

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218010Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number	218010		
Applicant Name	Glaukos Corporation		
Drug Product Name	iDose® TR (travoprost intraocular implant)		
Dosage Form	Implant		
Proposed Strength(s)	75 mcg		
NDA Classification	Type 3 - New Dosage Form		
Route of Administration	Ophthalmic		
Maximum Daily Dose	(b) (4)		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension		
Drug Product Description	Travoprost Intraocular Implant is comprised of a titanium reservoir with titanium anchor, containing 75 mcg of travoprost drug substance formulated with (b) (4) and preloaded on an inserter		
Co-packaged product information	NA		
Device information	Inserter. CDRH consult was attached in this IQA.		
Storage Temperature/ Conditions	2°C to 25 °C		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Joseph Leginus	Sithamalli Chandramouli
	<i>Drug Product/ Labeling</i>	Milton Sloan	Chunchun Zhang

	<i>Manufacturing</i>	Krishnakali Ghosh	Sateesh Sathigari
	<i>Biopharmaceutics</i>	Debasis Ghosh	Kevin Wei
	<i>Microbiology</i>	David Bateman	Laura Wasil
	<i>Other (specify)</i>	NA	
	<i>RBPM</i>	Shazma Aftab	
	<i>ATL</i>	Chunchun Zhang	
Consults	CDRH		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: The shelf life of 24 months for travoprost intraocular implant is granted when stored at 2°C to 25°C.

b. Additional Comments for Action: NA

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

Satisfactory information and responses have been submitted to support the drug substance, drug product, manufacturing process, biopharmaceutics and quality microbiology aspects.

The product is regulated as a drug and device combination product per the Genus decision. CDRH consults evaluated the device and found adequate on 10/3/2023.

The compliance status of the drug product manufacturing facility, Glaukos Corporation (FEI#3012341472) was determined acceptable based on the most recent pre-approval inspection. OPMA issued an overall recommendation of “approval” on Oct 5, 2023. Therefore, NDA 218010 is recommended Approval from Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Adequate
Manufacturing - Adequate
Biopharmaceutics - Adequate
Microbiology - Adequate

Environmental Assessment: Categorical Exclusion - Adequate

QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments: NA

Comparability Protocols (PACMP): No

Comments: NA

Additional Lifecycle Comments: NA

Application Technical Lead Name and Date: Chunchun Zhang, Ph. D., Oct 30, 2023

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CHAPTER III: ENVIRONMENTAL

[IQA NDA Assessment Guide Reference](#)

R REGIONAL INFORMATION

Environmental

Pursuant to 21 CFR 25.15(d) and 21 CFR 25.31(b), Glaukos Corporation claims a categorical exclusion from the requirement to prepare an Environmental Assessment (EA) or an Environmental Impact Statement (EIS) as the estimated concentration of the substance at the point of entry into the aquatic environment will be below one part per billion. To our knowledge, no extraordinary circumstances exist.

Assessment: **Adequate**

The claim of categorical exclusion is acceptable.

Primary Environmental Assessor Name and Date:

*Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div3/Branch 6*

Secondary Assessor Name and Date (and Secondary Summary, as needed):

*Chunchun Zhang, Ph.D.,
Quality Assessment Lead,
OPQ/ONDP/Div3/Branch 6*

CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Yes	iDose® TR (travoprost (b) (4) implant) 75mcg
Established name(s)	Yes	
Route(s) of administration	Yes	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	No	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

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

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Yes	
Dosage form(s) and route(s) of administration	Yes	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	Yes	
Pharmacological/therapeutic class	Yes	
Chemical name, structural formula, molecular weight	Yes	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)



Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
Available units (e.g., bottles of 100 tablets)	N/A	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant	N/A	

has a warning such as “Do not eat.”		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Yes	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)



Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Yes	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING



Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Yes	
Dosage strength	Yes	
Route of administration	Yes	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	N/A	
"Rx only" displayed on the principal display	Yes	
NDC number	Yes	
Lot number and expiration date	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code		

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	
Medication Guide (if applicable)	Yes	
No text on Ferrule and Cap over seal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: Adequate

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Acceptable pending final review negotiations

Primary Labeling Assessor Name and Date:

Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div3/Branch 6

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Chunchun Zhang, Ph.D.,
Quality Assessment Lead,
OPQ/ONDP/Div3/Branch 6



Milton
Sloan

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Chunchun
Zhang

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	The Applicant submitted an NDA under 505(b)(2) of the FD&C for Travoprost Intraocular Implant, 75 µg for the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or Ocular hypertension (OHT).
NDA Number	218010
Assessment Cycle Number	1
Drug Product Name/ Strength	iDose® TR ¹ (travoprost intraocular implant) 75 mcg
Route of Administration	Ophthalmic
Applicant Name	GLAUKOS Corporation
Therapeutic Classification/ OND Division	Division of Ophthalmology
Listed Drug	NDA 021257
Proposed Indication	Reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension

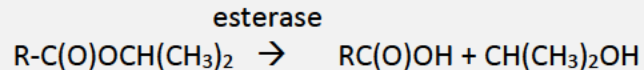
Assessment Recommendation: ADEQUATE

Assessment Summary:

On 22-FEB-2023, the Applicant submitted an original New Drug Application (NDA) under Section 505(b)(2) of FD&C Act seeking marketing approval for Travoprost Intraocular Implant, 75 µg for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension relying on the FDA's previous finding of safety (non-clinical) for the listed drug (LD) Travatan® (travoprost ophthalmic solution) 0.04% which was approved under NDA 021257 on 16-MAR-2001. While the marketing status of the LD is discontinued, based on Drugs@FDA, it was not discontinued for safety or effectiveness reasons.

The drug substance, travoprost, is a clear colorless oil and practically insoluble in water. The proposed product, Travoprost Intraocular Implant (also referenced as G2-TR-125 or G2-TR), is a sterile drug-eluting implant that is surgically delivered through a corneal incision and anchored in the anterior chamber angle of the eye. The implant is comprised of a titanium reservoir which is sealed with an ethylene vinyl acetate (EVA) membrane ((b) (4) and contains (b) (4) vinyl acetate) intended to deliver formulated drug product at a controlled rate for extended period of time for the management of open angle glaucoma or ocular hypertension. In the cornea, travoprost, an isopropyl ester, is converted by esterases to its biologically active free acid.

¹ Conditionally Acceptable by the Agency on 11/26/2019



During the development phase, drug elution method was developed to measure the release of travoprost from the Travoprost Intraocular Implant. The elution profile was measured in aqueous media meant to stimulate physiologically relevant conditions. However, it takes more than (b) (4) to get complete elution using initially developed drug elution method. Nevertheless, using this interim drug elution method, the release rate (not the cumulative release) of the early development as well as pivotal clinical batches were monitored (Day 1-21) for Quality Control (QC) purposes. However, the proposed initial elution method was not practical for routine QC test. Following Agency's recommendation during EOP2 meeting (12/17/2017), the Applicant developed an accelerated drug elution method where complete elution ((b) (4), cumulative) can be accomplished in 10 days (240 hours). The Applicant provided development report including discriminating ability of the method to detect changes to critical bioavailability attributes and validation report including robustness of the method during minor changes to method parameters. The proposed accelerated drug elution method involves the use of gradient elution method (variable ratio of THF/Water) at 50°C. The dissolution profile was generated at 6h, 24h, 72h and 240h (complete elution or (b) (4) time points. The proposed accelerated elution method is not a biorelevant method. However, the proposed method can be used for quality control (QC) purposes (e.g., release of the product, to justify post-approval changes, etc.). The Applicant provided technical report (TR-1134) to demonstrate that the drug elution performance was equivalent in both long-term and accelerated elution studies, regardless of material vendor or minor process changes.

Based on drug elution data from pivotal clinical batches, the Applicant proposed QC acceptance criteria for the proposed accelerated drug elution method. Since accelerated method was developed almost 2 years after the manufacture and release of pivotal clinical batches, the drug elution data of the pivotal clinical batches were originally characterized with initial long drug elution method. Later, aged (18-33 months; stored in long-term storage condition) pivotal clinical batches were characterized by accelerated drug elution method. While we recommend the use of drug elution data from pivotal clinical/biobatches at release, considering the unavailability of the accelerated method at the time of release of the clinical batches, it is acceptable to use the aged samples for setting QC acceptance criteria for accelerated drug elution method because drug elution data of one of the pivotal clinical batches were characterized with different aged samples and the data from that pivotal clinical batch (lot 119435), however, did not show any significant change of elution profile due to aging (approximately 18-33 months at 5°C, Table 3). Therefore, for the proposed product, the risk of using aged samples in lieu of fresh sample is low. The proposed drug elution acceptance criteria (Table 1) are reasonable. We note that all Registration batches and stability batches met the proposed drug elution acceptance criteria.

Table 1. Proposed and Approved QC Accelerated Elution Test Method and Acceptance Criteria

Source	Apparatus	Agitation rate (rpm)	Gradient Elution Media (Volume 1 mL)		Temp. (°C)	Acceptance Criterion
In-House	Air Incubator	20±5	Time Point	Elution Media	50±2	6h: (b) (4) 1 day: (b) (4) 3 Day: (b) (4) 10 Day: (b) (4)
			T=0	5% THF + 0.2 % Tween-20		
			0 hour – 6 hours	5% THF + 0.2 % Tween-20		
			6 hours – 24 hours	10% THF + 0.2 % Tween-20		
			24 hours – 96 hours	15% THF + 0.2 % Tween-20		
			96 hours – 240 hours	20% THF + 0.2 % Tween-20		

The Applicant made number of formulation and process changes during the development and clinical phases. Originally drug substance (an oil) was used in the formulation (b) (4). (b) (4) Later, (b) (4) was added (b) (4). (b) (4). No other formulation change was introduced. While the addition of an (b) (4) in the formulation may require bridging by in vivo studies, the (b) (4) added product was used for Phase 2 clinical trial to assess the safety as well as efficacy (Study#GC-009) whereas non-IND Phase 1 trial was used with no (b) (4) containing product to assess safety only. Therefore, no bridging between Phase 1 and Phase 2 products would be required because the Phase 1 study is not considered as the basis for approval. There are number of process changes noted from Phase 2 to Phase 3 products, however, the risk that the proposed changes may affect the product in vivo performance is low and the bridging between Phase 2 and Phase 3 products is established based on the comparable batch analysis data. The Applicant reported a vendor change for EVA membrane during post-Phase 3 Phase. Since EVA membrane is a critical component of the product performance, any change of EVA vendor would require bridging of Phase 3 and post-Phase 3 products. The Applicant provided a design of Experiment (DOE) study (3.2.P.2 TR-1134) to demonstrate that EVA vendor change and some process changes (b) (4) (b) (4) likely to have no effect on the drug elution characterized by either Real-time drug elution method or accelerated drug elution method (QC). Based on comparative drug elution data provided in the DOE study, the drug elution profile of pre-change (pivotal Phase 3) and post-change (to-be-marketed/post Phase 3) are similar ($f_2 > 50$). In addition, the vinyl acetate specification (b) (4) (b) (4) of previously and newly proposed EVA membranes remain unchanged. Therefore, the proposed change of rate controlling EVA membrane vendor and other minor process changes are not likely to impact the drug release and in vivo performance. We note post-Phase 3 product and to-be-marketed products have the same formulation and both manufactured using the same manufacturing process except some very minor changes in the process. Based on the overall data and information provided in the NDA, the pivotal clinical product and to-be-marketed product formulations are deemed adequately bridged, and no additional data/information is needed. From Biopharmaceutics' perspective, the Application is recommended for approval.

CQAs	Initial Risk Ranking#	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Critical Material Attributes: Vinyl Acetate (VA) content of EVA membrane	Medium	(b) (4)	Low	(b) (4)
	(b) (4)			
	Medium		Low	
	Medium		Low	
	Medium		Low	

#Risk to Drug Elution rate

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Original NDA (SN001)	22-FEB-2023
Amendment – Response to CMC information (SN0014)	03-AUG-2023

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues (list bullet points with key information and update as needed): None

B.1 BCS DESIGNATION

Assessment: NA

BCS classification is not applicable (NA) for Ophthalmic product.

Drug Substance: Travoprost is a clear, colorless to slightly yellow oil. It does not solidify at room temperatures or above (-)50°C.

Solubility:

Travoprost is practically insoluble in water but soluble in most of the organic solvents (alcohol, dichloromethane etc.).

Permeability: NA

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

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Proposed Accelerate Elution Method Parameters:

Item	Parameters												
Apparatus	Air Incubator												
Vessel Size/Type	4.0 mL glass vial												
Agitation Rate	20 ± 5 rpm												
Elution Media	<table border="1"> <thead> <tr> <th>Time Point</th> <th>Elution Media</th> </tr> </thead> <tbody> <tr> <td>T=0</td> <td>5% THF + 0.2 % Tween-20</td> </tr> <tr> <td>0 hour – 6 hours</td> <td>5% THF + 0.2 % Tween-20</td> </tr> <tr> <td>6 hours – 24 hours</td> <td>10% THF + 0.2 % Tween-20</td> </tr> <tr> <td>24 hours – 96 hours</td> <td>15% THF + 0.2 % Tween-20</td> </tr> <tr> <td>96 hours – 240 hours</td> <td>20% THF + 0.2 % Tween-20</td> </tr> </tbody> </table>	Time Point	Elution Media	T=0	5% THF + 0.2 % Tween-20	0 hour – 6 hours	5% THF + 0.2 % Tween-20	6 hours – 24 hours	10% THF + 0.2 % Tween-20	24 hours – 96 hours	15% THF + 0.2 % Tween-20	96 hours – 240 hours	20% THF + 0.2 % Tween-20
	Time Point	Elution Media											
	T=0	5% THF + 0.2 % Tween-20											
	0 hour – 6 hours	5% THF + 0.2 % Tween-20											
	6 hours – 24 hours	10% THF + 0.2 % Tween-20											
	24 hours – 96 hours	15% THF + 0.2 % Tween-20											
96 hours – 240 hours	20% THF + 0.2 % Tween-20												
Elution Media Volume	1.0 mL												
Temperature	50°C ± 2°C												
Pull Volume	(b) (4)												
Sampling Intervals (hours)	2, 6, 24, 48, 72, 96, 168 and 240												

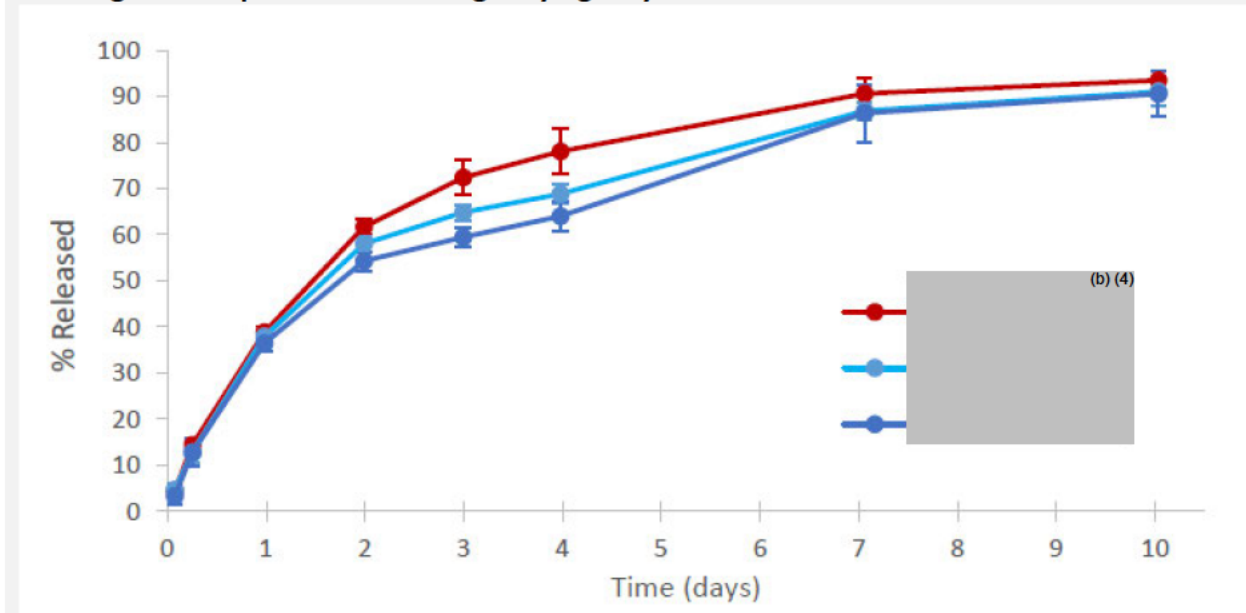
Discriminating Ability of the Proposed Elution Method:

Since EVA membrane controls the rate of elution from the reservoir, the vinyl acetate (VA) content in the EVA membrane (b) (4)

(b) (4) also plays a pivotal role in the elution process.

- **Vinyl Acetate Content:** A study was performed with different vinyl acetate content (b) (4) using the proposed elution method.

Fig 6. Travoprost Elution using varying vinyl acetate content in the EVA membrane



Based on the elution profile, the proposed method appears to differentiate the VA content of EVA membrane at Day 3 and Day 4. However, the differentiation at earlier or later time points are not apparent.

(b) (4)

Robustness of the proposed Elution Method:

Elution robustness was evaluated by changing several elution parameters (temperature, THF concentration, surfactant concentration and agitation rates).

(b) (4)

The result from the robustness study indicated that the method is robust to above changes.

Reviewer’s Comment: ADEQUATE

Based on the information provided in the drug elution development report, the selection of the apparatus, media, volume, incubation temperature, and other parameters were justified. During the development phase, we had concerns regarding the compatibility of EVA membrane in presence of 20%THF plus 0.2%TWEEN 20 at 50°C. While the Applicant provided image analysis at various time points to justify the use of 20%THF, we asked the Applicant to verify the integrity of the EVA membrane as worst case scenario. Since EVA membrane may also undergo a swelling or mass change in presence of 20%THF and (b) (4), a quantitative assessment such as weight change by gravimetric analysis was requested at the pre-NDA stage. The Applicant provided the requested information in the Version 2 of the elution development report.

The VA content in the EVA membrane (b) (4) affect the elution rate of travoprost from the reservoir. The method appears to detect large changes (b) (4) and also changes to VA content (b) (4).

The Applicant demonstrated robustness of the method by changing several elution parameters. The proposed accelerated elution method is not a biorelevant method. However, the proposed method can be used for quality control (QC) purposes (e.g., release of the product, to justify post-approval changes, etc.).

Acceptance Criteria:

The Applicant proposed following accelerated elution (M19382) acceptance criteria in Mod 3.2.P.5.1 Specification:

Test	Test Method	Acceptance Criteria
Accelerated Elution (%)	M19382 (HPLC/UV)	6 Hour: (b) (4) 1 Day: (b) (4) 3 Day: (b) (4) 10 Day: (b) (4) Conforms to L1, L2, or L3 Criteria ^b

^b Criteria as shown is aligned with USP<724> DRUG RELEASE

In the justification of elution acceptance criteria, the Applicant indicated that 4-time point (6h, 1 day, 3 days, 10 days) for elution acceptance criteria were selected based on Agency’s

recommendation. The proposed acceptance criteria are supported by the data from 4 clinical lots and 3 registration lots.

Reviewer's Comment: Adequate

We recommended 6h, 24h, 72h and 240h time points for setting acceptance criteria for accelerated elution of travoprost. We also indicated that the acceptance criteria should be established based on data from pivotal clinical batches. However, no drug elution data from clinical batches are available to assess the proposed acceptance criteria.

Comments communicated to the Applicant on 7/21/23:

Based on your submission, the proposed acceptance criteria for accelerated elution are not adequately justified. As we indicated in our response under IND 120995 meeting minutes (dated 06-29-2020), In absence of in vitro in vivo link, drug release acceptance criteria should be set based on the elution data of the pivotal clinical batches. In Module 2.7.1, you have indicated that "the drug elution rate for the implants used in the Phase 3 clinical trials was characterized with the accelerated elution method. The final proposed specification for drug elution were determined based on the data from the Phase 3 clinical trial batches and registration batches." However, we could not locate elution data for Phase 3 clinical trial materials characterized with the proposed accelerated elution method. In support of the proposed acceptance criteria for the proposed accelerated elution method, provide travoprost elution data for pivotal Phase 3 clinical trial batches characterized with the proposed accelerated elution method. Include drug release data of individual unit, mean and %CV, date of manufacture and test date for each batch tested.

A response was received on 8/3/2023 (SN 0014). The Applicant stated that the pivotal Phase 3 clinical batches of Travoprost Intraocular Implant (lot 103691K and Lot 119435) were manufactured in 2/2018 and 11/2018, respectively. At the time of release of these batches, 21-day elution (Long time elution method) was used because accelerated drug elution method was not available at that time. After the implementation of accelerated elution test method in 9/2020, the batches were tested using accelerated elution test method. The results of the accelerated elution test method are provided in Table 3.

Table 3. Results of the Accelerated Elution Testing for the Pivotal Phase 3 Batches

Lot No. Date of Manufacture Storage condition & Storage condition	Accelerated Elution Rate: Individual, Mean Results (%) and % RSD			
	6 Hour	1 Day	3 Day	10 Day
103691K DOM: 08Feb 2018 5°C/24 months Date of Testing: 05Oct2020 ¹	(b) (4)			
	Meets L1	(b) (4)		
		Meets L1	Meets L1	Meets L1
	(b) (4)			
	Meets L1	(b) (4)		
	Meets L1	Did not meet L1 ^a	Meets L1	
	Mean: 8 % RSD: 45.8	Mean: 38 % RSD: 7.2	Mean: 61 % RSD: 7.1	Mean: 97 % RSD: 3.5
119435 DOM: 20Nov 2018 5°C/18 months Date of Testing: 05Oct2020 ¹	(b) (4)			
	Meets L1	(b) (4)		
		Meets L1	Meets L1	Meets L1
	(b) (4)			
	Meets L1	(b) (4)		
	Meets L1	Meets L1	Meets L1	
	Mean: 10 % RSD: 16.4	Mean: 36 % RSD: 3.4	Mean: 61 % RSD: 5.2	Mean: 92 % RSD: 3.2
119435 DOM: 20Nov 2018 5°C/24 months Date of Testing: 01Mar2021	(b) (4)			
	(b) (4)			
	Meets L1	Meets L1	Meets L1	Meets L1
	(b) (4)			
	Meets L1	Meets L1	Meets L1	Meets L1
	Mean: 13 % RSD: 12.5	Mean: 40 % RSD: 4.1	Mean: 69 % RSD: 3.2	Mean: 99 % RSD: 4.4
119435 DOM: 20Nov 2018 5°C/33 months Date of Testing: 06Dec2021	(b) (4)			
	Meets L1	(b) (4)		
		Meets L1	Meets L1	Did not meet L1 ^a
	(b) (4)			
	Meets L1	(b) (4)		
	Meets L1	Meets L1	Meets L1	
	Mean: 9 % RSD: 21.2	Mean: 38 % RSD: 3.9	Mean: 65 % RSD: 3.2	Mean: 95 % RSD: 5.3

¹ The testing of these two batches at this time point was done under a stand-alone protocol (P38020); subsequent testing for Lot 119435 was done by amending the ongoing stability protocol.

^a With the exception of this data point, all other samples met the L1 requirement; the time point met the USP <724> L2 criteria for 12 units.

The data are generated from two sets of implants with 6 implant each per batch per time point (n=12). The individual variability at 6h time point was found to be higher, however, <10% or low individual variability at all other time points. Lot 103691K was tested with samples from more than 2 years (approximately 32 months) of long-term storage. There is no additional data to compare the trend of elution pattern in this case. We noted 3-Day time point required L2 testing but all other time points passed L1 requirements. Lot 119435 was tested after approximately 23 months, 27 months, and 34 months. No trend was noted during this time period. One of the samples at 10-Day time point did not meet the L1 criteria but met L2 criteria. While drug elution acceptance criteria should be based on clinical batch elution data at release, in absence of any

trend of elution pattern during long-term storage (5°C), the mean values from the batches may be considered for setting drug elution specification. The proposed drug elution specification is acceptable.

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Assessment: NA

The proposed accelerated elution method is intended to be used for QC purposes. Since setting of acceptance criteria for accelerated elution method is based on pivotal clinical batches, it is expected that from QC perspective, the batch-to-batch consistency can be established by the proposed acceptance criteria. However, in absence of additional information, the clinical relevance of the proposed acceptance criteria can't be established.

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: NA

No Quality by Design (QbD) approach is included for dissolution.

B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – In-Vitro Alcohol Dose Dumping

Assessment: NA

Since it is an ophthalmic product, in vitro alcohol dose dumping study is not required.

B.6 IN-VITRO SOFT-FOOD INTERACTION STUDY

Assessment: NA

Since it is an ophthalmic product, in vitro Soft-food interaction study is not required.

B.7 IN-VITRO RELEASE TESTING (IVRT) FOR SEMI-SOLID PRODUCTS

Assessment: NA

Since it is an ophthalmic product, in vitro release testing for semi-solid product is not required.

B.8 IN-VITRO PERMEATION TESTING (IVPT) FOR TRANSDERMAL/TOPICAL PRODUCTS

Assessment: NA

Since it is an ophthalmic product, in vitro permeation testing for transdermal/topical product is not required.

B.9 IN-VITRO DISSOLUTION TESTING FOR ABUSE-DETERRENT PRODUCTS

Assessment: NA

Since it is an ophthalmic product, in vitro dissolution testing for abuse deterrent is not required.

B.10 IN-VITRO BE EVALUATION FOR PULMONARY PRODUCTS

Assessment: NA

Since it is an ophthalmic product, in vitro BE evaluation for pulmonary product is not required.

B.11 EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Assessment: NA

No extended dosage form claim is proposed.

B.12 BRIDGING OF FORMULATIONS

Assessment: Adequate

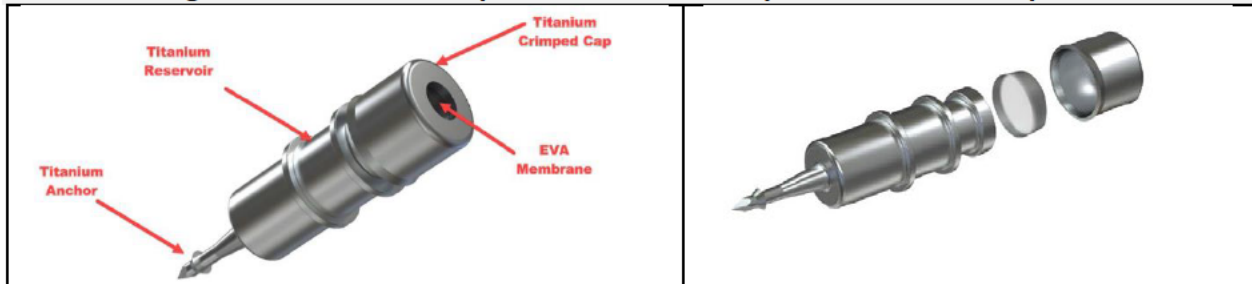
Summary of Formulation changes:

Following tabulated summary of Travoprost formulation history is provided in the submission (3.2.P.2.3):

Lot Number	Lot Size (units)	Lot Use	Manufacturer	Manufacturing Process Changes
72581E2	59	Phase 1/2a Clinical Trial, Stability	(b) (4)	(b) (4)
92631H0	160	Phase 2 Clinical Trial, Stability	(b) (4)	
103691K1 (Glaukos Batch 1)	502	Phase 3 Clinical Trial, Stability	(b) (4)	
119435 (Glaukos Batch 2)	1055	Phase 3 Clinical Trial, Stability	Glaukos	
130524 (Glaukos Batch 3b)	772	Stability (Also used in the non-IND IDOS-402-IVIV clinical trial)	Glaukos	
101698 (Glaukos Batch 4)	1450	Clinical IDOS-106-EXCH (Exchange Trial), Stability	Glaukos	
300723	2360	Registration	Glaukos	
300724	2137			
300725	2404			

The proposed intraocular implant is an anterior chamber implant that elutes travoprost drug product for the treatment of elevated intraocular pressure. The implant is comprised of a titanium reservoir containing approximately 75 µg of travoprost, an ethylene copolymer membrane and titanium cap.

Fig 9. Assembled and Exploded View of Travoprost Intraocular Implant



- Lot 72581E2 was manufactured by using travoprost only. No other inactive ingredient was used with oily API. This batch was used for non-IND clinical trial.
- Lot 92631H0 was manufactured (b) (4) as inactive ingredient and this lot was used for Phase 2 clinical study (GC-009).
- Lot 103691K1 (also known as Glaukos Batch 1) and Lot 119435 (also known as Glaukos Batch 2) were manufactured (b) (4) and manufacturing process were optimized. These lots were used for Phase 3 clinical trials (Study#GC-010, Study#GC012).
- Lot 101698 (also known as Glaukos Batch 4) was manufactured with some process improvement. One of the changes is the EVA (b) (4) supplier (b) (4) (b) (4). This lot was used for post-Phase 3 study (IDOS-106-EXCH; Obj: safety of the exchange of the travoprost implant).
- Registration Lots (to-be-marketed product): Lot 300723, 300724, and 300725 were manufactured using the same process as was used for Lot 101698 with minor process improvements.

Reviewer's Comment: ADEQUATE

- *Phase 1 Vs Phase 2 products:*

During non-IND Phase 1 study, the drug substance (an oil) was used in the formulation (b) (4) (b) (4). Later, (b) (4) was added (b) (4) (b) (4)

(b) (4). No other formulation change was introduced. While the addition of (b) (4) in the formulation may require bridging by in vivo studies, the (b) (4) added product was used for Phase 2 clinical trial to assess the safety as well as efficacy whereas non-IND Phase 1 trial was used with no (b) (4) containing product to assess safety only. Therefore, no bridging between Phase 1 and Phase 2 products would be required because the non-IND Phase 1 trial was not considered as the basis for approval (pivotal clinical study).

- *Phase 2 vs Phase 3 Products:*

Some minor process improvements were introduced for the manufacture of Phase 3 product (3.2.P.2.3 Manufacturing Process Development, Table 9). However, the process improvements (b) (4) is unlikely to have significant effect on the product in vivo performance.

Based on batch analysis data including drug elution data using real-time elution method at release, both Phase 2 and Phase 3 batches complies with all critical quality attributes including

interim real-time elution acceptance criteria (3.2.P.2 manufacturing Process Development – Table 3, 6 and 8). Therefore, considering the low risk of the changes, the bridging between the Phase 2 vs Phase 3 Products is adequately established based on the comparable/acceptable batch analysis data.

- Phase 3 vs post-Phase 3 Products:

During explant/implant phase (also known as post-Phase 3 phase), change of EVA source (b) (4) may have significant impact on the drug release rate. Therefore, a bridging is required. To justify the change, the Applicant indicated that (b) (4) previous and new suppliers have been evaluated against the same (b) (4) specifications² (b) (4), assessed for physicochemical equivalency as well as functional performance using the accelerated and real-time/long term drug elution methods for the finished implant.

A Design-of-Experiment (DOE) study was performed (3.2.P.2 Report#TR-1134) to evaluate the drug elution performance for pre-change (EVA from current supplier (b) (4) and post-change (EVA from new supplier Celanese VitalDose) products. Based on comparative drug elution data provided in the DOE study, the drug elution profile of pre-change (pivotal Phase 3) and post-change (to-be-marketed/post Phase 3) using either long-term or accelerated drug elution methods are similar ($f_2 > 50$).

Table 3. Similarity Factor f_2 values for long term elution profiles

Reference (Lot ID) Sample description	Test Sample (Lot ID) Sample description	f_2	Acceptance Criteria	Verdict
(1) (b) (4)-006	(2) (b) (4)006	(b) (4)	$f_2 > 50$	Similar
	(3) 006			Similar
	(4) 006			Similar
	(5) VitalDose (b) (4)083			Similar
	(6) VitalDose-083			Similar
	(7) VitalDose-083			Similar
	(8) VitalDose-083			Similar
	(9) VitalDose-086			Similar
	(10) VitalDose-086			Similar
	(11) VitalDose-086			Similar
	(12) VitalDose-086			Similar
	(13) VitalDose-084			Similar

² See 3.2.P.2 Manufacturing Process Development Table 21 for Comparison of the Physical and Chemical Properties of the (b) (4) and Celanese VitalDose EVA (b) (4)

Table 4. Similarity Factor f2 values for accelerated elution profiles

Reference (Lot ID) Sample description	Test Sample (Lot ID) Sample description	f ₂	Acceptance Criteria	Verdict
(1) (b) (4) 006	(2) (b) (4) 006	(b) (4)	f ₂ > 50	Similar
	(3) 006			Similar
	(4) 006			Similar
	(5) VitalDose (b) (4) 83			Similar
	(6) VitalDose- 83			Similar
	(7) VitalDose- 83			Similar
	(8) VitalDose- 83			Similar
	(9) VitalDose 86			Similar
	(10) VitalDose 86			Similar
	(11) VitalDose 86			Similar
	(12) VitalDose 86			Similar
	(13) VitalDose 84			Similar

Therefore, the proposed change of rate controlling EVA membrane vendor and other minor process changes are not likely to impact the drug release and no additional bridging data is needed.

- *Post-Phase 3 vs To-be-Marketed Products:*

The proposed to-be-marketed products (Registration lots) were manufactured using the same process and formulation except some minor process improvement (b) (4). Essentially, post-Phase 3 material is similar as the to-be-marketed product. However, the bridging can be established by the release/stability data.

B. 13 BIOWAIVER REQUEST

Assessment: NA

The proposed product is a single strength product. Therefore, no biowaiver request has been submitted.

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: NA

Post-Approval Commitments

Assessment: NA

Lifecycle Management Considerations: NA

BIOPHARMACEUTICS LIST OF DEFICIENCIES: None

Primary Biopharmaceutics Assessor's Name and Date:

Debasis Ghosh, Ph.D.

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Kevin Wei, Ph.D.



Debasis
Ghosh

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Date: 10/19/2023 10:46:11AM
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Kevin
Wei

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CHAPTER VII: MICROBIOLOGY

[IQA NDA Assessment Guide Reference](#)

Product Information	
NDA Number	218010
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Travoprost Intraocular Implant (iDose TR) 75 mcg implant
Route of Administration	Intraocular (Ophthalmic) implant
Applicant Name	Glaukos Corporation (Glaukos)
Therapeutic Classification/ OND Division	Division of Ophthalmology
Manufacturing Site	Glaukos Corporation 229, 236 Avenida Fabricante San Clemente, CA 92672
Method of Sterilization	(b) (4)

Assessment Recommendation: Adequate

Assessment Summary:

The drug product is sealed into trays (b) (4).

List Submissions being assessed (table):

Document(s) Assessed	Date Received
eCTD Seq #0001 (original)	February 22, 2023
eCTD Seq #0003 (Stability data)	March 21, 2023
eCTD Seq #0006 (Response Micro IRs)	April 24, 2023
eCTD Seq #0014 (Response Micro IR)	August 3, 2023

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The drug product is a drug device combination product that is surgically delivered through a clear corneal incision and anchored in the anterior chamber angle of the eye.

Concise Description of Outstanding Issues

(List bullet points with key information and update as needed): None

Supporting Documents: None

P.1 Description of the Composition of the Drug Product

- **Description of drug product:** A sterile drug eluting implant that is surgically delivered through a clear corneal incision and anchored in the anterior chamber angle of the eye. The implant is a drug device combination product with reservoir that is formulated with 75 μg of Travoprost with ethylene vinyl acetate (EVA) membrane, which allow the drug to elute at a controlled rate. An inserter is used to facilitate placement of the implant by a physician. The assembled implant and inserter are placed in a (b) (4) blister tray, sealed with a Tyvek lid (b) (4). The applicant provided the following images of the drug product and inserter (3.2.P.1, SEQ0001, description and composition of the drug product, pages 3, 4):

Figure 1: Assembled View of Travoprost Intraocular Implant



Figure 2: Exploded View of Travoprost Intraocular Implant

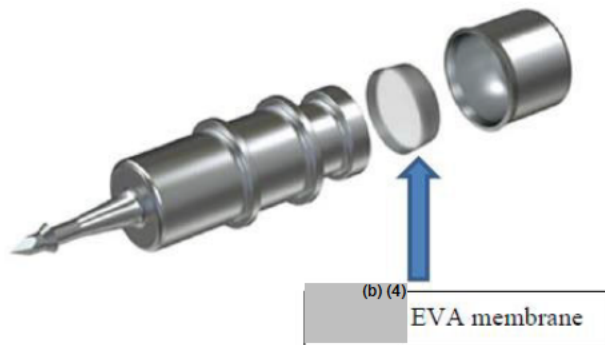
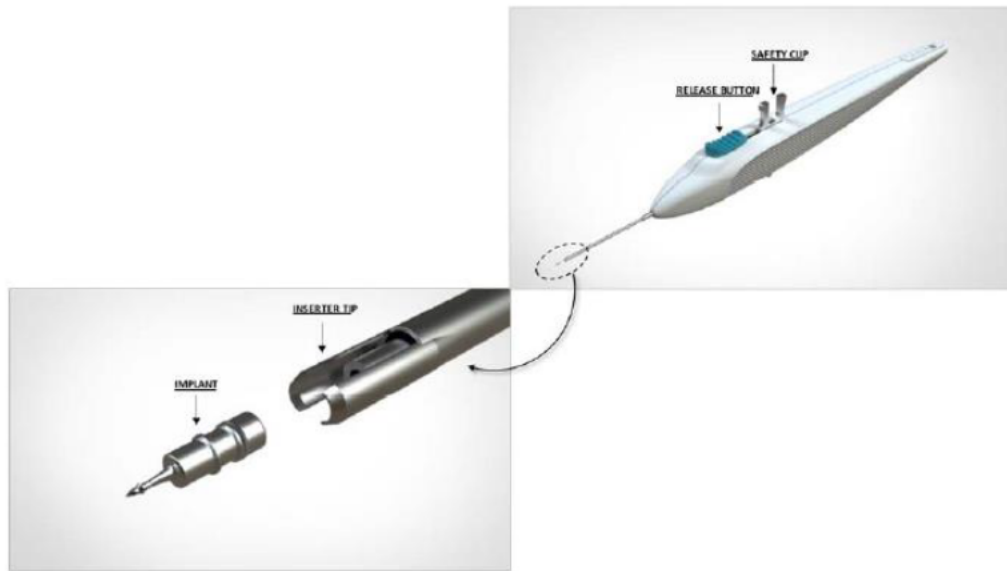


Figure 4: Inserter Loaded with Travoprost Intraocular Implant



- **Drug product composition:**

Ingredient	Content
Travoprost	75 µg/implant

(b) (4)

- **Description of container closure system:** The drug product implant is packaged in a blister tray with Tyvek lid and package in a unit carton. The applicant provided the following diagram of the container closure system (3.2.P.7, SEQ0001, Container closure system, page 7):



(b) (4)

Adequate

Reviewer's Assessment:

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2 Pharmaceutical Development

(b) (4)



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Biocompatibility review
NDA 218010: Travoprost Intraocular Implant, 75 µg (Model G2-TR-125)

To: CDER/OPQ/OPRO/DRBPMI/RBPMB2

Through: Damia Jackson, Regulatory Health Project Manager
CDRH/OHT1

From: Simona Bancos, Ph.D., Biologist,
CDRH/OHT1

Applicant: Glaukos

Recommendation: Approval

I. Purpose:

The current New Drug Application (NDA) was submitted on February 22, 2023 and requests marketing approval for Travoprost Intraocular Implant (TII), 75 µg (Model G2-TR-125) studied under IND 120995. The proposed marketed product is comprised of an implanted titanium reservoir containing the drug formulation and the inserter. TII is preloaded onto the inserter.

I was asked to perform the biocompatibility review of the device components.

II. Indication for Use

Travoprost Intraocular Implant, 75 µg is for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

III. Summary of clinical safety information:

While the sponsor considered 2 models of TII (i.e., Model G2-TR-063 and Model G2-TR-125) that were investigated under one Phase 2 trial (GC-009) and two Phase 3 trials (GC-010 and GC-012), based on the results of the Phase 2 clinical trial, Glaukos selected the Model G2-TR-125, 75 µg as the model for which they request marketing approval. Both models have the same travoprost formulation and composition and are differentiated by the drug release rate (b) (4)

Table 1: Overview of Clinical Trials

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects ^a	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
GC-009	Phase 2 safety and efficacy	Prospective, randomized, double-masked, active-controlled, parallel-group, multicenter trial	G2-TR-063 intraocular implant + placebo eyedrops BID in the study eye G2-TR-125 intraocular implant + placebo eyedrops BID in the study eye Sham surgery + Timolol 0.5% eye drops BID in the study eye	270	Males or females ≥ 18 years of age with OAG or OHT	36 months
US IDOS-106-EXCH	Phase 2 safety of the exchange of a Travoprost Implant	Prospective, open-label, multi-center, single arm study	G2-TR-125 intraocular implant in the study eye	33	Males or females ≥ 18 years of age with OAG or OHT	12 months
GC-010	Phase 3 safety and efficacy	Prospective, randomized, double-masked, active-controlled, parallel-group, multicenter trial	G2-TR-063 intraocular implant + placebo eyedrops BID in the study eye G2-TR-125 intraocular implant + placebo eyedrops BID in the study eye Sham surgery + Timolol 0.5% eye drops BID in the study eye	590	Males or females ≥ 18 years of age with OAG or OHT	36 months (12-Month analysis included in NDA)
GC-012	Phase 3 safety and efficacy	Prospective, randomized, double-masked, active-controlled, parallel-group, multicenter trial	G2-TR-063 intraocular implant + placebo eyedrops BID in the study eye G2-TR-125 intraocular implant + placebo eyedrops BID in the study eye Sham surgery + Timolol 0.5% eye drops BID in the study eye	560	Males or females ≥ 18 years of age with OAG or OHT	36 months (12-Month analysis included in NDA)

^a Intent-to-Treat Population

Timolol 0.5% = Timolol maleate ophthalmic solution USP, 0.5%

BID = twice daily; CSR = Clinical Study Report; N/A = not applicable; OAG = open-angle glaucoma; OHT = ocular hypertension

The two pivotal studies are ongoing and additional safety data will be provided in the 120-day safety update. The sponsor states that the most common ocular adverse reaction reported in the 3 randomized clinical trials was intraocular pressure (IOP) increase (5,5% of subjects). Other adverse events (AEs) reported in 2% - 5% of enrolled subjects were iritis, dry eye, cataract visual field defects, eye pain, conjunctival and ocular hyperemia, and decrease in visual acuity.

Table 10: Most Common Study Eye Adverse Events (Occurring in ≥ 1.0% of Subjects in Any Treatment Group) in the Pooled Population (Safety Analysis Set)

System Organ Class Preferred Term	G2-TR-063 Implant (N=436)	G2-TR-125 Implant (N=432)	Sham/Timolol (N=435)
Subjects with Any TEAEs	158 (36.2)	148 (34.3)	80 (18.4)
Eye disorders	127 (29.1)	124 (28.7)	56 (12.9)
Dry eye	15 (3.4)	12 (2.8)	10 (2.3)

System Organ Class Preferred Term	G2-TR-063 Implant (N=436)	G2-TR-125 Implant (N=432)	Sham/ Timolol (N=435)
Iritis	11 (2.5)	22 (5.1)	0
Conjunctival hyperaemia	11 (2.5)	8 (1.9)	2 (0.5)
Eye pain	9 (2.1)	11 (2.5)	1 (0.2)
Punctate keratitis	9 (2.1)	4 (0.9)	8 (1.8)
Ocular hyperaemia	12 (2.8)	7 (1.6)	1 (0.2)
Visual acuity reduced	5 (1.1)	12 (2.8)	3 (0.7)
Cataract	6 (1.4)	8 (1.9)	3 (0.7)
Conjunctival haemorrhage	6 (1.4)	10 (2.3)	0
Blepharitis	6 (1.4)	5 (1.2)	3 (0.7)
Photophobia	7 (1.6)	6 (1.4)	0
Eye irritation	7 (1.6)	3 (0.7)	2 (0.5)
Vitreous detachment	4 (0.9)	5 (1.2)	2 (0.5)
Conjunctivitis allergic	3 (0.7)	4 (0.9)	3 (0.7)
Eye inflammation	6 (1.4)	3 (0.7)	0
Foreign body sensation in eyes	3 (0.7)	6 (1.4)	0
Anterior chamber cell	2 (0.5)	6 (1.4)	0
Meibomian gland dysfunction	5 (1.1)	3 (0.7)	0
Vision blurred	6 (1.4)	1 (0.2)	0
Investigations	30 (6.9)	19 (4.4)	11 (2.5)
Intraocular pressure increased	29 (6.7)	19 (4.4)	10 (2.3)
Nervous system disorders	10 (2.3)	13 (3.0)	6 (1.4)
Visual field defect	10 (2.3)	13 (3.0)	5 (1.1)
Injury, poisoning and procedural complications	11 (2.5)	9 (2.1)	4 (0.9)
Corneal abrasion	7 (1.6)	3 (0.7)	1 (0.2)
Product issues	6 (1.4)	4 (0.9)	0
Device dislocation	6 (1.4)	4 (0.9)	0

Source: ISS Table 14.3-2.2.2

PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event

Note: If a subject experienced more than 1 TEAE within a SOC (or PT), the subject is counted once under that SOC (or PT). MedDRA dictionary Version 21.0 English is used for coding.

Percentages are based on the number of subjects in each treatment group.

Table 13: Most Common Non-study Eye or Non-ocular Treatment-Emergent Adverse Events (Occurring in $\geq 1.0\%$ of Subjects in Any Treatment Group) in the Pooled Population (Safety Analysis Set)

System Organ Class Preferred Term	G2-TR-063 Implant (N=436)	G2-TR-125 Implant (N=432)	Sham/ Timolol (N=435)
Subjects with Any TEAEs	143 (32.8)	119 (27.5)	123 (28.3)
Infections and infestations	34 (7.8)	29 (6.7)	38 (8.7)
Corona virus infection	9 (2.1)	4 (0.9)	14 (3.2)
Bronchitis	3 (0.7)	4 (0.9)	5 (1.1)
Pneumonia	5 (1.1)	3 (0.7)	2 (0.5)
Sinusitis	5 (1.1)	2 (0.5)	3 (0.7)
Eye disorders	34 (7.8)	25 (5.8)	22 (5.1)
Dry eye	8 (1.8)	2 (0.5)	6 (1.4)
Musculoskeletal and connective tissue disorders	22 (5.0)	13 (3.0)	15 (3.4)
Arthralgia	5 (1.1)	3 (0.7)	1 (0.2)
Metabolism and nutrition disorders	12 (2.8)	13 (3.0)	13 (3.0)
Diabetes mellitus	0	5 (1.2)	3 (0.7)
Vascular disorders	15 (3.4)	8 (1.9)	8 (1.8)
Hypertension	13 (3.0)	6 (1.4)	6 (1.4)
Investigations	8 (1.8)	10 (2.3)	11 (2.5)
Intraocular pressure increased	4 (0.9)	6 (1.4)	6 (1.4)

Source: ISS Table 14.3-2.2.3

AE = adverse event; PT = preferred term; SOC = system organ class; TEAE = treatment emergent adverse event

Note: If a subject experienced more than 1 TEAE within a SOC (or PT), the subject is counted once under that SOC (or PT). MedDRA dictionary Version 21.0 English is used for coding.

Percentages are based on the number of subjects in each treatment group.

The IDOS-106-EXCH trial was conducted to evaluate the exchange of TII in subjects who were previously implanted in the 36-month GC-009 study with either G2-TR-063 or G2-TR-125 models. This study also evaluated the manufacturing changes implemented to TII bridging the outcomes of TII used in Phase 3 clinical trial with the product intended for marketing. This approach was agreed upon with CDER during June 7, 2021 Type C meeting.

Table 11: Study Eye Adverse Events in IDOS-106-EXCH (Safety Analysis Set)

System Organ Class Preferred Term	Study Eye (N=33) n (%)
Subjects with Any TEAEs	13 (39.4)
Eye disorders	8 (24.2)
Eye irritation	2 (6.1)
Corneal pigmentation	1 (3.0)
Diabetic retinopathy	1 (3.0)
Iridodialysis	1 (3.0)
Photophobia	1 (3.0)
Posterior capsule opacification	1 (3.0)
Retinal haemorrhage	1 (3.0)
Retinal vein occlusion	1 (3.0)
Infections and infestations	1 (3.0)
Conjunctivitis viral	0
Hordeolum	1 (3.0)
Injury, poisoning and procedural complications	1 (3.0)
Corneal abrasion	1 (3.0)
Investigations	2 (6.1)
Intraocular pressure increased	2 (6.1)
Nervous system disorders	3 (9.1)
Visual field defect	3 (9.1)

Source: IDOS-106-EXCH Table 14.3-2.2.1

AE = adverse event; PT = preferred term; SOC = system organ class; TEAE = treatment emergent adverse event

Note: Percentages are based on the total number of subjects (N) in the Safety analysis set.

Overall presents the number of subjects with TEAEs occurring in at least one eye.

TEAEs are AEs that occur after initiation of the Exchange surgery.

AEs are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0.

Subjects experiencing more than one TEAE within a given SOC or PT are counted once within that SOC or PT.

SOCs are listed in alphabetical order and PTs within an SOC are listed in descending frequency.

While the sponsor proposes iDose TR as tradename of their product, in this submission the sponsor is also referring to their product as TII, G2-TR, G2TR, G2-TR-125, G2TR-125, and iDose.

IV. Relevant regulatory history (summary provided by the biocompatibility reviewer):

Below are the previous submissions on which I provided biocompatibility recommendations:

- February 26, 2014 - FDA received a meeting package (PIND 120995) containing information regarding the Dose Medical's TII and specific questions for a Pre-IND Type B meeting. The preliminary comments for the meeting were sent to the sponsor on March 20, 2014 and included biocompatibility recommendations regarding the test article preparation for the biocompatibility testing, genotoxicity testing on the finished sterilized device, long-term ocular implantation study, biocompatibility study on the inserter's component that have direct and indirect contact with the patient, and recommendations on additional testing if changes in material composition of the device will be implemented. The biocompatibility consult for this Type B meeting for PIND 120995 is available in [CDRH OPEQ OHT1 DHT1A Team - PIND 120995 Biocompatibility review 3-17-14.pdf - All Documents \(sharepoint.com\)](#).

The type B meeting with the sponsor was held on March 28, 2014. During the meeting, additional discussions were held regarding test article preparation (e.g., FDA recommended that

extractions be performed in both polar and non-polar vehicles and use of (b) (4) that are manufactured of the same materials and underwent the same manufacturing procedure).

- On July 18, 2014, the sponsor submitted a Pre-IND (Type B) meeting request (written response only). The sponsor asked for additional feed-back regarding the pre-clinical testing. Biocompatibility recommendations were sent to CDER on August 27, 2014. We reiterated that (b) (4) should be manufactured from the same material, using the same manufacturing procedure and sterilization process, and the sponsor should perform the leachable and extractions testing using polar, non-polar and the travoprost oil as vehicles, and follow the extraction conditions recommended in International Standard Organization (ISO) 10993-12, Biological evaluation of medical devices, Part-12: Sample preparation and reference materials. The biocompatibility consult for this 60-day meeting is available in [CDRH OPEQ OHT1 DHT1A Team - PIND 120995_Type B Biocompatibility answers.pdf - All Documents \(sharepoint.com\)](#).
- On April 2, 2015, the sponsor submitted a request for pre-IND (Type B meeting) for written responses only. The sponsor requested additional feed-back on biocompatibility, physico-chemical testing and pharmacokinetic (PK) and toxicity testing. Biocompatibility recommendations were conveyed to CDER on May 13, 2015. The sponsor proposed (b) (4). However, detailed recommendations could not be provided as the sponsor did not submit a comprehensive description (b) (4). It appeared that the (b) (4) will not be manufactured using the same materials (titanium and EVA) and same manufacturing procedure and sterilization process as the finished product. Therefore, we recommended that the sponsor provides comparison between the (b) (4) and the finished device, identifying any differences in the material composition, manufacturing process, etc. In addition, we recommended that the sponsor provides a justification on why despite the identified differences the (b) (4) is still acceptable to be used for biocompatibility testing in lieu of the finished implant. The sponsor proposed to change the material composition of the implant from titanium and EVA (b) (4). Therefore, we recommended that they perform biocompatibility on the new finished device. The biocompatibility consult is available in [CDRH OPEQ OHT1 DHT1A Team - PIND 120995 Biocompatibility review May 13 2015.pdf - All Documents \(sharepoint.com\)](#).
- The sponsor submitted an IND to request approval for Phase 2 trial (GC-009) on December 5, 2015. A biocompatibility consult was initially requested by CDER on December 7, 2015. However, subsequently we were informed that a biocompatibility consult is not required as they consider the titanium implant an ophthalmic dispenser. Therefore, the biocompatibility testing provided in the IND 120995 submission in December 2017 was not reviewed by CDRH.
- On September 27, 2017 the sponsor requested an End of Phase 2 (EOP2) Type B Meeting for TII, IND 120995. In my consult I included a note to CDER's project manager/team leader of this submission to indicate that CDRH had not been consulted on IND 120995 submission dated December 5, 2015 (please see the above paragraph) and therefore the biocompatibility consult provided for the type B meeting from 2017 focused on the changes proposed in the EOP2 Type B Meeting. In response to sponsor's questions, I recommended that the sponsor provides justification on why testing performed on the (b) (4) implant is applicable to the (b) (4) (b) (4) implant; provides justification on why change in (b) (4) inserter components do not impact the biocompatibility of the inserter; provides biocompatibility testing on all inserter components with direct and indirect tissue contact; and biocompatibility testing is performed on (b) (4) the finished sterile container. The biocompatibility consult is available in [CDRH OPEQ OHT1 DHT1A Team - IND 120995 Biocompatibility review November 24 2017.pdf - All Documents \(sharepoint.com\)](#)

- On October 17, 2022 the sponsor requested a pre-NDA meeting. The FDA preliminary comments were sent to the sponsor on November 17, 2022 and the sponsor provided their responses to this document on December 1, 2022. The meeting with the sponsor was held on December 8, 2022. In this pre-submission and during the meeting with the sponsor I provided recommendations on the biocompatibility assessment of the implant and delivery device. Briefly, I recommended that in their future NDA the sponsor provides:

- detailed description of the test articles used for biocompatibility assessment of the implant and inserter, how they differ from the finished sterile devices, and why these tests are applicable to the marketed device;
- description of material and manufacturing changes of the device components that were implemented after completion of biocompatibility assessments;
- additional assessment on non-genotoxic carcinogens that may be present in the implant component;
- justification on why analytical chemistry testing methodology used for evaluation of the implant and delivery device are adequate and comparable to analytical chemistry tests that are recommended in relevant device standards (e.g., ISO 10993-18: 2020 “Biological evaluation of medical devices – Part 18: Chemical characterization of medical device materials within a risk management process, American National Standard (ANSI) Z80.27 Implantable Glaucoma Devices, ISO 11979-5, Ophthalmic implants- Intraocular lenses- Part 5: Biocompatibility);
- additional information and justification on the method used for evaluation of particulate testing of the implant.

The sponsor provided a summary of discussion on December 20, 2022.

A summary of prior interactions with the Agency and copies of Agency’s feedback and meeting minutes is provided by the sponsor in [CDSESUB1\evsprod\NDA218010\0001](#)

V. TII description (excerpts from [CDSESUB1\evsprod\NDA218010\0001](#) “container-closure-system”):

TII is a sterile, drug-eluting implant that is surgically delivered through a clear corneal incision and anchored in the anterior chamber (AC) angle of the eye. The implant elutes formulated drug product (travoprost drug substance formulated (b) (4)).

TII is comprised of an implanted titanium reservoir with titanium anchor, containing the drug formulation. The titanium reservoir is sealed with an EVA membrane held in place with a titanium crimp cap. The EVA membrane is (b) (4) and contains (b) (4) vinyl acetate. The EVA membrane, which is in direct contact with the travoprost drug product formulation filled into the titanium reservoir, allows drug to elute through the membrane at a controlled rate. The nominal dimensions of the assembled implant are 1.84 mm long by 0.494 mm in diameter.

Figure 1: Travoprost Intraocular Implant (Assembled View)

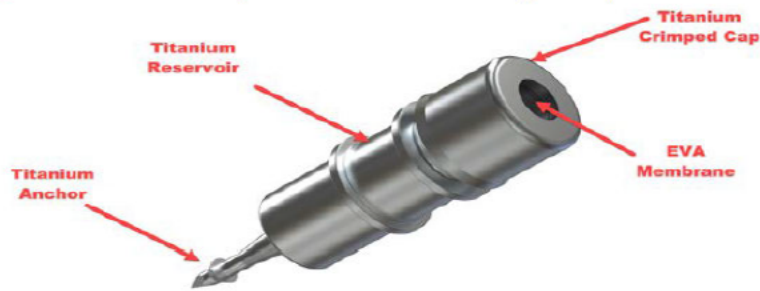


Figure 2: Travoprost Intraocular Implant (Exploded View)

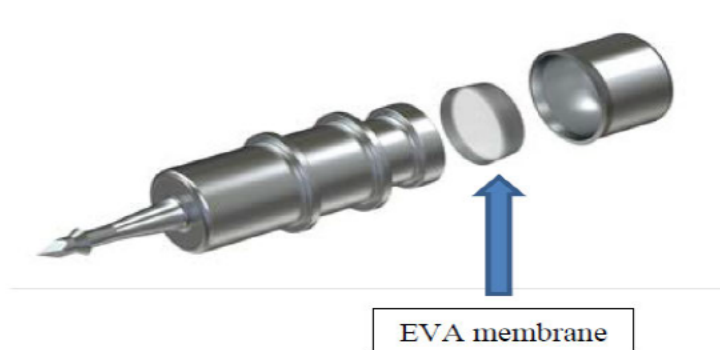
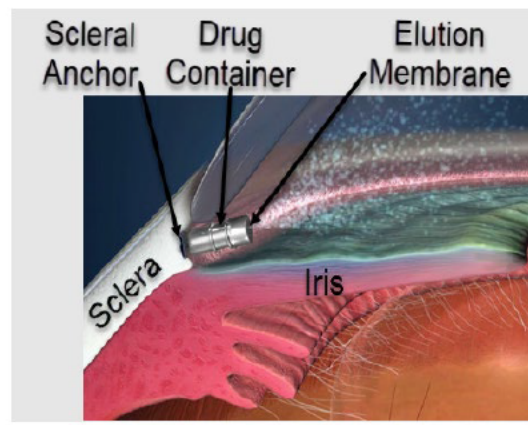
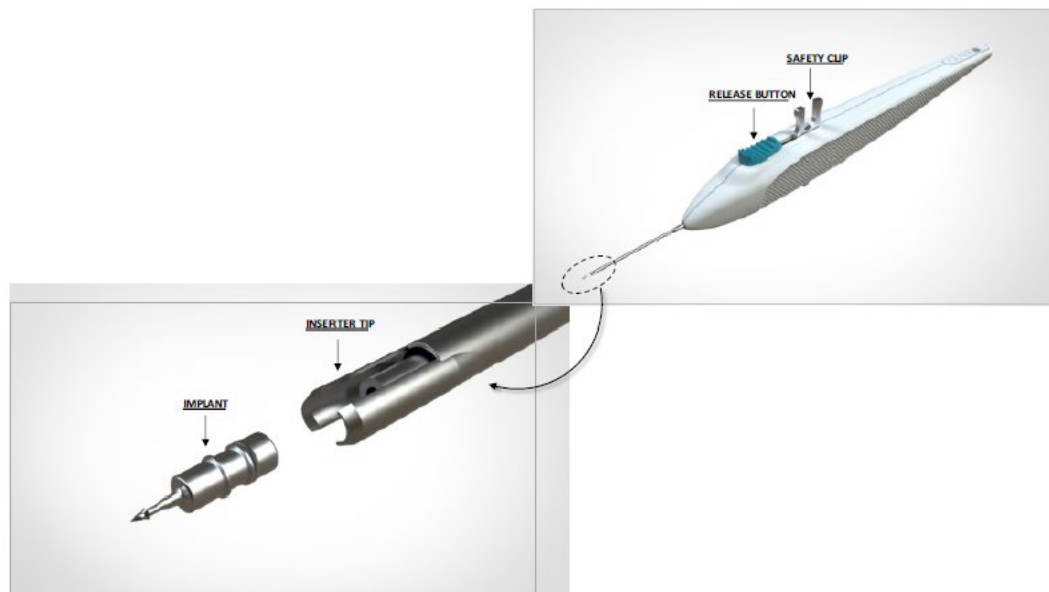


Figure 3. Implant Location in the Eye



The implant filled with the drug product is loaded onto the inserter. The inserter is composed of (b) (4). A safety clip holds the release button in the forward position during shipping, storage, and handling, thus preventing a premature release of the implant. The inserter handpiece is made from common medical grade (b) (4) and (b) (4) stainless steel (SS). The inserter material that enters the eye is SS.

Figure 3: Inserter Loaded with Travoprost Intraocular Implant



The assembled implant and inserter are placed in a (b) (4) blister tray that is sealed with a Tyvek lid (b) (4). The sealed tray is placed together with an oxygen absorbing packet into a transparent barrier pouch (b) (4) (secondary packaging), which is sealed and placed in a unit carton (tertiary packaging). (b) (4) the final labeling contents are added inside the unit carton (i.e., prescribing information and patient card).





Table 1: Travoprost Intraocular Implant Components (Up to Tertiary Packaging)

Component	Drug Product Constituent	Medical Device Constituent Implant	Medical Device Constituent Inserter	Primary Container Closure	Secondary Packaging	Tertiary Packaging	Material
Travoprost Drug Substance	X						Travoprost
(b) (4)	X						(b) (4)
Titanium Reservoir		X					Titanium, (b) (4)
EVA Membrane		X					Ethylene vinyl acetate
Titanium Cap		X					Titanium, (b) (4)
Inserter			X				stainless steel (b) (4)
Blister Tray				X			(b) (4)
Tyvek Lid				X			Tyvek (b) (4)
Radiation Indicator					X		(b) (4)
O ₂ Absorbing Packet					X		(b) (4)
Barrier Pouch					X		(b) (4)
Carton						X	The unit carton contains the barrier pouch packaging, prescribing information, patient card and label for the unit carton. A tamper evident seal is affixed to both ends of carton.

Reviewer's comment:

As indicated in the relevant regulatory summary provided above, during the IND review the implant was considered a (b) (4). In the pre-NDA submission the sponsor indicated that they consider the product as a drug-device but they characterized the implant as a (b) (4) Per Genus Medical Technologies LLS

versus FDA DC Circuit Court Decision issued on April 16, 2021

<https://www.federalregister.gov/documents/2021/08/09/2021-16944/genus-medical-technologies-llc-versus-food-and-drug-administration-request-for-information-and>) in response to the pre-NDA submission CDER informed the sponsor that we do not agree with the designation of the titanium implant (b) (4) and the sponsor should consider the blister tray with Tyvek lid as the primary container. However, the current submission was not updated to include CDER's recommendation and the sponsor refers to the inserter as a (b) (4) and to the Tyvek lid and blister tray as a (b) (4).

Per graphical representation provided for the inserter and primary packaging, the delivery device is held in place in the blister tray, with the "tip" located in a "dip" of the tray and it does not appear that the "tip" of the delivery device that contacts the tissue has direct contact with the tray. In addition, the sponsor conducted analytical chemical testing on the secondary packaging. Therefore, no additional biocompatibility assessment is needed for the blister tray and Tyvek pouch.

VI. Summary of manufacturing information:

The following are the summary of the manufacturing processes of TII product.



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



VIII. Summary of biocompatibility assessment (excerpts from attachment 3-1-vr-16-0008):

A. Biocompatibility assessment of the TII

Reviewer's comment:

As discussed in the relevant regulatory section of this document, CDRH provided recommendations during the pre-IND meetings but was not involved in the biocompatibility review of the IND. Therefore, the biocompatibility assessment may not follow the CDRH recommendations. In addition, the biocompatibility tests summarized below were performed prior to manufacturing changes implemented after Phase 2 and Phase 3 clinical trials.

The applicant states that the test samples used for biocompatibility testing (b) (4) were representative of the finished device:

Table 1. Test Article Description	
Material	Test Article Description
(b) (4) Titanium	(b) (4)
(b) (4)	(b) (4)
(b) (4) Titanium	(b) (4)
Ethylene Vinyl Acetate – EVA	(b) (4)

Table 2: Comparison of G2TR Final Device vs. G2TR Test Article

Component Material	G2TR Final Device	G2TR Test Article	Comment
	% of Unit Internal & External Surface Area (cm ²)		
(b) (4) Titanium (b) (4)	(b) (4)	(b) (4)	Representative
(b) (4)	(b) (4)	(b) (4)	Representative
Titanium (b) (4)	(b) (4)	(b) (4)	(b) (4)
Ethylene Vinyl Acetate – EVA (Membrane)	(b) (4)	(b) (4)	the EVA in the final device
(b) (4) Travoprost Oil	(b) (4)	(b) (4)	the Travoprost oil in the final device
Total Surface Area =	(b) (4)	(b) (4)	Acceptable

Reviewer's comment:

During the pre-IND submissions (please refer to the regulatory background summarized in this document), there were in-depth discussions regarding use of (b) (4) during which we emphasized that while (b) (4) can be considered (especially for devices that are small), the materials and manufacturing processes need to be identical/representative of the finished sterile device. While the sponsor provided the type of material (e.g., Titanium, EVA) and surface area used for each of the implant materials, they do not describe whether the manufacturing process is representative of the finished device and whether the same materials (i.e., same material from the same vendors) have been used in (b) (4) and finished device. It does not appear that during the IND review CDER requested information regarding whether the (b) (4) used for biocompatibility tests are representative of the finished implant.

The test article was extracted at a ratio of 3 cm²/ml at temperature of 50°C for 72 hrs. except for cytotoxicity test for which the test article was extracted at 37°C for 24 hrs. The applicant states that the test extracts were clear, free of particulates; the test extracts were not manipulated in any way.

Reviewer’s comment:

Except for cytotoxicity, extraction conditions are appropriate. For devices with permanent tissue contact we recommend that the extraction is performed under “worst case” conditions (i.e., 37°C for 72 hrs.) to ensure that all potential cytotoxicants are extracted from the device. It does not appear that CDER discussed with the sponsor the extraction conditions used for cytotoxicity during the IND review.

The applicant states that per ISO 10993-1 the following endpoints were evaluated: cytotoxicity, sensitization, irritation, acute systemic toxicity, material mediated pyrogenicity, genotoxicity, sub-chronic toxicity, chronic toxicity, and carcinogenicity.

All testing was conducted by an ISO 17025 accredited laboratory following Good Laboratory Practices (GLP) testing policies and procedures.

Reviewer’s comment:

The above identified endpoints are in line with CDRH 2016 Biocompatibility guidance/FDA 2020 Biocompatibility guidance for devices with permanent (>30 days) contact with tissue.

For assessment of subchronic toxicity endpoint, the sponsor is proposing to use the 6-mo intraocular implantation study which included ocular assessments as well as systemic endpoints (e.g., body weight, macroscopic observations of the main tissues and organs), which is acceptable.

In addition to MEM elution cytotoxicity test, the sponsor also performed agarose overlay cytotoxicity test. However, this indirect cytotoxicity tests is applicable only to those test articles that can penetrate the agarose overlay. Since we do not recommend use of this method for cytotoxicity, the agarose overlay method is not summarized below.

The biocompatibility tests performed on the implant (b) (4) are summarized below:

TABLE 4: SUMMARY OF <i>IN VITRO</i> CYTOTOXICITY ISO MEDIUM ELUATE METHOD (MEM) TEST RESULTS FOR THE GLAUKOS G2TR DRUG ELUTING INTRAOCULAR IMPLANT (b) (4) PROTOCOL NO. P15-0889-00A AND (b) (4) FINAL GLP REPORT NO. 15-02021-G1			
Test Method	Extraction Medium	Extraction Conditions Sample to Medium Ratio & Extraction Parameters	Results
ISO Medium Eluate Method (MEM) Elution Test	1x CMEM Cell Growth Medium (MEM supplemented with 10% fetal bovine serum extract)	60 cm ² /20 mL (3.0 cm ² /mL) at 37°C/24 hrs.	Test Article: Non-cytotoxic to cells at all the 24 and 48-hour readings for the 100% (neat), 75% and 50% extract concentrations. 0% cell lysis (score of 0 in all triplicate samples) at both the 24 and 48 hour readings.
Compliance with ISO 10993-5:2009 [EN ISO 10993-5:2009]			Negative Control (1x CMEM and retest (b) (4)). Non-cytotoxic to cells at all the 24 and 48-hour readings. 0% cell lysis (score of 0 in all triplicate samples) at both the 24 and 48 hour readings.
			Positive Control (b) (4). Severely cytotoxic to cells. >70 - 100% cell lysis (score of 4 in all triplicate samples) at both the 24 and 48-hour readings.
Acceptance Criteria: Scores of (b) (4) and non-cytotoxic. (b) (4) are considered passing			
Conclusion: The test article showed passing results and was determined to be non-cytotoxic by the MEM Elution Test procedure.			

Reviewer’s comment:

As indicated in a previous comment, for device with permanent tissue contact and per ISO 10993-12:2021 we recommend that the test articles are extracted at 37°C for 72 hrs for cytotoxicity.

TABLE 6: SUMMARY OF <i>IN VIVO</i> ISO KLIGMAN MAXIMIZATION IN GUINEA PIGS SENSITIZATION TEST RESULTS FOR THE GLAUKOS G2TR DRUG ELUTING INTRAOCULAR IMPLANT			
(b) (4) PROTOCOL NO. P15-0915-00A AND		(b) (4) FINAL GLP REPORT NO. 15-02021-G3)	
Test Method	Extraction Medium	Extraction Conditions Sample to Medium Ratio & Extraction Parameters	Results
ISO Kligman Maximization Test in Guinea Pigs Sensitization Test	Normal Saline	60 cm ² /20 mL (3.0 cm ² /mL) at 50°C/72 hrs.	All guinea pigs normal. No irritation was present on any of the test or negative control (0% sensitized) guinea pigs at any of the 24, 48 or 72-hour readings. Non-sensitizing.
Compliance with ISO 10993-10:2010	Vegetable (Cottonseed) Oil	60 cm ² /20 mL (3.0 cm ² /mL) at 50°C/72 hrs.	All guinea pigs normal. No irritation was present on any of the test or negative control (0% sensitized) guinea pigs at any of the 24, 48 or 72-hour readings. Non-sensitizing.
Acceptance Criteria:			(b) (4)
Conclusion: The test article showed passing results and was determined to show no sensitizing potential (0% sensitized).			

Reviewer's comment:

In the guinea pig sensitization study the sponsor reports that 5/10 animals that received the saline test extract and 1/10 animals that received the cotton seed oil test extract presented "large FCA-induced lesion sites." However, there is no additional discussion provided whether the injection sites "overlapped" due to the "large FCA-induced lesions" and whether there were any lesions at the injection sites where Freud's adjuvant was not used. It does not seem that this was discussed during the IND review.

TABLE 7: SUMMARY OF <i>IN VIVO</i> ISO INTRAOCULAR IRRITATION IN RABBITS TEST RESULTS FOR THE GLAUKOS G2TR DRUG ELUTING INTRAOCULAR IMPLANT			
(b) (4) PROTOCOL NO. TA044 800 AND		(b) (4) FINAL GLP REPORT NO. 15T_43842_03)	
Test Method	Extraction Medium	Extraction Conditions Sample to Medium Ratio & Extraction Parameters	Results
ISO Intraocular Irritation in Rabbits Test	Balanced Saline Solution (BSS) Extract	60 cm ² /20 mL (3.0 cm ² /mL) at 50°C/72 hrs.	Immediately following the injection procedure, an air bubble was present in the right eye of animal no. 5352. Both eyes of each animal were red at the end of day 0 with four (4) animals (animal nos. 5352, 5359, 5416, and 5330) extending to day 1 for both eyes and one (1) animal (animal no. 5356) for only the left eye on day 1. Animal no. 5416 had blood associated with fibrin present in the anterior chamber of the left eye on day 1. The amount of blood present was reduced on day 2 and further reduced on day 3 indicating resolution. The presence of fibrin was considered incidental and related to trauma during the injection procedure. Otherwise, all animals tolerated the procedure well and appeared healthy throughout the study. Macroscopic observations at the end of the treatment day (day 0) and at day 1 were considered acceptable for an invasive procedure of this nature. The slit-lamp examination was performed at the 24, 48, and 72-hour observation points. Synechia (iris to injection site) and fibrin were noted in some eyes throughout the study. Injection sites remained visible in all corneas throughout the 72-hour study. All changes were judged to be related to the dosing trauma and were considered acceptable following an invasive procedure of this kind. There were no significant differences between the test and control eyes. Therefore, the test article was determined to be non-irritating to intraocular tissues by the ISO Intraocular Irritation Test in Rabbits procedure.
Compliance with ISO 10993-10:2010			
Acceptance Criteria: Considered to be non-irritating and passing when			(b) (4)

Reviewer's comment:

For the ocular irritation study while the sponsor indicates that the test article is representative of the intraocular implant, the image of the test article included in the test report appears to show only the EVA membrane.

TABLE 8: SUMMARY OF <i>IN VIVO</i> ISO INTRACUTANEOUS REACTIVITY TEST RESULTS FOR THE GLAUKOS G2TR DRUG ELUTING INTRAOCULAR IMPLANT (b) (4) PROTOCOL NO. P15-0916-00A AND (b) (4) FINAL GLP REPORT NO. 15-02021-G4)			
Test Method	Extraction Medium	Extraction Conditions Sample to Medium Ratio & Extraction Parameters	Results
ISO Intracutaneous Reactivity Test Compliance with ISO 10993-10:2010	Normal Saline	60 cm ² /20 mL (3.0 cm ² /mL) at 50°C/72 hrs.	All rabbits normal. No evidence of irritation at all the 24, 48, and 72-hour readings as compared to the negative control (normal saline) exposed injection sites. Difference between test and control sites had a mean score of 0.0. Non-irritating.
	Vegetable (Cottonseed) Oil	60 cm ² /20 mL (3.0 cm ² /mL) at 50°C/72 hrs.	All rabbits normal. No evidence of irritation at all the 24, 48, and 72-hour readings as compared to the negative control (vegetable oil) exposed injection sites. . Difference between test and control sites had a mean score of 0.0. Non-irritating.
Acceptance Criteria: Considered to be non-irritating and passing when (b) (4)			(b) (4)
Conclusion: The overall mean score for the test article after subtraction of the corresponding negative control value was 0.0 for both the normal saline and vegetable (cottonseed) oil test article extracts. The test article showed passing results and was determined to be non-irritating by the Intracutaneous Injection Test procedure.			

TABLE 9: SUMMARY OF <i>IN VIVO</i> ISO SYSTEMIC INJECTION TEST IN MICE RESULTS FOR THE GLAUKOS G2TR DRUG ELUTING INTRAOCULAR IMPLANT (b) (4) PROTOCOL NO. P15-0917-00A AND (b) (4) FINAL GLP REPORT NO. 15-02021-G5)			
Test Method	Extraction Medium	Extraction Conditions Sample to Medium Ratio & Extraction Parameters	Results
ISO Systemic Injection Toxicity Test Compliance with ISO 10993-11:2006 [EN ISO 10993-11:2009]	Normal Saline	60 cm ² /20 mL (3.0 cm ² /mL) at 50°C/72 hrs.	All mice normal. No weight loss or systemic affects over the 72-hour observation period as compared to the negative control exposed mice. Non-toxic.
	Vegetable (Cottonseed) Oil	60 cm ² /20 mL (3.0 cm ² /mL) at 50°C/72 hrs.	All mice normal. No weight loss or systemic affects over the 72-hour observation period as compared to the negative control exposed mice. Non-toxic.
Acceptance Criteria: The test is considered negative and systemically non-toxic if (b) (4)			(b) (4)
Conclusion: The test article showed passing results and was determined to be systemically non-toxic by the Systemic Injection Test procedure for both the normal saline and vegetable (cottonseed) oil test article extracts.			

Reviewer's comment:

The sponsor states that there was no weight loss in the test animal groups as compared to the control groups in the acute systemic toxicity study. However, this is not accurate because 5/15 animals that were injected with the non-polar test extract presented a weight loss of ~ 4g at 72 hrs as compared to baseline. In addition, 5/15 animals that received the non-polar vehicle extract presented ~ 1g of weight loss at 72 hrs compared to baseline. The sponsor states that this is not a significant loss in weight. Also, while the protocol indicates that 20 animals are enrolled in this study and no deviations/amendments to the protocol were provided, the sponsor used 40 animals; 30 of these were used for the non-polar extract and non-polar vehicle. This seems to suggest that the sponsor may have repeated/amended the study to include additional animals for the non-polar extracts. It does not appear that CDER discussed these observations with the sponsor during the IND review.

TABLE 10 SUMMARY OF <i>IN VIVO</i> SYSTEMIC TOXICITY ISO RABBIT PYROGEN (MATERIAL-MEDIATED) TEST RESULTS FOR FOR THE GLAUKOS G2TR DRUG ELUTING INTRAOCULAR IMPLANT (b) (4) PROTOCOL NO. P15-0918-00A AND (b) (4) FINAL GLP REPORT NO. 15-02021-G6			
Test Method	Extraction Medium	Extraction Conditions Sample to Medium Ratio & Extraction Parameters	Results
ISO Rabbit Pyrogen (Material-Mediated) Test Compliance with ISO 10993-11:2006 [EN ISO 10993-11:2009]	Normal Saline	60 cm ² /20 mL (3.0 cm ² /mL) at 50°C/72 hrs.	All rabbits normal. Test Article: Total Rise in Temperature (°C) Rabbit No. 50375 = 0.0 Rabbit No. 50377 = 0.0 Rabbit No. 50382 = 0.0 Negative Control (Normal Saline): Total Rise in Temperature (°C) Rabbit No. 50384 = 0.0 All individual rabbits for both the test article and negative control showed a total rise in temperature of < 0.5°C and were determined to be non-pyrogenic.
Acceptance Criteria: A test article extract is considered non-pyrogenic if (b) (4)			(b) (4)
Conclusion: The test article showed passing results and was determined to be non-pyrogenic (material-mediated) by the Rabbit Pyrogen (Material-Mediated) Test procedure.			

TABLE 11: SUMMARY OF <i>IN VITRO</i> AMES TEST – <i>SALMONELLA TYPHIMURIUM</i> AND <i>ESCHERICHIA COLI</i> REVERSE MUTATION GENOTOXICITY TEST RESULTS – NORMAL SALINE (PRIMARY STUDY) FOR THE GLAUKOS G2TR DRUG ELUTING INTRAOCULAR IMPLANT (b) (4) PROTOCOL NO. P15-0162-00A AND (b) (4) FINAL GLP REPORT NO. 15-02021-G7						
ISO Ames Test Method Compliance with ISO 10993-3:2003 [EN ISO 10993-3:2009]	Sample Description Note = Sample extractions prepared at a sample to extract medium concentration of 3.0 cm ² /mL normal saline. Extracted at 50°C for 72 hours.	Average Number of Revertants per Plate (Initial Assay/Confirmatory Assay) Mean/Standard Deviation				
		TA98	TA100	TA1535	TA1537	WP2 <i>uvrA</i>
Plate Incorporation Non-Activated System	Positive Control * (varies according to strain)	304/10	900/91	138/8	198/8	551/55
	Normal Saline Spontaneous Mutation	12/3	66/24	7/5	3/1	67/27
	Test Extract – 3.0 cm ² /mL Normal Saline	13/3	66/20	7/3	5/3	50/11
Plate Incorporation Activated System with S-9	Positive Control * (varies according to strain)	165/1	323/54	72/5	111/22	199/20
	Normal Saline Spontaneous Mutation	17/2	143/12	13/3	9/2	71/25
	Test Extract – 3.0 cm ² /mL Normal Saline	17/8	154/6	9/2	5/2	80/12
Non-Activated Positive Controls: S. typhimurium TA98: 2-Nitrofluorene (10 µg/mL); TA 100: Sodium Azide (100 µg/mL); TA1535: Sodium Azide (5 µg/mL); TA1537: 9-Aminoacridine (800 µg/mL); E. coli WP2 <i>uvrA</i> : 4-Nitroquinoline 1-Oxide (100 µg/mL). Activated Positive Control: 2-Aminoanthracene at 5, 10, 20, 30, and 200 µg/mL (S. typhimurium TA98, TA100, TA1535, TA1537, and E. coli WP2 <i>uvrA</i> , respectively).						
Acceptance Criteria: A positive mutagenic response is identified when (b) (4)						(b) (4)
Conclusion: A statistically significant increase in the number of revertant colonies was not observed with the test article extract as compared to the negative control in both the non-activated and activated conditions. All positive controls exhibited a statistically significant increase in the number of revertant colonies as compared to the corresponding negative controls in both non-activated and activated conditions, validating the functioning of the assay. Based on the criteria of the study protocol, the test article was considered to be non-mutagenic.						

TABLE 12: SUMMARY OF <i>IN VITRO</i> AMES TEST – <i>SALMONELLA TYPHIMURIUM</i> AND <i>ESCHERICHIA COLI</i> REVERSE MUTATION GENOTOXICITY TEST RESULTS – NORMAL SALINE (CONFIRMATORY STUDY) FOR THE GLAUKOS G2TR DRUG ELUTING INTRAOCULAR IMPLANT (b) (4) PROTOCOL NO. P15-0162-00A AND (b) (4) FINAL GLP REPORT NO. 15-02021-G7)						
ISO Ames Test Method Compliance with ISO 10993-3:2003 [EN ISO 10993-3:2009]	Sample Description Note = Sample extractions prepared at a sample to extract medium concentration of 3.0 cm ² /mL normal saline. Extracted at 50°C for 72 hours.	Average Number of Revertants per Plate (Initial Assay/Confirmatory Assay) Mean/Standard Deviation				
		TA98	TA100	TA1535	TA1537	WP2 <i>uvrA</i>
Plate Incorporation Non-Activated System	Positive Control * (varies according to strain)	304/10	900/91	138/8	198/8	551/55
	Normal Saline Spontaneous Mutation	17/6	68/2	7/1	4/2	50/4
	Test Extract – 3.0 cm ² /mL Normal Saline	22/6	81/1	6/1	3/1	47/11
Plate Incorporation Activated System with S-9	Positive Control * (varies according to strain)	165/1	323/54	72/5	111/22	199/20
	Normal Saline Spontaneous Mutation	26/5	155/26	6/1	8/4	72/6
	Test Extract – 3.0 cm ² /mL Normal Saline	23/6	152/16	10/2	7/5	68/12
Non-Activated Positive Controls: <i>S. typhimurium</i> TA98: 2-Nitrofluorene (10 µg/mL); TA 100: Sodium Azide (100 µg/mL); TA1535: Sodium Azide (5 µg/mL); TA1537: 9-Aminocridine (800 µg/mL); <i>E. coli</i> WP2 <i>uvrA</i> : 4-Nitroquinoline 1-Oxide (100 µg/mL). Activated Positive Control: 2-Aminoanthracene at 5, 10, 20, 30, and 200 µg/mL (<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, and <i>E. coli</i> WP2 <i>uvrA</i> , respectively).						
Acceptance Criteria: A positive mutagenic response is identified when						(b) (4) (b) (4)
Conclusion: A statistically significant increase in the number of revertant colonies was not observed with the test article extract as compared to the negative control in both the non-activated and activated conditions. All positive controls exhibited a statistically significant increase in the number of revertant colonies as compared to the corresponding negative controls in both non-activated and activated conditions, validating the functioning of the assay. Based on the criteria of the study protocol, the test article was considered to be non-mutagenic.						

TABLE 13: SUMMARY OF <i>IN VITRO</i> AMES TEST – <i>SALMONELLA TYPHIMURIUM</i> AND <i>ESCHERICHIA COLI</i> REVERSE MUTATION GENOTOXICITY TEST RESULTS – 95% ETHANOL EXTRACT (PRIMARY STUDY) FOR THE GLAUKOS G2TR DRUG ELUTING INTRAOCULAR IMPLANT (b) (4) PROTOCOL NO. P15-0162-00A AND (b) (4) FINAL GLP REPORT NO. 15-02021-G7)						
ISO Ames Test Method Compliance with ISO 10993-3:2003 [EN ISO 10993-3:2009]	Sample Description Note = Sample extractions prepared at a sample to extract medium concentration of 3.0 cm ² /mL 95% ethanol. Extracted at 50°C for 72 hours.	Average Number of Revertants per Plate (Initial Assay/Confirmatory Assay)				
		TA98	TA100	TA1535	TA1537	WP2 <i>uvrA</i>
Plate Incorporation Non-Activated System	Positive Control * (varies according to strain)	304/10	900/91	138/8	198/8	551/55
	95% Ethanol Spontaneous Mutation	12/4	54/11	8/1	3/1	67/8
	Test Extract – 3.0 cm ² /mL 95% Ethanol	14/5	78/15	8/2	3/2	58/8
Plate Incorporation Activated System with S-9	Positive Control * (varies according to strain)	165/1	323/54	72/5	111/22	199/20
	95% Ethanol Spontaneous Mutation	19/6	154/20	15/2	8/2	69/13
	Test Extract – 3.0 cm ² /mL 95% Ethanol	19/10	129/19	11/1	6/3	72/4
Non-Activated Positive Controls: <i>S. typhimurium</i> TA98: 2-Nitrofluorene (10 µg/mL); TA 100: Sodium Azide (100 µg/mL); TA1535: Sodium Azide (5 µg/mL); TA1537: 9-Aminocridine (800 µg/mL); <i>E. coli</i> WP2 <i>uvrA</i> : 4-Nitroquinoline 1-Oxide (100 µg/mL). Activated Positive Control: 2-Aminoanthracene at 5, 10, 20, 30, and 200 µg/mL (<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, and <i>E. coli</i> WP2 <i>uvrA</i> , respectively).						
Acceptance Criteria: A positive mutagenic response is identified when						(b) (4) (b) (4)
Conclusion: A statistically significant increase in the number of revertant colonies was not observed with the test article extract as compared to the negative control in both the non-activated and activated conditions. All positive controls exhibited a statistically significant increase in the number of revertant colonies as compared to the corresponding negative controls in both non-activated and activated conditions, validating the functioning of the assay. Based on the criteria of the study protocol, the test article was considered to be non-mutagenic.						

ISO Chromosomal Aberration in CHO Test Method	Sample Description Note = Sample extractions prepared at a sample to extract medium concentration of 3.0 cm ² /mL Ham's F12 w/10% FBS cell growth medium or 95% ethanol. Extracted at 50°C for 72 hours.	Chromosomal Aberration Frequency (% Chromosomal Aberrations & p-value)	
3 HOUR TREATMENT, 21 HOUR RECOVERY PERIOD:			
Chromosomal Aberration in CHO Non-Activated System	Positive Control (MMC 0.075ug/mL)	Ham's F12	Ethanol
	Spontaneous Mutation	33.0% / 0.000	33.0% / 0.000
	Test Extract – 3.0 cm ² /mL (most elevated conc. evaluated)	4.5%	2.5%
Chromosomal Aberration in CHO Activated System with S-9	Positive Control (Cyclophosphamide 35 ug/mL)	2.5% / 0.276	1.5% / 0.475
	Spontaneous Mutation	58.0% / 0.000	58.0% / 0.000
	Test Extract – 3.0 cm ² /mL (most elevated conc. evaluated)	3.0%	5.5%
CONFIRMATORY ASSAY: 20 HOUR TREATMENT, 3 HOUR RECOVERY PERIOD			
Chromosomal Aberration in CHO Non-Activated System	Positive Control (MMC 0.075 ug/mL)	7.0% / 0.066	6.0% / 0.830
	Spontaneous Mutation	33.0% / 0.000	33.0% / 0.000
	Test Extract – 3.0 cm ² /mL (most elevated conc. evaluated)	2.5%	1.5%
Acceptance Criteria: A positive mutagenic response is identified when		(b) (4)	(b) (4)
Conclusion: The test article extracts prepared in the Ham's F12 cell growth and 95% ethanol extraction mediums and evaluated in both the non-activated and activated systems for both the standard and confirmatory treatment periods were determined to be non-clastogenic (non-mutagenic).			

TABLE 16: SUMMARY OF <i>IN VIVO</i> RODENT BLOOD MICRONUCLEUS TEST – REPEAT DOSE RESULTS NORMAL SALINE AND VEGETABLE (COTTONSEED) OIL EXTRACTS FOR THE GLAUKOS G2TR DRUG ELUTING INTRAOCULAR IMPLANT (b) (4) PROTOCOL NO. P15-0919-00A AND (b) (4) FINAL GLP REPORT NO. 15-02021-G9)					
ISO Rodent Blood Micronucleus Test	Sample Description Note = Sample extractions prepared at a sample to extract medium concentration of 3.0 cm ² /mL normal saline or 95% ethanol. Extracted at 50°C for 72 hours.	Reticulocytes Containing Micronuclei (MN-RET) (Mean % MN-RET / p-Value)			
		Normal Saline		Vegetable (Cottonseed) Oil	
		Male Mice (n = 5)	Female Mice (n = 5)	Male Mice (n = 5)	Female Mice (n = 5)
Mouse Micronucleus Test 36 - 48 Hour Exposure Duration	Positive Control (Cyclophosphamide 25 ug/gm)	1.0680 P = 0.0010	0.7200 P = 0.0060	1.0680 P = 0.0010	0.7200 P = 0.0070
	Spontaneous Mutation	0.1300	0.1140	0.1220	0.1540
	Test Extract – 3.0 cm ² /mL	0.1420 p = 0.4850	0.1560 p = 0.1490	0.1180 p = 0.9050	0.1320 p = 0.3790
Acceptance Criteria: A positive mutagenic response is identified when		(b) (4)	(b) (4)	(b) (4)	(b) (4)
Conclusion: All test article extracts prepared in the normal saline and vegetable (cottonseed) oil extraction mediums and evaluated in both male and female mice for the 36 - 48 hour exposure duration were determined to be non-mutagenic.					

TABLE 17: SUMMARY OF <i>IN VIVO</i> A 6-MONTH TOXICITY STUDY ASSESSING THE TRAVOPROST INTRAOCULAR IMPLANT IN MINIPIGS TEST RESULTS FOR THE GLAUKOS G2TR DRUG ELUTING INTRAOCULAR IMPLANT COMPLIANCE WITH ISO 10993-6:2007 [ISO 10993-6:2009] ADDRESSING IMPLANTATION, SUB-CHRONIC TOXICITY AND CHRONIC TOXICITY (b) (4) STUDY NO. (b) (4) 14-5048-P-TX (4)	
Test Article	Results
Glaukos G2TR Drug Eluting Intraocular Implant	There were no clinical signs of abnormality during the acclimation period and no clinically significant observations during the in-life period. There was no premature mortality and all animals survived to the terminal days of the study. The body weights of all animals in all groups increased during the study and were comparable between males and females in all groups and between all groups in the study. For all groups, the ophthalmology findings from slit lamp examination (SLE) performed on Day 7 were consistent with surgical trauma; the eyes which were implanted with the device exhibited mild conjunctival hyperemia, and chemosis along with corneal edema localized to the area surrounding the corneal incision. By Day 28, edema progressed to localized corneal fibrosis. Fundus examination including the retina, optic nerve, choroid and vitreous was normal at all time points. There were slight early decreases in IOP that resolved to baseline level over time. The present study was not intended to assess the efficacy of the implant, as the response of the mini pig to travoprost has not been established in the scientific literature. In human subjects, safety and efficacy of the implant was established in a Phase 1 study completed in Armenia. Electroretinography assessments did not suggest any deterioration in retinal function during the course of the study. Hematology, coagulation and clinical chemistry parameters were generally within the normal physiological values. Serum samples from all animals were analyzed for the concentration travoprost acid before dosing and again on Days 7, 30, 60, 90, 180 using a validated LC-MS/MS method. In all specimens, serum concentrations of travoprost acid were below the lower limit of detection (i.e. ≤ 0.2 ng/mL of travoprost acid). Animals of Groups 1 and 2 were sacrificed on Day 90 and animals of Groups 3 and 4 were sacrificed on Day 180. For all groups at Day 90 or 180, no test article related toxicity was observed at necropsy or histopathologically. In summary, the test article was well tolerated both locally and systemically and there were no lesions in either eye or adnexal structures that were toxicologically relevant indicating that both the device and the travoprost were well tolerated at both 3 and 6 months.
Acceptance Criteria: The acceptability of a test material is based upon (b) (4) (b) (4)	
Conclusion: The 6-Month Toxicity Study Assessing the Travoprost Intraocular Implant in Minipigs showed the Glaukos G2TR Drug Eluting Intraocular Implant to be biocompatible upon implantation with no untoward affects.	

Table 1. Summary of Study Design[†]

Group	Animal No. (male/female)	Necropsy Day	Day 0		Days 0-180
			OD (Travoprost)	OS (Empty)	
1	101-102 151-152	90	Single test article (b) (4)	None	- Clinical observations: Daily - Clinical ophthalmic observations: Daily - Body weights: Pre-dose and once weekly thereafter. - Ocular examinations (by ophthalmologist) and tonometry: pre-dose and Days 7$\pm$1, 28$\pm$1, 62, 84$\pm$1 and 176* - Blood for TK analysis: pre-dose and Days 7, 30, 90 and 180* - Blood for Clinical Pathology: pre-dose and Days 7, 30, 60, 90, 180* - EKG: pre-dose and Days 32, 89, and 180* - ERG: pre dose and Days 7$\pm$1, 28, 84, 176*
2	201-202 251-252		Two test articles (b) (4)	Single control article	
3	301-302 351-352	180	Single test article (b) (4)	None	
4	401-402 451-452		Two test articles (b) (4)	Single control article	

*Groups 3 and 4 only. #Control article is an unloaded titanium implant.

[†] Terminal procedures (Day 90 to 180) in all groups included 1) body weight, 2) blood for clinical pathology and TK, 3) sacrifice and necropsy for collection of complete tissue list, and 4) histopathology on eyes.

Reviewer's comment:

For the 6-mo ocular implantation study, the right eyes (OD) of animals in groups 1 and 2 presented mild corneal cloudiness. It is not clear how the posterior segment was graded. The histopathology of the explanted eyes did not identify safety concerns. Some animals presented thymus that "appeared black"/enlarged spleen/dark spots on pancreas, etc. It does not appear that these observations were discussed during the IDE.

Carcinogenicity assessment

The sponsor concluded that carcinogenicity assessment is not required based on negative genotoxicity test results and since the materials used in the G2TR ((b) (4) titanium, (b) (4) titanium, ethylene vinyl acetate and Travoprost oil) are commonly used for medical applications and recognized as inert and biocompatible.

Reviewer's comment:

The carcinogenicity assessment was discussed during the pre-NDA meeting with the sponsor on December 8, 2022 when I noted that in addition to genotoxic carcinogens, there may be non-genotoxic chemicals that may induce carcinogenicity. Per CDRH 2016/FDA 2020 Biocompatibility guidance, we recommend that carcinogenicity is assessed using an exhaustive extraction coupled with toxicological risk assessment. To address this recommendation, the sponsor provided additional justification as summarized below.

The mechanisms behind non-genotoxic carcinogenicity is diverse and not well understood. In general, it involves tissue- and species-specific disturbances in normal physiological control, gene expression patterns implicated in cellular proliferation, survival and differentiation. The safety of non-genotoxic compounds in man has mainly been concluded from repeat dose toxicity tests (implant, sub-chronic or chronic toxicity studies), toxicokinetics, rodent bioassays, if available, and by using threshold principle. The potential for leachable or extractable non-genotoxic carcinogens in the Glaukos iDose G2-TR implant was evaluated by the cell and tissue specific portion of the biocompatibility test battery in compliance with ISO 10993-1:2018 and included cytotoxicity and implantation which did not identify abnormal findings indicative of any potential abnormal cell growth.

Elemental Impurities Assessment (excerpt from “characterization-impurities”)

Elemental impurities are not being monitored as part of the product specifications. Glaukos has identified five potential sources of elemental impurities:

- the drug substance travoprost
- ^{(b) (4)} excipient
- the EVA membrane
- the titanium implant material
- the implant inserter.

Glaukos screened elemental impurity extractables from the EVA membrane, the inserter and titanium materials of Travoprost Intraocular Implant drug-eluting implants using ICP-MS. The ICP-MS method scans from mass range of 6 AMU to 238 AMU in sample solution. The potential for the presence of elemental impurities in Travoprost Intraocular Implant was assessed using ICH Q3D(R1) Guideline for Elemental Impurities. No elemental impurities were detected above 30% of the parenteral PDE defined by ICH Q3D.

In addition to biocompatibility tests, the following table summarizes the nonclinical studies conducted with Travoprost Intraocular Implants are:

Table 1: Overview of Nonclinical Studies Conducted by Glaukos

Study Type	Test Article/ Dose*	Species	Duration	Report	GLP
Pharmacology/ Primary pharmacodynamics	G2-TR-(b)(4)**	Cynomolgus monkeys	1 year	Bioanalytical Report 08-104 Dose Medical Final Report	No
Pharmacokinetics	G2-TR-125	New Zealand White (NZW) rabbits	28 days	12C94Q3R2	No
	G2-TR-063 & G2-TR-125	NZW rabbits	7 months	16C95Q2	No
	G2-TR-125	NZW rabbits	6 months	14C94Q1R1G62	Yes
	G2-TR-(b)(4)**	Cynomolgus monkeys	1 year	Bioanalytical Report 08-104 Dose Medical Final Report	No
Toxicology	G2-TR-125	NZW rabbits	28 days	12C94Q3R2	No
	G2-TR-125	NZW rabbits	6 months	14C94Q1R1G62	Yes
	G2-TR-125 1-2 implants/eye	Micro Yucatan miniature swine	6 months	(b)(4) 14-5048-P- TX	Yes
	G2-TR-(b)(4)**	Cynomolgus monkeys	1 year	Bioanalytical Report 08-104 Dose Medical Final Report	No

* Dose in in vivo implant studies is 1 implant/dose unless otherwise indicated

** The G2-TR (b)(4) implant (b)(4) vs. the G2-TR-063 and G2-TR-125 implants investigated in the clinical studies that had a fill volume of (b)(4) 75 µg travoprost. Upon review of the clinical study data G2-TR-125 was selected for commercialization.

The sponsor states that the adequacy of the non-clinical, including biocompatibility tests was initially discussed and agreed with the Agency during the pre- IND meeting on March 28, 2014 (FDA Meeting Minutes dated April 4, 2014). The Agency confirmed the adequacy of the nonclinical package at the End-of-Phase 2 meeting on December 4, 2017 (FDA Meeting Minutes dated December 17, 2017) and again at the Type C meeting on June 7, 2021 (FDA Meeting Minutes dated June 25, 2021). The clinical trials conducted to date did not identify any unanticipated safety concerns.

“Confirmatory” biocompatibility testing of the EVA membrane (excerpts from attachment “att3-2-report-eva-biocomp”)

An *in vitro* and *in vivo* confirmational biocompatibility study was performed to ensure the safety of the replacement Celanese VitalDose EVA Membrane component (Glaukos p/n 10-0660; Celanese p/n 21042856) for use in the Travoprost Intraocular Implant (iDose G2-TR). The Celanese VitalDose EVA Membrane is intended to replace the (b)(4) (b)(4) EVA Membrane (b)(4) component (b)(4) manufactured under an improved supplier quality system.

The EVA membrane has indirect tissue contact via the eluted drug.

To demonstrate the “equivalence” of the EVA membrane from (b) (4) and Celanese, the sponsor performed the following tests:

- Visual Appearance
- Identification by FT-IR (Fourier-transform Infrared) Spectroscopy
- (b) (4)
- Melt Index using ASTM D1236
- (b) (4)
- (b) (4)
- Evaluations addressing Physical Performance and Characteristics

Table 1: (b) (4) EVA and Celanese VitalDose EVA (b) (4) Comparison

Attribute	Test Method	Acceptance Criteria for Equivalency	Results		Met Acceptance Criteria?
			(b) (4) EVA L/N 600425006 (Control) GC-010/ GC-012	VitalDose EVA L/N 1222083 IDOS-106-EXCH	
Appearance	TM-0019	Colorless transparent to slightly opaque polymer pellets.	Colorless transparent to slightly opaque polymer pellets.	Colorless transparent to slightly opaque polymer pellets.	Yes
	(b) (4) TM-0017				(b) (4)
Melt Flow Index	Per Manufacturer’s COA & ASTM D1238				Yes
	(b) (4) Per Manufacturer’s COA				Yes
	Per Manufacturer’s COA				Yes
Additional Supporting Data					
(b) (4) EVA Membrane (%)	Modulated Differential Scanning Calorimetry			(b) (4)	Yes

Reviewer’s comment:

I defer to the chemistry reviewer to determine whether the methods and assessments listed above are adequate.

The Celanese VitalDose EVA contains (b) (4) (b) (4) (b) (4). The specification for (b) (4) was set at not more than (b) (4) (b) (4). Based on the conservative estimates of the maximum amount of (b) (4) (b) (4) potentially released into the iDose intraocular implant from the EVA membrane component at the (b) (4) proposed specification level would be (b) (4) (b) (4) per implant. These levels are (b) (4)-fold below the PDE levels for (b) (4) and (b) (4) fold below the TTC level for potentially carcinogenic aromatics established for daily lifetime exposure, so the risk to patient safety is minimal. Finally, since this (b) (4) specification is set for the EVA (b) (4) (b) (4), the final (b) (4) levels in the processed EVA membranes are expected to be even lower.

Therefore, the (b) (4) level for (b) (4) in the EVA (b) (4) is justified and is not expected to pose any safety concern for patients.

Reviewer's comment:

Using the total amount of (b) (4) present in the EVA membrane from Celanese, the sponsor calculated the level of (b) (4) that could be released /single dose. Per this calculation, the sponsor determined that the carcinogenicity and systemic toxicity risks are low/unlikely.

The sponsor states that the manufacturing, cleaning, assembly and sterilization operations used to produce the membrane component and the ultimate assembled final device are exactly the same between the iDose G2-TR version with the (b) (4) EVA Membrane and the Celanese VitalDose EVA Membrane.

The sponsor performed select biocompatibility testing that included MEM Elution cytotoxicity, 4-week intramuscular implantation study, extractable and leachable study.

The test article was the Celanese VitalDose EVA membrane material (Celanese p/n 21042856) that underwent all intended manufacturing (b) (4) operations as intended for the final clinical device. The test article used for cytotoxicity was extracted at 40 cm²/ml which is a worst-case extraction compared to the ratio recommended by ISO 10993-12 (i.e., 3 cm²/ml).

TABLE 6: SUMMARY OF <i>IN VITRO</i> CYTOTOXICITY ISO MINIMAL ESSENTIAL MEDIUM (MEM) ELUATE TEST RESULTS FOR THE CELANESE VITAL DOSE EVA MEMBRANE (b) (4) PROTOCOL NO. P22-0026-00A AND (b) (4) FINAL GLP REPORT NO. 22-01827-G1			
Test Method	Extraction Medium	Extraction Conditions Sample to Medium Ratio & Extraction Parameters	Results
ISO Minimal Essential Medium (MEM) Elution Test Compliance with ISO 10993-5:2009 [EN ISO 10993-5:2009]	1x CMEM Cell Growth Medium (MEM supplemented with 10% fetal bovine serum extract)	Twenty (20) devices/20 mL (10x maximum patient contact) at 37°C/72 hrs.	<u>Test Article:</u> Non-cytotoxic to cells at all the 24 and 48-hour readings. 0% cell lysis (score of 0 in all triplicate samples) at both the 24 and 48-hour readings.
			<u>Negative Control (1x CMEM and retest HDPE Plastic):</u> Non-cytotoxic to cells at all the 24 and 48-hour readings. 0% cell lysis (score of 0 in all triplicate samples) at both the 24 and 48-hour readings.
			<u>Positive Control (Natural Rubber):</u> Severely cytotoxic to cells. >70 - 100% cell lysis (score of 4 in all triplicate samples) at both the 24 and 48-hour readings.
Acceptance Criteria: Scores of (b) (4) are considered passing and non-cytotoxic.			
Conclusion: The test article showed passing results and was determined to be non-cytotoxic by the MEM Elution Test procedure.			

TABLE 7: SUMMARY OF <i>IN VIVO</i> ISO INTRAMUSCULAR IMPLANTATION WITH HISTOLOGY TEST RESULTS FOR THE FOUR (4) WEEK IMPLANT DURATION	
RESULTS FOR THE CELANESE VITAL DOSE EVA MEMBRANE	
(b) (4) PROTOCOL NO. P22-0029-00A AND (b) (4) FINAL GLP REPORT NO. 22-01827-G2)	
Test	Results
ISO Rabbit Implantation Test with Histology – 4 Week Implant Duration Compliance with ISO 10993-6:2016	All three (3) implanted rabbits appeared normal throughout the duration of the study and all increased in weight showing no weight loss. None of the test animals exhibited any signs of toxicity over the course of the study. All axillary lymph nodes appeared normal upon necropsy. All macroscopic observations showed no significant signs of inflammation, encapsulation, hemorrhage, necrosis, or discoloration at the end of the four (4) week implant duration. Based on the macroscopic evaluation, there was no gross evidence of bioreaction at any implantation site and the axillary lymph nodes from each animal were grossly normal in appearance. The muscle tissue samples were then submitted for histological evaluation. The histopathologist found the test article implant sites for the test article rod samples indicated a slight reaction as compared to the control sites. The test article implantation sites were effaced with moderate populations of inflammatory cells. Inflammation consisted of a mixture of granulocytes, lymphocytes, and macrophages. Robust neovascularization was present adjacent to test article implantation sites, characterized by bundles of capillaries and larger vessels. Negative control implantation sites were effaced with minimal to mild numbers of inflammatory cells and thin layers of fibrosis. The test article was slightly bioactive compared to the negative control based on histological Bioreactivity Rating = (b) (4) (average of the all three animals). The slightly bioactive finding for the implant sites was not unexpected given that the EVA material is a non-smooth surface designed with porosity for elution and it was compared to an accepted USP Negative Control HDPE material with a biologically non-reactive smooth surface. Therefore, the slight elevation in tissue response as compared to the negative control is considered to be an expected finding with the host tissue interaction. The Bioreactivity Rating (b) (4) is within the sight reaction classification scores of 3.0 – 8.9 and falls below the responses of moderate reaction (9.0 – 15.0) and severe reaction (> 15) that are considered unacceptable findings. Bioreactivity ratings of non-reactive (0 – 2.9) to slightly reactive are typically considered acceptable findings especially in
ISO Rabbit Implantation Test with Histology – 4 Week Implant Duration (continued)	consideration of the material characteristics. It is also important to note that the EVA Membrane has no direct patient contact. It is refrained from direct tissue contact by the Cap. The contact is considered to be indirect tissue contact due to the ingress of bodily fluids to contact the EVA Membrane and the elution of the Travoprost oil through the EVA Membrane to the anterior chamber of the eye. In summary, the test article was determined to be slightly reactive and biocompatible upon implantation for the duration of four (4) weeks. Based on the criteria of the protocol, the study met the requirement of ISO 10993-6:2016.
Acceptance Criteria:	The acceptability of a test material is based upon the Bioreactivity Rating as a result of the histopathologist's scoring. A sample is considered non-reactive and biocompatible upon implantation if (b) (4) and (b) (4) and may be considered biocompatible based on the review of the pathologist. Scores of 9.0 – 15.0 and > 15.0 are considered moderately reactive and severely reactive, respectively.
Conclusion:	All animals at the 4-week implant duration for the test article material were determined by the histopathologist to be non-reactive. All other aspects of the biocompatibility studies show no untoward effects. Therefore, the test article was determined to be biocompatible for implantation by the Intramuscular Implantation Test procedure.

Reviewer's comment:

The sponsor does not provide a justification for implanting the EVA membrane in the muscle. Since the device has permanent (>30 days) tissue contact, it is not clear how the sponsor determined that a 4 week implantation study is adequate to evaluate the change in the EVA membrane. In addition, the tissue responses in the eye would be different compared to the muscular tissue responses. It does not appear that CDER discussed this with the sponsor during the IDE review.

Toxicological assessment for packaging of G2TR Intraocular implants (excerpts from “att3-4-extractable” dated March 3, 2022)

The (b) (4) is a device consisting of a (b) (4) container with a cap and an EVA membrane. The container and the cap are made of titanium. The travoprost drug product is held in the container and capped with the membrane for elution. The (b) (4) packaging components includes the inserter that holds the G2-TR device and all packaging. The inserter is held in a blister tray and sealed with a Tyvek lid.

Reviewer's comment:

As indicated in a previous comment in this consult, in response to the pre-NDA submission CDER informed the sponsor that we do not agree with the designation of the titanium implant as the (b) (4) and

the sponsor should consider the blister tray with Tyvek lid as the primary container. However, the sponsor did not update the information included in this NDA to identify the Tyvek lid and blister tray as the primary container.

In addition to cytotoxicity and intramuscular implantation tests on the EVA membrane, the sponsor also conducted extractable and simulated use tests on Glaukos iDose G2-TR with both the (b)(4) EVA Membrane and Celanese VitalDose EVA Membrane. In the extraction study, the sponsor reports no volatile organic compounds (VOCs), semi-VOCs, and non-VOCs, no (b)(4) anions, and no elemental substances in the test extracts. In the simulated use study, the sponsor reports no extractables above the reporting threshold (1.5 µg/day).

Table 6. Summary of Extractable Results

Samples	Container Closure System Components Description	Number of Extractables Found			
		VOCs	Semi-VOCs	Non-VOCs	Elemental
Drug Delivery Components	Cap: titanium Reservoir: titanium Membrane: EVA	NR	NR	NR	NR
Inserter Device Metal Components	(b)(4)	NR	N/A	N/A	N/A
Inserter Device Components	(b)(4)	11	N/A	N/A	N/A
Pouch Contents: primary and secondary container closure components	Blister tray: (b)(4) Barrier pouch: (b)(4) Oxygen absorber packet: (b)(4)	11	N/A	N/A	N/A
Adhesive and Label Components	Lid: Tyvek for Blister tray Label set: (b)(4) Radiation sticker: (b)(4) Tamper evident seal: (b)(4) Unit carton adhesive: (b)(4)	13	N/A	N/A	N/A
Paper Items	Carton: (b)(4) Prescribing Information with ink: (b)(4) Implant card with ink: (b)(4)	49	N/A	N/A	N/A
Drug Formulation Contact Components during Manufacture	(b)(4)	NR	NR	NR	NR

NR: none reportable (< (b)(4) for any organic impurity and < (b)(4) for any elemental impurity)
N/A: not applicable, test not performed- component has no immediate contact with the drug product formulation

Reviewer's concluding comment regarding biocompatibility testing of the TII:

As summarized above, during the IND review the sponsor provided biocompatibility test reports on TII; however, CDRH had not reviewed these reports and this is the first submission where review of biocompatibility test reports for TII was performed. While the sponsor had identified the biocompatibility endpoints applicable for a device with permanent (>30 days) tissue contact, it is not clear whether the (b) (4) used for biocompatibility tests are representative of the finished sterile TII. Through this submission the sponsor emphasizes that the testing conducted and the proposed approach is in line with FDA's recommendations and prior discussions even though CDRH was not consulted on most of prior submissions. As discussed during the pre-NDA meeting, CDRH will consider the least burdensome approach and will evaluate the totality of information provided by the sponsor. Therefore, due to uncertainty on whether the (b) (4) used in the biocompatibility testing are representative of finished sterile TII, I considered the following:

- The materials used for TII are titanium (b) (4) and EVA membrane. The sponsor provided detailed description of manufacturing including the vendors of both materials.
- While CDRH recommends that each biocompatibility endpoint is evaluated performing standardized studies recommended by ISO 10993 standard series (e.g., MEM elution for cytotoxicity, intracutaneous reactivity for skin irritation), as mentioned above we will consider the totality of available information to evaluate the safety of the device.
 - For cytotoxicity, ocular irritation, and intracutaneous reactivity studies I considered the safety toxicology studies that were performed to evaluate product safety. The safety toxicology studies were reviewed by CDER and included 6-mo. implantation studies of the TII in rabbits and mini-pigs and 12-mo. implantation study in monkeys. It is likely that any adverse tissue reaction (e.g., irritation, cell death around the implantation site) and adverse implant/tissue interactions would have been identified during slit lamp microscopy and/or histology assessment during these long-term animal implantation studies.
 - For sensitization I considered the clinical experience with the device. As discussed in FDA's 2020 Biocompatibility guidance, clinical information is difficult to interpret because the enrolled subjects may have other underlying issues, may be administered medication that can decrease irritation, inflammation and other adverse responses to the device, and therefore, it may be difficult to determine that the adverse events reported are associated with the device. As indicated in the first section of this consult, there are >1000 subjects enrolled in the clinical studies for TII. While the pivotal studies are ongoing, the current available safety data did not indicate adverse events that may be related to sensitization (e.g., allergic reactions in subjects implanted with the device).
 - In lieu of systemic toxicity (acute, subacute/subchronic, chronic) I considered the safety toxicology studies that were reviewed by CDER (e.g. 6-mo implantation studies of the TII in rabbits and mini-pigs and 12-mo. implantation study in monkeys). While an acute systemic toxicity response may be difficult to decipher in a long-term implantation study, it does not appear that the sponsor reported adverse events (e.g., loss in appetite and/or body weight, change in grooming) that would be indicative of a systemic toxicity response.
 - In lieu of material mediated pyrogenicity I considered the material composition of TII and clinical experience with the device. In general, a material-mediated effects is associated with an increase in body temperature. While the body temperature may be due to surgery and/or other underlining conditions, it is likely that due to the high number of enrolled subjects an increase in body temperature in the subjects implanted with the investigational product vs control (e.g., sham surgery) would have been reported. In addition, there were no increase in the rate of AEs reported in IDOS-106-EXCH trial where subjects were implanted with TII after which the "original" TII was explanted followed by implantation of a "new" TII.
 - For genotoxicity and carcinogenicity I considered the material composition of TII and analytical chemistry testing performed which indicated either no detectable or very low levels of detected chemicals.
- As discussed in the manufacturing section of this consult, the sponsor had implemented several changes to TII after the biocompatibility assessment was concluded. As discussed in my previous comments, design changes (e.g., (b) (4)) that do not involve changes in materials and manufacturing processes do not

impact the biocompatibility profile of TII. However, change in vendor and manufacturing site will impact the biocompatibility of TII. To assess these changes, the sponsor performed a gap analysis and provided select biocompatibility assessments. I considered the following:

- TII that comprised of manufacturing changes implemented during Phase 2 was used for Phase 3 clinical trial. In addition, select number of subjects enrolled in Phase 3 clinical trial received TII that were “aged” under real-time shelf life conditions between 4 to 31 mo.
- The TII that incorporated the changes made after Phase 3 clinical trial (b) (4) were implanted in subjects enrolled in the IDOS-106-EXCH trial that enrolled 33 subjects followed for 12 mo. CDER agreed with this approach for evaluating the manufacturing changes to TII as part of the “exchange” clinical trial. The sponsor reported low rate of occurrence of ocular (e.g., eye irritation, n=2) and non-ocular AEs.
- Cytotoxicity, 4-week muscular implantation, and analytical chemistry testing of the EVA membrane from the “new” vendor (i.e., Celanese) did not identify safety concerns.
- Except for change in batch size and (b) (4) the TII implanted in the IDOS-106-EXCH study incorporated all the manufacturing changes implemented during Phase 2 and Phase 3 clinical studies.

Therefore, based on weight-of-evidence and least burdensome approach, I will not request additional biocompatibility assessment on the finished sterile TII as intended for marketing.

B. Biocompatibility testing of the delivery device (excerpts from “att3-3-biocomp” dated October 9, 2015)

The sponsor states that the (b) (4) are the only components of the inserter with direct and indirect tissue contact. The (b) (4) has direct contact with TII.

Table 3-4: Inserter Component Materials

No.	Part Name, Sub-Component (if any), & Part #	Raw Material (Chemical Name)	Current Standard
1	(b) (4)	(b) (4)	Complies with 21 CFR 177.1520(c) 3.2a
2		(b) (4)	Per manufacturer specification
3		(b) (4)	
4		(b) (4)	Per manufacturer specification AISI 304 / ASTM F899
5		(b) (4)	Per manufacturer specification ASTM A240
6		(b) (4)	Per manufacturer specification AISI 304 / ASTM F899
7		(b) (4)	Per manufacturer specification AISI 304

Reviewer's comment:

As summarized in the manufacturing section of this review, the (b) (4) used in Phase 3 clinical trial was manufactured (b) (4) at a third party (b) (4). The material (b) (4) was changed (b) (4). The manufacturing process and (b) (4) occurred at the third party (b) (4). This (b) (4) was used in the IDOS-106-EXCH study. The sponsor states that this change did not include additional manufacturing materials.

The inserter is a direct communicating device with direct tissue contact for a limited patient contact duration (< 24 hours) and per ISO 10993-1 the following assessments are recommended:

- Cytotoxicity
- Sensitization
- Intracutaneous reactivity
- Systemic toxicity
- Analytical chemistry testing

Reviewer's comment:

In response to question 12.c from the pre-NDA meeting request, we recommended that the sponsor categorizes the inserter components that contact the implant as permanent (>30 days) indirect tissue contact. While the inserter is intended to contact the patient for limited (<24 hrs.) time, the implant is preloaded in the inserter and resides in the inserter during packaging (b) (4) and shelf life. While the sponsor did not take into consideration our recommendation from the pre-NDA meeting, the biocompatibility endpoints identified for the inserter are acceptable and take into account the permanent indirect tissue contact of the components that contact the implant.

Components using the same stainless steel (b) (4) have been evaluated for use in the G2-W Injector. In addition, the sponsor provided tests on (b) (4) inserter comprising of a "comparable" (b) (4) material.

Table 1: (b) (4) Sample Configuration

Material	Configuration	Sample Detailed Information
Stainless Steel (b) (4)	(b) (4)	(b) (4)
Travoprost Drop (1.5 µL) (b) (4)		
Titanium (Implant Cap Material)		

Extracts were prepared at a ratio of 60 cm²/20 mL (3.0 cm²/mL) in compliance with ISO 10993-12 for a sample (b) (4) for the cell culture assays and at a ratio of 120 cm²/20 mL (6.0 cm²/mL) for the physicochemical test per the compendial method. The test article extract for the MEM Elution Test was prepared by extraction at 37°C for 24hrs per the compendial method. The test article extract for the insoluble inorganics was

prepared by extraction at 70°C for 24 hrs. The test article was exposed to all intended manufacturing (b) (4) processes intended for the final device. The samples presented for testing were identified as "Glaukos Travoprost Inserter (Stainless Steel (b) (4) Sample Representative of the Patient Contacting (b) (4) Components - with Exposure to the G2TR (b) (4) Titanium & Travoprost Oil)." A control sample with no oil was also included in the biocompatibility tests.

Reviewer's comment:

In response to question 12.c from the pre-NDA meeting request, we recommended that the sponsor provides a detailed comparison between the test article used and the finished sterile inserter. Except for the summary above, the sponsor did not clearly indicate all the differences in material and manufacturing between the test article used and the finished inserter. However, since the sponsor states that the (b) (4) were subjected to all manufacturing processes used for the finished device, I will not request additional information regarding the (b) (4) used for the inserter testing. It does not appear that CDER identified any concerns during IND regarding the biocompatibility tests performed in the inserter.

TABLE 3: SUMMARY OF CONFIRMATIONAL <i>IN VITRO</i> MEDIUM ELUATE METHOD (MEM) CYTOTOXICITY TEST RESULTS FOR THE TEST ARTICLE REPRESENTATIVE OF THE TRAVOPROST INSERTER STAINLESS STEEL (b) (4) INTERACTION WITH G2TR CAP (b) (4) TITANIUM (NO TRAVOPROST OIL PRESENT) (b) (4) (b) (4) PROTOCOL NO. P15-0889-00A AND (b) (4) FINAL GLP REPORT NO. 15-03061-G1			
Test Method	Extraction Medium	Extraction Conditions Sample to Medium Ratio & Extraction Parameters	Results
ISO Medium Eluate Method (MEM) Elution Test Compliance with ISO 10993-5:2009 [EN ISO 10993-5:2009]	1x CMEM Cell Growth Medium (MEM supplemented with 10% fetal bovine serum extract)	47.2 cm ² /15.9 mL (3.0 cm ² /mL) at 37°C for 24 hrs.	Control Article: No Travoprost Oil Non-cytotoxic to cells at all the 24 and 48-hour readings. 0% cell lysis (score of 0 in all triplicate samples) at both the 24 and 48 hour readings. Negative Control (1x CMEM and (b) (4)): Non-cytotoxic to cells at all the 24 and 48-hour readings. 0% cell lysis (score of 0 in all triplicate samples) at both the 24 and 48 hour readings. Positive Control (b) (4): Severely cytotoxic to cells. >70 - 100% cell lysis (score of 4 in all triplicate samples) at both the 24 and 48-hour readings.
Acceptance Criteria: Scores of (b) (4) are considered passing and non-cytotoxic.			
Conclusion: The test article showed passing results and was determined to be non-cytotoxic by the MEM Elution Test procedure.			

TABLE 7: SUMMARY OF USP PHYSICO-CHEMICAL TEST RESULTS FOR THE TEST ARTICLE REPRESENTATIVE OF THE TRAVOPROST INSERTER STAINLESS STEEL (b) (4) INTERACTION WITH G2TR CAP (b) (4) TITANIUM (NO TRAVOPROST OIL PRESENT) (b) (4) (b) (4) PROTOCOL NO. P15-1181-00A AND (b) (4) FINAL GLP REPORT NO. 15-03061-G3			
Test Method	Extraction Medium	Extraction Conditions Sample to Medium Ratio & Extraction Parameters	Results
USP Physico-Chemical Test – USP <661>	Purified Water	127.2 cm ² /21.2 mL (6 cm ² /mL) at 70°C for 24 hours	Control Article: No Travoprost Oil Heavy Metals: Passed with no significant heavy metals detected. Met the acceptance criteria of ≤ (b) (4) heavy metals. ≤ (b) (4) heavy metals.
Acceptance Criteria: • Heavy Metal Content: (b) (4) (b) (4)			
Conclusion: The test article showed passing results with no detectable heavy metals (≤ (b) (4)) and was determined to be met the acceptance criteria for the USP <661> Physico-Chemical Test – Section 7.3.3 Heavy Metals Assay.			

Reviewer's comment:

I defer to Dr. Hutter to comment if he has any concerns regarding the analytical chemistry testing summarized above.

The following tests were performed on the “predicate” (b) (4) Injector System (p/n 10- 0219) made with a comparable stainless steel (b) (4).

TABLE 9: SUMMARY OF CONFIRMATIONAL <i>IN VITRO</i> MEDIUM ELUATE METHOD (MEM) CYTOTOXICITY TEST RESULTS FOR THE MODIFIED (b) (4) ASSEMBLY (P/N 10-0259) FOR USE IN THE (b) (4) INJECTOR INCLUSIVE OF THE MODIFIED (b) (4) (P/N 10-0153 REV 2, DRAFT PENDING (b) (4) RELEASE) (b) (4) PROTOCOL NO. P14-1184-00A AND (b) (4) FINAL GLP REPORT NO. 15-00925-G1			
Test Method	Extraction Medium	Extraction Conditions Sample to Medium Ratio & Extraction Parameters	Results
ISO Medium Eluate Method (MEM) Elution Test Compliance with ISO 10993-5:2009 [EN ISO 10993-5:2009]	1x CMEM Cell Growth Medium (MEM supplemented with 10% fetal bovine serum extract)	Nine (9) Test Article Samples (Combined nine (9) End Mill and nine (9) EDM prepared samples) per 20 mL at 37°C for 24 hrs.	Test Article: Non-cytotoxic to cells at all the 24 and 48-hour readings. 0% cell lysis (score of 0 in all triplicate samples) at both the 24 and 48 hour readings. Negative Control (1x CMEM and (b) (4)): Non-cytotoxic to cells at all the 24 and 48-hour readings. 0% cell lysis (score of 0 in all triplicate samples) at both the 24 and 48 hour readings. Positive Control (b) (4): Severely cytotoxic to cells. >70 - 100% cell lysis (score of 4 in all triplicate samples) at both the 24 and 48-hour readings.
Acceptance Criteria: Scores of (b) (4) are considered passing and non-cytotoxic.			
Conclusion: The test article showed passing results and was determined to be non-cytotoxic by the MEM Elution Test procedure.			

TABLE 11: SUMMARY OF <i>IN VITRO</i> INHIBITION OF CELL GROWTH CYTOTOXICITY TEST RESULTS FOR THE DISTAL SECTION OF THE PREDICATE (b) (4) INJECTOR SYSTEM (P/N 10-0219) CONSIDERED REPRESENTATIVE OF THE (b) (4) INJECTOR (P/N 10-0227) (b) (4) PROTOCOL NO. P10-1854-00A AND (b) (4) FINAL GLP REPORT NO. 11-4096-G1 AMENDED)			
Test Method	Extraction Medium	Extraction Conditions Sample to Medium Ratio & Extraction Parameters	Results
ISO Inhibition of Cell Growth Test Compliance with ISO 10993-5:2009 [EN ISO 10993-5:2009]	Sterile Water for Injection (SWFI) then Mixed with an Equal Volume of 2x CMEM Cell Growth Medium (MEM supplemented with 10% fetal bovine serum extract)	Extraction used Twenty (20) samples representing the Distal Tip portions of the (b) (4) Injector device with intended patient contact and proximity to the adhesive bond and Forty (40) GTS400 Stents per 20 mL at 70°C/24 hrs. then mixed with an equal volume of 1x CMEM Cell Growth Medium to achieve a final concentration of 10 Distal Tips and 20 Stents per 20 mL.	Test Article: Non-cytotoxic and non-inhibitory to cells at the 72-hour endpoint. 15.8% cell growth inhibition for the 100% concentration. 15.5% cell growth inhibition for the 30% concentration. 5.4% cell growth inhibition for the 10% concentration. 0.0% cell growth inhibition for the 3% concentration. Negative Control (b) (4): Non-cytotoxic and non-inhibitory to cells at the 72-hour endpoint. 0.0% cell growth inhibition for the 100% concentration. Positive Control (b) (4): Cytotoxic and inhibitory to cells at the 72-hour endpoint. 78.8% cell growth inhibition for the 100% concentration.
Acceptance Criteria: Scores of (b) (4) are considered passing and non-cytotoxic/non-inhibitory to cell growth.			
Conclusion: The test article showed passing results and was determined to be non-cytotoxic by the Inhibition of Cell Growth Test procedure.			

TABLE 12: SUMMARY OF <i>IN VITRO</i> MEDIUM ELUATE METHOD (MEM) CYTOTOXICITY TEST RESULTS FOR THE DISTAL SECTION OF THE PREDICATE (b) (4) INJECTOR SYSTEM (P/N 10-0219) CONSIDERED REPRESENTATIVE OF THE (b) (4) INJECTOR (P/N 10-0227) (b) (4) PROTOCOL NO. P10-1855-00A AND (b) (4) FINAL GLP REPORT NO. 12-2656-G1			
Test Method	Extraction Medium	Extraction Conditions Sample to Medium Ratio & Extraction Parameters	Results
ISO Medium Eluate Method (MEM) Elution Test Compliance with ISO 10993-5:2009 [EN ISO 10993-5:2009]	1x CMEM Cell Growth Medium (MEM supplemented with 10% fetal bovine serum extract)	Ten (10) samples representing the Distal Tip portions of the G2-M-IS Injector device with intended patient contact and proximity to the adhesive bond per 20 mL at 37°C/24 hrs.	Test Article: Non-cytotoxic to cells at all the 24 and 48-hour readings. 0% cell lysis (score of 0 in all triplicate samples) at both the 24 and 48 hour readings.
			Negative Control (1x CMEM and (b) (4)) Non-cytotoxic to cells at all the 24 and 48-hour readings. 0% cell lysis (score of 0 in all triplicate samples) at both the 24 and 48 hour readings.
			Positive Control: (b) (4) Severely cytotoxic to cells. >70 - 100% cell lysis (score of 4 in all triplicate samples) at both the 24 and 48-hour readings.
Acceptance Criteria: Scores of (b) (4) are considered passing and non-cytotoxic.			
Conclusion: The test article showed passing results and was determined to be non-cytotoxic by the MEM Elution Test procedure.			

TABLE 13: SUMMARY OF CONFIRMATIONAL <i>IN VITRO</i> MEDIUM ELUATE METHOD (MEM) CYTOTOXICITY TEST RESULTS FOR THE TEST ARTICLE REPRESENTATIVE OF THE (b) (4) INJECTOR (P/N 10-0227) PATIENT CONTACTING DISTAL TIP (b) (4) PROTOCOL NO. P13-0760-00A AND (b) (4) FINAL GLP REPORT NO. 13-04010-G1			
Test Method	Extraction Medium	Extraction Conditions Sample to Medium Ratio & Extraction Parameters	Results
ISO Medium Eluate Method (MEM) Elution Test Compliance with ISO 10993-5:2009 [EN ISO 10993-5:2009]	1x CMEM Cell Growth Medium (MEM supplemented with 10% fetal bovine serum extract)	Ten (10) Test Article Samples (4.9 gm) per 20 mL at 37°C for 24 hrs.	Test Article: Non-cytotoxic to cells at all the 24 and 48-hour readings. 0% cell lysis (score of 0 in all triplicate samples) at both the 24 and 48 hour readings.
			Negative Control (1x CMEM and (b) (4)) Non-cytotoxic to cells at all the 24 and 48-hour readings. 0% cell lysis (score of 0 in all triplicate samples) at both the 24 and 48 hour readings.
			Positive Control: (b) (4) Severely cytotoxic to cells. >70 - 100% cell lysis (score of 4 in all triplicate samples) at both the 24 and 48-hour readings.
Acceptance Criteria: Scores of (b) (4) are considered passing and non-cytotoxic.			
Conclusion: The test article showed passing results and was determined to be non-cytotoxic by the MEM Elution Test procedure.			

TABLE 16: SUMMARY OF <i>IN VIVO</i> GUINEA PIG MAXIMIZATION SENSITIZATION TEST RESULTS FOR THE DISTAL SECTION OF THE PREDICATE (b) (4) INJECTOR SYSTEM (P/N 10-0219) CONSIDERED REPRESENTATIVE OF THE (b) (4) INJECTOR (P/N 10-0227) (b) (4) PROTOCOL NO. P10-1867-01A AND (b) (4) FINAL GLP REPORT NO. 11-4096-G2			
Test Method	Extraction Medium	Extraction Conditions Sample to Medium Ratio & Extraction Parameters	Results
ISO Guinea Pig Maximization Sensitization Test Compliance with ISO 10993-10:2010	Normal Saline	Ten (10) samples representing the Distal Tip portions of the (b) (4) Injector device with intended patient contact and proximity to the adhesive bond and Twenty (20) GTS400 Stents per 20 mL at 70°C/24 hrs.	All guinea pigs normal. No irritation was present on any of the test or negative control (0% sensitized) guinea pigs at any of the 24 or 48-hour readings. Sensitization rating/classification (b) (4) Non-sensitizing.
	Vegetable (Sesame) Oil	Ten (10) samples representing the Distal Tip portions of the (b) (4) injector device with intended patient contact and proximity to the adhesive bond and Twenty (20) GTS400 Stents per 20 mL at 70°C/24 hrs.	All guinea pigs normal. No irritation was present on any of the test or negative control (0% sensitized) guinea pigs at any of the 24 or 48-hour readings. Sensitization rating/classification (b) (4) Non-sensitizing.
Acceptance Criteria: Passing results considered to be (b) (4)			(b) (4)
Conclusion: The test article showed passing results and was determined to show no sensitizing potential (0% sensitized) and a sensitization rating/classification (b) (4)			

TABLE 17: SUMMARY OF <i>IN VIVO</i> INTRAOCULAR IRRITATION IN RABBITS TEST RESULTS FOR THE DISTAL SECTION OF THE PREDICATE (b) (4) INJECTOR SYSTEM (P/N 10-0219) CONSIDERED REPRESENTATIVE OF THE (b) (4) INJECTOR (P/N 10-0227) (b) (4) PROTOCOL NO. TA044 800 AND (b) (4) FINAL GLP REPORT NO. 11T_36952_02			
Test Method	Extraction Medium	Extraction Conditions Sample to Medium Ratio & Extraction Parameters	Results
Intraocular Irritation in Rabbits Test Compliance with ISO 10993-10:2010	Balanced Saline Solution (BSS) Extract	Ten (10) samples representing the Distal Tip portions of the (b) (4) (b) (4) injector device with intended patient contact and proximity to the adhesive bond per 20 mL Extracted at 70°C/24 hrs	Both eyes of each animal were red at the end of day 0 with two animals extending to day 1. Otherwise, all animals tolerated the procedure well and appeared healthy throughout the study. Macroscopic observations at the end of day 0 and at the 24-hour observation were considered acceptable for an invasive procedure of this nature. The slit-lamp examination was performed at the 24, 48, and 72-hour observation points. All animals showed minimal iritis in both the test and control eyes in about equal frequency and severity on day 1. By day 2, the iritis had completely disappeared in all eyes. Synechia (iris to injection site) was noted in the both the test and control eyes of a few animals throughout the study. Injection sites remained visible in all corneas throughout the 72-hour study. All changes were judged to be related to the dosing trauma and were considered acceptable following an invasive procedure of this kind. There were no significant differences between the test and control eyes. In summary, there were no significant differences observed between the test article and the negative control exposed eyes in the test procedure. Therefore, the test article was determined to be non-irritating to intraocular tissues by the Intraocular Irritation Test in Rabbits procedure.
Acceptance Criteria: Considered to be non-irritating and passing when			(b) (4) (b) (4)
Conclusion: The test article showed passing results and was determined to be non-irritating to intraocular tissues by the intraocular Irritation Test in Rabbits procedure.			

TABLE 18: SUMMARY OF <i>IN VIVO</i> INTRACUTANEOUS REACTIVITY TEST RESULTS FOR THE DISTAL SECTION OF THE PREDICATE (b) (4) INJECTOR SYSTEM (P/N 10-0219) CONSIDERED REPRESENTATIVE OF THE (b) (4) INJECTOR (P/N 10-0227) (b) (4) PROTOCOL NO. P10-1865-01A AND (b) (4) FINAL GLP REPORT NO. 11-4096-G3			
Test Method	Extraction Medium	Extraction Conditions Sample to Medium Ratio & Extraction Parameters	Results
ISO Intracutaneous Reactivity Study in the Rabbit Compliance with ISO 10993-10:2010	Normal Saline	Ten (10) samples representing the Distal Tip portions of the (b) (4) injector device with intended patient contact and proximity to the adhesive bond and Twenty (20) GTS400 Stents per 20 mL at 70°C/24 hrs.	All rabbits normal. No evidence of irritation throughout the 72-hour observation period as compared to the negative control exposed injection sites. Non-irritating.
	Vegetable (Sesame) Oil	Ten (10) samples representing the Distal Tip portions of the G2-M-IS Injector device with intended patient contact and proximity to the adhesive bond and Twenty (20) GTS400 Stents per 20 mL at 70°C/24 hrs.	All rabbits normal. No evidence of irritation throughout the 72-hour observation period as compared to the negative control exposed injection sites. Non-irritating.
Acceptance Criteria: Considered to be non-irritating and passing when			(b) (4) (b) (4)
Conclusion: The overall mean score for the test article after subtraction of the corresponding negative control value was 0.0 for both the normal saline and vegetable (cottonseed) oil test article extracts. The test article showed passing results and was determined to be non-irritating by the Intracutaneous Injection Test procedure.			

TABLE 19: SUMMARY OF <i>IN VIVO</i> SYSTEMIC TOXICITY STUDY IN MICE TEST RESULTS FOR THE DISTAL SECTION OF THE PREDICATE (b) (4) INJECTOR SYSTEM (P/N 10-0219) CONSIDERED REPRESENTATIVE OF THE (b) (4) INJECTOR (P/N 10-0227) (b) (4) PROTOCOL NO. P10-1864-00A AND (b) (4) FINAL GLP REPORT NO. 11-4096-G4			
Test Method	Extraction Medium	Extraction Conditions Sample to Medium Ratio & Extraction Parameters	Results
ISO Systemic Injection Toxicity Test Compliance with ISO 10993-11:2006 [EN ISO 10993-11:2009]	Normal Saline	Ten (10) samples representing the Distal Tip portions of the (b) (4) injector device with intended patient contact and proximity to the adhesive bond and Twenty (20) GTS400 Stents per 20 mL at 70°C/24 hrs.	All mice normal. No weight loss or systemic affects over the 72-hour observation period as compared to the negative control exposed mice. Non-toxic.
	Vegetable (Sesame) Oil	Ten (10) samples representing the Distal Tip portions of the G2-M-IS Injector device with intended patient contact and proximity to the adhesive bond and Twenty (20) GTS400 Stents per 20 mL at 70°C/24 hrs.	All mice normal. No weight loss or systemic affects over the 72-hour observation period as compared to the negative control exposed mice. Non-toxic.
Acceptance Criteria: The test is considered negative and systemically non-toxic if (b) (4)			(b) (4)
Conclusion: The test article showed passing results and was determined to be systemically non-toxic by the Systemic Injection Test procedure.			

Reviewer's concluding comment regarding biocompatibility testing of the inserter:

As discussed in my previous comments, during the IND review the sponsor provided biocompatibility test reports on the inserter; however, CDRH had not reviewed these reports and this is the first submission where review of biocompatibility test reports for the inserter was performed. While the sponsor had identified the biocompatibility endpoints applicable for the inserter and despite our pre-NDA recommendation, the sponsor categorizes all the inserter components as components with limited (<24 hrs) tissue contact. In addition, as summarized in the manufacturing section of this consult, the sponsor had implemented manufacturing changes to the inserter. Through this submission the sponsor emphasizes that the testing conducted and the proposed approach is in line with FDA's recommendations and prior discussions even though CDRH was not consulted on these submissions and discussions. As discussed during the pre-NDA meeting, CDRH will consider the least burdensome approach and evaluate the totality of information provided by the sponsor. Due to uncertainty on whether the (b) (4) used in the biocompatibility testing are representative of finished sterile injector and to determine whether the manufacturing changes made during the clinical trial raise safety concerns, I considered the following:

- The sponsor states that (b) (4) were used for biocompatibility testing and indicate that these were subjected to same manufacturing processes as the finished inserter. The test performed on (b) (4) comprised of only cytotoxicity testing. The other biocompatibility endpoints (i.e., irritation, sensitization, acute systemic toxicity) were performed on the "predicate" (b) (4) injector that is manufactured of a "similar" (b) (4) inserter is approved under P170043.
- The (b) (4) was used for the two Phase 3 clinical studies and was subsequently replaced with (b) (4) for the IDOS-106-EXCH clinical study. The composition of these SS materials is very similar (e.g., (b) (4)). The same (b) (4) used to manufacture the (b) (4) in the "exchange" trial will also be used for the marketed inserter.
- The sponsor performed USP <661> Heavy Metals Assay in which the extraction ratio and extraction conditions represent a worst case scenario (e.g., exaggerated extraction ratio, extraction temperature of 70°C for 24 hrs.).
- The SS used for the inserter has a (b) (4).
- Leachable testing was performed on the TII, inserter and on the (b) (4) tray and Tyvek pouch and the quantitation limit of each method was lower than the analytical evaluation threshold (AET). There were no extractables detected from the implant or the inserter.
- The "to be marketed" inserter was used in IDOS-106-EXCH clinical study in which 33 subjects were implanted with to be marketed TII. This study was completed and the subjects were followed up for 12-mo. There were 13 subjects (39%) that reported an AE. The AE included eye irritation (n=2; 6%), corneal pigmentation

(n=1, 3%), infection (n=1; 3%), corneal abrasion (n=1, 3%), increase in IOP (n=2, 6%), visual field defect (n=3, 9%), etc. As summarized here, except for eye irritation, there are no other AEs that would raise biocompatibility concerns for the inserter. The eye irritation was reported only in 2 subjects and this event was reported on day 166 and day 369, respectively and appeared to be related to increase IOP. After IOP lowering medication had been administered to these subjects, the IOP was reduced and no other AEs were reported in these 2 subjects.

IX. Particulate matter testing

To evaluate the particulate matter originating from TII the sponsor used the recommendations included in USP<789> using the light obscuration method. The sponsor states that they validated this method for TII to ensure that the method is able to identify subvisible particulates in small volume of vehicle.

The following table is the acceptance criteria per USP <789>. The sponsor states that this test and specifications were previously agreed upon with the Agency at the June 7, 2021 Type C meeting.

Table 1: Subvisible Particulate Matter Proposed Specifications

Particles per Implant		
≥ 10 µm	≥ 25 µm	≥ 50 µm
50	5	2

Reviewer’s comment:

During the pre-NDA meeting we stated that CDRH had not been involved in prior discussions regarding particulate matter testing and we recommended that since USP<789> provides recommendations for ophthalmic (drug) solutions in their future NDA the sponsor provide additional information to demonstrate that the method used was validated for ophthalmic devices. As summarized above, the sponsor states that the light obscuration method used was validated. However, this method may be unreliable because it will not detect visible particulates and/or particulates that vary in shape.

As summarized in the product description section of this memorandum, TII is manufactured of titanium and EVA membrane and the inserter components that contact the TII are manufactured of SS. In addition, the inserter components that contact TII are not coated (b) (4). Therefore, it is unlikely that TII and the inserter would generate particulates; the particulates that may be present in the product would likely be generated from the drug product (which is reviewed by CDER). In addition, particulate matter testing is not requested for glaucoma medical devices. I also discussed the particulate matter testing with Claudine Krawczyk, Assistant Director in Division of Ophthalmic Devices (OHT1) who confirmed that particulate testing is not requested for glaucoma stents and for ophthalmic inserters that are not-coated. She also agreed that if the source of particulate matter is the drug product, CDRH can defer to CDER regarding particulate testing of the drug/implant. Therefore, based on material composition of TII and inserter and based on regulatory precedent for glaucoma devices, I concluded that I will not request additional assessment of particulate matter for TII.

X. Labeling

I reviewed the labeling and have no biocompatibility concerns regarding the proposed labeling, including the Directions for Use.

Digital Signature Concurrence Table (Doc ID: 04503.02.03)

This document represents a high-level summary of the Agency's determination on whether the applicant's device is substantially equivalent to a legally marketed predicate device. In determining whether the subject device is substantially equivalent to a predicate device, we carefully considered the relevant regulatory and statutory criteria for Agency decision-making under 21 CFR part 807 and section 513(i) of the Federal Food, Drug and Cosmetic Act (FD&C Act). We considered the burden that may be incurred by the applicant's attempt to follow the premarket notification process. The deficiencies provided in this review, if any, represent the required minimum information necessary to support a substantial equivalence determination. Therefore, we believe that we have considered the least burdensome requirements, under section 513(i)(1)(D) of the FD&C Act, for a 510(k) determination of substantial equivalence.

For the specific issues identified in the deficiency section(s) above, I provided a statement of basis for the request(s) and either cited as part of it an available, applicable, and relevant final rule, statute, final guidance, or FDA-recognized consensus standard, or confirmed that there is no final rule, statute, final guidance, or FDA-recognized consensus standard available, applicable, and relevant to the deficiency request(s).

Reviewer Sign-Off



Subject Matter Expert (SME) Review

Date: October 2, 2023	
SME Reviewer: Keith Christopher	
Expertise: Engineering	
Applicable Review Guide (if used): Not Applicable	
Submission # NDA218010	
Applicant: Glaukos Corp	Device Trade Name: iDose® TR (travoprost intraocular implant)
Optional Classification Information:	
Pro Code(s):	Class: [Choose] Reg #:
Rx/OTC: Rx	Reg Name:

I. SME Review Summary

Original review of material that resulted in interactive requests:

The sponsor has submitted engineering and shipping information for the device system (injector and implant device). In the review, it details the package integrity testing, cap/crimp strength, leak testing method validation, implant device stability, insertion testing, physical stability testing, and surface/edge quality testing. The sponsor provided adequate information for the package integrity, implant device stability over the shelf life, and for the cap/crimp strength, which all demonstrated that the device is stable over the proposed 2 year shelf life and had adequate device assembly and packaging/transportation. However, the sponsor did not provide enough information regarding the leak testing or the insertion testing.

The sponsor provided the edge/surface quality testing that was validated through the SEM testing. They provided x115 images of the implant at t=0 and to demonstrate the device is stable over the entire use life of the device, they provided images of explanted devices to demonstrate the edge quality is maintained. The images demonstrated no device defects, scratches, or rough edges. This is adequate to demonstrate the stability of the edge and surface characteristics.

For the leak testing, they compared the leak rates between “reference” devices and ones that had holes made in them intentionally. However, it cannot be confirmed that the “reference” devices are similar to the ones used in the clinical studies. Therefore, it is unknown if these devices are accurate representations of the ones used in the clinical trial. A deficiency was drafted for them to provide the data from the leak test done in the pre-NDA submission and to compare those to the reference devices used in the method validation study.

For the insertion testing, it was conducted with an implant that was fixed to a rod and was inserted and removed from a simulated eye. The sponsor tested the implantation and explantation

of the device with a maximum applied force of (b) (4). Since this force adequately punctures the simulated eye model, which has similar properties to the trabecular meshwork, and this device has force that is only generated by the user and no internal spring component, this is a reasonable force to be used for the assessment. The sponsor compared the maximum force experience by the anchor during implantation, explantation, and under its own weight when in the eye and determined that the values were within a safety factor of (b) (4) respectively. The safety factor was a comparison of the minimum yield strength of titanium according to ASTM (b) (4). (b) (4) This testing demonstrates that the implant can withstand the exerted forces during the simulated implantation procedure with a force that is an adequate evaluation since there is no force applied other than that of the user.

The sponsor has noted that the AQL validation is not included in this package. However, they mentioned that it is available upon request. This is essential to demonstrate the consistent performance of the final and finished device product. There will be a deficiency asking for the AQL and quality assurance materials.

Interactive review notes after communicating deficiencies:

The sponsor was asked to provide responses to deficiencies that were related to a need for validation for leak testing and testing units, AQL for the EVA membrane, validation for the manufacturing changes to the (b) (4) and validation for the (b) (4) process. The sponsor provided responses to each of the deficiencies and demonstrated that the leak testing was adequate to demonstrate the safety and effectiveness profile, an adequate AQL plan, validation for the (b) (4), and the validation for the (b) (4). All of these were found adequate and the sponsor has resolved all the deficiencies. The recommendation is now CND (no deficiencies identified).

II. Recommended Communication

1. **Resolved:** In the submission, you provide a leak test method, the validation of the leak test method and the technical report for establishment of the evaluation criteria for the leak test (i.e., NMT (b) (4) Travoprost) in documents #DN-1447, #RN-0299, and #RN-0477, respectively. In the validation report, #RN-0299, and the establishment of the evaluation criteria, #RN-0477, you compared the leak rates between nominal units and ones that had holes made in them intentionally, or leaking units. However, it cannot be confirmed that the nominal test samples are similar to the ones used in the clinical studies and, therefore, it is not clear whether the evaluation criteria of NMT (b) (4) is representative of the clinical performance of the implant. Without this information, it cannot be determined whether the device components intended for marketing can be characterized as having similar safety and effectiveness as device components that were clinically studied with regards to implant leakage. Therefore, please clarify how the nominal samples are representative of the clinically studied versions.
2. **Resolved:** In the document titled "Device Constituent Summary for Travoprost Intraocular Implant NDA", you state (3.2.R DEVICE, page 150) that the the AQL validation (VR-1269) is available upon request. The quality inspection methods are critical to understanding the

ability to provide a consistent and reliable final product for the users and ensures the safety, effectiveness, and benefit/risk profile is consistent across all devices. Please provide the AQL validation and all quality assurance measures to demonstrate consistent reliability of the subject device.

3. **Resolved:** In your submission, you provided details of manufacturing changes to the (b) (4) (3.2.P.2.3 Manufacturing Process Development, page 33). In these changes, you detail how the process was altered (b) (4). However, it is not clear if this method was validated on the device version that is intended to be commercially distributed. Without validation, the safety and effectiveness of the device cannot be confirmed. Therefore, please provide the process validation testing on the device version that is intended to be commercially available or justification as to why it is not necessary.
4. **Resolved:** In your submission, you describe a new (b) (4) process for (b) (4) (3.2.P.2.3 Manufacturing Process Development, page 17). In the document titled “Device Constituent Summary for Travaprost Intraocular Implant NDA”, you indicate (page 178) that the (b) (4) process was validated in “Validation Report for (b) (4) System”, document #RN-0794. However, it does not appear that this document has been provided. Without this information, it cannot be determined whether the device components intended for marketing can be characterized as having similar safety and effectiveness as device components that were clinically studied with regards to the durability of the device to (b) (4). Therefore, to validate the performance of the (b) (4) process (b) (4), please provide this report.

III. Scope of Request/Information Reviewed

REGULATORY HISTORY:

Below is a table provided by the sponsor for previous interactions with the Agency regarding this device which was investigated under IND120995.

Table 2. Summary of Formal Meetings with FDA and Glaukos

Date of Meeting or Written Response	Meeting Type	Type of Advice	Date of Meeting Minutes or Response	Reference ID
28 Mar 2014	Type B	Pre-IND: CMC, Nonclinical, Clinical	04 Apr 2014	3493177
15 Sep 2014	Type B (WRO)	Pre-IND: CMC, Nonclinical	15 Sep 2014	3627620
19 May 2015	Type B (WRO)	Pre-IND: CMC, Nonclinical	19 May 2015	3760114
15 Jun 2015	Type B (WRO)	Pre-IND: CMC	15 Jun 2015	3779304
04 Dec 2017	Type B	End-of-Phase 2 Meeting	17 Dec 2017	4196564
04 Dec 2018	Type C	Clinical	21 Nov 2018 ^a	4353162 ^a
20 Mar 2020	Type C	CMC	15 Apr 2020	4592662
17 Feb 2021	Type B (WRO)	CMC	17 Feb 2021	4748393
07 Jun 2021	Type C	CMC, Nonclinical, Clinical	25 Jun 2021	4816756
15 Oct 2021	Type A	CMC (Microbiology)	02 Nov 2021	4882419
09 May 2022	Type B	Pre-NDA: Clinical (Biostatistics)	18 May 2022	4985069

a: Preliminary meeting comments

The following provides the history of CDRH consults provided for the IND:

March 28, 2014 – Biocompatibility and sterility for pre-IND feedback. In the consult memos, the biocompatibility reviewer, Simona Bancos, asked the sponsor to adhere to ISO 10993 for all device components and testing articles, including the inserter and the implant. It was also recommended that the sponsor include MRI labeling. The sterility reviewer, Jennifer Brown, advised that the sponsor adhere to an endotoxin limit of (b) (4) EU/implant. Additionally, she asked for shelf life and accelerated aging studies and that sterility testing be done (b) (4)

May 19, 2015 – Biocompatibility for pre-IND feedback. The biocompatibility reviewer, Simona Bancos, asked the sponsor to provide additional information and a comparison of the proposed (b) (4) and the finished device to demonstrate an adequate evaluation in addition to asking for the reasoning why the sponsor believes the (b) (4) are acceptable in place of the finished implant.

December 4, 2017 – Engineering and biocompatibility for post-Phase II testing. The biocompatibility reviewer, Simona Bancos, agreed with the sponsor that if the device’s titanium container was (b) (4) then it is a minor manufacturing change and it does not impact biocompatibility. Additionally, she recommended that the sponsor provide evidence that the inserter is not patient contacting if the (b) (4) vendor for the device fabrication has changed and that is because using materials from different vendors may change the material specification and

introduce new impurities in the inserter materials. The final feedback given by the biocompatibility reviewer is that testing should be done on the inserter according to ISO 10993. The engineering reviewer, Claudine Krawczyk, asked the sponsor to provide verification testing for the device to ensure the device cap properly retains the EVA membrane and to provide clarification on how a proposed [REDACTED] (b) (4) does not impact the final overall length of the device. Finally, the engineering reviewer also stated that additional verification testing will be needed if the sponsor decides to introduce new models of the device.

(b) (4)

November 17, 2022 (not listed) – Pre-NDA review and discussion about expected/required testing with the engineering, sterility, and biocompatibility review by myself, Jennifer Brown, and Simona Bancos respectively.

IV. Detailed Review

Glaukos proposes the following Indications for Use for iDose implant:

The proposed indication for the Travoprost Intraocular Implant is for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Engineering Reviewer Comment: From the device summary section of the NDA submission:

The Travoprost Intraocular Implant, Model G2-TR-125 contains 75 µg of travoprost in a drug delivery system. Travoprost Intraocular Implant is surgically anchored in the anterior chamber angle of the eye and designed to release travoprost slowly as a treatment for elevated IOP in patients with open-angle glaucoma or ocular hypertension.

The Travoprost Intraocular Implant is a sterile, drug-eluting implant that is surgically delivered through a clear corneal incision and anchored in the anterior chamber angle of the eye. The nominal dimensions of the assembled implant are 1.84 mm long by 0.494 mm in diameter. The Travoprost Intraocular Implant is comprised of a titanium reservoir (also referred to as titanium container) with titanium anchor, containing 75 µg of travoprost drug substance formulated with

(b) (4). It is capped with an ethylene vinyl acetate (EVA) copolymer (with (b) (4) vinyl acetate content) membrane (also referred to as the elution rate controlling EVA membrane) which is held in place by a titanium cap. The Travoprost Intraocular Implant is pre-loaded into the inserter. The assembled implant and inserter are then placed in a blister tray that is sealed with a Tyvek lid. The sealed tray is placed together with an oxygen absorbing packet into a transparent barrier pouch made of (b) (4), which is sealed and placed in a unit carton. The unit cartons are (b) (4) the final labeling contents are added in the unit carton (e.g., prescribing information and patient card).

The titanium materials used in the implant are Titanium (b) (4) and Titanium (b) (4).

Travoprost was chosen as the drug of choice in the implant based on its long history of safe and effective use worldwide. A schematic of the Travoprost Intraocular Implant is presented in Figure 2-10. The implant is placed into the eye through a small clear corneal incision. Placement of the implant within the eye is shown in Figure 2-11. While Figure 2-10 and Figure 2-11 are significantly magnified and not to scale, Figure 2-12 shows the actual size of the implant in relation to a human finger. Figure 2-4 shows the inserter loaded with the implant.

The function of the EVA membrane component is to retain the travoprost (when present) while facilitating the slow controlled release from the implant. The rate of elution is defined by the drug product specification and tested at release and on stability.

Travoprost is a prodrug, where enzymatic cleavage in vivo converts travoprost into its corresponding free acid form. Binding of the free acid to prostaglandin FP receptors results in lowering of IOP. The conversion of travoprost ester prodrug to travoprost acid is well established for topical eye drops containing travoprost. The Travoprost Intraocular Implant delivers travoprost ester prodrug directly into the eye, bypassing the cornea.

***Engineering Reviewer Comment:** It should be noted that the device is implanted in the target area through the release of the product (b) (4). A rod pushes the device (b) (4) and releases it (b) (4). There is no spring or force that is generated within the injector other than the direct force from the surgeon on to the end of the implant that pushes the implant (b) (4). Additionally, there is no method of controlling the implantation depth other than the tapered area of the implant where the anchor meets the reservoir. It appears that the sponsor relies on that tapered area of the device to provide consistency with the implantation depth.*

Figure 2-10: Travoprost Intraocular Implant (Assembled View)

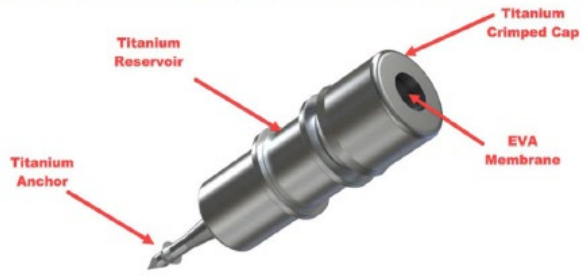
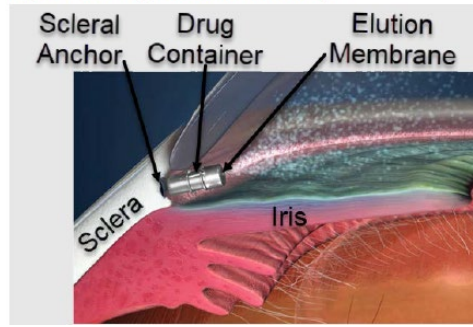


Figure 2-11: Implant Location in the Eye



(b) (4)

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Table 12: Travoprost Intraocular Implant Device Constituent Testing

Device Finished Product Test	Test Method	Acceptance Criteria
Physical Appearance	M16818 (Microscope 30X Magnification)	All components are present. Cap is secured to container and cap, membrane and container do not appear damaged. Packaging components do not appear damaged.
Bacterial Endotoxin – inserter hand piece / inserter tip and implant	USP <85>	NMT (b) (4) NMT
Sterility – inserter hand piece / implant*	USP <71>	Conforms to test requirements

* Glaukos reviews the sterilization documentation (Certificate of Processing) prior to final release, in accordance with the requirements for device testing requirements. The actual sterility testing as described in Table 1 is done to fulfil the requirements for the drug constituent of the drug led drug-device combination product.

Table 6: Manufacturing, Packaging and Control Sites of Travoprost Intraocular Implant

Site	Responsibility
Glaukos Corporation 229, 236 Avenida Fabricante San Clemente, CA 92672 FEI: 3012341472 DUNS: 012835406 Official Correspondent: Ted Wheeler 229 Avenida Fabricante San Clemente, CA 92672 Phone: (949) 481-0583 Email: twheeler@glaukos.com	(b) (4) component receiving inspection component release Manufacturing: • Component preparation • drug product formulation • Drug product filling • EVA disc (membrane) manufacture • Implant assembly • Inserter assembly Primary and secondary packaging Batch disposition and final release

Engineering Reviewer Comment: Please note that the sponsor has described the manufacturing process in the flow charts and tables included above. However, there is a lack of detail relating to the AQL vs visual inspection (VI) process and when each are used. This will be added to the deficiency that is requesting AQL certification. **NOT ACCEPTABLE**

Sponsor Response to Deficiency #2: Glaukos confirms that the AQL validation and all quality assurance measures are present to demonstrate consistent reliability of the device constituent of the Travoprost Intraocular Implant. Per the Agency’s request, the AQL validation (Protocol VP-1269 and Report VR-1269) for the EVA membrane produced at (b) (4) is provided with this response. The report concludes that an AQL= (b) (4) or (b) (4) can be applied to the laser cut membrane. The approach to this validation was agreed upon by CDER during the Type C Meeting on June 07, 2021, FDA Meeting Minutes dated June 25, 2021; Reference ID 4816756). Glaukos has the following quality assurance measures in place to demonstrate consistent reliability of the device constituent of the Travoprost Intraocular Implant:

- (b) (4) Quality Agreement
- (b) (4) AQL= (b) (4) inspection of critical dimensions as described in (b) (4) Performance Qualification, and 100% visual inspection
- AQL inspection by Glaukos upon receipt of the EVA membrane
- Glaukos thickness measurement (b) (4)
- Confirmation of membrane thickness (b) (4)
- Endotoxin testing (b) (4)

Engineering Reviewer Comment to the Sponsor Response: The sponsor has provided (VR-1269) the following acceptance criteria for the AQL (b)(4) for the EVA membrane (Section 11) and the results of the testing (Section 12):

11. ACCEPTANCE CRITERIA

- 11.1 Bioburden and Endotoxin (LAL) testing shall be performed per §8.3.3.2 and (b)(4) report shall be attached to the Validation Report.
- 11.2 Components per Table 1 shall undergo First Article Inspection per DN-0522 and results attached to the Validation Report.
- 11.3 AQL Sampling Plan shall be performed as outlined in §10.2 and assign an AQL sampling plan for the component listed in Table 1.
- 11.4 (b)(4) Laser Processing OQ/PQ performed and the (b)(4) final report documented in the Validation Report for this protocol.

Attribute Data Analysis	Variable Data Analysis	
For at least 3 separate lots, verify that at least 50 units were inspected with no failures observed.	Analyze the data from each lot using Distribution Analyzer per Appendix D of DN-0237 / QA-07-013. Verify that the data is normally distributed. Provide a justification for any non-normal data sets.	Confirm that the 95% confidence and 95% reliability that the tolerance interval generated using distribution analyzer is within the dimension's specification limit.
*Note that variable data may be analyzed as attribute data if at least 50 samples are measured.		

12. RESULTS

- 12.1 Bioburden testing performed per §8.3.3.2 by (b)(4) see Attachment 4. Bioburden was found to be below the detectable limit.
- 12.2 LAL testing was performed per §8.3.3.2 by (b)(4) see Attachment 5. Endotoxin was found to be below the detectable limit.
- 12.3 First Article Inspection was performed and met the acceptance criteria, see Attachment 3.
- 12.4 Inspection Results for 10-0636 are summarized in Table 7 and Table 8.

Characteristic	Glaukos Lot	(b)(4) Lot	# of Units Inspected	# of Rejected Units	Meets/Exceeds 95/95 Requirement?
Visual Inspection per Critical Feature #3	QA-19-0058-03	(b)(4)	100	0	Yes
	QA-20-0003-04	48154-1-5	100	0	Yes
	QA-20-0003-06	48154-1-6	100	0	Yes
Total	All	All	300	0	Yes

Characteristic	Sample Size
Visual	AQL = (b)(4)
Dimension #1	Maintain current method of sampling
Dimension #2	AQL = (b)(4)

The sponsor has demonstrated that an AQL of (b)(4) is an acceptable limit for the inspection of the devices which evaluates bioburden and endotoxin limits and with article inspection limits that evaluates critical dimension of the EVA membrane. The results described in this qualification indicate the PN 10-0636 components produced at (b)(4) meet and exceed the minimum requirements for adoption of an AQL sampling plan at Glaukos Receiving Inspection. The assessment is acceptable and the deficiency has been resolved. ACCEPTABLE

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Engineering Reviewer Comment: The sponsor has made several changes to the manufacturing process and design of the device. Most notably were the changes to (b) (4), which is acceptable from an engineering point of view and was discussed in TR-1134 which compared the long term elution rate (ug/day) for (b) (4) (Table 16 of TR-1134). The sponsor demonstrated that the elution rate is consistent between the two methods (see below).

Table 16. Equivalence test of long-term elution rate (µg/day) for process robustness assessment				
Time Points	Mean±STD (µg/day) (b) (4)	Mean±STD (µg/day) (b) (4)	Acceptance Criteria (b) (4)	Verdict
Day 7	0.82±0.17	0.92±0.16	95% Confidence Interval	Equivalent
Day 14	0.32±0.09	0.27±0.05		Equivalent
Day 21	0.23±0.06	0.20±0.02		Equivalent

However, the sponsor still needs to provide their inspection/AQL plan to fully assess this change adequacy. The next change, (b) (4) is acceptable as it has not impacted formulation load/content, raw component materials, mechanism of controlled release, and gross external dimensions: EVA membrane diameter, EVA membrane thickness, titanium cap hole diameter, titanium reservoir outer diameter, titanium reservoir inner diameter, titanium reservoir cavity volume, implant overall length, or the implant overall diameter. Therefore, the change is acceptable and does not impact safety or effectiveness. The final change, the (b) (4) manufacturing was amended to (b) (4) attempt to simplify the process. This is also acceptable as it allows more control over quality control. However, as mentioned before, the sponsor needs to provide the AQL and quality control measures for the full assessment of adequacy. **NOT ACCEPTABLE**

Sponsor Response to Deficiency #3: (b) (4) of the travoprost intraocular implant that is intended to be commercially available was qualified and validated through multiple steps, namely validation at the vendor, validation by Glaukos and validation in a clinical trial.

The vendor (b) (4) performed the requisite validation of this change. This validation, which was overseen by Glaukos, is summarized in Validation Report VR-1276 (Attachment 11 and Attachment 12) provided herein.

Glaukos further validated (b) (4) by (b) (4) conducting shipping and transportation studies to demonstrate that the (b) (4) performed as intended. The implant aging and shipping study (RN-0714), provided in 3.2.R Device Section 3.6 of the original NDA (Sequence Number 0001), demonstrated successful functionality of the (b) (4) after 2 years of accelerated aging.

The (b) (4) was used in the 12-month clinical trial IDOS-106-EXCH further demonstrating proper functionality. Therefore, this manufacturing change was validated in a 12-month clinical trial as agreed upon by CDER during the Type C Meeting on June 07, 2021, FDA Meeting Minutes dated June 25, 2021; Reference ID 4816756).

Engineering Reviewer Comment to the Sponsor Response: The sponsor has provided a validation report (VR-1276) for the testing of the (b) (4) which was overseen by Glaukos. Below is the acceptance criteria for the AQL of (b) (4) (Table 8).

Table 8. AQL Acceptance Criteria		
Attribute Data Analysis	Variable Data Analysis	
For at least 3 separate lots, verify that at least 92 units were inspected with maximum 4 failures observed.	Analyze the data from each lot using Distribution Analyzer, or Minitab per Appendix D of DN-0237 / SOP-0237 / QA-07-013. Verify that the data is normally distributed. Provide a justification for any non-normal data sets.	Confirm that the 95% confidence and 90% reliability that the tolerance interval generated using distribution analyzer is within the dimension's specification limit.

Table 10. (b) (4) Pull Test					
Sample Size (n)	Mean ($\bar{x}_l$)	Standard Deviation (s_l)	Normal ($p > .05$)	Distribution Analyzer k-factor analysis 95%/90%	Pass/Fail
30	4.1580	0.6979	Yes	Yes (b) (4)	Pass

Table 11. Trigger Force					
Sample Size (n)	Mean ($\bar{x}_l$)	Standard Deviation (s_l)	Normal ($p > .05$)	Distribution Analyzer k-factor analysis 95%/90%	Pass/Fail
30	0.1057	0.0483	Yes	Yes (b) (4)	Pass
*Original data set required transformation in order to satisfy normality.					

The sponsor provided measurements for a pull test (b) (4) (Table 10) and an analysis of the force exerted from the trigger force (Table 11) to ensure the force is less than the fail force found in the pull test. After testing, it has been shown that the force for implantation is far less than the force measured in the pull test. Therefore, this is acceptable. The sponsor has provided adequate analysis of the device inspection which has provided sufficient evidence to support the following sampling plans which are for the evaluation for various dimensions:

Table 12. PN 10-0705 Receiving Inspection Sampling Plan	
Characteristic	Specifications
Visual Inspection	(b) (4)
Dimension #1	
Dimension #2	
Dimension #3	
Dimension #4	
Dimension #5	
Dimension #6	

This AQL is acceptable (b) (4) to fix the injector features together. **ACCEPTABLE**

Also note that the sponsor has provided a traceability matrix in DRTM-0007 which details the document history, design specifications, user needs, design inputs, design outputs, and design verification output. The matrix demonstrates the flow of the design considerations and the stages of progression for each of them with references to the testing documentation.

Engineering Reviewer Comment: It was requested in the pre-NDA meeting in November 2022 that the sponsor provide package/shipping simulation testing, simulated insertion testing, strength testing for the anchor and cap/crimp strength, quality assurance measures, stability testing, surface and edge quality testing, physical stability testing, and shelf life performance/stability performance data in the future NDA. The following is a discussion and analysis of all testing included.

PACKAGE INTEGRITY AND PERFORMANCE VALIDATION (DOC #):

Engineering Reviewer Comment: The sponsor performed the following tests to validate the package integrity according to ASTM D4169 and ISTA 3A. From an engineering perspective, the testing must demonstrate that the device is in a condition that allows consistent performance over the shelf life following accelerated aging, simulated distribution, and environmental conditioning. Therefore, testing needs to demonstrate the ability of the inserter to implant the device, have functional trigger forces, and for the inserter to retain the implant over the shelf life prior to implantation. The following are the testing requirements, acceptance criteria, and applicable testing to demonstrate device stability after shipping and conditioning:

Table 9. Testing Requirements						
Test #	Test Description	Build Type	# of Units (Per Time Point)	Test Procedure	Testing Site	Comments
1	Visual Inspection: Seal Integrity	Simulation	60	ASTM F1886	(b) (4)	Both outer pouch and Tyvek sealed tray to be tested. Same units are to be used for Test #1 and Test #2.
2	Bubble Leak	Simulation	60	ASTM F2096		Both outer pouch and Tyvek sealed tray to be tested.
3	Peel Strength	Simulation	30	ASTM F88		Both outer pouch and Tyvek sealed tray to be tested.
4	Unit Carton Inspection	Full Assembly	60	See §10.9	Glaukos	Same units used for Test #4 – Test #9 & Test #11
5	Label Visual Inspection	Full Assembly	60	See §10.10	Glaukos	Not necessary for (b) (4) labels used for testing identification, potential human use stickers, or radiation indicators. Same units used for Test #4 – Test #9 & Test #11
6	Label Legibility	Full Assembly	60	See §10.11	Glaukos	Not necessary for (b) (4) labels used for testing identification, potential human use stickers, or radiation indicators. Same units used for Test #4 – Test #9 & Test #11
7	Prescribing Information Visual Inspection	Full Assembly	60	See §10.12	Glaukos	Same units used for Test #4 – Test #9 & Test #11
8	Safety Clip Removal and Visual Inspection: Implant Retention	Full Assembly	60	See §10.13	Glaukos	Same units used for Test #4 – Test #9 & Test #11
9	Functional: Implantation, Release, and Re-grasp	Full Assembly	60	See §10.14	Glaukos	Same units used for Test #4 – Test #9 & Test #11
10	Functional: Trigger Force	Full Assembly	60	See §10.15	Glaukos	N/A
11	Visual Inspection: Implant Stability	Full Assembly	60	See §10.16	Glaukos	Same units used for Test #4 – Test #9 & Test #11

Table 10. Testing Acceptance Criteria				
Test #	Test Description	Test Type	Risk Assessment	Acceptance Criteria
1	Visual Inspection: Seal Integrity	Attribute	See §11.4.1.1	The visual inspection report shall be in compliance with ASTM F1886, "Standard Test Method for Determining Integrity of Seals for Flexible Packaging by Visual Inspection". The seal area must have no channels in the seal.
2	Bubble Leak	Attribute	See §11.4.1.1	The Bubble Leak Test report shall be in compliance with ASTM F2096, "Standard test method for detecting gross leaks in medical packaging by internal pressurization", (Bubble Leak Test). The results of the tested samples must not show any visible leaks.
3	Peel Strength	Variable	See §11.4.1.2	The peel strength test report should be in compliance with ASTM F88, "Standard test method for seal strength of flexible barrier." The peel strength of the outer pouch must be (b) (4). The peel strength of the Tyvek sealed tray must be (b) (4).
4	Unit Carton Inspection	Attribute	See §11.4.1.1	Unit cartons must not be severely damaged. There should be no rips or holes. Unit cartons must have minimal to no smudging of the printing. Unit cartons must be legible after shipping and distribution.
5	Label Visual Inspection	Attribute	See §11.4.1.1	Labels must be adhered to the Tyvek lid and unit carton after shipping and distribution testing.
6	Label Legibility	Attribute	See §11.4.1.1	Labels and patient ID card must have minimal to no smudging of the printing. Labels and patient ID card must be legible after shipping and distribution.
7	Prescribing Information Visual Inspection	Attribute	See §11.4.1.1	Prescribing information inside the unit carton must not be torn or damaged. If prescribing information is lightly torn, ensure writing is still legible. Prescribing information must have minimal to no smudging of the printing. Prescribing information must be legible after shipping and distribution.
8	Safety Clip Removal and Visual Inspection: Implant Retention	Attribute	See §11.4.1.1	The implant must be present on the inserter after shipping and distribution testing.
9	Functional: Implantation, Release, and Re-grasp	Attribute	See §11.4.1.1	The implant must be delivered. The implant must be re-grasped and removed from the Gel.
10	Functional: Trigger Force	Attribute	See §11.4.1.1	The force to move the trigger shall be less than or equal to (b) (4). The implant must release.
11	Visual Inspection: Implant Stability	Attribute	See §11.4.1.1	At minimum (b) (4) magnification, the container tip must not be bent or blunt. The container must not have any jagged edges. The membrane must not be damaged.

Engineering Reviewer Comment: The sponsor performed the tests at the t=0 and t=2yr timepoint with the 2yr timepoint being done through accelerated aging. Environmental and atmospheric conditioning per ISTA 3A was performed on all samples to prove package and product integrity is not adversely affected by climate conditioning that can be observed in all climates across the US. Distribution simulation per ASTM D4169 was performed on all samples to simulate the various climate conditions that the device may experience. Testing was performed on conditioned samples to prove package and device integrity is not adversely affected during shipping and handling. Both of these standards are applicable and acceptable for the size of the package and the distribution cycle chosen. The following are the testing results:

Table 11. Summary of Results for Time T=0						
Test #	Test Description	Test Type	Sample Size	# of Failures	Pass / Fail	Results
4	Unit Carton Inspection	Attribute	60	0	Pass	- All units met the acceptance criteria. There was no severe damage and no rips or holes to the unit cartons prior to handling. After running a gloved finger over the samples, there was no smudging of printing and all information remained legible. - See Attachment 7 for completed inspection data sheets. - Note: Unit #50 was ripped while opening. It remained intact and undamaged prior to handling. Therefore, the unit is not a failure.
9	Functional: Implantation, Release, and Re-grasp	Attribute	60	0	Pass	- All units met the acceptance criteria. The implant was delivered and regripped from the Gel-Pak. - See Attachment 8 for completed inspection data sheets.
10	Functional: Trigger Force	Attribute	60	0	Pass	- All units met the acceptance criteria. The force to move the trigger was less than (b) (4) for all units. - See Attachment 8 for completed inspection data sheets. - See Deviation in §13.2.1 for clarifying acceptance criteria.
11	Visual Inspection: Implant Stability	Attribute	60	0	Pass	- All units met the acceptance criteria. The container tip was not bent or blunt, and the container had no jagged edges. The membrane was not damaged. - See Attachment 8 for completed inspection data sheets. - See deviation in §13.3.1.1 for the addition of this test.

Table 12. Summary of Results for Time T=2AA						
Test #	Test Description	Test Type	Sample Size	# of Failures	Pass / Fail	Results
4	Unit Carton Inspection	Attribute	60	0	Pass	- All units met the acceptance criteria. There was no severe damage and no rips or holes to the unit cartons prior to handling. After running a gloved finger over the samples, there was no smudging of printing and all information remained legible. - See Attachment 10 for completed inspection data sheets. - Note: Unit #3 and #23 were ripped while opening. They remained intact and undamaged prior to handling. Therefore, the units are not failures. See Attachment 10 for documented results.

9	Functional: Implantation, Release, and Re-grasp	Attribute	60	0	Pass	- All units met the acceptance criteria. The implant was delivered and regrasped from the Gel-Pak. - See Attachment 11 for completed inspection data sheets.
10	Functional: Trigger Force	Attribute	60	0	Pass	- All units met the acceptance criteria. The force to move the trigger was less than (b)(4) for all units. - See Attachment 11 for completed inspection data sheets. - Unit #32 was dropped prior to testing. See deviation in §13.3.2.1 for details.
11	Visual Inspection: Implant Stability	Attribute	60	0	Pass	- All units met the acceptance criteria. The container tip was not bent or blunt, and the container had no jagged edges. The membrane was not damaged. - See Attachment 11 for completed inspection data sheets. - See deviation in §13.3.2.2 for clarifying remarks regarding data.

All 60 samples at each of the timepoints passed the acceptance criteria which demonstrates adequate performance of the device. The testing demonstrated that the device is in acceptable working condition after passing all acceptance criteria and supports the device system, both the implant and injector, so that they provide consistent performance after distribution and over the product use life before implantation of the device. There was only one deviation that affected testing and that is one for the t=2yr; there was one device that was accidentally dropped to the floor and damaged before the trigger testing. Therefore, a device from a different unit was included as a replacement, which passed the performance criteria. After review of the shelf life performance validation and package distribution testing, the sponsor has demonstrated adequate performance. **ACCEPTABLE**

CRIMP/CAP STRENGTH (DOC #VR-1106, found under Section 3.2.P.2):

Engineering Reviewer Comment: The sponsor provided testing for the crimp strength with a sample size of 15 for each of the Phase 2 and Phase 3 INDs:

Table 6. Data Summary						
Group	Sample Size (n)	Mean ($\bar{x}_t$)	Standard Deviation (s_t)	Normal ($p > .05$)	k-factor analysis ($\geq 100\text{gf}$, 95%/90%)	Pass/Fail
Phase 2 IND	15	1138	32.1	Yes (b)(4)	Pass (b)(4)	Pass
Phase 3 IND	15	1141	49.6	Yes	Pass	Pass

*Original data set required transformation in order to satisfy normality.

The following is the testing method:



Figure 4. Capped device in test setup

1. The (b) (4) load cell should be attached to the Instron test machine with the adjustable chuck attached.
2. The test fixture is to be attached to the micrometer plate and crimped cap and container placed in the fixture as shown in Figure 4.
3. A gage pin or equivalent of diameter 0.011 should be attached to the adjustable chuck using a pin vise and the micrometer plate adjusted until the pin can easily go into the container.
4. Inspect and photograph the crimped cap of each test sample prior to testing.
5. Using a compression program on the Instron tester. Compress the membrane/cap until cap is removed from container. Program the compression rate to two (2) inches per minute.
6. Record peak force, raw data and force curve using the Instron output.
7. Remove the implant and cap from the fixture and capture images of both after disassociation or reaching maximum load.
8. Record which configuration was tested (Phase 2 or 3), peak force, and all pertinent information in the Data Sheet in VP-1106.
9. Repeat the test with a minimum of 15 samples of each assembly configuration (Phase 2 and Phase 3).

The following is the acceptance criteria:

- **Cap Strength**
 - The Validation report shall have a completed Data Sheet for both versions of the container.
 - Peak disassociation force shall be greater than (b) (4) for all assemblies meeting 95/90 for either variable or attribute analysis. This represents a (b) (4) safety factor for peak force as the force (b) (4) against the cap is exerted for 12 weeks.
 - Any units for which the pin either breaks or buckles and the load is above (b) (4) shall be acceptable and may be recorded as the peak force.
- A sample size of >29 with zero (0) failures will result in 95% Confidence and 90% Reliability for each group using attribute analysis. A minimum quantity of 15 is required for variable data analysis meeting 95/90.

The following observations were also made:

- *No pin buckling occurred. The same push pin was used across all 30 tested units.*
- *No caps disassociated within the Phase 2 group. Each failure mode for Phase 2 was the pin pressing through the small cap hole, shearing titanium as shown in Appendix F figures.*
- *Four caps out of 15 partially disassociated in the Phase 3 group. Although it is noted that all partially disassociated caps had the same peak values as the sheared caps.*
- *All pre and post testing images captured are archived in Appendix F figures .*
- *Both Phase 2 and Phase 3 met the required 95/90 requirement for greater than (b) (4) force, meeting the acceptance criteria that the Phase 3 version is equivalent to the Phase 2 version.*



The testing revealed that all acceptance criteria was met with no deviations in testing. This demonstrates that the cap stays intact to the body of the implant after significant force. Therefore, this testing is adequate to demonstrate the cap strength. However, the sponsor has not provided a validation of the (b) (4) process and this will be communicated in a deficiency.

NOT ACCEPTABLE

Sponsor Response to Deficiency #4: As per the Agency's request, RN-0794 (Validation Report for (b) (4) System) is provided with this response. In addition, we are providing RN-0657 (iDose (b) (4) System Validation Strategy) which prospectively outlined the strategy for validation of the (b) (4) and included a detailed comparison of the (b) (4) with the previously utilized semi-(b) (4)

Engineering Reviewer Comment to the Sponsor Response: The sponsor has provided the (b) (4) validation report (RN-0794) which involved a push off test to measure the resistance of the cap from pushing off the implant body, the accelerated elution test and leak test that was also provided in the original review. Here is the acceptance criteria:

13.3.1 Push Off Test

13.3.1.1 Acceptance criteria for the Cap Push Off Test is defined to be no less than (b) (4)

Using a safety factor (b) (4) the minimum required cap push off strength (b) (4)

13.3.1.2 Cap Push Off Test data for lot DN-1748-1 must demonstrate (b) (4) minimum strength requirement to a statistical criteria of 95/95 per 9.2.

13.3.2 Accelerated Elution

13.3.2.1 Acceptance criteria for Accelerated Elution testing is defined in SPEC-P-0003.

13.3.3 Leak Test

13.3.3.1 Acceptance criteria for the Leak Test is defined in DN-1604.

The results of the testing demonstrated that the cap is capable of a push off force of roughly (b) (4) grams, which is far above the (b) (4) value which is satisfactory given the weight of materials within the implant which is less than several grams. Additionally, the accelerated elution test and leak tests met the acceptance criteria which satisfied concerns with the (b) (4) process. Therefore, the (b) (4) is acceptable. **ACCEPTABLE**

LEAK TESTING (DOC #RN-0299, #DN-1447, and #RN-0477):

Engineering Reviewer Comment: The sponsor provided a leak test method validation report in response to our request in the pre-NDA meeting to demonstrate that the leak test accurately addressed concerns of drug leaking. The validation report demonstrates that the leak test method is capable of detecting the difference between a leaking and non-leaking implant. The sponsor compared the amount of eluted travoprost from "reference" implants and from "leaking" implants (in which a (b) (4) hole was deliberately created) following 24 and 48 hours agitation in media. Although this validation is limited in that it is not clear what path the eluted travoprost followed into the medium for the "reference" implants (i.e., the implants with no hole

deliberately created in them) (that is, it is possible that the travoprost is flowing from the implant into the medium both through the EVA membrane and through any weak spots around the crimping seal). However, this would not be a concern if “reference” samples used in the leak test method validation are representative of the clinical studied implants. The sponsor indicated in Table 5 of the Type B pre-NDA meeting materials (November 2022) that they performed leak testing of 30 clinical units and 180 units from 3 registration lots (prior testing units were R&D). This was discussed in another leak test document (RN-0477) which provided the “% elution” for “control” and “leaker” units (Table 5).

Parameters	Nominal Units (Control)	Leaker Units
Sample Size (n)	284	24
Mean (% Travoprost Eluted)	18	32
SD	1.77	3.85
Median (% Travoprost Eluted)	18	31
Minimum (% Travoprost Eluted)	(b) (4)	
Maximum (% Travoprost Eluted)		
99% Tolerance Interval		
p-value ¹	0.509	0.010

1. Anderson-Darling Normality Test

In this testing, they demonstrated that they were able to detect leaking units and demonstrated the difference in rate for different device lots. However, it is not known if these were clinically relevant samples. Therefore, the sponsor will be asked to confirm if these samples were similar to the ones that were clinically studied. **NOT ACCEPTABLE**

Sponsor Response to Deficiency #1: Glaukos confirms that the nominal units used for the leak test are representative of the clinical studied versions of the travoprost intraocular implant, as well as of the device components intended for marketing. The leak method validation report (RN-0299) systemically assessed multiple batches (which included those built using the proposed commercial manufacturing processes) to establish the evaluation criteria (RN-0477). The median % travoprost eluted was (b) (4) with a maximal travoprost elution of (b) (4) for nominal units. Based on statistical analysis of 99% tolerance interval, range, sensitivity, and specificity, the acceptance criteria for % travoprost elution of the leak test method at 2 days was determined to be NMT (b) (4) elution of travoprost (RN-0477).

Engineering Reviewer Comment to the Sponsor Response: The sponsor has provided additional information in the response to the CDRH deficiencies that summarize how the units used in the leak test validation are clinically relevant to those used in the clinical evaluations and other bench testing for the drug elution against time. They have stated that the nominal units from lot 126348 were built using the same manufacturing processes representative of the process used to manufacture clinical trial material for the Phase 3 clinical trials GC-010 and GC-012; similarly nominal units from lot 104594 were built using the same manufacturing processes representative of the process for clinical trial material used for the IDOS-106-EXCH clinical trial. The IDOS-106-EXCH study was a 12-month clinical trial conducted to validate the manufacturing changes from Phase 3. Therefore, the sponsor has resolved the deficiency (Deficiency #1). **ACCEPTABLE**

INSERTION TESTING (DOC #RN-0829):

Engineering Reviewer Comment: *The sponsor provided testing that involved gluing the implant to a rod that was used to insert the device into a silicone ball to simulate the eye. There were 10 testing samples used:*

(b) (4)



9. RESULTS

9.1. See Figure 8 below microscope images of the implantation/explantation test sequence.

(b) (4)



Figure 8. Implantation/Explantation Test Sequence, Microscope View



(b) (4)

Figure 9. Illustrated Events of Implantation/Explantation Cycle

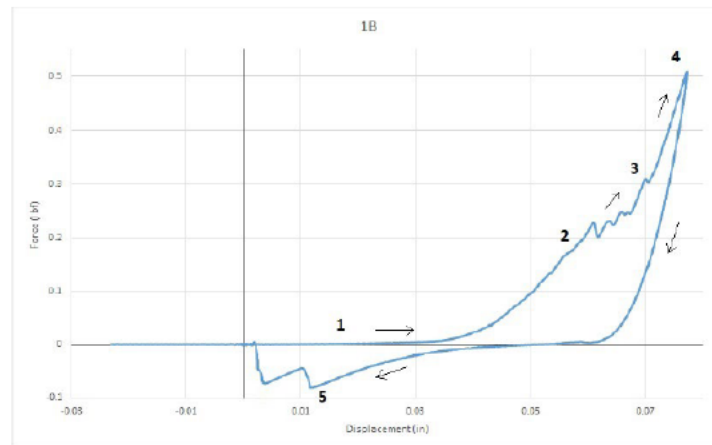


Figure 10. Typical Force/Displacement Curve with Numbered Implantation/Explantation Events

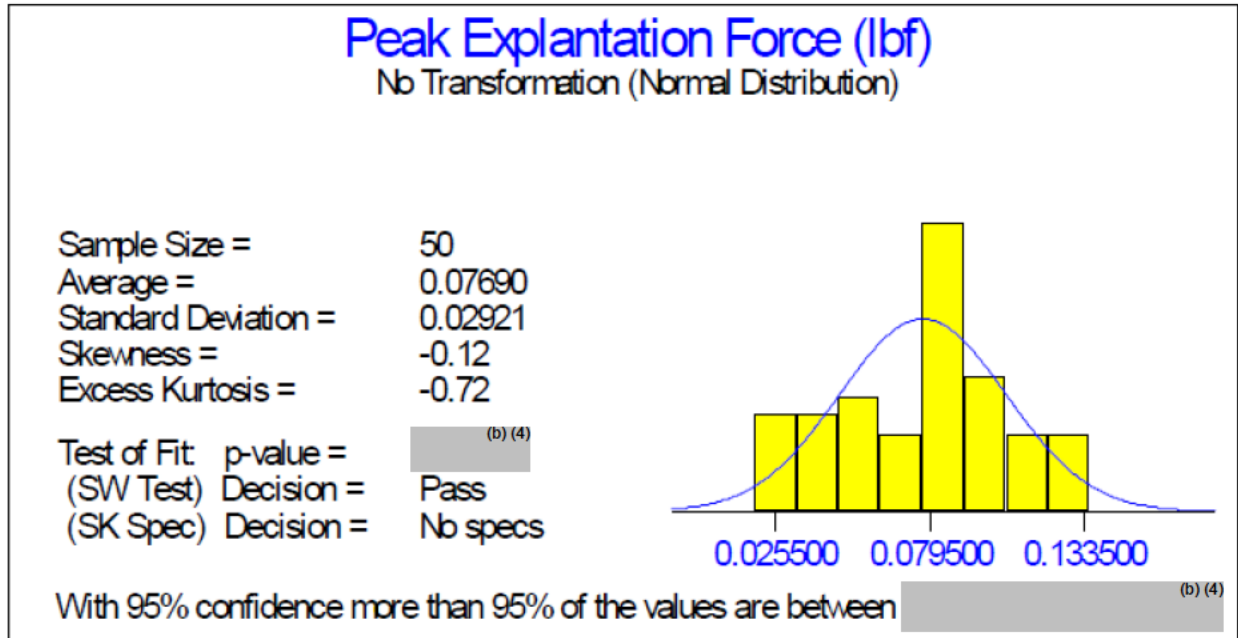


Figure 11. Distribution of Peak Explantation Force

- 10.2.1 The maximum implantation force recorded throughout testing was approximately (b) (4). This value was selected (and programmed into the Instron test sequence) to provide consistency and comparability of force/displacement data for all test samples.
- 10.2.2 A surgeon performing the G2-TR implantation procedure would apply as much force as the surgeon deems necessary to secure the implant. This amount could be greater than or less than the (b) (4) benchmark, and would vary from patient to patient.
- 10.2.3 With a nominal diameter of 0.80 mm, the anchor is the most delicate region of the distal end of the implant. As such, this study's analysis of implantation and explantation will assess the maximum forces experienced by the anchor.
- 10.2.4 Once the implant anchor has pierced to a certain depth, the implant body contacts the tissue and the implantation forces are distributed between both the anchor and body. The maximum force seen by the anchor is the force required to pierce the tissue. When a surgeon applies force in magnitude exceeding the 'piercing force', the additional load is distributed to the implant body rather than the anchor.
- 10.2.5 The 'piercing force' is the force required to cause the implant anchor to pierce and traverse into tissue. Within the force/displacement curve (Figure 10 above), this occurs during the turbulence between Event 2 and Event 3.
- 10.2.6 Review of the force/displacement curves within Appendix A indicate that the anchor pierces tissue between approximately (b) (4) as determined by identification of turbulent regions. However, this method therefore cannot be relied upon to provide a definitive value of piercing force.
- 10.2.7 All force/displacement curves show a beginning and end of a turbulent region. For each test, by the time the maximum force of (b) (4) has been applied, the anchor has pierced the tissue and implant body is contacting and dimpling the implantation site. Therefore (b) (4) is selected as a conservative upper-bound estimate of the piercing force experienced by the implant anchor.
- 10.3. Determination of Explantation Force
 - 10.3.1 See Figure 11 showing distribution of peak explantation force for all 50 test cycles.

The predicted maximum explantation force is (b) (4) per Figure 11 above.

- 10.3.3.1. The predicted maximum explanation force is less than the estimated piercing force ((b) (4) per 10.2.7) during implantation.
- 10.3.3.2. Therefore, the greater estimated piercing force will be used for assessments of anchor strength.
- 10.3.4 The predicted minimum explanation force is (b) (4) per Figure 11 above.
- 10.3.4.1. A filled and assembled G2-TR implant weighs approximately (b) (4).
- 10.3.4.2. The predicted minimum explanation force (b) (4) exceeds the weight of a G2-TR implant by a safety factor of more than (b) (4).
- 10.4. Anchor Resilience to Implantation and Explanation Forces
 - 10.4.1 Conservative Estimate of Anchor Resilience
 - 10.4.1.1. A conservative estimate of (b) (4) is used as the applied load for calculated anchor resilience to implantation and explanation forces (see 10.2.7).
 - 10.4.1.2. Finite Element Analysis (FEA) using estimated load was performed by consulting firm (b) (4). See FEA results in Attachment 1.
 - 10.4.1.3. Per Figure 12 below, an applied force of (b) (4) results in stress magnitude of approximately (b) (4) at the anchor. The minimum material yield strength (b) (4) per 10.4.1.4) of the anchor exceeds the estimated maximum applied load stress ((b) (4) per 10.4.1.3) by a safety factor of greater than (b) (4).
 - 10.4.1.5 is based on conservative estimates of loading and material strength.
 - 10.4.2.2. Per 10.2.6 and interpretation of the data plots in Appendix A, the anchor piercing force is more likely to be at most (b) (4).

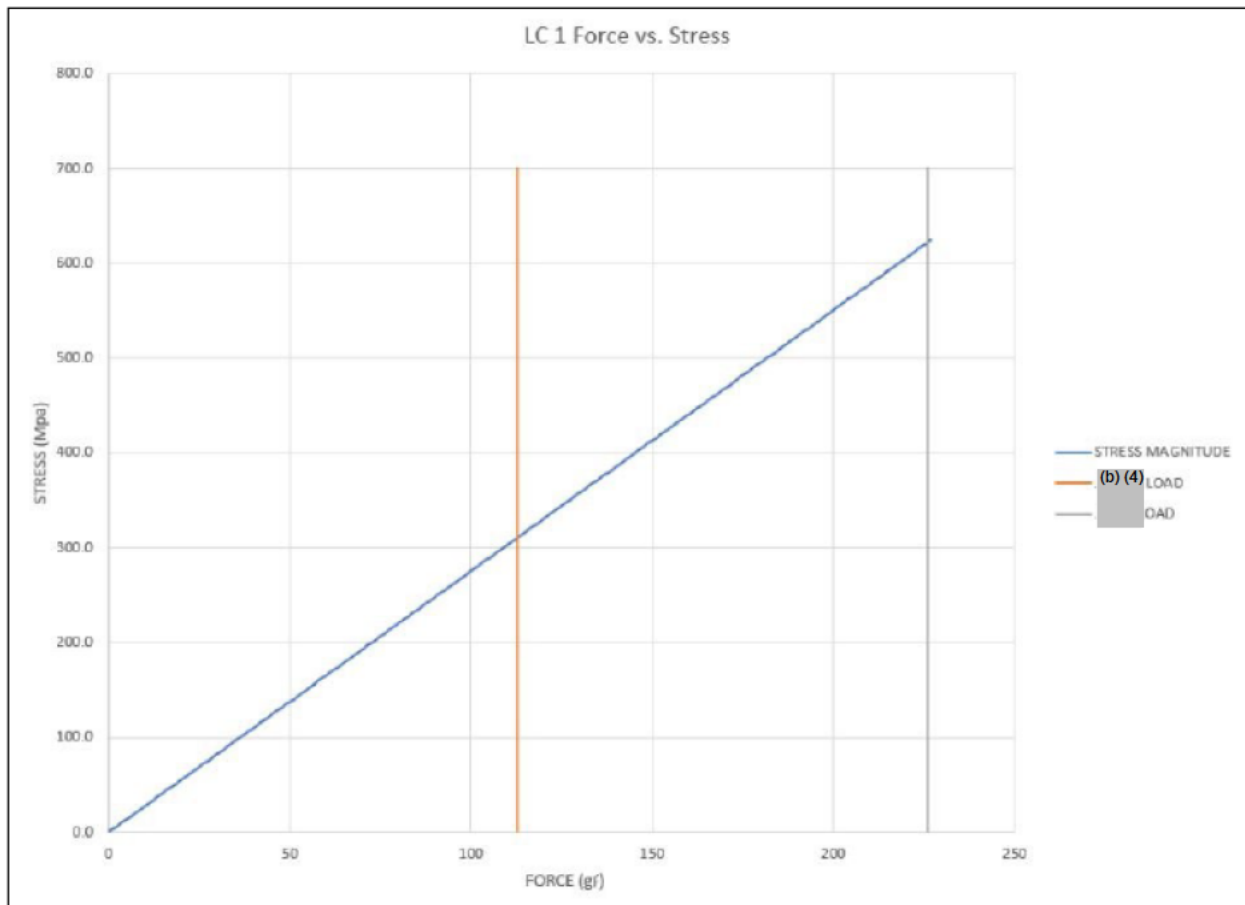


Table 4. Material Yield Strength of Typical G2-TR Container Lots		
Glaukos Lot#	Lot Receipt Date	Reported Yield Strength
004132	JUL 2016	(b) (4)
005279	DEC 2017	(b) (4)
008441	APR 2020	(b) (4)

Figure 10 details the forces are exerted on the silicone ball at the various stages of the insertion testing. The maximum force applied for insertion was (b) (4). This force was determined as a “conservative estimate” of the force applied by the user. Since this force adequately punctures the simulated eye model, which has similar properties to the trabecular meshwork, and this device has force that is only generated by the user and no internal spring component, this is a reasonable force to be used for the assessment. During the course of the implantation procedure, the peak explanation force was measured, which is the force exerted on the anchor when disengaging the implant and after the full insertion of the device (steps 5 and 4 respectively in Figure 9). According to Figure 11, the maximum explanation force measured was (b) (4) which is less than the piercing force used (b) (4). Additionally, the force of the weight of the implant is far less than the minimum explanation force of (b) (4) (sponsor uses safety factor of roughly (b) (4) where the safety factor is the ratio of yield strength of titanium in ASTM (b) (4) compared to the experienced yield strength), which demonstrates that if the anchor withstands the force of the implantation/explantation procedure, then there is no concern that the anchor will fail while implanted in the subject. Then the sponsor compared the yield strength of the explanation force to the yield strength found in ASTM (b) (4). At its narrowest point, the anchor measures (b) (4) and with an applied force of (b) (4) (which is not the implant force but the force applied specifically to that part of the anchor also known as the explanation force), the stress applied would be (b) (4). The sponsor provided the yield strengths of different G2-TR lots which have yield strengths of (b) (4) and above (Table 4). Therefore, the with an estimated applied force of (b) (4) which was more than double the explanation force measured, the yield strength for the containers provided in Table 4 are 2.8 times greater than the proposed applied explanation force. Furthermore, when comparing the applied force of (b) (4) the stress would be (b) (4) which compared to the ASTM (b) (4) minimum strength of (b) (4) the standard’s required force is 1.2 time greater than what is experienced. Therefore, the sponsor has demonstrated that the material has adequate strength to withstand all forces experienced during the implantation and explantation procedure. The testing is acceptable. **ACCEPTABLE**

IMPLANT STABILITY TESTING (DOC #RN-0892):

Engineering Reviewer Comment: The sponsor provided stability testing for the implants at T=0 and T=2AA (two years accelerated aging) with the following acceptance criteria for the 3 test methods:

Table 6. Testing Acceptance Criteria				
Test #	Test Description	Test Type	Risk Assessment	Acceptance Criteria
1	Implant Critical Dimension – Cap Hole Diameter	Attribute	§9.1.1.1	(b) (4)
2	Implant Critical Dimension – Container (b) (4) Outer Diameter	Attribute	§9.1.1.1	
3	Insertor Critical Dimension – (b) (4) Width	Attribute	§9.1.1.1	

The sponsor tested 8 implants for each of the tests described in the table. For all tests, there were no concerns noted and all demonstrated consistent results over the product lifetime. Therefore, the testing is acceptable. However, the sponsor has not provided sample sizes or how the testing sizes were calculated for the certification of the device dimensions. This is critical to ensure consistent product performance and will be requested in a deficiency. **NOT ACCEPTABLE**

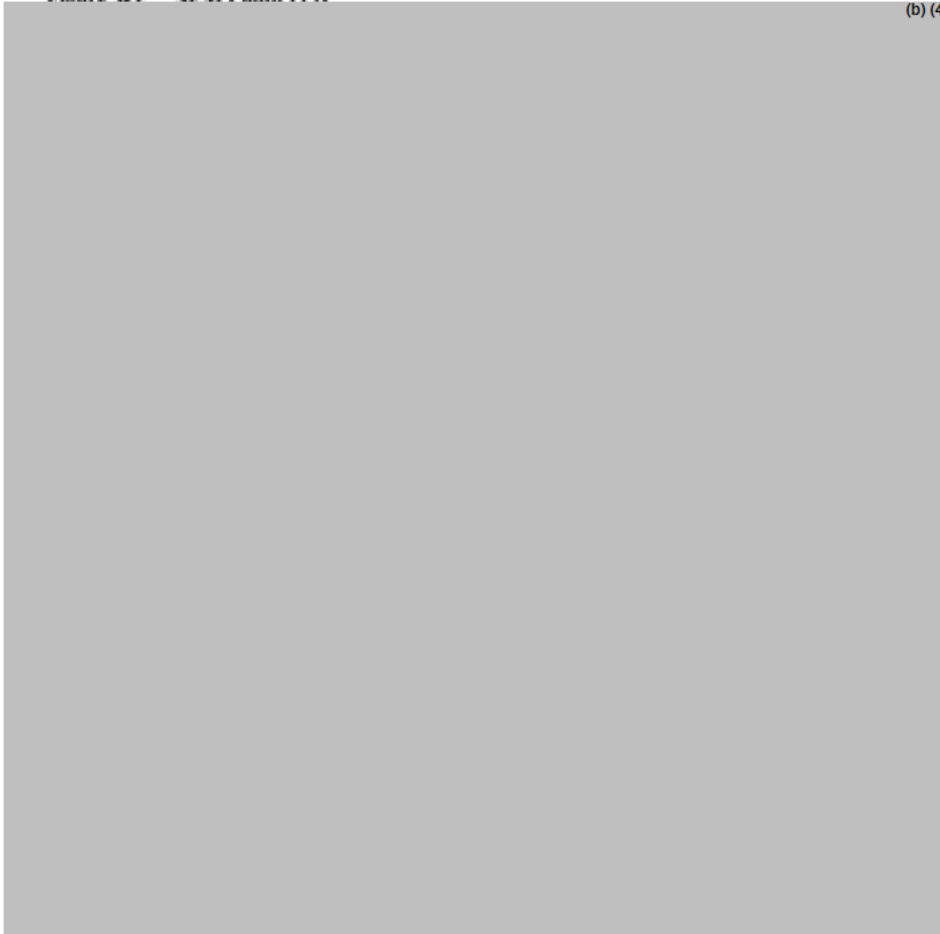
Engineering Reviewer Comment to the Sponsor Response: See the discussion above about the AQL and quality assurance in the final section. Please note that this deficiency (communicated in part of Deficiency #2) has been resolved after review of VR-1276 validation report.

ACCEPTABLE

SURFACE AND EDGE QUALITY (SEM) TESTING (Section 3.2.R under 3.4.3):

Figure 3-3: SEM Photo 115x

(b) (4)



Engineering Reviewer Comment: *The sponsor has included SEM testing to demonstrate the edge and surface quality of the implant device. The Figure 3-3 depict the implant free of any defects or corrosion. However, Figure 3-3 is of an implant at time $t=0$ and although the depiction is adequate for surface quality at $t=0$, there needs to be an evaluation of this after environmental aging. This was communicated to the sponsor in the previous pre-NDA meeting. They responded with the following information:*

- *868 eyes implanted up to 36 months*
- *The Corrosion Resistance testing performed per ASTM F2129-19a assessed the corrosion susceptibility of small, metallic, implant medical devices, or components thereof, using cyclic (forward and reverse) potentiodynamic polarization. No corrosion was observed on the test articles (see Section 3.4.4 of this document).*
- *The images shown below in Figure 3-5 are taken from explants for various reasons during GC-010 and GC-012 Phase 3 clinical trials. These images show the EVA membrane, titanium cap and titanium reservoir are all intact and not damaged or misplaced after implantation over time.*

Figure 3-5: Implant - GC-012

(b) (4)



*The sponsor has also included other images of the implants in other figures included in the same section and all of them demonstrate the ability of the implant to stay stable over the use life and are free of defects. This is acceptable to demonstrate that the implants have acceptable surface and edge quality. **ACCEPTABLE***

PHYSICAL STABILITY TESTING (DOC #RN-0892):

***Engineering Reviewer Comment:** The sponsor has not provided specific stability testing but has provide an analysis of several tests and how it establishes adequate physical stability:*

Accelerated Elution - the accelerated elution method is conducted at release and during stability studies to determine the elution rate of the travoprost formulation from the titanium reservoir from Travoprost Intraocular Implants (see document TR-1133 in Section 3 of 3.2.P.2.2.)

Appearance - appearance testing is conducted at release and during stability studies with the acceptance criteria of: "All components are present. Titanium cap is secured to container and cap, membrane and container do not appear damaged. Packaging components do not appear damaged."

Inserter shelf-life testing - (see Protocol DN-1501, Report RN-0714, and Report RN-0892 in Section 3.6.1), where dimensional inspection and simulated implantation was performed after accelerated aging.

Dimensional stability of the iStent and iStent inject stents made from (b) (4) titanium was submitted to FDA under PMA P080030 and P170043, respectively. The stents were shown to meet all dimensional requirements after three years of aging. The implant titanium reservoir and titanium cap are both made of (b) (4) titanium and therefore would be equivalent over time since the material and mechanical properties are very similar.

Pharmaceutical stability studies mentioned above inspect for accelerated elution and appearance of the implant. Current stability studies are ongoing and the protocol is designated for 3 years.

The crimped titanium cap testing for durability during qualification of the crimping method, which exceeds the design requirement of the titanium cap force (b) (4).

Further, stability of the titanium reservoir and titanium cap crimp has been demonstrated via the stability studies which show the units have passed the requirements for implant appearance and accelerated elution over time.

The titanium reservoir sees minimal external force over time as the inserter holds it in place throughout shelf-life. The stability studies show the appearance does not change over time where clasped, therefore no dimensional studies over time are needed.

The implant sees minimal internal forces during assembly and when the drug product expands under raised temperatures. Stability of the implant has been demonstrated via the stability studies which show the units have passed the requirements for implant appearance and Release Rate ($\mu\text{g}/\text{day}$)/Accelerated Release (Elution) over time. (b) (4)

(b) (4). Therefore, measurement of the EVA membrane post aging is not feasible, and thus EVA membrane physical stability is best supported by visual inspection and the implant elution performance during the pharmaceutical stability studies mentioned above.

Titanium was chosen as the implant material not only for its excellent biocompatibility and micro-machinability, but also because of its inherent strength. In addition, titanium is not a brittle material and has an elongated elasticity portion on its stress strain curve.

For this reason, catastrophic material failure such as cracking or fracture is unlikely to occur. Furthermore, the titanium reservoir and titanium cap are machined/formed from a single piece from (b) (4) titanium and assembled together. From published data, the yield strength of titanium (b) (4) is approximately (b) (4) ksi, and the ultimate tensile strength is approximately (b) (4) ksi. From published data, the yield strength of titanium (b) (4) is approximately (b) (4) ksi, and the ultimate tensile strength is approximately (b) (4) ksi. (b) (4)

The sponsor has discussed multiple ways how the device is stable over the use life and have adequately demonstrated that the device is stable. However, the sponsor has not provided any direct document describing the physical stability of the device, only the above summary of other testing used to demonstrate that the device is stable over the use life. But, this testing is thorough and the sponsor has demonstrated long term stability of the device with ones that were explanted from the patients and provided images (SEM imaging section). These images, in combination with the other tests listed above are adequate to demonstrate long-term stability of the device and has an acceptable safety profile from the viewpoint of physical stability over the use life.

ACCEPTABLE

QUALITY CONTROL (DOC #VR-1269):

Engineering Reviewer Comment: *The sponsor has stated in "Device Constituent Summary for Travoprost Intraocular Implant NDA", on p150 that the AQL validation is available upon*

request. This needs to be reviewed in order to be verified and found adequate. **NOT ACCEPTABLE**

Sponsor Response to Deficiency #2: Glaukos confirms that the AQL validation and all quality assurance measures are present to demonstrate consistent reliability of the device constituent of the Travoprost Intraocular Implant. Per the Agency's request, the AQL validation (Protocol VP-1269 and Report VR-1269) for the EVA membrane produced at (b) (4) is provided with this response. The report concludes that an AQL = (b) (4) or (b) (4) can be applied to the laser cut membrane. The approach to this validation was agreed upon by CDER during the Type C Meeting on June 07, 2021, FDA Meeting Minutes dated June 25, 2021; Reference ID 4816756). Glaukos has the following quality assurance measures in place to demonstrate consistent reliability of the device constituent of the Travoprost Intraocular Implant:

- (b) (4) Quality Agreement
- (b) (4) AQL = (b) (4) inspection of critical dimensions as described in (b) (4) Performance Qualification, and 100% visual inspection
- AQL inspection by Glaukos upon receipt of the EVA membrane
- Glaukos thickness measurement (b) (4)
- Confirmation of membrane thickness (b) (4)
- Endotoxin testing (b) (4)

Engineering Reviewer Comment to the Sponsor Response: The sponsor has provided (VR-1269) the following acceptance criteria for the AQL (b) (4) for the EVA membrane (Section 11) and the results of the testing (Section 12):

11. ACCEPTANCE CRITERIA

- 11.1 Bioburden and Endotoxin (LAL) testing shall be performed per §8.3.3.2 and (b) (4) report shall be attached to the Validation Report.
- 11.2 Components per Table 1 shall undergo First Article Inspection per DN-0522 and results attached to the Validation Report.
- 11.3 AQL Sampling Plan shall be performed as outlined in §10.2 and assign an AQL sampling plan for the component listed in Table 1.
- 11.4 (b) (4) Laser Processing OQ/PQ performed and the (b) (4) final report documented in the Validation Report for this protocol.

Attribute Data Analysis	Variable Data Analysis	
For at least 3 separate lots, verify that at least 50 units were inspected with no failures observed.	Analyze the data from each lot using Distribution Analyzer per Appendix D of DN-0237 / QA-07-013. Verify that the data is normally distributed. Provide a justification for any non-normal data sets.	Confirm that the 95% confidence and 95% reliability that the tolerance interval generated using distribution analyzer is within the dimension's specification limit.
*Note that variable data may be analyzed as attribute data if at least 50 samples are measured.		

12. RESULTS

- 12.1 Bioburden testing performed per §8.3.3.2 by (b) (4) see Attachment 4. Bioburden was found to be below the detectable limit.
- 12.2 LAL testing was performed per §8.3.3.2 by (b) (4) see Attachment 5. Endotoxin was found to be below the detectable limit.
- 12.3 First Article Inspection was performed and met the acceptance criteria, see Attachment 3.
- 12.4 Inspection Results for 10-0636 are summarized in Table 7 and Table 8.

Characteristic	Glaukos Lot	(b) (4) Lot	# of Units Inspected	# of Rejected Units	Meets/Exceeds 95/95 Requirement?
Visual Inspection per Critical Feature #3	QA-19-0058-03	(b) (4) 48154-1-4	100	0	Yes
	QA-20-0003-04	48154-1-5	100	0	Yes
	QA-20-0003-06	48154-1-6	100	0	Yes
Total	All	All	300	0	Yes

Characteristic	Sample Size
Visual	AQL = (b) (4)
Dimension #1	Maintain current method of sampling
Dimension #2	AQL = (b) (4)

The sponsor has demonstrated that an AQL of (b) (4) is an acceptable limit for the inspection of the devices which evaluates bioburden and endotoxin limits and with article inspection limits that evaluates critical dimension of the EVA membrane. The results described in this qualification indicate the PN 10-0636 components produced at (b) (4) meet and exceed the minimum requirements for adoption of an AQL sampling plan at Glaukos Receiving Inspection. The assessment is acceptable and the deficiency has been resolved. **ACCEPTABLE**

Digital Signature Concurrence Table (Doc ID: 04504.03.05)	
For each of the specific issues identified in the recommended requests to the applicant above, I and/or if applicable contributing consulting reviewer(s) (and or supervisors), have provided a statement of basis for the request(s); and either cited as part of it an available, applicable, and relevant final rule, statute, final guidance, or FDA-recognized consensus standard, or confirmed to the best of my ability for requests: add all relevant numbers here, else delete that there is no final rule, statute, final guidance, or FDA-recognized consensus standard available, applicable, and relevant to the request(s).	
Reviewer Sign-Off	



To: The Record, CDER Review

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

Subject: NDA 218010 Travoprost Intraocular Implant G2-TR-125 or G2-TR, Materials Review

Date: 3 May 2023

RECOMMENDATION – Tests support safety and effectiveness of the device, no additional information is needed.

DESCRIPTION OF DEVICE

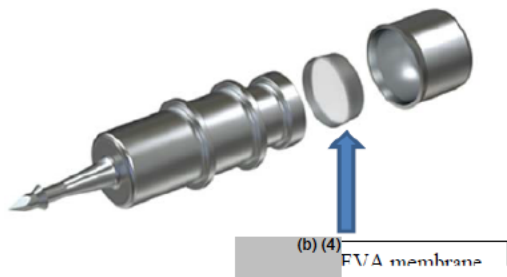
Table 2: Travoprost Intraocular Implant Drug Product Formulation

Component	Amount per Implant (µg)	Composition (%)	Function	Quality Standard
Travoprost	75	(b) (4)	Active Ingredient	USP
(b) (4)	(b) (4)	(b) (4)	(b) (4)	USP/NF
Total				

Figure 1: Assembled View of Travoprost Intraocular Implant



Figure 2: Exploded View of Travoprost Intraocular Implant



The Travoprost Intraocular Implant is comprised of a titanium reservoir (also referred to as titanium container) with titanium anchor, containing 75 µg of travoprost drug substance formulated with (b) (4). The titanium reservoir is sealed with an ethylene vinyl acetate (EVA) membrane held in place with a titanium crimp cap. The EVA membrane is (b) (4) and contains (b) (4) vinyl acetate. The EVA membrane, which is in direct contact with the travoprost drug product formulation filled into the titanium reservoir, allows drug to elute through the membrane at a controlled rate. The nominal dimensions of the assembled implant are 1.84 mm long by 0.494 mm in diameter.

An inserter is used to facilitate placement of the implant by the physician. The implant filled with drug product is loaded onto the inserter. A safety clip holds the release button in the forward position during shipping, storage, and handling, thus preventing the premature release of the implant. The inserter handpiece is made from common medical grade (b) (4), and (b) (4) stainless steels. The inserter material that enters the eye is stainless steel.

The assembled implant and inserter are placed in a (b) (4) blister tray that is sealed with a Tyvek lid. The sealed tray is placed together with an oxygen absorber packet into a transparent barrier pouch (b) (4), which is sealed and placed in a unit carton. (b) (4)

(b) (4) the final labeling contents are added inside the unit carton (i.e., prescribing information and patient card).

Comment – The proposed device drug is a titanium stent filled with an (b) (4) oily drug Travoprost (b) (4). (b) (4) . The drug is eluted from the device through a EVA (ethylene vinyl acetate) membrane. The membrane is (b) (4) not the typical EVA loaded drug delivery devices which have drug

particles dispersed in the polymer. The oily drug can diffuse out of the implant in a controlled release

The device is implanted with an inserter.

EXTRACTION STUDIES

Extractables for secondary packaging for G2-TR intraocular implant:

Table 2 Sample Set Information (Analytical Report 094533-01-01)

Sample Set No.	Sample Type	Component Type	Components
1	Secondary Packaging	Stainless steel	(b) (4) and safety clip
2			(b) (4)
3		Pouch	Blister tray, (b) (4) barrier pouch, and oxygen scavenger packet
4		Adhesive	Tyvek lid, label set, (b) (4) tamper proof seal, (b) (4) and portion of unit carton sealed with adhesive
5		Paper	Portion of unit carton without adhesive, IFU, and implant card
6-1	Manufacturing Components	(b) (4)	(b) (4)
6-2			
7		Travoprost DS shipping container	

Abbreviations: DS, drug substance; (b) (4) IFU, instructions for use; No., number.

Source: (b) (4) Protocol Number P34577.03, Project Number 094533-01-01, p. 6

Results reported in pdf att3-4

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

(b) (4)

Comment – Dilute components were extracted from the adhesive. The package is dry, these were extracted with solvents, it is unlikely these components could be transferred to the implant.

Method Implant

Extractions were performed in 72 hour increments until gravimetric analysis of non-volatile residue in successive replicates of the ethyl acetate and acetonitrile extracts indicated that extracted non-volatile residue was approximately 10% of the initially extracted amount, consistent with ISO 10993 Part 12. From the results of the non-volatile residue analysis of acetonitrile extraction, the extraction was considered exhaustive after the fourth extraction. While this feasibility study was performed using EVA (b) (4) pellets, the actual EVA container/closure used for the G2TR intraocular implant is a thin EVA membrane and therefore the migration of extractables from the membrane will be much faster than from the resin pellets and will reach exhaustive extraction in shorter time or fewer cycles than the (b) (4) pellets samples.

Results

1. Study Summary

This report summarizes an exhaustive extraction study performed on the EVA (b)(4) used for the EVA membrane of Glaukos Corporation (CA)'s G2TR intraocular implant. The goal of this study was to determine appropriate extraction solvents and an appropriate duration of the extraction to ensure the extraction conditions used for the subsequent controlled extraction study were exhaustive.

The extraction procedures used to achieve an exhaustive extraction of the EVA material were based on those specified in ISO standard 10993 part 12. Per the standard, moderately polar, and non-polar solvents were utilized to achieve the extraction of compounds with a wide range of polarities; specifically, acetonitrile, hexane, and ethyl acetate were initially screened for this purpose. Water, a polar solvent, was not screened during the feasibility testing as the organic solvents would represent a worst case extraction. Acetonitrile was the most appropriate solvent for the extraction as it is not reactive to the EVA material and is a semi-polar solvent capable of extracting polar and non-polar compounds. Hexane was not chosen as a non-polar solvent as dissolution of the EVA material was observed. Ethyl acetate did not dissolve the EVA material but swelling was observed. The extraction was facilitated by oven incubation with agitation (50 °C at 100 rpm).

Extractions were performed in 72 hour increments until gravimetric analysis of non-volatile residue in successive replicates of the ethyl acetate and acetonitrile extracts indicated that extracted non-volatile residue was approximately 10% of the initially extracted amount, consistent with ISO 10993 Part 12. From the results of the non-volatile residue analysis of acetonitrile extraction, the extraction was considered exhaustive after the fourth extraction. While this feasibility study was performed using EVA (b)(4) pellets, the actual EVA container/closure used for the G2TR intraocular implant is a thin EVA membrane and therefore the migration of extractables from the membrane will be much faster than from the (b)(4) pellets and will reach exhaustive extraction in shorter time or fewer cycles than the (b)(4) pellets samples.

Comment – These results support the use of acetonitrile as a solvent to evaluate the EVA material. Hexane is a solvent for EVA so dissolution will not separate leachables but dissolve the entire membrane. Water does not have a high affinity for organic polymer residuals. I agree with their assessments to use acetonitrile.

Table 4-1. Non-volatile Residue from Reflux Extraction of Placebo Implant
 (b) (4) **Sample ID 094533-01-01-0006**

Extraction Solvent	Weight (mg)			
	First Extraction	Second Extraction	Third Extraction x	Fourth Extraction
Acetonitrile	(b) (4)			
Ethyl acetate				

Executive Summary

A controlled extraction study was performed on the primary packaging, secondary packaging and manufacturing components used for Glaukos Corporation (CA)'s G2TR intraocular implant.

- The primary packaging materials, including EVA membranes and Ti materials, were extracted and analyzed for volatile, semi-volatile, non-volatile and elemental extractables. In addition, the water extracts of the EVA membranes were analyzed for extractable acetate and formate anions. Reportable extractables are shown in [Table 10-6](#) through [Table 10-12](#).
- The secondary packaging materials were extracted and analyzed for volatile extractables. Reportable extractables are shown in [Table 10-1](#) through [Table 10-5](#).
- The manufacturing components were extracted and analyzed for volatile, semi-volatile, non-volatile and elemental extractables. Reportable extractables are shown in [Table 10-13](#) through [Table 10-15](#).

An in-use simulation study was performed on EVA membranes, Ti materials and the inserter tip used for the implanting, targeted the volatile, semi-volatile, non-volatile and elemental leachables from those components. In addition, the simulation solutions of the EVA membranes were analyzed for leachable acetate and formate anions. The extractable profiles from the controlled extraction study for the EVA membranes and TI materials were used for the search of the leachables. As shown in [Table 10-16](#) through [Table 10-22](#), no reportable leachables were found in the simulation solutions.

A controlled extraction study was performed on the secondary packaging components which were combined as follows:

- Sample Set 1: Secondary packaging: stainless steel components: (b) (4)
 (b) (4) safety clip
- Sample Set 2: Secondary packaging: (b) (4) components: (b) (4)
 (b) (4)
- Sample Set 3: Secondary packaging: pouch components: blister tray, (b) (4) barrier pouch, and oxygen scavenger packet
- Sample Set 4: Secondary packaging: adhesive components: Tyvek lid, label set, radiation sticker, tamper proof seal, (b) (4)
 (b) (4) and portion of unit carton sealed with adhesive
- Sample Set 5: Secondary packaging: paper components: portion of unit carton without adhesive, IFU, and (b) (4) card

Comment – Sample set 1 is critical as this is the implanted component. Other sample sets are possible sources of incidental contamination. Controlled extraction conditions – 50 deg C 72 h, simulated extractions 24 h 37 deg C.

Table 1-1. Schemes for Controlled Extraction Study of Device Components

Component	Target Compounds	Extracts	Analytical Techniques
EVA membrane and Ti Materials	Volatiles Extractables	Dry Heat	HS/GC/MS
EVA membrane and Ti Materials	Semi-volatiles Extractables	Water	DI/GC/MS
		Acetonitrile (ACN)	
		Ethyl acetate (EtOAc)	
EVA membrane and Ti Materials	Non-volatiles Extractables	Water	UHPLC/UV/MS
		ACN	
		EtOAc	
EVA membrane and Ti Materials	Elemental Extractables	2% Nitric Acid	ICP/MS
EVA membrane	Acetate and Formate Anions	Water	IC

HS/GC/MS = Headspace gas chromatography with a mass spectrometer detector.

DI/GC/MS = Direct injection gas chromatography with mass spectrometer detector.

UHPLC/UV/MS = Ultra high performance liquid chromatography with both ultraviolet and mass spectrometer detectors.

ICP/MS = Inductively coupled plasma mass spectrometry

IC = Ion chromatography

6.2. Controlled Extraction in Oven with Agitation

Material:	Sample Set 6-1, Sample Set 6-2, Sample Set 7, Ti material and EVA membrane material, extracted separately
Solvent:	Water, ACN, EtOAc and DMF ^f
Amount of Solvent:	1.69 mL for EVA materials, 2 mL for Ti material ^g and 50 mL for API shipping container and manufacturing components.
Temperature:	50 °C
Time:	72 Hours

6.4. In-Use Simulation

Material:	Ti materials, EVA membrane materials and inserter, simulated separately
Solvent:	Saline and 50/50 IPA/Water
Amount of Solvent:	1.69 mL for EVA membrane material, and 2 mL for Ti material and inserter
Temperature:	37 °C
Time:	24 Hours

1. Study Summary

This report summarizes the controlled extraction and in-use simulation studies for the primary packaging, secondary packaging and manufacturing components used in Glaukos Corporation (CA)'s G2-TR intraocular implant. The goal of these studies is to provide a qualitative assessment of the extractables/leachables, identify the extractables/leachables, and provide a semi-quantitative estimate of their levels.

A controlled extraction study was performed on the primary packaging components, including the EVA membrane and Ti container with cap. Two EVA membrane materials and five Ti materials were extracted with water, EtOAc, ACN and 2% nitric acid. The resulting extracts were analyzed for volatile, semi-volatile, non-volatile and elemental extractables. In addition, the water extracts of EVA membranes were analyzed for extractable acetate and formate anions. Reportable extractables are summarized in [Table 10-6](#) through [Table 10-12](#).

Table 5-1. HS/GC/MS Analysis Results for Controlled Extraction by Dry Heat: Sample Set 1

RT (min)	CAS Number	Identification	Report Label	Amount (µg/sample set)
No reportable volatile extractables				

Table 5-2. HS/GC/MS Analysis Results for Controlled Extraction by Dry Heat: Sample Set 2

RT (min)	CAS Number	Identification	Report Label	Amount (µg/sample set)
(b) (4)		(b) (4)	Tentative	(b) (4)
			Confident	
			Confident	
			Confident	
			Confident	
			Confident	
			Tentative	
			Tentative	
			Confident	
			Confident	
			Confident	

Comment – Head space results indicate no volatiles in implant Set 1. Secondary package Set 2 residuals at low levels were detected by head space as noted above. Similar results were reported for other package materials. Ti components such as device and insert had NO volatiles by the headspace method. EVA samples also were clean, ND.

ANALYSIS OF SEMI-VOLATILES OF IMPLANT SETS BY DI/GC/MS (DIRECT INJECTION GC MS)

Water, EtOAC, ACN extracts of Sets to detect residuals.

NO PEAKS DETECTED IN WATER, EtOAC, OR ACN BY DI/GC/MS

Table 6-31 through Table 6-40.

Table 6-1. DI/GC/MS Analysis Results for Controlled Extraction: Sample Set 6-1
Extracted by Water

RT (min)	CAS Number	Identification	Report Label	Amount (µg/sample set)
No reportable semi-volatile extractables				

Comment- Nothing was found in water extracts of other Sets.

Also, the firm submitted several pages of results from these extractions, they did not find any semi-volatiles from the DI GC MS in any of the solvents tested.

These tests indicate that all extractables are below detection limits for the implant. Nothing was found in the other sets either...

Simulated use extractions showed similar results, nothing detected.

EVALUATION OF NON-VOLATILES BY UHPLC UV MS

Tables 7-1 to 7-44 in the report showed ND for any of the samples.

EXTRACTION IN 2 WT% NITRIC ACID

They were able to detect residues from stainless steel in these tests. I do not expect this is a problem since the stainless steel components of the injector should not be exposed to nitric acid in general use.

CONCLUSIONS ON EXTRACTION STUDIES

They were able to detect packaging residuals, [REDACTED] (b) (4) [REDACTED] (b) (4) when the packaging was aggressively extracted. None of these components were detected when the separate device was extracted alone. This indicates that the device is not cross-contaminated by impurities in the packages. Aggressive extractions of the device and samples sets that could have patient contact generally did not find anything in selected solvents except for 2 wt% nitric acid. The nitric acid would be corrosive to stainless steel components in the injector and ICP analysis detected the expected residuals from the metals. Since the device is not exposed to nitric acid in use, these components are unlikely to be bioavailable and are not a concern. They are more indicative of the quality of the stainless steel alloy components. The device is acceptable for use based on these tests.

LEACHABLE STUDIES

The device was aged in its packaging with the following tests:

Interval	Finished Product Lot Number	Storage Condition	Sample Orientation	(b) (4) Sample ID
0 Month	300723	Ambient	NA	094533-02-01-0001
	300724			094533-02-01-0002
	300725			094533-02-01-0003
1 Month	300723	40 °C/NMT 25% RH	Horizontal	094533-02-02-0001
	300724			094533-02-02-0002
	300725			094533-02-02-0003
3 Month	300723	40 °C/NMT 25% RH	Horizontal	094533-02-03-0001
	300724			094533-02-03-0003
	300725			094533-02-03-0005
	300723	25 °C/40% RH		094533-02-03-0002
	300724			094533-02-03-0004
	300725			094533-02-03-0006
6 Month	300723	40 °C/NMT 25% RH	Horizontal	094533-02-04-0001
	300724			094533-02-04-0003
	300725			094533-02-04-0005
	300723	25 °C/40% RH		094533-02-04-0002
	300724			094533-02-04-0004
	300725			094533-02-04-0006
9 Month	300723	25 °C/40% RH	Horizontal	094533-02-05-0001
	300724			094533-02-05-0002
	300725			094533-02-05-0003
12 Month	300723	25 °C/40% RH	Horizontal	094533-02-06-0001
	300724			094533-02-06-0002
	300725			094533-02-06-0003

Data References

Stability Interval	Result Set ID	Description	Data References	Analysis Date(s)
Initial	1325	Volatile Leachables (HSGC-FID)	84-0807	15-Mar-2022
1 Month	1325		84-0807	15-Mar-2022
3 Month	1565		93-1788	01-Jul-2022
6 Month	1900		110-1753	26-Sep-2022
9 Month	3016		122-0469	30-Nov-2022
12 Month	4160		135-0496	25-Jan-2023

Tests were done by headspace analysis as shown above. The implant is made from Ti and EVA, both materials are known to be robust and unlikely to degrade in storage. The results they reported confirmed no degradation was detected.

6.2. Lot 300723, 25 °C/40% RH

Sample Name: Travoprost Intraocular Implant, G2-TR-125
Dose/Strength/Formulation: 75 µg implant
Finished Product Lot Number: 300723
Container Lot Number: 300710
Storage Condition: 25 °C/40% RH (ambient at initial)
Sample Orientation: Horizontal

(b) (4) Sample ID	094533-02-01-0001	094533-02-03-0002	094533-02-04-0002	094533-02-05-0001
Analysis	Storage Time (months)			
	0	3	6	9
Volatile Leachable Analysis (µg/device)				
(b) (4)	ND	ND	ND	ND
	ND	ND	ND	ND
	ND	ND	ND	ND
	ND	ND	ND	ND
	ND	ND	ND	ND
	ND	ND	ND	ND
	ND	ND	ND	ND
	ND	ND	ND	ND
	ND	ND	ND	ND
	ND	ND	ND	ND
	ND	ND	ND	ND
	ND	ND	ND	ND
	ND	ND	ND	ND

Sample Name: Travoprost Intraocular Implant, G2-TR-125
Dose/Strength/Formulation: 75 µg implant
Finished Product Lot Number: 300723
Container Lot Number: 300710
Storage Condition: 25 °C/40% RH
Sample Orientation: Horizontal

(b) (4) Sample ID	094533-02-06-0001			
Analysis	Storage Time (months)			
	12	18	24	36
Volatile Leachable Analysis (µg/device)				
(b) (4)	ND			
	ND			
	ND			
	ND			
	ND			
	ND			
	ND			
	ND			
	ND			
	ND			
	ND			

CONCLUSIONS LEACHABLE STUDIES

No degradation was detected in storage period. 1 year stability confirmed.

CORROSION TEST

2. SCOPE

- 2.1. This testing is specific to the Travoprost Intraocular Implant 75 µg, G2-TR using the manufacturing methods listed in DN-1880.
- 2.2. Glaukos submitted samples of the Travoprost Intraocular Implant to (b) (4), for electrochemical evaluation in accordance with ASTM F2129, "Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices" per DN-1880.
- 2.3. Test samples were manufactured by Glaukos per DN-1880, see Attachment 1. Test samples were empty (not filled with Bulk Drug Product) as the drug product will interfere with the corrosion testing of the implant. The test samples were attached to titanium wire through the top of the cap after manufacturing steps are completed and then delivered to (b) (4) to facilitate testing (see Attachment 4).

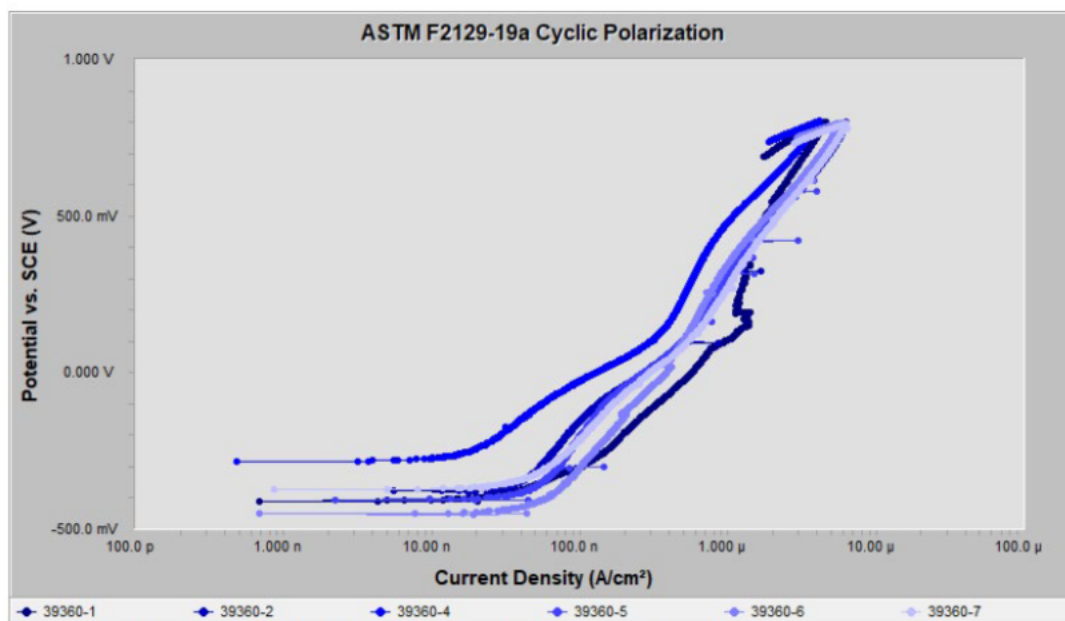


Figure 4. Overlay of ASTM F2129 test results for the six Glaukos devices.

Table 4. Electrochemical Data Summary						
Test Article	E_r	E_b	E_v	E_p	Hysteresis	Pitting
39360-1			(b) (4)	N/A	No	No
39360-2				N/A	No	No
39360-4				N/A	No	No
39360-5				N/A	No	No
39360-6				N/A	No	No

14. CONCLUSIONS

- 14.1. Per the discussion of the results performed by (b) (4) the data indicates that the implants are passive and exhibit corrosion resistant behavior.
- 14.2. The six (6) test results show reasonably reproducible results and with high confidence, additional tests would likely yield similar results.

CONCLUSIONS

Device completed polarization tests indicated corrosion of the Ti material should be minimal.

QUESTIONS FROM BIOCOMPATIBILITY REVIEWER ATT3-2 REPORT EVA
BIOCOMPATIBILITY

S Bancos had the following concerns about the tests in this report:

Reviewer's comment:

I defer to the chemistry reviewer to determine whether the methods and assessments listed above are adequate.

Comment - I copied the relevant test summary of concern below:

- (b) (4) EVA Membrane (b) (4) with the replacement Celanese VitalDose EVA Membrane (Celanese p/n 21042856). Equivalence was confirmed by:
- Visual Appearance
 - Identification by FT-IR (Fourier-transform Infrared) Spectroscopy
 - (b) (4) Content using H-NMR (Proton Nuclear Magnetic Resonance Spectroscopy)
 - Melt Index using ASTM D1236
 - (b) (4)
 - (b) (4)
 - Evaluations addressing Physical Performance and Characteristics

The following is a summary of the physical and chemical properties of the (b) (4) EVA and Celanese VitalDose EVA (b) (4), as well as functional performance in the drug elution tests.

Table 1: SPP EVA and Celanese VitalDose EVA (b) (4) Comparison

Attribute	Test Method	Acceptance Criteria for Equivalency	Results		Met Acceptance Criteria?
			(b) (4) EVA L/N 600425006 (Control) GC-010/ GC-012	VitalDose EVA L/N 1222083 IDOS-106-EXCH	
Appearance	TM-0019	(b) (4)	Colorless transparent to slightly opaque polymer pellets.	Colorless transparent to slightly opaque polymer pellets.	Yes
	(b) (4) TM-0017			(b) (4)	Yes
Melt Flow Index	Per Manufacturer's COA & ASTM D1238			Yes	
	(b) (4) Per Manufacturer's COA			Yes	
	Per Manufacturer's COA	Yes			
Additional Supporting Data					
Crystallinity, EVA Membrane (%)	Modulated Differential Scanning Calorimetry	(b) (4)	(b) (4)	(b) (4)	Yes

Comment - The above tests support the equivalence of the VitalDose EVA to the previous (b) (4) EVA. The (b) (4) content is nearly identical and the small difference should not affect

permeability significantly (see next page for confirmation). The melt index is slightly lower but this will only be a minor change in the time needed when the product is molded, not significant since dimensional tolerances are still met in the final device. Crystallinity is about the same, and (b) (4) are slightly improved in the new product.

Attribute	Test Method	Acceptance Criteria for Equivalency	Results		Met Acceptance Criteria?
			(b) (4) EVA L/N 600425006 (Control) GC-010/ GC-012	VitalDose EVA L/N 1222083 IDOS-106-EXCH	
Oxygen Transmission Rate (cc/m ² /day)	ASTM F1927	(b) (4)	(b) (4)		Yes
Water Vapor Transmission Rate (g/m ² /day)	ASTM F1249		Yes		
Molecular Weight, Relative (Dalton)	Gel Permeation Chromatography		Yes		
Polydispersity	Gel Permeation Chromatography		Yes		
Melting Temperature (°C)	Modulated Differential Scanning Calorimetry		Yes		
Long-term Elution, (µg/day)	Elution HPLC/UV		Yes		
			Yes		
Accelerated Elution, Accumulated Release, (%)	Elution HPLC/UV M19382		Yes		
		Yes			

Comment – The test for O₂ transfer is a direct measure of permeability which is critical for the CDER application of drug release. (b) (4) is within (b) (4) of their target. Also, they have independent checks of drug release. Therefore, I agree that this material is an acceptable

replacement. MW is lower, but is high enough so EVA mechanical stability should be adequate. Elution results show residues are equivalent. These tests support the use of this new EVA material in this application. This change is unlikely to significantly affect biocompatibility. Acceptable.

QUESTION ABOUT METALS TESTS

TABLE 7: SUMMARY OF USP PHYSICO-CHEMICAL TEST RESULTS FOR THE TEST ARTICLE REPRESENTATIVE OF THE TRAVOPROST INSERTER STAINLESS STEEL (b) (4) INTERACTION WITH G2TR CAP (b) (4) TITANIUM (NO TRAVOPROST OIL PRESENT) (b) (4) PROTOCOL NO. P15-1181-00A AND (b) (4) FINAL GLP REPORT NO. 15-03061-G3			
Test Method	Extraction Medium	Extraction Conditions Sample to Medium Ratio & Extraction Parameters	Results
USP Physico-Chemical Test – USP <661>	Purified Water	127.2 cm ² /21.2 mL (6 cm ² /mL) at 70°C for 24 hours	Control Article: No Travoprost Oil Heavy Metals: Passed with no significant heavy metals detected. Met the acceptance criteria of ≤ (b) (4) heavy metals. • ≤ (b) (4) heavy metals.
Acceptance Criteria:			(b) (4)
Conclusion: The test article showed passing results with no detectable heavy metals (≤ (b) (4)) and was determined to be met the acceptance criteria for the USP <661> Physico-Chemical Test – Section 7.3.3 Heavy Metals Assay.			

Reviewer's comment:

I defer to Dr. Hutter to comment if he has any concerns regarding the analytical chemistry testing summarized above.

Comment – This test assesses heavy metal contamination of the inserter when exposed to extraction with water at 70 deg C @ 24 h. Using purified water, they were un-able to detect any heavy metals above (b) (4). Acceptable.

Consulting Memorandum

To: Shazma Aftab (CDER/OPQ/OPRO)
From: Sam Fielden
 Division of Radiological Imaging Devices and Electronic Products (DHT8B)
 Office of Radiological Health (OHT8)
 Office of Product Evaluation and Quality | Center for Devices and Radiological Health

Digital Signature Concurrence Table	
For each of the specific issues identified in the recommended requests to the applicant below, I and/or if applicable contributing consulting reviewer(s) (and/or supervisors), have provided a statement of basis for the request(s); and either cited as part of it an available, applicable, and relevant final rule, statute, final guidance, or FDA-recognized consensus standard, or confirmed to the best of my ability for requests: N/A that there is no final rule, statute, final guidance, or FDA-recognized consensus standard available, applicable, and relevant to the request(s).	
Reviewer Sign-Off	

Subject: MRCOMP Consult
 NDA218010 / ICC2300356 / ICC2300357
 iDose TR (Travoprost Intraocular Implant)
 Glaukos Corporation

I. Summary

The sponsor is leveraging MR testing from a similar device to inform MR Conditional labeling. I agree with their rationale, and only have one minor request intended to align the labeling format to that recommended in the MRI Testing/Labeling Guidance.

Response Update: After some interaction with the sponsor, labeling has been updated appropriately. I have no further concerns.

II. Background and scope

The scope of this consult is limited to MR safety and compatibility of the Travoprost Intraocular Implant. Specifically, I have only reviewed the physically implanted components of the submission, as the drug product constituents and packaging are not magnetic and/or are not anticipated to enter the MR Environment. I reviewed documents, “32r-device-summary-nda.pdf,” “att3-7-tr-16-0011.pdf,” “Draft Container Label – iDose TR – Implant Card.pdf,” and “Draft Labeling Text – pdf.pdf.”

III. Device Description

Excerpts from the sponsor’s Device Description, beginning on p11 of “32r-device-summary-nda.pdf”:
Travoprost Intraocular Implant (alternatively referred to as G2-TR-125 or G2-TR) is a sterile, drug-eluting implant that is surgically delivered through a clear corneal incision and anchored in the anterior chamber

angle of the eye. The implant elutes formulated drug product (travoprost drug substance formulated with (b) (4) and is designed for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. The Travoprost Intraocular Implant is a single entity drug-led drug-device combination product.

The Travoprost Intraocular Implant is comprised of a titanium reservoir (also referred to as titanium container) with titanium anchor, containing 75 µg of travoprost drug substance formulated with (b) (4). The titanium reservoir is sealed with an ethylene vinyl acetate (EVA) membrane held in place with a titanium crimp cap. The EVA membrane is (b) (4) and contains (b) (4) vinyl acetate. The EVA membrane, which is in direct contact with the travoprost drug product formulation filled into the titanium reservoir, allows drug to elute through the membrane at a controlled rate. The nominal dimensions of the assembled implant are 1.84 mm long by 0.494 mm in diameter.

The Travoprost Intraocular Implant titanium reservoir is comprised of Titanium (b) (4). Incoming titanium reservoirs are sourced from (b) (4).

Figure 2-1: Titanium Reservoir Drawing



The Travoprost Intraocular Implant titanium cap is comprised of Titanium (b) (4). Incoming titanium caps are sourced from (b) (4).

Figure 2-2: Titanium Cap Drawing

(b) (4)

To summarize the size of composition of the physical implant:

- Titanium Reservoir (b) (4) 1.73 x 0.494 mm
- Titanium Cap (b) (4): 0.386 x 0.474 mm
- EVA copolymer membrane (Ethylene vinyl acetate): (b) (4)

The maximum dimensions of the total implant are: 1.84 x 0.494 mm.

Lead Reviewer or Consulting Reviewer Comments for Internal Discussion Only

The dimensions and composition of the device would not suggest concern from an MR compatibility standpoint. The EVA copolymer membrane (and drug products) are nonmetallic and nonmagnetic. The titanium alloys are not expected to produce significant force or torque ([Woods et al. J Test Eval 49\(2\):783-795](#)), and the overall dimensions, being less than 2 cm, are expected to generate a temperature increase of less than 2 °C in Normal Operating Mode over the course of 1 hour of exposure (FDA Guidance document, [Testing and Labeling Medical Devices for Safety in the Magnetic Resonance \(MR\) Environment](#)).

IV. Review of Testing

The sponsor is leveraging MRI Compatibility testing from a previous study performed on a 22x scaled-up test article representing a similar implant, the iStent Inject, Model G2-W that is in commercial distribution in the U.S. under PMA P170043/S005. The rationale behind using MR testing from another device and proposed MRI Safety Information are found beginning on page 71 of “32r-device-summary-nda.pdf.”

Table 3-8: Comparison of iStent inject Model G2-W MRI Test Article to Travoprost Intraocular Implant Components

	Diameter	Mass	Material	%Fe
MRI Test Article	(b) (4)	(b) (4)	Ti 6Al4V ELI	(b) (4)
Titanium cap	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Titanium reservoir	(b) (4)	(b) (4)	(b) (4)	(b) (4)

From that rationale:

The MRI test article was a titanium alloy model scaled up by 22-fold in diameter relative to the G2-W stent, and by 11,000-fold relative to the G2-W mass. Relative to the Travoprost Intraocular Implant metallic components (titanium cap and titanium reservoir), the MRI test article was scaled up by 16-fold in diameter, and by 1,600-fold in mass. Because the test article was scaled up by large safety margins relative to the diameter and mass of the Travoprost Intraocular Implant metallic components, the MRI test article is considered a valid surrogate for the Travoprost Intraocular Implant.

The MRI test article material was made from Ti6Al4V, (b) (4). The iron content of Ti6Al4V is specified to be (b) (4). Like the MRI test article, the implant is comprised mainly of titanium. Other materials used in the construction of the implant are nonmetallic: ethylene vinyl acetate and travoprost.

More specifically, the implant metallic components are comprised of a reservoir of (b) (4) titanium (b) (4) and a titanium cap (b) (4). The iron content (b) (4) is specified to be (b) (4). The overall implant metallic composition is therefore (b) (4). Because this metallic composition is very similar to that of the (b) (4) test article, the MRI test article is considered a valid surrogate for the Travoprost Intraocular Implant.

The original MR Test Report (TR-16-0011) was provided for review in “att3-7-tr-16-0011.” Tests were conducted according to relevant ASTM standards at 3T and found:

- Minor amount of translational attraction (deflection angle 4°) and no torque
- 1.8 °C maximum heating
- Moderate imaging artifacts

Lead Reviewer or Consulting Reviewer Comments for Internal Discussion Only

I agree with the sponsor’s rationale that the testing of a scaled-up G2-W is applicable to the subject device. Combined with the low level of concern based on the size and composition of the device (see Reviewer Comments above), this approach is acceptable.

V. Review of Labeling

Based on the leveraged testing described above, MRI Safety Information labeling identical to the G2-W is proposed on page 72 of “32r-device-summary” and found on the proposed Implant Card (“Draft Container Label – iDose TR – Implant Card.pdf”):

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

Lead Reviewer or Consulting Reviewer Comments for Internal Discussion Only

Labeling information is appropriate; however, the recent MRI Testing/Labeling Guidance recommends a tabular format and to remove specific test results from labeling to increase clarity and consistency across devices. See Section VI, below, for a **potential request** to the sponsor.

Response Update: The final revised card contains the recommended format for MR Safety information and is acceptable.

VI. Potential Requests for Additional Information

1. You have provided MR Conditional labeling in Section 3.4.2 of the Travoprost Intraocular Implant Device Summary (page 72), which is reproduced on draft implant cards. However, the labeling is inconsistent with current practice and does not follow our recommendations in the FDA Guidance [Testing and Labeling Medical Devices for Safety in the Magnetic Resonance \(MR\) Environment](#), issued May 20, 2021. MRI safety labeling is important to inform safe scanning of patients implanted with medical devices, and as a result of a request for more clarity and consistency in MRI safety labeling from the MRI user community at a recent FDA workshop on MRI safety, we request that device manufacturers use the format for the MRI safety labeling given in the guidance.
 - a. Please revise your proposed MRI Conditional labeling using the format recommended in the guidance (You may find Table 3 in Appendix 2 of the above-cited guidance a relevant example for your device).
 - b. To reduce irrelevant and distracting information, please note that the guidance does not recommend inclusion of the methods or results of specific tests. Specifically, because the extent of image artifact is affected the choice of imaging parameters, please revise the MR Image Artifact line of your MR Safety Information table to remove the specific extent of image artifact

(b) (4)

Response and Review: The deficiency above was sent to the sponsor on July 7, 2023. On July 21, 2023, the sponsor responded with an updated card following the format recommendations outlined in the deficiency. However, review found that the updated card restricted use to 3.0T, which was inconsistent with the information included in the original submission. On 8/22/2023, the following interactive request was sent to the sponsor:

As requested, you have provided updated MR Safety Information aligned with the format recommendations in the Testing and Labeling Medical Devices for Safety in the Magnetic Resonance (MR) Environment Guidance in Section 1.14.1. In your updated table, you have changed safe use from (b) (4) to “3.0-Tesla.” Please confirm that you wish to label your device as MR Conditional at 3.0T only; alternatively, please provide MRI Safety information with revised field strength information consistent with the original submission. The Agency is committed to ensuring that MR Conditional labeling, supported by appropriate data and scientific rationale, is inclusive of as wide range of conditions as possible so as not to impede patient access to important diagnostic imaging technologies. On 9/11/2023 the sponsor responded with the revised card included in Section V, above. The revised card is consistent with the information in the original submission and follows Guidance recommendations. I have no further concerns.

The Agency informed the Applicant at a Type B meeting on December 8, 2022 that the subject device will be regulated as a single entity, drug-led, drug-device combination product. As such, the Center for Drug Evaluation and Research (CDER), Division of Ophthalmology leads the review, with the Center for Devices and Radiological Health (CDRH) providing consult reviews.

I have been asked to perform a Sterility review and identify any remaining questions or deficiencies to be conveyed from CDRH to the Applicant. My initial Sterility filing review identified three (3) potential concerns that were discussed with the CDER Microbiology reviewer, Dr. David Bateman, to ensure consistency with CDER review requests. However, based upon submission documents brought to my attention by THT1A4 Assistant Director and review team point person, Ms. Claudine Krawczyk, two (2) of these potential concerns regarding shelf life and transport stability have been alleviated. One (1) Interactive Review request regarding sterile barrier (e.g., Tyvek lidding) and outer carton labeling was forwarded to the Applicant via CDER on 07/09/2023. On 07/19/2023, the Applicant provided responses to all Interactive Review requests, including revised copies of the sterile barrier and outer carton labeling, as well as updated physicians labeling (e.g., instructions for use). The Applicant's revised documents fully address my concerns. No additional concerns have been identified during the current review. The device aspects of the submission are acceptable from a CDRH Sterility perspective.

Device Description:

The Applicant provides a general device description for their drug product in their "Quality Overall Summary – Drug Product" document, found in section 2.3.P, beginning on page 4. The Applicant states:

The Travoprost Intraocular Implant (alternatively referred to as G2-TR-125 or G2-TR) is a sterile, drug eluting implant that is surgically delivered through a small clear corneal incision and anchored in the anterior chamber angle of the eye. The implant elutes drug product (travoprost drug substance [REDACTED] (b) (4) and is designed for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT). The Travoprost Intraocular Implant is a single entity drug led drug-device combination product. The quantitative composition, based on the target implant fill weight, for the Travoprost Intraocular Implant bulk drug product contained within a single implant is shown in Table 1. Table 2 in Section 2.3.P.2.1 summarizes the drug product and medical device constituents, and primary, secondary, and tertiary packaging components of the Travoprost Intraocular Implant.

Regarding the device implant, the Applicant states:

The Travoprost Intraocular Implant is comprised of a titanium reservoir (also referred to as titanium container) with titanium anchor, containing 75 µg of travoprost drug substance (b) (4). The titanium reservoir is sealed with an ethylene vinyl acetate (EVA) membrane held in place with a titanium crimp cap. The EVA membrane is (b) (4) and contains (b) (4) vinyl acetate. The EVA membrane, which is in direct contact with the travoprost drug product formulation filled into the titanium reservoir, allows drug to elute through the membrane at a controlled rate. The nominal dimensions of the assembled implant are 1.84 mm long by 0.494 mm in diameter.

With respect to the implantation procedure, the Applicant describes their device inserter, as follows:

An inserter is used to facilitate placement of the implant by the physician. The implant filled with drug product is loaded onto the inserter. A safety clip holds the release button in the forward position during shipping, storage, and handling, thus preventing the premature release of the implant. The inserter handpiece is made from common medical grade (b) (4) and (b) (4) stainless steels. The inserter material that enters the eye is stainless steel.

A brief description of the device packaging (including the sterile barrier system) is also provided, as follows:

The assembled implant and inserter are placed in a (b) (4) blister tray that is sealed with a Tyvek lid. The sealed tray is placed together with an oxygen absorber packet into a transparent barrier pouch (b) (4) which is sealed and placed in a unit carton. The unit cartons are (b) (4) (b) (4) the final labeling contents are added within the unit carton (i.e., prescribing information and patient card).

The following table (Table 2, 2.3.P, p.5) is provided listing the materials used:

Table 2: Travoprost Intraocular Implant Components (Up to Tertiary Packaging)

Component	Drug Product Constituent	Medical Device Constituent Implant	Medical Device Constituent Inserter	Primary Container Closure	Secondary Packaging	Tertiary Packaging	Material
Travoprost Drug Substance	X						Travoprost
(b) (4)	X						(b) (4)
Titanium Reservoir		X					Titanium, (b) (4) (b) (4)
EVA Membrane		X					Ethylene vinyl acetate
Titanium Cap		X					Titanium, (b) (4) (b) (4)
Inserter			X				(b) (4) stainless steel (b) (4) (b) (4)
Blister Tray				X			(b) (4)
Tyvek Lid				X			Tyvek and (b) (4) adhesive, (b) (4) (non- printed side only) (b) (4)
(b) (4)					X		(b) (4)
O ₂ Absorbing Packet					X		(b) (4)
Barrier Pouch					X		(b) (4)
Carton						X	The unit carton contains the barrier pouch packaging, prescribing information, patient card and label for the unit carton. A tamper evident seal is affixed to both ends of carton.

Container Closure System

The Applicant provides their container closure system description, including illustrations, beginning on page 7 of 2.3.P. The Applicant states:

2.3.P.2.4 Container Closure System

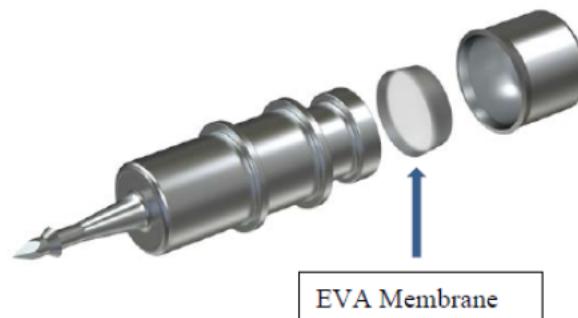
Travoprost Intraocular Implant (alternatively referred to as G2-TR-125 or G2-TR) is a sterile, drug-eluting implant that is surgically delivered through a clear corneal incision and anchored in the anterior chamber angle of the eye. The implant elutes formulated drug product (travoprost drug substance (b) (4)) and is designed for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. The Travoprost Intraocular Implant is a single entity drug led drug-device combination product. Section 3.2.P.1 Table 1 summarizes the drug product and medical device constituents, and primary, secondary, and tertiary container closure (packaging) components of Travoprost Intraocular Implant.

Assembled and exploded views of the device are provided on page 8:

Figure 1: Assembled View of Travoprost Intraocular Implant

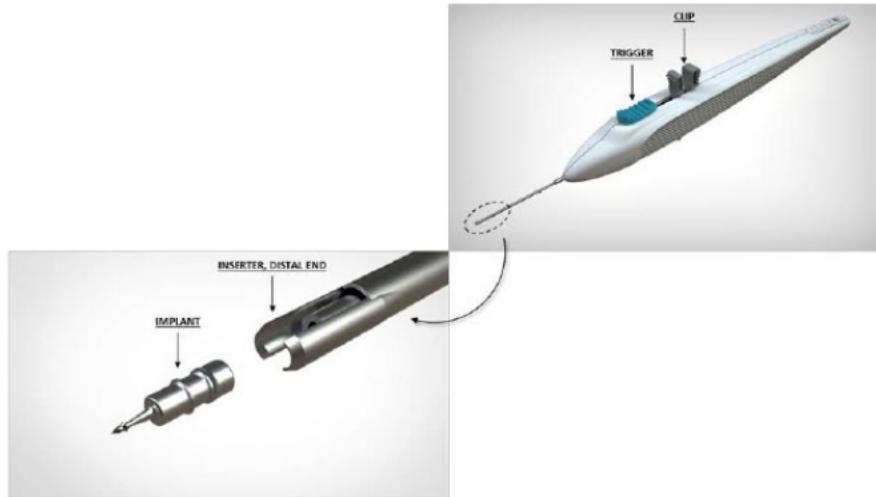


Figure 2: Exploded View of Travoprost Intraocular Implant



An additional image provides an illustration of the implant injector:

Figure 3: Inserter Loaded with Travoprost Intraocular Implant



Engineering drawings for the above components is included in the Container Closure System section, 3.2.P.7.

The Applicant goes on to provide a description and engineering drawings for the primary device packaging in 3.2.P.7, beginning on page 23. Regarding the blister tray, the Applicant states:

1.4.1. Blister Tray and Lid

The function of the blister tray is to hold the pre-loaded inserter containing the implant securely during shipment and storage. The blister tray is (b) (4)

(b) (4). The lid is comprised of Tyvek (b) (4)

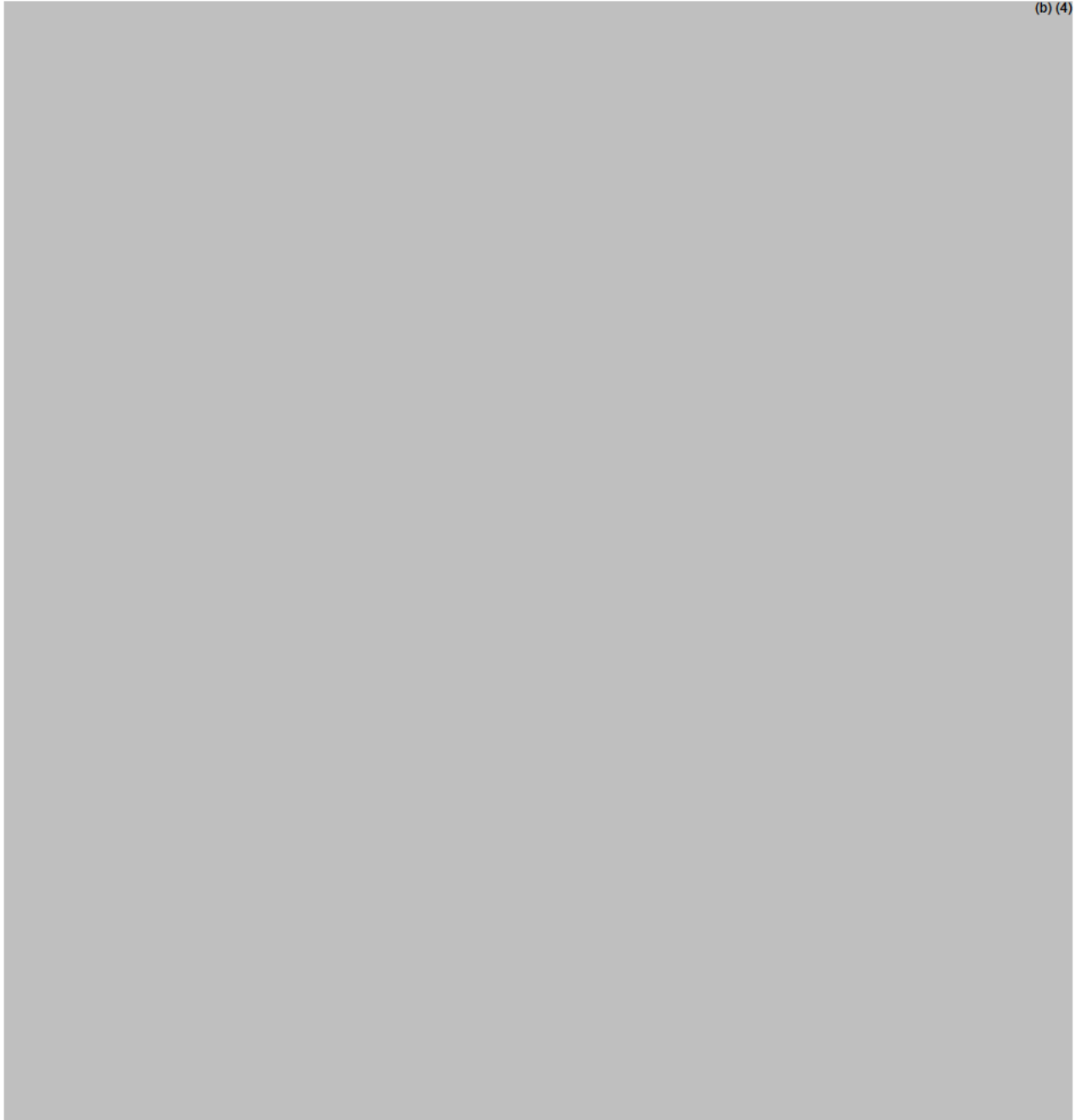
(b) (4). Current drawings of the tray and lid are provided in [Figure 16](#) and [Figure 17](#), respectively. Previous version of the drawings used in the manufacture of the registration batches had minor dimensional changes to the non-critical dimensions that did not impact the overall form fit or function of the product. Glaukos receives the trays and lids and releases the components for drug product manufacturing per the specifications outlined in [Table 11](#) and [Table 12](#), respectively.

Figures 16 (Tray Drawing) and 17 (Lid Drawing) are included, as follows:

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The Applicant also employs a barrier pouch. (b) (4). This is described on page 26 of 3.2.P.7, as follows:

1.5.1. Barrier Pouch



An exploded diagram of the complete packaging configuration is included in document 2.3.P, on page 33, as follows:

Figure 6: Travoprost Intraocular Implant Packaging (Exploded View)



Finally, photographs illustrating the device packaging are included in the Container Closure System document, 3.2.P.7, on page 37, as follows:



Reviewer Comments: *I have reviewed the device description information provided by the Applicant in the current submission. The information is adequate and includes relevant details of the drug substance, the drug delivery implant, the implant injector, and the device*

packaging (inclusive of primary blister tray with Tyvek lid, and (b) (4) pouch (b) (4) (b) (4)). This information provides the necessary level of detail to perform my Sterility review. Therefore, the device description is ACCEPTABLE from a Sterility perspective.

Indications for Use

The Applicant provides the following draft Indications for Use statement in their Draft Labeling Text document, 1.14.1.3:

(b) (4)

Reviewer Comments: The draft Indications for Use statement is ACCEPTABLE from a Sterility perspective.

Sterility Review

Manufacturing Process

The Applicant discusses their manufacturing process across multiple documents in the submission. The Applicant specifically includes the document, "Description of Manufacturing Process and Process Controls," as Section 3.2.P.3.3 of the submission.

Beginning on page 2 of 3.2.P.3.3, the Applicant includes 4 flow chart figures illustrating their manufacturing process, as follows:

(b) (4)

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Table 1: In-Process Controls

(b) (4)



In the Quality Overall Summary document (2.3.P, p.28), the Applicant lists out the release testing performed on the implant device, in its final finished form:

Table 12: Travoprost Intraocular Implant Device Constituent Testing

Device Finished Product Test	Test Method	Acceptance Criteria
Physical Appearance	M16818 (Microscope 30X Magnification)	All components are present. Cap is secured to container and cap, membrane and container do not appear damaged. Packaging components do not appear damaged.
Bacterial Endotoxin – inserter hand piece / inserter tip and implant	USP <85>	NMT (b) (4) NMT
Sterility – inserter hand piece / implant*	USP <71>	Conforms to test requirements

* Glaukos reviews the sterilization documentation (Certificate of Processing) prior to final release, in accordance with the requirements for device testing requirements. The actual sterility testing as described in Table 1 is done to fulfil the requirements for the drug constituent of the drug led drug-device combination product.

Also in 2.3.P, the Applicant lists out the various manufacturing and testing locations, beginning on page 14. The Applicant states:

Table 6: Manufacturing, Packaging and Control Sites of Travoprost Intraocular Implant

Site	Responsibility
Glaukos Corporation 229, 236 Avenida Fabricante San Clemente, CA 92672 FEI: 3012341472 DUNS: 012835406 Official Correspondent: Ted Wheeler 229 Avenida Fabricante San Clemente, CA 92672 Phone: (949) 481-0583 Email: twheeler@glaukos.com	(b) (4) component receiving inspection (b) (4) component release Manufacturing: • Component preparation • (b) (4) drug product formulation • Drug product filling • EVA disc (membrane) manufacture • Implant assembly • Inserter assembly Primary and secondary packaging Batch disposition and final release

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(b) (4)

***Reviewer Comments:** The Applicant describes their manufacturing process, inclusive of the Sterility/Microbiology controls in place to ensure product safety. The Applicant indicates that Bioburden and Endotoxin testing are performed on (b) (4) drug product, (b) (4)*

. This routine/release testing approach is ACCEPTABLE. The respective specification limits that are in place for Bioburden and Endotoxin testing are also ACCEPTABLE, with the implant Endotoxin limits set at the intraocular device limit.

(b) (4)

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As such, the shelf life and transport stability information is ACCEPTABLE.

Draft Labeling

The Applicant includes draft labeling in the Labeling section, 1.14. The following blister tray Tyvek lid draft labeling is included in section 1.14.1.1:

(b) (4)

The draft outer carton label is also included in section 1.14.1.1, as follows:



As shown, the outer carton contains essentially the same information as the Tyvek lid. There are no symbols on either label.

The draft Directions for Use are included in the “Draft Labeling Text” section 1.14.1.3. This document contains detailed directions, including images to illustrate steps of implant insertion. There is minimal information related to device sterility (e.g., do not re-use, do not re-sterilize).

Reviewer Comments: The Applicant has provided drafts of their Directions for use, blister tray Tyvek lid label and outer carton labeling. The Tyvek lid and outer carton labeling do not contain any symbols, including Sterility-related symbols (e.g., sterilization modality, do not reuse, do not resterilize, etc.). It is unclear, therefore, if text-only labeling is common for CDER.

Similar to my shelf life study questions, I discussed my labeling concerns with Microbiology CMC reviewer from CDER, Dr. David Bateman, to determine what is typical practice for CDER with respect to establishing shelf-life for a combination drug device. This discussion took place during the same phone call on 05/25/2023 mentioned above. Dr. Bateman confirmed that the absence of symbols on labeling was odd, and noted that CDER utilizes separate reviewers that focus on labeling when reviewing proposed drug labeling. As above, Dr. Bateman stated that my concerns should be interactively conveyed to the Applicant, particularly because the Applicant has many approved devices and should have an understanding of the information (including Sterility-specific symbols) required for labeling approval.

As a result, the following Sterility Interactive Review request were conveyed to the Applicant via CDER Project Manager, Ms. Shazma Aftab, on 07/07/2023 as “Agency Comment 6”:

You provide your draft labeling in the Labeling section, 1.14. However, your draft Tyvek lid and outer carton labeling do not contain any symbols, including any Sterility-related symbols (e.g., sterilization modality, “do not reuse,” “do not resterilize,” or expiration date symbols). Therefore, due to potential safety concerns, please provide updated draft labeling that includes all relevant commonly used symbols. Please also ensure that your “Draft Labeling Text” (section 1.14.1.3) includes a key that describes all symbols used on your draft Tyvek lid and outer carton labeling. This is important to ensure that end users are fully aware of all instructions that will maintain device sterility before and during use.

On 07/19/2023, the Applicant provided the following written response to my request:

Glaukos’ Response:

Glaukos provides herein updated proposed draft labeling in Section 1.14.1 for the **Tyvek lid**, **carton**, and prescribing information (**redline** and **clean**) with the applicable ISO 15223 symbols added including sterility-related symbols. Glaukos considers the newly proposed labeling addresses the Agency’s (i.e., CDRH review team) comments above while also being compliant with the CDER labeling guidelines.

The Tyvek lid is part of the primary container closure and has a long lead time. Glaukos intends to commence the process validation of the commercial product as early as possible. Because the Tyvek lid will be used in the planned commercial manufacturing process, we are kindly asking the Agency to evaluate the herein submitted version of the Tyvek lid at the upcoming mid-cycle review meeting, so that Glaukos might obtain feedback from the CDER and CDRH review teams as part of the Agency’s mid-cycle communication to Glaukos.

The revised draft Tyvek lid labeling was included as follows:

(b) (4)

As shown, the revised draft Tyvek lid labeling now includes all relevant Sterility information as requested.

Similarly, the following revised draft outer carton labeling was provided as follows:

(b) (4)

Again, the revised draft carton labeling now includes all relevant Sterility information as requested.

Accordingly, the draft physician labeling (e.g., instructions for use) was revised to include a symbol key for those symbols now appearing on the Tyvek lid and outer carton labeling:



(b) (4)

Based upon the new revised information provided interactively, the Labeling is ACCEPTABLE from a Sterility perspective.

Recommendation: CND – Completed – No Deficiencies

In the current submission, the Applicant, Glaukos Corp., requests marketing approval for their iDose TR travoprost intraocular implant. The device consists of a travoprost-releasing titanium implant that is preloaded in a single-use inserter. (b) (4)

(b) (4)

The current review was aimed at identifying any last questions/concerns to be interactively addressed with the Applicant ahead of the final review. Based upon my initial filing review (and multiple discussions [internal to CDRH and external with CDER], my recommendation was to FILE from a CDRH Sterility perspective. The Applicant has provided information describing the subject device, device packaging, the manufacturing process, (b) (4), all Sterility-related test methods (b) (4), (b) (4), and accelerated aging shelf-life study results to perform my Sterility review. Based on my most recent review, one (1) questions/concerns was identified regarding the absence of Sterility-related symbols in the draft labeling. This concern has been fully addressed interactively with the Applicant with the new information that was provided on 07/19/2023. Therefore, I have no additional questions/concerns for the Applicant and recommend for CND. I recommend for approval from a CDRH Sterility perspective.

ICCR Inspectional Guidance Template

Document Type: Template

Date Effective: 3/23/2022

Point of Contact: Bertram, James

Use FEEDBACK ✓ CDRH  to provide comments on this document (include Doc # [03994](#))

COMBINATION PRODUCT INSPECTIONAL GUIDANCE

Date: June 8, 2023
Amended: October 27, 2023

To: Krishnakali Ghosh, Office of Process and Manufacturing Assessment (OPMA) Division IV Krishnakali.Ghosh@fda.hhs.gov

Vidya Pai, Office of Process and Manufacturing Assessment (OPMA) Division IV Vidya.Pai@fda.hhs.gov

Office of Combination Products at combination@fda.gov

RPM: Shazma Aftab, Shazma.Aftab@fda.hhs.gov

Through: Claudine Krawczyk, Acting Assistant Director, Glaucoma, Cornea, and Surgical Devices Team, OHT1, OPEQ, CDRH

Claudine H. Krawczyk -S  Digitally signed by Claudine H. Krawczyk -S
Date: 2023.06.08 11:58:14 -0400

From: CAPT Dimitrus Culbreath, Restorative and Surgical Dental Devices Team, OHT1, OPEQ, CDRH

Applicant: Glaukos Corporation
229 Avenida Fabricante
San Clemente, CA 92672
FEI# 3012341472

Application # NDA# 218010

Consult #
ICC#2300245

Product Name: iDose® TR (travoprost intraocular implant)

Combination Product

Intended Use: Treatment of reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension.

Pre-Approval Inspection: Yes

The Office of Ophthalmic, Anesthesia, Respiratory, ENT and Dental Devices at CDRH received a consult from CDER requesting the identification of the device manufacturing sites for NDA#218010 for iDose® TR (travoprost intraocular implant) which will require a device inspection.

Inspectional Assignment

Firm to be inspected:

1. Glaukos Corporation

229 Avenida Fabricante
San Clemente, CA 92672
FEI# 3012341472

CDRH recommends a preapproval inspection under the applicable Medical Device Regulations of Glaukos Corporation, located in San Clemente, USA (FEI # 3012341472).

A limited inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30) for the iDose® TR (NDA# 218010).

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

INSPECTIONAL GUIDANCE

Perform an inspection based on the recommendations (for applicable locations) of this Inspectional Guidance, and the Quality System Inspection Technique (QSIT) Guide:

Note: As per usual inspection, please use your discretion to determine which documentation should be collected to support the observations.

21 CFR 820.20 Management Responsibility

For the iDose® TR, Firm 1: Glaukos Corporation:

Determine if the firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements.

1. Collect the firm's basic quality system procedure(s). The basic quality system procedure(s) should include:
 - a. Quality audit or internal audit procedure(s);
 - b. Management review procedure(s);
 - c. Outline of the structure of the quality system documentation;

21 CFR 820.30 Design Controls

For the iDose® TR, Firm 1: Glaukos Corporation:

Each manufacturer shall establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met:

2. Determine if the iDose® TR, Firm 1: Glaukos Corporation has established and maintained design control records for the iDose® TR. Determine if design changes were implemented, including those related to corrective actions. Determine if the design changes have been verified and validated. Determine if design changes adversely affect the finished device.

3. Records reflecting design development, design input and output, design review, design verification, validation and transfer as well as design changes for the iDose® TR should be collected and reviewed by Glaukos Corporation.
4. Determine if Glaukos Corporation has a Risk Management Program. Does the Risk Management Program extend through the various Quality System processes such as Design Controls, CAPA, and Complaint Handling and integrated with Purchasing Controls and Acceptance activities?

21 CFR 820.50 Purchasing Controls

For the iDose® TR, Firm 1: Glaukos Corporation:

Each manufacturer shall establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements;

1. Evaluation of the firm's purchasing control over its suppliers
 - a. Identify the sources of raw materials for the iDose® TR, and their components.
 - b. Are these components purchased sterile, sterilized in-house, or sterilized by a contract sterilizer?
 - c. Review the Purchasing Control procedures for the iDose® TR, and their components.
 - i. Evaluate the agreement between the supplier and the manufacturer, taking note whether the supplier is required to notify the manufacturer of changes in the product that may affect the quality of the finished device.
 - ii. Collect documentation regarding audit procedures the manufacturer may have on their suppliers.
 - d. Does Glaukos Corporation have a written purchasing agreement with (b) (4) (b) (4)? Does Glaukos Corporation audit these suppliers?

21 CFR 820.100 Corrective and Preventive Action (CAPA)

For the iDose® TR, Firm 1: Glaukos Corporation:

Each manufacturer shall establish and maintain procedures for implementing corrective and preventive action to include: analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems.

1. In addition to the normal QSIT CAPA review, please review any CAPAs performed specifically for this combination product or another similar product.
2. Collect and review the firm's final release testing procedures and results.

21 CFR 820.80 Acceptance Activities

For the iDose® TR, Firm 1: Glaukos Corporation:

Each manufacturer shall establish and maintain procedures for acceptance activities. Acceptance procedures include inspections, test, or other verification activities.

1. Review the firm's acceptance process for purchased supplies and services and document how the firm handles deviations from its established acceptance criteria.
 - a. Review the firm's qualification of their component supplier and associated acceptance testing.
 - b. Review documentation of the firm's audit checks on their suppliers.
2. Identify and review the firm's acceptance criteria and any acceptance testing performed on purchased supplies or services specifically for the components of the iDose® TR.
 - a. What type of testing is done as part of the final release criteria for the iDose® TR.
 - b. Are incoming products tested and the functionality verified prior to final release?
 - c. What is the firm's procedure for receipt of non-conforming products from suppliers?
 - d. Are device constituents ever rejected on incoming inspection? Is there a written procedure for this activity? What is the rejection rate – if any?

AMENDED, October 26, 2023:

The recommended device inspection of the Glaukos facility, FEI 3012341472 was conducted (7/10-19/2023) and deemed acceptable (see NAI/VAI EIR Checklist).

I reviewed the EIR. In particular, from device perspective (i.e., 21 CFR 820 considerations), I reviewed the following information provided in the EIR.

CDRH Call out	EIR Section	Page
21 CFR 820.20 - Management responsibility	Quality Control/Quality Assurance Laboratory System Non-Conformance, Out of Specifications, OOS	p.12-14 P.16-17 p.18-25
21 CFR 820.30 - Design controls	Production and Process Control	p. 5-11
21 CFR 820.50 - Purchasing controls	Purchasing Control, Incoming acceptance testing and Raw Material testing	p. 28-30
21 CFR 820.100 - Corrective and preventive action	Non-Conformance, Out of Specifications, OOS	p.18-25
21 CFR 820.170 – Installation	Equipment Control	p.12-15
21 CFR 820.200 – Servicing	Equipment Control	p. 12-15

I identified no concerns based on the information provided in the EIR. No 483 was issued but this inspection resulted in 4 verbal observations that were discussed with management. The verbal observations raise no new concerns.

CDRH Decision: Approvable (Recommend approval to CDER)

CDRH Concurrence:

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/

CHUNCHUN N ZHANG
10/30/2023 05:55:05 PM