CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210331Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

NDA 210331
Review # 1
Oct 5, 2018

Drug Name/Dosage Form	***YUTIQ® (Fluocinolone Acetonide Intravitreal Implant)***
Strength	*0.18 mg*
Route of Administration	*Intravitreal Implant*
Rx/OTC Dispensed	*Rx*
Applicant	*EyePoint Pharmaceuticals, Inc (formally known as pSivida US, Inc)*
US agent, if applicable	*NA*

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	*1/5/2018*
Amendment	*3/20/2018*
Amendment	*4/4/2018*
Amendment	*7/6/2018*
Amendment	*7/20/2018*
Amendment	*7/23/2018*
Amendment	*8/7/2018*
Amendment	*8/13/2018*
Amendment	*8/23/2018*
Amendment	*8/31/2018*
Amendment	*9/14/2018*
Amendment	*9/21/2018*
Amendment	*9/26/2018*
Amendment	*9/28/2018*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Application Technical Lead	Chunchun Zhang	NA
Drug Substance	Gaetan Ladouceur	Charles Jewell
Drug Product	Yong Wang	Balajee Shanmugam
Microbiology	Jennifer Sykora	Elizabeth Bearr
Biopharmaceutics	Akm Khairuzzaman	Jing Li
Process	Steve Rhieu	Maotang Zhou
Facility	Steve Rhieu	Cassandra Abellard

Regulatory Business Process Manager	Kristine Leahy	NA
ORA Lead	NA	NA
Laboratory (OTR)	NA	NA
Environmental Assessment (EA)	Yong Wang	Balajee Shanmugam

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

DMFs:

	Type			Status[1]	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	12/14/2017	LoA: 5/22/2018 Reviewed by Weixiang Dai
	Type III			NA		LoA: 10/23/2017
	Type III			NA		LoA: 7/10/2018

(There is enou re the DMF did not need to be reviewed).

ther Docum *lications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	113140	
NDA	210923	LoA: 6/1/2018

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Adequate		10/1/2018	Aling Dong
CDRH	Adequate		7/12/2018	Simona Bancos
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

Satisfactory information and response have been submitted to support the quality of the drug substance, drug product, manufacturing process, biopharmaceutics, and quality micro aspects.

The Office of Process and Facilities has issued an overall acceptable recommendation on 10/1/2018. In agreement with the above recommendation, NDA 210331 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.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	For the treatment of non-infectious uveitis affecting the posterior segment of the eye.
Duration of Treatment	Approximately 36 months. 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, fluocinolone acetonide, is a white or almost white, microcrystalline powder. It is manufactured by (b) (4) The drug substance referenced in DMF (b) (4) was found adequate by Weixiang Dai on 12/14/2017.

ii. Drug Product Quality Summary

Fluocinolone Acetonide Intravitreal Implant, 0.18 mg is indicated to treat non-infectious uveitis affecting the posterior segment of the eye. The drug product is a

light brown 3.5mm x 0.37mm implant and is loaded into a single (b) (4) applicator and then is placed inside a sealed sterile foil pouch inside a (b) (4) pouch.

The inactive ingredients include polyimide tube, polyvinyl alcohol, silicone adhesive, and water for injection. All excipients used in the formulation are adequately qualified. No novel excipients are used in the formulation. The drug product specification includes tests for appearance, two non-specific identification tests by HPLC and TLC, assay, impurities (specified, unspecified and total), release rate, content uniformity, bacterial endotoxins, Container Closure Integrity, and sterility. Evaluation of the risk assessment of the elemental impurities was performed and indicates the results are lower than the permitted daily exposure (PDE) as noted in ICH Q3D guidance. The proposed specification is acceptable to ensure quality of the product over its expiration period. All analytical methods are described in reasonable detail and have been adequately validated. The applicant performed extractable study, (b) (4)

(b) (4)

The CDRH reviewer Dr. Simona Bancos has found the biocompatibility profile of the polyimide tubing is acceptable and has recommended conducting biocompatibility tests (cytotoxicity, sensitization and irritation) for the applicator. The applicant submitted cytotoxicity test result on 9/21/2018 which was found acceptable by CDRH on 10/3/2018. The other aspects of biocompatibility, sensitization and irritation tests are currently pending and the applicant proposes to submit the results post approval. We note the applicant has used the drug products (Batch 13-0014, Batch 14-0001 and Batch 15-0016) which have been stored for about 12 months for use in clinical trial studies PSV-FAI-001 and PSV-FAI-006, using the proposed applicators. The lack of any reported adverse events caused by the applicator with the drug suggests compatibility. Additionally, Dr. Chambers indicates that the non-clinical study supports the biocompatibility for the applicator. Therefore, the biocompatibility of the applicator is considered of low risk with no apparent concern for the applicator at this point.

The proposed commercial scale is (b) (4) Batch analyses are provided for 6 batches on the commercial scale and manufactured in the commercial site pSivida US, Inc. All batches complied with the proposed specification.

Drug product stability data is available to 24 months at long term storage 25°C/60%RH and 6 months at 40°C/75%RH for three registration batches. The attributes are within proposed specifications. The shelf life of 24 months when stored at 15°C-30°C is granted.

Biopharmaceutics has found the proposed drug release acceptance criterion of (b) (4) µg/day is acceptable. The bridging between the clinical and commercial formulation-products is not needed as the formulation of the drug

(b) (4)

(b) (4)

(b) (4)

The drug product facility Eyepoint Pharmaceuticals, Inc., FEI 3005508657 is found acceptable from outcome of the recent re-inspection. Therefore, the overall recommendation of "Acceptable" was entered for the NDA into Panorama by OPF on 10/1/2018.

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		Final Risk Eval.	Lifecycle Considerations Comments
Sterility	Formulation Container closure[1] Process parameters Scale/equipment Site[3]	H	(b) (4)	L	(b) (4)
Endotoxin Pyrogen	Formulation Container closure[1] Process parameters Scale/equipment	L		L	

			(b) (4)		
Assay (API), stability	Formulation Container closure[1] Raw materials	L		L	
Release rate	Formulation Process parameters	H		L	
Content uniformity	Formulation Container closure[1] Process parameters Scale/equipment	M		L	
Extractables and Leachables	Formulation Container closure[1] Process parameters Scale/equipment	M		L	

[1]Stability studies demonstrate container closur roduct for all quality attributes.

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BIOPHARMACEUTICS

NDA: 210331
Drug Product Name/Strength: YUTIQ® (Fluocinolone Acetonide Intravitreal Implant) / 0.18 mg
Route of Administration: Intravitreal implantation
Applicant Name: pSivida US, Inc.

Background: pSivida US, Inc. is seeking approval for Yutiq® (Fluocinolone Acetonide Intravitreal Implant) 0.18 mg for Intravitreal Injection under the 505 (b)(1) path. The drug product is a sterile sustained release delivery system containing fluocinolone acetonide (an insert) to be administered intravitreally for the treatment of non-infectious uveitis affecting the posterior segment of the eye. The drug product is designed in a way so that it can release sub-microgram levels of fluocinolone acetonide into the ocular vitreous chamber for as long as three years. This product is the same by design with that of another product, ILUVIEN, approved under NDA 201923. They are nearly identical, differing only in strength, manufacturing site and inserter. The dimension of the subject insert is 3.5 mm (L) x 0.37 mm (D). The summary of the biopharmaceutics study of Fluocinolone Acetonide (FA) release for this product submitted under this NDA is also cross referenced with NDA 201923.
The Applicant also owns other similar products such as Vitrasert® (surgical ocular implant to deliver ganciclovir for over 5-8 months), Retisert® (surgical implant to deliver fluocinolone acetonide for over 30 months).

The clinical package in support of this NDA for Yutiq® (Fluocinolone Acetonide Intravenous Implant) 0.18 mg includes the results of 3 phase III safety and efficacy studies. The primary efficacy endpoint was defined as the proportion of subjects who had a recurrence of uveitis in the study eye within 6 months following treatment.

REVIEW SUMMARY

The product is an ocular implant. The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall relevant information/data supporting **1)** in vitro drug release method and acceptance criterion for the proposed drug product, and **2)** bridging throughout product development.

Based on the review of the provided information/data, Division of Biopharmaceutics has the following comments:

1) ***Drug Release Method and Acceptance Criterion:*** The Applicant's proposed method [1.7 mL micro centrifuge tube filled with 1 ml of 0.1M phosphate buffer solution, pH 7.4 immersed into a water bath at 37°C] which was also used for another similar approved product is **acceptable** to monitor drug release from the implant. The proposed drug release acceptance

criterion of (b) (4) µg/day is **acceptable**. An **appropriate level** of drug release characterization was done during product development stage while manufacturing the clinical study batches.

2) ***Bridging of Formulations:*** The formulation of the drug product used in the pivotal clinical studies is reported to be the same as that of the commercial drug product. The manufacturing site of the drug product-batches used in the Phase 3 clinical and registration-stability studies is the proposed commercial site. Therefore, bridging between the clinical and commercial formulation-products is not needed. **Acceptable**.

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 210331 for YUTIQ® (Fluocinolone Acetonide Intravitreal Implant) 0.18 mg for Intravitreal Implantation, is recommended for **APPROVAL**.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

Akm Khairuzzaman, PhD — ***7/4/2017***
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Secondary Biopharmaceutics Reviewer Name and Date:

Jing Li, PhD — **8/6/2017**
Division of Biopharmaceutics
Office of New Drug Products, OPQ

BIOPHARMACEUTICS ASSESSMENT

➢ LIST OF SUBMISSIONS BEING REVIEWED:

eCTD # (SND #)	Received date	Document
0000 (1)	01/05/2018	Original submission
0007 (7)	3/26/2018	Quality/Response to information request

➢ DRUG PRODUCT:

The drug product is a sterile non-biodegradable sustained release delivery system (an insert) to be administered Intravitreally for the treatment of non-infectious uveitis affecting the posterior segment of the eye. The drug product is designed in a way so that it can release sub-microgram level as three year design is show

(b) (4)

As de (b) (4) over a total period of approximately 36

months. (b) (4)

(b) (4)

➢ **DRUG RELEASE METHOD & ACCEPTANCE CRITERION**

- ***Proposed Drug Release Method and Acceptance Criterion:*** The dissolution method and dissolution acceptance criterion proposed by the Applicant for the proposed drug product are presented below.

Apparatus	Medium	Volume/Temp (mL/°C)	Analytical Method	Proposed Drug Release Rate Acceptance Criterion
1.7 mL micro centrifuge tube	0.1 M phosphate buffer solution (pH 7.4)	1 ml /37 °C	HPLC	(b) (4) µg/day

The device is placed into the centrifuge tube followed by enclosing by cap. The tube is then immersed into water bath (temp 37 °C). Samples are collected every 24 hours. The volume of 1ml was selected based on FA solubility in physiological pH ((b) (4) µg/ml) and FA implant release rate specification ((b) (4) µg/day). Sink conditions are maintained for a 24-hour period. No agitation is used in the release rate test, due to the small volume (1ml). The test time points are set for every 24 hours for 8 consecutive days.

- ***Physicochemical properties affecting drug release***: The drug is practically insoluble in water and has solubility in pH 7.4 phosphate buffer solution as follows: (b) (4) µg/ml at 37 °C. It

(b) (4)

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(b) (4)

se from drug product was adapted from methods previously developed by pSivida to measure the rate of drug release from Vitrasert® and Retisert. It was also used for the very similar product ILUVIEN which also contains FA. This method was validated to support the approved product, ILUVIEN. Therefore, the method was found to be relevant for this implant and considered adequate for the quality control purposes based on the availability of sufficient sink condition, as well as, discriminating ability of the method towards critical formulation, process and raw material variables (b) (4)

(b) (4)

The proposed acceptance criterion for rate of FA release in commercial YUTIQ drug product of (b) (4) µg/day (target initial release rate of (b) (4) µg/day ± (b) (4) µg/day) is reasonable based on the daily average drug release rate (with low and high) from the clinical batches, registration batches as well as stability data.

- ***BRIDGING OF FORMULATIONS***

The formulation of the drug product used in the pivotal clinical studies is reported to be the same as that of the commercial drug product. The manufacturing site of the drug product-batches used in the Phase 3 clinical and registration-stability studies is the proposed commercial site. Therefore, bridging between the clinical and commercial formulation-products is not needed.

Reviewer's Assessment: ADEQUATE

[1] \\cdsesub1\evsprod\NDA210331\0007\m3\32-body-data\32p-drug-prod\uviey\32p2-pharm-dev

- **OVERALL RECOMMENDATION:**

From a Biopharmaceutics perspective, NDA 210331 for YUTIQ® (Fluocinolone Acetonide Intravitreal Implant) 0.18 mg for Intravitreal Implantation, is recommended for **APPROVAL**.

Akm Khairuzzaman

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Jing Li

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MICROBIOLOGY

IQA Review Guide Reference

Product Background:

NDA: 210331

Drug Product Name / Strength: (b) (4) **Fluocinolone Acetonide, 0.18 mg**

Route of Administration: Intravitreal Implant

Applicant Name: pSivida Corp

Manufacturing Site: pSivida US, Inc, 480 Pleasant Street, Watertown, MA 02472, USA

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary: Recommended as Approvable on the basis of sterility assurance.

List Submissions Being Reviewed: 01/05/2018; 06/22/2018; 7/20/2018; 8/23/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: None

Concise Description Outstanding Issues Remaining: None

Supporting Documents:

- **Microbiology review** (b) (4) **describes the bubble leak test for Container Closure Integrity Testing.**

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance – The drug substance is (b) (4)

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – (b) (4) (Fluocinolone Acetonide (FA), 0.18 mg) is a sterile intravitreal implant designed to release submicrogram levels of FA. This implant is (b) (4) loaded into an applicator that has a 25-guage needle. The drug product consists of the implant and device inside a foil (b) (4) pouch.

- **Drug product composition** (b) (4)

Ingredient	Function	Amount per implant
Fluocinolone Acteonide (FA), USP		(b) (4)

- (b) (4)

- (b) (4)

(b) (4)

[redacted]

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

(b) (4)

[redacted]

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(b) (4)

Revie

The firm provided sufficient information for validation of sterility testing of the drug product.

P.7 Container Closure – See P.1

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(See 3.2.P.8.1 in "Stability Summary and Conclusions.pdf")

Proposed Expiry: 24 months at RT

Stability testing includes testing under accelerated (40ºC ± 2ºC/ 75% ± 5%RH) and long-term (25ºC ± 2ºC/ 60% ± 5%RH) conditions. Accelerated conditions are tested at 1, 3, and 6 months and the long-term conditions are tested at 1, 2, 4, 6, 9, 12 ,18, 24, and 36 months. Sterility testing is performed as per USP <71> and has an acceptance criteria of "sterile."

Reviewer's Assessment: ***Adequate***

The firm provided sufficient information in the stability summary to support the proposed expiry of the drug product.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(See 3.2.P.8.2)

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Sterility	USP <71>	Sterile

Endotoxin testing will be performed at release only (see page 11).

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: 25ºC ± 2ºC/ 60% ± 5%RH

Test	Time (Months)								
	0	3	6	9	12	15	18	24	30
Sterility	X				X			X	X

Post Approval Stability Commitment

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

Reviewer's Assessment: ***Adequate***

The firm provided sufficient information on the post-approval stability protocol and stability commitment for the drug product.

P.8.3 Stability Data

For 25ºC ± 2ºC/ 60% ± 5%RH:

Lot numbers 13-0014, 14-0001, 15-0006 passed sterility testing at 0, 12, and 24 months. Lot numbers 13-0014 and 14-0001 also passed sterility testing at 36 months. Lot numbers 17-0005, 17-0006, 17-0007 also passed sterility testing at time 0.

40°C ± 2°C/ 75% ± 5%RH:
Lot numbers 13-0014, 14-0001, 15-0006 passed sterility testing at 0 and 6 months. Lot numbers 17-00058, 17-0006, and 17-0007 also passed sterility testing at time 0.

Reviewer's Assessment: ***Adequate***

The firm provided sufficient information on the stability data for the finished batches.

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: ***N/A***

A.2.1 Materials of Biological Origin

Reviewer's Assessment: ***N/A***

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: ***N/A***

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: ***N/A***

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: ***N/A***

R Regional Information

Executed Batch Records

Executed lot #(s): 17-0005, 17-0006, and 17-0007

(b) (4)

Note to Reviewer: This reviewer located the sterility documents from (b) (4) in 3.2.R in documents titled "Lot # - FG-XXX.pdf." The documents provide QC documentation of the Final Microbiology Results. It appears that Sterility testing was performed using methods in AAMI TIR 333:2005 and resulted was recorded as "sterile." Furthermore endotoxin testing was performed by USP <85> and resulted in (b) (4) EU/implant. (b) (4) (b) (4)

Reviewer's Assessment: ***Adequate***

Comparability Protocols - No CP was included in the application.
Reviewer's Assessment: ***N/A***

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

- **Post-dilution/constitution hold time** – N/A
  (1.14.1.3)

  Storage temperature: Room temperature; Route of administration: Intravitreal Implant ; Container: Single (b) (4)

Reviewer's Assessment: ***Adequate***

The firm provided sufficient information on the package insert for the storage conditions and route of administration for the sterile drug product.

Post-Approval Commitments: **None**

Reviewer's Assessment: ***N/A***

List of Deficiencies: **None**

Primary Microbiology Reviewer Name and Date: **Jennifer Sykora, Ph.D. on Sep 5, 2018**

Secondary Reviewer Name and Date (and Secondary Summary, as needed): **Elizabeth Bearr, Ph.D. on Sep 5, 2018**

Jennifer Sykora

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Elizabeth Bearr

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M E M O R A N D U M

U.S. FOOD & DRUG ADMINISTRATION

DATE: 3 Oct 2018

TO: Kristine Leahy
Regulatory Health Project Manager
CDER/OPQ/OPRO/DRBPMI/RBPMBI

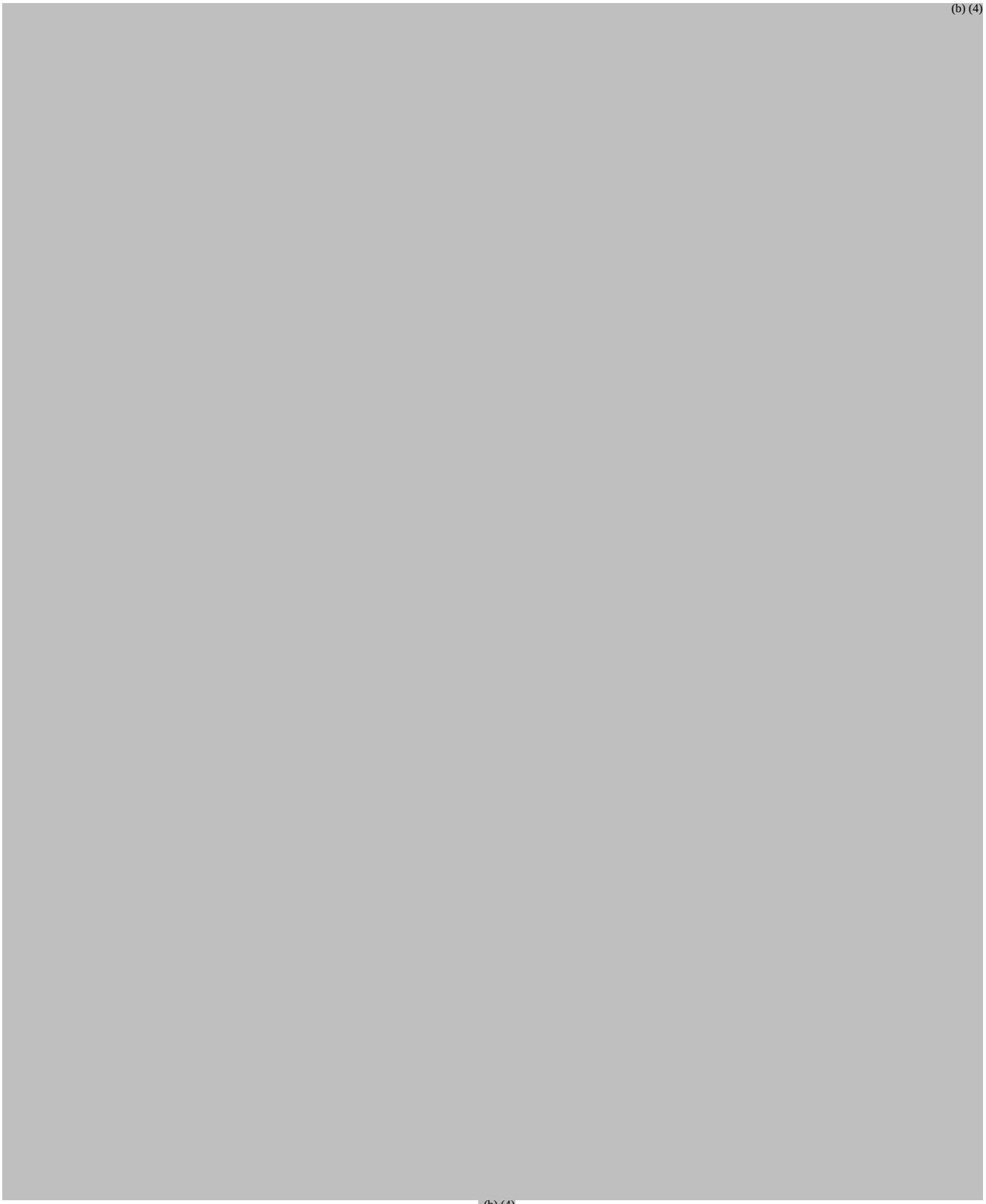
FROM: Jennifer Sykora, Ph.D.
Microbiologist
CDER/OPQ/OPF/DMA/Branch I

THROUGH: Elizabeth Bearr, Ph.D.
Microbiologist
CDER/OPQ/OPF/ DMA/Branch I

SUBJECT: NDA: 210331
Submission date: 28 Sep 2018
Drug Product (b) (4) Fluocinolone Acetonide, 0.18 mg
Applicant: pSivida Corp

NDA 210331 was submitted to the Agency on 1/5/2018 and a Microbiology review of the original

(b) (4)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Acceptable

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Chunchun Zhang

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