8/19/16

Received Date: 8/19/16

SDN-825

Submission Date: 9/22/16

Received Date: 9/22/16

Review Date: 10/3/16

Sponsor:

Genentech, Inc.
1 DNA Way, MS 321B
South San Francisco, CA 94080-4990

Drug:

Lucentis (ranibizumab injection)

Pharmacologic Category:

VEGF inhibitor

Dosage Form and

Route of Administration:

intravitreal injection

Indication:

Treatment of patients with treatment of patients with neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), and diabetic retinopathy in patients with DME

Submitted:

This supplemental application proposes the addition of a Lucentis 0.5 mg prefilled syringe (PFS) with associated changes to the labeling. A Type C meeting (teleconference) had previously been held on May 19, 2015, to discuss a change in the presentation of Lucentis 0.5mg from a single-use vial to a single-use pre-filled syringe. This PFS product is considered a biologic and not a combination product.

Reviewer's Comments:

Genentech conducted an actual use study (GX30020) for the Lucentis PFS to evaluate whether healthcare providers could follow the Lucentis PFS Instructions for Use while maintaining aseptic conditions in the intended use environment.

A teleconference was held on August 15, 2016, regarding the Agency's concern on Step 6 of the PFS Instructions for Use (IFU). The Agency did not agree that the diagram and instructions provided in Step 6 were consistent with standard physician practice with syringes.

Step 6 of the IFU instructed users to align the edge below the dome of the rubber stopper with the 0.05 mL dose mark. The applicant was asked to include their analysis of the stopper position and corresponding drug product volume expelled from the PFS as well as the human factors engineering summary report referenced by Genetech during the call. Genetech was also asked to provide a sample of the Lucentis PFS.

Original Figure 5**Step 6: Expel air and adjust drug dose**

- Hold the syringe at eye level, and carefully push the plunger rod until the **edge below the dome** of the rubber stopper is aligned with the 0.05 mL dose mark (see Figure 5).

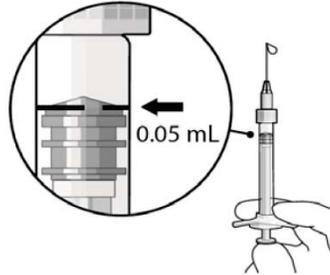


Figure 5

Note: The plunger rod is not attached to the rubber stopper – this is to prevent air being drawn into the syringe.

Genentech had previously agreed to incorporate the PFS IFU within Section 2, Dosage and Administration of the USPI and amended draft labeling with this change is provided in the 8/19/16 submission.

A second teleconference was held on September 12, 2016; Genentech revised Figure 5 to increase clarity on how to adjust the dosage for the PFS. Per the submission, "...The updated figure reflects that when a healthcare professional (HCP) aligns the bottom edge of the dome with the dose mark, the dose mark is also concurrently aligned to the top of the first rib, where the stopper meets the wall of the glass barrel. When adjusted as instructed, the dose mark aligns with both features of the stopper. Additionally, Figure 5 has been improved for clarity by adding the inner walls of the glass barrel and by more clearly depicting the dome of the stopper and the dose mark."

Revised Figure 5**Step 6: Expel air and adjust drug dose**

- Hold the syringe at eye level, and carefully push the plunger rod until the **edge below the dome** of the rubber stopper is aligned with the 0.05 mL dose mark (see Figure 5).

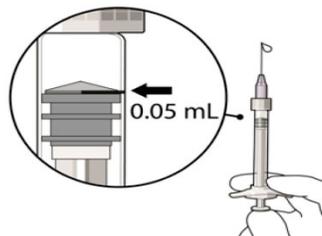


Figure 5

Note: The plunger rod is not attached to the rubber stopper – this is to prevent air being drawn into the syringe.

Following is the package insert submitted on 9/22/16. Applicant additions to the approved package insert are noted by underline and deletions are noted by

CDRH Intercenter Consult

CDRH (Office of Device Evaluation Division of Anesthesiology, General Hospital, Respiratory, Infection Control, and Dental Devices) recommends approval in their review dated 9/29/16.

Reviewer's Comments:

There is a typographical error on the first page of the consult review; the reviewer states the prefilled syringe is a combination product. Because this prefilled syringe presentation for Lucentis is for ophthalmic use, it is not considered a combination product (21 CFR 200.50). This is acknowledged on page 2 of the consult.

CDRH has no recommend revisions to the labeling.

Division of Medication Error Prevention and Analysis (DMEPA)

DMEPA completed a review on 10/3/2016. DMEAP has no recommend revisions to he package insert but has suggested revisions to the carton and container labeling:

A. Carton Labeling

(b) (4)

2. Consider increasing the prominence (i.e., font size) of the NDC. Since NDC number is often used as an additional verification prior to drug dispensing in the pharmacy, it is an important safety feature that should be prominently displayed in the top third of principal display panel of the labeling in accordance with 21 CFR 207.35(b)(3)(i).

Reviewer's Comments: *Disagree. The NDC number is appropriately placed and appropriately prominent on the top of the carton. This is the portion of the carton most visible when the product is stored.*

3. Decrease the prominence of the statement "Rx Only" as this information appears more prominent than the established name on the principal display panel.

Reviewer's Comments: *Disagree. Rx is not more prominent that the established name of the product.*

B. ^{(b) (4)} Labeling

1. The strength lacks prominence. Increase the prominence (i.e., font size) of the strength taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.15(a)(6).

Reviewer's Comments: *Disagree. This is a prefilled syringe in sterile packaging for administration by an ophthalmologist in a clean, surgical setting. The strength is of adequate prominence.*

2. We recommend that you apply the same color scheme as the corresponding commercialized 0.5 mg vials to the (b) (4) labeling.

Reviewer's Comments: *Disagree. There is no approved 0.3 mg prefilled syringe configuration. The proposed color scheme is acceptable.*

3. As currently presented, the route of administration is not present. We recommend including the statement "For intravitreal injection only" to minimize the risk of administering the drug as an intravenous bolus.

Reviewer's Comments: *Disagree. This is a prefilled syringe in sterile packaging for administration by an ophthalmologist in a clean, surgical setting.*

4. We recommend including the statement "Single Dose" to ensure that the product is safely used and handled.

Reviewer's Comments: *Disagree. This is a prefilled syringe in sterile packaging for administration by an ophthalmologist in a clean, surgical setting.*

(b) (4)

(b) (4)

Reviewer's Comments: *The Quick response code (QR) that currently only contains lot information can be removed. Lot information is already provided on the (b) (4) labeling.*

C. Prefilled Syringe Label

1. Based on the syringe samples provided, we note that there is inadequate contrast when the syringe label information is printed against the transparent syringe. We recommend increasing the contrast of the text against the syringe to improve readability, while following the same color scheme as the corresponding commercialized 0.5 mg vials.

Reviewer's Comments: *Disagree. There is adequate contrast on the syringe label; and the printed text is easily legible.*

2. The strength lacks prominence. Increase the prominence (i.e., font size) of the strength taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR

201.15(a)(6). Additionally, please consider following the same color scheme as the corresponding commercialized 0.5 mg vials.

Reviewer's Comments: *Disagree. This is a prefilled syringe in sterile packaging for administration by an ophthalmologist in a clean, surgical setting. There is no approved 0.3 mg prefilled syringe configuration. The proposed color scheme is acceptable.*

3 Page(s) of Draft Labeling have been Withheld in Full as b4
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Recommended Regulatory Action:

This supplemental application providing for a Lucentis 0.5 mg prefilled syringe (PFS) with associated changes to the labeling is NOT recommended for approval until:

1. The Office of Biologic Products review is completed.

2.

(b) (4)

William M. Boyd, M.D.
Clinical Team Leader

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/s/

WILLIAM M BOYD
10/05/2016

WILEY A CHAMBERS
10/11/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125156Orig1s110

CHEMISTRY REVIEW(S)



Memorandum of Review

Date: October 5, 2016

To: File for STN: 125156/110

From: Sarah Kennett, Ph.D.

Through: Kathleen A. Clouse, Ph.D., Director DBRRI

Subject: PAS for 0.5 mg prefilled syringe presentation

Applicant: Genentech

Product: Lucentis (ranibizumab)

Filing Action Date: 8/15/16 **Status:** Filed

Action Due Date: 10/16/16

Review Recommendation: Approval

Review Comments:

Tables and Figures were copied directly from the sponsor's submission (125156/110), and other statements copied directly from the submission are in quotation marks. Reviewer comments are indicated by italics.

This PAS is for the introduction of a prefilled syringe presentation for Lucentis, which is currently marketed in 0.3 mg and 0.5 mg vial (solution) presentations. The current data were submitted in support of a 0.5 mg PFS (b) (4)

(b) (4) The change to a PFS led to updates to the prescribing information. The changes to the labeling will be reviewed by the OBP labeling reviewer and OND.

The PFS has been marketed outside the US (Europe, Canada, and Japan) for more than two years. The container closure and filling and sterilization processes used outside the US are identical to those currently proposed for US licensure.

This product is not considered a biologic/device combination product [per 21 CFR 200.50(c), which states that ophthalmic dispensers are regulated as drugs]; therefore, the package submitted in support of the PFS is not a standard device package. However, a CDRH evaluation of the PFS information and data associated with development and validation was requested to ensure that the sponsor gave appropriate consideration to patient safety when selecting and testing the syringe. The CDRH/General Hospital Devices Branch review recommendation is approval (September 29, 2016).



Kathleen
Clouse Strebel

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125156Orig1s110

MICROBIOLOGY/VIROLOGY REVIEW(S)



Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: August 18, 2016
To: Administrative File, STN 125156/110
From: Candace Gomez-Broughton, Ph.D., Reviewer CDER/OPQ/OPF/DMA/ Branch IV
Endorsed: Colleen Thomas, Ph.D. Acting Team Lead CDER/OPQ/OPF/DMA/Branch IV
Subject: Prior Approval Supplement for the approval of the Lucentis 0.5 mg prefilled syringe (PFS) (b) (4)
US License: 1048
Applicant: Genentech, Inc.
Facilities: (b) (4)
Product: Lucentis® (ranibizumab)
Dosage: liquid single use vial, prefilled syringe, intravitreal injection (10 mg/mL, 0.5 mg dose)
Indication: Treatment for wet acute macular degeneration
Due date: October 16, 2016

Recommendation: The supplement is recommended for approval from a microbiology product quality perspective.

INTRODUCTION

Genentech Inc. has submitted a Prior Approval Supplement (PAS) for the approval of the Lucentis 0.5 mg prefilled syringe (PFS) presentation. Currently, only the vial presentation is approved for use in the United States. Novartis and Genentech have a partnership that consists of (b) (4) (b) (4) that was approved by the European Commission in November 2013. (b) (4) commercially available in the US.

(b) (4)

Changes Being Effective in 30 Days (CBE-30) supplement is acceptable.

CONCLUSION

- I. The supplement is recommended for approval from a microbiology product quality perspective.
- II. Product quality data not reviewed here should be reviewed by OBP and CDRH.
- III. No additional inspectional follow-up items were identified.

Information Requested During Review Cycle

1. In the description of the manufacturing process (Section 3.2.P.3.3); it states that [REDACTED] (b) (4). Samples for microbial testing should be collected [REDACTED] (b) (4). Please implement these changes in sample location and amend the BLA to reflect the changes.
2. Provide summary data from the three most recent requalification studies for [REDACTED] (b) (4). The studies should be relevant to the ranibizumab drug product manufacturing process.
3. Clarify if parameters used in requalification studies for [REDACTED] (b) (4) represent worst-case conditions and compare these to those parameters used during routine operations.
4. With regard to media fill studies, please describe the worst-case conditions used. What are the routine parameters compared those used in the media fill simulations?
 - a. Describe growth promotion studies and submit results from three most recent requalification
 - b. Clarify the fill speeds used during the media and routine production fills.

Reviewer comments: Responses to the information requests were adequate.

Candace Y. Gomez-
broughton -A

Digitally signed by Candace Y. Gomez-
broughton -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2000640207,
cn=Candace Y. Gomez-broughton -A
Date: 2016.10.13 11:56:14 -04'00'



Colleen
Thomas

Digitally signed by Colleen Thomas
Date: 10/13/2016 12:01:01PM
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125156Orig1s110

OTHER REVIEW(S)

HUMAN FACTORS RESULTS, LABEL, LABELING, AND PACKAGING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: September 28, 2016

Requesting Office or Division: Division of Transplant and Ophthalmology Products (DTOP)

Application Type and Number: BLA-125156/S-110

Product Name and Strength: Lucentis
(ranibizumab)
Injection
0.3 mg and 0.5 mg

Product Type: Single ingredient, combination product

Rx or OTC: Rx

Applicant/Sponsor Name: Genentech, Inc.

Submission Date: June 16, 2016

OSE RCM #: 2016-2106

DMEPA Primary Reviewer: Madhuri R. Patel, PharmD.

DMEPA Team Leader: Mishale Mistry, PharmD., MPH

DMEPA Associate Director for Human Factors: QuynhNhu Nguyen, MS

1 REASON FOR REVIEW

This review evaluates the Human Factors (HF) validation study report, proposed container label, carton labeling, and Prescribing Information (PI) for Lucentis (ranibizumab) Injection (BLA 125156/S-110). Genentech submitted a Prior Approval Supplement (PAS) on June 16, 2016, which proposes a 0.5 mg prefilled syringe. Subsequently, Division of Transplant and Ophthalmology Products (DTOP) requested that DMEPA review the HF validation report and proposed labels and labeling as part of their evaluation of the PAS for Lucentis.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 HUMAN FACTORS VALIDATION STUDY

Genentech performed an HF validation study to evaluate the safe and effective use of the proposed Lucentis 0.5 mg prefilled syringe (PFS), the associated label and packaging, and the Instructions for Use (IFU). Lucentis is currently approved in 0.3 mg and 0.5 mg single-dose vials. DMEPA did not previously review the HF study protocol for the proposed PFS prior to the Applicant initiating the study. After the initial submission for Supplement 110, DTOP raised concerns regarding the dose mark on the proposed PFS and the accuracy to which it can be aligned to the dome when drawing up a dose. Specifically, the Division noted that Step 6 of the Instructions for Use instructs users to align the edge below the dome of the rubber stopper with the 0.05 mL dose mark, rather than other locations of the rubber stopper which may call out of the attention of the healthcare providers. We agreed with the Division's concern regarding the need for users to align the edge below the dome of the rubber stopper with the

0.05 mL dose mark as we do not believe that this is consistent with other currently marketed prefilled syringes and may potentially lead to dosing errors

In response, Genentech submitted a HF validation study report on August 19, 2016. In addition, DTOP held a teleconference with Genentech on September 12, 2016 to discuss their concerns. Subsequently, Genentech submitted a revised figure in the prescribing information on September 22, 2016 which instructs health care providers to align the dose mark to the top of the first rib, where the stopper meets the wall of the glass barrel.

Previous Figure 5

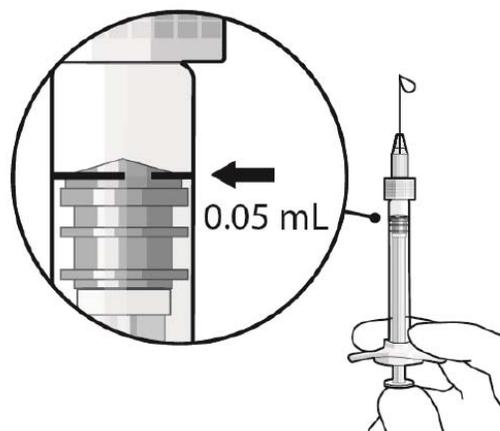


Figure 5

Updated Figure 5

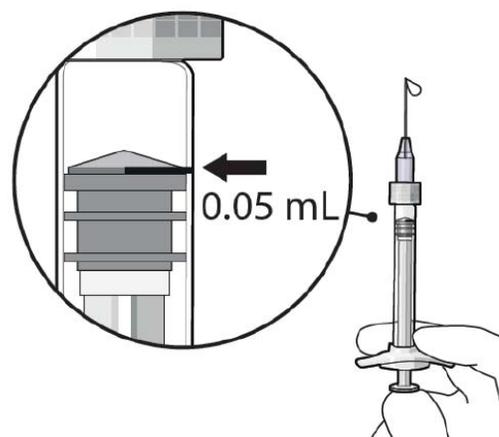


Figure 5

The HF validation study results showed no use errors or close calls. There were operational difficulties that occurred with following essential (E) and safety critical (SC) tasks:

1. Snap off Syringe Cap (E): 0/30 for retina specialists; 2/30 for retina specialist assistants
2. Remove Injection Needle Cap (E): 1/30 times for retina specialists; task not assessed for retina specialist assistants
3. Adjust Drug Dose (E, SC): 2/30 for retina specialists; task not assessed for retina specialist assistants

The subjective data from study participants indicated that the one participant who rated "Correctly align the rubber stopper with dose mark" as "Very difficult" found the required feature of the plunger stopper caused the difficulty. Despite the participant's reported difficulties, the participant successfully adjusted an acceptable dose on first and second simulated use. There were other difficulties reported amongst the non-critical tasks such as the one participant who rated "Snap off the syringe cap" as "Very Difficult". Root cause analysis indicated that the participant had deviated from the IFU (pulled the cap instead of snapping it) during both simulated uses.

We anticipate that the proposed product will be used by health care providers (HCPs), who are familiar with the use of PFS for intravitreal injections. Additionally, the use of this prefilled syringe is not different from what the HCPs are currently doing for the Lucentis vial (i.e.,

drawing up product from a vial into a syringe, adjusting dose, and administering). In such situations, we typically would not review a HF validation study. Nevertheless, we find the HF study results and the revised figure in the prescribing information submitted on September 22, 2016 acceptable.

We note that the Applicant submitted a formative actual use study with the supplement at the advice of DTOP during a Type C Meeting held on May 19, 2015. DMEPA was not involved in the meeting; therefore, we defer to the Division with regard to the acceptability of the formative actual use study.

3.2 LABELS AND LABELING

In addition, DMEPA reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors. DMEPA finds the prescribing information acceptable from a medication error perspective. However, we note that the syringe label, ^{(b) (4)} container labeling, and carton labeling can be improved to enhance the readability and prominence of important information to promote the safe and effective use of the product, to mitigate confusion, and to clarify information. We provide recommendations in Section 4 to address these concerns.

Additionally, we note the use of the terminology 'single use' throughout the labels and labeling. We defer to the Office of Biological Products (OBP) on the appropriate terminology.

4 CONCLUSION & RECOMMENDATIONS

DMEPA finds the HF validation study acceptable. DMEPA also finds the Prescribing Information acceptable from a medication error perspective. However, our review indicates that the proposed container labels and carton labeling can be improved to increase the readability and prominence of important information. Please see our letter-ready recommendations in Section 4.1 below for the container labels and carton labeling.

We recommend that DTOP consult the Office of Biological Products (OBP) on the appropriate terminology of 'single use' that was found throughout the product labels and labeling.

4.1 RECOMMENDATIONS FOR GENENTECH, INC.

We recommend the following be implemented prior to approval of this BLA supplement:

A. Carton Labeling

1.



2. Consider increasing the prominence (i.e., font size) of the NDC. Since NDC number is often used as an additional verification prior to drug dispensing in the

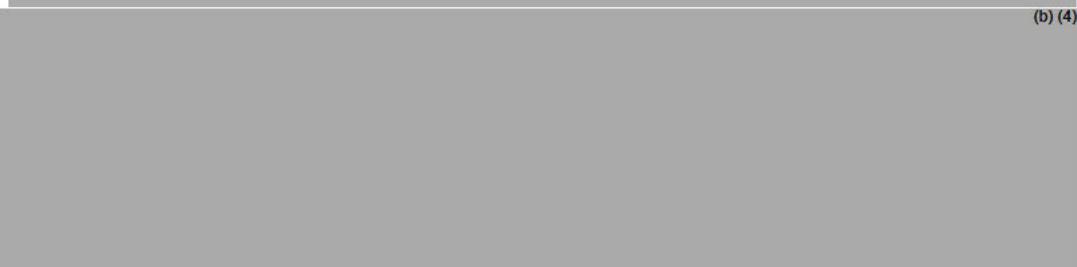
pharmacy, it is an important safety feature that should be prominently displayed in the top third of principal display panel of the labeling in accordance with 21 CFR 207.35(b)(3)(i).

3. Decrease the prominence of the statement “Rx Only” as this information appears more prominent than the established name on the principal display panel.

B. (b) (4) Labeling

1. The strength lacks prominence. Increase the prominence (i.e., font size) of the strength taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.15(a)(6).
2. We recommend that you apply the same color scheme as the corresponding commercialized 0.5 mg vials to the (b) (4) labeling.
3. As currently presented, the route of administration is not present. We recommend including the statement “For intravitreal injection only” to minimize the risk of administering the drug as an intravenous bolus.
4. We recommend including the statement “Single Dose” to ensure that the product is safely used and handled.

5.  (b) (4)

6.  (b) (4)

C. Prefilled Syringe Label

1. Based on the syringe samples provided, we note that there is inadequate contrast when the syringe label information is printed against the transparent syringe. We recommend increasing the contrast of the text against the syringe to improve readability, while following the same color scheme as the corresponding commercialized 0.5 mg vials.
2. The strength lacks prominence. Increase the prominence (i.e., font size) of the strength taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.15(a)(6). Additionally, please consider following the same color scheme as the corresponding commercialized 0.5 mg vials.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lucentis that Genentech, Inc. submitted on June 16, 2016.

Table 2. Relevant Product Information for Lucentis	
Initial Approval Date	June 30, 2006
Active Ingredient	ranibizumab
Indication	Neovascular (Wet) Age-Related Macular Degeneration (AMD) Macular Edema Following Retinal Vein Occlusion (RVO) Diabetic Macular Edema (DME) Diabetic Retinopathy in patients with DME
Route of Administration	Intravitreal Injection
Dosage Form	Solution for injection in vial Solution for injection in prefilled syringe (proposed)
Strength	0.3 mg and 0.5 mg
Dose and Frequency	<ul style="list-style-type: none">• 0.5 mg by intravitreal injection once a month (approximately 28 days)• 0.5 mg once every 3 months after 4 monthly doses• 0.3 mg by intravitreal injection once a month (approximately 28 days)
How Supplied	0.3 mg and 0.5 mg single-use vials 0.5 mg single-use prefilled syringe (proposed)
Storage	Refrigerated at 2 ^o -8 ^o C (36 ^o -46 ^o F). Do not freeze.
Container Closure	N/A

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On September 15, 2016, we searched the L:drive and AIMS using the terms, ranibizumab to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 1 previous proprietary name review that is not relevant to this review.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design

Human factors validation testing was performed in a simulated use environment, representative of actual conditions of end use. It was conducted in three US Locations. Participants were provided with a presentation tray consisting of the Lucentis PFS product, an injection needle, a cotton-tipped applicator, and a caliper. A dummy patient was fixed to an adjustable stand on a table.

Participants:

A total of n=15 Retina Specialists (RS) and n=15 Retina Specialist Assistants (RSA) participated in the validation study. Retina Specialists were required to have experience adjusting the dose and administering intravitreal injections, while the Retina Specialist Assistants were required to have experience assisting Retina Specialists during the administration of intravitreal injections. No training was provided to participants in the HF validation testing.

Procedure:

Participants were introduced to the Lucentis PFS presentation tray and asked to do everything they would do in a clinical environment if they were about to prepare an injection for a patient with a new drug product. Participants were provided with the IFU but were not prompted to read it. Participants were instructed to perform different tasks based on their specialty as follows:

- Retina Specialists were asked to prepare and administer an intravitreal injection into the dummy patient eye placed in a mannequin head.
- Retina Specialist Assistants were asked to prepare the PFS for a Retina Specialist to administer an injection to a patient.
- The participants were only assessed on the use of the product for tasks which they routinely perform during their standard practice.

After first simulated use, the Study Moderator asked the participant if they were confident that the dummy patient had received the required dose and for a reason behind their response. If a participant was not confident that the dummy patient would have received the required dose, the Study Moderator asked the participant for reasons why and what they would do next if they were in their clinic. The Study Moderator did not explore any issues observed during first simulated use at this point to avoid influencing the participant's behavior during second simulated use. Participants were then asked to perform a second simulation with the Lucentis PFS. If participants were observed to experience operational difficulties or commit use errors on first and/or second simulated use, they were asked to perform a third simulation. Prior to performing this simulation, the participant was directed back to those section(s) of the IFU where they were observed to experience difficulties and asked to reflect their understanding to the Study Moderator. On completion of the simulated use assessments, each participant was asked to comment on their experiences of using the Lucentis PFS including whether they found

any aspect of preparing and/or administering a dose with the PFS confusing or difficult. If the participant acknowledged difficulties or errors, these were discussed thoroughly with the Study Moderator. Similarly, if the Study Moderator identified any deviations, operational difficulties, close calls or use errors that were not acknowledged by the participant, these were also discussed in detail.

After their simulated use assessment, participants were asked additional questions as follows:

- Knowledge Based Assessments (KBAs): Any items that could not be assessed via observation during simulated use were assessed through KBAs.
- Subjective Feedback: Participants were asked to rate the ease of use of various aspects of the Lucentis PFS.

Critical Tasks:

Task	Task Type	Assessment Method	Assessment Criteria	Task Executed By
Unpack carton: Open the carton	Essential	KBA; Performance	During observed use, participants must be able to open the Lucentis PFS carton, and during comprehension questioning, participants must identify if the packaging of the Lucentis PFS has been tampered with	RS; RSA
Unpack carton: Remove contents from carton (blister pack with PFS and USPI/IFU)	Essential	Performance	During observed use participants must be able to remove the blister pack and IFU from the Lucentis PFS carton	RS; RSA
Unpack PFS: Peel the lid off the blister pack	Essential	Performance	During observed use, participants must be able to remove the lid from the blister pack without dropping the PFS outside of the clean field	RS; RSA
Unpack PFS: Carefully remove the PFS using aseptic technique*	Essential	Performance	During observed use, participants must demonstrate careful removal of the PFS from the blister pack using aseptic technique	RS; RSA
Attach needle: Snap off PFS cap	Essential	Performance	During observed use, participants must demonstrate that they are able to snap off the syringe cap from the PFS	RS; RSA
Attach needle: Firmly screw the needle onto the Luer lock of the PFS	Essential	KBA; Performance	During observed use, participants must demonstrate that they can securely and firmly attach the injection needle to the Lucentis PFS and perform an intravitreal injection without the injection needle becoming detached. During comprehension questioning, participants must identify a compatible needle by reading and understanding the guidance provided in the IFU	RS; RSA
Attach needle: Remove needle cap	Essential	Performance	During observed use, participants must demonstrate that they are able to remove the needle cap from the PFS	RS
Adjust dose: Carefully align the stopper with the dose line	Essential; Safety-critical	Performance	During observed use, participants must demonstrate that they can adjust to the required dose	RS
Insert PFS at injection site	Essential	Performance	During observed use, participants must demonstrate that they can insert the PFS into the injection site	RS
Slowly inject full dose**	Essential	KBA; Performance	During observed use, participants must demonstrate correct injection technique into the injection site. During comprehension questioning, participants must be able to verify that the full dose has been administered	RS
Remove PFS from injection site	Essential	Performance	During observed use, participants must demonstrate that they can remove the PFS from the injection site	RS
Dispose of used PFS and needle	Safety-critical	KBA; Performance	During observed use and/or comprehension questioning, participants must demonstrate correct understanding of safe disposal techniques and dispose of the used PFS in the sharps disposal container provided	RS; RSA

* Only removing the PFS from the blister pack is essential.

** Only the full injection of the drug product is essential.

C.2 Results

Overall task step performance by all participants:

Use Tasks	Use Task completion per User Group							
	Retina Specialists (n=15)				Retina Specialist Assistants/ Technicians (n=15)			
	Successful	Use Errors	Close Calls	Operational Difficulties	Successful	Use Errors	Close Calls	Operational Difficulties
Unpack Carton (E)	24/24*	0/24*	0/24*	0/24*	30/30	0/30	0/30	0/30
Unpack PFS (E)	24/24*	0/24*	0/24*	0/24*	30/30	0/30	0/30	0/30
Snap off Syringe Cap (E)	30/30	0/30	0/30	0/30	30/30	0/30	0/30	2/30
Attach Injection Needle (E)	30/30	0/30	0/30	0/30	30/30	0/30	0/30	0/30
Remove Injection Needle Cap (E)	30/30	0/30	0/30	1/30	*	*	*	*
Dislodge Air Bubble Inside PFS	30/30	0/30	0/30	0/30	*	*	*	*
Expel Air from Inside PFS	30/30	0/30	0/30	0/30	*	*	*	*
Adjust Drug Dose (E, SC)	30/30	0/30	0/30	2/30	*	*	*	*
Administer Intravitreal Injection (E)	30/30	0/30	0/30	0/30	*	*	*	*
Remove PFS from Injection Site (E)	30/30	0/30	0/30	0/30	*	*	*	*
Dispose of Used PFS (SC)	30/30	0/30	0/30	0/30	30/30	0/30	0/30	0/30

*Task Not Assessed for some/all participants: Users were only assessed on tasks they routinely perform.

- All participants (n=30/30, 100%) successfully performed all essential (E) and safety-critical (SC) task steps during the validation study without use error.
- Participants who performed the dose adjustment step (Retina Specialists only, n=15) successfully adjusted the dose in 30/30 (100%) instances.
- No close calls or use errors were recorded during the validation study. There were five operational difficulties observed.

- Three instances of recapping injection needle were also observed but were attributable to the participant's previous experience and/or professional training or to test artifact

Knowledge-Based Assessment:

All participants correctly answered the Knowledge-Based Assessment questions and were able to locate the specific information on the Lucentis PFS carton, label and IFU without difficulty or direction from the study moderator.

Subjective Feedback:

The majority of participant responses (n=196/216, 91%) rated the tasks required to use the Lucentis PFS as 'Easy' or 'Very Easy'. A total of n=5/216 (2%) responses, across five participants and three task steps, rated a task as either 'Difficult' or 'Very Difficult' to perform. These are summarized below.

- *Remove the PFS from the blister pack:* Rated as 'Difficult' by three participants. Two of these ratings were due to the force needed to remove the PFS from the blister pack; the third was due to the participant's initial technique to remove the PFS. Despite the rated difficulties, all three participants successfully removed the PFS from the device packaging without damaging or dropping the PFS on first and second simulated use.
- *Snap off the syringe cap:* Rated as 'Very Difficult' by one participant, who deviated from the IFU (pulled the cap instead of snapping it) during both simulated uses. During root cause analysis, the participant removed a cap from a spare device using the method described in the IFU. Once the participant understood the correct method for removal, he rated the task as 'Easy' or 'Very Easy' and successfully removed the cap without difficulty.
- *Correctly align the rubber stopper with dose mark:* Rated as 'Very Difficult' by one participant. The participant explained that she found it difficult to align the dose mark with the required feature of the plunger stopper. Despite the participant's reported difficulties, the participant successfully adjusted an acceptable dose on first and second simulated use.

IFU Review:

Three participants (one RS, two RSAs) were unfamiliar with the term 'aseptic technique.' These participants explained that they had not seen the term 'aseptic' before, but understood that a clean technique according to clinical standard of care should be used.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On September 16, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care Community Nursing Long-Term Care
Search Strategy and Terms	Match Exact Word or Phrase: Lucentis

D.2 Results

Our search identified three newsletters mentioning Lucentis, two of which are not relevant to this review as they are regarding Avastin being used off-label for a condition that Lucentis is indicated for.^{1,2} The third result was a safety brief regarding Lucentis which was unrefrigerated for at least 2 days and possibly used.³ We reviewed the PI, and the labels/labeling which clearly states the product is to be refrigerated, and we have no recommendations at this time.³

¹ Institute for Safe Medication Practices. Safety briefs: ISMP resolve for compounding oversight strengthens. ISMP Med Saf Alert Acute Care. 2011;16(8):2-3.

² Institute for Safe Medication Practices. Safety briefs: Need for compounding oversight. ISMP Med Saf Alert Community/Ambulatory Care. 2010;10(5):1-2.

³ Institute for Safe Medication Practices. Safety briefs: Warning! Do not use unrefrigerated Avastin and Lucentis. ISMP Med Saf Alert Acute Care. 2012;17(20):1-2.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on September 14, 2016 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.^d

Table 3: FAERS Search Strategy	
Date Range	Start-September 01, 2016
Product	Lucentis [product name]
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT) Intercepted Drug Administration Error Intercepted Drug Dispensing Error Intercepted Drug Prescribing Error Intercepted Medication Error Intercepted Product Selection Error

E.2 Results

^d The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

Our search retrieved 77 cases, but after further evaluation, we didn't identify any medication error cases that were relevant for this review and could be addressed by labels and labeling revisions.

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^e along with postmarket medication error data, we reviewed the following Lucentis labels and labeling submitted by Genentech on June 16, 2016.

- Carton labeling
- ^{(b) (4)} labeling
- Container label

^e Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MADHURI R PATEL
09/28/2016

MISHALE P MISTRY
09/28/2016

QUYNHNHU T NGUYEN
10/03/2016



**GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM**

Date: September 29, 2016
From: LCDR Keith Marin, Nurse Reviewer, WO66, RM 2604
General Hospital Devices Branch, DAGRID, ODE, CDRH
To: Christina Marshall, WO22, RM 6241, Regulatory Health Project Manager
OMPT/CDER/OND/OAP/DTOP
Subject: CDRH Consult for Lucentis (ranibizumab) pre-filled syringe/BLA 125156/S110,
DMF (b) (4), ICC1600554

Applicant	Genentech
Indication for Use	For the treatment of neovascular (wet) age-related macular degeneration (nAMD) and macular edema (ME) following retinal vein occlusion (RVO), diabetic macular edema (DME), and diabetic retinopathy (DR) in patients with DME.
Biologic Constituent	Lucentis® (ranibizumab, rhuFab V2)
Device Constituent	Pre-filled syringe

Consultants: None

Recommendation: Based on information reviewed BLA 125156/S110, the sponsor has provided sufficient information related to the bench performance testing, biocompatibility, sterility, shelf life, and shipping studies to support the safe and effective use of the device. As a result, CDRH/ODE recommends approval for the BLA for this combination product.

Digital Signature Concurrence Table	
Reviewer	Keith G. Marin -A Digitally signed by Keith G. Marin -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Keith G. Marin -A, 0.9.2342.19200300.100.1.1=0011250397 Date: 2016.09.29 15:06:22 -04'00'
Branch Chief	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2016.09.29 15:13:26 -04'00'

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1. Purpose/Background

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding a review request for BLA 125156/S110. The device constituent of this combination product consists of a pre-filled syringe designed to deliver Lucentis (ranibizumab) for injection.

The original consult request from CDER indicates that, *“this submission is for the introduction of a prefilled syringe presentation for Lucentis (currently supplied as a solution in a vial). Because this is a presentation for ophthalmic use, it is not considered a combination product (21 CFR 200.50). However, we would appreciate your evaluation of the supporting data provided for the use of the syringe as a container closure and ophthalmic dispenser. The majority of the information is presented in the Module 3 Regional section (3.2.R.2) and the DP container closure section (3.2.P.7).*

Reviewer’s Note: CDER was contacted to get clarification on what was meant in the consult form that this device is not a combination product. Based on an email from Dr. Sarah Kennett, the CMC reviewer, as this is a biologic plus device combination and the fact that the syringe is considered a ophthalmic dispenser, this device/biologic is not considered a combination product according to 21CFR 200.50 (“...These articles, which are regulated as drugs if packaged with the drugs...”. However, while this isn’t regulated as a device, it still is a pre-filled syringe, so CDER wants us to evaluate the functional performance of the syringe. CDRH was previously involved in ICC1500208 where we were asked to evaluate the proposed device specifications on May 11, 2016. Based on our recommendations, we recommended the sponsor provide a complete description of the device system and components, provide labeling and instructions for use, provide a listing of combination product requirements/specifications critical for achieving essential performance, and a risk analysis describing the risk to the user and/or patient during normal and potential misuse.

Product	Indications for Use
Lucentis® (ranibizumab, rhuFab V2)	For the treatment of neovascular (wet) age-related macular degeneration (nAMD) and macular edema (ME) following retinal vein occlusion (RVO), diabetic macular edema (DME), and diabetic retinopathy (DR) in patients with DME.

2. Administrative

Documents Reviewed:

Document Title	Document Number	Date -Version	Location
Container closure system	ranibizumab.PFS.F01.P.7.CCS	06/16/2016	GSR Sequence 0168(798) / Section 3.2.P.7
Specifications	ranibizumab.PFS.F01.P.5.1.SPE	06/16/2016	GSR Sequence 0168(798) / Section 3.2.P.5.1

CDRH Review Team:

Team Member	Role	Deficiencies
LCDR Keith Marin, CDRH/ODE/GHDB)	Lead Reviewer – Nurse Consultant	#...

3. Device Description and Performance Requirements

Figure R.2-1 Schematic Representation of the Ranibizumab Bulk PFS and Assembled, Labelled PFS



The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad spectrum microbicide should be given prior to the injection.

Administration instructions:

1. Snap off the syringe cap.
2. Attach a 30G x 0.5- inch sterile needle and remove the needle cap.
3. Expel air and adjust to the 0.05 mL dose mark.
4. Inject the solution
5. Dispose of the PFS into a sharps container.

Each prefilled syringe or vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new prefilled syringe or vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter needle (vial only), and injection needles should be changed before LUCENTIS is administered to the other eye.



(b) (4)

Reviewer's Note: DMF (b) (4) for the plunger stopper and tip cap are all drug contacting. As such, review of these drug master files will be deferred to CDER. In terms of the DMF for the syringe, the sponsor has referenced DMF (b) (4). There is not any functional assessment within this DMF. The only value noted is the technical drawings of the 1ml syringe barrel. All testing appears to be within the BLA.

4. Design Control Review

A. Design Review Summary

The sponsor has described within BLA 125156/S110 that the primary drug container consists of a glass syringe barrel with rubber tip cap and plunger stopper closures. The tip cap is part of the syringe cap, which also includes a Luer lock connection and a rigid, white outer shell that serves as a tamper-evident seal. The (b) (4)

(b) (4). The Luer lock on the PFS is designed to be compatible with commercially available Luer lock needles. A 30Gx 0.5-inch needle is recommended as the established standard of care for intravitreal injection. The syringe barrel has a single-dose mark to be aligned with the plunger stopper to achieve the 0.05 mL injection volume. The plunger rod is (b) (4)

(b) (4)

B. Design Control Documentation Check

Design Control Requirement*	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	X		3.2.P.5.1 3.2.P.7 3.2.R
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		3.2.R
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	X		3.2.R
Validation Data <ul style="list-style-type: none"> • Human factors • Clinical data 		X	The Applicant had provided in the pre-meeting package an overview of the proposed human factors program, including a human factors summative study (simulated-use) as part of design validation. FDA indicated that the product is a biologic, not a combination with a device and a human factors study is not required (refer to the DTOP Meeting Minutes
	X		

			issued on 01 June 2015). Clinical testing was conducted using the 0.5ml pre-filled syringe in Research report 1068559 (5.2.5.4)
Traceability Documentation		X	No software present in this device

C. Design Verification and Validation Review

Summary of Design V&V Attributes:

Design Verification / Validation Attributes		Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing		X		
To-be-marketed device was used in the pivotal clinical trial?		X		
Selectable dose range on device matches the labeled dose range for the medication?				X
Verification methods relevant to specific use conditions as described in design documents and labeling		X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)				X
Traceability demonstrated for specifications to performance data				X
Conformance to applicable standards demonstrated	ISO 14971: Risk Management	X		
	ISO 62366-1: Usability Engineering			X
	ISO 10993-5/10/11: Biocompatibility	X		
	ISO 594-2: Luer connectors	X		
Adherence to FDA Guidance: Use of international standard ISO-10993, "Biological evaluation of medical devices Part 1: Evaluation and testing		X		
Stability and simulated shipping / transport data adequately verifies device will meet essential performance requirements at expiry		X		
Discipline -Specific Design Verification / Validation adequately addressed	Biocompatibility	X		
	Sterility	X		
	Software / Cybersecurity			X
	Electrical Safety / EMC			X
	Human Factors			X

Design Validation Review

Design Validation Attributes	Yes	No	N/A
The Open-Label, Single-Arm Phase IIIb Study utilized the to-be-marketed device	X		
Bioequivalence Study utilized to-be-marketed device		X	
Simulated Actual Use Study utilized to-be-marketed device		X	

Reviewer's Note: CDER has stated via email on August 30, 2016 that they are not asking CDRH for a review of a Human Factor's study as there is not one to review and they believe that the information in the clinical trials is sufficient for demonstrating the safety and efficacy of the revised product. They are also not asking CDRH for a review of the bioequivalence of the biologic product.

Design Verification Review

Lead Reviewer's Note: Review of the stability testing demonstrates that the functional characteristics of the pre-filled syringe are maintained during the [REDACTED] (b) (4).

Biocompatibility Testing

The sponsor has stated that the ranibizumab PFS was evaluated for biocompatibility, according to the requirements of ISO 10993-1, USP <1031>, and FDA Guidance document on the use of International Standard ISO- 10993-1, Evaluation and Testing. Furthermore, the needle the user attaches to the PFS during use is commercially available (not provided with the product), and therefore not included in the biocompatibility assessment.



Lead Reviewer's Note: The sponsor has provided a summary table of the biocompatibility testing conducted and provided the protocols and complete test reports. All results meet established acceptance criteria. Complete reports can be found in global submit 0177 (820) 09/08/2016 under CMC Response to FDA Request for Information.

Shipping Studies

No non-conforming samples were observed. The bulk PFS and packaging system passed the visual inspection, with no defects observed, and all PFS passed CCI. The semi-finished product shipping qualification demonstrated the Lucentis bulk PFS – truck shipping method is suitable for shipment of bulk Lucentis PFS from [REDACTED] (b) (4).

[REDACTED] (b) (4)

Table 3 Test Overview



(b) (4)



Lead Reviewer's Note: Shipping qualification was performed to support the Lucentis PFS. All tests passed the acceptance criteria.

D. Risk Analysis

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities			X

Summary of Risk Analysis

The sponsor's risk management team conducted pFMEAs by identifying potential failure modes, their causes, and effects associated with the manufacturing processes for the ranibizumab PFS.

Risks:

- Overdose or underdose delivery due to difficulties or errors in priming and alignment to dose mark or due to needle not firmly attached to the PFS
- Injection of air bubble due to use-errors during priming (e.g., needle attached after priming)
- Fast injection rate
- Product damaged and drug quality impacted due for example to exposure to excessive temperature, light or due to damaged package
- Risk of needle stick injury to unused and used needle
- Abrasion of cornea during needle removal after injection
- Foreign particulates from PFS contaminating injection
- Risk of injury to eye due to incorrect injection location, needle movement or needle detachment during injection
- Incorrect needle type is attached to the PFS

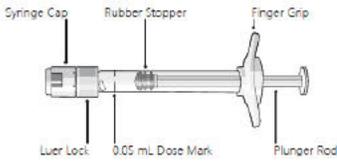
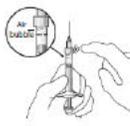
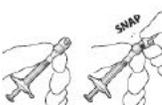
- CCI breach due to lack of seal of PFS components
- Leachables from PFS components (refer to P.2.4 Container Closure System)
- Biological contaminants on the PFS surface

Benefit: The sponsor has argued that the PFS configuration is designed as alternative to the vial presentation to ease the IV injection procedure. With a PFS, the preparation for injection has fewer steps, which improves the convenience of use for physicians, and potentially reduces risks of contamination. The PFS has a single dose mark, to be aligned with the rubber plunger stopper to achieve the 0.05 mL injection volume. The single dose mark simplifies the dose adjustment procedure in comparison to graduation marks that are standard in the off-the-shelf 1 mL disposable plastic syringe currently used for the administration of vial product.

(b) (4)
 (b) (4). Packaging of the PFS in a (b) (4) will maintain syringe surface sterility during transport and storage of the product.

Reviewer's Note: This reviewer agrees with the identified hazards by the sponsor. Based on the mitigation posed including process improvement, verification, validation, and implementation of inspections, it is this reviewer's belief that the risk can be adequately mitigated.

E. Labeling

Device description	
 <p>Figure 1</p>	<p>Step 4: Attach needle</p> <ul style="list-style-type: none"> • Attach a 30G x 1/2 inch sterile injection needle firmly onto the syringe by screwing it lightly onto the Luer lock (see Figure 3). • Carefully remove the needle cap by pulling it straight off. <p>Note: Do not wipe the needle at any time.</p>  <p>Figure 3</p>
<p>Step 1: Prepare</p> <ul style="list-style-type: none"> • Make sure that your pack contains a sterile prefilled syringe in a sealed tray. • Peel the lid off the syringe tray and, using aseptic technique, remove the syringe. 	<p>Step 5: Dislodge air bubbles</p> <ul style="list-style-type: none"> • Hold the syringe with the needle pointing up. • If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 4).  <p>Figure 4</p>
<p>Step 2: Inspect syringe</p> <ul style="list-style-type: none"> • LUCENTIS should be colorless to pale yellow. • Do not use the prefilled syringe if: <ul style="list-style-type: none"> - the syringe cap is detached from the Luer lock. - the syringe is damaged. - particulates, cloudiness, or discoloration are visible. 	<p>Step 6: Expel air and adjust drug dose</p> <ul style="list-style-type: none"> • Hold the syringe at eye level, and carefully push the plunger rod until the edge below the dome of the rubber stopper is aligned with the 0.05 mL dose mark (see Figure 5). <p>Note: The plunger rod is not attached to the rubber stopper – this is to prevent air being drawn into the syringe.</p>  <p>Figure 5</p>
<p>Step 3: Remove syringe cap</p> <ul style="list-style-type: none"> • Snap off (do not turn or twist) the syringe cap (see Figure 2).  <p>Figure 2</p>	<p>Step 7: Inject</p> <ul style="list-style-type: none"> • The injection procedure should be carried out under aseptic conditions. • Insert the needle into the injection site. • Inject slowly until rubber stopper reaches the bottom of the syringe to deliver the volume of 0.05 mL. • After injection, do not recap the needle or detach it from the syringe. Dispose of the used syringe together with the needle in a sharps disposal container or in accordance with local requirements.

Labeling packaging Testing:



Note: Testing under 2°C – 8°C storage conditions is ongoing, data are not yet available.
 Abbreviations: PFS=prefilled syringe.

F. Design Transfer Activities – Release Specifications

The following release specifications are included for the device constituent within eCTD
 Module 3.2.P.5:

Attribute	Specification	Results
<i>Appearance</i>	<i>0.5 mL colorless glass syringe, grey rubber plunger stopper, white tamper-evident tip cap</i>	<i>Meets specification</i>
<i>Extractable volume</i>	(b) (4)	<i>Batch B0001B01: 0.097, 0.116, 0.114, 0.113, 0.120 Batch B0002B01: 0.117, 0.115, 0.110, 0.108, 0.113 Batch B0003B01: 0.116, 0.125, 0.119, 0.118, 0.120</i>
<i>Break Loose</i>	(b) (4)	<i>Batch B0001B01: 3.5N, Batch B0002B01: 3.1N, Batch B0003B01: 2.9N</i>
<i>Glide Force</i>	(b) (4)	<i>Batch B0001B01: 5.4N, Batch B0002B01: 5.5N, Batch B0003B01: 5.4N</i>

5. Information Requests – Sent August 29, 2016

- A. Please address the following:
 - i. Specify the exact location of the human factors validation study which validates the design specifications defined by you. You have stated that the clinical study was to be completed by Jan 2016 but we cannot locate it.
 - ii. Provide the location of the bioequivalence study

- iii. Provide the location of the complete biocompatibility testing for the syringe (protocol, acceptance criteria, results, conclusion). It is alluded to throughout the submission, but testing cannot be located.
- iv. Provide the location for the complete shipping studies. You reference ASTM 7386, but the testing cannot be located.
- v. Specify exactly what volume of the DMF is being referenced? It isn't clear from the LOA as it simply states "original 12/21/2000, revision 12/05/11"

Please provide this information by September 7, 2016 COB.

Lead Reviewer's Note: CDER stated that they they are not asking CDRH for a review of a Human Factor's study. There is not a Human Factor's study. We believe that the information in the clinical trials is sufficient for demonstrating the safety and efficacy of the revised product. They are also not asking CDRH for a review of the bioequivalence of the biologic product. The DMF reference is to the DMF in its entirety, it is not limited to any volume. The sponsor has provided the request biocompatibility and shipping study information. This reviewer considers this IR resolved.

- VII. Outstanding Deficiencies
None
- VIII. Post-Market Commitments / Post-Market Requirements
None
- IX. Recommendation
Approval

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/s/

LOIS A ALMOZA
09/30/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125156Orig1s110

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



BLA 125156

**FULFILLMENT OF POSTMARKETING
COMMITMENT**

Genentech, Inc.
Attention: Philippe Egler
Associate Regulatory Program Director
1 DNA Way
South San Francisco, CA 94080

Dear Mr. Egler:

We refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Lucentis (ranibizumab).

We have received your submission dated August 3, 2017, containing the final report for the following post-marketing commitment listed in the October 13, 2016 approval letter for BLA 125156/110.

PMC 3134-1: Perform a shipping study designed to confirm stability of Lucentis drug product during shipping under conditions and through a route that are representative of commercial drug product shipping. The study will include testing of pre- and post-shipping samples for product quality (container closure integrity, purity by SEC, nrCE-SDS, IE-HPLC, sub-visible particles, and potency of ranibizumab).

We have reviewed your submission and conclude that the above commitment was fulfilled.

This completes all of your postmarketing commitments acknowledged in our October 13, 2016 approval letter.

If you have any questions, call Truong Quach, Regulatory Business Process Manager, at (240) 402-5826.

Sincerely,

{See appended electronic signature page}

Kathleen A. Clouse, Ph.D.
Director
Division of Biotechnology Review and Research I
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

KATHLEEN A CLOUSE STREBEL
11/09/2017

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125156
Product Name: Lucentis (ranibizumab)

PMC #1 Description: Perform a shipping study designed to confirm stability of Lucentis drug product during shipping under conditions and through a route that are representative of commercial drug product shipping. The study will include testing of pre- and post-shipping samples for product quality (container closure integrity, purity by SEC, nrCE-SDS, IE-HPLC, sub-visible particles, and potency of ranibizumab).

PMC Schedule Milestones:	Final Protocol Submission:	<u>12/16/2016</u>
	Study/Trial Completion:	<u>06/16/2017</u>
	Final Report Submission:	<u>08/04/2017</u>
	Other: _____	<u>MM/DD/YYYY</u>

PMC #2 Description: _____

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other: _____	<u>MM/DD/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDA AA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Data from a vibration simulation study and different temperature-based stability studies were provided in the BLA. Shipping container qualification studies have also been performed. The additional studies provide assurance of the safety and quality of the product when the drug product undergoes actual shipping.

2. Describe the particular review issue and the goal of the study.

Shipping validation studies did not evaluate the impact to drug product under actual shipping conditions, including the combination of potential effects of vibration and pressure changes and moderate temperature fluctuations in the presence of silicon oil and tungsten found in the syringe barrel. This study will provide confirmation that shipping the PFS drug product will not significantly impact product quality through an evaluation of product quality parameters pre- and post-shipment.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

A study will be performed using drug product shipped through shipping lanes and under conditions representative of commercial shipping to assess the impact of shipping on product quality.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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/s/

SARAH B KENNETT
10/12/2016

KATHLEEN A CLOUSE STREBEL
10/12/2016



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION SHEET

DATE: October 6, 2016

To: Key Kang	From: Lois Almoza, M.S. Regulatory Health Project Manager
Company: Genetech, Inc.	Division of Transplant and Ophthalmology Products
Email: key@gene.com	Email: lois.almoza@fda.hhs.gov
Phone Number: 415-269-4995	Phone number: 301-796-1600

Subject: BLA 125156/S-110/ Lucentis (ranibizumab injection)/Genentech, Inc. – information request

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Dear Mr. Kang,

Please refer to your June 16, 2016, submission to BLA 125156 for Lucentis (ranibizumab injection). This submission contained a Supplemental Biologics License Application (sBLA). We request the following information to continue our review:

1. In the description of the manufacturing process (Section 3.2.P.3.3), it states that [REDACTED] (b) (4). Samples for microbial testing should be collected [REDACTED] (b) (4). Please implement these changes in sample location and amend the BLA to reflect the changes.
2. Provide summary data from the three most recent requalification studies for the [REDACTED] (b) (4). The studies should be relevant to the ranibizumab drug product manufacturing process.
3. Clarify if parameters used in requalification studies for [REDACTED] (b) (4) represent worst-case conditions and compare these to those parameters used during routine operations.
4. With regard to media fill studies, please describe the worst-case conditions used. What are the routine parameters compared those used in the media fill simulations?
 - a. Describe growth promotion studies and submit results from three most recent requalification
 - b. Clarify the fill speeds used during the media and routine production fills.
 - c. Provide a description of the growth promotion test.

Please submit the information mentioned above by COB Thursday, October 6, 2016, where possible. If you need additional time to submit the information requested please let us know. Your response should be submitted via e-mail and to the application on file.

If you have any questions regarding this communication, please contact me at (301) 796-1600.

Sincerely,

Lois Almoza, M. S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

LOIS A ALMOZA
10/06/2016



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION SHEET

DATE: October 3, 2016

To: Key Kang	From: Lois Almoza, M.S. Regulatory Health Project Manager
Company: Genetech, Inc.	Division of Transplant and Ophthalmology Products
Email: key@gene.com	Email: lois.almoza@fda.hhs.gov
Phone Number: 415-269-4995	Phone number: 301-796-1600

Subject: BLA 125156/S-110/ Lucentis (ranibizumab injection)/Genentech, Inc. – information request

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES NO

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Dear Mr. Kang,

Please refer to your June 16, 2016, submission to BLA 125156 for Lucentis (ranibizumab injection). This submission contained a Supplemental Biologics License Application (sBLA). We request the following information to continue our review:

1. Regarding the August 30, 2016 response to the August 15, 2016 information request:
 - a. You stated that breakloose and glide force testing will be implemented as part of the release specification and that Section 3.2.P.5.1 was updated (Question 4 and Table 7). However, Table P.5.1-1 (Release and Stability Specifications for Ranibizumab PFS) still states that these tests are not performed at release. Update this section to include testing and the acceptance criteria presented in Section 3.2.P.5.6.
 - b. You provided a list of analytical methods that were transferred to new QC testing sites and the sites to which each method was transferred (Question 1). Each site is responsible for only a fraction of the complete set of release or stability test methods, and it is not acceptable to perform QC testing at alternative sites; however, the appropriate sections of the BLA were not updated with the specific testing site information. Update Form 356h and Section 3.2.P.3.1 (Manufacturers) to clarify the testing site(s) responsible for each test.
 - c. Stability data were referenced to support the maintenance of product quality during shipping of the finished PFS from the manufacturing site to the US distributor (Question 6). However, the response does not include information to support that the conditions selected are representative of actual DP shipping conditions. Provide information/data to clarify how the (b) (4) and the temperature cycling studies compare to actual conditions encountered during shipping and how the separate studies cover the combination of conditions to which the DP is exposed during shipping. Alternatively, provide data to demonstrate that 0.5 mg PFS DP that has been shipped through a similar route has not been impacted by the shipping conditions (e.g., if samples shipped to SSF or RSTO have been tested for product quality attributes in addition to the identity or potency testing routinely performed at those sites).
2. The Master Batch Record states that refiltration is allowed; however, refiltration is not included in Section 3.2.P.3.3 (Description of Manufacturing Process and Process Controls). Reprocessing steps should be clearly identified and described in Section 3.2.P.3.3, and data from commercial scale reprocessing should be provided to demonstrate validation of the reprocessing process as performed at the site of manufacture. If reprocessing cannot be supported and added to Section 3.2.P.3.3, the option to reprocess should be removed from the Master Batch Record.

Please submit the information mentioned above by COB Tuesday, October 4, 2016. If you need additional time to submit the information requested please let us know. Your response should be submitted via e-mail and to the application on file.

If you have any questions regarding this communication, please contact me at (301) 796-1600.

Sincerely,

Lois Almoza, M. S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

LOIS A ALMOZA
10/03/2016

REQUEST FOR CONSULTATION

TO (Division/Office):
Mail: OSE

FROM: **Lois Almoza, M.S.**
**RHPM/Office of Antimicrobial Products/Division of
Transplant and Ophthalmology Products**

DATE September 14, 2016	BLA NO. 125156/s-110	NDA NO.	TYPE OF DOCUMENT CMC Labeling Supplement	DATE OF DOCUMENT August 19, 2016
NAME OF DRUG Lucentis		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE September 28, 2016

NAME OF FIRM: **Genentech, Inc.**

REASON FOR REQUEST

I. GENERAL

- | | | |
|---|---|--|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> PRE--NDA MEETING
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY/EFFICACY
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input checked="" type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|---|--|

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|---|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---|--|

IV. DRUG EXPERIENCE

- | | |
|--|---|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|--|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS:

The purpose of the submission was to provide the required information for approval of the Lucentis 0.5 mg prefilled syringe (PFS). In addition to CMC information, proposed updates to the Lucentis U.S. Prescribing Information and Instructions for Use for the Lucentis 0.5 mg PFS are included.

Please review substantially complete labeling named 8-19 redlined-label-text in the SharePoint link below and provide comments by September 28, 2016.

<http://sharepoint.fda.gov/orgs/CDER-OND/dtopndas/BLA%20125156/Forms/AllItems.aspx>

EDR Location: \\CDSESUB1\evsprod\BLA125156\125156.enx

SIGNATURE OF REQUESTER Lois Almoza, M.S.		METHOD OF DELIVERY (Check all that apply)		
		<input type="checkbox"/> MAIL	<input checked="" type="checkbox"/> DARRTS	<input type="checkbox"/> HAND
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

06/18/2013

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/s/

LOIS A ALMOZA
09/14/2016

From: Almoza, Lois

Sent: Tuesday, August 30, 2016 9:47 AM

To: 'Key Kang'

Subject: Information Request - BLA 125156/s-110/Lucentis (ranibizumab)/Genentech

Hi Key,

Please see the information request below and try to respond by September 7, 2016.

1. Provide the location of the complete biocompatibility testing for the syringe (protocol, acceptance criteria, results, conclusion). It is alluded to throughout the submission, but testing cannot be located.
2. Provide the location for the complete shipping studies. You reference ASTM 7386, but the testing cannot be located.

Thanks,

Lois

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/s/

LOIS A ALMOZA
08/31/2016

From: Almoza, Lois

Sent: Tuesday, August 16, 2016 4:19 PM

To: Key Kang

Subject: Information Request - sBLA 125156/s-110/Lucentis (ranibizumab injection)/Genentech, Inc.

Good Afternoon,

Please respond to the information request below on or before August 30, 2016.

1. The majority of the analytical methods were transferred from the currently approved testing sites to a number of (b) (4) sites; however, no data were provided to support the transfers. Submit the method transfer reports for each method and each site to which the method was transferred; for compendial methods that were not formally transferred, submit the verification/validation reports. In addition, submit the method validation reports for all the new analytical methods and method transfer reports for any subsequent testing sites.
2. The data from the study performed to compare the ranibizumab quality attributes in paired bulk PFS and finished PFS batches are difficult to evaluate in the forms provided (Table P.2-19 and Figures P.2-8 through P.2-15). These data provide critical support for the proposal to perform the majority of the PFS release testing on the bulk PFS. Submit the actual quantitative data for each datapoint (e.g., in a tabular format) to allow for a sufficiently complete comparison of the bulk and finished materials.
3. Regarding the Description of Manufacturing Process and Process Controls (Section 3.2.P.3.3):
 - a. The description of the process does not include sufficient detail to support that the process is routinely run following a process that is supported by validation and development studies. Add the following operating parameters and operating limits/ranges that are supported by the studies that have been performed:
 - i. DS thawing/storage time
 - ii. Thawed DS recirculation time
 - iii. Thawed DS recirculation speed
 - iv. Compounded bulk mixing speed
 - v. Compounded bulk mixing time

- vi. Syringe filling time (from time of transfer from filtered DP solution hold; broken into any units that would be applicable)
 - vii. Syringe filling speed
 - viii. Total time at room temperature (e.g., to include 100% visual inspection, assembly, etc.)
- b. No product quality data were provided to support the upper limits of the validation study operating ranges for the DS thawing time, recirculation time (no limit), compounded bulk mixing time (no limit), and syringe filling time (based on media fill only). Hold times and mixing can impact critical product quality attributes. If the time limits incorporated in response to request 3a are the limits used in the validation studies, provide appropriate data to support these limits.
4. Regarding in-process testing (Section 3.2.P.3.4):
- a. The fill weight/fill volume is currently proposed to be controlled through in-process “action” limits, and fill weight is “verified at regular intervals throughout the filling process.” Syringes that are outside the acceptable fill weight range should not be released to the market. Update the control strategy to clearly indicate that syringes that fail the syringe weight check will be rejected (those between a passing and failing weight check may be appropriately screened for passing units, if an acceptable system is in place).
 - b. The limits currently proposed to control syringe breakloose and glide force at release are the in-process “action” limits. Action limits are not acceptable as the primary controls for these attributes; syringes not meeting these limits should not be released. Update the control strategy to include acceptance/rejection limits for in-process testing or implement breakloose and glide force testing as part of the release specifications.
5. The validation section (3.2.P3.5.2.1) states that “based on validated bulk PFS process, some adjustments and additions were made to the in-process control settings and limits.” The timing of the changes is not clear, although, given the location of the comment, we infer that there were changes made between the (b) (4). The changes made can impact the level of support provided by the (b) (4). Clarify the timing of the changes and identify the adjustments and additions to the process.
6. Shipping studies were performed to assess the capability of the cold chain to support transit of the materials at the appropriate temperatures. However, other than the data that happens to be available as part of other studies (e.g., end-to-end validation of the process that includes shipping to (b) (4)), no data were provided to demonstrate that

shipping does not impact product quality. The data available do not appear to cover the potentially more stressful transit routes for the finished PFS. Provide data from PFS shipping studies performed to evaluate impact to ranibizumab product quality attributes.

7. Leachables studies have been initiated to support the new container closure; however, very limited data are available to date, and the identification of some leachable/extractable compounds is ongoing. The leachables studies data should be submitted to provide assurance of the safety of the product. Commit to updating the study data in the annual reports submitted subsequent to obtaining new study data.

Thanks,

Lois

Lois Almoza, M.S.

Regulatory Health Project Manager

Division of Transplant and Ophthalmology Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue

Building 22, Room 6241

Silver Spring, MD 20993

Phone: 240-402-5146

Fax: 301-796-9881

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/s/

LOIS A ALMOZA
08/17/2016



BLA 125156/S110

**ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT**

Genentech, Inc.
Attention: Kay Kang, M. Sc.
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Mr. Kang:

We have received your Supplemental Biologics License Application (sBLA) submitted under section 351(a) of the Public Health Service Act for the following:

BLA NUMBER:	125156
SUPPLEMENT NUMBER:	110
PRODUCT NAME:	Lucentis (ranibizumab injection)
DATE OF SUBMISSION:	June 16, 2016
DATE OF RECEIPT:	June 16, 2016

This supplemental application proposes the addition of a Lucentis 0.5 mg prefilled syringe (PFS)

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 15, 2016, in accordance with 21 CFR 601.2(a). If the application is filed, the user fee goal date will be October 16, 2016.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me at 301-796-0763.

Sincerely,

{See appended electronic signature page}

Judit Milstein
Chief, Project Management Staff
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JUDIT R MILSTEIN
08/03/2016
sBLA 125156/S110 Acknowledgment Letter

MANDATORY: Send a copy of the consult request form to the

Office of Combination Products as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-427-1935

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: CDRH

Division: DAGRID

Mail Code: HF

Consulting Reviewer Name:

Building/Room #:

Phone #:

Fax #:

Email Address:

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER

Division: OPQ/OBP/DBRRI

Mail Code: HF

Requesting Reviewer Name: Sarah Kennett

Building/Room #: 71/2322

Phone#: 240-402-9243

Fax #:

Email Address: sarah.kennett@fda.hhs.gov

RPM/CSO Name and Mail Code: Christina Marshall HFD 590

Requesting Reviewer's Concurring Supervisor's Name: Kathleen Clouse

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 7/25/16

Requested Completion Date: 9/16/16

Submission/Application Number: 125156/110
(Not Barcode Number)

Submission Type: BLA (supplement)
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: 6/16/16

Official Submission Due Date: 10/14/16

Name of Product: Lucentis (ranibizumab)

Name of Firm: Genentech

Intended Use: intravitreal injection for neovascular age-related macular degeneration, macular edema following retinal vein occlusion, diabetic macular edema, diabetic retinopathy in patients with diabetic macular edema

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Link to the submission: \\CDSESUB1\evsprod\BLA125156\125156.enx

LoA for (b) (4) DMF (b) (4); Section 2.3 Quality Overall Summary; Section 3.2.P.7 Container Closure System; Section 3.2.R.2 Delivery Device 0.5 mg PFS

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

This submission is for the introduction of a prefilled syringe presentation for Lucentis (currently supplied as a solution in a vial). Because this is a presentation for ophthalmic use, it is not considered a combination product (21 CFR 200.50). However, I would appreciate your evaluation of the supporting data provided for the use of the syringe as a container closure and ophthalmic dispenser. The majority of the information is presented in the Module 3 Regional section (3.2.R.2) and the DP container closure section (3.2.P.7).

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/s/

CHRISTINA D MARSHALL
07/28/2016