CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210565Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approval

NDA 210565
Review # 1
Jul 24, 2018

Drug Name/Dosage Form	***INVELTYS (Loteprednol etabonate ophthalmic suspension)***
Strength	*1%*
Route of Administration	*Topical ophthalmic*
Rx/OTC Dispensed	*Rx*
Applicant	*Kala Pharmaceuticals*
US agent, if applicable	*NA*

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	*10/24/2017*
Amendment	*1/8/2018*
Amendment	*1/16/2018*
Amendment	*1/22/2018*
Amendment	*3/20/2018*
Amendment	*3/22/2018*
Amendment	*3/30/2018*
Amendment	*4/18/2018*
Amendment	*6/4/2018*
Amendment	*6/27/2018*
Amendment	*6/28/2018*
Amendment	*7/12/2018*
Amendment	*7/23/2018*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Application Technical Lead	Chunchun Zhang	NA
Drug Substance	Sharon Kelly	Charles Jewell
Drug Product	Shrikant Pagay	Balajee Shanmugam
Microbiology	Andrew Pike	John Metcalfe
Biopharmaceutics	Akm Khairuzzaman	Jing Li
Process	Feiyan Jin	Dan Obrzut
Facility	Wenzheng Zhang	Christina Capacci-Daniel

QUALITY ASSESSMENT

Regulatory Business Process Manager	Kristine Leahy	NA
ORA Lead	Caryn McNabb	NA
Laboratory (OTR)	NA	NA
Environmental Assessment (EA)	Shrikant Pagay	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)	loteprednol etabonate drug substance (b) (6)	Adequate	7/15/2018	LoA: 6/15/2017 Reviewed by Sharon Kelly
	Type III			NA		LoA: 8/4/2017
	Type III			NA		LoA: 8/17/2017
	Type III			NA		LoA: 5/25/2017
	Type III			NA		LoA: 7/5/2017
	Type III			NA		LoA: 7/17/2017
	Type III			NA		LoA: 7/5/2017
	Type III			NA		LoA: 5/29/2018

[1]NA (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	117192	This product during IND development

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

NDA 210565, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product INVELTYS (Loteprednol etabonate ophthalmic suspension), 1%. All information requests and review issues have been addressed.

The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on 7/13/2018.

Therefore, NDA 210565 is recommended for 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 of post-operative inflammation and pain following ocular surgery.
Duration of Treatment	Instill one to two drops of INVELTYS™ into the affected eye twice daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period. 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, Loteprednol etabonate, is a white to almost white crystalline powder. It is manufactured by (b) (4) The drug substance referenced in DMF (b) (4) was found adequate by Sharon Kelly on 7/15/2018.

ii. Drug Product Quality Summary

Loteprednol etabonate ophthalmic suspension is corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery. The drug product is provided in a 5 mL LDPE (b) (4) with 2.8 mL fill for the commercial supply and 1.2 mL fill for the physician samples. Each (b) (4) is packaged in an individual carton with black/white printed package insert.

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, identity, assay, impurities (specified, unspecified and total), BAC assay, EDTA assay, pH, osmolality, (b) (4) sterility, particle size, and minimum fill volume. (b) (4) "shake for 1 to 2 seconds before using". (b) (4) is not included in the drug product specification which was found acceptable. 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. Extractable and leachable studies were performed and no leachable were detected in the 12 months' stability data provided in the submission. The updated specification was submitted on 7/23/2018 with the revised limits on the related impurities/degradants and it 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.

Batch analyses are provided for 3 registration batches for the commercial fill configuration and 3 registration batches for the physician samples manufactured at the commercial site (b) (4). All batches complied with the proposed specification.

The applicant proposed a (b) (4) to stability study for the commercial drug product: (b) (4) the bottles (b) (4) stored at 15°C- 25°C for 24 months. Drug product stability data for the commercial fill bottles is available for (b) (4) Twelve months stability data for the physician sample stored at (b) (4) 25°C/40%RH, and 6 months stability data at 30°C/35%RH are provided. All the quality attributes remain within the proposed specifications. Therefore, the expiration date granted for (b) (4) commercial fill bottles (b) (4) stored at 15°C- 25°C, an

expiration date of 24-months is granted. The physician samples (1.2 mL fill) when stored upright at 15°C- 25°C is recommended an expiration date of 12 months.

The storage statement is "Store upright at 15°C to 25°C (59°F to 77°F). Do not freeze" and will be finalized at the OND's labeling meeting.

The proposed drug product manufacturing process consists of: (b) (4) During the NDA review several information requests regarding to in-process controls, batch records and extractable/leachable were conveyed to and addressed by the applicant. The overall information regarding the manufacturing process provided in the NDA submission and subsequent amendments was found acceptable. The drug product is manufactured at a series of facilities with a (b) (4) It is found acceptable from quality micro perspective.

Biopharmaceutics reviewer Dr. Akm Khairuzzaman has found bridging between the clinical and commercial formulation-products is not needed. However, one PMC on improving the dissolution method has been recommended in Dr. Khairuzzaman's review chapter. During the clinical meeting on 7/16/2017, Dr. Wiley Chambers disagreed with the proposed PMC, therefore, this PMC hasn't been communicated to the applicant, please refer to Dr. Chambers' review for the further discussion. Below is the proposed Biopharmaceutics PMC:

(b) (4)

(b) (4)

All the facilities are acceptable based on the profile. No pre-approval inspection is required at this review cycle. Therefore, the overall recommendation of "Approve" was entered for the NDA into Panorama by OPF on 7/13/2018.

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	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	Formulation Container closure[1] Process parameters Scale/equipment Site	H	Sterilization has been validated.	L	Post-approval stability protocol will test sterility.
Endotoxin Pyrogen	Formulation Container closure[1] Process parameters Scale/equipment	L	This is a topical product and therefore does not require testing for endotoxin.	L	No endotoxin testing required.
Assay (API), stability	Formulation Container closure[1] Raw materials	L	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification. Label claim will be delivered.	L	

Assay (preservative)	Formulation Container closure[1] Process parameters Scale/equipment	L	Preservative benzalkonium chloride is added in the formulation.	L	
Uniformity of Dose (Fill Vol/ Deliverable volume)	Formulation Container closure[1] Process parameters Scale/equipment	M	5 mL LDPE (b) (4) with 2.8 mL fill volume for the commercial bottles and 1.2 mL fill for the physician sample. (b) (4) (b) (4) performed to support "Shake for 1 to 2 seconds before using".	L	
pH	Formulation Container closure[1] Process parameters Scale/equipment	L	(b) (4) No trend on stability observed. Impact on other quality attributes is very minimal.	L	
Particulate matter	Formulation Container closure[1] Process parameters Scale/equipment	M	(b) (4) test was included in the drug product specification	L	

[1]Stability studies demonstrate container closure compatibility with the drug product for all quality attributes.

This NDA is recommended for approval from the Product Quality Perspective.

On behalf of the OPQ team
Chunchun Zhang, Ph.D. ATL for NDA 210565

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MICROBIOLOGY

IQA Review Guide Reference

Product Background:

NDA: 210565

Drug Product Name / Strength: Loteprednol Etabonate ophthalmic suspension, 1%

Route of Administration: Topical

Applicant Name: Kala Pharmaceuticals, Inc

Manufacturing Sites:

(b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

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

Justification (ANDA only): N/A

Review Summary: (b) (4)
(b) (4)

List Submissions Being Reviewed: 10/24/2017, 01/22/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting Documents: N/A

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

S Drug Substance

The drug product is sterilized [redacted] (b) (4) The drug substance was not reviewed.

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – The drug product is a sterile [redacted] (b) (4)
- **Drug product composition** – The drug product composition is displayed in the table below (from section 3.2.P.1 Description and Composition of the Drug Product).

Ingredient	Standard	Function	Amount (mg) per mL of product	Concentration
Loteprednol etabonate	[redacted] (b) (4)	API	10	1
Glycerin	USP-NF	[redacted] (b) (4)	[redacted] (b) (4)	[redacted] (b) (4)
Sodium citrate dihydrate	USP-NF			
Poloxamer 407	USP-NF			
Sodium chloride	USP-NF			
Edetate disodium dihydrate	USP-NF			
Citric acid [redacted] (b) (4)	USP-NF			
Benzalkonium chloride	USP-NF	Preservative		0.01
WFI	USP-NF	[redacted]		(b) (4)

- **Description of container closure system** – The drug product will be packaged in a 5 mL white low density polyethylene (LDPE) dropper bottle with a controlled-drop linear LDPE tip [redacted] (b) (4), a pink high density polyethylene (HDPE) cap and a white LDPE overcap. [redacted] (b) (4) will contain either 1.2 mL of KPI-121 1% solution as physician samples or 2.8 mL of KPI-121 1% solution as commercial bottles.

Adequate

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

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

(b) (4)

(b) (4)

Results are provided in section 3.2.P.2 Attachment PCL pgs. 22-23 of 25. The applicant states that all acceptance criteria were met.

Adequate

Reviewer's Assessment: The applicant provided an acceptable description of the container closure integrity test, and the container meets regulatory expectations for demonstrating container closure integrity.

Antimicrobial Effectiveness Testing

Section 3.2.P.2 Microbiological Attributes and Section 3.2.P.2 Attachment KPI-121-T-024

The drug product contains 0.01% benzalkonium chloride (BAK) as a preservative. Antimicrobial effectiveness testing was performed in accordance with USP <51> on batch 00516A1 both at product release and after 12 months. All five compendial organisms were reduced from > (b) (4) CFU/mL to < (b) (4) CFU/mL at 7, 14 and 28 days post-inoculation, yielding satisfactory results. The applicant also states that the antimicrobial effectiveness of BAK was confirmed down to (b) (4)% w/v, which is (b) (4)% of the label claim for BAK, leading them to create a release specification of (b) (4)% of BAK label claim. AET is to be performed at release and at full shelf life for all products, as described in the 26th February 2017 Type C meeting and response provided in section 1.6.3 Attachment 5.

Adequate

Reviewer's Assessment: The applicant has met regulatory expectations for demonstrating the antimicrobial effectiveness requirement for a multiple dose drug product.

P.3 Manufacture

P.3.1 Manufacturers

Drug product: The drug product will be manufactured and packaged at the facilities listed below (Section 3.2.P.3.1 Manufacturers):

(b) (4)

P. 3.3 Description of the Manufacturing Process and Process Controls

Overall Manufacturing Operation

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(b) (4)

Adequate

Reviewer's Assessment: The applicant has met regulatory expectations with regard to the test method and verification of the use of the sterility test that will be performed on the drug product prior to release.

P.7 Container Closure

See P.1

P.8 Stability

P. 8.1 Stability Summary and Conclusion

Sterility will be tested in accordance with USP <71> at release and at 12, 24 and 36 months for commercial fill bottles and at 12 months for physician sample bottles (b) (4) Additionally, sterility will be tested at release and 12 and 18 months after storage at 5° C, then at 30, 42 and 54 months with storage at 25° C. All samples will be tested after upright storage, and the 12 month timepoint will also be tested in horizontal and inverted storage. In accordance with an agreement with the FDA, antimicrobial effectiveness testing will also be performed after 12, 24 and 36 months of storage (b) (4)

The proposed shelf life for the 1.2 mL physician samples is 12 months at 15-25° C and the proposed shelf life for the 2.8 mL commercial bottles is 24 months at 15-25° C.

(b) (4)

Adequate

Reviewer's Assessment: The applicant has provided an acceptable description of their microbiology stability monitoring program, and the program meets regulatory expectations with regard to the proposed expiration date.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant commits to perform post-approval stability studies on the first three commercial batches of the drug product. Additionally, stability studies will be performed on one batch for each calendar year that the drug is manufactured. (b) (4)

Adequate

Reviewer's Assessment: The applicant provided an adequate (b) (4)

P.8.3 Stability Data

The applicant provided sterility data for three batches of commercial fill and three batches of physician sample bottles. For commercial fill batches, data were provided for all storage conditions up to 12 months, and all samples conformed to USP <71>. For physician sample batches, data were provided for (b) (4) 25° C storage up to 12 months, and all samples conformed to USP <71>. Antimicrobial Effectiveness Testing was also performed after 12 months of storage at (b) (4) 25° C, and all samples passed.

Adequate

Reviewer's Assessment: The applicant provided sufficient microbiological data to support the microbiological quality of the drug product.

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

Section 3.2.R Executed Batch Records

The applicant has provided the following batch records:

- CSR KPI-121-C-001 (b) (4)

- CSR KPI-121-C-005 (b) (4)
- CSR KPI-121-C-008 (b) (4)

Adequate

Reviewer's Assessment: The applicant has provided detailed batch records for three batches of KPI-121 1%. This meets the regulatory expectations regarding the executed batch records.

Comparability Protocols

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**

Adequate

Reviewer's Assessment: The applicant has provided acceptable instructions for product use to maintain acceptable microbiological conditions.

Post-Approval Commitments:

Reviewer's Assessment: N/A

List of Deficiencies: N/A

Primary Microbiology Reviewer Name and Date: Andrew Pike, PhD; 31 January 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): John W. Metcalfe, Ph.D.; 08 February 2018. I concur with the primary reviewer's assessment.

Andrew Pike

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John Metcalfe

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Comments: I concur with the primary reviewer's assessment.

BIOPHARMACEUTICS

NDA: 210565
Drug Product Name/Strength: INVELTYS (Loteprednol Etabonate) 1% Ophthalmic Suspension)
Route of Administration: Ophthalmic
Applicant Name: Kala Pharmaceuticals, Inc.

Background: The drug (Loteprednol etabonate) product is an ophthalmic suspension. Loteprednol etabonate was first approved in 1998 under NDA 20-583 as Lotemax® ophthalmic suspension, 0.5% (Bausch & Lomb) and, most recently, in 2013 under NDA 202-872 as Lotemax® ophthalmic gel, 0.5%. Kala Pharmaceuticals, Inc developed this product as 1% ophthalmic suspension claiming that their suspended (b) (4) particles can enhance penetration of the drug through the mucous layer of the tear film and into ocular tissues.

This 505(b)(2) NDA relies in part on the FDA's findings of safety for Lotemax® 0.5% loteprednol etabonate ophthalmic suspension. The clinical package in support of this NDA includes the results of 2 PK and tolerability studies, and 5 efficacy and safety studies.

REVIEW SUMMARY

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting; **1)** the dissolution method used in product development, and **2)** bridging throughout product development.

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

1) ***Dissolution/In Vitro Drug Release:*** *Acceptable with PMC*
   Applicant did not propose any dissolution test in their product specification. An IR letter was sent out to the Applicant on Feb 23, 2018 requesting for dissolution method used for the product development. While applicant responded with the details of their dissolution method, the method was not used for QC test for dissolution, instead it was used for product development with very limited information revealed. The dissolution method was found to be not suitable for the proposed drug product (b) (4)
   (b) (4)

2) ***Bridging of Formulations:*** *Acceptable*

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.

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 210565 for INVELTYS (Loteprednol Etabonate) 1% Ophthalmic Suspension, is recommended for **APPROVAL with** (b) (4)

(b) (4)

- (b) (4)

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

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

I concur with Dr. Akm Khairuzzaman's recommendation.
Secondary Biopharmaceutics Reviewer Name and Date:

Jing Li, PhD **7/7/2017**
Division of Biopharmaceutics
Office of New Drug Products, OPQ

BIOPHARMACEUTICS ASSESSMENT

➢ LIST OF SUBMISSIONS BEING REVIEWED:

eCTD # (SND #)	Received date	Document
0000 (1)	10/24/2017	Original submission
0014 (14)	3/22/2018	Quality/Response to information request

➢ DRUG PRODUCT:

The proposed drug product is a sterile ophthalmic suspension containing (b) (4)-sized Loteprednol Etabonate (b) (4) Each milliliter of KPI-121 1% (INVELTYS (Loteprednol Etabonate) 1% Ophthalmic Suspension) contains 10 mg LE as the active ingredient. Inactive ingredients are glycerin, sodium citrate dihydrate, poloxamer 407, sodium chloride, edetate disodium dihydrate, citric acid, benzalkonium chloride and water for injection.

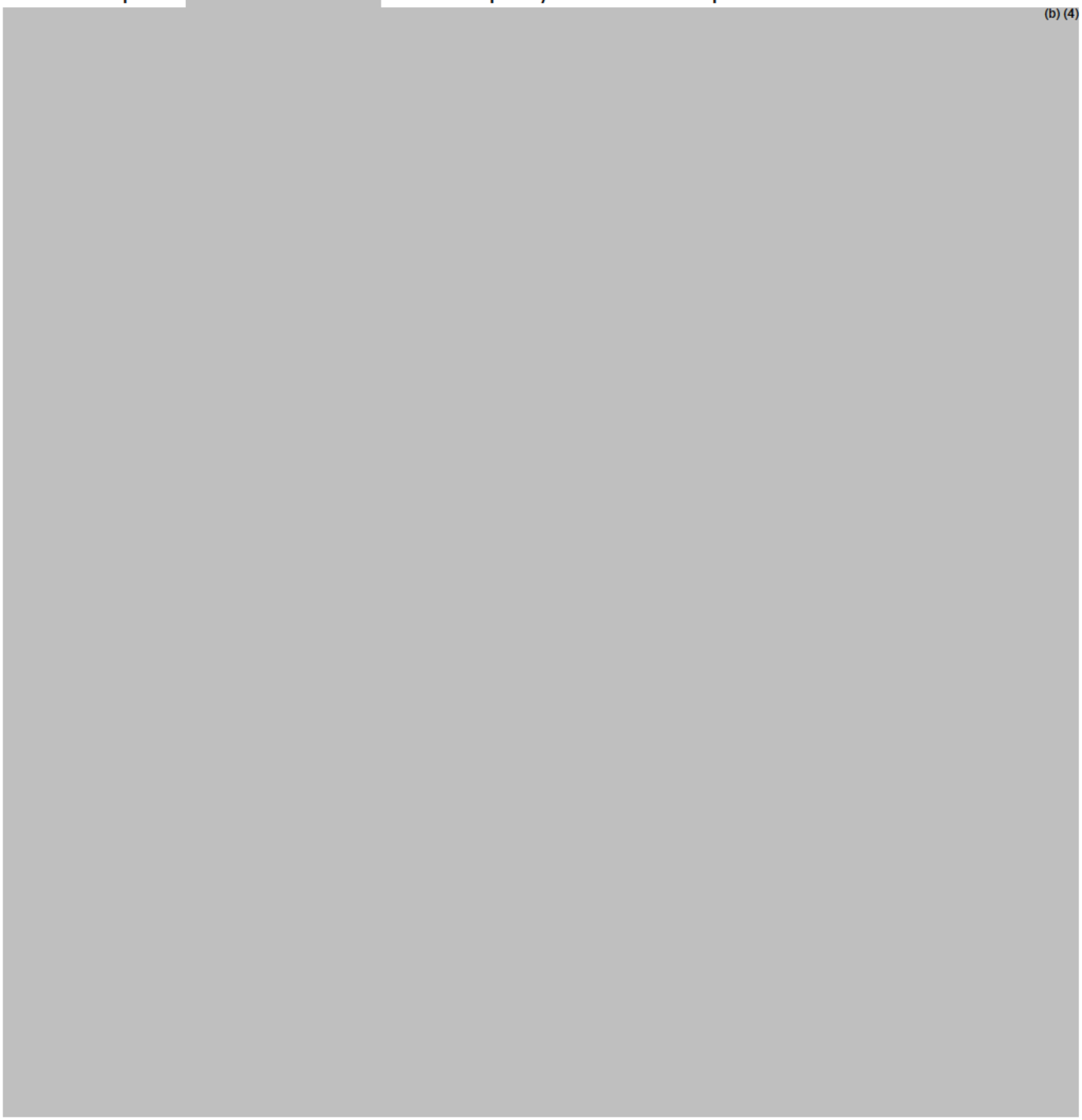
➢ *DISSOLUTION INFORMATION:*

The following dissolution method was used for the product development.

(b) (4)

The following figures (taken from the IR response) provides information of the method's sensitivity with respect to (b) (4) and other quality attributes of the product.

(b) (4)



(b) (4)

[redacted]

- ***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

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.

- ***BIOWAIVER REQUEST***

None.

- **OVERALL RECOMMENDATION:**

From a Biopharmaceutics perspective, NDA 210565 for INVELTYS (Loteprednol Etabonate) 1% Ophthalmic Suspension, is recommended for **APPROVAL with a PMC**.

Akm Khairuzzaman

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Jing Li

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Chunchun Zhang

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