CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761197Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 20, 2021

To: Lois Almoza, Regulatory Health Project Manager
Division of Ophthalmology (DO)

From: Carrie Newcomer, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for SUSVIMO™ (ranibizumab injection) for intravitreal use via SUSVIMO ocular implant

BLA: 761197

In response to the Division of Ophthalmology (DO) consult request dated May 21, 2021, OPDP has reviewed the proposed product labeling (PI), Instructions for Use (IFU), Medication Guide (MG), and carton and container labeling for the original BLA submission for SUSVIMO™ (ranibizumab injection) for intravitreal use via SUSVIMO ocular implant.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DO (Lois Almoza) on October 6, 2021 and are provided below.

OPDP's comments on the proposed IFU are based on the draft IFU received by electronic mail from DO (Lois Almoza) on October 18, 2021 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed MG were sent under separate cover on October 15, 2021.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor and received by electronic email from DO (Lois Almoza) on October 18, 2021 and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at (301) 796-1233 or Carrie.Newcomer@fda.hhs.gov.

93 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4875236

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARRIE A NEWCOMER
10/20/2021 09:33:24 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 15, 2021
To:	Lois Almoza, M.S. Senior Regulatory Health Project Manager **Division of Ophthalmology (DO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Carrie Newcomer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	SUSVIMO (ranibizumab injection)
Dosage Form and Route:	for intravitreal use via SUSVIMO ocular implant
Application Type/Number:	BLA 761197
Applicant:	Genentech, Inc.

1 INTRODUCTION

On April 23, 2021, Genentech, Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761197 SUSVIMO (ranibizumab injection) for the use of Port Delivery System as a treatment for neovascular (wet) age-related macular degeneration (AMD).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Ophthalmology (DO) on May 21, 2021 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for SUSVIMO (ranibizumab injection).

2 MATERIAL REVIEWED

- Draft SUSVIMO (ranibizumab) MG received on April 23, 2021, and received by DMPP and OPDP on October 6, 2021.
- Draft SUSVIMO (ranibizumab) Prescribing Information (PI) received on April 23, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 6, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY E CARROLL
10/15/2021 10:02:31 AM

CARRIE A NEWCOMER
10/15/2021 10:05:29 AM

MARCIA B WILLIAMS
10/15/2021 10:17:54 AM

LASHAWN M GRIFFITHS
10/15/2021 10:30:05 AM

HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING 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:	October 8, 2021
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	BLA 761197
Product Type:	Combination Product
Drug Constituent Name and Strength	Susvimo (ranibizumab) Injection, 10mg/0.1 mL
Device Constituent:	Port Delivery System
Rx or OTC:	Rx
Applicant/Sponsor Name:	Genentech
Submission Date:	4/23/2021
OSE RCM #:	2021-873
DMEPA 1 Human Factors Specialist:	Jason Flint, MBA. PMP
DMEPA 1 Safety Evaluator:	Nasim Roosta, PharmD
DMEPA 1 Team Leader (Acting)	Murewa Oguntimein PhD, MHS, CHES, CPH
DMEPA 1 Division Director (Acting):	Irene Z. Chan, PharmD, BCPS

Reference ID: 4870032

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under BLA 761197 for Susvimo (ranibizumab) injection. Additionally, this review evaluates the results of a clinical use observation report from a human factors perspective.

1.1 PRODUCT DESCRIPTION

This is a combination product with a proposed Port Delivery System (PDS) device constituent part that is intended to treat neovascular age-related macular degeneration (nAMD).

The PDS consists of a PDS implant, vial, Initial Fill Needle (IFN), Insertion Tool (IT) Carrier, IT Handle, Refill Needle (RFN), and Explant Tool (see Figure 1).

Figure 1: Susvimo Port Delivery System

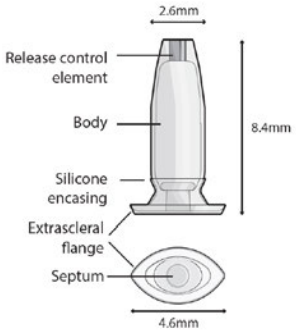


Figure 1 – PDS implant

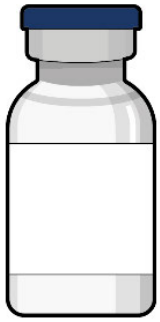


Figure 2 – Vial containing ranibizumab

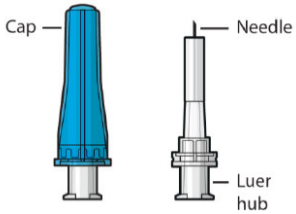


Figure 3 – Initial fill needle (IFN)

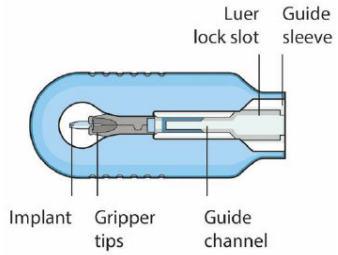


Figure 4 – Insertion tool carrier

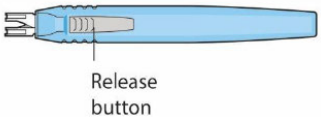


Figure 5 - Insertion tool handle

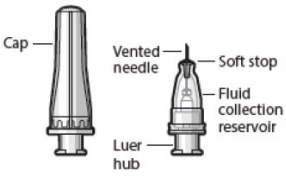


Figure 6 – Refill needle (RFN)

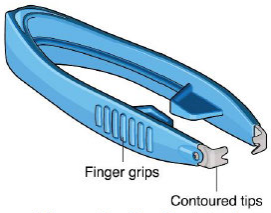


Figure 7 – Explant tool

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

We reviewed the human factors validation study protocol for this product in January, 2020[1] and confirmed that the Applicant addressed our recommendations.

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F
Clinical Use Observation Report	G

[1] Flint, J. Human Factors Validation Study Protocol and Label and Labeling Review for Susvimo (ranibizumab Port Delivery System IND 113552. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020JAN15 RCM No.: 2019-2452.

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed , and our analysis to determine if the results indicate that the user interface has been optimized to support the safe and effective use of the proposed product. As part of our review, we sent an information request for clarification on the training program. See Appendix E for more information.

We also consulted the Center for Devices and Radiological Health (CDRH) Human Factors team to review the study report. The CDRH HF reviewer identified similar deficiencies, which we already incorporated in our recommendation number one in the Training section of table A below.

2.1 SUMMARY OF STUDY DESIGN

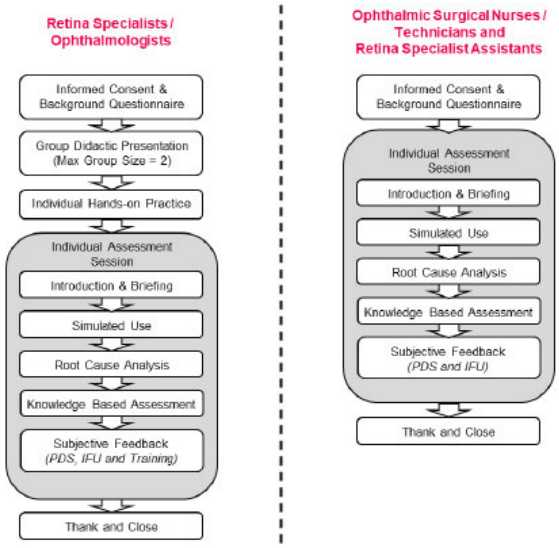
2.1.1 HUMAN FACTORS VALIDATION STUDY

Table 2 presents a summary of the HF validation study design.

Table 2. Study Methodology for Human Factors (HF) Validation Study

Study Design Elements	Details
Participants	<table><tr><th>Group</th><th>Use Environment</th><th>Number of Study Participants</th><th>Procedures Assessed</th><th>Participant Identifier</th></tr><tr><td rowspan="3">Retina Specialists / Ophthalmologists</td><td>Surgical</td><td>8</td><td>• Initial fill and implant • Implant removal</td><td>RS</td></tr><tr><td>Clinic</td><td>8</td><td>• Refill-exchange</td><td>RC</td></tr><tr><td>Both (surgical and clinic)</td><td>7</td><td>• Initial fill and implant • Refill-exchange • Implant removal</td><td>RB</td></tr><tr><td>Ophthalmic Surgical Nurses / Technicians (scrub/circulating)</td><td>Surgical</td><td>15</td><td>• Initial fill and implant • Implant removal</td><td>S</td></tr><tr><td>Retina Specialist Assistants</td><td>Clinic</td><td>15</td><td>• Refill-exchange</td><td>A</td></tr></table>
Training	Training facilitated by trained PDS representatives was provided for the retina specialists. Training consisted of a group or individual didactic presentation, individual hands-on practice, and an individual subjective feedback interview. Following both the presentation and the hand-on practice, participants were free to ask the PDS representatives questions individually. The PDS representatives only answered questions pertaining to information covered during the training session and provided in the IFU. They did not provide participants with any information about the subsequent simulated use session. The training session was followed by a training decay period of 24-72 hours. Retina specialist assistants and ophthalmic surgical nurses/technicians were not trained by a PDS representative in the commercial setting.
Test Environment	The test environment was not representative of a surgical environment, and this may have impacted the results of the HF validation study.

Reference ID: 4870032

	(b) (4)
Sequence of Study	

2.1.2 CLINICAL USE OBSERVATION STUDY

We reviewed the Clinical Use Observation Report (CUOR) from a human factors perspective. The CUOR focused on assessing the ability of HCPs to:

- Perform the initial fill of the PDS implant using final commercial configuration of the IFN (with integrated filter) in accordance with the IFU in patients in the surgical environment
- Perform the PDS refill exchange procedure using the final commercial configuration of the RFN (with integrated filter) in accordance with the IFU in patients in the office room environment

Table 3 presents a summary of the Clinical Use Observation Study design. See Appendix C for more details on the study design.

Table 3. Study Methodology for Clinical Use Observation Report	
Study Design Elements	Details

Participants	18 physicians • 13 IFN uses • 21 RFN uses
Training	Trained user group
Test Environment	IFN - surgical environment RFN – office room environment
Sequence of Study	The study was limited to observation of use. No follow up subjective interview or root cause analysis was performed.

3 RESULTS AND ANALYSES

3.1 CLINICAL USE OBSERVATION REPORT (CUOR)

The CUOR results were of limited utility from a human factors perspective. For example, the description of the study environment was limited, not all tasks associated with the use of the product were assessed, and data on any use difficulties or close calls were not recorded. Generally, from a human factors perspective, we would expect that the study moderator would identify use errors, use difficulties, and close calls on the task level, collect subjective feedback, and conduct a robust root cause analysis to determine what elements of the user interface may have contributed to the use errors. Despite these limitations, there were two use errors identified in the CUOR:

- During the initial fill procedure, one participant depressed the plunger too quickly, introducing bubbles into the implant. The Applicant indicates that this use error was identified during inspection but does not indicate whether the participant or the moderator identified the bubbles. We note that there were also use errors in the HF validation study regarding air bubbles in the syringe and in the implant. We discuss this use error further in Section 3.2.2.
- During the refill procedure, one participant did not use the standard luer lock syringe, instead the participant used a tapered syringe. This use-related error is not identified in the use-related risk analysis and was not assessed in the human factors validation study.

Reference ID: 4870032

3.2 HUMAN FACTORS VALIDATION STUDY REPORT

The summative validation testing results revealed use errors, close calls, and use difficulties that may not be fully mitigated with labeling alone. We find that further development of the training materials, train-the-trainer materials, and hands-on practices may further reduce the residual risks identified. We make a recommendation for the Applicant in the Training section of table A below

3.2.1 SURGICAL TASKS

We note that there were use errors and use difficulty with some of the surgical tasks assessed during the HF validation study. These tasks appear to be independent of the PDS user interface. We defer to the Division of Ophthalmology to assess the impact of task failures for the tasks included in Table 4:

Table 4: Identified Issues and DMEPA's Findings – Surgical Tasks

	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
1.	For the Perform scleral incision task, there were 2 use errors. For example, one participant cut down too far during the incision, and one failed to use the MVR blade to make the incision. The subjective data and the Applicant's root cause analysis stated: Test Artefact due to use of a porcine eye. Clinical Judgement – participant used a larger surgical blade than recommended The Applicant has not proposed mitigation strategies for these use errors.	Based on the URRA, if this task is omitted or not performed correctly there is risk of suprachoroidal hemorrhage, vitreous hemorrhage, retinal detachment, cataract, vitreous prolapse, implant dislocation, foreign body sensation, conjunctival erosion, and disease progression. These tasks do not appear to be related to the product design, rather they appear to be related to clinical judgement/practice of medicine. We shared these concerns with our clinical colleagues, and they indicated that the type of blade used, and depth of incision is not a concern, rather the length of the incision was more critical. They have addressed this concern from a clinical perspective in their review. We do not have any recommendations to address this use error.
2.	For the task Perform pars plana incision there was 1 use error. This participant incised the pars plana with the MVR blade instead of the slit knife.	Based on the URRA, if this task is omitted or not performed correctly there is risk of Suprachoroidal hemorrhage, vitreous hemorrhage. These tasks do not appear to be related to the product design, rather they appear to be related to clinical judgement/practice of medicine.

Reference ID: 4870032

	The subjective data and the Applicant's root cause analysis stated: Participant forgot what tool was supposed to be used for this procedure. The Applicant has not proposed mitigations for this use error.	We shared these use errors with our clinical colleagues, and they indicated that the type of blade used is not a concern. We do not have any recommendations to address this use error.

3.2.2 INITIAL FILL AND IMPLANT PROCEDURE

We separated the initial fill and implant scenarios by user groups because different users performed different tasks. Table 5 addresses use errors, use difficulties and close calls experienced by the Retina Specialists during the initial fill and implant scenario.

Table 5. Identified Issues and DMEPA's Findings – Initial Fill and Implant, Retina Specialists

	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
1.	For the Stabilize the globe task, there were two use errors, and three use difficulties during the implant procedure, and an additional two use errors during the refill and implant removal procedure. The subjective data and the Applicant's root cause analysis stated: Participants used two hands for the implant tool handle. One participant noted that the IT handle release button required them to use two hands. Test Artifact – the porcine eye was stable and did not require additional stability. The Applicant has not proposed mitigations for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of retinal detachment and cataract. Our review of the study results identified subjective feedback that indicated some participants had difficulty with releasing the implant, and that the implant tool required both hands for them to operate. This left them unable to stabilize the globe. Our review of the labels and labeling (user interface, etc.) finds that the initial fill implant procedure, refill procedure, and implant removal procedure IFUs contain images and instructions to support this step. We discussed this use error with our colleagues in the Division of Ophthalmology, who indicated that the use of the porcine model may have contributed to this use errors, and that stabilization of the globe is very different in actual surgical practice.

		We discussed the difficulty with the IT handle release button with our colleagues at the Center for Devices and Radiological Health (CDRH), who indicated that the button force was within the proposed specification. Additionally, we discussed and agreed that decreasing the force for the button may introduce a risk of inadvertent activation and dropping the implant. We find that changes to the button activation force may have unintended consequences. We find that the residual risk in this case is acceptable.
2.	For the Screw filter needle onto syringe task, there was one use error. For example, the participant did not use gloves to attach the filter needle. The subjective data and the Applicant's root cause analysis stated: Study artifact. Due to the nature of the simulated use study, the participant opted to not use proper aseptic technique. The Applicant has not proposed mitigations for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of endophthalmitis, conjunctivitis, keratitis, inflammatory response due to endotoxins, and disease progression. We note that several of the use errors were related to test artifact because the test environment was not representative of actual use, however, we also note in an actual surgical setting, this type of error would be unusual. That is, there is a clear expectation in the surgical setting to maintain the sterile field. One participant mentioned it could be made clearer in the IFU which materials are supposed to be treated with aseptic technique. The Division of Ophthalmology sent an information request asking the Applicant to "Please revise the labeling of the outside of the packaging of the Initial Fill Needle, Ocular Implant with Insert Tool Assembly and Refill Needle to clearly advise users that the contents of these cartons must only be opened onto a sterile field." In response, the Applicant noted that the labeling on the cartons for the Insertion Tool Assembly, Initial Fill Needle, Refill Needle, and Explant Tool have been updated to advise users to transfer the contents of the blister tray on to a sterile field.

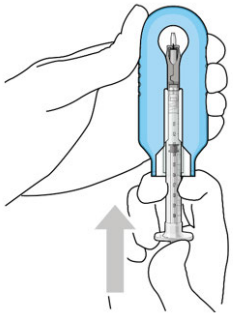
		We have not identified additional changes to the user interface to further reduce the risks associated with this use error. With the recently implemented change, we find that the residual risk in this case is acceptable.
3.	For the task "Withdraw all the drug product from vial through filter needle into syringe", there was one use error. For example, the participant did not use gloves to attach the filter needle. The subjective data and the Applicant's root cause analysis stated: Study artifact. Due to the nature of the simulated use study, the participant opted not to use proper aseptic technique. In the real world, the retina specialist participant would not perform this task themselves and would have assistance from a scrub nurse who would help them, using aseptic technique. The Applicant did not provide mitigation strategies for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of endophthalmitis, conjunctivitis, keratitis, inflammatory response due to endotoxins, and disease progression. We note that this use error was related to test artifact because the test environment was not representative of actual use, however, we also note that in an actual surgical setting this type of error would be unusual. That is, there is a clear expectation in the surgical setting to maintain the sterile field. The Division of Ophthalmology sent an information request asking the Applicant to "Please revise the labeling of the outside of the packaging of the Initial Fill Needle, Ocular Implant with Insert Tool Assembly and Refill Needle to clearly advise users that the contents of these cartons must only be opened onto a sterile field." In response, the Applicant noted that the labeling on the cartons for the Insertion Tool Assembly, Initial Fill Needle, Refill Needle, and Explant Tool have been updated to advise users to transfer the contents of the blister tray on to a sterile field. We have not identified additional changes to the user interface to further reduce the risks associated with this use error. We find that the residual risk in this case is acceptable.
4.	For the task "crew IFN onto syringe", there was one close call. The participant tried to load the syringe into the insertion tool carrier without attaching the IFN.	Based on the URRA, if this task is omitted or not performed correctly there is risk of disease progression. Our review of the labels and labeling (user interface, etc.) finds that the initial fill implant procedure IFU contains images and instructions to

	The root cause analysis indicated that the participant experienced a lapse in memory, that is, the participant indicated that the instructions were clear, they just forgot to attach the IFN. The Applicant did not provide risk mitigation strategies for this use error.	support this step. Additionally, we expect that a clinician would recognize and correct this error – as seen with this participant – when they realized that they could not fill the implant without a needle attached to the syringe. We find that the residual risk in this case is acceptable.
5.	For the task "Remove air from the syringe", there were four use errors. The Applicant's root cause analysis for the use errors were incomplete, indicating that participants had lapses, or made mistakes. We note that this use error also occurred in the CUOR. The Applicant has not provided risk mitigation strategies for these use errors and use difficulty.	Based on the URRA, if this task is omitted or not performed correctly there is risk of disease progression. Our review of the study results identified subjective feedback that some participants did not adequately prime the syringe and did not use the instructions during the use scenario. Our review of the labels and labeling (user interface, etc.) finds that the initial fill implant procedure IFU contains images and instructions to support this step. We discussed this use error with our colleagues in the Division of Ophthalmology, who sent an information request to the Applicant for additional information on the impact of air in the implant. The Applicant responded that: ▪ Based on the outcomes of the Phase II clinical study (GX28228, Ladder), simulations using a PK/PD model confirmed that a ranibizumab release rate of (b) (4) µg/day at 26.3 weeks is required to achieve efficacious vitreous concentrations. This release rate requirement can be met via a minimum implant volume of (b) (4) µL. ▪ The implant fillable volume is >=- (b) (4) µL. The difference between the implant fillable volume and the minimum required volume is >= (b) (4) µL.

		▪ The volume of air bubble corresponding to 1/3 of the widest implant diameter is (b) (4) µL. ▪ Therefore, it is acceptable to have an air bubble no larger than 1/3 of the widest diameter of the implant without having an impact on disease progression as described above. Our discussions with the Division of Ophthalmology indicated that the clinical team found this explanation acceptable. Based on our expert review, we find that the residual risks associated with these use errors are acceptable.
6.	For the task "Inspect syringe and IFN for air bubbles", there were two use errors and one use difficulty. We note that this use error also occurred in the CUOR. The Applicant's root cause analysis for these use errors and use difficulty was incomplete, indicating that participants had lapses, or made mistakes. The Applicant has not provided risk mitigation strategies for these use errors and use difficulty.	Based on the URRA, if this task is omitted or not performed correctly there is risk of disease progression. Our review of the study results identified subjective feedback that indicated one participant did not think it mattered if they removed the IFN cap, and one participant indicated they forgot to inspect the syringe, and they did not use the instructions. Our review of the labels and labeling (user interface, etc.) finds that the initial fill implant procedure IFU contains images and instructions to support this step. We discussed this use error with our colleagues in the Division of Ophthalmology, who sent an information request to the Applicant for additional information on the impact of air in the implant. The Applicant responded that: ▪ Based on the outcomes of the Phase II clinical study (GX28228, Ladder), simulations using a PK/PD model confirmed that a ranibizumab release rate of (b) (4) µg/day at 26.3 weeks is required to achieve efficacious vitreous

		concentrations. This release rate requirement can be met via a minimum implant volume of (b) (4) µL. ▪ The implant fillable volume is >=- (b) (4) µL. The difference between the implant fillable volume and the minimum required volume is >= (b) (4) µL. ▪ The volume of air bubble corresponding to 1/3 of the widest implant diameter is (b) (4) µL. ▪ Therefore, it is acceptable to have an air bubble no larger than 1/3 of the widest diameter of the implant without having an impact on disease progression as described above. Our discussions with the Division of Ophthalmology indicated that the clinical team found this explanation acceptable. Based on our expert review, we find that the residual risks associated with these use errors and use difficulty are acceptable.
7.	For the task "Align syringe luer with luer collar slot in IT carrier", there were five use errors. Participants loaded the syringe from the back of the IT carrier. The subjective feedback indicated participants did not know why this step was important. The Applicant proposed changing the instruction in step 5 of the IFU from "Align the syringe Luer lock above the Luer lock slot in the carrier." to "Align the syringe Luer lock above the Luer lock slot in the carrier to protect the needle from being damaged.""	Based on the URRA, if this task is omitted or not performed correctly there is risk of conjunctival abrasion, erosion, or disease progression. Our review of the subjective feedback and study results indicated that it was not clear to some participants why they should complete this task. The Applicant proposed adding some information to the IFU on why this step was important. Our review of the labels and labeling (user interface, etc.) finds that that the initial fill implant procedure IFU contains images and instructions to support this step. Additionally, we note that the participants in the study that experienced this use error corrected their mistake and were able to align the syringe with the implant.

		Based on our overall assessment, we find that the proposed mitigation may reduce the likelihood of occurrence of this use error, and we have not identified additional changes to the user interface to further reduce the risk.
8.	For the task "Push the syringe forward until it stops", there was one use difficulty. The participant was unable to push the syringe forward because they bent the needle in the previous step. The Applicant has not proposed risk mitigations for this step.	Based on the URRA, if this task is omitted or not performed correctly there is risk of Disease progression, conjunctival abrasion or hemorrhage, or conjunctival erosion. The root cause analysis is incomplete because it does not indicate why the needle was bent in the previous step. Our review of the labels and labeling (user interface, etc.) finds that the initial fill implant procedure IFU contains images and instructions to support this step. Our review of the study results identified that this participant previously loaded the IT carrier incorrectly, which may have led to damaging the needle. The participant recognized that the IFN needle was bent, started over with another kit, and was able to successfully complete the task. We note that this participant bent the needle based on the use error identified in #7 above. The mitigation proposed above may also address this potential use error. We have not identified additional changes to the user interface to further reduce the risk.
9.	For the tasks "Depress plunger slowly to inject the contents of the syringe into the implant under microscope" and "Inspect the implant for air bubbles" there were four use errors and one use difficulty. Four participants did not fill the implant under the microscope.	Based on the URRA, if this task is omitted or not performed correctly there is risk of disease progression. Our review of the study results identified subjective feedback that indicated participants used their clinical judgement to complete this task. Our review of the labels and labeling (user interface, etc.) finds that while the initial fill and implant procedure IFU includes text to support

	The root cause analysis indicated that the participants used their usual practice of using their naked eye to fill the implant instead of a microscope. One participant indicated that microscopes were not usually available in their work setting. The Applicant did not provide any risk mitigation strategies to address this use error.	this task, the associated image shows a user filling the implant while holding the insertion tool carrier. This image does not indicate that the implant should be filled under the microscope.  Based on our expert review, we find the user interface can be improved. We provide a recommendation in Table A to address this concern. We have determined that this change can be implemented without additional HF validation testing to be submitted for review.
10.	For the task "Withdraw the IT guide sleeve with syringe from carrier", there was one use difficulty. The root cause analysis indicated that the participant was concerned with introducing air bubbles and was being cautious. The Applicant did not provide risk mitigation strategies for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of pain. Our review of the study results identified subjective feedback that indicated that the participant was ultimately successful but was using caution with their initial use of the product. Our review of the labels and labeling (user interface, etc.) finds that the initial fill implant procedure IFU contains images and instructions to support this step. Based on our expert review, additional labeling mitigations in the IFU are unlikely to further reduce the residual risk associated with this use error.

11.	For the task “Set IT handle with filled implant aside”, there were two use errors. Participants removed the IT handle with the filled implant and set it onto the sterile field. The root cause analysis indicated that the two participants did not use the IFU for these steps. The Applicant did not provide risk mitigation strategies for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of endophthalmitis, conjunctivitis, keratitis, or inflammatory response due to endotoxins. Our review of the study results identified that the subjective feedback and subsequent root cause analysis for this use error was limited. Our review of the labels and labeling (user interface, etc.) finds that the initial fill implant procedure IFU contains images and instructions to support this step. Based on our expert review, additional labeling mitigations in the IFU are unlikely to further reduce the residual risk associated with these use errors.
12.	For the Slowly insert the implant through the incision perpendicular to the globe until the IT handle gripper tips abuts the sclera task, there was one use difficulty. The participant did not recall how far to insert the implant, and had difficulty opening the release button. The root cause analysis was incomplete, because it focused on the participants memory lapse, and not the difficulty opening the release button. The Applicant did not provide mitigation strategies for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of retinal detachment or cataract. Our review of the study results identified that the subjective feedback and subsequent root cause analysis for this use error was limited. Our review of the labels and labeling (user interface, etc.) finds that the initial fill implant procedure IFU contains images and instructions to support this step. We discussed the difficulty with the IT handle release button with our CDRH colleagues, who indicated that the button force was within the proposed specification. Additionally, we discussed and agreed that decreasing the force for the button may introduce a risk of inadvertent activation and dropping the implant. Based on our expert review, additional labeling mitigations in the IFU are unlikely to further reduce the residual risk associated with this use difficulty.

13.	For the Release the implant by depressing the IT handle release button completely task, there were three use difficulties. Two participants had difficulty pressing the release button, and one participant came close to touching the implant septum with forceps. The root cause analysis for these use difficulties were incomplete because they focused on the user's "mistakes" and not elements of the IT handle that may have contributed to the use errors. The Applicant did not provide mitigation strategies for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of pain, disease progression, or intraocular inflammation. Our review of the study results identified that the subjective feedback and subsequent root cause analysis for these use difficulties were limited. Our review of the labels and labeling (user interface, etc.) finds that the initial fill implant procedure IFU contains images and instructions to support this step. We discussed the difficulty with the IT handle release button with our colleagues at the Center for Devices and Radiological Health (CDRH), who indicated that the button force was within the proposed specification. Additionally, we discussed and agreed that decreasing the force for the button may introduce a risk of inadvertent activation and dropping the implant. Based on our expert review, additional labeling mitigations in the IFU are unlikely to further reduce the residual risk associated with these use errors.
14.	For the knowledge task "According to the instructions, can you locate the information to be filled in the patient implant card?" there were three use errors, and one use difficulty. Participants selected the wrong lot number for the implant. The root cause analysis indicates that participants experienced negative transfer and chose the lot number for the drug product, not the implant. The Applicant proposed changing the implant card to read "Implant Lot Number" instead of "(b) (4)" to address these use errors and use difficulty.	Based on the URRA, while there are no direct risks to the patient if the task is not completed or is not completed correctly, the Implant lot number provides traceability and added information to the patient regarding their implant. Our review of the study results identified subjective feedback that indicated they experienced negative transfer because their normal practice is to record the lot numbers for drug products. Our review of the implant card indicates that the applicant's proposal to clarify that the implant lot number should be recorded may help address these use errors and use difficulty. We have not identified

		mitigations for other elements of the user interface that could address these use errors and use difficulty.

Table 6 addresses use errors, use difficulties and close calls experienced by the Surgical Nurses/Technicians during the initial fill and implant scenario.

Table 6. Identified Issues and DMEPA's Findings – Initial Fill and Implant, Surgical Nurse/Technicians

	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
1.	For the tasks associated with removing the contents from cartons there were: • Two use errors for the task "Remove contents from ranibizumab vial-IFN kit carton " • One use error for the task "Remove contents from IFN carton" • One use difficulty for the task "Open ITA carton" • Four use errors for the task "Remove IFN from SBS using aseptic technique and place onto sterile field" • Three use errors and one use difficulty for the task "Remove ITA with implant from SBS using aseptic technique and place onto sterile field" The root cause analysis indicated: • Some participants experienced negative transfer of experience from other products • Study Artifact – participants were not clear which tables were meant to be the sterile field	Based on the URRA, if this task is omitted or not performed correctly there is risk of endophthalmitis, conjunctivitis, keratitis, inflammatory response due to endotoxins, and disease progression. Our review of the study results identified that one participant was not a representative user for this task because they did not usually set up the sterile field. We note that several of the use errors were related to test artifact because the test environment was not representative of actual use, however, we also note that these use errors do not seem to be a result of the product packaging, and that in an actual surgical setting, these types of errors would be unusual. That is, there is a clear expectation in the surgical setting to maintain the sterile field. One participant mentioned it could be made clearer in the IFU which materials are supposed to be treated with aseptic technique. The Division of Ophthalmology sent an information request asking the Applicant to "Please revise the labeling of the outside of the packaging of the Initial Fill Needle, Ocular Implant with Insert Tool Assembly and Refill Needle to clearly advise users that the contents of these cartons must only be opened onto a sterile field." In response, the Applicant noted that the labeling on the cartons for the Insertion Tool Assembly, Initial Fill Needle, Refill Needle, and Explant Tool has been updated to advise users to transfer the contents of the blister tray on to a sterile field.

	• Accident – one participant dropped the ITA onto the floor while attempting to drop it onto the sterile field The Applicant did not provide mitigation strategies for these use errors and use difficulties.	We have not identified additional changes to the user interface to further reduce the risks associated with these use errors.
2.	For the task "Disinfect vial septum with alcohol pad", there were four use errors. The root cause analysis indicates: Negative Transfer of experience – participants expected that the top of the vial was already sterile. Lapse – One participant indicated that they forgot to wipe the vial. The Applicant did not propose risk mitigations for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of Endophthalmitis, conjunctivitis, keratitis. Our review of the study results identified subjective feedback that indicated participants were not aware that wiping the vial was necessary. Our review of the labels and labeling (user interface, etc.) finds that the IFU contains instructions to support this use step. Additionally, we note that in the surgical setting, it would be good clinical practice to disinfect the vial septum with alcohol. We have not identified additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risk in this case is acceptable.
3.	For the task "Screw filter needle onto syringe", there were 5 use errors. For example, participants handled the filter needle and syringe using "clean technique" instead of Aseptic technique. The subjective data and the Applicant's root cause analysis stated: Negative transfer. This is an issue of negative transfer from the knowledge provided at their workplace regarding aseptic technique. Test Artifact: The simulated use environment was not representative of an actual use environment	Based on the URRA, if this task is omitted or not performed correctly there is risk of endophthalmitis, conjunctivitis, keratitis, and inflammatory response due to endotoxins. Our review of the study results identified subjective feedback that indicated that one of the root causes for the use errors was negative transfer from their clinical experience, however, it appears that the study design contributed to this use error because the use environment was not representative of a surgical theater. Additionally, we note there is a clear expectation in the surgical setting to maintain the sterile field. One participant mentioned it could be made clearer in the IFU which materials are supposed to be treated with aseptic technique.

	The Applicant did not propose risk mitigations for these use errors.	The Division of Ophthalmology sent an information request asking the Applicant to "Please revise the labeling of the outside of the packaging of the Initial Fill Needle, Ocular Implant with Insert Tool Assembly and Refill Needle to clearly advise users that the contents of these cartons must only be opened onto a sterile field." In response, the Applicant noted that the labeling on the cartons for the Insertion Tool Assembly, Initial Fill Needle, Refill Needle, and Explant Tool has been updated to advise users to transfer the contents of the blister tray on to a sterile field. We have not identified additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risk in this case is acceptable.
4.	For the task "withdraw all the drug product from vial through filter needle into syringe", there were 4 use errors, and one use difficulty. For example, participants did not use aseptic technique, or did not withdraw all of the medication from the vial. The participant that did not withdraw all of the medication withdrew enough to fill the implant, so this was considered a use difficulty. The subjective data and the Applicant's root cause analysis stated: Negative transfer. This is an issue of negative transfer from the knowledge provided at their workplace regarding aseptic technique. Test Artifact: The simulated use environment was not representative of an actual use environment Technique – One use difficulty was related to the participant not inverting the vial completely	Based on the URRA, if this task is omitted or not performed correctly there is risk of disease progression. Our review of the study results identified subjective feedback that indicated that one of the root causes for the use errors was negative transfer from their clinical experience, however, it appears that the study design contributed to this use error because the use environment was not representative of a surgical theater. Additionally, we note there is a clear expectation in the surgical setting to maintain the sterile field. One participant mentioned it could be made clearer in the IFU which materials are supposed to be treated with aseptic technique. The Division of Ophthalmology sent an information request asking the Applicant to "Please revise the labeling of the outside of the packaging of the Initial Fill Needle, Ocular Implant with Insert Tool Assembly and Refill Needle to clearly advise users that the contents of these cartons must only be opened onto a sterile field." In response, the Applicant noted that the labeling on the cartons for the Insertion Tool Assembly, Initial Fill Needle, Refill Needle, and Explant Tool has been updated to advise users to transfer the contents of the blister tray on to a sterile field.

	The Applicant did not propose risk mitigations for this use error.	We have not identified additional changes to the user interface to further reduce the risks associated with these use errors.
5.	For the task "Remove filter needle", there was one use error – the participant did not remove the filter needle. The subjective data and the Applicant's root cause analysis stated: Mistake (knowledge). The participant was not familiar with the standard, off-the-shelf filter needle and the intended use of the system. The Applicant did not propose risk mitigations for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of disease progression. Our review of the study results identified subjective feedback that indicated the participant was not familiar with filter needles. Our review of the labels and labeling (user interface, etc.) finds that there are instructions and illustrations on removing the filter needle and replacing it with the IFN. We have not identified additional changes to the user interface to further reduce the risks associated with this use error. We find that the residual risk in this case is acceptable.
6.	For the task "Screw IFN on to syringe", there was one use error. For example, the participant tried to load the syringe into the IT carrier without the IFN attached. The subjective data and the Applicant's root cause analysis stated that this participant had a lapse. The Applicant did not provide mitigation strategies for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of disease progression. Our review of the study results identified subjective feedback that indicated although the participant initially forgot to attach the IFN, they recognized their error during the next step and corrected it. Our review of the labels and labeling (user interface, etc.) finds that there are instructions and illustrations on attaching the IFN prior to loading the syringe into the carrier. We have not identified additional changes to the user interface to further reduce the risks associated with this use error. We find that the residual risk in this case is acceptable.
7.	For the knowledge tasks, for storage temperature for the Insertion Tool Assembly and drug product cartons, there were two use errors; the participants	Based on the URRA, if this task is omitted or not performed correctly there is risk of degradation of the drug product or damage to the implant leading to disease progression, inflammation, immunogenicity, and pain.

	provided the storage temperature from the wrong carton. Lapse – the participant located storage information from the wrong carton The Applicant has not proposed mitigations for this use error.	Our review of the study results identified that this participant looked at the wrong carton to retrieve this information. Our review of the labels and labeling (user interface, etc.) finds that the carton for the insertion tool assembly displays the storage temperature. Based on our expert review, we have not identified additional changes to the user interface to address these use errors. We find that the residual risk in this case is acceptable.
8.	For the knowledge task "According to the instructions, can you locate the information to be filled in the patient implant card?", there were eight use errors. Participants selected the wrong lot number for the implant. The root cause analysis indicates that participants experienced negative transfer and chose the lot number for the drug product, not the implant. The Applicant proposed changing the implant card to read "Implant Lot Number" instead of "(b) (4) " to address this use error.	Based on the URRA, while there are no direct risks to the patient if the task is not completed or is not completed correctly, the Implant lot number provides traceability and added information to the patient regarding their implant. Our review of the study results identified subjective feedback that indicated participants experienced negative transfer because their normal practice is to record the lot numbers for drug products. Our review of the implant card indicates that the Applicant's proposal to clarify that the implant lot number should be recorded may help address this use error. We have not identified mitigations for other elements of the user interface that could address these use errors.

3.2.3 REFILL EXCHANGE PROCEDURE

Table 7 addresses use errors, use difficulties and close calls experienced by the Retina Specialists during the initial fill and implant scenario.

Table 7. Identified Issues and DMEPA's Findings – Refill Exchange, Retina Specialists		
	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
1.	For the tasks associated with drawing up the medication, there were:	Based on the URRA, if this task is omitted or not performed correctly there is risk of endophthalmitis, conjunctivitis, keratitis, inflammatory response due to endotoxins, and disease progression.

Reference ID: 4870032

	• Three use errors for the task "Screw filter needle into syringe" • Two use errors for the task "Withdraw all the drug product from vial through filter needle into syringe" The root cause analysis for these tasks indicated that negative transfer of experience and test artifact contributed to these use errors. The Applicant did not provide mitigation strategies for this use error.	Our review of the study results identified subjective feedback that indicated participants used non-sterile gloves during training which led them to believe they should do the same during the study. Additionally, some participants expected the injection to be similar to an intravitreal injection and used clean technique instead of sterile technique. The Division of Ophthalmology sent an information request asking the Applicant to "Please revise the labeling of the outside of the packaging of the Initial Fill Needle, Ocular Implant with Insert Tool Assembly and Refill Needle to clearly advise users that the contents of these cartons must only be opened onto a sterile field." In response, the Applicant noted that the labeling on the cartons for the Insertion Tool Assembly, Initial Fill Needle, Refill Needle, and Explant Tool has been updated to advise users to transfer the contents of the blister tray on to a sterile field. We have not identified additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risk in this case is acceptable.
2.	For the task "Remove Filter Needle", there was one use error. One participant had difficulty removing the filter needle, causing the needle cap to come off. This participant experienced a needle stick injury as a result. The root cause analysis indicated that the participant was grabbing the wrong part of the filter needle when trying to remove it. The Applicant did not provide mitigation strategies for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of pain or cut. Our review of the study results indicates that the root cause analysis was incomplete because the Applicant did not identify why the participant was grabbing the wrong part of the filter needle. Our review of the labels and labeling (user interface, etc.) finds that the IFU shows the IFN with and without the blue cap while attached to the syringe. Additionally, the IFU includes a clear depiction of the cap removal step, which should aid the user in perceiving which is the cap, and which is the needle hub.

		We have not identified additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risk in this case is acceptable.
3.	For the task "Remove air from syringe", there were four use errors. The root cause analysis indicated that the participants made mistakes. The Applicant did not provide mitigation strategies for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of disease progression. Our review of the study results identified that the root cause analysis was incomplete because the Applicant did not identify why participants did not remove the air from the syringe. Our review of the labels and labeling (user interface, etc.) finds that that the initial fill implant procedure IFU contains images and instructions to support this step. We discussed this use error with our colleagues in the Division of Ophthalmology, who sent an information request to the Applicant for additional information on the impact of air in the implant. The Applicant responded that: ▪ Based on the outcomes of the Phase II clinical study (GX28228, Ladder), simulations using a PK/PD model confirmed that a ranibizumab release rate of (b) (4) µg/day at 26.3 weeks is required to achieve efficacious vitreous concentrations. This release rate requirement can be met via a minimum implant volume of (b) (4) µL. ▪ The implant fillable volume is >=- (b) (4) µL. The difference between the implant fillable volume and the minimum required volume is >= (b) (4) µL. ▪ The volume of air bubble corresponding to 1/3 of the widest implant diameter is (b) (4) µL.

		▪ Therefore, it is acceptable to have an air bubble no larger than 1/3 of the widest diameter of the implant without having an impact on disease progression as described above. Our discussions with the Division of Ophthalmology indicated that the clinical team found this explanation acceptable. Based on our expert review, we find that the residual risks associated with these use errors are acceptable.
4.	For the task "Inspect syringe and RFN for air bubbles", there were 3 use errors. Participants did not remove the cap to inspect the RFN for air bubbles. The root cause analysis indicated that some participants did not want to remove the cap prematurely to maintain sterility of the needle. The Applicant did not provide mitigation strategies for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of disease progression. Our review of the study results identified that some participants used clinical judgement to leave the cap on to maintain the sterility of the needle. We discussed this use error with our colleagues in the Division of Ophthalmology, who sent an information request to the Applicant for additional information on the impact of air in the implant. The Applicant responded that: ▪ Based on the outcomes of the Phase II clinical study (GX28228, Ladder), simulations using a PK/PD model confirmed that a ranibizumab release rate of (b) (4) µg/day at 26.3 weeks is required to achieve efficacious vitreous concentrations. This release rate requirement can be met via a minimum implant volume of (b) (4) µL. ▪ The implant fillable volume is >=- (b) (4) µL. The difference between the implant fillable volume and the minimum required volume is >= (b) (4) µL. ▪ The volume of air bubble corresponding to 1/3 of the widest implant diameter is (b) (4) µL.

		▪ Therefore, it is acceptable to have an air bubble no larger than 1/3 of the widest diameter of the implant without having an impact on disease progression as described above. Our discussions with the Division of Ophthalmology indicated that the clinical team found this explanation acceptable. Based on our expert review, we find that the residual risks associated with these use errors are acceptable.
5.	For the task "stabilize the globe", there were two use errors. The root cause analysis indicated that the participants used their typical technique for intravitreal injections. Additionally, test artifact may have played a role because the porcine eye was stable as part of the test setup. The Applicant did not provide mitigation strategies for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of disease progression or cataract. Our review of the subjective feedback indicated that these participants experienced negative transfer of experience, that is, they relied on previous experience with intravitreal injections. We discussed this use error with our colleagues in the Division of Ophthalmology, and they indicated that the use of the porcine model may have contributed to this use errors, and that stabilization of the globe is very different in actual surgical practice. Based on our expert review, we find that additional changes to the user interface are unlikely to further mitigate these use errors. We find that the residual risk in this case is acceptable.
6.	For the task "Insert the RFN through the conjunctiva and the center of the implant septum until the RFN soft stop is in contact with the conjunctiva", there were two use difficulties. Participants had difficulty locating the center of the septum. The root cause analysis indicated that the participants knew what cues to look for, but had difficulty locating the center of the septum.	Based on the URRA, if this task is omitted or not performed correctly there is risk of Pain, retinal detachment. Our review of the study results identified subjective feedback that indicated these participants made several attempts, however they were ultimately successful at performing the refill procedure. Our review of the labels and labeling (user interface, etc.) finds that the IFU contains instructions and images to support this task.

	The Applicant did not provide mitigation strategies for this use difficulty.	Based on our expert review, we find that additional changes to the user interface are unlikely to further mitigate these use errors. We find that the residual risk in this case is acceptable.

Table 8 addresses use errors, use difficulties and close calls experienced by the Retina Specialist Assistants during the Refill Exchange Procedure.

Table 8. Identified Issues and DMEPA's Findings – Refill Exchange, Retina Specialist Assistants

	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
7.	For the tasks associated with removing the carton contents using aseptic technique there were: • Four use errors for "Remove contents from ranibizumab vial carton (vial and USPI)" • 11 use errors for "Remove contents from RFN carton (SBS)" • 14 use errors for "Remove RFN from SBS using aseptic technique and place onto sterile field" These participants placed the non-sterile contents of the vial carton on the sterile field and did not maintain aseptic technique. The root cause analysis for these tasks indicated that negative transfer of experience contributed to these use errors. The Applicant did not provide mitigation strategies for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of endophthalmitis, conjunctivitis, keratitis, or inflammatory response due to endotoxins. Our review of the study results identified subjective feedback that indicated these participants approached the procedure as they would an intravitreal injection and use a "clean technique" ensuring that they avoided touching surfaces that contact either the medication or the patient directly. The Division of Ophthalmology sent an information request asking the Applicant to "Please revise the labeling of the outside of the packaging of the Initial Fill Needle, Ocular Implant with Insert Tool Assembly and Refill Needle to clearly advise users that the contents of these cartons must only be opened onto a sterile field." In response, the Applicant noted that the labeling on the cartons for the Insertion Tool Assembly, Initial Fill Needle, Refill Needle, and Explant Tool has been updated to advise users to transfer the contents of the blister tray on to a sterile field. We have not identified additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risk in this case is acceptable.

8.	For the task “Disinfect vial septum with alcohol pad”, there was one use error. The root cause analysis indicates that the participant thought the vial was already sterile. The Applicant did not provide mitigation strategies for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of Endophthalmitis, conjunctivitis, keratitis, or inflammatory response due to endotoxins. Our review of the study results identified subjective feedback that indicated this participant relied on previous experience and clinical judgement, thinking that the vial septum was already sterile. Our review of the labels and labeling (user interface, etc.) finds that the IFU contains instructions to support this use step. Additionally, we note that in the surgical setting, it would be good clinical practice to disinfect the vial septum with alcohol. We have not identified additional changes to the user interface to further reduce the risks associated with this use error. We find that the residual risk in this case is acceptable.
9.	For the knowledge task “Can you tell me what temperature the Refill Needle must be stored at?” there was one use error. The root cause analysis indicated that the participant selected the wrong temperature information. The Applicant did not provide mitigation strategies for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of pain, retinal detachment, or ocular discomfort. Our review of the study results identified subjective feedback that indicated the participant was focused on the drug product storage information. Our review of the labels and labeling (user interface, etc.) finds that the carton for the insertion tool assembly displays the storage temperature. Based on our expert review, we have not identified additional changes to the user interface to address this use error. We find that the residual risk in this case is acceptable.

3.2.4 IMPLANT REMOVAL PROCEDURE

Table 9 addresses use errors, use difficulties and close calls experienced by the Retina Specialists during the implant removal procedure.

Reference ID: 4870032

Identified Issues and DMEPA's Findings – Implant Removal, Retina Specialist		
	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
1.	For the task "Grasp underneath the long axis of the implant flange with the Explant Tool tips", there was one use difficulty. The root cause analysis indicated that the participant was holding the explant tool too far back, so the tool was not gripping the implant completely. The Applicant did not provide mitigation strategies for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of retinal detachment, cataract, and pain . Our review of the study results identified subjective feedback that indicated that the participant eventually realized that the ridges on the explant tool were for grasping. Once this perception occurred, the participant was able to perform the task. Our review of the explant tool finds that there is a design affordance of ridges to indicate to the user where they should grasp. We did not identify additional changes to the user interface to address this use difficulty. We find that the residual risk in this case is acceptable.
2.	For the task stabilize globe, there were two use errors. The root cause analysis indicated that the stability of the porcine eye in the test environment contributed to these use errors. The Applicant did not provide mitigation strategies for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of retinal detachment, or cataract . Our review of the study results identified subjective feedback that indicated the participants would stabilize the globe if needed, but the porcine eye was stable enough that it did not require additional stabilization. We discussed this use error with our colleagues in the Division of Ophthalmology, and they indicated that the use of the porcine model may have contributed to this use errors, and that stabilization of the globe is very different in actual surgical practice. Based on our expert review, we find that additional changes to the user interface are unlikely to further mitigate these use errors. We find that the residual risk in this case is acceptable.

3.	For the task "Gently pull the implant from eye with Explant Tool in a perpendicular motion", there was one use difficulty. The root cause analysis indicated that the participant wanted to stay away from the implant to maintain sterility, so they grasped the explant tool too high. The Applicant did not provide mitigation strategies for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of pain, retinal detachment, cataract. Our review of the study results identified subjective feedback that indicated that the participant eventually realized that the ridges on the explant tool were for grasping. Once this perception occurred, the participant was able to perform the task. Our review of the explant tool finds that there is a design affordance of ridges to indicate to the user where they should grasp. We did not identify additional changes to the user interface to address this use difficulty, however, we add a general recommendation regarding the training program in Table A.

Table 10 addresses use errors, use difficulties and close calls experienced by the Retina Specialist Assistants during the implant removal procedure.

Table 10. Identified Issues and DMEPA's Findings – Implant Removal, Retina Specialist Assistants		
	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
1.	For the task "Remove ET from SBS using aseptic technique and place onto sterile field", there was one use error. The root cause analysis indicated that the participant confused the use environments because they work part time in the clinic and part time in surgery. The Applicant did not provide mitigation strategies for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of endophthalmitis, conjunctivitis, or keratitis. Our review of the study results identified subjective feedback that indicated that the test environment was not representative of actual use, which contributed to this use error. We also note that this use error does not seem to be a result of the product user interface, and that in an actual surgical setting, these types of errors would be unusual. That is, there is a clear expectation in the surgical setting to maintain the sterile field. One participant mentioned it could be made clearer in the IFU which materials are supposed to be treated with aseptic technique. The Division of Ophthalmology sent an information request asking the Applicant to "Please revise the labeling of the outside of the packaging of

		the Initial Fill Needle, Ocular Implant with Insert Tool Assembly and Refill Needle to clearly advise users that the contents of these cartons must only be opened onto a sterile field." In response, the Applicant noted that the labeling on the cartons for the Insertion Tool Assembly, Initial Fill Needle, Refill Needle, and Explant Tool has been updated to advise users to transfer the contents of the blister tray on to a sterile field. We have not identified additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risk in this case is acceptable.

3.3 LABELS AND LABELING

Tables 11 and A below include the identified medication error issues with the submitted Prescribing Information (PI), Medication Guide, Instructions for Use (IFU), container labels, carton labeling and packaging, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 11: Identified Issues and Recommendations for Division of Ophthalmology			
	Identified Issue	Rationale for Concern	Recommendation
Prescribing Information- General Issues			
1.	The non-proprietary name suffix is denoted by the placeholder "-xxxx"		Replace "-xxxx" with the conditionally acceptable non-proprietary name suffix when it is determined.
Highlights of Prescribing Information: Dosage and Administration			
1.	There is no direction to follow the Initial Fill Implant Procedure IFU and the Implant Removal Procedure IFU documents while preparing to administer the product.	Clear direction for the user to follow the appropriate IFU is necessary to mitigate the risk of preparation and administration errors.	In the *Dosage and Administration* section of the Highlights, add directions for the user to use the Initial Fill Implant Procedure IFU and the Implant Removal Procedure IFU when preparing to administer or remove the implant.
2.	The incorrect concentration is displayed in the second bullet point e.g., (0.02 mL of 100 mg/mL solution).	The correct product concentration should be displayed for dosing calculations and administration in order to mitigate the risk of dosing error.	Revise "100 mg/mL" to "10 mg/0.1 mL" so that the second bullet point reads: "...(0.02 mL of 10 mg/0.1 mL solution)..."
Highlights of Prescribing Information: Dosage Forms and Strength			
3.	The strength dose not match the strength in the rest of the PI and the container label and carton labeling.	The correct strength should be displayed in order to mitigate the risk for dosing errors.	In the *Dosage Forms and Strengths* section of the highlights, change "100 mg/1 mL" to "10 mg/ 0.1 mL".
Full Prescribing Information: Dosage and Administration			

1.	Section 2.1, (b) (4) .	Revise the title of Section 2.1 to *General Information*.
2.	The sections within Section 2 of the FPI are not in correct numerical order.	Correct the numbering of the sections within Section 2 of the FPI.

Table A: Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Training			
1.	The summative validation testing results revealed that the Retina Specialists/Ophthalmologists, Ophthalmic Surgical Nurses/Technicians, and Retina Specialist Assistants experienced serious use errors on observational task performance and labeling comprehension failures and close calls associated with critical tasks.	These failures would have impacted the PDS system use-safety and potentially cause serious clinical harm to the patient in a "real-world" setting.	We recommend using the findings of the root cause analysis to further develop your training materials, train-the-trainer materials, hands-on practices, and certification (if applicable) program specific to each distinct user group. For example, consider including information on proper use of the tools provided (such as where to grasp) to your training material.
Instructions for Use (IFU) (Initial Fill Implant Procedure/ Implant Removal Procedure) and Medication Guide			
1.	The non-proprietary name suffix is denoted by the placeholder "-xxxx".		Replace "-xxxx" with the conditionally acceptable non-proprietary name suffix when it is determined.
Container Label, Carton Labeling and Packaging			

1.	The format for the expiration date is not defined.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	The non-proprietary name suffix is denoted by the placeholder "-xxxx"		Replace "-xxxx" with the conditionally acceptable non-proprietary name suffix when it is determined.
3.	The net quantity of drug product contained in the vial is not displayed on the container label, carton labeling or the packaging (kit carton).	The net quantity of drug product contained in the vial is not displayed on the appropriate labeling.	Add the net quantity to the PDP of the container label, carton labeling and the packaging (kit carton).
Carton Labeling and Packaging (kit carton)			
1.	We note that the carton labeling and	In September 2018, FDA released draft guidance on	Add the machine-readable 2D data matrix barcode on the carton labeling and packaging .

	packaging (kit carton) do not include a machine-readable 2D data matrix barcode.	product identifiers required under the Drug Supply Chain Security Act.2 The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	

[2] Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act-Questions and Answers. Food and Drug Administration. 2018. Available from https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

4 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated several use errors/close calls/use difficulties with critical tasks that may result in harm. However, the Division of Ophthalmology requested labeling changes in an information request on July 16, 2021 to further mitigate the identified risks. The Applicant responded with additional information and proposed labeling changes on July 22, 2021, and we find their response to be acceptable.

Furthermore, our evaluation of the proposed user interface, proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 11 for the Division and Table A for the Applicant. We ask that the Division convey Table A in its entirety to the Applicant. In addition, we provide our recommendations for the Applicant related to the HF validation study in section 4.1 below. We ask that the Division convey Table A in its entirety to the Applicant so that recommendations are implemented prior to approval of this BLA 761197.

4.1 RECOMMENDATIONS FOR GENENTECH

The results of the human factors (HF) validation study demonstrated several use errors/close calls/use difficulties with critical tasks that may result in harm to the patient. However, the Division of Ophthalmology requested labeling changes in an information request on July 15, 2021 to further mitigate the identified risks. Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table A and we recommend that you implement these recommendations prior to approval of this BLA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Susvimo that Genentech submitted on April 23, 2021.

Table 5. Relevant Product Information	
Initial Approval Date	06/30/2006 – (Lucentis)
Therapeutic Drug Class or New Drug Class	humanized anti-vascular endothelial growth factor (VEGF) Fab
Active Ingredient (Drug or Biologic)	ranibizumab
Indication	Age related macular degeneration
Route of Administration	intravitreal injection
Dosage Form	Injection
Strength	100 mg/mL (10 mg/0.one mL)
Dose and Frequency	Q 24 weeks
Storage	refrigerated at 2º-8ºC (36º-46ºF). DO NOT FREEZE.
Container Closure/Device Constituent	a surgically implanted, refillable intraocular device, ancillary devices for the surgical implantation, initial fill, refill, and explant (if needed) procedures
Intended Users	Retinal specialists
Intended Use Environment	Implanted surgically in an Operating Room (OR) environment Refilled in a clinic environment

APPENDIX B. BACKGROUND INFORMATION

B.one PREVIOUS HF REVIEWS

B.1.1 Methods

On September 3rd, 2021, we searched the L:drive and AIMS using the terms, "ranibizumab" to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified one previous review[1], and we confirmed that our previous recommendations were implemented.

Reference ID: 4870032

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in the HF results report. See Appendix D.

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:

\\CDSESUB1\evsprod\bla761197\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\neovascular-amd\5354-other-stud-rep\hfe-summary-report\hfe-summ-report.pdf

The Clinical Use Observation Report can be accessed in EDR via:

\\CDSESUB1\evsprod\bla761197\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\neovascular-amd\5354-other-stud-rep\clinical-use-observation-report\clinical-use-observation-report.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

The Division of Ophthalmology sent an information request on July 16, 2021 for information relevant to the HF validation study:

> 1. The Human Factors Engineering Summary Report for the Port Delivery System with Ranibizumab describes disease progression as a potential harm if air bubbles are not identified and removed. Please provide data to support this association and using this data, an estimate of the number/size of bubbles which can be retained without having an impact on disease progression.
> 2. The Human Factors Engineering Summary Report for the Port Delivery System with Ranibizumab describes multiple instances in which maintenance of sterile conditions cannot be assured. Please revise the labeling of the outside of the packaging of the Initial Fill Needle, Ocular Implant with Insert Tool Assembly and Refill Needle to clearly advise users that the contents of these cartons must only be opened onto a sterile field.

The Applicant's response is located in the EDR here:
\\CDSESUB1\evsprod\bla761197\0016\m1\us\clinical-resp-fda-req-info-20210722.pdf

We sent an information request for additional information on the Applicant's training program. The Applicant's response is located in the EDR here:

\\CDSESUB1\evsprod\bla761197\0027\m1\us\cmc-response-fda-req-20210913.pdf

APPENDIX F. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[3] along with postmarket medication error data, we reviewed the following Susvimo labels and labeling submitted by Genentech on April 23, 2021.

Type of Label and Labeling	Location Link
Vial Label	\\CDSESUB1\evsprod\bla761197\0003\m1\us\10-mg-vial-label-10233584.pdf
Vial Carton Labeling	\\CDSESUB1\evsprod\bla761197\0003\m1\us\10-mg-vial-carton-10233583.pdf
Kit Carton Labeling	\\CDSESUB1\evsprod\bla761197\0003\m1\us\10-mg-kit-carton-10233586.pdf
Implant Tool Assembly Label	\\CDSESUB1\evsprod\bla761197\0003\m1\us\implant-tool-assembly(b) (4)-label-10233596.pdf
Implant Tool Carton Labeling	\\CDSESUB1\evsprod\bla761197\0003\m1\us\implant-tool-assembly-carton-10233581.pdf
Initial Fill Needle	\\CDSESUB1\evsprod\bla761197\0003\m1\us\initial-fill-needle-(b) (4)-label-10233594.pdf
Initial Fill Carton Labeling	\\CDSESUB1\evsprod\bla761197\0003\m1\us\initial-fill-needle-carton-10233578.pdf
Refill Needle Label	\\CDSESUB1\evsprod\bla761197\0003\m1\us\refill-needle(b) (4)-label-10233593.pdf
Refill Needle Carton Labeling	\\CDSESUB1\evsprod\bla761197\0003\m1\us\refill-needle-carton-10233579.pdf
Implant Removal Tools	\\CDSESUB1\evsprod\bla761197\0003\m1\us\implant-removal-too(b) (4)-label-10233595.pdf
Implant Removal Tool Carton Labeling	\\CDSESUB1\evsprod\bla761197\0003\m1\us\implant-removal-tool-carton-10233577.pdf
USPI	\\CDSESUB1\evsprod\bla761197\0003\m1\us\clean-label-text.doc
Initial Fill IFU	\\CDSESUB1\evsprod\bla761197\0003\m1\us\initial-fill-implant-proc-ifu.doc
Removal IFU	\\CDSESUB1\evsprod\bla761197\0003\m1\us\implant-removal-proc-ifu.doc

[3] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JASON A FLINT
10/08/2021 01:27:38 PM

NASIM N ROOSTA
10/08/2021 05:03:23 PM

OLUWAMUREWA OGUNTIMEIN
10/08/2021 05:09:12 PM

IRENE Z CHAN
10/08/2021 05:49:20 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Date	5/19/2021		
To:	Lois Almoza, Sr. Regulatory Health Project Manager		
Requesting Center/Office:	CDER/OND	**Clinical Review Division:**	DROSM
From	David Wolloscheck, PhD, Chemist OPEQ/OHT3/DHT3C		
Through (Team)	Suzanne Hudak, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Division Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	BLA 761197 , Ranibizumab ICC2100392, ICC2100442 00080659, 00085003		
Recommendation	**Filing Recommendation Date: 5/19/2021** ☐ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☑ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: 8/19/2021 ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☑ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 9/24/2021 ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
David Wolloscheck -S Date: 2021.09.30 14:34:03 -04'00'	Suzanne J. Hudak -S Digitally signed by Suzanne J. Hudak -S Date: 2021.09.30 15:43:01 -04'00'	

FDA

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761197
Sponsor	Genentech, Inc.
Drug/Biologic	Ranibizumab
Indications for Use	Neovascular wet AMD
Device Constituent	Co-Packaged Needles
Related Files	IND 113552 (ICC 1800880, ICCR#00066395)

Review Team		
Lead Device Reviewer	*David Wolloscheck, PhD, Chemist*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
Chemistry	Gang Peng (CDRH/OPEQ/OHT3/DHT3C)	CON2116414 CON2120293
Toxicology	Dr. Tromondae Feaster (CDRH/OSEL/DBP)	CON2116588 CON2120294
Chemistry	Dr. Berk Oktem (CDRH/OSEL/DBCMS)	CON2122623

Important Dates	
Discipline-Specific Review Memos Due	September 10, 2021
Final Lead Device Review Memo Due	September 23, 2021
Interim Due Dates	**Meeting/Due Date**
Filing	5/19/2021
74-Day Letter	July 6, 2021
Mid-Cycle	July 23, 2021
Primary Review	September 23, 2021 (primary reviews); September 26, 2021 (secondary reviews)

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☑ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews	X			Chemical Characterization was found deficient. However, no additional biocompatibility information is needed. See Section 9.5 detail.
Clinical Validation	X			
Human Factors Validation			X	Deferred to DMEPA/CDRH HF consultant (A separate HF ICCR was issued)
Facilities & Quality Systems			X	Deferred to CDRH/OHT1

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

TABLE OF CONTENTS

Reference ID: 4868317

Reference ID: 4868317

3. PURPOSE/BACKGROUND

3.1. Scope

Genentech, Inc. is requesting approval of Ranibizumab. The device constituent of the combination product is a Co-Packaged Needles.

CDER/OND has requested the following consult for review of the device constituent of the combination product:

Please review the needle device constituents for BLA 761197.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

For the needle device constituents:

- Device performance
- Biocompatibility
- Sterilization

This review will not cover the following review areas:

A review of the other device constituents is deferred to OHT 1.

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

The needles were previously reviewed and found approvable under ICC 18008800 and a subsequent design change of the needles was submitted and reviewed under ICCR 00066395 (reviewed by OHT 1). These reviewed were requested by CDER as part of the review of IND 113552 for Phase II and Phase III studies.

3.2.1. Related Files

IND 113552 (ICC18008800 (reviewed by OHT 3) and ICCR 00066395 (reviewed by OHT 1)

3.3. Indications for Use

Combination Product	Indications for Use
Ranibizumab	Neovascular wet AMD
Co-Packaged Needles	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
0003	M2, M3

Reference ID: 4868317

4. DEVICE DESCRIPTION

4.1. Device Description

There are a total of 5 device constituent parts in this BLA submission. These are:

- Ocular Implant / Port Delivery System (PDS)
- Insertion Tool
- Explant Tool
- Initial Fill Needle
- Refill Needle

Of these components, the ocular implant, insertion tool, and explant tool are reviewed by CDRH/OHT1. Hence, these components are outside the scope of this review memorandum. The initial fill needle (IFN) and refill needle (RF) are reviewed by CDRH/OHT3 and are in scope of this review.

The insertion tool and ocular implant are co-packaged together in one single carton and are provided sterilized in a blister pack. The initial fill needle is co-packaged with the drug vial in a separate carton. The needle is individually packaged into a sterile blister as the primary sterile barrier system. The refill/exchange components (a new drug vial and the refill needle) are packaged in two separate cartons with the refill needle being packaged in a sterile blister as the primary sterile barrier system. The implant removal tool is separately supplied in another carton and also placed in a sterile blister. Hence, the initial fill needle and refill needle are packaged separately from the drug product and the sterilization of these device constituents are in scope of this memorandum.

The following descriptions of the IFN and RF were provided by the Sponsor:

Initial Fill Needle

The PDS IFN is used to fill the PDS implant with drug prior to implantation. The IFN is designed to only fill the PDS implant and is not intended for direct intravitreal injection.

The IFN consists of a 34 G (b) (4) *x 1/10-inch stainless steel cannula, Luer body (hub), integrated filter,* (b) (4) *and cap (Figure 2.3-7).* (b) (4)

Figure 2.3-7 Illustration of IFN

During the PDS initial fill and implant procedure, drug is withdrawn from the vial using a commercially available 1 mL Luer lock syringe and filter transfer needle. The transfer needle is then removed and discarded. The IFN is then attached to the filled syringe, primed to remove air, and loaded into the insertion tool carrier to fill the implant with approximately 20 µL drug prior to implant insertion.

Refill Needle

The PDS RFN is designed to simultaneously exchange the contents of the PDS implant reservoir with fresh ranibizumab PDS drug product.

The RFN consists of a 34 G (b) (4) *1/6-inch stainless steel cannula,* (b) (4) *outer cannula sleeve* (b) (4) *, a silicone soft stop (bumper), a fluid collection reservoir tip,* (b) (4) *, a Luer body (hub), integrated filter,* (b) (4) *, and a cap (Figure 2.3-7).* (b) (4)

Figure 2.3-9 Illustration of RFN

The refill-exchange procedure begins with the insertion of the RFN cannula into the implant septum. The RFN is inserted perpendicular to the implant flange surface until the silicone bumper (soft stop) contacts the conjunctiva. The user performs the
refill-exchange procedure using 100 µL of fresh drug from a primed 1 mL Luer lock syringe.

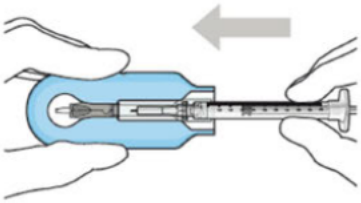
The RFN allows fresh drug to flow through the 34 G (b) (4) *inner, stainless steel cannula and enter the implant. As the new drug is introduced into the implant, the contents of the implant (comprising any remaining drug previously filled and vitreous fluid) are flushed out of the implant* (b) (4) *. Exchanged fluid is collected inside the tip reservoir,* (b) (4) *. The tip reservoir has the capacity to hold approximately* (b) (4) *µL of fluid. The target refill volume is 100 µL. A study demonstrated that increasing the refill volume above 100 µL does not result in an appreciable improvement in refill efficiency, which is defined as the percentage of new drug remaining in the implant after completion of the refill-exchange procedure.*

4.2. Steps for Using the Device

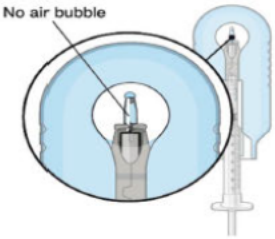
The IFN will be used with a syringe to fill the PDS implant. The refill needle is similarly used with a primed 1 mL Luer lock syringe. It is inserted into the implant and facilitates the exchange of 100 microliter of "fresh" drug.

1. Initial Fill and Implant Insertion Procedure

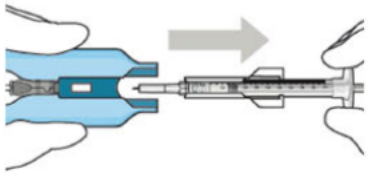
(a) ITA holds the implant and guides the syringe and IFN to target the implant septum during implant filling



(b) Visual confirmation that the implant is filled and does not contain bubbles

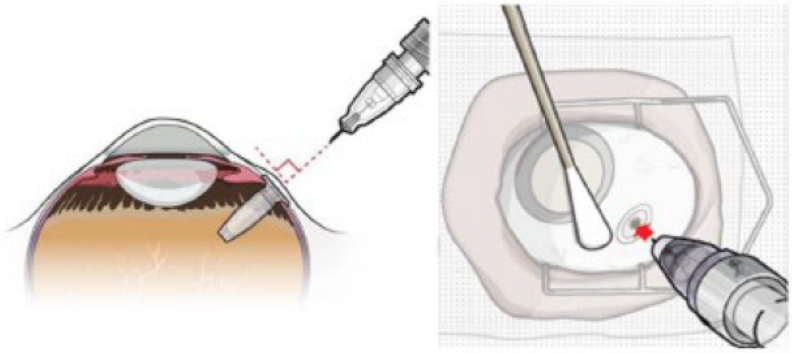


(c) Removal of syringe after filling of the implant



2. Refill-Exchange Procedure

RFN inserted perpendicular to implant flange *in situ* to perform the refill-exchange procedure



4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The Sponsor provided a complete description of the device and how the device operates. The provided information is acceptable.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent:	Date/Sequence Received:
	7/7/2021	7/14/2021 Seq 14
Information Request #1	(b) (4)	

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

	(b) (4)
Reviewer Comments	The response is reviewed under Section 9 (Design verification) of this memo.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent:	**Date/Sequence Received:**
	7/7/2021	**7/14/2021 Seq 14**
Information Request #2	(b) (4)	
Sponsor Response		

Reference ID: 4868317

	(b) (4)
Reviewer Comments	The provided reports are reviewed under Section 9.5 of this memo.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent:	**Date/Sequence Received:**
	7/7/2021	**7/14/2021 Seq 14**
Information Request #3	(b) (4)	
Sponsor Response		

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

	(b) (4)
Reviewer Comments	The Sponsor clarified that drug-device compatibility test included an evaluation of particulates per USP <789>. The following table was taken from 3.2.R.4.3:

Table R.4.3-6 **Product Quality of 100 mg/mL Ranibizumab PDS Drug Product in 1 mL Syringe with IFN at 25°C and 15 min after Priming**

Analytical Procedure	Acceptance Criteria	T=0	3-y Accelerated Aging
Physical State	Liquid	Liquid	Liquid
Color (Ph. Eur. color scale)	Not more colored than (b) (4)	≤B7	≤B7
Clarity/Opalescence (Ph. Eur. opalescent value)	(b) (4)	≤Ref I	≤Ref I
Strength (% change)		0.92% change (100.92 mg/mL)	1.05% change (101.05 mg/mL)
Visible Particles		No visible particles observed	No visible particles observed
Subvisible Particles (light obscuration/microscope)			
>10 µm		2	1
>25 µm		0	0
>50 µm		0	0
pH		5.5	5.5
Purity by SE-HPLC (area%)			
Main Peak		99.9	99.9
Sum of HMW Form		0.1	0.1
Purity by IE-HPLC (area%)			
Main Peak		98.6	98.6
Acidic Region		0.4	0.4
Basic Region		1.0	1.0
Purity by Non-Reduced CE-SDS (%CPA)			
Main Peak		98.4	98.6
Sum of LMW Forms		0.6	0.5
Potency by Bioassay (×10⁴ U/mg)		1.01	0.98

Table R.4.4-6 **Product Quality of 100 mg/mL Ranibizumab PDS Drug Product in 1 mL Syringe Used with the RFN at 25°C and 15 min after Priming**

Analytical Procedure	Acceptance Criteria	T=0	3-y Accelerated Aging
Physical State	Liquid	Liquid	Liquid
Color (Ph. Eur. color scale)	Not more colored than (b) (4)	≤B7	≤B7
Clarity/Opalescence (Ph. Eur. opalescent value)	(b) (4)	≤Ref I	≤Ref I
Strength (% change)		0.90% change (100.90 mg/mL)	1.67% change (101.67 mg/mL)
Visible Particles		No visible particles observed	No visible particles observed
Subvisible Particles (light obscuration/microscope)			
>10 µm		5	15
>25 µm		0	1
>50 µm		0	0
pH		5.5	5.5
Purity by SE-HPLC (area%)			
Main Peak		99.9	99.9
Sum of HMW Form		0.1	0.1
Purity by IE-HPLC (area%)			
Main Peak		98.5	98.0
Acidic Region		0.4	0.5
Basic Region		1.0	1.6
Purity by Non-Reduced CE-SDS (%CPA)			
Main Peak		98.4	98.4
Sum of LMW Forms		0.5	0.6
Potency by Bioassay (×10⁴ U/mg)		1.00	1.04

The results suggest low levels of particulates and conformance USP <789>. This is acceptable.

Response Adequate: ☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent:	**Date/Sequence Received:**
Information Request #4	**7/7/2021**	**7/14/2021 Seq 14**

(b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

	(b) (4)
Reviewer Comments	The provided response is reviewed under Section 9.5 (biocompatibility) of this memo.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent:	**Date/Sequence Received:**
	7/7/2021	**7/14/2021 Seq 14**
Information Request #5	(b) (4)	
Sponsor Response		

	(b) (4)
Reviewer Comments	The response is reviewed under Section 9.4 (Sterilization) of this memo.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

5. FILING REVIEW

CDRH performed Filing Review	☑
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist				
Description		**Present**		
		Yes	**No**	**N/A**
Description of Device Constituent		X		
Device Constituent Labeling		X		
Letters of Authorization		X		
Essential Performance Requirements defined by the application Sponsor		X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing		X	
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)	X		
	Reliability	X		
	Biocompatibility	X		
	Sterility	X		
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors			X
	Shelf Life, Aging and Transportation	X		
	Clinical Validation	X		
	Human Factors Validation	X		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure	X		
	Control Strategy provided for EPRs	X		

Reviewer Comment

An initial review of the file indicates that the majority of the required documentation is present. The Submission includes information regarding the device performance (including design control documentation), biocompatibility, sterilization, and shelf-life. Complete protocols for the in-house developed test methods for the two needles are missing. However, as test results are provided, the missing protocols should not lead to a negative decision regarding the filing of this submission. I am recommending that an IR is issued with the 74-day letter to provide the missing documents.

5.2. Facilities Information

Firm Name:	Genentech SSF
Address:	1 DNA Way, South San Francisco, CA
FEI:	2917293
Responsibilities:	Applicant of BLA for PDS combination product; Design owner of the PDS devices Preparation and primary storage of MCB and WCB.

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☐ Inspection was conducted Click or tap to enter a date. to Click or tap to enter a date.. The inspection covered Choose an item. and was classified Choose an item..

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☑ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☑ A routine surveillance inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm has not been performed.

☐ An inspection is not required because the manufacturing site does not require an inspection at this time given the risk of the combination product.

Firm Name:	Phillips-Medisize, LLC
Address:	409 Technology Dr. West, Menomonie, WI
FEI:	3002919960
Responsibilities:	Manufacturer of the finished, (b) (4) standalone PDS device constituents Device contract manufacturing and supplier

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☑ Inspection was conducted 9/3/2019 to 9/5/2019. The inspection covered medical device QS and was classified NAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

Reference ID: 4868317

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product
Inspection Recommendation: ☐ A choose an item inspection is required because: The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and, A recent medical device inspection of the firm Choose an item. ☑ An inspection is not required because A recent medical device inspection of the firm was acceptable.

Firm Name:	Genentech, Inc (Hillsboro)
Address:	4625 NE Brookwood Parkway, Hillsboro, OR
FEI:	3007232634
Responsibilities:	Co-packaging of drug product vial and IFN Labeling and secondary packaging, finished product identity testing, release of finished drug product.
Inspectional History An analysis of the firm's inspection history over the past 2 years: ☑ Inspection was conducted Click or tap to enter a date. to Click or tap to enter a date.. The inspection covered Choose an item. and was classified Choose an item.. ☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected. ☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product	
Inspection Recommendation: ☐ A choose an item inspection is required because: The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and, A recent medical device inspection of the firm Choose an item. ☑ An inspection is not required because The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.	

5.3. Quality System Documentation Triage Checklist

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☐ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☐ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☐ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☐ Yes ☐ No ☐ UNK

Reference ID: 4868317

Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☐ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☐ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☐ No ☐ UNK
cGMP Risk:	
☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☐ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

Reviewer Comment

A facility review for this submission will be conducted by Alan Gion

5.4. Filing Review Conclusion

FILING REVIEW CONCLUSION

Acceptable for Filing: ☑ Yes ☐ No (Convert to a RTF Memo) ☐ N/A

Facilities Inspection Recommendation:
☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance
☐ No Inspection ☑ N/A

Site(s) needing inspection:

N/A – An evaluation of the facilities is conducted by Alan Gion from OHT1.

Reviewer Comments

The Submission is acceptable for filing. An information request is recommended to provide full verification test reports for the needle tests.

Refuse to File Deficiencies: ☐ Yes ☑ No ☐ N/A

74-Day Letter Deficiencies: ☑ Yes ☐ No ☐ N/A

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors	X (Review deferred to DMEPA and CDRH HF consultant)		
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols	X (MR conditional)		
RF/Wireless Labeling/Symbols			X

(b) (4)

Reviewer Comments

The labeling contains all required elements. A usability review is conducted by DMEPA and CDRH. CDER has consulted a CDRH HF consult separately. Please note that this review is only limited to the initial fill needle (IFN) and refill needle (RFN). Needles do not have a device specific FDA guidance and no particular labeling requirements. The Sponsor included the gauge size and length of the needle in the labeling. A clinical labeling review of the implant is deferred to OHT1 or the relevant CDER review division.

6.2. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The labeling of the two needles contains all required elements. The Sponsor included the full product name, relevant device symbols (i.e., rx only, no reuse, sterile), and the contact information of the manufacturer. A separate usability consult from the CDRH human factors team.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	**X**		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	**X (FMEA)**		

Mitigations are adequate to reduce risk to health	**X**	**X Unclear, individual dFMEAs not provided.**	
Version history demonstrates risk management throughout design / development activities	**X**		
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	**X**		
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 – Applicant stated that commercial needles were modified with a filter.**	
Bioequivalence Study utilized to-be-marketed device			**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**		

Reviewer Comments

The Applicant has not provided a full dFMEA for the two needles. While a risk management report was provided in 3.2.R, no individual dFMEAs were provided for the device constituents. Additionally, it is unclear if the needle with filter has been used during a clinical study before. While the Sponsor stated that the filter component is new for the commercial presentation, an IND was previously filed for this device constituent. Clarification is needed if this presentation has been used clinically before.

(b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4868317

(b) (4)

[redacted]

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	N/A
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	N/A
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	N/A
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Y

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
ISO 7864 ***Sterile hypodermic needles for single use – Requirements and Test Methods***	Y	Y
ISO 9626 ***Stainless steel needle tubing for the manufacture of medical devices – Requirements and test methods***	Y	Y
ISO 80369-7 ***Small-bore connectors for liquids and gases in healthcare applications – Part 7: Connectors for intravascular or hypodermic applications***	Y	Y

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies:	**Mid-Cycle Deficiencies:**	**Final Deficiencies:**

Reference ID: 4868317

☐ Yes ☑ No ☐ N/A	☑ Yes ☐ No ☐ N/A	☐ Yes ☑ No ☐ N/A

Reviewer Comments

The Sponsor demonstrated that the device was developed using design controls. Traceability of design inputs was provided by the Sponsor for both the refill and the initial fill needle. However, some information was found missing in the submission. While the Sponsor provided a risk management plan that references individual FMEAs for the device constituents, the FMEAs were not provided in the submission. Furthermore, it remains unclear if the commercial presentation of the two needles (inclusive of the filter) was used during clinical studies.

Update: An information request was issued to the Sponsor on 8/06/2021 to clarify if the commercial version of the device was used in a clinical study. Please see Section 10 of the memo for additional information.

CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes see IR#7 ☐ No

8. RISK ANALYSIS

8.1. Risk Management Plan

(b) (4)

[redacted]

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

8.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The provided risk management and dFMEA documentation is acceptable. No specific concerns regarding the provided information were identified.		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

(b) (4)

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Initial Fill Needle					
Maximum Glide Force	≤ (b) (4) N	Y, see below	Y, clinical and HF study	Y (accelerated aging done; real-time in progress)	Y (T=0 testing was done after simulated shipping)
Needle Peak Insertion Force into Implant	≤ (b) (4) N	Y, see below	Y, clinical and HF study	Y (accelerated aging done; real-time in progress)	Y (T=0 testing was done after simulated shipping)
Needle Peak Removal Force from Implant	≤ (b) (4) N	Y, see below	Y, clinical and HF study	Y (accelerated aging done; real-time in progress)	Y (T=0 testing was done after simulated shipping)
Refill Needle					
Maximum Glide Force	≤ (b) (4) N	Y, see below	Y, clinical and HF study	Y (accelerated aging done; real-time in progress)	Y (T=0 testing was done after simulated shipping)
Refill Efficiency	≥ (b) (4) %	Y, see below	Unclear: while the specification for refill efficiency is unchanged from the clinical verification, the actual performance of the device is much higher than (b) (4) % (Avg. 104%). This specification should be tightened, or additional validation information is needed. Update: This issue was resolved in response to IR#7.	Y (accelerated aging done; real-time in progress)	Y (T=0 testing was done after simulated shipping)
Needle Peak Insertion Force into Implant	≤ (b) (4) N	Y, see below	Y, clinical and HF study	Y (accelerated aging done; real-time in progress)	Y (T=0 testing was done after simulated shipping)

Needle Peak Removal Force from Implant	≤ (b) (4) N	Y, see below	Y, clinical and HF study	Y (accelerated aging done; real-time in progress)	Y (T=0 testing was done after simulated shipping)

Reviewer Comment

As noted above, the specification for refill efficiency appears very broad and, given that the device performs much closer to 100%, it is unclear how this broad specification is validated through clinical testing. An information request will be sent to the Sponsor to clarify this specification or tighten it (See IR#7). Please see below for a review of the design verification activities.

(b) (4)

16 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: 8/20/2021	Date/Sequence Received: 8/27/2021 Seq. 0022
Information Request #7	(b) (4)	
Sponsor Response		

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

	(b) (4)
Reviewer Comments	The Sponsor stated that the minimum refill efficiency was derived based on the above equation with a minimum drug release of (b) (4) µg/day. This approach appears reasonable overall as the equation accounts for the needle refill performance, implant release performance, and drug concentration. A review of the minimum drug release specification is deferred to the relevant review division(s) in CDER (i.e., clinical pharmacology and clinical). The refill dosage volume was determined based on this analysis. The following study provided in R.4.4 correlates the refill efficiency with the injected drug volume into the implant. The study demonstrates that there was no appreciable difference in the refill efficiency when increasing the injected volume beyond 100 µL. **Table R.4.4-1 Effect of Injected Drug Volume during Refill** Injected Drug Volume (µL) / Refill Efficiency (%)[a] 10 — (b) (4) 20 40 60 80 100 120 [a] The precision requirement for the UV-Vis analytical method is ≤5% RSD. During method validation studies, the actual achieved precision was ≤1.34% RSD; therefore, the measured (b) (4)% refill efficiency is within the experimental error range of the maximum 100% (±1.34%) refill efficiency The final specification (delivered volume ≥ (b) (4) mL and ≤ (b) (4) mL) is based on the accuracy of an ISO compliant syringe (ISO 7886-1) with a target injection volume of 0.1 mL. As shown from the table above, the lower specification limit, (b) (4) µL, ensures a refill efficiency of around (b) (4)%.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

9.3. Discipline Specific Sub-Consulted Review Summary

☐ No Additional Discipline Specific Sub-Consults were requested
☑ The following additional Discipline Specific Sub-Consults were requested:

Discipline-Specific Design Verification / Validation adequately addressed						
Discipline	**Consult needed**			**Consultant**	**Section**	**Adequately Addressed (Y/N/NA)**
	Yes	**No**	**N/A**			
Engineering (Materials, Mechanical, General)						
Biocompatibility	X			Gang Peng (Chemistry), Tromondae Feaster (Toxicology)		
Sterility						
Software / Cybersecurity						
Electrical Safety / EMC						
Human Factors					11	
Clinical						

9.4. STERILIZATION AND PACKAGING

(b) (4)

f

20 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

For these reasons, I believe that the Sponsor has provided sufficient biocompatibility information to support use of the device for the indications stated in the submission. This was confirmed by discussions with OHT1 who came to a similar conclusion during the review of the IND for use of the modified needles in clinical studies. Hence, the Sponsor has ADEQUATELY addressed the biocompatibility of the device.

CDRH sent Deficiencies or Interactive Review Questions to the Sponsor	☑ Yes ☐ No

Discipline: Sterility	**Date Sent:** 7/22/2021	**Date/Sequence Received:** 8/11/2021 Seq. 0019
Information Request #6	(b) (4)	
Sponsor Response		

6 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

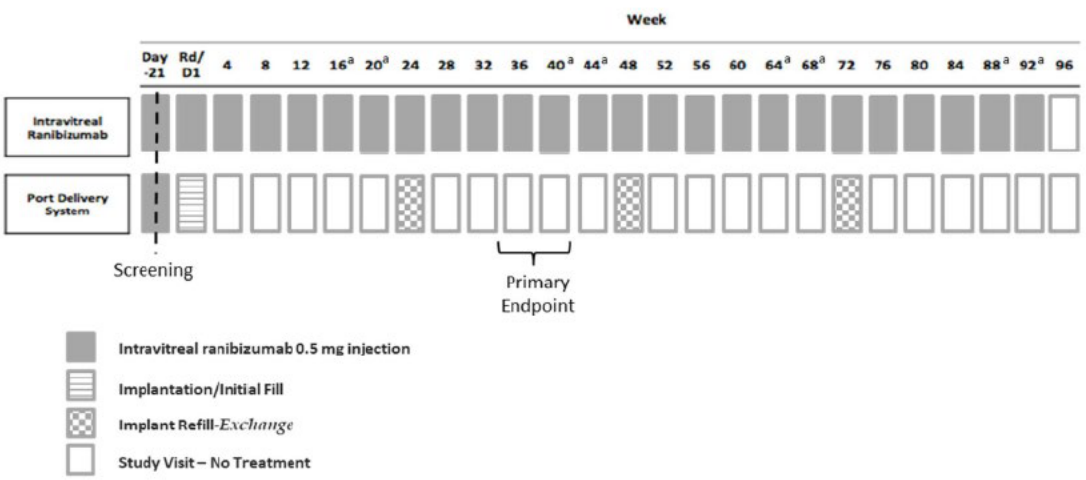
10.CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

☐ There is no device related clinical studies for review
☑ There are clinical studies for review
This information was obtained from the following **documents**:

Study Name	
Study Type	Phase III; Primary Clinical Study Report (CSR) Study GR40548, (Archway): A Phase III, Multicenter, Randomized, Visual Assessor□Masked, Active Comparator Study of the Efficacy, Safety, and Pharmacokinetics of the Port Delivery System with Ranibizumab in Patients with Neovascular Age-Related Macular Degeneration. Report No. 1100486. October, 2020
Objectives/Endpoints	**Primary Efficacy Objective** • To evaluate the non-inferiority and equivalence in efficacy of ranibizumab delivered via the Port Delivery System (PDS) every 24 weeks (Q24W) with the 100 mg/mL formulation compared with that of 10 mg/mL (0.5 mg dose) every 4 weeks (Q4W) intravitreal ranibizumab injections **Secondary Efficacy Objectives** • To evaluate the relative efficacy of ranibizumab delivered via the PDS Q24W with the 100 mg/mL formulation compared with that of 10 mg/mL (0.5 mg dose) Q4W intravitreal ranibizumab injections, as assessed by visual acuity • To evaluate the relative efficacy of ranibizumab delivered via the PDS Q24W with the 100 mg/mL

	formulation compared with that of 10 mg/mL (0.5 mg dose) Q4W intravitreal ranibizumab injections, as assessed by center point thickness (CPT) on spectral domain optical coherence tomography (SD-OCT) • To evaluate the proportion of patients who undergo supplemental treatment with intravitreal ranibizumab 0.5 mg **Safety Objective** • To evaluate the safety and tolerability of ranibizumab, delivered via the PDS Q24W with the 100 mg/mL formulation compared with that of 10 mg/mL (0.5 mg dose) Q4W intravitreal ranibizumab injections **Pharmacokinetic Objective** • To characterize the serum pharmacokinetics of ranibizumab in patients after the initial fill and subsequent refill-exchanges in patients with the PDS **Immunogenicity Objective** • To investigate the formation of serum anti-ranibizumab antibodies **Exploratory Patient Experience Objectives** • To evaluate the preference of patients for ranibizumab delivered via the PDS for 40 weeks compared to intravitreal anti-VEGF treatment received in the 6 months prior to Day 1 • To evaluate patient-reported treatment satisfaction with ranibizumab delivered via the PDS for 40 weeks compared with that of Q4W intravitreal ranibizumab injections, as assessed by the MacTSQ
Drug/Device Studied	0.5 mg / intravitreal / Q4W / 92 weeks Port Delivery System with ranibizumab (PDS)
Number and Type of Subjects	360 planned (216 in the PDS 100 mg/mL arm and 144 in the intravitreal arm); due to a high speed of enrollment combined with a lower screen failure rate than expected, 418 enrolled (251 and 167, respectively).
Brief description of protocol	Study GR40548 (Archway) is an ongoing Phase III, randomized, multicenter, open-label (visual acuity assessor [VAE]–masked), active comparator study designed to assess the efficacy, safety, and pharmacokinetics of ranibizumab 100 mg/mL Q24W delivered via the PDS compared with ranibizumab intravitreal 0.5 mg injections every 4 weeks (Q4W) in patients with neovascular agerelated macular degeneration (nAMD).

	Study Schema 
Results	• The PDS 100 mg/mL Q24W regimen was non-inferior (LL CI > –4.5 letters) and equivalent (LL CI > –4.5 letters and UL CI limit < +4.5 letters) to the intravitreal ranibizumab 0.5 mg Q4W regimen, as measured by the change from baseline in BCVA at the average of Week 36 and Week 40. The difference in adjusted means was -0.3 letters (95.03% CI [–1.7, 1.1]). • The results of the sensitivity analysis, trimmed mean analysis, and supplemental analyses were consistent with the primary efficacy endpoint analysis, supporting the robustness of the primary analysis. • The change in BCVA from baseline in the PDS 100 mg/mL arm was generally similar to the intravitreal arm after Week 8. • Similar proportions of patients in the PDS 100 mg/mL arm and intravitreal arm had BCVA scores of 69 letters or better (and similar proportions had a BCVA score of 38 letters or worse) at the average of Weeks 36 and 40. • Similar proportions of patients in the PDS 100 mg/mL arm and intravitreal arm had and losses of <5 letters, <10 letters and <15 letters or gains of ≥ 0 letters and >15 letters in change from baseline BCVA score at the average of Weeks 36 and 40. • With the PDS 100 mg/mL Q24W regimen, the majority of PDS 100 mg/mL patients, 98.4% did not receive supplemental treatment before the first refill-exchange interval (including 238 patients [96.0%] who had their first refill without supplemental treatment and 6 patients [2.4%] who withdrew from treatment prior to the first refill). • Ranibizumab serum concentrations were maintained within the range experienced with monthly intravitreal ranibizumab 0.5 mg injections. • Overall, the PDS has a favorable benefit-risk profile. The PDS implant insertion surgery and refill-exchange procedure were generally well tolerated by patients. Systemic safety of the PDS was sufficiently characterized through Week 40 and comparable to intravitreal injections of ranibizumab. • The majority (93%) of patients in the PDS arm expressed a preference for PDS treatment over intravitreal treatment, with 74% of patients with a very strong preference.
Device Related Comments	The PDS implant was generally well tolerated. As expected following intraocular surgery, a higher percentage of patients in the PDS 100 mg/mL arm experienced ocular AEs within the postoperative period compared with patients in the intravitreal arm. Most

<table>
<tr><td></td><td>ocular AEs within the postoperative period were mild in severity and surgical complications were thoroughly investigated and well characterized and manageable. Following the postoperative period, a similar incidence of ocular AEs between arms was observed through Week 40. Refill-exchange was well tolerated, with 6.0% of patients
reporting an ocular AE suspected to be related to the first refill-exchange.
The systemic safety profile of the PDS was comparable to intravitreal ranibizumab 0.5 mg Q4W regimen with similar incidence of non-ocular SAEs between arms and no new safety signals.</td></tr>
<tr><td>Reviewer Comments</td><td>The Sponsor stated in the submission that the final commercial version of the needles has not been used in a clinical study. The difference between the clinical version and commercial version of the needles is the addition of a filter in the commercial version. It is to note that the Sponsor has previously agreed to use the commercial version of the device in a clinical study prior to submission of the BLA.

An information request was issued to the Sponsor on 8/06/2021 to clarify if the commercial version of the device was used in a clinical study. The following was provided:

QUESTION 1
Please confirm that the amended quality information data submitted to IND 113552 on April 29, 2021 was implemented (devices used in the clinical studies) prior to the submission of BLA 761197.

ANSWER 1
<table>
<tr><th>Component(s)</th><th>Submission Amendment Reference</th><th>Clinical Distribution Date</th></tr>
<tr><td>Drug Product and Drug Substance</td><td>22-Jan-2021 (Serial No. 0201)</td><td>Feb-2021</td></tr>
<tr><td>Devices: To-Be-Commercialized Initial Fill Needle (IFN) and Refill Needle (RFN)</td><td>12-Feb-2021 (Serial No. 0206)</td><td>To-be-commercialized IFN and RFN were distributed in limited supply to sites to accomplish the clinical observation study that was requested by the Agency (2-Nov-2020 Type C Meeting)</td></tr>
<tr><td>Devices: To-be-Commercialized Devices (all devices)</td><td>29-Apr-2021 (Serial No. 0222)</td><td>To-be-commercialized devices have not been distributed to PDS clinical studies at this time; once supply of the phase III devices is depleted, these devices will be distributed to the ongoing PDS clinical studies.</td></tr>
</table>
Abbreviations: PDS = Port Delivery System with ranibizumab.

Based on this, it appears that the to-be-marketed version of the needles is currently part of the clinical program.</td></tr>
<tr><td>Reviewer Conclusion</td><td>No particular concerns regarding the use of the needles were identified. A review of the clinical data is deferred to the clinical review division.</td></tr>
</table>

10.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The Sponsor clarified that the to-be-marketed version of the device is used in the clinical study. No particular concerns were identified with the device.		
CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA and CDRH HF team. A CDRH HF consult was separately requested and the review is not included in this memo.	☑

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
CDRH Facilities Inspection Review was not conducted. The facilities review is deferred to OHT1.	☑

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☐
CDRH Quality Systems Documentation Review was not conducted. The QS review is deferred to OHT1.	☑

12.3. Control Strategy Review

(b) (4)

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☑ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☑ N/A
Reviewer Comments A facilities/QS desk review is deferred to OHT1.		

CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No

	Date Sent:	**Date/Sequence Received:**
	8/20/2021	**8/27/2021 Seq. 0022**

(b) (4)

[redacted]

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

<<END OF REVIEW>>

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4868317

(b) (4)

14.APPENDIX B (CONSULTANT MEMOS)

14.1. Chemistry Review Memo – Gang Peng

14.2. Toxicology Review Memo – Dr. Tromondae K. Feaster

Reference ID: 4868317

eConsult Cover Sheet

Consult Number: CON2120293

Document Number: BLA761197

Applicant: Genetech

Trade Name: Port Delivery System

Consult Type: Chemistry

Requestor: David Wolloscheck

Requestor Home: CDRH\ OPEQ\OHT3\DHT3c

Gatekeeper / Consultant: Gang Peng

Consultant Home: CDRH\ OPEQ\OHT3\DHT3c

Due Date: 9/10/2021

Instructions: Hi TK/Gang,

Just a heads up that Genentech has submitted a response to your deficiencies. Please see the response document attached. I will assign new consults in CTS shortly. If you identify any issues that would rise to the level of a CR (i.e., not approvable) decision, please let me know as soon as possible.

Thanks,

David

Recommendation: Additional information needs/does not need to be requested from the sponsor.

DEVICE DESCRIPTION

The Port Delivery System with ranibizumab (PDS, also referred to as RPDS) is an innovative drug delivery technology that enables physicians to use a customized formulation of ranibizumab to provide a continuous drug delivery profile. The PDS is a system composed of an intraocular implant (hereafter referred to as the implant), a

Reference ID: 4868317

customized formulation of ranibizumab, and four ancillary devices (insertion tool assembly, initial fill needle, refill needle, and explant tool). The customized formulation of ranibizumab (100 mg/mL) tailored for continuous delivery is provided in a vial.

The PDS implant is a refillable, permanent, intraocular device uniquely designed for continuous delivery of ranibizumab (100 mg/mL). The PDS is designed to maintain therapeutic drug concentrations in the vitreous for longer durations than the available anti-VEGF treatments administered by intravitreal injection. The implant is surgically placed through the pars plana of the eye.

Contact device: permanent/implant tissue and permanent/externally communicating tissue

BACKGROUND/SCOPE

This review is a continuation of previous Agency responses and request. Specifically, on pg 5 of the cmc response fda req 20210714 document, Question 2, the lead reviewer has requested full reports of chemical characterization on the fill needle and refill needle. The associated documents are in attachment 2-2(initial) and 2-4(refill).

SUMMARY OF CONSULTATION

(b) (4)

6 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4868317

Gang Peng -S Digitally signed by Gang Peng -S
Date: 2021.09.10 11:12:40 -04'00'

Reference ID: 4868317

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration

Memorandum

Consult Number:	CON2116588
File Number	ICC2100442
BLA#	BLA761197
Applicant:	Genentech, Inc.
Trade Name:	Port Delivery System with Ranibizumab (PDS)
Consult Type:	Toxicological Risk Assessment
Requestor:	David Wolloscheck [DAVID.WOLLOSCHECK] David.Wolloscheck@fda.hhs.gov
Requestor Home:	CDRH\OHT3\DHT3C\THT3C1
Gatekeeper / Consultant:	Tromondae K. Feaster [TROMONDAE.FEASTER], Caroline Pinto [CAROLINE.PINTO1], Ju Young Park [JUYOUNG.PARK], Alan Hood [ALAN.HOOD] Tromondae.Feaster@fda.hhs.gov; Caroline.Pinto1@fda.hhs.gov; JuYoung.Park@fda.hhs.gov
Consultant Home:	CDRH\ OSEL\ DBCMS, CDRH\ OSEL\ DBP
Date Requested:	July 16, 2021
Due Date:	August 6, 2021
Recommendation(s):	Recommend requesting additional toxicological risk assessment information

SUMMARY

The purpose of this memorandum is to document the outcome of the DBCMS review of the sponsor's toxicological risk assessment report in the document(s) titled "Port Delivery System (PDS) Commercial Accelerated Launch Line (ALL) Design Verification Report: Initial Fill Needle (IFN) Biological Evaluation Report" (Document Number: VAL-0203376, 05-Jan-2021) and "Port Delivery System (PDS) Commercial Accelerated Launch Line (ALL) Design Verification Report: Refill Needle (RFN) Biological Evaluation Report" (Document Number: VAL-0203380, 05-Jan-2021).

SCOPE

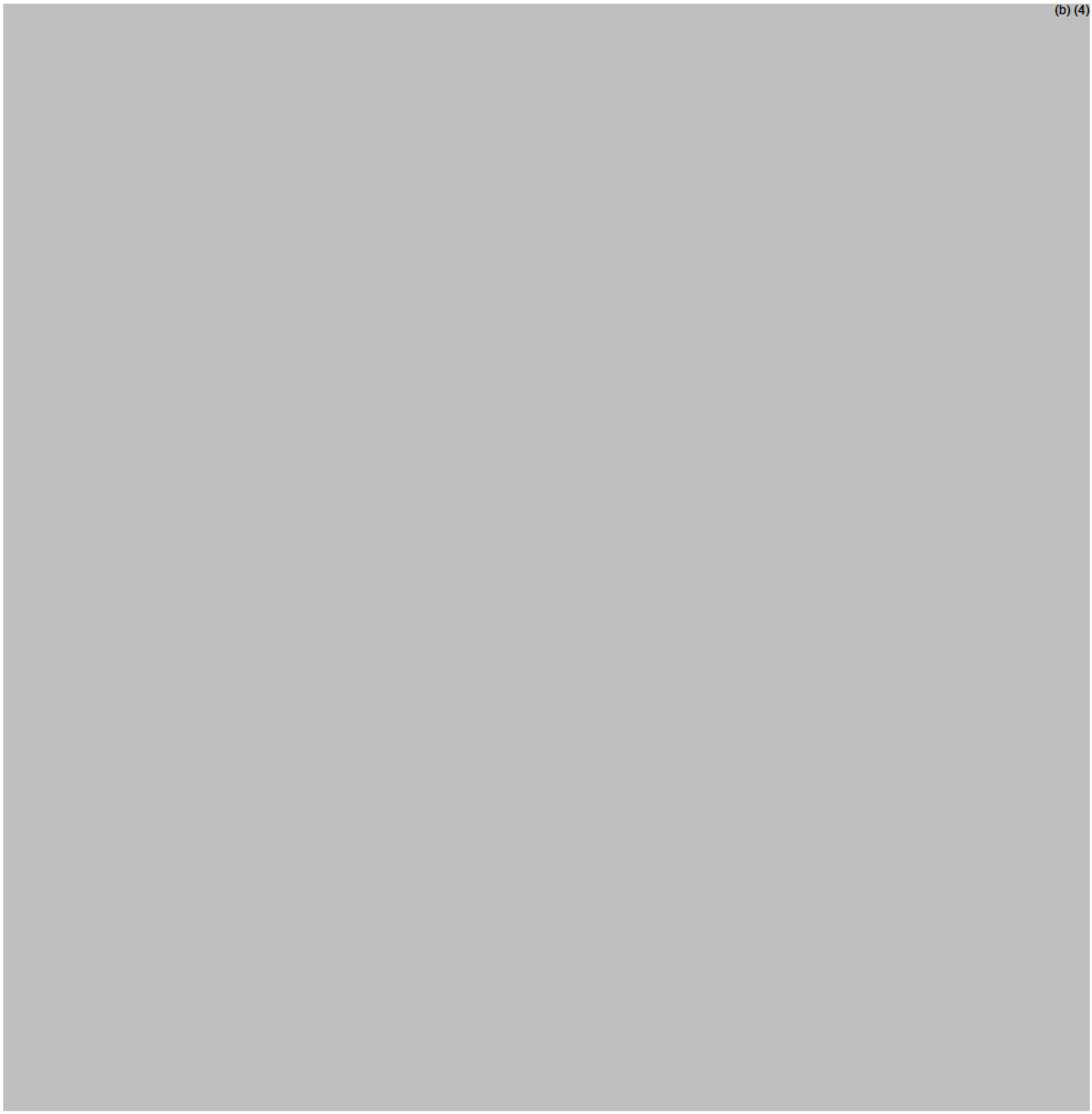
The focus of this consult is the device design change for the commercial PDS configuration (the addition of a filter [redacted (b) (4)]) to the IFN and RFN devices. Specifically, the sponsor conducted a toxicological risk assessment of device extractables to address the acute systemic toxicity endpoint.

DEVICE DESCRIPTION

The sponsor reports the following device description and intended use information for IFN (VAL-0203376) and RFN (VAL-0203380) devices.

7 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4868317



RECOMMENDATIONS

Recommend requesting additional toxicological risk assessment information. Please see deficiency for justification.

SIGNATURE

Tromondae Feaster -S

Digitally signed by Tromondae Feaster -S
Date: 2021.08.09 08:29:00 -04'00'

Tromondae K. Feaster, PhD
Staff Fellow (Pharmacology)
Division of Biomedical Physics
Office of Science and Engineering Laboratories
DBP / OSEL / CDRH / FDA

Caroline L. Pinto -S

Digitally signed by Caroline L. Pinto -S
Date: 2021.08.09 09:31:20 -04'00'

Caroline Pinto, PhD
Staff Fellow
Division of Biology, Chemistry, and Material Science
Office of Science and Engineering Laboratories
DBCMS / OSEL / CDRH / FDA

Ju Young N. Park -S

Digitally signed by Ju Young N. Park -S
Date: 2021.08.09 09:51:50 -04'00'

Ju Young Park, PhD
Staff Fellow (toxicology)
Division of *Biology, Chemistry, and Material Science*
Office of Science and Engineering Laboratories
DBCMS / OSEL / CDRH / FDA

Please note that this toxicology consult review only pertains to the Sponsor's Toxicological Risk Assessment and is based on chemistry information provided by the Sponsor, including accuracy of identification and quantification. I defer to the chemistry consultant (Dr. Gang Peng) to make a determination about the acceptability of this chemical characterization information. Our evaluation of the toxicological risk assessment may not be applicable if the chemistry information is determined to be inadequate.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration

Memorandum

Consult Number:	CON2120294
File Number	ICC2100442
BLA#	BLA761197
Applicant:	Genentech, Inc.
Trade Name:	Port Delivery System with Ranibizumab (PDS)
Consult Type:	Toxicological Risk Assessment
Requestor:	David Wolloscheck [DAVID.WOLLOSCHECK] David.Wolloscheck@fda.hhs.gov
Requestor Home:	CDRH\OHT3\DHT3C\THT3C1
Gatekeeper / Consultant:	Tromondae K. Feaster [TROMONDAE.FEASTER], Caroline Pinto [CAROLINE.PINTO1], Ju Young Park [JUYOUNG.PARK], Alan Hood [ALAN.HOOD] Tromondae.Feaster@fda.hhs.gov; Caroline.Pinto1@fda.hhs.gov; JuYoung.Park@fda.hhs.gov; Alan.Hood@fda.hhs.gov
Consultant Home:	CDRH\ OSEL\ DBCMS, CDRH\ OSEL\ DBP
Date Requested:	August 27, 2021
Due Date:	September 10, 2021
Recommendation(s):	No additional toxicological risk assessment information is requested.

SUMMARY

The purpose of this memorandum is to document the outcome of the DBCMS review of the sponsor's responses to request for Additional Information in Sponsor's submission document (ICC2100442) on the Port Delivery System with Ranibizumab (PDS). Specifically, we reviewed toxicological risk assessment-related question, Question #8. Please refer to the attachment titled PDS_CON2116588_TRA_memo_20210809_Signed.pdf in the email sent to Dr. David Wolloscheck on August 9, 2021 for background information, including device description, materials of construction, device categorization, and previous report from chemical characterization and toxicological risk assessment. In this consult review, no additional information is requested.

FDA REQUESTED FOR ADDITIONAL INFORMATION

(b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4868317

(b) (4)

(b) (4)

RECOMMENDATIONS

(b) (4)

The information provided by the Sponsor in response to FDA's request for additional information is adequate. Therefore, no additional information is requested.

SIGNATURE

Tromondae Feaster -S

Digitally signed by Tromondae Feaster -S
Date: 2021.09.09 08:42:35 -04'00'

Tromondae K. Feaster, PhD
Staff Fellow (Pharmacology)
Division of Biomedical Physics
Office of Science and Engineering Laboratories
DBP / OSEL / CDRH / FDA

Caroline L. Pinto -S

Digitally signed by Caroline L. Pinto -S
Date: 2021.09.09 09:00:58 -04'00'

Caroline Pinto, PhD
Staff Fellow
Division of Biology, Chemistry, and Material Science
Office of Science and Engineering Laboratories
DBCMS / OSEL / CDRH / FDA

Ju Young N. Park -S

Digitally signed by Ju Young N. Park -S
Date: 2021.09.09 09:08:16 -04'00'

Ju Young Park, PhD
Staff Fellow (Toxicology)
Division of *Biology, Chemistry, and Material Science*
Office of Science and Engineering Laboratories
DBCMS / OSEL / CDRH / FDA

Please note that this toxicology consult review only pertains to the Sponsor's Toxicological Risk Assessment and is based on chemistry information provided by the Sponsor, including accuracy of identification and quantification. Our evaluation of the toxicological risk assessment may not be applicable if the chemistry information is determined to be inadequate.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LOIS A ALMOZA
10/06/2021 10:21:17 AM

Memorandum

DATE: September 9, 2021; Amended September 28, 2021

FROM: Claudine H. Krawczyk -S
Digitally signed by Claudine H. Krawczyk -S
Date: 2021.09.28 16:52:13 -04'00'

Claudine Krawczyk
Mechanical Engineer
Glaucoma, Cornea, and Surgical Devices Team
CDRH/OPEQ/OHT1/DHT1A

TO: Record through
ICCR Coordinator: Ms. Damia Jackson

SUBJECT: BLA 761197 (ICC2100385, ICCR# 00079832), Engineering Review
Genentech

DEVICE: Ranibizumab Port Delivery System (PDS)

BACKGROUND:

An Inter Center Consult Request was received on April 27, 2021 with the following information for the request:

Product Information: BLA 761197 Port Delivery System with ranibizumab
Applicant/Sponsor: Genentech, Inc.
Indication for use: To treat neovascular wet AMD
ICCR Request Type(s): Routine (Tier 2)
Consult Expertise/Keywords: Technical Engineering - Delivery device (e.g., autoinjectors, on-body infusion pumps, electroporation devices)
Request Details: We are requesting a CDRH consultative review of BLA 761197 for Port Delivery System with ranibizumab which is a combination product, composed of a biological product (ranibizumab) and five device constituent parts as detailed below.

Link to file: *\\CDSESUB1\evsprod\BLA761197\0003*

ICCR Submitted Date: 4/26/2021
ICCR Due Date: 9/9/2021

Genentech's Ranibizumab Port Delivery System (PDS) is currently under investigation in phase III clinical studies in IND 113552. The product is intended for the treatment of patients with neovascular (wet) age-related macular degeneration. The PDS for intravitreal delivery of

Reference ID: 4865571

ranibizumab consists of an implant, the insertion tool, the initial fill needle (IFN), the refill needle (RFN), and the explant tool.

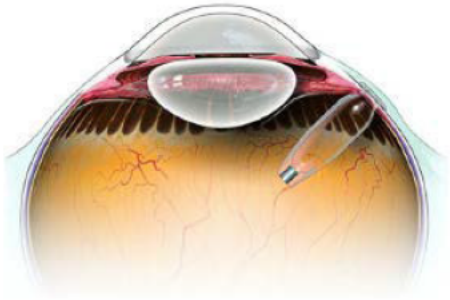
This engineering review will be limited to relevant performance testing for the constituent device components excluding the initial fill needle and refill needle as these will be reviewed by David Wolloscheck.

INDICATIONS FOR USE:

The PDS is intended for the intravitreal delivery of ranibizumab for the treatment of nAMD, (b) (4) .

PRODUCT DESCRIPTION:

The PDS includes ranibizumab (100 mg/mL) sterile drug product for injection and five devices including a permanent implant and ancillary devices used to fill, insert, refill and explant the implant. The implant is a refillable drug reservoir that is inserted into the eye through the pars plana. The implant is secured within the sclera, with an injection port that remains visible through the conjunctiva following insertion. Once filled with ranibizumab, the implant is designed to provide sustained release of ranibizumab. The implant may be refilled with ranibizumab in situ via an injection through the conjunctiva and implant septum. The image below depicts placement of the implant in the eye.



(b) (4)

33 Pages have been Withheld in Full as b4 (CCI/ TS) immediately following this page

Reference ID: 4865571

(b) (4)

CONCLUSION:

Genentech provided this Biologics License Application (BLA) for their Port Delivery System with ranibizumab (PDS). The product has been investigated under IND 113552. CDER has requested CDRH review of the device components and the associated verification testing. This review focuses on the engineering aspects of the device description and verification testing of the implant, insertion tool, and explant tool.

Reference ID: 4865571

Prior engineering review of the device description and verification testing for the implant, insertion tool and explant tool were performed under IND 113552. These prior submissions included verification testing of the device components, all of which was found acceptable. For the relevant device components, engineering conclusions are summarized as follows:

- Implant – My reviews of IND 113552 (SDN unknown) dated January 28, 2019, IND 113552 (SDN 210) dated March 18, 2021, and IND 113552 (SDN 225) dated August 2, 2021, all included review of the implant device description and verification testing (updated as needed with additional shelf-life and/or use-life testing). In both this BLA and IND 113552 (SDN 225), the sponsor refers to the previously submitted verification testing to support the safety and effectiveness of the implant. They also state that minor changes were made to the implant which do not impact the verification testing. However, they do not provide any details of the minor modifications that were made to the implant. Details regarding the modifications were provided in response to an interactive review request of August 6, 2021 under the review of IND 113552 (SDN 225). The information provided regarding modifications to the implant supports reference to the prior testing to verify the clinical performance of the implant. Since the sponsor adequately addressed this concern, prior testing supports a (b) (4) year shelf-life for the implant.

  Note that in my prior reviews of the implant, my reviews were limited to the evaluation of the physical properties of the implant and included evaluation for shelf-life and transport stability. In this review, I was asked to also comment on the information provided regarding the drug release rate of the implant. The sponsor has demonstrated stability of the implant over the proposed use-life in the ocular environment. However, the sponsor has not demonstrated stability of the implant (beyond (b) (4) months) from long-term exposure to the drug product. I defer to CBER and their experience with the drug as to whether they believe long-term exposure of the implant to the drug product will affect the overall effectiveness of the product.

- Insertion Tool Assembly – My reviews of IND 113552 (SDN unknown) dated January 28, 2019, and IND 113552 (SDN 225) dated August 2, 2021, included review of the insertion tool assembly device description and verification testing (updated as needed with additional shelf-life and/or use-life testing). In both this BLA and IND 113552 (SDN 225), the sponsor refers to the previously submitted verification testing to support the safety and effectiveness of the insertion tool assembly. They also state that minor changes were made to the insertion tool assembly which do not impact the verification testing. However, they do not provide any details of the minor modifications that were made to the insertion tool assembly. Details regarding the modifications were provided in response to an interactive review request of August 6, 2021 under the review of IND 113552 (SDN 225). The information provided regarding modifications to the insertion tool assembly supports reference to the prior testing to verify the clinical performance of the insertion tool assembly. Since the sponsor adequately addressed this concern, prior testing supports a (b) (4) year shelf-life for the insertion tool assembly.

- Explant Tool – The most recent review for IND 113552 (SDN 225) dated August 2, 2021 summarizes changes to the explant tool and the verification testing performed to support

Reference ID: 4865571

those modifications. I concluded that, as a manual surgical instrument, little to no performance testing is needed for the explant tool. Regardless, the sponsor provided results of testing that demonstrates that the explant tool remains within acceptable performance parameters following (b) (4) years of aging and simulated shipping.

RECOMMENDATION:

The device description and testing information for the implant, insertion tool assembly and explant tool support marketing approval of these device components to the Ranibizumab Port Delivery System (PDS) from Genentech.

Reference ID: 4865571

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LOIS A ALMOZA
09/30/2021 11:40:58 AM

Memorandum

DATE: July 2, 2021, Updated July 21, 2021, Final September 17, 2021

FROM:
Jennifer N. Brown
Lead Biologist
OHT1/DHT1A/Glaucoma, Cornea & Surgical Devices Team

TO: **The Record through**
ICCR Coordinator: Ms. Damia Jackson

SUBJECT: **ICC2100385 Micro Review**
BLA 761197

DEVICE: **Port Delivery System (PDS) with ranibizumab**

Background:
An Inter Center Consult Request was received on April 27, 2021with the following information for the request:

Product Information: BLA 761197 Port Delivery System with ranibizumab
Applicant/Sponsor: Genentech, Inc.
Indication for use: To treat neovascular wet AMD
ICCR Request Type(s): Routine (Tier 2)
Consult Expertise/Keywords: Technical Engineering - Delivery device (e.g., autoinjectors, on-body infusion pumps, electroporation devices)
Request Details: We are requesting a CDRH consultative review of BLA 761197 for Port Delivery System with ranibizumab which is a combination product, composed of a biological product (ranibizumab) and five device constituent parts as detailed below

Link to file: \\CDSESUB1\evsprod\BLA761197\0003

ICCR Submitted Date: 4/26/2021
ICCR Due Date: 9/16/2021, **Clarified later to be 9/27/21 with supervisor signature**
I'm going to follow-up with the project manager about the five device constituent parts referenced above.

Reference ID: 4860243

Note that we reviewed a consult request in March for an IND from Genentech for their port delivery system with ranibizumab. We provided CDER with sterility, engineering, and material reviews by Claudine, Dan, and Joe.

There were no specifics provided to me as to what was being requested for review from a sterility perspective. Before the planning meeting dated May 19, 2021, an email circulated that indicated David Wolloscheck will be covering the preclinical assessment for the two needles (performance/sterility/biocompatibility). Therefore, this review memo will focus on the sterility-related aspects of the implant, insertion tool and explant tool only.

Of note, the InterCenter Consult Coordinator for OHT1 (Ms. Damia Jackson) mentioned that Dr. Dan Fedorko previously reviewed device components for the PDS system for the IND submission for which the subject device is the same system. However, when I reviewed the memo for the IND, it appears that Dr. Fedorko only reviewed the two needle components for the system. Therefore, it is unclear if a CDRH representative has previously assessed the sterility aspects of the implant, insertion tool, and explant tool, which appears to be covered in Rolling Submission Part 3 for this BLA. My review memo focuses on the sterility related information provided in Part 3 received on April 23, 2021. Note that Parts 1 and 2 did not appear to include any sterility related information for the implant, insertion tool or explant tool.

28 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4860243

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LOIS A ALMOZA
09/21/2021 09:42:09 AM

Memorandum

DATE: September 9, 2021

FROM: Claudine H. Krawczyk -S
Digitally signed by Claudine H. Krawczyk -S
Date: 2021.09.09 08:38:15 -04'00'

Claudine Krawczyk
Mechanical Engineer
Glaucoma, Cornea, and Surgical Devices Team
CDRH/OPEQ/OHT1/DHT1A

TO: Record through
ICCR Coordinator: Ms. Damia Jackson

SUBJECT: BLA 761197 (ICC2100385, ICCR# 00079832), Engineering Review
Genentech

DEVICE: Ranibizumab Port Delivery System (PDS)

BACKGROUND:

An Inter Center Consult Request was received on April 27, 2021 with the following information for the request:

Product Information: BLA 761197 Port Delivery System with ranibizumab
Applicant/Sponsor: Genentech, Inc.
Indication for use: To treat neovascular wet AMD
ICCR Request Type(s): Routine (Tier 2)
Consult Expertise/Keywords: Technical Engineering - Delivery device (e.g., autoinjectors, on-body infusion pumps, electroporation devices)
Request Details: We are requesting a CDRH consultative review of BLA 761197 for Port Delivery System with ranibizumab which is a combination product, composed of a biological product (ranibizumab) and five device constituent parts as detailed below.

Link to file: *\\CDSESUB1\evsprod\BLA761197\0003*

ICCR Submitted Date: 4/26/2021
ICCR Due Date: 9/9/2021

Genentech's Ranibizumab Port Delivery System (PDS) is currently under investigation in phase III clinical studies in IND 113552. The product is intended for the treatment of patients with neovascular (wet) age-related macular degeneration. The PDS for intravitreal delivery of

Reference ID: 4854648

ranibizumab consists of an implant, the insertion tool, the initial fill needle (IFN), the refill needle (RFN), and the explant tool.

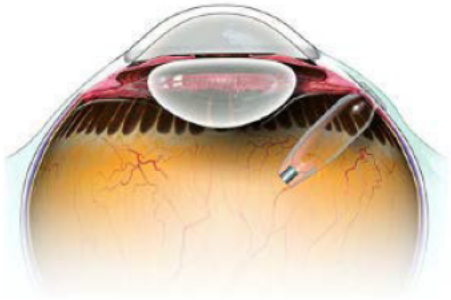
This engineering review will be limited to relevant performance testing for the constituent device components excluding the initial fill needle and refill needle as these will be reviewed by David Wolloscheck.

INDICATIONS FOR USE:

The PDS is intended for the intravitreal delivery of ranibizumab for the treatment of nAMD, (b) (4) .

PRODUCT DESCRIPTION:

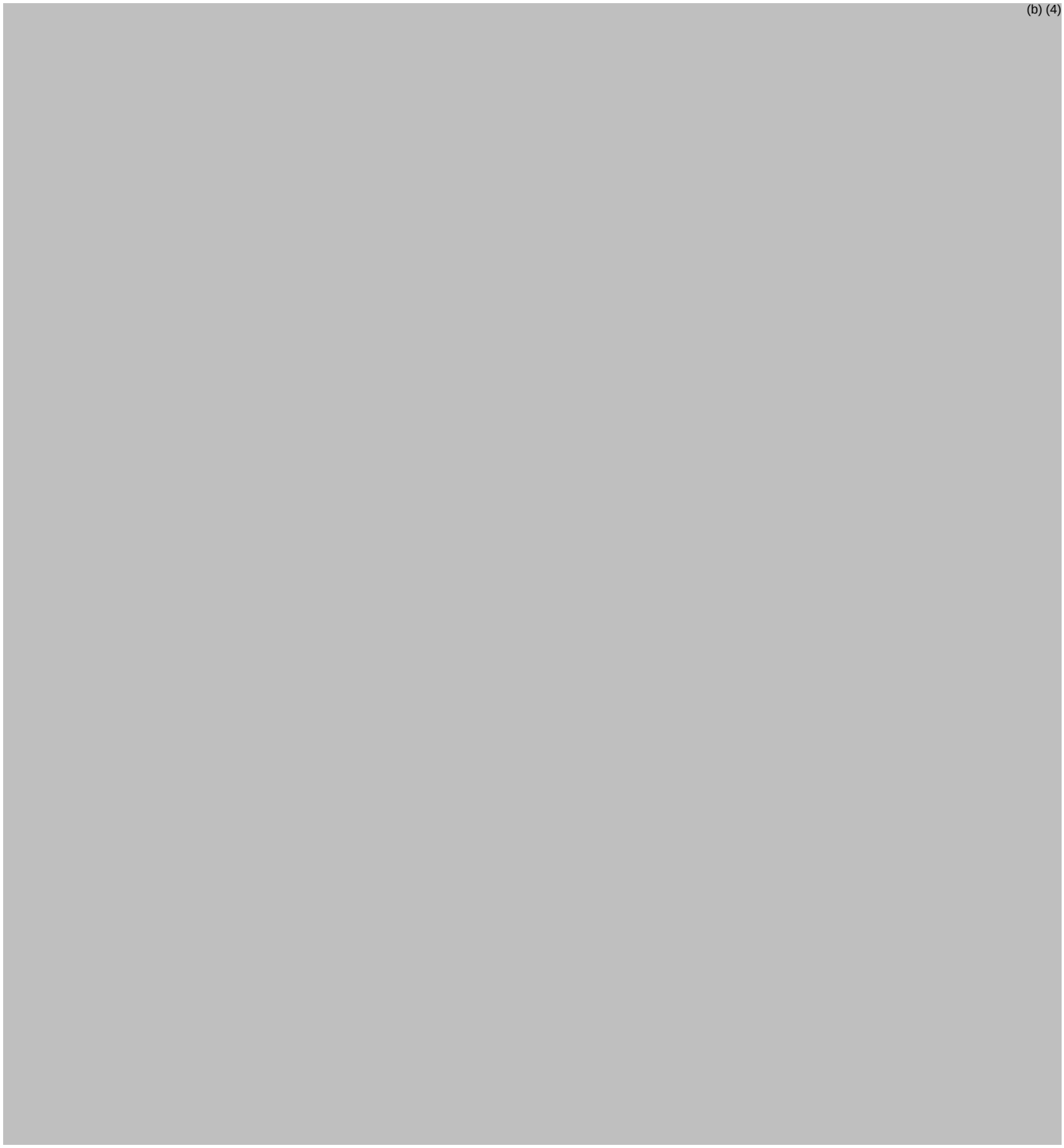
The PDS includes ranibizumab (100 mg/mL) sterile drug product for injection and five devices including a permanent implant and ancillary devices used to fill, insert, refill and explant the implant. The implant is a refillable drug reservoir that is inserted into the eye through the pars plana. The implant is secured within the sclera, with an injection port that remains visible through the conjunctiva following insertion. Once filled with ranibizumab, the implant is designed to provide sustained release of ranibizumab. The implant may be refilled with ranibizumab in situ via an injection through the conjunctiva and implant septum. The image below depicts placement of the implant in the eye.



(b) (4)

34 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4854648



CONCLUSION:

Genentech provided this Biologics License Application (BLA) for their Port Delivery System with ranibizumab (PDS). The product has been investigated under IND 113552. CDER has requested CDRH review of the device components and the associated verification testing. This review focuses on the engineering aspects of the device description and verification testing of the implant, insertion tool, and explant tool.

Reference ID: 4854648

Prior engineering review of the device description and verification testing for the implant, insertion tool and explant tool were performed under IND 113552. These prior submissions included verification testing of the device components, all of which was found acceptable. For the relevant device components, engineering conclusions are summarized as follows:

- Implant – My reviews of IND 113552 (SDN unknown) dated January 28, 2019, IND 113552 (SDN 210) dated March 18, 2021, and IND 113552 (SDN 225) dated August 2, 2021, all included review of the implant device description and verification testing (updated as needed with additional shelf-life and/or use-life testing). In both this BLA and IND 113552 (SDN 225), the sponsor refers to the previously submitted verification testing to support the safety and effectiveness of the implant. They also state that minor changes were made to the implant which do not impact the verification testing. However, they do not provide any details of the minor modifications that were made to the implant. Details regarding the modifications were provided in response to an interactive review request of August 6, 2021 under the review of IND 113552 (SDN 225). The information provided regarding modifications to the implant supports reference to the prior testing to verify the clinical performance of the implant. Since the sponsor adequately addressed this concern, prior testing supports a (b) (4) year shelf-life for the implant.

  Note that in my prior reviews of the implant, my reviews were limited to the evaluation of the physical properties of the implant and included evaluation for shelf-life and transport stability. In this review, I was asked to also comment on the information provided regarding the drug release rate of the implant. The sponsor has not supported the claimed (b) (4) use life of the implant as it relates to the drug release rate. Since it is not possible to simulate fouling of the RCE from the ophthalmic environment and/or drug product over the use-life, I propose a post-approval study to evaluate the long-term effectiveness of the implant for acceptable drug delivery.

- Insertion Tool Assembly – My reviews of IND 113552 (SDN unknown) dated January 28, 2019, and IND 113552 (SDN 225) dated August 2, 2021, included review of the insertion tool assembly device description and verification testing (updated as needed with additional shelf-life and/or use-life testing). In both this BLA and IND 113552 (SDN 225), the sponsor refers to the previously submitted verification testing to support the safety and effectiveness of the insertion tool assembly. They also state that minor changes were made to the insertion tool assembly which do not impact the verification testing. However, they do not provide any details of the minor modifications that were made to the insertion tool assembly. Details regarding the modifications were provided in response to an interactive review request of August 6, 2021 under the review of IND 113552 (SDN 225). The information provided regarding modifications to the insertion tool assembly supports reference to the prior testing to verify the clinical performance of the insertion tool assembly. Since the sponsor adequately addressed this concern, prior testing supports a (b) (4) year shelf-life for the insertion tool assembly.

- Explant Tool – The most recent review for IND 113552 (SDN 225) dated August 2, 2021 summarizes changes to the explant tool and the verification testing performed to support those modifications. I concluded that, as a manual surgical instrument, little to no

Reference ID: 4854648

performance testing is needed for the explant tool. Regardless, the sponsor provided results of testing that demonstrates that the explant tool remains within acceptable performance parameters following (b) (4) years of aging and simulated shipping.

RECOMMENDATION:

The device description and testing information for the implant, insertion tool assembly and explant tool support marketing approval of these device components to the Ranibizumab Port Delivery System (PDS) from Genentech. However, the following condition of approval is recommended:

You propose a (b) (4) year use-life for the implant (Section 6.1.7 of R.4.1, page 27/111). You state in Section 6.1.8.5 of R.4.1 (page 42/111) that the key device attributes that determine drug release over the use-life of the implant are (b) (4) . You also state (page 42/111 of R.4.1) that it is impractical to generate real-time (b) (4) year drug release use-life data due to the length of the study and that accelerated conditions cannot be utilized due to the negative impact on the chemical stability of the drug at elevated temperatures. The verification testing provided establishes acceptable internal volume of the implant, RCE properties and mechanical integrity of the implant (b) (4) . However, these verification tests do not address the implant integrity over the use-life. In Section 6.1.8.5, you attempt to address these same attributes following "exposure to drug product and the intraocular environment" with the following studies:

- Drug Release Characterization of Explanted Implants from Phase II Ladder Clinical Trial (Section 6.1.8.5.3) – You perform in vitro drug release testing of 13 implants that were explanted during Phase II of the clinical study. However, you did not state the use-age of the explanted implants. In Section 6.1.8.5.2, you indicate that the median time of the study was 20.9 months in all PDS-treated patients (range: 0.26-37.52 mo). Assuming the explanted implants were removed over the entire range of the study, any testing of these implants may only support up to (b) (4) years of use-life for the implant. In addition, it is not clear why the incon stencies noted at 8 weeks for 4 of the evaluated implants (31%) attributed to "experimental start-up noise following the in vivo exposure of the implants" (Section 6.1.8.5.3) are considered "exceptions" since the point of the study was to evaluate the implant for changes to the release rates following "in vivo exposure of the implants". These data from explanted implants of unknown use-age are not sufficient to support the (b) (4) -year use-life.

- Phase II Use Life Drug Release Design Verification Study (Section 6.1.8.5.1) – You perform in vitro drug release testing of Phase II hydrolytically aged implants (aged to (b) (4) years). Although this testing supports the conclusion that there is no degradation of the physical properties of the RCE over the proposed use-life, this testing in which the implants were hydrolytically aged in phosphate buffered saline (PBS) is not sufficient to demonstrate that "exposure to the drug product

Reference ID: 4854648

and the intraocular environment" over the use-life will not result in fouling of the RCE which could potentially impact the effectiveness of the implant for the proposed (b) (4) year use life.

- Extended Phase III Drug Release Design Verification Study (Section 6.1.8.5.4) – You perform in vitro drug release testing of Phase III implants following (b) (4) months of exposure of the RCE to the drug product. Although this testing supports the conclusion that there is no degradation of the physical properties of the RCE following (b) (4) months exposure to the drug product, this testing fails to account for fouling of the RCE from the intraocular environment and does not support the proposed (b) (4) year use life in terms of the impact on the RCE from long-term exposure to the drug product beyond (b) (4) months.

You have not supported the claimed (b) (4) year use life of the implant as it relates to the drug release rate. We agree that it is not feasible nor possible to simulate fouling of the RCE from the ophthalmic environment and/or drug product over the use-life. Therefore, the long-term effectiveness of the implant for acceptable drug delivery should be confirmed in a post-approval study in which the premarket cohort is followed for the proposed (b) (4) year use-life.

Reference ID: 4854648

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LOIS A ALMOZA
09/09/2021 08:03:09 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES | Public Health Service

Food and Drug Administration

Memorandum

DATE: July 2, 2021, Updated July 21, 2021

FROM: _____
Jennifer N. Brown
Lead Biologist
OHT1/DHT1A/Glaucoma, Cornea & Surgical Devices Team

TO: The Record through
ICCR Coordinator: Ms. Damia Jackson

SUBJECT: ICC2100385 Micro Review
BLA 761197

DEVICE: Port Delivery System (PDS) with ranibizumab

Background:
An Inter Center Consult Request was received on April 27, 2021with the following information for the request:

Product Information: BLA 761197 Port Delivery System with ranibizumab
Applicant/Sponsor: Genentech, Inc.
Indication for use: To treat neovascular wet AMD
ICCR Request Type(s): Routine (Tier 2)
Consult Expertise/Keywords: Technical Engineering - Delivery device (e.g., autoinjectors, on-body infusion pumps, electroporation devices)
Request Details: We are requesting a CDRH consultative review of BLA 761197 for Port Delivery System with ranibizumab which is a combination product, composed of a biological product (ranibizumab) and five device constituent parts as detailed below

Link to file: \\CDSESUB1\evsprod\BLA761197\0003

ICCR Submitted Date: 4/26/2021
ICCR Due Date: 9/16/2021
I'm going to follow-up with the project manager about the five device constituent parts referenced above.

Reference ID: 4829985

Note that we reviewed a consult request in March for an IND from Genentech for their port delivery system with ranibizumab. We provided CDER with sterility, engineering, and material reviews by Claudine, Dan, and Joe.

There were no specifics provided to me as to what was being requested for review from a sterility perspective. Before the planning meeting dated May 19, 2021, an email circulated that indicated David Wolloscheck will be covering the preclinical assessment for the two needles (performance/sterility/biocompatibility). Therefore, this review memo will focus on the sterility-related aspects of the implant, insertion tool and explant tool only.

Of note, the InterCenter Consult Coordinator for OHT1 (Ms. Damia Jackson) mentioned that Dr. Dan Fedorko previously reviewed device components for the PDS system for the IND submission for which the subject device is the same system. However, when I reviewed the memo for the IND, it appears that Dr. Fedorko only reviewed the two needle components for the system. Therefore, it is unclear if a CDRH representative has previously assessed the sterility aspects of the implant, insertion tool, and explant tool, which appears to be covered in Rolling Submission Part 3 for this BLA. My review memo focuses on the sterility related information provided in Part 3 received on April 23, 2021. Note that Parts 1 and 2 did not appear to include any sterility related information for the implant, insertion tool or explant tool.

24 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4829985

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DIANA M WILLARD
07/22/2021 11:48:13 AM
CDRH Consult Review in Response to April 27, 2021 ICCR (ICCR placed in DARRTS May 11, 2021)

U.S. FOOD & DRUG ADMINISTRATION

To: CDER

From: Joseph C. Hutter, Chemical Engineer, CDRH/OPEQ/OHT1/DHT1A/CLDT

Subject: ICCR2100414, IND 113552 Port Deliver System with Ranibizumab, Genentech, Materials Review

Date: 30 June 2021

SCOPE OF REVIEW

The following updated sections (R.4, R.4.1, R.4.2, R.4.5, R.4.9, R.4.10) were reviewed:

Regional (Device)	The following sections were updated to reflect relevant information for the commercial PDS devices: Section R.4 *Devices [Port Delivery System]* Section R.4.1 *Implant* Section R.4.2 *Insertion Tool* Section R.4.5 *Explant Tool* Section R.4.6 *Biocompatibility* Section R.4.8 *Risk Management* Additionally, Section R.4.9 *Initial Fill Needle with Integrated Filter (IFN)* and Section R.4.10 *Refill Needle with Integrated Filter (RFN)* were renumbered in eCTD to Sections R.4.3 and R.4.4, respectively, to replace the previous information for the phase III clinical needles. This renumbering of the eCTD leaves is for life-cycle management, as the phase III clinical needles are no longer manufactured and the commercial needles will be used for future clinical resupply. No changes were made to the content of these sections as part of this renumbering.

Analysis – Most of the significant changes were done to the initial fill and refill needles. The device and implant/explant tools had either none or very minor changes as noted in this

review.

DRUG STABILITY

Analysis- These sections were NOT reviewed, defer to CDER.

P.8.1 STABILITY SUMMARY AND CONCLUSION [RANIBIZUMAB PDS, SOLUTION FOR INJECTION, 100 MG/ML] MANUFACTURING SITE: SOUTH SAN FRANCISCO

Note: Definitions of abbreviations are provided in Subsection 3 *Abbreviations*.

1. OVERVIEW

The ranibizumab for Port Delivery System (ranibizumab PDS) drug product is a liquid formulation, supplied in single-use 2 mL USP/Ph. Eur. glass Type (b) (4) vials containing (b) (4) of ranibizumab. The drug product is formulated as 100 mg/mL ranibizumab in (b) (4) histidine HCl, 240 mM sucrose, 0.01% (w/v) polysorbate 20, pH 5.5.

Data supporting the drug product shelf life are described in Subsection 2 *Results from Stability Studies*.

The long-term storage is tested at 5°C (5°C±3°C) and accelerated stability studies are tested at 30°C (30°C±2°C [65% RH±5% RH]) or at 25°C (25°C ±2°C [60% RH±5% RH]). In this section, these temperatures will be indicated as 5°C, 30°C, and 25°C, respectively.

Table P.8.1-1 lists the drug product batches used to monitor stability and their respective studies.

Table P.3.2-1 Batch Formula for 100 mg/mL Ranibizumab PDS Drug Product

Ingredients	Nominal Amount per Vial	Nominal Amount per 1 L
Ranibizumab	10 mg	100 g
(b) (4) Histidine HCl		(b) (4)
		(b) (4)
Sucrose	8.2 mg	82.2 g
Polysorbate 20	0.01 mg	0.1 g
Water		(b) (4)

DESIGN VERIFICATION

INITIAL FILL NEEDLE

42 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

CONCLUSIONS

The proposed changes to the device should not affect performance. Therefore, I recommend that this product can be approved for use. CDER should verify MRI labeling meets CDRH recommendations as per this review when the final labels are available.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DIANA M WILLARD
07/21/2021 02:45:30 PM
CDRH Consult REview in response to April 27, 2021, ICCR (ICCR placed in DARRTS May 11, 2021)

Biocompatibility review
BLA 761197/Susvimo (ranibizumab)

Date: June 22, 2021
To: Lois Almoza and Diana Willard (on detail at CBER), Project Managers
Through: Damia Jackson, GWCPM, Regulatory Project Manager, CDRH/OHT1
From: Simona Bancos, Ph.D., Biologist, OHT1/DHT1A
Sponsor: Genentech, Inc.

Purpose:
I was assigned this ICC to review the biocompatibility information included in BLA 761197.

The current consult contains the biocompatibility review of the implant, insertion tool and explant tool. The other device components (i.e., initial fill needle and refill needle) are reviewed by David Wolloscheck, Ph.D. (CDRH/OHT3).

The biocompatibility assessment provided for the implant, insertion tool, and explant tool is acceptable. There are no biocompatibility concerns regarding these device components.

Indication for Use (IFU)
SUSVIMO (ranibizumab-xxxx) is indicated for the treatment of patients with Neovascular (wet) Age-Related Macular Degeneration (AMD).

Device Description (excerpts from m003 and m3/32-body-data/32-reg-info):
The Port Delivery System with ranibizumab (PDS) is an innovative intraocular drug delivery system that consists of an ocular implant, a customized formulation of ranibizumab (100 mg/mL), and 4 single use ancillary devices used to fill, insert, refill, and explant the implant.

Table 1 Device Components of Port Delivery System with Ranibizumab

Device	Purpose
Implant	To provide continuous delivery of ranibizumab to the eye
Insertion tool	To hold the implant during the initial filling and insertion procedures
Initial fill needle	To fill the implant with ranibizumab prior to implantation
Refill needle	To refill (in situ) the implant with ranibizumab when needed
Explant tool	To surgically remove the implant from the implantation site in the eye when as needed

The PDS is designed to continuously release the customized formulation of ranibizumab into the eye over time. The recommended dose of ranibizumab is 2 mg (0.02 mL of solution) continuously delivered via the implant with refills administered every 24 weeks (approximately 6 months).

Reference ID: 4815149

Ranibizumab is a sterile, clear preservative-free aqueous solution and is the antibody fragment (Fab) of a recombinant humanized monoclonal antibody (rhuMAb) anti-VEGF. It consists of a 214-residue light chain linked by a disulfide bond at its C-terminus to the 231-residue N-terminal segment of the heavy chain.

Implant and insertion tool

The implant is a drug delivery device constructed from (b) (4) polysulfone (b) (4), an (b) (4) silicone septum, and a porous titanium release control element (RCE) (see Figure 1).

Figure 1 Illustration of the Implant

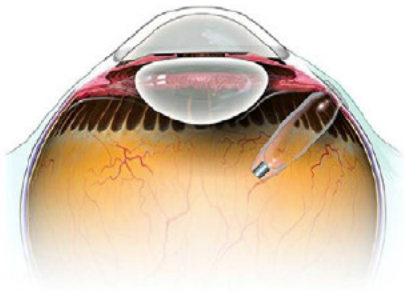
The interior of the device is hollow and is designed to hold approximately 20 µL of Drug Product. The components are (b) (4). The implant is approximately the size of a grain of rice.

Ranibizumab diffuses into the vitreous through the distal tip of the device through a porous titanium component (i.e., RCE), which controls the rate of ranibizumab release from the device. The proximal end of the implant resides in the subconjunctival space, with the flange and septum of the device visible through the conjunctiva (see Figure 7).

The implant is designed to be refillable in situ, via an injection through the conjunctiva and through the device septum using the refill needle.

Reference ID: 4815149

Figure 7 Illustration of the Implant after Surgical Placement in the Supero-Temporal Quadrant of the Eye



Note: Relative scale of the eye and implant are approximate.

23 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4815149

Summary and conclusion:

I was asked to evaluate the biocompatibility of the implant, insertion tool and explant tool device components of Port Delivery System with ranibizumab (PDS).

- The implant is a permanent (>30 days) implant in contact with tissue. The implant is manufactured of polysulfone, silicone (b) (4), titanium and (b) (4). The manufacturing process of the commercial version of the implant differs from the manufacturing procedures used for Phase 2 and 3 implants due to use of (b) (4). The sponsor performed analytical chemistry on Phase 2 and commercial version of the device which demonstrated that the chemical profile of the 2 versions is very similar and that there are no new/higher levels of extractables identified in the commercial version vs. Phase 2 device version. Therefore, the biocompatibility testing performed on Phase 2 device version is applicable to the commercial version of the device.

  Per ISO 10993-1, the implant was tested for cytotoxicity (ISO MEM Elution), sensitization (guinea pig maximization), ocular irritation (intravitreal injection), intramuscular implantation, subchronic toxicity and local toxicity (6-mo ocular implantation), and genotoxicity (Ames assay and mouse lymphoma assay). In addition, the acute systemic toxicity and carcinogenicity were assessed via analytical

Reference ID: 4815149

chemistry which identified low levels of extractables (up to (b) (4) µg/device). These low levels are unlikely to lead to local and systemic toxicity, and carcinogenicity.

The implant did not induce cytotoxicity, sensitization, irritation, genotoxicity, and local toxicity and was determined that it is unlikely to induce systemic toxicity and carcinogenicity. The biocompatibility assessment including the 6 months. ocular implantation study did not identify safety concerns.

The implant is preloaded onto the insertion tool.

- The insertion tool is an external communicating device with limited (≤24 hrs.) contact with tissue. However, since the implant is preloaded, the insertion tool has permanent contact (>30 days) with the implant. The insertion tool is manufactured of (b) (4), (b) (4). The manufacturing process of the commercial version of the insertion tool differs from the manufacturing procedures used for Phase 3 insertion tool due to updates to the (b) (4). The sponsor had performed analytical chemistry on the commercial version of the insertion tool and identified relatively low level of (b) (4) on the insertion tool. The insertion tool was only tested for cytotoxicity. However, the analytical chemistry performed on the finished sterile implant indicated that (b) (4) is not transferred to the implant. In addition, the analytical chemistry performed on the insertion tool did not identify any extractables. Therefore, since the analytical chemistry testing identified only low levels of (b) (4) and testing on the finished implant did not identify safety concerns, I concluded that the sponsor has addressed the biocompatibility of the insertion tool.

- The explant tool is an external communicating device with limited (≤24 hrs.) contact with tissue. The explant tool is manufactured of stainless steel and (b) (4). There are no changes reported to the commercial version of the explant tool as compared to the explant tool used in Phase 3.

  The explant tool was tested for cytotoxicity (ISO MEM Elution), sensitization (guinea pig maximization), and ocular irritation (intravitreal injection) and indicated that the explant tool does not induce cytotoxicity, sensitization and irritation. The explant tool is used to remove, as needed, the implant from the eye; hence, the contact with tissue is brief and localized. Therefore, it is unlikely that during this short time the explant tool would have systemic exposure. In addition, only the stainless-steel component of the explant tool has tissue contact.

Reference ID: 4815149

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DIANA M WILLARD
06/22/2021 03:44:33 PM
CDRH Biocompatibility Review in Response to May 11, 2021, ICCR