

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211950Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 211950 Assessment # 2

Drug Product Name	XIPERETM (triamcinolone acetonide injectable suspension)
Dosage Form	Injectable suspension
Strength	40 mg/ mL
Route of Administration	Suprachoroidal injection
Rx/OTC Dispensed	Rx
Applicant	Clearside Biomedical, Inc
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission	Apr 30, 2021	All disciplines
Quality Amendment	Jun 10, 2021	Quality microbiology, Manufacturing process
Quality Amendment	Jul 16, 2021	Quality microbiology
Quality Amendment	Jul 27, 2021	Drug product
Quality Amendment	Aug 6, 2021	Manufacturing process
Quality Amendment	Aug 31, 2021	Manufacturing process
Quality Amendment	Sep 2, 2021	Manufacturing process
Quality Amendment	Sep 14, 2021	Manufacturing process
Quality Amendment	Sep 23, 2021	Manufacturing process
Quality Amendment	Oct 5, 2021	CDRH
Quality Amendment	Oct 6, 2021	Manufacturing process
Quality Amendment	Oct 15, 2021	CDRH

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Ben Zhang	Suong Tran
Drug Product	Chunchun Zhang	Danae Christodoulou
Manufacturing	Rose Xu	Sateesh Sathigari



QUALITY ASSESSMENT



Microbiology	Eric Adeeku	Elizabeth Berr
Biopharmaceutics	NA	NA
Regulatory Business Process Manager	Kelly Ballard	
Application Technical Lead	Chunchun Zhang	
Laboratory (OTR)	NA	
Environmental	Chunchun Zhang	Danae Christodoulou

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	5/29/2019 reviewed by Ben Zhang	LoA: 6/22/2018
	Type III			NA		LoA: 5/23/2018
	Type III			NA		LoA: 5/28/2018

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	115683	This product during IND development

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH		Adequate	10/18/2021	Alan Stevens
Clinical				
Other				

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Satisfactory information and responses have been submitted to support product quality (biopharmaceutics, drug substance, quality microbiology, and drug product), refer to IQA#1 dated 9/10/2019 and these disciplines uphold the approval recommendation in this resubmission.

The product was determined to be a drug device combination product per the Genus decision in Sep 2021. OND revisited the CDRH deficiencies identified in the consult review during the original review cycle dated Aug 12, 2019 and sent the first three deficiencies to the applicant on Sep 20, 2021. The response was received on 10/1/2021 and Dr. Alan Stevens (CDRH) found the response acceptable with the inclusion of plunger aspiration force and plunger depression force tests in the drug product specification on Oct 18, 2021. Dr. Ashley Boam discussed the (b) (4), (b) (5)

The applicant was notified that the product is regulated as a combination product and the 356h form including device facilities was updated per the Agency's request on 10/5/2021. The device facilities were acceptable from the original CDRH consult review. Dr. Ashley Boam indicated on Sep 28, 2021 that OPQ/OPPQ and CDRH have determined that although this device constituent part is not necessarily a standard syringe, a CDRH facility consult is not necessary for this particular application; however, the device facility (b) (4) FEI (b) (4) has never been inspected by the Agency, OPQ and CDRH recommend a post-approval inspection for this facility.

The drug product manufacturing site is transferred to (b) (4) from (b) (4) in the resubmission. All the manufacturing sites are currently acceptable. The Office of Pharmaceutical Manufacturing Assessment (OPMA) has issued an overall acceptable recommendation for all the facilities with post-approval inspection recommendations for Alcami (FEI 1000110990) and (b) (4) (FEI (b) (4) on (b) (4). Additionally, all the manufacturing process deficiencies have been resolved with adequate (b) (4) (IPCs) or appropriate justifications. Therefore, NDA 211950 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.

We have one non-approvability comment to be included it as an "additional comment" from biopharmaceutics in the action letter:

We acknowledge your commitment to perform additional in vitro drug release studies post-approval. We recommend that you submit the following data/information in a supplement when they are available: (1) data demonstrating the discriminating ability of the proposed in vitro drug release method (M20682) against smaller particle size distributions that is representative of meaningful changes; (2) multi-point drug release profiles (individual, mean, %RSD) for the clinical batches and registration stability batches.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

XIPERETM (triamcinolone acetonide injectable suspension), 40 mg / mL is a sterile, preservative-free aqueous suspension and packaged in a 2 mL / 13 mm glass vial with a rubber stopper and an aluminum seal for the single use. The fill volume is 0.9 mL and the injection volume of the dose is 0.1mL. The drug product will be administered by a SCS Microinjector.

Proposed Indication(s) including Intended Patient Population	For the treatment of macular edema associated with uveitis.
Duration of Treatment	See package insert for the recommended dosage in patients.
Maximum Daily Dose	As above (see the package insert for details).
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance, triamcinolone acetonide, is a white or almost white crystalline powder. The drug substance referenced in DMF (b) (4) was found adequate by Ben Zhang on 5/29/2019. No update was submitted since the last review.

Drug Product: Adequate

General drug product information is referred in the review #1. The proposed drug product is the subject of a USP monograph. In the resubmission, the drug product manufacturing site is transferred to (b) (4) from (b) (4). Three registration batches (B200466, B210103 and B210104) were manufactured at the commercial scale (L) at Alcami Corp. Composition and specifications are identical to the original submission. The comparability report demonstrated that manufacturing processes from both sites are comparable. Six months

stability data for one registration batch (B200466) and one month for 2 other registration batches (B210103 and B210104) stored in inverted orientation at both long term (25°C/60%RH) and accelerated condition (40°C/75%RH) was submitted in the resubmission on 4/30/2021 and the quality amendment dated on 7/27/2021. Additionally, stability data from original three registration stability batches were updated: 48 months for Lot FG-15-0349 and 36 months for Lot FG-17-0087 at 25°C/60%RH. All the quality attributes met the proposed specifications.

Refer to IQA # 1 on the SCS microinjector evaluation from CDRH and section I in this IQA. Three performance tests including dispensability, functionality and injection volume in container have been included in the DP specifications. Per the agency's request, plunger aspiration force and plunger depression force tests are included in the drug product specifications on 10/18/2021. Major update on the SCS microinjector in this resubmission was ethylene oxide sterilization validation for the addition of new facilities (b) (4) in (b) (4) and (b) (4). Quality microbiology reviewer Dr. Eric Adeeku reviewed the sterilization validation report and found it adequate on 7/29/2021. Refer to Dr. Adeeku's review in Panorama.

Drug product review #1 recommended Approval and this review upholds the Approval recommendation from drug product perspective.

Based on stability data provided, the shelf life for XIPERETM (triamcinolone acetonide suprachoroidal injectable suspension) 40 mg/mL is granted for 36 months when "stored at 15°C to 25°C (59°F to 77°F). Do not freeze. The drug vial should be protected from light by storing in the carton". Please note the drug product has an overfill (0.9 mL fill in 2 mL glass vial but only 0.1 mL administered), the following statements will be included based on the discussion with OND, OPPQ and DMEPA on 9/8/2021: (b) (4) and "Discard unused portion".

Labeling: Adequate

Labeling recommendations from the Product Quality perspective will be communicated to the OND PM.

Manufacturing: Adequate

The proposed drug product manufacturing process consists: (b) (4)

The process related deficiencies have been resolved with adequate IPCs or appropriate justifications. All the manufacturing facilities are currently acceptable or at low risk. However, the product is currently regulated as a drug device combination product, and the drug product

manufacturing site is identified as a new profile, Device Kit Assembler (DKA). Additionally, the device facility has never been inspected by the Agency. Therefore, post approval inspections are recommended for the drug product manufacturing site Alcamí (FEI 1000110990) and the device facility (b) (4) (FEI (b) (4)).

Biopharmaceutics: Adequate

The Applicant developed an in vitro drug release testing method for the proposed triamcinolone acetonide suprachoroidal injectable suspension per the Agency's PMC in the original review cycle. The Applicant commits to perform additional studies on discriminating ability of the method against smaller particle size distributions post approval. The application upholds an approval recommendation from biopharmaceutical perspective. A general comment regarding submitting the additional in vitro drug release data as the Applicant committed will be conveyed in the action letter:

We acknowledge your commitment to perform additional in vitro drug release studies post-approval. We recommend that you submit the following data/information in a supplement when they are available: (1) data demonstrating the discriminating ability of the proposed in vitro drug release method (M20682) against smaller particle size distributions that is representative of meaningful changes; (2) multi-point drug release profiles (individual, mean, %RSD) for the clinical batches and registration stability batches.

Microbiology (if applicable): Adequate

The sterility assurance of the SCS microinjector was reviewed and found adequate by CDRH (ICC1900093) during the original review cycle dated 05/15/2019. Ethylene oxide sterilization validation for the SCS microinjector for the addition of new facilities (b) (4) in (b) (4) and (b) (4) was reviewed and found it adequate on 7/29/2021.

C. Risk Assessment

I. From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations

Sterility	Formulation Container closure Process parameters Scale/equipment Site	H	(b) (4)	L	Post-approval stability protocol will test sterility.
Bacterial Endotoxin	Formulation Container closure Process parameters Scale/equipment	H		L	
Assay (API), stability	Formulation Container closure Raw materials	L		L	
Uniformity of Dosage unit	Formulation Container closure Process parameters Scale/equipment	M		L	
pH	Formulation Container closure Process parameters Scale/equipment	L		L	
Particle size distribution	Formulation Container closure Process parameters Scale/equipment	M		L	
SCS microinjector	Formulation Container closure	H		L	

D. List of Deficiencies for Complete Response

- Overall Quality Deficiencies (*Deficiencies that affect multiple sub-disciplines*)

NA

2. Drug Substance Deficiencies

NA

3. Drug Product Deficiencies

NA

4. Labeling Deficiencies

Communicate to the OND PM

5. Manufacturing Deficiencies

NA

6. Biopharmaceutics Deficiencies

NA. One general comment is proposed to be included in the action letter.

7. Microbiology Deficiencies

NA

8. Other Deficiencies (*Specify discipline, such as Environmental*)

NA

Application Technical Lead Name and Date:***Chunchun Zhang, Ph. D., Oct 18, 2021***

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

BIOPHARMACEUTICS**Product Background:****NDA/ANDA:** 211950**Drug Product Name / Strength:** XIPERE (triamcinolone acetonide suprachoroidal injectable suspension)**Route of Administration:** Suprachoroidal**Applicant Name:** Clearside Biomedical, Inc.***Review Summary:***

The Applicant developed an in vitro drug release testing method for the proposed triamcinolone acetonide suprachoroidal injectable suspension using (b) (4). However, the discriminating ability of the proposed method against critical quality attributes, such as API particle size distribution, was not demonstrated. The Applicant commits to perform additional studies on discriminating ability of the method against smaller particle size distributions post-approval. The Applicant does not plan to use the method for routine batch-to-batch quality control test but will use it to support future post approval changes. In the current Drug Product Specification, particle size distribution is controlled at "D10<(b) (4) μm, D50<(b) (4) μm, D90<(b) (4) μm". Due to the existing controls on particle size which may impact drug release, and the Applicant's ongoing efforts in optimizing the in vitro drug release method, the Applicant's plan is acceptable. NDA 211950 for triamcinolone acetonide suprachoroidal injectable suspension is recommended for approval from a Biopharmaceutics perspective. A comment regarding submitting the additional in vitro drug release data as the Applicant committed will be conveyed in the action letter.

List of Submissions being reviewed:

NDA resubmission, eCTD sequence #0017, dated 04/30/2021

Response to Biopharmaceutics IR, eCTD sequence #0023, dated 08/06/2021

Highlight Key Outstanding Issues from Last Cycle:FDA recommended the Applicant to develop an appropriate in vitro drug release method for quality control purpose.¹

¹ Meeting minutes- 2019 Aug CMC meeting. [\\CDSESUB1\evsprod\nda211950\0017\m1\us\16-meet\correspond-typea-20190920.pdf](#)

Concise Description Outstanding Issues Remaining:

The Applicant commits to submit additional studies post-approval on discriminating ability of the proposed in vitro drug release method against smaller API particle size distributions.

Biopharmaceutics Assessment:

BCS Designation: BCS classification is not applicable to this ophthalmic product.

Solubility: Triamcinolone acetonide is practically insoluble in water. The Applicant conducted a shake flask study to determine the solubility of the Triamcinolone Acetonide Reference Standard material in various media. The results are shown in Table 1.

Table 1². shake flask solubility study results

(b) (4)

**Matrix Evaluation**

(b) (4)



(b) (4)

Reviewer's Assessment:

The method (b) (4) % SDS, (b) (4) mL/min) is shown to be able to differentiate the proposed drug product (with PSD specification: D10<(b) (4) μm, D50<(b) (4) μm, D90<(b) (4) μm) from the product prepared with (b) (4). However, the (b) (4) have significantly larger particle size than the proposed drug product, which may not be a meaningful comparison. In addition, the method used was not the final proposed method (b) (4) mL/min).

In the IR response, Clearside commits to perform additional analysis at smaller particle size distributions using the current method M20682 post approval, in order to demonstrate whether the current method M20682, with a flow rate of (b) (4) mL/min, is discriminating against smaller particle size distributions.

In vitro drug release test is not included in the Drug Product Specification⁸ for quality control at batch release and during long term storage. No acceptance criteria were proposed. Through an IR, the Applicant was asked to clarify their plan. In the response, Clearside noted that it plans to establish an IVR acceptance criteria based on clinical and registration batch data and provide clinical and registration batch data in the post-approval annual report. Consistent with the FDA recommendations at the August 20, 2019 meeting and SUPAC-SS, Section C, Item 2, the IVR acceptance criteria will be established for effective evaluation of post approval changes and is not intended as a routine batch-to-batch quality control test.

⁷ Figure 5-1 from Page 41 of the updated method development report.

⁸ Drug Product Specifications (b) (4)

Overall, the discriminating ability of the proposed *in vitro* drug release method was not adequately investigated, and Clearside commits to perform additional studies on discriminating ability of the method against smaller particle size distributions. Clearside does not plan to use the method for routine batch-to-batch quality control test but will use it to support post approval changes. Because the existing Drug Product Specifications provides controls on particle size distribution which may impact on drug release, the Applicant's plan is reasonable. The Applicant will be advised to provide the additional data it commits to collect to a supplement for FDA review.

R Regional Information

Comparability Protocols

The Applicant submitted a comparability protocol⁹ attempting to demonstrate that the commercial manufacturing process of CLS-TA (triamcinolone acetonide injectable suspension) 40 mg/mL at (b) (4) (b) (4) (b) (4) (b) (4) is substantially equivalent to the manufacturing process at (b) (4) (b) (4) (b) (4) Manufacturing process information and batch analysis data were provided to support the comparison. Comparative *in vitro* drug release data between the new registration batches manufactured using the commercial manufacturing process at (b) (4) and the original registration (clinical) batches manufactured at (b) (4) were also submitted (Figure 2).



⁹ Comparability Protocol. [\\CDSESUB1\evsprod\nda211950\0017\m3\32-body-data\32r-reg-info\32r3-comp-prot\comp-report.pdf](#)

¹⁰ Plotted based on data from Table 14 and 15 of Comparability Report

Reviewer's Assessment:

Though the in vitro drug release data showed similar drug release profiling between the pre- and post-change batches, the in vitro drug release method has not been found adequate, especially its discriminating ability has not been demonstrated. Biopharmaceutics defers to Drug product and Process review teams to evaluate the adequacy of the comparability protocol.

List of Biopharmaceutics Comments:

1. We acknowledge your commitment to perform additional in vitro drug release studies post-approval. We recommend that you submit the following data/information in a supplement when they are available: (1) data demonstrating the discriminating ability of the proposed in vitro drug release method (M20682) against smaller particle size distributions that is representative of meaningful changes; (2) multi-point drug release profiles (individual, mean, %RSD) for the clinical batches and registration stability batches.

Primary Biopharmaceutics Reviewer Name and Date: Jing Li, Ph.D., 8/18/2021

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Poonam Delvadia, Ph.D., 08/18/2021



Jing
Li

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Date: 8/19/2021 11:12:41AM

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Delvadia

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	211950
Assessment Cycle Number	02
Drug Product Name/ Strength	Triamcinolone acetonide suprachoroidal Injectable suspension / 40 mg/mL
Route of Administration	Suprachoroidal
Applicant Name	Clearside Biomedical, Inc.
Therapeutic Classification/ OND Division	N/A
Manufacturing Site	Alcami Carolinas Corporation, 4221 Faber Place Drive Charleston, SC 29405
Method of Sterilization	(b) (4)

Assessment Recommendation: Adequate

Assessment Summary: The submission is **recommended** for approval.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
17 (eCTD seq. #0017)	04/30/2021
19 (eCTD seq. #0019)	06/10/2021
21 (eCTD seq. #0021)	07/16/2021

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
04/30/2021	04/30/2021	N/A	05/06/2021
06/10/2021	06/10/2021	N/A	06/15/2021
07/16/2021	07/16/2021	N/A	07/22/2021

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks:

This is an electronic submission.
No CP was included in the application.
The goal date is 10/30/2021

Response to the Agency's 05/25/2021 and 07/08/2021 information request letters were provided in the 06/10/2021 and 07/16/2021 submissions.

The sterility assurance of the injector was reviewed and found adequate by CDRH during the first cycle of NDA 211950 review in sterility consult review CON1999832 (ICC1900093), dated 05/15/2019. On 06/24/2021, the CDER/OPMA/DMA reviewers were asked to review ethylene oxide sterilization validation information for the injector submitted in NDA 211950 for the addition

of new facilities (b) (4) in (b) (4)
and (b) (4)

Concise Description of Outstanding Issues: No outstanding issues remain.

Supporting Documents:

DMF (b) (4) (Type V): – (b) (4) – (b) (4)
Manufactured in (b) (4)
(b) (4).

(b) (4) docx – Sterility assurance review of the depyrogenation of the stoppers that was found adequate in the 01/29/2020 microbiology review.

(b) (4) docx – Sterility assurance review of (b) (4) studies that was found adequate in the 04/16/2018 microbiology review.

(b) (4) docx – Sterility assurance review of the depyrogenation of the drug product glass vials that was found adequate in the 10/30/2020 microbiology review.

(b) (4) docx – Sterility assurance review of drug product glass vials depyrogenation requalification that was found adequate in the 05/12/2021 microbiology review.

This review contains original information as well as response to microbiology deficiencies conveyed to the sponsor in the Agency's information request letters dated 05/25/2021 and 07/08/2021 respectively. The most recent deficiencies are italicized.

(b) (4)



DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	10/18/2021
To:	Kelly Ballard
Requesting Center/Office:	CDER/OPQ
From	CAPT Alan M. Stevens* OPEQ/OHT3/DHT3C
Subject	NDA 211950 , XIPERE (triamcinolone acetonide ophthalmic suspension) ICC2100835 ICCR 00790392
Recommendation	Final Recommendation Date: Click or tap to enter a date. ☐ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies

*The review was initiated by Michaela Schulman, who left FDA on October 8, 2021. Alan Stevens completed the review. Comments from each reviewer are denoted in the memo below.

Digital Signature Concurrence Table

Reviewer	Team Lead	Division (Optional)

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 211950
Sponsor	Clearside Biomedical, Inc.
Drug/Biologic	XIPERE (triamcinolone acetonide ophthalmic suspension)
Indications for Use	For suprachoroidal injection, treatment of macular edema associated with uveitis
Device Constituent	Co-Packaged Syringe
Related Files	ICC1900093 / ICCR 00006653 (CR recommendation) ICC1800493 / ICCR 00007716 (meeting request)

Review Team	
Lead Device Reviewer	<i>Alan Stevens & Michaela Schulman</i>

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

- ☐ Approvable – the device constituent of the combination product is approvable for the proposed indication.
- ☐ Approvable with PMC or PMR, [See Section 2.3](#)
 - ☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, [see Section 2.2](#).

3. Comments to the Review Team

- ☒ CDRH does not have any further comments to convey to the review team.
- ☐ CDRH has the following comments to convey to the review team:

4. Complete Response Deficiencies

- ☐ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.
- ☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

5. Recommended Post-Market Commitments/Requirements

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

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6. PURPOSE/BACKGROUND

7. Scope

Clearside Biomedical, Inc. is requesting approval of XIPERE (triamcinolone acetonide ophthalmic suspension). The device constituent of the combination product is a Co-Packaged Syringe, with vial adapter and needles.

CDER/OPQ has requested the following [consult](#) for review of the device constituent of the combination product:

Consult review from CDRH in 2019 contains deficiencies. We are asking the CDRH team to review the response for these deficiencies sent by OND on 9/20/2021.

The goal of this memo is to provide a recommendation of the approvability of the proposed supplement; specifically related to changes that may impact the device constituent of the combination product. The Sponsor is addressing the following CR Deficiencies:

1, 2 and 3

This review will cover the following [review areas](#):

Verification Test Methods, EPR Validation, Control Strategy, and Risk Management

This review will not cover the following review areas:

All other areas as they remain unchanged from the previous review done by Rumi Young

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

8. Prior Interactions

Rumi Young reviewed the original NDA 211950 on 8/14/2019 and the file was CR. She issued 3 CR Deficiencies which the sponsor has responded to and are reviewed in this document (refer to ICC1900093 / ICCR 00006653 – CR recommendation).

9. Related Files

ICC1900093 / ICCR 00006653 (CR recommendation)

ICC1800493 / ICCR 00007716 (meeting request)

10. Indications for Use

Combination Product	Indications for Use
XIPERE (triamcinolone acetonide ophthalmic suspension)	For suprachoroidal injection, treatment of macular edema associated with uveitis
Co-Packaged Syringe	Delivery of the Drug Product

11. CR Responses

CR Deficiency #1	1. You provided numerous specifications for your SCS Microinjector Delivery System. However, you did not identify the essential performance requirements (EPRs), requirements essential to the safety and effectiveness of your device, as requested in our feedback to IND 115683 (07 AUG 2018). Provide essential performance requirements and specifications for the following: volume delivered, Plunger depression force, Plunger aspiration force, 900µM needle length, 1100µM needle length and Vial adapter insertion force, and Needle cap tip distance. For each EPR, address the following:
------------------	--

a. You provided the release and stability testing plan in 3.2.P.5.1. However, it is unclear

(b) (4)

b. You propose test methods (b) (4) to SCS Microinjector delivery system related test specifications (b) (4) Functionality and Injection Volume in Container, respectively. However, your proposed methods do not adequately assess the functional performance the specifications (b) (4) Functionality and Injection Volume in Container) for the following reasons:

(b) (4)

**Sponsor
Response**

(b) (4)

**Reviewer
Comments****Michaela Schulman Review**

See the sponsor's response for all figures included in their CR deficiency responses.

ai. The sponsor provided stability testing with accelerated and real-time aging equivalent to 36 months (see ENG-0418). They provided T=0 stability testing for the 900 um needle length and needle cap tip distance. They provided stability testing at T=0 & T=12 months for the 1100 um needle length. Testing on samples that have been aged 36 months for all EPRs (except needle length and needle cap tip distance) is acceptable to support a 36-month shelf-life. Additionally, per the deficiency, testing at T=0 for the needle lengths and needle cap tip distance is sufficient.

They claim that their sample size supports

(b) (4)

They don't justify why (b) (4) reliability is acceptable. **Deficiency**

Alan Stevens Review:

This deficiency is not supportive of a CR recommendation in this context.

Michaela Schulman Review

The sponsor noted that per the ISO standards (noted in Seq 0017, 3.2.P.7 Container Closure System – SCS Microinjector Table 4), distilled water was utilized as the test medium for three EPR evaluations where drug product-device interactions would be expected: volume delivered, plunger depression force and plunger aspiration force. These EPRs would be impacted by glide force which is impacted by the drug product. Therefore, they did not address our CR concerns to perform all EPR stability testing using the drug product.

(b) (4)

FDA responded that while their proposal appears reasonable, a determination cannot be made until it is submitted and reviewed. Therefore, they have not adequately addressed the CR deficiency to demonstrate that their combination product (with the drug product) meets all EPRs following aging. **Deficiency**

Alan Stevens Review:

(b) (4)

The deficiency is considered resolved.

Michaela Schulman Review:

aii. The sponsor provided ENG-0361 which includes the updated EPR controls. These include

(b) (4)

since the sponsor is not performing release testing for all EPRs but adequately justified how the EPRs are controlled (b) (4) this appears reasonable.

(b) (4)

(b) (4) Relevant functional performance of the SCS Microinjector with CLS-TA is included in the post-approval commitment. **This appears reasonable.**

CR Deficiency #2	2. You provided a vial adapter insertion force specification. However, you did not provide evidence that you validated that specification. Provide validation data demonstrating that your intended user is capable of exerting (b) (4) N forces.
Sponsor Response	(b) (4)

Reviewer Comments	The sponsor references studies, specifically one that notes the force range of one-handed strength to push down for adults between 21-60 years old. Since the device is intended to be administered by medical professionals (likely over 18 years old), this appears reasonable to validate the specification. Additionally, the usability study also supports the validation of the spec for vial adapter insertion force.
--------------------------	--

CR Deficiency #3	3. Your submission did not provide a process risk assessment identifying and mitigating the risks associated with kitting the tray with the vial. Provide a process risk assessment identifying and mitigating the risks associated with the manufacturer of your system. Also provide definitions of severity, occurrence and detection scoring.
-------------------------	---

Sponsor Response

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
10/18/2021 10:09:21 AM

Recommendation: Complete Response

NDA 211950

Review # 1

Sep 10, 2019

Drug Name/Dosage Form	<i>XIPERETM (triamcinolone acetonide injectable suspension)</i>
Strength	<i>40 mg/mL</i>
Route of Administration	<i>Injection</i>
Rx/OTC Dispensed	<i>Rx</i>
Applicant	<i>Clearside Biomedical, Inc.</i>
US agent, if applicable	<i>NA</i>

SUBMISSION(S) REVIEWED	DOCUMENT DATE
<i>Original</i>	<i>12/19/2018</i>
<i>Amendment</i>	<i>1/22/2019</i>
<i>Amendment</i>	<i>2/28/2019</i>
<i>Amendment</i>	<i>3/21/2019</i>
<i>Amendment</i>	<i>4/15/2019</i>
<i>Amendment</i>	<i>6/28/2019</i>
<i>Amendment</i>	<i>7/2/2019</i>
<i>Amendment</i>	<i>7/19/2019</i>

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Application Technical Lead	Chunchun Zhang	NA
Drug Substance	Ben Zhang	Su (Suong) Tran
Drug Product	Yong Wang/Chunchun Zhang	Balajee Shanmugam
Microbiology	Eric Adeeku	Elizabeth Berr
Biopharmaceutics	Akm Khairuzzaman	Jing Li
Process	Lixia Cai	Dan Obrzut
Facility	Lixia Cai	Dan Obrzut
Regulatory Business Process Manager	Kristine Leahy	NA
ORA Lead	Caryn McNabb	NA
Laboratory (OTR)	NA	NA
Environmental Assessment (EA)	Yong Wang	Balajee Shanmugam

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status ¹	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	5/29/2019 reviewed by Ben Zhang	LoA: 6/22/2018
	Type III		(b) (4)	NA		LoA: 5/23/2018
	Type III		(b) (4)	NA		LoA: 5/28/2018
	Type III		(b) (4)	NA		LoA: 5/23/2018

¹NA (There is enough data in the application, therefore the DMF did not need to be reviewed).

B. Other Documents: IND, RLD, or sister applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	115683	

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	CR	Major deficiencies	8/14/2019	Rumi Young
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

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

*The compliance status of the drug product manufacturing facility, (b) (4) (FEI (b) (4) was determined unacceptable based on the most recent inspection performed ending (b) (4). Therefore, OPF has issued an overall recommendation of "Withhold" on Aug 14, 2019. Additionally, there are outstanding deficiencies from the manufacturing process perspective. CDRH was consulted to review the SCS microinjector and has found several major deficiencies in the consult memo dated on 8/14/2019. In agreement with the above recommendation, NDA 211950 is recommended **Complete Response** from Product Quality perspective.*

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

The following CR statement about the unacceptable manufacturing facility (b) (4) and CDRH deficiencies should be included in the CR letter:

- 1. During the pre-approval inspection of (b) (4) [FEI (b) (4) manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.*

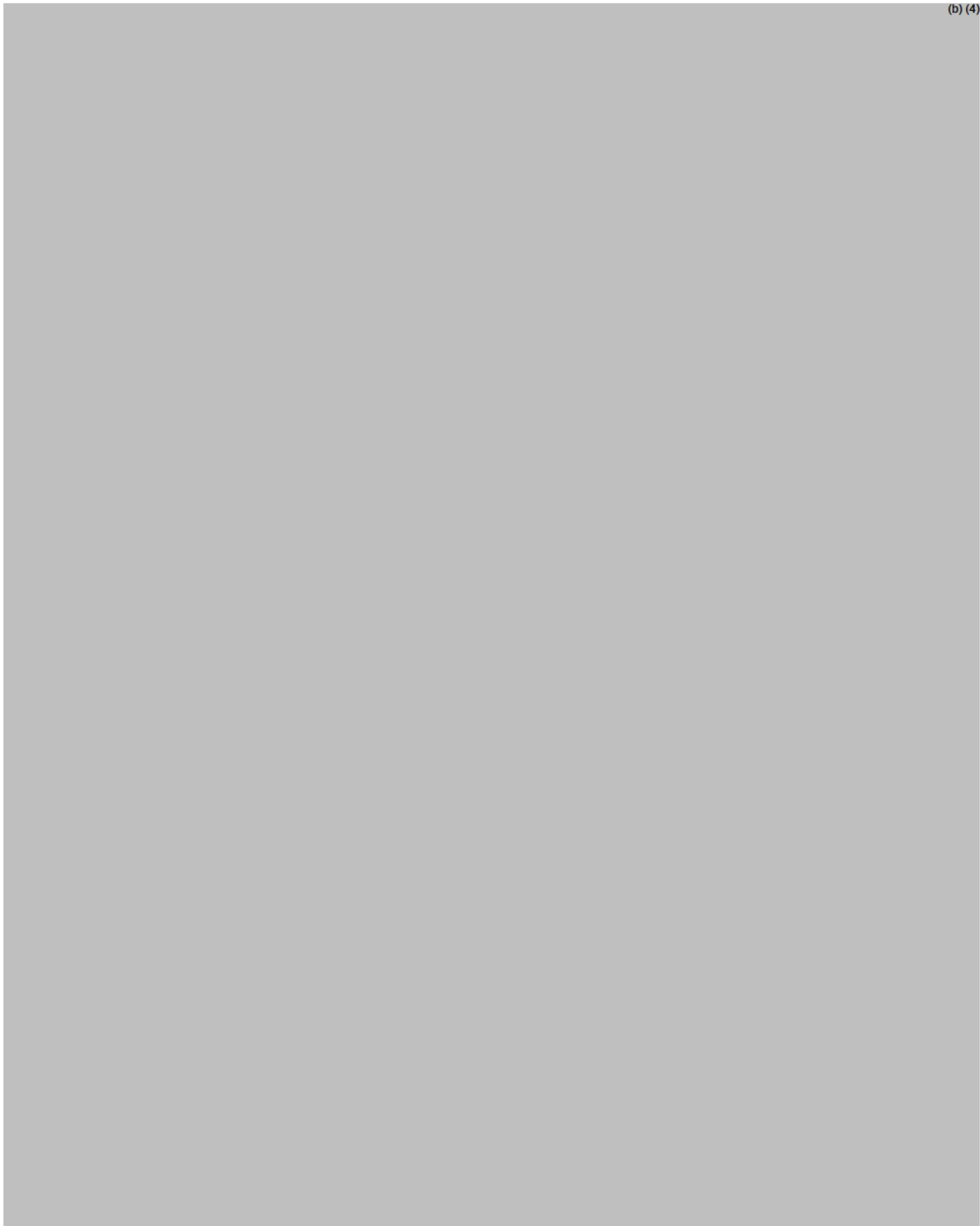
(b) (4)

Below are the non-CR comments for the applicant:

1. *The drug product is an ophthalmic suspension. Therefore, FDA recommends that for quality control purposes, you develop an in vitro drug release method and include the dissolution test in the specifications of the product. We have the following comments and request for information for the in vitro drug release test:*
 - a. *Submit the development and validation report for the proposed in vitro drug release method. Include justifications and enough data supporting the selection of the dissolution testing conditions (equipment/apparatus, in vitro drug release media, agitation/rotation speed, pH, sink conditions, use of surfactant if applicable, etc.). Provide data/information supporting the discriminating ability of the method with respect to the most relevant critical material attributes (CMAs, e.g., PSD), critical formulation variables, and critical process parameters (CPPs).*
 - b. *Collect and submit in vitro drug release profile data for the clinical batches and upcoming stability time points of the registration batches using the proposed drug release method. Based on the collected data, provide your proposal for the in vitro drug release acceptance criterion/criteria of the proposed drug product.*
2. *Update manufacturing process flow diagram to include all individual process step enhancements and all applicable recommendations noted in this Information Request.*
3. *We recommend you provide data generated from three new registration batches using the proposed commercial process to demonstrate process robustness and product meeting quality standards of efficacy, stability, and safety. Provide one*

registration batch with 3 months stability data at long term storage and 3 months stability data at accelerated condition.

(b) (4)



II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	For the treatment of macular edema associated with uveitis.
Duration of Treatment	See package insert for the recommended dosage in patients.
Maximum Daily Dose	As above (see the package insert for details).
Alternative Methods of Administration	NA

B. Quality Assessment Overview

i. Drug Substance Quality Summary

The drug substance, triamcinolone acetonide, is a white or almost white crystalline powder. The drug substance referenced in DMF (b) (4) was found adequate by Ben Zhang on 5/29/2019.

ii. Drug Product Quality Summary

XIPERETM (triamcinolone acetonide injectable suspension), 40 mg /mL is a sterile, preservative-free aqueous suspension and packaged in a 2 mL / 13 mm glass vial with a rubber stopper and an aluminum seal for the single use. The fill volume is 0.9 mL and the injection volume of the dose is 0.1mL. The drug product will be administered by a SCS Microinjector.

All excipients used in the formulation are adequately qualified. No novel excipients are used in the formulation. All excipients are the same as the approved products Triesence (NDA 22223) except the amount of polysorbate. The drug product specification includes tests for appearance, identity, assay, impurities (specified, unspecified and total), pH, osmolality, viscosity, sterility, visual inspection for particulate, particle size distribution, resuspendability/redispersibility, (b) (4) functionality, bacterial endotoxin, uniformity of dosage units and injection volume in container. All analytical methods are described in reasonable detail and have been adequately validated. The applicant has performed extractable and leachable studies, no reportable extractable or leachable was detected. A risk assessment on the elemental impurity was performed and indicate the results are lower than PDE.

The applicant has submitted two registration batches (Lots FG-15-0349 and FG-17-0087) at the commercial scale (b) (4) L and one batch (Lot FG-13-0174) at the (b) (4) L scale using the commercial process and packaging. Stability data of 12 months for batch FG-13-0174, 24 months for batch FG-15-0349 and 48 months for batch FG-

17-0087 at 25°C/60%RH at inverted orientation is provided. Stability data for six months at 40°C/75% RH for three registration batches are provided. All the quality attributes remain within the proposed specifications. Therefore, the expiration date of (b) (4) months is granted when stored at 15 °C- 25 °C.

The storage statement is “Protect from light. Don’t freeze. Store at 15°C to 25°C (59°F to 77°F). Discard unused portion” and will be finalized at the OND’s labeling meeting.

The proposed drug product manufacturing process consists: 1 (b) (4). During the NDA review several information requests regarding to critical process parameters and hold time for bulk solution etc. were conveyed to by the applicant. However, the issues haven’t been fully resolved. Therefore, the overall information regarding the manufacturing process provided in the NDA submission and subsequent amendments was found inadequate. The quality micro reviewer Dr. Eric Adeeku has found the (b) (4) acceptable.

Biopharmaceutics reviewer Dr. Akm Khairuzzaman has found the bridging of formulations is not needed as the proposed commercial formulation is identical to the formulation used in the clinical studies. However, Dr. Khairuzzaman has recommend that the Applicant should develop a dissolution method for quality control purpose as a PMC commitment (see the attached review).

CDRH was consulted to review the SCS microinjector and has identified several major deficiencies. Those deficiencies had been discussed with the clinical division on 7/22/2019. The clinical division indicated that the deficiencies are not needed to assess the potential safety and efficacy of the drug product since this is not a combination product. See the attached consult memo from CDRH for the detailed discussion. However, we recommend communicate these deficiencies as CR comments to the applicant from the product quality perspective.

OPF has issued a withhold recommendation for the drug product manufacturing site, (b) (4) (FEI (b) (4) from the outcome of the recent inspection ending 5/24/2019. All the other facilities are acceptable based on the profile. Therefore, the current overall recommendation of “withhold” was entered for the NDA into Panorama by OPF on 8/14/2019.

C. Special Product Quality Labeling Recommendations (NDA only)

NA

D. Final Risk Assessment (see Attachment)

I. From Initial Risk Identification	Review Assessment
-------------------------------------	-------------------

Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	Formulation Container closure ¹ Process parameters Scale/equipment Site	H	(b) (4)	L	Post-approval stability protocol will test sterility.
Endotoxin Pyrogen	Formulation Container closure ¹ Process parameters Scale/equipment	H		L	Endotoxin testing is included in the drug product specification.
Assay (API), stability	Formulation Container closure ¹ Raw materials	L		L	
Assay (preservative)	Formulation Container closure ¹ Process parameters Scale/equipment	L		L	
Uniformity of Dose (Fill Vol/ Deliverable volume)	Formulation Container closure ¹ Process parameters Scale/equipment	M		L	
pH	Formulation Container closure ¹ Process parameters Scale/equipment	L		L	
Particle size distribution	Formulation Container closure ¹ Process parameters Scale/equipment	M		L	

¹Stability studies demonstrate container closure attributes.

Product for all quality

This NDA is recommended for **Complete Response** from the Product Quality erspective.

On behalf of the OPQ team

Chunchun Zhang, Ph.D. ATL for NDA 211950

CHAPTER VII: BIOPHARMACEUTICS

Product Information	XIPERE (triamcinolone acetonide suprachoroidal injectable suspension)
NDA Number	211950
Assessment Cycle Number	SDN 001
Drug Product Name/ Strength	Triamcinolone acetonide suprachoroidal injectable suspension/40 mg/mL
Route of Administration	Suprachoroidal
Applicant Name	Clearside Biomedical, Inc.
Therapeutic Classification/ OND Division	Ophthalmic
LD/RS Number	TRIESENCE (NDAs # 022048, 022223)
Proposed Indication	Treatment of macular edema associated with uveitis

Overall Recommendation: Inadequate

REVIEW SUMMARY:

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting; 1) the dissolution method and acceptance criteria, and 2) bridging of the clinical and commercial drug products. Based on the review of the provided information/data, Biopharmaceutics has the following comments:

1. DISSOLUTION TEST: Pending

The submission did not include a dissolution test for this product. However, because the drug product is an ophthalmic biphasic system, dissolution from the suspended drug-particles is expected to occur. Therefore, for quality control purposes, the dissolution test should be included in the specifications of the proposed drug product. In the meeting to be held on August 20, 2019, the Applicant is being requested to develop an optimal dissolution method and set adequate dissolution acceptance criteria/criterion for the proposed drug product (refer to section 8).

2. BRIDGING: Adequate

Human clinical trials for safety and efficacy were conducted. The formulation of the proposed commercial product is identical to the formulation of the drug product used in the clinical studies. Therefore, bridging is not needed.

3. RISK ASSESSMENT: Adequate

The table below shows the initial and final review risk assessment with respect to biopharmaceutics.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Dissolution	Medium to Low	Intraocular ophthalmic suspension. Drug release is dependent on (b) (4) Poorly soluble drug.	Low	The drug product is administered into the suprachoroidal space. Human PK studies show that plasma TA concentrations are always below 100 pg/mL indicating that systemic exposure is negligible, and the drug is confined within the suprachoroidal space. Therefore, there is limited absorption and distribution of the drug from its local acting site. The efficacy of the drug product was demonstrated in the clinical trials.

REVIEWER's NOTES

1. List of Submissions being assessed (table):

Document(s) Assessed	Date Received
SDN-001	12/19/2018

2. Highlight Key Issues from Last Cycle and Their Resolution:

Not Applicable

3. Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

The drug product is an ophthalmic suspension. Therefore, for quality control purposes, the Applicant will be requested to develop an appropriate in vitro drug release method and set adequate acceptance criteria/criterion for their drug product.

4. BCS Designation - Not Applicable

Triamcinolone acetonide is practically insoluble in water.

5. Dissolution Method and Acceptance Criteria

The submission did not include any dissolution information.

Reviewer's Comments:

The proposed drug product (1 mL) is administered into the suprachoroidal space using the proprietary SCS Microinjector™ to restrict the delivery of TA to a focused anatomical location in the eye while limiting collateral exposures in other portions of the eye or systemically. Both human PK studies (study # CLS 1001-301 & CLS 1001-302) showed that plasma TA concentrations in all 19 subjects were always below 100 pg/mL across the studies, indicating that the systemic exposure is negligible, and the drug is confined within the suprachoroidal space.

However, because it is an ophthalmic biphasic system, dissolution from the suspended particle is expected to occur. The current submission does not include the in vitro drug release information/data that is needed to ensure that the drug will be bioavailable at the site of administration over the targeted period of time.

6. Bridging of Formulations

The formulation of the proposed commercial product is identical to the formulation of the product used in the clinical studies. Therefore, bridging is not needed.

7. Regional Information

- Comparability Protocols

None

- Post-Approval Commitments -None

None

8. BIOPHARMACEUTICS LIST OF DEFICIENCIES

1. Because your proposed drug product is an ophthalmic suspension, FDA recommends that for quality control purposes, you develop an in vitro drug release method and include the dissolution test in the specifications of the product.
2. We have the following comments and request for information for the in vitro drug release test:
 - (a) Submit the development and validation report for the proposed in vitro drug release method. Include justifications and enough data supporting the selection of the dissolution testing conditions (equipment/apparatus, in vitro drug release media, agitation/rotation speed, pH, sink conditions, use of surfactant if applicable, etc.).
 - (b) Provide data/information supporting the discriminating ability of the method with respect to the most relevant critical material attributes (CMAs, e.g., PSD), critical formulation variables, and critical process parameters (CPPs).
 - (c) Collect and submit in vitro drug release profile data for the clinical batches and upcoming stability time points of the registration batches using the proposed drug release method.
 - (d) Based on the collected data, provide your proposal for the in vitro drug release acceptance criterion/criteria of the proposed drug product.



Akm
Khairuzzaman

Digitally signed by Akm Khairuzzaman
Date: 8/15/2019 08:30:32AM
GUID: 502d1ab500002aef5afaa6f74ddf7e69



Angelica
Dorantes

Digitally signed by Angelica Dorantes
Date: 8/16/2019 06:46:28PM
GUID: 502d0913000029d59f1c87e0a380c7f7

CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	211950
Assessment Cycle Number	01
Drug Product Name/ Strength	Triamcinolone acetonide suprachoroidal Injectable suspension / 40 mg/mL
Route of Administration	Suprachoroidal
Applicant Name	Clearside Biomedical, Inc.
Therapeutic Classification/ OND Division	N/A
Manufacturing Site	(b) (4) (b) (4) (b) (4) (b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: Adequate

Assessment Summary:

Document(s) Assessed	Date Received
0001	12/19/2019
0005	02/28/2019

List Submissions being assessed (table):

Submit	Received	Review Request	Assigned to Reviewer
12/19/2018	12/19/2018	N/A	12/21/2019
02/28/2019	02/28/2019	N/A	02/28/2019
04/15/2019	04/15/2019	N/A	04/15/2019

Highlight Key Issues from Last Cycle and Their Resolution:

None

Remarks:

This is an electronic submission.
No CP was included in the application.
The goal date is 10/10/2019

Review also contains responses to the Agency's 02/21/2019 and 03/28/2019 information requests that were provided in the 02/28/2019 and 04/15/2019 submissions respectively.

The following sterile components for administration, sealed in a Tyvek-covered tray included with the drug product are reviewed by CDRH:

- ❖ One SCS Microinjector® syringe with vial adapter attached
- ❖ One 30-G x 900-µm needle
- ❖ One 30-G x 1100-µm needle

Concise Description of Outstanding Issues

N/A

Supporting Documents:

DMF (b) (4) (Type V): — (b) (4) — (b) (4)

Manufactured in (b) (4)

(b) (4) .

(b) (4) docx – Sterility assurance review of the depyrogenation of the (b) (4) stoppers that was found adequate in the 02/03/2017 microbiology review.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(section 3.2.P.2).

Component	Function	Unit (mg/mL)
Triamcinolone acetonide, USP	Active	40
Carboxymethylcellulose sodium, USP	(b) (4)	5.0
(b) (4) (polysorbate 80), USP/NF	(b) (4)	0.2
Sodium chloride, USP	Isotonicity	5.5
Potassium chloride, USP	(b) (4)	(b) (4)
Calcium chloride dihydrate, USP	(b) (4)	(b) (4)
Magnesium chloride hexahydrate, USP	(b) (4)	(b) (4)
Sodium acetate trihydrate, USP	(b) (4)	(b) (4)
Sodium citrate dihydrate, USP	(b) (4)	(b) (4)
(b) (4) hydrochloric acid, NF	pH adj.	(b) (4)
Water for Injection, USP	(b) (4)	(b) (4)

Adequate

(b) (4)



DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	8/1/2019		
To:	Kristine Leahy		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Other
From	Rumi Young OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject	NDA 211950 , XIPERE ICC1900093 00006653 ICC1900258 (Facilities) 00010343 (Facilities)		
Recommendation	Filing Recommendation Date: ☐ CDRH did not provide a Filing Recommendation Mid-Cycle Recommendation Date: 5/24/2019 ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A. No inspection is required. See Comments to CDER in Section 2.1 Final Recommendation Date: 8/1/2019 ☐ Device is Approvable. ☐ Device is Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device is Not Approvable - See Section 2.2 for Complete Response Deficiencies and Section 2.1 for Comments #4-6 to CDER		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 211950
Sponsor	Clearside Biomedical
Drug/Biologic	XIPERE
Indications for Use	treatment of macular edema associated with uveitis
Device Constituent	Co-Packaged Syringe
Related Files	ICC1800493

Review Team		
Lead Device Reviewer		<i>Rumi Young</i>
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	CON #
Extractables	Srilekha Das	CON198760
Biocompatibility	Gang Peng	CON198320
Toxicological Risk Assessment	Alan Hood	CON198761
Sterility	Ryan Ortega	CON199832

Important Dates	
Discipline-Specific Review Memos Due	5/21/2019
Final Lead Device Review Memo Due	8/1/2019
Interim Due Dates	Meeting/Due Date
Mid-Cycle	5/29/2019
Primary Review	8/14/2019

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the device is:

- ☐ Approvable – the device is approvable for the proposed indication.
- ☐ Approvable with PMC or PMR, [See Section 2.3](#)
 - ☐ Not Acceptable – the device is not approvable for the proposed indication. We have Major Deficiencies to convey, [see Section 2.2](#).

Section	Adequate			Reviewer <u>Notes</u>
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls		X		See Complete Response 1 and 2
Risk Analysis		X		See Complete Response 3
Design Verification		X		See Complete Response 1 and 2
Consultant Discipline Reviews		X		See Complete Response 4
Clinical Validation		X		See Complete Response 1
Human Factors Validation			X	Defer to CDER/DMEPA
Facilities & Quality Systems		X		See Complete Response 1

2.1. **Comments to the Review Team**

- ☐ CDRH does not have any further comments to convey to the review team.
- ☐ CDRH has the following comments to convey to the review team:

Comment #1 - Comment was communicated to CDER at the midcycle milestone 5/24/2019

In the IND 115683 we recommended to CDER that summative validation testing be provided by the sponsor to demonstrate that they validated their device interface and labeling. During the internal meeting we recommended that DMEPA is consulted. A review of the labeling and submission shows there is the risk of user errors with the administration technique due to the device design that cannot be addressed through the verification testing provided by the sponsor.

- Adjustments needed to reach the suprachoroidal injection site (repeat injection with new needle) [Step 16]
- Syringe has graduations, but they are not used in IFU.
- IFU has instruction that would allow for reconnection to vial after drawing solution. Risks associated with multi-dosing [Step 10]
- Two needle lengths provided. Will HCP know which needle length is appropriate or would they use a new needle after the 900uM does not work.

In addition, the sponsor provide clinical data from AZALEA CLS1001-302 and MAGNOLIA CLS1001-303 to validate the following requirements from their design control documentation:

#27 Device should conform to latest FDA human Factors recommendations (-302)

#28 Device should be easy to handle, prime and use (-303)

Therefore, we defer adequacy of the user labeling and validation of the requirements 27-28 to DMEPA.

Comment #2 – Comment was communicated to CDER at the midcycle milestone 5/24/2019

All verification (bench) testing was done to a ^{(b) (4)}% reliability. This was supported by the risk assessments in the ^{(b) (4)} except for the needle cap tip distance were and Midcycle IR# 16 was issued. Is a ^{(b) (4)}% reliability adequate for the given indications for use. For syringes we typically accept 95-99% depending on the indication and characteristic (EPR vs non-

EPR). If the reliability is not adequate, we recommend the following IR. In bold is where the IR can be modified in terms of proposed reliability, whether it should apply to all requirements or just EPRs and if the proposed reliability is different than the needle cap tip distance.

Your verification testing was done at a 95% confidence (b) (4) reliability. However, a (b) (4) reliability is not consistent with the risks associated with the indication and intended use of your proposed injection system. We recommend a XX% reliability level for essential performance requirements [all requirements] [except for needle cap tip distance (see IR #x)]. Update your analysis to demonstrate that you verified your essential performance requirements [all requirements] to a 95 % confidence and XX %reliability [except for needle cap tip distance (see IR #X)]. Alternatively, explain why a (b) (4) % reliability is adequate given the indication and intended use.

Comment #3 – Comment was communicated to CDER at the midcycle milestone 5/24/2019

A general IR should be included in the midcycle letter regarding the deficient MAF (b) (4) Defer to CDER for typical language.

Comment #4

Please issue the following MAF deficiencies to the MAF holder:

1. In your response to Question 5 you stated that

is not adequate

Comment #5

As communicated in midcycle meeting on 6/3 and follow-up email with CMC team on 6/10, the extractables and leachables testing for this delivery system will be reviewed by CDER CMC team. Please see MAF holder's response to Questions 11 and 12 regarding extractables and leachables. In addition, please consider the IRs not communicated in Section 9.3.1 Extractables Review of this memo.

Comment #6

Consistent with CDRH feedback provided at the July 23, 2019 internal meeting, CDRH is concerned that because the device quality information recommended in our midcycle IRs has not been provided, we are unable to assure the device will consistently achieve safe and reliable performance. We are also concerned about maintaining consistent regulatory review of devices indicated for injection of drugs irrespective of submission pathway. Therefore, we recommend that CR deficiencies identified in Section 2.2 be issued to the manufacturer.

2.2. Complete Response Deficiencies

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

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

CDRH is providing the following 'letter-ready' Major Deficiencies written so they can be directly communicated to the Sponsor:

Major Deficiencies:

1. You provided numerous specifications for your SCS Microinjector Delivery System. However, you did not identify the essential performance requirements (EPRs), requirements essential to the safety and effectiveness of your device, as requested in our feedback to IND 115683 (07 AUG 2018). Provide essential performance requirements and specifications for the following: volume delivered, Plunger depression force, Plunger aspiration force, 900µM needle length, 1100µM needle length and Vial adapter insertion force, and Needle cap tip distance. For each EPR, address the following:

- a. You provided the release and stability testing plan in 3.2.P.5.1. However, it is unclear from the list of specifications if the EPRs are being adequately controlled.

(b) (4)

- b. You propose test methods (b) (4) related test specifications (b) (4) ^{(u) (4)} Functionality and Injection Volume in Container, respectively. However, your proposed methods do not adequately assess the functional performance the specifications (b) (4) ^{(b) (4)} Functionality and Injection Volume in Container) for the following reasons:

(b) (4)

There
control your SCS microinjector delivery system related specifications. Update your test methods for testing (b) (4) ^{(b) (4)} Functionality and Injection Volume in Container.

2. You provided a vial adapter insertion force specification. However, you did not provide evidence that you validated that specification. Provide validation data demonstrating that your intended user is capable of exerting (b) (4) N forces.
3. Your submission did not provide a process risk assessment identifying and mitigating the risks associated with kitting the tray with the vial. Provide a process risk assessment identifying and mitigating the risks associated with the manufacturer of your system. Also provide definitions of severity, occurrence and detection scoring.

(b) (4)

2.3. Recommended Post-Market Commitments/Requirements

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

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3. PURPOSE/BACKGROUND

3.1. Scope

Clearside Biomedical is requesting approval of XIPERE. The device is a Co-Packaged Syringe, with vial adapter and needles.

CDER/OPQ has requested the following [consult](#) for review of the device:

Standard, 10-Month Review with a Division (DTOP) Signatory. It's a 505(b)(2), studied under IND 115683.

The goal of this memo is to provide a recommendation of the approvability of the device. This review will cover the following [review areas](#):

Device performance
Biocompatibility (syringe, vial transfer device, needles)
Sterility (syringe, vial transfer device, needles)
Stability – device performance on stability
Essential performance Requirements (EPR) control strategy
Extractables
Tox Risk assessment

This review will not cover the following review areas:

Human Factors (deferred to DMEPA)

3.2. Prior Interactions

IND 115683

We agreed that the sponsor can use the MAF to reference device information. However, we stated that they had to define the EPRs and design inputs for the device.

3.2.1. [Related Files](#)

ICC1800493

3.3. Indications for Use

Product	Indications for Use
XIPERE	treatment of macular edema associated with uveitis
Co-Packaged Syringe System	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	Module(s)
0001	1.14.1.3 Draft Labeling Text
0001	1.14.1.1 Draft Carton and Container Labels
0001	3.2.P.7 Container Closure System
0001	3.2.P.3.1 Manufacturer(s)
0001	3.2.P.2 Pharmaceutical Development
0001	1.4.2 Statement of Right of Reference
0001	5.2 Tabular listing of All clinical Studies
0001	5.3.4.1. CLS1001-301 (PEACHTREE) – PEACHTREE: A Phase 3, Randomized, Masked, Controlled Clinical Trial to Study the Safety and Efficacy of Triamcinolone Acetonide Injectable suspension (CLS-TA) for the

	Treatment of Subjects with Macular Edema associated with Non-infections Uvelitis
0001	5.3.5.2 CLS1001-302 (AZALEA)-Open label Safety Study of Suprachoroidal Triamcinolone Acetonide Injectable Suspension in Patients with non-infectious Uvelitis.
0001	5.3.5.2 CLS1001-303 (MAGNOLIA) -MAGNOLIA: Multicenter, Non-Interventional Extension Study of the Safety and Efficacy of CLS-TA for the treatment of Macular Edema Associated with Non-infectious Uveitis
0001	3.2.P.5.1 Specification(s)
N/A	(b) (4) Clearside Biomedical
0009	1.11.1 Quality Information Amendment
0009	2.3.P. CLS-TA – Injectable Suspension – (b) (4)
0009	3.2.P.7 Container Closure System

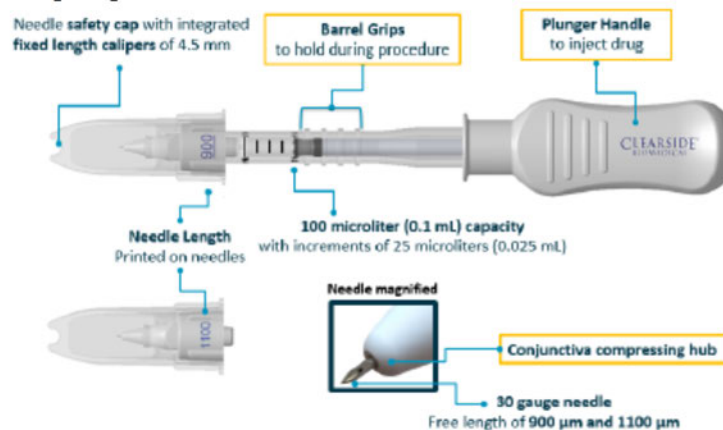
4. DEVICE DESCRIPTION

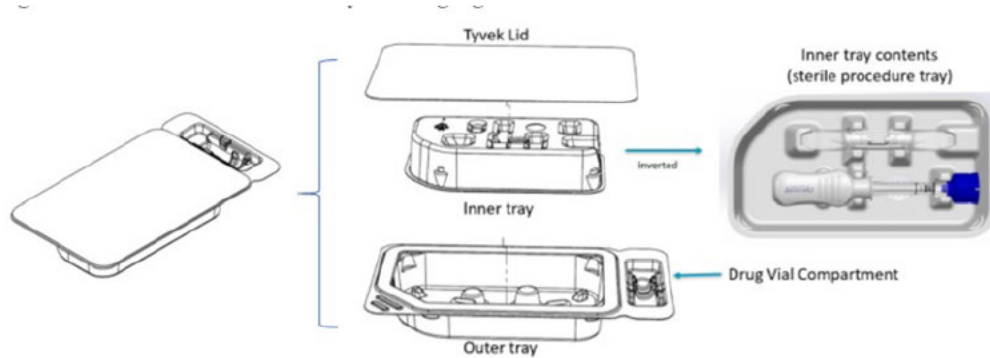
4.1. Device Description

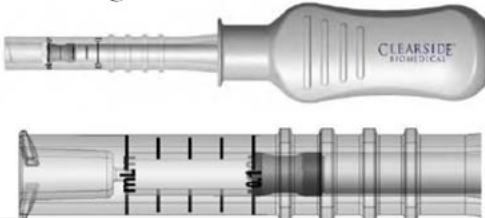
The following information was obtained from:

- Container Closure System
- Proposed Labeling Text
- Container Closure System – SCS Microinjector

The SCS Microinjector is a sterile empty luer syringe with a vial adapter attached that is packaged in a tray with two needles (900uM and 1100um) and the vial. The SCS microinjector is designed to administer the drug product to the eye via suprachoroidal injection in the pars plana.





Requirement	Reviewer Comment
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Healthcare provider
Injection Site	Eye, 4-4.5 mm posterior to the limbus
Injection tissue and depth of injection	Suprachoroidal , 900 um or 1100uM depending on the needle selected.
Type of Use (e.g. single use, disposable, reusable, other)	Single
Environments of use (e.g. home, clinic)	Healthcare environment
Storage conditions and expiry	36 month, 15C to 25C, protect from light (vial)
Needle connection (e.g. luer, slip tip, staked)	Female Luer (syringe) to male luer of vial adapter
Syringe Volume	0.1ml nominal, Dose accuracy: 0.1mL +/- (b)(4) mL
Device materials including lubricant	Silicone oil
Requirement	Reviewer Comment
Hypodermic Needle: length, gauge, and configuration of the tip.	900uM+/- (b)(4) uM 1100uM+/- (b)(4) uM 30G Tri-bevel tip
Markings (graduated scale, position of scale, length of scale, numbering of scale, and legibility criteria (for insulin syringes). Insulin Syringes: The scale on the barrel should be in units of insulin.	0.025mL graduations. 
Reuse Durability (for reusable piston syringes): number of times the device can be sterilized and still meet specifications (using sterilization method indicated in the labeling).	N/A
Safety Features (e.g. Needle safety component/device)	None
Automated Functions	None
Sterilization method	ETO

4.2. Steps for Using the Device

1. Remove tray from carton

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
Reviewer Comments Device description is complete.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

5. FILING REVIEW

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

6. LABELING

6.1. General Labeling Review

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

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

Reviewer Comments

There is limited evidence that the sponsor validated the IFU and device user interface through summative HF testing. See comment to CDER #1. Comment was communicated to CDER at the midcycle milestone 5/24/2019.

6.2. Device Specific Labeling Review

Device Specific Labeling Review Checklist	Adequate?		
	Yes	No	N/A
N/A	N/A	N/A	N/A

Reviewer Comments : There is no ocular syringe specific labeling checklist requirements outside the checklist in Section 6.1.

6.3. Clinical Labeling Review

The following Clinical Labeling Review was completed by

- Insert Consultant Name ; The full memo is located in [Appendix B](#).
- The Lead Reviewer

Below is a summary of the review & [recommendation](#):

Deferred to CDER.

- The IFU states that the user would feel resistance in the plunger rod if they do not reach the appropriate space and should check injection and make small adjustments in positioning as necessary. It is unclear if this is the appropriate

clinical recommendation (Comment to CDER #1). Comment was communicated to CDER at the midcycle milestone 5/24/2019.

- The sponsor provides two microneedle lengths. How will the HCP know the correct length to use? Could they change the needle if 900uM needle is too short? Is this clinically acceptable? Comment to CDER #1. Comment was communicated to CDER at the midcycle milestone 5/24/2019.

6.4. Labeling Review Conclusion

LABELING REVIEW CONCLUSION								
Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:		
☐ Yes	☐ No	☐ N/A	☐ Yes	☐ No	☐ N/A	☐ Yes	☐ No	☐ N/A
<u>Reviewer Comments</u>								
None.								
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No								

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)		X	
Mitigations are adequate to reduce risk to health		X	
Version history demonstrates risk management throughout design / development activities	X		
Design Inputs/Outputs	Yes	No	N/A
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing		X	
To-be-marketed device was used in the pivotal clinical trial		X	
Bioequivalence Study utilized to-be-marketed device		X	
Verification methods relevant to specific use conditions as described in design documents and labeling		X	
Device reliability is acceptable to support the indications for use (i.e. emergency use product may require separate reliability study)		X	
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments

See individual Section (8, 9, 10) for review and any deficiencies, if identified.

7.2. Design Inputs and Outputs

(b) (4)

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	N/A
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	N/A
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	N/A

Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	N/A
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Unknown – Defer to CDER (Comment 1)

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
ISO 14971:2012 Medical devices. Application of risk management to medical devices	Y	Y
ISO 7864:2016 Sterile Hypodermic needles for single use	Y	Y
ISO 7886-1:2017 Sterile hypodermic syringe for single use – Part 1: syringes for manual use	Y	Y
ISO 9626:2016 Stainless steel needle tubing for the manufacture of medical devices	Y	Y
ISO 80369-7:2016 Small-bore connectors for liquids and gases in healthcare applications – Part 7: Connectors for intravascular or hypodermic applications	Y	Y

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
Reviewer Comments See Complete Response 1 and 2 in Section 2.2		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

(b) (4)

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

The following information was obtained from (b) (4) Appendix H Verification and validation Planning

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method <u>Acceptable</u> (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Plunger depression force (item 96/9.1.21/9.3.3-9.3.4)	$\leq \frac{(b)}{(4)} N$	N – Needle was not assembled during testing See Complete Response 1	Y*	Y*
Plunger aspiration force (Item 3, Item 95/9.1.13/9.1.21/9.3.2 and 9.3.4)	$\leq \frac{(b)}{(4)} N$	N – Needle was not assembled during testing See Complete Response 1	Y*	Y*
Distance between cap tips (item 19/9.2.5)	4.5 mm $\pm \frac{(b)}{(4)}$ mm	Y	N/A	N/A
Vial adapter insertion force (Item 1/9.1.11 DVT)	$\leq \frac{(b)}{(4)} N$ – Not Validated See Complete Response 2	Y	Y*	Y*
Volume delivered (Item 15/9.3.8)	$\pm \frac{(b)}{(4)} uL$ target volume from 0 - 100uL	Y	Y	Y
900uM needle length (item 87/9.3.7)	900 uM $\pm \frac{(b)}{(4)} uM$	Y	N/A	N/A
1100 uM needle length (item 87/9.3.7)	1100uM $\pm \frac{(b)}{(4)} uM$	Y	N/A	N/A

*Y – the stability and transportation preconditioning approach was adequate. However, the test method or specification for individual EPR, which was also used at T=0, was not.

Reviewer Comment

- Validation of the user interface is done through summative HF testing, which is deferred to CDER/DMEPA.
- Adequacy of the EPR specification is assessed in Section 7.2 of this memo.
- The sponsor states that validation of items 13, 27, 28 and 29 were validated via the clinical trial. The listed items relate to the device operation. Therefore, it should cover the EPRs listed once they address what the EPRs are, and if they used a representative device in the clinical study.
- The proposed sample sizes were adequate for testing.

- The aging and shipping condition testing was performed adequately in terms of sample conditioning and sample size. However, since the aging/shipping testing repeated the testing described for T=0 the IRs identified for those test approaches also apply for the aging/shipping reports. See below for details.
- The sponsor provided stability testing for the needle length (900um) and needle tip cap distance. However, this is unnecessary because these dimensions would not vary over stability. Therefore, N/A is listed for those EPRs.

9.1.2. Verification of Design Inputs Evaluation/Methods

The following information was obtained from MAF (b) (4) and submission 3.2.P.7 Container Closure System – SCS Microinjector:

- Container Closure System – SCS microinjector

(b) (4)

(b) (4)

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION								
Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:		
☐ Yes	☐ No	☐ N/A	☐ Yes	☐ No	☐ N/A	☐ Yes	☐ No	☐ N/A
<u>Reviewer Comments</u>								
See complete response 1 and comment to cder 4								
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No								

(b) (4)

9.3. Discipline Specific Sub-Consulted Review Summary

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

<u>Discipline</u> -Specific Design Verification / Validation adequately addressed						
Discipline	Consult needed			Consultant	Section	Adequately Addressed (Y/N/NA)
	Yes	No	N/A			
Engineering (Materials, Mechanical, General)		X				
Extractables		X – See comment below		Srilekha Das	9.3.1	Defer to CDER
Biocompatibility		X - See comment below		Gang Peng	9.3.2	Defer to CDER
Toxicological risk assessment		X- See comment below		Alan Hood	9.3.3	Defer to CDER
Sterility	X			Ryan Ortega	9.3.4	Y, No IRs
Software / Cybersecurity			X			
Electrical Safety / EMC			X			
Human Factors			X		11	
Clinical		X				

Reviewer Comment: At the midcycle meeting on 6/3 it was discussed that the CMC would review the material extractable and leachables data for the delivery system as part of the drug product quality review. In addition, CDER

stated that biocompatibility of the system is not needed for this application. On 6/10 the CMC team agreed to take over the review for this data. Although some of the IRs were communicated to the sponsor relating to the extractables/leachables and biocompatibility were communicated to the sponsor, the responses were not reviewed by CDRH per the agreement on 6/3 or 6/10. **See Comment to CDER #5**
In addition, there was a meeting on 7/23 to discuss why some of the IRs (i.e. particulate testing) were not communicated. See Section 9.3.1-9.3.3 for details.

9.3.1. Extractables Review

The following Extractables review was completed by Srilekha Das. The full memo is located in **Appendix B**. Below is a summary of the recommendation:

Additional information should be requested from the sponsor. In the MAF, there are two chemical characterization reports containing information about chemical extractions and toxicological risk assessment for microinjector and needle. The first one is in Section 1.4.4/Page 32 of the container-closer system; and the second one is in volume 013/Page 193 of Appendix K-6. The sponsor provided a toxicological risk assessment for the vial adapter, which was review by consultant Alan Hood.

IRs were issued to get clarification on the test/extraction approach and data reported.

(b) (4)

9.3.2. *Biocompatibility Review*

The following Biocompatibility review was completed by Gang Peng. The full memo is located in **Appendix B**. Below is a summary of the recommendation:

Two deficiencies are recommended. The contact classification for the device is externally communicating limited contact. Therefore the endpoints are:

- Cytotoxicity

- Sensitization
- Irritation or Intracutaneous reactivity
- Acute systemic toxicity
- Material mediated pyrogenicity

The sponsor did not test all endpoints for the vial adapter. There were also questions regarding the test approach for material mediated pyrogenicity.

It was noted that the consultant did not request Hemocompatibility which is recommended as an endpoint for the contact classification or particulates per USP. Gang Peng discussed this endpoint with Sarah Mollo and determined that Hemocompatibility is not necessary because a suprachoroidal injection would be considered tissue contacting. However, they did add an IR regarding particulates.

(b) (4), (b) (5)

Consultant:

Click or tap to enter a date.

Click or tap to enter a date.

(b) (4), (b) (5)

9.3.3. *Toxicological Risk Assessment Review*

The following Toxicological Risk Assessment review was completed by Alan Hood. The full memo is located in **Appendix B**. Below is a summary of the [recommendation](#):

Based on the information in the (b) (4) further toxicological risk evaluation for extractables, as well as the (b) (4) additive in (b) (4) is not recommended for the intended use of the device.

9.3.4. *Sterility Review*

The following Sterility review was completed by Ryan Ortega. The full memo is located in **Appendix B**. Below is a summary of the [recommendation](#):

The sponsor provided complete sterilization (b) (4) validation information for the proposed EO sterilization cycle. They provided an assessment of (b) (4) a plan to use a LAL assay as a lot release criteria, and the results of

package integrity testing which supports the proposed 36 month shelf-life. The sterility information is complete and acceptable. There is an outer tray and box that includes the vial. However, no additional sterilization steps are performed. Sterility of the Drug product is deferred to CDER.

10. CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

There is no device related clinical studies for review

There are clinical studies for review

In (b) (4) the sponsor stated that clinical studies CLS1001-301, CLS1001-302 and CSL1001-303 validated the following requirements:

13 Device must allow the user to change needle length via needle replacement (-302)

27 Device should conform to latest FDA human Factors recommendations (-302) DEFER TO CDER/DMEPA **Comment #1.** Comment was communicated to CDER at the midcycle milestone 5/24/2019

28 Device should be easy to handle, prime and use (-303). DEFER TO CDER/DMEPA **Comment #1** Comment was communicated to CDER at the midcycle milestone 5/24/2019.

29 Device should provide feedback to inform the user when sufficient force has been applied on plunger (initiate change to different needle length). (-302)

Reviewer Comment: Requirement #13 does not require a study for validation since the design provide two needles and there is lot release and inspections to ensure the kit is packaged with two needles. Requirements 27-28 are deferred to CDER since they validate the device interface.

Therefore, the study -302 will be evaluated to determine if it validated requirement 29. However, all listed studies were reviewed to determine if the to-be marketed device was used.

This information was obtained from the following [documents](#):

- Tabular listing of all clinical studies
- Study CLS1001-301-Study Report Body (PEACHTREE)
- Study CLS1001-302 – Study Report Body (AZALEA)
- Study CLS1001-303 – Protocols and Amendments (MAGNOLIA)

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3	CLS1001-301 PEACHTREE	5.3.5.1	Evaluate the safety and efficacy of CLS-TA administered via SC injection	Randomized, masked, multicenter, sham-controlled	4 mg CLS-TA or sham; 2 unilateral injections, 12 weeks apart; suprachoroidal injection or sham injection procedure	160	Subjects with ME associated with NIU of any etiology/ disease diagnosis and from any anatomic location ^a	24 weeks	Complete; Full Clinical Study Report

Phase 3	CLS1001-302 AZALEA	5.3.5.2	Evaluate safety of CLS-TA administered via SC injection	Open-label, multicenter	4 mg CLS-TA; 2 unilateral injections, 12 weeks apart; suprachoroidal injection	38	Subjects with NIU of any etiology/ disease diagnosis and from any anatomic location ^a	24 weeks	Complete; Full Clinical Study Report
Phase 3 (Non-interventional Extension Study of CLS1001-301 PEACHTREE)	CLS1001-303 MAGNOLIA	5.3.5.2	Evaluate the maintenance of efficacy and safety of CLS-TA, up to 6 months following exit from Parent study, CLS1001-301 (PEACHTREE)	Non-interventional Extension Study	None	33	Subjects with ME associated with NIU who completed PEACHTREE without receiving additional therapy for uveitis in the study eye	Up to 24 weeks	Ongoing

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
User Evaluation	Microinjector User Experience Report	5.3.5.4	Evaluate the use of the suprachoroidal microinjector and injection instructions in the AZALEA study	Open-label, multicenter	4 mg CLS-TA; 2 unilateral injections, 12 weeks apart; suprachoroidal injection	38	Subjects with NIU of any etiology/ disease diagnosis and from any anatomic location ^a	Not applicable	Complete; Abbreviated Clinical Study Report
Usability Study	SCS Microinjector Preparation Evaluation Study	5.3.5.4	Assess if subjects, after reading the user/ administration instructions, can demonstrate the proper assembly of the SCS Microinjector components and prime the microinjector with drug, in preparation for a suprachoroidal injection.	Face-to-face, individual interviews conducted by an independent moderator	SCS Microinjector Preparation Instructions	20	Not applicable ^b	Not applicable ^b	Complete; Summary Report

Reviewer Comment: Usability studies which would validate the user interface of the device was deferred to CDER. See **Comment #1**. Comment was communicated to CDER at the midcycle milestone 5/24/2019
Note, the usability studies were a sub-analysis of testing conducted for AZALEA.

Reviewer Comment :

Phase 3 clinical studies PEACHTREE, AZALEA, and MAGNOLIA, were reviewed to determine if the to be marketed device or representative device was used.

The clinical study summary does not mention the use of the to be marketed microinjector aside from the user evaluations. Below are comments when the reports of the Phase 3 studies were reviewed.

- PEACHTREE LCS1001-301 – Used Active and Sham Kits. Active kits comprised of Vial, clearside microinjector syringe, vial access device, 900uM needle and 1100uM needle. Lot numbers are provided. However, they do not say if it is representative of to be marketed design iteration.
- AZALEA CLS1001-302- Two different microinjectors were mentioned one of which was considered “updated”. It is unclear if either is representative of the to be marketed product. It is also unclear what “updated” included in terms of design or manufacture. See in section below (excerpt from AZALEA) for additional review of this study.
- MAGNOLIA CLS1001-303- This study is an extension of PEACHTREE. However the protocol and amendment. Therefore, a microinjector was used. However, like the parent study, it is unclear if the device used is representative of the to be marketed product design iteration.

Therefore, the sponsor should confirm that the to be marketed design of the microinjector was used in the clinical studies CLS1001-301, CLS1001-302, and CLS1001-303 . If not, they should compare the design iteration used in the clinical studies and provide justification why any differences would not impact the clinical study outcomes/endpoints and validation of requirements listed 27-29. **Midcycle IR #31. Unresolved- sponsor did not provide an adequate rationale comparing their clinical and commercial designs. See Complete Response 1ai.**

Below are excerpts from the AZALEA study with respect to the usability of the device.

Table 14.3.4.4.1
Summary of User evaluation and information pertaining to the use of the microinjector during the injection procedure in the Study Eye, by Visit (Safety Population)

Category/Questions	Response	4 mg CLS-TA SC Injection (N=38)	
		Visit 2 (Week 0) n(%)	Visit 5 (Week 12) n(%)
Study Eye: Response from Observer	n	38	35
Did the physician review injection instructions?	Yes	37 (97.4)	35 (100)
	No	1 (2.6)	0
Were there any issues opening and removing components from their packaging?	Yes	1 (2.6)	0
	No	37 (97.4)	35 (100)
Was the physician able to fill the injector appropriately utilizing the vial adaptor?	Yes	37 (97.4)	35 (100)
	No	1 (2.6)	0
Did the physician have difficulty attaching the microneedle to the syringe?	Yes	0	0
	No	38 (100)	35 (100)

Note: Injector use is collected only at Visit 2 and Visit 5. Percentages are determined using the number of subjects with response at the visit.

Reviewer Comment: Highlighted is evidence that the injection aspiration force may have been too high. See **Midcycle IR#5 Resolved** – sponsor provided the specification for aspiration force.

Table 14.3.4.4.1
Summary of User evaluation and information pertaining to the use of the microinjector during the injection procedure in the Study Eye, by Visit (Safety Population)

Category/Questions	Response	4 mg CLS-TA SC Injection (N=38)	
		Visit 2 (Week 0) n(%)	Visit 5 (Week 12) n(%)
Did the physician measure the distance from the limbus to the injection site?	Yes	38 (100)	35 (100)
	No	0	0
If yes, what method			
Cap		30 (78.9)	29 (82.9)
Caliper		8 (21.1)	6 (17.1)
Other		0	0
Did the physician use the 900 µm needle first?	Yes	38 (100)	34 (97.1)
	No	0	1 (2.9)
Did the physician need to change needles?	Yes	14 (36.8)	14 (40.0)
	No	24 (63.2)	21 (60.0)
Did the physician appear to have difficulty with the injection?	Yes	5 (13.2)	3 (8.6)
	No	33 (86.8)	32 (91.4)

Note: Injector use is collected only at Visit 2 and Visit 5. Percentages are determined using the number of subjects with response at the visit.

Reviewer Comment:

- The use of the cap over calipers is overwhelming (80%) to determine the injection site. Therefore, if the sponsor's response to **Midcycle IR #16** (Resolved by providing data) is that the HCP could use calipers then it would not be an adequate mitigation.
- The physician needed to change the needles ~37-40% of the time. This indicates that the 900uM needle was not adequate and the sponsor may need to only provide the 1100uM needle to ensure they reach the target injection space. **Midcycle IR #3**. CDER did not communicate the IR to the sponsor. Deferred to CDER for adequacy.
- The physician had difficulty performing the injection 9 to 13% of the time. The physicians even say the force of injection was unacceptable (11% to 3%, depending on microinjector used). Note: An updated microinjector was used for visit #5. This supports the need for an adequate plunger depression force specification **Midcycle IR #1 and 18**. **IRs unresolved due to lack of performance data and inadequate methods. See Complete Response 1.** The current reliability of the EPR is 90%. See **Comment to CDER #2** regarding acceptability. Comment to CDER was communicate at 5/24 midcycle milestone.

Table 14.3.4.4.1
Summary of User evaluation and information pertaining to the use of the microinjector during the injection procedure in the Study Eye, by Visit (Safety Population)

Category/Questions	Response	4 mg CLS-TA SC Injection (N=38)	
		Visit 2 (Week 0) n(%)	Visit 5 (Week 12) n(%)
Was the force required for the needle to penetrate the eye appropriate?	Yes	32 (84.2)	22 (62.9)
	No	6 (15.8)	13 (37.1)
How do you rate the force necessary for the injection?	Acceptable	34 (89.5)	34 (97.1)
	Not Acceptable	4 (10.5)	4 (11.4)
Did you change needles?	Yes	15 (39.5)	14 (40.0)
	No	23 (60.5)	21 (60.0)
If so, why?			
a. Was unable to inject with the 900 micron needle		14 (36.8)	10 (28.6)
b. Physical or mechanical problem with the needle		1 (2.6)	0
c. Other		0	4 (11.4)
In your experience, did the suprachoroidal injection procedure present any new challenges as compared to other types of injections?	Yes	6 (15.8)	4 (11.4)
	No	31 (81.6)	31 (88.6)

Note: Injector use is collected only at Visit 2 and Visit 5. Percentages are determined using the number of subjects with response at the visit.

Table 14.3.4.4.1
Summary of User evaluation and information pertaining to the use of the microinjector during the injection procedure in the
Study Eye, by Visit
(Safety Population)

Category/Questions	Response	4 mg CLS TA SC Injection (N=38)	
		Visit 2 (Week 0) n(%)	Visit 5 (Week 12) n(%)
Did you have difficulty with any of the steps in the procedure?	Yes	5 (13.2)	2 (5.7)
	No	33 (86.8)	33 (94.3)
Were you able to inject all of the contents of the syringe?	Yes	38 (100)	32 (91.4)
	No	0	3 (8.6)
If not, estimate the volume injected:			
a. < 50 %		0	3 (8.6)
b. Approximately 50%		0	0
c. > 50%		0	0

Note: Injector use is collected only at Visit 2 and Visit 5. Percentages are determined using the number of subjects with response at the visit.

Reviewer Comment:

- 9% of physicians reported that <50% of volume was injected. The reliability for volume delivered and plunger depression force (force to high to complete injection) is 90%. See **comment to CDER #2**. Comment to CDER was communicate at 5/24 midcycle milestone.

10.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
Reviewer Comments See complete response 1		
CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

(b) (4)

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	
Human Factors deferred to DMEPA	

See Comment to CDER #1 in Section 2.1 of this memo. This comment was communicated in midcycle milestone 5/24.

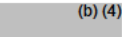
12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	
CDRH Facilities Inspection Review was not conducted	

The following information was obtained from:

Manufacture (2.3.P)

 (b) (4) – Section 12 Summary of Manufacturing Processes and Lot Release activities

Facility Regulatory History Review	
Firm Name:	(b) (4)
Address & FEI:	
Responsibilities:	Final Assembly of drug product/microinjector kit and secondary packaging
Site Inspection Recommendation:	NAI. (b) (4)

Reviewer Comments : Eventhough the last inspection was 6 years ago no inspection is recommended because of the last inspection decision (NAI), device type(co-package syringe) and indication (non-emergency use),.

Facility Regulatory History Review	
Firm Name:	(b) (4)
Address & FEI:	
Responsibilities:	Microinjector device manufacturer: Component injection molding, component pad printing, syringe assembly, needle assembly, inspection and lot release testing of components, packaging (placing device components in tray) and tyvek sealing of device componenes side of tray.
Site Inspection Recommendation:	NA.

Reviewer Comments: The Sponsor states that the (b) (4) site is not yet registered with FDA, but will comply with the FDA registration requirements for Contract medical device manufacture per 21 CFR 807.20 (a)(6). They are a Facility manufacturing the co-packaged syringe for the sponsor. The SCS microinjector is the only device being manufactured in the facility. They must register and list their manufacturing site prior to approval. See **Midcycle IR 32**. Resolved – the sponsor acknowledge the request to register and list.

Facilities Review Conclusion		
The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.	☐ Yes	☐ No

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☐
CDRH Quality Systems Documentation Review was not conducted	☐

A quality system documentation review was not conducted because the device is an ocular syringe system not for emergency use.

12.3. Control Strategy Review

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer Comments

- Control of the EPRs was inferred from the stability and release plan in Specifications. However, it is still unclear from the submission how the sponsor proposed to control proposed EPRs. **Midcycle IR 33**. Unresolved
Note: The sponsor may address **Midcycle IR 34** if they adequately address Midcycle IR 33

(b) (4)

(b) (4)

Midcycle IR 34. unresolved

- The MAF provided a high level description in Section 12.2 of what is tested but does not tie it to the EPRs or provide the specifications of the attributes tested. The control strategy is the responsibility of the Sponsor and is done from the perspective of the final finished product, not the subassembly (SCS Microinjector delivery system).

Midcycle IR 33 and 34 were not communicated. Therefore, we could not make a determination regarding the product quality (i.e., adequacy of control strategy). See Complete Response 1

Control Strategy Conclusion

The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the product.

☐ Yes

☒ No

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION

Filing Deficiencies:

☐ Yes ☐ No ☐ N/A

Mid-Cycle Deficiencies:

☐ Yes ☐ No ☐ N/A

Final Deficiencies:

☐ Yes ☐ No ☐ N/A

Reviewer Comments

See complete response 1

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

(b) (4)

<<END OF REVIEW>>

Ryan
Ortega -S

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by Ryan Ortega -S
Date: 2019.05.15
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Reviewer

Branch Chief

6 – CON199832 (ICC1900093)



Chunchun
Zhang

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